Europäisches Patentamt
European Patent Office
Office européen des brevets

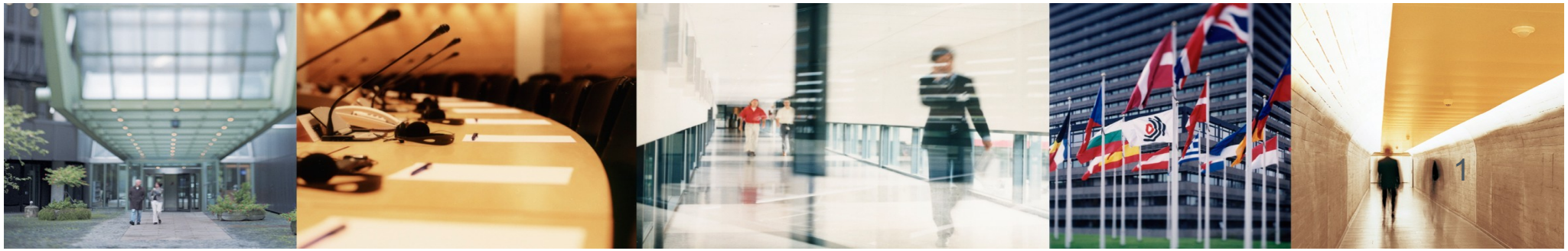
THE FUTURE OF THE PATENT SYSTEM IN EUROPE:

NOSTALGIA IS NOT A GOOD ADVISER

EPIP Conference, Lund

Alison Brimelow
President of the EPO

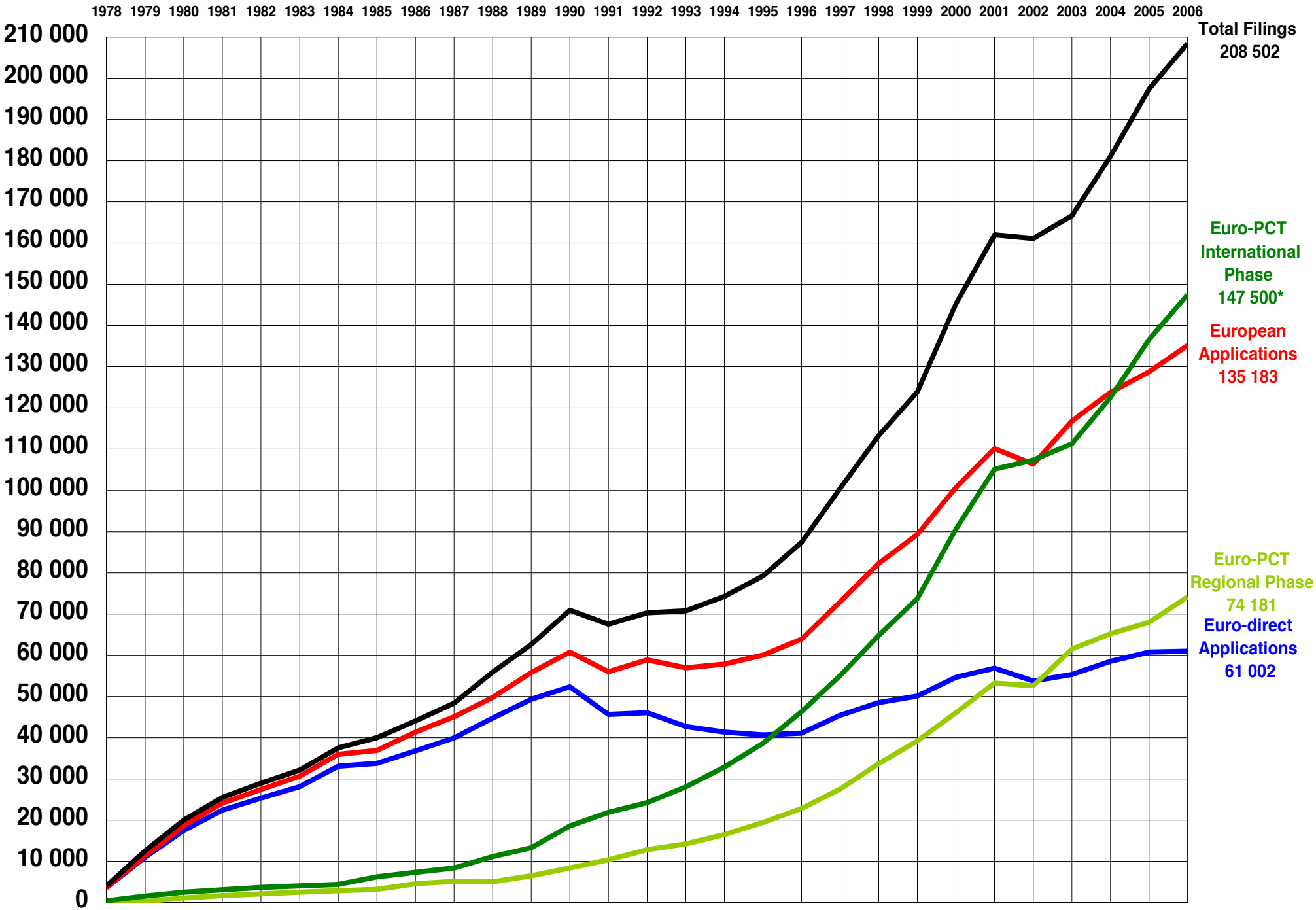
September, 2007, Lund



Italian Presidency / European Commission Conference 2003 "IP Quo Vadis?"

- "Business as usual"
- "If only they understood"
- "We may have a problem here"

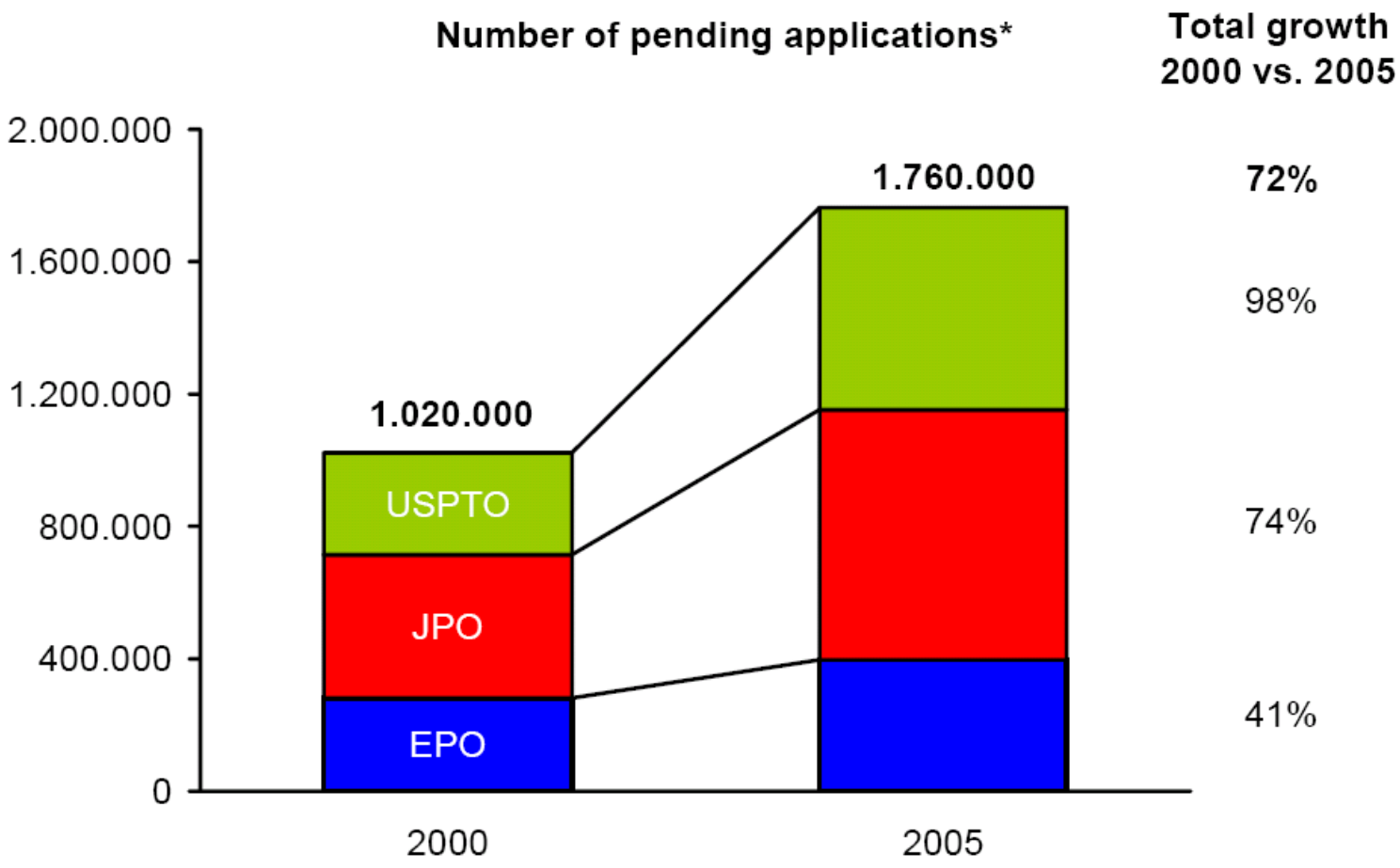
European filings



- **Globally, patent systems face a boom in filings…**
  - Globalization of markets,
  - Harmonization of patent systems (PCT,…)
  - New and dynamic countries in the arena (BRICS)
  - New technologies (Bio, nano…)
  - New actors (SMEs, universities)
  - New management of R&D: open innovation
  - New strategies (portfolio, thickets, flooding, standards…)
  - Active promotion of patenting by governments e.g. Japan

- **Growth much stronger than growth in R&D**

Increase in backlogs = increase in uncertainty + scope for new games

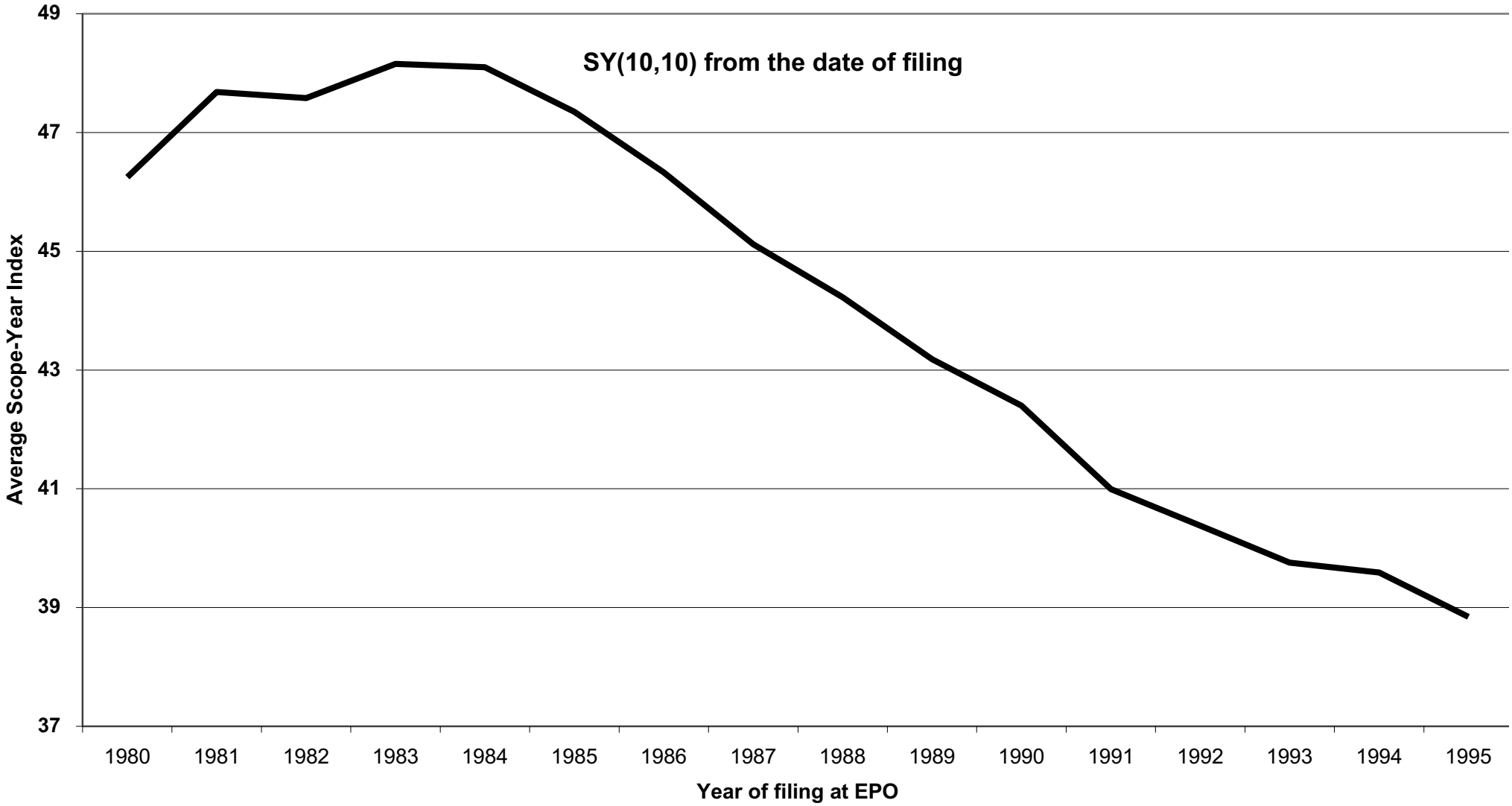


*in search and examination, excluding applications awaiting request for examination
Note: Figures are rounded
Source: Trilateral Statistical Reports (EPO & JPO figures), USPTO Annual Report 2006 (USPTO FY figures)

Audi’s recent A6 ad campaign claimed:

« To date NASA has filed 6,509 patents. In developing the A6, Audi filed 9,621 ». Patenting is identified as a proof of innovation...

The Scope-Year index...
The average value of EP patents has decreased by 9 SY



Source: van Pottelsberghe and van Zeebroeck (2008)

And EPO performance has some weak points

- Productivity ↓
- Unit costs ↑
- 2005 and 2006 results - € 70 m

On the other hand...

EPO strategic debate

- European office strong centre = focus on core business
- Developing role of National Offices in a changing world
- Engaging with how to utilise

Strategic Renewal

- Raising the bar
- The future of work and working
- Managing Performance
- The European Patent Network
- E2E
- Governance

Scenarios - thinking about "what if" globally -

and here are some ways forward.

Challenge	Operational Tools	Most relevant Scenario(s)
Costs	London Agreement	
	EPLA/Community Patent	
	EPN/Trilateral/3+3 (re-use of work)	
	Procedural Efficiency	
	Financial IP-support for SMEs	

Challenge	Operational Tools	Most relevant Scenario(s)
Quality Workload	• Fee Policy (Shift to Upfront)	
	• Fee Policy (Fees as a function of examination time)	
	• Restrict possibility for divisionals	
	• EPN	
	• Applicant Training	
	• Trilateral	
	• 3+3	
	• Peer Review (peer-to-patent)	
	• Publication of reasoned votum for grant	

Challenge	Operational Tools	Most relevant Scenario(s)
Quality Workload (continued)	• Request for examination by third parties (+ deferred examination)	
	• Credit for Refusals	
	• Efficient procedures	
	• Increased threshold for inventive step/sufficiency of disclosure/clarity	
	• Quality control (internal/external audits	

Challenge	Operational Tools	Most relevant Scenario(s)
Blockage	• Consistent high quality	
	• Reduced scope of rights (e.g. patent term, limits to injunctions, compulsory licensing, license of right)	
	• Fixation of patent rights to the extent of usage by patentee	
	• Broadening of exclusions from patentability	

Challenge	Operational Tools	Most relevant Scenario(s)
Ethical, political debate	• Regular dialogue with all stakeholders	
	• Advisory boards	
	• Involvement of national and EU parliaments	
	• Intensive contact with international bodies (WHO, WIPO, WTO)	
	• Contact with competition and standard governing bodies	

EPC @ 30

Time to abandon nostalgia and deliver some change

The European Community Patent - A Realisable Dream

The Vice-President of the European Commission, Günter Verheuegen, stated at the European Patent Forum in Munich in April 2007 that "an incomplete European patent system puts European businesses at a competitive disadvantage" and that he expected the Community Patent to become reality “in the next five years”.

It is unfortunate that many others do not see the Community Patent as realisable, due to the well known translation and jurisdictional problems. They are instead focusing efforts on patent litigation systems such as the European Patent Litigation Agreement (EPLA) and on the London Agreement on translations as partial solutions to the problems.

Speaking at the European Patent Forum in Munich in April 2007, Hans-Ulrich Maerki, IBM's EMEA Chairman, pointed to the increasing importance of collaborative innovation and stressed the need for a balance between open and proprietary development based on standards. Leading on from this, he emphasised that we need intellectual property protection that serves both open and proprietary innovation. Society stands to benefit from both these models.

At the same event, the European Patent Office (EPO) announced the Scenarios projects and one of the four, the Blue Skies scenario, presented a novel idea for the future of IP. A break-out session followed and one of the suggestions was that a new form of IP is required. . “Soft IP” was the name given to this new form of IP.

Soft IP is a system that enables efficient capture and protection of IP, with provision for making licenses available to all interested parties. This is particularly applicable to patents. This scenario acknowledged the value of IP in a licensing context, the need for balance between uses of IP in various industries and development models and the fact that the value of a patent does not always reflect the value of the invention but more the cost of being unable to continue using the invention when an injunction is given. While the injunction based leverage available from a patent is perfectly appropriate in some contexts (e.g., pharmaceuticals), it may not be appropriate or fair in other contexts such as standards and interoperability in industries with significant network effects.

The Soft IP approach would be particularly attractive in situations involving the so-called honest concurrent user (to borrow the trademark term) of the invention. Such people are, of course “innocent” infringers. Innocent infringers have not engaged in any nefarious or unprincipled behaviour but need to use patented invention(s), for example, inventions essential for software interoperability, essential for Internet use, for telecommunication projects where interoperability is a must-have, or for Open Source projects.

Patent law already recognises the concept of the “innocent infringer - one who did not know of the patent or could not reasonably be expected to have known of the patent. The "Soft IP" concept would extend the notion of the innocent infringer. One context within which this has been discussed is the European Community Patent where the cost of the patent would be prohibitive if translation into all the languages of the European Community were required, and yet those potential infringers in countries not using the language of filing of the patent application will be vulnerable to being an innocent infringer simply because the patent is not in their own language.

The European Community Patent would be a valuable right with wide geographic spread; covering the whole of the Community of 27 countries (with more to join). The long term problem to implementing the European Patent has been languages, with translations being required of the whole specification or the claims (or both) into all the languages of the Community, thereby making the cost prohibitive and legal scope uncertain. Proposals have been made for a single or three language solution to solve the cost problem for applicants; however, as indicated above, infringers are vulnerable if they cannot understand the language of the patent.

Under the Soft IP proposal, the Community Patent route would be optional, and the alternative European (bundle of national patents) and National routes to patents would remain. The

language of these granted national patents would remain as now, subject to the London Agreement on translations when it comes into force.

The opportunity, therefore, is to provide an alternative patent system. The Community Patent system would be a different route to those presently available - a new system in addition to the existing systems.

The Community Patent would not be translated into all the Community languages but would in be in the language of filing with the EPO **and** it would be automatically endorsed Licenses of Right.

The License of Right endorsement means that injunctions to stop infringement would not be available. Instead the patent owner would acknowledge that some form of compensation for infringement would be acceptable - the compensation could be monetary with perhaps a cross license being taken into account if appropriate. The fact that Licenses of Right are available greatly assists innocent infringers since they would be assured of obtaining a license, and would not be faced with the prospect of their business being disrupted or closed down.

As with the existing License of Right systems in the UK, and Germany, if parties cannot agree on terms, terms would be decided by the courts. The court system currently proposed for the Community Patent would be perfectly capable of dealing with the Licenses of Right requests in addition to handling normal infringement and validity questions.

An important consideration, as indicated above, is that the proposed Community Patent would be an optional system and an additional system, therefore full cost national patents obtained directly or through the EPO would still be available.

The proposal would require that the applicant for the patent applies via the EPO in an official language as at present. On grant, the applicant would choose whether it wants a Community Patent automatically endorsed Licenses of Right or whether it wants to use the existing routes to national patents.

The Community Patent would not need to be translated and renewal fees would be payable to a single body, whereas the national patents would still need to be translated, the translations filed with national patent offices and renewal fees paid to the national offices. If national patents are selected, injunctions would be available before national courts.

An advantage of the proposal is that it removes vulnerability of innocent infringers to injunctions because there is a certainty that licenses will be available. In the case of disputes over license terms, the terms and royalty would be settled by the courts under reasonable and non-discriminatory terms.

Another advantage is that, because it is an optional system and leaves the existing system in place, there is no disruption to existing businesses, and valuable business models such as those for the pharmaceutical industry would not be adversely affected.

It might be expected that new business models would be developed to take advantage of the "reward" based system of the Community Patent. In effect the patent would be a Non-exclusionary Community Patent, open for all in the community to be able to obtain a license – it would thus be a true community patent.

Perhaps there could be other advantages for the Non-exclusionary Community Patent with standards bodies or similar bodies directing technology adoption to those inventions covered by the Community Patent where Licenses of Right are therefore available.

National patent offices and national patent attorneys would play an important role in providing the infringement and validity opinions essential for the potential infringers. National patent offices would have the advantage of their close working relationship with the EPO giving them access to information and examiner resources with the required language skills, where necessary, to assist with preparation of the opinions. It would be hoped that the national patent offices would provide low cost high quality infringement and validity opinions such as those currently available from the UK Intellectual Property Office.

There are serious concerns that EPLA as currently proposed will be favourable to patent trolls on the one hand and a poor forum for consideration of highly valuable patents on the other. The USA Supreme Court in the eBay case reduced the power of trolls by introducing the discretion for courts not to grant injunctions if the equity of the situation indicates otherwise - in Europe, there would be no such protection against trolls under EPLA. Rather than pursue an unsatisfactory EPLA, efforts should be put into the Community Patent of the type proposed under a Soft IP regime and keep the current EPO/national system as an option.

National states should perceive the Community Patent proposal as less of an attack on the sovereignty of their courts; it reduces the Community Patent Court to a more administrative and technical tribunal role (along the lines of the EPO Boards of Appeal) because it can only decide validity, infringement and license terms. National courts could be asked to grant a prohibition on use of the patented invention if the infringer failed to pay under the agreed terms of the license. Most importantly, injunctions are left to national courts alone and directed to those patent owners that really need injunctions and are willing to use the current patent system for the privilege.

EPIP 2007
The Future of the patent system in Europe
Contribution by Gun Hellsvik

With my background from the Swedish Patent Office I will use my time to share with you some of the thoughts from my office concerning the development of the national patent offices and their relationship with EPO.

Patents are, of course, legal instruments, but the patent system as such is intended as a means of stimulating innovation and economical growth. We have together with the other Nordic countries made a study that confirms this by providing clear evidence of a direct correlation between the level of innovation of a country and good national framework conditions for patenting. It also underpins that the national patent offices are an important part of these national framework conditions.

NPO´s fulfil their role in two different ways. The role that traditionally has attracted most attention is that of providing an efficient patent protection system and patent granting procedure (the statutory role).

There is, however, an increasing awareness of the fact that the patent system cannot merely be seen as a legal instrument. It must be seen also as an instrument for stimulating and enhancing innovation, and a national patent office must therefore be seen in a broader perspective, too, that is as being part of the national infrastructure for innovation.

Hence, a national patent office must also take care of a number of additional tasks (the non-statutory role) including
-Acting as national competence centre for IP matters, being accessible and communicative to the public
-Promoting understanding of all aspects of IP, including business and management related aspects
-Being active in improving general and specialist IP knowledge in society and among companies, research institutions etc
-Providing assistance in getting access to information contained in patent literature
-Taking part in national policy making within the innovation field.

In formal, analytical terms, the two roles of the NPO´s are distinct and serve different purposes. In practical terms, however, they are closely interrelated and require a number of similar fundamental competencies and skills.

It takes a great deal of expertise and experience to make sensible use of the patent system, in particular at an international level. Different users have different needs and competencies in this respect, and this is also reflected in their different needs for a national patent office.

For big companies (in the Nordic countries, at least), the situation generally is as follows
-They have a deep knowledge of the patent system, and they are capable of making their own competent assessment of the patentability of an invention before spending money on patents
-They draw up their first filings in English anywy, since they need global protection, and they may therefore use an international patenting route right away

-A number of reasons often make big companies prefer another patent office than their national office, for exampel specific patent legislation in certain countries like the US or the quality level of a specific office.

Many small and medium sized enterprises, however, prefer or even need to start by consulting their national patent office for a number reasons
-They have no knowledge of prior art and are not capable of making their own searches and assessments prior to filing a patent application
-Their financial situation is very fragile and they must keep costs at a minimum until they have some certainty of the prospects of their invention. A positive report from their national patent office may be a precondition for getting financial backing
-They cannot afford a patent agent, and in a number of countries, SME´s are not in command of any of the official EPO languages; they therefore need assistance and advice from their national office
-Some of them may not even want or need international patent protection.

