Patent Seminar Barcelona, Sept. 29, 2003

Screening Methods and Research Tool Patents

- selected topics -

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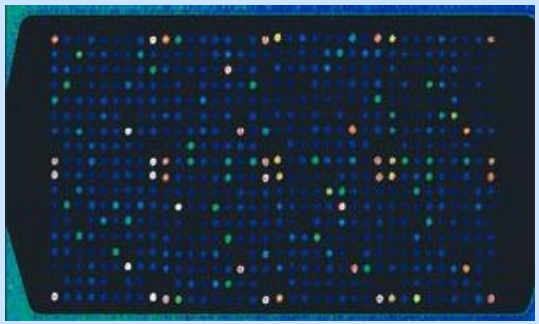
Talk Outline

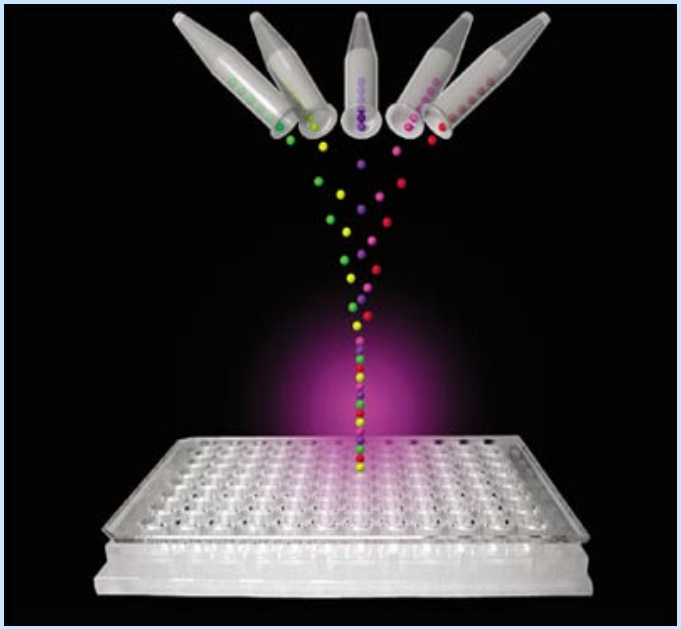
- Patentability of Screening Method / Research Tool Patents
  - EPO Practice – Case Study EP 0 624 100 B1
  - Claim Drafting
  - Sufficiency of Disclosure
- Enforcement of Screening Method / Research Tool patents
  - *Housey* vs. *Bayer* - EP 0 403 506
  - Research Exemption
  - Scope of Protection

Quantum Leaps in Synthesis

Miniaturization and Automatization

- Combinatorial Chemistry
- High Throughput Screening
- Parallel Analysis/Sequencing

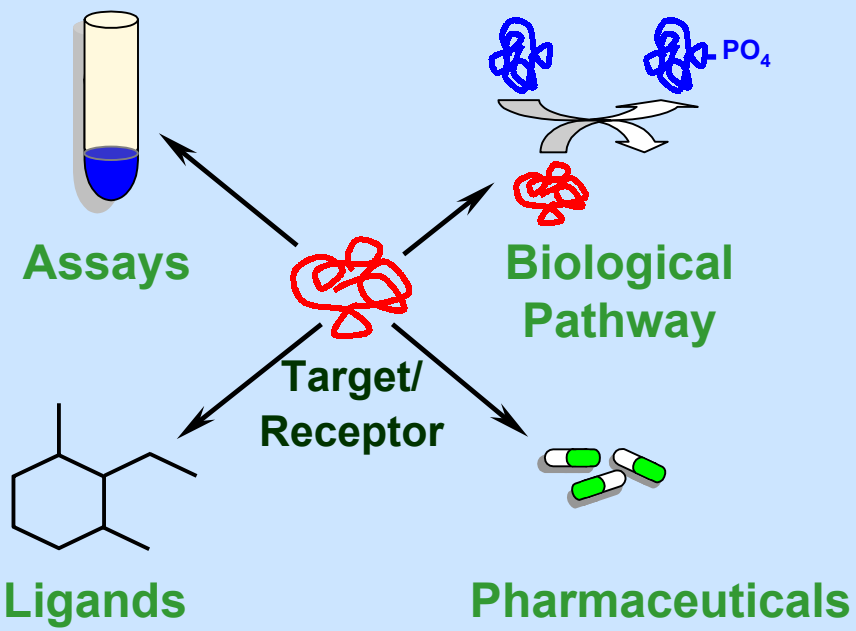




Research Tools

Research Tools aim at Biochemical Targets

- Eukaryotic Transcription Factors
- Nuclear Receptors
- Ligands of Orphan Receptors
- Development of Cell Cycle
- Control of Metabolic Pathways
- Activity is ligand-dependent



