UNEP

CBD

CONVENTION ON BIOLOGICAL DIVERSITY

Distr.
GENERAL

UNEP/CBD/WG-ABS/3/INF/4
11 January 2005

ENGLISH ONLY

AD HOC OPEN-ENDED WORKING
GROUP ON ACCESS AND
BENEFIT-SHARING
Third meeting
Bangkok, 14-18 February 2005

GLOBAL STATUS AND TRENDS IN INTELLECTUAL PROPERTY CLAIMS: GENOMICS, PROTEOMICS AND BIOTECHNOLOGY

Submission by the European Community

Note by the Executive Secretary

1. At the request of the European Community, the Executive Secretary is pleased to circulate herewith, for the information of participants in the third meeting of the Ad Hoc Working Group on Access and Benefit-sharing, a paper on intellectual property trends and genomics, proteomics and biotechnology. In making that request, the European Community stated that it should be made clear that the paper is the result of independent research and should by no means be taken as expressing the point of view of the Community.

2. The paper is being circulated in the form and the language in which it was received by the Convention Secretariat.

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Global Status and Trends in Intellectual Property Claims:

Genomics, Proteomics and Biotechnology

Submission to the Executive Secretary of the Convention on Biological Diversity by Dr. Paul Oldham from the ESRC Centre for Economic and Social Aspects of Genomics (CESAGen), United Kingdom.

Global Status and Trends in Intellectual Property Claims. Issue No. 1.
ISSN: 1745-3941 (Print)
ISSN: 1745-395X (Online)

About CESAGen:

The ESRC Centre for Economic and Social Aspects of Genomics is a Research Centre of the Economic and Social Research Council, United Kingdom and is a collaboration between Lancaster and Cardiff Universities. CESAGen forms part of the national ESRC Genomics Network. CESAGen's work is directed towards analysis of the social, economic, ethical and environmental implications of genomics across the spectrum of red and green genomics issues.

About this Series:

This series has been established as a contribution to the development of evidence based approaches to analysis of the potential role of intellectual property instruments within the development of an international regime on access to genetic resources and benefit-sharing under the Convention on Biological Diversity. The series aims to provide independent information and analysis of intellectual property issues to assist policy-makers and other participants within debates surrounding the development of the international regime.

Acknowledgements:

The research upon which the paper is based was funded by the UK Economic and Social Research Council (ESRC) through the ESRC Centre for Economic and Social Aspects of Genomics (CESAGen), a Lancaster-Cardiff University collaboration (http://cesagen.lancs.ac.uk). Dr. Paul Oldham is Research Associate at CESAGen, Lancaster University and a member of the Development Research Group, Anthropology Department, University of Durham. The author thanks Mr. Mark Cutter who served as Research Assistant for the project for his assistance with generating the underlying patent dataset upon which this review is based and which constitutes the results of our joint work. The author thanks Professor Peter Whittaker and Professor Brian Wynne for their valuable scientific advice and comments and thanks staff at the European Patent Office and the Japan Patent Office for their generous assistance in clarifying the characteristics of the esp@cenet database and interpreting statistical data from the Trilateral Offices. The author also thanks Ms. Roberta Stout and Mr. James Lamouche of the National Aboriginal Health Organisation (NAHO), Canada, for their kind assistance in attempting to trace the origins of the indigenous peoples thanksgiving address presented in this review. The views expressed are those of the author and not necessarily those of the ESRC, CESAGen or any other institution or individual named above. Responsibility for any errors, omissions or misinterpretations resides solely with the author.

Executive Summary:
This paper has been prepared as a contribution to analysis and discussion surrounding the development of an international regime on access to genetic resources and benefit-sharing under the Convention on Biological Diversity (Decision VII/19).

The paper provides a review and assessment of the implications of trends in relation to genomics, proteomics and biotechnology for the development of an international regime. The results of the review are also relevant to the ongoing work of the WIPO Intergovernmental Committee on Intellectual Property and Genetic Resources, Traditional Knowledge and Folklore, the International Treaty on Plant Genetic Resources for Food and Agriculture, and other relevant bodies.

Section I examines the challenges and potential opportunities represented by the growth of bioinformatics and international electronic transfers of genetic data for the development of an international regime. The review reveals that by the end of 2003 the international DNA sequence depositary known as GenBank contained 30,968,418 DNA sequences from an estimated 130,000 organisms. The review concludes that further attention could be paid to the potential of bioinformatics and "open source" models to provide alternative forms of benefit-sharing directed towards conservation and development objectives and the cost-effective regulation of biopiracy. However, the relevance of bioinformatics to the needs of developing countries and substantive issues surrounding the human rights and ethical dimensions of bioinformatics merit careful analysis and evaluation.

Section II considers the challenges involved in tracking intellectual property claims in relation to genetic material on the global level. The review presents the results of a search of available patent publications from 73 national patent offices, four regional patent offices, and WIPO contained within the European Patent Office esp@cenet worldwide database between 1990 and 2003 using a working definition of biotechnology developed by the Organisation for Economic Co-operation and Development (OECD). The search reveals that biotechnology patent publications (consisting of applications and grants) are primarily awarded international patent sub-classes concerned with microorganisms and enzymes. In the period 1990-2000 demand for patent protection for the main biotechnology sub-class (C12N microorganisms or enzymes) reached approximately 188,213 patent publications rising to a preliminary total of 299,163 patent publications by the end of 2003.

The search results reveal the ongoing internationalisation of the patent system under the Patent Cooperation Treaty (PCT) and the wider implications of the requirement for protection of microorganisms and microbiological processes under Article 27.3(b) of the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) under the World Trade Organization (WTO). The review suggests that further work and methodological refinement to develop reliable and verifiable indicators for patent trends may be desirable to enhance the visibility of trends to policy-makers and participants within debates surrounding the development of an international regime. The review also highlights that the European Patent Office esp@cenet worldwide database represents a key resource for enhancing the visibility of international trends.

Section III considers the complexity and scope of intellectual property claims in relation to biological and genetic material in the context of the rise of genomics, proteomics and biotechnology. The review examines the complexity of patent applications in these arenas and

the challenges such claims present for patent examiners and patent offices in a context of increasing workloads. Thus, an estimated 3,433,022 patent applications were reported to be awaiting request for examination or pending at various stages of the patent procedure in the year 2000 by the Trilateral Offices (consisting of the European Patent Office, the Japan Patent Office and the United States Patent and Trademark Office). Wider international trends in pendency are unknown, however, the USPTO has estimated that upto 7 million patent applications may be pending worldwide.

The Trilateral Offices are seeking to respond to trends in demand through the adoption of information technology, including electronic filing software, electronic signatures, and the establishment of DNA and Amino Acid sequence listings. These developments may present potential opportunities in relation to the development of an international certificate of origin under an international regime. However, the existence of in excess of three million outstanding patent applications within the major patent offices raises substantive questions surrounding the ongoing integrity of the patent system. Furthermore, the review of trends in patenting in the realm of genomics and proteomics supports the wider and substantive concerns expressed by specialist and United Nations bodies surrounding the wide-ranging and unforeseen implications of permitting patent claims in this arena for health, agriculture, development, human rights, science, innovation and trade.

These issues are explored through a detailed case study of a Patent Cooperation Treaty application arising from the completion of the draft of the rice genome in 2001. The application designates 115 States Parties to the Patent Cooperation Treaty in both developed and developing countries and seeks protection over DNA, amino acids and proteins involved in the development and timing of flower formation in plants and plant architecture (morphology). The case study reveals that genetic-similarities ("homologies") in the genetic make-up of plants and other organisms permits intellectual property claims that extend beyond individual varieties, species and genera to incorporate key elements of genomes across classes. These claims may also extend to species and genera that have yet to be described by taxonomists.

The review concludes that the practical significance of the rise of genomics and proteomics is that intellectual property protection may exist over key genetic elements and regulatory mechanisms of biological organisms in multiple jurisdictions before access and benefit-sharing arrangements are put into place.

In considering this problem the review notes that genomics and the emerging science of proteomics are commonly described as a "revolution" or a "new era". This "revolution" or "new era" is at an early stage but is gathering pace. Thus, between the 14th of September 2003 and the 14th of September 2004 the number of registered genome mapping projects increased from 803 projects to 1182 projects. This represents a 47% increase in a twelve month period.

The completion of an increasing number of genome maps has led to the realisation that genomes are much smaller, in terms of the number of genes within an organism, than had previously been thought and that there are significant genetic similarities or "homologies" across species, genera and classes of organism. This is reconfiguring scientific understandings in two important ways: a) the rise of phylogenetic taxonomy and systems biology is increasingly leading to an emphasis on the relatedness between organisms, including proposals to extend the genus *Homo* to include chimpanzees; b) the completion of the first genome maps has revealed that the differences in the

order of biological complexity between a nematode worm, a mouse, and a human being cannot be explained by the number of genes within an organism but can only be explained by the realisation that one gene may encode multiple proteins.

The nature of genetic homologies between organisms signifies that intellectual property claims in relation to the biological or genetic components of one organism may permit intellectual property claims in relation to the biological or genetic components of other organisms (i.e. primate embryonic stem cells and human stem cells). Furthermore, given that it is now known that single genes are involved in the expression of multiple proteins, permitting patent claims in relation to DNA and genes is likely to have unforeseen consequences for science and innovation as science moves into the realm of proteomes where key developments in relation to health are predicted.

The review also reveals that it is increasingly observed that the extension of intellectual property protection to biological and genetic material and internationalisation of the patent system has not been based on economic evidence or analysis. The central dogma that 'science + intellectual property protection = innovation + revenue', is questionable when viewed from a wider innovation perspective. While it has been assumed that the internationalisation of intellectual property protection may lead to increased trade in goods and services, foreign direct investment (FDI) and technology transfer, the evidence for such effects is presently both limited and mixed. In practice, permitting strong intellectual property claims over genetic material may also serve as a vehicle for unproductive rent extraction and produce a chilling effect on research and innovation at the expense of wider policy objectives directed towards the conservation and sustainable use of biodiversity, public health, agriculture, development, human rights and trade.

The review also reveals that the rise of genomics, proteomics and biotechnology is associated with a marked shift in the balance of relationships within the "triple helix" of government, universities and industry towards universities. Thus, the majority of registered worldwide genome mapping projects are in fact conducted by universities or non-profit organisations. This shift in the structure of innovation towards publicly funded research may provide important ways forward in developing an international regime directed towards the conservation and sustainable use of biodiversity, health, development and human rights goals. Specifically, the dominance of publicly funded Research & Development in the arena of genomics and proteomics provides opportunities to develop alternative incentives directed towards internationally agreed goals and alternative models for access and benefit-sharing that minimise the externalities of the patent system and maximise the benefits for global welfare.

The review further concludes that while recognising the potential of genomics and proteomics in arenas such as health, agriculture and enhancing understanding of biological diversity, it is also necessary to recognise that these emerging sciences should not be privileged at the expense of other sciences and areas of innovation. In particular, the knowledge, innovations and practices of indigenous peoples and local communities and the customary law based common resource regimes that these peoples and communities have developed over the course of generations represent vital elements of human cultural diversity and the international science and resource management base.

The review highlights that sciences such as systems biology increasingly emphasise relatedness, complexity and ultimately risk in understanding biological diversity and the impacts of human

intervention upon biological diversity. An emphasis upon relatedness, complexity and the need to manage risk in human interactions with biological diversity are also central features of the sciences and philosophies of indigenous peoples and local communities. This emerging convergence between 'cutting edge' science and the sciences of indigenous peoples and local communities may offer new opportunities to bridge the epistemological gap between different forms of knowledge to promote common understanding and contribute to the realisation of the objectives of the Convention and wider international policy goals.

The review closes by concluding that the genomes and proteomes of biological organisms constitute a significant gap within the existing international policy framework established under the United Nations system. In considering genomes and proteomes as a gap within existing international regimes the review notes that genomes and proteomes may extend beyond individual lands or territories, the jurisdictions of individual states, regions, population groups and ultimately generations. The review proposes that genomes and proteomes could usefully be seen as "global public goods". Addressing genomes and proteomes as a form of global public goods may best be achieved by recognising the legitimate rights and interests of indigenous peoples and local communities, the legitimate rights and interests of States, and the need to promote research and innovation which advances implementation of the Convention and wider international policy goals. In considering the appropriate arena for the development of an international regime, the United Nations General Assembly has provided the Convention on Biological Diversity with the mandate to pursue fairness and equity in benefit-sharing arising from the utilisation of genetic resources. Decision VII/19 provides a clear mandate for a deliberative and participatory process to address the challenges and opportunities of this new era.

Introduction:

Genomics can be briefly defined as "the study of genes and their function" and is concerned with the mapping and analysis of the entire genetic make-up of an organism constituting its genome.[1] Genomics provides the foundation for the science of proteomics which is concerned with the mapping and analysis of the protein make-up within an organism (the proteome).[2]

Relative to the estimated number of species the mapping of the genome of organisms remains in its infancy. The first map of the genome of an organism, the bacterium (*Haemophilus influenzae*) with 1,743 genes was announced in 1995.[3] The first complete genome of a plant, Thale cress (*Arabidopsis thaliana*) containing an estimated 25,498 genes, was completed in 2000.[4] This was followed by the mapping of the Nippon Bare variety of rice (*Oryza sativa ssp. japonica*) with an estimated 32,000 to 50,000 genes, by Syngenta Biotechnology and Myriad Genetics in 2001 and *Oryza sativa ssp. indica* by a team of researchers from the Beijing Genomics Institute (BGI).[5] In other areas, the map of the genome of a nematode worm (*Caenorhabditis elegans*) with over 19,000 genes was completed in 1998.[6] In the case of mammals the draft of the human genome was published in February 2001 with an estimated 30,000 – 40,000 genes with estimates suggesting that there will be in the region of 30,000 genes.[7] This was followed by the mouse genome in 2002, with an estimated 30,000 genes, and a partial map of the dog genome (a poodle named Shadow) in 2003.[8] In the case of insects, the draft of the fruit fly (*Drosophila melanogaster*) genome with an estimated 13,600 genes was published in 2000 and a draft of the honey bee (*Apis mellifera*) genome was announced in January 2004.[9]

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[1] Nuffield Council on Bioethics (2002) *The ethics of patenting DNA: a discussion paper*. London: Nuffield Council on Bioethics, Location: <http://www.nuffieldbioethics.org/fileLibrary/pdf/theethicsofpatentingdna.pdf>. Citation at 90.

[2] *Nature* magazine provides a 'genome gateway' website contains a section on ´post-genomics´ including proteomics <http://www.nature.com/genomics/post-genomics/action.html> . See also the Nature (2003) special ' Insight' supplement, 'Proteomics'. *Nature*, Vol. 422, No. 6928. Location: <http://www.nature.com/nature/insights/6928.html>.

[3] Fleischmann, R et al. (1995) 'Whole-Genome Random Sequencing and Assembly of *Haemophilus influenzae* Rd', *Science*, 269, 496-512. For an accessible free summary see Henahan, S (nd) 'First Complete Genome Sequenced', *Science Updates*, Access Excellence @ the National Health Museum.

Location: <http://www.accessexcellence.org/WN/SUA06/hflu.html>.

[4] The Arabidopsis Initiative (2000) 'Analysis of the genome sequence of the flowering plant *Arabidopsis thaliana*.' *Nature*, Special edition. Dec. 14; Vol. 408, 796-815.

[5] Science (2002) The Rice Genome. Vol. 296, 1-203. See also the Science magazine feature on the Rice Genome. Location: <http://sciencemag.org/feature/data/rice/index.shtml>. See also Torrey Mesa Research Institute 'Frequently Asked Questions – Rice Genome', 4th April 2002. Location: <http://www.tmri.org/en/partnership/access_faq.aspx>.

[6] BBC (1998) 'Small worm makes history', Thursday, 10 December, 1998. Location: <http://news.bbc.co.uk/1/hi/sci/tech/232608.stm>.

[7] See Science (2001) 'The Human Genome', *Science*, 16th February 2001, Vol. 291, 1145-1434 and Nature (2001) 'The Human Genome', *Nature*, 15th February 2001, Vol. 409, 928-933.

[8] Nature (2002) 'The Mouse Genome'. *Nature*, Vol. 420, 509-590. See also, Kirkness, E. F. et al. (2003) 'The dog genome: survey sequencing and comparative analysis', *Science*, 301**,** 1898-1903.

[9] See: a) Adams et al. (2000) 'The Genome Sequence of *Drosophila melanogaster*', *Science* Vol. 287, 2185-2195; b) Pilcher, H (2004) 'Honey bee genome sequenced', *Nature*, Science Update, 9th of January 2004. Available via <http://www.nature.com/news/2004/040105/full/040105-7.html>; c) NIH News Advisory 'Honey Bee Genome Assembled', National Institutes of Health/National Human Genome Research Institute press release, January 7th 2004. Location: <http://www.genome.gov/11509819>.

According to the Genomes Online Database (GOLD) as of September the 14th 2004, 1182 genome-mapping projects have been recorded.[10] 219 projects have been completed, including the mapping of 4 chromosomes, and a further 963 are in progress of which 522 focus on Prokaryotic organisms and 441 on Eukaryotic organisms. As this suggests many mapping efforts are focused on prokaryotes, (divided into the kingdoms of Archaebacteria and Eubacteria), or "Any organism in which the genetic material is not enclosed in a cell nucleus"."[11] In contrast, eukaryotes are organisms "consisting of cells in which the genetic material is contained within a distinct nucleus" (i.e. humans, plants, animals etc.).[12]

Seen from the perspective of an estimated 14 million species worldwide, progress in the mapping of genomes and proteomes may presently appear to be limited.[13] However, the mapping of the genome of model species i.e. *Arabidopsis thaliana* and varieties of *Oryza sativa*, provide important keys to unlocking the genome within a particular class and across classes (i.e. monocots and dicots in the case of plants). Thus, the mapping of the genome of the Fugu puffer fish (*Fugu rubripes*) within the Class Osteichthyes has assisted in the identification of almost 1,000 human genes within the Class Mammalia.[14] Growing recognition that genetic similarities ("homologies") exist between organisms which cross the boundaries of species, genera, families, classes and ultimately perhaps kingdoms and domains has important implications for the development of an international regime. The implications of intellectual property claims arising from genome mapping for the development of the international regime are explored below in a case study of a 2002 Patent Cooperation Treaty application concerning genes and proteins regulating flowering in plants.

The mapping of genomes provides the foundation for the science of proteomics.[15] "The term proteome defines the entire protein complement in a given cell, tissue or organism."[16] Estimating the size of a proteome is a significant challenge, however, one "ball park" suggestion is that a proteome may be three times as large as the protein-coding elements of a genome.[17] Thus, if the human genome consists of approximately 30,000 protein-coding genes, the human proteome may consist of up to 300,000 proteins.[18] Mapping and analysis of the proteome is likely to

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[10] The GOLD database is located at <http://www.genomesonline.org>. See Bernal, A., Eur, U., Kyripides, N (2001) 'Genomes Online Database (GOLD): a monitor of genomics projects world-wide. *Nucleic Acids Research* (NAR) Vol. 29, No. 1, 126-127. Location: <http://nar.oupjournals.org/cgi/content/full/29/1/126>.

[11] "prokaryote" *A Dictionary of Biology*. Oxford University Press, 2000. For an accessible guide to classifications by leading biologists see the *Tree of Life Web Project*. Location: <http://www.tolweb.org>.

[12] "eukaryotes" *A Dictionary of Biology*. Oxford University Press, 2000. For an accessible guide to classifications by leading biologists see the *Tree of Life Web Project*. Location: <http://www.tolweb.org>.

[13] Secretariat of the Convention on Biological Diversity (2001) *Global Biodiversity Outlook*. Montreal: Secretariat of the Convention on Biological Diversity. Citation at 61.

[14] OECD (2002) *Genetic Inventions, Intellectual Property Rights and Licensing Practices: Evidence and Policies*. Paris: Organization for Economic Co-operation and Development. Citation at 33, citing Wade 2002. See also, Campbell, N and Reece, J and Mitchell, L (1999) *Biology*. Menlo Park, California: Addison Wesley Longman. Citation at 639. See also Institute of Molecular and Cell Biology 'IMCB Fugu Genome Project' website. Location: <http://www.fugu-sg.org/>.

[15] Nature (2003) *Proteomics*, Vol. 422. Location: <http://www.nature.com/nature/insights/6928.html>.

[16] Ibid., Nature 2003 *Proteomics*. See also, McNally, R and Glasner, P (2004) 'Beyond genomics: Post-genomics, proteomics & the other Omics', Extract from BSA Conference Paper, York, March 2004. CESAGen, unpublished ms.

[17] Fields, S (2001) 'Proteomics in Genomeland', *Science*, Vol. 291, 1221-1224. See also, Harrison, P, Kumar A, Lang, N, Snyder, M and Gerstein, M (2002) 'A question of size: the Eukaryotic proteome and the problems in defining it,' *Nucleic Acids Research*, Vol. 30, No. 5, 1083-1090.

[18] For recent discussion of the challenges in identifying the protein-coding portion of the human genome see Southan, C (2004) 'Has the yo-yo stopped? An assessment of human protein coding gene number', *Proteomics*, June 2004, 4(6): 1712-1726.

provide a much fuller understanding of organisms and the role of proteins in disease and may provide a route to developing new therapies.[19]

The rise of genomics and proteomics is intimately associated with two developments with important implications for debates surrounding the establishment of an international regime on access to genetic resources and benefit-sharing:

a) The relationship between genomics, proteomics and biotechnology and information technology ("bioinformatics");
b) Trends in intellectual property protection claims over genetic materials, genetic components, technology, and research methods.

I. Bioinformatics and Electronic Transfers

Bioinformatics consists of the computer-based analysis of biological materials.[20] The application of computational techniques to genetic material has revolutionised the biotechnology and genomics sector and encouraged major companies, such as IBM, to develop life-sciences divisions.[21] One estimate suggests that the bioinformatics sector will constitute a US$38 billion sector by 2006.[22]

The key innovation in bioinformatics has been the invention of the microarray or 'gene chip'. A microarray is a small glass slide which may be ordered as a series of slides, "…containing thousands of DNA sequences in an ordered array, which allows simultaneous analysis of thousands of genetic markers or cDNA sequences".[23] The invention of the microarray has enabled the rapid electronic sequencing of genetic material and entire genomes. Thus, using a technique known as BLAST (Basic Local Alignment Search Tool), Syngenta Biotechnology Inc. and Myriad Genetics were able to complete the draft of the rice genome in a total of around fourteen months.[24] Trends in the rapid sequencing of genomes are set to accelerate with the invention of the "genome chip" containing "the entire protein-coding portion of the human genome".[25] This advance will permit the analysis of the entire coding DNA of the human genome in a day.

The emergence of bioinformatics is revolutionising the science of biology. This is reflected in the rapid growth of "systems biology" focusing on mathematical algorithms and modelling of

[19] See a) Nature (2003) *Proteomics*, Vol. 422. Location: <http://www.nature.com/nature/insights/6928.html> b) An up to date collection of literature on proteomics is provided by Dr. Yuk Fai Leung at *Y.F Leung's Functional Genomics*. Location: <http://ihome.cuhk.edu.hk/%7Eb400559/>

[20] Science (2000) 'Bioinformatics for Biodiversity', *Science*, 29th September 2000, Vol. 289, No. 5488.

[21] The Economist 'The race to computerize biology', *The Economist*, 12th of December 2002.

[22] Ibid., The Economist 2002.

[23] Ibid., Nuffield Council on Bioethics 2002 at 91. See also Raven, P and Johnson, G (2002) *Biology*. Boston: McGrawHill.

[24] See: a) Myriad Genetics. Location: <http://www.myriad.com.>; b) See Karlin, S and Altschul, SF (1990) 'Methods for Assessing the Statistical Significance of Molecular Sequence Features by Using General Scoring Schemes', *Proceedings of the National Academy of Science*, Vol. 87, 2264-2268.

[25] See: a) Hitt, E (2004) 'One Chip, One Genome', *The Scientist*, Volume 18, Issue 13, 38, July 5th 2004. Location: <http://www.the-scientist.com/yr2004/jul/tech2_040705.html.>; b) Scott, A (2003) 'The human genome on a chip', *The Scientist*, October 3rd, 2003. Location: <http://www.biomedcentral.com/news/20031003/07>.

biological processes.[26] The scientific promise of the application of computational techniques to the analysis of genetic data is that it will provide a much fuller understanding of the genetic make-up of organisms and relationships between varieties, species, genera and families within and across classes. In the arenas of agriculture and medicine, the rise of bioinformatics provides opportunities for the rapid screening of genomics data and selection of potential compounds for further testing. In the context of debates surrounding the assessment of the role of intellectual property in relation to access to genetic resources and benefit-sharing arrangements, developments in this area are important for three main reasons.

a) Research and Development costs:

The application of computational techniques to the identification of candidate compounds potentially promises to reduce the costs of the development of new pharmaceuticals and other products.[27] Estimates for the costs of Research and Development to develop a new drug presently range between US$231 and US$500 million to US$800 million and US$1.7 billion.[28] It is also estimated to take an average of 15 years to bring a new product to market and the length of product development increased significantly in the late 20th Century to the point that a crisis is emerging in new product delivery.[29] In particular, claims surrounding the high costs of R & D provide the foundation for arguments for intellectual property protection over genetic material, limitations on prior informed consent requirements from governments, indigenous peoples and local communities, and the curtailment of benefit-sharing expectations. The analysis of trends in R & D costs and time to market in the context of the rise of bioinformatics may therefore merit closer attention in establishing effective and equitable access and benefit-sharing arrangements.[30] The rise of bioinformatics may also provide potential alternative forms of benefit-sharing targeted towards health and development needs (see below).

