Intellectual Property and Molecular Biology: Biomedicine, Commerce, and the CCR5 Gene Patent

Myles W. Jackson
Caltech
New York University

Outline the Project

CCR5 gene as a heuristic tool to probe the boundaries between science and society

Biography of a scientific object (gene and its protein project)

Genes as commodities: intellectual property and molecular biology

BigPharma's use of high-throughput screening (HTS) and structure-activity relationships (SARs) to identify and synthesize small molecules as inhibitors

Genes and natural selection: resistance to disease

'Race' at the level of the DNA

Age of 'biocapitalism'

Introduction

Stephenson-Wydler Technology Innovation Act of 1980

Bayh-Dole Act of 1980

Bill Clinton's "Biotech Directive" of January 2001

The Human Genome Project

What is at stake?

The CCR 5 Story

J. Craig Venter, Wallace Steinberg, and William Haseltine: HealthCare Investment Corporation, The Institute for Genomic Research (TIGR), and Human Genome Sciences (HGS)

Yi Li and Steven M.Ruben, HGS
Human G-protein chemokine
receptor HDGNR 10: 6 June 1995

FASTA and BLAST: computer algorithms
to find sequence homologies

chemokines

Research on the Receptor

National Institutes of Health, Aaron Diamond AIDS Research Center-Rockefeller University, New York
University School of Medicine, University of Pennsylvania School of Medicine, and Dana-Farber Cancer Institute

HDGNR10 = CCR5= HIV-1 Co-Receptor

HIV-1 entry into CD4+ cells is mediated by the chemokine receptor CC-CKR-5

Tatjana Dragic*, Virginia Litwin†, Graham P. Allaway†, Scott R. Martin*, Yaoxing Huang*, Kirsten A. Nagashima†, Charmagne Cayanan*, Paul J. Maddon†, Richard A. Koup*, John P. Moore* & William A. Paxton*

* The Aaron Diamond AIDS Research Center, The Rockefeller University, New York, New York, 10016, USA
† Progenics Pharmaceuticals, Inc., Tarrytown, New York 10591, USA

The β-chemokines MIP-1α, MIP-1β and RANTES inhibit infection of CD4+ T cells by primary, non-syncytium-inducing (NSI) HIV-1 strains at the virus entry stage, and also block *env*-mediated cell–cell membrane fusion. CD4+ T cells from some HIV-1-exposed uninfected individuals cannot fuse with NSI HIV-1 strains and secrete high levels of β-chemokines. Expression of the β-chemokine receptor CC-CKR-5 in CD4+, non-permissive human and non-human cells renders them susceptible to infection by NSI strains, and allows *env*-mediated membrane fusion. CC-CKR-5 is a second receptor for NSI primary viruses.

The replication of primary, non-syncytium-inducing (NSI) human immunodeficiency virus (HIV)-1 isolates in CD4+ T cells is inhibited by the β-chemokines macrophage inflammatory protein 1α (MIP-1α), MIP-1β and regulated-upon-activation, normal T expressed and secreted (RANTES)[1–5], but T-cell line-adapted (TCLA) or syncytium-inducing (SI) primary strains are insensitive to these β-chemokines[2,3]. CD4+ T cells from some HIV-1-exposed uninfected (EU) persons resist infection with NSI strains, but can be infected by TCLA and SI strains, and lymphocytes from some EU individuals secrete high concentrations of β-chemokines[1]. The β-chemokines are proteins of relative molecular mass 8,000 (*6*, *8*). They are active on lymphocytes and monocytes by means of cell-surface receptors belonging to the family of G-protein-coupled seven-transmembrane-domain proteins[6–8]. One of these is the LESTR (also known as fusin) orphan receptor, the second receptor for TCLA HIV-1 strains[9], which is not a receptor for known β-chemokines[10].

