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July 26, 2018 @ 3-3pm ET
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Pitfalls and Promise of Central Nervous System Drug Discovery
Session 6 of the 2018 Drug Design and Delivery Symposium

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What We Will Discuss in the Webinar

1) **What constitutes the CNS and why is CNS drug discovery so difficult**

2) **Categories of targets for drug discovery in the CNS** (types of diseases and conditions)

3) **What has happened to CNS drug discovery programs over the last 2 decades**

4) **Notable failures and successes**

5) **What has changed/is changing that should increase interest in CNS targets**
Drug Discovery is Very Difficult

- Pharmaceutical industry among the most heavily regulated

- As of Dec., 2013, only **1500 drugs** (new molecular entities, or NMEs) had been approved by the FDA since its creation in 1938, and only a handful had been developed prior to this.

- Failure rates for drug candidates at the pre-clinical stage is **>99%**, from **Phase 1 >90%**. This varies by discipline, with CNS drugs failing at a higher rate than most other areas. Successes in the CNS area are dominated by psychiatric drugs.

- Drug discovery is expensive. Tufts study suggests **~$1B and >12 years to market**. This cost estimate is probably inaccurate, but it’s expensive. The time required from benchtop to bedside has been improved where possible, but long timelines are anathema to activist investors.

- The CNS is a particularly difficult organ system.

**The Central Nervous System**

*not shown: retina, cranial nerves, olfactory system*
The Central Nervous System as a Drug Target

• Ultimate targets are usually **neurons and glia**, primary cells of the CNS
  Billions of neurons, many different types, numerous functional regional differences.

• Many **different neurotransmitter systems** with specific receptors, hormonal systems, many voltage-gated and ligand-gated ion channels and ion pumps, enzyme systems, and metabolic pathways.

• Complexity of biology means **diseases may affect many different systems**

• For many conditions similar disease phenotypes may result from very **different underlying pathologies**

• **Neurons, for the most part, do not regenerate**. Function that is already lost to disease may not be re-attained even with successful drug treatment

• Difficult to get drugs into the brain

• **Behavior is easily affected by drugs that enter CNS**; this can be therapeutic, or a negative side-effect

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The Blood-Brain Barrier

• Formed by capillary endothelium in most brain regions, exclude hydrophobic compounds and pathogens

• Specific transporter systems (mediated by p-glycoprotein) also exist to exclude specific lipophobic compounds and toxins

• Excludes nearly all large molecule therapeutics and greater than 95% of small molecule drugs

• Significant barrier to development of CNS drugs

• Often require highly lipophobic compounds in order to circumvent BBB

• Different barriers determine entry into and out of the cerebrospinal fluid and the retina
CNS Diseases and Conditions

- **Genetic/Developmental Disorders**: Fragile-X, Tourette’s, Seizure disorders of infancy (e.g. MMPSI), Autism. Many other CNS disorders have some degree of genetic linkage (e.g. neurodegenerative disorder cohorts, schizophrenia).

- **Degenerative** (e.g. Huntington’s, Alzheimer’s, Parkinson’s, ALS, MS and other neuromuscular disorders)

- **Psychiatric** (e.g. schizophrenia, depression, anxiety, ADHD…)

- **Infectious Diseases** and their sequelae (e.g. meningitis, encephalitis…)

- **CNS Injury** (e.g. TBI, spinal trauma, ischemic and hemorrhagic stroke, epilepsies…)

- **Pain Syndromes** including migraine (include central and peripheral components)

- **Brain Cancers** (e.g. glioma)

- **Addiction**

If you live long enough, you will almost certainly exhibit some form of CNS disorder or condition
Can you think of a single CNS disease or indication that has been adequately treated by existing therapy?

Despite many clinical attempts to treat Alzheimer’s Disease, there is no successful disease-modifying treatment yet available.

Why do you think this is?

According to the Alzheimer’s Association® how many people are living with this disease in 2018?

• **500,000** (about the population of Atlanta)
• **1.5 Million** (about the population of Philadelphia)
• **2.7 Million** (about the population of Chicago)
• **5.7 Million** (about the population of Los Angeles, San Diego, and Oakland combined)
• **8.5 Million** (about the population of New York City)
The Problem: CNS Drug Discovery Is Uniquely Challenging

- Failure rates for some CNS targets have been extremely high
- For disease modifying treatments of chronic neurodegenerative disorders (NDDs) the failure rate has been 100% with the exception of MS

<table>
<thead>
<tr>
<th>Chronic NDDs</th>
<th>Acute NDDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer's Disease (AD) 5.7 M in US 2018</td>
<td>Stroke (with the exception of clot dissolving/removal agents such as tPA)</td>
</tr>
<tr>
<td>Parkinson's Disease (PD) 1M in US in 2018</td>
<td>Traumatic Brain Injury (TBI)</td>
</tr>
<tr>
<td>Huntington's Disease 30,000 in US in 2018</td>
<td></td>
</tr>
<tr>
<td>Amyotrophic Lateral Sclerosis (ALS) 15,000 in US in 2018</td>
<td></td>
</tr>
<tr>
<td>Multiple Sclerosis (MS) 400,000 in US in 2015</td>
<td></td>
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</tbody>
</table>

Many CNS treatments are palliative, providing relief of some symptoms (often temporary) without significantly affecting the course of the disease. E.g. acetylcholinesterase (AChE) inhibitors for AD-Aricept®

Many CNS diseases and conditions have a genetic component, or are hereditary diseases. Many of the changes to the CNS are created during early development, prior to symptom appearance. It is unclear what can be done once the disease has progressed.

