

Stanford Law School

Current Issues Surrounding the Non-Obviousness Doctrine

John Fitzgerald Duffy, George Washington University Law School

Robert P. Merges, UC Berkeley Boalt School of Law; Berkeley Center for Law and Technology

Brian P. Barrett, Eli Lilly and Company

Arti K. Rai, Duke Law School

Moderator: Jane M. Love, WilmerHale

The Future of the Invention Standard

John F. Duffy

Oswald Symister Colclough Research

Professor of Law

George Washington University Law School

Timing Theory and Obviousness

- Fundamental Paradox: “If the new, valuable innovation were obvious, why was it not created before?”

Timing Theory and Obviousness

- Fundamental Paradox: “If the new, valuable innovation were obvious, why was it not created before?”
- Two solutions:
 - The invention was nonobvious.
 - Something happened just prior to the innovation that made it obvious or valuable.

Timing Theory and Obviousness

- Money in the street paradox: If it is so easy to see and pick up money lying openly in a street, how can it still be there?
 - It's been dropped **recently**.
- Ob – via: Latin – “in the street.”

Timing Theory and Obviousness

- Obvious, valuable innovations have either just become valuable or just become obvious.
- Thus, in every case of obviousness, it should be possible to identify relatively recent “exogenous” changes (changes other than the inventive work of the patent applicant) that are responsible for rise of the innovation.

Does a Timing Approach Explain the Cases?

- KSR – yes.
- Hotchkiss v. Greenwood – almost certainly.
- Graham v. John Deere – yes.
- United States v. Adams – yes.
- Almost every other case too.

In re Kubin

- Sambrook et al., *Molecular Cloning: A Laboratory Manual* (1989) – basic cloning and sequencing technologies.
- Valiante et al., U.S. Patent No. 5,688,690 (filed Sept. 16, 1994; issued Nov. 18, 1997) – discloses protein that “is the same protein as NAIL.”
- Kubin application filed September 20, 2000. DNA sequences encoding NAIL.

In re Kubin

- But ...

Because of NAIL's important role in the human immune response, the Board further found that "one of ordinary skill in the art would have recognized the value of isolating NAIL cDNA, and would have been motivated to apply conventional methodologies, such as those disclosed in Sambrook and utilized in Valiante, to do so."

Kubin, ___ F.3d at ___ (quoting the BPAI).

- Why three - six years? Is this a long or short time?

Does a Timing Approach Have Doctrine Support?

- Yes, it is similar to, though more theoretically rigorous than, the current use of “secondary considerations” (what used to be called “objective considerations”).
- If courts become less certain that any particular verbal formulation of the legal standard supplies a good test, they will naturally turn to secondary considerations to judge obviousness.
- The approach is closest to that taken by Learned Hand in his obviousness / inventive step cases.

Learned Hand's "History of the Art"

- From *Bresnick v. U S Vitamin Corp.* (Hand, J.):
 - We have repeatedly said that in judging whether a new combination is an invention, we regard **the history of the art** as of much greater importance than our own untutored judgment as to what advances demand imaginative originality in specialized fields. Nothing can be less reliable than our naive impressions based upon gross appearances; the books never tire of warnings against them. [W]e should resort to them only when all other means have failed.

Learned Hand's "History of the Art"

- From *Bresnick v. U S Vitamin Corp.* (Hand, J.):
 - In the case at bar the history of the art very clearly indicates that the problem of preserving and masking vitamins derived from fish-livers was no different from that of doing the same to those derived from vegetables, or from mammalian livers. Certainly nothing suggests any difference. Yet even so, had the art waited long for the step (especially if there had been intermediate unsuccessful efforts) and if the step, when made, had been an answer for which the art had been looking, we might have yielded. That was not the situation. The interval was short; it was not filled by a single unsuccessful effort The history of the art assures us that the disclosure was an obvious and valueless variant of a well-known process.

