Patenting and Licensing of Research Elements and Biomedical Innovation

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www7.nationalacademies.org/step

World Health Organization
Geneva, Switzerland
September 8, 2004
Evolution of the U.S. Patent System Since 1980

• Patenting extended to
  – new technology (biotechnology)
  – technologies previously without or subject to different forms of IP protection (business methods, software)
  – upstream scientific research tools, materials, and discoveries

• Emergence of new players (universities and public research institutions)

• Position of patent holders strengthened vis-à-vis alleged infringers
  – Court of Appeals for the Federal Circuit higher validity rates from 1982
  – Major damage awards (e.g. Polaroid v. Kodak, 1991)
  – TRIPS Agreement, 1994
  – No research exemption (Madey v. Duke, 2002)

• Antitrust constraints on patent use relaxed
Changing Context of Biomedical Innovation

Patents provide important incentives for biomedical innovation, but

- Technological changes
- Policy changes
- Industry structure changes

More patenting of upstream discoveries and research tools and patenting by public research institutions and biotechnology firms
Total Biotechnology Patents Granted per Year

Source: BIO

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DNA/RNA Fragment (USPTO Class 536/23.1) Patent Grants

Note:
A. Utility and written description guidelines implemented

Source: USPTO
Initial Concerns

- Patenting of “information” encroaching on the public domain of science
- Research impeded by the practical difficulty of acquiring rights to use all of the needed patenting elements of research held by diverse parties ("anti-commons")
- Access restrictions on upstream, foundational discoveries limit subsequent discovery and improvement
- Access is possible, but on terms that make use of the inventions too costly, especially for nonprofit research performers
“Information” Patents

• Examples: at least 2 patents with claims to computer programs containing protein coordinates, but apparently at odds with USPTO guidelines (Shimbo, et al., 2004)

Questions:
• Has the line between practical invention and pure information been breached?
• If so, an aberration or a trend?
• Addressable under other standards, e.g. non-obviousness, utility?
Commissioned Study

Effects of Research Tool Patenting and Licensing on Biomedical Innovation – J. Walsh, A. Arora, and W. Cohen

70 interviews:
• 10 pharma firms, 15 biotech firms
• University personnel
• Patent attorneys, government officials, technology transfer officers
Preconditions for Breakdown Exist

- Growing number of patents
- Many biotech firms patenting
- Increase in university patenting, esp. in biotechnology
- Defensive patenting

Thus, a much more complex patent landscape
Anti-commons “Tragedies”?

• 90% of respondents say “never happens”
• Royalty stacking “manageable”
• Projects not undertaken?
  – Commercially/technically marginal projects may be affected, but
  – Mitigated by ample technological opportunities

Overall conclusion: IP is manageable
**Restricted Access?**

**Forms:**
- Exclusive licensing, exclusive use by owner, high fees

**Facts:**
- Many research tools and drug targets have limited access (50+% of university licenses exclusive)
- Licensing fees sometimes “too high” for universities and small firms, but frequently benefit from price discrimination
- Exclusivity can promote follow-on investment and commercialization
Cases with Access Issues

- NF-κB
- COX-2 Enzyme
- CD34
- OncoMouse
- Embryonic Stem Cells
- BRCA1
Clinical Use of Diagnostics Using Patented Genes

- “High” royalties can be 100% of test costs
- Diagnostic clinical tests integral to research
- But tests earn revenue for academic health centers
Overcoming the Anti-Commons and Access Restrictions

- Number of relevant patents is moderate: 1-12
- Negotiated license
  - General purpose tools are widely licensed
  - Some targets are licensed non-exclusively
- Inventing around
- Off-shore
- Patents challenged in court
- Research infringement prevalent
  - Indifference to IP
  - Presumption of a shield from liability
- Institutional response to encourage “openness”
  - NIH Research Tool Guidelines and advocacy (OncoMouse, stem cells)
  - SNPs Consortium
Research Exemption


In short, regardless of whether a particular institution or entity is engaged in an endeavor for commercial gain, so long as the act is in furtherance of the alleged infringer’s legitimate business and is not solely for amusement, to satisfy idle curiosity, or for strictly philosophical inquiry, the act does not qualify for the very narrow and strictly limited experimental use defense. Moreover, the profit or non-profit status of the user is not determinative.”
Concerns Going Forward

• Standards for patents less rigorous
• Examination quality uncertain
• No open forum for considering subject matter appropriateness
• Delayed, costly correction of USPTO errors
• Universities’ vulnerability to patent assertions and inability to perform due diligence
• Restrictions on access to “rival-in-use” foundational research tools inhibiting realization of their full potential
Recommendations