Some CNS diseases/conditions have become very politicized. Think autism and vaccines.

Many CNS diseases have a behavioral phenotype that is uniquely human. Treatment of these diseases requires the use of animal models, and these models often lack both face and predictive validity (psychiatric disorders). Even worse, when they have face validity, the model looks like the condition, they often lack predictive validity (pain models).

The BBB represents a significant impediment to treatment with existing medications. E.g. brain cancers and CNS infections.
Consequences

- Many billions of dollars have been spent in select CNS areas without any real success (NDDs, non-opiate pain treatments, ischemic stroke).
- Success has been limited even in relatively successful areas such as the epilepsies. While there are many effective anti-epileptic drugs (AEDs), from 25-35% of all patients are refractory to existing treatments and a further 25-35% are not fully stabilized with treatment (at risk for seizure).
- Many CNS programs have been scaled back or shut down entirely, particularly in large pharma companies. Capital has been hard to obtain for biopharm ventures targeting the CNS.

Why Did This Happen?

- Neuroscience came of age in the decades between the 1970s and 1990s.
- Building on new knowledge, hypotheses were generated, and drug discovery programs were initiated based on these hypotheses. This is as it should be.
- We often thought we knew more than we did. Hubris, and an example of the over-reliance on academic ‘experts’. This would be fine, as long as everyone pinky-swear to go where the drug discovery data indicated.
- Hypotheses became political, with much time and money spent defending hypotheses rather than thinking deeply and freely about alternatives.
- Failures, which should be informative, often did not lead to retooling of hypotheses, but rather to program rejection and the wholesale abandonment of certain diseases.
- Animal models, even in areas where there was seemingly good face validity, were often constructed for convenience and hence resulted in little predictive validity.
- Marketing often dictated what science we could do, rather than the other way around. I’ll explain with an example below.
- Regulatory agencies took a dim view of multi-drug approaches to many CNS diseases in areas where no single drug had shown approvable efficacy.

I promise this will end on a positive note after a few examples.
What do I mean when I say that hypotheses became politicized, and what were the outcomes of this?

Did disease foundations play a role?

Can you give any examples of a disease area where this occurred, in either CNS or another DD field?

Ischemic Stroke

- About 87% of all strokes; nearly 800,000 strokes/yr. in US
  5th leading cause of death; ~140,000 deaths/yr. in US
- Caused by a blood clot (thrombotic) or an embolism
- ~7 million survivors with varying degrees of disability

Cost of strokes ~$34B/yr in US; stroke is the leading cause of long-term disability
- Many improvements in emergency and post-stroke care and support

Clot reduction/dissolution remains most effective intervention
Limited time window for treatment

An ischemic stroke occurs when an artery in the brain becomes blocked.
Ischemic strokes consist of a core region of dead tissue, and a penumbra of potentially salvageable tissue.

The difference between diffusion-weighted MRI (DWI) and perfusion-weighted CT (PWI) images reveals the area of reduced blood flow and areas ‘at risk’ for the spread of the core stroke.

Increasing the flow of blood to the penumbra can reduce or eliminate further risk. In the figure on the right, recanalization of the vascular blockage seen in 'b.' (white arrow) results in salvage of most of the tissue in the penumbra.

Recanalization has a limited time window, although it is longer than once thought.

Efforts to ‘protect’ the penumbral neurons, even in the absence of clot-busting therapy, formed the basis of most efforts at stroke therapeutics.


Ischemic Stroke Intervention: Why We Thought This Would Work

- Ischemic neurons lose their membrane potential (ischemic depolarization)
  - Massive release of neurotransmitter, particularly glutamic acid
  - Pathological levels of calcium entry and intracellular calcium release
  - Calcium initiates a number of processes leading to cell death
- Excitotoxic cascade hypothesis
- A number of mechanisms were postulated to protect neurons at risk from this cascade; receptor antagonists, calcium channel blockers, potassium channel openers, caspase inhibitors...
- Many of these mechanisms looked very good in the animal models used.
- Many were tested in the clinic
- All failed to demonstrate any significant efficacy (est. $2B spent)
- Almost all efforts at neuroprotection were ended
- **I don’t think any of these hypotheses were adequately tested**, and I’ll explain why below. Note that they may not be valid, I just don’t think they were tested properly.
Which of the following contributed to clinical failure in stroke neuroprotection and loss of industry participation?