Speaking in somewhat general terms, therefore, SME´s have a pressing need for national patent authorities for statutory as well as non-statutory tasks. They also need a PCT authority within their region, in particular due to language problems and communication issues in general. Big companies might find national offices convenient and even useful, but only if quality and efficiency is at an absolute top level and competitive with the EPO quality.

Quality and efficiency depends on a number of parameters, including the competence of the examiners, the search tools available to the examiners, and the quality assurance system. Even the size of the staff is of significance, since a high number of specialists will allow for a higher degree of specialisation than a small number.

Patent acitivy on a global level has been increasing for many years, and there is every reason to believe that this trend will continue in the foreseeable future. The patent activity of Nordic companies is also increasing.

It has furthermore been shown that SME´s are likely to play an increasingly important role in innovation in the Nordic countries in the future, and that the proportion of patents granted to SME´s can be expected to increase in the future.

Despite the global development in patent activity, however, there is a decrease or stagnation in workload at national patent offices. This may soon make it difficult in particular for the smaller offices to maintain quality and efficiency of work since this reguires a certain minimum amount (critical mass) of examiners(which means workload). This will have an impact on statutory as well as non-statutory work. It may even be difficult in the long run to maintain a national PCT authority.

As I already mentioned, there is a clear correlation between innovation and good framework conditions for patenting. Since NPO´s are an essential part of these framework conditions, and since SME´s in particular need qualified national patent offices, the situation calls for action.

Between EPO-memberstates a discussion related to this development started a few years ago and resulted in a joint statement accepted by the Administrativ Council. Today preparation for a network between the national offices and EPO is under its way. The principles that guide the work are

1. EPO´s specific role as the sole European Authority for granting European Patents must be maintained and reinforced. However, the delegations were concerned about EPO´s financil situation, decreasing productivity, cost-effectiveness, quality of patents and patent examination, lack of timeliness and high cost of patents.
2. EPO should concentrate itself on its core business which means patent granting, It should decrease its expanding involvement in training and education activities for third parties as well as in promotion and marketing business. These activities divert EPO from its key role and impact the role of the NPO´s negatively. To optimize the proper functioning of the patent system in Europe and to increase it competitiveness a closer co-operation is necessary between the NPO´s and EPO. To summerize this, EPO should
    - stick to its core business
    - recognize and accept the specific responsibility of the NPOs
    - recognize and accept NPO´s role as part of the overall patent network
    - accept and obey the principle of subsidiarity in relation to the contribution of the NPOs.

3 The European Patent Convention together with the Protocol on Centralization are the backbones on the Organization. They should stay unchanged. However, this does not impede future adaptations.

4 It was also emphasized that the political role of the AC should be strengthened and the AC should concentrate its work on strategic issues.

5 EPO and the NPOs have to cooperate as much as possible. They together can contribute a lot to reach the Lisbon goals by taking advantage of each others competence and to avoid duplication of work as much as possible.

6 The network model could be based on interlinked principles such as
    - free choice for applicants
    - no compulsory outsourcing
    - no automatic utilization by EPO of the work of NPOs
    - equal treatment of all member States
    - introduction and assurance of equal quality standards

In May 2005 Sweden contributed with some thoughts on how to assure equal quality standards and I will now share with you some of our thoughts.

We believe a future PCT system in Europe must be recognised by its effective use of resources, its high standard regarding ability to retrieve relevant prior art documentation, predictability in the assessment of patentability and last but not least timeliness in issuing reports.

It is our opinion that to ensure an efficient system in Europe it has to be built without duplication of work. We think that an efficient and reliable future PCT system is based on the utiliztion of the work done by the International Searching Authorities. This aspect however, puts the focus on how to establish a system where not only the consistency in the PCT system is met, but also on the fact that it has to be in line with the standards established in the European patent system.

To accomplish this we think a quality model for the procedure introduced by UK is necessary. From UK was suggested a quality system for the PCT procedure featuring common quality standards for search and examination, a model of quality management system to support the

search and examination process, and a transparent, as well as an objective and independent review mechanism, for assessing compliance with the standards.

It is often commented in the Administrativ Council what a success the European Patent System is. And of course the system compared to the situation before 1978 is indeed a success in the sense that the applicant no longer needs to apply for a patent in each single country in Europe. However, looking at the patent process in Europe from a perspective of efficiency and quality aspects, one can certify that there is everything but a perfect process. The duplication of work in the present procedure is tremendously resource consuming and brings very litte value to the products.

The patent process in Europe lacks a structured way of handling the result from the initial stage in the process(NPO´s) and the use of it in the final stage(EPO). The communication and cooperation between the authorities in this aspect is the time being, negligible.

It is obvious that the European patent process should have a lot to gain from a structured work along the entire process. It is our opinion that the total amount of available resources concerning search and examination in Europe is more than sufficient to handle the total workload of patent applications filed here, provided a cooperation between NPO´s and the EPO could take place. This is applicable for the PCT procedure as well as for national/EP procedures.

Despite the fact that the EPO has existed for 30 years and that the EPO procedure gives the applicants the possibility to obtain a patent in their own country, the vast majority of the applicants still choose their NPO for the first filings. A strategy to centralise the patent process in Europe leading to the elimination of the search and examination work done in the NPO´s would obviously be an action narrowing the possibility to priority choice for the applicant in Europe.

A strategy for the patent process in Europe, which supports the present behaviour of the applicants and possibly even enlarges the possibilities to a priority choice, has to be built on using the resources in the patent process in Europe in a more efficient way, which could be obtained by analysing the present patent process in Europe and establishing a deeper cooperation between the EPO and the NPO´s.

NPO´s which perform search and examination put a lot of useful information into the application, which, if structured and standardised, could be of significant use for the EP procedure.

When discussing the patent system in Europe we have to contemplate the entire procedure, from the filing of a national application to the final grant in the EPO. We have to look at how the work done in the NPO`s can be used by the EPO in the grant procedure. To establish a cost effective and an efficient patent process in Europe it is essential that the resources in the European patent process are used in an effective way and that the quality of the search and examination meet the expectations of the applicants.

In order to achieve this we have to establish a close cooperation between the NPO´s and the EPO and setting a common level for a European Standard for Search and Examination (ESSE). This standard also has to be valid for the PCT procedure in Europe, which will result in a further harmonisation between the PCT and EPC regulations.

EPIP Annual Conference
Lund, 20 September 2007

Harmonisation of the Biotechnology Patent Landscape in Europe

Prof. Dr. Geertrui Van Overwalle

Centre for Intellectual Property Rights
University Leuven, Belgium
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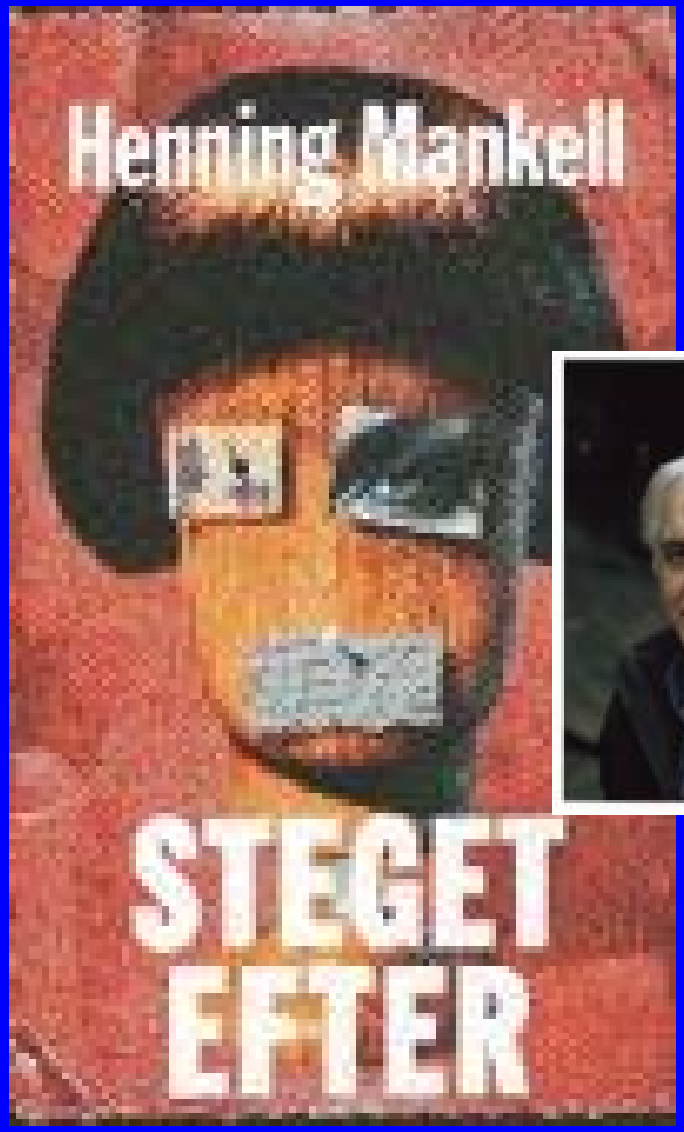
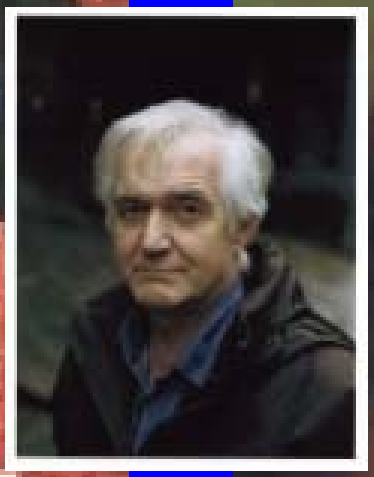




RYDBERG:

“Fighting crime is always a matter of perseverance. Who can hang in the longest? “

Outline

1. *Existence* of patent rights

   Pre-grant issues

   European umbrella legislation (Bt) and national implementation

2. *Exercise* of patent rights

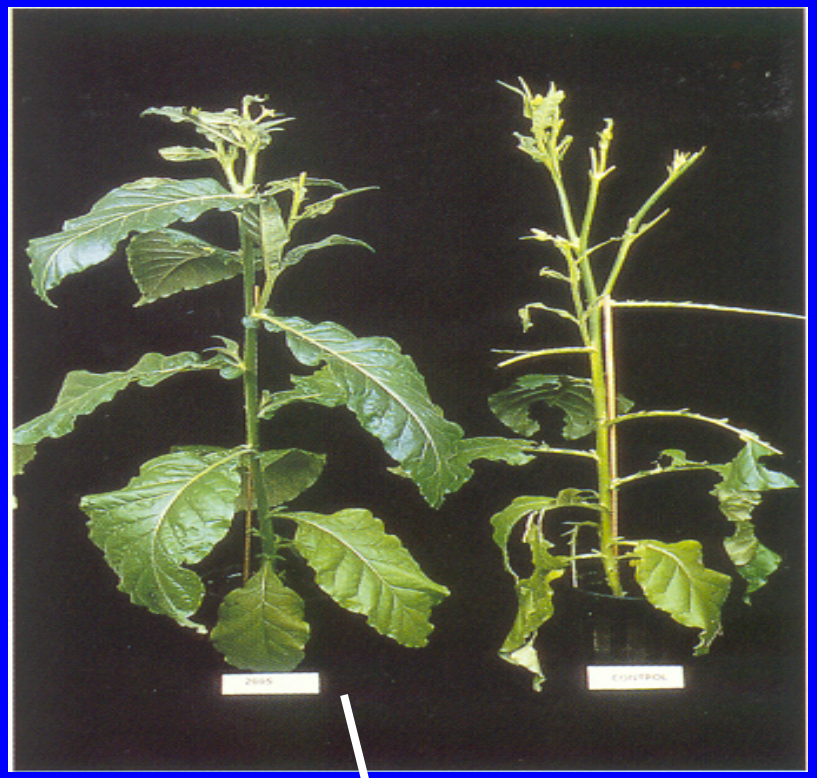
   Post-grant arena

   National legislation prevails (Bt+)

1. *Existence* of patent rights

- European Patent Convention, 1973
  - **No** explicit provisions relating to biotech
    - Except implicit for micro-organisms
    - Morality clause
  - Diverging national viewpoints
- EU Biotechnology Directive, 1998
  - **Explicit** provisions relating to biotech
    - Confirmation patentability 'biological material'
    - Detailed provisions for plants, animals, human material
    - Morality clause refined, ethical assessment
  - Aim: Harmonisation
    - Member states
    - EPO

Plants



Genetically modified tobacco

Genetically modified tomato

Technical Dimension

- EPC "European patents shall **not** be granted in respect of:

  (b) plant or animal varieties or essentially biological processes for the production of plants or animals; … " (art. 53, b)

- EU Biotechnology Directive

  "1. The following shall **not** be patentable:

  (a) plant and animal varieties

  2. Inventions which concern plants or animals **shall** be patentable if the technical feasibility of the invention is not confined to a particular plant or animal variety" art. 4

Claims

1. A transformed plant cell containing a chimeric gene which: is stably integrated in the genome of said cell, is capable of being expressed in differentiated cells of a plant derived from said cell, and

comprises:

(a) a promoter region derived from a gene which is naturally expressed in a plant cell; and
(b) a DNA fragment obtained by truncation of a DNA coding for a crystal protein produced by Bacillus thuringiensis or having substantial sequence homology thereto; said truncated fragment (b) coding for at least a polypeptide toxin of said crystal protein and providing an insect controlling amount of said polypeptide toxin in said cell as a result of intracellular expression of said truncated fragment (b).

20. A plant or differentiated plant cell progeny which comprises the plant cell as claimed in any of claims 1 to 19.

21. A seed of a plant or progeny thereof as claimed in claim 20.

22. A method of protecting a plant against a specific insect pest which comprises transforming the genome of said plant with said chimeric gene as claimed in any of claims 1 to 19 whereby an insect controlling amount of said polypeptide toxin is expressed in cells of said plant.

23. A method of transforming a plant to protect it against a specific insect pest which comprises stably integrating, in the genome of said plant, said chimeric gene as claimed in any of claims 1 to 19 whereby an insect controlling amount of said polypeptide toxin is expressed in cells of said plant.

Ethical Dimension

- EPC

  'European patents shall **not** be granted in respect of

  (a) inventions the *publication* or *exploitation* of which would be contrary to 'ordre public' or morality, provided that the exploitation shall not be deemed to be so contrary merely because it is prohibited by law or regulation in some or all of the Conctracting States" = 'Morality clause'

  (art. 53 a)

- EU Biotechnology Directive
  - Article 6 (1)

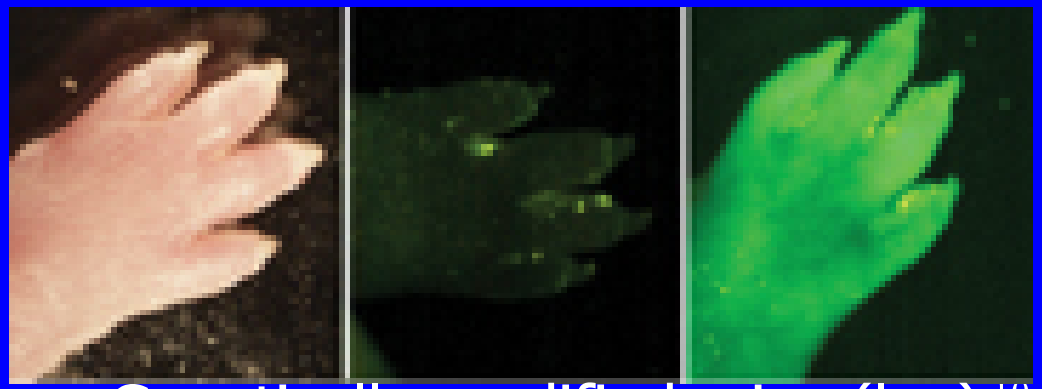
    « Inventions shall be considered **un**patentable where their *commercial exploitation* would be contrary to ordre public or morality; however, exploitation shall not be deemed to be so contrary merely because it is prohibited by law or regulation. = 'Morality clause'
  - Recital 27: refinement Morality clause

    "Whereas if an invention is based on biological material of plant or animal origin or if it uses such material, the patent application should, where appropriate, include information on the geographical origin of such material, *if known*; whereas this is *without prejudice* to the processing of patent applications or the validity of rights arising from granted patents'

Animals

(Belgian) genetically modified rabbits

(Dutch) genetically modified bull



Genetically modified mice (leg)

- Technical dimension
  - EPC, art. 53 (b)

    "European patents shall **not** be granted in respect of:

    (b) plant or animal varieties…"
  - EU Biotechnology Directive

    "1. The following shall **not** be patentable:

    (a) plant and animal varieties

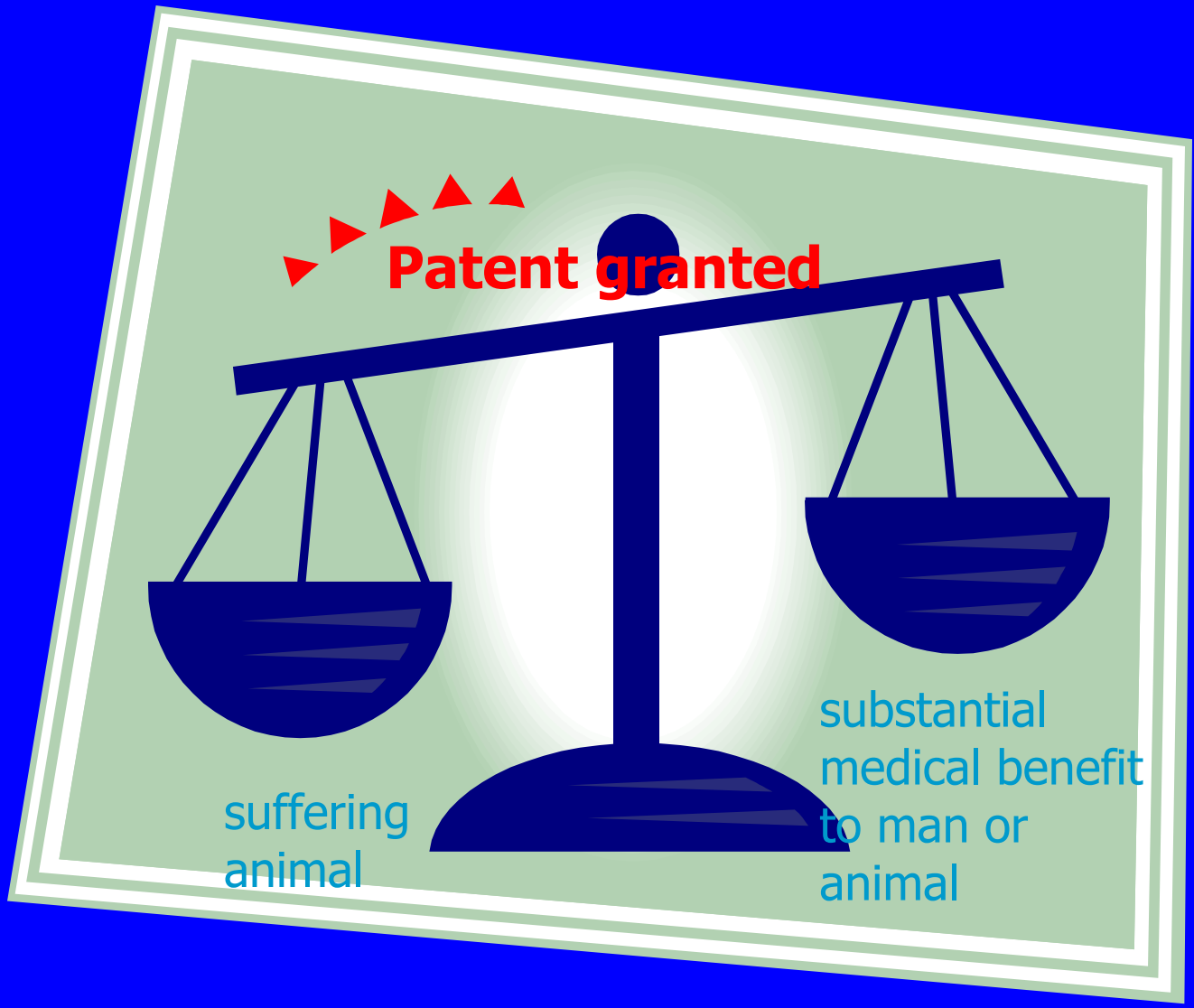
    2. Inventions which concern plants or animals **shall be** patentable if the technical feasibility of the invention is not confined to a particular plant or animal variety

- Ethical dimension
  - EPC

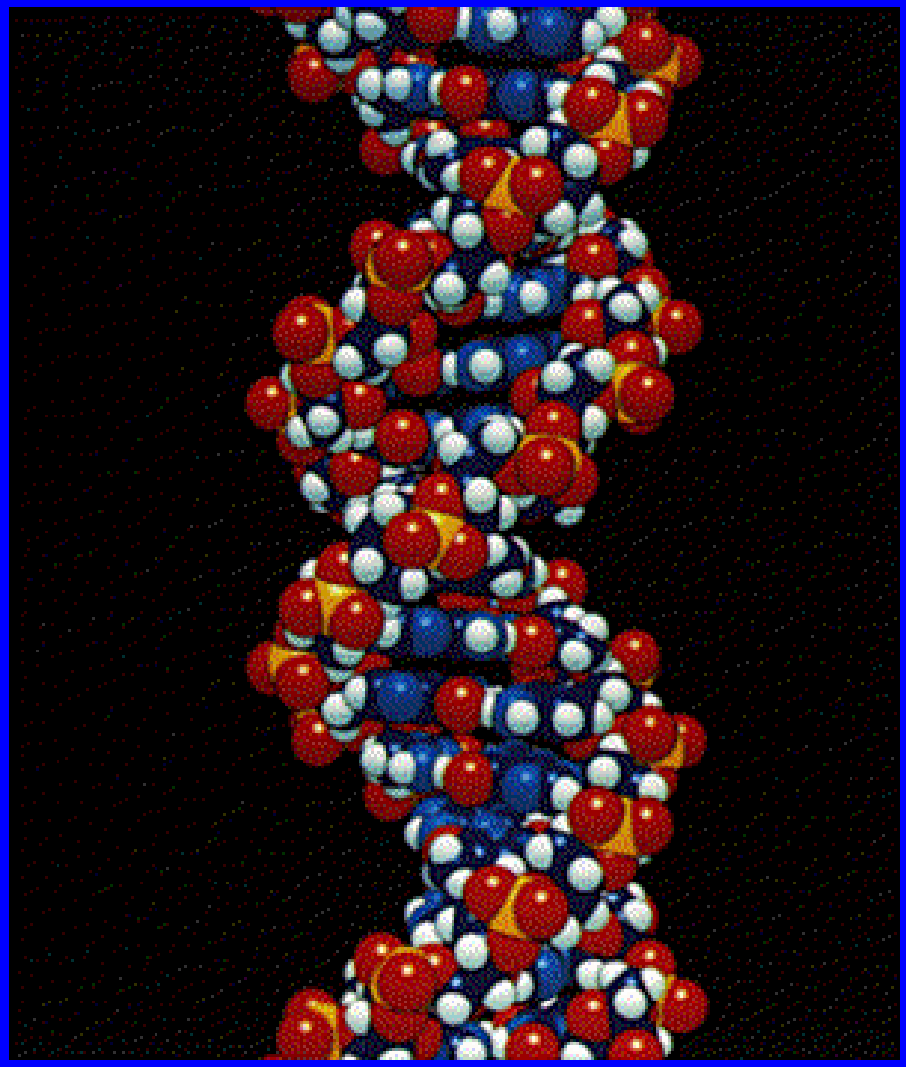
    Morality clause
  - EU Biotechnology Directive: refinement morality clause

    "The following shall be considered **un**patentable

    processes for modifying the genetic identity of animals which are likely to cause them suffering without any substantial medical benefit to man or animal, and also animals resulting from such processes."(art. 6 (2)(d)) [contrary public order/morality]


Patent granted
suffering animal
substantial medical benefit to man or animal

Human material



Human genes

Claims

1. A DNA fragment encoding human H2-preprorelaxin, said H2-preprorelaxin having the amino acid sequence set out in Figure 2.

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 112 149 B1**

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication of patent specification: **10.04.91**

(51) Int. Cl.5: **C12N 15/16**, C12P 21/02, C07K 13/00, C07K 7/00

(21) Application number: **83307553.4**

(22) Date of filing: **12.12.83**

Divisional application 88110103 filed on 24.06.88.

