RESEARCH TOOL PATENTS WITH REACH-THROUGH CLAIMS AND LICENSING AGREEMENTS WITH REACH-THROUGH ROYALTY CLAUSES

A RESOURCE FOR RESEARCHERS & PRACTITIONERS IN SINGAPORE

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CHAPTERS AND APPENDICES

APPENDICES TO THE CHAPTERS

CHAPTER 1

VALIDITY OF REACH-THROUGH PATENT CLAIMS

The patent system is intended to reward inventors who, in return for certain, time-limited exclusive rights, disclose their new inventions to the public. By rewarding them in that way, the system seeks to encourage or promote technical innovation. That basic aim or reason would be subverted if a patent were to be granted for an invention (or alleged invention) that could not be applied or practised in any industry or that has yet to be identified; and such a patent could hinder the efforts of others wanting to pursue a particular line of research or product development[1]. A patent cannot be granted for something that is not a patentable invention within the meaning of the applicable law.

A patent is a contract with the public, in which the *quid pro quo* for the disclosure of an invention is the grant of certain exclusive rights in respect of the invention. These rights give the owner of a patent an opportunity to develop the invention and to profit from it if there is a market for it. A research tool is, for present purposes, a method which scientists or technicians can use to identify or discover biologically active compounds for further possible development. The tool itself is not a feature of a marketable end-product but it can be an essential for identifying or testing a compound that in time and with further development may become a marketable end-product. Being a method, it may easily be misappropriated by being used without a licence from the owner of the patented tool. A patented method can be very difficult to police against infringers.

The inventor of a research tool who applies to patent it must show that the invention meets the criteria for the grant of a patent, that it is a patentable invention. If the patent applied for is granted, the owner (patentee) can exploit the patented invention exclusively or by licensing it. The grant of a patent does not mean that the patent or any claim in the patent is unquestionably valid, although there is a rebuttable legal presumption of validity[2]. A patent claim is the inventor's written definition of the invention (or alleged invention)[3]; it is a carefully-worded statement of the technical features of the new and

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[1] The English courts were alert to this consequence from the earliest days of the English patent system. For example, in Morgan v Seaward (1837) 150 ER 874 (English Court of Exchequer) Parke B. said that the grant of a monopoly "for an invention which is altogether useless may well be considered as 'mischievous to the state, to the hurt of the trade, or generally inconvenient', within the meaning of the statute of Jac 1 which requires, as a condition of the grant, that it should not be so, for no addition or improvement of such an invention could be made by any one during the continuance of the monopoly, without obliging the person making use of it to purchase the useless invention…"

[2] See, for example, section 282, US Patent Code: "A patent shall be presumed valid. Each claim of a patent (whether in independent, dependent, or multiple dependent form) shall be presumed valid independently of the validity of other claims; dependent or multiple dependent claims shall be presumed valid even though dependent upon an invalid claim…"

[3] It is beyond the scope of this report to discuss the drafting of patent claims. A claim drafted for the purposes of, say, US patent law may need to be redrafted for, say, an application under the European Patent

inventive product or process that the inventor wants to patent or, in a granted patent, what is protected by the patent owner's exclusive rights[4]. Usually there is more than one claim in a patent specification[5]. A patent or patent claim can be invalidated after grant for failure to satisfy one or more of the criteria for the grant of a patent.

1 Some Relevant Rules

A patentable invention must be new, involve an inventive step and be industrially applicable[6]. The criteria for the grant of a patent also include the disclosure requirement: a patent application or granted patent must specify or describe the claimed invention in terms sufficient for a skilled person in the art to which the invention contributes, to be able to make, reproduce or perform the invention without undue effort.

The rule on industrial application in section 16 of the Singapore Patents Act (Chapter 221)[7] states that "an invention shall be taken to be capable of industrial application if it can be made or used in any kind of industry, including agriculture."[8] A method of treatment of the human or animal body by surgery or therapy or of diagnosis practised on the human or animal body is deemed not to be capable of industrial application but this does not apply to a product consisting of a substance or composition which is invented for use in such a method[9].

Convention. An inventor should always seek advice on drafting a patent claim from a patent attorney practising in the particular field of technology to which the invention contributes.

[4] Natural Color Kinematograph Co Ltd v Bioschemes Ltd [1915] 32 Reports of Patent Cases 236: "It is the duty of the patentee to state clearly and distinctly, either in direct words or by clear and distinct reference, the nature and the limits of what he claims. If he uses language which, when fairly read, is avoidably obscure and ambiguous, the patent is invalid, whether the defect be due to design, or to carelessness or to want of skill. Where the invention is difficult to explain, due allowance will, of course, be made for any resulting difficulty in the language. But nothing can excuse the use of ambiguous language when simple language can easily be employed, and the only safe way is for the patentee to do his best to be clear and intelligible" (Lord Loreburn).

[5] A claim that stands on its own is known as an *independent* claim. *Dependent* claims depend on a single claim or on several claims and generally express particular embodiments. A dependent claim has to be read in conjunction with the claim on which it depends. It provides a fall-back position in case the independent claim is invalidated by the courts.

[6] The novelty and inventive step criteria in the Singapore Patents Act is comparable to the US requirement that the invention must be new and must not be obvious (35 USC 102 and 103). In fact, the Patent Cooperation Treaty, which streamlines the filing process in its member countries, also requires that an invention be novel and involve an inventive step, but states that being non-obvious is sufficient to involve an inventive step. A European patent application involves an inventive step if it solves a technical problem in a non-obvious way, that is to say, it must solve a problem (if no problem is solved there is no inventive step) and that problem must be technical (if the problem solved is economic or social there is no inventive step).

[7] The Singapore Act is, in many of its provisions, modelled on the UK Patents Act 1977; and the UK Act's provisions on patent applications and the granting of patents are aligned with the European Patent Convention.

[8] Where the invention resides in a sequence or partial sequence of a gene, industrial application must be disclosed in the filed application, and under EPO, UK and USPTO rules the utility or industrial application must be shown to be specific, substantial and credible.

[9] See also section 4, UK Patents Act 1977

Section 25 of the Act[10] requires every patent application to contain "a specification containing a description of the invention, a claim or claims and any drawing referred to in the description or any claim"[11]. The specification must "disclose the invention in a manner which is clear and complete for the invention to be performed by a person skilled in the art" [12]. The claim or claims in the specification must "define the matter for which the applicant seeks protection, be clear and concise and be supported by the description"[13].

The level of sufficiency of the disclosure in the specification can vary; and in some instances not every product or process covered by the invention has to be disclosed[14]. An invention is sufficiently disclosed if at least one way is clearly indicated that will enable the person skilled in the art to carry out the invention[15], although a specification with a broad claim should, or perhaps must, disclose several ways of performing the claimed invention[16].

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[10] See also section 14, UK Patents Act 1977

[11] See also section 14(2), UK Patents Act 1977 and Article 78 EPC

[12] Genentech Inc's Patent [1989] RPC 147 (English Court of Appeal): "[The] skilled person should be taken to be a worker who is aware of everything in the state of the art and who has the skill to make routine developments but not to exercise inventive ingenuity. The 'person skilled in the art' may be a multi-disciplinary team rather than a single individual." See also section 14(3), UK Patents Act 1977 and the UK Patent Office Manual of Patent Practice, April 2007, pages 15 to 23, http://www.ipo.gov.uk/p-law-manual-practice.htm and http://www.ipo.gov.uk/practice-sec-014.pdf. See further EPO Enlarged Board of Appeal Decision G2/93 (1994): "In order to meet the requirements of Article 83 EPC, a European patent application must therefore contain sufficient information to allow a person skilled in the art, using his common general knowledge, to perceive the technical teaching inherent in the claimed invention and to put it into effect accordingly."

[13] See also section 14(5), UK Patents Act 1977 and Article 84 EPC.

[14] See, for example, Biogen Inc v Medera Plc [1997] Reports of Patent Cases 1 (UK House of Lords, Lord Hoffman): "[T]he specification must enable the invention to be performed to the full extent of the monopoly claimed. If the invention discloses a principle capable of general application the claims may be in correspondingly general terms. The patentee need not show that he has proved his application in every individual instance. On the other hand if the claims include a number of discrete methods or products the patentee must enable the invention to be performed in respect of each of them. Thus if the patentee has hit upon a new product which has a beneficial effect but cannot demonstrate there is a common principle by which the effect will be shared by other products of the same class, he will be entitled to a patent for that product but not for the class, even though some may subsequently turn out to have the beneficial effect … On the other hand if he had disclosed a beneficial property which is common to the class he will be entitled to a patent for all the products of that class (assuming them to be new) even though he has not himself made more than one or two of them." Whether this statement still represents English law on the question of sufficiency seems moot, having regard to suggestions in later English Court of Appeal decisions (e.g. Amgen v TKT [2002] EWCA Civ 1096) that broad claims may fail, whether or not the patent discloses a principle of general application, where an opponent can demonstrate examples of embodiments that would fall within the claims but would not 'work' in the manner of the patented invention.

[15] See, for example, Genentech I (Polypeptide expression) EPO Official Journal 1989, 275 (T 0292/85).

[16] A broad claim will not be granted if the skilled person, after reading the description, is not able readily to perform the invention over the whole area claimed without undue burden and without needing inventive skill.

The US rule corresponding to section 25 of the Singapore Act is set down in section 112 of the Patent Code (Title 35)[17]: "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention. The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention."

The information in a US patent application must be sufficient to teach the public how to make and use the invention (the enablement requirement), the best mode of practising the invention must be set out in the disclosure[18], and the description must be sufficient for the public to ascertain that, as of the filing date, the applicant was in possession of every element claimed in the invention. The enablement requirement is satisfied if any person skilled in the art can make and use the invention without undue experimentation. The section 112 requirement serves the important purpose of preventing an applicant from asserting that he invented that which he did not.

Utility or usefulness (industrial application) is a basic requirement for the grant of a US patent[19]. It means that an invention must perform some function of positive benefit to society - but the invention does not have to be superior to existing products or processes. The utility, either as asserted in the specification or as well established in the art, must be a specific and substantial credible utility and must be available as of the filing date.

There may be no insurmountable obstacle in the foregoing criteria to the grant of a patent for a research method (or tool). But as was said earlier in this Report, a claim in a patent application or granted patent to future unidentified results obtained through use of the method may be seriously and incurably deficient for lack of industrial application (utility) and/or adequate disclosure[20]. That said, patents are being granted with reach-through claims that could well be deficient and this may need to be borne in mind when negotiating licences for research tools, particularly licences with reach-through royalty

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17 See further the US PTO's MPEP 2163 Guidelines for the Examination of Patent Applications under 35 USC 112, paragraph 1, http://www.uspto.gov/web/offices/pac/mpep/documents/2100_2163.htm#sect2163.

18 This way, the inventor cannot get a patent and still keep some essential or advantageous aspect a secret. In contrast, patent laws in Singapore and Europe have no such requirement. At least one way of practising the invention must be included in the application, but there is nothing that states this way must be the best way, or even a good way.

19 Section 101, US Patent Code, states: "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvements thereof, may obtain a patent, subject to the conditions and requirements of this title." The utility requirement has been used to prevent the patenting of inoperative devices or methods such as perpetual motion machines (e.g. Newman v Quigg (1989) 877 F2d 1575 (US Court of Appeals, Federal Circuit)), a device that allegedly expanded powers of extra-sensory perception, methods of retarding aging and curing male baldness, and uncharacterised compositions for curing a wide array of cancers.

20 A reach-through claim may be vulnerable also to attack for lack of novelty and/or inventive step if the claim embraces as-yet unidentified products (e.g. activating compounds) which turn out to been known already.

clauses. Typical of European patents with reach-through claims is EP0724637 B2[21], in which claims 25 and 30 are clearly for method, and claim 39 is for a product (a receptor antagonist):

> ….
> 25. A method for detecting the presence of a compound which binds to a CRF2 receptor, comprising:
> (a) exposing one or more compounds to cells that express CRF2 receptors under conditions and for a time sufficient to allow binding of said compounds to said receptors; and
> (b) isolating compounds which bind to said receptors, such that the presence of a compound which binds to a CRF2 receptor may be detected.
> …
> 30. A method for determining whether a selected compound is a CRF2 receptor antagonist, comprising:
> (a) exposing a selected compound in the presence of a CRF2 receptor agonist to a recombinant CRF2 receptor coupled to a response pathway under conditions and for a time sufficient to allow binding of the compound to the receptor and an associated response through the pathway; and
> (b) detecting a reduction in the stimulation of the response pathway resulting from the binding of the compound to the CRF2 receptor, relative to the stimulation of the response pathway by the CRF2 receptor agonist alone, and therefrom determining the presence of a CRF2 antagonist.
> …
> 37. A method for treating Alzheimer disease, comprising administering to a patient a therapeutically effective amount of a CRF2 receptor antagonist.
> …
> 39. A CRF2 receptor antagonist for use in the manufacture of a medicament for treating cerebrovascular disorders.

According to this patent, "the invention provides a variety of methods for detecting the presence of compounds which bind to CRF2 [corticotropin-releasing factor] receptors. For example, within one embodiment of the invention methods for detecting such compounds are provided, comprising the steps of (a) exposing one or more compounds to

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[21] http://v3.espacenet.com/textdoc?DB=EPODOC&IDX=EP0724637&F=1. Another example is European Patent EP0680517 (http://v3.espacenet.com/textdoc?IDX=EP0680517) which summarises the invention as follows: "This invention provides methods and diagnostic kits for identifying and characterizing toxic compounds. These methods and diagnostic kits measure transcription or translation levels from genes linked to native eukaryotic stress promoters, especially those of mammals. The kits and methods of this invention utilize at least one stress promoter from each of the following groups: redox stress, DNA stress, protein stress and energy/ionic stress. The invention also provides methods and diagnostic kits for identifying and characterizing compounds that are toxic to specific organs, such as skin and the eye, as well as for each of the individual stresses indicated above. The methods and diagnostic kits of this invention yield information concerning the action of a compound on a subcellular level. This information may be utilized to design antitoxins to compounds found to be toxic and in active drug design." US Patent 6048850 (**University of Rochester v. G.D. Searle & Co**. (2004) 358 F.3d 916 (US Court of Appeals, Federal Circuit)) relates to the gene encoding the mammalian prostaglandin H synthase-2 and its product. The abstract in the Rochester patent, granted on 11 April 2000, reads: "More specifically, the invention relates to the diagnosis of aberrant PGHS-2 gene or gene product; the identification, production, and use of compounds which modulate PGHS-2 gene expression or the activity of the PGHS-2 gene product including but not limited to nucleic acid encoding PGHS-12 and homologues, analogues, and deletions thereof, as well as antisense, ribozyme, triple helix, antibody, and polypeptide molecules as well as small inorganic molecules; and pharmaceutical formulations and routes of administration for such compounds."

cells that express CRF2 receptors under conditions and for a time sufficient to allow binding of the compounds to the receptors, and (b) isolating compounds which bind to the receptors, such that the presence of a compound which binds to a CRF2 receptor may be detected…In addition to providing assays which detect the presence of compounds which bind to CRF2 receptors, the present invention also provides methods for detecting both CRF2 receptor agonists and CRF2 receptor antagonists. Within the context of the present invention, CRF2 receptor agonists should be understood to refer to molecules that are capable of binding to the cell-surface receptor, thereby stimulating a response pathway within the cell. In contrast, CRF2 receptor antagonists should be understood to refer to molecules that are capable of binding to a CRF2 receptor, but which prevent stimulation, or exhibit greatly reduced stimulation of a response pathway within the cell…Within a preferred aspect of the invention, the screening of chemical libraries (including peptide, small organic molecule or combinatorial chemistry-derived compound libraries) can be assessed in a high-throughput format using the expressed CRF2 receptors… Once purified partially, or to homogeneity, as desired, both CRF2 receptor agonists and antagonists may be used therapeutically."

2 Reach-Through Claims and Patentability Criteria

In the tripartite "Report on Comparative Study on Biotechnology Patent Practices"[22] the European, Japanese and US Patent Offices assessed the patentability under their respective criteria of four examples involving reach-through claims[23]. The form of these claims, including the claims that reach through to compounds yet to be discovered, is typical of claims found in research tool patent applications and granted patents.

2.1 The **first** example discussed in the report had the following claims:

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[22] http://www.trilateral.net/projects/biotechnology/reach_through_claims/B3b_reachthrough_text.pdf For the USPTO's comments, see http://www.trilateral.net/projects/biotechnology/reach_through_claims/B3b_reachthrough_annex_1.pdf; for Japanese Patent Office's comments, see http://www.trilateral.net/projects/biotechnology/reach_through_claims/B3b_reachthrough_annex_3.pdf; for the European Patent Office's comments, see http://www.trilateral.net/projects/biotechnology/reach_through_claims/B3b_reachthrough_annex_2.pdf.

[23] See also Grassler, US Treatment of Reach-Through Claims and Reach-Through Royalties, http://www.sdipla.org/events/past/grassler/ReachThru.htm; Lonati, Patentability of Receptors and Screening Methods, 4 Bio-Science Law Review 144 (2000/2001); Lim and Christie, Reach-Through Patent Claims in Biotechnology, IPRIA Working Paper (University of Melbourne), March 2005 – hereinafter "Lim and Christie"; Kunin, Reach-Through Claims in the Age of Biotechnology, 51 American University Law Review 609 (2002) – hereinafter "Kunin"; Tessensohn and Yamamoto, Enthusiasm Curbed: A Japanese View of Biotechnology Reach-Through Claims, 21 Biotechnology Law Report 426-434 (October 2002, No. 5).

1. An isolated and purified receptor[24] the sequence of which consists of SEQ ID NO 1:

2. A method of identifying an agonist[25] of the receptor of claim 1 comprising:

preparing a candidate compound,

contacting a cell which expresses said receptor on its surface with said candidate compound, and

determining whether said candidate compound activates the receptor of claim 1, wherein a compound that activates the receptor of claim 1 is an agonist of said receptor.

3[26]. An isolated and purified receptor agonist identified by the method of claim 2.

4[27]. (EPO Version) Use of a receptor agonist for the manufacture of a medicament for treating a disease treatable by said agonist, wherein said receptor agonist is identified by the method of claim 2[28].

(JPO Version) Composition comprising a receptor agonist for use in treating a disease treatable by said agonist, wherein said receptor agonist is identified by the method of claim 2, as an active ingredient.

(USPTO Version) A method for the treatment of disease treatable by the agonist of claim 2, comprising administering to a host in need thereof a therapeutically effective amount of the agonist identified by the method of claim 2.

5[29]. A monoclonal antibody which recognizes the receptor of claim 1.

Having regard to the outline specification for the first example, the claims are deficient in several respects:

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[24] Based on a homology analysis, the specification discloses that the receptor belongs to the prior art family of R-receptors and different members of this family are important in a wide variety of physiological processes. But no particular biological or biochemical process is disclosed for this new receptor.

[25] This is a molecule that activates the receptor.

[26] This claim is typical of the form in which reach-through claims are framed. Such claims were likened by a US court to the patenting of a "philosopher's stone" for transmuting lead into gold. The purported inventor of a reach-through claim is no more in possession of the compound than a medieval alchemist possessed the mythical stone based on the desire to turn lead into gold and the hope that such a stone will be found. An alternative form of this type of claim in US Patent 6083705 reads: "A process for determining whether a chemical compound is a human α1C adrenergic receptor agonist which comprises contacting cells transfected with and expressing DNA encoding the α1C adrenergic receptor with the compound under conditions permitting the activation of the α1C adrenergic receptor, and detecting an increase in α1C adrenergic receptor activity, so as to thereby determine whether the compound is an α1C adrenergic receptor agonist."

[27] This is another type of reach-through claim.

[28] Methods of medical treatment are not patentable under the European Patent Convention. This form of claim is known as the "Swiss form".

[29] A third type of reach-through claim. Lim and Christie, page 6, describe this type as a "quasi reach-through" claim.

- Notwithstanding disclosure of the receptor sequence, claim 1 lacks utility or industrial application because no specific function is assigned in the specification to the receptor of claim 1 nor can one be inferred[30].
- Notwithstanding disclosure of the receptor sequence in a manner sufficiently clear and complete for a skilled person to prepare the receptor, claim 1 is non-enabling[31] because the specification does not disclose a specific function of the receptor.
- A method of identifying an agonist in accordance with claim 2, even though it lacks industrial application (utility) because the receptor of claim 1 has no specific function[32], satisfies the requirement for a written description. But it fails to meet the sufficiency (enablement) criterion – the skilled person would need to determine the specific function that is to be stimulated by the receptor agonist[33].
- Claim 3 claims a non-specified agonist identified by the method of claim 2[34]. It lacks industrial application (utility) also for the foregoing reason. Neither does it meet the written description requirement[35]. A non-specified agonist described

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[30] The specification does not say, nor can it be inferred, that the receptor can be used to treat a specific disease. In the second example, the specification discloses that the receptor of claim 1 is useful in treating obesity. See pages 5 to 9 of the tripartite report at http://www.trilateral.net/projects/biotechnology/reach_through_claims/B3b_reachthrough_text.pdf Kunin, page 17, believes it "may be possible to overcome a rejection of claims 1-6 for failure to comply with the utility requirement by presenting objective evidence that supports the position that one of ordinary skill in the art would have recognized that each member of the R-receptor protein family would have been reasonably expected to have a particular specific and substantial function or activity, or that a specific and substantial purpose for agonizing such function was known to those of skill in the art."

[31] The disclosure is insufficient under Article 83 EPC. It fails also to meet the "how to use" requirement of 35 USC 112 because a patent specification that provides only a starting point or direction for further research is not enabling as it does not provide full and clear terms that teach others how to make and to use an invention that will be discovered sometime in the future..

[32] The tripartite report, page 10: "there can be no industrial applicability (application)/ utility for methods of identifying agonists that are asserted to stimulate an unknown function."

[33] The tripartite report, page 10: "since the specification does not provide any guidance with respect to the activity of the receptor, nor give any working examples, the person skilled in the art cannot use the claimed assay without undue experimentation. Since the description does not describe how the "agonist compound" can be used, the claim lacks enablement."

[34] UK Patent Office, Examination Guidelines for Patent Applications relating to Biotechnological Inventions in the UK Patent Office (May 2005), paragraph 64: "…Such speculative claims differ from "product by process" claims because the product of a process requires repetition of the process to obtain more product, whereas the subject of a "reach though" claim does not. It follows that "reach through" claims may even extend to known materials which are not modified in any way by the process used to identify them. Examples of such claims are those directed towards candidate compounds that are identified by the use of screening methods. Such compounds are generally only defined by their function eg as modulators of receptor X, and no relationship between this function and the structural features of the compounds is described. In the absence of any knowledge of any relationship, either from the specification or from common general knowledge, the skilled person would not know how to produce and use the compounds. Moreover, the skilled person would not know before undertaking the laborious task of performing the screening assay if any given compound would fall within the scope of the claim. It would require an undue burden of experimentation to screen undefined compounds for the desired activity. There will also be a lack of support where the function of the compounds identified is not specified."

[35] University of Rochester v Searle, supra. The University spent more than ten years investigating the physiological pathways underlying the highly successful painkiller Celebrex® before identifying the particular cellular receptors that produced the desirable and undesirable reactions that accompany

only by the ability to bind to a particular receptor does not distinguish the agonist identified in the claim 2 method from agonists in the prior art. A claim lacks clarity if a person reading it cannot easily determine what is or is not covered by the claim.

- Claim 4 does not satisfy the industrial application (utility), written description or enablement criteria. Utility is not described in the specification and cannot be inferred. It is a claim for the treatment of an unknown disease. To comply with the criteria the specification must disclose a specific disease.
- Claim 5 (monoclonal antibody) lacks industrial application because the receptor it recognises also lacks industrial application. The tripartite report concluded that the claim is not enabling, "since although the person skilled in the art can make the antibody using routine procedures, it would require undue experimentation (or be an undue burden) for the person skilled in the art to determine the specific function of the antibody and thus determine how to use the antibody"[36].

2.2 The **second** example discussed in the report had the following claims:

> 1. An isolated and purified receptor the sequence of which consists of SEQ ID NO 2:
>
> 2. A method of identifying an agonist of the receptor of claim 1 comprising:
> preparing a candidate compound,
> contacting a cell which expresses said receptor on its surface with said candidate compound, and
> determining whether said candidate compound activates the receptor of claim 1, wherein a compound that activates the receptor of claim 1 is an agonist of said receptor.
>
> 3. An isolated and purified receptor agonist identified by the method of claim 2.

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conventional painkillers. Although the University's patents included disclosure of specific assays for finding effective human medicinal compounds, the patents did not disclose any sample compounds that operated according to the discoveries. Because of this omission, the court ruled that the University's claims covering the treatment of a patient using a drug that was found by using the assays failed to comply with the statutory requirements for a written description and enablement. *Cf*. Regents of the University of California v Eli Lilly & Co. (1997) 119 F.3d 1559, 43 USPQ2d 1398 (US Court of Appeals, Federal Circuit): a description of how to obtain compounds was insufficient without description of what the compounds were; and the court ruled that "a description of what the genetic material does, rather than of what it is, does not suffice".

[36] E.g. Mentor v Hollister [1991] FSR 557 (English Court of Appeal): the skilled person "… may need to carry out the ordinary methods of trial and error, which involve no inventive step and generally are necessary in applying the particular discovery to produce a practical result. In each case, it is a question of fact as to whether the steps needed to perform the invention are ordinary steps of trial and error which a skilled man would realise would be necessary and normal to produce a practical result." Pharmacia Corporation v Merck & Co. Inc [2002] RPC RPC 77 & 709 (English Court of Appeal): the specification provided the skilled man with a class comprising an enormous number of compounds, many hundreds if not thousands of which did not have the quality of the class. The patent did not indicate a common element which underpinned success and avoided failure in identifying compounds in the class. It was invalidated for insufficiency.

4[37]. (EPO Version) Use of a receptor agonist for the manufacture of a medicament *for inhibiting obesity*, wherein said receptor agonist is identified by the method of claim 2.

(JPO Version) Composition comprising a receptor agonist for use in treating obesity, wherein said receptor agonist is identified by the method of claim 2, as an active ingredient.

(USPTO Version) A method for the treatment of obesity, comprising administering to a host in need thereof a therapeutically effective amount of the agonist identified by the method of claim 2.

5. A monoclonal antibody which recognises the receptor of claim 1.

- Unlike in the first example, the receptor is useful in diagnostic methods relating to obesity and claim 1 therefore complies with industrial application or utility requirement. The claim also satisfies the requirement of enablement, support, clarity, and/or written description.
- Unlike in the first example, the claimed method in claim 2 for identifying agonists is industrially applicable or useful in view of the proven pharmaceutical relevance of the receptor. Again, the claim complies with the requirement for enablement, support, clarity, and/or written description. The description provides general reference toward standard screening methods. Although the description does not provide working examples, the description teaches a method for measuring the biochemical and binding activity of the specific receptor, and the person skilled in the art can understand how to use the screening method considering the common general knowledge.
- The agonist (activating compound) claim is seen in the tripartite report[38] as encompassing "a genus of compounds defined only by their function wherein the relationship between the structural features of the members of the genus and said function has not been defined. In the absence of such a relationship either disclosed in the as-filed application or which would have been recognised based upon information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition. The fact that one could have assayed a compound of interest using the claimed assays does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound (other than those that might be particularly disclosed in an application) would fall within the scope of what is claimed. It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity."
- Unlike in the first example, claim 5 (monoclonal antibody) complies with the industrial application (utility), clarity, and/or written description requirements. It

[37] Lim and Christie, Reach-Through Patent Claims in Biotechnology, IPRIA Working Paper (University of Melbourne), March 2005, page 10, describe this type of claim as a "quasi reach-through" claim. It embraces a specified agonist, identified by the claimed method, for the treatment of a specific disease.

[38] See page 10 of the tripartite report at http://www.trilateral.net/projects/biotechnology/reach_through_claims/B3b_reachthrough_text.pdf

also complies with the enablement and/or support requirements since the person skilled in the art could obtain a monoclonal antibody specific to a given protein, using routine and well known methods, and use the antibodies in diagnostic methods.

2.3 The specification for the **third** example discussed in the report discloses three working examples wherein compounds activating the receptor, namely X, Y, and Z were identified using the disclosed screening procedure but it gives no structural information for compounds other than X, Y, or Z or methods of making compounds other than X, Y, or Z. In other words, it gives no functional or structural relationship between these compounds and any other compound that might be found using the claimed method. Furthermore, although the receptor of SEQ ID NO: 3 was expressed in an animal cell, antibodies that recognise the receptor were not actually produced.

The following claims are given in the example:

> 1. An isolated and purified receptor the sequence of which consists of SEQ ID NO 3:
>
> 2. A method of identifying an agonist of the receptor of claim 1 comprising:
> preparing a candidate compound,
> contacting a cell which expresses said receptor on its surface with said candidate compound, and
> determining whether said candidate compound activates the receptor of claim 1, wherein a compound that activates the receptor of claim 1 is an agonist of said receptor.
>
> 3. An isolated and purified receptor agonist identified by the method of claim 2.
>
> 4. (EPO Version) Use of a receptor agonist for the manufacture of a medicament for treating a disease treatable by said agonist, wherein said receptor agonist is identified by the method of claim 2.
>
> (JPO Version) Composition comprising a receptor agonist for use in treating a disease treatable by said agonist, wherein said receptor agonist is identified by the method of claim 2, as an active ingredient.
>
> (USPTO Version) A method for the treatment of disease treatable by the agonist of claim 2, comprising administering to a host in need thereof a therapeutically effective amount of the agonist identified by the method of claim 2.
>
> 5. (EPO Version) Use of compound X for the manufacture of a medicament for treating a disease treatable by said compound.
>
> (JPO Version) Composition comprising compound X for use in treating a disease treatable by said compound, as an active ingredient.
>
> (USPTO Version) A method for treating a disease treatable by compound X comprising administering to a host in need thereof a therapeutically effective amount of compound X.
>
> 6. A monoclonal antibody which recognises the receptor of claim 1.

Much of what has been said about the claims in the first example can be repeated for these claims. Claim 5 refers to a treatable disease, not to a specific disease, and so it lacks industrial application (utility); and for the same reason, it is unlikely to fulfil the requirements of enablement, support, clarity, and/or written description.

2.4 Claim 5 in example **four** contrasts with the corresponding claim in example three, in that it refers to a specific disease (obesity). A skilled person could practise the invention without inventiveness or undue burden.

> 4. (EPO Version) Use of a receptor agonist for the manufacture of a medicament *for inhibiting obesity*, wherein said receptor agonist is identified by the method of claim 2.
> (JPO Version) Composition comprising a receptor agonist for use in treating obesity wherein said receptor agonist is identified by the method of claim 2, as an active ingredient.
>
> (USPTO Version) A method for the treatment of obesity comprising administering to a host in need thereof a therapeutically effective amount of the agonist identified by the method of claim 2.
> 5. (EPO Version) Use of compound X for the manufacture of a medicament *for inhibiting obesity*.
> (JPO Version) Composition comprising compound X for use in treating obesity, as an active ingredient.
> (USPTO Version) A method for the treatment of obesity comprising administering to a host in need thereof a therapeutically effective amount of compound X.

3 Tripartite Report Conclusions

SUBJECT MATTER	PATENTABLE
Receptor with known function	Yes
Screening method using the receptor	Yes
Compounds (agonists or antagonists) in general discovered with preceding method	No
Method of treatment using agonists compounds in general discovered with preceding method	No
Specific disclosed compounds discovered with preceding method	Yes
Methods of treatment using specific disclosed compounds discovered with preceding method	Yes

3.1 No Specific Function Disclosed for Receptor

In cases where the specific function (e.g., the relationship to a specific disease) of a receptor protein is not disclosed, the claims for (1) the receptor, (2) screening methods using said receptor, (3) agonists (activating compounds) in general identified by said screening methods, (4) methods, uses, or medicaments using said agonists in general, (5) methods, uses, or medicaments using the specific agonists and (6) monoclonal antibodies

which recognise the receptor, do not comply with one or more of the requirements of industrial applicability (utility), enablement, support, clarity, and/or written description.