β-Chemokines inhibit HIV-1 replication

To study how β-chemokines inhibit HIV-1 replication, we first used a virus entry assay based on single-cycle infection by an *env*-deficient virus, NL4/3Δenv, which also carries the luciferase reporter gene, complemented by envelope glycoproteins expressed *in trans*[10,11]. The use of PM1 cells, a variant of HUT-78 that supports replication of primary and TCLA HIV-1 strains, allowed comparison of *env* functions against a common cellular background[3,5]. The β-chemokines MIP-1α, MIP-1β and RANTES are most active against HIV-1 in combination[2,3], and strongly inhibited infection of PM1 cells by viruses complemented with envelopes from the NSI strains ADA and BaL (Table 1a). Individually, RANTES and MIP-1β were more strongly active than the other β-chemokines tested[2–5] (Table 1a). MIP-1α, MIP-1β and RANTES in combination did not inhibit infection of PM1 cells by the TCLA strains NL4/3 and HxB2 (Table 1a). Thus phenotypic characteristics of the HIV-1 envelope glycoproteins influence their sensitivity to β-chemokines in a virus entry assay.

EU CD4+ T cells and NSI virus entry

The *env*-complementation assay was used to assess HIV-1 entry into CD4+ T cells from two individuals, EU2 and EU3, which are exceptionally resistant to infection by NSI strains in conventional HIV-1 infection assays[1]. The cells of neither individual supported efficient entry of the NSI strain, JR-FL, but both allowed HxB2 entry; luciferase activity in cells from EU2 and EU3 after exposure to JR-FL was 300 and 200 c.p.m., respectively, compared with 5,440 and 29,560 c.p.m. from the same cells infected with HxB2. In contrast, JR-FL-infected CD4+ T cells from control individuals LW4 and LW5 produced luciferase counts of 814,670 and 77,880 c.p.m. The cells of EU2 and EU3 were therefore capable of efficiently replicating the HIV-1 genome once virus entry had been achieved. MIP-1α, MIP-1β and RANTES strongly inhibited JR-FL infection of the CD4+ T cells of LW4 and LW5, and weakly reduced HxB2 infection of both LW and EU cells (Table 1c).

To examine whether EU2 and EU3 had a generic or acquired block to infection, we isolated CD4+ T cell clones. All 21 clones from EU2 and the one clone isolated from EU3 produced high levels of β-chemokines (especially RANTES), irrespective of their Th phenotype. They were resistant to infection by the SF162 NSI strain, compared to 22 readily infectable CD4+ clones from LW4 and LW5 (Table 2). The SI variant of SF162, R3H5, was significantly more replication competent than SF162 in the EU clones, but the two strains replicated comparably in the LW clones. However, some EU clones resisted infection by both SF162 and R3H. That all the EU clones were essentially uninfectable by SF162 suggested that the mechanism of resistance had a genetic basis. One possibility was that constitutive overproduction of β-chemokines in the CD4+ T cells of EU2 and EU3 rendered them resistant to infection. Anti-β-chemokine antibodies partly abolished resistance to HIV-1 SF162 infection of CD4+ T cells from LW4 when they were co-cultured with cells from EU2 (and hence were exposed to β-chemokines secreted from the cells of EU2). However, CD4+ cells from EU2 remained resistant to SF162 infection in the presence of these antibodies (Fig. 1a), suggesting that the resistance mechanism may be more complex than an overproduction of endogenous β-chemokines.

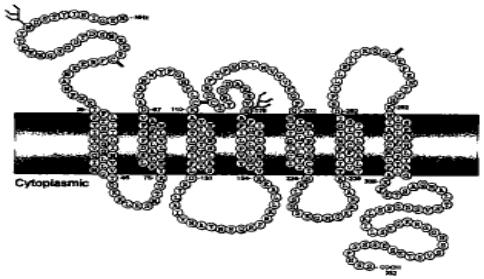
Inhibition early in HIV-1 infection

We determined when β-chemokines inhibited HIV-1 replication by showing that complete inhibition of the infection of PM1 cells required the continuous presence of β-chemokines for up to 5 h after the addition of BaL *env*-complemented HIV-1 (Fig. 1b). Pretreatment of the cells with β-chemokines for 2 or 24 h before infection had no inhibitory effect if the cells were subsequently washed before virus addition. Furthermore, adding β-chemokines