Screening Method Patent

- Selection and Characterization of Receptor Modulators
- High-Throughput Screening
- Structure-based Drug Design
- Virtual / *in silico* Screening
- Reach-Through to Active Ingredients

EPO Case Study: EP 0 624 100 B1

- "DNA Encoding a Human Serotonin Receptor (5-HT 4B) And Uses Thereof"
  - Applicant: Synaptic Pharmaceutical Corp. Paramus, N.J., USA
  - Date of Filing: 29.10.1993
  - Grant of Patent: 03.05.2000
  - **No Opposition Filed !**

EP 0 624 100 B1 – Claims (i)

47. A process for ***identifying*** ***a chemical compound which specifically binds to a 5-HT4B receptor***, […] which comprises contacting non-neuronal cells expressing on their cell surface the 5-HT4B receptor […] with the chemical compound ***under conditions suitable for binding***, and ***detecting*** specific binding of the chemical compound to the 5-HT4B receptor.

EP 0 624 100 B1 – Claims (ii)

48. A process *involving competitive binding* for identifying a chemical compound which *specifically binds* to a 5-HT4B receptor, […] which comprises *separately* contacting non-neuronal cells […] with the chemical compound and *a second chemical compound known to bind to the 5-HT4B receptor*, […], and *detecting* […] the decrease in the binding of the second chemical compound […] in the presence of the chemical compound *indicating that the chemical compound binds to the 5-HT4B receptor*.

EP 0 624 100 B1 – Claims (iii)

49. A process for *determining* whether a chemical compound specifically binds to and *activates a 5-HT4B receptor*, […] which comprises […] *measuring the second messenger response* in the presence and in the absence of the chemical compound, a *change* in the second messenger response […] *indicating that the chemical compound activates the 5-HT4B receptor*.

EP 0 624 100 B1 – Claims (iv)

50. A process for *determining* whether a chemical compound specifically binds to and *inhibits a 5-HT4B receptor*, […] which comprises […] *measuring the second messenger response* […], a smaller *change* in the second messenger response […] *indicating that the chemical compound inhibits activation of the 5-HT4B receptor*.

EP 0 624 100 B1 - Screening Method (i)

- What is the screening aimed at?
  - ***Identifying*** a chemical substance that specifically ***binds*** to the receptor
  - ***Determining*** a substance that ***activates*** the receptor
  - ***Determining*** a substance that ***inhibits*** the receptor

EP 0 624 100 B1 - Screening Method (ii)

- ***Identifying a binding substance***:
  - *Functional language* (under conditions *suitable* for binding chemical compound)
  - Involving competitive binding
  - *Comparison* of measured results (second messenger response)
  - Specific result (decrease in second messenger response) *indicates* that compound binds specifically to receptor

EP 0 624 100 B1 - Screening Method (iii)

- ***Determining a modulator***:
  - *Comparison* of measured results (second messenger response)
  - Specific result (change in second messenger response) *indicates* that compound is an ***activator*** of receptor
  - Specific result (smaller change in second messenger response) *indicates* that compound is an ***inhibitor*** of receptor

EP 0 624 100 B1 – Claims (v)

65. A method of *preparing a pharmaceutical composition* which comprises *obtaining* a chemical compound, *identifying* a chemical compound as one which specifically binds to a 5-HT4B receptor according to the method of any of claims 47, 48, 49 or 50, and *admixing* the compound with a pharmaceutically acceptable carrier.