3.2 Specific Function Disclosed for Receptor

Where the specific function (e.g., the relationship to a specific disease) of a receptor is disclosed, claims for the receptor meet all the patentability requirements: industrial applicability (application), utility, enablement, support, clarity and written description.

Claims for screening methods using said receptor meet all the requirements of industrial applicability (application), utility, enablement, support, clarity and written description if

- there is a working example of the screening method, or
- there is a general reference to standard screening methods that can be applied with a reasonable expectation of success, together with the disclosure of a method for measuring the biochemical and binding activity of the specific receptor, or
- the person skilled in the art can understand how to use the screening method, considering the common general knowledge.

But notwithstanding disclosure of the specific function (e.g., the relationship to a specific disease) of a receptor protein, the claims for agonists (activating compounds) in general identified by said screening methods and for methods, uses, or medicaments using said agonists in general do not meet enablement and/or support requirements, considering the general scope of the claims. The claims encompass a genus of compounds defined only by their function wherein the relationship between the structural features of the members of the genus and said function has not been defined.

In the absence of such a relationship either disclosed in the as-filed application or which would have been recognised based upon information readily available to one skilled in the art, the skilled person would not know how to make and use compounds that lack structural definition. The fact that one could have assayed a compound of interest using the claimed assays does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound (other than those that might be particularly disclosed in an application) would fall within the scope of what is claimed. It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity.

3.3 Specific Agonists Identified

Where the specific function (e.g., the relationship to a specific disease) of a receptor protein is disclosed, and specific agonists (activating compounds) are identified (found) by screening methods using said receptor, the claims for methods, uses, or medicaments utilising the specific agonists meet all the requirements of industrial applicability (utility), enablement, support, clarity and written description as long as there is adequate guidance with respect to how such uses would be put into effect.

Furthermore, claims limited to the specific agonists identified (found) by the screening method using the receptor would meet all the requirements of industrial applicability (utility), enablement, support, clarity and written description if the agonists could be made by the person skilled in the art in view of the description in the specification and the common general knowledge in the art.

3.4 Monoclonal Antibodies

Where the specific function (e.g., the relationship to a specific disease) of a receptor protein is disclosed, the claims for monoclonal antibodies which recognise the receptor meet all the requirements of industrial applicability (application), utility, enablement, support, clarity and written description if the receptor is clearly described[39].

4 University of Rochester v Searle & Co.[40]

There are no reported decisions by courts in Singapore or Europe, in which the validity of a reach-through claim has been contested. To date, only courts in the USA have considered the issue of validity. The background to the Rochester case begins in 1992 when scientists at the University of Rochester developed a screening method that would determine whether a substance could help relieve arthritis pain without irritating the gastrointestinal track. Previously, anti-inflammatory pharmaceuticals such as aspirin and ibuprofen inhibited COX-1 and COX-2 enzymes. As a result, they reduced arthritic pain but also caused upset stomachs and potentially dangerous side effects like ulcers. Rochester scientists found a method to determine whether a pharmaceutical could inhibit the harmful COX-2 inflammatory enzymes without inhibiting the beneficial COX-1 enzymes. The contested patent, US Patent 6048850, was granted for this work. This patent was invalidated for failure to meet the enablement and written description requirements in 35 USC 112, partly because it was directed to the administration of an unidentified compound that exhibited properties identified using the patented screening method.

The eight claims contested before the Court of Appeals for the Federal Circuit were directed to methods "for selectively inhibiting PGHS-2 activity in a human host" by "administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product to [or in] a human host in need of such treatment." Claim 1 covered methods of treatment using any PGHS-2 inhibitor, even though the patent only disclosed tests of a few well-known compounds. The patent also did not identify any specific

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[39] The European Patent Office often accepts (quasi-reach-through) claims to all monoclonal antibodies having sufficiently precisely defined immune reactivity towards new and inventive antigens. Hindle, Reach-Through Claims, http://www.hindlelowther.com/article_reach.htm.

[40] See (2003) 249 F. Supp. 2d 216, 236 (US District Court, W.D.N.Y.), (2004) 358 F.3d 916 (US Court of Appeals, Federal Circuit). For commentaries on this case, see Mehta, University of Rochester Corp. v G.D. Searle & Co. Inc.: How to Lose Millions in Patent Royalties, 29 Delaware Journal of Corporate Law 547 (2005); Pierce, University of Rochester v G.D. Searle: Writing on the Wall, 4 The John Marshall Review of Intellectual Property Law 406 (2005), http://www.hbsr.com/filelibrary/pierce.pdf, although most of Pierce's commentary is concerned with the interpretation of section 112, US Patent Code (Title 35).

inhibitor in structural terms to assist one of ordinary skill in visualising the inhibitor without first screening it for inhibitory activity.

The three independent claims (1, 5 and 6), each of them a reach-through claim, read as follows:

> 1. A method for selectively inhibiting PGHS-2 activity in a human host, comprising administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product to a human host in need of such treatment.
> 5. A method for selectively inhibiting PGHS-2 activity in a human host, comprising administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product in a human host in need of such treatment, wherein the activity of the non-steroidal compound does not result in significant toxic side effects in the human host.
> 6. A method for selectively inhibiting PGHS-2 activity in a human host, comprising administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product in a human host in need of such treatment, wherein the ability of the non-steroidal compound to selectively inhibit the activity of the PGHS-2 gene product is determined by:
> a) contacting a genetically engineered cell that expresses human PGHS-2, and not human PGHS-1, with the compound for 30 minutes, and exposing the cell to a pre-determined amount of arachidonic acid;
> b) contacting a genetically engineered cell that expresses human PGHS-1, and not human PGHS-2, with the compound for 30 minutes, and exposing the cell to a pre-determined amount of arachidonic acid;
> c) measuring the conversion of arachidonic acid to its prostaglandin metabolite; and
> d) comparing the amount of the converted arachidonic acid converted by each cell exposed to the compound to the amount of the arachidonic acid converted by control cells that were not exposed to the compound, so that the compounds that inhibit PGHS-2 and not PGHS-1 activity are identified.

The central issue was whether a written description for a claimed method of treatment[41] is adequate where a compound that is necessary to practise that method is described only in terms of its function, and where the only means provided for finding such a compound is essentially a trial-and-error process. Without the compound, the patentee did not possess the claimed method for its use. "The claimed method depends upon finding a compound that selectively inhibits [Cox-2] activity. Without such a compound, it is impossible to practise the claimed method of treatment. It means little to 'invent' a method if one does not have possession of a substance that is essential to practising that method. Without that substance, the claimed invention is more theoretical than real; it is, as defendants argue, akin to 'inventing' a cure for cancer by utilizing a substance that attacks and destroys cancer cells while leaving healthy cells alone. Without possession of such a substance, such a 'cure' is illusory, and there is no meaningful possession of the method." (Larimer J., US District Court)

The district court ruled that the patent merely described the desired function of the compound called for. There was no information by which a person of ordinary skill in the art would understand that the inventors possessed the claimed invention. "At best, it

[41] New and inventive methods of medical treatment can be patented under US law.

simply indicates that one should run tests on a wide spectrum of compounds in the hope that at least one of them will work."

In its appeal before the Federal Circuit Court, the University argued that there was no requirement that inventions be described separate from the requirement that the patent should enable skilled persons to work the invention. In the alternative, it asserted that the patent adequately described the invention and gave sufficient guidance to skilled persons. Pfizer contended that a patent fails to satisfy the written description requirement if it claims a method of achieving a biological effect, but discloses no compounds for use with the method that could accomplish that result.

The appeals court upheld the lower court's ruling, and remarked in doing so that "generalized language may not suffice if it does not convey the detailed identity of an invention" in a patent application under 35 USC 112. "In this case, there is no language here, generalized or otherwise, that describes compounds that achieve the claimed effect." The university failed to provide a significant written description of a compound that would effectively inhibit COX-2 enzymes without reducing COX-1 enzymes; and the patent application gave no guidance that would steer the skilled practitioner towards compounds that can be used to carry out the claims made in the patent application. Instead, said the court, the patent "discloses nothing more than a hoped-for function for an as-yet-to-be-discovered compound, and a research plan for trying to find it." Common sense, said the court, "dictated that a method of treatment with a drug cannot be disclosed if neither the drug to be applied nor the existence of the drug is disclosed". A patent is not "a hunting licence. It is not a reward for the search, but compensation for its successful conclusion."

5 Enzo Biochem v Gen-Probe[42]

The patent claims of US Patent 4900659 in issue before the Federal Circuit Court in the Enzo case relates to nucleic acid probes that selectively hybridize to the genetic material of the bacteria that cause gonorrhea, Neisseria gonorrhoeae. The patented DNA probes are essentially DNA sequences having a much higher hybridization ratio of selectivity for N. gonorrhoeae over selectivity for Neisseria meningitidis[43], when compared to other probes known in the industry. Three DNA sequences were deposited at the American Type Culture Collection. The validity of six claims was contested. It was alleged that

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[42] (2002) 296 F.3d 1316 (US Court of Appeals, Federal Circuit). For commentary on this judgment see, for example, Blaug, Shuster and Su, Enzo Biochem v Gen-Probe: Complying with the written description requirement under US patent law, 21 Nature Biotechnology 97 (January 2003), http://www.fenwick.com/docstore/477/Enzo_Biochem.pdf; Morgan, After the Fire and Rain, Lilly Still Stands, 30 University of Daytona Law Review 123 (2005), http://law.udayton.edu/lawreview/documents/31-1/Morgan.pdf; Zuhn and Berghoff, The Evolution of the Written Description Requirement in the Context of Biotechnological Inventions (8 November 2006), http://patentdocs.typepad.com/patent_docs/new_biotech_opinions/index.html; Manak, The Law of Written Description in Pharmaceutical and Biotechnology Patents, 23 Biotechnology Law Report 30, Number 1 (February 2004) http://www.gtlaw.com/pub/articles/2004/manakj04a.pdf.

[43] N. gonorrhoeae and N. meningitidis have about 93% homology, and this resulted in false positive results for tests for gonorrhea because the test probes were actually detecting N.meningitidis.

these claims (they were not reach-through claims) were invalid for failure were to meet the written description requirement in section 112, 35 USC[44]. The Federal Circuit Court ruled initially that the claims were invalid but later vacated its ruling as incorrect and remanded the case to the District Court for a further hearing on certain questions.

In its judgment the Federal Court said that the six claims of the '659 patent would meet the written description requirement if the functional characteristic of the sequences' selective hybridization to N. gonorrhoeae were coupled with a disclosed correlation between that function and a structure that is sufficiently known or disclosed. The US PTO's Written Description Guidelines recognise that the written description requirement can be met if the description of the ability to hybridise to a known or disclosed structure corresponds to the description of a function and of a correlation between the said function and a structure[45]. It remained however for Enzo to show that the three deposited sequences represented the broader invention claimed in the patent.

The Enzo judgment may provide an answer, in the context of reach-through claims, where, for example, a claimed agonist is only described by its function, that is, by its ability to link to a disclosed receptor. But there must be a correlation between the function and a structure. Thus, a claim to an agonist identified by a screening method would have to describe the structure of the claimed molecule[46]. Véron and Moussa suggest using X-ray crystallography to determine the three-dimensional coordinates – the space structure – of the target molecule[47]. "A three-dimensional model of the analysed target is thus obtained which can be used to identify by their spatial conformation the compounds likely to act on the target." This spatial structure can be used to "create a graphic representation thereof on a computer and to superpose it on the representation of

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[44] In addition to a written description, section 112 also requires enablement and disclosure of the best mode.

[45] Blaug, Shuster and Su, *supra*: "Descriptions should include information about the structure, the properties, or other identifying characteristics of the compound, molecule, or biologic whenever practicable. A description of function alone probably will not be sufficient. It should be accompanied by an explanation of the relationship between the function described and the structure or properties of the compound, molecule, or biologic. Consequently, it is important to include adequate and real data with the filed patent application to meet the [written description] requirement."

[46] Moreover, as Blaug, Shuster and Su, *supra*, conclude: "Broad claims, such as those drawn to a genus of compounds, will be especially vulnerable to invalidation unless the disclosure identifies characteristics or properties that determine membership in the genus based on the data derived from the species that have been isolated or synthesized." Yet, as the authors of the BSK Memo entitled The Scope of Patent Protection Available to Research Entities in the Wake of Recent Cases Rejecting 'Reach Through' Claims" (October 2003) point out, "… a specification that includes a description of the physical structure of a potential drug that will result in a positive assay response may be sufficient to support generic "reach through" claims to any drugs discovered by assays using the nascent compound. While the entire physical structure of every potentially effective drug is likely too difficult to determine, drugs responding favorably to an assay may have some common structural elements that are responsible for the physical interaction with the nascent compound. By defining and detailing these generic structural portions, a patentee can cross the threshold from invalid claims that rely strictly on a mere hoped-for function to valid "reach through" claims that are based on an actual description of structure of commercially viable products." (http://www.bsk.com/archives/infomemo.dbm?StoryID=383)

[47] Protecting the Results of Future Research: Reach-Through Claims in European and US Laws, http://www.veron.com/files/publications/Protecting_the_results_of_future_research.pdf.

the structure of the target, in order to check whether the compound links to a sufficient number of active sites of the target. According to some authors, the inventor of a screening method of this type could perhaps claim the compounds identified by means of this method. One can consider that the requirement of description is met since the crystalline coordinates of the target provide enough information to allow identification of the molecules covered by said claim. The patentee would not merely claim all the molecules able to link to the target but he would actually describe them by means of their spatial structure. However, such a patent may be invalidated for lack of novelty if a compound known in the prior art was included in the scope of the claim."

6 Conclusion

Current legal opinion has it that reach-through claims are likely to be deficient under patent laws of most countries, and particularly under patent laws in Europe, Japan and USA, for want of industrial application (utility) or sufficiency or both. If no specific function is assigned to the claimed subject matter or can be inferred, a reach-through claim to a genus of compounds will lack industrial application (utility). Even if a specific function (e.g. inhibiting obesity) is assigned thereto or can be inferred, the claim will be invalid for insuffiency if it encompasses a genus of compounds but does not define the relationship between the structural features of the member compounds and the specific function. Yet the likelihood of invalidity has not deterred patent applicants from seeking, and indeed patent offices from allowing, reach-through claims. Techniques, such as X-ray crystallography, may enable future patent applicants to satisfy the written description requirement. Thus a claim which is not allowed today may be unobjectionable in a few years from now[48]. New matter, although it cannot be added to an existing application, might support a new application[49] for the claim and patent attorneys will be mindful of that when advising their clients on patenting strategies. Limited reach-through claims relating to monoclonal antibodies may be accepted by some patent offices, including the European Patent Office which is known to accept claims to monoclonal antibodies having precisely defined immune reactivity towards new and inventive antigens.

The potential impact on Singapore's medical sciences industry is fairly clear: new research tools devised by the industry, or by local research centres serving the industry, can be patented in Singapore and in foreign jurisdictions, and of course foreign private and public enterprises can patent new research tools in Singapore, provided the patent application or granted patent satisfies the patentability criteria, including the disclosure requirement. But under Singapore law and foreign patent laws, most reach-through claims encompassing a future or as-yet unidentified compound or genus of compounds

[48] Sonnenfeld and Wittmayer, Broader Patent Claims for the Pharmaceutical and Biotech Industry, http://www.touchbriefings.com/pdf/17/pt031_t_morg&finn.pdf: "As technology progresses and more powerful techniques and instruments become available, as well as an increased understanding of the basis of molecular interactions, one's ability to deduce molecular structure increases. The anatomical principle that form follows function may well have a molecular counterpart in molecular biology and provide a basis to reasonably predict molecular structure based on the requirements of interacting with other molecular entities."

[49] However, novelty or inventive step could be a problem since the earlier application may have enough information in it to invalidate a later application.

are unlikely *at present* to satisfy those requirements – although it should not be forgotten that even a potentially invalid claim may not be entirely worthless in commercial negotiations and, until it is declared by a court to be invalid, its worth might be realised in preliminary legal proceedings to delay the entry of imports to the patent jurisdiction.

Consideration of the validity, or likely invalidity, of a reach-through claim can deflect attention from method claims in the patent, difficult though these claims may be to police effectively. Because of that difficulty a researcher may be inclined to ignore method claims. A further reason why a researcher may ignore such claims could be a belief that a patent cannot be enforced to prevent scientific experimentation, but as the next chapter explains such a belief is largely unfounded.

CHAPTER 2

EXPERIMENTAL USE AND PATENT INFRINGEMENT

Experimentation is part of the human condition, somewhat like inventiveness. Humans are instinctive experimenters, at times against our own or others' well-being or interests and perhaps fatally so. Society regulates experimentation, out of a regard for the safety and security of others and their property, but recognises, by the limits it sets, that without experimentation humanity might still be in the trees. The patent system, an expression of society's desire for technological advancement, allows unlicensed use of others' patented inventions in specified circumstances provided the use is not a disguised form of theft[50].

Patent laws in Singapore and Europe[51] recognise *post-grant* use of a patented invention for experimental purposes as an exception[52] to a patentee's exclusive rights, yet the scope of the exception can vary with the jurisdiction. The exception is not inconsistent with the WTO TRIPS Agreement which states in Article 30 that "Members may provide limited exceptions to the exclusive rights conferred by a patent, provided that such exceptions do not unreasonably conflict with a normal exploitation of the patent and do not unreasonably prejudice the legitimate interests of the patent owner, taking account of the legitimate interests of third parties."

Beyond the experimental purposes exception, using a patented process to identify agonists of a specified receptor[53], for example, or using, offering for sale, selling, or importing in the patent jurisdiction the product obtained directly by the process, are *prima facie* infringements of the patent[54]. A new agonist identified by using a method for identifying such agonists would be a product obtained directly by that process; and even if the agonist is comprised in a composition for treating a specified disease, it remains a directly-obtained product if it retains its essential characteristics. If the invention is a process for obtaining a new product and the same product is produced by other than the patentee or his licensee, there is a presumption that that product has been obtained by that process unless the contrary is proved[55].

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[50] Patent law (e.g. in the USA, 35 USC 102) may also tolerate public disclosure by way of experimental use of the invention *prior to* filing a patent application, on the basis that such use allows inventors to perfect their inventions. See, for example, Pfaff v Wells Electronics (1998) 525 US 28 (US Supreme Court), where the court approved the experimental use doctrine recognised in the leading case, City of Elizabeth v American Nicholson Pavement Co. (1877) 97 U.S. 126 (US Supreme Court); SmithKline Beecham Corporation v Apotex Corporation (2004) 359 F.3d 1361 (US Court of Appeals, Federal Circuit).

[51] The phrase "European patent law" refers in this paper to the national patent laws of the Member States of the European Union.

[52] An exception differs conceptually from a defence, in that the burden of proof in a defence lies with the defendant. Post-grant experimental use may afford a defence to infringement under US patent law.

[53] Such as the process covered by claims discussed in the preceding chapter of this Report.

[54] WTO TRIPS Agreement, Article 28(1)(b); section 66(1)(c), Singapore Patents Act (Chapter 221).

[55] WTO TRIPS Agreement, Article 34; section 68(1), Singapore Patents Act (Chapter 221); section 100(1), UK Patents Act 1977

Scientists, particularly in universities, have been known to see no violation of patent rights in using others' patented inventions in experimental scientific work and to defend that view by reference to the experimental purposes exception. But the rule is not so widely cast in their favour as scientists may believe or suppose: the exception is limited to acts "relating to the subject-matter of the invention". The unlicensed use of another's patented method to identify a biologically active molecule or substance may well infringe the patent; and even if it does not infringe because the use falls within the experimental purposes exception, a downstream or end-product comprising or containing the molecule could infringe a reach-through claim in the patent. A method that is not patented in the jurisdiction is 'free game' for all there; but if the method is patented in other jurisdictions then imports of a product obtained directly by use of the method or of a product falling within the scope of a patent claim could be excluded from those jurisdictions[56].

1 Singapore Patent Law

An act which would infringe a Singapore patent does not do so[57]

- if it is done for experimental purposes relating to the subject-matter of the invention (section 66(2)(b));
- if it consists of the doing of anything in relation to the subject-matter of the patent to support any application for marketing approval for a pharmaceutical product, provided that any thing produced to support the application is not
    - made, used or sold in Singapore or
    - exported outside Singapore

  other than for purposes related to meeting the requirements for marketing approval for that pharmaceutical product (section 66(2)(h)).

The phrase "done for experimental purposes relating to the subject matter of the invention", which is found also in the (European) Community Patent Convention and European patent law, is likely to be construed by the Singapore courts in much the same, if not in an identical, way as it is read by UK courts.

The section 66(2) exception relating to marketing approval for pharmaceutical products[58] corresponds in its basic objective to the exceptions in EC Directives on clinical trials: Article 13, Directive 2001/82 (veterinary) and Article 10, Directive 2001/83 (human-use).

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[56] The Cohen-Boyer method was patented only in the USA yet licences with reach-through royalty obligations were sold to companies in Europe and Japan. The Cohen-Boyer patents claimed the method and products made or obtained by the method.

[57] Section 66(2), Patents Act (Chapter 221).

[58] The exception does not distinguish between pharmaceutical products for human use from those for animal (veterinary) use.

2 European Patent Law

European patent law on post-grant experimental use of patented inventions is in general more liberal than US law[59]. Activities which would infringe a patent in Europe do not infringe if they are done "for experimental purposes relating to the subject-matter of the invention". This phrase encompasses experiments done for the purpose of confirming patentability of the patented invention, confirming the function and results thereof if described in the patent specification, and improving on the patented invention[60]. But if the patented invention is used in experiments directed to research on subject matter other than the invention itself, this use is not covered by the exemption and is an infringement of the patent.

2.1 Scope of Experimental Purposes Exception

An early case on the scope of the experimental purposes exception was the English case of Monsanto Company v Stauffer Chemical Company[61]. The court ruled that trials carried out on a patented herbicide by the defendant's personnel at its own farm did not infringe but trials carried out elsewhere, whether by the defendant's personnel or third parties, would infringe. Lord Justice Dillon stated "trials carried out in order to demonstrate to a third party that a product works, or in order to amass information or to

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[59] Except with regard to clinical trials.

[60] Judge Michael Fysh (English Patents County Court) suggested (in Legal Issues in Exploiting Drug Patents in Europe, LES-Italy Conference, December 2002) that the experimental use exception is rather narrow in UK/Irish law: "The qualification may cover such acts as verification of various kinds (such as seeing whether a compound can be made as proposed or will work in a particular climate), assessment of validity, and in-house experiment for the purposes of improvement and modification etc. But the exception would in my view exclude the use of a patented process in experiments specifically to test some other product or process with a view to the direct use of the results thereof for a commercial purpose." See also Fischer, Reach-through and experimental use, Managing Intellectual Property: IP Strategy Yearbook 2001, where the author observes that "the experimental use exemption would no longer apply when the research tool is used in a way which is taking its claimed function as granted, in order to develop a result that can typically be achieved by conducting research with the tool. In this case, the research acts performed with the tool would no longer relate to the subject matter of the invention, as required by established statutory law on the experimental use exemption. Regarding this criterion, an earlier Decision of the Berlin District Court of 1984 can be cited (Klinischer Test; rendered under the old German Patent Act of 1968), where the Court basically distinguished between experiments on the invention and experiments with the invention - the latter not relating to the subject matter of the invention. In the case of a research tool, a line between verifying its functioning and taking its claimed function as granted seems artificial and difficult to draw. In any case, it should be clear that one may not conclude from the intrinsic purpose of a research tool that the use of such a tool automatically amounts to an experimental use act in the legal sense. Rather, it should be hard to believe that a party using a patented research tool to a certain extent just uses it, for instance, for verifying its functioning or for testing its economic value. In practice, the problem is rather how to prove that a patented research tool is being used at all by another party, and if so to what extent, if one wants to establish acts of infringement."

[61] [1985] RPC 515 (Court of Appeal); c*f*. "Ethofumesat", German Federal Supreme Court, 21 February 1989, decided under the German Patent Act 1968, where the court ruled that it was an infringement of the patent to use a herbicide containing the patented substance in field tests during the term of the patent in order to research the effectiveness and the environmental friendliness of the composition, in order to obtain regulatory approval before marketing the herbicide. Trials were exempted only if their sole purpose was to improve and to perfect the protected invention.

satisfy a third party ... that the product works as it claims are not, in my judgment, to be regarded as acts done for experimental purposes".

The patent in Auchincloss v Agricultural & Veterinary Supplies[62] had a claim for compositions for destroying viruses and other micro-organisms. The claimed composition contained a number of ingredients in stated proportions by weight. One batch of NaDCC had been used only to produce a sample of the defendants' composition for submission to the regulatory authority for official approval. The defendants argued that this was not an infringement by virtue of section 60(5)(b) of the Patents Act 1977, but the court ruled – and the Court of Appeal agreed with this – that making (and indeed experimenting) merely for the purpose of getting an official approval was not a defence under section 60)(5)(b).

The English position on the experimental purposes defence was at odds with the views of the German courts. In Klinische Versuche (Clinical Trials) 1 and 2[63] the German Federal Supreme Court ruled that activities for research purposes relating to the object of the patented invention were permitted, in accordance with the experimental purposes of the exemption, if they were aimed at clearing up lack of certainty regarding the object of the invention, or bringing out a new discovery about it. All experimental activities which related to the object of the invention were exempted, and these activities included commercially-oriented trials.

The exemption in the German Patent Act 1981 applied regardless of any additional motivation and purpose that the findings might serve. Commercial orientation does not turn the experimental activity into an infringement. The clinical trials in the case before the German court were intended to confirm results obtained in animal tests, and to supply data necessary for official permission to market the product. The defendant wanted to determine the clinical differences in effectiveness and digestibility of its products and the marketed products. The Federal Supreme Court ruled that these tests were exempted by section 11(2) of the 1981 Act, although it said that trials could be not conducted in a volume that would not be justified by the purpose of the trials or for the purpose of interfering with the marketing efforts of the patent proprietor. The Federal Supreme Court's ruling was challenged unsuccessfully in the German Constitutional Court.

In France, according to the case law of the Paris Court of Appeal, clinical trials performed only with the aim of obtaining governmental approval constituted patent infringement[64] whereas trials done, as in Welcome Foundation Limited v Parexel

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62 [1997] RPC 649 (English Patents High Court)

63 [1997] RPC 623 and [1998] RPC 423 (German Federal Supreme Court)

64 The Paris Court of First Instance disagreed with this view in Science Union v AJC Pharma (20 October 2001) and Science Union v Biophelia (25 January 2002). Further, an attempt to amend French law via Article 31 of French Social Security Act 1999 failed. Article 31 said that "studies to show bio-equivalency with an original drug for the purpose of obtaining a marketing authorisation for a generic drug are regarded as acts of experimental use within the meaning of L. 613-5 of French Intellectual Property Code". It was declared invalid by the

International (20 February 2001), to compare different methods of administration of the patented molecule came within the experimental purposes exception[65]. Large scale phase III trials were carried out by Flamel Technologies, the owner of a patent for a micro-encapsulation technology, in which Flamel compared its own products with Wellcome's Zovirax. The aim of the trials was apparently (the judgment is vague on the precise details) to compare different modes of administration of Aciclovir, and to research effective dosing regimes. The court decided that the experiments were done for experimental purposes relating to the subject matter of the invention. It went on to say that the trials did not become infringing acts despite their desired aim, namely, future commercialisation. The experimental character of these trials was said to be apparent by virtue of the fact that they were a pre-requisite to the grant of a marketing authorisation.

2.2 Exceptions in EC Directives 2001/82 and 2001/83

Quite clearly then there was a significant divide between national courts in Europe on the issue of clinical trials of medicinal products and the experimental purposes exception. The English courts, there being no reported case from the Scottish courts, regarded such clinical trials as a patent infringement; and this would appear to have been the view also in France and Sweden. Legal opinion in Denmark appeared to agree with the German view.

The differing legal opinions and national court rulings in the European Community on clinical trials under the experimental purposes exemption prompted the Community to address the issue in both Article 13 of Directive 2001/82 (veterinary medicines)[66] and Article 10 of Directive 2001/83[67] (medicinal products for human use). Article 10 reads (as far as is relevant here) as follows:

> 1. By way of derogation from Article 8(3)(i), and without prejudice to the law relating to the protection of industrial and commercial property, the applicant shall not be required to provide the results of pre-clinical tests and of clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal

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Constitutional Court on the ground that such a provision could not be validly included in a law on the financing of French social security.

65 Science Union and Servier v Corbière and Bellon (27 November 1984): the Paris Court of Appeal ruled that the manufacture of pharmaceutical samples in order to obtain marketing authorization had a commercial purpose and was therefore an infringement. In a different context, the same court held in Parienti v Peugeot (3 July 3 2002) that the submission to local authorities of a new type of transportation system fell outside the experimental use exception, notably because the event had been widely publicised.

66 As amended by Directive 2004/28 of the European Parliament and of the Council.

67 As amended by Directive 2002/98/EC of the European Parliament and of the Council, by Commission Directive 2003/63/EC and by Directives 2004/24/EC and 2004/27/EC of the European Parliament and of the Council.

> product which is or has been authorised under Article 6 for not less than eight years in a Member State or in the Community.
>
> …
>
> 6. Conducting the necessary studies and trials with a view to the application of paragraphs 1, 2, 3 and 4 and the consequential practical requirements shall not be regarded as contrary to patent rights or to supplementary protection certificates for medicinal products[68].

Article 10 has been implemented in the United Kingdom by the Medicines (Marketing Authorisations Etc.) Amendment Regulations 2005 (SI 2005 No. 2759). Section 60(5)(i), UK Patents Act 1977, exempts studies, tests and trials on generic medicines required to show that the generic product is bioequivalent to an approved patented product where these acts are required to obtain marketing authorisation. Article 10 applies only to medicinal products. Studies, tests and trials of non-medicinal products[69] for which marketing approvals are required are not covered by the exception.

The UK Patent Office believes that the Article 10 and Article 13 exceptions cover the following activities[70]:

- the carrying out of chemical and biological synthetic processes suitable for the making, disposal or keeping of the active substance(s) including the manufacture or the import of batches in quantities sufficient to provide material for preparing investigative batches of the medicinal product and to validate the processes to the satisfaction of the competent authorities;
- the development, testing and use of the associated analytical techniques for the above;
- the development of the final pharmaceutical composition and manufacturing processes for the medicinal product to be marketed including the making, disposal or keeping or import of product batches in quantities sufficient to conduct the necessary pre-clinical tests, clinical and bioavailability trials and stability studies of the medicinal product and to validate the processes to the satisfaction of the competent authorities;
- the development, testing and use of the associated analytical techniques for the above;
- the manufacture and supply to the competent authorities of samples of active substances, their precursors, intermediates or impurities and of finished product samples;
- the compilation and submission of a marketing authorisation or variation application and application for a marketing authorisation.

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68 The same statement can be found in Article 13, paragraph 6 of the directive on veterinary medicinal products.

69 Such as herbicides.

70 http://www.patent.gov.uk/about/ippd/issues/pharmleg.htm.

This view of the exceptions Articles 10 and 13 would seem to exclude the use of research tools to identify or obtain biologically active molecules or compounds for possible further development as pharmaceutical compositions.

3 US Patent Law

It is not necessary for the purposes of this Report to discuss in any detail the law on experimental use of patented inventions in the USA. Suffice to say that experimental use of a patented invention by unlicensed users is strictly limited under US common law to "philosophical experiments" [71]. The strictness of the common law is relaxed by the US Patent Code which allows a patented product to be used solely for purposes reasonably related to testing requirements under Federal law which regulates the manufacture, use or sale of drugs – the so-called Bolar exemption[72].

Section 271(e)(1), US Patent Code (Title 35), states that it is not an infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention (other than a new animal drug or veterinary biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Act of March 4, 1913) which is primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology, or other processes involving site specific genetic manipulation techniques) *solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products*. A product in this context does not include information about a product; and importing such information into the jurisdiction is not a patent infringement under section 271[73].

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71 See generally, http://www.fas.org/sgp/crs/RL32651.pdf, Thomas, Scientific Research and the Experimental Use Privilege in Patent Law, 28 October 2004, CRS Report for Congress; Iles, A Comparative Analysis of the Impact of Experimental Use Exemptions in Patent Law on Incentives to Innovate, 4 Northwestern Journal of Technology and Intellectual Property 61 (2005).