Judge Posner (2009)

- From *Ritchie v. Vast Resources* (Posner, J.):
 - [A]n invention that has commercial value is likely to come on the market very shortly after the idea constituting the invention ... became obvious; if the invention did not appear so soon despite its value in the market, this is some evidence that it wasn't obvious after all.
 - But ...
 - Among the inventions that the law deems obvious are those modest, routine, everyday, incremental improvements of an existing product or process that confer commercial value (otherwise they would not be undertaken) but do not involve **sufficient inventiveness** to merit patent protection.

Biotechnology Nonobviousness: Back to Basics

Prof Robert Merges

UC Berkeley

- **In re Kubin, 561 F.3d 1351 (Fed. Cir. 2009)**
- **Held: “[T]his court determines that the Board had substantial evidence to conclude that appellants used conventional techniques, as taught in Valiante and Sambrook, to isolate a gene sequence for NAIL.” – 561 F.3d at 1366.**

- **Natural Killer (“NK”) cells, thought to originate in the bone marrow, are a class of cytotoxic lymphocytes that play a major role in fighting tumors and viruses. NK cells express a number of surface molecules which, when stimulated, can activate cytotoxic mechanisms. NAIL is a specific receptor protein on the cell surface that plays a role in activating the NK cells.**

The claim

73. An isolated nucleic acid molecule comprising a polynucleotide encoding a polypeptide at least 80% identical to amino acids 22-221 of SEQ ID NO:2, wherein the polypeptide binds CD48.

In other words, appellants claim a genus of isolated polynucleotides encoding a protein that binds CD48 and is at least 80% identical to amino acids 22-221 of SEQ ID NO:2-the disclosed amino acid sequence for the CD48-binding region of NAIL.

The prior art

- **Regarding obviousness, the Board rejected appellants' claims over the combined teachings of U.S. Patent No. 5,688,690 (“Valiante”) and 2 Joseph Sambrook et al., Molecular Cloning: A Laboratory Manual 43-84 (2d ed.1989) (“Sambrook”).**

- **Valiante: P38 receptor on NK cells**
- **Valiante teaches that “[t]he DNA and protein sequences for the receptor p38 may be obtained by resort to conventional methodologies known to one of skill in the art.”**

- The Board found as a factual matter that appellants used conventional techniques “such as those outlined in Sambrook” to isolate and sequence the gene that codes for NAIL. Id. The Board also found that appellants' claimed DNA sequence is “isolated from a cDNA library ... using the commercial monoclonal antibody C1.7 ... disclosed by Valiante.” Id. With regard to the amino acid sequence referred to as SEQ ID NO:2, the Board found that

Valiante's disclosure of the polypeptide p38, and a detailed method of isolating its DNA, including disclosure of a specific probe to do so, i.e., mAb C1.7, established Valiante's possession of p38's amino acid sequence and provided a reasonable expectation of success in obtaining a polynucleotide encoding p38, a polynucleotide within the scope of Appellants' claim 73. (See Valiante, col.7, l.48 to col.8, l.7.)

- **Insofar as Deuel implies the obviousness inquiry cannot consider that the combination of the claim's constituent elements was “obvious to try,” the Supreme Court in KSR unambiguously discredited that holding. In fact, the Supreme Court expressly invoked Deuel as a source of the discredited “obvious to try” doctrine.**

**KSR INTERNATIONAL CO. v.
TELEFLEX INC.**

127 S.Ct. 1727 (April 30, 2007)

When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability.



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Boult Hall
School of Law
University of
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Merges, “*Uncertainty and the Standard of Patentability*,” 7 [Berkeley] High Tech. L.J. 1 (1993).

35 U.S.C. §103

**Non-Obviousness Is Critical to a Good Patent,
*But of No Necessary Relevance to Whether a
Molecule Can Ever Become a Good Medicine***

Brian P. Barrett, Associate General Patent Counsel
Eli Lilly and Company

BIO/PhRMA Industry Background

- Scientific discoveries often build on prior art discoveries and inventions often use common building blocks (atoms, amino acids, nucleic acids, chemical/biological reactions, cells lines, vectors, salts, formulation excipients).
- Prior art is generated daily - a multitude of structurally diverse molecules are tested against disease targets (often computer generated and tested), suggestions from scientists to change the “building blocks” to alter molecular activities, etc.