- Re-invigorate standards, esp. non-obviousness
- Increase USPTO resources, examination corps
- Institute an “Open Review” procedure
- Shield some research from infringement liability by
  - Statutory research exemption
  - Administrative action under 28 USCA Sec. 1948(a) (“authorization and consent”)
Current Study

Title: Intellectual Property in Genomic and Protein Research and Innovation

Sponsor: U.S. National Institutes of Health

Chair: Shirley M. Tilghman, chair

Roderick McKelvie, vice chair

Report due: March 2005
Charge to the Committee

Study the granting of intellectual property rights and licensing on discoveries relating to genes and proteins and the effects of these practices on research and innovation, including

- trends in the number and nature of U.S.-issued patents being granted on technologies related to genes and proteins;
- the standards the U.S. Patent and Trademark Office and other patent offices are applying;
- how the patenting and licensing of genetic and protein inventions is affecting research and innovation; and
- steps the NIH and others might take to ensure the productivity of research and innovation involving human genes and proteins.
Data Gathering

- Patent mapping of key technologies
- Licensing practices of government, PROs, and firms
- Survey of 1200-1500 investigators public and private
Categories Examined

- Categories
  - Genes and gene regulatory sequences
  - Protein structures
  - Protein-protein interactions
  - Software
  - Algorithms
  - Single Nucleotide Polymorphisms (SNPs) / Haplotypes
  - Gene expression
  - Genetically modified animals
Categories Examined

continued

• Diseases (committee and staff recommendations, reviewed by NHGRI)
  – Multiple sclerosis & arthritis
  – Breast cancer (profile only)
  – Pseudoxanthoma elasticum (PXE)

• Pathways (committee and staff recommendations, reviewed by NHGRI)
  – NF-kB
  – Vascular endothelial growth factor (VEGF)
  – Endodermal growth factor (EGF)
  – P53
  – Cystic fibrosis transmembrane conductance regulator (CFTR)
Trends in DNA patents

number of patents granted

0 100 200 300 400 500 600 700 800 900 1000 1100 1200


SNP/ Haplotype
Genes/ Gene Regulatory Sequences
Gene Expression

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Trends in protein patents

Protein structure patents

- **Protein structure**
- **Protein-protein interactions**

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Trends in disease patents

- MS/Arthritis
- Autism
- PXE

The number of patents granted for various diseases over the years from 1995 to 2003.
# Summary of Historic Trends

<table>
<thead>
<tr>
<th></th>
<th>Increasing</th>
<th>Stable</th>
<th>Declining</th>
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<tbody>
<tr>
<td><strong>DNA</strong></td>
<td></td>
<td>Genes and gene regulatory sequences</td>
<td>SNPs?</td>
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<tr>
<td></td>
<td></td>
<td>Gene expression</td>
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<td></td>
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<td>SNPs</td>
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<tr>
<td><strong>Proteins</strong></td>
<td>Protein structure</td>
<td>Protein-protein interactions</td>
<td></td>
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<tr>
<td><strong>Diseases</strong></td>
<td>Autism, MS/arthritis</td>
<td>PXE</td>
<td></td>
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<td><strong>Pathways</strong></td>
<td>NF-kB?, p53, VEGF</td>
<td>CFTR, EGF</td>
<td></td>
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<tr>
<td><strong>Tools</strong></td>
<td></td>
<td>Modified animals, Databases, Software, Algorithms</td>
<td></td>
</tr>
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</table>
Is the Plateauing Real and Continuing

• Considerations:
  – Began very recently; experience brief
  – We have only begun to look at pending applications, new submissions
  – Science and patenting “move on,” may be a transition hiatus (reflecting completion of human and other genome sequences)
  – Improvements in methods and processes
  – Patent pendency is increasing
Summary of Assignee Trends

- U.S. leads by factors ranging from 2 to 20
- “Second tier” nations
  - Canada, France, German, Japan, UK
- “Up and coming” nations
  - Australia, Belgium, Denmark, Finland, Israel, Italy, Korea, Netherlands, Spain, Switzerland, Taiwan
- Ranked order varies by field
Assignee Country Protein-Protein Interactions

Number of Patents Granted

Australia
Belgium
Denmark
France
Israel
Italy
Netherlands
Switzerland
Sweden
Germany
Japan
Canada
UK
US
# Top 5 Assignees: DNA

| Gene Expression Profiles, Genes/Gene Reg. Seq., SNPs/Haplotypes |
|-----------------|-----------------|-----------------|-----------------|
| **Univ./Inst.** | **Biotech** | **Pharma** | **Govt.** |
| University of California (181) | Incyte Inc. (125) | Pioneer Hi-Bred (110) | DHHS (USA) (55) |
| General Hospital (37) | Affymetrix Inc. (56) | Monsanto Co. (43) | MRC (UK) (11) |
| Institut Pasteur (35) | Genentech (51) | SmithKline-Beecham (29) | CNRS (France) (7) |
| Ludwig Institute for Cancer Research (34) | Perkin-Elmer Co. (46) | Aventis SA Abbott (17) | USDA (5) |
| Harvard (23) | Applera Co. (44) | Eli Lilly Amoco Becton & Dickinson (13) | |
## Top 5 Assignees: Protein