[26] See: a) Westerhoff, H and Palsson, B (2004) 'The evolution of molecular biology into systems biology', *Nature Biotechnology* Vol. 22, No. 10. October 2004; b) European Commission (2003) *Bioinformatics – Structures for the Future*. June 2003. <http://www.cordis.lu/lifescihealth/genomics/home.htm>; c) Marcus, F, Mulligan, B, Sansom (eds.) (2004) *Computational Systems Biology (CSB) – Its future in Europe*. European Commission, DG Research, 8th of March 2004. Location: <ftp://ftp.cordis.lu/pub/lifescihealth/docs/csbworkshop_2004_03_en.pdf>; d) Ibid., The Economist 2002.

[27] Ibid., The Economist 2002.

[28] See: a) Laird, S and ten Kate, K (1999) 'Natural Products and the Pharmaceutical Industry', in ten Kate, K and Laird, S (1999) *The Commercial Use of Biodiversity*. London: Earthscan. Citation at 34 and see discussion section 3.4.2 at page 47; b) Food and Drug Administration (2004) *Innovation or Stagnation? Challenge and Opportunity on the Critical Path to New Medical Technologies*. White Paper, U.S Department of Health and Human Services, Food and Drug Administration, March 2004 (revised ed.). Citation at 3. Location: <http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.pdf>; c) In practice these claims are contested i.e. Goozner, M (2004) *The $800 Million Pill: The Truth Behind the Cost of New Drugs*. Berkeley: University of California Press. at Chapter 9; d) The Global Alliance for TB Drug Development (2001) *The Economics of TB Drug Development*'. Location: <http://www.tballiance.org/pdf/Economics%20Report%20Full%20(final).pdf>; e) the World Health Organisation has established a Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH). Location: <http://www.who.int/intellectualproperty/en/>.

[29] See: a) Ibid., US Food and Drug Administration (2004) op. cit. 29; b) ten Kate, K and Laird, S (1999) *The Commercial Use of Biodiversity*. London: Earthscan.

[30] The US Food and Drug Administration endorses bioinformatics in providing a potential contribution to overcoming the crisis in drug development, Ibid., US Food and Drug Administration 2004. See also Constans, E (2004) 'Desktop Drug Discovery', *The Scientist*, Vol. 18, Issue 4, 33, March 1st 2004. Location: <http://www.the-scientist.com/yr2004/mar/tech1_040301.html>.

b) Accessible and Affordable Technologies:

The technology and software associated with the rise of bioinformatics is increasingly accessible, standardised and affordable.[31] Thus, Dell and IBM have entered this market and a number of specialist companies offer software, including "open source" and free software, and other specialised services for the storage and analysis of bioinformatics data.[32] The European Commission is also actively supporting the development of bioinformatics software platforms and on a wider level is promoting "open source" software models as part of initiatives involving "Free/Libre and Open Source Software" (F/OSS).[33] Other important initiatives include the European Molecular Biology Open Software Suite (EMBOSS) project established with support from the UK Medical Research Council (MRC) which offers a suite of freely available "open source" bioinformatics software resources.[34] The Ford Foundation has also recently announced a US$1 million initiative to promote "open source" tools in the realm of genomics and biotechnology.[35]

The challenges and costs associated with bioinformatics merit further consideration that can be provided here. However, the rise of bioinformatics presents potential opportunities to link access and benefit-sharing agreements with bioinformatics technology and knowledge transfers in accordance with Articles, 16, 17, 18 and 19 of the Convention and may merit further consideration. A 2002 study of the top ten biotechnologies for improving health in developing countries ranked bioinformatics as the 7th most important technology.[36] However, a 2003 report from a workshop sponsored by the European Commission highlights that it is important not to underestimate the significant technical and human resource challenges represented by bioinformatics.[37] Furthermore, the rise of bioinformatics raises significant issues surrounding

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[31] Ibid., European Commission (2003). See also Laird, C (2002) 'Open source in the Biosciences: freely available software plays special role for big Pharma and others'. IBM website. Location: <http://www-106.ibm.com/developerworks/linux/library/l-osbio.html>

[32] See: a) Ibid., European Commission (2003); b) Bioinformatics.org at <http://bioinformatics.org>; c) For recent discussion see 'Open Bioinformatics', Editorial, *Bioinformatics* 19(6) 679-680. Location: <http://bioinformatics.oupjournals.org/cgi/reprint/19/6/679.pdf>; d) See also the European Bioinformatics Institute (EMBL-BI) website which forms part of the European Molecular Biology Laboratory (EMBL).

Location: <http://www.ebi.ac.uk/Information/funding/temblor.html>.

[33] See European Commission website 'Free and Open Source Software'

Location : <http://europa.eu.int/information_society/activities/opensource/index_en.htm>.

[34] EMBOSS. Location: <http://emboss.sourceforge.net/what/> . Rice, P, Longden I, Bleasby, A (2000) 'EMBOSS: The European Molecular Biology Open Software Suite' *Trends in Genetics* 16, (6) pp276—277. See also, The Bioinformatics Resource (TBR). Location: <http://www.hgmp.mrc.ac.uk/CCP11/whatistbr.jsp>. See also, Counsell, D (forthcoming 2004) 'Condemned by your genes', *Linux User*. Location: **<**http://www.linuxuser.co.uk/**>.**

[35] Dennis, C (2004) 'Biologists launch 'open-source movement'', *Nature* 431, 494, 30 September 2004.

[36] See: a) Daar, A et al. (2002) 'Top ten biotechnologies for improving health in developing countries', *Nature genetics*, Volume 32, October 2002, 229-232; b) Daar, A et al. *Top ten biotechnologies for improving health in developing countries*, Program in Applied Ethics and Biotechnology – Canadian Program on Genomics and Global Health. University of Toronto Joint Centre for Bioethics. Location: <http://www.utoronto.ca/jcb/genomics/documents/toptenreportfinal.pdf>; c) Genomics Working Group of the Science and Technology Task Force of the United Nations Millennium Project (2004) *Genomics and Global Health*. A Report of the Genomics Working Group of the Science and Technology Task Force of the United Nations Millennium Project. Location: <http://www.utoronto.ca/jcb/home/documents/Genomics_Global_Health.pdf>.

[37] See: a) European Commission (2003) *Bioinformatics – Structures for the Future*. June 2003. <http://www.cordis.lu/lifescihealth/genomics/home.htm>; b) Ibid., *The Economist*.; c) Marcus, F, Mulligan, B, Sansom, M (eds.) (2004) *Computational Systems Biology (CSB) – Its future in Europe*. European Commission, DG Research, 8th of March 2004. Location: <ftp://ftp.cordis.lu/pub/lifescihealth/docs/csbworkshop_2004_03_en.pdf>.

[37] Ibid., European Commission 2003.

human rights, research ethics and prior informed consent that merit further and detailed consideration.

c) Electronic Transfers and International Collaboration:

The rise of bioinformatics reflects a growing trend towards the electronic transfer of data on biological materials across frontiers and the promotion of international collaborative ventures. These trends are observable in the case of the establishment of online genetics databases, such as the publicly accessible international depositary known as GenBank, maintained by the National Institutes of Health (NIH), which forms part of the wider International Nucleotide Sequence Database Collaboration.[38] At the end of 2003 GenBank contained 30,968,418 DNA sequences from an estimated 130,000 organisms.[39] Developments in this arena are also reflected in the establishment of the Single Nucleotide Polymorphism Consortium (SNP Consortium) as a public/private initiative to map DNA variations among individuals and to place such material in the public domain.[40] As of July 2004, an estimated 1.8 million SNPs (pronounced "snips") have been identified through the initiative.[41]

Other important international collaborative research initiatives include the International Rice Genome Sequencing Project (IRGSP).[42] The IRGSP was established in 1997 as a collaborative venture to map the rice genome between publicly funded laboratories in China, Japan, the USA, Brazil, Thailand, France, India, Taiwan, the Republic of Korea and the United Kingdom.[43] In December 2002 IRGSP announced that it had completed the mapping of the rice genome (*Oryza sativa ssp.japonica*) using a BAC (Bacterial Artificial Chromosome) or "clone by clone shotgun sequencing strategy".[44] The information on the rice genome comprising 367Mb of "non-overlapping nucleotide sequence" data is now publicly available.[45] In 2003, the IRGSP received the World Technology Award for what the Prime Minister of Japan described in 2002 as: "…an epoch making achievement comparable to the completion of the first survey of the entire human genome two years ago".[46] Similar international initiatives are underway in the area of disease, such as the quest to eradicate malaria following the mapping of the genome of the *Plasmodium falciparum* human malaria parasite.[47]

A fuller review of international collaborative initiatives involving genomics and proteomics may be desirable in the context of the development of an international regime. However, for governments, scientists, indigenous peoples, local communities and civil society organisations concerned with issues surrounding access to genetic resources and benefit-sharing, trends

[38] See GenBank website. Location: <http://www.ncbi.nlm.nih.gov/Genbank/index.html>.

[39] See a) GenBank Statistics 'Growth of GenBank'. Location: <http://www.ncbi.nlm.nih.gov/Genbank/genbankstats.html>; b) NCBI Resource Guide 'GenBank – General Information'. Location: <http://www.ncbi.nlm.nih.gov/Sitemap/index.html#Overview>.

[40] SNP Consortium website. Location: <http://snp.cshl.org/>.

[41] Ibid., SNP Consortium website.

[42] International Rice Genome Sequencing Project (IRGSP). Location: <http://rgp.dna.affrc.go.jp/IRGSP/>.

[43] Ibid., IRGSP.

[44] Ibid., IRGSP, 'Guidelines'. Location: <http://rgp.dna.affrc.go.jp/IRGSP/>.

[45] Ibid., IRGSP

[46] IRGSP, news 18 December 2002. Location: <http://rgp.dna.affrc.go.jp/rgp/Dec18_NEWS.html>.

[47] See for example the Malaria Sequencing Consortium <http://www.wellcome.ac.uk/en/malaria/TheParasite/pbgeno1.html>.

towards the electronic transfers of genetic data are likely to present both challenges and potential opportunities.

Challenges:

In the case of existing debates under the Convention on Biological Diversity, notably the establishment of the Bonn Guidelines, considerable attention has focused on the elaboration of a model Material Transfer Agreement (MTA) to assist governments and other actors in regulating access to genetic resources and benefit-sharing.[48] In the context of debates surrounding the establishment of an international regime, important proposals have also emerged in connection with the use of the existing international customs regime and creation of an international certification system.[49]

However, trends in the genomics sector suggest a decreasing dependence on physical transfers of biological material and increasing trends towards electronic transfers because genetic material can be readily expressed as *information* in the form of A (adenine), G (guanine), C (cytosine) and T (thymine) bases in the case of DNA (deoxyribonucleic acid), and ACG and U (uracil) for RNA (ribonucleic acid). This also extends to amino acids which form the basis of proteins. Thus, there are 20 common amino acids and these and other amino acids may also be expressed as information organised in sequences relative to DNA sequences i.e. G or Gly (Glycine), A or Ala (Alanine), V or Val (Valine) etc.[50] To date the implications of these trends have not been considered in debates surrounding access to genetic resources and benefit-sharing under the Convention.

In considering the implications of such trends for the development of an international regime four initial questions arise: a) what are the terms and conditions under which international electronic transfers are made?; b) should electronic transfers be regulated?; c) what are the potential costs and benefits of the regulation of electronic transfers?; d) what forms of regulation of electronic transfers might be appropriate?

These questions are particularly important in a context in which DNA sequence data, relating for example to a particular medicinal plant, may be uploaded to a website or partially transferred as an attachment within electronic mail. Furthermore, the extraction of genetic data has classically depended upon the collection, taxonomic identification and storage of field samples, i.e. within

[48] a) Decision VI/24 'Access and benefit-sharing as related to genetic resources', Location <http://www.biodiv.org/decisions/default.asp?lg=0&dec=VI/24>; b) Decision VII/19 'Access and benefit-sharing as related to genetic resources'. Location <http://www.biodiv.org/decisions/default.aspx?m=COP-07&id=7756&lg=0>.

[49] See: a) WIPO (2003) 'Proposals by Switzerland regarding the declaration of the source of origin of genetic resources and traditional knowledge in patent applications', Working Group on Reform of the Patent Cooperation Treaty (PCT), Fifth Session, Geneva, November 17 to 21, 203. Document PCT/R/WG/5/11 Rev. Location: <http://www.wipo.int/pct/en/meetings/reform_wg/pdf/pct_r_wg_5_11_rev.pdf>; b) WIPO (2004) Additional comments by Switzerland on its proposals regarding the declaration of the source of genetic resources and traditional knowledge in patent applications', Working Group on Reform of the Patent Cooperation Treaty (PCT), Sixth Session, Geneva, May 3 to 7, 2004. Document PCT/R/WG/6/11. Location: <http://www.wipo.int/pct/en/meetings/reform_wg/pdf/pct_r_wg_6_11.pdf>; c) UNU (2003) *User Measures: Options for Developing Measures in User Countries to Implement the Access and Benefit-Sharing Provisions of the Convention on Biological Diversity*, 2nd Edition. UNU-IAS report. United Nations University Institute of Advanced Study. Tokyo: UNU-IAS. Location: <http://www.ias.unu.edu/binaries/UNUIAS_UserMeasures_2ndEd.pdf>.

[50] Ringo, J (2004) *Fundamental Genetics*. Cambridge: Cambridge University Press. See for example, Medical Research Council 'Amino Acid Codes'. Location: <http://www.hgu.mrc.ac.uk/Softdata/Misc/aacode.htm>.

herbaria. However, it is conceivable that technological innovation may one-day permit the *in situ* extraction of genetic material and transfer of data to electronic form without the necessity of the collection, taxonomic identification and storage of field samples. While this is presently speculative, it is worth noting that DNA testing kits for humans are already available over the internet and a 'DNA Explorer Kit' for children is now available.[51] In the era of the single "genome chip", and the recent announcement of a new technique to replicate DNA (HDA or helicase-dependent amplification) which may permit the development of hand-held DNA diagnostic devices, this suggests a need for flexibility to accommodate emerging developments in establishing an international regime.[52]

The emergence of bioinformatics may also present potential opportunities for governments, the scientific community, indigenous peoples and local communities, and civil society organisations. Two areas stand out for possible further discussion and exploration.

Potential Opportunities:

First, the rise of electronic transfers of genetic data raises the possibility of the creation of electronic certificates or passports to accompany genetic data throughout its journey. Such measures could complement existing proposals for certification and enhanced disclosure and may potentially provide a possible, if partial, route to regulation of the problem of "biopiracy" and scientific fears surrounding the emergence of a so-called "anticommons".[53] These opportunities may extend to alternative forms of protection or licensing arrangements to enhance collaboration and benefit-sharing (see below).[54]

In this regard it is important to note that the major patent offices and the World Intellectual Property Organisation (WIPO) are increasingly adopting regulations and procedures to permit electronic deposits of DNA/Amino Acid sequences. This forms part of a wider shift towards the electronic submission and administration of patent applications within the major patent offices and WIPO. For the purposes of the administration of Patent Cooperation Treaty (PCT) applications, WIPO has established a publicly accessible electronic listing of "Nucleotide and/or Amino Acid Sequences" contained within PCT patent applications.[55] In 2001 a total of 90

[51] The Discovery company markets a 'DNA Explorer Kit' for children aged ten and over for $79.95.

Location: <http://shopping.discovery.com/stores/servlet/ProductDisplay?catalogId=10000&storeId=10000&productId=53965>.

[52] On the genome chip see: a) Hitt, E (2004) 'One Chip, One Genome', *The Scientist*, Vol. 18, Issue 13, 38, July 5th 2004, and; b) Scott, A (2003) 'The human genome on a chip', *The Scientist*, October 3, 2003. On HDA see: a) EurekAlert 'A better way to copy DNA' press release 14th July 2004. Location: <http://www.eurekalert.org/pub_releases/2004-07/embl-abw071404.php>; b) See also, Vincent, M. Xu, Y & Kong, H (2004) 'Helicase –dependent isothermal DNA amplification' EMBO reports Vol. 5, Issue 8. pp 795-800. Location: <http://www.nature.com/cgi-taf/DynaPage.taf?file=/embor/journal/v5/n8/full/7400200.html>.

[53] See: a) WIPO (2003) 'Convention on Biological Diversity: Disclosure Requirements Concerning Genetic Resources and Traditional Knowledge', World Intellectual Property Organisation, WO/GA/30/7, August 15th 2003. Location: <http://www.wipo.org/documents/en/document/govbody/wo_gb_ga/doc/wo_ga_30_7.doc>; b) WIPO (2004) 'Traditional Knowledge within the Patent System', Intergovernmental Committee on Intellectual Property and Genetic Resources, Traditional Knowledge and Folklore, Seventh Session, Geneva, November 1 to 5, 2004. Document WIPO/GRTKF/IC/7/8, July 23 2004. Location: <http://www.wipo.int/edocs/mdocs/tk/en/wipo_grtkf_ic_7/wipo_grtkf_ic_7_8.doc>; c) In relation to biopiracy see the Action Group on Erosion, Technology and Concentration (ETC Group). Location: <http://www.etcgroup.org/>; d) Heller, M and Eisenberg, R (1998) 'Can Patents Deter Innovation? The Anticommons in Biomedical Research', *Science*, Vol. 280, 698-701.

[54] UNEP/CBD/WG-ABS/2/2 'Further consideration of outstanding issues related to access and benefit-sharing: use of terms, other approaches and compliance measures: Note by the Executive Secretary', United Nations Convention on Biological Diversity. Location: <http://www.biodiv.org/doc/meetings/abs/abswg-02/official/abswg-02-02-en.doc>.

[55] The WIPO sequence listing can be accessed at <http://www.wipo.int/pct/en/sequences/listing.htm>.

sequences were deposited rising to 121 sequences in 2002 and falling to 81 sequences in 2003.[56] Between January the 15th and September the 2nd 2004, 70 sequences had been deposited with the listing. The sequences are downloadable in plain text format setting out the DNA sequence in terms of A (adenine) C (cytosine), T (thymine) and G (guanine) and corresponding amino acid sequences. Similar measures have been adopted, or are in the process of being adopted, by the Trilateral Offices consisting of the United States Patent and Trademark Office (USPTO), the European Patent Office (EPO) and the Japan Patent Office (JPO) and have been accompanied by the introduction of electronic filing software and electronic signatures. [57] These trends are particularly relevant in relation to proposals to introduce an international certificate of origin system in relation to traditional knowledge and genetic resources within access and benefit-sharing arrangements.[58] An electronic international certification system could potentially be employed to preclude the possibility of submission of traditional knowledge and genetic material for patent protection where this is deemed desirable.

Second, in the case of health, it is well established that the existing model of innovation within the pharmaceuticals sector is oriented towards developed country markets: only a small percentage of new compounds are directed towards diseases which primarily affect developing country residents. Thus, the World Health Organisation estimates that between 1975 and 1996 of 1,223 new chemical pharmaceutical compounds only 11 were targeted towards tropical diseases.[59] As the Director of the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases has recently observed: "The total R &D activity for diseases of poverty currently ranks at the level of a small pharmaceutical company…".[60] While R&D expenditure in this area is expected to double in the next five years, this will nevertheless result in investment ranking at the level of a small to medium pharmaceutical company. Similar problems are encountered in the case of rare, or "orphan", diseases where low population levels of sufferers make pharmaceutical development commercially unattractive in the absence of special incentives.[61] Furthermore, in the case "bioprospecting" projects involving traditional

[56] Ibid., WIPO sequence listing.

[57] The USPTO has developed regulations surrounding sequence deposits, provides software to facilitate deposits and has created a new sequence search facility (see for example: <http://seqdata.uspto.gov/>). The status of such developments at the EPO and JPO is unclear at the time of writing.

[58] See COP7 Decision VII/19, Annex, para. (d) small roman (xiii) concerning an "Internationally recognized certificate of origin/source/legal provenance of genetic resources and associated traditional knowledge".

[59] Cullet, P (2003) 'Patents and medicines: the relationship between TRIPS and the human right to health', *International Affairs* Vol. 79, 1 pp. 139-160. Citation at 142.

[60] Mr. Ridley goes on to add that "…but there is a likely doubling of size in the coming five years resulting in many thousands more individuals being engaged in product R&D for diseases of poverty". This issue is addressed elsewhere in the review. See Ridley, R (2004) 'Product development Public Private Partnerships for Diseases of Poverty. Are there more efficient alternatives? Are there limitations? Paper presented at IPPPH Meeting, London, April 15th and 16th 2004, Combating Diseases Associated with Poverty: Financing Strategies for Product Development and the Potential Role of Public-Private Partnerships. Location: <http://www.who.int/entity/intellectualproperty/documents/en/R.Ridley.pdf>.

[61] The US Orphan Drug Act is a primary example of an incentive targeted towards orphan diseases. See Food and Drug Administration 'The Orphan Drug Act (as amended)'. Location: <http://www.fda.gov/orphan/oda.htm>. For a critical perspective on the relationship between the biotechnology sector and the Orphan Drug Act, see Goozner, M (2004) *The $800 Million Pill: The Truth Behind the Cost of New Drugs*. Berkeley: University of California Press.

knowledge testing of compounds appears to be primarily directed towards the demands of developed country markets.[62]

On a wider level, bioinformatics and genomics promises to contribute to the conservation and sustainable use of biodiversity by providing greater insights into the biology of species, relationships between species, and processes within particular environments. The promotion of research collaborations (which could be virtual) could potentially provide an alternative form of benefit-sharing directed towards local conservation, sustainable use and development needs and attract public support.

However, in considering these potential opportunities three important caveats are appropriate:

a) Developments in the biotechnology sector over the last ten years have been characterised by a high level of promise with respect to the delivery of new products relative to levels of delivery of such products.[63] Such promises at times appear to have more to do with attracting venture capital and the demands of stock flotation than product delivery. In the absence of convincing evidence, and taking into account the limited resources and many pressing priorities within developing countries and among indigenous peoples and local communities, scepticism with respect to the promises of advocates of biotechnology appears to appropriate.
b) In the absence of certainty surrounding respect for the rights and interests of indigenous peoples and local communities in relation to their knowledge and resources, it is unlikely to be logical for indigenous peoples and local communities to participate in such initiatives. Bioinformatics and related developments such as databases and "biobanks" also raise significant human rights and ethical issues which are particularly marked in the case of indigenous peoples, local communities and other vulnerable groups.[64]

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[62] This issue merits further research. However, a case in point is provided by *hoodia* (P57), which has traditionally been used as an appetite suppressant by the San peoples of Southern Africa. Anticipated developments relating to *hoodia* are primarily directed towards developed country markets (obesity and diabetes). See Stephenson, D (2003) *The Patenting of P57 and the Intellectual Property Rights of the San Peoples of Southern Africa*. Location: <http://www.firstpeoples.org>. The same issue is also reported in the case of the ICBG-Aguaruna project in the Peruvian Amazon. See Greene, S (2004) 'Indigenous People Incorporated? Culture as Politics, Culture as Property in Pharmaceutical Bioprospecting', *Current Anthropology*, Vol. 45, No.2, April 2004. 211-237. See also the International Cooperative Biodiversity Groups website. Location: <http://www.fic.nih.gov/programs/icbg.html>.

[63] See for example, Ernst and Young (2002) *Beyond Borders: The Global Biotechnology Report 2002*. See also, the Global Biotechnology Reports series 2004. Location: <http://www.ey.com/global/content.nsf/International/Biotechnology_Reports_2004>.

[64] There is no single comprehensive review of these issues across the spectrum of red and green genetic issues. However, the following are useful resources: a) Motoc, I-A (2003) 'Human Rights and Bioethics', Expanded working paper submitted by Ms. Iulia-Antoanella Motoc in accordance with Sub-Commission decision 2002/114, Sub-Commission on the Promotion and Protection of Human Rights. Document E/CN.4/Sub.2/2003/36, 10th of July 2003. Location: <http://www.unhchr.ch/huridocda/huridoca.nsf/(Symbol)/E.CN.4.Sub.2.2003.36.En?Opendocument>; b) CESCR (2001) Human Rights and Intellectual Property: Statement by the Committee on Economic Social and Cultural Rights. Document E/C.12/2001/15. Location: <http://www.unhchr.ch/tbs/doc.nsf/0/1e1f4514f8512432c1256ba6003b2cc6?Opendocument>; c) WHO (2002) *Genomics and World Health*. Canada. World Health Organization, see in particular chapter eight 'Ethical Issues in Genetic Research, Screening, and Testing, with Particular Reference to Developing Countries'. Location: <http://www3.who.int/whosis/genomics/genomics_report.cfm#>; d) HUGO (2002) Statement on Human Genomic Databases. Location: <http://www.gene.ucl.ac.uk/hugo/HEC_Dec02.html>; e) TRAMES, Journal of the Humanities and Social Sciences, Vol. 8 No.1/2, Special issue, *Human genetic databases: ethical, legal and social issues*; f) Alexander, M et al. (2003) *The Role of Registers & Databases in the Protection of Traditional Knowledge: A Comparative Analysis*. UNU-IAS Report. Tokyo: United Nations University, Institute of Advanced Study. Location: <http://www.ias.unu.edu/binaries/UNUIAS_TKRegistersReport.pdf>.

c) Trends towards the patenting of key genetic components and regulatory mechanisms of organisms arising from genome mapping may result in intellectual property claims existing before access and benefit-sharing arrangements are put in place.