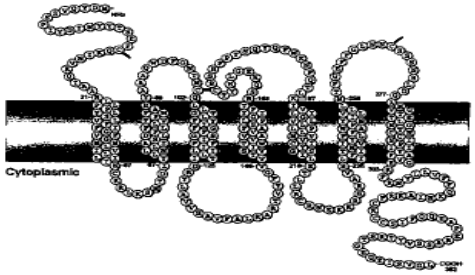
CCR 5

Figure 2

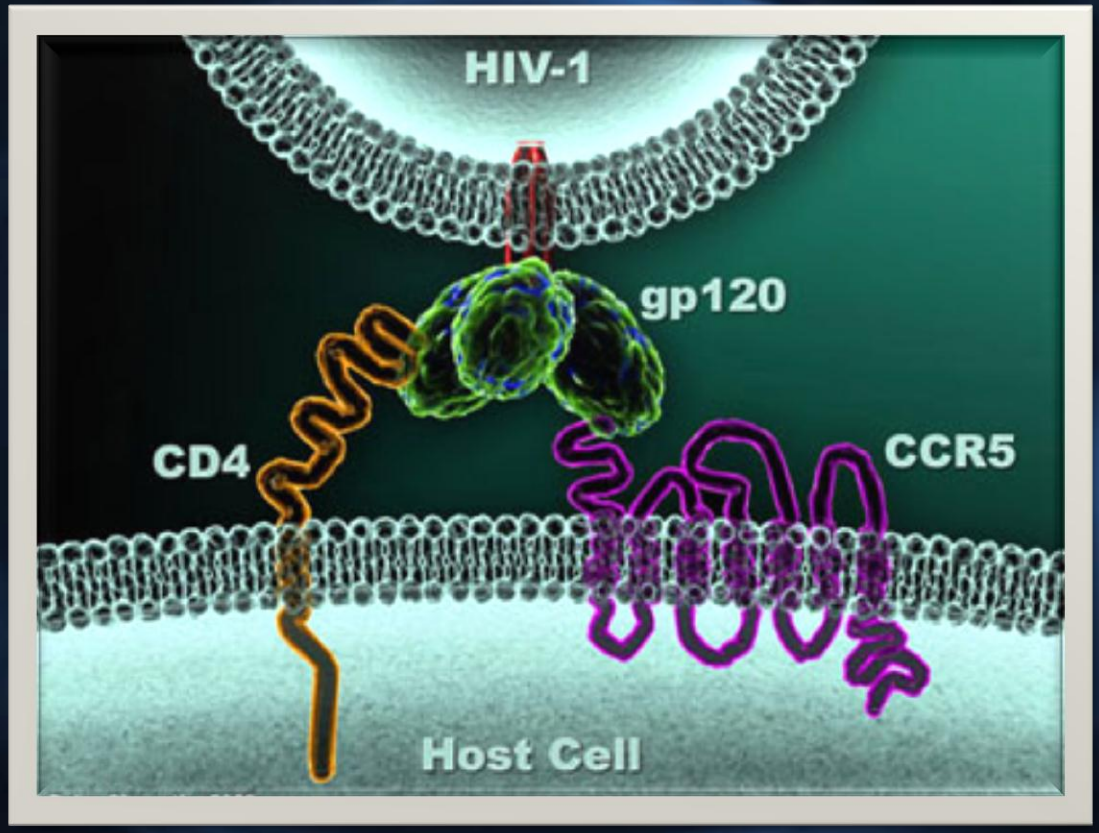
A. CXCR4



B. CCR5



Models of CXCR4 and CCR5. Reprinted with permission from Doranz, et al., 1997c.

