Central Nervous System Drug Design

MacMillan Group Meeting
Stefan McCarver
November 8th, 2017
Why is Central Nervous System Drug Discovery Important?

- Neurodegenerative Disease
  - Almost 6 million Americans suffer from either Alzheimer’s or Parkinson’s
  - There is a greater than 50% chance of dementia by age 90

Despite the size of this societal burden, no effective treatments exist!

β-Amyloid Hypothesis in Alzheimer’s Disease

Shih, H-P.; Zhang, X.; Aronov, A. M. Nat. Rev. Drug Discov. 2017
β-Amyloid Hypothesis in Alzheimer’s Disease

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Why is Central Nervous System Drug Discovery Important?

- Mood Disorders - Depression
  - Overall lifetime prevalence rate of 17% (21% of women, 13% of men)
  - Depression is the second leading cause of disability worldwide
  - Responses are often delayed and many patients do not respond to treatment

Existing Antidepressant Treatments

most best-selling antidepressants have identical biological targets

sertraline (Zoloft®)
selective serotonin reuptake inhibitor

escitalopram (Lexapro®)
selective serotonin reuptake inhibitor

fluoxetine (Prozac®)
selective serotonin reuptake inhibitor

duloxetine (Cymbalta®)
serotonin-norepinephrine reuptake inhibitor
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Existing Antidepressant Treatments

serotonin reuptake inhibitor target

Existing Antidepressant Treatments

Innovation Gap in CNS Drug Development

- investment in CNS drug design has decreased rapidly in recent years
  - CNS drugs cost more and take longer to bring to market than most other therapies
  - Only 8% of clinical compounds are approved, about half the average success rate

<table>
<thead>
<tr>
<th>Disease Area</th>
<th>Clinical Phase</th>
<th>Approval Phase</th>
<th>Total Time (years)</th>
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<tbody>
<tr>
<td>Antineoplastic</td>
<td>7.9</td>
<td>0.8</td>
<td>8.7</td>
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<tr>
<td>CNS</td>
<td>7.1</td>
<td>1.7</td>
<td>8.8</td>
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<tr>
<td>Endocrine</td>
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<td>8.4</td>
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<tr>
<td>Anesthetic/Analgesic</td>
<td>6.5</td>
<td>1.9</td>
<td>8.4</td>
</tr>
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<td>Anti-infective*</td>
<td>6.0</td>
<td>1.7</td>
<td>7.7</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>5.2</td>
<td>1.7</td>
<td>6.9</td>
</tr>
<tr>
<td>AIDS Antiviral</td>
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<th>Disease Area</th>
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<tr>
<td>Sys. Anti-infective</td>
<td>23.9%</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>20.4%</td>
</tr>
<tr>
<td>Oncology/Immunology</td>
<td>19.4%</td>
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<tr>
<td>GI/Metabolism</td>
<td>9.4%</td>
</tr>
<tr>
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Halted drug discovery in pain, depression, and anxiety

Halted drug discovery in bipolar disorder, depression, schizophrenia, and anxiety
Designing Therapies for Neuropsychiatric Diseases is Challenging

- Inadequate Pre-Clinical Models
- Challenging Target Validation
- Mechanisms Poorly Understood
Pre-Clinical Models Possess Limited Predictive Value

“There is growing agreement that there are no animal models of psychiatric disorders such as depression that capture the relevant pathophysiology”

Pre-Clinical Models Possess Limited Predictive Value

Mobile rat = “happy rat”
Immobile rat = “depressed rat”

“Forced Swim Test”
Human brain biology is incredibly complex

- Significant differences from animal models
- Surgical procedures are impossible in most cases
- Brain disorders are not cell autonomous
How Do Molecules Enter and Exit the Brain?
I. The free drug concentration at the site of action is responsible for pharmacological activity *in vivo*

II. At steady state in the absence of active transport, free drug concentration is the same on both sides of any biomembrane
How Do Molecules Enter and Exit the Brain?

Blood-Brain Barrier: Endothelial cells with very tight intracellular junctions

- $C_{b,u}$: unbound brain concentration
- ISF: interstitial fluid
- ICF: intracellular fluid
- A number of transport proteins regulate drug or other molecule concentration in the brain via active transport mechanisms

Crossing the Blood-Brain Barrier

Most common route: Passive permeation

Crossing the Blood-Brain Barrier

Blood-brain barrier permeable

Blood-brain barrier impermeable
Crossing the Blood-Brain Barrier

Abbott, N. J.; Rönnbäck, L.; Hansson, E. *Nature Reviews Neuroscience*
Efflux mechanisms need to be avoided!