As this discussion suggests, a balanced and evidence based approach which recognises the variety of rights, interests and perspectives involved in, or affected by, the rise of bioinformatics is likely to be desirable in considering the potential opportunities and costs presented by bioinformatics. In an era when biological and genetic material is merging with information technology enhancing the visibility of global trends in intellectual property claims in relation to genetic material is particularly desirable.

II. Status and Trends in Patenting of Genetic Material

A patent is a legal certificate which awards temporary protection over a claimed invention for a period that is generally twenty years.[65] Patents are awarded in accordance with three criteria, they must be: a) new (or novel); b) involve an inventive step (be non-obvious), and; c) be capable of industrial application (be useful or of utility). A patent awards an exclusive temporary protection to its holder including the right to exclude others from "making, using, offering for sale, or selling" or "importing" the protected invention into a jurisdiction where the patent protection is in force, or to charge others for any uses or purposes involving the protected invention within such jurisdictions (i.e. through licensing).[66]

Patenting and licensing practices in connection with genetic 'inventions' have recently been the focus of an important 2002 report by the OECD Working Party on Biotechnology entitled *Genetic Inventions, Intellectual Property Rights and Licensing Practices: Evidence and Policies* (hereafter the OECD Working Party report) upon which the following discussion draws extensively.

It is frequently asserted that patent protection has a vital role to play in stimulating commercial innovation in the life sciences. This view is reflected in the OECD Working Party report in the following terms:

> "The economic value of patent protection in the life sciences, and especially in the pharmaceutical and agrochemical industries, is widely recognised. In no other fields is the relationship between patent protection and incentives to innovate so strong".[67]

In practice the rise of patent protection in these arenas is highly contested in both developed and developing countries, among indigenous peoples and local communities, civil society organisations, members of the scientific community, economists, and increasingly industry.[68] These diverse and substantive concerns merit further detailed attention than can be provided here but may be briefly summarised as follows:

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[65] WIPO 'Inventions (patents)'. Location: <http://www.wipo.int/about-ip/en/patents.html>.

[66] United States Patent and Trademark Office 'General Information Concerning Patents' online brochure. Citation at 'What is a patent?'. Location: <http://www.uspto.gov/web/offices/pac/doc/general/>.

[67] OECD (2002) *Genetic Inventions, Intellectual Property Rights and Licensing Practices: Evidence and Policies*. Paris: Organisation for Economic Co-operation and Development. Citation at 27.

[68] See for example industry submissions to the United States Federal Trade Commission (FTC) and discussion surrounding economic analysis in the FTC report *To Promote Innovation: The Proper Balance of Competition and Patent Law and Policy*. A Report by the Federal Trade Commission, October 2003. Location: <http://www.ftc.gov/os/2003/10/innovationrpt.pdf>.

a) Whether the extension of patent protection to genetic material is justifiable on ethical or human rights grounds;
b) Whether the "identification", "isolation" or "purification" of genetic material meets the criteria of "inventive step" or constitutes mere "discovery" for the purposes of determining patentability;
c) Whether claimed inventions meet the criteria of being capable of industrial application (or "utility" for the United States);
d) The impacts of permitting patent claims that are very broad in scope;
e) The economic evidence upon which the extension of patentability to biological and genetic material has been based and implications for competition and innovation;
f) The impacts of multiplying patent protection claims for public health, agriculture, human rights, development, scientific research, industry and trade.

The well-known and widely cited 1980 United States Supreme Court case *Diamond v. Chakrabarty* surrounding the patentability of a 'modified' microorganism proved critical in opening the way for the patenting of genetic material and its components.[69] In reaching this judgement the Court recalled the observation that emerged during the 1952 Congressional recodification of the Patent Law (U.S.C. 35) that the law should be expanded to "include anything under the sun that is made by man".[70] This decision overturned the earlier doctrine which excluded biological organisms and genetic material from eligibility for patentability on the grounds that they are a "product of nature" and replaced this with what may be called the "hand of man" doctrine.[71]

Attitudes and legislation concerning the patentability of genetic material vary significantly between the United States, Europe and Japan.[72] A 1994 European Patent Office Board of Appeals decision V0008/94 concerning a patent claim over a human DNA fragment clarified the position of the EPO in relation to the patenting of genetic material.[73] In response to a challenge to the patent on the grounds of morality the Board of Appeals declared:

> "It is worth pointing out that DNA is not "life", but a chemical substance which carries genetic information and can be used as an intermediate in the production of proteins which may be medically useful. The patenting of a single human gene has nothing to do

[69] For an accessible interview based discussion of the case see, Kevles, D (2002) *A history of patenting life in the United States with comparative attention to Europe and Canada*. European Group on Ethics in Science and New Technologies to the European Commission. 12 January 2002. Luxembourg: Office for Official Publications of the European Communities. Location: <http://europa.eu.int/comm/european_group_ethics/docs/study_kevles.pdf>. See also *Diamond v. Chakrabarty*. Location: <http://supct.law.cornell.edu/supct/cases/patent.htm>.

[70] Royal Society (2003) *Keeping Science Open: The Effects of Intellectual Property Policy on the Conduct of Science*. London: Royal Society, Location: <http://www.royalsoc.ac.uk/files/statfiles/document-221.pdf>. Citation at 7. *Diamond v. Chakrabarty* Location: <http://supct.law.cornell.edu/supct/cases/patent.htm>. The quotation is commonly attributed to Chief Justice Burger (i.e. Nuffield Council on Bioethics 2002). In fact, in delivering the opinion of the Court, Chief Justice Burger was citing Congressional Committee Reports S. Rep. No. 1979, 82d Cong., 2d Sess., 5 (1952).

[71] WO/03000904 at 22, line 21.

[72] See: a) Ibid., Kevles (2002); b) See also, Motoc, I-A (2003) 'Human Rights and Bioethics', Expanded working paper submitted by Ms. Iulia-Antoanella Motoc in accordance with Sub-Commission decision 2002/114 Sub-Commission on the Promotion and Protection of Human Rights. Document E/CN.4/Sub.2/2003/36, 10th of July 2003. Location: <http://www.unhchr.ch/huridocda/huridoca.nsf/(Symbol)/E.CN.4.Sub.2.2003.36.En?Opendocument>; c) Llewelyn, M (2000) 'The Patentability of Biological Material: Continuing Contradiction and Confusion', *European Intellectual Property Review*, Vol. 22 Issue 5.

[73] Ibid., Nuffield Council on Bioethics 2002.

> with the patenting of human life. Even if every gene in the human genome were cloned (and possibly patented), it would be impossible to reconstitute a human being from the sum of its genes."[74]

The patentability of genetic material is a focus of ongoing debate within the European Union.[75] However, patent practice within the European Union is informed by European Directive 98/44/EC "on the legal protection of biotechnological inventions".[76] Article 5.1 of Directive 98/44/EC specifies that: "…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".

It is important to note that Article 5.1 of Directive 98/44/EC remains controversial.[77] However, as of 2004, thirteen of the now twenty-five member states have implemented the directive.[78] Further questions have been raised surrounding the qualifications of the EPO Board of Appeals to deliberate on such weighty matters as the nature of life on behalf of citizens of the European Union and its member states.[79] However, in practice, for the purposes of patent law in the United States, Europe, and also Japan, patent protection in relation to DNA and biotechnology is presently treated in much the same way as chemical compounds and microorganisms.[80]

Tracking Gene Patent Claims:

A major constraint confronting the analysis of patenting activities in the arena of genomics, proteomics and biotechnology is the difficulty of tracking gene patent claims.[81] Thus, the Working Party reports that:

> "Gene or DNA patents do not coincide with a specific International Patent Classification (IPC) category. Very few groups, patent offices included, consistently track gene patent applications or grants. In addition, there is no easy way to make cross-country comparisons of patent activity, as no group has yet compiled a database of DNA-based patents worldwide…"[82]

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[74] EPO Board of Appeals Decisions, case V0008/94 - Opposition Division, 8th December 1994.

[75] See also A. Scott, "The Dutch Challenge to the Bio-Patenting Directive" (1999) *European Intellectual Property Review*, Vol. 21, 212; b) Schiemeier, Q (2000) "German Government takes a Narrow View of Gene Patents", *Nature* Vol. 406, 664. c) Schiemeier, Q (2000) 'German agencies sound alarm on risks of broad gene patents…', *Nature*, Vol. 406, 111.

[76] Ibid., Nuffield Council on Bioethics 2002 at 22. Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions. *Official Journal of the European Communities* L213/13 30.7.98. Location: <http://europa.eu.int/eur-lex/pri/en/oj/dat/1998/l_213/l_21319980730en00130021.pdf>.

[77] For a review of the history of the Directive see: a) Gold, R and Gallochat, A (2001) 'The European Biotech Directive', *European Law Journal*, Vol. 7, No. 3, September 2001, 331-366; b) Scott, A (2003) European court action over biotech patents', *The Scientist*, July 17 2003. Location: <http://www.biomedcentral.com/news/20030717/06>; c) Gold, R and Gallochat, A (2001) 'European Directive on the Legal Protection of Biotechnological Inventions: History, Implementation, and Lessons for Canada'. Location: <http://cbac-cccb.ic.gc.ca/epic/internet/incbac-cccb.nsf/en/ah00383e.html >.

[78] Ibid., Royal Society 2003. Further clarification is required of the status of the Directive among new member states of the European Union.

[79] See for example: a) Ibid., Gold and Gallochat (2001); b) See also Greenpeace. Location: <http://archive.greenpeace.org/pressreleases/geneng/2000nov19.html>.

[80] See: a) Ibid., OECD 2002; b) See Ibid., Motoc (2003) for discussion of the significant differences between legislation in this area within the United States, Europe and Japan.

[81] Ibid., OECD 2002.

[82] Ibid., OECD 2002 at 34.

The OECD Working Party report also reveals that in the case of the United States, biotechnology patents fall under class 435 of the United States Patent and Trademark Office (USPTO) classification system ("Molecular biology and microbiology").[83] In the case of the European Patent Office, biotechnology patents are awarded under five main classes ranging through "apparatus for enzymology or microbiology" (C12M), "microorganisms or enzymes" (C12N), "…fermentation or enzyme using processes for synthesising compounds" (C12P), "…measuring or testing processes" involving enzymes/microorganisms (C12Q), and "Processes using enzymes or microorganisms to liberate, separate or purify a pre-existing compound or composition" (C12S).[84]

Notwithstanding these constraints the OECD Working Party reports that patent grants in the arena of biotechnology "…have been growing more quickly than the rate of growth of all patents granted by USPTO and the EPO".[85] Thus, in "…2001 alone over 5000 DNA patents were granted by the USPTO…" of which 1,500 are thought to cover human genes.[86]

In an effort to identify trends in this area the OECD Working Party adopted an approach involving searching the major patent office databases for applications including the phrase "nucleic acid" and a range of other terms. In the case of the USPTO database, this approach yielded 9,456 patents granted of which 8,334 had been granted since 1996. A search of the Japan Patent Office (JPO) database revealed 5,652 patents granted between 1996 and 2001 featuring "…the terms genes, nucleic acid, DNA, RNA, or genome in the claims".[87] In the case of the European Patent Office (EPO) the data was less certain with a reported 30,000 biotechnology related applications received by the EPO between 1998 and 2001 "…of which about 10,000 pertain to 'mutations or genetic engineering'" where an estimated "...40% of the latter are for microorganisms, plants and/or animals and 60% relate to human or animal DNA sequences".[88] In the case of the EPO, data on actual patent grants in the biotechnology arena are unclear as a result of the nature of the esp@cenet database.

In response to these difficulties the Trilateral Offices are engaged in studies to reach agreement on the treatment of biotechnology patents.[89] The 2001 and 2002 Trilateral Statistical Reports incorporate biotechnology patents into the category of "high technology".[90] The inclusion of aviation, semi-conductors and lasers within this same category raises questions surrounding the utility of such a category for the purposes of tracking intellectual property trends in the arena of genomics, biotechnology and emerging arenas such as proteomics. Furthermore, in the context of the routinization of DNA replication and mapping through computerization, the application of the term "high" to such technologies is potentially open to question.[91] However, the Trilateral

[83] Ibid., OECD 2002 at 35.

[84] Ibid., OECD 2002 at 35.

[85] Ibid., OECD 2002 at 33.

[86] Ibid., OECD 2002 at 34, citing Rivers 2002.

[87] Ibid., OECD 2002 at 38.

[88] Ibid., OECD 2002 at 38.

[89] See the EPO/JPO/USPTO 'Trilateral Studies'. Location: <http://www.european-patent-office.org/tws/sr-3.htm>.

[90] Ibid. EPO/JPO/USPTO.

[91] i.e. Ibid., Nuffield Council on Bioethics 2002.

Offices are engaged in further work to refine the treatment of biotechnology statistics which will make an important contribution to the assessment of trends within the major patent offices.[92]

As this suggests, existing approaches commonly focus on identifying trends in the major patent offices (i.e. the EPO, JPO and USPTO) which account for the majority of patent activity world-wide.[93] This is logical when we consider that the Trilateral Offices accounted for an estimated 82% of patent activity world-wide in 2002.[94] One important initiative to enhance the tracking of gene patents is the *DNA Patent Database* established by the Kennedy Institute of Ethics at Georgetown University and the non-profit organisation Foundation for Genetic Medicine Inc.[95] This database provides full-text records of patents issued in the United States between 1971-2004 and a search algorithm for United States patents which may be used with the commercial DELPHION database operated by the Thomson Corporation.[96] However, while valuable, the analysis of trends within the major patent offices does not provide an adequate indicator of wider trends in the internationalisation of demand for patent protection for which alternative approaches are needed.[97]

This problem is particularly marked as a result of the growing prominence of regional and international patent instruments in the internationalisation of demand for patent protection. The main international instrument in terms of operationalising international patent protection is the 1970 Patent Cooperation Treaty (PCT) (amended 1979, modified 1984 and 2001).[98] Under the PCT residents of a Contracting State may submit a single application which can be "designated" for consideration by patent offices within other Contracting States and regional patent offices (i.e. ARIPO, the EPO, OAPI, EAPO).[99] There were 109 Contracting States to the PCT in 2000 rising to 115 in 2001, 118 in 2002 and 123 in 2003.[100] Patent filings under the PCT are an increasing feature of the international intellectual property regime and according to the Trilateral Offices, when combined with regional instruments, accounted for an estimated 75% of cumulative global demand for patent protection in 2000 rising to 78.9% in 2001.[101] As of the 1st

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[92] Japan Patent Office 'Summary Report of the Trilateral Technical Meeting. May 18 (Tue) - May 20 (Thu), 2004, in Arlington, U.S.' Location: <http://www.jpo.go.jp/torikumi_e/kokusai_e/3kyoku_e_arlington.htm>.

[93] See the Trilateral Statistical Reports available at Location: <http://www.uspto.gov/web/tws/sr-2.htm>.

[94] EPO/JPO/USPTO (2003) Trilateral Statistical Report 2002. Location: <http://www.uspto.gov/web/tws/tsr2002/>. Citation at Chapter 2: The Trilateral Offices. Location: <http://www.uspto.gov/web/tws/tsr2002/ch2/index.html>.

[95] See Kennedy Institute of Ethics/Foundation for Genetic Medicine Inc. 'DNA Patent Database'. Location: <http://dnapatents.georgetown.edu/oshtml/>.

[96] See Thomson – Delphion database. Location: <http://www.delphion.com>.

[97] The most detailed recent discussion of patent count methodologies is provided by Dernis, H and Guellec, D and Pottelsberghe, B (2001) *Using Patent Counts for Cross-Country Comparisons of Technology Outputs*. Economic Analysis and Statistics Division of the OECD Directorate for Science, Technology and Industry, and Free University of Brussels. Location: <http://www.oecd.org/dataoecd/26/11/21682515.pdf>.

[98] See WIPO website for the Patent Cooperation Treaty. Location: <http://www.wipo.int/pct/en/index.html>. The Regional Patent Organisations are a) the African Regional Industrial Property Organization (ARIPO); b) the European Patent Office (EPO); c) the Eurasian Patent Organization (EAPO); c) the Organisation Africaine de la Propriété Intellectuelle (OAPI).

[99] The Patent Cooperation Treaty was amended in 1979 and modified in 1984 and 2001. For the text of the Treaty and administrative arrangements, see WIPO <http://www.wipo.int/pct/en/texts/pdf/pct.pdf>.

[100] Sources: a) WIPO (2001) 'Information Note: The Patent Cooperation Treaty (PCT) in 2000', paragraph 4. Location: <http://www.wipo.int/pct/en/activity/2000/>; b) WIPO (2002) Information Note: The Patent Cooperation Treaty (PCT) in 2001', paragraph 4. Location: <http://www.wipo.int/pct/en/activity/2001/pct_2001.htm> ; c) WIPO (2003) *Yearly Review of the PCT: 2002*. page 12. Location: <http://www.wipo.int/pct/en/activity/pct_2002.pdf> ; d) See also WIPO (2004) *Yearly Review of the PCT: 2003*. Citation page 2. Location: <http://www.wipo.int/pct/en/activity/pct_2003.pdf>.

[101] Ibid., EPO/JPO/USPTO (2003) *Trilateral Statistical Report 2002*, at 18.

of January 2004, PCT applications automatically designate all Contracting States (123 Contracting States).[102]

Achieving a truly global perspective on status and trends in patent claims in relation to biological and genetic material is rendered challenging by the lack of integration of patent office databases world-wide. However, the European Patent Office esp@cenet "worldwide" database provides coverage of seventy three national patent offices, regional patent offices and WIPO (for the Patent Cooperation Treaty) and contains an estimated 45 million patent related publications. As such it is the largest database of its type and broadly corresponds with a world "master" database.

As a contribution to methodological development and evaluation a key word search was conducted of the esp@cenet worldwide database for a series of seventeen key terms related to genomics, proteomics and biotechnology. The outcomes of the search were verified during a second test and ranked to identify the top five key terms. [103] The results of this search are presented in Figure One and the underlying search result data including data for individual target years 1990, 1995, 2000, and preliminary data for 2003 is presented in Table One. The full thirteen year dataset is presented in Annex 1.

In approaching this data, it is important to note that the search is confined to the title and abstracts of patent publications within the esp@cenet "worldwide" database.[104] In contrast with the USPTO database (which is confined to US patent publications) it is not possible to search the claims section of publications within esp@cenet. Furthermore, the search results are confined to those patent publications which possess a title and/or abstract in English. In practice, a review of the detailed coverage of titles and abstracts within the worldwide database reveals very significant variation in country coverage.[105] Thus, in the case of Brazil none of the 278,133 patent publications within the database contained titles or abstracts in English while in contrast in the case of Canada 99.5% of 883,947 publications possessed titles in English and 70.8% possessed abstracts in English.[106] A review of the availability of titles and abstracts for the estimated 36,165,421 industrial patent publications within

[102] Ibid., WIPO (2004) *Yearly Review of the PCT: 2003*. These issues are considered in further detail in the companion paper in this series *Global Status and Trends in Intellectual Property Claims: Global Patent Trends*.
[103] Methodological issues including data verification are addressed in further detail in the companion paper in this series *Global Status and Trends in Intellectual Property Claims: Patent Dataset*.
[104] EPO esp@cenet 'Worldwide Database – Detailed Coverage Abstracts', Table current as of 2nd of August 2004. Location: <http://ep.espacenet.com/espacenet/ep/en/helpV3/detailedcoverageab.html>.
[105] Ibid., EPO esp@cenet 'Worldwide Database – Detailed Coverage Abstracts'.
[106] Ibid., EPO esp@cenet 'Worldwide Database – Detailed Coverage Abstracts'.

Figure One: esp@cenet Keyword Rankings for Patent Publications 1990-2003

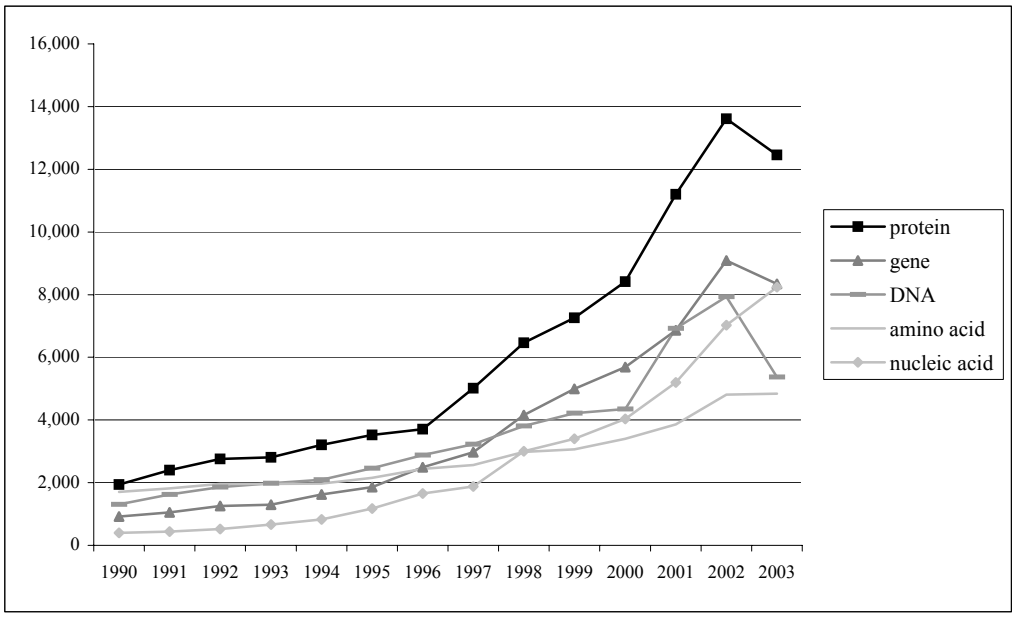

Table One: esp@cenet Keyword Rankings for Patent Publications 1990-2003

Keyword	1990	1995	2000	2003*	Total 1990-2000	Total 1990-2003*	2000-2003* +/-
							%
protein	1,937	3,524	8,411	12,460	47,480	84,751	78
gene	923	1,860	5,685	8,343	28,308	52,604	86
DNA	1,303	2,459	4,347	5,371	29,801	50,025	68
amino acid	1,708	2,156	3,403	4,837	26,027	39,534	52
nucleic acid	403	1,173	4,035	8,238	17,994	38,453	114
enzyme	1,229	1,593	2,563	3,586	19,320	29,105	51
polypeptide	469	786	1,967	4,815	10,557	27,113	157
peptide	784	1,406	2,357	3,489	16,194	25,734	59
nucleotide	218	541	1,371	2,209	7,048	13,165	87
RNA	173	439	950	1,422	6,041	10,060	67
microorganism	521	611	845	1,102	6,915	10,024	45
human gene	134	281	896	1,521	4,476	9,019	101
genome	94	165	544	1,046	2,676	5,716	114
plant gene	40	150	570	683	2,459	4,429	80
animal gene	17	53	203	430	906	1,968	117
microbe	39	89	131	255	875	1,471	68
deoxyribonucleic	20	23	24	6	270	336	24
ribonucleic	4	27	34	45	197	331	68
proteome	0	0	4	60	7	107	1,429

*Data for the period 2001-2003 is preliminary

the worldwide database reveals that an average of 52% (18,806,018 publications) possess titles in English and an average of 11% (3,978,196 publications) possess abstracts in English.[107] As this suggests, while useful, the keyword methodology does not address translation issues across jurisdictions and possesses significant limitations in mapping status and trends in international demand for patent protection. Further details of country coverage within the worldwide database are provided in Annex 3.

However, the keyword search methodology does serve to reveal trends in the use of terms in the titles and abstracts of patent publications that are available in English and to permit the ranking of terminology. This methodology also permits an insight into emerging areas of demand for patent protection, notably the emergence of the term "proteome" within patent titles and abstracts in the period from 1998 onwards. While presently small in number trends in this area are set to accelerate following the completion of an increasing number of genome mapping projects which provide the foundation for "post-genomic" analysis such as proteomics.

An alternative approach to tracking international trends in demand for patent protection is to carry out a patent class search using the International Patent Classification (IPC) system.[108] The IPC is a hierarchical classification system which employs approximately 69,000 classifiers to

[107] The database is reported to contain 45 million patent related publications, including utility models and legal documentation (XP documents). The estimate of industrial property publications employed in this review excludes utility models and patent related documentation.

[108] WIPO 'International Patent Classification (IPC)'. The present edition is the 7th edition. Location: <http://www.wipo.int/classifications/ipc/en/preface.htm>.

categorise patent publications in terms of sections, classes, sub-classes, groups and sub-groups.[109] In contrast with key terms, patent filings are generally awarded International Patent Classification codes to describe the claimed invention. Thus, in the case of Brazil, 99.3% of publications within esp@cenet contain IPC classifiers while 87.1% contain IPC classifiers in the case of Canada. Once again, the use of IPC classifiers may vary significantly between countries. However, a detailed review of data coverage suggests that an average of 82% of the 36,165,421 industrial patent publications within the esp@cenet "worldwide" database, consisting of approximately 29,655,645 documents, possessed IPC classifiers (Annex 3).[110]

In response to the problems surrounding tracking trends in biotechnology the OECD Economic Analysis and Statistics Division has developed a preliminary working definition of biotechnology based on the International Patent Classification system (6th edition).[111] The results of a patent class search of the EPO esp@cenet database employing this definition for the period 1990-2000 including target years 1990, 1995, and 2000 and preliminary data for 2001-2003 are provided in Table Two. A summary of trends in the main areas of demand based on the ranking of results is provided in Figure Two. The full thirteen year dataset is provided in Annex 2.