EP 0 624 100 B1 – Pharmaceutical Composition (i)

- Process of ***Manufacturing*** a Product:
  - ***Scope of Protection*** extends to product immediately obtained by manufacturing process
  - Actual ***process steps*** (obtaining compound; admixing carrier) are not defined
  - ***Active ingredient*** (chemical compound) identified by screening method

EP 0 624 100 B1 – Claims (vi)

66. A process of *obtaining a chemical compound* which comprises *identifying* a chemical compound which specifically binds to a 5-HT4B receptor according to the method of any of claims 47, 48, 49 or 50, and *preparing* the chemical compound.

EP 0 624 100 B1 – Chemical Compound

- Legal Validity - Sufficiency of Disclosure
  - Skilled person must be in a position to manufacture chemical compound that has been identified by screening method just relying on his common general knowledge
  - NOTE: Identification of compound does not necessarily provide sufficient information to manufacture it (e.g. structural formula)!

EP 0 624 100 B1 – Claims (vii)

38. A ***pharmaceutical composition*** comprising an amount of a ***substance*** *effective to alleviate the abnormalities resulting from* ***over-expression*** *of a human 5-HT4B receptor*, wherein the […] *receptor* has an amino acid sequence […] encoded by the nucleic acid of claim 1 to 3 […].

EP 0 624 100 B1 – Claims (viii)

39. A ***pharmaceutical composition*** comprising an amount of a ***substance*** *effective to alleviate the abnormalities resulting from* ***under-expression*** *of a human 5-HT4B receptor*, wherein the [...] receptor has an amino acid sequence [...] encoded by the nucleic acid of claim 1 to 3 [...].

EP 0 624 100 B1 – Pharmaceutical Composition (ii)

- Disease to be treated characterized by functional features relating to underlying biochemical mechanism:

  Over / Under-Expression of receptor

- Patentable in the view of T241/95 „Serotonin Receptor / ELI LILLY“?
  - Decision issued (14.07.2000) after grant
  - Medical condition must be a *“real life disease”*

EP 0 624 100 B1 – Pharmaceutical Composition (iii)

- Support in the description:
  - Patent discloses receptor and manufacture thereof
  - Patent discloses method of detecting expression of receptor in tissue
  - Patent discloses method of determining the physiological effects of expression varying levels of receptor (by creating a non-human transgenetic animal)
  - Patent gives concrete examples of compounds and diseases
- ***Sufficient to comply with Art. 83 EPC?***

Legal Questions resulting from EP 0 624 100 (i)

- What is the **result** of a screening method: ***product*** *or* ***information?***
  - If it is a ***product***, does scope of protection also extend to products ***identifiable*** by said screening method ("*Reach-Through Claim*")?
  - If it is ***information***, does including trivial process steps turn the claim into a true ***process of manufacture*** claim?

Legal Questions resulting from EP 0 624 100 (ii)

- If the claim is directed to a ***cell-based*** method of identifying a modulator of a target:
  - Is claim infringed if activity of substance was ***known*** before testing?
  - Is claim infringed if activity was known only ***in vitro*** and is now verified ***in vivo***?
  - Is claim infringed by activity verification during ***drug optimization***?

Legal Questions resulting from EP 0 624 100 (iii)

- If the claim is directed to a *cell-based* method of identifying a modulator of a target:
  - Is claim infringed by determination of ***degree of purification*** of mixtures of many substances (vs. screening of many individual substances)?
  - Is claim infringed if screening method itself is ***established*** (e.g. verification that cloning of recombinant cell line was successful using known modulator)?

Legal Questions resulting from EP 0 624 100 (iv)

- If the claim is directed to a ***cell-based*** method of identifying a modulator of a target:
  - Can alleged infringer use the defense that screening method was ***not enabled***?
  - Method not able to distinguish between
    - an **activator** or ***inhibitor***
    - a ***specific*** or ***non-specific*** modulator

EP 0 403 506 B1 – Claim 3 (i)

3. Method of *determining whether a substance is an inhibitor or activator of a protein* whose presence in a cell line evokes a *phenotypic characteristic* other than the level of said protein in said cell per se, which comprises:
   […]

EP 0 403 506 B1 – Claim 3 (ii)

[…] which comprises:

(a) providing a *first cell line* which *overproduces* said protein and exhibits said phenotypic response to the protein;

(b) providing a *second cell line* which produces the protein at a lower level than the first cell line, or does not produce the protein at all, and which exhibits said phenotypic response to the protein to a lesser degree or not at all;

EP 0 403 506 B1 – Claim 3 (iii)

[…]

(c) incubating the first and second cell line with the substance; and

(d) *comparing* the phenotypic response of the first cell line to the substance with the phenotypic response of the second all line to the substance.

