Contemporary Discovery Research Processes and Strategies: Avoiding Risks, Collaborating, and Finding Success

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Purdue Pharma LP, Cranbury NJ
Presentation Outline

• About Purdue Pharma

• Current Purdue pain and CNS research interests

• How pharma companies evaluate academic research

• Productive alliances between pharma and academia
Global coverage across 4 regions and 45 independent affiliated companies in 87 countries

Capabilities that span the globe:
- Global capabilities, customized with local knowledge
- Regional ability to fully develop and commercialize products

Proven performance:
- Worldwide sales of ~$4 billion
- Active in 87 countries

Consensus driven governance:
- Business heads report to the Boards of Directors
- Global strategies require agreement from all business heads

Asia Pacific, Latin America, and Middle East / Africa
Purdue’s Flexible Interests in External Relationships

- Late-stage asset acquisition
- Strategic alliance
- Joint venture
- Start-up equity
- Early stage research funding

- Purdue is opportunistically interested in deals from any stage of development
External Scouting at Purdue

Complementary to Internal Research With a Common Goal of Broadening the Development Pipeline & Enhancing Innovation
Virtual Discovery: Our Approach

Three Step, Science-Led Process

<table>
<thead>
<tr>
<th>(1) Science evaluation</th>
<th>Detailed scientific analysis including past, present, &amp; future directions</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2) Landscape analysis</td>
<td>Cross reference the science with 3 key measures of research success</td>
</tr>
<tr>
<td></td>
<td>(1) Institutional Funding</td>
</tr>
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<td>(2) Applied &amp; Issued Patents</td>
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<tr>
<td></td>
<td>(3) Peer-Reviewed Publications</td>
</tr>
<tr>
<td>(3) Strategic actions</td>
<td>(1) Create a “watch-list”</td>
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<td>(2) Create a “contact-list”</td>
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<td>(3) Negotiate collaborations &amp; other deals</td>
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Many of the most prescribed psychiatric drugs target older mechanisms.
## CNS Diseases: Current & Future Mechanisms of Interest

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<th>Target Class</th>
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<th>2000’s</th>
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<td>VMAT2</td>
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<tr>
<td>OTHER</td>
<td>α-synuclein</td>
<td></td>
<td>LRRK2</td>
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<tr>
<td>KINASE</td>
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### Latest Research
- Significant research funding, patents, and publications are directed towards α-synuclein aggregation, LRRK2 inhibition, TAAR1 inhibition, and VMAT2 inhibition.
- TAAR1 activation modifies DAT function and localization
- VMAT2 regulates loading of neurotransmitter into vesicles
- α-synuclein aggregation is a signature of most Lewy bodies
- LRRK2 mutation is the most common cause of familial and sporadic PD
# CNS Diseases: Current & Future Mechanisms of Interest

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<th>Discovery by Decade</th>
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## Latest Research
- Significant research funding, patents, and publications are directed towards **α-synuclein** aggregation, **LRRK2** inhibition, **TAAR1** inhibition, and **VMAT2** inhibition.
LRRK2 Funding by Institution & Investigator
2011-2015

NIH, NSF, MJF-funded research activities
Molecules, diagnostics, animal models, mechanisms

TOP 5 NIH-funded institutions
Johns Hopkins
UCLA
University of Alabama
Harvard
University of Minnesota

Immediate contacts & watch-list
Identification of KOLs
Cross-reference with USPTO & publications
LRRK2 US Patents & Applications
2012-2014

Top 10 Patent Holders

(1) Roche  (6) Factor Bioscience
(2) Merck  (7) Genosco
(3) Origenis (8) Lundbeck
(4) Elan    (9) Ipsen
(5) Glaxo  (10) Oncodesign

- Significant competition in big pharma
- Mergers & acquisitions already taking place
- Company “IP turf” identified & monitored

LRRK2 Intellectual Property Landscape

NEW Pharmaceutical (2011)
US Patent 8,791,112 (Sept. 2014)
NEW-1104: IND studies in progress/complete?

Competitive area, but there are opportunities!
Neuropathic Pain MOAs Overlap With CNS Diseases and Represent Targets of Significant Interest

Anticonvulsants & anti-depressants are the most common drugs for neuropathic pain
## Existing Treatments for Neuropathic Pain

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<th>Example(s)</th>
<th>Published Mechanism(s)</th>
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<td>Amitriptyline</td>
<td>Na_v, Ca_v, NMDA, sigma 1, Muscarinic, 5HT/NE reuptake inhibitor</td>
</tr>
<tr>
<td></td>
<td>Cymbalta</td>
<td></td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Carbamazepine</td>
<td>Na_v, GABA, L-type calcium channel, α2δ subunit</td>
</tr>
<tr>
<td></td>
<td>Gabapentin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lyrica</td>
<td></td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td>Phenytoin</td>
<td>Na_v</td>
</tr>
<tr>
<td>Spinal infusions &amp; Other</td>
<td>Ziconotide</td>
<td>Ca_v 2.2, mu / kappa opioid</td>
</tr>
<tr>
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<td>Opioids</td>
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<td>Local Anesthetics</td>
<td>Lidocaine</td>
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- Mechanisms are validated in man but existing drugs are sub-optimal.
- New pharmacological approaches to these proven targets may produce enhanced treatments.
- Risk of POC failure within this class is significantly lower than with other proposed mechanisms, unproven in man.
# Neuropathic Pain Mechanisms of Interest