[109] The development of the International Patent Classification (IPC) is governed by the Special Union for the International Patent Classification (IPC Union) established under the 1971 Strasbourg Agreement Concerning the International Patent Classification (amended 1979). Location: <http://www.wipo.int/classifications/ipc/en/reform/ipc_reform.html>.

[110] EPO esp@cenet 'Worldwide Database – Detailed Coverage Abstracts', Table current as of 2nd of August 2004. Location: <http://ep.espacenet.com/espacenet/ep/en/helpV3/detailedcoverageab.html>.

[111] Devlin, A (2003) 'An Overview of Biotechnology Statistics in Selected Countries'. *STI Working Paper 2003/13*. Statistical Analysis of Science, Technology and Industry. Directorate for Science, Technology and Industry. DSTI/DOC (2003) 13. Organisation for Economic Co-operation and Development. Paris: OECD. Citation at 13. Location: <http://www.olis.oecd.org/olis/2003doc.nsf/linkto/dsti-doc(2003)13>.

Figure Two: Trends in Patent Publications for the Top Five IPC Biotechnology Classifications 1990-2003

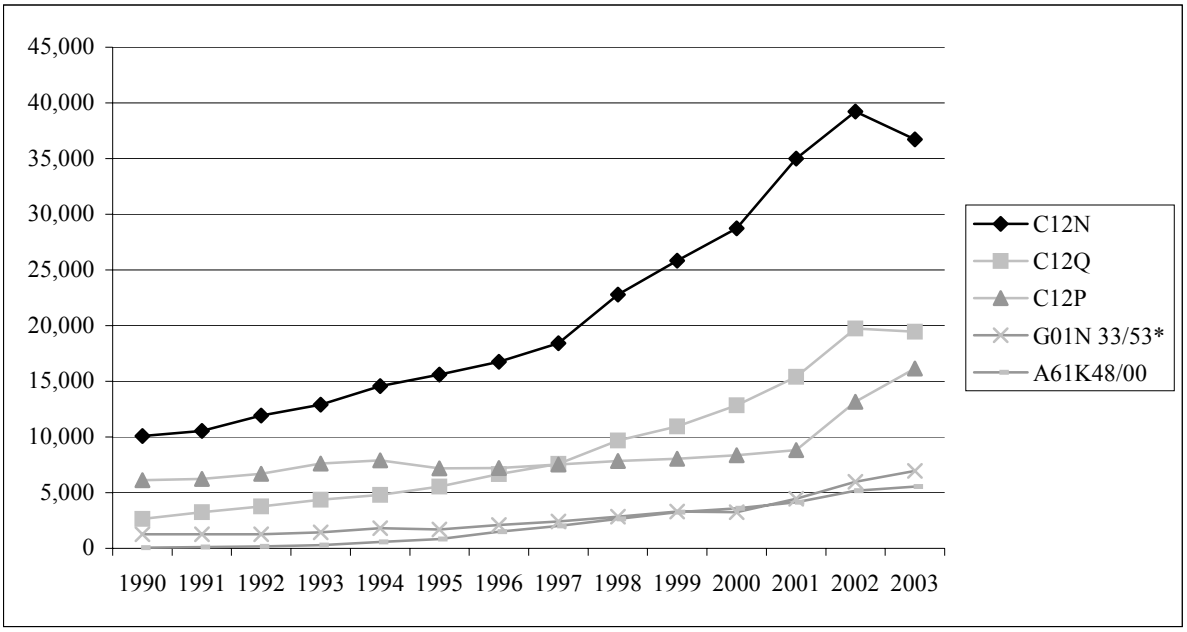

Table Two: Trends in Patent Publications for Biotechnology

Biotechnology OECD		**1990**	**1995**	**2000**	**2003**	**Total 1990-2000**	**Total 1990-2003****	**2000-2003 +/-**
Human Necessities								**%**
plants, processes for modifying genotypes	A01H1/00	126	138	441	802	2,189	3,864	77
plant reproduction by tissue culture techniques	A01H4/00	175	210	425	226	3,111	3,883	25
Medicinal preparations containing peptides	A61K38/00	58	2,222	2,721	3,767	15,169	26,966	78
Medicinal preparations containing antigens or antibodies	A61K39/00	411	716	1,494	2,002	9,520	15,203	60
Treatments for genetic diseases, Gene therapy	A61K48/00	47	823	3,605	5,546	15,004	29,866	99
Chemistry								
Biological treatment of water wastewater, or sewage characterised by microorganism used	C02F3/34	173	337	445	452	3,675	4,945	35
Antibiotics	C07G11/00	68	39	15	22	443	495	12
Vitamins	C07G13/00	4	1	0	4	24	32	33
Hormones	C07G15/00	4	4	2	0	42	45	7
Peptides with more than 20 amino acids in undefined/partially defined sequence, derivatives thereof	C07K4/00	1	73	55	140	421	762	81
Peptides with more than 20 amino acids Gastrins; Somatostatins; Melanotropins; Derivatives thereof	C07K14/00	56	1,012	1,624	1,533	7,572	15,253	101

Table Two (Continued): Trends in Patent Publications for Biotechnology

Biotechnology OECD		1990	1995	2000	2003*	Total 1990-2000	Total 1990-2003*	2000-2003 +/-
								%
Immunoglobulins, e.g. monoclonal or polyclonal antibodies	C07K16/00	22	356	1,047	1,056	4,497	10,536	134
Carrier-bound or immobilised peptides	C07K17/00	90	264	323	647	2,331	4,149	78
Hybrid peptides	C07K19/00	40	304	748	1,082	3,513	6,716	91
Chemistry (Microbiology)								
Apparatus for Enzymology or Microbiology	C12M	1,255	1,310	1,648	3,612	15,016	24,273	62
Microorganisms or Enzymes' compositions thereof	C12N	10,092	15,602	28,748	36,738	188,213	299,163	59
Fermentation or Enzyme using processes to synthesise chemical compounds	C12P	6119	7,170	8,374	16,156	80,743	118,877	47
Measuring or testing processes involving enzymes or microorganisms	C12Q	2,642	5,547	12,841	19,455	72,086	126,684	76
Processes using enzymes or microorganisms to liberate, separate or purify pre-existing compound or composition	C12S	77	345	163	206	2,633	3,165	20
Physics								
Biochemical Electrodes	G01N27/327	110	128	231	393	1,629	2,648	63
Immunoassay; Biospecific binding assay; Materials thereof	G01N 33/53*	1,254	1,696	3,258	6,942	22,653	40,026	77
as above, double or second antibody etc.	G01N33/54*	8	0	1	1	17	22	29
as above, relating to type of carrier etc.	G01N33/55*	1	1	1	2	6	15	150
as above, relating to specific disease i.e. hepatitis, cancer etc.	G01N33/57*	0	0	0	1	2	5	150
as above, involving proteins, peptides or amino acids etc.	G01N33/68	402	890	2,244	2,277	11,582	19,400	68
as above, involving hormones	G01N33/74	75	149	126	164	1,397	1,868	34
as above, Human chorionic gonadotropin	G01N33/76	42	53	31	29	480	567	18
as above, Thyroid gland hormones	G01N33/78	34	35	12	9	315	361	15
as above, involving prostaglandins	G01N33/88	4	7	4	13	49	72	47
as above, involving lipids, e.g. cholesterol	G01N33/92	67	78	120	185	915	1,373	50

* Captures relevant sub-groups **Data for 2001-2003 is preliminary

In approaching the data presented in Figure Two and Table Two it is immediately apparent that the patent class search provides a much higher level of data capture of patent publications than a key word search methodology. However, in approaching this data it is also important to note three main points.

First, individual patent applications are generally awarded more than one patent classifier in order to adequately describe the claimed invention. As a consequence, an individual application and subsequent publications may appear in the statistics for more than one patent classifier. Any temptation to cumulate data across classifiers should therefore be resisted in order to avoid over-counting.

Second, the working definition may not capture all relevant sub-classes, groups and sub-groups and problems of under-counting may occur in the case of sub-classes, groups, and sub-groups due to changes in the International Patent Classification over the data period. Problems of over-counting may also occur in the case of regional and international instruments when an individual application is published (A2), republished with the international search report (A3), and granted (B). These issues merit further investigation and refinement in any future work on patent trends.

Third, trends in patent publications provide an indicator of demand for patent protection on the international level (since a patent application must be published at various stages of the procedure in order to become a patent grant). However, publications in a given year do not provide a reliable indicator of future trends since the publication and subsequent grant of a patent may be affected by a number of factors including, inter alia: a) decisions by the applicant on which countries or regions to enter into the national/regional procedure in the case of regional/international instruments; b) time limits for publication established under regional and international instruments; c) issues surrounding pendency including the availability of trained examiners (see below).

These issues are particularly marked in the case of recent publication trends. Thus, Figure Two suggests a marked drop in patent publications between 2002 and 2003 for C12N (Microorganisms and Enzymes) and C12Q (Measuring or testing processes involving enzymes or microorganisms). This may potentially correspond with the delayed impact of a reported downturn in biotechnology patents in the United States between 2000 and 2001 resulting from an economic downturn in the sector and subsequent decisions not to pursue international protection in multiple jurisdictions.[112] However, this apparent dip may also reflect a lack of submissions to the esp@cenet database for the corresponding period. In particular, repeat searches of the database to verify the results revealed the greatest degree of variance in results in the period between 2001 and 2003. This variability reflects the active nature of the database.[113] For this reason, data for the period 2001 to 2003 is classified as preliminary.

However, the most striking feature of the patent class search for patent publications employing the OECD working definition of biotechnology is the dominance of sub-classes relating to Microorganisms and Enzymes (C12N, C12Q and C12P) within the top three of the top five of

[112] Nature Biotechnology (2004) 'Patent drop reveals pressure on industry', *Nature Biotechnology*, Vol. 22, No. 8, August 2004, page 930.

[113] An initial search was conducted on the 27th of June 2004 and 2nd of July followed by a full search on the 15th of July 2004. A second full search was conducted on the 24th of September 2004 in order to validate the results. For discussion see the companion paper *Global Status and Trends in Intellectual Property Claims: Patent Dataset*.

thirty categories. These trends reveal the underlying significance of the requirement within Article 27.3 (b) of the agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) that member states of the World Trade Organisation (WTO) provide protection for microorganisms and microbiological processes.[114] Specifically, a review of the first page of patent search results for these sub-classes combined with analysis of the International Patent Classification system rapidly reveals the prominence of human, animal and plant DNA and related biological and genetic material such as stem cells. Furthermore, the role of the Patent Cooperation Treaty in operationalising the internationalisation of patent protection is suggested by the existence of an estimated 42,279 PCT (WO) patent publications under class C12N within the "worldwide" database which may translate into patent grants in multiple jurisdictions. Thus, a single PCT application filed in 2004 may potentially generate patent grants in 123 Contracting States to the PCT.[115] As such, the Patent Cooperation Treaty introduces a very significant multiplier effect into international demand for patent protection.

In closing this discussion of global trends in patent claims in relation to genomics, proteomics and biotechnology further methodological development and refinement may be desirable in order to provide a foundation to inform decision-making surrounding the potential role of patent protection in the development of an international regime on access to genetic resources and benefit-sharing. This discussion suggests that further methodological development could usefully focus on developing the keyword and patent class search techniques, improving country level coverage, and refining techniques in order to produce reliable, verifiable and repeatable methodologies.

A variety of tools, such as the USPTO database, the JPO database and private databases such as the Thomson DELPHION database are available for patent research. However, in seeking to assess international trends in intellectual property claims the European Patent Office esp@cenet worldwide database represents a vital resource. At present, the esp@cenet database does not offer tools to facilitate statistical analysis and all data searches must be conducted, and cross-checked, by hand. This is a very time-consuming and unnecessarily laborious process which could readily be remedied through further development of the interface. Furthermore, opportunities to address potential under-counting and over-counting of publications, such as A1, A2 and A3 publications for regional and international applications, and data-capture issues resulting from updating of the IPC, are limited with the existing interface. The development of readily accessible statistical tools to interrogate esp@cenet would make a valuable contribution to enhancing the capacity of governments, analysts, and civil society to track, monitor and assess status and trends in intellectual property claims. Such tools would ideally be publicly available and could potentially include "open source" models of development to facilitate collaborations to enhance analytical capacity. Furthermore, a number of organisations, including the Trilateral

[114] Article 27.3 (b) of the TRIPS Agreement reads: "Members may also exclude from patentability: (b) plants and animals other than micro-organisms, and essentially biological processes for the production of plants or animals other than non-biological and microbiological processes. However, Members shall provide for the protection of plant varieties either by patents or by an effective *sui generis* system or by any combination thereof. The provisions of this subparagraph shall be reviewed four years after the date of entry into force of the WTO Agreement." Location:<http://www.wto.org/english/docs_e/legal_e/27-trips_01_e.htm>.

[115] These issues are discussed in further detail in the companion paper in this series *Global Status and Trends in Intellectual Property Claims: Microorganisms*.

Offices, WIPO and the OECD possess staff with expertise in the analysis of patent trends which could contribute to generating indicators of patent trends.[116]

Taking into account the range of legitimate concerns that surround the patenting of genetic material, the development of indicators may best be pursued through a participatory process to ensure the transparency, intelligibility and utility of indicators. It should also perhaps be noted that these suggestions do not constitute endorsement of the patenting of biological and genetic material. Instead, the development of indicators may be desirable in order to enhance the visibility of intellectual property claims as a basis for evidence based assessment of the potential role of intellectual property protection and intellectual property instruments in the course of the development of an international regime.

In practice, the rise of intellectual property claims in relation to genomics, proteomics and biotechnology poses significant challenges for the international patent system. Wider analysis of trends within the major patent offices also raises significant questions surrounding the ongoing integrity of the patent system. It is to trends in these areas to which the review now turns.

III. The Complexity, Scope and Implications of Patent Claims

The challenges involved in tracking status and trends in genomics, proteomics and biotechnology across multiple areas of the patent classification system reflect the complex and emerging nature of intellectual property claims in these arenas. This extends to the incorporation of biological and genetic material within copyright, database rights and so-called "software patents".[117] The implications of tends in these related areas of intellectual property protection merit further attention but are beyond the scope of this review.

As the OECD Working Party report highlights, the technical complexity and length of patent applications in the realm of genomics, proteomics and biotechnology poses a formidable challenge to patent examiners and anyone seeking to track gene patent claims.[118] Specifically, we learn that:

> "Compounds are being claimed, not in the traditional form based on chemical structure, but in terms of their ability to bind to regions of the three-dimensional configuration of target enzymes and other proteins. Enzymes and enzyme inhibitors themselves are claimed in terms of *in silico* determination of spatial numerical co-ordinates rather than by their chemical characteristics, such as their primary or secondary amino acid sequences. For such applications, patent searchers and examiners encounter difficulties for performing the necessary search and evaluation of prior art."[119]

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[116] WIPO has recently introduced an Industrial Property Statistics Online Directory. Location: <http://www.wipo.int/ipstats/en/links/index.jsp>. A WIPO-OECD Workshop on the Use of Patent Statistics is also planned for October 2004. Location: <http://www.wipo.int/patent/meetings/2004/statistics_workshop/en/index.html>. The OECD Statistical Analysis of Science, Technology and Industry website 'Current Work on Patents' also serves as a very useful resource.

Location: <http://www.oecd.org/document/10/0,2340,en_2649_34409_1901066_1_1_1_1,00.html>.

[117] See: a) Ibid., Royal Society 2003; b) David, P (2000) 'A Tragedy of the Public Knowledge "Commons"? Global Science, Intellectual Property and the Digital Technology Boomerang', SIEPR Discussion Paper no. 00-02, Stanford Institute for Economic Policy Research. Location: <http://siepr.stanford.edu/papers/pdf/00-02.pdf>.

[118] Ibid., OECD 2002 at 65.

[119] Ibid., OECD 2002 at 66.

These complexities, including the merging of genomics with bioinformatics, make it difficult for examiners to assess inventiveness and as the OECD Working Party report puts it "…securing adequate protection for inventors on the basis of the inventive contributions made."[120]

This in turn has wider implications linked with trends in overall demand for patent protection. Thus, the OECD Working Party report highlights that in the industry and research sphere, one consequence of the complexity of patent applications is that "…many contracts and licenses have to be concluded while patent applications are pending and R & D is far from complete."[121] This may potentially contribute to a lowering of standards and the creation of uncertainties in the public research and commercial sectors surrounding the legitimacy of intellectual property claims.

These difficulties are likely to be exacerbated by a reported "workload crisis" within the main patent offices.[122] As of 2000, 2,585,436 applications were reported to be awaiting request for examination or pending at various stages of the procedure in the case of JPO rising to 2,654,102 in 2001.[123] In the case of the USPTO, 547,626 application were reported to be pending in examination in the year 2000.[124] In the case of the EPO, 299,960 applications were reported to be pending in 2000 rising to 338,920 in 2001.[125] The Trilateral Offices report that the majority of applications are awaiting action by the applicant, notably in the case of JPO.[126] In particular, 2,175,739 applications to the JPO were described as awaiting request for examination in 2001 (the latest year for which full data is available). However, pendency to first action by a patent office between 2001 and 2002 has increased from 20.7 months to 23 months at the EPO, from 22 months to 24 months at JPO and 14.4 months to 16.6 months at the USPTO.[127]

The 2003 USPTO *21st Century Strategic Plan* suggests that accelerating demand for patent protection has precipitated a crisis within intellectual property offices world-wide:

> "Today, the United States Patent and Trademark Office (USPTO) is under siege. Patent application filings have increased dramatically throughout the world. There are an estimated seven million pending applications in the world's examination pipeline, and the annual workload growth rate in the previous decade was in the range of 20-30 percent."[128]

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[120] Ibid., OECD 2002 at 66.

[121] Ibid., OECD 2002 at 65.

[122] USPTO (2003) *21st Century Strategic Plan*, United States Patent and Trademark Office, February 2003. Location: <http://www.uspto.gov/web/offices/com/strat21/stratplan_03feb2003.pdf> .

[123] Consisting of 2,152,416 applications awaiting request for examination and 433,020 applications pending in examination in 2000 rising to 2,175,739 applications awaiting request for examination and 478,363 pending in examination in 2001. EPO/JPO/USPTO (2002) *Trilateral Statistical Report 2001*. Citation at Table 4 at 36-37. Location: <http://www.jpo.go.jp/torikumi_e/kokusai_e/tws/tsr2001/> or see Table 4: Statistics on Procedures online. Location: <http://www.jpo.go.jp/torikumi_e/kokusai_e/tws/tsr2001/ch4/4_4.html>.

[124] At the USPTO the filing of an application is classified as a request for examination. No information is available on pendency rates in 2001. Ibid., EPO/JPO/USPTO (2002) at 36-37.

[125] In 2000 at the EPO, 90,100 applications were pending in search, 15,790 were awaiting request for examination, 191,600 were pending in examination and 2,470 were pending in opposition. Ibid., EPO/JPO/USPTO (2002) at 36-37.

[126] In the case of JPO applicants were previously granted a seven year period before being required to request examination. This period was reduced to three years from October 2001 onwards. Ibid., EPO/JPO/USPTO (2002) at 37.

[127] Ibid., EPO/JPO/USPTO (2002) at 37 and Ibid., EPO/JPO/USPTO (2003) at 38.

[128] USPTO (2003) *21st Century Strategic Plan*, United States Patent and Trademark Office, February 2003. Location: <http://www.uspto.gov/web/offices/com/strat21/stratplan_03feb2003.pdf>. See also, the Opening Address by the President of the European Patent Office, Dr H.C. Ingo Kober, to a 2003 Customer Workshop entitled *Mastering the Workload*. Location: <http://mtw.european-patent-office.org/workload/site/en/keynote_session.html>.

In practice, accurately assessing international trends in demand for patent protection is made challenging by the multiple designation system employed under the Patent Cooperation Treaty. Thus, it is not presently possible to readily assess how many "designations" under the PCT translate into the national/regional phase of the procedure and become applications in the true sense of the term.[129] However, the existence of an estimated 3,433,022 patent applications awaiting request for examination or pending in the procedure within the world's major patent offices suggests that the patent system is confronting escalating demand and raises wider questions surrounding the ongoing integrity of the patent system (see below).

The challenges confronting the major patent offices are also highlighted by the 2004 report of the United States National Research Council *A Patent System for the 21st Century*:

> "The sheer volume of applications to the U.S. Patent and Trademark Office—more than 300,000 a year—threatens to overwhelm the patent examination corps, degrading the quality of their work or creating a huge backlog of pending cases, or both. The costs of acquiring patents, promoting or securing licenses to patented technology, and defending against infringement allegations in court are rising rapidly. The benefits of patents in stimulating innovation appear to be highly variable across technologies and industries, but there has been little systematic investigation of the differences. In some cases patenting appears to have departed from its traditional role, as firms build large portfolios to gain access to others' technologies and reduce their vulnerability to litigation."[130]

The Trilateral Offices are seeking to respond to increases in demand for patent protection through a combination of measures which rely heavily on information technology.[131] However, as the 2002 report of the UK Commission on Intellectual Property Rights (CIPR) has highlighted, the availability of such options is likely to be limited in many developing countries.[132]

When viewed from a wider international perspective, this problem can perhaps be characterised as one of a shift within the international patent protection system away from providing temporary protection to inventors based on rigorous scrutiny of the claimed contribution to reward innovation, to one of *presumed invention* which rewards those with access to the patent system. This shift suggests that the patent system may be becoming de-anchored from its original function. Notwithstanding the substantive concerns that surround the patenting of genetic material it is unclear whose interests the wider de-anchoring of the patent system is likely to serve.

In considering the implications of these trends for the establishment of an international regime on access to genetic resources and benefit-sharing it is also important to consider two additional factors:

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[129] This issue is addressed in a forthcoming paper in this series, *Global Status and Trends in Intellectual Property Claims: Global Patent Trends*.

[130] Merrill, S, and Levin, R and Myers, M (eds.) (2004) *A Patent System for the 21st Century*. Committee on Intellectual Property Rights in the Knowledge-Based Economy, Board on Science, Technology and Economic Policy and Global Affairs Division. National Research Council of the National Academies. Washington: National Academies Press. Citation at 1-2. Location: <http://www.nap.edu/html/patentsystem/0309089107.pdf>.

[131] These issues are considered in further detail in a forthcoming companion paper in this series *Status and Trends in Intellectual Property Claims: Global Patent Trends*.

[132] Ibid., CIPR 2002.

a) the scope of patent claims relating to genetic material;
b) the implications of patent claims arising from genome mapping.

The Scope of Patent Claims in Biotechnology and Genomics:

A number of recent reports have highlighted growing concerns surrounding the implications of the scope of intellectual property protection claims over genetic material for science, public health, agriculture, human rights, trade and developing countries.[133] Table Three provides a preliminary introductory guide to the nature of patent claims in the realm of genomics, proteomics and biotechnology compiled from a variety of sources as a basis for further development.[134] The table has been adapted

[133] In addition to the reports highlighted above (i.e. Nuffield Council on Bioethics 2002, OECD 2002, Royal Society 2003, National Research Council 2004) see also: a) CIPR (2002) *Integrating Intellectual Property Rights and Development Policy*. Report of the Commission on Intellectual Property Rights, September 2002. London: Commission on Intellectual Property Rights: Location: <http://www.iprcommission.org/graphic/documents/final_report.htm>; b) Food Ethics Council (2003) *TRIPS with everything? Intellectual property and the farming world*. Halifax, UK: Food Ethics Council. Location: <http://www.foodethicscouncil.org/library/reportspdf/trips.pdf>; c) Australia Law Reform Commission (2004) *Genes and Ingenuity: Gene Patenting and Human Health*. Australia Law Reform Commission (ALRC 99, 2004) Location: <http://www.austlii.edu.au/au/other/alrc/publications/reports/99/>. The Intellectual Property section of the SciDev.net website provides recent news on developments in this area. Location: <http://www.scidev.net.>

[134] Sources: a) Ibid., Nuffield Council on Bioethics 2002; Ibid., OECD 2002 - citing University of Pennsylvania, Center for Bioethics "Who Owns Life?" <http://www.bioethics.upenn.edu/prog/wol/glossary.shtml> and Crespi, R and the Report of the National Institutes of Health (NIH) Working Group on Research Tools (1998). Location: <http://www.nih.gov/news/researchtools/>. Entries for expression cassettes, primers, and single sequence repeats are adapted from Syngenta Participations AG, PCT publication WO/03000904. Corrections to the Nuffield Council on Bioethics entry for RNA by Professor Peter Whittaker, CESAGen UK. Entries for promoters, stem cells, meristems and probes courtesy of Professor Peter Whittaker, CESAGen UK.