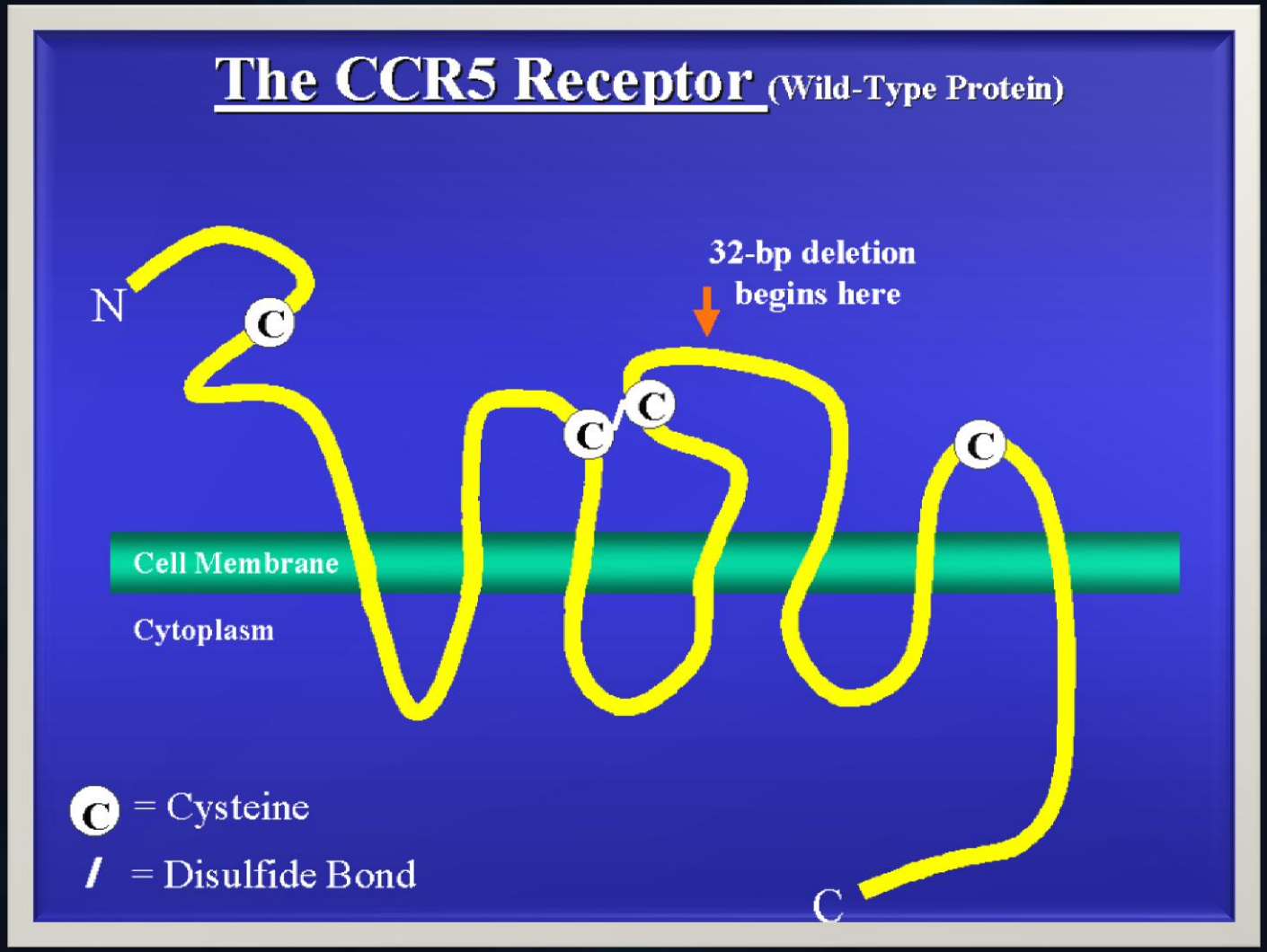

HIV-1
gp120
CD4
CCR5
Host Cell

The Brussels Group

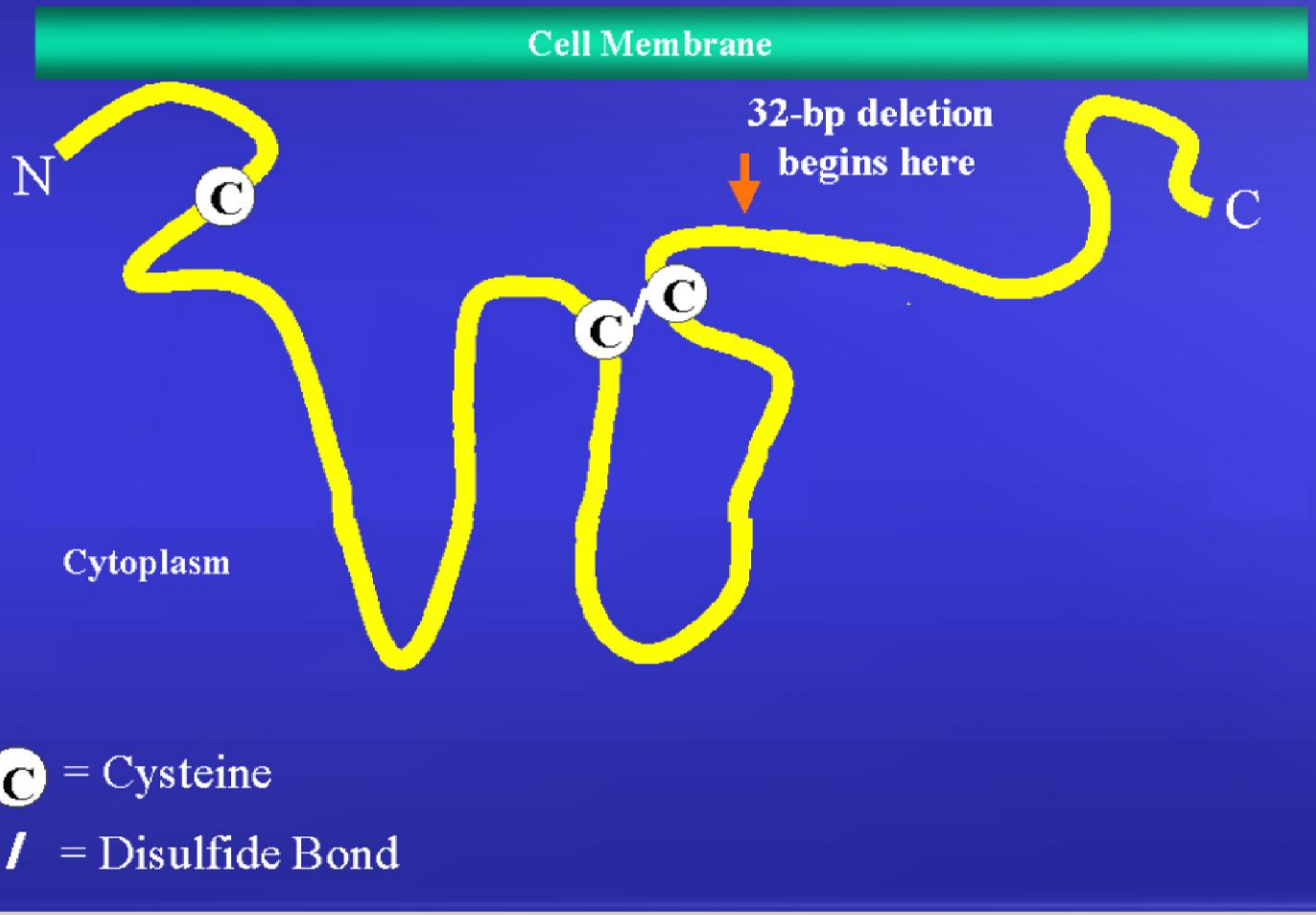
Euroscreen, Free University of Brussels, and U Penn School of Medicine:

Δ32 mutation of the CCR5 gene: those who are homozygous for this allele are (by and large) immune to AIDS

They file a patent application on the CCR5 gene and the Δ32 mutation (do not know about HGS' application). They cite HIV-1 recognition.