(54) **Molecular cloning and characterization of a further gene sequence coding for human relaxin.**

(30) Priority: **13.12.82 AU 7247/82**

(43) Date of publication of application:
27.06.84 Bulletin 84/26

(45) Publication of the grant of the patent:
10.04.91 Bulletin 91/15

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(56) References cited:
EP-A- 0 068 375
EP-A- 0 086 649
EP-A- 0 101 309

TELEGEN TECHNICAL FEATURE, 82000533, abstract 31808, 1982, Environment Information Center, New York, US;H. NIAL:"Hormones and genetic engineering":paper presented at the Genetic Engineering Symposium in Sydney, November 18-20, 1981

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EP 0 112 149 B1

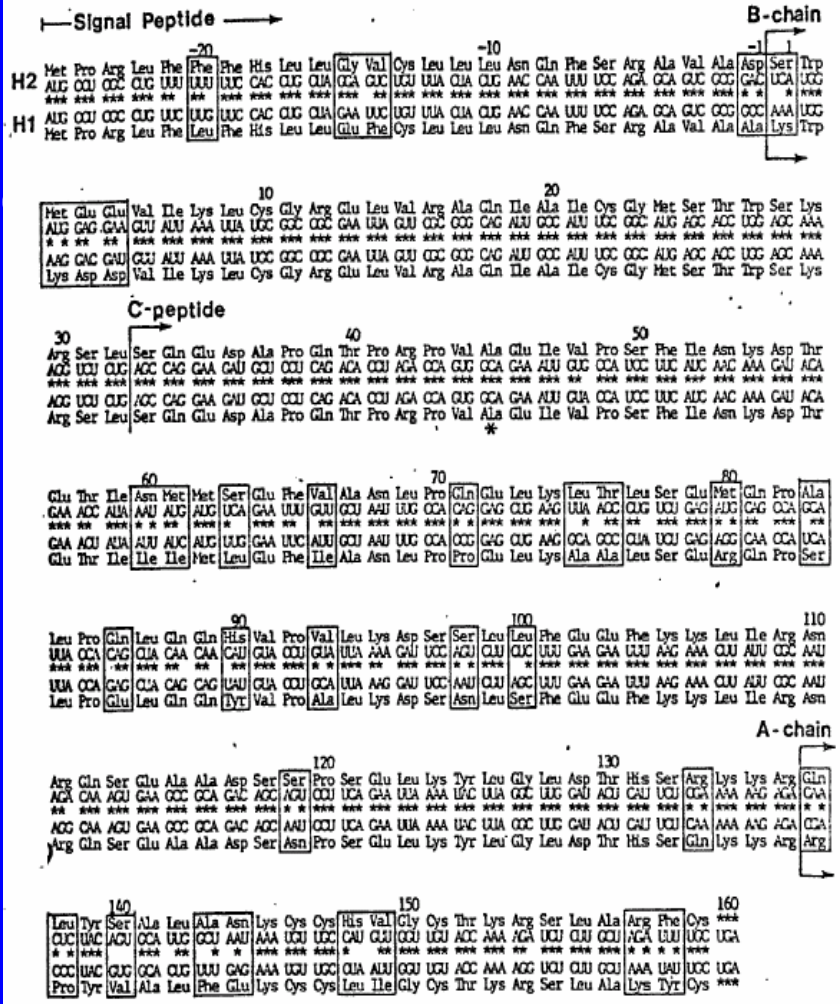
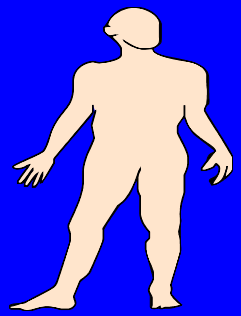


FIGURE 2.

EU Biotechnology Directive

- Technical Dimension

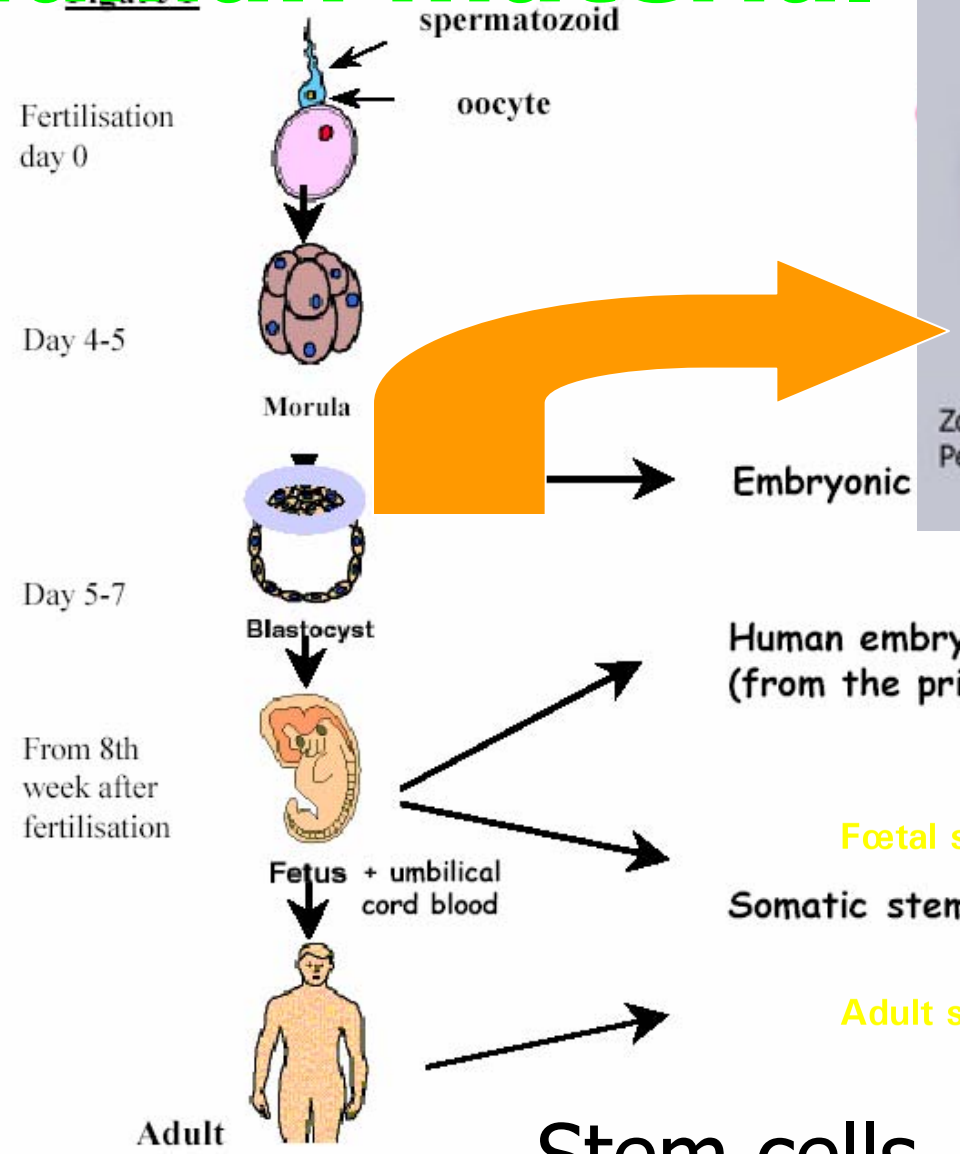


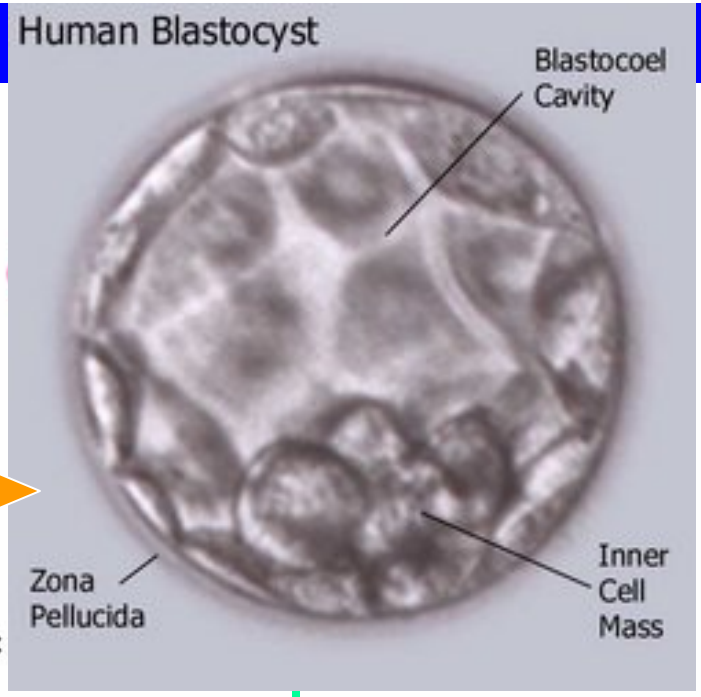
"1. The human body, at the various stages of its formation and development, and the simple discovery of one of its elements, including the sequence or partial sequence of a gene, **cannot** constitute patentable inventions.

2. An element isolated from the human body or otherwise produced by means of a technical process, including the sequence or partial sequence of a gene, **may** constitute a patentable invention, even if the structure of that element is identical to that of a natural element

(art. 5 EU-Bt-Directive)"

Human material





Embryonic

Human embryonic germ cells
(from the primordial germ cells of the foetus)

Pluripotent
any cell type
unlimited

Fœtal stem cells

Somatic stem cells

Adult stem cells

Multipotent
differentiated cell types
limited life span

Stem cells

US006200806B1

(12) **United States Patent**
Thomson

(10) **Patent No.: US 6,200,806 B1**
(45) **Date of Patent: Mar. 13, 2001**

(54) **PRIMATE EMBRYONIC STEM CELLS**

(75) Inventor: **James A. Thomson**, Madison, WI (US)

(73) Assignee: **Wisconsin Alumni Research Foundation**, Madis

(*) Notice: Subject to any discl
patent is extended
U.S.C. 154(b) by 0

This patent is subj
claimer.

(21) Appl. No.: **09/106,390**

(22) Filed: **Jun. 26, 1998**

Related U.S. Applicati

(60) Division of application No. 08/59
1996, now Pat. No. 5,843,780, and
application No. 08/376,327, filed
abandoned.

(51) **Int. Cl.**[7] C

(52) **U.S. Cl.** .....

(58) **Field of Search** .....

Damjanov, Ivan., et al., Retinoic Acid–Induced Differentiation of the Developmentally Pluripotent Human Germ Cell Tumor–Derived Cell Line, NCCIT, *Laboratory Investigation*, 68(2):220–232 (1993).

I claim:

1. A purified preparation of pluripotent human embryonic stem cells which (i) will proliferate in an in vitro culture for over one year, (ii) maintains a karyotype in which the chromosomes are euploid and not altered through prolonged culture, (iii) maintains the potential to differentiate to derivatives of endoderm, mesoderm, and ectoderm tissues throughout the culture, and (iv) is inhibited from differentiation when cultured on a fibroblast feeder layer.

2. The preparation of claim **1**, wherein the stem cells will spontaneously differentiate to trophoblast and produce chorionic gonadotropin when cultured to high density.

3. A purified preparation of pluripotent human embryonic stem cells wherein the cells are negative for the SSEA-1 marker, positive for the SSEA-4 marker, express alkaline phosphatase activity, are pluripotent, and have euploid karyotypes and in which none of the chromosomes are altered.

4. The preparation of claim **3**, wherein the cells are positive for the TRA-1-60, and TRA-1-81 markers.

5. The preparation of claim **3**, wherein the cells continue to proliferate in an undifferentiated state after continuous culture for at least one year.

6. The preparation of claim **3**, wherein the cells will differentiate to trophoblast when cultured beyond confluence and will produce chorionic gonadotropin.

7. The preparation of claim **3**, wherein the cells remain euploid for more than one year of continuous culture.

8. The preparation of claim **3**, wherein the cells differentiate into cells derived from mesoderm, endoderm and ectoderm germ layers when the cells are injected into a SCID mouse.

9. A method of isolating a pluripotent human embryonic stem cell line, comprising the steps of:

(a) isolating a human blastocyst;

(b) isolating cells from the inner cell mass of the blastocyte of (a);

(c) plating the inner cell mass cells on embryonic fibroblasts, wherein inner cell mass-derived cell masses are formed;

(d) dissociating the mass into dissociated cells;

(e) replating the dissociated cells on embryonic feeder cells;

(f) selecting colonies with compact morphologies and cells with high nucleus to cytoplasm ratios and prominent nucleoli; and

(g) culturing the cells of the selected colonies to thereby obtain an isolated pluripotent human embryonic stem cell line.

10. A method as claimed in claim **9**, further comprising maintaining the isolated cells on a fibroblast feeder layer to prevent differentiation.

11. A cell line developed by the method of claim **9**.

* * * * *

- EU Biotechnology Directive
  - Technical dimension

    "1. The human body, ... **cannot** constitute patentable inventions.

    2. An element isolated from the human body or..., **may** constitute a patentable invention. "

    - germ cells, oocytes: excluded
    - quid embryonic stem cells?

  - Ethical dimension: refinement morality clause

    "The following shall be considered **un**patentable

    (a) processes for cloning human beings;

    (b) processes for modifying the germ line genetic identity of human beings;

    (c) uses of human embryos for industrial or commercial purposes" (art. 6 (2))

    - definition "embryo"?

- Ethical dimension: further refinement

"Whereas if an invention is based on biological material of human origin or if it uses such material, where a patent application is filed, the person from whose body the material is taken must have had an opportunity of expressing free and informed consent thereto, in accordance with national law"

1. *Existence* of patent rights

A harmonized European bio-patent framework?

Yes, with regard to
- Principle patenting biological material
- Patents for animals
- Exclusion patents causing pain to animals
- List exclusions delicate human material from patentability

No, with regard to
- Patents for plants
- Origin indication plant material
  Diverging national interpretations
- Gene patents
  Diverging national interpretations
- List exclusions delicate human material
  Diverging national interpretations
- Informed consent

2. *Exercise* of patent rights

TWO PROBLEMATIC PHENOMENA

- **Patent explosion - "patent thicket"**
- **Refusal to license**

First inventions

Multiple patents

"Royalty stacking"

Patent "thicket"

SHAPIRO, 2001

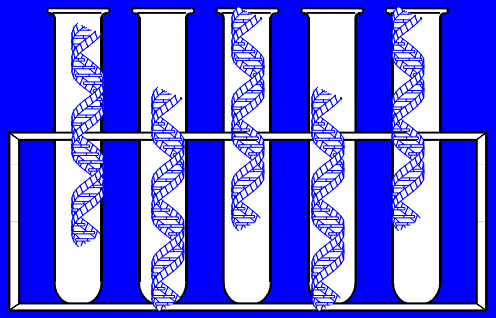
No use

No final product

Subsequent innovation

Cumulative innovation

"Shoulders" Newton v. block on "Pyramid"



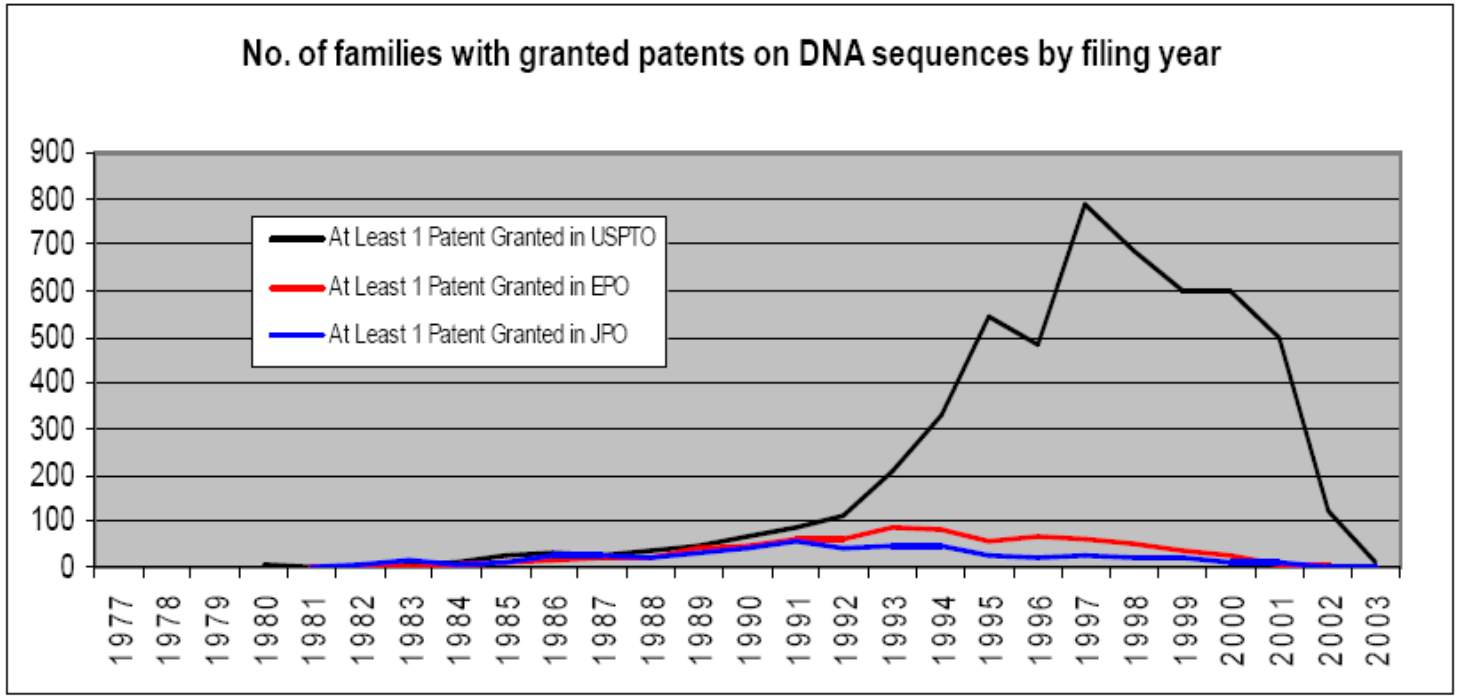
'Tragedy of the anti-commons'

Patent thicket

EMPIRICAL EVIDENCE ?

– At first sight: tremendous increase patents claiming human DNA sequences

Figure 1. Trends in granting by the EPO, USPTO, and JPO



HOPKINS, M.M., MAHDI, S., PATEL, P. & THOMAS, S., 'DNA patenting: the end of an era?', 25 *Nature Biotechnology,* 2007, 185-187; Ibidem, *Final Project Report,* 2006, p. 14

– Closer look

- No patent thicket in genetics (yet)

REAPING THE BENEFITS OF GENOMIC AND PROTEOMIC RESEARCH:

Intellectual Property Rights, Innovation, and Public Health

Committee on Intellectual Property Rights in Genomic and Protein Research and Innovation

Board on Science, Technology, and Economic Policy

Committee on Science, Technology, and Law

Policy and Global Affairs

NATIONAL RESEARCH COUNCIL
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Report U.S. National Research Council, december 2005

POLICY FORUM

INTELLECTUAL PROPERTY

Intellectual Property Landscape of the Human Genome

Kyle Jensen and Fiona Murray*

Gene patents are the subject of considerable debate and yet, like the term "gene" itself, the definition of what constitutes a gene patent is fuzzy (*1*). Nonetheless, gene patents that seem to cause the most controversy are those claiming human protein-encoding nucleotide sequences. This category is the subject of our analysis of the patent landscape of the human genome (*2*).

Enhanced online at www.sciencemag.org/cgi/content/full/310/5746/239

Critics describe the growth in gene sequence patents as an intellectual property (IP) "land grab" over a finite number of human genes (*3*, *4*). They suggest that overly broad patents might block follow-on research (*5*). Alternatively, gene IP rights may become highly fragmented and cause an anticommons effect, imposing high costs on future innovators and underuse of genomic resources (*6*). Both situations, critics argue, would increase the costs of genetic diagnostics, slow the development of new medicines, stifle academic research, and discourage investment in downstream R&D (*7*–*11*).

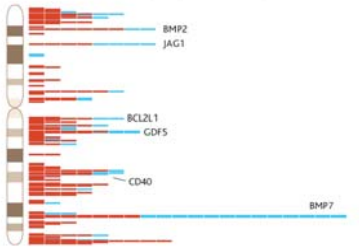
In contrast, the classic argument in support of gene patenting is that strong IP protection provides incentives crucial to downstream investment (*12*, *13*) and the disclosure of inventions. Patents are also regarded as the cornerstone of vibrant markets for ideas (*14*) and central to the biotech boom of the 1980s and 1990s (*15*).

Policy-makers are hampered by the lack of empirical data on the extent of gene patenting. Most analyses have relied on anecdotal evidence (*11*, *16*–*18*) and empirical analyses have been hindered by (i) limited (and poorly defined) coverage of DNA sequence patents (*17*, *19*); (ii) difficulty separating patents that claim gene sequences per se from those merely disclosing DNA sequences (*20*–*22*); and (iii) distinguishing patents on the human genome from those on other species (*23*).

Our detailed map was developed using bioinformatics methods to compare nucleotide sequences claimed in U.S. patents to the human genome. Specifically, this map is based on a BLAST (*24*) homology search linking nucleotide sequences disclosed and claimed in granted U.S. utility patents to the set of protein-encoding messenger RNA transcripts contained in the National Center for Biotechnology Information (NCBI) RefSeq (*25*) and Gene (*26*) databases. This method allows us to map gene-oriented IP rights to specific physical loci on the human genome (*27*) (see figure, right). Our approach is highly specific in its identification of patents that actually claim human nucleotide sequences. However, by limiting the search to patents using the canonical "SEQ ID NO" claim language we do not consider claims on genes defined through amino acid sequences. (See table S1 for a sensitivity analysis.)

Our results reveal that nearly 20% of human genes are explicitly claimed as U.S. IP. This represents 4382 of the 23,688 genes in the NCBI's gene database at the time of writing (see figure, right). These genes are claimed in 4270 patents within 3050 patent families (*28*). Although this number is low compared with prior reports, a distinction should be made between sequences that are explicitly claimed and those that are merely disclosed, which outnumber claimed sequences roughly 10:1. The 4270 patents are owned by 1156 different assignees (with no adjustments for mergers and acquisition activity, subsidiaries, or spelling variations). Roughly 63% are assigned to private firms (see figure, above). Of the top ten gene patent assignees, nine are U.S.-based, including the University of California, Isis Pharmaceuticals, the former SmithKline Beecham, and Human Genome Sciences. The top patent assignee is Incyte Pharmaceuticals/Incyte Genomics, whose IP rights cover 2000 human genes, mainly for use as probes on DNA microarrays.

Although large expanses of the genome are unpatented, some genes have up to 20 patents asserting rights to various gene uses and manifestations including diagnostic uses, single nucleotide polymorphisms (SNPs), cell lines, and constructs containing the gene. The distribution of gene patents was nonuniform (see figure, page 240, top right): Specific regions of the genome are "hot spots" of heavy patent activity, usually with a one-gene-many-patents scenario (see figure, below). Although less common, there were cases in which a single patent claims many genes, typically as complementary DNA probes used on a microarray (see figure, p. 240, bottom).



Physical mapping of patent activity on chromosome 20, divided into 300-kb segments. Each horizontal bar represents a unique patent claiming a gene sequence located in that region. Orange represents the number of unique patent families in a region (*28*). Labels show the loci of highly patented genes (see table S1).

BMP7, an osteogenic factor, and CDKN2A, a tumor suppressor gene, were the most highly patented genes in the genome [their sequences were each claimed in 20 patents (table S2)]. The patents on CDKN2A are distributed between nine different assignees and, collectively, claim all three splice variants of the gene. Nearly all of these patents are directed toward diagnostic applications. In contrast, the patents on BMP7 are for the use of BMP7 proteins in implants to stimulate bone growth. However, a number are directed towards more speculative utilities, such as drug-screening probes, which suggests a strategy of "science-

K. Jensen is in the Department of Chemical Engineering, F. Murray is in the Sloan School of Management, Massachusetts Institute of Technology, Cambridge, MA 02139, USA.