Table Three: A Preliminary List of Patent Claims in the Realm of Genomics

IP claims	Description
DNA Sequences (partial or complete)	Deoxyribonucleic acid (DNA) molecules, consisting of A (adenine), C (cytosine), G (guanine), and T (thymine).
RNA	Ribonucleic acid: "A single stranded nucleic acid molecule comprising a linear chain made from four bases (A, C, G and U)" (NCB 2002). There are several types of RNA of which three main types are involved in gene expression: messenger (mRNA), transfer (tRNA) and ribosomal (rRNA). The importance of RNA relative to DNA is increasingly recognised.
cDNA	"DNA within a nucleotide sequence that is complementary to RNA." A complementary sequence to G-U-A-C is C-A-T-G. cDNA constitutes a stable copy of fragile mRNA and is created using an mRNA template (NCB 2002 with corrections and OECD 2002 citing University of Pennsylvania).
Promoters	A region of DNA to which the enzyme complex RNA polymerase must bind in order to initiate transcription. Particular promoters may be used to enhance or modulate transcription rates.
Enhancers	DNA sequence increasing the rate of transcription (copying of DNA into RNA). The sequence may be distant from the DNA to be transcribed.
Exons	"The region of DNA within a gene that codes for a polypeptide chain or domain. Usually a protein is made up of multiple domains, each coded for by different exons within a single gene". (NCB 2002).
Gene fragments	"…pieces of genes containing only the exons (those parts of the gene which actually encode the protein sequence). They are composed of cDNA" (OECD 2002, citing University of Pennsylvania.
Expressed Sequences (Expressed Sequence Tags or ESTs)	Short sequences of complementary DNA (cDNA) isolated from mRNA where the location and nucleotide sequences are known. Applications include 'fishing' for whole genes, new genes and genome mapping.
Single Nucleotide Polymorphisms (SNPs)	DNA sequence resulting from variation/alteration in a single nucleotide base within a genome. The occurrence of the same SNP within a specific population may be significant in identifying particular traits (i.e. disease resistance/susceptibility).
Single Sequence Repeats (ssr)	For use in the identification of polymorphisms, creating genetic markers and mapping.
Stem cells (animals) or meristems (plants)	Cells which are able to divide to give rise either to cells like themselves (proliferation) or to particular types of specialised cells (differentiation). They are consequently very important in the development of an animal or plant.
Vectors (cloning and expression)	"An agent, often a virus or plasmid, used to carry foreign DNA into a cell" (OECD 2002, citing University of Pennsylvania). A plasmid is: "A small circular form of DNA found in bacteria which carries certain genes, such as for antibiotic resistance, and which replicates independently of the host cell" (University of Pennsylvania).
Proteins/Polypeptides	Chains of amino acids
Antibodies	For use as markers
Probes	A fragment of DNA used to locate particular parts of nucleic acid sequences. They can have a fluorescent or radioactive tag to enable detection.
Microarrays	'Gene chips' used for the identification of gene sequences and the mapping of genomes. Microarrays may contain many thousands of DNA probes with known or unknown function (The Economist December 12th 2002).
Expression cassettes	A DNA sequence capable of directing expression of a particular nucleotide sequence in a host cell consisting of a promoter for the nucleotide sequence of interest and/or termination signals. Also sequences required for translation of the nucleotide sequence coding for a protein or functional RNA (i.e. antisense RNA).
Primers	Oligonucleotides (fragments of DNA or RNA) corresponding to nucleotide sequences for use in probing or amplification generally of +14 nucleotides in length.
Methods for identifying a DNA sequence, mutation, or deletion	
Whole genomes/proteomes	All genes within an organism (genome) or all proteins within an organism (proteome)
A transgenic embryo or seed	
A plant or animal from the above	
Transgenic progeny of the above	

to cover animal and plant claims and provides brief explanations for readers unfamiliar with the language of genomics.

As a starting point in considering Table Three, it should be noted that Article 2 of the Convention on Biological Diversity concerning the "Use of Terms" establishes that: "'Genetic material' means any material of plant, animal, microbial or other origin containing functional units of heredity" while "'Genetic resources' means genetic material of actual or potential value." However, in practice, the wider terminology employed in the realm of genomics, proteomics and biotechnology represents a significant challenge for anyone who is not a biologist.

The difficulties confronting policy-makers and participants within debates under the Convention are perhaps illustrated by the lengthy discussions surrounding "derivatives" which took place during the negotiation of the Bonn Guidelines in 2001 and 2002 and more recent debates surrounding the establishment of an international regime in 2003 and 2004. However, it is also important to recognise that considerable variation exists within the scientific community surrounding the meaning and significance of the apparently straightforward concept of the "gene".[135] In the case of genomics and proteomics, definitional problems are also exacerbated by the emerging nature of scientific understanding in these areas. Thus, genome mapping has revealed that the one gene = one protein (polypeptide) model (originally, the one-gene/one-enzyme hypothesis) dating from 1941 is outdated because a single gene may be involved in the expression of multiple proteins.[136]

In considering potential ways forward in providing policy-makers and participants in debates under the Convention with the tools to address the complexity and emerging nature of scientific understanding in the realm of genomics and proteomics, relevant terminology and key concepts could perhaps usefully be incorporated into a proposal to compile "existing national definitions or other relevant definitions" relating to the use of terms under the Bonn Guidelines adopted by COP7 (Decision VII/19).[137] In connection with assessing the relationship between the use of terms and the patent system, further work in relation to national definitions and the International Patent Classification (IPC) system may also be desirable.[138]

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[135] See for example: a) Fox Keller, E (2000) *The Century of the Gene*. Cambridge: Harvard University Press; b) Stotz, K and Griffiths, P (2003) 'How Biologists Conceptualize Genes: An empirical study'. Department of History and Philosophy of Science, University of Pittsburgh. Location: <http://philsci-archive.pitt.edu/archive/00001241/>.

[136] Raven, P and Johnson, G (2002) *Biology*. New York: McGrawHill. Citation at 296.

[137] Decision VII/19 'B Use of terms, definitions and/or glossary, as appropriate,' para 1(a) and 1(b). Location: <http://www.biodiv.org/decisions/default.aspx?m=COP-07&id=7756&lg=0>.

[138] See the Special Union for the International Patent Classification (IPC Union) established under the 1971 Strasbourg Agreement Concerning the International Patent Classification (amended 1979). Location: <http://www.wipo.int/classifications/ipc/en/reform/ipc_reform.html>.

The Structure of Patent Claims in Biotechnology and Genomics:

Patent applications surrounding genetic 'inventions' vary according to the kinds of claims that are advanced and the structure of such claims.[139] According to the OECD Working Party report at least three categories of patent claims are common, notably in the arena of human genetics. These can be briefly paraphrased as follows:

1. 'DNA coding for industrially useful expression products (i.e. a therapeutic protein). This results in claims over: a) DNA of specific function; b) recombinant vectors; c) a genetically modified organism, and; d) a method for producing a polypeptide from the claimed DNA.
2. Genes as diagnostic tools (i.e. identification of genes involved in disease). This results in claims over: a) the DNA sequence of a wild-type gene (allele); b) mutated forms of the allele; c) DNA primers for amplification of the sequence; d) testing methods for mutations; d) reagent kits; e) screening methodology using the gene/polypeptide as a target for identifying potential therapeutic products.
3. Genes controlling biological pathways (i.e. for preventing the entry of pathogens such as viruses into a cell). This results in claims over: a) a receptor peptide/polypeptide for a defined DNA sequence; b) "DNA coding for the receptor"; c) "a transformed cell expressing the receptor"; c) "an assay system comprising the transformed cell"; d) a method for identifying an agonist(s)/ antagonist(s) of the claimed receptor(s); e) agonist(s)/antagonist(s) of the claimed receptor(s) identified by the claimed method.'[140]

The structure and content of patent claims in the realm of genomics are of particular relevance to the scope of an international regime on access to genetic resources and benefit-sharing and further work may be desirable in this area. As noted in Table Three, claims surrounding genetic materials occur at the level of DNA or RNA bases and amino acids. In a context in which the development of a product may involve genetic material from many different sources (e.g. enhancers) this raises the question of how the use of such material might effectively be tracked? Furthermore, in this scenario, how would benefit-sharing be determined?

However, the scope and structure of patent claims in the realm of genomics, proteomics and biotechnology have far reaching implications that are likely to require careful consideration in the course of the development of an international regime.

[139] Ibid., OECD 2002 at 25

[140] Ibid., OECD 2002 at 25.

Intellectual Property and Genome Mapping: the Genome Submarine

The term "patent submarine" has been applied in the case of human genome research to describe a situation in which, drawing on published sources, a company or Public Research Organisation (PRO), such as a university, develops a method for genetic testing or analysis using genetic material and subsequently discovers that such methods infringe a patent.[141] This may lead to costly licensing arrangements or to the abandonment of the method. Concern surrounding such patents has primarily focused on human genetic testing, such as the BRCA1 and BRCA2 "research tool" patents relating to breast cancer which have been the focus of expensive legal challenges mounted by European public health institutions.[142] This discussion extends the concept of the "patent submarine" to a case study of a patent claim arising from the mapping of a plant genome in order to explore the potential implications of such claims for the development of an international regime.

In December 2001 Syngenta Biotechnology Inc. and Myriad Genetics announced the completion of the draft sequence of the rice genome (*Oryza Sativa, ssp. japonica* –NipponBare cultivar). Syngenta Biotechnology Inc. is the largest crop protection company in the world with sales of US$6.1 billion in 2002 and pre-tax profits of US$445 million.[143] Myriad Genetics is a biopharmaceutical company specialising in bioinformatics and high-throughput DNA sequencing and claims the capacity to sequence the human genome in 12 months. [144]

The rice genome consists of 12 chromosomes and approximately 32,000-50,000 genes in 420 million DNA bases.[145] The mapping of the rice genome was achieved over a fourteen-month period and represents a major achievement as the first map of the genome of a major cereal. Myriad Genetics received a $3 million cash bonus from Syngenta for completing the mapping with 99.5% accuracy six months ahead of schedule.[146] Myriad will receive 50% of profit generated from the exploitation of the genome data. [147] As Myriad Genetics makes clear on its website:

> "Rice is the largest commercial crop in the world, nourishing over half of the World's population. There is tremendous potential to improve the world's ability to feed its people through improving yields and reducing the rice plant's dependence upon fertilizer and

[141] Ibid., Nuffield Council on Bioethics 2002 at 79. The term patent submarine or its variant 'submarine patent' has also been used to describe patents applications that lie dormant for a long period and are asserted when a competitor produces a product or process which infringes the claim through exploitation of the 'priority' claim system.

[142] See: a) Lecrubier, A (2002) 'Patents and Public Health: European institutions are challenging Myriad Genetic's patent monopoly on the *brca1* gene', *EMBO Reports*, Vol.3, No. 12, 1120-1122; b) Ibid., Nuffield Council on Bioethics 2002 at 39; c) See EPO (2004) '"Myriad/breast cancer" patent revoked after public hearing', EPO Press Release, Munich, 18 May 2004. Location: <http://www.european-patent-office.org/news/pressrel/2004_05_18_e.htm>; c) See also, New Scientist (2004) 'Europe revokes controversial gene patent', 19th May 05, NewScientist.com news service. Location: <http://www.newscientist.com/news/news.jsp?id=ns99995016>.

[143] Syngenta (2003*) Annual Report 2002*. Located at <http://www.syngenta.com>. Syngenta was formed in the year 2000 from the merger of Novartis Agribusiness and Zeneca Agrochemicals.

[144] Myriad Genetics 'Investor Relations'. <http://www.myriad.com>.

[145] Torrey Mesa Research Institute 'Frequently Asked Questions – Rice Genome', 4th April 2002. Location: <http://www.tmri.org/en/partnership/access_faq.aspx>.

[146] Myriad Genetics (2001) 'Myriad Genetics And Syngenta Complete Rice Genome Map', News Release - 26-Jan-2001. Location: <http://www.corporate-ir.net/ireye/ir_site.zhtml?ticker=mygn&script=410&layout=9&item_id=210304>.

[147] Ibid., Myriad Genetics (2001).

> pesticides. Rice is also a key to knowledge of other cereal crops such as corn and wheat."[148]

The mapping of the genome took place in similar circumstances to the competition that erupted between public and private sector interests over the mapping of the human genome.[149] Syngenta and Myriad Genetics were engaged in direct competition to map the genome with Monsanto and to a certain degree with the publicly funded IRGSP, both of which used the slower, but more accurate, clone by clone (BAC) sequencing technique.

However, all teams approached the mapping of the rice genome using experience gained with the mapping of Thale cress (*Arabidopsis thaliana*) which is used as a model to identify homologies (genetic similarities) within other plants. Angiosperms (flowering plants) are divided into two classes (or for descriptive purposes lineages) each with a presumed common ancestor.[150] *Arabidopsis thaliana* is a dicot (dicotyledon) and rice, along with the other major world cereals, is a monocot (monocotyledon). The use of the *Arabidopsis* genome data to identify and map homologies within the rice genome illustrates the way that genomics data can be used to map genomes across classes. As a consequence Syngenta and Myriad Genetics have been able to generate "…a virtual map of all cereal species".[151]

Controversy surrounding the mapping of the rice genome emerged when Syngenta initially chose not make the genome publicly available by depositing the genome data with GenBank and instead placed the genome in escrow with *Science* prior to publication.[152] This aroused concerns that the company would seek to patent the genome and thereby establish a temporary monopoly over the DNA make-up of the world's major cereal. This did not come to pass and the company subsequently announced that it would provide access to the genome data under a series of access arrangements managed by its then research subsidiary the Torrey Mesa Research Institute (TMRI).[153] In 2001 Syngenta announced a Technology Transfer Policy for developing countries and in 2002, following an earlier lead set by Monsanto, made its genome sequence data available to the IRSGP under an access agreement for participating organisations.[154]

However, the company's decision not to patent the rice genome and to make the sequence data available to IRSGP disguises a more complex situation. On the 24th of June 2002 Syngenta Participations AG (the intellectual property arm of the company) and employees within the subsidiary Torrey Mesa Research Institute accompanied by former employees now based at the

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[148] Ibid., Myriad Genetics (2001).

[149] Smaglik, P (2000) 'Forces for collaboration falter with human genome in sight', *Nature* 408, 758.

[150] For a free and accessible source of high quality information on taxonomy see the *Tree of Life Web Project*. See for example 'Monocotyledons'. Location: <http://tolweb.org/tree?group=Monocotyledons&contgroup=Angiosperms>.

[151] Ibid., Myriad Genetics (2001).

[152] See: a) Science (2002) The Rice Genome. Vol. 296, 1-203 and Science magazine feature on the Rice Genome. Location: <http://sciencemag.org/features/data/rice/index.shtml>; b) Butler, D (2002) Geneticists get steamed up over public access to rice genome', *Nature*, 416, 111 - 112 (14 Mar 2002) News; c) Walgate, R (2001) 'Syngenta claims ownership of rice – but will give data away', *The Scientist*, 1st February 2001. Location: <http://www.biomedcentral.com/news/20010201/05>; d) BBC (2002) 'Rice genome data row'. Location:<http://news.bbc.co.uk/1/hi/sci/tech/1879346.stm>.

[153] The Torrey Mesa Research Institute has now closed and the rice genome data and access arrangements are managed directly by Syngenta. Location: <http://www.tmri.org/en/Site/home.aspx>. For details of access conditions see 'Access to Rice Genome Sequence'. Location: <http://www.tmri.org/en/partnership/access.aspx>.

[154] IRGSP (2002) 'International Rice Genome Sequencing Project and Syngenta Announce Agreement that Will Accelerate Completion of a Finished Rice Genome Sequence', IRGSP-Syngenta Rice Genome Announcement Release, 23 rd of may 2002. Location: <http://www.nias.affrc.go.jp/pressrelease/2002/20020523/announcement.html>.

University of Minnesota, the University of Toronto and Diversa Inc., filed international Patent Cooperation Treaty application number PCT/EP02/06968 which is linked by priority to patents in the United States dated between June and November 2001.[155] The patent application was published on the 3rd of January 2003 with the international patent publication number WO/03000904.[156] As of September 2004 the patent forms part of a wider patent family of a total of 21 patents derived from 14 applications.[157]

The Patent Cooperation Treaty (PCT) application is designated for consideration by 115 Contracting States to the PCT either through the national patent office or regional patent offices (ARIPO, EAPO, the EPO and OAPI). Further details of the designations are provided in Annex 4.

The patent application is structured into four main parts: a) abstract; b) technical description; c) claims; d) drawing/mosaics (the DNA and amino acid sequence listing). The contents of the main sections of the 323 page application are briefly summarised in Box One.

[155] To locate the application go to the EPO esp@cenet database, click advanced search and enter the patent number WO03000904 in the publication number box. Note that the 'O' in 'WO' is alphabetical as in 'O' for 'Oscar' followed by '0' for zero. Failure to use the correct combination will not reveal the application. Location: <http://ep.espacenet.com/>.

[156] Patent publication WO03000905 is concerned with transgenic rice and is beyond the scope of this study The abstract to patent publication WO03000905 reads: "The invention discloses a set of genes the expression products of which are up-regulated during the grain filling process in rice and active in different metabolic pathways involved in nutrient partitioning. The invention also discloses the use of said genes to modify the compositional and nutritional characteristics of the plant grain." Source: European Patent Office Database. Location: <http://ep.espacenet.com/>.

[157] EPO esp@cenet database search, July 2004. Location: <http://ep.espacenet.com/>.

Box One:
PCT Patent Application PCT/EP02/06968 (WO/03000904)
Identification and Characterization of Plant Genes

Abstract: "The present invention relates to nucleic acid molecules obtainable from the rice genome that encode protein products that are involved in the development and timing of flower formation in plants and which can be used to modulate flower development, architecture and flowering time."

Description: The description explains that the biological pathways controlling meristem activity in flowering plants are poorly understood and sets out four "collective embodiments" of the claimed invention.

1. Nucleotide sequences encoding polypeptides involved in the development and/or timing of flower formation and/or whole plant architecture, the encoded polypeptides and antigene sequences'.
2. Ability to modulate development and/or timing of flower formation and/or whole plant architecture in plants, by modulating gene expression (e.g. over-expressing, under-expressing or knocking out) one or more genes involved in regulation in a host cell, preferably a plant cell, *in vitro* or *in planta.*
3. A transformed plant host cell, or one obtained through breeding, capable of over-expressing, underexpressing, or knock out of a flower development or flower time gene or a gene regulating these processes and/or its gene products.
4. DNA molecules, or parts, for use in hybridization-based assays to detect and identify DNA molecules encoding protein products involved in the development and/or timing of flower formation in plants and/or whole plant architecture other than rice, …especially…the cereal group.'

Description of DNA Sequence Listings: for a) rice, and homologous sequences for b) maize, c) banana, d) wheat;

Definitions: "…an 'isolated' or 'purified' DNA molecule or an 'isolated' or 'purified' polypeptide is a DNA molecule or polypeptide that, by the hand of man, exists apart from its native environment and is therefore not a product of nature."

Justification: 'The transition between vegetative growth and flowering (reproduction) is a major transition and identification and modulation of flowering genes can enable flower timing and plant architecture to be altered. This has important agricultural implications for extending growing period and increasing yield with multiple crops per year (i.e. rice), adaptation to cold climates, and directing more energy into vegetative growth than reproduction (flowering).'

Specific Embodiments: 20 specific embodiments, preferred embodiments, and 13 examples of application, to establish the scope of the claimed invention.

Scope of application: "…any plant species" can be transformed, followed by a list of 40 individual species, (i.e. maize, banana, sorghum, millet etc), all genera and species of duckweed (Lemna) including those as yet unknown, 6 genera of vegetables, 10 ornamentals, 11 conifers (i.e. pines), 3 cedars, 11 leguminous plants (beans, peas), +8 legumes, 6 forage/turf grasses, 55 other plants, including 20 members of the Brassica complex (i.e. broccoli, cabbage), and 28 specific ornamental plants.

Claims: 83 claims in 31 groups involving gene function, transgenic plant, seed, methods, expression cassette, computer medium, etc. For example:

"37. An isolated nucleic acid molecule comprising a nucleotide sequence encoding a polypeptide the activity of which is involved in specifying flower-meristem identity, which nucleic acid molecule is substantially similar to a nucleic acid encoding a polypeptide as given in SEQ ID NOs: 2,48,58, and 60, or a partial-length polypeptide having substantially the same activity as the full-length polypeptide, e. g., at least 50%, more preferably at least 80%, even more preferably at least 90% to 95% the activity of the full-length polypeptide."

40. The isolated nucleic acid molecule of claim 37 comprising a nucleotide sequence a) as given in SEQ ID NOs: 1, 47,57, and 59, or a fragment thereof encoding a partial-length polypeptide having substantially the same activity as the full length polypeptide, e. g., at least 50%, more preferably at least 80%, even more preferably at least 90% to 95% the activity of the full-length polypeptide; b) having substantial similarity to (a); c) capable of hybridizing to (a) or the complement thereof; d) capable of hybridizing to a nucleic acid molecule comprising 50 to 200 or more consecutive nucleotides of nucleotides given in SEQ ID NOs: 1, 47,57, and 59, or the complement thereof…."

The case study patent application discloses a remarkable achievement: the DNA that regulates flowering development, flower formation, whole plant architecture and flower timing in rice and, it is claimed, other plants. In particular, the application claims to have identified the biological pathways controlling plant meristems. A plant meristem can be defined as:

> "A plant tissue consisting of actively dividing cells that give rise to cells that differentiate into new tissues of the plant. The most important meristems are those occurring at the tip of the shoot and root…and the lateral meristems in the older parts of the plant..."[158]

The identification of the biological pathways controlling plant meristems (in particular the shoot tip meristem) has been something of a holy grail in plant genomics as meristems are the equivalent of stem cells in humans and animals.[159] However, while recognising that this is a very significant achievement, in approaching the question of whether this achievement merits twenty years of exclusive protection, it is useful to recall the following words of one of the framers of the first United States Patent Act and former patent examiner, Thomas Jefferson:

> "Considering the exclusive right to invention as given not of natural right, but for the benefit of society, I know well the difficulty of drawing a line between the things which are worth to the public the embarrassment of an exclusive patent, and those which are not."[160]

According to the Food and Agriculture Organisation (FAO), rice is cultivated in 113 countries and constitutes the main staple for over half the world's population.[161] Furthermore, the claims within the patent extend to other major cereals and plants in general. In considering a request for a grant of intellectual property protection over key genetic elements of the world's major cereal and other plants, from a Jeffersonian perspective, hard questions appear to be in order.

Would a reasonable person regard the mapping and isolation of genes and proteins and the identification of their biological properties as a discovery or an invention? Does the act of mapping and identifying the properties of a genome amount to an inventive step? Should this be regarded, as a number of critics have asserted, as a form of genetic plagiarism little different to copying a document and claiming authorship? Alternatively, do such claims represent the commodification of life?[162]

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[158] "meristem" *A Dictionary of Biology*. Oxford University Press, 2000.

[159] See for example, Overwalle, G (2002) *Study on the patenting of inventions related to human stem cell research*. European Group on Ethics in Science and New Technologies to the European Commission. 30 December 2001. Luxembourg: Office for Official Publications of the European Communities. Location: <http://europa.eu.int/comm/european_group_ethics/docs/stud-vanoverw.pdf>.

[160] Thomas Jefferson (1813) 'To Isaac McPherson, August 13, 1813', in Appleby, J and Ball, T (1999) *Jefferson: Political Writings*. Cambridge: Cambridge University Press. Citation at 581. Also available via the University of Virgina *Thomas Jefferson Digital Archive*. Location: <http://etext.lib.virginia.edu/jefferson/>.

[161] FAO (2004) 'Rice is Life: Increased, sustainable rice production key to global food security', Food and Agriculture Organisation Newsroom, 12 February 2004. Location: <http://www.fao.org/newsroom/en/focus/2004/36887/>.

[162] For discussion see for example: a) Shiva, V (1998) *Biopiracy: The Plunder of Knowledge and Nature*. Totnes: Green Books/Gaia Foundation; b) Boyle, J (2003) 'The Second Enclosure Movement and the Construction of the Public Domain'. *Law and Contemporary Social Problems*, Vol. 66: 33, 33-74. Location: <http://www.law.duke.edu/pd/papers/boyle.pdf>.

Another way to approach these questions is to consider the nature of DNA as a code. This can be briefly illustrated by a partial extract from Sequence ID 1 of the 161 pages of DNA and amino acid sequences provided in the patent application.

Table Four: DNA from the Rice Genome (Oryza sativa)

atggggcgag ggaaagtaga gctgaaagcg gatcgagaac aagataagcc ggcaggtgac 60

gttcgcgaag aggaggaacg ggctgctgaa gaaggcgtac gagctgtccg tgctctgcga 120

cgccgaggtc gccctcatca tcttctccac ccgcggccgc ctcttcgagt tctccacctc 180

The DNA sequences (measured in terms of bases) (A – adenine, C – cytosine, G, guanine, T – thymine) bind to each other in a regular pattern (A with T and C with G) to form the rungs of the twisting ladder of the double helix of DNA. Within this structure, individual nucleotide bases (i.e. A – adenine) form groups of three nucleotide bases called codons corresponding with an amino acid in a protein.[163] Thus, the first three nucleotides in the partial sequence in Table Four "atg" correspond with the common amino acid Methionine (Met).[164] The amino acids of the corresponding DNA form the basis of proteins (polypeptides). The sequence provided above is a partial DNA sequence involved in flower meristem identity and according to the application correspond with the amino acid sequence in Sequence ID 2 which, for the sake of brevity, is also partially illustrated in Table Five.

Table Five: Amino Acids from the Rice Genome (Oryza sativa)[165]

Met Gly Arg Gly Lys Val Glu Leu Lys Arg Ile Glu Asn Lys Ile Ser Arg Glu Val Thr
5 10 15 20
Phe Ala Lys Arg Arg Asn Gly Leu Leu Lys Lys Ala Tyr Glu Leu Ser Val Leu Cys Asp
25 30 35 40
Ala Glu Val Ala Leu Ile Ile Phe Ser Thr Arg Gly Arg Leu Phe Glu Phe Ser Thr Ser
45 50 55 60
(60 = 180 nucleotide bases/3)

The patent applicant appears to have successfully mapped the DNA sequences and identified the amino acid sequences for the proteins (peptides and polypeptides) involved in plant flowering, morphology etc. However, as this partial illustration from a large number of sequences reveals we are dealing with what may be described as biological algorithms. When seen from this perspective it appears that the applicants have succeeded in mapping the biological algorithms involved in rice and related cereals and have identified the functions of components of the algorithms. However, is it reasonable to conclude that the applicants have thereby 'invented' these algorithms?