72 See, for example, Integra Life Sciences v Merck (2003) 331 F3d 860; (2005) 545 US … (US Supreme Court) http://www.law.cornell.edu/supct/pdf/03-1237P.ZO. The Canadian Patent Act 1985 states in section 55.2(1) that "is not an infringement of a patent for any person to make, construct, use or sell the patented invention solely for uses reasonably related to the development and submission of information required under any law of Canada, a province or a country other than Canada that regulates the manufacture, construction, use or sale of any product." The Canadian common law on experimental use of patented inventions is discussed in Micro Chemicals Ltd. v. Smith Kline & French Inter-American Corp. (1971) 2 C.P.R.(2d) 193 (Supreme Court of Canada). The Federal Court of Canada decided in Wellcome Foundation Ltd. v Apotex Inc. [1991] 32 CPR (3d) 350 that the importation of a small quantity of a patented medicine for experimental use in hospitals, in order to obtain a notice of compliance before a compulsory licence was delivered to the defendants, did not constitute a bona fide experimental use without the idea of making profit, and was therefore an infringement.

73 Bayer AG v Housey Pharmaceuticals (2002) 340 F.3d 1367 (US Court of Appeals, Federal Circuit); Synaptic Pharmaceutical v MDS Panlabs Inc (2002) 265 F.Supp.2d 452 (US District Court, New Jersey).

The phrase "reasonably related" in 35 USC 271(e)(1) has been interpreted liberally by the US courts; and in Merck KGaA v Integra Lifesciences I Ltd (2005)[74] the Supreme Court said that the section covered (i) the use of patented materials both before and after clinical trials have been approved by the Federal Food and Drug Administration (FDA), (ii) carrying out research beyond issues pertaining to human safety, and (iii) failing to submit an investigational new drug application to the FDA on research that used the patented compounds[75]. Integra owned five patents related to the tripeptide sequence Arg-Gly-Asp ("RGD peptide") which promotes cell adhesion. As part of a research project aimed at identifying and developing potential compounds inhibiting for angiogenesis, Merck sponsored research that used the RGD peptides as "positive controls" in the experiments. Integra sued Merck for patent infringement, alleging that Merck wilfully infringed and induced others to infringe its RGD peptide patents. Merck argued that its research involving the RGD peptides did not infringe by virtue of 35 USC 271(e)(1). The Supreme Court concluded that the section extends to all uses of patented inventions that are reasonably related to the development and submission of any information to the FDA. However, the Court expressly avoided the issue of whether the use of a patented research tool in pre-clinical research comes within section 271(e)(1).

4 Conclusion

The unauthorised use or enjoyment of a person's property is an invasion of that person's rights or a misappropriation of his entitlement. This general principle applies no less to intellectual property than it does to property in general. Moreover, while a court may have regard to the good or laudable intentions of a trespasser when it comes to penalising a trespass, good intentions will not excuse a trespass or exonerate a trespasser. Thus, a researcher in Singapore who, without a licence, uses a research tool patented in Singapore when seeking a potential cure or treatment for a horrible human disease is, despite this laudable motive, nonetheless an infringer of the patent. Use of a patented research tool at the discovery stage in pharmaceutical research, for example, with the intention of seeking a licence from the patentee if the tool should yield commercially promising results, is also an infringement notwithstanding this intention.

The exception in section 66(2)(b), Singapore Patents Act, is limited to acts relating to the subject matter of the invention under Singapore law and therefore the use of a patented research tool in commercial research to discover or identify new therapeutic compounds is likely to fall outside the exception. It is likely also to fall outside the section 66(2)(h) exception relating to marketing approval for pharmaceutical products. That being so, if a licence is sought from the patent owner after a new compound has been identified, the price of a retrospective licence is apt to be higher than it would have been for a licence

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74 125 Supreme Court 2372; (2005) 545 US …

75 The Court's judgment in Merck has been said by Rubin, Merck KGaA v Integra Lifesciences I Ltd: Greater Research Protection for Drug Manufacturers, 1 Duke Journal of Constitutional Law & Public Policy 79 (2006), to reflect "a pro-development and concomitant anti-property right policy acknowledging that in reality, scientific testing is a process of 'trial and error' and the safety of proposed clinical experiments cannot be evaluated 'in a vacuum'" and as being "likely to affect the future of research exemptions.". http://www.law.duke.edu/journals/djclpp/index.php?action=downloadarticle&id=20

granted before the research started; and yet higher still the further down the line towards a marketable product that a compound has progressed. The price of a retrospective licence will include an element of compensatory damages for the earlier infringement.

CHAPTER 3

IMPORTATION OF PRODUCTS OF PATENTED PROCESSES

The unauthorised importation of the product of a patented process (such as a research tool) may infringe the exclusive rights of the patent owner. The WTO TRIPS Agreement, Article 28(1), requires signatories to grant the owner of a patent the following exclusive rights:

> (a) where the subject matter of a patent is *a product*, to prevent third parties not having the owner's consent from the acts of making, using, offering for sale, selling, or *importing* for these purposes that product;
>
> (b) where the subject matter of a patent is a *process*, to prevent third parties not having the owner's consent from the act of using the process, and from the acts of using, offering for sale, selling, or *importing for these purposes at least the product obtained directly by that process*.

Article 34, WTO TRIPS Agreement provides for reversal of the burden of proving infringement of a process patent[76].

> 1. For the purposes of civil proceedings in respect of the infringement of the rights of the owner referred to in paragraph 1(b) of Article 28, if the subject matter of a patent is a process for obtaining a product, *the judicial authorities shall have the authority to order the defendant to prove that the process to obtain an identical product is different from the patented process.* Therefore, Members shall provide, in at least one of the following circumstances, that any identical product when produced without the consent of the patent owner shall, in the absence of proof to the contrary, be deemed to have been obtained by the patented process:
>
> (a) if the product obtained by the patented process is new;
>
> (b) if there is a substantial likelihood that the identical product was made by the process and the owner of the patent has been unable through reasonable efforts to determine the process actually used.
>
> 2. Any Member shall be free to provide that the burden of proof indicated in paragraph 1 shall be on the alleged infringer only if the condition referred to in subparagraph (a) is fulfilled or only if the condition referred to in subparagraph (b) is fulfilled.

[76] See for example: section 295, US Patent Code; section 121, Australian Patent Act 1990.

> 3. In the adduction of proof to the contrary, the legitimate interests of defendants in protecting their manufacturing and business secrets shall be taken into account.

Assuming these WTO rules are enacted in national patent law, a patented product (e.g. a receptor agonist or antagonist the subject of a reach-through claim) or any product obtained directly by use of a patented process (e.g. a research tool) cannot be imported to the jurisdiction without the patentee's consent, unless of course the patent (or patent claim) is shown to be invalid. Moreover, where a substantial likelihood exists that a product was made[77] by the patented process and the patentee has been unable through reasonable efforts to determine that the process was actually used, the defendant must prove that he did not use the patented process to obtain the product[78]. A new product is deemed to have been obtained by the patented process – but if the product is new, it can also be patented if the other criteria for patentability (including the disclosure requirement) can be met. However, as discussed in an earlier chapter, a claim for a new compound with no specific function will be invalid for lack of industrial application (or utility); and even if a specific function (e.g. inhibiting obesity) is assigned thereto or can be inferred, the claim will be invalid for insuffiency if it encompasses a genus of compounds but does not define the relationship between the structural features of the member compounds and the specific function. That may leave the process claims as the only enforceable claims in the patent.

1 Direct Products of Patented Process

The obligations in Articles 28(b) and 34 WTO are expressed in sections 66(1)(c) and 68, Singapore Patents Act[79]. Section 66(1)(c) declares a patent to be infringed "where the invention is a process, [if without the patent owner's licence any person] disposes of, offers to dispose of, uses or imports any product obtained directly by means of that process or keeps any such product whether for disposal or otherwise." The key words in the section are "any product obtained directly"[80]. It might be said that "any product" refers only to a physical or tangible product and that information about a product (e.g. that it is an activating compound) falls outside section 66(1)(c). But surely that misses the point. The word "obtained" is not limited to a product that is made by the process. Any product identified or tested by the patented process is also "obtained" thereby. In other words, a product identified by using a patented process (as in a claim to an "isolated and purified receptor agonist identified by the method…") is a product obtained directly by

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[77] The verb "made" in Article 34(1)(b) might suggest that "obtain" in Articles 28 and 34(1)(a) also means "made".

[78] Infringement of a process patent can be hard to detect unless the process leaves its "mark" or "fingerprint" on products made by the process.

[79] Certain acts are exempted by section 66(2) from infringement provisions in section 66(1). The section 66(2) exceptions cover, among other things, acts done for experimental purposes; acts done to support any application for marketing approval for a pharmaceutical product; and the import, disposal or offer to dispose of a patented pharmaceutical product for use by or on a specific patient in Singapore, or the use of that product by or on that patient. The corresponding provisions in the UK Patents Act 1977 are insections 60(1)(c) and 100.

[80] The corresponding section in the US Patent Code, section 271(g), is limited to a product which is "made" by a process. Section 271(g) is discussed below.

the process or method. Incidentally, even if the process is used only once, rather than repeatedly as when a product is made by a process, there is an infringement under paragraph (c).

Whether a product incorporating an ingredient developed from molecule, substance or compound identified and evaluated outside the jurisdiction using a research tool patented in the jurisdiction, would infringe if imported into the jurisdiction, can be explored through the following example.

> X uses in Ruritania a screening process patented in Singapore by P, to identify a molecule or substance (a compound) which is used in the manufacture of a medicament. The process is not patented in Ruritania; alternatively it is patented in Ruritania but X's activities cannot be shown to infringe the Ruritanian patent. X imports or intends to import the medicament into Singapore.

Do the imports infringe, or threaten to infringe, the Singapore patent, owned by P? Is there in the medicament a product obtained directly by means of that process? What did X obtain directly by use of the process in Ruritania? A physical product or simply information about a physical product?

1.1 Pioneer Electronics v Warner Music

Pioneer Electronics is the leading UK case on the meaning section 60(1)(c), UK Patents Act 1977[81]. The patents in suit related to processes used in the manufacture of optical discs (compact discs or CDs). One of the patents allegedly to have be infringed had a claim for a method for forming a metallic layer for use as a 'stamper' in moulding disc replicas. A metallic film was first evaporated onto the recording layer of a master recording, the inventive step lying in the lowness of the pressure at which this was done, and another metallic film was then superimposed by electroplating to form an integral metallic layer which was then separated from the rest of the material. In the other action, the three patents alleged to be infringed related to the production of the master recording.

Warner applied to strike out the writs and statements of claim. They admitted the manufacture in Germany and the sale in the United Kingdom of the allegedly infringing discs. It was agreed for the purpose of the case that the defendants' manufacture included steps as claimed in the patents. The metallic layer (referred to as the "father") was then used to produce a number of positive impressions ("mothers") each of which was used to produce a number of negative impressions ("sons"). These "sons" were then used in the pressing process by which the CDs were mass-produced. Warner contended that there had been no infringement because the CDs were not obtained directly by means of the processes claimed in the patents as required by section 60(1)(c), and the Patents High Court agreed with Warner ([1995] RPC 487).

Pioneer appealed, arguing that the judge had been wrong in holding that the infringing product must be the immediate product of the patented process. The patented processes

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[81] [1997] RPC 757.

were used in the production of discs which were identical with the masters in that the physical configuration of the surfaces and the information obtained from them were the same. The essential characteristics of the finished discs were largely determined by the use of the patented processes. Warner accepted that a product could be further processed without losing its identity, so that it remained a product obtained directly by means of the patented process. They submitted however that there was no identity between the master and the finished CDs. Pioneer's appeal was dismissed.

The Appeal Court ruled that, by confining infringement to products 'directly obtained', section 60(1)(c) would appear to have altered the previous English law that there was infringement where an imported product had been obtained directly or indirectly by means of a patented process provided always that the use of the patented process had been substantial. The requirement in section 60(1)(c) – that the product in question be obtained directly by means of the patented process – came via the European Patent Convention, from German law and, the English court said, the relevant German authorities supported these conclusions:

- The product obtained directly by means of a patented process is the product with which the process ended. It does not cease to be the product so obtained if it is subjected to further processing which does not cause it to lose its identity, there being no such loss where it retains its essential characteristics.
- There is no free-standing "essential characteristics" test. Those characteristics are relevant only to the question whether the product with which the patented process ended has lost its identity or not.
- The "loss of identity" test represents the test adopted by European law.

It was not correct to say that the finished CD was an identical copy of the master. It differed in material from the master and was the result of three further stages of production. From each stage emerged a new and different product which was a necessary instrument in the production of the finished disc. Neither the master nor any of the intermediate products was capable of performing the same function as the finished CD: none of them could be put in a compact disc player and played in the home.

The question whether the product with which the patented process ended retains its essential characteristics or not is one of fact and degree, and there will often be difficulty in applying the test to the facts of particular cases. In the Pioneer case, on the factual analysis put forward by the parties and even allowing for the possibility of further argument as to the facts and the law at a trial, there was no such difficulty and Pioneer was bound to fail if it pursued its case against Warner.

1.2 Applying the Pioneer Ruling

What was obtained directly by means of the process patented in Singapore but used in Ruritania? If information about the biological activity of a compound, rather a physical product *per se*, was obtained by using the process in Ruritania and this information allowed the user to identify the compound for further development, then arguably the

compound is a product "obtained directly" by using the patented process. As said earlier, the verb "obtained" is not limited to making a product. Testing a product to identify its qualities or characteristics should come within the meaning of "obtained", leaving it to be decided in Singapore whether the medicament made in Ruritania for importation to Singapore is or contains the immediate (or direct) product, the compound, obtained by X's use of the patented process. If the medicament is or contains that compound, then arguably importation of the medicament into Singapore infringes (or would infringe) P's patent[82]. But if, in the manufacture of the medicament, that compound (the direct or immediate product of the patented process) loses its identity, importation of the medicament will not infringe P's patent under section 66(1)(c) of the Singapore Act.

2 Importation and 35 USC 271(g)

The US Patent Code (35 USC) declares that anyone who "without authority makes, uses, sells, or offers to sell any patented invention, within the United States during the term of the patent therefor, infringes the patent" (section 271(a))[83]; and that importation, sale or use of a product made by a patented process is an infringement except where the "product" is either "materially changed by subsequent processes" or is "a trivial and nonessential component of another product" (section 271(g))[84]. Paragraph (g) reads as follows:

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[82] It will be recalled from Chapter 3 of this Report that section 66(2), Singapore Patents Act, creates an exception relating to marketing approval for pharmaceutical products. This corresponds in its basic objective to the exceptions in EC Directives on clinical trials: Article 13, Directive 2001/82 (veterinary) and Article 10, Directive 2001/83 (human-use). Studies, tests and trials on generic medicines required to show that the generic product is bioequivalent to an approved patented product where these acts are required to obtain marketing authorisation are covered by the exception.

[83] See generally, http://www.oblon.com/media/index.php?id=166, Signore, Michon, The Impact of U.S. Patents on International Business, Managing Intellectual Property, Issue 144, page 28. Columbia University v Roche Diagnostics (2001) 150 F. Supp.2d 191; 57 USPQ2d 1825 (US District Court, Mass.): Columbia sued Roche under section 271(a) for infringement of patents relating to methods and products to make erythropoietin (EPO). Roche obtained the cell lines that it used in Germany from its collaborator (Genetics Institute) in the USA. But because the acts that allegedly infringed Columbia's patents for methods of genetically transforming cells to get them to produce EPO did not occur in the USA, there was no infringement under section 271(a). Importation of EPO, an unpatented by-product of Columbia's patented methods, did not infringe either, because it could not be proven that the importer used the patented process to manufacture the serum-free EPO. See further, Ewing and Heide, "Case Cautions Collaborators", The National Law Journal 16 December 2002.

[84] Ajinomoto Co. Inc. v Archer-Daniels-Midland Co. (2000) 228 F.3d 1338, 56 USPQ2d 1332 (US Court of Appeals, Federal Circuit): the claims in Ajinomoto were for a method of modifying bacteria to improve their ability to express the amino acid threonine. The actual bacteria made by the claimed process were imported to the United States, and the infringement action was based on the alleged use of the bacteria in the USA. Pfizer Inc. v Aceto Corp. (1994) 853 F. Supp. 104 (USDC, SD New York): an action was brought under section 271(g) against a foreign manufacturer located and operating in China, for infringement of a United States patent for a process of making flavour enhancers. The manufacturer did not itself import the product of the allegedly infringing process into the USA, but sold the product in China to another Chinese company, and the latter in turn sold it to a Delaware corporation that imported the product. The court granted the manufacturer's motion for summary judgment. Liability does not follow under section 271(g) simply because a foreign manufacturer can foresee that a buyer of its product may ultimately import it into the United States. Since the Chinese manufacturer did not bring the product into the United States (nor did it foresee its importation there), it was not an "importer" within the meaning of section 271(g). See also, Cybiotronics, Ltd. v Golden Source Electronics Ltd (2001) 130 F. Supp. 2d 1152 (USDC,

> Whoever without authority imports into the United States or offers to sell, sells, or uses within the United States a product which is made by a process patented in the United States shall be liable as an infringer, if the importation, offer to sell, sale, or use of the product occurs during the term of such process patent. In an action for infringement of a process patent, no remedy may be granted for infringement on account of the noncommercial use or retail sale of a product unless there is no adequate remedy under this title for infringement on account of the importation or other use, offer to sell, or sale of that product. A product which is made by a patented process will, for purposes of this title, not be considered to be so made after—
> (1) it is materially changed by subsequent processes; or
> (2) it becomes a trivial and nonessential component of another product.

Imagine now that the earlier example falls to be decided under 35 USC 271(g). X uses in Ruritania a screening process patented in the USA, to identify a compound which is used in the manufacture of a medicament. The process is not patented in Ruritania; alternatively it is patented in Ruritania but X's activities cannot be shown to infringe the Ruritanian patent (e.g. because of the wording of the Ruritanian claims). X imports or intends to import the medicament into the USA. Would this infringe under section 271(g)? Was the compound made by the patented process?

2.1 Scope of 35 USC 271(g)

The scope and limits of section 271(g) were explained in Eli Lilly & Co. v American Cyanamid Co.[85] and in Mycogen Plant Science v Monsanto[86].

The patent in issue in Eli Lilly was for a process of making an intermediate compound. The alleged infringer used the process outside the jurisdiction (in Italy) to make the intermediate, and used other processes to convert the intermediate into a final antibiotic product before importing it into the jurisdiction. The Federal Circuit Court ruled that there was no infringement because the final antibiotic product differed in its chemical structure from the product of the patented process (the intermediate compound) and it possessed different properties. The court also noted that the intermediate resulting from the patented process could be used to make more than one final product. If the process claim had included the three additional steps for converting the intermediate to the final product, the court may have found an infringement under section 271(g).

The independent process claim of the '831 patent in Mycogen read:

> A method of designing a synthetic Bacillus thuringiensis gene to be more highly expressed in plants, comprising the steps of:
> analyzing the coding sequence of a gene derived from a Bacillus thuringiensis which encodes an insecticidal protein toxin, and

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CD California); Tellekson and Bernard, Have Patent, Will Travel, Intellectual Property Today, July 2004, page 40; Petersen, US Infringement Liability for Foreign Sellers, Duke Law and Technology Review 32 (2003); Signore and Michon, The Impact of US Patents on International Business, Managing Intellectual Property, Issue 144, page 28 (November 2004).

85 (1996) 82 F.3d 1568 (US Court of Appeals, Federal Circuit).

86 (2001) 58 USPQ2d 1991, 243 F.3d 1316 (US Court of Appeals, Federal Circuit).

> modifying a portion of said coding sequence to yield a modified sequence which contains a greater number of codons preferred by the intended plant host than did said coding sequence.

This claim relates to the technology of genetically engineering plant genes to protect plants from insect pests.

Monsanto argued that it had not infringed under section 271(g) because it performed the process before the '831 patent was granted. After the codon optimisation was completed, the host cell expressing the optimised sequence would reproduce itself and there was no need to repeat the steps ever again. Section 271(g) refers to "a product which is made by a process patented in the United States", meaning that the process must be patented at the time the product is made before section 271(g) is violated[87].

2.2 Bayer AG v Housey Pharmaceuticals[88]

Housey Pharmaceuticals was the assignee of four U.S. patents all entitled "Method of Screening for Protein Inhibitors and Activators", in which the claimed methods are directed to the identification of compounds having pharmaceutical potential to treat a particular disease, and accordingly the methods could assist a researcher to predict whether a drug comprising a particular pharmacological agent may be beneficial in treating a disease known to involve the protein of interest[89]. For example,

> A method of determining whether a substance is an inhibitor or activator of a protein whose production by a cell evokes a responsive change in a phenotypic characteristic other than the level of said protein in said cell per se, which comprises:
>
> (a) providing a first cell line which produces said protein and exhibits said phenotypic response to the protein;
>
> (b) providing a second cell line which produces the protein at a lower level than the first cell line, or does not produce the protein at all, and which exhibits said phenotypic response to the protein to a lesser degree or not at all;
>
> (c) incubating the substance with the first and second cell lines; and
>
> (d) comparing the phenotypic response of the first cell line to the substance with the phenotypic response of the second cell line to the substance.

Bayer sought a declaratory judgment that the Housey patents were invalid, unenforceable, and not infringed by Bayer. The patent owner responded with a

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87 Moreover, products made by the process prior to patenting can be sold under US law without violating section 271(g). Proof that an alleged infringer had actual knowledge of a published process claim may create provisional rights under the American Inventors Protection Act if the patent is granted with a process claim substantially identical to the published process claim.

88 (2002) 340 F.3d 1367 (USCA, FC).

89 The claimed methods involve the preparation of a cell line having a relatively high concentration of a protein of interest relative to an original cell line. When a particular pharmacologic agent is applied to both cell lines, the methods allow a researcher to determine whether the applied agent activates, or inhibits, the activity of the protein of interest.

counterclaim against Bayer for patent infringement, including a claim under 35 USC 271(g), alleging a substantial likelihood that Bayer had used the Housey methods overseas to "make the characterization of a pharmacologically active agent" and that thereafter Bayer had imported to the jurisdiction both information gathered from practising the patented testing process and a pharmaceutical composition identified by the patented testing process.

2.2.1 Section 271(g): Physical Product Required

The US District Court for the District of Delaware rejected Housey's counterclaim, and Housey appealed to the US Court of Appeals for the Federal Circuit. The Federal Circuit Court reviewed the history of section 271(g) and concluded the section protects only *manufactured products* and not information derived from patented processes. If the section were interpreted to cover information generated by a patented process then the mere entry into the United States of an individual who observed and possessed knowledge of the operation of a patented process overseas could arguably constitute infringement. Accordingly, the court ruled that for a product to have been made by a process patented in the United States, it must have been a physical article that was 'manufactured' and the production of information was not covered.[90]

2.2.2 Use of Information

As to the second element of Housey's counterclaim, the Federal Circuit Court ruled, in dismissing the counterclaim, that the sale, use or importation of a medicament manufactured through the use of information received from practising the patented process overseas does not violate Section 271(g) either. Patented screening methods, though useful in identifying and developing a compound with medicinal properties, do not "make" a product within the meaning of Section 271(g). As the Appeals Court said[91], "The process must be used directly in the manufacture of the product, and not merely as a predicate process to identify the product to be manufactured. A drug product, the

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[90] See also, Synaptic Pharmaceutical v MDS Panlabs Inc (2002) 265 F.Supp.2d 452 (US District Court, New Jersey). In June 2000, the patentee, Synaptic Pharmaceutical Corporation, sought to enforce patents directed to cloned human receptor genes, cells expressing those receptors, and the use of such cloned receptors in biological testing. Synaptic alleged that laboratory research service organisation MDS infringed Synaptic's patents by importing reports from MDS's Taiwanese affiliate that comprised the results of tests performed in Taiwan using Synaptic's patented testing methods. The District Court ruled that that these reports did not constitute a "product" protected by Section 271(g).

[91] In Bio-Technology General Corporation v Genetech, Inc. (1996) 80 F.3d 1553, 1561 (USCA, FC), the Federal Circuit affirmed the district court's ruling that a protein (human growth hormone) made in Israel by a host organism expressing an inserted plasmid was a product "made by" the patented process for creating the plasmid itself. The patent in issue had claims to (i) a method for making a vector or microorganism containing DNA encoding the protein and (ii) methods for making the DNA encoding the protein. The appeal court found that it would not have been possible to make the vector (or microorganism), ie the product expressing the protein outside the USA, without using the patented method. Unlike the process in Bio-Technology, the Housey process was not used in the actual synthesis of the drug product; and unlike Eli Lilly, discussed above, where the intermediate had different uses, the plasmid in B-TG was only used to make one final product. That said, had the process claim in B-TG included additional steps of transforming a host to express a protein encoded by the plasmid and collecting the protein end product from the culture, the litigation with Genentech could have been avoided.

characteristics of which were studied using the claimed research processes, therefore, is not a product "made by" those claimed processes."

2.2.3 Method of Manufacture Claims

The ruling in Housey suggests that, to improve their chances of meeting the requirements of section 271(g), inventors of new screening methods should consider adding claims that include a step of making a medicament or compound identified in the screening process.

3 Conclusion

The owner of a patented research tool who seeks to gain the maximum benefit from its use by another will want to reach through, whether by agreement or through patent infringement damages, to commercial products or services which, but for the other's use of the tool, would not have been made or would not be provided. If the patent for the tool includes a reach-through claim, for example in the general form of "an isolated and purified X identified by the method of claim Y", the claim may be attacked for invalidity if the patent owner seeks to enforce it.

With that in mind, the patent owner may argue, where the evidence supports this, that the defendant to an infringement action is, for example, importing a product obtained directly by means of the patented method, contrary to section 66(1)(c), Singapore Patents Act or its equivalent in European jurisdictions. Arguably, an isolated and purified agonist identified outside the jurisdiction by the method patented in the jurisdiction is a product "obtained" directly thereby. But did that product 'lose its identity' during further development or processing? If it lost its identity, section 66(1)(c) or its European equivalent will not apply.

It would be different under US law following the ruling in Bayer v Housey. This case rests on the meaning of certain key words in 35 USC 271(g), and the court ruled that the section applies only to manufactured products, as distinct from information obtained from testing the pharmacological activity of products. Patented screening methods, though useful in identifying and developing a medicine or pharmaceutical, do not "make" a product within the meaning of Section 271(g).

Having regard to the foregoing, a researcher or enterprise outside the patent jurisdiction may learn ultimately, and at no small (and possibly very significant) cost, that research tools are not a form of 'free beer'. Patent laws in Europe equivalent to section 66(1)(c), Singapore Patents Act, have yet to be interpreted by the national courts in the context of patented research tools but it may be unwise to assume that the meaning of "obtained" will be limited to a product *made* by a patented process. Whether the product thereby obtained (e.g. identified) lost its identity during further processing is a different issue. It would be sensible therefore to obtain a licence to use the method and pay a royalty rather risk the loss of a significant investment in research and development, even though the

research tool is not patented in the jurisdiction where it is being used[92]. A negotiated royalty is almost certain to cost less than a judicial award of compensatory damages, alternatively an account of profits, as discussed in the next chapter.

[92] The claims in the Cohen-Boyer 'gene-splicing' patents – US Patent 4740470, US Patent 4237224 and US Patent 4468464 – covered not only the enabling technology but also any recombinant organisms created through use of the technology. These patents can be found in the appendices to this Report. Although no corresponding patents were granted in Europe or Japan, companies there paid for licences since otherwise the US patents could have been enforced to exclude from US markets imported products made with or expressing the technology.

CHAPTER 4

MONETARY REMEDIES FOR INFRINGEMENT OF RESEARCH TOOL PATENTS

The remedies provisions in the WTO TRIPS Agreement, Article 45 (Damages), require the judicial authorities of signatory States to have the authority to order the infringer to pay the right holder damages and also expenses:

1. … damages adequate to compensate for the injury the right holder has suffered because of an infringement of that person's intellectual property right by an infringer who knowingly, or with reasonable grounds to know, engaged in infringing activity.

2. … expenses, which may include appropriate attorney's fees. In appropriate cases, Members may authorise the judicial authorities to order recovery of profits and/or payment of pre-established damages even where the infringer did not knowingly, or with reasonable grounds to know, engage in infringing activity.

Damages, alternatively recovery of profits, for infringement of a patent are meant to encourage technical innovation by compensating the patent owner for profits lost to or appropriated by the infringer. An injunction seeks to prevent harm, or further harm, to the patentee's economic interests. If an injunction by itself does not do so then an award of damages, alternatively recovery of profits, coupled with legal costs, may threaten the survival of an enterprise, if it does not eliminate the enterprise altogether.

1 Some General Principles

The common law of compensatory damages aims to compensate the claimant for the loss or harm caused by the wrongdoer's act[93]. Damages for a breach of contract are intended to compensate for the loss suffered as a result of the breach, and so the law endeavours to put the claimant in the position he would have been in had the contract been performed. A claimant seeking substantial damages for a breach of contract must prove that actual loss has been caused by the breach, that the type loss is recognised by the law as giving a right to damages and that the loss is not too remote (that is, ought reasonably to have been foreseen when the contract was made). If no actual loss can be proven, the claimant will only be entitled to nominal damages. Damages for a tort (or legal wrong), such as infringement of an intellectual property right[94], seek to return the claimant to the position he was in before the wrongdoing. The claimant must prove that the loss he suffered was

[93] Damages claims in Civil Law jurisdictions (e.g. Japan, the countries of Continental Europe) are beyond the scope of this Report. But see Reitzig et al., Who Really Profits from Patent Infringements? (8 May 2003) http://www.druid.dk/uploads/tx_picturedb/ds2003-805.pdf

[94] Infringement of a patent claim is analogous to trespass to land. Patent infringement is a statutory tort. Common law torts include negligence, unlawful interference with contractual relations, and passing-off (misrepresentation of goods or services).

caused by the defendant's wrongdoing, that that loss was reasonably foreseeable, and that recovery of the loss is not excluded by public and social policy[95]. A tort which also is a breach of contract – for example where a patent licensee exceeds the limits of the licence – can be pursued on either basis.

Compensatory damages are often classified as substantial, restitutionary, aggravated or additional. Exemplary or punitive damages[96] are extra-compensatory, as is nominal damages[97]. Nominal (or vindicatory) damages recognise the existence of a claimant's right where the claimant suffers no consequential loss as a result of the wrongful act. Substantial damages are awarded where the claimant can prove actual loss (although it may be a trivial loss) resulting from the wrongdoer's act. Restitution is an alternative method of assessing damages; and restitutionary damages are intended deprive a defendant of some or all of the gains arising from his wrongdoing. Aggravated damages seek to compensate the claimant for conduct which has increased the seriousness of the wrong inflicted on him and, accordingly, increased the degree of the insult, hurt feelings or harmed reputation for which compensation must be paid. Additional damages can be awarded for infringement of copyright under section 119(4), Singapore Copyright Act, if the court is satisfied that it is proper to do so, having regard to the flagrancy of the infringement, any benefit shown to have accrued to the defendant by reason of the infringement, and all other relevant matters[98]. Exemplary damages, which are punitive in nature, are available under English law in a limited number of non-IP cases, where ordinary damages calculated on a compensatory basis would be inadequate[99].

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[95] Gerber Garment Technology v Lectra Systems Ltd (1997) Reports of Patent Cases 443 (English Court of Appeal).

[96] US patent law authorises the courts to award treble damages for wilful and wanton patent infringement or proceedings brought in bad faith.

[97] Lord Scott, in his paper given at the Chancery Bar Association Conference held in London on 20 January 2006, http://www.chba.org.uk/downloads/Lord%20Scott%20lecture%20on%20Damages.doc, remarks that "This proliferation of adjectives suggests a variety of different purposes for the award of damages. It underlines the over-complication of what should be a simple jurisprudential concept and prompts a re-examination of the purpose or, perhaps purposes, for which damages are awarded in our civil law… So-called "restitutionary" damages, too, are in my opinion, best explained as compensatory damages; awarded to compensate for a loss caused by a wrong. A distinction needs to be drawn between proprietary monetary claims, where the claimant is alleging that the defendant is holding a fund that belongs to the claimant, and restitutionary damages claims. The former are not damages claims at all. They are proprietary claims."