Background (cont.)

- Patent applications are often filed on structural changes to prior art molecules designed to alter activity - improve medical efficacy, reduce a side effect, improve product formulation or delivery, etc.
- A company tests thousands of molecules for activities against disease targets; some molecules advance to testing in animal models; a few may advance to a decade of clinical testing; and if all goes well after about \$1B is spent, an approved medical therapy may result.

Background (cont.)

- Fewer than half of approved products provide a positive return on their R&D investment.
- An approved “drug” may get 3-5 years of data protection (DP – the period of time a copied product cannot be approved based on an innovator’s data – a copy must undergo the “full testing” imposed on the innovator).
- Biologics currently have unlimited DP.

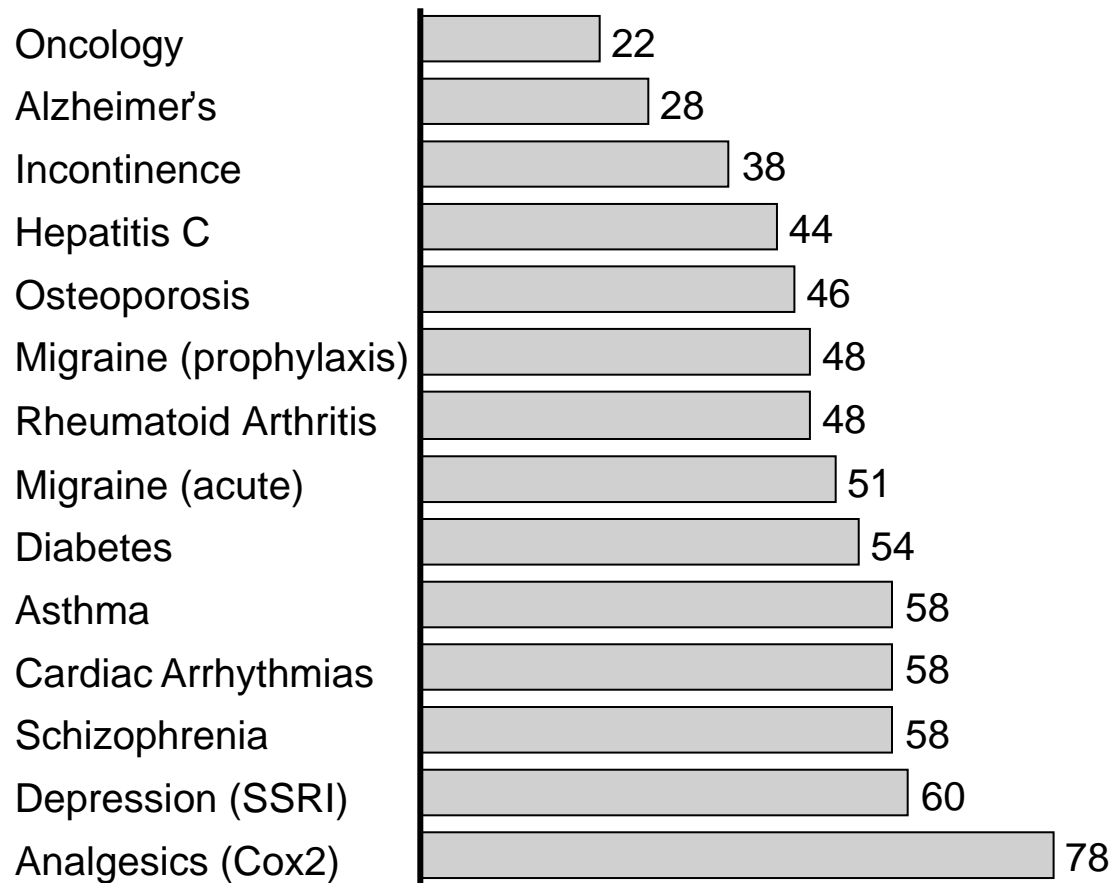
Background (cont.)