*Author for correspondence. E-mail: fmurray@mit.edu

Published by AAAS

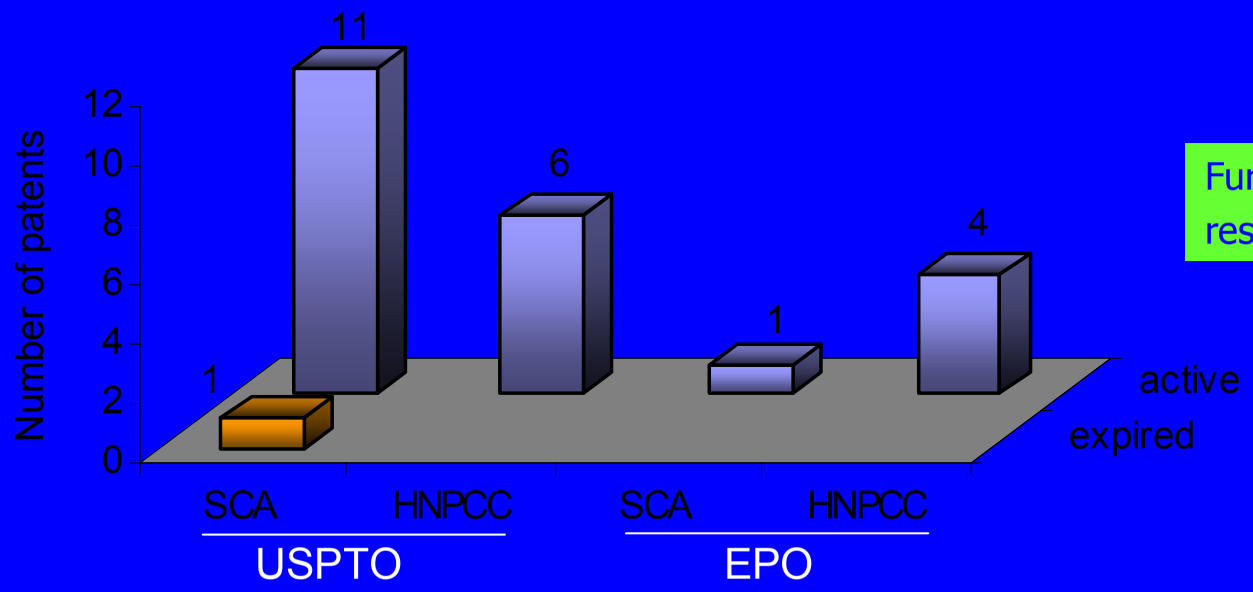
JENSEN, K. & MURRAY, F., 'Intellectual Property Landscape of the Human Genome', *Science,* 2005

- May be in diagnostics…
  - Initial findings: search algorythm + one "patent landscape"

    VERBEURE, B., MATTHIJS, G. & VAN OVERWALLE, G., 'Analysing DNA patents in relation with diagnostic genetic testing', 14 *European Journal of Human Genetics,* vol. 1, January 2006, 26-33
  - Recent (unpublished) findings: 2 additional patent "landscapes"

    BERTHELS, N. & VERBEURE, B., 2007

**Granted patents related to SCA and HNPCC genes*
USPTO vs. EPO**



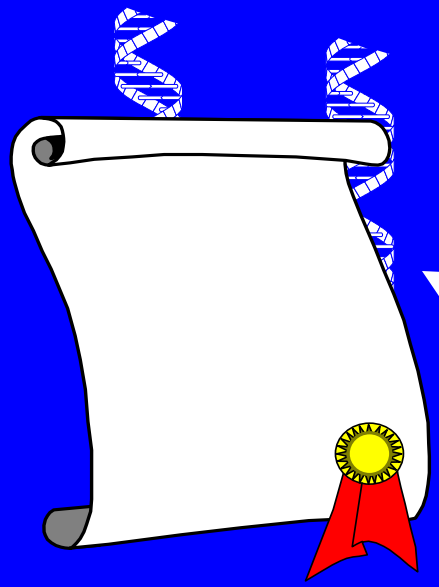
Further empirical research needed

SCA: Spinocerebellar ataxia
HNPCC: Hereditary Non-Polyposis Colon Cancer

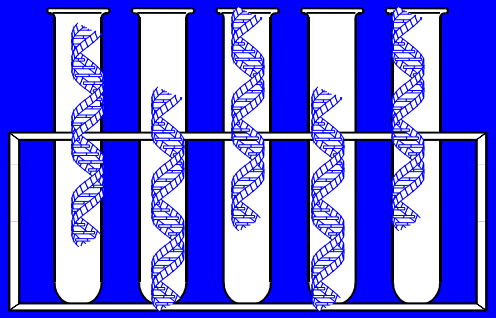
First inventions

Subsequent innovation

Cumulative innovation
"Shoulders" Newton v. block on "Pyramid"



No use
No final product



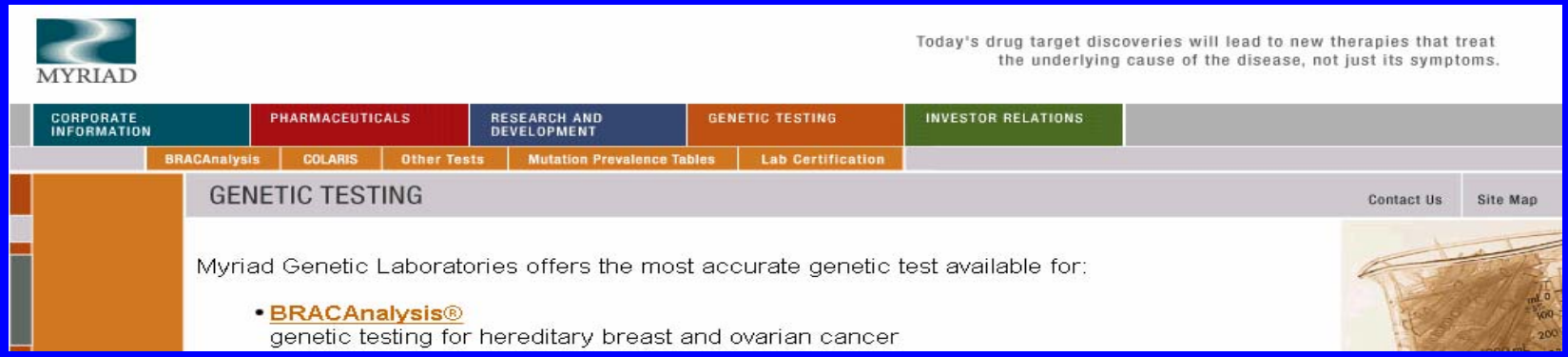
No license

No reasonable license

Refusal to license

EMPIRICAL EVIDENCE ?

- Refusal to license
  - No license
  - No reasonable license
    - No wide evidence, one (a few?) cases



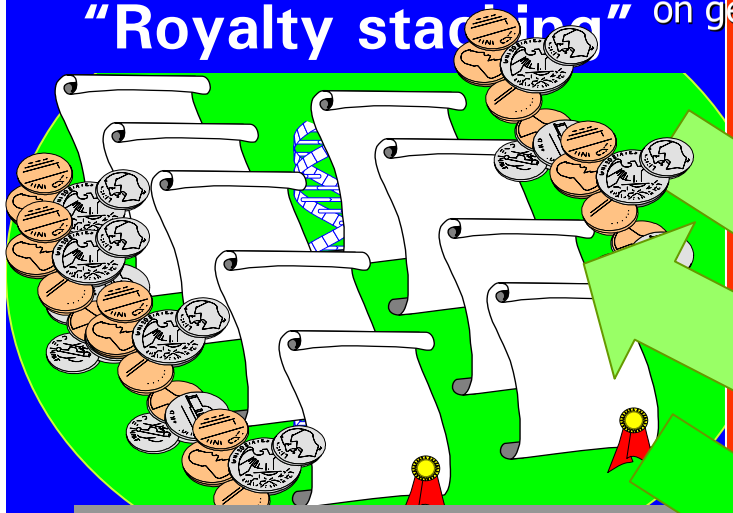
MATTHIJS, G. & HALLEY, D., 'European-wide opposition against the breast cancer gene patents', 10 *European Journal of Human Genetics*, 2002, 783-784;

MATTHIJS, G., Patenting Genes, *BMJ,* 2004, 1358-1360

First inventions

Multiple patents

"Royalty stacking"



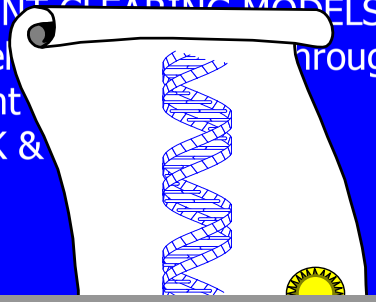
Patent "thicket"

SHAPIRO, 2001

PATENT CLEARING MODELS

Model[illegible]hrough the patent

BURK &



Refusal to license,

Unreasonable licensing conditions

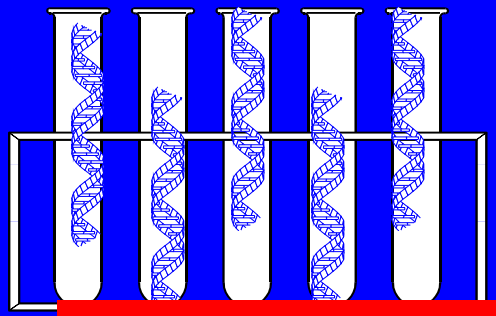
REMEDIES

VAN OVERWALLE, G., et al. , 'Models for facilitating access to patents on genetic inventions', 7 *Nature Review Genetics,* February 2006, 143

Subsequent innovation

Cumulative innovation

"Shoulders" Newton v. block on "Pyramid"



Hardly any direct remedy in competion law

Compulsory license

'general intrest', 'public h'

Research exemption

Licenses

Cross Licenses

Patent pools

One stop licensing

Clearing house

2. *Exercise* of patent rights

A harmonized European bio-patent framework?

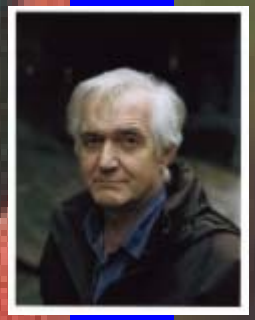
Yes, with regard to **concerns**

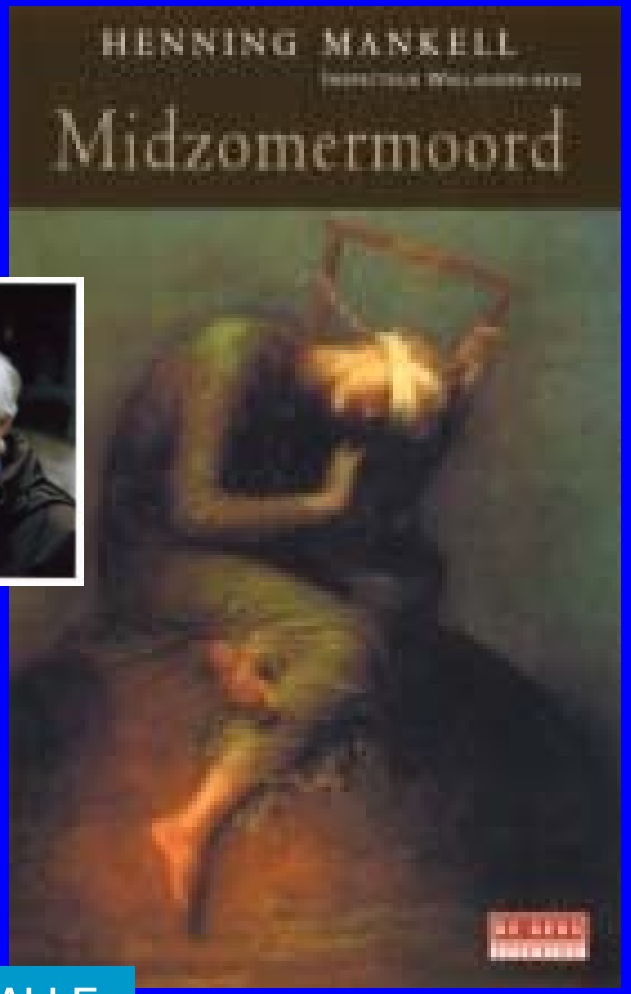
- access to healthcare
- 'stacking problem'
- abuse dominant market position

No, with regard to **remedies**

- Scope research exemption
- Compulsory license regime (National legislation)
- Compulsory license regime export to developing countries (EU legislation)
- 'New' licensing models? (EU legislation)

Conclusion





VAN OVERWALLE:

"Shaping the law is always a matter of perseverance. Who can hang in the longest?"

Genes (scope), origin requirement, informed consent requirement (Bt)
Research exemption, compulsory licensing (Bt+)

FRØLUNDWINSLØW

Patents & Competition – different angles

EPIP 2nd Conference, Sept. 21st 2007, Lund
Round Table – Plenary Session IV

Per Mejer, Attorney, Partner
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Involved Parties

- Universities
  - Science / Research
- Industrial / Production
  - Research & Development
  - Production
  - E.g. Medical, Technical, Consumer Goods, Information Technology
- Service Sectors
  - E.g. Financial (Banking / Insurance)
- Public Sector
  - Service citizens and commercial entities

Different Aims?

- Combination of Parties with different aims? E.g.:
- University & Industrial entities cooperate in projects
- Service Sector & Customers
  - IT Vendor deliverance to Customer
- What are the Aims and what are the means to reach them?

Monopoly

- By … e.g. :
- Patent
- Copyright
- Closed Systems
- Agreement based

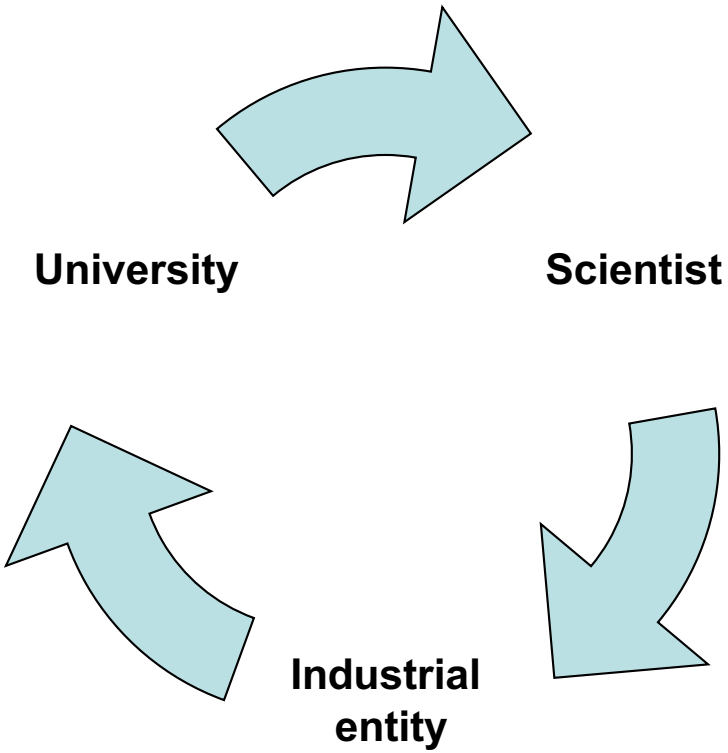
Clash of Aims ?

- R *and* D

Become

- R *or* D

”From Thought to Invoice”



Directions of Competitional Enviroment

- Awareness
- Knowledge
- Explanation
- Consideration
- Guidance

SCIENCE AND SOCIETY

Models for facilitating access to patents on genetic inventions

Geertrui Van Overwalle, Esther van Zimmeren, Birgit Verbeure and Gert Matthijs

Abstract | The genetics community is increasingly concerned that patents might lead to restricted access to research and health care. We explore various measures that are designed to render patented genetic inventions accessible to further use in research, and to diagnosis and/or treatment. They include the often-recited research or experimental-use exemption, conventional one-to-one licensing and compulsory licensing, as well as patent pools and clearing-house mechanisms. The last two alternatives deserve special attention in the area of human genetics.

Many patents have been granted in genetics in recent years. For example, up to the end of 2004, the European Patent Office granted 2,913 patents containing the term 'nucleic acid' in the claims, and 549 of these were granted in 2004 alone. The omnipresence of genetic patents has raised serious concerns about access to and use of genome-related inventions, as the expansion of genetic patents might result in a patent thicket. As it is unlikely that patents for genetic inventions will be carved out from patent law, it is extremely important to develop alternative strategies to maximize access to and use of genetic inventions. Some models already exist for facilitating access to patented gene technology. Research exemptions create access for research purposes, and licensing agreements and compulsory licences are well-known tools for encouraging access. Other models that could render proprietary genetic inventions accessible for further use are under discussion, such as patent pools and clearing-house mechanisms. Patent pools and clearing-house mechanisms have been suggested by various governmental and non-governmental organizations as useful mechanisms to deal with the specific problems of access and use of patented genes, diagnostic methods, technologies and tools that are used in genetics.

We briefly describe research exemptions, licensing agreements and compulsory licensing, and extensively examine patent pools and clearing-house mechanisms. We explore to what extent the last two mechanisms could become leading models for enhancing access to and use of patented genetic inventions.

> "The omnipresence of genetic patents has raised serious concerns about access to and use of genome-related inventions…."

Exemptions

A first possibility for guaranteeing the freedom to use patented technology is to exempt certain activities from infringement. An example of this is the research or experimental-use exemption that qualifies scientific research for immunity from infringement.

In Europe, the research exemption is part of patent law. The original provision, which was laid down in the Community Patent Convention, states that the rights that are conferred by a patent shall not extend to "acts done for experimental purposes relating to the subject-matter of the patented invention". The equivalent provisions in the European member-states mirror but sometimes also deviate from this wording. Because different national legislations and court rulings exist, the exact scope of the exemption differs from country to country. There seems to be a general consensus that the exemption applies irrespective of the way the patented subject matter has been put into operation and the place of the experiment, be it a public laboratory, hospital or private company. But doubts arise about the scale, nature (experiments 'on' versus experiments 'with' the patented subject matter) and final purpose of the experiment (commercial versus non-commercial goal), and whether these fall within the exemption[1–4]. At present, it is unclear to what extent the research exemption can shield diagnostic testing. On the one hand, one could argue that diagnostic testing falls within the research exemption, because patient blood or tissue sampling is often necessary to do research. On the other hand, one could claim that diagnostic testing cannot fall within the exemption because once a diagnostic test is established, the act of diagnosis could be defined as and/or confined to the act of providing the referring medical doctor with an opinion as to whether or not the patient carries a deleterious mutation.

In the United States the research exemption is not part of the patent act but exists as a judicially created theory. The theory has a very narrow scope of application. In the landmark case *Madey v. Duke University*[5] — which in fact involved electron laser technology, not genetics — it was recalled that: "Regardless of whether a particular institution or entity is engaged in an endeavour for commercial gain, so long as the act is in furtherance of the alleged infringer's legitimate business and is not solely for amusement, to satisfy idle curiosity, or for strict philosophical inquiry, the act does not qualify for the very narrow and strictly limited experimental use defence." Furthermore, the profit or non-profit status of the user is not decisive for the applicability of the doctrine. Research projects that are financed by major research universities but that have no prospect of commercialization further the institution's legitimate business objectives, including: "educating and enlightening students and faculty participating in these projects", and "serve to increase the status of the institution and lure lucrative research grants, students and faculty"[5]. This means that, after the *Madey v. Duke University* case, universities can no longer invoke experimental use in their defence. Concerns have been raised about this extremely limited interpretation by the US Federal Circuit of the experimental-use theory[6,7]. In practice,

however, the research exemption is administered more flexibly because companies hardly ever sue universities[8].

In 1984 US Congress enacted an exemption from patent infringement "solely for uses reasonably related to the development and submission of information under a Federal law which regulated the manufacture, use, or sale of drugs" use in the so-called the Hatch–Waxman act[9]. Recently, the Supreme Court held in *Merck v. Integra* — a case about the use of the Arg–Gly–Asp (or RGD) tripeptide in cell-adhesion experiments — that the use of patented inventions in preclinical research, the results of which are not ultimately included in a submission to the Food and Drug Administration (FDA), also falls within the scope of this exemption[10]. This interpretation of the exemption that is defined in the Hatch–Waxman act seems to be broad when compared with the limited interpretation of the common law experimental-use exemption in the *Madey v. Duke University* case. However, one should take into consideration the limited scope of application of this statutory exemption: it only applies to research that is related to drug development. It remains to be seen to what extent this case will influence the interpretation of the common law experimental-use exemption.

The research exemption is a powerful model for accommodating further research, but it suffers from legal uncertainty. The situation in the United States could be improved by introducing an explicit and clear-cut experimental-use exception in patent law, whereas the situation in Europe could be remedied by clarifying existing research exemptions and carefully defining the delicate borderline between commercial and non-commercial research in biotechnology and biomedicine. The optimal solution would be to adopt a clear and well-balanced exemption at the international level.

Licensing agreements

For activities that seem not to be covered by the research exemption, licensing is probably the instrument that is used most regularly for gaining access to patented technology. The licensor and licensee have considerable freedom to choose the appropriate contract modalities and clauses as long as they do not have an anti-competitive effect. Royalties and transaction costs might be reduced to a minimum by negotiating cross licences. Cross licensing might be attractive in various settings, including cases of complementary patents and blocking patents. The exchange might concern more than two patents, or in some cases even entire portfolios. Moreover, royalty stacking might be alleviated to a certain extent by bargaining a reduced royalty provision or a cap on royalties by using '(anti) royalty stacking clauses'[11,12].

> "The research exemption is a powerful model for accommodating further research … [t]he optimal solution would be to adopt a clear and well-balanced exemption at the international level."

The use of licensing agreements is routine practice in genetics. Roughly speaking, four approaches towards exploiting and licensing patents are known in the diagnostic field.

The first approach, which is universally accepted, has been followed by major research institutes that have granted free access to gene sequences for diagnostic testing using commonly available technologies for mutation analysis, but have collected royalties on gene-based commercial test kits. The best-known example relates to the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that was cloned in 1989 and patented by the Hospital for Sick Children of Toronto and the University of Michigan (WO 91/02796).

The second approach has been taken by Bio-Rad, the company that acquired the patent on the hereditary haemochromatosis (*HFE*) gene after Mercator Genetics went out of business[13] (WO 96/35802, WO 96/35803, WO 97/38137 and WO 98/14466). The company offers to license laboratories to carry out testing, but at a cost that makes Bio-Rad's own, commercial test kit more economically attractive owing to their requirement of up-front payments and a per-test fee of US$20 (for 2 mutations).

The third approach has been put into practice by Myriad Genetics for the screening of the breast cancer 1 and 2, early onset (*BRCA1* and *BRCA2*) genes (*BRCA1*: WO 96/05306, WO 96/05307 and WO 96/05308; and *BRCA2*: WO 97/22689). They licensed the test exclusively to a limited number of commercial genetic laboratories within specific geographical regions. However, these laboratories are apparently allowed to carry out testing of only a limited set of *BRCA1* and *BRCA2* mutations, while the complete sequence analysis is still carried out only by Myriad Genetic Laboratories in Salt Lake City, USA[14]. This highly restrictive licensing policy has given rise to a strong and worldwide reaction[15,16].

Recently, a fourth and unique type of licensing agreement has emerged — the so-called BiOS (Biological Innovation for Open Society) licence. BiOS is an initiative of the Centre for Applications of Molecular Biology in Agriculture (CAMBIA) and aims to develop new means for cooperative invention, improvement and delivery of technologies for life sciences. Research tools that have resulted from the BiOS initiative are made available on the basis of a BiOS licence. Instead of paying royalties, BiOS licensees should, in order to obtain a licence, agree to the legally binding conditions that improvements to the patented technology are shared, and that licensees will not "appropriate the fundamental 'kernel' of the technology and improvements exclusively for themselves". In this way, a BiOS licence not only guarantees access to the basic technology, but also to downstream improvements.

The variety of licensing agreements currently in place demonstrates that the one-to-one licensing mechanism is a flexible model that offers a wide opportunity to tailor access and use to specific needs and circumstances. However, users who do not have any assets to offer in return might find themselves in a weak bargaining position when entering into licence negotiations.

Patent pools

When access and use are hindered by the existence of multiple patents, held by multiple patent owners, patent pools might be a useful model to gain access to patented technology. A patent pool is an agreement between two or more patent owners to license one or more of their patents to one another, or to license them as a package to third parties who are willing to pay the royalties that are associated with the licence. Licences are provided to the licensee, either directly by the patentee, or indirectly through a new entity that is specifically set up for the administration of the pool[17–19]. Therefore, a patent pool is formed by the patent holders, acting as shareholders of the pool and as financiers of the licensing entity. Consequently, patent holders retain authority over the licensing conditions.

Patent pools might have significant benefits: elimination of stacking licences[17]; reduction of licensing transaction costs through the introduction of a system of 'one-stop licensing' for non-member licensees; decrease in patent litigation; and institutionalized exchange of technical information that is not covered by patents, through a mechanism for sharing technical information relating to the patented technology, which would otherwise be kept as a trade secret[17,19,20]. Furthermore, patent pools offer

an interesting instrument for government policy: it is better to encourage companies to establish patent pools than to force them into a compulsory licensing scheme[19] (see below). Such a suggestion seems to ignore the fact that the main prerequisite for establishing patent pools is the voluntary participation of all patent holders, whereas the compulsory licensing mechanism is the last-resort instrument for patent holders who do not voluntarily wish to enter into (reasonable) licensing negotiations.

Patent pools might also carry some risks: they might shield invalid patents[20] and entail the risk of inequitable remunerations, although expert valuation could settle disagreements on the value of the patents[18]. Additionally, patent pools might cover for a cartel and, subsequently, have anti-competitive effects[19–23].

The establishment of patent pools in genetics was suggested by the Organisation for Economic Co-operation and Development (OECD). The OECD considers the patent-pool concept to be interesting for biotechnology, but calls for further study[12]. It fears that the fact that biotechnological companies rely heavily on their intellectual property (IP) and foster what has been called a 'bunker mentality' might cause difficulties in the process of creating a pool.

Nevertheless, there are already some patent pools in genetics. A first, instructive genetic patent pool, which gained wide attention, is the Golden Rice pool. Potrykus succeeded in genetically enriching rice grains with β-carotene[24] and wanted to transfer the Golden Rice materials to developing countries for further breeding in order to introduce the trait into local varieties that are consumed in these countries. Six key patent holders were approached and an agreement was reached that allowed Potrykus to grant licences, free of charge, to developing countries, with the right to sub-license[25–27]. This agreement is an example of how private and public organizations, in a combined effort, dealt with the surrounding patents to create a non-profit humanitarian (and therefore probably atypical) patent pool in the form of a single licensing authority[28–30].