[98] Additional damages are available also for infringement of copyright, design right or performers' right under the UK Copyright, Designs and Patents Act 1988; and under schedule A1 of the UK Patents Act 1977, which concerns the provision of false information relating to biotechnological innovations. There has been uncertainty as to how the term "additional" should be interpreted, and it has been suggested in the UK Government's Consultation Paper on the Law of Damages (CP 9/07, 4 May 2007) that the term 'additional damages' be replaced with 'aggravated and restitutionary damages'. This would ensure that damages awarded under the 1977 and 1988 Acts could include, for example, restitutionary elements such as the recovery of profits from the infringer as well as aggravated damages.

[99] Following the ruling of the House of Lords in Kuddus v Chief Constable of Leicestershire Constabulary [2001] UKHL 29, exemplary damages may now be available under English law in patent infringement cases to supplement an award of compensatory damages, but as yet there is no reported patent (or indeed any IP) case on the award of such damages. In Catnic v Hill & Smith [1983] FSR 512 the defendants manufactured lintels which infringed the plaintiff's patent. The defendants, knowing that an adverse judgment would be given (and an injunction granted against further sales), sold the remaining stock

2 Damages or Account of Profits?

Section 67(1), Singapore Patents Act provides for damages or an account of profits, but the court cannot, in respect of the same infringement, both award the patentee damages and order that he shall be given an account of the infringer's profits[100]. An account of profits requires all profits made by the defendant as a result of the infringement to be paid over to the successful plaintiff. The principle is that a person who appropriates the property of another (e.g. infringes a patent) should not gain in any way, either directly or indirectly from that appropriation[101].

There are significant differences between damages and an account of profits. An inquiry as to damages aims to determine what loss the claimant has actually suffered. The claimant's loss may far exceed any gain made by the infringer through the infringing activity, and it will be all the more so if the infringer violates different rights of different claimants because he will have to compensate each of them for the damage each suffered. There is no upper limit to the compensation the infringer may have to pay. The more damage he inflicts, the greater the financial burden imposed on him.

An account of profits is very different. The court looks not at the harm done by the infringer to the claimant but at the profit made by the infringer – who is treated as if he conducted his business and made profits on behalf of the claimant[102]. It follows that the maximum payment which can be ordered is the total profit made by the infringer, and that profit may far exceed the damage suffered by the claimant. That said, there is only one profits "pot". If different claimants seek accounts in respect of different infringing

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of lintels at a discount before the House of Lords ruling. If the lintels had not been sold, then an order for destruction of the lintels would probably have been made. The court ruled that this sale had been calculated to produce a gain, since it was better to sell the lintels, rather than to have them destroyed, notwithstanding a patent damages claim based on a loss of profits basis. Exemplary damaged might have been awarded in such circumstances.

[100] Damages or an account of profits cannot be awarded against a defendant who proves that at the date of the infringement he was not aware, and had no reasonable grounds for supposing, that the patent existed. Section 69(1), Singapore Patents Act and section 62, UK Patents Act

[101] In Dyson Appliances Ltd v Hoover Ltd (No. 3) (2001) (English Patents High Court) the infringer had to provide the claimant-patentee with an audited financial statement in order to enable claimant to make an informed and timely election between seeking an inquiry for damages or an account of profits as a result of the infringement proved at the substantive hearing. The particular order (a so-called "Tring" order in the English courts) is frequently made today following a finding of infringement in cases involving IP rights and originates from Island Records Ltd v Tring International Limited [1995] FSR 560.

[102] Spring Form Inc v Toy Brokers Limited [2002] FSR 17 (English Patent High Court): "An account [of profits] is a restitutionary remedy whose purpose is to deprive the infringer of the profits which he has improperly made by wrongful acts committed in breach of the claimant's rights and to transfer those profits to the claimant. The test is, in effect, a 'but for' test." When intellectual property is a part in a multi-stage production process, it can be extremely difficult to determine the profit attributable to that property. In Celanese International Corporation v BP Chemicals Limited [1998] 25 Fleet Street Reports 586, [1999] Reports of Patent Cases 203 (English High Court) the claimant elected for an account of profits in the sum of approximately £180 million. The defendant claimed that the property had no value and there were no profits attributable to it. The parties settled their claim too late to prevent the issue of the judgment assessing the profits attributable to the patent in dispute at £375,000 only – the judge had apportioned the profits due to the claimant at £567,840 subject to tax.

activities of an infringer within a single business, the totality of the profits ordered to be paid must not exceed the total profits made by the infringer in that business.

Although an account of profits may give rise to a very different figure to that obtained in a damages inquiry, both remedies proceed on a common principle of legal causation. In a damages action the court is trying to determine what damage has been caused by the infringer's wrongful acts. Was the wrongdoing the cause of the loss or merely the occasion of it? In an account of profits the court is trying to determine what profits have been caused by the infringing acts. Thus, where only part of a product or process infringes, the profits attributable to the non-infringing parts were not caused by or attributable to the unauthorised use of the invention even if the use of the invention was the occasion for the generation of those profits.

3 Assessment of Damages

The measure (or quantum) of damages is the sum of money which will put the injured party in the same position as if he had not sustained the wrong (or infringement); and where secondary losses are a foreseeable consequence of patent infringement, the secondary losses can be recovered[103]. Patent damages should be liberally assessed provided the assessment does not go as far as to punish the defendant.

Damages for infringement may be measured on these bases:

- loss of profits on sales (lost-profit damages) which the patentee did not make but otherwise would have made;
- diminution in the patentee's profits on sales due to the defendant's activities;
- where the patentee would not have made the sales himself, a fair and proper royalty as the price or hire which should have been paid for the use of the patentee's invention to legalise those sales;
- where the patentee does not exploit the patent by manufacture and sale, a fair and proper royalty on all sales or use made by the defendant.

Thus, in a claim for loss of profits, the plaintiff must show both that the loss was caused by the defendant's infringement and that the loss was foreseeable[104]. If that cannot be shown, the plaintiff is entitled to a fair and proper royalty.

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[103] Gerber Garment Technology Inc. v Lectra Systems Ltd. (1997) R.P.C. 443 (English Court of Appeal): "(1) … the overriding principle is that the victim should be restored to the position he would have been in if no wrong had been done; and (2) … the victim can recover loss which was (i) foreseeable, (ii) caused by the wrong, and (iii) not excluded from recovery by public or social policy."

[104] If the plaintiff did not have and could not acquire the means or capacity to manufacture (directly or by sub-contract) the patented products then he would not have made the sales or the additional sales that he claims the defendant took from him.

4 Lost-Profits Damages

In Gerber Garment Technology Ltd v Lectra Systems[105] the plaintiff claimed damages of US$9.757 million from Lectra, the claim comprising

- lost profit on lost sales of the patented machines (automatic cutting machines (CAM) used in the clothing industry),
- lost profit on lost sales of associated products and services, e.g. CAD systems, service contracts and spare parts,
- lost profit on sales Gerber did make due to price depression caused by Lectra's presence in the market,
- lost profit on machine sales made by Lectra after expiry of the patent, and
- royalties on sales that could not have been made by Gerber.

In addition to these lost-profit damages, Gerber claimed damages for profits on lost sales of its subsidiaries and royalties on sales in Ireland of machines shipped via the UK by Lectra. The amount claimed from Lectra was nearly three times what the defendant had received from selling the infringing machines. Lectra argued, not surprisingly, that the damages should be based only on lost sales of the CAM machines that were within the claims of the patent.

Gerber was entitled to damages in respect of profits from lost sales of the CAM and CAD machines and to damages from the sales lost from its subsidiaries; and because Gerber expected to make sales of ancillary equipment following the primary sales and obtain a good proportion of the service contracts and sale of spare parts, it was entitled to lost-profits damages on these items. The effect of price depression due to Lectra's presence in the market was also taken into account in calculating damages. Although an offer made near to expiry of the patent to take orders to supply after expiry is not an infringement if it causes the patentee's customers to wait until the patent expires, because in this case Lectra and its customers involved in the near-expiry negotiations did not care whether delivery took place before or after expiry, these negotiations were regarded as an offer to supply during the life of the patent[106]. Gerber was also entitled to damages in the form of royalties for sales that Lectra made to Irish customers. There were two other minor infringers in the market and the court took into account their sales and their effect on price depression when calculating damages.

The Court of Appeal which, except on minor point, agreed with the High Court's ruling, said that

- there is no rule of law limiting damages for infringement of a patent to lost sales of the patented items, and the general rule is that the patentee should be restored to the position that he would have been in had the wrong in question not been

[105] [1995] Reports of Patent Cases 383 (English Patents High Court); [1997] RPC 443 (English Court of Appeal)

[106] These are often called "bridgehead" or "springboard" damages.

done, as long as there was no exclusion of damages by way of public or social policy;

- in principle a patentee can obtain damages for losses incurred by their subsidiaries;
- in cases where the patentee lost opportunities to make ancillary sales as a result of the infringement it was proper to seek to average the loss incurred as a result of these lost opportunities.

5 Royalty Damages

Consider the following example. P owns a patent for a research method. A licence to use the method is granted by P to anyone who buys directly or indirectly from P materials (e.g. reagents) or a device for use in the method[107]. D uses the method in a research project to discover or identify new molecules with promising medicinal properties. If D buys such materials or device not from P or his licensee but from an unlicensed supplier (S), D's use of the method will infringe the patent if D does not hold or obtain a separate licence to use the method from P; and it may be possible to pursue S as a contributory infringer[108].

Damages in the form of a reasonable royalty[109] are the most likely damages to be sought in a case for infringement of a patented research tool, such as a screening process. Unless the patentee and the infringer are competitors in the relevant product market, the patentee will not lose sales as a result of the infringement, although it will lose royalties.

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[107] See also Stimson, Damages for Infringement of Research Tool Patents, 3 Stanford Technology Law Review 8 (2003), paragraph 21, http://stlr.stanford.edu/STLR/Articles/03_STLR_3/contents_f.htm; Beck, Do you have a license? Products Licensed for PCR in Research Applications, The Scientist 1998, 12(12):21, 8 June 1998. PCR is used to amplify a short, well-defined part of a DNA strand. This can be a single gene, or just a part of a gene. The PCR reaction is carried out in a thermal cycler. This is a machine that heats and cools the reaction tubes within it to the precise temperature required for each step of the reaction. To prevent evaporation of the reaction mixture, a heated lid is placed on top of the reaction tubes or a layer of oil is put on the surface of the reaction mixture.

[108] Under section 60(2) of the UK Patents Act 1977, S may infringe P's patent by supplying or offering to supply D (if he does not hold P's licence) "with any of the means, relating to an essential element of the invention, for putting the invention into effect when he knows, or it is obvious to a reasonable person in the circumstances, that those means are suitable for putting, and are intended to put, the invention into effect in the United Kingdom." The damages claimed by P from D and/or S cannot exceed P's loss, even though use contrary to section 60(1) and supply contrary to section 60(2) are separate torts. If D's use of P's invention is for experimental purposes then it will come within the exception to patent infringement. This will not avail S because section 60(2) creates a separate tort. There is no equivalent provision in the Singapore Patents Act to section 60(2) of the UK Act, so presumably the old law applies. Section 271(c), US Patent Code, states: "Whoever offers to sell or sells within the United States or imports into the United States a component of a patented machine, manufacture, combination, or composition, or a material or apparatus for use in practicing a patented process, constituting a material part of the invention, knowing the same to be especially made or especially adapted for use in an infringement of such patent, and not a staple article or commodity of commerce suitable for substantial non-infringing use, shall be liable as a contributory infringer." Unlike section 60(2) of the UK Act, section 271(c) does not appear to create an independent tort.

[109] In the foregoing example, the price charged by P would comprise a price for the materials and a royalty to use the method. P would seek damages for lost sale of the materials and for unlicensed use of the patented process.

Moreover, if the infringer identifies a marketable medicinal compound, this is unlikely to damage the interests of the patentee unless the latter and the infringer compete in the relevant market.

Courts in Singapore and the UK have yet to provide guidelines or a list of factors to consider when determining a reasonable royalty in the hypothetical negotiations between a willing licensor and a willing licensee[110]. Royalties actually agreed in comparable licences between real parties are preferred to complicated valuation formulae[111]. Where there are no comparables, a reasonable royalty is reached by the profits-available method. That said, a reasonable royalty as damages for patent infringement ought to be higher than a royalty negotiated voluntarily between an actual patentee and an actual licensee.

5.1 Comparable Licence Royalties

The royalty for assessing damages is the royalty that a willing licensor and a willing licensee would have agreed before the infringement occurred. Where there are truly comparable licences in the relevant field these provide the most useful guidance for the court as to the reasonable royalty.

The comparable-licence method requires the parties who negotiated the comparable(s) to have bargained on equal terms[112], that is to say (a) the prospective licensor must have been willing to grant a licence on such terms as would give him a fair return, (b) the prospective licensee must have been willing to make a fair payment for permission to use the invention or other matter, (c) the prospective licensee must have recognised and intended to honour the prospective licensor's monopoly right, or, in other words, he must not have disputed the validity of the exclusive right and must not have been minded to infringe it if he were unsuccessful in obtaining a licence, and (d) there were no other circumstances weighing the balance in favour of either party.

Where an established royalty or going rate exists and there is no circumstance indicating that the bargaining positions of the licensor and the licensee were not equal, this rate may justifiably be regarded as a fair royalty negotiated on equal terms[113]. A going-rate is a rate that is found in a number of licensing agreements with similar terms which the infringer

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[110] See below, Georgia-Pacific Corp. v. U.S. Plywood-Champion Papers (1970) 318 F. Supp. 1116 (US District Court, S.D.N.Y.), (1971) 446 F.2d 295 (US Court of Appeals, Second Circuit) where the court listed 15 factors representing the guidelines given by earlier courts for determining what would be a reasonable royalty based upon a hypothetical negotiation following a finding of patent infringement in that case.

[111] UK courts, and likely Singapore's courts also, are apt to regard patent (and indeed other IP) valuation techniques as unreliable. Some trade mark valuation techniques have grossly (if not fraudulently) overvalued trade marks in company accounts.

[112] In the real world the prospective licensee is likely to have the stronger hand except where a research tool involves a major breakthrough.

[113] Gerber Garment Technology Ltd v Lectra Systems [1995] Reports of Patent Cases 383 (English Patents High Court), per Jacob J.: "Before a 'going rate' of royalty can be taken as the basis on which an infringer should be held liable, it must be shown that the circumstances in which the going rate was paid are the same, or at least comparable with those in which the patentee and the infringer are assumed to strike their bargain."

would have to accept if he wanted to avoid the infringement. The rate in a single licence agreed with a small company is unlikely to be regarded as the going rate for a licence.

The rate of royalty is one element, the base (e.g. sales revenue less specified costs) to which the rate is applied is the other. The licensor will take a reasonable share of the licensee's "profit".

5.2 Available Profits

Where there are no comparables, the court must determine by other means what a willing licensor and a willing licensee would have agreed as a reasonable royalty. The profits-available method involves an assessment of the profits that would be available to the licensee, absent a licence, and apportionment of those profits between the licensor and the licensee[114].

The method was preferred by the first instance court in Gerber Garment Technology Ltd v Lectra Systems[115] because no proper comparables were available[116]. The trial judge (Jacob J.) explained his application of the method thus:

> This involves ascertaining the 'profit' made by the licensee absent a licence and apportioning this between the patentee and the licensee… Each party engaged an expert in licensing who gave the usual kind of evidence about rule of thumb splits of

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[114] E.g. Ultraframe (UK) Ltd v Eurocell Building Plastics Ltd [2004] 1785 EWHC (English High Court); 2005] EWCA Civ 761 (English Court of Appeal); 2006] EWHC 1344 (English Patents High Court)

[115] [1995] Reports of Patent Cases 383 (English Patents High Court). For example, in Catnic Components v Hill and Smith [1983] RPC 533 (English High Court) the plaintiff sought a royalty of 20% of the defendant's gross sales, because the plaintiff earned a profit margin of almost 25% on its own sales. The defendant argued that the rate should be no more than 2.5% because that represented the savings it made in production costs through use of the patentee's invention. The court set the royalty at 10% of pre-tax profits, or net of income tax at 7%. In a judgment on an application for a compulsory licence, Smith Kline & French Laboratories Limited's (Cimetidine) Patents [1990] RPC 203 (English Court of Appeal), a royalty rate of 45% on SKF's selling price represented a division of 64% of the profits available between the patentee and the licensee in the approximate proportions of five-sixths and one-sixth, the one-sixth equal to a return of about 11% on the licensee's likely selling price. While this was a small share for the licensee, set against the fact that the licensee was entering a very large, established market with a proven product which cost comparatively little to manufacture, and given the risks taken by SKF in discovering and proving the product and establishing the market, the division was not regarded by the court as manifestly unreasonable to the licensee. *Cf*. TWM Manufacturing Co. v Dura Corporation (1986) 789 F2d 895 (United States Court of Appeal, Federal Circuit), where the court used the internal memoranda prepared by the infringing company's senior executives to determine a reasonable royalty. These memoranda showed that the infringer expected to earn a gross profit of around 53% from infringing sales. Operating profit was calculated (by subtracting overhead costs) at between 37% and 42%. Having regard to the standard, normal profit (between 6.6% and 12.5%) in the industry at the time of the infringement, the court determined that 30% of profits would represent a reasonable royalty for the purposes of calculating infringement damages.

[116] "Reference was made to the rates fixed by the Comptroller in a number of compulsory licence and licence of right applications. These have been of the order of 5% in the case of non-medical inventions. I find little value in this sort of comparison. One has to know the circumstances of each case. There is an enormous difference, for instance, between the case where a man wants a licence to exploit a hitherto unused invention and the case where the invention is fully developed with a large and active market…" (Jacob J.)

> profits between licensor and licensee… All I know is that the parent made a reasonable profit and so did the subsidiary and that in some cases Lectra were able to cut their quoted prices considerably and still make a reasonable profit.
> I think it likely that the profits available were quite high. I say this because Gerber were working on a gross margin of 60% prior to Lectra. Lectra were cheaper, but I think there must have been a substantial difference between costs and price… As to how the "available profits" were to be split, absent the extra profits from spares etc it was agreed that the split would be 25% to the patentee. Gerber's expert suggested that this ought to be doubled because the licensee would be competing, leading to a royalty of 50% of the licensee's sales revenue. As I have indicated I think this wrong -- we are here talking about the non-competing sales. Lectra's experts suggested the 25% should be cut down for various reasons. He ended up with 1-1 1/2% of sales revenue, upon the assumption that the net profit level of the licence was 10%.
> Given these widely differing views I must do the best I can. I have come to the conclusion that 15% is a fair figure. It is admittedly a "jury" figure, but I think it fairly takes into account the sort of profits Lectra were, I think, making at the marginal rate, and the extra benefits they would be getting by way of profits from sales of ancillary items.
> 15% of what? I have already decided that I cannot reasonably identify particular Lectra sales which would not have been got by Gerber. So it must be on the average, namely 11/26 of the total revenue on Lectra's sales, coupled with 15% on the two identified Irish sales.

When applying the profits available method:

- The gross profit from relevant sales made by the licensee, absent the licence, must be determined.
- Profit from associated sales may be a relevant factor.
- Certain costs may be allowed against the gross profit, including all or part of R&D costs (including safety and testing costs in the case of a pharmaceutical product), marketing costs and overhead costs.
- The net profit must be shared between the patentee and the licensee.

5.3 Research Tool Patents

When assessing damages for infringement of a patent for a research method[117] the question may arise with, for example, a patented method for screening compound libraries to identify compounds with particular medicinal properties or a patented method for testing the safety or efficacy of a medicinal compound[118], whether infringement damages in the form of a reasonable royalty should reach through to sales of an end product containing a compound that would not have been identified or verified as safe or efficacious but for the infringer's unauthorised use of the patented method – the key that

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117 It will be recalled from the general introduction in Chapter 1 that the term 'research tool' covers a broad range of biological or biotechnological discoveries. The Report of the [US] National Institutes of Health Working Group on Research Tools (4 June 1998) says that "The label 'research tool' may apply less equivocally to the multitude of biological discoveries that precede the identification of new therapeutic compounds, including DNA sequences, databases, clones, cell lines, animal models, receptors and ligands involved in disease pathways, or laboratory techniques used to create or identify these discoveries..."

118 E.g. Harvard mouse used to screen for carcinogens.

unlocked the door, so to speak. If we assume that a compound claim would not be granted by the patent office, or if granted would be invalidated by the courts, an award of damages that reached through to the end product might be seen as unjustified – and yet, were it not for the research tool the compound would not have been identified or verified in the first place.

A reasonable royalty for infringement of patented research method should reflect or reach through to the value to the infringer of the product identified or verified using the method. The product could be a highly-profitable pharmaceutical or a foodstuff[119]. Damages which do not reflect that value will not compensate the patentee properly for unauthorised use of his invention. In hypothetical licence negotiations the patentee would almost always seek, yet may not always get, a share (by means of a reach-through royalty) of the revenue derived by the prospective licensee from sales of products which incorporate a molecule or substance identified or tested using the patented method; and the more unique the patented invention, the fewer the alternative methods, the more likely it is (if it were not a certainty) that a prospective licensee would concede a reach-through royalty in the price for a licence. There being no sales of a patented product, and it being difficult to value use of the patented method to identify a compound (which may or may not become a successful product), a royalty which reaches through to revenue from a marketable product may be the only way left to the patentee to obtain a fair and proper reward for his invention[120].

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[119] See, for example, US Patent 6955887 covering the use of the human sweet taste receptor to screen for compounds that can be used to modulate sweet taste. The patentee asserts that the patented invention can screen and identify rapidly an unprecedented number of potential new sweet flavour ingredients which may have applications in multiple product categories such as confectionaries, cereal, ice cream, beverages, yogurt, desserts, spreads, and bakery products, each of which represents a sizeable commercial market opportunity.

[120] Cullem, Panning for Biotechnology Gold: Reach-Through Royalty Damage Awards for Infringing Uses of Patented Molecular Sieves, 39 IDEA: The Journal of Law and Technology 553 (1999): "The inclusion of hypothetical reach-through royalties in the calculation of damages would most likely occur within the context of a reasonable-royalty determination. However, for new research tools with limited market penetration, the reach-through royalty may be the most relevant of the factors examined, and may represent the ultimate reasonable royalty… Lost profits and traditional reasonable royalty awards (i.e., those failing to consider the value of products developed via the infringing use) do not adequately compensate the owner of an infringed patented drug discovery tool, such as a molecular sieve. In contrast, a damage calculus that contemplates reach-through royalties or up-front licensing fees on drugs that have yet to be identified and developed seems an appropriate and fair means of adequately compensating the patentee… Nonetheless, when infringement occurs, the clock must be turned back to a pre-infringement period to assess what the parties would have done as willing licensor/patentee and licensee. During pre-infringement, there is no traditional royalty base the patentee can rely on in calculating the value of a license. There are no immediate product sales, based either on the licensed technology or on unpatented products produced by the technology. Yet a vast potential market exists and significant profits may be realized from identifying and subsequently developing a drug candidate using the patented discovery tool. This very profit potential - and the particular value of the molecular sieve in attaining it - drives the infringer to use the technology. As a hypothetical licensee, the infringer probably would have agreed to a reach-through royalty on future sales of drugs identified via the technology, especially since there would have been no other appropriate royalty base."

6 Account of Profits

A person who appropriates the property of another (e.g. infringes a patent) should not gain in any way, either directly or indirectly from that misappropriation. The wrongdoer or infringer is seen as claimant's trustee. An account of profits in a patent infringement action proceeds on the basis that all profits made by the infringer as a result of the infringement should be paid over to the successful claimant-patentee. But the claimant is only entitled to that portion of the infringer's profit which is causally attributable to the patentee's invention[121]. The main principles of account are these[122]:

> First, the infringer must disclose fully the revenues made and this amount must be paid to the claimant-patentee subject only to such bona fide expenses as the infringer can by positive evidence establish as having actually been incurred.
>
> Second, the infringer is allowed to deduct from the revenue derived from sales of infringing products (i) the variable costs attributable to the infringing products, and (ii) any increase in the fixed costs attributable to the infringing products.
>
> Third, if the infringer improves the infringing product in a way that increases its marketability, he may be allowed to retain profits resulting from the improvement(s).
>
> Fourth, the infringer is deemed to have benefited from the profits retained and must pay interest at the current rate on the amount of the profits

An infringer who, for example, uses a patented screen to identify a medicinal compound that becomes the active ingredient in a highly successful medicine, would have to hand over to the patentee the profits[123] resulting from the infringement[124]. But for the infringing use, would the infringer have identified the compound? If he would not have done so, it should not bar the remedy of an account of profits that the infringer only used the screen to identify the compound and thereafter reproduced the compound or medicine using standard manufacturing processes. The infringer may contend that he should not have to pay all his total profits during the infringing period to the patentee, but only such part of the profits as reasonably reflects the value that the patented screen brought to the infringer's business; and if the court accepts that argument, it will proceed to assess the

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[121] Spring Form Inc v Toy Brokers Ltd [2002] FSR 17 (English Patents High Court); Celanese Corp. v BP Chemicals Ltd., [1999] R.P.C. 203 (English Patents High Court); Lubrizol Corp. v Imperial Oil Ltd., [1997] 2 F.C. 3 (Canadian Court of Appeal); Monsanto Canada Inc. v Schmeiser [2004] 1 SCR 902 (Canadian Supreme Court)

[122] See generally Teledyne Industries Inc v Lido Industrial Products Ltd (1982) 68 CPR (2d) 204 (Canadian Federal Court, Trial Division); Potton v Yorkclose [1990] FSR 11 (English High Court); Dart Industries Inc v Decor Corporation Pty Ltd (1993) 26 IPR 193 (High Court of Australia); Celanese International Corporation v BP Chemicals Limited [1999] RPC 203 (English High Court).

[123] These profits (sales revenue less costs) could well be very substantial where a medicine or pharmaceutical costs pennies to make yet sells for a high price in the market.

[124] In Celanese Corp v BP Chemicals Ltd [1999] RPC 203 (English High Court), Mr Justice Laddie gave this example: "Imagine a case where the plaintiff invents and patents an entirely new process for making an entirely new product. The defendant infringes the patent by using the process to make the products which he sells at a profit. There is little doubt that he would have to account to the patentee for the profits so made…"

proportion of the infringer's total profits that are attributable to the patented technology (apportionment)[125].

7 Assessment of Damages under US Patent Code

Section 284, US Patent Code, entitles the patentee to "damages adequate to compensate for the infringement but in no event less than a reasonable royalty for the [infringing] use" where the court finds that the patent in suit has been infringed[126]. Damages are split between the lost profits caused by the infringing acts and a reasonable royalty when a patentee cannot sufficiently prove lost profits. But the patentee cannot claim the infringer's profits as such[127], as an alternative to damages. Damages can also be claimed for contributory infringement contrary to section 271(c).

The federal courts use one or other of two models (or methods) for assessing patent damages. The deterrence model (which some commentators see as being of limited application[128]) includes a punitive element. According to the court in Panduit Corp. v. Stahlin Bros. Fibre Works (1978) 575 F.2d 1152 (US Court of Appeals, Sixth Circuit), a patentee may recover lost profits if he proves: (1) a demand for the patented product; (2) the absence of acceptable (available), non-infringing substitutes; (3) the patentee's capacity to exploit the demand; and (4) the profits lost due to infringement. Would the patentee have made the sale "but for" the infringement[129]; and if so how much is the patentee entitled to? The compensatory model (which the Court of Appeals for the Federal Circuit seems to prefer) considers a broader range of factors than the deterrence model. A court may consider economic evidence of a demand curve (showing the effect of demand on sales), price erosion (showing how higher prices result in fewer sales), and the way an infringer's presence in the market depresses the price a plaintiff can charge[130].

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[125] Celanese Corp v BP Chemicals Ltd [1999] RPC 203 (English High Court): the court identified a three-step method for assessing apportionment: first, calculate a base allocated profits (allowing the patentee a proportion of the infringer's total profits equal to the proportion of the infringer's total expenditure on the infringing activity); second, weight the base allocation up or down (to reflect the value of the technology); third, add any differential profits (where extra profits can be attributed to the infringing activity). On apportionment, see also Wellcome Foundation Ltd.v Apotex Inc. [2001] 2 F.C. 618 (Canadian Court of Appeal).

[126] See generally Pincus, The Computation of Damages in Patent Infringement Actions, 5 Harvard Journal of Law and Technology 95 (1991).

[127] The Patent Act was amended in 1946 to eliminate a patentee's right to recover the infringer's profits. The patentee can only have as damages his actual, proven pecuniary loss. See also, Aro Manufacturing Co. v Convertible Top Replacement Co. (1964) 337 US 476 (US Supreme Court). That said, an infringer's actual profits are highly relevant to determining reasonable-royalty damages.

[128] See, for example, http://www.ftc.gov/os/comments/intelpropertycomments/obrien.pdf, O'Brien, Economics and Key Patent Damages Cases, 9 University of Baltimore Intellectual Property Law Journal 1 (2000).

[129] Micro Chemical Inc v Lextron Inc (2003) 318 F3d 1119 (US Court of Appeals, Federal Circuit): "to recover lost profits, a patentee must show that 'but for' [the] infringement it reasonably would have made the additional profits enjoyed by the infringer."

[130] See, for example, Grain Processing Corporation v. American Maize-Products Co**.** (1999) 185 F.3d 1341 (US Court of Appeals, Federal Circuit).

In an action for infringement of a research tool patent, the more likely basis for calculating damages is that of a reasonable royalty[131].

> The very nature of the lost-profit award makes this traditional remedy inappropriate for addressing infringement of the technologies discussed here. In the case of infringement of a patented molecular sieve, infringement results not in the form of a competing sieve that leads to lost sales or decreased prices of the patentee's molecular sieve. Rather, the damage suffered by the patentee is the loss of bargaining power the patentee would have had to negotiate deals with the infringer. Unfortunately, the patentee will likely be unable to show that "but for" the infringement, the patentee himself would have identified the same drug candidate with corresponding financial success. Consequently, in the absence of any quantifiable lost opportunity, such as sales of a competing product, the lost-profits damage calculus seems ill-suited to adequately compensate for the infringement of a patented molecular sieve[132].

But could a damages award reach through to, or reflect the value of, a medicinal compound obtained through the unauthorised use of the patented tool; and if it could then on what legal basis could it do so?

7.1 Reasonable Royalty

Where lost-profits damages cannot be proven or awarded, the patentee is entitled to a reasonable royalty for infringement of the patented research tool[133]. If there is an established royalty for patented inventions in the field wherein the patented tool is used then the court will regard that royalty (or rate of royalty) as the best measure of a reasonable royalty. Where an established royalty cannot be proven, a reasonable royalty will have to be divined from hypothetical pre-infringement licence negotiations between a willing licensor and a willing licensee of a valid and enforceable patent[134]. This rate can

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131 Lost-profits damages require evidence that the patented product was made for sale and that sales were lost as a result of the infringer's wrongdoing. Lost-profits damages based on the sales of a medicinal compound discovered, developed or produced using the patented tool would require proof that the patentee and the infringer were competitors on the market for the medicinal compound.

132 Cullem, Panning for Biotechnology Gold: Reach-Through Royalty Damage Awards for Infringing Uses of Patented Molecular Sieves, 39 IDEA: The Journal of Law and Technology 553 (1999).

133 See generally, http://stlr.stanford.edu/STLR/Articles/03_STLR_3/contents_f.htm, Stimson, Damages for Infringement of Research Tool Patents, 3 Stanford Technology Law Review 8 (2003); Pincus, The Computation of Damages in Patent Infringement Actions, 5 Harvard Journal of Law and Technology 95 (1991); http://www.howrey.com/docs/MarkWhitakerPlacement.pdf; Whitaker, Challenging IP Damages Experts; http://www.hoffmanclark.com/Litigation/BAMSLFall2000.htm, Walsh, Injunctive and Damages Remedies Available in a Patent Infringement Case; Linck, Patent Damages: The Basics, 33 IDEA: The Journal of Law and Technology 13 (1993), http://www.idea.piercelaw.edu/articles/34/34_1-2/p13.Linck.pdf; http://law.wfu.edu/prebuilt/IPLJ_Winter2005_Barnhardt.pdf, Barnhardt, Revisiting a Reasonable Royalty as a Measure of Damages for Patent Infringement.