A further approach is to consider the potential consequences of a grant of patent protection using the Jeffersonian standard. Will the award of patent protection over key elements of the genome

[163] See Raven, P and Johnson, G (2002) *Biology*. Boston: McGrawHill, at 302 for discussion.

[164] Ibid., Raven, P and Johnson, G (2002) *Biology*, at 303.

[165] The amino acids in order of appearance are: Met (Methionine), Gly (Glycine), Arg (Arginine), Lys (Lysine), Val (Valine), Glu (Glutamic Acid), Leu (Leucine), Ile (Isoleucine), Asn (Asparagine), Ser (Serine), Thr (Threonine), Phe (Phenylalanine), Ala (Alanine), Tyr (Tyrosine), Cys (Cysteine), Asp (Asparatic Acid).

of rice and other plants in up to 115 countries serve to benefit society (from a global perspective) or represent what Jefferson termed an "embarrassment" or burden to that society?[166]

In considering this question, from an innovation perspective the promise of intellectual property protection may be said to have provided an incentive to produce a map of the rice genome. However, viewed from a wider innovation or competition perspective is it logical to award strong intellectual property protection over key genetic resources to a single company or alternatively a Public Research Organisation such as a university? Does twenty years of patent protection over key genetic materials in up to 115 countries over-reward patent holders? Furthermore, what are the wider implications of permitting such claims for food security, development objectives and human rights obligations? In considering these questions it is important to examine the implications of the language of patent claims in the realm of genomics.

The Language of Genomic Patent Claims:

"Comprising":

The first point to be considered is the use of the term "comprising" in connection with nucleotide sequences, polypeptides, single sequence repeats (ssr) and methods within the application (see Box 1). As the Nuffield Council on Bioethics highlights in the case of Expressed Sequence Tags (ESTs):

> "The claims in these patents have tended to use what is called 'comprising' language meaning that a patent with a claim to a sequence 'comprising' or containing an identified EST sequence would be infringed by a patent application that claimed the full-length gene that included the EST."[167]

In the case of the case study application we are considering here, the term "comprising" occurs 208 times of which 91 occurrences are located within the 83 specific claims set out in the claims section of the application. The use of "comprising" mainly occurs in connection with the claimed nucleotide sequences and polypeptides (proteins) but also appear in the methods claims involving the sequences (below). The practical significance of this is that strong property claims are being made over the nucleotide sequences, amino acids, and polypeptides, and the use of such materials within the methods claims.

"Substantially Similar":

The second point to be considered is the use of the phrase "substantially similar". As the application explains, "substantially similar" refers to a corresponding reference nucleotide sequence, amino acid sequence and polypeptide.[168]

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[166] Ibid., Jefferson 1813.

[167] See: a) Robertson, D (1999) 'EST patent granted on human kinase homologs', *Nature biotechnology*, Vol. 17, February 1999, at 125; b) Ibid., Nuffield Council on Bioethics 2002 at 33; c) See also the 1995 'HUGO Statement on the Patenting of DNA Sequences', and the 1997 HUGO Statement on Patenting Issues Related to Early Release of Raw Sequence Data. Human Genome Organisation. Location: <http://www.gene.ucl.ac.uk/hugo/ethics.html>; d) The USPTO issued guidelines in this area in 2001, See *Federal Register*. Vol. 66, No. 4, Friday, January 5, 2001, Notices. Location: <http://www.uspto.gov/web/offices/com/sol/notices/utilexmguide.pdf>.

[168] WO/03000904 at 18, line 17-20.

Taking the case of the claims surrounding flower meristem identify (illustrated in Box 1) as an example we can see that the term "comprising" is directly linked to the term "substantially similar" which is in turn defined in terms of percentages of activity of full-length polypeptides (proteins). The significance of this is that there is a very strong possibility that nucleotide sequences and expressed polypeptides, either whole or partial, may be discovered in other plants with at least 50%, 70% or 90% "substantial similarity" to the reference sequences claimed in the application in terms of activity in determining flower meristem identity. This is also true in the case of the genes for flower timing and whole plant architecture (morphology) claimed elsewhere within the application.

"Homologous Genes and Polypeptides":

It is important to note that the claimed sequences include "homologous" DNA and polypeptide sequences for maize, banana, and wheat. As the application explains, homology "… in the context of nucleotide sequence identity refers to the similarity between the nucleotide sequence of two nucleic acid molecules or between the amino acid sequences of two protein molecules".[169] Homology is established through the use of publicly available mathematical algorithms.[170]

This data can be used to map the homologous genes and polypeptides in other cereals and flowering plants. As the definition provided above makes clear, "homology" defined in terms of "similarity" is thus directly linked to the term "substantially similar". Where the DNA and polypeptides within other plants can be classified as "substantially similar" to the claimed reference sequences (i.e. +50% or above in terms of activity) it could be argued that they fall within the scope of the patent. The wider significance of "homology" and "substantial similarity" comes into greater focus in the original article in *Science* where the researchers announced their findings:

> "At significant similarity levels, almost every cereal protein was found to have a related gene in rice. At higher stringency, 80 to 90% of cereal gene queries identified rice homologs. These observations suggest that most genes are conserved across cereals, and that phenotypic variation is due to a small number of different genes or functional differences within similar genes."[171]

It is here that it is important to consider the treatment of the sequences within the method claims.

"Methods Claims"

Within the realm of biotechnology the most common method for the introduction of genetic material is using a "vector" which consists of a virus or a plasmid (DNA from bacteria) which expresses the desired DNA within the organism concerned. This is a standard research and industrial genetic engineering technique and a wide range of viruses and plasmids exist which

[169] WO/03000904 at 16, line 7-9.

[170] Mathematical algorithms have historically not been eligible for patentability and this essentially appears to remain the case. However, in the context of the rise of software patents, database rights and bioinformatics this exclusion is under increasing pressure. Academic literature in relation to this specific topic presently appears to be limited, see for example: a) Ibid., Royal Society 2003; b) de Laat, P (2000) 'Patenting mathematical algorithms: What's the Harm? A thought experiment in algebra', *International Review of Law and Economics* 20, 187-204.

[171] Goff, S et al. (2002) 'A Draft Sequence of the Rice Genome (*Oryza sativa* L. ssp. *japonica*)', *Science*, 296, 92 (2002). Citation at 97, table references removed.

may be used to insert genetic material from a different species or from the same variety/species. The use of such techniques are thus linked with the issues addressed under the Cartagena Protocol on Biosafety and wider debates surrounding Genetically Modified (GM) foods.[172]

In the case of the case study application, the term "vector" is "…defined to include, inter alia, any plasmid, cosmid, phage or Agrobacterium binary vector in double or single stranded linear or circular form which may or may not be self transmissible or mobilizable, and which can transform prokaryotic or eukaryotic host either by integration into the cellular genome or exist extrachromosomally (e. g. autonomous replicating plasmid with an origin of replication)."[173] As such, and taking due account of the use of the term "inter alia", the term vector can be said to extend to the use of any vector for delivering the claimed nucleotide sequences into a plant or plant tissue.

A total of ten method claims are set out in the claims section of the application. Method claims concern the use of the DNA and amino acid sequences to:

a) modulate flowering time and/or whole plant architecture (including antisense);
b) identify/isolate orthologs for flowering time and plant architecture in other plants; [174]
c) detect the polynucleotides, including a detection kit;
d) modify the frequency of a flowering time gene in a plant;
e) select for, or against, particular traits through plant breeding including the use of single sequence repeats (ssr);
f) determine the varietal identity of a plant;
g) develop a primer consisting of bases from the claimed sequences, and;
h) develop a computer readable medium.

In considering the implications of the incorporation of the sequences within method claims it is important to recall that genes, and the products of gene expression, are notoriously difficult to "invent around" and delivery methods are limited.[175] Thus, while science has had some success in creating synthetic nucleotide sequences of a few hundred bases, the synthetic development of sequences, amino acids and proteins of the complexity found within organisms is presently beyond the reach of science. Within this context the classification of DNA, amino acids and proteins as "research tools" and the inclusion of such materials within the method claims of patent applications has emerged as a major focus of concern highlighted within the reports of specialist bodies.[176] Thus, the techniques for mapping and identifying genes are increasingly standardised and there appears to be nothing particularly novel in the other methods claims except the inclusion of the particular nucleotide, amino acids and polypeptides. The problem that emerges here is that if the patent application is successful anyone using the sequences, or

[172] See the home page of the Cartagena Protocol on Biosafety. Location: <http://www.biodiv.org/biosafety/default.aspx>

[173] WO/03000904 at 26, line 9-13.

[174] An ortholog is described within the application as a sequence with "…a high degree of sequence similarity to a known sequence or gene of interest, with the similarity often occurring along the entire length of the coding portion of the gene. The terms 'orthologous sequence' and 'ortholog' …encompass both full-length genes and regions and fragments thereof."

[175] See for example, Ibid., Nuffield Council on Bioethics 2002

[176] This issue is highlighted in the majority of the major reports referenced in this review. See also: a) National Research Council (1996) *Intellectual Property Rights and Research Tools in Molecular Biology*. Summary of a Workshop Held at the National Academy of Sciences, February 15-16, 1996. See Section 5 Case Studies. Location: <http://books.nap.edu/html/property/>; b) Rai, A and Eisenberg, R (2003) 'Bayh-Dole Reform and the Progress of Biomedicine', Law and Contemporary Social Problems, Winter/Spring 2003, Vol. 66: 289-314. Location: <http://www.law.duke.edu/journals/66LCPRai>.

"substantially similar" or "homologous" sequences for trait selection, identifying varieties, and plant breeding may run the risk of patent infringement. This extends to the use of the sequences within a primer and computer readable medium.

Thus, it is conceivable that in the case of rice, publicly funded or private initiatives will independently discover "substantially similar" or "homologous" genes within rice, maize, banana and other plants but may be required to seek licensing arrangements with relevant patent holders to use and manipulate such DNA for research and plant breeding purposes that may lead to the development of a product. This is particularly likely in the case of commercial competitors engaged in similar work but may also extend to Public Research Organisations (PROs) such as universities. Thus, the company that is the focus of this case study has agreed to make the rice genome data available under a series of access arrangements, including for research in relation to the needs of developing countries.[177] However, in a context in which Public Research Organisations are increasingly pursuing patent protection as part of a process that has been described by the OECD as "Turning Science into Business" the so-called "experimental use defense" or "research exemption" is reported to be facing increasing challenges in the United States which provides the model for this process.[178]

It is here that the wide-ranging scope of intellectual property claims made possible by genome mapping become important. As we have seen, the application considered in this case study includes homologous sequences for maize, banana and wheat. Does this imply that public and private research initiatives may be required to enter into agreements with patent holders for the use of the DNA sequences, or "homologous" or "substantially similar" sequences, or risk potential litigation?

Furthermore, at least 23 species and genera listed within the case study application are included in the list of major food crops contained within Annex 1 of the International Treaty on Plant Genetic Resources for Food and Agriculture.[179] One of the compromises that emerged in the seven years of negotiations surrounding the Treaty was that intellectual property claims would be permitted where the material has been modified.[180] In the absence of criteria for assessing modification, and taking into account the significance of the genetic homologies revealed by genome mapping, this raises the question of whether initiatives seeking to employ publicly accessible Annex 1 accessions to explore the possibilities of genomics for plant breeding purposes (i.e. improving yields, adaptation to climate etc.) may be required to enter into licensing agreements with entities holding patents over the underlying genetic frameworks and regulatory mechanisms of Annex 1 plants or risk litigation?

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[177] For details of the existing access conditions see 'Access to Rice Genome Sequence'. Location: <http://www.tmri.org/en/partnership/access.aspx>.

[178] See: a) OECD (2003) *Turning Science into Business: Patenting and Licensing at Public Research Organisations*. Paris: Organisation for Economic Co-operation and Development. Available from: <http://www.oecd.org/document/61/0,2340,en_2649_34797_2513917_1_1_1_1,00.html>; b) Eisenberg, R (2003) 'Patent Swords and Shields', *Science*, 299: 1018-1019; c) Bok, D (2003) *Universities in the Marketplace: The Commercialization of Higher Education*. Princeton, N.J.: Princeton University Press; d) Stein, D (ed.) (2004) *Buying in or Selling Out? The Commercialization of the American Research University*. Rutgers, N.J.: Rutgers University Press.

[179] WO/03000904 at 79-82. The application specifically includes 20 members of the Brassica complex. However, one difficulty in assessing claims relative to Annex 1, is a lack of specificity in Genera covered in the application. For the text of International Treaty on Plant Genetic Resources for Food and Agriculture, see <http://www.fao.org/ag/cgrfa/itpgr.htm>.

[180] Ibid., CIPR 2002 at 79 for discussion.

On a still wider level the application makes clear that: "The present invention may be used for transformation of any plant species" across the monocots and dicots. While existing concerns have focused on alleged 'species' claims (i.e. Golden Rice), and 'genus patent' claims (i.e. transgenic Brassica) the rise of genomics permits intellectual property claims across species, genera and classes.[181] This may also present a situation in which intellectual property claims will be extended to species and varieties that have yet to become known to taxonomists. As the patent application puts it in connection with Duckweed (a family of floating aquatic plants): "Any other genera or species of Lemmaceae, if they exist, are also aspects of the present invention."[182]

This in turn raises the issue of the relationship between intellectual property claims over plant genetics and plant variety and plant patent protection. In the case of rice there may be 140,000 varieties of which an unclear number will be subject to Plant Variety Protection (PVP) or plant patent protection.[183] On a wider level, the Union for the Protection of New Varieties of Plants (UPOV) estimates that in 2002 a total of 59,200 plant variety protection certificates and plant patents were in force among UPOV member states.[184] In addition, utility patent claims in relation to plants are an increasing feature of international demand for patent protection.[185] Where the owners of such intellectual property seek to use genomics techniques or breeding techniques involving the claimed materials (i.e. the DNA involved in expressing the proteins within plant meristems) to alter flowering time, heading date, plant architecture etc. will they be required to enter licensing negotiations with companies or other bodies or risk litigation? That is, what are the implications of intellectual property claims over the underlying genetic regulatory mechanisms controlling plant flowering and plant morphology for other intellectual property claims surrounding plants?

Patent Cooperation Treaty application PCT/EP02/06968 (WO/03000904 A3) was subjected to an international search report conducted by the European Patent Office on the 29th of July 2003 (mailed on the 24th of October 2003). In relation to the DNA and amino acids involved in plant meristems discussed above, the international search report specifies that:

> "This International Searching Authority found multiple (groups of) inventions in this international application as follows:

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[181] The Golden Rice case also demonstrates the misunderstandings that may arise from patent claims. As the CIPR (2002) highlights patent protection only applies in the country where protection is granted. The rights to Golden Rice were subsequently acquired by Syngenta which then allowed royalty free use of the seed by farmers in developing countries earning less than US $10,000 per year. Syngenta also persuaded other companies to make Golden Rice technology available royalty free (See Ibid., CIPR 2002 at 147 for discussion). However, claims in relation to plant genetics may also form a barrier to entry to markets where intellectual property protection is in force and serve as a barrier to fair trade. For discussion of trade issues and poverty, see Kamal, M (lead author) (2003) *Making Global Trade Work for People*. United Nations Development Programme/Heinrich Boll Foundation/Rockefeller Brothers Fund/Rockefeller Foundation/Wallace Global Fund. London: Earthscan.

[182] WO/03000904 at 80, line 23-24.

[183] International Rice Institute. Location: <http://www.irri.org/GRC/GRChome/..%5Cirg%5Cbiodiv-genebank.htm>.

[184] UPOV (2003) 'Plant Variety Protection Statistics for the period 1998-2002'. Document: C/37/7, dated 2003-10-17. Location: <http://www.upov.int/en/documents/c/37/c_37_7.pdf>.

[185] See the companion paper in this series *Global Status and Trends in Intellectual Property Claims: Plants*. This issue has also increasingly been a focus for the work of WIPO and UPOV, See for example: a) WIPO-UPOV/SYM/02/4 'Patent protection for plant material: Lecture by Mrs. Victoria Henson-Apollonio, Manager, The Consultative Group on International Agricultural Research (CGIAR), The Hague, Netherlands'. WIPO-UPOV Symposium on the Co-Existence of Patents and Plant Breeders' Rights in the Promotion of Biotechnological Developments. October 21, 2002. Location: <http://www.upov.int/en/documents/Symposium2002/pdf/wipo-upov_sym_02_4.pdf>; b) WIPO-UPOV Symposium on Intellectual Property Rights in Plant Biotechnology. Geneva, October 24, 2003. Location: <http://www.upov.int/en/documents/Symposium2003/index.html>.

> Invention 1: claims 1-81, 83 (all partially and in so far as applicable)
>
> an isolated nucleic acid molecule encoding a polypeptide involved in control of flowering time; a polypeptide encoded by said polynucleotide; vectors containing said polynucleotide; plants transformed with said vector;
>
> methods of modulating flowering time and/or whole plant architecture of a plant using said polynucleotide; wherein said isolated nucleic acid molecule is represented by SEQ ID NO: 1 and the encoded protein is represented by SEQ ID No: 2
>
> Inventions 2 to 45: claims 1-81, 83 (all partially and in so far as applicable)."[186]

In one case, patent claim 82 concerning "an oligonucleotide primer consisting of between 8 and 150 bases which comprises at least 14 bases selected from…", the examiner found a claim to be unsearchable due to a lack of "clarity and conciseness".[187] under Article 6 of the Patent Cooperation Treaty.[188] However, the examiner also explains to the applicant that if this problem is overcome a search may be conducted during the examination procedure.[189]

In practice, the results of the search report reveal the significant challenges confronting patent searchers and patent examiners in relation to genomics. Thus, in considering the treatment of DNA and amino acid sequences as natural biological algorithms noted above the author of the present review engaged in a hand coding exercise to check the correspondence between the partial 180 DNA sequences set out in Table Four and the amino acid sequences set out in Table Five (i.e. atg = Met). The results of this exercise revealed that the 180 DNA base sequences from Sequence ID 1 do not in fact code for the corresponding 60 amino acids in Sequence ID 2. In order to test this conclusion a hand-coding exercise was conducted by Professor Peter Whittaker which was found to match the findings of the first test. An anonymous blind test was then conducted by a molecular biologist at Lancaster University as a third check and was found to correspond with the previous two results. The amino acid sequence for which the first 180 DNA bases disclosed in Sequence ID 1 is claimed to code is set out in Table Six.

Table Six: Amino Acids from the Rice Genome in SEQ ID: 2 (claimed)

Met	Gly	Arg	Gly	Lys	Val	Glu	Leu	Lys	Arg	Ile	Glu	Asn	Lys	Ile	Ser	Arg	Glu	Val	Thr
				5				10				15					20		
Phe	Ala	Lys	Arg	Arg	Asn	Gly	Leu	Leu	Lys	Lys	Ala	Tyr	Glu	Leu	Ser	Val	Leu	Cys	Asp
				25				30				35					40		
Ala	Glu	Val	Ala	Leu	Ile	Ile	Phe	Ser	Thr	Arg	Gly	Arg	Leu	Phe	Glu	Phe	Ser	Thr	Ser

[186] WO/03000904 A3 'International Search Report: Further Information' at 1.

[187] WO/03000904 A3 'International Search Report' at 2.

[188] In full claim 82 reads as follows. "An oligonucleotide primer consisting of between 8 and 150 bases which comprises at least 14 bases selected from the group of flanking sequences obtainable from a nucleotide sequence provided in SEQ ID NOs: 1 to 65, which at least 14 bases are immediately adjacent to at least two consecutive repeat units of an SSR." WO/03000904 at 161. Article Six of the Patent Cooperation Treaty specifies that: "The claim or claims shall define the matter for which protection is sought. Claims shall be clear and concise. They shall be fully supported by the description." Location: <http://www.wipo.int/pct/en/texts/articles/a6.htm#_6>.

[189] Under European Patent Office Guideline C-VI, 8.5., Ibid., WO/03000904 A3 'International Search Report'.

45 50 55 60
(60 = 180 nucleotide bases/3)

The amino acids which the first 180 DNA bases set out in Sequence ID 1 of the patent application actually code are set out in Table Seven.

Table Seven: Amino Acids from the Rice Genome SEQ ID: 2 (actual)

Met Gly Arg Gly Lys Val Glu Leu Lys [Ala] Asp Arg Glu Gln Asp Lys Pro Ala Gly
5 10 15
Asp Val Arg Glu Glu Glu Glu Arg Ala Ala Glu Glu Gly Val Arg Ala Val Arg Ala
20 25 30 35
Leu Arg Arg Arg Gly Arg Pro His His Leu Leu His Pro Arg Pro Pro Leu Arg Val
40 45 50 55
Leu His Leu
60 (60 = 180 nucleotide bases/3)

Further analysis of the DNA sequence listing to attempt to understand this discrepancy revealed that an extra base (G – Guanine) appears at base number 28 in the sequence. For the purpose of clarity and for verification purposes this is set out in Table Eight.

Table Eight: DNA from the Rice Genome (Oryza sativa) SEQ ID: 1

atggggcgag ggaaagtaga gctgaaa[g]cg gatcgagaac aagataagcc ggcaggtgac 60
28

gttcgcgaag aggaggaacg ggctgctgaa gaaggcgtac gagctgtccg tgctctgcga 120

cgccgaggtc gccctcatca tcttctccac ccgcggccgc ctcttcgagt tctccacctc[c?] 180

If this base is excluded then the amino acid sequence reads correctly. However, the effect of the presence of this additional base is to create a "frame shift" resulting in a "nonsense" amino acid sequence and a "nonsense" protein. This is significant because the synthesis of proteins within biological organisms is initiated by the "start" codon "atg" (Methionine). Computer programmes for coding amino acids from DNA bases also use the three base "atg" codon (Methionine) as the start point for mapping amino acids. The effect of the presence of the additional base "g" at point 28 is to change the reading frame so that the amino acid "Arg" (Arginine) reads as Ala (Alanine) and all subsequent amino acids in the sequence, underlined in Table Seven, become nonsense. Furthermore, with the exception of the initial nine amino acids, the 248 amino acids coded by the 747 bases in Sequence ID 1 are also nonsense as a result of this error. Given, that the 180 bases correctly code for the first 60 amino acids set out in the Sequence ID: 2 if the erroneous base "g" at point 28 is removed, it is reasonable to conclude the DNA listing was originally correct and that the error emerged at some point in the preparation of the Sequence ID document.

The problem of lack of verification and errors within DNA and amino acid sequences set out in genomics patent applications is increasingly recognised.[190] The practical effect of such errors is

[190] Cook-Deegan and McCormack, (2001) 'Intellectual Property: Patents, Secrecy, and DNA', *Science*, Vol. 293, 217. The major patent offices and WIPO have responded to this problem by introducing a requirement for the deposit of electronic sequences (see above). See also, European Patent Office 'STorage &Retrieval of Aminoacid & Nucleotide Data [STRAND]', Location: <http://www.european-patent-office.org/filingsoft/strand/patentin31.htm>.

that a person "skilled in the art" would not be readily able to reproduce the amino acids and proteins set out in the application. The scale of the challenge confronting patent searchers and patent examiners in verifying the correspondence between DNA and amino acid sequences in genomics related patent applications is perhaps revealed by the presence of an estimated 98,605 individual DNA bases in the case study application of which only the first 180 have been examined for the purposes of this review.[191] The introduction of requirements for the use of electronic software and electronic sequence deposits will undoubtedly assist patent examiners. However, as this case study reveals, the challenges remain significant.[192]

The case study patent application (as EP1409696) entered the regional examination phase of the procedure in Europe without the international search report on the 21st of April 2004. The European Patent application covers Austria, Belgium, Switzerland, Cyprus, Germany, Denmark, Spain, Finland, France, the United Kingdom, Greece, Ireland, Italy, Liechtenstein, Luxembourg, Monaco, the Netherlands, Portugal, Sweden, and Turkey and has been extended to include Albania, Lithuania, Latvia, Macedonia, Romania and Slovenia. The outcome of the application remains unknown at the time of writing in September 2004.

Conclusion:

In closing this review of the implications of intellectual property claims in the arena of genomics, proteomics and biotechnology for the development of an international regime, it is useful to recall that genomics and proteomics are commonly described as a "revolution" or a "new era." This "revolution" opens new vistas in scientific understandings of the relationships between organisms within and across kingdoms and domains and produces new challenges and potential opportunities. This new era introduces a requirement to think on the molecular level and at the same time to expand those horizons to the level of the complex and overlapping genetic make-up of organisms represented by genomes and proteomes.

In the twelve months between the 14th of September of 2003 and the 14th of September 2004 the number of genome mapping projects registered with the Genomes Online Database (GOLD) increased from 803 to 1182 projects, of which 219 had been completed. This represents a 47% increase in the number of mapping projects over the twelve month period and a 37% increase in the number of completed genome maps.[193] These trends are likely to accelerate with the completion of additional genome maps which will provide the foundation for unlocking the genomes of other organisms and technological developments such as the "whole genome chip".

The completion of the map of the human genome has been described as the "end of the beginning" of the genome era.[194] This end of the beginning is increasingly leading to the proclamation of arrival of the "post-genomic" era of the proteome.[195] However, the completion of

[191] It is for this reason that electronic DNA sequence listings have been established and software also exists to facilitate this task.

[192] For information on EPO and Patent Cooperation Treaty requirements for sequences listing deposits, see European Patent Office 'STorage & Retrieval of Aminoacid & Nucleotide Data [STRAND]'. Location: <http://www.european-patent-office.org/filingsoft/strand/patentin31.htm>.