Another genetic pool, supported by the World Health Organization (WHO), is under way — the SARS (Severe Acute Respiratory Syndrome) corona virus pool. The relevant patent holders have been identified and agreement has officially been gained by the signing of a letter of intent (J. Simon, personal communication). The SARS pool highlights the opportunities that are offered by the patent-pool concept for biomedical genetic inventions.

Patent pools that comprise sequence data for genetic testing purposes are also worth investigating. Most prone to the patent-pool concept are cases where a disease is caused by various mutations in one gene, or by one or more mutations in any one of several possible genes, as such cases are more likely to give rise to patent thickets[20,40]. However, it remains to be seen whether a gene patent pool that covers only one disease syndrome will reach a fair balance between the costs of creating a pool and adequate revenue, and whether small pools prove to be viable.

As well as providing a possible solution to the problem of patent thickets, the creation of a patent pool might also stimulate funding for research and development, benefiting all partners in the pool. As has been demonstrated in the electronics and telecommunications sector[21,22], the main incentive to setting up a patent pool is the generation of an internationally accepted technical standard. It has been claimed that such a standard is missing in genetics[12]. However, in the context of genetic testing, standards could be defined by establishing a set of mutations that are recognized by the international scientific community, or by reflecting national or international best-practice guidelines relating to genetic testing for a particular disease[31].

> "…the one-to-one licensing mechanism is a flexible model that offers a wide opportunity to tailor access and use to specific needs and circumstances."

Clearing houses

Clearing-house models might be another approach to facilitate access when many patents are present. The term 'clearing house' is derived from banking institutions and refers to the mechanism by which cheques and bills are exchanged among member banks to transfer only the net balances in cash. Nowadays the concept has acquired a broader meaning that refers to any mechanism by which providers and users of goods, services and/or information are matched[32].

Based on this contemporary interpretation, several clearing-house models can be distinguished. The first model is the information clearing house, which provides a mechanism for exchanging technical information and/or information that is related to the IP status of that information. Information mechanisms are relatively easy to set up but require constant maintenance and updating[28,32]. They include general patent search sites, which can be either freely accessible — such as the European Patent Office (EPO) esp@cenet web site — or fee-based. In addition, there are specific search platforms for biotechnological patents, such as Patent Lens. Patent Lens is established in the framework of the BiOS initiative and offers a fully text-searchable database of US, European, Australian and international agricultural and life-science patents, and is complemented by advisory and educational services.

The second model, the technology-exchange clearing house, is inspired by the internet-based business-to-business (B2B) model. This model provides an information service that lists the available technologies to allow technology owners and/or buyers to initiate negotiations for a licence. Additionally, it may provide more comprehensive mediating and managing services[28,32]. An example of a global technology-exchange model is BirchBob, which is an internet-based platform that brings together offers and demands for innovations, and provides services dedicated to finding and facilitating contacts between technology holders and technology seekers. More than 25,000 innovations from 1,900 organizations worldwide are currently searchable on BirchBob by investors, entrepreneurs and scientists who are looking for new business or scientific opportunities. Specific health-care technology platforms include Pharmalicensing and TechEx, which provide online support for partnering and licensing in the biopharmaceutical and biomedical industry. Specific biotechnology platforms include the Public Intellectual Property Resource for Agriculture (PIPRA) — a collaboration among universities, foundations and non-profit research institutions that aims to make agricultural technologies more easily available.

An example of an upcoming, worldwide technology-exchange model is Science Commons. Science Commons aims to encourage technology transfer and intellectual property licensing by stimulating stakeholders to adopt standardized licences to create transparency in the use of patented technology in science, as Creative Commons does for copyright issues in the use of copyrighted material. Science Commons is therefore a more advanced technology-exchange model, as it does not merely link offers to demands, but its main objective is to provide standardized licences worldwide.

The technology-exchange clearing-house model is generally cheap to maintain and generates only low operating costs. However,

it might be difficult to bring together the critical mass of genetic patents that would be needed to turn platforms of this type into useful tools. At present, most of the platforms offer only a small proportion of the market and a low density of patents, and one has to search various web sites (sometimes paying considerable registration fees). Moreover, this model might only be suitable for technologies that can be easily defined and valued. Therefore, it might be limited as a model for general-purpose research methods, such as PCR, and for patents that protect specific and well-defined improvements to familiar downstream products or processes[28,32].

The third model is the royalty-collection clearing house, which would comprise major aspects of the technology-exchange scheme. On top of this, royalty-collection clearing houses would cash licence fees from users on behalf of the patent holder in return for the use of certain technologies or services[33]. The patent holder would be reimbursed by the clearing house pursuant to a set allocation formula. Classical examples of such clearing houses in other sectors include copyright societies for playing music on air and during public performances, such as the American Society of Composers, Authors and Publishers (ASCAP), the Authors Licensing and Collecting Society (ALCS) in the United Kingdom, the Japanese Society for Rights of Authors, Composers and Publishers (JASRAC), and other national agencies.

It has been suggested that royalty-collection clearing houses should be set up in the field of patents and genetic inventions[12,28,32,34–38]. At present, there are no working examples in this field. A praiseworthy attempt to design a royalty-collection clearing-house model in the life sciences — the Global Bio-Collecting Society (GBS)[39] — did not materialize, probably because no consensus could be reached among the stakeholders and because the necessary political support was missing. The GBS was designed to be an efficient, fair and equitable model for the exchange of indigenous knowledge between knowledge holders (indigenous groups) and knowledge users (the life-science industry) in the commerce of biodiversity. Although the GBS model was constructed to encourage arrangements between merely non-IP holders (indigenous groups) and IP holders, the concept could be applied to the more classical IP holder (patentee) and IP user (licensee) situation.

A royalty-collection clearing house would be more complicated to set up in comparison to the previous two clearing-house models; however, once established, it could facilitate the collection of royalties. Although the concerns of the authorities overseeing free competition might vary according to the actual legal structure chosen for the clearing house (for example, a private entity that comprises patent holders as its members, or a neutral, independent, public clearing institution), one should always be aware of potential anti-competitive effects. Furthermore, this type of clearing house would only be useful if there was a recurring need to transact in the patents that were included, and if many patent holders or an entire branch of industry would participate.

A fourth and unique model is the open-source clearing house that fosters the free exchange of technology. A good example in the life sciences is the SNP Consortium. The goal of the SNP Consortium, which is a non-profit entity, is to identify and collect SNPs, and create and make publicly available a map of all catalogued SNPs of the human genome without any proprietary rights being retained by the members of the consortium to allow further drug discovery.

Open-source clearing houses might be a readily available model for sharing and exchanging unpatented technology. However, most genetic inventions are the outcome of long-lasting research that requires high levels of investment. Both private enterprises and universities wish to recover those investments and so do apply for patent protection. Therefore, the scope of application for this model might be limited in the area of genetic inventions, at least in the near future.

A clearing house in genetics might combine various clearing-house models and fulfil different functions such as: identifying all essential claims that are related to a specific technology and indicating the scope of availability for licensing (information clearing house); matching licensees with licensors (technology-exchange clearing house) on the basis of standardized yet flexible royalties and licensing agreements; providing a royalty disbursement accounting system (royalty-collection clearing house); monitoring and enforcing agreements; and resolving disputes.

A clearing house in genetics might be set up by a public entity that would act as financier of the collection society, and could be implemented as a statutory framework on a mandatory basis. Alternatively, it could be set up by a not-for-profit or profit-making (private) organization as a voluntary scheme. Various clearing houses that deal with patent rights in different countries could be coordinated by regional clearing houses (for example, European, North American or Asian), or possibly even by a worldwide, 'umbrella' clearing house. Such a global approach could increase the incentives for patent holders to participate voluntarily in the model by limiting the points of registration. Additionally, owing to the global character of the genetics market place, potential licensees would be better served by a global check-point for existing patent rights. The Human Genome Organization (HUGO) has already suggested that the clearing-house model could also lead to increased levels of

Glossary

Blocking patents
Patents that block further development and commercialization of a product because they might be infringed when the product is used, manufactured or sold.

Community Patent Convention
A convention that was signed in Luxemburg on 15 December 1975, with the aim of creating a community patent: a single patent that is legally valid throughout the European Community. The expected advantages of this system include a substantial reduction in patenting costs (particularly those relating to translation and filing), simplification of application procedure (one single application procedure) and harmonization of interpretation (thanks to the establishment of a single centralized system of litigation). The convention has never entered into force. The discussions were resumed in 1989, but the convention is still not in place.

Complementary patents
Two patents are complementary when they are both required to produce the product or carry out the methods to which they relate.

Cross licence
A cross licence is a bilateral mutual exchange of licences between unrelated parties.

Hatch–Waxman act
This is the Drug Price Competition and Patent Term Restoration Act of 1984, which provides incentives to support the development of generic versions of off-patent drugs and allows patent owners to recover time that is lost during the FDA procedure for approval.

Patent thicket
An overlapping set of patent rights, which requires those who seek to commercialize new technology to obtain licences from multiple patentees.

Royalty stacking
The accumulation of royalties that have to be paid when confronted with a patent thicket.

Standard
A norm or a measure that might be the result of a formal consensus-building procedure that is managed by a standardization body (*de jure* standards) or arise spontaneously owing to the degree of market penetration of a particular technical solution (*de facto* standards).

licensing and to options for researchers to secure licences to sequences and genes at a reasonable cost, which might encourage the pursuit of research in areas from which they might have been deterred in the past[38].

A genetic clearing-house mechanism might facilitate access to multiple patents and so help remove patent thickets. Being a multifaceted model, it could even become a pivotal platform, allowing a mixture of complementary functions and offering information exchange, technology partnering, royalty collection, monitoring, enforcement and dispute resolution simultaneously.

Compulsory licences

Under the compulsory licence mechanism the government or a court can compel a patent holder to license his rights. The 1994 worldwide WTO (World Trade Organization) Agreement on Trade Related Aspects of Intellectual Property Rights affirms the right of member states to grant compulsory licences and implicitly confirms their current autonomy to determine the grounds on which such licences can be granted.

In general, compulsory licences are provided in cases of dependency of a downstream patent holder on an upstream patent holder, and in cases in which the invention is not (or insufficiently) exploited. Recently, it has been suggested that the compulsory licensing mechanism can be invoked to address the potential hindering effects of patents in public health care[41–43]. Such an approach was formally recognized during the WTO Ministerial Conference in Doha, Qatar, confirming that the Agreement on Trade Related Aspects of Intellectual Property Rights and the compulsory licensing regime is part of the wider national and international action that is being taken to address public-health problems[43,44]. In this regard, the European Union has not only taken the necessary steps to put the compulsory licence for public health to work for the benefit of developing countries[45], but various European countries have also designed specific public-health licences for domestic use. France has recently implemented an *ex officio* licence for national public-health reasons in its patent act[46] and Belgium has accepted a special compulsory licensing regime for national health reasons[47].

Unlike most countries, the United States has no general compulsory licensing provision in its patent laws, but makes provision for only a number of specific instances in which such licences might be granted (for example, government use, 28 U.S.C. (United States Code) § 1498; Atomic Energy Act, 42 U.S.C. § 2183, Clean Air Act, 42 U.S.C. § 7608; Plant Variety Protection Act, 7 U.S.C. § 2404; and March in Right, Bayh–Dole Act, 35 U.S.C. § 203).

Although various international treaties offer a firm legal basis for the introduction of a compulsory licence in the member states, no apparent use of the compulsory licensing mechanism has been made by potential licensees in genetics so far. This could indicate a need to re-assess the conditions and procedures for granting compulsory licences.

The compulsory licence regulatory scheme was conceived to resolve a bilateral problem of access between a patent holder and a downstream user. One can well imagine that the compulsory licensing mechanism can also be applied in public health care and genetics to settle access problems between multiple patent holders and multiple technology users. A 'compulsory patent pool', in which a patent-pool entity seeks a compulsory licence from a patent holder of an essential technology who does not voluntarily engage in the pool, should be further explored. A statutory, mandatory clearing house should also be investigated more closely.

Conclusions

Patents considerably limit the freedom to use protected inventions in genetics. Various measures can facilitate access to patented technology and render proprietary genetic and genomic inventions accessible for further use. One possibility for guaranteeing the freedom to operate is to exempt certain activities from infringement. Examples include exemptions for scientific research or submission of information. For activities that do not fall under the research exemption, licensing is probably used most regularly to gain access to patented technology, at least when not too many patent holders are concerned. Patent-pool schemes and clearing-house models might be helpful to settle the presence of multiple patents and multiple patent holders and offer a solution for inventors who wish to gain access to a patent thicket. Nevertheless, parties to licensing agreements should always be aware of the potentially anti-competitive restrictions in their agreement that might lead to a violation of competition law. When patent holders do not voluntarily wish to enter into (reasonable) licensing negotiations, the compulsory licensing mechanism might be a last-resort instrument.

Various governmental and non-governmental institutions, such as the WHO, OECD, HUGO or the US NIH (National Institutes of Health) have suggested the creation of patent pools and clearing-house mechanisms to tackle problems of access and use in genetics. If they wish these models to break through, they might have to promote patent pools by funding the set-up costs for genetic pools, or to take the lead as initiators and co-founders of clearing-house mechanisms by triggering the creation of a mixed information, technology exchange and a royalty-collection clearing house in genetics.

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Competing interests statement
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DATABASES
The following terms in this article are linked online to:
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BRCA1 | *BRCA2* | *CFTR* | *HFE*

FURTHER INFORMATION
BiOS: http://www.bios.net
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CAMBIA: http://www.cambia.org
Convention on Biological Diversity — Clearing House Mechanism: http://www.biodiv.org/chm
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Patent Lens: http://www.bios.net/daisy/bios/patentlens.html
Pharmalicensing: http://pharmalicensing.com
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OPINION

Decoding the research exemption

Jordan Paradise and Christopher Janson

Abstract | While debate continues as to whether genetic sequences, which many argue represent natural phenomena rather than inventions, should be subject to standard patent protections, issuance of patents that claim DNA sequences remains common practice. In an attempt to insulate researchers from patent claims that could hinder scientific progress, many countries have provided general exemptions for scientific research. However, there is no international consensus about the extent of required protections, and even existing exemptions vary widely in clarity and are limited in practical application. We believe that gene patents raise several unique issues that are inadequately handled by the current research exemptions.

Despite serious concerns by many researchers and the public, patents are currently awarded that directly claim physical and computer-readable human gene sequences, which represent both the tangible and abstract informational content of DNA molecules. A fundamental question remains about whether DNA should even be eligible for patent protection, and legal challenges to the existing policy that allows gene patents are imminent. Critics of gene patents argue that DNA and its implicit informational basis represents an irreducible constituent or law of nature, which, under existing United States (US) and European Union (EU) law, is not statutory subject matter. Some have highlighted as especially problematic gene patents that stake claims to basic genetic research, genetic testing and gene therapy [1–3]. This interpretation of the law contrasts with the permissive practices of the US Patent and Trademark Office and European Patent Office, which currently allow broad patents on partial and complete genes, genomes and even social or ethnic classifications of DNA, such as Ashkenazi-specific gene sequences[4,5].

Increasingly, medical research institutes, hospitals, physicians, scientists and patients are questioning the purpose and scope of gene patents, arguing that allowing exclusive rights to the information that is contained in specific manifestations of the universal genetic code has restricted scientific research and health-care delivery, while adding to its overall cost[6,7].

A clearing house for diagnostic testing: the solution to ensure access to and use of patented genetic inventions?

Esther van Zimmeren,[a] Birgit Verbeure,[a] Gert Matthijs,[b] & Geertrui Van Overwalle[a]

Abstract In genetic diagnostics, the emergence of a so-called "patent thicket" is imminent. Such an overlapping set of patent rights may have restrictive effects on further research and development of diagnostic tests, and the provision of clinical diagnostic services. Currently, two models that may facilitate access to and use of patented genetic inventions are attracting much debate in various national and international fora: patent pools and clearing houses. In this article, we explore the concept of clearing houses. Several types of clearing houses are identified. First, we describe and discuss two types that would provide access to information on the patented inventions: the information clearing house and the technology exchange clearing house. Second, three types of clearing houses are analysed that not only offer access to information but also provide an instrument to facilitate the use of the patented inventions: the open access clearing house, the standardized licences clearing house and the royalty collection clearing house. A royalty collection clearing house for genetic diagnostic testing would be the most comprehensive as it would serve several functions: identifying patents and patent claims essential to diagnostic testing, matching licensees with licensors, developing and supplying standardized licences, collecting royalties, monitoring whether users respect licensing conditions, and providing dispute resolution services such as mediation and arbitration. In this way, it might function as an effective model for users to facilitate access to and use of the patented inventions. However, it remains to be seen whether patent holders with a strong patent portfolio will be convinced by the advantages of the royalty collection clearing house and be willing to participate.

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Voir page 357 le résumé en français. En la página 357 figura un resumen en español. يمكن الاطلاع على الملخص بالعربية في صفحة 357.

Introduction

Scientists, patent attorneys and academics have expressed concerns about the emergence of a "patent thicket" in the biomedical sciences. Many patents have been granted in this specific technical field, leading to concern among researchers and companies that they will encounter serious difficulties cutting through the bulk of patents and paying the associated licensing fees.[1] Heller and Eisenberg developed the idea that such an increase in property rights will ultimately lead to a "tragedy of the anticommons".[2,3] By this, they refer to the situation where there are so many property rights in the hands of various owners — with whom parties must reach agreements to enable them to aggregate the rights they need access to in order to legally perform their activities — that it will prove difficult to bargain licences to the patented inventions successfully. High transaction costs may stand in the way of an agreement.[4] If a high number of agreements with right holders is required, transaction costs may lead parties to decide that the bargaining process is not worthwhile. Hence, a socially optimum level of consumption of the resource may not be achieved, resulting in "under-use" of the property which will have a blocking effect on further innovation.[2,3,5] Moreover, the fact that licensees have to acquire many licences in order to avoid patent infringements may lead to elevated royalty fees, caused by royalty stacking. Because the licensee will usually pass on the cost of these fees to the final consumer, the final development and manufacture of products may be obstructed.

A recent study from the Committee on Intellectual Property Rights in Genomic and Protein Research and Innovation (US National Research Council of the National Academies) shows that at present there is no substantial evidence for the existence of a patent thicket or a patent-blocking problem in genetics.[6] However, we note that this study mainly focuses on the consequences of a potential patent thicket on genetic research. Established companies may be reluctant to pursue active licensing policies or even litigation against universities and research institutes. This may not be the case in more commercially competitive relationships.

Moreover, there are factors that may lead to the emergence of a patent-blocking problem in genetics in the future: increased awareness among researchers; and growing rate of patent enforcement caused by the strategic enforcement of their rights by patent holders and the proliferating complexity of biomedical research requiring a broader range and greater number of

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inputs of which a growing number is patented.[6]

Several studies have, however, highlighted that in the field of gene-based diagnostics, patent holders are already more active in asserting their patents, which seems to be inhibiting research and clinical practice. Indeed, some laboratories have — as a result of such patent enforcement policies — ceased to perform tests and/or refrained from test development.[6–11]

In order to overcome the difficulties created by the overall presence of patents in genetic diagnostics, several national, regional and international organizations together with scientists, the pharmaceutical industry and academics are debating alternative licensing models. These alternative models aim to allow effective access to and use of diagnostic testing services, essential in the light of public health, and to enable further research on related technologies. The two models attracting most interest are patent pools and clearing houses.[12] So far, most contributions have focused on patent pools.[13–16] Patent pools have been in existence for decades in the field of electronics and telecommunications. More recently some pools are being established in biotechnology, such as the Golden Rice-pool,[13] the SARS (severe acute respiratory syndrome) pool[13,16] and the GFP (green fluorescent protein) pool.

The clearing house model, however, is rarely investigated, let alone put into practice. Of the few papers available in this area, Krattiger[17] focused on collaborative and technology transfer mechanisms for biotechnology and Graff et al.[18,19] on an intellectual property clearing house for agricultural biotechnology. In Van Overwalle et al.,[12] we recently reviewed which licensing models might facilitate access to and use of patented genetic inventions for research and public health purposes. The aim of this paper is to further explore the clearing house model, in particular its use in the field of genetic diagnostics. Starting with a description of the concept of the clearing house and a brief survey of the different types of clearing houses, the potential functions, features, advantages and disadvantages of a clearing house for diagnostic testing will be analysed.

What is a clearing house?

The term clearing house is derived from banking institutions and refers to the mechanism by which cheques and bills are exchanged among member banks in order to transfer only the net balances in cash. More recently, the concept has acquired a much broader meaning and is used to describe almost any mechanism whereby providers and users of goods, services and/or information are matched.[17]

Types of clearing houses

The Organisation for Economic Co-operation and Development (OECD),[20] the Human Genome Organisation (HUGO)[21] and the Nuffield Council of Ethics[22] support the idea of a clearing house in order to facilitate access to patented genetic inventions. However, none of these organizations has precisely defined what type of clearing house would be optimal. In view of the previously mentioned broad contemporary interpretation of the term and the clearing houses that currently exist, it is important to be precise about the desirable functions and features of such models.

We have identified five types of clearing houses. The first two models merely provide access to (protected) information. This might be basic information related to the technology, the patents, or claims covering these technologies (information clearing house) and/or lists of technologies available through licensing, thereby providing a platform for technology owners and users to enter into bilateral negotiations (technology exchange clearing house).

The remaining three more advanced clearing house types aim to not only provide access to but also to standardize the use of the (patented) inventions. Access and use can be offered by a clearing house on a royalty-free open-access basis (open access clearing house), or via standardized licences (standardized licences clearing house and royalty collection clearing house). In addition to providing standardized licences, a royalty collection clearing house may offer monitoring of the patents transferred to the clearing house and an independent dispute resolution mechanism.

Facilitating access

The information clearing house provides a mechanism for the exchange of technical knowledge and/or information related to its intellectual property status. Information mechanisms are relatively easy to set up but require constant maintenance and updating.[17–19] Examples include general patent search sites, either freely accessible, such as Espacenet from the European Patent Office (EPO), or fee-based, like Delphion, STN International, Dialog or Micropatent. There are also specific patent biotech search platforms, such as Patent Lens. Patent Lens is established in the framework of the BiOS initiative and offers a free, fully text-searchable database of US, European and Australian agricultural and life science patents, as well as complementary advisory and educational services.

The technology exchange clearing house is inspired by the basic Internet business-to-business (B2B) model. This type of clearing house offers an information service that lists available inventions. These lists will allow buyers to initiate negotiations for a licence. Furthermore, partnering, mediating and managing facilities may be provided.[17,18]

BirchBob is an interesting example of a global technology exchange model. It is an Internet platform that brings together offers and demands for innovations with services to find and facilitate contacts between technology holders and technology seekers. Specific healthcare technology exchange platforms include Pharmalicensing or TechEx. They provide online partnering support that enables companies in the biopharmaceutical and biomedical industry to find licensing partners and conclude licensing contracts. Specific biotechnology clearing houses include PIPRA (Public Intellectual Property Resource for Agriculture), a collaboration between universities, foundations and non-profit research institutions to make agricultural technologies more easily available for humanitarian use.

The technology exchange clearing house model will, in general, be cheap to maintain and relatively inexpensive to operate. However, it might be difficult to bring together a large enough number of genetic patents to establish the clearing house as a useful tool that ensures effective access to a comprehensive body of patented inventions. At present, most clearing houses only offer a small proportion of the market and a low density of patents, and one has to search several web sites, some of which impose considerable registration fees. Moreover, this model might only be suitable for technologies that can be easily defined and valued: for example, general purpose research methods, such as PCR, and for patents protecting very specific and well defined improvements to familiar

upstream products or processes.[17,18]

It is important to underline that actual access to the patented inventions is not usually granted by the technology exchange clearing house but by the individual patent holder after one-to-one licensing negotiations have taken place with the licensee. These negotiations are, however, based on the information on the inventions which was provided by the clearing house.

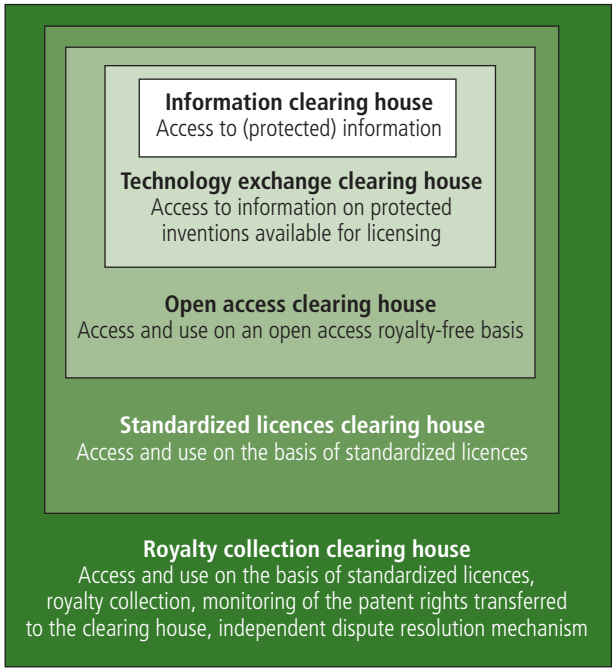
Facilitating access and use

Another type of a clearing house is the open access clearing house. This type of clearing house does not only foster free access to information about inventions, as its name may suggest, but also to standardized free use of inventions. A well known example in the life sciences is the SNP Consortium. The goal of the non-profit SNP Consortium is to identify and collect single nucleotide polymorphisms (SNPs) and create and make the SNP map of the human genome publicly available, without any proprietary rights, in order to enable further drug discovery.