Abbott, N. J.; Rönnbäck, L.; Hansson, E. *Nature Reviews Neuroscience*
**P-Glycoprotein Mediated Efflux**

P-Glycoprotein

- Highly expressed at the blood-brain barrier
- Serves as a molecular “pump”
- Very broad substrate specificity

P-Glycoprotein Mediated Efflux

Critical Parameters and How They Are Measured

1. $C_{b,u}$: unbound brain concentration

2. $K_{p,uu}$: unbound brain to plasma ratio

3. $P_{app}$: rate of brain permeability

4. $ER$: efflux ratio
Critical Parameters and How They Are Measured

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4. ER : efflux ratio
Measurement of Unbound Drug Concentration in the Brain

Unbound drug concentration is the most important parameter for CNS pharmacokinetics.

\[ C_b \times f_{u,b} = C_{u,b} \]
Measurement of Unbound Drug Concentration in the Brain

In humans, CSF concentration approximates brain concentration when transporters are not involved.

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Parallel Artificial Membrane Permeability Assay

The amount of drug in each compartment is measured following an incubation period.

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Measuring Efflux Ratio with MDR1-MDCK

Efflux Ratio (ER) = (compound in apical chamber)/(compound in basal chamber)

highly effluxed compounds are prevented from diffusing to the basal chamber

Culture Cells

Madin Darby canine kidney
transfection with MDR1

Measure Concentration

Measuring Receptor Occupancy

How can you tell if a drug is reaching its target?
Measuring Receptor Occupancy

vehicle administration

tracer administration

drug administration

inistration
Measuring Receptor Occupancy

Measuring Receptor Occupancy

- Receptor occupancy studies provide the most direct information on drug exposure.

- Cost and time concerns preclude their use for all but the most advanced compounds.
# Optimization of Compounds for CNS Penetration

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<th>Consequences</th>
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Optimization of Compounds for CNS Penetration

analysis of 119 marketed CNS drugs and 108 Pfizer CNS candidates

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Optimization of Compounds for CNS Penetration

LogP = a determination of lipophilicity based on partitioning between octanol and water

LogD = a pH dependent counterpart to logP, measured at a specific pH using a buffer

\[
\log P_{oct/wat} = \log \left( \frac{[\text{solute}]_{octanol}}{[\text{solute}]_{\text{un-ionized}}_{\text{water}}} \right)
\]
Increased Lipophilicity Leads to Higher Permeability

Passive permeability ($P_{\text{app}}$) as a function of pH - dependent partition coefficient

Reducing Lipophilicity to Improve Unbound Brain Concentration

selective muscarinic M$_1$ agonist from a GSK high throughput screen

receptor is highly expressed in the hippocampus and cerebral cortex

potential targets for treatment of cognitive deficits including in Alzheimer’s and schizophrenia

previous compounds showed some clinical efficacy, discontinued due to side effects

Reducing Lipophilicity to Improve Unbound Brain Concentration

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Optimization of Compounds for CNS Penetration

Polar surface area: surface sum over all polar atoms (O, N, etc.) including attached hydrogens

Typically < 140 Å² for cell membrane permeability and < 90 Å² for BBB permeability
Higher Polar Surface Area Reduces CNS Exposure

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|                           | Can be improved by IMHB and cyclization                                       |

Optimization of Compounds for CNS Penetration

- PDE10A inhibitors for the treatment of schizophrenia (Amgen)
- regulates cAMP and cGMP in signaling pathway downstream from dopamine receptors

![Chemical structures]

- initial HTE hit ($IC_{50} = 10 \text{ nM}$)
- after optimization ($IC_{50} = 5 \text{ nM}$)
Optimization of Compounds for CNS Penetration

- PDE10A inhibitors for the treatment of schizophrenia (Amgen)
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Hydrogen Bond Donors Can Lead to P-gp Efflux

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<tr>
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<td>3</td>
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Intramolecular Hydrogen Bonding Generally Improves PK

ER = 3.1

ER = 1.1

$K_p = 0.4$, MED = 30 mg/kg

$K_p = 6.0$, MED = 1 mg/kg
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**α7 Nicotinic Acetylcholine Receptor Agonists**

- Target of growing interest for cognitive deficits and negative symptoms in schizophrenia
- Several α7 nAChR agonists have demonstrated efficacy in preclinical models

High Throughput Evaluation

**Lead Compound**

\[ \alpha_7 EC_{50} = 1.3 \mu M \]

good selectivity over 5HT\(_3\) receptor

α7 Nicotinic Acetylcholine Receptor Agonists

High $pK_a$ Can Lead to Reduced CNS Exposure

Attenuated basicity leads to significantly reduced efflux and good brain/plasma distribution

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Rigid Structures are Often More Membrane Permeable

crizotinib
anaplastic lymphoma kinase inhibitor
non-small cell lung carcinoma

*in some patients, point mutations and cancer metastasis into the brain is observed
a compound effective against mutant ALK and CNS penetrant was needed*

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\[
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<th>$K_i$ (nM)</th>
<th>RB #</th>
<th>PSA ($\text{Å}^2$)</th>
<th>cLogP</th>
<th>$P_{app}$</th>
<th>ER</th>
<th>CSF/C$_{u,p}$</th>
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<tr>
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<td>86</td>
<td>2.2</td>
<td>18.8</td>
<td>7.6</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
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<td>0</td>
<td>110</td>
<td>1.6</td>
<td>28.8</td>
<td>1.5</td>
<td>0.31</td>
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Questions?