- No longer a large unmet medical need, since clot dissolution/removal adequately treats stroke patients
- Lack of understanding of the disease process
- Marketing groups insisted that successful treatments could only be given for the period of current insurance-driven standard of care
- Only gyrencephalic species were used as stroke models, and they were too expensive
- Animal models did not adequately represent the disease

What We Got Wrong And Why

- Nearly everything except the need to initiate treatment quickly
- While mechanisms of ischemic cell death and neuroprotection may have been valid, we did not understand the disease target
- Assumptions were made about how to treat that resulted from incomplete clinical knowledge and market driven priorities
  - Stroke evolves over a much longer time course, and treatment has to be continued during the period of potential risk
  - Other aspects of the natural history of the disease were ignored or unappreciated (e.g. role of inflammation)
  - You can’t ignore the BBB
  - Inclusion in clinical trials was probably not restrictive enough
  - Not enough attention paid to dosage form
  - Drug cocktails, exploiting multiple neuroprotective mechanisms, might be more effective
- Animal models used to propel drugs into the clinic were badly designed, and we knew it
  - Non-gyrencephalic (lissencephalic, smooth cortex) species used almost exclusively (mice and rats, as opposed to pigs, cats, dogs, most primates)
  - Short-duration treatment, damage assessed usually after only a few days to a week
  - Young adult animals used, whereas most human strokes occur in older patients, and older patients have much less ability to repair damage (neuronal plasticity)

In other words, almost everything we did was too permissive, and led to poor trial clinical trial design
Another Question

Is what we have discussed with the history of ischemic stroke treatment unique, or are there other equally compelling examples of missteps in CNS drug discovery and development?

Examples of Other CNS Disease Areas Where We Could Readily Learn From Our Past Mistakes

- **Alzheimer’s Disease**
  Many failures, no real success; current treatments are palliatives (temporary cognition enhancement)

- **Amyotrophic Lateral Sclerosis**
  Many failures, riluzole remains only successful drug and extends life only by several months

- **Parkinson’s Disease**
  Palliative treatments only

- **Pain**
  Opiates and NSAIDS remain most effective treatments

Many other examples…
That Positive Note I Mentioned Earlier

- **The pivotal mistakes were not on the medicinal chemistry side**, and target identification was largely competent if incomplete. Candidate molecules were usually quite good as target ligands. We now better understand that disease models will greatly affect probability of success or failure.

- **Much has been done to improve our understanding of disease processes.** Understanding of mutations leading to CNS disease has advanced meteorically, although the relationship to sporadic disease (often the vast majority of cases) remains unclear (AD and ALS are 2 good examples).

- Future clinical trials should benefit greatly from enhanced knowledge about disease causation and natural history. **Companies have learned that it’s better to have a successful treatment and learn how to market it**, than to try and force-fit discovery and development of a treatment to existing markets and standards of care....I hope.

- **The FDA is more willing to entertain the idea of cocktail treatments**, although the logistics of such ventures are still a significant hurdle.

- **There is renewed interest in many CNS targets**: the diseases remain large unmet medical needs, and the financial rewards are significant. Many efforts are targeting orphan populations with the hope that these successes may have wider implications.

- **Programs more likely to find traction in small companies, with VC support**, while larger companies wait to step in at a time when large investments in clinical trials are required. As a model this is not new but is more frequent and is a good one.

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Still Positive!

- Much of the work in CNS drug discovery is now carried out in small, targeted biopharmaceutical companies. Venture capital has been increasingly interested in CNS indications, and big pharma remains involved, particularly as a development engine for advanced projects.

- Many CNS diseases represent a collection of similar symptoms, with multiple underlying causes (epilepsies, autism, perhaps AD and ALS). It has become increasingly easier to target sub-populations of patients as this is recognized, and industry takes advantage of orphan drug status.

- Older mechanisms and molecules are finding new life, and new programs are being started based on these earlier efforts.

- WE, the scientists at the bench level, the clinicians at the bedside, the administrators of commercial entities, the distributors of capital and the public at large and their representatives ALL remain committed to finding new treatments for CNS diseases and conditions.
I would like to acknowledge the help of my colleague Prof. Leonard Kaczmarek, Dept. of Pharmacology, Yale University School of Medicine, and the many colleagues I have worked with over the years at BMS and at several small companies, including Dr. Nicholas Meanwell, at whose invitation I prepared this talk.
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What You Will Learn

- What are the Med Chem strategies, tactics and work flows to quickly optimize CNS agents
- What are the assay caveats to ensure successful translation from cells to in vivo proof target validation
- What Chemotypes or usual suspects and heteroarenes to avoid and why to take caution with CNS multiparameter optimization scores

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