- 3-5 years of DP is commercially meaningless.
- If patent protection exists, research on the molecule continues after approval - secondary indications, dose regimens to target individual patient needs or improve safety, formulations to improve dosing frequency or to enable an intravenous medicine available orally.
- Public disclosure of innovation also stimulates further research on other molecules to the same target or to better treat patients with the same or similar condition.

Unmet Medical Needs Continue to Exist

Average response rate* to current drug treatments
Percent

McKinsey&Company



Low response rates to existing treatments

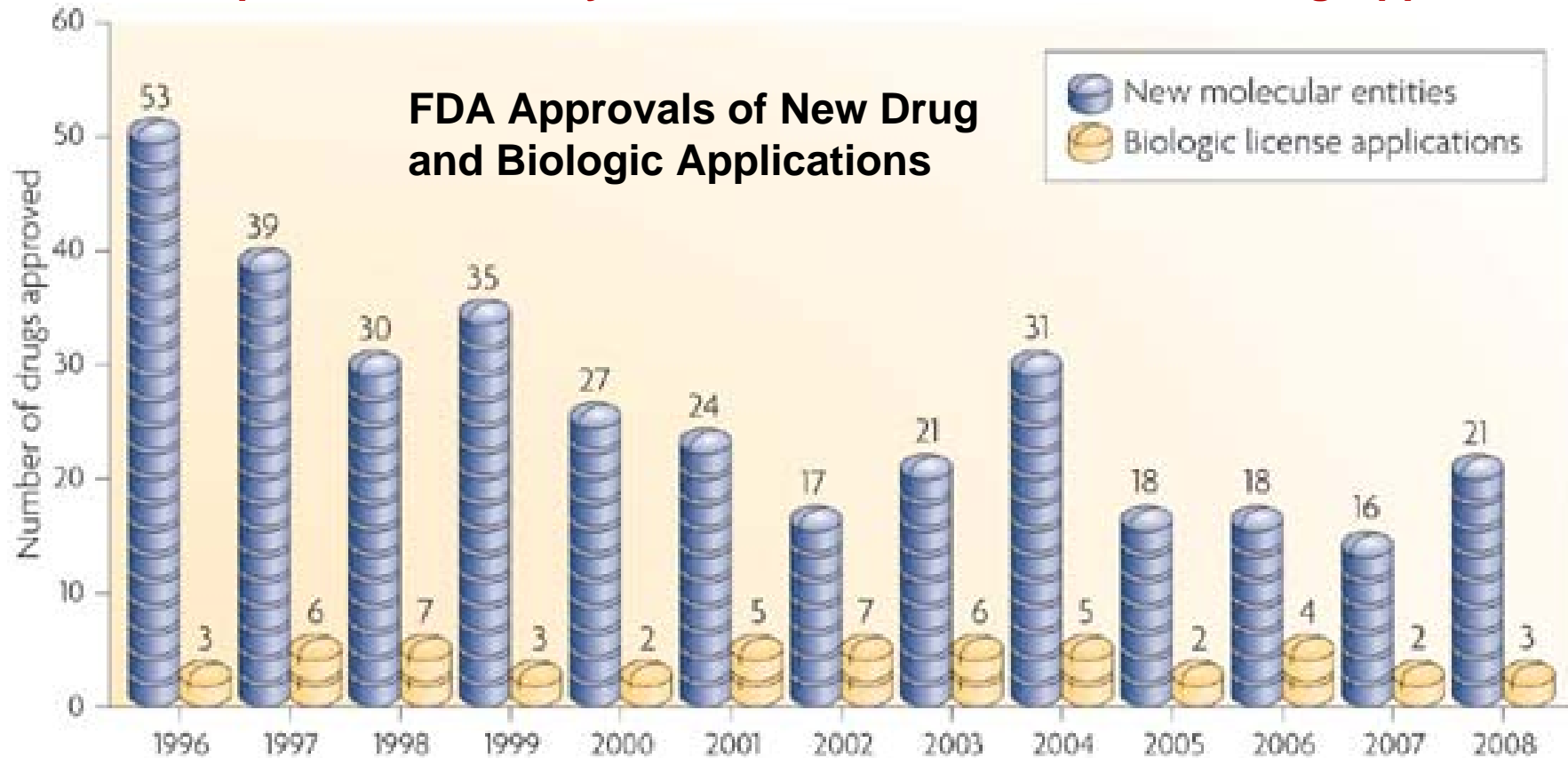
Continued unmet needs even where response rates are high

