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Section Leader,
Biotransformation & Drug Disposition
DMPK, RD Platform Technology & Science
GlaxoSmithKline Pharmaceuticals

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Thursday, July 9, 2015
“The Entrepreneurial Chemist: Bridging the Bench and the Boardroom”
Tashni-Ann Dubroy, President-Elect, Shaw University and Entrepreneur, Tea and Honey Blends
Steven Isaacman, Founder and CEO, Biosciences

Thursday, July 16, 2015
“Catalyzing Innovation through Molecular Design”
LIVE From the Green Chemistry & Engineering Conference
Brian Laird, Professor of Chemistry, University of Kansas
Anthony Rappé, Professor of Chemistry, Colorado State University
Joe Fortunak, Professor of Chemistry, Howard University

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2015 Drug Design & Delivery Symposium

### Module 1: Improving Drug Design Efficiency and Efficacy

<table>
<thead>
<tr>
<th>Date</th>
<th>Topic</th>
<th>Speaker(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jan 29</td>
<td>Designing Better Drug Candidates</td>
<td>Dr. Paul Leeson</td>
</tr>
<tr>
<td>Feb 26</td>
<td>Strategies to Improve Solubility of Drug Candidates</td>
<td>Dr. Michael Walker</td>
</tr>
</tbody>
</table>

### Module 2: Activity/Potency Screening for Drug Lead & Candidate Optimization

<table>
<thead>
<tr>
<th>Date</th>
<th>Topic</th>
<th>Speaker(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mar 19</td>
<td>Fragment-Based Drug Design Strategies</td>
<td>Dr. Dan Ehrman</td>
</tr>
<tr>
<td>Apr 30</td>
<td>Screening Strategies</td>
<td>Dr. David Swinney</td>
</tr>
<tr>
<td>May 28</td>
<td>PAINS (Pan-Assay Interference Compounds)</td>
<td>Dr. Jonathan Baed</td>
</tr>
<tr>
<td>June 25</td>
<td>Positron Emission Tomography (PET) Labeling in Drug Discovery &amp; Development</td>
<td>Dr. Lei Zhang</td>
</tr>
<tr>
<td>July 30</td>
<td>X-Ray Crystallography in Drug Discovery</td>
<td>Dr. Jon Mason &amp; Dr. Miles Congreve</td>
</tr>
</tbody>
</table>

### Module 3: Enabling Drug Discovery

<table>
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<tr>
<th>Date</th>
<th>Topic</th>
<th>Speaker(s)</th>
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<tbody>
<tr>
<td>Aug 27</td>
<td>Choices and Trends in Solid Dosage Form Section</td>
<td>Dr. Scott Trzaska &amp; Dr. Roe Smith</td>
</tr>
<tr>
<td>Sept 24</td>
<td>Delivery Options to Support Dose Escalation in Preclinical Toxicology and Pharmacodynamic Activity Studies</td>
<td>Dr. Evan Thackaberry</td>
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### Module 4: Pharmacokinetics

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<th>Date</th>
<th>Topic</th>
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</thead>
<tbody>
<tr>
<td>Oct 29</td>
<td>Pharmacokinetic Considerations in Drug Design and Development</td>
<td>Dr. Punit Marathe</td>
</tr>
<tr>
<td>Nov 19</td>
<td>Prodrugs in Drug Discovery</td>
<td>Dr. John Higgins</td>
</tr>
</tbody>
</table>
Join us July 30, 2015 for the 7th Session!

“X-ray Crystallography in Drug Discovery”
with Jon Mason and Miles Congreve of Heptares and Gregory Petsko of Cornell University

www.acs.org/content/acs/en/events/upcoming-acs-webinars/drug-design-2015.html

“2015 Drug Design and Delivery Symposium:
Accelerating CNS Positron Emission Tomography Ligand Discovery”

Lei Zhang
Senior Principal Scientist, Pfizer Inc.