The CCR5 Receptor (Wild-Type Protein)
32-bp deletion
begins here
N
C
C
C
C
C
Cell Membrane
Cytoplasm
= Cysteine
= Disulfide Bond

The Δccr5 Receptor (Mutant Protein)

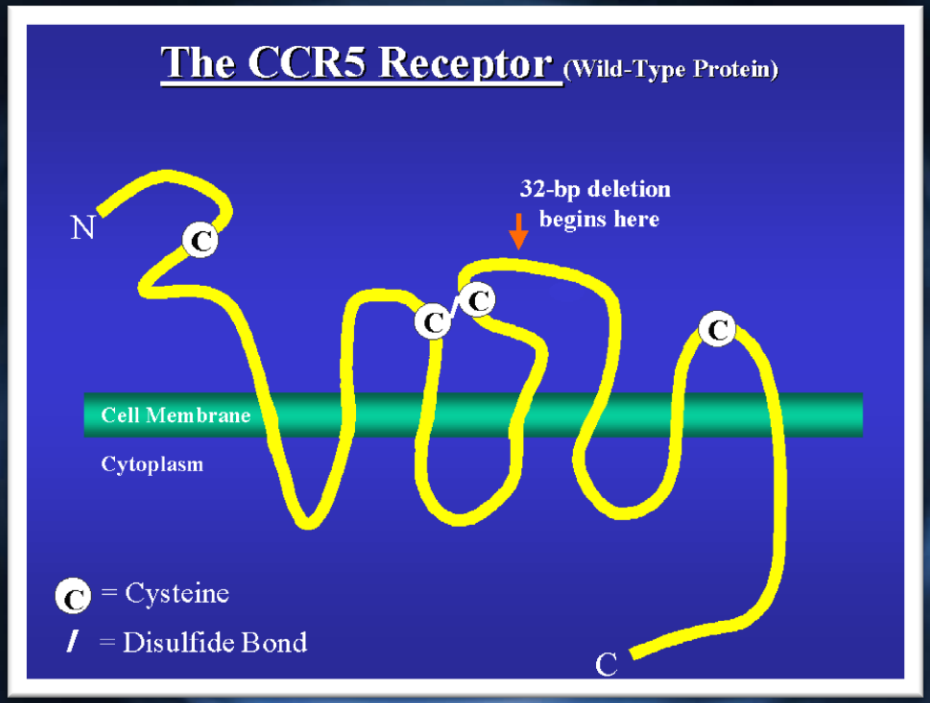


Responses to the the HGS Patent

Wall Street: HGSI stock soars over 50% in two days, nearly $1 billion in a nearly a year

Biomedical Researchers:
Robert Gallo, Dan Littman, Eric Lander

The incorrect sequence


The CCR5 Receptor (Wild-Type Protein)
32-bp deletion
begins here
N
C
C
C
C
C
Cell Membrane
Cytoplasm
= Cysteine
= Disulfide Bond

The Plot Thickens

USPTO awards the patent to HGS
on 15 February 2000

USPTO awards the patent for the same gene to
Euroscreen on 10 September 2002

USPTO awards patents for the same gene to ICOS on
24 and 31 July 2001 and 28 September 2004

CCR Patents

- CCR 1 US Department of Health
- CCR 2 Regents of the University of California
- CCR 3 Merck
- CCR 4 Glaxo
- CCR 5 HGS
- CCR 6 Schering
- CCR 7 SmithKline Beecham
- 25% of the top selling drugs worldwide regulate G-protein-receptor activity: e.g. Claritin and Prozac

CCR5 Patent : Emblematic of the Problems with Gene Patenting

- Patenting products of nature
- The relationship between written specification and the object patented
- The sufficiency of sequence homology in determining function/utility
- Broad utility patents- claims not mentioned in the patent specification

Diamond v. Chakrabarty (1980)

- "The laws of nature, physical phenomena, and abstract ideas have been held not patentable."
- "Thus, a new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter. Likewise, Einstein could not patent his celebrated law that $E=mc^2$; nor could Newton have patented the law of gravity."