134 Real-world negotiations will consider validity of the patent and possible defences to an infringement action before settling on a royalty. Validity and defences are tried before and decided by the court before it turns to the hypothetical negotiations for a licence and decides what rate of royalty would have been agreed by a willing licensor and a willing licensee. Panduit Corporation v Stahlin Brothers Fibre Works (1978) 575 F.2d 1152, 197 USPQ 726 (United States Court of Appeals, Sixth Circuit): "Determination of a 'reasonable royalty' after infringement, like many devices in the law, rests on a legal fiction. Created in an effort to 'compensate' when profits are not provable, the 'reasonable royalty' device conjures a 'willing' licensor and licensee, who like Ghosts of Christmas Past are seen dimly as

be adjusted by the court to reflect the circumstances of the case and it should normally be higher than a royalty negotiated on a voluntary basis[135].

US courts have identified the main factors (usually referred to as the Georgia-Pacific[136] factors) to be considered when determining a reasonable royalty and these are: the relative bargaining strengths of the parties; the anticipated amount of profits that the prospective licensor reasonably thinks he would lose as a result of licensing the patent as compared to the anticipated royalty income; the anticipated amount of net profits that the prospective licensee reasonably thinks he will make; the commercial past performance of the invention in terms of public acceptance and profits; the market to be tapped; and any other economic factor that normally prudent businessmen would, under similar circumstances, take into consideration in negotiating the hypothetical licence.

> In calculating a reasonable royalty award for infringement of patented molecular sieves, some Georgia-Pacific factors will receive great weight, while others will receive none at all. For example, since many novel drug discovery tools, such as molecular sieves, were previously unavailable in the research industry, commercial past performance of the invention may be irrelevant. Further, the number of previous licenses for the technology may be insufficient to prove an established royalty rate. Likewise, if the patentee is not active in the pharmaceutical market (e.g., a small research firm or university), anticipated profits foregone by licensing the technology will be given little weight because the patentee's intention to utilize the technology themselves to identify and market drug candidates is not evident. On the other hand, factors such as the relevant target market and the licensee's expected profits will likely be significant in determining an appropriate and fair reasonable royalty… Similarly, factors such as the utility and advantages of the technology over alternative technologies and the portion of realizable profits creditable to the technology are likely to be important in determining the royalty rate[137].

A research tool which is unique and likely to contribute significantly to the value of an end product would be a factor that would prompt a normally prudent businessman to seek a share of future profits resulting from the use of the tool; and, according to a number of commentators, this should be a factor in the court's calculation of reasonable-royalty

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'negotiating' a 'license'. There is, of course, no actual willingness on either side and no license to do anything, the infringer being normally enjoined...from further manufacture, use, or sale of the patented product." The Federal Circuit court in Fromson v W. Litho Plate and Supply Co. (1988) 853 F.2d 1568, 1575 described the task of determining a fair and reasonable royalty as being often "a difficult judicial chore, seeming often to involve more the talents of a conjurer than those of a judge. . . . The methodology encompasses fantasy and flexibility; fantasy because it requires a court to imagine what warring parties would have agreed to as willing negotiators; flexibility because it speaks of negotiations as of the time infringement began, yet permits and often requires a court to look to events and facts that occurred thereafter and that could not have been known to or predicted by the hypothesized negotiators."

[135] Otherwise, as the court pointed out in Panduit Corporation v Stahlin Brothers Fibre Works (1978) 575 F.2d 1152, 197 USPQ 726 (United States Court of Appeals, Sixth Circuit), "the infringer would have nothing to lose and everything to gain if it could count on paying only the normal, routine royalty non-infringers might have paid. The infringer would be 'in a heads-I-win, tails-you-lose position'."

[136] The court in Georgia-Pacific Corp. v. U.S. Plywood-Champion Papers (1970) 318 F. Supp. 1116 (US District Court, S.D.N.Y.), (1971) 446 F.2d 295 (US Court of Appeals, Second Circuit) listed 15 factors representing the guidelines given by earlier courts for determining what would be a reasonable royalty based upon a hypothetical negotiation following a finding of patent infringement in that case.

[137] Cullem, Panning for Biotechnology Gold: Reach-Through Royalty Damage Awards for Infringing Uses of Patented Molecular Sieves, 39 IDEA: The Journal of Law and Technology 553 (1999).

damages[138]. Although the case was not concerned with a research tool, in Ajinomoto Co. v Archer-Daniels-Midland Co.[139] the US District Court calculated reasonable-royalty damages by applying a fixed per unit royalty rate of $1.23 per kilo of threonine produced by the infringer's use of the patented process (and so, in effect, reached through to the product of the patented process). Neither party to the action contested this.

It would not therefore be inconsistent with legal precedents on the calculation of a reasonable royalty under US law, for the calculation of reasonable-royalty damages for infringement of a patented tool at least to have regard to the ultimate value (in terms of sales) to the infringer of the product that would not have been obtained or identified but for the unauthorised use of a patented research tool. But there may be less reason for that where the patented tool is used for verifying an existing product's safety or efficacy.

7.2 SIBIA Neurosciences v Cadus Pharmaceutical

SIBIA, a commercial offshoot of the Salk Institute, owned US Patent 5,401,629 ("the 629 patent"), granted on 28 March 1995, for a cell-based screening method useful for the identification of compounds that exhibit agonist and antagonist activity with respect to particular cell surface proteins[140].

The patent broadly disclosed, among other things, "novel recombinant cells which are useful for assaying compounds for their agonist or antagonist activity with respect to specific ion channels and/or specific cell surface localized receptors ... rapid, reliable methods to identify compounds which interact with, and thereby affect the function of, specific ion channels and/or specific cell surface-localized receptors; [and] rapid reliable methods to determine if cells are producing specific functional ion channels and/or cell specific functional surface-localized receptors." The claimed methods "for identifying compounds that modulate cell surface protein-mediated activity..." were said to be particularly effective because, by allow a scientist rapidly and reliably to screen large numbers of compounds for agonist and antagonist activity, the scientist could quickly develop a list of candidate compounds that would merit further in-depth studies for

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[138] E.g. http://stlr.stanford.edu/STLR/Articles/03_STLR_3/contents_f.htm, Stimson, Damages for Infringement of Research Tool Patents, 3 Stanford Technology Law Review 8 (2003); Cullem, Panning for Biotechnology Gold: Reach-Through Royalty Damage Awards for Infringing Uses of Patented Molecular Sieves, 39 IDEA: The Journal of Law and Technology 553 (1999) writes: "Thus, for patented molecular sieves that represent the only practicable means of identifying drug candidates to tap potential multi-million dollar markets, reach-through royalties can serve as a central factor in calculating an appropriate infringement damage award. …However, for new research tools with limited market penetration, the reach-through royalty may be the most relevant of the factors examined, and may represent the ultimate reasonable royalty."

[139] (2001) 228 F.3d 1338 (US Court of Appeals, Federal Circuit). The patent was for a method of modifying the genetic structure of bacterial strains to produce amino acids in increased quantities. The patent described a mutation of a gene in E. coli bacteria that controls the synthesis of the amino acid threonine, and subsequent insertion of the modified genetic material into a host bacterial strain modified in order to produce excess quantities of threonine.

[140] High throughput screening was a new, advanced technology in 1990 and a strong patent was likely to be of substantial value.

therapeutic applications. The patent had no claims to products or compositions identifiable through that claimed method.

Claim 1, the only independent claim, read as follows:

> 1. A method for identifying compounds that modulate cell surface protein-mediated activity by detecting intracellular transduction of a signal generated upon interaction of the compound with the cell surface protein, comprising:
>
> comparing the amount of transcription of a reporter gene or the amount of reporter gene product expressed in a first recombinant cell in the presence of the compound with the amount of transcription or product in the absence of the compound, or with the amount of transcription or product in a second recombinant cell; and
>
> selecting compounds that change the amount of transcription of a reporter gene or the amount of reporter gene product expressed in the first recombinant cell in the presence of the compound compared to the amount of transcription or product in the absence of the compound, or compared to the amount of transcription or product in the second recombinant cell, wherein:
>
> the cell surface protein is a surface receptor or ion channel;
>
> the first recombinant cell contains a reporter gene construct and expresses the cell surface protein;
>
> the second recombinant cell is identical to the first recombinant cell, except that it does not express the cell surface protein; and
>
> the reporter gene construct contains:
>
> (a) a transcriptional control element that is responsive to the intracellular signal that is generated by the interaction of an agonist with the cell surface protein; and
>
> (b) a reporter gene that encodes a detectable transcriptional or translational product and that is in operative association with the transcriptional control element.

As well as disclosing prophetic examples that could be used in the disclosed method, the specification disclosed as actual examples (i) the activation of the M1 muscarinic receptor by its agonist carbamylcholine in the presence or absence of its antagonist atropine; and (ii) the activation of gene expression by carbachol, bovine serum, or atropine.

Cadus developed a line of yeast cells expressing heterologous mammalian cellular receptors and containing reporter genes. SIBIA sued Cadus for infringement, arguing that the word "cell" in the 629 patent covered any cell, including the Cadus yeast cell libraries. But because a mammalian host cell line was the only embodiment of the assay disclosed in the 629 patent, Cadus asked the court to limit the word "cell" to "mammalian cells" only[141]. The district court rejected this limitation, ruling that "cell" referred to all

[141] When Cadus tried to reduce the screening assay to practice using yeast, it found that the description in the 629 patent was non-enabling for yeast. In fact, as other independent researchers had also found, the teachings of the SIBIA patent offered no guidance for those working with yeast.

eukaryotic cells. SIBIA was given reasonable-royalty damages of US$18 millions by the US district court, based on Cadus's actual and potential profits on its commercialised products.

SIBIA's claim for damages comprised (a) $5 million by way of an initial fee for the licence, (b) $1.6 million 4% equity stake in Cadus as of March 1995, (c) $3 million for 30 targets allegedly delivered to Cadus' corporate partners between March 1995 and December 1998 at $100,000 per target, and (d) $8.7 million, being SIBIA's share of the royalty payments from pharmaceuticals that could eventually be put on the market[142]. Cadus challenged the figure in (d) on the ground that, as no marketable products had been found, there was little prospect for future profits, let alone profits to a level reflected in (d). The paragraph (d) figure involved too much speculation and too little fact[143]. There was much discussion in the case about target "hit rates", with SIBIA contending for industry average primary hit rates, rather than actual hit rates and, in so contending, over-estimating the value of SIBIA's invention to Cadus. Royalty provisions in licensing agreements for patented research tools typically included a payment based on primary hits and a payment for a marketable compound resulting from a primary hit.

Cadus's appeal to the US Federal Circuit court resulted in the 629 patent being invalidated for obviousness, and therefore the appeal court did not have to consider the reasonableness of the royalty.

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[142] This information comes from http://stlr.stanford.edu/STLR/Articles/03_STLR_3/contents_f.htm, Stimson, Damages for Infringement of Research Tool Patents, 3 Stanford Technology Law Review 8 (2003). The judgment of the district court could not be found on the internet. See, as a further example, the settlement agreement between Ligand Pharmaceuticals Inc and Pfizer Inc at http://contracts.onecle.com/ligand/pfizer.settle.1996.04.22.shtml. Briefly, this settlement followed litigation in 1994 in the California Superior Court for breach of contract. Ligand sued Pfizer for milestone payments and royalties related to an osteoporosis-screening project. The parties had entered into a five- year collaboration wherein Pfizer funded research using Ligand's intracellular receptor technology for the treatment of diseases. Under the settlement, Pfizer received exclusive worldwide rights to market any products resulting from the collaboration and Ligand was entitled to royalties on the sales. As part of the settlement, Pfizer paid Ligand in excess of US$1.3m and agreed to make additional payments as Pfizer developed future compounds, with the expectation that pharmaceuticals would be marketed.

[143] Stimson, Damages for Infringement of Research Tool Patents, 3 Stanford Technology Law Review 8 (2003), paragraph 41: "Speculative profits projections potentially over-compensate patentees by giving them damages that extend beyond their injuries. Furthermore, speculative profits projections potentially create additional and unnecessary hardships on infringers, and deter the use of research tools when potential researchers forego their use for fear of disproportionate liability or because of prohibitive transaction costs." Grassler, US Treatment of Reach-Through Claims and Reach-Through Royalties http://www.sdipla.org/events/past/grassler/ReachThru.htm: "The Cadus appeal in the SIBIA case is a good illustration of some of the problems that arise in trying to calculate reach-through royalties that would have been paid to the patentee for infringement of a research tool patent. At trial SIBIA's expert estimated: (1) the probability that a molecular target supplied by Cadus would yield a "primary hit" when tested against the compound libraries of its collaborators; (2) as well as the probability that such a primary hit compound would be developed; (3) tested in clinical trials; (4) approved by the FDA; and (5) marketed successfully to; (6) become one of the top 300 drugs sold in the US. Whatever statistical basis may have been offered to support these assumptions, it is difficult to see how such testimony avoids lapsing into pure speculation, vague estimation and/or gross extrapolation…"

7.3 Integra v Merck

Integra Lifesciences I, Ltd., and the Burnham Institute, own five patents relating to the tripeptide sequence Arg-Gly-Asp, known in single-letter notation as the "RGD peptide". This peptide attaches to the avß3 receptors on the surface of cells and induces better cell adhesion and growth which should promote wound healing and biocompatibility of prosthetic devices. Merck used the Integra peptides to help develop new peptide drugs that could potentially be used to treat certain diseases including cancer, diabetic retinopathy and arthritis. Integra offered Merck a licence under its patents but the two sides could not agree on the licence terms. Integra sued Merck for patent infringement[144].

The lower court's award to Integra of a reasonable royalty of $15,000,000 was reversed on appeal by the Federal Circuit court because the award was not supported by the evidence. A reasonable royalty is based upon a hypothetical negotiation between the parties that would have occurred at a time before the infringement began. The value to a licensee of research tools lies, in part, in the point at which those tools are employed in pharmaceutical development. A research tool that enables the identification of a medicinal compound during high throughput screening may supply more value to the ultimate invention than a research tool used to confirm the safety or efficacy of an existing compound. Royalties negotiated at a stage when it was uncertain whether Merck would be able to identify any useful product using Integra's peptides were likely to be much smaller than a royalty calculated after the identification of a useful compound.

In summary, the Federal Circuit court mentioned several factors that should be considered when calculating reasonable-royalty damages and these factors included the time at which the infringement took place, the purpose of using the research tool (e.g. obtaining a new compound as distinct from confirming its safety or efficacy), and royalty stacking (e.g. the number of patent licences needed to develop or commercialise a medicinal compound).

8 Conclusion

Damages for infringement of a patent are meant to compensate the patentee for losses caused by the infringer. An account of profits, as an alternative to damages, gives the patentee the profits made by the infringer as a result of the infringement. If the infringer made little profit from the infringement but caused thereby considerable loss to the patentee, the choice between the alternatives is obvious. Where the patentee and the infringer compete for sales, the patentee can claim by way of damages (i) the profit from sales that, but for the infringement, he would have made but did not make, or the reduction in profit from sales he made, or (ii) if he would not have made the sales, a fair

[144] Merck argued, inter alia, that its actions came within the clinical testing exception in 35 USC 271(e)(1), which states that it is not act of infringement to use a patented invention "solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products". The Federal Circuit court rejected this argument. The Supreme Court judgment reversed the Federal Circuit's interpretation.

and reasonable royalty; and where the two do not compete, damages in the form of a reasonable royalty can be claimed from the infringer.

In many (if not most) cases, the holder of a patent for a research tool and the infringer will not be competitors and damages for infringement will be calculated on the basis of a reasonable royalty. In a minority of cases, the patentee may lose sales to a supplier, as where for example a third-party supplies the infringer with reagents for use in particular method. The patentee may be able to pursue the third-party supplier as a contributory infringer. Package licensing involves the grant of a licence to the purchaser of a quantity of materials for use in a patented process, the licence being limited to the quantity bought from the patentee or his licensee. Part of the profit from the sale would be equivalent to (although likely less than) the royalty for a straight licence, that is, a licence which allowed the licensee to purchase supplies for use in the process from wherever he could get the best deal. If the process is used without the patentee's licence and necessary supplies are bought from a third party, royalty damages could be claimed from the user and lost-profits damages from the user's supplier[145].

In an appropriate case, where a valuable molecule or substance has been identified or obtained directly by the unauthorised use of a patented research tool, royalty damages could (and maybe should) reach through to the profits from commercial products (e.g. pharmaceuticals) embodying the substance, and royalty damages which do not reach thereto will not compensate the patentee properly for unauthorised use of his invention. An account of profits, on the other hand, would require the infringer to hand over, if not all the profits from commercial products embodying the identified substance, at least such part of the profits as reasonably reflects the value of the patented invention in the infringing business.

[145] The user may come within one of the exceptions to patent infringement (e.g. experimental use) and the supplier may be able to show that what he supplied to the user was a staple product.

CHAPTER 5

REACH-THROUGH CLAUSES IN LICENSING AGREEMENTS

The wisdom of taking a licence from the owner of a patented research tool before using the method, other than for experimental purposes, in biomedical research was suggested or implied in earlier chapters. A licence will cost less than paying, in addition to damages or profits, the legal costs of the infringement action. Seeking a licence after the event, when a promising discovery has been made with the patented tool, can be a flawed strategy. The owner could refuse to license the patent, although he would more likely license it on terms less attractive than if a licence had been sought and granted before the research began. If a licence were refused after the event, the erstwhile user could be faced with abandoning a promising research project, or commencing proceedings to invalidate the patent, or, where the law provides for compulsory licensing, applying for a compulsory licence.

The owner of a patent for a research tool can do one or more of the following[146]:

- exploit[147] it exclusively;
- license another to exploit it, in return for a money consideration or other advantage or benefit;
- assign ownership of the patent or a share in it, or mortgage the same, to another in return for a money consideration or other advantage or benefit.

An untried or unproven patent, with no market share to speak of, is unlikely to secure a sale price beyond a mere token – except where the patented invention represents a major breakthrough in the technology, and then there would be the difficulty of trying to put a realistic sale price on the asset if an outright sale and assignment were contemplated[148]. This exception aside, for the vast majority of patents the choices come down to exploitation exclusively by the patentees or exploitation (usually subject to limitations) by licensees, assuming in either case that the necessary resources (financial, technical, managerial, etc) are available and that exploitation of the patent or licence would yield worthwhile or attractive returns to the invested resources.

The patentee may be able to exploit the patent exclusively for certain purposes or markets and license it for other purposes; but if the patentee (e.g. a university) does not have the resources needed for exclusive exploitation then licensing the patented invention is likely

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146 Section 41, Singapore Patents Act (Chapter 221).

147 That is, manufacture, sell, use, export or import.

148 See http://www.fenwick.com/docstore/Publications/IP/IP_Articles/Assessing_Patent_Value.pdf, 'Assessing Patent Value' by Amir Raubvogel.

to be the only alternative – assuming always that there is a licensee who would be willing to pay a worthwhile money consideration or give some other economic or tactical advantage for a licence, for example, a cross-licence. A patent does not guarantee commercial success and, at the end of the day, it may prove to have little or no tactical or commercial value.

Whatever the reason(s) for licensing a patent (or indeed any other form of intellectual property), each party to the contract will usually seek to secure certain of its commercial interests by imposing on the other party (or parties) terms that restrict the other's economic freedom. Virtually all licensing agreements, except the barest or simplest of contracts, will have restrictive terms, and such terms may raise questions as to the compatibility of an agreement with laws (national or supra-national) intended to protect economic competition.

A patented technology may be licensed to enable or facilitate research and/or development. For example, a joint venture enterprise established to carry out research or development may license-in necessary technology from the venture parties to enable the enterprise to perform its designated task(s); and, depending on the nature and scope of the joint venture and the commercial interests of the venture parties, each of the venture parties may be entitled to licences from their enterprise in respect of R&D results. Or a developer may license-in a research tool to enable him to identify a molecule for possible development or to evaluate the efficacy or safety of a product under development.

1 Licences for Patented Research Tools

A licence is required only to do that which, absent the licence, the law would forbid, to do that which in the context of intellectual property would come within the exclusive rights of the owner of the property. A patent, for example, forbids all who do not hold a licence from the patentee, from exploiting commercially the invention defined by the claims of the patent. If the claims are granted for a process (or method), the patentee's exclusive rights extend beyond the process *per se* to "any product obtained directly by means of that process"[149].

The terms of an agreement granting a licence for a patented research tool may require payment of a flat fee, milestone payments, and reach-through royalties on 'downstream' products, for example, marketable products incorporating biologically active molecules identified by a patented screening method. Research tools can be very difficult to value for licensing purposes because, as Eisenberg notes[150], "The serendipitous nature of research discoveries may make it difficult to place a value on the right to use a patented invention before the outcome of a research project is known."

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149 Singapore Patents Act (Chapter 221), section 66(1), UK Patents Act 1977, section 60(1).

150 Proprietary rights and the norms of science in biotechnology research, 97 Yale Law Journal 177, 217 (1987); http://pharmalicensing.com/features/disp/963567614_396edffe132c5, Kowalski and Smolizza, Reach through licensing: A US perspective: "the measure of value of a basic research tool is not merely the costs for developing and patenting the basic research tool; but rather the extent to which the basic research tool enables the development of further products and the value of those products; namely, market-place forces."

A reach-through royalty clause requires the licensee to pay a royalty on sales of downstream products developed from, made with or containing a compound identified or tested using a patented the research tool, the compound *per se* being the subject matter of a reach-through claim in the licensed patent, or on such sales where there is no such reach-through claim in the licensed patent[151]. But in either case, the royalty helps to attribute a realistic value to a research tool used to find or validate that compound[152].

Where different research tools may be needed to develop a product (e.g. a medicament, a food product)[153] and where each tool may be licensed to the developer on terms that include a reach-through royalty clause, the licensee should provide in each licensing agreement for royalty-stacking, with the consequence that the royalty income each licensor receives may be reduced to a basic (floor) rate by having to share with the other licensors the overall amount allocated to royalties by the developer[154]. The royalty rate is likely to vary according to the technical and/or economic importance of each tool to the licensee's task.

A reach-through royalty involves this consequence: if notwithstanding diligent use of the tool the licensee does not discover, create or validate any product of marketable value with the tool then, if the only consideration for the licence were the reach-through royalty, the patent owner might be seen to get a fair measure of the worth of his patent to

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[151] Eisenberg refers to the sales royalties on *patented* downstream products in the Cohen-Boyer Licensing Agreement (in the appendices) as reach-through royalties.

[152] Despite an extensive search of the literature, only a few examples of actual reach-through royalty clauses were found. See, for example, the Cohen-Boyer Licensing Agreement in the appendices. A sub-clause from a more complex set of reach-through provisions in a licensing agreement made available to the authors of this Report, read as follows on the issue of post-patent-expiry royalties, a possible issue for competition law: "If an End Product that is not a Licensed Product and is not covered per se or for a given purpose by any patents obtained by LICENSEE, the obligation to pay royalties shall end ten (10) years after the last to expire of the patents in the Licensed Patent Rights having a claim or claims for a Licensed Method used in discovering, creating, identifying, characterizing, isolating, developing, manufacturing, evaluating or establishing the pharmacological properties or condition of use of the End Product (or a component thereof) for the given purpose."

[153] For example, X owns a patent with claims to a specific agonist and to use of the agonist in the manufacture of medicinal product and Y owns a patent with claims to a method for determining the toxicity of a compound, a method for decreasing its toxicity and a modified compound produced by the method. An example where access to different technologies was needed to develop a product can be found in the so-called Golden Rice case (http://www.goldenrice.org/). Golden Rice is designed to raise the levels of vitamin A in rice. Three proprietary genes were inserted into the rice plant to complete the beta-carotene biosynthetic pathway. Also used in the development of the improved rice plant were plant transformation vectors, promoters and antibiotic resistance markers, all of which (totalling 70 items) were covered by patents owned by different patentees or by material transfer agreements. On the Golden Rice licensing agreement see http://www.goldenrice.org/Content2-How/how9_IP.html. See also 'Monsanto provides royalty-free golden rice technology', http://www.gene.ch/gentech/2000/Aug/msg00072.html. But now see 'The Golden Rice hoax', http://online.sfsu.edu/~rone/GEessays/goldenricehoax.html.

[154] The royalty-stacking clause might be in these words: "If Licensee is required to obtain additional licenses not covered by this Agreement in order to develop, manufacture, sell or market Licensed Product(s), Licensee may reduce its royalty payments to Licensor by an amount equal to the sum of royalties payable under additional licence(s) provided that the royalty paid to Licensor will not be less than [X %] of the rates specified above."

the licensee – that is to say, he would get nothing from the licensing deal if there was no marketable outcome. Few patentees are likely to license their research tools for a reach-through royalty only.

Thus, a reach-through royalty gives the patent owner an appropriate share of the profits (if any) made by the licensee from selling the thing or substance created, identified, or assessed with the patented tool. Flattmann and Kaplan explain why a patentee will seek to obtain a reach-through royalty from a licensee: "Reach-through royalty licenses are increasingly common because (i) they are more profitable than licenses based solely on sales or use of the research tool, (ii) they may be easier to enforce than licenses based solely on sales or uses of the research tool, and (iii) they potentially maximize the patentee's return on investment in otherwise limited markets (for example, if only one or a few potential licensees conduct experiments using their patented tools)."[155]

Although the patent owner may press a prospective licensee for a reach-through royalty, in many cases he may have to settle for royalties based on the licensee's actual use of the patented method, that is, on the number of times the method is used or as measured by an input (e.g. a reagent) necessary for its use, or for a once-only licence fee. A particularly valuable or unique screening method may command, for example, an up-front licence fee, a fee for each target compound identified with the licensed method, a fee for each such compound selected for or entering product efficacy or safety trials, and a reach-through royalty based on sales revenue from a compound that reaches the market[156].

2 Competition Law

A royalty clause that reaches beyond the licensed research tool to the exploitation of any chemical compound which is identified with the tool but which does not embody the claimed invention, may violate competition law[157] and so be unenforceable except where the compound itself is within the scope of a claim in the licensed patent. Competition law in Singapore, as set down in the Competition Act 2004 (Chapter 50), is expressed in terms similar to the provisions in the UK Competition Act 1998 which, in turn, is modelled on Articles 81 (restrictive agreements) and 82 (abuse of dominant position) in the European Communities Treaty. An agreement which offends, or would be likely to offend, the ban on restrictive agreements in Article 81(1) is prohibited unless it qualifies for an exemption under Article 81(3).

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155 Flattmann and Kaplan, Licensing research tool patents, 20 Nature Biotechnology 945-947 (2002). The authors offer no supporting evidence for their alleged 'increasing commonality' of reach-through royalties. Other commentators share this view but again they give no evidence for it. On the other hand, Abrams and Kaiser, Licensing Transgenic Mice, state that MIT found it difficult to get would-be licensees to agree to pay reach-through royalties because the patented mouse did not enable "the identification of the drug candidate but rather the validation of its therapeutic value". (The Abrams and Kaiser paper seems no longer to be available as a free download from the internet.)

156 See, for example, the terms of the agreement in SIBIA Neurosciences v Cadus Pharmaceutical (2000) 225 F.3d 1349 (US Court of Appeals, Federal Circuit).

157 A royalty based on sales of a product outside the scope of the licensed patent may be seen also as an unlawful extension (abuse or misuse) of the licensed patent.

Basing a royalty on sales of an unpatented product, for example, a product in which the patented invention is a component, does not without more offend the competition rules relating to restrictive agreements; and as if to underscore that, in a patent infringement action the court can give damages for lost sales of unpatented products, that is, sales the patentee would have made but did not make because of the infringement[158]. But if a research tool patent includes a claim to, for example, "an isolated and purified receptor agonist identified by the method of claim …", and even though such a claim may be of questionable validity, it would answer competition law concerns about the legality of imposing a royalty on a downstream product incorporating the patented molecule. Therefore, with a view to licensing a research tool, an application for patent for the tool should include a product-by-process claim.

3 Technical Improvements Clauses

An improvement (or grant-back) clause in a bilateral licensing agreement requires a licence party to transfer (assign or license) to the other licence party any improvement that the former may make to the licensed technology. A typical improvements clause tends to be reciprocal, that is to say, both the licensor and the licensee are bound by the contractual obligation to license each other for their respective improvements. The improvements clause is a form of reach-through clause, in that it reaches through the licensed technology to capture or gain access to improvements within the scope of the clause that are made by the licence party bound by the obligation. An improvement may be severable from the licensed technology, that is to say, the improvement can be exploited without infringing the intellectual property in the licensed technology[159].

An obligation on a licensee to assign or to license exclusively severable improvements to or new applications of the licensed technology to the licensor or the licensor's nominee may be unacceptable under competition law[160], but if an improvement is non-severable the obligation is unlikely to contravene the competition rules because the improvement cannot be exploited independently of the licensed technology.

4 Conclusion

Reach-through royalties are calculated on sales of final end-products. The licensed technology may be incorporated in the end product, for example, as the active ingredient of a pharmaceutical, or it may be used to develop that product but not otherwise be a part of it. A patent claim in the form, for example, of "an isolated and purified receptor agonist identified by the method of claim …" is in the main a broad claim to products

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158 See, for example, Gerber Garment Technology Ltd v Lectra Systems [1995] Reports of Patent Cases 383 (English Patents High Court); [1997] RPC 443 (English Court of Appeal).

159 See, for example, Article 1(1)(n), EC Regulation 772/2004 on Technology Transfer Agreements (27 April 2004).

160 See, for example, Article 5(1), EC Regulation 772/2004 on Technology Transfer Agreements (27 April 2004) and the EC Guidelines on Technology Transfer Agreements, paragraph 109. On the other hand, an obligation on the contract parties to communicate non-exclusively to one another any experience gained in exploiting the licensed technology and to grant one another non-exclusive licences in respect of improvements and new applications of the licensed technology is exempted by EC Regulation 772/2004.

unidentified at the time of the filing of the patent application but discoverable through the use of the claimed method; and this form of claim allows the patentee to seek reach-through royalties based on sales of undisclosed products discovered by a licensee using the claimed method. A licensee could agree to pay a reach-through royalty "on sales of any product which comes within a valid claim of the licensed patent" and, if the royalty clause were enforced, attack the patent claim for invalidity. Thus, the licensor should consider carefully the base for a reach-through royalty lest it allows the licensee to undermine the royalty obligation or it conflicts with competition law. A royalty based on sales of an end product such as a medicine or therapy created, identified, or tested with a patented research tool can be a fair way of valuing the tool's contribution to the end product. An improvements clause reaches through to future inventions and/or know-how and as long as the clause is kept within limits it will not raise an issue for competition law. A reach-through royalty clause is analogous in certain respects to an improvements grant-back clause: the former gives the licensor a right to a share of future profits made by the licensee from exploiting an as-yet unidentified invention and the latter gives the licensor a right to a licence for, or possibly ownership of, as-yet unidentified inventions made by the licensee.

APPENDICES TO THE CHAPTERS

APPENDIX 1

RESEARCH TOOLS

During the gold rushes in the 1800s in Australia, Canada and the United States, many of the businesses that supplied the gold miners with 'tools' (food, tents, pack animals, picks, shovels, etc.) made fortunes[161], while many of the miners lost everything within a relatively short time of arriving in the gold fields. Today, the diverse fields of biology (human, animal and plant) and the biological sciences can provide rich seams for individuals and companies looking for biotechnological or biomedical 'gold' (new medicines, therapies, manufacturing methods, etc.) and, as in the 1800s, there are those who prosper or hope to prosper by supplying the 'miners' with tools to help them discover or 'mine' seams in their specialised fields. Some of the tools (the picks and shovels, you might say), such as PCR and the Cohen-Boyer (or recombinant DNA) method, have broad applications and can be found in many research settings or incorporated into other research techniques. Other tools, such as ESTs and drug targets, are more problem-specific and have narrower applications. The following sections will provide a brief summary of some of the common research tools used by researchers in the biotechnology and bio-medical sciences.