David Donnelly
Senior Research Investigator II, Bristol-Myers Squibb

Slides available now! Recordings will be available to ACS members after one week

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The 2015 Drug Design and Delivery Symposium is co-produced by the ACS Medicinal Chemistry Division and the AAPS
Strategies to Accelerate the Discovery of Novel CNS PET Ligands

Lei Zhang
ACS Webinar
June 25th, 2015

Positron Emission Tomography (PET)

• A non-invasive imaging method to provide high resolution and quantifiable 3-dimensional (3D) images of radioligand distribution → Visualize the “the invisibles”
• Requires a target-specific radioligand labeled with a positron emitting nuclide, typically $^{11}$C ($t_{1/2} = 20$ min) or $^{18}$F ($t_{1/2} = 110$ min)
PET ligands play important roles in CNS drug discovery

Measures target occupancy (TO):
- Support Proof of Mechanism
- Optimize clinical dose selection
- Facilitate clinical go/no go decision

Disease state biomarker:
- Diagnostic tools, e.g. Florbetapir®
- Patient enrichment

Brain permeability
Target Occupancy (TO)

Disease state biomarker:
- Diagnostic tools, e.g. Florbetapir®
- Patient enrichment

Audience Survey Question #1

Which of the following properties are required for a CNS PET ligand?

(i) Brain permeable
(ii) Orally available
(iii) weak off-target activity
(iv) Labeling site for C-11 or F-18

A) (i), (ii) and (iii)  B) (i), (ii) and (iv)
C) (i), (iii) and (iv)  D) All of above
**Desired attributes of CNS PET Ligands**

- Structural handle for $^{18}$F or $^{11}$C labeling
- Brain Permeable
- Safe for clinical dosing (µg)
- Amenable for late-stage labeling
- No brain-permeable radioactive metabolites
- Low non-specific binding (NSB)
- Brain Permeable
- Brain Permeable
- Brain Permeable
- Low non-specific binding (NSB)
- High potency (Low to sub-nM)
- High Selectivity
- Safe for clinical dosing (µg)

**PET ligand discovery process historically suffered from high attrition rates**

- Med Chem Publications
- Close-in analogs of Clinical Candidate
- GLP tox, dosimetry and eIND filing
- Clinical PET Imaging
- NHP PET imaging
- 5HT1B

- Average cost: $80-120K /ligand for PET assessment in NHPs
- $1-1.5 million to identify a PET lead prior to GLP safety studies
There is a clear need in a more efficient and resource-sparing PET ligand discovery process.

Our Strategy to improve the CNS PET ligand discovery process:

- $B_{\text{max}}$ and Bio-distribution
- Lead Triaging and PET-specific SAR
- Assessing In vivo specific binding
- PET imaging in NHP
- GLP tox, dosimetry and eIND filing

- Gain early read on cross-species target expression ($B_{\text{max}}$) and biodistribution to inform PET viability and study design
- Define design and selection parameters to enable facile lead prioritization/rational ligand design
- Explore cost-effective alternatives for in vivo specific binding assessment
Our Strategy to improve the novel CNS PET ligand discovery process

**B**\textsubscript{\text{max}} and Bio-distribution | Lead Triaging and PET-specific SAR | Assessing In vivo specific binding | PET imaging in NHP | GLP tox, dosimetry and eIND filing

*Gain early read on cross-species target expression (B\textsubscript{\text{max}}) and biodistribution to inform PET viability and study design*

---

Gain an early understanding on B\textsubscript{\text{max}} to inform PET viability

\(B\textsubscript{\text{max}}/\text{biodistribution}\) is typically determined by saturation binding (brain tissue homogenate) and in vitro autoradiography (brain slices) studies using a \([^3\text{H}]\) or \([^{125}\text{I}]\) ligand:

Important to be highly selective; brain permeability not necessary

**Target 1**

<table>
<thead>
<tr>
<th>Species</th>
<th>B\textsubscript{\text{max}}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mice</td>
<td>0.3 nM</td>
</tr>
<tr>
<td>Human</td>
<td>0.2 nM</td>
</tr>
</tbody>
</table>