Many conditions (e.g., cancer, Alzheimer's) remain largely unsolved

*% of patients that achieve a clinically significant response (definition of response varies by disease state) at steady state (e.g., several courses of therapy)

Source: Paul Waring, Genentech; Felix Frueh, CDER; Parexel R&D Statistical Sourcebook 2007/2008

R&D is Expensive and Risky and Fewer New Products are Being Approved



\$50 Billion Annual Industry R&D Produces Two Dozen New Medicine Approvals Each Year

Nature Reviews | Drug Discovery

http://www.nature.com/nrd/journal/v8/n2/fig_tab/nrd2813_F1.html

Background (cont.)

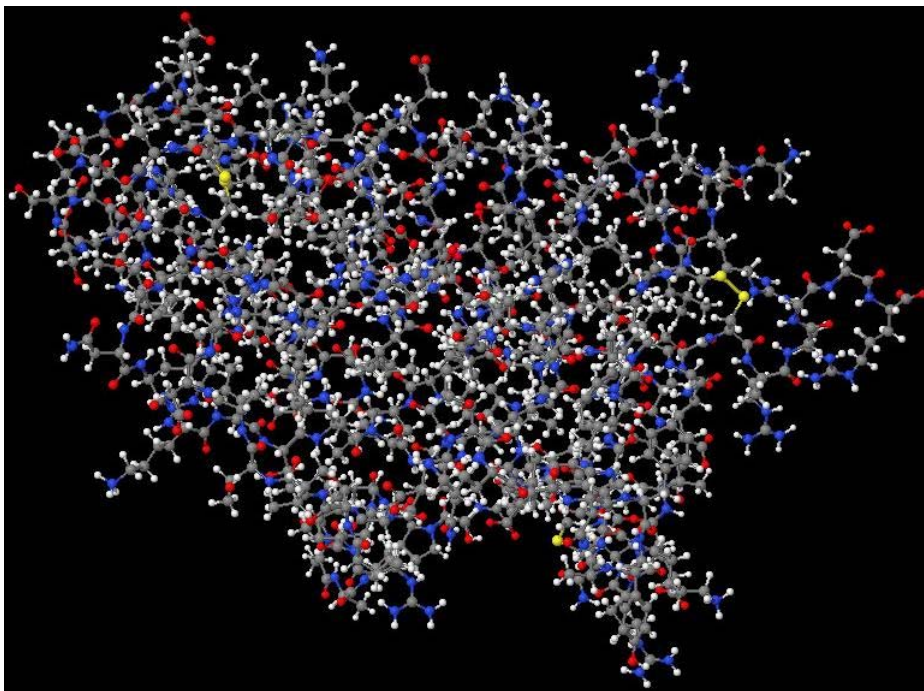
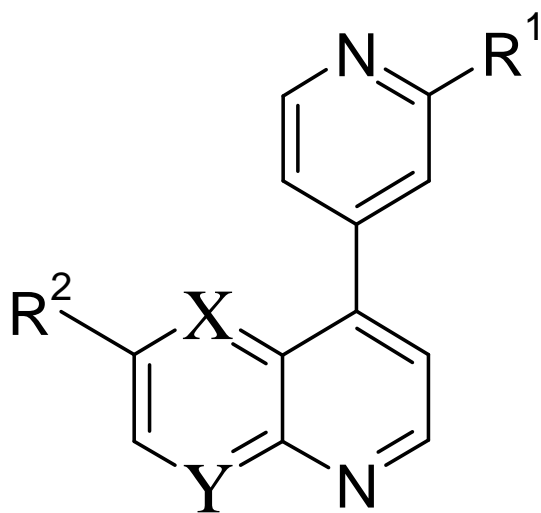
- Four (4) years after FDA approval, generic ANDA filings and patent attacks begin – all relevant patents protecting the product will be challenged – many based on alleged obviousness and inequitable conduct – an 180-day generic exclusivity period serves as the bounty.
- Primary patents provide a greater chance of surviving multi-million dollar generic patent challenges.
- Patent challenges drastically slow or stop further R&D spending until there is greater certainty on exclusivity because absent patent protection, generics will completely overtake the market. Generics may also “launch-at-risk” before a final patent decision.