Open access clearing houses may be particularly well suited to sharing and exchanging unpatented inventions. However, most of the genetic inventions are the result of long and expensive research initiatives. Both private enterprises and universities usually seek to recover their investments in such research and, therefore, apply for patent protection. For this reason, apart from situations where the patent rights are extremely fragmented, as illustrated by the SNP Consortium, holders of patents related to genetics will probably not have an incentive to voluntarily cooperate in a scheme where the patented inventions will end up in the public domain. Therefore, the scope of application for this type of clearing house in genetic diagnostics is expected to be rather limited, at least in the near future.

An upcoming model is the clearing house that provides access to and standardized licences for the use of protected inventions, hereinafter called the "standardized licences clearing house". An example of this scheme is Science Commons. This organization aims to encourage data sharing, technology transfer and intellectual property licensing, by stimulating stakeholders to adopt standardized licences in order to create greater transparency. Its sister organization, Creative Commons, has already been in operation for a couple of years facilitating the use of copyrighted material (such as music, movies, photos, books, course materials, scientific literature (e.g. PLoS Biology)) by way of standardized, simplified licences and it has been very successful.

Fig. 1. **Five types of clearing house**



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Finally, the royalty collection clearing house comprises all the functions of the information clearing house, the technology exchange clearing house and the standardized licences scheme (Fig. 1). In addition to these functions, the royalty collection clearing house sets up a mechanism to cash licence fees from users on behalf of the patent holders in return for the access to and use of the inventions.[23] The patent holders will be reimbursed by the clearing house in accordance with a set allocation formula. Well known examples include copyright societies for playing music on air and public performances such as ASCAP (the American Society of Composers, Authors and Publishers), ALCS (the Authors Licensing and Collecting Society in the UK) or JASRAC (the Japanese Society for Rights of Authors, Composers and Publishers) and other national agencies. These copyright collecting societies vary between countries with respect to their make-up, in particular their legal basis, legal structure, decision-making procedures, price-setting procedures, and licensing conditions. In general, however, they are subject to competition law. Therefore, they should refrain from discriminatory practices and set reasonable prices.

An important prerequisite for the royalty collection clearing house to be effective is that there should be a continuous and ongoing demand for patents included in the clearing house. Moreover, the establishment of this type of clearing house is only worthwhile if many patent holders or an entire branch of industry participates. It remains to be seen whether patent proprietors with a strong portfolio would be willing to voluntarily participate in such a clearing house.

At present, no examples of a royalty collection clearing house exist in the field of patents. The Global Bio-Collecting Society (GBS)[24] was a praiseworthy attempt to design a royalty collection clearing house model in life sciences. It was designed to function as an efficient, fair and equitable exchange model of indigenous knowledge between knowledge holders (indigenous groups) and knowledge users (life science industry). The GBS model was never realized, probably because traditional knowledge is a highly sensitive issue, and no consensus could be reached among the stakeholders, nor was there the necessary political support. The GBS model was devised to encourage arrangements between indigenous groups (who generally did not hold any

intellectual property rights) and private and public entities (who did have intellectual property rights) to clear controversies with respect to biodiversity and indigenous knowledge. However, the model might also be applicable to the more classic intellectual property relationship between patent holders (licensors) and users of the patented inventions (licensees).

A royalty collection clearing house in genetic diagnostics?

It has been suggested that a royalty collection clearing house should be set up in the field of patents related to genetic inventions.[12,17,18,20–22,25–27] We take the view that such a clearing house in genetic diagnostics may indeed be able to guarantee both access to and use of patented genetic inventions by serving as a multifaceted platform encompassing as many functions as a clearing house might possibly fulfil.

In a royalty collection clearing house, patent holders would licence their patents to the clearing house in order to enable the clearing house to issue sublicences to the sub-licensees (hereinafter simply "licence" and "licensees"). The clearing house would develop standard licensing agreements in consultation with the patent holders. Such standardized licences could be differentiated in accordance with the nature of the user, the intended use and the profile of the eventual product to be developed by the licensee.

Forms could be drafted with tick-boxes related to the nature of the user, the specific goal of the intended use (such as research, product development (an improvement or a new product), or diagnostic testing), followed by a list of the different patented genetic inventions (such as DNA sequences, mutations, proteins, or technical applications) included in the clearing house. Any potential licensee could tick boxes according to his or her needs, and royalties would be calculated accordingly. Royalty fees would entitle the licensee to access all the essential patents in accordance with the standardized licence drafted for the objective pre-specified by the licensee.

Although the clearing house would facilitate access to and use of multiple patents, the simple "ticking of boxes" related to the relevant genetic inventions by the licensee entails a risk of accumulation of royalties. Such an accumulation may result in a fee that is prohibitively expensive for licensees. To solve this problem, the clearing house might insist on reduced or capped royalties through so-called "royalty stacking clauses" that may be stipulated in the standardized licence.

The clearing house would provide information to the potential licensees on patents and claims relevant to a specific application in genetic diagnostics and indicate to what extent licences are available. Potential licensees would be provided with information about all licences included in the clearing house that might be relevant to their project, much like an information and technology clearing house. It would then "match" licensees and the patented inventions (like a technology exchange clearing house) while at the same time offering the previously mentioned standardized licensing agreements, which could provide flexible yet standardized, reasonable royalties (like the standardized licences clearing house).

Additionally, a royalty disbursement accounting system would be established in the framework of the clearing house. The clearing house would collect the royalties from the licensees and compensate patent holders in accordance with a set allocation formula after deduction of administration costs. Furthermore, the clearing house might also monitor infringements of patents (and notify the patent holder) and provide dispute resolution services by way of mediation or arbitration by a neutral board (Fig. 1).

A royalty collection clearing house in genetic diagnostics could be set up as a neutral, independent agency by a public entity, or as a private initiative by the stakeholders involved who might become members of the collection society. In principle, it might be implemented by a not-for-profit or profit (private) organization as a voluntary scheme or as a statutory framework on a mandatory basis. However, implementation of a statutory organization with an obligation to participate should be a last resort.

Various national or regional clearing houses (North American, Asian, European, etc.) could be set up to identify, match, negotiate, collect royalties, monitor infringements and assist in dispute resolution. All these services could be coordinated by a worldwide, overreaching "umbrella" organization. Such a global approach would not only be cost-effective but could also encourage patent holders to participate in the model by limiting the points of registration yet increasing their visibility for technology users.

Certainly, the global character of the genetics marketplace means that potential licensees would be better served with a global checkpoint for existing patent rights. We note, however, that this suggestion is complicated by the fact that patents operate on a national level. Therefore, standardized licences should be drafted in such a way that the territorial scope of the patents may be taken into consideration. For instance, the licensee would only need to apply for a licence for the countries for which a patent has been granted and for those territories where he wishes to exploit the invention.

Industry standards, which serve as an important incentive for the establishment of patent pools in electronics and telecommunications,[12–14,20] could be another useful tool for managing the royalty collection clearing house. Generally, industry standards are technical specifications related to a product or an operation, and which are recognized by a large number of manufacturers and users.[28] However, a genetic standard should not necessarily be looked at in terms of a technical specification, but could present itself as a set of mutations, recognized by the international scientific community, or reflecting national or international best practice guidelines for genetic testing for a particular disease. Good examples are the standards and guidelines issued by the American College of Medical Genetics for Cystic Fibrosis.[12–14,29]

The rights collected in the clearing house for genetic diagnostics could be identified and grouped on the basis of such best practice guidelines to increase transparency and effectiveness. All the patented products and methods that such guidelines deem to be essential for genetic testing for a particular disease could be made available by the royalty collection clearing house as a bundled set, with a standardized licence at a reasonable royalty fee. In addition to sets of patented inventions, it is very important that the royalty collection clearing house continues to allow scientists, clinical geneticists, laboratories or clinics the option to pick and choose individual licences relevant to their practice. To

limit licensees to buying sets of patents might have anti-competitive effects: users would no longer be free to determine their (competitive) business strategy. Moreover, as the best practice guidelines are subject to continuous review following research and development in the field of genetics, the sets of patented inventions and the related standardized licences should be dynamic as well.

Hence, the clearing house would bridge the gap between patent holders and potential licensees, while at the same time obviating the need for licensees to enter into time-consuming and costly negotiations with the various market players. Thus, transaction costs could be reduced and the potential anticommons effect partly avoided. Because of this collaborative mechanism of centralizing rights, the stacking of royalties could be taken into consideration in the establishment of standardized royalties, and clauses to avoid such stacking could be incorporated into those standardized licences.

Strengths and weaknesses of a royalty collection clearing house

A royalty collection clearing house definitely has certain advantages. From the perspective of a user, such an organization would simplify licensing negotiations in genetic diagnostics and, therefore, facilitate access to and use of the patented inventions. For the patent holder, increased visibility of the patent rights and the streamlining of royalty collection and monitoring, may lead to a rise in licensing and, thus, licensing revenue. At the same time, awareness and respect for intellectual property rights may grow among researchers and their public and private institutions, leading to decreased enforcement costs through fewer infringements. Hence, a reasonable price for licensees (royalties, transaction costs) and licensors (royalties, transaction costs, and enforcement costs) may be achieved.

However, a royalty collection clearing house might have some drawbacks. First, the clearing house might have potential anti-competitive effects, depending on the legal structure chosen for the clearing house. Second, patent holders may be reluctant to voluntarily participate in a royalty collection clearing house. They would have to grant a licence to the clearing house which would then issue licences to all applicants without discrimination and on a non-exclusive basis in accordance with competition law. As a consequence, patent holders would lose some control over their business licensing strategy. Third, unless the clearing house represents a high proportion of all relevant patented inventions, it might not be a viable and effective alternative nor could it prevent the emergence of an anticommons effect. Fourth, royalty clearing houses might be more complicated and costly to set up in comparison with the other clearing house models. Highly educated scientists and experienced lawyers will have to be hired to evaluate the often very complex patents, to match licensees with the patented inventions, to develop standardized licence agreements, and for monitoring and dispute resolution. Fifth, the standardized licences might not allow for measures highly appreciated in commercial licensing practices, such as the setting of milestones, due diligence and the maintenance of long-term business relationships. Sixth, the exchange of relevant technical know-how is often fundamental for the smooth application and further development of the patented invention. Know-how is generally protected as a business secret, but the clearing house will probably not be able to guarantee the exchange of know-how and maintain secrecy. Thus, with respect to complex technologies, direct negotiations between the licensor and the licensee on the issue of know-how may still be required, which might cancel out some of the advantages of the royalty collection clearing house. This drawback might be a reason to advocate the establishment of a royalty collection clearing house that is limited to inventions that do not require the exchange of technical know-how, such as patented DNA sequences and mutations, and a handful of commonly used diagnostic tools.

Admittedly, the analysis we present here is based on preliminary research, and a full economic examination of the model by economists is still required. However, such an examination is beyond the scope of this paper. For now, the leap forward to a royalty collection clearing house may be too big, especially since biotech companies rely heavily on their patent portfolio, and foster what has been called a bunker mentality: that is, a defensive attitude focused on self-protection and secrecy.[30] More realistic might be the emergence of a global technology exchange clearing house for genetic diagnostics that may eventually develop into a royalty collection clearing house when the concept has matured, when economists have delivered favourable reports on the potential efficiency of a royalty collection clearing house and when there is a greater willingness to cooperate within the biomedical industry.

Conclusion

The royalty collection clearing house model could be very useful in providing access to and use of patented inventions in genetic diagnostics. HUGO has already suggested that the clearing house model could also lead to increased levels of licensing and options for researchers to secure licences to sequences and genes at a reasonable cost. HUGO also suggested that these benefits might encourage scientists to pursue research in areas from which they might have been deterred in the past.[21]

Nevertheless, the establishment of a royalty collection clearing house on a national or regional basis covered by a global umbrella organization would without doubt be a complex, time-consuming and costly endeavor. Therefore, before it can be implemented as a workable alternative, it is essential that further exploration and discussion of this model takes place with a wide range of experts (such as economists, lawyers, patent attorneys, social scientists, ethics committees) and stakeholders (such as clinical geneticists, big pharmaceutical companies, biotech companies, and patients' organizations). WHO might play a prominent role in the initiation of this consultation process by organizing and funding workshops of experts to investigate what might be a solution to the patent thicket problem in genetic diagnostics.

Further reading and online links are available from: http://www.who.int/Bulletin ■

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Résumé

Un office central pour les tests diagnostiques : la solution pour que les inventions brevetées dans le domaine génétique soient accessibles et exploitables ?

Dans le domaine du diagnostic génétique, l'apparition de ce qu'on appelle un «taillis de brevets» est imminente. Un tel ensemble de droits de propriété empiétant les uns sur les autres pourrait avoir des effets restrictifs sur la poursuite des travaux de recherche et développement sur les tests diagnostiques, ainsi que sur la prestation de services de diagnostic clinique. Actuellement, deux concepts susceptibles de faciliter l'accessibilité et l'exploitabilité des inventions brevetées dans le domaine génétique sont au centre de bien des débats menés dans les divers forums nationaux et internationaux : la communauté de brevets et l'office central des brevets. L'article explore la notion d'office central et identifie plusieurs types de dispositifs y répondant. Il commence par décrire et examiner deux types d'offices centraux qui permettraient d'accéder aux informations sur les inventions brevetées : un centre d'échange des données et un centre d'échange des technologies. Puis il analyse trois autres types d'offices centraux offrant non seulement accès à l'information, mais également un instrument facilitant l'exploitation des inventions brevetées : l'office central en libre accès, l'office central délivrant des licences normalisées et l'office central de collecte des redevances sur les brevets. Un office central de collecte des redevances sur les brevets relatifs aux tests diagnostiques génétiques constituerait la solution la plus complète dans la mesure où il assurerait plusieurs fonctions : identifier les brevets et les demandes de brevets essentiels dans ce domaine, mettre en relation les octroyeurs et les porteurs de licences, développer et délivrer des licences normalisées, collecter les redevances sur les brevets, veiller au respect des conditions de licence par les utilisateurs et fournir des services pour le règlement des contentieux, tels que la médiation et l'arbitrage. Cet office central pourrait ainsi jouer le rôle de modèle efficace de dispositif facilitant l'accessibilité et l'exploitabilité des inventions brevetées. Il reste cependant à convaincre les détenteurs de gros portefeuilles de brevets des avantages d'un office central de collecte des redevances sur les brevets et d'y recourir.

Resumen

Centro coordinador para las pruebas diagnósticas: ¿la solución para asegurar la accesibilidad y el uso de las invenciones genéticas patentadas?

En el campo del diagnóstico genético, se considera inminente la aparición de lo que se ha calificado como «maraña de patentes». Un conjunto imbricado de derechos de patente puede tener efectos restrictivos en la realización de nuevas actividades de investigación y desarrollo de pruebas diagnósticas, así como en la prestación de servicios de diagnóstico clínico. Dos modelos que pueden favorecer el acceso a las invenciones genéticas patentadas y el uso de las mismas están suscitando actualmente un amplio debate en diversos foros nacionales e internacionales. Se trata de las patentes mancomunadas y los centros coordinadores. En este artículo se analiza el concepto de centros coordinadores y se describen varios tipos de centros con esa función. En primer lugar, describimos y examinamos dos tipos que ofrecerían acceso a información sobre las invenciones patentadas: el centro coordinador de información y el centro coordinador para intercambio de tecnologías. En segundo lugar, analizamos tres tipos de centros de coordinación que no sólo ofrecen acceso a información sino que además brindan un instrumento para facilitar el uso de las invenciones patentadas: el centro coordinador de libre acceso, el centro coordinador de licencias normalizadas y el centro coordinador de percepción de regalías. Un centro coordinador de percepción de regalías para las pruebas diagnósticas genéticas sería el instrumento más exhaustivo pues permitiría asegurar varias funciones: identificación de las patentes y las solicitudes de patentes esenciales para las pruebas diagnósticas, emparejamiento de licenciadores y licenciatarios, desarrollo y suministro de licencias normalizadas, percepción de regalías, vigilancia de la observancia de las condiciones de la licencia por los usuarios, y prestación de servicios de resolución de controversias, como mecanismos de mediación y arbitraje. De esta forma, podría ser un modelo eficaz para los usuarios, que facilitaría el acceso a las invenciones patentadas y el uso de las mismas. Sin embargo, habrá que ver si quienes poseen una buena cartera de patentes reconocen las ventajas de un centro coordinador de esas características y están dispuestos a participar en él.

ملخص

مركز تبادل للمعلومات حول الاختبارات التشخيصية: هل هو الحل لضمان إتاحة واستخدام الابتكارات المسجلة الملكية في الوراثيات؟

لقد أصبح إطباق ((مجالات تسجيل حقوق الملكية)) على المواد التشخيصية في الوراثيات أمراً وشيك الوقوع. وقد يؤدي تراكب مجموعة من حقوق الملكية إلى تأثيرات محددة على زيادة البحوث والتنمية في الاختبارات التشخيصية وعلى إيتاء الخدمات التشخيصية السريرية (الإكلينيكية). ويتعالى الجدل هذه الأيام في مختلف المنتديات الوطنية والدولية حول نموذجين قد يسهلان إتاحة واستخدام الابتكارات المسجلة الملكية في الوراثيات، وأول هذين النموذجين هو مراكز تبادل المعلومات وثانيهما هو مراكز تجميعها. ونستقصي في هذا المقال مفهوم مراكز تبادل المعلومات، ونميز أنماطاً مختلفة لها. وقد قمنا أولاً بوصف ومناقشة نمطين من أنماط إتاحة المعلومات حول الابتكارات المسجلة الملكية، أول هذين النمطين هو مراكز تبادل المعلومات وثانيهما هو تقنيات تبادل المعلومات في تلك المراكز. ثم قمنا ثانياً بتمييز ثلاثة أنماط من مراكز تبادل المعلومات التي تم تحليلها والتي لا تقتصر على تقديم إتاحة المعلومات بل تتعدى ذلك أيضاً لتقديم أداة لتسهيل استخدام الابتكارات المسجلة الملكية؛ وهي مراكز تبادل المعلومات ذات الإتاحة المفتوحة ، ومراكز تبادل المعلومات ذات الرخص (أو الإجازات) المعيارية)، ومراكز تبادل المعلومات ذات مجموعات من حقوق الملكية.

ويعد مركز تبادل المعلومات ذو مجموعات حقوق ملكية الاختبارات التشخيصية في الوراثيات الأكثر شمولاً من بين هذه المراكز، لما يقدمه من

خدمات لوظائف عديدة: التعرُّف على حقوق الملكية المسجلة وطلبات تسجيل حقوق الملكية الضرورية في مجال الاختبارات التشخيصية، ومواءمة الرخص أو الإجازات مع أصحابها، وإعداد الرخص أو الإجازات المعيارية وتقديمها، وتجميع حقوق الملكية ورصد مدى احترام المستخدمين لشروط الرخص أو الإجازات وتقديم خدمات لحل الخلافات مثل التواسط والتحكيم.

وبهذا يمكنه أن يصبح نموذجاً فعَّالاً للمستخدمين لتسهيل إتاحة واستخدام الابتكارات المسجلة الملكية؛ إلا أنه لابد من البحث عمن يحمل حقوق الملكية بشكل شديد الوضوح وإقناعهم بفوائد مراكز تبادل المعلومات التي تجمع حقوق الملكية ولابد من إقناعه بالمبادرة بالمشاركة في هذه المراكز.

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Glossary

Competition or antitrust law: antitrust law is a term primarily used in the United States, while in many other countries the term "competition law" is used. Most antitrust or competition laws have provisions dealing with mergers, abuse of a dominant position and anticompetitive practices.

Industry standard: a norm or a measure that might be the result of a formal consensus-building procedure that is managed by a standardization body (de jure standards) or arise spontaneously owing to the degree of market penetration of a particular technical solution (de facto standards).

Licence: a licence permits the **licensee** to use the patented inventions or product in a defined way and territory for a specific purpose. The use of the patented invention would be unlawful in absence of that permission.

Licensor: the entity that delivers a licence to the licensee, allowing the licensee to use the patented inventions in accordance with the **licensing conditions** (with respect to for instance royalties, territorial restrictions, (non-)exclusivity, obligations to grant back a non-exclusive licence to improvements of the patented inventions). Generally, the licensor will be the **patent holder**, but it may also be a licensee competent to grant sublicences.

Patent: a patent is a right granted by the government to an inventor that confers on that person the exclusive right to prevent others from making, using, selling or importing the invention without his or her permission, for a limited period of time and for a specific (national) territory. For a patent to be granted the invention has to be new, there has to be an inventive step and the invention has to be eligible for industrial application.

Patented genetic inventions: inventions for which a patent has been granted in the field of genetics. These include patents on DNA sequences and mutations, gene-constructs encoding therapeutic proteins, as well as genetic technologies such as amplification or sequencing techniques.

Patent pool: an agreement between two or more patent owners to license one or more of their patents to one another and to license them as a package to third parties willing to pay the royalties associated with the licence. Licences are provided to the licensee either directly by one of the patentees, or indirectly through a new entity that is specifically set up for the administration of the pool.

Patent thicket: an overlapping set of patent rights, which requires those who seek to commercialize new inventions to obtain licences from many patent holders.

Royalties: fees to be paid in exchange for the use of the licence. Such fees may, for instance, be upfront payments and/or a percentage of the net sale price of any resultant product or invention that results from use of the invention covered by the patent.

Royalty stacking: the accumulation of royalties that have to be paid when several licences must be obtained from many patent holders.

Further reading and online links

- American Society of Composers, Authors and Publishers: http://www.ascap.com/
- Authors Licensing and Collecting Society: http://www.alcs.co.uk/
- BiOS: http://www.bios.net
- BirchBob: http://www.birchbob.com
- Creative Commons: http://creativecommons.org
- Delphion: http://www.dephion.com
- Dialog: http://dialog.com
- Espacenet: http://www.ep.espacenet.com
- GFP-pool: http://www.amershambiosciences.com
- Japanese Society for Rights of Authors, Composers and Publishers: http://www.jasrac.or.jp/ejhp/index.htm
- MicroPatent: http://www.micropatent.com/static/index.htm
- Patent Lens: http://www.bios.net/daisy/bios/patentlens.html
- Pharmalicensing: http://www.pharmalicensing.com
- PIPRA: http://www.pipra.org
- SNP Consortium: http://snp.cshl.org
- Science Commons: http://sciencecommons.org/
- STN International: http://www.stn-international.de
- TechEx: http://www.techex.com

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ARTICLE

Analysing DNA patents in relation with diagnostic genetic testing

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In the ongoing debate concerning DNA patents, there is a need for empirical data. We aim at creating this data set for DNA patents related to diagnostic genetic testing. To this end we developed two tools to facilitate this process. First, we set up a search strategy to find the relevant patents. Second, we provide a claim classification template to assist the user in the assessment of the subject matter covered by the patent claims and in creating a comprehensive overview of the patent situation within this field. These tools have been used in a pilot study on 11 selected hereditary disorders. In addition, a detailed analysis of the familial breast and ovarian cancer genes patents retrieved by the developed search strategy and their claim classification, after meticulous reading of the documents, allowed us to better describe the problems which medical geneticists and researchers might face when dealing with the patented technology.
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Keywords: gene patents; diagnostic testing; breast cancer genes; BRCA1; BRCA2

Introduction

The appropriateness of patenting DNA sequences and genetic technologies is, still, a matter of debate and controversy. Initially, DNA patents were mainly focused on newly cloned genes encoding therapeutic proteins, for example, human t-Pa (EP0093619) or human insulin (EP0055945). Hence, in this area of research and in the development of therapeutics, gene patents were considered equivalent to patents on new chemical entities with a therapeutic use where patenting was accepted as an established management strategy. But underlying science advanced. Newer and faster tools and techniques became available for identifying genes and their involvement in diseases. Today, genetic sequence information no longer has its main application in recombinant technology and the supply of therapeutics, but the data are used in the much broader context of life science research, drug development, diagnostics, etc.[1] This evolution generated patents that play different roles in management strategies in the biomedical community: the scope of patents on DNA sequences evolved from patents on gene-constructs encoding therapeutic proteins, to patents on DNA sequences including not only their therapeutic utility in encoding the protein, but also the application of the knowledge regarding a gene sequence in diagnosis and research. Therefore, the interests at stake and the group of professionals affected changed and set off a delayed but persistent concern about patenting genes and the approach to be taken in this field.[2]

Regarding diagnostics, several studies have been published on the possible influence of patents and licensing strategies on the provision of clinical genetic testing services.[3–8] The main focus has been on analyzing licensing practices and understanding the strategies of companies and research organizations in their attempt to exploit acquired rights over their inventions. Publications mostly result from surveys held with companies, research centers and diagnostic service providers, both public and private.[9,10] Two major concerns have been put forward: first, clinical geneticists feel that the service towards

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patients is hampered, and second, research and new test development may be inhibited by patents.[11–13]

Despite the value of these studies by illustrating an important issue in the relation between patenting and (public) health services, no in-depth data are available yet on the scope and effective characteristics of the problem described. Most of the reports contain only anecdotal evidence to support their conclusions, probably because broadly based evidence is not readily available. Additionally, the reports available to a large extend focus on ownership and licensing practices and not necessarily on the patents and the scope of patent protection. Only a few papers discuss the patentability itself, whereby a recent American study questioned the patentability requirements for DNA sequences in detail.[14] In any case, the emphasis in the published surveys lies with the patent situation in the US, Canada and Australia. We aim at creating a better understanding of DNA-patents and the actual protection that they confer by the wording of the claims, while focusing on the European situation. Our methodology is based on gathering empirical data by collecting and studying in an exhaustive way the patents that are of importance for genetic diagnostic testing. In this way, a valuable tool and an empirical basis for policy development are created. At the same time, the developed tools could assist those working in the field of diagnostic testing to find and read patents related to their specific scientific needs.