**Target 2**

<table>
<thead>
<tr>
<th>Species</th>
<th>B\textsubscript{\text{max}}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mice</td>
<td>98 nM</td>
</tr>
<tr>
<td>NHP</td>
<td>75 nM</td>
</tr>
<tr>
<td>Human</td>
<td>TBD</td>
</tr>
</tbody>
</table>

**Target 3**

![Image of Target 3]

**Target 4**

![Image of Target 4]

**PET viability:** in vitro binding potential (BP) \(\text{Bmax}/Kd > 10\); if \(\text{Bmax} < 1\) nM, low PET viability

**Bio-distribution:** Widespread or enriched in certain brain regions? is there a reference region within the brain?

---

Our Strategy to improve the novel CNS PET ligand discovery process

- **B<sub>max</sub> and Bio-distribution**
- **Lead Triaging and PET-specific SAR**
- **Assessing In vivo specific binding**
- **PET imaging in NHP**
- **GLP tox, dosimetry and eIND filing**

*Define design and selection parameters to enable facile lead prioritization/rational ligand design*

---

**Audience Survey Question #2**

➢ Which of the following physicochemical parameter(s) one should consider when designing a CNS PET ligand?

(A) cLogP
(B) LogD
(C) Molecular Weight (MWt)
(D) Polar Surface Area (PSA)
(E) Number of H-bond donors
Define design and selection parameters to enable rational PET ligand design/selection

**Lead Triaging and PET-specific SAR**

Key knowledge gap:
- Lack of understanding in the preferred property space for CNS PET ligands, in particular how to minimize non-specific binding (NSB)

**PET Ligand Database**
- 62 Validated PET ligands ("Yes" category)
- 15 ligands failed due to NSB ("No" category)

**Physicochemical properties:**
- MWt, tPSA, cLogP, LogD, PKa, HBD

**In vitro ADME Properties:**
- HLM, MDR, RRCK, Fu_b, Fu_p

**Spotfire® Analysis**


---

Define design and selection parameters to enable rational PET ligand design/selection

**Lead Triaging and PET-specific SAR**

- Identify key property differences between two categories and define design parameters that would enable facile lead prioritization and rational PET ligand design

**PET Ligand Database**
- 62 Validated PET ligands ("Yes" category)
- 15 ligands failed due to NSB ("No" category)

**Physicochemical properties:**
- MWt, tPSA, cLogP, LogD, PKa, HBD

**In vitro ADME Properties:**
- HLM, MDR, RRCK, Fu_b, Fu_p

**Spotfire® Analysis**

In vitro ADME properties: Brain Free Fraction (Fu_b) can serve as a useful predictor for NSB

**Brain Free Fractions (Fu_b)**
- X > 0.15: 27% (Yes) 33% (No)
- 0.05 < X ≤ 0.15: 40% (Yes) 87% (No)
- X ≤ 0.05: 27% (Yes) 87% (No)

Human use
- Yes
- No

Low non-specific binding
- Fu_b > 0.05
- High risk of NSB
- If both Fu_b and Fu_p < 0.05

**Plasma Free Fractions (Fu_p)**
- X > 0.15: 60% (Yes) 16% (No)
- 0.05 < X ≤ 0.15: 24% (Yes) 40% (No)
- X ≤ 0.05: 40% (Yes) 40% (No)

Human use
- Yes
- No

Moderate to high passive permeability and low Pgp liability are preferred for brain permeability

**RRCK P_{app, AB} (10^{-6} cm/sec)**
- X > 10: 8% (Yes) 40% (No)
- 5 < X ≤ 10: 68% (Yes) 33% (No)
- X ≤ 5: 13% (Yes) 20% (No)

Human use
- Yes
- No

Brain Permeability
- RRCK > 5 \times 10^{-6} cm/s; MDR BA/AB ≤ 2.5
CNS MPO (Multi-parameter Optimization)