Background (cont.) - A Typical Scenario

- A company scientist discloses to a patent attorney a molecule having good activity in a test (in vitro or animal model) indicative of disease, or the molecule is disclosed (with or without data) to a company by a 3rd party seeking financial and R&D assistance.
- The “patent” question is the same – **will there be enough exclusivity in view of the nearly certain early generic patent attack to justify the R&D risk and financial investment?**

Typical Scenario (cont.)

- Prior art searches often identify structurally similar molecules, and the patent attorney considers the POSITA when advising whether the company should develop the molecule.



What a Patent Attorney Considers Re §103

- Obviousness determinations are complicated - no case provides a key to the legal test.
- The conclusion requires *an expansive and flexible approach* that depends on *Graham* factors.
- *Where appropriate*, secondary considerations may prove instructive.
- The POSITA is expected to use common sense, make inferences and be creative.
- Any need or problem known in the field can provide a POSITA reason to combine elements of an invention.

Patent Attorney Considerations (cont.)

- If a POSITA can implement a *predictable* variation, §103 likely bars its patentability.
- The combination of familiar elements according to known methods is likely to be obvious when it only yields *predictable* results.
- Obvious-to-try might show an invention was obvious when there are a finite number of identified, *predictable* solutions.
- Obviousness does not require absolute predictability of success - a *reasonable* expectation of success will do.
- A POSITA in the chemical and biotech arts is likely well educated, has practical experience, and has access to a lot of prior art.

Patent Attorney Considerations (cont.)

- FDA testing requirements, improving common problems, improving human health, and/or \$\$ may provide at least general motivation to solve a known problem.
- It may be generally known how to at least try to tackle common problems - substitute certain atoms or amino acids, formulation excipients, identify 1 isomer with the best or worst activity, etc.
- “Drug” molecules – although the teaching *need not be explicit*, it is necessary to identify a reason a POSITA would have modified a known compound to arrive at the claimed invention.
- A lot of \$\$ and lawyering will continue to go into why a POSITA would or would not have started with a particular Lead molecule and/or modified a prior art molecule.

Patent Attorney Considerations (cont.)

- Isomers-beware, perhaps a finite number of choices, FDA provides motivation to resolve isomers, resolution techniques often within a POSITA's grasp, and 1 isomer is expected to have superior properties - even 18X more potent than any other. *Aventis v. Lupin*
- DNA molecules-beware, if the protein is in the prior art (even if not isolated or sequenced) and there is nothing difficult about isolating the DNA. *Kubin*
- Salts or optimization of ranges/variables—beware, district court non-obviousness determination overturned for a claim to 1 salt in view of a “small” number (53) because the evidence “easily satisfies us” a POSITA “would have been motivated to combine the prior art teaching to produce the besylate salt” and a POSITA “would have had a reasonable expectation of success” *Pfizer v. Apotex*

Patent Attorney Considerations (cont.)

- Substantial evidence of secondary considerations may be insufficient to overcome a legal conclusion of obviousness. *Leapfrog; Boston Scientific; Aventis*
- Structurally similar compounds are presumed to have similar properties - finding an unexpected property is critical. *Papesch, Chupp*
- To properly evaluate whether a superior property was unexpected, the court must consider what properties are expected. *Apotex*

Practical Considerations

- Obvious determinations remain very fact/case specific and unpredictable – what does POSITA know, what would he do given the unique facts, how creative is he, what would he find obvious to try, and what property or level of activity would he expect?
- Primary patent protection (the molecule in the bottle) is more important than ever.
- Should be better if the problem solved by the claimed invention isn't disclosed to the POSITA. *Chapman v. Casner* (J. Rader's dissent)
- When a specific problem is known in the field, chances are there will be an incentive (\$\$ or health need) to solve it, so a claimed solution better be unpredictable to a POSITA.