[193] As of the 14th of September 2003, 160 genome maps had been completed, including the mapping of 4 chromosomes, and a further 643 were in progress of which 393 focused on Prokaryotic classes and 250 on Eukaryotic classes. Search of the GOLD database conducted on the 14th of September 2003.

[194] Claverie, J-M (2001) 'What If There Are Only 30,000 Human Genes?', *Science*, Vol. 291, 1255-1257. Citation at 1256, citing Brenner, S (2000)' The End of the Beginning', *Science*, Vol. 287, 2173-2174.

[195] Fields, S (2001) 'Proteomics in Genomeland', *Science*, Vol. 291, 1221-1224.

each map of a genome provides new insights into the relationships between the biological organisms that make up the world's biological diversity. Thus, the realisation that the human genome is only one third larger than the genome of the nematode worm and approximately the same size as that of the average mouse has been a surprising and humbling one for science.[196]

To date, with the partial exception of the human genome, the genomes and proteomes of plants, animals and microorganisms can be said to have been treated as a form of *Terra nullius* or empty lands.[197] The key to unlocking the potential of these new lands has been held to be incentives in the form of intellectual property protection to promote investment and innovation. This process occurred in a period when it was thought that the human genome might contain as many as 80,000 to 100,000 genes and policy-making in relation to DNA was informed by the hypothesis dating from 1941 that one gene = one protein (polypeptide).[198] However, the completion of the first genome maps has revealed that these lands are not as vast as had been imagined.

The rise of genomics and phylogentic taxonomic classification are also reconfiguring scientific understandings and assumptions surrounding the relatedness between biological organisms. Thus, the realisation that humans and chimpanzees share 99.4% and 98.4% of genetic relatedness and that this relatedness extends to the great apes has led to a proposal that all apes should be included in the family Hominidae (hominids) and the genus *Homo* should be expanded to include *Homo (Homo) sapiens* (humankind), and the sub-genera of *Homo (Pan) troglodytes* (the common chimpanzee), and *Homo (Pan) paniscus* (the bonobo chimpanzee).[199]

This is linked with growing recognition that there are major similarities ("homologies") in the genetic make-up of biological organisms across species, genera and classes. The case study of a patent application arising from the completion of a map of the genome of the world's major cereal, reveals that the identification and characterization of genetic homologies permits wide-ranging intellectual property claims over the genetic components of organisms across varieties, species, genera and classes. The issues raised by such claims also extend to the realm of animals and ultimately to humans. Thus, in December of 1998 a patent was issued for "Primate Embryonic Stem Cells" based on research with rhesus monkeys (*Macaca mulatta*) and the

[196] Ibid., Science (2001) The Human Genome; b) Ibid., Nature (2001) The Human Genome.

[197] See: a) UNESCO *Universal Declaration on the Human Genome and Human Rights 1997*. Location: <http://www.unesco.org/shs/human_rights/hrbc.htm>; b) HUGO (1995) HUGO Statement on the Patenting of DNA Sequences, Human Genome Organisation. Location: <http://www.gene.ucl.ac.uk/hugo/patent.htm>; c) HUGO (2000) HUGO Statement on Patenting of DNA sequences - In Particular Response to the European Biotechnology Directive - April 2000', Human Genome Organisation. Location: <http://www.gene.ucl.ac.uk/hugo/patent2000.html>; d) For other Human Genome Organisation statements and reports see <http://www.gene.ucl.ac.uk/hugo/publications-reports.html>; e) UNESCO 'Towards a declaration on universal norms on bioethics', Location: <http://portal.unesco.org/shs/en/ev.php-URL_ID=1883&URL_DO=DO_TOPIC&URL_SECTION=201.html>.

[198] See: a) Petsko, G (2001) 'Size doesn't matter', *Genome Biology*, 2002, 2(3): comment 1003.1-1003.2. Location: <http://genomebiology.com/2001/2/3/comment/1003.1>; b) This hypothesis arose from the work of George Beadle and Edward Tatum at Stanford University in 1941 and was originally known as the "one gene/one enzyme hypothesis". See Raven, P and Johnson, G (2002) *Biology*. Sixth Edition. Boston: McGrawHill. Citation at 295-296.

[199] Wildman, D, Uddin, M, Guozhen, L, Grossman, L and Goodman, M (2003) 'Implications of natural selection in shaping 99.4% nonsynonymous DNA identity between humans and chimpanzees: Enlarging genus Homo,' *Proceedings of the National Academy of Sciences of the United States of America*, June 10, 2003, Vol. 100, No.12. 7181-7188. See also, Black, R (2003) 'Chimps genetically close to humans,' BBC News website, UK edition, Tuesday, 20 May, 2003. Location: <http://news.bbc.co.uk/1/hi/sci/tech/3042781.stm>.

common marmoset (*Callithrix jacchus*).[200] Given that humans are also primates this has made possible intellectual property claims in relation to human embryonic stem cells.[201]

In considering these issues in relation to science and innovation a growing body of specialist bodies and analysts are observing that the extension of patentability to biological and genetic material and the wider internationalisation of the patent system to promote innovation has not been based on evidence. As the OECD has recently observed in the 2004 report *Patents and Innovation: Trends and Policy Challenges,* "The paucity of economic evaluation of the patent system is striking. Most of the changes to patent regimes implemented over the past two decades were not based on hard evidence or economic analysis."[202] Instead, it has been suggested that this could better be understood as a result of "policy capture" in developed countries and may ultimately lead to unforeseen "boomerang" effects on innovation.[203]

The wider social and economic impacts of the internationalisation of patent protection are reflected in an increasing number of reports by specialist and United Nations organisations and bodies concerning food security, public health, human rights and world trade. As the World Bank has noted in the case of the TRIPS agreement "…one impact of TRIPS will be to transfer economic rents from technology importers to technology developers"[204] While it has been asserted that intellectual property protection may promote trade in goods and services, foreign direct investment (FDI) and technology transfer, in practice it is far from clear whether such positive benefits exist or whether rent transfers lead to unproductive rent extraction at a cost to global welfare.[205] Thus, an econometric model employed by the World Bank to examine rent transfers from patents for 26 developed and developing countries under full TRIPS conditions reveals very significant rent transfers that are only partly offset by Foreign Direct Investment (FDI).[206] Furthermore, a recent substantive review of the implications of the internationalisation of intellectual property rights for world trade and innovation has highlighted that:

> "It is well to remember that the law and economics disciplines still know relatively little about how an incipient transnational system of innovation should best be organized and

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[200] See US patent 5,843,780. Source: Rai, A and Eisenberg, R (2003) 'Bayh-Dole Reform and the Progress of Biomedicine', *Law and Contemporary Social Problems*, Winter/Spring 2003, Vol. 66: 289-314. Location: <http://www.law.duke.edu/journals/66LCPRai>. See also, Overwalle, G (2002) *Study on the patenting of inventions related to human stem cell research*. European Group on Ethics in Science and New Technologies to the European Commission. 30 December 2001. Luxembourg: Office for Official Publications of the European Communities. Location: <http://europa.eu.int/comm/european_group_ethics/docs/stud-vanoverw.pdf>; For detailed consideration, see European Group on Ethics in Science and New Technologies to the European Commission (2002) *Opinion on Ethical Aspects of Patenting Inventions involving Human Stem Cells*. 7th May 2002. Luxembourg: Office for Official Publications of the European Communities. Location: <http://europa.eu.int/comm/european_group_ethics/docs/avis16_en_complet.pdf>.

[201] See US patent 6,200,806. Source: Ibid., Rai and Eisenberg (2003). Ibid., Overwalle (2002)

[202] OECD (2004) *Patents and Innovation: Trends and Policy Challenges*. Paris: Organisation for Economic Co-operation and Development. Citation at 26. Location: <http://www.oecd.org/dataoecd/48/12/24508541.pdf>.

[203] Maskus, K and Reichman, J (2004) 'The Globalization of Private Knowledge Goods and the Privatization of Global Public Goods', *Journal of International Economic Law* 7(2), 279-320. Citation at 286. See also, Ibid., Maskus, K and Reichman (2004) citing David, P (2000) 'A Tragedy of the Public Knowledge "Commons"? Global Science, Intellectual Property and the Digital Technology Boomerang', SIEPR Discussion Paper no. 00-02, Stanford Institute for Economic Policy Research. Location: <http://siepr.stanford.edu/papers/pdf/00-02.pdf>. For a critical perspective on the negotiating history of the TRIPS agreement see, Drahos, P and Braithwaite, J (2002) *Information Feudalism: Who Owns the Knowledge Economy?* London: Earthscan.

[204] World Bank (2001) *Global Economic Prospects and the Developing Countries 2002*. Washington: The International Bank for Reconstruction and Development/The World Bank. Citation at 136.

[205] Ibid., World Bank 2001.

[206] Ibid., World Bank 2001 Table 5.1 TRIPS: who gains?, at 133 and discussion at 137.

> regulated in the short to medium term. Countries big and small, rich and poor, find themselves at the start of a new era, in which serious thought and bold experimental undertakings will be needed to identify the optimal mix of public and private goods in this broadened but largely uncharted domain."[207]

The outcomes of the present review suggest that the emergence of intellectual property claims over genetic material that crosses varieties, species, genera and classes may also hold unforeseen consequences for future scientific research and innovation. The completion of the first maps of genomes and the realisation that genomes are far smaller than expected has also revealed that differences in the order of biological complexity between a nematode worm, a mouse and a human being can only be explained by the realisation that "a single gene can encode multiple different proteins."[208]

As science moves into the realm of proteomes in the pursuit of potential new therapies in the realm of medicine and greater understanding of the biology of plants in relation to agriculture, the existence of a large number of overlapping intellectual patent grants over DNA that is found across organisms may generate significant negative "anticommons" effects on future scientific research and innovation.[209] The costs or externalities generated by such effects are likely to impact upon both present and future generations and draw our attention to the inter-generational dimensions of fairness and equity in benefit-sharing arising from the utilisation of genetic resources.

Drawing directly on the reports of the world's major patent offices, this review has also revealed that the patent system is confronting a significant, if presently unrecognised, crisis in addressing demand for patent protection arising from the internationalisation of the patent system. As the President of the European Patent Office has recently highlighted, this crisis is primarily a consequence of the entry into force of the TRIPS agreement.

> "On entry into force of the TRIPs agreement, the patent system was hit by a virtual explosion in the demand for patent rights, and patent offices found themselves facing a flood of applications which they could no longer treat within acceptable time limits. As a result, backlogs started to build up which soon began to exceed the examining capacities of most offices."[210]

A fuller understanding of levels of international demand for patent protection is desirable in order to appreciate the true scale of this problem. However, the existence of in excess of three million patent applications awaiting request for examination or pending in the procedure within the world's major patent offices suggests that substantive questions surround the ongoing integrity of the patent system. While recognising the substantive concerns expressed by an increasing number of civil society organisations, specialist bodies and United Nations bodies

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[207] Maskus, K and Reichman, J (2004) 'The Globalization of Private Knowledge Goods and the Privatization of Global Public Goods', *Journal of International Economic Law* 7(2), 279-320. Citation at 320.

[208] Ibid., Fields, S (2001) at 1221. See also, Strohman, R (2002) 'Maneuvering in the Complex Path from Genotype to Phenotype,' *Science*, Vol. 296, 701-703.

[209] Heller, M and Eisenberg, R (1998) 'Can Patents Deter Innovation? The Anticommons in Biomedical Research', *Science*, Vol. 280, 698-701. Location: <http://www.sciencemag.org/cgi/content/full/280/5364/698>.

[210] Dr H. C Ingo Kober, (2003) 'Opening Address' *Mastering the Workload: A European Patent Office Customer Workshop on the Patenting System in Europe*, 18th of February 2003, Munich. Location: <http://mtw.european-patent-office.org/workload/site/en/keynote_session.html>.

with respect to the implications of the internationalisation of the patent system in relation to pharmaceuticals and biological and genetic material, on a wider level it is unclear whose interests will ultimately be served by the emerging crisis within the patent system.

Thus, the wider patent system may have an important role to play in protecting the public from false claims for protection in multiple arenas of invention and promoting openness through disclosure to serve the public good. However, the ability of the patent system and professional patent examiners to fulfil these functions across multiple arenas of invention appears to have been undermined by the "virtual explosion" in the number of patent claims arising from the entry into force of the TRIPS agreement and the internationalisation of patent protection under the Patent Cooperation Treaty. It is unclear whether this process of de-anchoring of the patent system across multiple arenas of invention serves the interest of science, industry, government, and the public good. In particular, in the case of the extension of patentability into the realm of biological organisms and genetic materials it is becoming clear that there may be arenas where the resources concerned are simply too important, in terms of the present and future public good, to be subject to strong intellectual property protection.

There is an emerging and increasingly widespread view that *sui generis* alternatives to patent protection may be preferred in the case of biological and genetic material and traditional knowledge. However, the outcomes of this review also suggest that if such options are pursued it will be important to learn the lessons of the incorporation of traditional knowledge and genetic materials into the realm of patents and to recognise that the pressures which led to such changes are unlikely to disappear under alternative systems.

In considering this problem from an innovation perspective it is useful to recall that the origins of the decision to extend patentability to microorganisms and microbiological processes embodied within Article 27.3 (b) of the TRIPS agreement are found within the 1980 United States Supreme Court Decision *Diamond v. Chakrabarty*.[211] In delivering this narrow 5-4 judgement Chief Justice Burger observed that:

> "The grant or denial of patents on micro-organisms is not likely to put an end to genetic research or to its attendant risks. The large amount of research that has already occurred when no researcher had sure knowledge that patent protection would be available suggests that legislative or judicial fiat as to patentability will not deter the scientific mind from probing into the unknown any more than Canute could command the tides. Whether respondent's claims are patentable may determine whether research efforts are accelerated by the hope of reward or slowed by want of incentives, but that is all." [212]

In short, and notwithstanding the substantive concerns that surround genetic research and biotechnology, the Court recognised that innovation would take place irrespective of whether patent protection was provided over microorganisms and genetic material. On this occasion the Court adopted the view that permitting the claim would provide further incentives for research. Twenty four years later the wider consequences of the internationalisation of that reasoning are a focus of the deliberations of an increasing number of United Nations Conventions and bodies

[211] For discussion of the negotiating history of the TRIPS agreement see, for example, Drahos, P and Braithwaite, J (2002) *Information Feudalism: Who Owns the Knowledge Economy?* London: Earthscan.

[212] See *Diamond v. Chakrabarty*. Location: <http://supct.law.cornell.edu/supct/cases/patent.htm>.

ranging across a spectrum from biological diversity, to development, human rights, health, agriculture and trade.

Much attention has understandably focused on issues surrounding patents and transnational corporations in the critical arenas of health and agriculture. However, it is important to recognise that the rise of genomics and proteomics is reported to be producing a marked shift in the balance of relationships within what has been called the "triple helix" of innovation, consisting of government, universities and industry.[213] This shift in emphasis is moving away from industry and towards universities and is reflected in the emergence of regional research strategies and the establishment of regional bioscience centres.[214] In contrast with the hierarchical and discipline based nature of earlier patterns of innovation this shift is reported to be marked by innovation that is networked, transdisciplinary and reflexive in nature.[215]

This shift in emphasis within the structure of innovation raises questions surrounding the implications of multiplying intellectual property claims for publicly funded and public-private research initiatives directed towards public health and related objectives and thus to enhancing public welfare.[216] However, this shift may also provide potential ways forward in developing an international regime on access to genetic resources and benefit-sharing directed towards conservation, health, agriculture and related goals that do not necessarily produce the externalities and costs of the patent system.[217] In particular, it has been argued that in some areas "…public spending is the most efficient way to fund R&D" and, if made publicly available, the results of R & D generate "…spillover effects across borders."[218] The development of an international regime could potentially seek to foster such effects, including collaborative research networks, through the development of alternative *sui generis* models such as "open source" style models which seek to avoid the externalities generated by the patent system and foster innovation.

It is also important to recognize that genomics and proteomics do not constitute the unique, or indeed most important, areas of innovation in arenas such as health and agriculture or in understanding the complex relationships between humanity and biological diversity. It is here that it is useful to recall the following guidance from the Secretariat of the Convention in relation to the development of an international regime:

> "…in regime theory the term 'international regime' has been defined as 'a set of principles, norms, rules and decision-making procedures around which actors' expectations converge in a given area of international relations".[219]

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[213] Cooke, P (2004) 'The molecular biology revolution and the rise of bioscience megacentres in North America and Europe', in *Environment and Planning C: Government and Policy*, Vol.22. pp. 161-177. Citing Etkowitz, H

and Leydesdorff, L (1997) *Universities and the Global Knowledge Economy*. London: Pinter. Location: <http://www.envplan.com/epc/abstracts/c22/c0344.html>.

[214] Ibid., Cooke 2004.

[215] Ibid., Cooke 2004 at 162, citing Gibbons et al. (1994).

[216] Ibid., Rai, A and Eisenberg, R 2003.

[217] Scotchmer, S (2004) 'The Political Economy of Intellectual Property Treaties', *The Journal of Law, Economics, & Organization*, Vol. 20, No. 2. 415-436. Location: <http://socrates.berkeley.edu/~scotch/treaties.pdf>.

[218] Ibid., Scotchmer 2004 at 436.

[219] UNEP/CBD/MYPOW/6 International Regime on Access and Benefit-Sharing: proposals for an international regime on access and benefit-sharing. Note by the Executive Secretary. 7th January 2-003. Citation at page 5 para. 19, footnotes removed. Location: <http://www.biodiv.org/doc/meetings/cop/mypow-01/official/mypow-01-06-en.doc>.

In conducting this review of trends in relation to proteomics, genomics and biotechnology, the cutting edge of science represented by systems biology emphasises relatedness, complexity and ultimately risk in understanding the relationships between biological organisms and the potential impacts of human interventions. In practice, there are other dynamic sciences that emphasise relatedness, complexity and risk in understanding human relationships with biological diversity. These sciences and philosophies are embodied in the diverse knowledge, innovations and practices of indigenous peoples and local communities around the world and the customary law based common resource regimes that they have developed to govern human interactions with biological diversity.[220]

Encapsulating the diversity and complexity of human knowledge and understanding of human relations with biodiversity across an estimated 5,000 to 7,000 spoken languages world-wide is a formidable and ultimately impossible challenge.[221] However, the following thanksgiving that is commonly heard among the indigenous peoples of Canada provides an insight into the sophistication of these views:

> "For all our relations - not only the two legged, but the winged ones, the crawling ones, the four legged, the plants, the trees and those that live in the water. We must look after those that nurture life - the fire, the earth, the water and the air. We must find the balance."[222]

In an era when the messages of seemingly remote "cutting edge" science represented by genomics, proteomics and systems biology are converging with other dynamic sciences which emphasise relatedness, complexity, risk and respect in managing relations between humanity and biological diversity, the privileging of particular forms of knowledge and intellectual property is likely to represent a lost opportunity to bridge the epistemological divide between so-called "local" and "global" science in order to advance human knowledge and common understanding

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[220] See: a) Ostrom, E (1990) *Governing the Commons: The Evolution of Institutions for Collective Action*. Cambridge: Cambridge University Press; b) Hess, C and Ostrom, E (2003) 'Ideas, Artifacts, and Facilities: Information as a Common-Pool Resource', *Law and Contemporary Problems*, Vol. 66: 111-145. Location: <http://www.law.duke.edu/shell/cite.pl?66+Law+&+Contemp.+Probs.+111+(WinterSpring+2003)>; c) Posey, D (ed.) (1999) *Cultural and Spiritual Values of Biodiversity*. United Nations Environment Programme. London: Intermediate Technology Publications; d) Bollier, D (2004) 'The Clash of Markets and Commons – and How It Affects Science, Economic Performance and Democracy'. Conscience and Science Forum, Simon Fraser University, University of Victoria and The Innovation and Science Council of British Columbia. Vancouver, British Columbia, April 29, 2004. Location: <http://www.bollier.org/pdf/Vancouverspeech.pdf>.

[221] See Maffi, L (1999) 'Language and the Environment', in Posey, D (ed.) (1999) *Cultural and Spiritual Values of Biodiversity*. United Nations Environment Programme. London: Intermediate Technology Publications. pp. 22-35.

[222] This version of the thanksgiving prayer is taken from the 1995 Annual Report of the Manitoba Model Forest a non-profit organisation with responsibility for an area of over one million hectares of forest north of Winnipeg in Manitoba, Canada. Location: <http://www.manitobamodelforest.net/>. The organization was established as a partnership between the Canadian Forest Service, business, local communities, universities, environmental organizations, and indigenous peoples organisations. The organization has also established an international conservation partnership in Mexico. The newsletter of the organisation "for all our relations" places an emphasis on training for First Nations youth. Annual report location: <http://www.manitobamodelforest.net/publications/anuuals/REPORT95.PDF>. The 2003 report discusses indigenous peoples participation in detail. Location: <http://www.manitobamodelforest.net/publications/anuuals/2003Annual/2003E.htm#106>. The origins of the thanksgiving are uncertain at the time of writing but may potentially be an abbreviated form of the Thanksgiving Address of the Haudenosaunee, or Six Nations, consisting of the Seneca, Cayuga, Onondaga, Oneida, Mohawk and Tuscarora Nations and also known as the Iroquois Confederacy. Location: <http://www.sixnations.org/>.

in pursuit of the realisation of the objectives of the Convention and wider internationally agreed goals.[223]

As this review has sought to highlight the genomes and proteomes of organisms and the transformation in scientific understandings of the relationships between biological organisms made possible by genome mapping and proteomics, constitutes a major new development in human understanding of biodiversity and a significant "gap" in international policy measures.[224] This presents the challenge of considering how this gap might best be addressed while recognising the existence and rights of indigenous peoples and local communities, the legitimate rights and interests of states, and the need to foster research and innovation directed towards the objectives of the Convention on Biological Diversity and international objectives in relation to health, agriculture, development and human rights. [225]

If the announcement of the working draft of the map of the human genome in 2000 and the completion of the first draft of a plant genome, *Arabidopsis thaliana*, in that same year can be taken as the starting point in the new "era" of genomics and proteomics, it becomes clear that this new era is barely four years old at the time of this review. In approaching the challenges and opportunities represented by genomes and proteomes that transcend the territories and lands of indigenous peoples and local communities, the jurisdictions of sovereign states, regions, population groups and ultimately generations, the international community is presented with what may be described as a "global public goods" problem.[226]

> "Global public goods are public goods with benefits – or costs, in the case of such "bads" as crime and violence – that extend across countries and regions, across rich and poor population groups, and even across generations."[227]

The concept of global public goods has been endorsed by the Secretary General of the United Nations in the following terms:

> "Global public goods are an often ignored but enormously important aspect of multilateralism. Whether we are talking about preserving biodiversity, preventing climate change, fighting the spread of communicable diseases, establishing rules for trade and aviation, or setting global standards of human rights, it is impossible for any single state to secure such goods on its own. Quite the contrary, global public goods can only be attained if countries work together, and globalization has only increased this fundamental interdependence."[228]

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[223] An example of such an initiative is provided by the Millennium Ecosystem Assessment which convened a conference *Bridging Scales and Epistemologies: Linking Local Knowledge and Global Science in Multi-Scale Assessments*, in Alexandria, Egypt, March 17-20, 2004. Location: <http://www.millenniumassessment.org/en/about.meetings.bridging.proceedings.aspx>.

[224] See Decision VII/19 Annex, para. (a) small roman (ii). Location: <http://www.biodiv.org/decisions/default.aspx?m=COP-07&id=7756&lg=0>.

[225] Plan of Implementation of the World Summit on Sustainable Development. Location: <http://www.johannesburgsummit.org/html/documents/summit_docs/2309_planfinal.htm>.

[226] Office of Development Studies, United Nations Development Programme website 'Providing Global Public Goods'. Location: <http://www.undp.org/globalpublicgoods/globalization/index.html>.

[227] Kaul, I et al. (1999) 'Why Do Global Public Goods Matter Today', in Kaul, I et al. (eds.) *Providing Global Public Goods: Managing Globalization*. Oxford: Oxford University Press. Citation at 3. Location: <http://www.undp.org/globalpublicgoods/globalization/pdfs/Overviews.pdf>.

[228] Kofi A. Annan, Secretary-General, United Nations, July 2002. Location: <http://www.undp.org/globalpublicgoods/globalization/endorsements.html>.

The analysis presented above suggests that genomes and proteomes, as fundamental biological properties of living organisms, are global public goods that are not presently recognised and addressed within the multilateral system established under the United Nations.[229] As the main international instrument concerned with the conservation and sustainable use of biodiversity and the fair and equitable sharing of the benefits arising from the utilisation of genetic resources it is reasonable to conclude that the Convention on Biological Diversity could logically play the leading role in confronting the challenges and opportunities represented by genomes and proteomes as global public goods.

In considering this issue it is useful to recall that in resolution 57/260 of the 20th of December 2002, the United Nations General Assembly invited the Conference of the Parties to the Convention on Biological Diversity to take appropriate steps "to negotiate within the framework of the Convention on Biological Diversity, bearing in mind the Bonn Guidelines, an international regime to promote and safeguard the fair and equitable sharing of benefits arising out of the utilization of genetic resources."