Results and discussion

Gathering the empirical data consists of two aspects for which tools were developed. On the one hand, the patents relating to genetic diagnostic testing have been searched in an existing database. On the other hand, after careful reading of the resulting patents, the claims were analyzed in detail and classified. The presented search and classification tools were formed gradually throughout and were applied in a pilot study that was performed on a select number of genetic disorders and the genes involved.

The patent search

The number of patents filed and granted at the European Patent Office (EPO) is large. For example, 5474 European patent documents in the field of biochemistry and genetic engineering (international patent class C12) were published in 2004. It is therefore imperative to use a good search strategy in order to find the relevant documents.

Different patent databases were tested in order to set up a robust search strategy and to find the patents relevant to this area of practice. A more complete list of patent resources can be found on the EPO website (http://www.european-patent-office.org/online/index.htm#databases). A main distinction can be made between the noncommercial and freely accessible databases of which most are supported by patent offices, and the fee-based commercial databases. A key example of a noncommercial database is Espacenet® (http://ep.espacenet.com/), a patent resource from the EPO. This database is freely accessible and comprises a worldwide patent collection. Unfortunately, in Espacenet® only a limited number of search terms is accepted by the search engine and text is only searchable on title and abstract. The United States Patent and Trademark Office (USPTO) also offers a freely accessible on-line database which unfortunately is limited to US patents and patent applications, although the documents are full-text searchable (http://www.uspto.gov/patft/index.html). Commercial databases such as Delphion® (http://www.delphion.com/), STN International® (http://www.stn-international.de/), Dialog® (http://www.dialog.com/) or Micropatent® (http://www.micropatent.com/static/index.htm) are supported by a more performing search platform, thereby responding to the need of patent professionals for the use of more complex search algorithms.

Nevertheless, finding the relevant patents might remain a cumbersome undertaking. Already several initiatives led to the construction of 'subset patent databases'. These subset databases offer a collection of patents limited to a certain technological area. Several of these databases focus on biotech patents and aim to assist both professionals and nonprofessionals to understand and navigate the biotech patent landscape. An interesting example is the DNA Patent Database (DPD, http://dnapatents.georgetown.edu). DPD is a joint project of Georgetown University's Kennedy Institute of Ethics and the Foundation for Genetic Medicine. The DPD contains DNA patents issued by the USPTO. DPD is created to make full-text patents available at no cost and to define a searchable set of patents of interest to those studying genomics, genetics, biotechnology and other fields. Another example is the BiOS patent database for life sciences (http://www.bios.net) that contains patents relating to a rather broad area of life sciences, covering biology, biotechnology, medicine, chemistry, agriculture, food science, etc. The BiOS collection currently consists of life science patents from the US, Australia and Europe and contains a subset of all patents, extracted on the basis of the International Patent Classification (IPC) codes pertaining to the life sciences encompassing a rather broad range. All patents in the life sciences, impacting public health, medicine, pharmaceuticals, chemistry, environmental management and genetic resources, as well as food, nutrition, agriculture and biotechnology are taken up in this database. Both these subset databases – DPD and BiOS – did not exactly correspond to our needs for identifying patents defined to the field of diagnostics but were very helpful in the development of our search strategy.

We developed a patent search strategy that runs in two steps. At the first stage, a general search algorithm was

constructed. The aim was to obtain a first collection containing essentially all DNA-patents relating to genetic diagnostic testing while reducing the amount of interfering nonrelevant patents. The general search algorithm set up for this study is similar to the search algorithm underlying the DPD. Patents included in the DPD were identified by virtue of their USPTO classification codes and the presence of keywords in the claims such as 'DNA'. This combination of USPTO classification codes and keywords is called the Cook–Deegan algorithm developed by Robert Cook–Deegan at Duke University.

By reducing the noise, this first selection greatly facilitates the search in the second stage: the search for diagnostic DNA patents on a specific gene or hereditary disorder. Indeed, we were interested in a subset of the collection gathered for the DPD, namely patents concerning the information relevant to diagnostic testing only. Also, because our primary focus is the situation in Europe, we based our search on the relevant IPC codes instead of DPD's combination of USPTO classification codes. The BiOS patent database, although set up on the basis of IPC codes, does not offer an advantage over the conventional databases either since it encompasses a selection that is too broad when considering DNA patents related to diagnostic genetic testing only.

For the selection of the IPC codes for our search algorithm, the major hurdle to overcome was that gene or DNA patents do not coincide with a specific IPC category. Therefore, a group of IPC codes has been selected encompassing the various IPC codes that have been given by the patent offices to the DNA patents that we aim to retain by our search (see Table 1). The combination of IPC codes in our search algorithm is the result of an iterative process which we performed, starting from a group of codes attributed to a set of manually searched patents relevant to our goal. This initial list has been narrowed down on the basis of our own analysis of the patents and our insight in the field of diagnostics, in a way to reduce the amount of nonrelevant patents without loosing the intended documents in the result of the search.

The group of patents thus obtained was then further limited by a keyword search string in the claims. For the keyword selection, a similar process was conducted as for the IPC code selection, starting from the list of keywords used in the Cook–Deegan algorithm. The resulting algorithm that we used for a first selection of patents, combines IPC codes and keywords appearing in the claims as shown in Table 1. The search algorithm was set up in the commercial database of Micropatent®. Unfortunately, the available free of charge patent databases such as Espacenet® are not equipped with a search engine that allows the degree of complexity of the developed algorithm.

The resulting collection of DNA patents was used in the next step of our search: finding DNA patents relevant to genetic diagnostic testing on a specific gene or for a specific hereditary disorder. To this end, the collection has been searched on the basis of keywords specifically associated with the gene (name of the gene and gene product and the relevant synonyms, the gene's letter code etc.) and/or the disorder related to the gene. For example, for Huntington's Disease the keyword selection included huntington, huntingtin, 'HD' and 'IT15'.

In a pilot study, a set of hereditary disorders was used to optimize and test the developed search strategy. The disorders included in this test, together with the relevant genes searched and patent entries found, are listed in Table 2. They represent key examples selected on criteria such as disease frequency, inheritance pattern, frequency in the population, clinical importance, types of testing available (diagnostic, predictive, prenatal), availability of alternative testing techniques, and whether or not treatment is available. Patents were selected in function of their relevance to genetic diagnostic testing. In practice, essentially all patents that could affect genetic diagnostic testing based on the cited genes were selected from the search results list. This includes patents with product claims on the gene itself or on mutated forms, as well as on diagnostic methods or kits involving the gene. Although emphasis of this study is put on the European patent situation, US patents were included for comparison.

Apparent from this pilot study is the difference in number of patents issued at the present time in Europe compared to the US: in general more US than EP patent documents are retrieved. At least three reasons can be put

Table 1 General search algorithm for DNA patents relevant to diagnostics

(IPC: C07H021* OR C07K014* OR C12N0151* OR C12N0152* OR C12N0153* OR C12N0154* OR C12N0155* OR C12N0156* OR C12Q00168 OR G01N0335* OR G01N0336*) and (keywords in claims: 'gene' or 'genes' or genetic or genomic or genotype or haplotype or DNA or DNAs or cDNA* or RNA or RNAs or mRNA* or 'nucleic acid' or 'nucleotide sequence' or polynucleotide or exon or exons or intron or introns or probe or probes or primer or primers or hybridisation or hybridization or polymorphi* or marker or mutation* or mutant or mutated or allelic or allele or 'wild type' or substitution or deletion or insertion or alteration or diagnos* or predisposition or susceptibility)

The search results in a collection of patent documents classified according to one of the IPC codes listed in the algorithm, and containing at least one of the listed keywords in the claims.
* = Wild card character (no limit on characters added, eg, polymorphi* encompasses polymorphic, polymorphism etc);
'…' = Exact phrasing only. The definition of IPC codes used in this search algorithm (C07H 21, C07K 14, C12N 15, C12Q 01/68, G01N 33) can be found on http://www.wipo.int/classifications/fulltext/new_ipc/index.htm.

Table 2 Listing of a set of hereditary diseases and their genes (as indicated on Genetest website and OMIM entries) taken up in the pilot study

Disease	*Gene*	*European patents*	*US patents*
Achondroplasia	*FGFR3*	One application	—
Alzheimer (late-onset)	*APO-E*	Six granted patents	Five granted
Canavan	*ACY2*	—	One granted, one application
Gaucher	*GBA*	Two applications (one refused, one withdrawn)	Two granted
Hereditary breast and ovarian cancer	*BRCA1*	Five granted (one revoked and two amended after opposition procedures), five applications (one withdrawn)	15 granted, seven applications
	BRCA2	Two granted (one amended) three applications	Four granted, one application
Hereditary hemochromatosis	*HFE*	One granted, seven applications	Six granted,
	TFR2	Two applications	Seven applications
	Ferroportin	One application	
Hereditary nonpolyposis colorectal cancer (HNPCC)	*MLH* genes *MSH* genes *PMS* genes	Four applications	Eight granted, 10 applications
Huntington	*HD*	One granted, one application (withdrawn)	Two granted
Neurofibromatosis	*NF1*	Two applications	Four granted, one application
	NF2	One granted	One granted
Tuberous sclerosis	*TSC1*	—	Two granted
	TSC2	One application	Two granted
Short stature	*SHOX*	One granted	One application

The patent count includes all patents that could affect genetic diagnostic testing based on the cited genes thus including patents with product claims on the gene itself or mutated forms, as well as diagnostic methods or kits involving the gene (last updated 16 August 2005).

forward to explain this difference. Part of this phenomenon has been attributed to a backlog in the granting procedure at the EPO,[15] so that a lot of the applications are still pending (eg Hereditary Hemochromatosis, Hereditary Non-Polyposis Colorectal Cancer (HNPCC)). Alternatively, it has been indicated that the EPO would employ higher standards than the USPTO although no data effectively substantiated this statement. We also noticed that in some of these cases either the inventors applied for a patent in the US but not in Europe (eg *TSC1*, *ACY2*), or some of the EP patent applications of which the US counterpart has been granted, have been refused or withdrawn from the European procedure (eg *HD*, *GBA*), or revoked after opposition (*BRCA1*, first instance, the patent proprietors filed an appeal against the decision) (Table 2).

Another important remark resulting from this pilot study is that one also has to be cautious in focusing on the number of patents resulting from a search. Differences in patent law between the US and Europe can result in a different number of patents, covering the same subject matter. An important reason for this is for example that a product claim on the nucleic acid sequence and a product claim on a protein sequence can occur in the same EP patent, whereas in the US two different patents have to be filed for each type of product claim.

Patent characterization

Subsequent to the collection of relevant patents, we gathered additional information with regard to the type of claims. The claims of a patent define the scope of protection conferred by the patent. As already indicated above, some of the collected DNA patents are more fundamental than others. For example, a patent covering the full cDNA sequence as a product is more fundamental than a patent disclosing a method for using this sequence in a diagnostic method. In the report of the Nuffield Council of Bioethics,[8] serious concern was raised on the granting of inappropriately broad patents where the actual utility disclosed in the patent only relates to a specific application or use of the claimed subject matter: '*protection is sought primarily for DNA sequences as such and extended with their application in method or use-claims*'. Within the variety of possible applications of genetics, in terms of patent protection, distinction has been made in four main method or use categories: the production of therapeutic proteins, diagnostic methods, research tools and gene therapy. Patents cast in broad terms of the gene sequence as such, effectively give the patent holder the exclusive right to control all downstream uses of the sequence, including research and development of tests, therapy and a whole range of diagnostics. The actual wording of the claims in those patents can have important bearings on the effect patents have both on health care services and on future research and innovation. It is therefore imperative to have actual data on the types of claims that have been granted to assess the breath of the assumed problem.

To this end, we have designed a detailed template to classify the claims after a thorough analysis of the granted European patents. The result is a detailed overview of the different types of product, method and use claims. This classification of claims will help in creating a better general understanding of the scope of protection conferred by the

DNA patents granted. Within the three main claim types, subdivisions were made as listed in Table 3, panel A. A direct comparison of claim classifications of different patents will also visualize where interferences between different patents might exist and hence where a conflict of interest between different patent proprietors might occur.

The template could assist the user when trying to assess what subject matter is covered by the patent claims. It presents a comprehensive overview of patented materials, methods or uses regarding a certain gene sequence. The template could also be useful for researchers and other professionals in the field of genetics, to whom the patent language can be obscure and confusing, to help them in a useful direction. The classification might thus help '*to render the massive, complex and opaque world of patents and IP into a transparent and stimulating structure for the public good, as originally intended by framers of patent systems*' (citation from www.bios.net), not only at the level of patent search but also at the level of understanding the scope of protection. Although the claims of the patents have been read carefully and in light of the specification for their classification in the template, one still needs to read the patent itself to know exactly what is covered by the claims. This is inevitable because of the importance of the wording of the claims and of the support for those claims that has to be found in the patent specification.

We have illustrated the utility of the classification template by applying it to the patents on the familial breast and ovarian cancer genes *BRCA1* and *BRCA2* (see Table 3, panel B). Oppositions were filed at the EPO against three of the patents related to *BRCA1*. This resulted in one patent being revoked (EP0699754)[16] and two patents upheld in amended form (EP0705902 and EP0705903)[17] (decision for EP0699754 and minutes of the oral proceedings for EP0705902 and EP0705903 are available for download at the EPO's Online Public File Inspection on http://ofi.epoline.org/view/GetDossier). For the purpose of comparison and for its illustrative value on the gene patenting issue, the set of claims as originally granted as well as the amended set of claims for these patents are retained in this study. Meanwhile, the proprietors of the patent EP0699754 filed appeal against the decision to revoke. Oppositions have also been filed against the *BRCA2* patents. EP0785216 has been upheld in amended form after recent proceedings at the EPO.[18] The breast cancer genes' patent situation has been amply commented on in the recent past and left a tumultuous trail throughout the research, medical and patent law community. Nevertheless, a comparative and in-depth analysis of all the granted patents to date and the scope of their claims has not been reported in the literature. We have tried through this claim analysis to further clarify the situation under debate.

As can be read from the claim classification templates for both *BRCA1* and *BRCA2* (Table 3), inventors aim at claims in the product category that cover the full cDNA sequence (line I.2) as a prime objective due to the broad protection it confers. Methods related to diagnosis (line II.1–6) constitute another main category, ranging from a claim covering the determination of a variation in the cDNA sequence (deleterious or not, lines II.1 and 2), or more specifically by claiming diagnostic methods based on the cDNA sequence and identified/disclosed deleterious mutations (line II.5). A last major group of claims comprises methods or products covering the therapeutic application of the knowledge that stems from the genetic sequence in gene therapy or recombinant production of the protein for therapeutic purposes (lines I.19, I.21–27, II.9, III.1–3 and III.7–8).

Products that are not perceived as having that much direct commercial utility, seem to get much less coverage despite their importance for more fundamental research purposes. This seems to be the case for the genomic sequence (line I.5). Besides possibly the unavailability of the genomic sequence at the time of the invention, this may also be due to a lack of interest from a commercial point of view at that time. Only a minor percentage of deleterious mutations were found in intronic parts of the gene and hence it was uncertain whether it was worth the financial effort and the strategic risk in waiting for the genomic sequence before filing the patent. Another argument for patenting the cDNA sequence is patent technical in nature and is the non-natural character of that sequence. The generation of a cDNA sequence implies a process of isolation and purification since cDNA does not occur in nature as a DNA molecule. Support for this theory can be found in the Rule 23c(a) European Patent Convention and Article 5 and Recital 22 EU Directive 98/44/EC.

Besides the cDNA sequence, claims frequently cover fragments of the cDNA sequence (lines I.7 and 8). In some cases, this may result from the fact that these fragments were the only actual sequence data available to the inventors for disclosure in the patent application at the time of filing. This was the case with one of the *BRCA2* patents (EP0858467). In most other cases, cDNA fragments are usually claimed in terms of necessary tools for diagnostic and therapeutic purposes, for example, primers for PCR amplification, (labeled) probes for mutation detection etc.

This distribution of the subject matter illustrates that the scope of protection sought by the inventors, clearly reflects the economic incentive to file patents. Indeed, research on the *BRCA1* and *BRCA2* genes was spurred by their involvement in the etiology of breast and ovarian cancer, consequently by their utility in carrier identification and diagnosis through genetic testing, and ultimately, by the prospect of developing gene specific disease therapy for example, through gene therapy or production of therapeutic proteins using recombinant technology. It is therefore not surprising that patent protection is sought in those areas of possible commercialization on a larger scale: diagnostics and therapeutics.

Table 3 Classification template for the subject matter covered by the claims with application to the BRCA1 and BRCA2 patents (A): Different categories of claims covering product, method or use claims. (B): classification of European patents related to the BRCA1 and BRCA2 gene

A		*B*								
			BRCA1					*BRCA2*		
		EP0699754 [1] 11.08.1995[a]	*EP0705902 [1] 11.08.1995*[a]		*EP0705903 [1] 11.08.1995*[a]		*EP0820526 [2] 12.02.1997*[a]	*EP0821733 [3] 19.04.1996*[a]	*EP0785216 [1] 17.12.1996*[a]	*EP0858467 [4] 25.11.1996*[a]
I	***Product***									
	Locus-related sequences									
1	Markers									
	Nucleic acid									
2	cDNA		***1***, 2				1		***1***, ***2***	**3**, **4**
3	Individual exons									
4	Individual exons with flanking intron									**1**, **2**
5	Genomic sequence									
6	Complementary seq.		***5***							
7	Fragment									**1**, **5**
8	Primers/probes		***6***, *7*, *8*	1	***3***, ***31***	1[b]			***6***	
	Variation/mutation									
9	% Identical/variation		***3***							
10	Nonspecific mutation									
11	Specific mutation		***4***		***1***, ***2***, ***30***			**1–5**	*3*, ***4***, ***5***	
	Peptide									
12	Wild type		***15–16***, *18*, *21*				*2*			**11** (full), **12** and **13** (fragment)
13	Mutated		***17***, *18*, *21*, *22*, ***19***, *20*		***13***			**6–10**		
14	Antibody									
	Diagnostic kit comprising:									
15	Nucleic acid		***25***, ***26***							
16	Peptide									
17	Antibody									
	Composition/preparation									
18	Nucleic acid									
19	Peptide				***9–11***, ***12***, ***32***				***11***, *12*	
	Purpose-limited product									
20	Nucleic acid		*27*						***16***	10
21	Peptide		*29*							14
	Recombinant technology									
22	Vector		***9***, ***10***, ***11***	2	***4***, ***5***	2[b]			***7***	**6**
23	Host		***12***	3	***6***	3[b]			***8***	**7**
24	Peptide									
25	Antibody									**15**
26	Organism producing Ab									
27	Transgenic organism		***34***							
II	***Method***									
	Determination of a variation									
1	Mutation not specified								***15***	
2	Mutation specified									
	Diagnostic method (NA)									
3	Linkage analysis									
4	Mutation scanning	***1***, ***2***, *3–8*, *14*, *15*, *17*, *18*, *21–23*					**3**, 4, **5**, 6[c]			**16**[d]
5	Mutation analysis	9, *16*, *19*, *20*, *24*			***16–17***, *18–29*, *33*			**11**		
6	Quantitative	***25***, ***26***, *27–28*								
7	Diagnostic method peptide	*5*, *10–13*, *25–27*, *29*			*19*			**12**		**16**
8	Diagnostic method antibody									
9	Recombinant expression		***13***, *14*		***7***, *8*				*9*, *10*	**8**, 9
10	Screening for therapeutics		***31***, ***32***, *33*							
III	***Use***									
	Medical use: treatment									
1	As such									
2	Disease oriented								***17*** (NA)	

Table 3 *Continued.*

A		*B*						
			BRCA1				*BRCA2*	
		EP0699754 [1] 11.08.1995[a]	*EP0705902 [1] 11.08.1995*[a]	*EP0705903 [1] 11.08.1995*[a]	*EP0820526 [2] 12.02.1997*[a]	*EP0821733 [3] 19.04.1996*[a]	*EP0785216 [1] 17.12.1996*[a]	*EP0858467 [4] 25.11.1996*[a]
3	Method oriented		***28*** (NA), ***30*** (pept)		**7** (NA) **8** (pept)		***18*** (pept)	
	Medical use: diagnostic							
4	As such							
5	Disease oriented							**1**
6	Method oriented							
	Use in recombinant technology							
7	Of nucleic acid							
8	Of peptide		***23***, *24*	***14***, 15			***13***, *14*	

Independent claims are in bold. Claims in the patents as originally granted but revoked or amended during opposition procedures at the EPO are in italic and separated from the current enforceable set of claims by a dotted line. [1] The patent has been jointly filed by Myriad Genetics, the University of Utah Research Foundation and the United States of America. Recently, Myriad Genetics transferred its rights on the invention in Europe over to the University of Utah Research Foundation; [2] The patent was originally filed by Oncormed that has been taken over by Gene Logic; [3] The patent proprietor is the Regents of the University of California; [4] the patent was originally filed by Cancer Research Campaign Technology Limited and Duke University, the former merged with the Imperial Cancer Research Fund and formed Cancer Research UK.
[a]Date of filing the patent application.
[b]Claim refers to one specific mutation only (185delAG).
[c]Claim disclaims diagnostic methods determining mutations known in prior art.
[d]Claim covers mutation scanning in part of the BRCA2 gene only.
(NA): method or use based on the nucleic acid, (pept): method or use based on the peptide.

Not only the profiling of the patented subject matter in these gene patents in general, but also the comparative analysis between patents in the same field is interesting. It is striking that the cDNA sequences of both *BRCA1* and *BRCA2* (line I.2, *BRCA1* claims before amendment during opposition procedures) seem to be covered by two different patent families and according to our information, to be owned by two different proprietors. To know how and why this was possible, one has to look at the claims themselves. For example, both patents on the *BRCA2* gene originally claimed a cDNA sequence. After a long and cumbersome examination procedure (see examination procedure at the EPO, available online at http://ofi.epoline.org/view/GetDossier), a patent (EP0858467) for the full *BRCA2* coding sequence encompassing all allelic variants was granted through a product-by-process claim (line I.2). The inventors eventually got awarded the full coding sequence of the different allelic variants by disclosing already in their priority documents part of the sequence and methods using the sequence data and thereby teaching the person skilled in the art to arrive at the full sequence. Another application resulted in the grant of a downstream patent (EP0785216) with protection for a single allelic variant by disclosing the actual full coding sequence of that *BRCA2* allele. Looking further into the method claims, the situation got more complicated. On the one hand, EP0785216 empowered the rights for a method for determining any variation in the full *BRCA2* cDNA sequence but in reference to the cDNA sequence of one specific allele only (line II.1). On the other hand, EP0858467 entitles the owner to the rights for diagnostic testing on BRCA2 in reference to all its allelic variants but not on the full-length cDNA sequence (EP0858467 line II.4). Thus, despite the fact that the EP0858467 proprietors hold the primary rights over the full-length cDNA sequence, for their diagnostic claim they may only refer to the part of the wild-type *BRCA2* cDNA (approximately 70% of the full cDNA) of which they effectively disclosed the sequence in their second priority document (GB9525555).

Before the amendment of the claims of EP0705902 during the opposition proceedings at the EPO last January, a similar situation characterized the *BRCA1* patent landscape. Claim 1 of the patent with the earliest filing date (EP0705902) was drafted in a way to encompass all allelic variants possibly coding for a *BRCA1* polypeptide. The main cDNA claim in the later filed patent EP0820526 covers only one possible coding sequence. The fact that the latter sequence is a consensus sequence (corresponding to only one be it the most frequently occurring allele) was considered to be the special and unexpected feature of this specific cDNA sequence, and considered as a further advancement in the technological field. This situation led to a conflict of interest between the different proprietors.[19]

The above analysis already illustrates how one patent does not necessarily preclude further patenting within a technological field, but allows further advancements and refinements to the state of the art to be rewarded by patents as well. Hence, the existence of a patent application or a granted patent on the general technological feature in the field, the full cDNA sequence, does not preclude opportunities for innovation. Although a patent application is not enforceable before grant, its existence

implies the risk that future developments will be infringing once granted. At the same time, the principle of 'protection for disclosure' to stimulate innovation, a founding incentive for the patent system, seems to work in this technological field. An upstream patent covering the cDNA sequences leaves the possibility for others to file patent applications for new uses of the patented product, and even for new methods for producing the products, under the provision that the patent holder of the product patent could not have foreseen the new process or method. For genetic testing purposes, a key example is the patenting of newly identified mutations. For both the *BRCA1* and *BRCA2* gene, various patent applications have been filed claiming newly identified mutations, and in the case of BRCA1, one such patent has recently been granted (see Table 3, EP0821733, line I.11). However, the fact that this might be patentable subject matter does not automatically allow the inventor to exploit his invention. By carrying out this invention one could be infringing an upstream patent. Besides their potential impact on further research and innovation, the powerful position of such upstream patents vis-à-vis the genetic testing practice thus remains.