Practical Considerations (cont.)

- Applicants should understand the prior art very well before filing.
- Understand both sides of the litigation arguments - why the POSITA would/wouldn't have arrived at the claimed invention.
- Narrow claims may be easier to prosecute (provide evidence of an unexpected property).
- It may be better if the prior art teaches away from the Lead. *Takeda v. Alphapharm*
- When the art is close, be prepared to submit declarations that will survive litigation attacks questioning every word and data point.
- The more relevant, significant and unexpected a compound's property, the better.

Practical Considerations (cont.)

- More declarations will mean even more inequitable conduct allegations and even more costly litigation.
- More likely to dispute who a POSITA is – the more educated, the more creative.
- Summary judgments may be more common – other than a “relevant” secondary consideration, other *Graham* factors aren't often disputed in molecule cases.
- Obvious-to-try will be alleged more, especially for optimization inventions – did a POSITA consider the art to provide a *finite number of predictable* solutions?

Bottom Line – POSITA's Influence on Medicine

- A patent attorney's view of our highest Court's cases involving knobs, plow blades, and pedal assemblies is critical to which medicines are developed for patients' most critical medical needs.
- What will POSITA (a patent examiner, district court judge or appellate panel) think of a prior art change (methyl, ethyl, halogen, 1 or 2 amino acids) or whether a property was expected when considered at a remote point in time (perhaps in 10-15 years)?
- Is there a better way to encourage innovators to pursue the best medicines, not just medicines with the best patent protection?

Suggestion – Provide Meaningful Data Protection

- There is no correlation between what a POSITA would know or expect and FDA standards.
- The vast majority of non-obvious (patented) molecules will fail the FDA tests for safety and effectiveness for human use.
- Safe and effective medicines, including breakthrough innovations, often fail the technical and uncorrelated standards for patentability – under §103 or otherwise.

Meaningful Data Protection (cont.)

- A long-lived patent covering a molecule will not yield a great medicine.
- However, the safety and efficacy data defining the patients for whom the medicine may be uniquely beneficial defines what makes a great new medicine.
- Data protection—reduces the role of a POSITA and may provide a better incentive for high risk R&D for medical breakthroughs.

Potential Benefits of Meaningful Data Protection

- Help ensure the best potential medicines get into clinical development – not just those with the best patent protection
- Greatest unmet medical needs can be more frequently studied
- Fullest and most complete use can be studied for new medicines
- Predictable generic entry after DP expiry
- Optimizes opportunity for return on R&D investment
- Medicines can be developed without a need for long and strong patents and expensive patent challenges

When DNA Is No Longer Special:

What's Old and New in Life Sciences
Obviousness

Arti K. Rai

Duke Law School & Center for Public
Genomics

Old and New

- *Largely old*: application to non-genomic technologies (especially small molecules)
- *Quite new*: application to genomic technologies (DNA's informational content recognized)

Small Molecules

- Standard strategy: start with promising structure for problem, try variations that may yield desirable results
- *Compare KSR*: “Where there is . . . [a] need . . . to solve a problem and there are a *finite number of identified, predictable solutions*, a [POSITA] has good reason to pursue the known options”
- *Post-KSR*: was structural starting point obvious; was number of variations finite and (reasonably) predictable

Strong similarity to chemical *prima facie* test

- *In re Dillon* (1990): 1) structural similarity between claimed and prior art subject matter; 2) prior art gives reason to make claimed variation
 - See also *In re O'Farrell* (1988) “reasonable expectation of success” standard (i.e. where variation has reasonable expectation of success, can be obvious)

Takeda v. Alphapharm (2007)

- Patented diabetes drug is variation of prior art “compound b”
- Lourie: *KSR* does not change *Dillon*’s prima facie test
- Prior art as a whole would **not** have led person of ordinary skill to compound b (prior art said compound b was toxic and increased brown fat)
- Also, prior art did not suggest patentee’s changes to compound b (replacing ethyl group with methyl, switching position)