<table>
<thead>
<tr>
<th>Properties</th>
<th>Function</th>
<th>Weight</th>
<th>CNS MPO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>More desirable range (T0 = 1.0)</td>
</tr>
<tr>
<td>ClogP</td>
<td>Monotonic decreasing</td>
<td>1.0</td>
<td>ClogP ≤ 3</td>
</tr>
<tr>
<td>ClogD</td>
<td>Monotonic decreasing</td>
<td>1.0</td>
<td>ClogD ≤ 2</td>
</tr>
<tr>
<td>MW</td>
<td>Monotonic decreasing</td>
<td>1.0</td>
<td>MW ≤ 360</td>
</tr>
<tr>
<td>TPSA</td>
<td>Hump Function</td>
<td>1.0</td>
<td>40 &lt; TPSA ≤ 90</td>
</tr>
<tr>
<td>HBD</td>
<td>Monotonic decreasing</td>
<td>1.0</td>
<td>HBD ≤ 0.5</td>
</tr>
<tr>
<td>pKₘ</td>
<td>Monotonic decreasing</td>
<td>1.0</td>
<td>pKₘ ≤ 8</td>
</tr>
</tbody>
</table>

- Functions set to favor CNS drug space
- Score each property ranging from 0 to 1
- Total CNS MPO = 0 (low) – 6 (high); A single parameter to track all 6 physicochemical properties


CNS MPO (Multi-parameter Optimization)

<table>
<thead>
<tr>
<th>Properties</th>
<th>Function</th>
<th>Weight</th>
<th>CNS MPO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>More desirable range (T0 = 1.0)</td>
</tr>
<tr>
<td>ClogP</td>
<td>Monotonic decreasing</td>
<td>1.0</td>
<td>ClogP ≤ 3</td>
</tr>
<tr>
<td>ClogD</td>
<td>Monotonic decreasing</td>
<td>1.0</td>
<td>ClogD ≤ 2</td>
</tr>
<tr>
<td>MW</td>
<td>Monotonic decreasing</td>
<td>1.0</td>
<td>MW ≤ 360</td>
</tr>
<tr>
<td>TPSA</td>
<td>Hump Function</td>
<td>1.0</td>
<td>40 &lt; TPSA ≤ 90</td>
</tr>
<tr>
<td>HBD</td>
<td>Monotonic decreasing</td>
<td>1.0</td>
<td>HBD ≤ 0.5</td>
</tr>
<tr>
<td>pKₘ</td>
<td>Monotonic decreasing</td>
<td>1.0</td>
<td>pKₘ ≤ 8</td>
</tr>
</tbody>
</table>

CNS MPO Distribution (0-6)
- Drugs (N = 119)
- Candidates (N = 108)

74%

### Definition of CNS PET MPO

<table>
<thead>
<tr>
<th>Properties</th>
<th>Function</th>
<th>Weight</th>
<th>CNS MPO</th>
<th>CNS PET MPO</th>
</tr>
</thead>
<tbody>
<tr>
<td>ClogP</td>
<td>Monotonic decreasing</td>
<td>1.0</td>
<td>ClogP ≤ 3</td>
<td>ClogP ≤ 1.0</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>ClogP &gt; 5</td>
<td>ClogP &gt; 4.0</td>
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<tr>
<td>ClogD</td>
<td>Monotonic decreasing</td>
<td>1.0</td>
<td>ClogD ≤ 2</td>
<td>ClogD ≤ 1.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ClogD &gt; 4</td>
<td>ClogD &gt; 2.8</td>
</tr>
<tr>
<td>MW</td>
<td>Monotonic decreasing</td>
<td>1.0</td>
<td>MW ≤ 360</td>
<td>MW ≤ 305.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MW &gt; 500</td>
<td>MW &gt; 350.5</td>
</tr>
<tr>
<td>TPSA</td>
<td>Hump Function</td>
<td>1.0</td>
<td>40 &lt; TPSA ≤ 90</td>
<td>TPSA ≤ 63.3</td>
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<td>TPSA &gt; 86.2</td>
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<tr>
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<td>HBD ≤ 0.5</td>
<td>HBD ≤ 1.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HBD &gt; 3.5</td>
<td>HBD &gt; 2.0</td>
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<td></td>
<td>pKₐ &gt; 10</td>
<td>pKₐ &gt; 9.5</td>
</tr>
</tbody>
</table>