Conclusion

In our research program we aim at creating an empirical data set for DNA-patents related to diagnostic genetic testing. We developed two tools to facilitate this process. First, we set up a search strategy to find the relevant patents. Second, we provide a claim-classification template to enable an immediate comprehensive overview of the patent situation for topics – genes or diseases – within this field. The claim classification brings sought-after added value to the collection of patents in support of the study of the legal framework. Apart from the controversy on the patenting of DNA, this classification of the claims related to the *BRCA1* and *BRCA2* genes nicely illustrates that patents in a research intensive technological field may well lead to a complicated situation causing difficulties in interpretation for third parties to know who effectively does own which rights and for which activities a license should be obtained.

The empirical data should be analyzed in view of the current legal framework on the patenting of human genes, gene products and diagnostic methods. Continuous care should be taken to confer a justifiable scope of protection to gene patents. Accordingly, the issue is not necessarily whether or not gene patents as such are justified but the way these patents are enforced and used in society, thereby taking into account both an appropriate award for the innovator as well as a guaranteed access to state of the art public health services for all. Due to the recent events, there is a strong feeling of breach of the implicit social contract comprised in the patenting system that needs to be addressed.

Disclaimer: the contents of these pages are informational only and should not be substituted for legal advice.

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Patent pools and diagnostic testing

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There is increasing concern that overlapping patents in the field of genetics will create a costly and legally complex situation known as a patent thicket, which, along with the associated issues of accumulating royalty payments, can act as a disincentive for innovation. One potential means of preventing this is for the patent holders to enter into a so-called patent pool, such as those established in the electronics and telecommunications industries. Precedents for these also exist in the field of genetics, notably with the patents pertaining to the SARS genome. In this review, we initially address the patent pool concept in general and its application in genetics. Following this, we will explore patent pools in the diagnostic field in more detail, and examine some existing and novel examples of patent pools in genetics.

Patent thickets and royalty stacking

The essence of innovation is cumulative investigation where each invention builds on many previous findings. However, if these previous findings are patented, each person who previously contributed must grant permission for their work to be used [1]. This leads to the emergence of a patent thicket (see Glossary), through which anyone who wishes to develop and eventually commercialize a new product must navigate his or her way [2].

Recent studies have reported on the licensing practices of the owners of patents for genetic inventions [3–6], and concerns have been raised that patent thickets, resulting in royalty stacking (see Glossary), block access to patented technology through the accumulated license fees that a downstream inventor has to pay to upstream patent holders. Although the existence of an anticommons effect (see Glossary) of patents [7,8] has not been validated by comprehensive empirical data, it is pertinent to reflect on ways to remedy this in the event that facts and cases arise that substantiate such an effect.

The patent pool model

Various mechanisms have been suggested to clear patent thickets [9], including patent pools, which are agreements between two or more patent owners to license one or more of their patents as a package to one another, and to third parties willing to pay the associated royalties (Figure 1). Agreements with third parties can be accomplished directly, between patentees and licensees, or indirectly, through the establishment of a body specifically set up to administer the pool [1,9–11].

Patent thickets have arisen in technical fields other than genetics, and patent pools have emerged previously to deal with overlapping patents [11,12]. For example, in 1917 an aircraft pool was formed that encompassed almost all aircraft manufacturers [13] and was crucial to the US entering World War I. In the late 1990s, several patent pools were formed in the electronics and telecommunications industries, starting with the moving picture experts group (MPEG)-2 pool in 1997 for inventions relating to the MPEG-2 standard (see Klein, J.I. (1997) Business Review Letter to Gerald R. Beeny), with others to follow (see Klein, J.I. Business Review Letter to Gerald R. Beeney regarding DVD (1998) and to Carey R. Ramos (1999) both regarding DVD–Video and DVD–ROM; and James, C.A. Business Review Letter to Ky P. Ewing regarding Third Generation Mobile Communication Systems (2002): available at http://www.usdoj.gov/atr/public/busreview/letters.htm).

In an attempt to deal with any potential anticompetitive effects of multiparty licensing agreements, such as patent pools, both the US antitrust agencies and the European Commission have established guidelines. The US antitrust agencies have developed the *Antitrust Guidelines for the Licensing of Intellectual Property (IP Licensing Guidelines)* [14]. In the European Union, the major competition laws (see Glossary) relating to technology licensing are laid down in the *Commission Block Exemption Regulation (EC) No. 772/2004 on Technology Transfer Agreements* [15] and the *Guidelines on the Application of Article 81 of the EC Treaty to Technology Transfer Agreements* [16]. Recently, the Japanese Fair

Glossary

Anticommons effect. An effect arising from the situation where multiple owners each have the right to exclude others from the use of a resource and no one has an effective privilege of use: this results in under use of the resource [7,8].

Antitrust or competition law. Antitrust law is a term primarily used in the US, while in many other countries the term competition law is used. Most antitrust or competition laws have provisions dealing with mergers, abuse of a dominant position and anticompetitive practices.

Patent thicket. The intellectual property portfolios of several companies that form a dense web of overlapping intellectual property rights [1].

Royalty stacking. The accumulation of royalties that have to be paid when confronted with a patent thicket [8].

Stacking licenses. Give the owner of a patented invention used in upstream research rights in subsequent downstream innovations [7].

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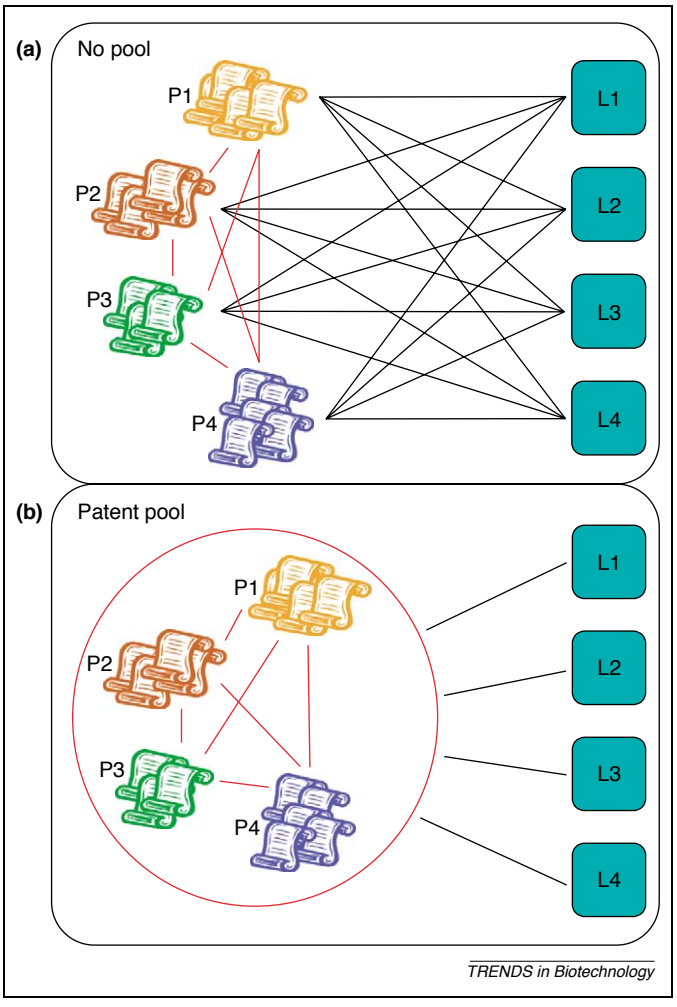

Figure 1. Comparative illustration of the different licenses needed in the absence **(a)** or presence **(b)** of a patent pool. P1–P4 represents the patent holders. L1–L4 represents the licensees. In the absence of a patent pool, licensees have to enter into negotiations with all the patent holders, which is a time consuming and expensive process. By contrast, in the presence of a patent pool licensees turn to the patent pool for acquiring the rights as one package, which results in simplification and a significant reduction of transaction costs.

Trade Commission issued its *Guidelines on Standardization and Patent Pool Arrangements* [17], which apply the same general principles. Close examination of foregoing guidelines, regulations and related decisions provides valuable information on the attitude of the US, European [18] and Japanese authorities towards patent pools. In short, patent pools should avoid creating anticompetitive restraints and will most probably be accepted if they meet the conditions set out in Box 1.

The establishment of a patent pool is a long, complex, multi-step process. In view of the varied issues and interests at stake, the expertise and joint collaboration of highly qualified patent attorneys, technical experts in the relevant field and legal advisors, both in the field of patent law and competition law, are required (Figure 2).

Benefits and risks

The successful set-up of the electronics and telecommunications pools demonstrates that patent pools can have significant benefits, the first of which is the elimination of stacking licenses (see Glossary) [10]. A second benefit is the reduction of licensing transaction costs through the introduction of a system of 'one-stop licensing' for non-member licensees [10,11], which provides an alternative to having to negotiate and acquire separate licenses directly from each of the patent owners (Figure 1). However, the initial cost of setting up and negotiating a pool agreement will often be high: all steps in the process involve costs [11] (Figure 2). A third benefit is a decrease in patent-related litigation [1,10].

A patent pool also leads to the exchange of technical information that is not covered by patents, through a mechanism for sharing technical information relating to the patented technology that would otherwise be kept a trade secret [11]. Furthermore, patent pools can forestall government policy: it is better to encourage companies to establish patent pools than force them into a compulsory licensing scheme [11]. Such a suggestion, however, seems to ignore the fact that the major prerequisite for

Box 1. Checklist for a patent pool arrangement

- **Validity of the patents**: a patent is valid from the date of grant until the date of expiration, as defined by law, which is usually 20 years from the date of the filing provided the annual maintenance fees are paid.
- **Essentiality of the patents**: a technology or patent is deemed to be essential if there are no substitutes for that technology inside or outside the pool and the technology in question constitutes a necessary part of the package of technologies for the purposes of producing the product(s) or carrying out the process(es) to which the pool relates.
- **Independent expert**: an independent expert identifies and evaluates the essential patents related to the technology.
- **Non-exclusive licenses to the pool**: a license is non-exclusive when one or more licensees are granted the right to use licensed technology covered by the patent(s) during the term of the license and when the licensor retains the right to use the licensed technology and the associated patent(s) as well.
- **Alternative technologies**: licensees are free to develop and use alternative technologies.
- **Grantback provisions**: a licensee should grant the licensor non-exclusive licenses for improvements on the licensed technology. This should be limited to essential patents and be settled on reasonable terms in order not to discourage further innovation.
- **Royalty allocation formula**: royalties are distributed among the licensors according to an agreed allocation formula set forth in the patent pool agreement.
- **FRAND terms**: royalties paid to the pool by the licensees should be fair, reasonable and non-discriminatory (the so-called FRAND terms), and licenses granted by the pool should be non-exclusive.
- **Safeguards for sensitive business information**: competitively sensitive business information on the licensee is safeguarded in case auditing mechanisms for the management of royalties are established.
- **Mechanism for dispute resolution**: an independent and, therefore, neutral dispute resolution mechanism in the agreements setting up the pool is desirable.

These are based on the guidelines laid down by the *US IP Licensing Guidelines* and Business Review Letters, the *EU Transfer of Technology Guidelines* and individual decisions, and the *Japanese Guidelines on Standardization and Patent Pool Arrangements*.

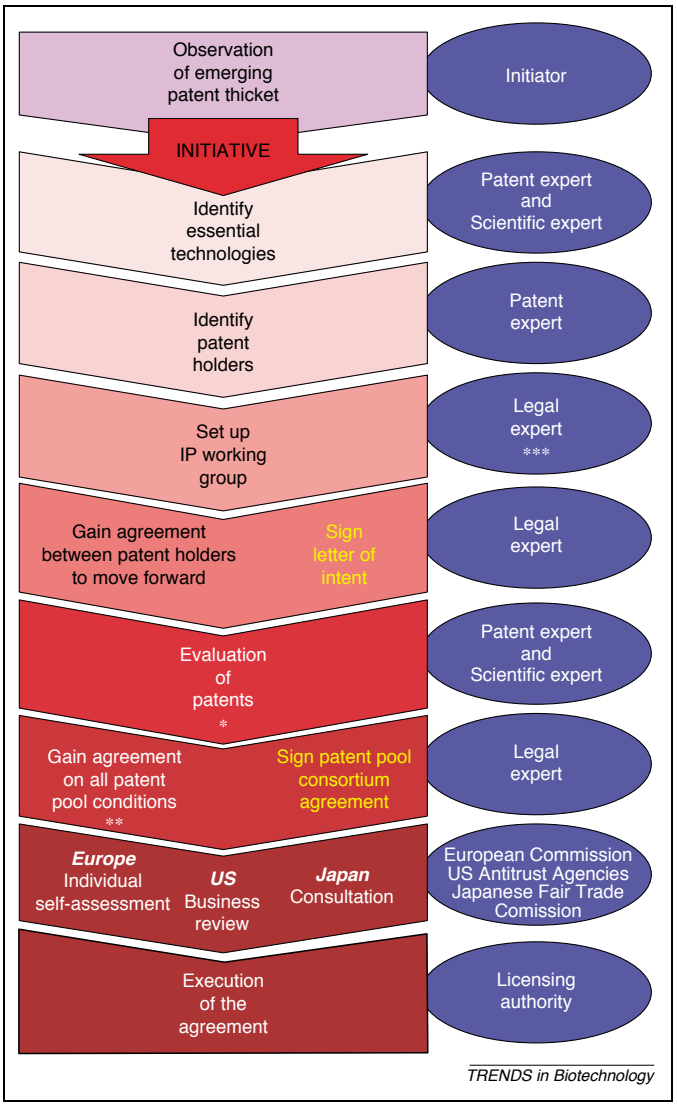

Figure 2. Overview of successive steps in the process of setting up a patent pool (block arrows on the left) and professional expertise needed at every step (associated balloons on the right). * Essential/non-essential character, ** Structure, technologies, royalties, dispute settlement system, etc., *** Legal expert: Attorneys and academic advisors This scheme is based on a document by James Simon.

establishing patent pools is the voluntary participation of all patent holders, whereas the compulsory licensing mechanism is the last resort for patent holders who do not wish to enter into (reasonable) voluntary licensing negotiations.

Patent pools are, however, not without potential risks, for example, they might shield invalid patents [19] or entail the risk of inequitable remunerations (although expert valuation could settle disagreements on the value of the patents) [11]. The major criticism, however, is the danger of covering for a cartel and the subsequent anticompetitive effects this would have [1,11,19].

Patent pools for genetic inventions

To what extent the patent pool mechanism can be applied to genetic inventions, and whether such a scheme leads to the expected benefits are important questions. The Organization for Economic Co-operation and Development (OECD; www.oecd.org) considers the concept of a patent pool to be an interesting one for biotechnology but has some doubts as to whether the technologies and markets for genetic inventions are amenable to patent pools [20]. The medical biotechnology industry is perceived as fundamentally different from the electronics and telecommunications sectors, particularly as the generation of standards, as used in electronics and telecommunications, for the interoperability of electronic devices is seen as a strong incentive for setting up a patent pool. In the absence of this type of standard-driven incentive, dominant players in the biotech industry might be reluctant to join a pool because there is no apparent gain. Additionally, biotech companies rely heavily on their patent portfolio, and foster what has been called a bunker mentality: a defensive attitude focused on self-protection and secrecy [19]. In light of these considerations, the OECD recommends further study [20]. In the meantime, some valuable contributions to the debate, which focus on the importance of standard setting for diagnostic testing, have been reported [21,22].

Golden rice

An instructive case on patterns of protection, and on negotiation through patent thickets, was published in the field of agricultural biotechnology [23,24]. In the Golden Rice case, Potrykus succeeded in genetically enriching rice grains with β-carotene, the precursor to vitamin A, which gives them a yellow hue: hence, they are called Golden Rice. Potrykus wanted to transfer the Golden Rice materials to developing countries for further breeding, and to introduce the trait into the local varieties consumed in developing countries. However, a freedom-to-operate survey initially uncovered 70 patents, belonging to 32 different companies and universities, embedded in Golden Rice. The six key-patent holders were approached, and an agreement was reached that allowed Potrykus to grant licenses, free of charge, to developing countries, with the right to sub-license (press releases 16 May 2000; 22 January 2001; and 14 October 2004; see www.syngentia.com). Consequently, a humanitarian board (HumBo; www.goldenrice.org) was established as a voluntary association to assist in the associated governance and decision making [25]. So far, approximately 20 master licenses have been granted to institutions in developing countries in Asia (Anatole F. Krattiger, personal communication).

The Golden Rice case is an example of how private and public organizations, in a combined effort, dealt with the patent thicket by creating a non-profit, humanitarian (and, therefore, probably atypical) patent pool in the form of a single licensing authority [26–29].

SARS patent pool

A recent case in which overlapping patents are emerging, and in which laboratories try to remove the thicket by way of a pool, relates to the biomedical field, specifically to the severe acute respiratory syndrome (SARS) corona virus [30]. In response to the outbreak of SARS, the World Health Organization (WHO; www.who.int/en/) set up a network of laboratories to help control the disease, which led to the isolation of the causative virus and the sequencing of its genome. Two groups are credited with discovering the SARS genome, independently from each

other [31,32], and several of the contributing laboratories filed patent applications incorporating SARS genomic sequence data. Further research then led to the filing of additional patent applications by a multitude of public and private sector entities [30]. The WHO set up a SARS consultation group, who proposed 'that a strategy be developed, in consultation with stakeholders, to address potential SARS corona virus related intellectual property issues and, thus, enhance development of intervention approaches'.

At present, the relevant parties have been identified, and principal agreement has been gained, officially, by the signing of a letter of intent. Highly qualified technical and legal experts have assisted the parties during the chain of negotiations. The resulting pool, should the parties conclude a full agreement, will be set-up in the USA, followed by attempts to set up pools elsewhere [30].

HNPCC patent pool: a test for diagnostic testing?

Genetic diseases are caused by mutations in genes. In some cases, such as hereditary non-polyposis colorectal cancer (HNPCC), the disease can be caused by a variety of mutations in one gene, or by one or more mutations in several genes. The diagnosis of HNPCC in a particular family is, in part, based on molecular genetic testing for germline mutations in one of the mismatch-repair (MMR) genes. Typically, patients are being tested for mutations in two or more out of four candidate genes (MLH1, MSH2, MSH6, and PMS2; see review of HNPCC on www.genetests.org). However, other genes involved in the MMR pathway have been reported to be associated with HNPCC (e.g. MLH2, MLH3, PMS1, MSH3, MSH5, MYH; see OMIM entries on http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM), and the number of genes identified as being involved in familial colorectal cancer is expected to grow. Some of these newly identified genes might soon be included on the shortlist for routine testing, and, as various patents have been filed, it is possible that overlapping patents might occur on the genetic data necessary to test for HNPCC. Should a patent thicket arise, an HNPCC patent pool, encompassing essential genomic patents, could help to eliminate the thicket and render proprietary genomic data more accessible for use. Additionally, such a patent pool should be considered a dynamic model with regard to both size and use, whereby the size and content of the pool will differ over time: competition law requires that additional essential patents, once granted, will enter the pool (e.g. relating to other genes with a role in the same pathology and on particular mutations in those genes) and others will disappear when no longer valid. Furthermore, the granting of licenses to a subset of patents should also be possible. Here, some genetic laboratories offering testing for the clinical condition as a whole might be interested in the entire pool, whereas other laboratories might only be interested in a license to a subset of patents in the pool, a subset of disease genes or mutations (which are of specific interest in view of the geographical heterogeneity of the distribution of mutations), a specific gene, or a particular mutation for the development of an antibody or another therapeutic or research tool. In addition, the licenses granted by the pool should be non-exclusive and non-discriminatory, thereby imposing fair and reasonable conditions and royalty rates.

Incentives

The initial impetus for patenting an invention is to award original research and recuperate investment through revenue from the royalties due on the commercialization of the invention; however, will the creation of a patent pool still provide the patentee with such significant gains?

Standards

Standards are technical specifications relating to a product or an operation, which are recognized by a large number of manufacturers and users [33]. Standards can be an important trigger to set up a pool, as illustrated in the electronics and telecommunications sectors, and this might also be true in the field of genetics [20,21]. A genetic standard should not necessarily be looked at in terms of a technical specification but could present itself as a set of mutations recognized by the international scientific community. Alternatively, it could reflect national or international best practice guidelines for genetic testing for a particular disease, such as the standards and guidelines issued by the American College of Medical Genetics (www.acmg.net) for cystic fibrosis [34] or Huntington's disease [35] – such guidelines could facilitate the establishment of corresponding patent pools. They could also be an important asset in the dissemination of knowledge of patent coverage for genetic inventions, and could promote the collection of licensing fees.

Potential revenue

The potential revenue from a patent will depend on the total number of patients eligible for a genetic test; however, the actual revenue will be determined by the amount of diagnostic kits sold by the manufacturers and the number of tests effectively carried out in diagnostic testing centers. At present, owners of genetic patents predominantly provide licenses to companies developing commercial kits and to large diagnostic laboratories. Patent pools might constitute the ideal means for raising the visibility and accessibility of smaller or public genetic laboratories and, thus, increase the actual amount of collected royalties, bridging the gap between potential and actual revenue. For example, some laboratories still use in-house methods to test for cystic fibrosis, although several appropriate kits are available commercially. For some genes, the diagnostic method for the detection of mutations is less amenable to the production of a commercial kit, which is presently the case for breast and ovarian cancer, tuberous sclerosis and neurofibromatosis. In such instances, litigation is difficult because data informing on the number of tests being performed are hard to find and legal action is costly; however, the introduction of one-stop licenses, through the establishment of patent pools, might promote a spontaneous registration by the users and simplify the collection of license fees.

For molecular diagnostic laboratories, a patent pool comprising the widely owned rights to diagnostic genes

can help these institutions to adjust to the emerging phenomenon of patents in their practice, and facilitate the regularization of their service by creating clarity and legal certainty, in addition to lowering the barrier to entry into this field. For similar reasons, a patent pool can remove the reluctance to enter into research, and incite innovation and the development of new tests.

Some remaining hotspots

There are many remaining issues that must be considered when further exploring the patent pool model for genetic inventions. First, patent pools are designed to remove the stacking of multiple patents and multiple patent holders. Hence, the model is not applicable when a single patent holder controls all the patents relevant for the genetic testing for a particular disease, for example, one patent owner holds the different patents covering the diagnosis of hemochromatosis [36]. The three biotech cases discussed in this review – Golden Rice, SARS and the hypothetical example of HNPCC – involve multiple patents belonging to two or more patent holders.

Secondly, patent pools rely on the voluntary engagement of the patent owners; therefore, they do not offer a solution in cases where patent holders do not wish to grant reasonable licenses or refuse to license at all. In both the Golden Rice and the SARS cases, voluntary negotiations appear to have been successful and it can only be hoped that the same will be true in future cases. If not, a compulsory patent pool, in which the administering body would seek a compulsory license for essential technology from all patent holders that do not voluntarily engage in the pool, could be further investigated. However, it remains to be seen whether these measures will be permitted within the confines of intellectual property and competition law.

Finally, the major incentive for all parties is economic benefit. In order for a patent pool to be an effective solution, the right balance has to be achieved between the cost of creating a pool and the prospect of adequate revenue generated by royalties on the end-product. It remains to be seen whether a diagnostic-gene patent pool covering only one disease syndrome will reach such a balance, and to what extent small size pools will prove to be viable. Extending those pools to a wider range of, or to all, genetic disorders could prove to be more useful from an economic or a clearing point of view but might lead to some delicate problems from the perspective of competition law.

Conclusions

Given their specific features, and the potential for stacking licenses (see Glossary) in the genetics sector, setting up patent pools might prove to be helpful in the area of genetic testing by clearing patent thickets. Patent pools can be particularly useful for disorders caused by multiple defects in a single gene, diseases caused by one or more defects in multiple genes or for the more common multifactorial diseases, for which complex genetic associations are being discovered and, consequently, a larger thicket could emerge.

The emerging standards for good practice in medical and laboratory genetics can be helpful in setting up patent pools and, conversely, the thorough scientific evaluation of the patent portfolio in the framework of a patent pool could help to establish, or to adjust, those standards.

However, when setting up pools for the clearance of stacking licenses for diagnostic purposes, competition law has to be taken into account to avoid potential anticompetitive effects.

Various governmental and non-governmental institutions, such as WHO, OECD, HUGO and the National Institutes of Health (NIH; www.nih.gov), and professional societies, such as the American Society of Human Genetics (ASHG; www.faseb.org/genetics/ashg/ashgmenu.htm) and the European Society for Human Genetics (ESHG; http://www.eshg.org/), might act to promote the formation of patent pools in this area. Well-tailored pools could, indeed, serve economic and societal public-health goals. To prevent the establishment of such pools becoming prohibitively expensive as a result of the costly expertise required, funding from such organizations to aid setting up the pools will be more than welcome.

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