Product of Screening Method (i)

- **BAYER AG vs HOUSEY PHARMACEUTICALS**

  Infringement under 35 U.S.C. §271(g)

  - Whoever without authority imports into the US […] a ***product which is made by a process patented*** in the US shall be liable as an infringer […].
  - A product which is made by a patented process will […] not be considered to be so made after
    (1) it is ***materially changed by subsequence processes***; or
    (2) it becomes a ***trivial*** and ***non-essential component of another product***.

Product of Screening Method (ii)

- **Decision of Fed. Circuit 02-1598 (22.08.03)**
  - Scope of protection is limited to ***physical goods*** that were manufactured
  - Does not include ***information generated by a patented process***
  - Does not include ***importation of a product*** that has been ***identified by the screening method outside*** the US
  - ***Congress*** should expand statute if court is wrong in their interpretation

Claim Construction (i)

- **Phenotypic Characteristic**
  (Interpretation of US District Court):
  - ***Observable trait*** **of a cell**
  - **Does not include characteristics of a *temporary* or *transient* nature (e.g. levels of concentration of ions or other chemical substances)**
  - **Preferably „*cultural*“ or „*morphological*“ characteristics as stable, non-transient traits**

Claim Construction (ii)

- US position may ***not*** be followed by German Court:
  - Phenotypic response may be **every effect** which is somehow affect by target
    - Efflux of ions through an ion-channel protein
    - Level of product catalyzed by an enzyme, even if of transient nature
      (level of second messenger cGDP)

Arguments in German Litigation (i)

- **Defendant:**
  - Method of Identifying whether a substance is an inhibitor or activator of a POI is not infringed if it was *known before* that substance had this activity
- **Plaintiff:**
  - Method proves whether a substance that may be known as an inhibitor or activator in vitro shows also this activity *in vivo*

Arguments in German Litigation (ii)

- **Defendant:**
  - To verify that establishment of a recombinant cell line was successful, a substance known for its activatory or inhibitory activity was used – *no method of determining* whether a substance is a ***modulator*** of a POI
- **Plaintiff:**
  - All claimed method steps are used

Arguments in German Litigation (iii)

- **Defendant:**
  - Where an actual screening is described, ***no second cell line*** (control cell) is used
- **Plaintiff:**
  - Comparison with second cell line ***not obligatory for each substance tested***, only when substance is tested positive with first cell line

Arguments in German Litigation (iv)

- **Defendant:**
  - **Establishment of recombinant cell line is in any case excluded from infringement by *experimental use exemption***
- **Plaintiff:**
  - **In the actual screening assay several thousand substances have been tested**

Hatch-Waxman Act 1984

- Patent Term Extension
- ANDA Filing (Abbreviated New Drug Application)
- Research Exemption (§ 271(e)(1) of 35 U.S.C)
  - Designation of compound as a candidate for FDA approval is sufficient to invoke the exemption

US Case Law: *Integra vs. Merck*

- Decision of Fed. Circuit 2003 WL 21299492 (06.06.2003):

  Is drug discovery reasonably related to FDA approval processes?

  - ***No*** drug was identified by plaintiffs
  - Plaintiffs activities to drug hunting only a purely speculative process of "***general biochemical experimentation***"

Arguments in German Litigation (v)

- **Defendant:**
  - **Third party cannot evaluate whether claim is infringed or not because claimed method is not enabled, i.e. cannot distinguish between *specific* or *non specific* inhibition / activation**
- **Plaintiff:**
  - **Plaintiff / Opponent did only make arguments based on plausibility, but *did not provide experimental evidence***

Outlook

- *Housey* vs. *Bayer* to be decided by end of October 2003 (1. instance LG Düsseldorf)
- Applicants will come up with more sophisticated claim language in research tool / screening method patents
- Some limited reach-through claims may be granted
- Attitude of Infringement Courts remains to be seen

End of Talk

THANK YOU FOR YOUR ATTENTION !