USPTO, EPO, JPO Joint Communiqué of 1988

- “Purified natural products are not regarded under any of the three laws [35 U.S.C. 101] as products of nature or discoveries because they do not in fact exist in nature in an isolated form. Rather, they are regarded for patent purposes as biologically active substances and chemical compounds and are eligible for patents on the same basis as chemical compounds.” At first cDNA required (not product of nature); shortly thereafter, mere isolation suffices.
- First legal case to challenge this claim: ACLU vs. Myriad Genetics (2009)

Patenting Products of Nature

- Supreme Court decisions: products of nature are not patentable
  - American Wood-Paper Patent (1874)
  - Cochrane v. Badische Anilin & Soda Fabrik (1884)
  - Funk Bros. Seed Co. v. Kalo Inoculate (1948)

Patented Products of Nature

- Parke-Davis & Co. v. H. K. Mulford Co. (1911-12): purified adrenaline, case misinterpreted by Judge Learned Hand

Errors of Judge Learned Hand

- Initial ruling: Judge Littlewood finally agreed that Adrenalin was not a product of nature (it took 7 attempts by Parke-Davis). Patent approved in 1903
- Infringement case (H. K. Mulford Co.) 1912-13: Judge Learned Hand claimed that Littlewood agreed to a patent for a natural product.
- Hand claims that Littlewood's initial rejections were based on a misunderstanding American Wood Paper Patent
- Hand never referred to *Ex parte Latimer* (1889)
  - "Even if it were merely an extracted product without change, there is no rule that such products are patentable.

Hand admits his own befuddlement with the chemistry. U.S. should adopt the German legal system of expert judges.

Hand influences P. J. Federico, one of the architects of 1952 Patent Reform

Other cases purportedly supporting gene patents

- Merck Co. Inc. v. Olin Mathieson Chemical Company (1958): purified vitamin B_{12}: uses Hand's decision as legal precedent
- Diamond v. Chakrabarty (1980) ??!!
- Amgen, Inc. v. Chugai Pharmaceutical Co. (Fed. Cir. 1991) takes Joint Communiqué of 1988 as doctrine

Amgen, Inc. v. Chugai Pharmaceutical Co. (1991)

- "[P]urified and isolated gene sequences are different from those occurring in nature."
- "[A] gene is a chemical compound, albeit a complex one."
- Key: problem with gene patenting is the application of chemical IP to genes.

Incorrect Sequence

- 35 U.S.C. Section 112, paragraph 1: “The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art in which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.” (1952)
- Patent claim includes all nucleic acid sequences with a 70% [now 90%] or greater sequence homology! Markush series in chemistry

What about the Written Description vs. Deposit?

- Genes deposited in American Tissue Culture Collection in Virginia.
- *Guaranty Trust Co. v. Union Solvents Corp* (District of Delaware, 1931)
- *In re Argoudelis* (1970)
- Fed. Cir. 1985: "The PTO must continue to adapt its procedures to facilitate the advance of science and technology, since it is the public interest in the progress of useful arts that is benefitted as new technologies evolve." Unique and burdensome description requirements create barriers to patentability.

University of California v. Eli Lilly (Fed. Cir. 1997)

- Rat vs. human insulin cDNA: UCal Berkeley scientists claimed patents for the insulin sequences from different species, although the different sequences were not specified.
- "An adequate description requires a kind of specificity usually achieved by means of recitation of nucleotides that make up the cDNA." Therefore, no infringement by Eli Lilly, as patent was invalid.
- So, as of 1997, it appears that one needs to specify the sequence in the written description …. however, ….

Enzo Biochem, Inc. v. Gen-Prob Inc. (2002)

- US District Court of Southern New York: patent infringement on a patent on three nucleic acid sequences of bacteria. Patent's description listed the function of gene products, not their sequences. Court sides with defendant, no infringement, as patent was invalid.
- Federal Circuit Court Ruling 1 (Enzo I, citing U. Cal. v. Eli Lilly, 1997). Decision upheld.
- Federal Circuit Court Ruling 2 (Enzo II). Court redressed issue 3 ½ months later: fear of problems with thousands of gene patents with incorrect sequences. Decision overturned. So as of 2003, it seems that one does not need to cite the sequence in the specification.
- Disagreement among Federal Circuit Judges: dangerous conflation of written description (possession) and enablement
- Enzo II: Overturned, March 2010 by Federal Circuit Court of Appeals in Ariad Pharmaceuticals v. Eli Lilly and Co. The situation is rather fluid!