1 Recombinant DNA (rDNA)

The term 'recombinant DNA' or rDNA refers to a new combination of DNA molecules that are not found together naturally, i.e. the molecules come from different biological sources. rDNA is generally recognised as the first research tool in modern biology[162]. The technique was invented by Stanley Cohen[163] and Herbert Boyer in 1973[164]. It was patented in the USA[165] and the patents[166] were granted to Stanford University and the

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161 See, for example, http://www.isu.edu/~trinmich/goldcountry.html.

162 See, for example, http://www.druid.dk/wp/pdf_files/05-21.pdf, Feldman et al, Commercializing Cohen-Boyer 1980-1997, DRUID Working Paper No. 05-21, page 1.

163 In the 1950's Cohen, working with Rita Levi-Montalcini, discovered proteins called cell growth factors that directed the growth of certain cells. For this work, Cohen and Levi-Montalcini were awarded the 1986 Nobel Prize in Physiology.

164 The first patent application was filed by Stanford University in November 1974. The technique was made possible by the discovery of restriction endonucleases by Arber, Nathans, and Smith, for which they received the 1978 Nobel Prize in Medicine.

165 An international application was precluded by disclosure of the technique in the USA prior to the filing date of the US patent application. The original US application in 1974 had claims to both the rDNA technique and any products resulting from use of the technique. The product claim was rejected by the US Patent Office. This resulted in two divisional product applications, one with claims to rDNA products produced in prokaryotic cells and the other with claims to rDNA products produced in eukaryotic cells. Patents granted on these divisional applications were subject to a terminal disclaimer – which meant that they expired on the same expiry date as the original patent, that is, on 2 December 1997.

University of California, San Francisco. Stanford University licensed the technology to 467 companies including Amgen, Eli Lilly, Genentech, Johnson & Johnson and Schering Plough. Using the technique, these licensees developed and sold products that included tissue plasminogen activator for heart attacks, erythropoeitin for dialysis patients, insulin for the treatment of diabetes, growth hormone for children with growth deficiencies and interferon for cancer patients[167]. The success[168] of the licensing strategy relating to the Cohen-Boyer technique is attributed to number of factors: it was easy and inexpensive to use; there were no significant impediments to widespread dissemination; there were no alternative technologies; and it played a critical and broad role in molecular biology research[169].

rDNA can be made by three methods: bacterial transformation, non-bacterial transformation and phage introduction[170]. Each of these methods aims to introduce recombinant genes into a host cell along with an expression factor, so that the host cell expresses the desired protein. *Transformation* begins with the selection of a piece of DNA which is cut with a restricted enzyme[171] and inserted into a plasmid vector[172]. The insert contains a selectable marker, often an antibiotic marker[173], which allows for identification of recombinant molecules. A host cell with the vector will survive exposure

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166 See Appendix 2.1 for extracts from the three patents. Unlike many patents for basic techniques, the Cohen-Boyer patents were licensed non-exclusively. The original licence required licensees to pay a $10,000 signing-up fee, plus a minimum annual advance of $10,000 for a licence, plus earned royalties of between 0.5% and 3% of sales, depending on the nature and sales volume of recombinant DNA products.

167 rDNA products being used in human therapy also include insulin for diabetics, factor VIII for males suffering from hemophilia A, factor IX for hemophilia B, human growth hormone (GH), erythropoietin (EPO) for treating anaemia, granulocyte-macrophage colony-stimulating factor (GM-CSF) for stimulating the bone marrow after a bone marrow transplant, granulocyte colony-stimulating factor (G-CSF) for stimulating neutrophil production, e.g., after chemotherapy and for mobilizing hematopoietic stem cells from the bone marrow into the blood, tissue plasminogen activator (TPA) for dissolving blood clots, adenosine deaminase (ADA) for treating some forms of severe combined immunodeficiency (SCID), angiostatin and endostatin for trials as anti-cancer drugs, parathyroid hormone, leptin, hepatitis B surface antigen (HBsAg) to vaccinate against the hepatitis B virus.

168 The first licensing agreement was signed on 15 December 1981. By the 13th of February 1995 the royalties from licensing agreements was $139 million; and for the period 1990-1995, the licensing fees totalled $102 million.

169 Feldman et al, Commercializing Cohen-Boyer 1980-1997, DRUID Working Paper No. 05-21

170 See, for example, http://www.rpi.edu/dept/chem-eng/Biotech-Environ/Projects00/rdna/rdna.html, The Basics of Recombinant DNA; Cloning Genes, http://web.mit.edu/esgbio/www/rdna/cloning.html; Genetic Engineering and Biotechnology, http://cwx.prenhall.com/brock/chapter10/objectives/deluxe-content.html.

171 There are a hundred plus such enzymes, and each enzyme cuts in a very precise way a specific base sequence of the DNA molecule.

172 Plasmids are relatively small, double-stranded, closed-circular DNA molecules that exist apart from the chromosomes of their hosts. The plasmid pBR322 constructed by Francisco Bolivar and others in Herbert Boyer's laboratory in the 1970s. pBR322's usefulness lies with the fact that contains an ampicillin resistance gene and a tetracycline resistance gene. Small plasmids, the pUC (pronounced PUCK) plasmids, e.g. pUC18, carry an ampicillin resistance gene and an origin of replication, both from pBR322.

173 Markers can be selected for antibiotic resistance, colour changes or any other trait which can distinguish transformed host cells from untransformed hosts.

to the antibiotic, while one without the marker will die when exposed thereto. The process of transformation inserts the vector into a specially prepared host cell, such as *Escherichia coli*. The host cell, and each generation that follows, carries out the particular set of instructions that was passed to it during the transformation process, to produce the recombinant protein.

In *non-bacterial transformation*, the DNA is injected directly into the nucleus of the cell to be transformed. Biolistics is where a host cell is bombarded with high velocity micro-projectiles e.g. particles of gold or tungsten coated with DNA. With *phage introduction*, a phage (such as lambda, P1 or M13)[174] is used to get the DNA into the host cell. A bacteriophage (phage) is a virus whose host is a bacterial cell. Outside of its host, a phage is metabolically inert. In order to reproduce, it infects the host cell and takes over the cell's machineries to create copies of itself. The result of the infection can be and often is total devastation of the cell.

2 Polymerase Chain Reaction (PCR)

PCR was invented by Kary Mullis at the Cetus Corporation in 1983[175] and the patent for the technique was granted to the company in 1987. Cetus then sold the PCR patent to Hoffman-La Roche for $300 million in 1991. The technique allows the specific and rapid amplification *in vitro* of targeted DNA or RNA sequences using an enzyme – DNA polymerase[176]. The enzyme that is widely used in current PCR practice is the thermostable Taq polymerase that is derived from the hot springs bacteria *Thermus aquaticus*.

PCR is a common tool used in medical and biological research for a broad range of applications. Examples include the detection of hereditary diseases, identification of genetic fingerprints, diagnosis of infectious diseases, cloning of genes, paternity testing, and DNA computing[177].

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174 Large numbers of different lambda strains have been created that allow efficient cloning of a variety of foreign DNA's.

175 Mullis won a Nobel Prize for his work 8 years after the first paper was published in 1985. For a general description of the process see Powledge, http://advan.physiology.org/cgi/content/full/28/2/44, The polymerase chain reaction. See also http://www.bioteach.ubc.ca/MolecularBiology/PolymeraseChainReaction/index.htm; http://library.thinkquest.org/24355/data/light/details/techniques/polymerase.html; animated picture of PCR http://users.ugent.be/~avierstr/principles/pcrani.html and narrated presentation http://www.biotechnologyonline.gov.au/popups/vid_pcr.cfm.

176 See Appendix 1.2. A polymerase is a naturally occurring enzyme, a biological macromolecule that catalyzes the formation and repair of DNA (and RNA). Taq polymerase comes from hot springs bacteria (Thermus aquaticus)and can tolerate the intense heat of a PCR reaction. For high precision, the Pfu polymerase derived from Pyrococcus furiosus is used. This is even better suited to high temperatures (around 100 degrees Celsius) than Taq and it incorporates an additional step known as proofreading. http://sunsite.berkeley.edu/PCR/whatisPCR.html

177 http://www.americanscience.org/journals/am-sci/0103/01-0198-%20mahongbao-am.doc

3 Cre-lox, FLP-FRT and Mouse Models

Cre-lox is a tool developed in the 1980s by Dupont for site-specific recombination of DNA in eukaryotic cells. The company patented the technology in 1990[178]. Cre-lox allows researchers to regulate the expression of engineered genes at Lox sites, through activation of a regulatory sequence that controls the expression of the recombinase Cre gene[179].

FLP-FRT[180] is a site-directed recombination technology that is analogous to Cre-lox. It involves using flippase (FLP) recombinase which is derived from *Saccharomyces cerevisiae* (yeast). FLP recognises a pair of FLP recombinase target (FRT) sequences that flank a genomic region of interest[181].

Both technologies enable the creation of a variety of genetically-modified animals and plants with the gene of their choice being externally regulated. Prominent among the examples, they allow scientists to make 'knock-out' mice by deleting a single gene from specific cells. In this way, they can be used to identify gene function[182]. Knocking out the activity of a gene provides valuable clues about its functions. Since humans share many genes with mice, knock-out mice give researchers information that can be used to understand how a similar gene may cause or contribute to diseases in humans[183]. Mouse models have been used for studying various diseases, including different kinds of cancer, obesity, heart disease, diabetes, arthritis, substance abuse, anxiety, aging and Parkinson

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178 US Patent 4,959,317 was granted to DuPont on 25 September 1990 for a method for producing site-specific recombination of DNA in eukaryotic cells, comprising (a) introducing into the cells a first DNA sequence comprising a first lox site and a second DNA sequence comprising a second lox site, and (b) contacting the lox sites with Cre, thereby producing the site specific recombination.

179 Pechisker, Targeting your DNA with the cre-lox system, http://www.scq.ubc.ca/?p=287: "The *cre* gene, short for **c**yclization **re**combination, encodes a site-specific DNA recombinase (**Cre**). A site-specific DNA recombinase means that the Cre protein can recombine DNA when it locates specific sites in a DNA molecule. These sites are known as ***loxP*** (locus of X-over P1) sequences, which are 34 base pairs long and magnets for the Cre to recombine the DNA surrounding them… The *loxP* sequence originally comes from the P1 bacteriophage, which is a bacterial virus that, quite reasonably, contains DNA that is not found in animals or plants." See also http://jaxmice.jax.org/models/cre_intro.html.

180 US Patent 6,140,129 was granted to the Wisconsin Alumni Research Foundation on 31 October 2000 for a method of chromosomal targeting in bacteria using FLP recombinase.

181 See http://jaxmice.jax.org/models/cre_intro.html

182 More generally, a gene knockout is a genetically engineered organism that carries one or more genes in its chromosomes that have been made inoperative. So far such organisms have been engineered chiefly for research purposes. Also known as knockout organisms or simply knockouts, their most direct use is for learning about a gene that has been sequenced, but has an unknown or incompletely known function. See Walinski, Studying gene function: creating knockout mice, http://www.scq.ubc.ca/?p=264.

183 Knockout Mice, http://www.genome.gov/12514551; researchers can purchase knockout mice or have them created on a contract basis by specialist companies. See further, A cocktail of experimental tools, http://www.sciencemag.org/products/ddbt_31904.dtl. Schultz, Some Model Organisms Mightier than the Mouse, Drug Discovery and Development (http://www.dddmag.com/default.aspx), April 2004; Shah, Mouse Model Makeovers Knock Genes Around, Drug Discovery and Development, August 2004.

disease. The results have been used to develop and test pharmaceuticals and other therapies.

Abrams and Kaiser describe transgenic mice as follows[184]: "What are transgenic or knock-out mice and how are they made? The term transgenic mouse is the colloquial term for any genetically-engineered mouse. In scientific terms, a transgenic mouse is one that has a foreign gene added to all of its cells. A knock-out mouse is one that has had a specific gene deleted (or made inactive) in all of its cells. The making of a transgenic mouse is a long and laborious process that can take up to a year. First, the genetic change is engineered in a single mouse embryonic stem cell—an undifferentiated cell that has the potential to turn into any cell in the body. The altered stem cell is then added to an early-stage mouse embryo that is implanted into a surrogate mother. The researchers will then breed the progeny of these mice for several generations to obtain mice that have the genetic alteration in all of their cells."

Knock-out mice are usually named after the inactivated gene. For example, the p53 knockout mouse is named after the p53 gene, which codes for a protein that normally suppresses the growth of tumours by arresting cell division. Humans born with mutations that inactivate the p53 gene suffer from Li-Fraumeni syndrome, a condition that dramatically increases the risk of developing bone cancers, breast cancer and blood cancers at an early age[185]. 'Methuselah' is a knockout mouse model noted for longevity, and 'Frantic' is a model useful for studying anxiety disorders.

Animal disease models such as mouse models have made significant impact on target and phrmaceuticals discovery and development; and their use to establish gene function is well documented in the literature.

4 Expressed-Sequence Tags

An expressed-sequence tag (EST) is part of a sequence from a complementary DNA (cDNA) clone that corresponds to a messenger RNA (mRNA). It can be used to identify an expressed gene and as a sequence-tagged site marker for locating that gene on a physical map of the genome. In other words, it can be used to selectively extract the rest of the gene out of the chromosome, by matching base pairs with part of the gene. ESTs provide researchers with a quick and inexpensive route for discovering new genes, for obtaining data on gene expression and regulation, and for constructing genome maps. The

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184 Abrams and Kaiser, Licensing Transgenic Mice (this paper seems no longer to be available as a free download.)

185 Knockout Mice, http://www.genome.gov/12514551. To produce knockout mice, researchers use one of two methods – gene targeting and gene trapping – to insert artificial DNA into the chromosomes contained in the nuclei of embryonic stem (ES) cells. Both methods are carried out in vitro, that is, in cultured cells grown in laboratory conditions. The advantage of gene targeting is that if the DNA sequence of the target gene is known, researchers can precisely knock out the gene at a high rate of efficiency. The advantage of gene trapping is that researchers do not need to know the DNA sequences of specific genes in order to knock them out. The disadvantage of gene trapping is that researchers often must spend considerable time conducting tests to identify ES cells in which gene(s) actually have been knocked out.

identification of ESTs has proceeded rapidly, with approximately 40 million ESTs now available in public databases[186]. Using ESTs, scientists have rapidly isolated some of the genes involved in Alzheimer's disease and colon cancer.

5 Antisense and RNA Interference [187]

Antisense molecules are small pieces of DNA or RNA that bind to a cell's mRNA during translation and interfere with its activity. Researchers use antisense molecules to selectively block the expression of certain genes and then measure the resulting biochemical or visible changes[188]. This allows them to understand the relationship between the specific genes, proteins and traits.

RNA interference (RNAi), or post-transcriptional gene silencing, is a related method for selective blocking of gene expression that works through a different mechanism. While antisense molecules work by using single strand DNA or RNA to physically block protein production during the translation process, RNAi works by having small, double-stranded pieces of RNA that trigger a process ending with the enzymatic degradation of the mRNA. RNA interference appears to be a natural mechanism that virtually all organisms use to defend their genomes from invasion by viruses[189].

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186 Available on GenBank, the NIH's genetic sequence database, as of December 2006.

187 See Antler, Antisense RNA, http://www.scq.ubc.ca/?p=265, http://www.ambion.com/techlib/resources/RNAi/overview/index.html and http://www.scq.ubc.ca/?p=265 for illustrations of antisense and RNAi. See also, Susan Schultz, The Wonderful World of Antisense Technology, http://www.bio.davidson.edu/Courses/Molbio/MolStudents/01suschultz/homepage.html. Antisense technology has been extensively patented, with Isis Pharmaceuticals owning more than 1,500 patents covering most angles of antisense technology: Chemical & Engineering News, 17 April 2006, page 16 (http://pubs.acs.org/cen/coverstory/84/8416cov2.html). Among these patents is European Patent 0618925 (granted 29 August 2001 and upheld on 5 December 2006) which broadly covers antisense compounds with 'chimeric' or 'gapmer' structures. The claims cover a class of antisense compounds, any of which is designed to have a sequence of phosphorothioate-linked nucleotides having two regions of chemically modified RNA flanking a region of DNA. Virtually all antisense drugs currently in development, or likely to be developed in the near future, have gapmer compositions pioneered by Isis and covered by this European patent.

188 Schultz gives as an example of antisense technology the Flavr Savr tomato. Antisense was used to block the enzyme that is involved in spoilage, thereby increasing the length of time a tomato could be sold. See also Enzo Biochem v Calgene (1999) 188 F3d 1362 (U.S. Court of Appeals, Federal Circuit), involving the patents on the Flavr Savr tomato: http://www.law.washington.edu/casrip/newsletter/Vol7/newsv7i1us2.pdf.

189 See "An Unusual Path for RNAi Technology", Dmitry A. Samarsky and Peter J. Welch, Bio-IT World, http://www.bio-itworld.com/archive/121504/rnai_path.html; Arnaud, Delivering RNA Interference, Chemical & Engineering News, 13 November 2006, http://pubs.acs.org/cen/coverstory/84/8446cover.html; http://www.bio.csiro.au/Projects/RNAInterference.htm. Among the patents for the technology are U.S. Patent 6,573,099 ("Genetic constructs for delaying or repressing the expression of a target gene") and U.K. Patent 2353282 ("Control of gene expression"), which claim a method for silencing any gene in any cell using DNA directed RNA interference (ddRNAi). DNA directed RNAi (ddRNAi) triggers the natural gene suppression process called RNAi that operates by destroying messenger RNA (mRNA), the courier that delivers instructions to the ribosomes within the cell to manufacture the proteins coded for by DNA. By introducing a DNA construct into a cell, ddRNAi technology triggers the production of double stranded (dsRNA), which is then

RNAi has also been used to study the function of genes in model organisms. When double-stranded RNA for the gene of interest is introduced into a cell or organism, it often causes a drastic decrease in production of the protein that is coded by the gene. This allows researchers to gain an understanding of the protein's role and function. As RNAi may not totally suppress the expression of the gene, this technique is sometimes referred to as a "knockdown"[190]. In other words, genes are silenced in a sequence-specific manner through targeted mRNA degradation.

6 DNA Microarray[191]

A DNA microarray is a tool used to analyse simultaneously the activity of thousands of genes in a cell. The first patents covering DNA microarrays were issued in the 1990s. Hyseq (USA), Affymetrix (USA), Oxford Gene Technologies (UK) and Stanford University (USA) were granted patents covering microarray manufacturing, experimental processing and genomic profiling[192]. A series of infringement actions ensued as these patent owners sought to determine the scope and validity of their patents[193].

Although the concept of using microarrays can be traced back more than two decades, modern microarray analysis has been credited to a Stanford University research team led by Patrick Brown and Ron Davis back in 1995[194]. A DNA microarray consists of an orderly arrangement of DNA fragments, often called probes, which are immobilised on a piece of glass the size of a microscope slide. Each fragment represents a gene of an organism and is assigned a specific spot on the array. When the microarray is doused with a test sample, DNA or RNA strands in the sample will bind (through a process called hybridization) with complementary strands in the spots thereby creating a picture of which genes in the sample are active.

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cleaved into small interfering RNA (siRNA) as part of the RNAi process, resulting in the destruction of the target mRNA and knocking-down or silencing the expression of the target gene.

190 A 'knockout' is where expression of a gene is eliminated altogether by removing or destroying its DNA sequence.

191 See http://www.scq.ubc.ca/?p=272 for illustration of the technique.

192 See Rouse and Hardiman, Microarray technology – an intellectual property retrospective, available online at http://microarrays.ucsd.edu/biogem/pdf/Rouse%20R%20and%20Hardiman%20G.pdf.

193 See also, Oxford Gene Technology Ltd v Affymetrix Inc [2000] EWHC Patents 111 (English High Court); [2000] EWCA Civ 272 (English Court of Appeal) – dispute over the meaning of a licensing agreement between OGT and Beckman Coulter; Hyseq v Affymetrix (2001) 132 F. Supp. 2d 1212 (U.S. District Court, N.D. Cal.). For a brief history of the litigation, see Bridges, Significant DNA Array Suits Conclude, Kirkland & Ellis Biotech Update, http://www.kirkland.com/files/tbl_s14Publications/Document1303/845/Kirkland_BioUpdate.pdf. Affymetrix and Oxford Gene Technologies are major players in the microarray business. Hyseq moved out of the microarray market and refocused on building a biopharmaceutical business. It incorporated Callida Genomics Inc (and assigned all of its microarray related IP rights to the company) in partnership with Affymetrix and changed its name to Nuvelo.

194 See Brewster et al., The Microarray Revolution: Perspectives from Educators, 32 Biochemistry and Molecular Biology Education 217-227 (2004)

Microarrays allow researchers to monitor the expression of hundreds and thousands of genes at one time. This helps to shed the light on many basic biological functions. For example, researchers are using microarrays to observe the changes in gene activity that occur as normal cells turn cancerous.

Besides the DNA microarray, other types of microarrays that are based on the same concept have since been developed, including protein microarrays, tissue microarrays, whole-cell microarrays and small-molecule microarrays.

7 Monoclonal Antibodies[195]

Antibodies are proteins that are made by the immune system, specifically the white blood cells. They are produced in response to the introduction of foreign bodies (known as antigens) such as microbes and viruses; and they are used in Western blotting[196] (also known as immunoblotting), a common method in molecular biology, biochemistry and immunogenetics, to detect particular proteins in a given sample of tissue homogenate or extract. In Western blotting, gel electrophoresis is used to separate denatured proteins by mass. The proteins are then transferred out of the gel and onto a membrane (typically nitrocellulose), where they are "probed" using antibodies specific to the protein. As a result, researchers can examine the amount of protein in a given sample and compare levels between several groups. Other techniques also using antibodies allow detection of proteins in tissues (immunohistochemistry) and cells (immunocytochemistry).

Monoclonal antibodies were discovered by Georges Köhler and Cesar Milstein at the Medical Research Council (MRC) Laboratory of Molecular Biology in Cambridge, England in 1975. The scientists constructed a hybrid between an antibody-producing, mortal, lymphoid cell which has been immunized with a target antigen, and a malignant, or "immortal", myeloma cell. The resulting "hybridoma" cell continuously secreted antibodies having a single, selected specificity for the antigen. Given the right nutrients and conditions, hybridomas will grow and divide almost indefinitely, enabling the mass production of a single type of antibodies. Notably, monoclonal antibody technology was never patented by its inventing scientists. In 1976, in a now famous decision, the National Research and Development Corporation (NRDC), which was responsible for patenting inventions in public research such as those coming from the MRC, stated that the technology was not patentable because it could not be shown to have utility[197]. However, just two years later, scientists at the Wistar Institute (USA) successfully applied for two US patents on hybridomas they had developed, using melanoma cell lines given to them by Köhler and Milstein.

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195 See Kohler and Milstein, Continuous cultures of fused cells secreting antibody of predefined specificity, 256 Nature 495-7 (1975); Riechmann et al., Reshaping human antibodies for therapy, 332 Nature 323-7 (1988).

196 So-called Western blotting is similar to Southern blotting which was invented by and named after the inventor E. M. Southern. See, on the Western technique, http://www.chemicon.com/resource/ANT101/a2B.asp

197 A copy of the original letter can be found in: http://www.path.cam.ac.uk/~mrc7/mab25yrs/index.html.

Monoclonal antibodies have a wide variety of uses – in basic research, diagnostics and therapeutics, due to their high specificity to antigens[198]. They can detect the presence of miniscule amounts of substances and measure them with great accuracy. For instance, monoclonal antibodies are used in Western blot tests to detect proteins on a membrane and in immunofluorescence tests to detect substances in a cell. They are also used in ELISA. Monoclonal antibodies can also be used to purify a substance with techniques such as immunoprecipitation and affinity chromatography.

8 ELISA[199]

Enzyme-Linked ImmunoSorbent Assay (ELISA) is yet another method that makes use of the binding affinity and specificity of antibodies for their antigens. It was invented in 1971 by Eva Engvall and Peter Perlman but was never patented by its inventors[200].

ELISA is a biochemical test that is frequently used in immunology to detect and measure antigens or antibodies in a sample. The test uses two antibodies – one is specific to the target antigen while the other reacts to antigen-antibody complexes and is coupled to an enzyme. This enzyme can cause a chromogenic or fluorogenic substrate to produce a signal.

ELISA has numerous applications and is still widely used today. For instance, in medical laboratories, clinicians use it to detect diseases such as AIDS and malaria, while in homes it can be found in pregnancy kits. It has also found applications in the food industry in detecting potential food allergens such as milk, peanuts, walnuts, almonds, and eggs.

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198 Among the many patents for monoclonal antibodies, U.S. Patent 6927035 is directed to a monoclonal antibody which reacts strongly with uracil and thymine but scarcely with N-carbamyl-β-alanine; a hybridoma producing this monoclonal antibody; a method of immunochemically assaying uracil or thymine characterized by using the above-described monoclonal antibody; and diagnostics for DPD deficiency containing the above monoclonal antibody. Because of high sensitivity and specific reaction with uracil and thymine, the above-described monoclonal antibody enables convenient, quick, and selective assaying of uracil and thymine in a sample. The antibody is useful in screening patients with DPD deficient cancer with contraindication to the administration of pyrimidine fluoride-based anti-tumor agents. See also U.S. Patent 7115716 (tumor specific monoclonal antibodies).

199 See Engvall and Perlman, Enzyme-linked immunosorbent assay (ELISA). Quantitative assay of immunoglobulin G, Immunochemistry (1971) Sep 8(9):871-4; Goldsby et al., Enzyme-Linked Immunosorbent Assay, Immunology, 5th edition.(2003), pages 148-150, W. H. Freeman, New York.

200 See http://www.npr.org/templates/story/story.php?storyId=5420914 and Lequin, Enzyme Immunoassay (EIA)/Enzyme-Linked Immunosorbentassay (ELISA), 51 Clinical Chemistry 2415-2418 (2005)

9 High-Throughput Screening

Screening chemical compounds for medicinal or other properties has been commonplace for many years in the pharmaceutical and food industries. Compound libraries are screened against targets in order to discover compounds that, usually after extensive development (including trials), may become marketable products[201]. For example, US Patent 6955887 ("Use of T1R Hetero-Oligomeric Taste Receptor to Screen for Compounds that Modulate Taste Signaling") issued on 18 October 2005 covers receptor-based screening methods that allow for rapid screening and identification of potential new sweet flavour ingredients. The opening claim of this patent reads:

> A method of screening for a compound that modulates sweet taste signaling in taste cells, the method comprising the steps of: (i) contacting the compound with a hetero-oligomeric taste transduction G-protein coupled receptor that responds to sweet taste stimuli; wherein said hetero-oligomeric receptor comprises a polypeptide that is encoded by a nucleic acid sequence that specifically hybridizes under stringent hybridization conditions to a human T1R2 nucleic acid comprising the nucleotide sequence of SEQ ID NO:3, and further comprises a polypeptide that is encoded is by a nucleic acid sequence that specifically hybridizes under stringent hybridization conditions to the human T1R3 nucleotide sequence of SEQ ID NO: 5; wherein stringent hybridization conditions comprise conducting the hybridization reaction at 42 degrees C. in a solution comprising …; and (ii) determining whether said compound binds to and/or affects the activity of said hetero-oligomeric sweet receptor[202].

High-throughput screening screens large numbers of compounds for binding or biological activity (e.g. as agonists or antagonists) against target molecules (e.g. receptors)[203]. A pharmaceutical company may screen as many as 1,000,000 compounds over several months to obtain half-a-dozen lead compounds. Screening 100,000 to 300,000

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201 For an example of a "Library Sample Evaluation Agreement", go to http://contracts.onecle.com/cubist/pharmacopeia.supply.1996.09.11.shtml.

202 Claim 2: "A method of screening for a compound that enhances or inhibits the binding of a sweet compound to and/or activation by a sweet compound of a hetero-oligomeric taste transduction G-protein coupled receptor that responds to sweet taste stimuli, by a sweet compound the method comprising the steps of …"

203 Fattinger, High Throughput Screening, Innovation 12, Carl Zeiss, 2002, http://www.zeiss.com/C125716F004E0776/0/F79C10F9D863005BC125717700453A84/$File/Innovation_12_4.pdf. Agonists and antagonists are key agents in the chemistry of the human body and important players today in pharmacology. An agonist binds to a receptor of a cell and triggers a response by the cell. It often mimics the action of a naturally occurring substance. It is the opposite of an antagonist which acts against and blocks an action. For example, dopamine agonists mimic the effects of dopamine in the brain by stimulating dopamine receptors with a lower risk of the uncontrollable and irreversible dyskinesias often associated with levodopa therapy used in the treatment of Parkinson's disease.

compounds can yield 100 to 300 "hits" (positive results) but on average only two lead compounds[204].

10 Combinatorial Chemistry and Compound Libraries

Mario Geysen has been credited as being the "father" of combinatorial chemistry[205]. In the early 1980s, Geysen developed a methodology to synthesize simultaneously arrays of peptides on polymer-based solid supports. He created the world's first "library" of mimotopes, peptides that mimic the reaction of antibodies and antigens and which are critical to drug discovery[206].

Since then, combinatorial chemistry refers to a range of techniques that allows for the synthesis of libraries of structurally-distinct molecules which can be subsequently screened with pharmacological assays. Like traditional methods, combinatorial chemistry relies mainly on organic synthesis methodologies[207]. The difference is that instead of synthesizing a single compound, combinatorial chemistry provides a diversity of products that can be made separately or in mixtures, using either solid-phase[208] or liquid-phase techniques. Using automation and miniaturisation, the process is systematic and repetitive, allowing the creation of libraries of molecules from sets of chemical "building blocks" in a short time. Productivity therefore is greatly increased.

Aside from the synthesis of compounds, the other crucial aspect of combinatorial chemistry is characterising and identifying the resulting compounds. Depending on the nature of the chemical compounds that have been synthesised, different analytical methods such as mass-spectrometry are used. Once the process of establishing the library of compounds is completed, it can then be subjected to various screens to identify potential lead compounds[209]. With the best candidate compounds screened, researchers can then use computational (*in silico*) chemistry[210] to enhance the leads.

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204 See Appendix 2.10 for illustration of high throughput screening.

205 Geysen is a 2000 Kilby Laureate, http://www.kilby.org/kl_past_laureates.html

206 See Geysen et al., 23 Molecular Immunology 709-15 (1986)

207 See Miertus et al, Concepts of combinatorial chemistry and combinatorial technologies, 94 Chem. Listy 1104-1110 (2000); available online at http://www.combichemistry.com/statdir/stat.php?id=pdf10

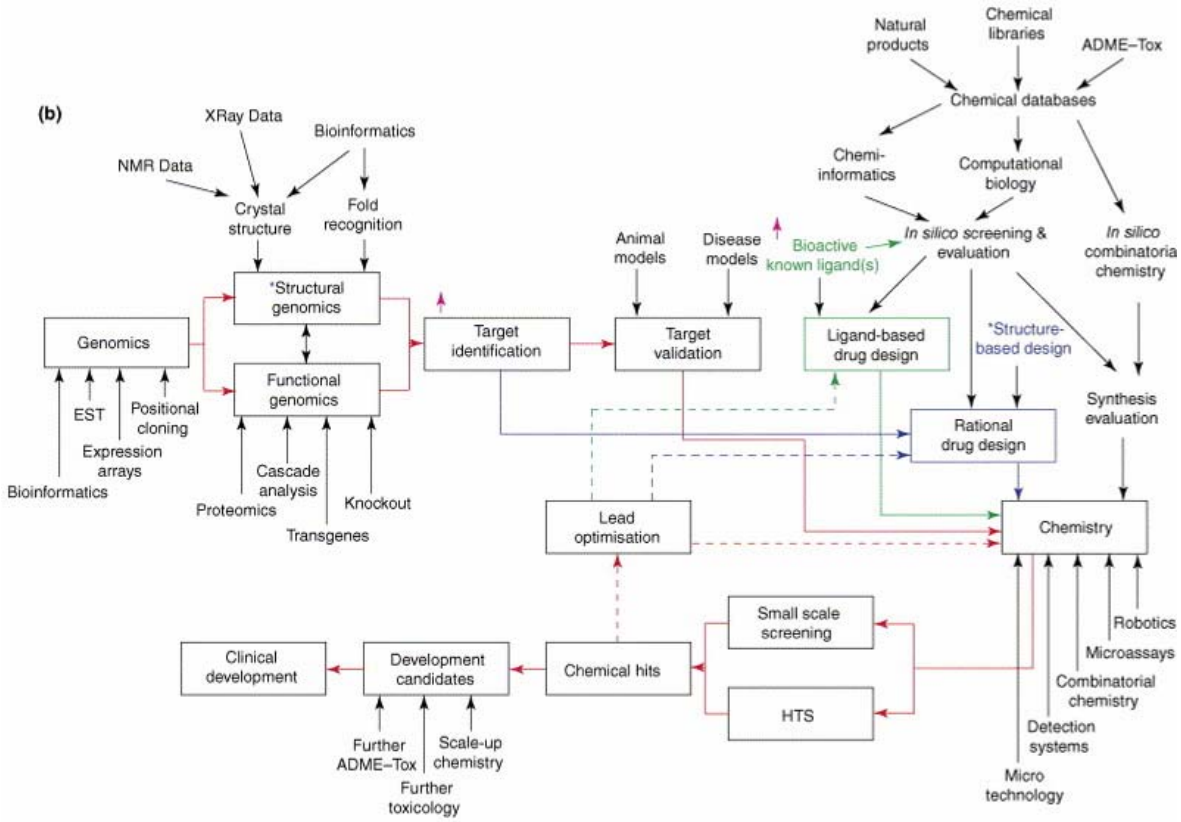
208 See IPTS report: http://www.jrc.es/home/report/english/articles/vol18/COM1E186.htm and http://www.combichemistry.com/solid_phase_synthesis.html for illustration of solid phase synthesis.