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| Tricyclic Antidepressants       | Amitriptyline               | Na
, Ca
, NMDA, sigma 1, Muscarinic, 5HT/NE reuptake inhibitor                           | PAM/NAM Allostery                    |
| Anticonvulsants                 | Carbamazepine               | Na
, GABA, L-type calcium channel, α2δ subunit                                         | Subunit Selectivity                  |
|                                 | Gabapentin                  |                                                                                      | Subtype Selectivity                  |
|                                 |                             |                                                                                      | Biased Ligands                       |
|                                 |                             |                                                                                      | State Dependency                     |
|                                 |                             |                                                                                      | Indirect Modulation                  |
| Antiarrhythmics                 | Phenytoin                   | Nav                                                                                 |                                      |
| Spinal infusions & Other        | Ziconotide                  | Ca
 2.2, mu / kappa opioid                                                            |                                      |
|                                 | Opioids                     |                                                                                      |                                      |
|                                 |                             |                                                                                      |                                      |
|                                 |                             |                                                                                      |                                      |
|                                 |                             |                                                                                      |                                      |
| Local Anesthetics               | Lidocaine                   | Na
                                                                        |                                      |
Considerations While Interfacing With Pharma

Internal Pharma Assessment Processes
Stage-Dependent Strategies for Evaluation of In-Licensed Programs & Assets

### DISCOVERY RESEARCH

**STRATEGY: “PLAY THE FIELD”**
- Want excellence in science & high caliber staff, board members, academic integration, with high degree of skill in the field.
- Want novelty in the approach, FTO, IP & evidence of ability to compete.
- Want access to pipeline as the “target concept” matures over time.
- Want a strong front-runner POC molecule.

### CLINICAL DEVELOPMENT

**STRATEGY: “CHERRY PICK”**
- Want an excellent, low risk molecule, IP, FTO, with strong data-driven evidence supporting advancement in the pipeline.
- Want an acceptable competitive landscape
- Want a suitable backup molecule.
- Want favorable market & a fail-fast strategy.

**Mechanistic target & experimental molecules maturing over time**
- **TARGET SELECTION** ➔ **LEAD DISCOVERY** ➔ **LEAD OPTIMIZATION** ➔ **IND-ENABLING**

**Specific molecule advancing on it’s own merits**
- **PHASE 1 CLINICAL** ➔ **PHASE 2 CLINICAL** ➔ **PHASE 3 CLINICAL** ➔ **LAUNCH**
Typical Pharma Process and Major Milestones
Preferred Drug Target Check-List

- MOA is validated in man *via* experimental or commercial drugs or genetics
- Validation in animals using various techniques/models
- Proper & proven anatomical placement and regulation of target expression in disease
- “Druggable” target (selectivity & potency are feasible/proven)
- Acceptable competitive landscape
- Known target-mediated physiological or behavioral safety risks are acceptable
Typical Pharma Process and Major Milestones

Expectations by Stage

- A proposal to pharma that leads from target checklist, then shows data to meet expectations by stage is more likely to progress to a higher value deal.

**Synthetic scalability**
**Intellectual property strength**
**Off-target risks (Cerep screen)**
**Drug-Drug interaction risks**
**hERG inhibition**
**Metabolite formation**
**Stability**
**Efficacy in animal model(s)**

**Rodent & non-rodent PK/TOX**
**NOAEL versus ED$_{50/80}$ (TI)**
**Safety margins (most sensitive species)**
**Commercial/Medical indication(s)**
**Human dosing form**
**Analytical references synthesized**
**Analytical methods validated**
Typical Pharma Process, Major Milestones, and Synergies With Academia

**DISCOVERY RESEARCH**
- Target Selection
- Lead Discovery
- Lead Optimization

**CLINICAL DEVELOPMENT**
- DC
- IND
- IND-Enabling
- Phase 1 Clinical
- Phase 2 Clinical
- Phase 3 Clinical
- NDA
- Launch

Research expertise typical in pharma & academia

Regulatory/drug safety/CMC expertise typical in Pharma

Clinical expertise typical in Pharma & academia but international regulatory/marketing experience typical in pharma

External relationships extend the scope of Pharma
Summary

• Purdue is a science-led, outward-facing R&D company with broad therapeutic interests & global capabilities.
• Our external early-stage scouting is currently focused on CNS diseases, pain, and possible mechanistic intersections between them.
• We appreciate that academic research represents a life’s work and our goal is to find the path(s) forward to maximize the chance of success.
• We appreciate that student education and exposure is integral in the academic process and we create opportunities to facilitate that in our collaborations.
• Understanding the expectations that pharma has for new drug development can effectively guide your research process and strategies toward successful relationships.
• There are many complementary skills between pharma and academia such that healthy collaborations should be fruitful and efficient.
• Cultural differences, for example “publish-or-perish”, stage-gated milestones, and time-bounded objectives can be overcome for mutual benefit.