Ortho-McNeil Pharmaceutical v. Mylan (2008)

- M's argument: small, finite number of options for epilepsy drug (topiramate)
- Rader → M failed to demonstrate:
 - person of ordinary skill would have used starting point, even for diabetes drug;
 - Would have chosen among unpredictable alternatives;
 - would have stopped when drug intermediate for unrelated properties
- Secondary considerations

Ex Parte Whalen (2008)

- Pharmaceutical composition capable of embolizing aneurysm at vascular site
- Improvement → higher viscosity
- Examiner: POSITA would have optimized viscosity to achieve safest clinical outcome
- BPAI: examiner had not demonstrated why those skilled in the art would have *increased* viscosity (references suggested lower viscosity was desirable)

In sum (small molecules)

- Impact on core composition of matter patents may not be high
 - Perhaps more “battles of the experts” on level of skill in the art, what would be reasonably predictable
- Some impact on other patents
 - Especially for PIs, when combined with *Ebay* in cases where there is no automatic 30-month stay

Genomics

- Where “new world of obviousness” may have greater bite
 - “Research Tools”
 - Diagnostics
 - Therapeutics

Genomic Technologies: Old Learning

- *In re Deuel*
 - Main holding: methods are not prior art for DNA sequence claims
 - Formalistic test
 - “Obvious to try” issue noted in passing
 - Much criticized (well before *KSR!*) for blanket exclusion of certain prior art
 - E.g., Rader dissent in *In re Fisher*

New Learning: Kubin

- cDNA claim to Natural Killer Activation Inducing Ligand (NAIL)
 - Receptor that, when bound (here by CD48 protein), can stimulate cytotoxicity
 - cDNA claim: “isolated nucleic acid molecule comprising a polynucleotide encoding a polypeptide at least 80% identical to amino acids 2-221 of SEQ ID NO:2, wherein the polypeptide binds CD48”

Kubin

- BPAI and CAFC decisions both stress importance of *factual* findings regarding what prior art would teach (subject to deferential review post *Zurko*)
- BPAI picks up on *KSR* criticism of “obvious to try”
- Rader notes compatibility of *KSR* with *In re O’Farrell*
- Does not reach 112 issues (*Deuel* and 112)
 - *But* see Linn concurrence in *Ariad v. Eli Lilly*

Impact

- Not necessarily “NAIL in the Coffin” for DNA patents
 - Kubin *per se* is “old school” DNA sequence identification (Cook-Deegan and Rai 2009)
- But a threat
 - Genomic research tools → role of patents mixed (small firms vs. large firms)
 - Mendelian DNA diagnostics → role of patents unclear (Chandrasekharan et al. 2009) (vs. IVDMIAs)
 - Therapeutics (!!)

Is “prospecting” bad for therapeutic innovators?

- Prospect theory: patent system should allow early patents so as to prevent races, induce development
- Therapeutics a celebrated application
- But this means obviousness is judged early (and by wrong standard?) – Rai 2008)
 - FDA-administered exclusivities for therapeutics (Roin 2009) (revocable pre-approval exclusivity to get advantages of prospecting?)
 - Already have various data exclusivities

Therapeutics: A Perfect Storm?

- *Kubin*
- “Generic” biologics legislation with limited data exclusivity (e.g. Waxman bill)
- Mandated substitution of generics by insurers

On the other hand . . .

- May not have many true “generic” biologics
 - “Innovation ecosystem”: therapeutic-specific regulation (FDA regulation plus health insurance) provides protection for therapeutic innovator (Rai 2008)
- Perhaps genomics patents will be broader (a NAIL in the coffin for written description?)
 - In follow-on biologics debate, innovator biologics firms have argued scope too narrow

In sum . . .

- DNA is no longer special (and other life sciences tech never was)
 - Informational content of DNA more important than “structure” (Art Unit 1631)
- Results for innovation are a mixed bag
- But important to see whole “innovation ecosystem,” not just patents