209 See above, on high-throughput screening. Virtual HTS is used to find "hit" compounds *in silico*, using commercial chemical compounds databases. VHTS applications (e.g. Grid MP) can screen thousands of virtual molecules in a fraction of the time and cost it would take to synthesize and test molecules in a laboratory. With the average drug taking 12-15 years and $500 million to $600 million to get to market, there could be huge cost savings by *in silico* screening of potential compounds. Since each drug is said to be the result of more than 10,000 screened compounds, the ability to screen out unpromising drug candidates quickly and cheaply would make computational drug discovery a huge potential growth market. See also Heal, *In silico* structure-based drug design, http://www.ddw-online.com/data/pdfs/in%20silico%20drug%20design.pdf.

210 The term *theoretical* chemistry may be defined as a mathematical description of chemistry, whereas *computational* chemistry is usually used when a mathematical method is sufficiently well developed that it can be automated for implementation on a computer. See generally Bussiere,

11 *In-Silico* Tools[211]

In modern life sciences R&D, *in-silico* tools are used in nearly every stage of the discovery and development process. The following figure illustrates the typical drug discovery workflow and the roles that computational tools play at each step.



Impact of *in silico* methods in the life sciences R&D process[212]

These tools are used to aid or accelerate R&D in 5 broad aspects:

11.1 Upstream Bioinformatics and Software Applications

With high-throughput techniques becoming common, researchers now have to contend with an ever increasing amount of research data and information. Software applications such as those for genomics, sequence analysis, micro-array analysis and proteomics, are developed specifically to help researchers manage and understand the data they have at hand.

Biotechnology, Drug Discovery, and Biomedical Research In Silico, http://www.nsti.org/procs/MSM99/2/T23.00; Sinskey et al., Getting to Rational Drug Design – at last, PharmaGenomics, November/December 2002, page 18.

211 This section was contributed by Anita Suresh, research associate at the Bioinformatics Institute, Singapore.

212 Drug Discovery Today 11:895-904, October 2006

11.2 Molecular Modeling

Molecular modeling tools help researchers construct, visualise, and analyse models of 3D molecular structure of proteins, chemical compounds and complex macromolecules[213]. Using the models, researchers are able to derive useful functional information about a compound, which in turn helps them design new and more potent drugs.

11.3 Atomistic Simulation

Researchers have developed methods to predict interactions, structural impact, dynamics and effects based on molecular models. For instance, molecular dynamics models the behaviour of the system over time.

11.4 Statistical Methods

Researchers also use a range of techniques, for example, the Quantitative Structure Activity Relationships (QSAR) method, to build and apply predictive models for activity and interactions based on analysis of computational and experimental results. A QSAR is a multi-variant statistical correlation between a property and the key geometric or chemical characteristics of a molecular system. By computing and analysing QSARs, researchers can identify the factors which are important to the property of interest, i.e. information that is useful in identifying or optimizing lead compounds.

11.5 Rational Drug Design Tools

A range of algorithms and techniques, including combinations of those mentioned above, are available to researchers to help them identify and optimise leads in the drug discovery process. These tools provide assistance in a number of ways including *de novo* design (refers to construction of virtual lead compounds entirely through computer simulation),

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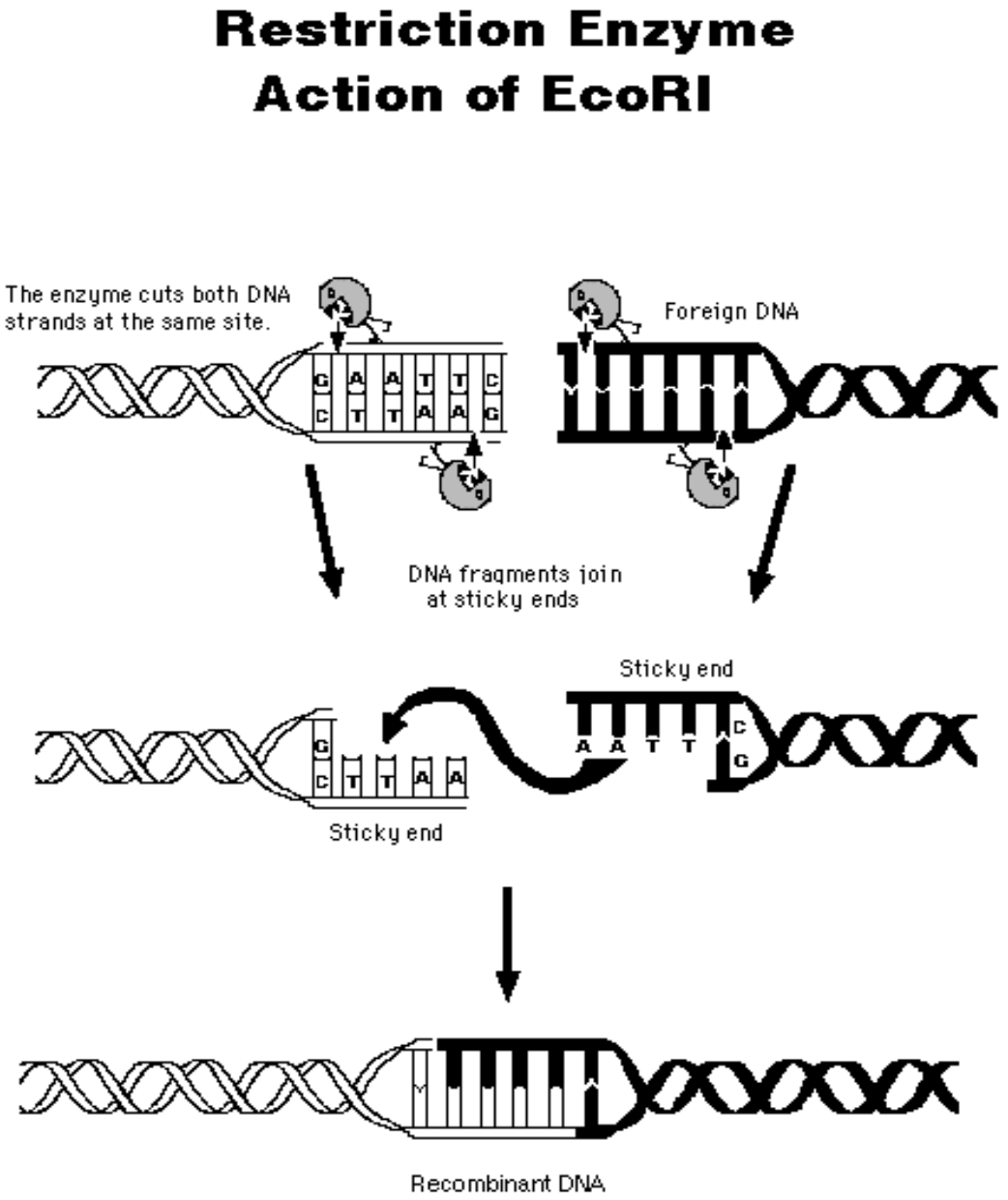
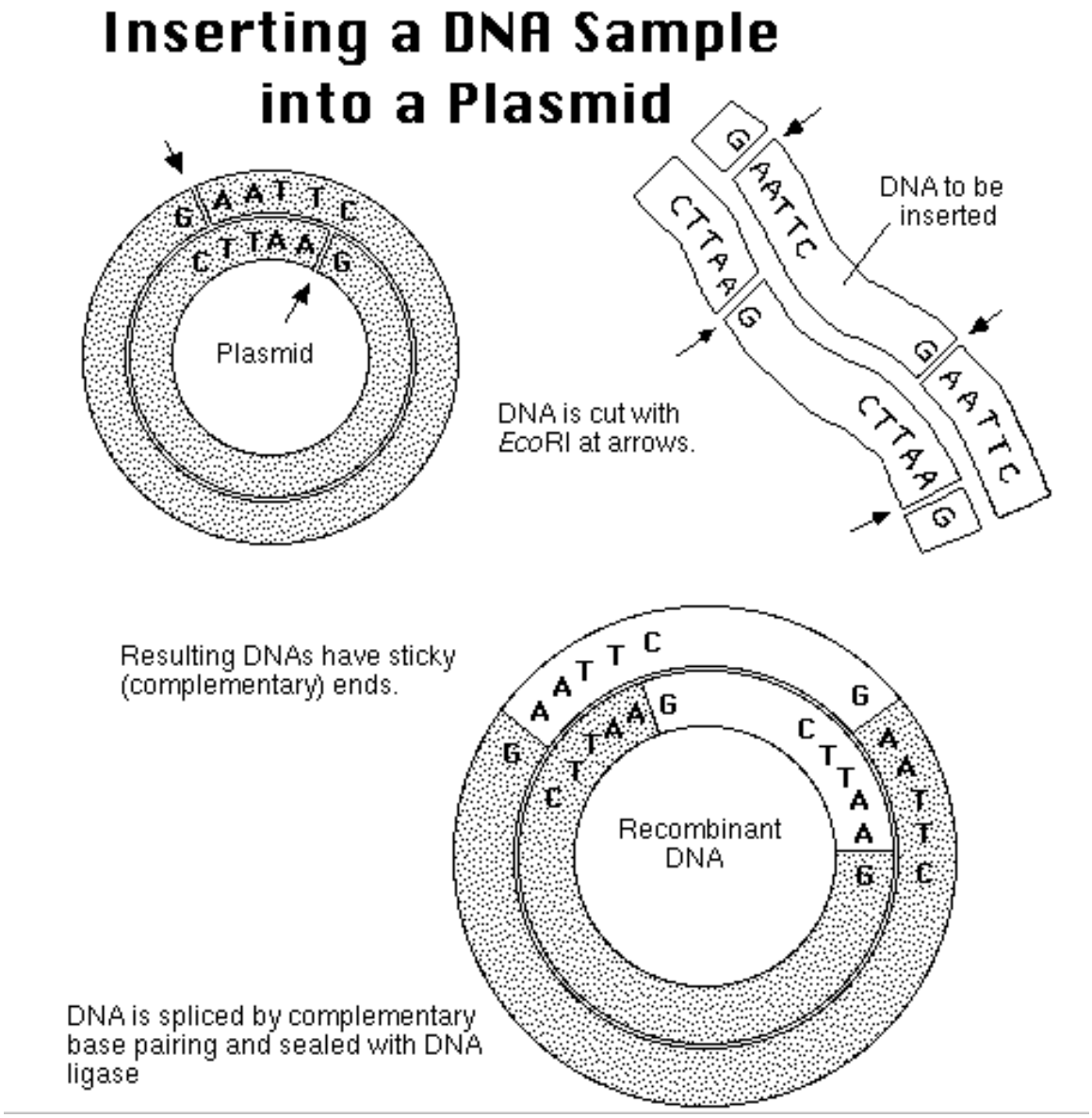
213 In **Fujitsu's Application** (1996) Reports of Patent Cases 511 (English Patents Court); (1997) RPC 608 (English Court of Appeal), the applicant tried unsuccessfully to patent a method and apparatus for modelling a synthetic crystal structure for designing inorganic materials and a computer programmed so that an operator could select an atom, a lattice vector and a crystal face in each of two crystal structures displayed by the computer. The computer then converted data representing the physical layouts of the two crystal structures into data representing the crystal structure that would have been obtained by combining the original two structures in that way. The resulting data was then displayed to give an image of the resulting combined structure. Accordingly, a scientist wishing to investigate what would result if he made a new material consisting of a combination of two existing compounds would enter into a computer data representing those compounds and how they should be joined. The computer then automatically generated and displayed the new structure using the data supplied. Previously, the same effect could only have been achieved by assembling plastic models by hand - a time consuming task. For the judgment of the Court of Appeal: http://www.bailii.org/ew/cases/EWCA/Civ/1997/1174.html. A patent claim for a computational research tool might read as follows: "A method for identifying herbicides comprising the following steps: generating a structural model of [XX inhibitors] by computer modelling techniques; designing a compound into the structure of said generated structural model; testing the compound of step (ii) for its herbicidal activity."

docking and scoring (e.g. to predict protein-ligand binding affinities), library design screening (to rationalise compound selection using virtual screeners), ADMET models for drug development as well as pharmacophore design and pharmacokinetics.

Appendix 1.1: Recombinant DNA



(Cloning Genes, http://web.mit.edu/esgbio/www/rdna/cloning.html)



(Cloning Genes, http://web.mit.edu/esgbio/www/rdna/cloning.html)

Transfer and Cloning of the Insulin Gene

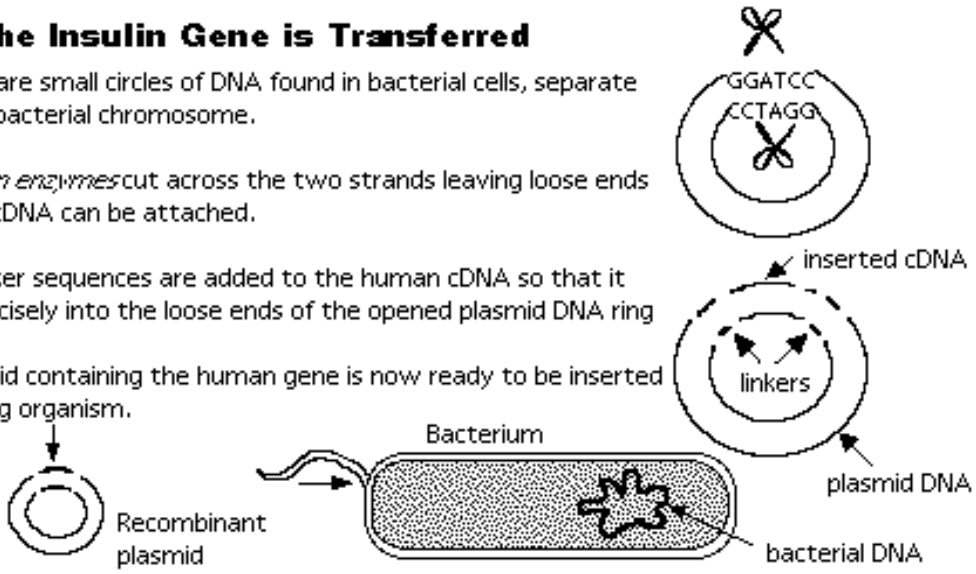
How the Insulin Gene is Transferred

Plasmids are small circles of DNA found in bacterial cells, separate from the bacterial chromosome.

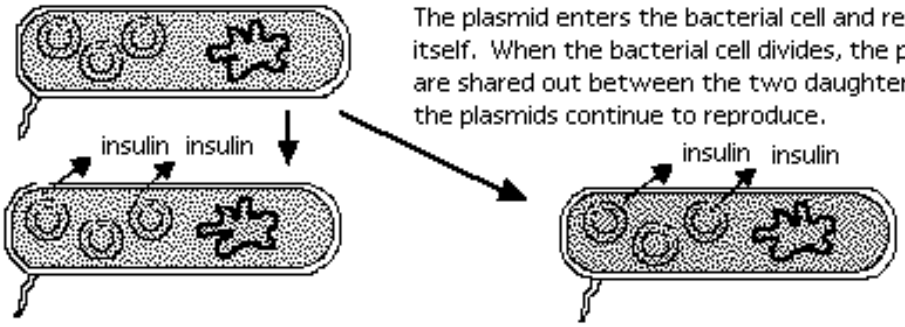
Restriction enzymes cut across the two strands leaving loose ends to which cDNA can be attached.

Special linker sequences are added to the human cDNA so that it will fit precisely into the loose ends of the opened plasmid DNA ring

The plasmid containing the human gene is now ready to be inserted into a living organism.



Cloning the Human Insulin Gene

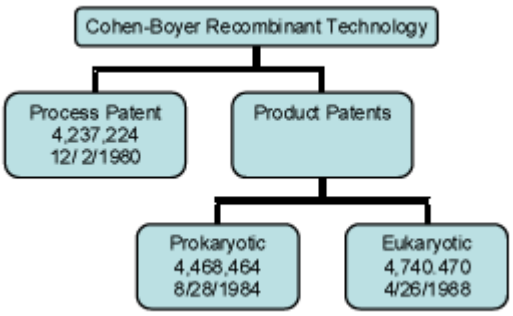


The plasmid enters the bacterial cell and reproduces itself. When the bacterial cell divides, the plasmids are shared out between the two daughter cells and the plasmids continue to reproduce.

In this way a clone of identical cells is formed and if the human gene incorporated encodes for the hormone insulin, then such a clone can provide a reliable insulin source.

(Cloning Genes, http://web.mit.edu/esgbio/www/rdna/cloning.html)

Appendix 1.2: US Patents for Cohen-Boyer Recombinant Technology



United States Patent [19]

Cohen et al.

[11] **4,237,224**

[45] **Dec. 2, 1980**

[54] **PROCESS FOR PRODUCING BIOLOGICALLY FUNCTIONAL MOLECULAR CHIMERAS**

[75] Inventors: **Stanley N. Cohen,** Portola Valley; **Herbert W. Boyer,** Mill Valley, both of Calif.

[73] Assignee: **Board of Trustees of the Leland Stanford Jr. University,** Stanford, Calif.

[21] Appl. No.: **1,021**

[22] Filed: **Jan. 4, 1979**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 959,288, Nov. 9, 1978, which is a continuation-in-part of Ser. No. 687,430, May 17, 1976, abandoned, which is a continuation-in-part of Ser. No. 520,691, Nov. 4, 1974.

[51] **Int. Cl.**[3] **C12P 21/00**

[52] **U.S. Cl.** ..... **435/68;** 435/172; 435/231; 435/183; 435/317; 435/849; 435/820; 435/91; 435/207; 260/112.5 S; 260/27R; 435/212

[58] **Field of Search** ..... 195/1, 28 N, 28 R, 112, 195/78, 79; 435/68, 172, 231, 183

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Singer et al., Science vol. 181, p. 1114 (1973).
Itakura et al., Science vol. 198, pp. 1056–1063 Dec. 1977.
Komaroff et al., Proc. Nat. Acad. Sci. USA, vol. 75, pp. 3727–3731, Aug. 1978.
Chemical and Engineering News, p. 4, May 30, 1977.
Chemical and Engineering News, p. 6, Sep. 11, 1978.

Primary Examiner—Alvin E. Tanenholtz
Attorney, Agent, or Firm—Bertram I. Rowland

[57] **ABSTRACT**

Method and compositions are provided for replication and expression of exogenous genes in microorganisms. Plasmids or virus DNA are cleaved to provide linear DNA having ligatable termini to which is inserted a gene having complementary termini, to provide a biologically functional replicon with a desired phenotypical property. The replicon is inserted into a microorganism cell by transformation. Isolation of the transformants provides cells for replication and expression of the DNA molecules present in the modified plasmid. The method provides a convenient and efficient way to introduce genetic capability into microorganisms for the production of nucleic acids and proteins, such as medically or commercially useful enzymes, which may have direct usefulness, or may find expression in the production of drugs, such as hormones, antibiotics, or the like, fixation of nitrogen, fermentation, utilization of specific feedstocks, or the like.

14 Claims, No Drawings

that certain changes and modifications may be practiced within the scope of the appended claims.

We claim:

1. A method for replicating a biologically functional DNA, which comprises:

transforming under transforming conditions compatible unicellular organisms with biologically functional DNA to form transformants; said biologically functional DNA prepared in vitro by the method of:

(a) cleaving a viral or circular plasmid DNA compatible with said unicellular organism to provide a first linear segment having an intact replicon and termini of a predetermined character;

(b) combining said first linear segment with a second linear DNA segment, having at least one intact gene and foreign to said unicellular organism and having termini ligatable to said termini of said first linear segment, wherein at least one of said first and second linear DNA segments has a gene for a phenotypical trait, under joining conditions where the termini of said first and second segments join to provide a functional DNA capable of replication and transcription in said unicellular organism;

growing said unicellular organisms under appropriate nutrient conditions; and

isolating said transformants from parent unicellular organisms by means of said phenotypical trait imparted by said biologically functional DNA.

2. A method according to claim 1, wherein said unicellular organisms are bacteria.

3. A method according to claim 2, wherein said transformation is carried out in the presence of calcium chloride.

4. A method according to claim 3, wherein said phenotypical trait is resistance to growth inhibiting substance, and said growth is carried out in the presence of a sufficient amount of said growth inhibiting substance to inhibit the growth of parent unicellular organisms, but insufficient to inhibit the growth of transformants.

5. A method according to claim 1, wherein said unicellular organism is *E. coli*.

6. A method according to claim 1, wherein said predetermined termini are staggered and cohesive.

7. A method according to claim 6, wherein said joining conditions includes enzymatic ligation.

8. A method according to claim 6, wherein said cohesive ends are formed by staggered cleavage of said viral or circular plasmid DNA and a source of said second segment with a restriction enzyme.

9. A method acording to claim 6 wherein said cohesive termini are formed by addition of nucleotides.

10. A method according to claim 1, wherein said predetermined termini are blunt end and said joining conditions include enzymatic ligation.

11. A method for replicating a biologically functional DNA comprising a replicon compatible with a host unicellular organism joined to a gene derived from a source which does not exchange genetic information with said host organism, said method comprising:

isolating said biologically functional DNA from transformants prepared in accordance with claim 1;

transforming unicellular microorganisms with which said replicon is compatible with said isolated DNA to provide second transformants; and

growing said second transformants under appropriate nutrient conditions to replicate said biologically functional DNA.

12. A method for producing a protein foreign to a unicellular organism by means of expression of a gene by said unicellular organism, wherein said gene is derived from a source which does not exchange genetic information with said organism, said method comprising:

growing transformants prepared in accordance with any of claims 1 and 11 under appropriate nutrient conditions, whereby said organism expresses said foreign gene and produces said protein.

13. A method according to claim 12, wherein said protein is an enzyme.

14. A method according to claim 11, wherein said method is repeated substituting said biologically functional DNA from transformants prepared in accordance with claim 1 with second or subsequent transformants to produce additional transformants.

* * * * *

United States Patent [19]

Cohen et al.

[11] **Patent Number: 4,468,464**

[45] **Date of Patent: * Aug. 28, 1984**

[54] **BIOLOGICALLY FUNCTIONAL MOLECULAR CHIMERAS**

[75] Inventors: **Stanley N. Cohen,** Menlo Park; **Herbert W. Boyer,** Mill Valley, both of Calif.

[73] Assignee: **The Board of Trustees of The Leland Stanford Junior University,** Stanford, Calif.

[*] Notice: The portion of the term of this patent subsequent to Dec. 22, 1998 has been disclaimed.

[21] Appl. No.: **959,288**

[22] Filed: **Nov. 9, 1978**

Related U.S. Application Data

[63] Continuation of Ser. No. 687,430, May 17, 1976, abandoned, which is a continuation-in-part of Ser. No. 520,691, Nov. 4, 1974, abandoned.

[51] **Int. Cl.**[3] **C12N 1/00;** C12N 15/00; C12N 1/20; C12P 21/00

[52] **U.S. Cl.** **435/317;** 435/68; 435/253; 435/820; 435/172.3; 935/6; 935/29; 935/56; 935/60; 935/67; 935/68; 935/73; 935/84; 535/23

[58] **Field of Search** 435/172, 68, 317, 91, 435/253

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Attorney, Agent, or Firm—Bertram I. Rowland

[57] **ABSTRACT**

Method and compositions are provided for replication and expression of exogenous genes in microorganisms. Plasmids or virus DNA are cleaved to provide linear DNA having ligatable termini, which are bound to a gene having complementary termini, to provide a biologically functional replicon with a desired phenotypical property. The replicon is inserted into a microorganism cell by transformation. Isolation of the transformants provides cells for replication and expression of the DNA molecules present in the modified plasmid. The method provides a convenient and efficient way to introduce genetic capability into microorganisms for the production of nucleic acids are proteins, such as medically or commercially useful enzymes, which may have direct usefulness, or may find expression in the production of drugs, such as hormones, antibiotics, or the like, fixation of nitrogen, fermentation, utilization of specific feedstocks, or the like.

The invention was supported by generous grants of NIH, NSF and the American Cancer Society.

11 Claims, No Drawings

The vehicle is combined with DNA indigenous to a biological organism other than the cell which provides replication and provides a genotypical or phenotypical property which is alien to the cell. The source of the DNA can be prokaryotic or eukaryotic, thus including bacteria, fungi, vertebrates, e.g. mammals, and the like.

The plasmid vehicle and the alien DNA having complementary cohesive termini can be annealed together and covalently linked to provide a recombinant plasmid, which is capable of transforming a bacterial cell, so as to be capable of replication, transcription, and translation. As a result, a wide variety of unique capabilities can be readily introduced into bacteria, so as to provide convenient ways to obtain nucleic acids and to study nucleic acids from a foreign host. Thus, the method provides the ability to obtain large amounts of a foreign nucleic acid from bacteria in order to be able to study the function and nature of the nucleic acid. In addition, the subject method provides means for preparing enzymes and enzymic products from bacteria where the natural host is not as convenient or efficient a source of such product. Particularly, bacteria may allow for more ready isolation of particular enzymes, uncontaminated by undesirable contaminants, which are present in the original host. In addition, the products of the enzymic reactions may be more readily isolated and more efficiently produced by a transformant than by the original host. Besides enzymes, other proteins can be produced such as antibodies, antigens, albumins, globulins, glycoproteins, polysaccharides, and the like.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be obvious that certain changes and modifications may be practiced within the scope of the appended claims.

What is claimed is:

1. As a composition of matter, a biologically functional recombinant plasmid capable of selection and replication in a prokaryotic cell comprising:

a first DNA segment containing an intact replicon recognized by said cell derived by cleaving a virus or plasmid compatible with said cell at other than the replicon site, which segment is covalently joined in vitro at its ends to the complementary ends of a second DNA segment foreign to said cell and having at least one intact gene, said second DNA segment derived from a source which does not exchange genetic information with said cell.

2. As a composition of matter, a biologically functional recombinant plasmid having been cloned at least once and capable of selection and replication, said plasmid having first and second linear segments, wherein said first segment has an intact replicon recognized by a prokaryotic host and said second segment is a gene derived from a source which is foreign to and does not exchange genetic information with a prokaryotic host for said replicon.

3. A composition of matter according to claim 2, wherein said second segment is derived from eukaryotic source.

4. A composition of matter according to claim 2, wherein said first segment has a basis for selection.

5. A composition of matter according to claim 2, wherein said second segment has a basis for selection.

6. As a composition of matter, a biologically functional recombinant plasmid having been cloned at least once and capable of selection and replication, said plasmid having first and second linear segments, wherein said first segment has an intact replicon derived from a prokaryotic plasmid and said second segment is a gene derived from a source which is foreign to and does not exchange genetic information with a prokaryotic host for said prokaryotic plasmid.

7. A composition of matter according to claim 6, wherein said second segment is derived from a eukaryotic source.

8. A composition of matter according to claim 6, wherein the basis for selection is resistance to a growth inhibiting substance.

9. A composition of matter according to claim 2, wherein the basis for selection is resistance to a growth inhibiting substance.

10. A composition of matter according to claim 8, wherein said growth inhibiting substance is an antibiotic.

11. A composition of matter according to claim 9, wherein said growth inhibiting substance is an antibiotic.

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United States Patent [19]

Cohen et al.

[11] **Patent Number: 4,740,470**

[45] **Date of Patent: * Apr. 26, 1988**

[54] **BIOLOGICALLY FUNCTIONAL MOLECULAR CHIMERAS**

[75] Inventors: **Stanley N. Cohen**, Menlo Park; **Herbert W. Boyer**, Mill Valley, both of Calif.

[73] Assignee: **The Board of Trustees of the Leland Stanford, Jr. University**, Stanford, Calif.

[*] Notice: The portion of the term of this patent subsequent to Dec. 2, 1997 has been disclaimed.

[21] Appl. No.: **602,294**

[22] Filed: **Apr. 20, 1984**

Related U.S. Application Data

[63] Continuation of Ser. No. 959,288, Nov. 9, 1978, Pat. No. 4,468,464, which is a continuation of Ser. No. 687,430, May 17, 1976, abandoned, which is a continuation-in-part of Ser. No. 520,691, Nov. 4, 1974, abandoned.

[51] **Int. Cl.**[4] **C12N 15/00**; C12N 5/00; C12N 1/20; C12N 1/00; C12P 19/34

[52] **U.S. Cl.** **435/172.3**; 435/91; 435/320; 435/240.2; 435/253; 935/27; 935/31; 935/32

[58] **Field of Search** 435/172.3, 91, 317, 435/253, 240, 320, 240.2; 935/27, 31, 32

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Primary Examiner—Alvin E. Tanenholtz

Attorney, Agent, or Firm—Bertram I. Rowland

[57] **ABSTRACT**

Method and compositions are provided for replication and expression of exogenous genes in microorganisms. Plasmids or virus DNA are cleaved to provide linear DNA having ligatable termini, which are bound to a gene having complementary termini, to provide a biologically functional replicon with a desired phenotypical property. The replicon is inserted into a microorganism cell by transformation. Isolation of the transformants provides cells for replication and expression of the DNA molecules present in the modified plasmid. The method provides a convenient and efficient way to introduce genetic capability into microorganisms for the production of nucleic acids and proteins, such as medically or commercially useful enzymes, which may have direct usefulness, or may find expression in the production of drugs, such as hormones, antibiotics, or the like, fixation of nitrogen, fermentation, utilization of specific feedstocks, or the like.

The invention was supported by generous grants of NIH, NSF and the American Cancer Society.

23 Claims, No Drawings

morphological properites, color, or the like, and production of growth factors, e.g. amino acids.

The vehicle is combined with DNA indigenous to a biological organism other than the cell which provides replication and provides a genotypical or phenotypical property which is alien to the cell. The source of the DNA can be prokaryotic or eukaryotic, thus including bacteria, fungi, vertebrates, e.g. mammals and the like.

The plasmid vehicle and the alien DNA having complementary cohesive termini can be annealed together and covalently linked to provide a recombinant plasmid, which is capable of transforming a bacterial cell, so as to be capable of replication, transcription, and translation. As a result, a wide variety of unique capabilities can be readily introduced into bacteria, so as to provide convenient ways to obtain nucleic acids and to study nucleic acids from a foreign host. Thus, the method provides the ability to obtain large amounts of a foreign nucleic acid from bacteria in order to be able to study the function and nature of the nucleic acid. In addition, the subject method provides means for preparing enzymes and enzymic products from bacteria where the natural host is not as convenient or efficient a source of such product. Particularly, bacteria may allow for more ready isolation of particular enzymes, uncontaminated by undesirble contaminants, which are present in the original host. In addition, the products of the enzymic reactions may be more readily isolated and more efficiently produced by a transformant than by the original host. Besides enzymes, other proteins can be produced such as antibodies, antigens, albumins, globulins, glycoproteins, polysaccharides, and the like.