During the Seventh Conference of the Parties, in Kuala Lumpur, Malaysia between the 9th to the 20th of February 2004, Parties established the terms of reference for the negotiation of an international regime by the Working Group on Access and Benefit-Sharing in collaboration with the Working Group on Article 8(j) and related provisions. The terms of reference for the negotiation of an international regime set out in COP7 Decision VII/19 include a wide range of elements relating to, inter alia; research, ethics, benefit-sharing, transboundary genetic resources, respect for the human rights of indigenous peoples and local communities, consent, certification and development goals, that form a well balanced foundation for the development of an international regime. Decision VII/19 also breaks new ground by promoting a deliberative and participatory process for the elaboration of an international regime, involving Parties, delegates of indigenous peoples and local communities, the scientific community, industry and civil society organizations. While the proposed development of an international regime has understandably been met with resistance or uncertainty within certain sectors, the present review of trends in genomics, proteomics and biotechnology would suggest that the Convention on Biological Diversity is the multilateral arena that is best placed to confront the challenges and opportunities of this new era.

[229] For discussion of genomics 'knowledge' as a global public good in the arena of health see: a) Smith, R et al. (2004) 'Genomics knowledge and equity: a global public goods perspective on the patent system', *Bulletin of the World Health Organization*, April 2004, 385-389; b) Thorsteindóttir, H et al. (2003) 'Genomics – a global public good?', *Lancet*, 361, 891-2.

Annex 1

Dataset: EPO esp@cenet Worldwide Database Keyword Rankings for Patent Publications 1990-2003

Notes:

1. Search of European Patent Office esp@cenet worldwide database conducted on the 24th of September 2004 and verified against a search conducted on the 15th of July 2004.
2. Search conducted for keywords within titles and abstracts by publication date using the advanced search function of esp@cenet.
3. Data for 2001 to 2003 is preliminary and reflects the active nature of the database for these target years.

Keyword	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	Total 1990-2000	Total 1990-2003	2000-2003 +/-	2001-2003 +/-	Database Total
																	%	No.	No.
protein	1,937	2,401	2,752	2,808	3,204	3,524	3,707	5,018	6,461	7,257	8,411	11,205	13,606	12,460	47,480	84,751	78	37,271	+100,000
gene	923	1,052	1,261	1,299	1,624	1,860	2,490	2,973	4,151	4,990	5,685	6,864	9,089	8,343	28,308	52,604	86	24,296	62,051
DNA	1,303	1,624	1,860	1,979	2,090	2,459	2,882	3,229	3,811	4,217	4,347	6,918	7,935	5,371	29,801	50,025	68	20,224	56,736
amino acid	1,708	1,822	1,963	1,956	1,968	2,156	2,439	2,565	2,982	3,065	3,403	3,856	4,814	4,837	26,027	39,534	52	13,507	79,223
nucleic acid	403	437	519	668	828	1,173	1,651	1,881	2,999	3,400	4,035	5,199	7,022	8,238	17,994	38,453	114	20,459	43,197
enzyme	1,229	1,238	1,376	1,355	1,521	1,593	1,720	1,925	2,392	2,408	2,563	2,706	3,493	3,586	19,320	29,105	51	9,785	42,104
polypeptide	469	507	624	588	711	786	894	1,027	1,367	1,617	1,967	5,809	5,932	4,815	10,557	27,113	157	16,556	31,555
peptide	784	911	1,039	1,030	1,215	1,406	1,606	1,650	2,113	2,083	2,357	2,554	3,497	3,489	16,194	25,734	59	9,540	32,673
nucleotide	218	267	321	376	406	541	659	812	930	1,147	1,371	1,816	2,092	2,209	7,048	13,165	87	6,117	15,338
RNA	173	260	274	316	352	439	589	651	923	1,114	950	1,171	1,426	1,422	6,041	10,060	67	4,019	11,598
microorganism	521	488	476	549	588	611	610	659	813	755	845	957	1,050	1,102	6,915	10,024	45	3,109	14,383
human gene	134	173	196	214	250	281	363	436	681	852	896	1,273	1,749	1,521	4,476	9,019	101	4,543	9,868
genome	94	107	162	163	168	165	223	282	358	410	544	725	1,269	1,046	2,676	5,716	114	3,040	6,337
plant gene	40	86	94	122	112	150	191	287	363	444	570	564	723	683	2,459	4,429	80	1,970	5,041
animal gene	17	29	27	23	40	53	91	86	132	205	203	238	394	430	906	1,968	117	1,062	2,311
microbe	39	35	76	55	85	89	74	75	106	110	131	121	220	255	875	1,471	68	596	1,851
deoxyribonucleic	20	21	19	32	29	23	27	24	26	25	24	32	28	6	270	336	24	66	479
ribonucleic	4	11	8	8	16	27	19	18	26	26	34	39	50	45	197	331	68	134	533
proteome	0	0	0	0	0	0	0	0	1	2	4	10	30	60	7	107	1,429	100	152

Source: Oldham, P and Cutter, M (2004) *Global Status and Trends in Intellectual Property Claims: Patent Dataset*. CESAGen, UK.

Annex 2

Dataset: EPO esp@cenet Worldwide Database Patent Publications for Biotechnology 1990-2003

Notes:

1. Search of the European Patent Office esp@cenet worldwide database conducted on the 24th of September 2004 and verified against an identical search conducted on the 15th of July 2004.
2. Search conducted using International Patent Classification (IPC) classifiers (Seventh edition) and publication date.
3. Search conducted using OECD working definition of biotechnology in OECD publication *STI Working Paper 2003/13*, 26 November 2003.
4. Data for 2001-2003 is preliminary and reflects the active nature of the database.
5. Whole database entries +/- 100,000 reflect the limitation of individual search results to 100,000 records.

Biotechnology OECD		**1990**	**1991**	**1992**	**1993**	**1994**	**1995**	**1996**	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**Total 1990-2000**	**Total 1990-2003**	**2000-2003 +/-**	**2000-2003 +/-**	**Whole Database**
Human Necessities																		**%**	**No.**	**No.**
plants, processes for modifying genotypes	A01H1/00	126	133	114	161	195	138	140	181	265	295	441	385	488	802	2,189	3,864	77	1,675	5,426
plant reproduction by tissue culture techniques	A01H4/00	175	246	239	235	269	210	274	236	359	443	425	320	226	226	3,111	3,883	25	772	3,966
Medicinal preparations containing peptides	A61K38/00	58	98	135	116	146	2,222	2,126	2,145	2,600	2,802	2,721	3,475	4,555	3,767	15,169	26,966	78	11,797	29,025
Medicinal preparations containing antigens or antibodies	A61K39/00	411	479	588	793	801	716	828	931	1,137	1,342	1,494	1,725	1,956	2,002	9,520	15,203	60	5,683	19,945
Treatments for genetic diseases, Gene therapy	A61K48/00	47	104	159	299	569	823	1,502	2,005	2,635	3,256	3,605	4,133	5,183	5,546	15,004	29,866	99	14,862	32,435
Chemistry																				
Biological treatment of water wastewater, or sewage characterised by microorganism used	C02F3/34	173	222	250	279	353	337	331	389	519	377	445	367	451	452	3,675	4,945	35	1,270	6,610
Antibiotics	C07G11/00	68	46	81	63	56	39	25	21	11	18	15	11	19	22	443	495	12	52	3,146
Vitamins	C07G13/00	4	2	3	2	5	1	1	4	1	1	0	2	2	4	24	32	33	8	108
Hormones	C07G15/00	4	8	7	5	4	4	1	2	1	4	2	2	1	0	42	45	7	3	331

Peptides with more than 20 amino acids in undefined/partially defined sequence, derivatives thereof	C07K4/00	1	9	9	11	10	73	60	70	51	72	55	78	123	140	421	762	81	341	896
Chemistry																		**%**	**No.**	**No.**
Peptides with more than 20 amino acids Gastrins; Somatostatins; Melanotropins; Derivatives thereof	C07K14/00	56	91	115	144	96	1,012	880	888	1,291	1,375	1,624	2,874	3,274	1,533	7,572	15,253	101	7,681	15,756
Immunoglobulins, e.g. monoclonal or polyclonal antibodies	C07K16/00	22	30	45	40	57	356	493	621	804	982	1,047	2,309	2,674	1,056	4,497	10,536	134	6,039	11,402
Carrier-bound or immobilised peptides	C07K17/00	90	95	127	185	253	264	260	253	257	224	323	334	837	647	2,331	4,149	78	1,818	4,915
Hybrid peptides	C07K19/00	40	66	65	82	71	304	469	548	572	548	748	946	1,175	1,082	3,513	6,716	91	3,203	7,348
Apparatus for Enzymology or Microbiology	C12M	1,255	1,184	1,358	1,365	1,431	1,310	1,349	1,292	1,387	1,437	1,648	2,231	3,414	3,612	15,016	24,273	62	9,257	34,586
Microorganisms or Enzymes'compositions thereof	C12N	10,092	10,560	11,938	12,892	14,582	15,602	16,747	18,427	22,787	25,838	28,748	35,002	39,210	36,738	188,213	299,163	59	110,950	+/- 100,000
Fermentation or Enzyme using processes to synthesise chemical compounds	C12P	6119	6,225	6,702	7,616	7,892	7,170	7,200	7,542	7,858	8,045	8,374	8,830	13,148	16,156	80,743	118,877	47	38,134	+/- 100,000
Measuring or testing processes involving enzymes or microorganisms	C12Q	2,642	3,241	3,765	4,354	4,805	5,547	6,681	7,594	9,682	10,934	12,841	15,415	19,728	19,455	72,086	126,684	76	54,598	+/- 100,000

Source: Oldham, P and Cutter, M (2004) *Global Status and Trends in Intellectual Property Claims: Patent Dataset*. CESAGen, UK.

Processes using enzymes or microorganisms to liberate, separate or purify pre-existing compound or composition	C12S	77	154	266	224	334	345	297	277	276	220	163	135	191	206	2,633	3,165	20	532	3,312
Physics																		**%**	**No.**	**No.**
Biochemical Electrodes	G01N27/327	110	82	98	122	129	128	142	187	165	235	231	293	333	393	1,629	2,648	63	1,019	3,200
Immunoassay; Biospecific binding assay; Materials thereof	G01N 33/53*	1,254	1,260	1,277	1,428	1,809	1,696	2,097	2,414	2,846	3,314	3,258	4,453	5,978	6,942	22,653	40,026	77	17,373	48,519
as above, double or second antibody etc.	G01N33/54*	8	2	0	3	0	0	0	2	0	1	1	2	2	1	17	22	29	5	4,060
as above, relating to type of carrier etc.	G01N33/55*	1	0	0	1	1	1	0	0	0	1	1	4	3	2	6	15	150	9	14
as above, relating to specific disease i.e. hepatitis, cancer etc.	G01N33/57*	0	0	0	1	0	0	0	1	0	0	0	1	1	1	2	5	150	3	4
as above, involving proteins, peptides or amino acids etc.	G01N33/68	402	513	607	562	764	890	1,014	1,133	1,516	1,937	2,244	2,597	2,944	2,277	11,582	19,400	68	7,818	22,310
as above, involving hormones	G01N33/74	75	126	129	113	141	149	152	127	141	118	126	126	181	164	1,397	1,868	34	471	2,503
as above, Human chorionic gonadotropin	G01N33/76	42	42	44	49	58	53	40	45	42	34	31	20	38	29	480	567	18	87	779
as above, Thyroid gland hormones	G01N33/78	34	38	33	31	45	35	23	22	23	19	12	18	19	9	315	361	15	46	504
as above, involving prostaglandins	G01N33/88	4	4	4	5	6	7	3	4	6	2	4	4	6	13	49	72	47	23	91
as above, involving lipids, e.g. cholesterol	G01N33/92	67	70	63	73	75	78	104	79	90	96	120	110	163	185	915	1,373	50	458	1,915

*Indicates inclusion of relevant sub-groups.

Annex 3:

European Patent Office esp@cenet Worldwide Database Coverage

The following table has been adapted from the original European Patent Office publication providing an overview of the contents of the worldwide database.[230] The table provides details of the coverage of industrial patent publications within the esp@cenet worldwide database and is current as of the 2nd of August 2004.

Explanations of the table fields:

1. Country code – WIPO Country Code.
2. TI - (Title), AB - (Abstract), EC - (European Classification), IC - International Patent Classification, PD - Publication Date.
3. Most recent: the most recent document available when the monthly screening has taken place.

	Country	Country Code	Number	TI %	AB %	EC %	IC %	PD %	Most recent
1	Argentina	AR	**40,755**	0	0	0	76.3	100	(30/12/1991)
2	Austria	AT	**497,623**	1.6	1.6	7.9	51.2	99.5	(15/07/2004)
3	Australia	AU	**1,042,670**	95.5	0	5.2	93.8	99.8	(15/07/2004)
4	Bosnia and Herzegovina	BA	**215**	0	0	0	100	100	(14/09/2001)
5	Belgium	BE	**536,719**	0.9	0.9	97.5	31.8	50.7	(01/06/2004)
6	Bulgaria	BG	**47,043**	81.4	11.8	0	99.3	100	(31/05/2004)
7	Brazil	BR	**278,133**	0	0	0.1	99.3	100	(13/07/2004)
8	Canada	CA	**883,947**	99.5	70.8	5.2	87.1	99.7	(19/07/2004)
9	Switzerland	CH	**692,770**	4.9	3.6	78.7	43.8	99.9	(30/07/2004)
10	China	CN	**416,294**	97.6	44.2	0.9	99.9	100	(31/03/2004)
11	Czechoslovakia (up to 1993)	CS	**173,992**	81.8	0	0.2	98.9	99.1	(12/11/2003)
12	Cuba	CU	**2,250**	88.5	0	0	98	100	(11/12/1995)
13	Cyprus	CY	**2,302**	100	0	0	81	100	(04/07/2003)
14	Czech Republic	CZ	**62,931**	99	12.4	0.1	100	100	(14/07/2004)
15	Germany, excluding the territory that, prior to October 3 1990, constituted the Federal Republic of Germany	DD	**226,810**	0	0	1.5	73.5	73.9	(22/04/1999)
16	Germany	DE	**2,990,574**	16.5	18.3	98.1	53.5	88.4	(29/07/2004)
17	Denmark	DK	**241,104**	1.9	1.9	0.3	63.2	97.9	(01/07/2004)

[230] EPO esp@cenet 'Worldwide Database – Detailed Coverage Abstracts', Table current as of 2nd of August 2004. Location: <http://ep.espacenet.com/espacenet/ep/en/helpV3/detailedcoverageab.html>.

	Country	Country Code	Number	TI %	AB %	EC %	IC %	PD %	Most recent
18	Estonia	EE	**5,811**	0	0	0	99.9	100	(15/06/2004)
19	Egypt	EG	**9,829**	39.2	0	0	97.7	100	(28/04/2004)
20	Spain	ES	**230,082**	9.4	9.4	0.1	99.5	100	(16/07/2004)
21		FA	**1**	0	0	0	0	0	(//0)
22	Finland	FI	**128,358**	4.8	4.8	0.2	96.8	99.9	(15/07/2004)
23	France	FR	**2,117,810**	7.2	8.5	99	39.9	91.4	(30/07/2004)
24	United Kingdom	GB	**2,215,342**	90.7	78.5	88.5	31.6	98	(28/07/2004)
25	Greece	GR	**39,964**	53.3	4.3	0.1	21.5	100	(19/07/2004)
26	Hong Kong	HK	**40,009**	100	0	0	99.9	100	(08/04/2004)
27	Croatia	HR	**6,634**	99.8	0	0	100	100	(30/06/2004)
28	Hungary	HU	**131,960**	93.5	1.2	0.1	99.7	100	(28/07/2004)
29	Indonesia	ID	**14,586**	0	0	0	89.9	100	(03/01/2002)
30	Ireland	IE	**52,240**	100	0.9	0.1	99.7	100	(14/07/2004)
31	Israel	IL	**61,412**	100	0	0.1	99.2	100	(28/03/2004)
32	India	IN	**50,329**	99.8	0	0.2	99.4	99.9	(02/11/2003)
33	Italy	IT	**459,758**	5.8	5.8	0.6	82.9	99.2	(02/02/2004)
34	Japan	JP	**8,661,837**	91.5	0	10.8	96.3	100	(24/06/2004)
35	Kenya	KE	**1,336**	0	0	0	98.1	100	(01/09/1989)
36	Republic of Korea	KR	**543,217**	99.6	13.9	0.1	99.6	100	(31/12/2003)
37	Lithuania	LT	**2,440**	100	12.7	0.2	100	100	(26/07/2004)
38	Luxembourg	LU	**60,191**	0.3	0.1	97.6	34.2	82.4	(21/06/2004)
39	Latvia	LV	**3,730**	99.9	13.9	0.2	100	100	(20/12/2002)
40	Morocco	MA	**7,380**	0	0	0	94.9	99.9	(01/10/2003)
41	Monaco	MC	**2,560**	0	0	31.8	97.3	100	(26/05/2004)
42	Republic of Moldova	MD	**1,652**	75.7	39.2	0	99.9	100	(30/06/2004)
43	Mongolia	MN	**233**	0	0	0	97.9	100	(15/06/1989)
44	Malta	MT	**545**	0	0	0	0	100	(08/05/1992)
45	Malawi	MW	**732**	100	0	0	96	100	(12/10/1994)
46	Mexico	MX	**48,858**	0	0	0	99	100	(27/01/2003)
47	Malaysia	MY	**9,618**	0	0	0	94.6	100	(31/12/1996)
48	New Caledonia	NC	**46**	0	0	100	0	0	(//0)
49	Netherlands	NL	**521,572**	2.1	2.1	94.4	53.6	64.5	(11/05/2004)
50	Norway	NO	**163,800**	0	0	0.1	94.3	99.7	(26/01/2004)
51	New Zealand	NZ	**78,029**	99.8	22.8	0.1	86.9	99.8	(25/06/2004)
52	Philippines	PH	**18,947**	0	0	0	97.9	100	(02/04/1998)
53	Poland	PL	**202,263**	83	0	0.1	99.8	100	(30/06/2004)
54	Portugal	PT	**37,961**	3.4	3.4	0	96.4	100	(30/04/2004)
55	Romania	RO	**55,589**	86.7	9.6	0.6	97.9	100	(30/06/2004)

	Country	Country Code	Number	TI %	AB %	EC %	IC %	PD %	Most recent
56	Russian Federation	RU	**227,862**	100	50.8	0.7	99.8	100	(27/05/2004)
57	Sweden	SE	**522,740**	2.5	2.5	0.4	64.6	65.8	(20/07/2004)
58	Singapore	SG	**21,980**	100	0	0.1	99.8	100	(29/04/2004)
59	Slovenia	SI	**5,258**	100	17.2	0	100	100	(30/06/2004)
60	Slovakia	SK	**23,768**	99.9	22.3	0.1	100	100	(07/07/2004)
61	Union of Soviet Socialist Republics (USSR)		**1,159,629**	84.7	0	2.8	76.1	99.9	(10/03/1999)
62	Thailand	TH	**3**	0	0	0	0	0	(//0)
63	Tajikistan	TJ	**278**	92.8	0	0	100	100	(28/07/2003)
64	Turkey	TR	**16,668**	0	0	0	79.2	100	(23/02/2004)
65	Trinidad and Tobago	TT	**3**	100	0	0	0	100	(08/12/1995)
66	Taiwan (China)	TW	**87,967**	100	93.8	0.1	100	100	(11/01/2004)
67	United States of America	US	**7,384,459**	81.2	43.8	78.9	53.5	81.6	(27/07/2004)
68	Uzbekistan	UZ	**1**	0	0	0	100	100	(30/12/1997)
69	Vietnam	VN	**112**	42.9	0	0	99.1	100	(25/04/1997)
70	Yugoslavia	YU	**40,684**	0	0	0	94.7	100	(28/05/1992)
71	South Africa	ZA	**194,826**	99.8	0	0.1	97.3	100	(19/02/2004)
72	Zambia	ZM	**2,730**	99.7	0	0	94.1	100	(25/05/1994)
73	Zimbabwe	ZW	**2,639**	99.9	0	0	98.7	100	(11/01/1995)
1	ARIPO	AP	**1,165**	100	0	66.6	99.5	100	(30/06/2003)
2	EAPO	EA	**4,740**	93.1	79.9	0	100	100	(29/04/2004)
3	EPO	EP	**1,440,769**	100	54.7	68.2	99.9	100	(28/07/2004)
4	OAPI	OA	**11,445**	18.8	0	69.2	99.9	100	(17/05/2004)
5	WIPO	WO	**892,902**	100	81.9	93.1	99.8	100	(29/07/2004)
Total:			**36,165,421**	**52**	**11**	**15**	**82**	**93**	

Annex 4

Country and Regional Designations International Patent Application PCT/EP02/06968 (Publication Number WO03/000904)

Designated States (national); AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW; **ARIPO patent:** GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW; **Eurasian patent:** AM AZ BY KG KZ MD RU TJ TM; **European patent:** AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR; **OAPI patent:** BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG.

Country Code Explanations and National/Regional Designations

	Code	Country/ Organisation	Designation		Code	Country/ Organisation	Designation
1	AE	United Arab Emirates	Y	30	DK	Denmark	Y and EP
2	AG	Antigua and Barbuda	Y	31	DM	Dominica	Y
3	AL	Albania	Y	32	DZ	Algeria	Y
4	AM	Armenia	Y and EAPO	33	EC	Ecuador	Y
5	AT	Austria	Y and EP	34	EE	Estonia	Y
6	AU	Australia	Y	35	ES	Spain	Y and EP
7	AZ	Azerbaijan	Y and EAPO	36	FI	Finland	Y and EP
8	BA	Bosnia and Herzegovina	Y	37	FR	France	EP route
9	BB	Barbados	Y	38	GA	Gabon	OAPI
10	BE	Belgium	EP	39	GB	United Kingdom	Y and EP
11	BF	Burkina Faso	OAPI	40	GD	Grenada	Y
12	BG	Bulgaria	Y	41	GE	Georgia	Y
13	BJ	Benin	OAPI	42	GH	Ghana	Y and ARIPO
14	BR	Brazil	Y	43	GM	Gambia	Y and ARIPO
15	BY	Belarus	Y and EAPO	44	GN	Guinea	OAPI
16	BZ	Belize	Y	45	GQ	Equatorial Guinea	OAPI
17	CA	Canada	Y	46	GR	Greece	EP
18	CF	Central African Republic	OAPI	47	GW	Guinea-Bissau	OAPI
19	CG	Congo	OAPI	48	HR	Croatia	Y
20	CI	Côte d'Ivoire	OAPI	49	HU	Hungary	Y
21	CH	Switzerland	Y and EP	50	ID	Indonesia	Y
22	CM	Cameroon	OAPI	51	IE	Ireland	EP
23	CN	China	Y	52	IL	Israel	Y
24	CO	Colombia	Y	53	IN	India	Y
25	CR	Costa Rica	Y	54	IS	Iceland	Y
26	CU	Cuba	Y	55	IT	Italy	EP

	Code	Country/ Organisation	Designation		Code	Country/ Organisation	Designation
27	CY	Cyprus	EP	56	JP	Japan	Y
28	CZ	Czech Republic	Y	57	KE	Kenya	Y and ARIPO
29	DE	Germany	Y and EP	58	KG	Kyrgyzstan	Y and EAPO
59	KP	Democratic People's Republic of Korea	Y	93	SG	Singapore	Y
60	KR	Republic of Korea	Y	94	SI	Slovenia	Y
61	KZ	Kazakhstan	Y and EAPO	95	SK	Slovakia	Y
62	LC	Saint Lucia	Y	96	SL	Sierra Leone	Y and ARIPO
63	LI	Liechtenstein	N	97	SN	Senegal	OAPI
64	LK	Sri Lanka	Y	98	SZ	Swaziland	ARIPO
65	LR	Liberia	Y	99	TD	Chad	OAPI
66	LS	Lesotho	Y and ARIPO	100	TG	Togo	OAPI
				101	TJ	Tajikistan	Y and EAPO
67	LT	Lithuania	Y	102	TM	Turkmenistan	Y and EAPO
68	LU	Luxembourg	Y and EP	103	TN	Tunisia	Y
69	LV	Latvia	Y	104	TR	Turkey	Y and EP
70	MA	Morocco	Y	105	TT	Trinidad and Tobago	Y
71	MC	Monaco	EP	106	TZ	United Republic of Tanzania	Y and ARIPO
72	MD	Republic of Moldova	Y and EAPO	107	UA	Ukraine	Y
73	MG	Madagascar	Y	108	UG	Uganda	Y and ARIPO
74	MK	The former Yugoslav Republic of Macedonia	Y	109	US	United States of America	Y
75	ML	Mali	OAPI	110	UZ	Uzbekistan	Y
76	MN	Mongolia	Y	111	VN	Viet Nam	Y
77	MR	Mauritania	OAPI	112	YU	Serbia and Montenegro	Y
78	MW	Malawi	Y and ARIPO	113	ZA	South Africa	Y
79	MX	Mexico	Y	114	ZM	Zambia	Y and ARIPO
80	MZ	Mozambique	Y and ARIPO	115	ZW	Zimbabwe	Y and ARIPO
81	NE	Niger	OAPI		EA	Eurasian Patent Organization (EAPO)	Y
82	NL	Netherlands	EP		AP	African Regional Industrial Property Organization (ARIPO)	Y
83	NO	Norway	Y		EP	European Patent Office (EPO)	Y
84	NZ	New Zealand	Y		OA	African Intellectual Property Organization (OAPI)	Y
85	OM	Oman	Y				
86	PH	Philippines	Y				
87	PL	Poland	Y				
88	PT	Portugal	Y and EP				
89	RO	Romania	Y				
90	RU	Russian Federation	Y and EAPO				

	Code	Country/ Organisation	Designation		Code	Country/ Organisation	Designation
91	SD	Sudan	Y and ARIPO				
92	SE	Sweden	Y and EP				