Sequence Homology

- USPTO Revised Interim Utility Guidelines Training Materials (1999)
- Jack Spiegel, Director of the Division of Technology Transfer & Development, NIH
- One skilled in the art needs to decide whether specific properties require experimental substantiation.
- Unpredictable vs. predictable arts: DNA vs. ‘more traditional’ chemicals

Chemical Patents Based on Structural Homology

- "A *prima facie* case of obviousness may be made when chemical compounds have very close structural similarities. Homologs (compounds differing regularly by the successive addition of the same chemical group) are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties." In re Wilder (CCPA 1977) and In re May (CCPA 1978)
- Again, basing gene IP law on chemical IP is the problem.

Broad Utility Patents

- HIV-1 recognition not mentioned in the patent: actually not a problem: chemical IP law, Jorge A. Goldstein, and John Barton

Problem with Broad Utility Patents

- National Advisory Council for Human Genome Research of the NIH criticizes 1999 Utility Guidelines of the USPTO: specifically they point to the CCR5 patent as one that should not have been granted.

- “We believe a broad allowance of claims is unjustified and will strongly discourage the further research efforts that will be necessary to translate gene discovery into medically important therapies. To avoid stifling scientific discovery and commercial application, we believe that allowances in these instances must be restricted to those utilities that are enabled by the patent.
- An example of speculative broad claims, which were in our opinion inappropriately allowed, is seen in the recently granted patent on CCR5. Based on sequence similarity, a patent was granted on a new gene that was claimed to be a putative chemokine receptor. No evidence was given to define the ligand or for any biological role for the putative receptor, but broad claims about the utility of the receptor were allowed. […] Independent of knowledge of the filing of the patent, other investigators established that CCR5 is the key co-receptor for HIV, making CCR5 a very important potential drug target. That patent taught nothing that contributed to these later important discoveries, but now the holders can dominate the field. Moreover, this broad allowance makes no concession to the discoverers of the key piece of intellectual property, namely that CCR5 is a HIV co-receptor. Allowing broad, poorly substantiated claims create, *de facto*, an unacceptable monopoly on all fields[,] which the new gene might be found to be of use.”

Problem with Broad Utility Patents

- Francis Collins and Harold Varmus: “We are very concerned with the PTO’s apparent willingness to grant broad utility claims to polynucleotides for which a theoretical function of the encoded protein based on sequence homology serves as the sole basis of the asserted utility.”

USPTO's response of 5 January 2001 to the scientists' objections

1. Name one utility, lock up all others: no change
2. Broad utility patents: increase stringency on broad utilities
3. Gene patents lack originality and ingenuity. John Sulston, "But who took the inventive step? Was it the company that made a lucky match with the right gene? Or was it the researchers who determined that HIV-resistant individuals had a defective genes?" Patentability cannot be negated by the method by which the invention was made (Patent Act of 1952).
4. Computer-base sequence homology: Aaron Klug and Bruce Alberts "a trivial matter"- does not serve science or society well. USPTO decided to judge this on a case-by-case basis. By 2002, a number of patent examiners felt that sequence homology alone should not suffice for utility claims. This was confirmed in 2007.

Conclusion

- What is the status of the CCR5 patent now?
- EPO: Strawman Ltd., Hoffmann-LaRoche AG, and Progenics Pharmaceuticals, Inc. Patent revoked December 2011
- US: effects on medical diagnostics
  - Pfizer's Selzentry (Maraviroc)
  - M- vs. T-tropic HIV-1
  - Monogram Biosciences/LabCorp test (Trofile Assay): $2,800

- Simultaneous instability of a scientific claim and a patent claim
- Role of historian in the controversy: history of patenting natural products
- Role of historian in public policy and the public understanding of science
- Much was, and still is, at stake.

- For further questions and comments, please email me at myles.jackson@nyu.edu, myles@caltech.edu