Although the foregoing invention has been described in some detail by way of illustration and example for purpsoes of clarity of understanding, it will be obvious that certain changes and modifications may be practiced within the scope of the appended claims.

What is claimed is:

1. A method for replicating biologically functional circular recombinant DNA molecules in transformed host cells, which comprises:

(1) preparing biologically functional circular recombinant DNA molecules by: joining first and second DNA linear segments, said first and second DNA segments having termini of a predetermined character at least in part complementary, at least one of said first and second DNA linear segments having a gene for a phenotypical trait, said first DNA linear segment having an intact extrachromosomal replicon recognized by said host cell, and said second DNA linear segment having foreign DNA derived from a source which does not exchange genetic information with said host cells;

(2) transforming said host cells with said biologically functional recombinant DNA molecules;

(3) growing said host cells under appropriate nutrient conditions; and

(4) isolating said transformant cells with said biologically functional recombinant DNA molecules by means of said phenotypical trait imparted by said biologically functional recombinant DNA molecules.

2. A method according to claim **1** wherein said host cells are unicellular organisms.

3. A method according to claim **1**, wherein said host cells are prokaryotic organisms.

4. A method according to claims **1**, **2** or **3** wherein said foreign DNA of said segment includes an intact gene capable of expression in said host cells, and including the additional step of growing said isolated transformant cells in an appropriate medium, whereby said intact gene is expressed and protein produced.

5. A method for producing foreign RNA from biologically functional circular recombinant DNA molecules in transformed host cells, which comprises:

(1) preparing biologically functional circular recombinant DNA molecules by: joining first and second DNA linear segments, said first and second DNA segments having termini of a predetermined character at least in part complementary, at least one of, said first and second linear DNA segments having a gene for a phenotypical trait, said first DNA linear segment having an intact extrachromsomal replicon recognized by said host cells, and said second DNA linear segment having foreign DNA derived from a source which does not exchange genetic information with said host cells;

(2) transforming said host cells with said biologically functional recombinant DNA molecules;

(3) growing said host cells under appropriate nutrient conditions; and

(4) isolating said RNA containing transformant cells with said biologically functional recombinant DNA molecules by means of said phenotypical trait imparted by said biologically functional recombinant DNA molecules.

6. A method for replicating biologically functional circular recombinant DNA molecules in transformed host cells, which comprises:

(1) preparing biologically functional circular recombinant DNA molecules by: joining first and second DNa linear segments, said first and second DNA segments having termini of a predetermined character at least in part complementary, at least one of said first and second DNA linear segments having a gene for a phenotypical trait, said first DNA linear segment having an intact replicon recognized by said host cells from plasmid or viral DNA, and said second DNA linear segment having foreign DNA derived from a source which does not exchange genetic information with said host cells;

(2) transforming said host cells with said biologically functional recombinant DNA molecules;

(3) growing said host cells under appropriate nutrient conditions; and

(4) isolating said transformant cells with said biologically functional recombinant DNA molecules by means of said phenotypical trait imparted by said biologically functional recombinant DNA molecules.

7. A method according to claim **6**, wherein said host cells are unicellular organisms.

8. A method according to claim **6**, wherein said host cells are prokaryotic organisms.

9. As an article of manufacture, a cloned biologically functional circular recombinant DNA molecule capable of selection and replication in a host cell comprising: a first DNA segment containing an intact extrachromsomal replicon recognized by said host cell, said first segment being joined to a second DNA segment having foreign DNA derived from a source which does not exchange genetic information with said host cell.

10. An article of manufacture according to claim **9**, wherein said host cell is a unicellular organism.

11. An article of manufacture according to claim **9**, wherein said host cell is a prokaryotic organism.

12. As an article of manufacture, a cloned biologically functional circular recombinant DNA molecule capable of selection and replication in a host cell comprising: a first DNA segment containing an intact replicon recognized by said host cell from plasmid or viral DNA joined to a second DNA segment comprising a foreign gene capable of expression in said host cell wherein said foreign gene is derived from a source which does not exchange genetic information with said host cell.

13. An article of manufacture according to claim 12, wherein said host cell is a unicellular organism.

14. An article of manufacture according to claim 12, wherein said host cell is a prokaryotic organism.

15. An article of manufacture according to claims 12, 13, or 14, wherein said gene has as a phenotypical property expression of an enzyme.

16. As an article of manufacture, a cloned biologically functional circular recombinant DNA molecule capable of selection and replication in a host cell comprising: cloned copies of a first DNA segment containing an intact extrachromsomal replicon recognized by said host cell from a plasmid or viral DNA joined to a second DNA segment comprising a foreign gene capable of expression in said host cell, wherein said foreign gene is derived from a source which does not exchange genetic information with said host cell.

17. A transformant cell comprising a biologically functional circular recombinant DNA molecule capable of selection and replication in said cell, said DNA molecule comprising: a first DNA segment containing an intact extrachromsomal replicon recognized by said cell, said first segment being joined to a second DNA segment having foreign DNA, wherein said foreign DNA is derived from a source which does not exchange genetic information with said host cell.

18. A transformant cell according to claim 17, wherein said cell is a unicellular organism.

19. A transformant cell according to claim 17, wherein said cell is a prokaryotic organism.

20. A transformant cell comprising a biologically functional circular recombinant DNA molecule capable of selection and replication in said cell, said DNA molecule comprising: a first DNA segment containing an intact extrachromsomal replicon recognized by said cell from plasmid or viral DNA, said first segment being joined to a second DNA segment comprising a foreign gene capable of expression in said cell wherein said foreign gene is derived from a source which does not exchange genetic information with said host cell.

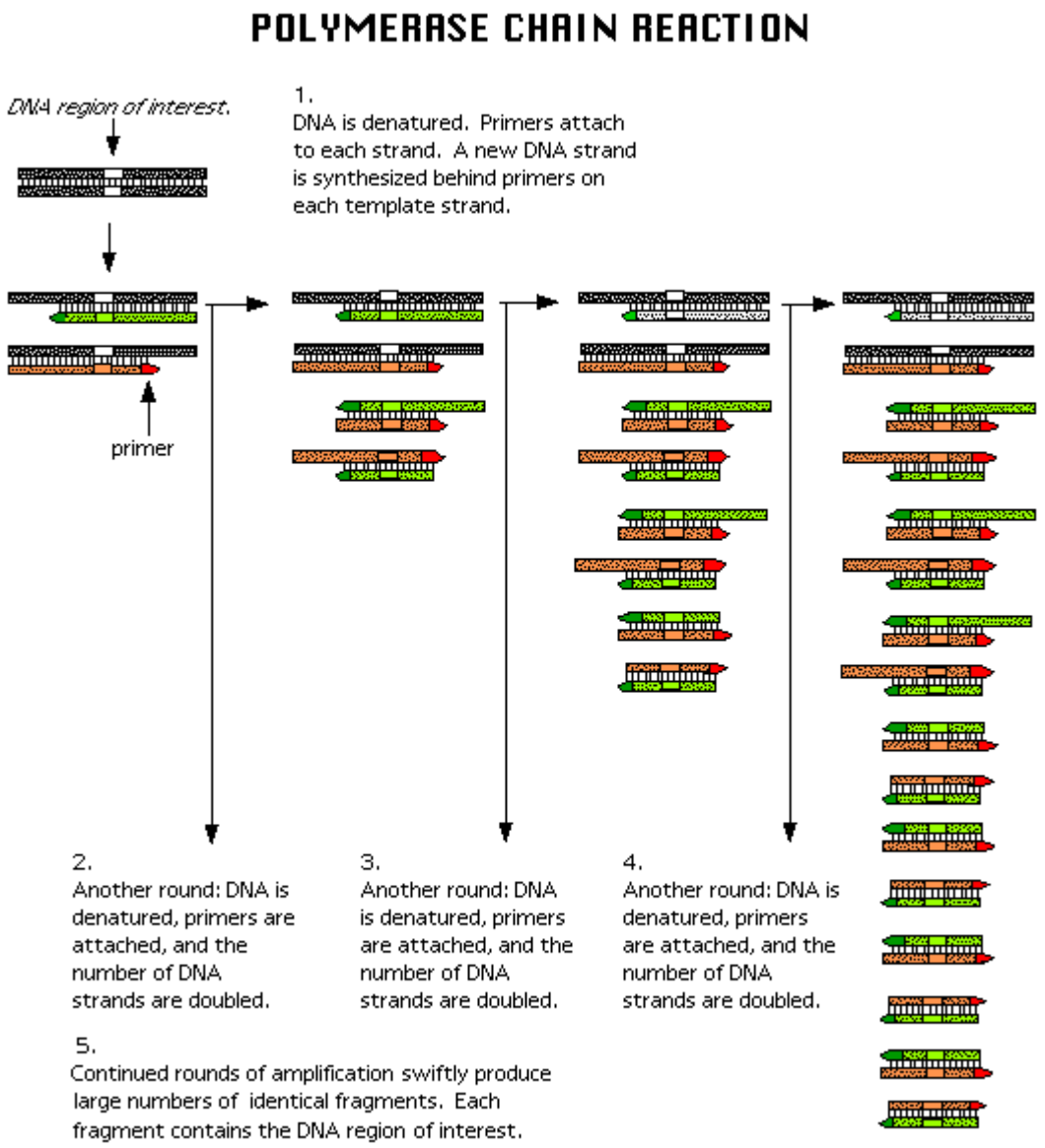
21. A transformant cell according to claim 20, wherein said cell is a unicellular organism.

22. A transformant cell according to claim 20, wherein said cell is a prokaryotic organism.

23. A transformant cell according to claims 20, 21, or 22 wherein said cell includes the expression product of said foreign gene.

* * * * *

Appendix 1.3: Polymerase Chain Reaction



http://www.accessexcellence.org/RC/VL/GG/polymerase.html

Appendix 1.4: Drug Screening

Extract from Dengue Digest, Volume 2, Number 1, April 2005

SpeedScreen

SpeedScreen is a new methodology developed at Novartis Pharma for HTS which identifies compounds that can bind to a particular protein target. The target molecule is first incubated with a mixed pool of compounds (or ligands), and then target-ligand complexes are separated from non-binders by chromatography (based on differences in mobility between smaller ligands and larger protein-ligand complexes). The target:ligand complex is then dissociated by chemical means, and the identity of the ligand is determined by mass spectroscopy (Figure 1).

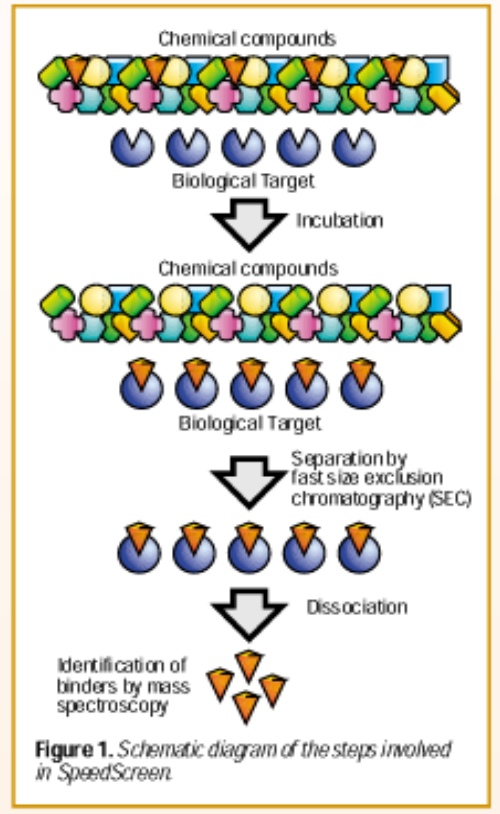


Figure 1. *Schematic diagram of the steps involved in SpeedScreen.*

The ligand is detected after electrospray ionization (ESI), ie. production of charged droplets of the charged ligand in solution and evaporation of solvent from these droplets, to determine its mass-to-charge (m/z) ratio for identification. This approach is currently among the most straightforward strategy for drug discovery on targets with unknown biological function (”orphan targets”) or targets that are incompatible for screening in the conventional HTS format (also known as “non-tractable targets”). In the case of Dengue virus, this method can be used to search for second site binders, ie. for compounds that bind outside of the catalytic site of the viral protease, polymerase or helicase but can still inhibit their enzymatic activities. of this method are the short assay development time of less than a day (neither the protein nor the compounds need to be labeled or modified in any way), the low protein consumption (several mg protein per 1’000’000 compounds), and the relatively short read-out and data processing times compared to other technologies.

Virtual Screening in Lead Discovery

Structure-based virtual screening (VS) of compound libraries has become an established method for drug discovery. This method uses computational exploitation or modelling to “dock” molecules into experimentally determined three-dimensional protein structures of targets which have been obtained by x-ray crystallography. For example in the case of the dengue NS3 protease for which the crystal structure is available, compounds can be assessed to see if they bind into the catalytic pocket of the enzyme using available docking software. Such molecular docking algorithms attempt to generate and identify the most complementary match between a compound and its target NS3 protease. The speed at which a virtual screen can be completed makes it effective at jump-starting a project for which there are few or no compelling leads. Additionally, it is highly cost effective since it is not manpower-intensive, and circumvents the need for robotics, reagent acquisition or production, or compound storage facilities. Virtual collections of proprietary, commercially available, and synthetically accessible molecules can be evaluated for potential binders. For this technology to be truly valuable it is imperative that a variety of in vitro and in vivo assays are available for testing the hits. We also work with Prof Torsten Schwede from the Biozentrum at University of Basel who has selected Dengue for extensive in silco docking studies to address neglected diseases.

Fragment Based Screening

Fragment-based screening is aimed at evolving a new tight binder based on a step-by-step chemical reconstruction approach and is different from HTS where this step is leap-frogged by screening full-size ligands. Compounds with typically a molecular weight of less than 250 Da are screened, and hits are expanded in a second step (see Figure 2). Even though the small compounds at best only bind with moderate affinity, if the interaction with the target protein is specific and understood (preferably on the basis of a three-dimensional structure of the complex obtained by NMR or crystallography), high affinity can be achieved by building up a ligand from the initial fragment hits by chemical modification or using a combination of different binders. In this step, either an individual fragment is expanded to fill empty pockets, or two or more fragments are combined by linking (see Figure 2) or merging of chemical features. This chemical work-up is an integral part of the fragment-based approach to lead finding. The technique is so powerful it is envisioned that fragment-based screening as well as HTS will be applied for drug screening, and that their complementary features will be combined and further integrated with virtual screening, and all together expand the tool box for finding leads against targets of a variety of therapeutic areas, including dengue disease!

Figure 2. *Schematic representation of fragment-based screening. A small library (< 10^3) of compounds (< 250 Da) is screened for binding (0.05-1 mM) to sub-pockets of a protein target. The hits are chemically expanded to fill out the pocket and gain high affinity.*

GLOSSARY OF SCIENTIFIC TERMS

Animal model
A non-human animal with a disease or injury that is similar to a human condition. These test conditions are often termed as animal models of disease. The use of animal models allows researchers to investigate disease states in ways which would be inaccessible in a human patient, performing procedures on the non-human animal that imply a level of harm that would not be considered ethical to inflict on a human.

Antibody
A Y-shaped protein on the surface of B cells that is secreted into the blood or lymph in response to an antigenic stimulus, such as a bacterium, virus, parasite, or transplanted organ, and that neutralizes the antigen by binding specifically to it.

Antibody, monoclonal
Monoclonal antibodies are proteins produced in the laboratory from a single clone of a B cell, the type of cells of the immune system that make antibodies. All monoclonal antibodies of a particular type bind to the same antigen, which distinguishes them from polyclonal antibodies.

Antigen
A substance that, when introduced into the body, stimulates the production of an antibody. Antigens include toxins, bacteria, foreign blood cells, and the cells of transplanted organs.

Antisense molecules
Conventional medicines bind directly with disease-causing protein molecules, but their imperfect specificity may lead them to bind with other protein molecules, resulting in unwanted side effects. Antisense molecules are extremely specific. Antisense techniques are used to deactivate disease-causing or undesirable genes so that they cannot produce harmful or unwanted proteins. Antisense has been used in medicine, especially in cancer and antiviral therapy; and in agriculture, for example, to deactivate the gene that causes softening in tomatoes.

Assay, biological (bioassay)

A bioassay determines the strength or biological activity of a substance such as a pharmaceutical or hormone, by comparing its effects with those of a standard preparation on a test organism. Bioassays may be qualitative or quantitative, the latter often involving an estimation of the concentration or potency of a substance by measurement of the biological response that it produces.

Bacterium (bacterial)
A single-celled or non-cellular spherical or spiral or rod-shaped organism lacking chlorophyll that reproduces by fission. Bacteria are found almost everywhere, being

abundant, for example, in soil, water, and the alimentary tracts of animals. Each kind of bacterium is fitted physiologically to survive in one of the innumerable habitats created by various combinations of space, food, moisture, light, air, temperature, inhibitory substances, and accompanying organisms. Dried but often still living bacteria can be carried into the air. Bacteria have a practical significance for humans. Some cause disease in humans and domestic animals, thereby affecting health and the economy. Some bacteria are useful in industry, while others, particularly in the food, petroleum, and textile industries, are harmful. Some bacteria improve soil fertility.

Base pair
One of the pairs of chemical bases joined by hydrogen bonds that connect the complementary strands of a DNA molecule or of an RNA molecule that has two strands; the base pairs are adenine with thymine and guanine with cytosine in DNA and adenine with uracil and guanine with cytosine in RNA.

Cell
The smallest structural unit of an organism that is capable of independent functioning, consisting of one or more nuclei, cytoplasm, and various organelles, all surrounded by a semi-permeable cell membrane. A cell line is cells grown in tissue culture and representing generations of a primary culture.

Cell, lymphoid
A lymphoid cell is a cell derived from stem cells of the lymphoid lineage. It is a type of white blood cell. Lymphocytes have a number of roles in the immune system, including the production of antibodies and other substances that fight infection and diseases. The lymphatic system is a system of thin tubes that runs throughout the body.

Cell, myeloma
A cancerous cell that arises in the bone marrow and involves plasma cells, a type of white blood cell that produces proteins called immunoglobulins.

Cell, hybridoma
A cell that is produced in the laboratory from the fusion of an antibody-producing lymphocyte and a non-antibody-producing cancer cell, usually a myeloma or lymphoma. It proliferates and produces a continuous supply of a specific monoclonal antibody.

Cell, melanoma
A dark-pigmented, usually malignant, tumour arising from a melanocyte and occurring most commonly in the skin

Chromatography
A physical separation method in which the components of a mixture are separated by differences in their distribution between two phases, one of which is stationary while the other moves through it in a definite direction. The substances must interact with the stationary phase to be retained and separated by it.

Chromosome
A threadlike linear strand of DNA and associated proteins in the nucleus of eukaryotic cells that carries the genes and functions in the transmission of hereditary information. Chromosomes are found in all organisms with a cell nucleus (eukaryotes) and are located within the nucleus.

Clone
A cell, group of cells, or an organism that is descended from and genetically identical to a single common ancestor, such as a bacterial colony whose members arose from a single original cell. A DNA sequence, such as a gene, that is transferred from one organism to another and replicated by genetic engineering techniques.

Combinatorial (matrix) chemistry
A method in which very large numbers of chemical entities are synthesized by condensing a small number of reagents together in all combinations defined by a small set of reactions. The main objective of combinatorial chemistry is synthesis of arrays of chemical or biological compounds called libraries. These libraries are screened to identify useful components, such as drug candidates.

DNA
Discovered in the late-1800s, DNA is a nucleic acid that carries the genetic information in the cell and is capable of self-replication and synthesis of RNA. DNA consists of two long chains of nucleotides twisted into a double helix and joined by hydrogen bonds between the complementary bases adenine and thymine or cytosine and guanine. The sequence of nucleotides determines individual hereditary characteristics. The other type of nucleic acid is RNA.

rDNA (recombinant DNA)
Recombinant DNA refers to a collection of techniques for creating (and analysing) DNA molecules that contain DNA from two unrelated organisms. One of the DNA molecules is typically a bacterial or viral DNA that is capable of accepting another DNA molecule – this is called a vector DNA. The other DNA molecule is from an organism of interest, which could be anything from a bacterium to a whale, or a human. Combining these two DNA molecules allows for the replication of many copies of a specific DNA. These copies of DNA can be studied in detail, used to produce valuable proteins, or used for gene therapy or other applications.

Enzyme
Enzymes are biological catalysts, or chemicals that speed up the rate of reaction between substances without themselves being consumed in the reaction. As such, they are vital to such bodily functions as digestion, and they make possible processes that normally could not occur except at temperatures so high they would threaten the well-being of the body.

Erythropoietin
A hormone that stimulates the production of red blood cells by stem cells in bone marrow. It is produced mainly by the kidneys and is released in response to decreased

levels of oxygen in body tissue. Synthetic erythropoietin has been used to increase the red blood cell count in patients who are anaemic before they have surgery. This can decrease the risk of needing blood transfusions.

Escherichia coli
This one of several types of bacteria that normally inhabit the intestine of humans and animals. Some strains of E. coli are capable of causing disease under certain conditions when the immune system is compromised or disease may result from an environmental exposure. Other strains have been used experimentally in molecular biology.

Eukaryotic (eukaryote)
This describes an organism that has cells containing nuclei. A prokaryote (a bacterium) is any cellular organism that lacks a distinct nucleus. Many prokaryotes also contain additional circular DNA molecules called plasmids.

Expressed sequence tag (EST)
An expressed sequence tag is a short sub-sequence of a transcribed spliced nucleotide sequence (either protein-coding or not). ESTs are intended as a way to identify gene transcripts, and are instrumental in gene discovery and gene sequence determination. The identification of ESTs has proceeded rapidly, with approximately 42 million ESTs now available in public databases.

Gene, gene expression
An hereditary unit consisting of a sequence of DNA that occupies a specific location on a chromosome and determines a particular characteristic in an organism. Genes undergo mutation when their DNA sequence changes. Gene expression is the process by which a gene's DNA sequence is converted into the functional proteins of the cell. Non-protein coding genes (e.g. rRNA genes, tRNA genes) are not translated into protein.

Fluorogenic
A non-fluorescent material that is acted upon by an enzyme to produce a fluorescent compound

Genome, genome map
A genome is the complete collection of hereditary information for an individual organism. In cellular life forms, the hereditary information exists as DNA. A genome map helps scientists navigate around the genome. Like road maps and other familiar maps, a genome map is a set of landmarks that tells people where they are, and helps them get where they want to go. The landmarks on a genome map might include short DNA sequences, regulatory sites that turn genes on and off, and genes themselves. Often, genome maps are used to help scientists find new genes. A genome map looks like a straight line with landmarks noted at irregular intervals along it, much like the towns along the map of a highway. The landmarks are usually inscrutable combinations of letters and numbers that stand for genes or other features—for example, D14S72, GATA-P7042, and so on.

Genomics
The study of all of the nucleotide sequences, including structural genes, regulatory sequences, and non-coding DNA segments, in the chromosomes of an organism.

Growth factor
A substance that affects the growth of a cell or an organism

HTS (high-throughput screening)
This is an automated method for rapidly analysing the activity of thousands of chemical compounds. It has become a key tool in modern pharmaceuticals discovery. Paired with combinatorial chemistry and bioinformatics, HTS allows potential pharmaceuticals to be quickly and efficiently screened to find candidates that should be explored in more detail.

Immunohistochemistry (IHC)
This is a method of analysing and identifying cell types based on the binding of antibodies to specific components of the cell.

Immunocytochemistry
This relates to chemicals interacting with immune responses of cells within the host. It involves the use of antibodies that recognise parts of the receptor that are exposed to the outside environment when expressed at the cell surface.

In vitro, *in vivo*
In vitro means literally "in glass" (laboratory experiments are often carried out in glass containers). In vitro conditions are distinguished from conditions that actually apply in nature. In vivo takes place inside an organism.

In silico
This means "performed on computer or via computer simulation".

Insulin
Insulin is a hormone that regulates the amount of glucose (sugar) in the blood and is required for the body to function normally. Insulin is produced by cells in the pancreas, called the islets of Langerhans. These cells continuously release a small amount of insulin into the body, but they release surges of the hormone in response to a rise in the blood glucose level.

Interferon
Interferons are proteins called cytokines produced by white blood cells, fibroblasts, or T-cells as part of an immune response to a viral infection or other immune trigger. The name of the proteins comes from their ability to interfere with the production of new virus particles.

Metabolism (metabolic)
Metabolism refers to all of the chemical reactions by which complex molecules taken into an organism are broken down to produce energy and by which energy is used to build up complex molecules.

Micro array
A semiconductor device that is used to detect the DNA makeup of a human cell. Micro arrays are revolutionising medicine by being able to pinpoint a very specific disease or the susceptibility to it.

Mimotope
A mimotope is a macromolecule, often a peptide, which mimics the structure of an epitope. Because of this property it causes an antibody response identical to the one elicited by the epitope. An antibody for a given epitope antigen will recognise a mimotope which mimics that epitope. A peptide is an organic compound composed of amino acids linked together chemically by peptide bonds. An epitope is a localised region on the surface of an antigen that is capable of eliciting an immune response and of combining with a specific antibody to counter that response.

Molecule
A molecule is the smallest particle of a substance that retains the chemical and physical properties of the substance and is composed of two or more atoms. It is a group of like or different atoms held together by chemical forces. A compound, on the other hand, is a substance made up of more than one type of atom – in other words, more than one type of element.

Nucleotide
Nucleotides are the building blocks of DNA and RNA. Individual nucleotide monomers (single units) are linked together to form polymers, or long chains. DNA chains store genetic information, while RNA chains perform a variety of roles integral to protein synthesis. Individual nucleotides also play important roles in cell metabolism.

Peptide

An organic compound composed of a series of amino acids linked by peptide bonds between a carbon atom of one and a nitrogen atom of the next. Peptide chains longer than a few dozen amino acids are called proteins. Many hormones, antibiotics, and other compounds that participate in life processes are peptides.

Phage (bacteriophage)
A virus which uses a bacterium to produce more phage until the bacterium is destroyed and phage is released to invade surrounding bacteria. Discovered in the early 20th century, bacteriophages were used unsuccessfully to treat human bacterial diseases such as bubonic plague and cholera. Bacteriophages were abandoned with the advent of antibiotics in the 1940s. The rise of drug-resistant bacteria in the 1990s focused renewed

attention on the therapeutic potential of bacteriophages. Thousands of varieties exist, each of which may infect only one or a few types of bacteria.

Plasmid (cloning) vector
Plasmid vectors are small circular molecules of double stranded DNA derived from natural plasmids that occur in bacterial cells. A plasmid cloning vector is a plasmid that accepts foreign DNA and is therefore used in recombinant DNA experiments. A plasmid is a circular, double-stranded unit of DNA that replicates within a cell independently of the chromosomal DNA. Plasmids are most often found in bacteria and are used in recombinant DNA research to transfer genes between cells. They similar to viruses but lack a protein coat and cannot move from cell to cell in the same fashion as a virus.

Polymerase
A polymerase is an enzyme whose central function is associated with polymers of nucleic acids such as RNA and DNA.

Polymerase chain reaction
A technique for amplifying DNA sequences *in vitro*. It can amplify a specific sequence of DNA by as many as one billion times and is important in biotechnology, forensics, medicine, and genetic research.

Protein
Proteins are fundamental components of all living cells and include many substances, such as enzymes, hormones, and antibodies that are necessary for the proper functioning of an organism. They are essential in the diet of animals for the growth and repair of tissue and can be obtained from foods such as meat, fish, eggs, milk, and legumes.

Proteomics
This involves the identification of proteins in the body and the determination of their role in physiological and pathophysiological functions. It is the systematic study of all of the proteins in a cell, tissue, or organism.

RNA
One of the two main types of nucleic acid (the other being DNA), which functions in cellular protein synthesis in all living cells and replaces DNA as the carrier of genetic information in some viruses. Like DNA, it consists of strands of repeating nucleotides joined in chainlike fashion, but the strands are single (except in certain viruses), and it has the nucleotide uracil (U) where DNA has thymine (T).

RNAi (RNA interference)
RNA interference is a process in which translation of some of a cell's messenger RNA (mRNA) sequences is prevented. RNA interference is believed to protect the cell against viruses and other threats. “Interference” refers to the interruption of the cell's translation of its own mRNA. RNA interference is also called posttranscriptional gene silencing, since its effect on gene expression occurs after the creation of the mRNA during transcription.

mRNA (messenger RNA)
Messenger RNA, a single strand copied from a DNA strand that acts as its template, carries the message of the genetic code from DNA (in chromosomes) to the site of protein synthesis (on ribosomes).

Reagent
A substance used in a chemical reaction to detect, measure, examine, or produce other substances. The word also describes chemical substances of sufficient purity for use in chemical analysis, chemical reactions or physical testing.

Receptor
A molecular structure or site on the surface or interior of a cell that binds with substances such as hormones, antigens, pharmaceuticals or neurotransmitters. A specialised cell or group of nerve endings that responds to sensory stimuli. The discovery of a new cell receptor that controls physiological events in the human body or the animal body may lead to the use of the receptor as a therapeutic agent. The receptor also may result in the future discovery of compounds such as hormones that activate the receptor or that inhibit the receptor. Future discoveries may be made when the new receptor is used as a screening reagent in assays to identify and purify previously unknown hormones.

Recombinase
An enzyme that catalyses the exchange of short pieces of DNA between two long DNA strands, particularly the exchange of homologous regions between the paired maternal and paternal chromosomes.

Screening
The process of finding a new molecule or substance against a chosen target for a particular disease usually involves high-throughput screening (HTS), wherein large libraries of chemicals are tested for their ability to modify the target. While HTS is a commonly used method for discovering new pharmaceuticals, it is not the only method. It is often possible to start from a molecule which already has some of the desired properties. Such a molecule might be extracted from a natural product or even be a drug on the market which could be improved upon. Other methods, such as virtual high throughput screening, where screening is done using computer-generated models and attempting to “dock” virtual libraries to a target, are also often used.

Sequence analysis
Sequence analysis encompasses the use of various bioinformatic methods to determine the biological function and/or structure of genes and the proteins they code for.

Target
Pharmaceutical companies working on the discovery and development of small molecule therapeutics distinguish between new targets and established targets. “Established targets” are those for which there is a good scientific understanding, supported by a lengthy publication history, of both how the target functions in normal physiology and

how it is involved in human pathology. “New targets” are all those targets that are not “established targets” but which have been or are the subject of pharmaceutical research. These typically include newly discovered proteins, or proteins whose function has now become clear as a result of basic scientific research.

Tissue plasminogen activator
A clot-dissolving enzyme that is produced naturally by cells in the walls of blood vessels and catalyses the conversion of plasminogen to plasmin. This enzyme is also produced by genetic engineering and used to dissolve clots blocking coronary arteries in heart attack and cranial arteries in certain cases of stroke.

Transcription
The process by which messenger RNA is synthesised from a DNA template resulting in the transfer of genetic information from the DNA molecule to the messenger RNA

Transgenic mouse
A transgenic mouse is a mouse whose genome has been altered by the transfer of a gene or genes from another species or breed. Transgenic mice have become models for studying human diseases and their treatments. They allow researchers to observe experimentally what happens to an entire organism during the progression of a disease.

Virus
A virus is a parasite that must infect a living cell to reproduce. Viruses are distinguished from free-living microbes, such as bacteria and fungi, by their small size and relatively simple structures. Although viruses share several features with living organisms, such as the presence of genetic material (DNA or RNA), they are not considered to be alive. Many illnesses in humans, including AIDS, influenza, Ebola fever, the common cold, and certain cancers, are caused by viruses. Viruses also exist that infect animals, plants, bacteria, and fungi.

Western blot test
A Western blot (or immunoblot) is a method to detect viral or other antibodies in a sample of serum or other body fluid by their reaction with target antigens that have been immobilised onto a membrane by blotting. It is usually used to confirm a positive result obtained with a screening test.