### Protein Structure, Protein-Protein Interactions

<table>
<thead>
<tr>
<th>Univ./Inst.</th>
<th>Biotech</th>
<th>Pharma</th>
<th>Govt.</th>
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</thead>
<tbody>
<tr>
<td>University of California (85)</td>
<td>Genentech (57)</td>
<td>Bristol-Myers Squibb (20)</td>
<td>DHHS (USA) (37)</td>
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<tr>
<td>General Hospital (26)</td>
<td>Immunex (32)</td>
<td>Abbott (11)</td>
<td>MRC (UK) (17)</td>
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<tr>
<td>Scripps (19)</td>
<td>Human Genome Sciences (21)</td>
<td>Bayer (9)</td>
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<td>Salk Institute Harvard (17)</td>
<td>Chiron (18)</td>
<td>Aventis SA (8)</td>
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<tr>
<td>Yale (13)</td>
<td>Millenium (13)</td>
<td>Boehringer-Manheim Rohe Schering (7)</td>
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</table>
# Top 5 Assignees: Disease

## MS/arthritis, PXE, Autism

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<th>Biotech</th>
<th>Pharma</th>
<th>Govt.</th>
</tr>
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<tbody>
<tr>
<td>University of California (4)</td>
<td>Chiron Co. Incyte (2)</td>
<td>Bristol-Myers Squibb (10)</td>
<td>DHHS (USA) (1)</td>
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<tr>
<td>General Hospital (3)</td>
<td>Syntex Amgen (1)</td>
<td>Merck &amp; Co. (7)</td>
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<tr>
<td>University of Kansas (2)</td>
<td></td>
<td>Vertex Pharma (5)</td>
<td></td>
</tr>
<tr>
<td>University of Alabama Michigan State University of Texas CNRD (France) (1)</td>
<td>Pfizer (4)</td>
<td>Pharmacia &amp; Upjohn (3)</td>
<td></td>
</tr>
</tbody>
</table>

**Of note:**
- NO pharma/biotech presence in PXE
- NO govt. activity in PXE/autism

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# Top 5 Assignees: Pathways

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<th>Pharma</th>
<th>Govt.</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Texas (14)</td>
<td>Genentech (23)</td>
<td>Bristol-Myers</td>
<td>DHHS (USA) (11)</td>
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<tr>
<td></td>
<td></td>
<td>Squibb/Merck &amp; Co. (8)</td>
<td></td>
</tr>
<tr>
<td>University of California (12)</td>
<td>Sugen Inc. (12)</td>
<td>Agouron Pharma (6)</td>
<td>MRC (UK) CNRS (France) (2)</td>
</tr>
<tr>
<td>Johns Hopkins University (8)</td>
<td>Transgene SA (7)</td>
<td>Aventis SA (5)</td>
<td></td>
</tr>
<tr>
<td>Cold Spring Harbor Laboratory (6)</td>
<td>Genzyme/Imclone (4)</td>
<td>Abbott Labs (4)</td>
<td></td>
</tr>
<tr>
<td>Ludwig Institute for Cancer Research (5)</td>
<td>Tularik Inc. (3)</td>
<td>Novartis (3)</td>
<td></td>
</tr>
</tbody>
</table>

**Of note:**
- NO biotech presence in p53
- NO govt. activity in VEGF
### Top 5 Assignees: Tools

#### Animal, Algorithms, Software, Databases

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<th>Pharma</th>
<th>Govt.</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of California (35)</td>
<td>Affymetrix Inc. (63)</td>
<td>Cytokinetica (38)</td>
<td>DHHS (USA) (5)</td>
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<tr>
<td>University of Texas (17)</td>
<td>DeKalb Genetics (50)</td>
<td>Pioneer Hi-Bred (27)</td>
<td>Japan Sci and Tech Corp. (3)</td>
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<tr>
<td>Johns Hopkins University (11)</td>
<td>Agilent (20)</td>
<td>Eli Lilly (11)</td>
<td>CNRS (France) (2)</td>
</tr>
<tr>
<td>Columbia University (8)</td>
<td>Millenium Pharma (12)</td>
<td>Pfizer (4)</td>
<td>Riken (2)</td>
</tr>
<tr>
<td>Baylor Medical College (6)</td>
<td>Harris Moran Seed Co. (7)</td>
<td>Regeneron Pharma (3)</td>
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