Actual median and the 75th percentile values of marketed CNS drugs


### Physicochemical properties: CNS PET MPO shows differentiation between two categories

![Physicochemical properties diagram]

CNS MPO: 62 (45% Yes, 15% No); CNS PET MPO: 15 (40% Yes, 60% No).

Physicochemical Properties

CNS PET MPO > 3
Majority of the successful PET ligands have ClogD \leq 3 (47 out of 62) and ClogP \leq 4 (50 out of 62)

CNS PET MPO: Better probability to align all three in vitro ADME properties

Alignment of ADME Properties vs. CNS PET MPO (PET Ligands Set)

Alignment of ADME Properties vs. CNS PET MPO (Broader Compound Set)
Design and selection parameters for CNS PET ligand development

Lead Triaging and PET-specific SAR

- Identify key property differences between two categories and define design parameters that would enable facile lead prioritization and rational PET ligand design

Physicochemical Properties
- CNS PET MPO > 3

Brain Permeability
- RRCK > 5 x 10^{-6} cm/s; MDR BA/AB ≤ 2.5

Low non-specific binding
- Fu_b > 0.05
- High risk of NSB if both Fu_b and Fu_p < 0.05,

Prospective PET ligand design
- (All properties can be calculated via *in silico* models prior to synthesis)

Application of the PET design parameters in PDE2 PET ligand development

1154 Cmpds
- RRCK >5 and MDR < 2.5

327 Cmpds
- cFu_b > 0.05

202 Cmpds
- CNS PET MPO > 3

172 Cmpds
- IC_{50}<10 nM

17 Cmpds
- Radiolabel moiety

8 leads

Prospective PET ligand design

- Rank order by potency

**PDE2 IC_{50}: 2.3 nM**

- >600x selective over other PDEs
- Clean in CEREP

- CNS MPO= 5.62
- CNS PET MPO= 4.94
- LogD = 1.48
- RRCK = 21.5
- MDR BA/AB = 1.46
- Fu_b= 0.09
- Fu_p= 0.23
NHP PET images of Compound 1 and optimization strategy

Baseline
In vivo BP 0.8

Blocking
Pretreatment with a selective PDE2 inhibitor

- High in striatum and frontal cortex
- Low in Cerebellum (reference region)

Maintain favorable PET parameters:
CNS PET MPO, RRCK, MDR, Fu_b

Improve Potency:
incorporate moiety beneficial for PDE2 activity

Introduce labeling handle:
- OMe, F-azetidine, etc

PET specific SAR guided by the Design Parameters

<table>
<thead>
<tr>
<th>Compound #</th>
<th>CNS PET MPO</th>
<th>cRRCK (x 10^6 cm/sec)</th>
<th>cMDR1 BA/AB</th>
<th>cFu_b</th>
<th>Human PDE2 IC_{50} (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>4.55</td>
<td>25.5</td>
<td>1.36</td>
<td>0.21</td>
<td>0.8</td>
</tr>
<tr>
<td>3</td>
<td>4.55</td>
<td>23.5</td>
<td>1.87</td>
<td>0.21</td>
<td>0.6</td>
</tr>
<tr>
<td>4</td>
<td>4.55</td>
<td>23.9</td>
<td>1.48</td>
<td>0.18</td>
<td>1.1</td>
</tr>
<tr>
<td>5</td>
<td>4.81</td>
<td>21.5</td>
<td>1.32</td>
<td>0.10</td>
<td>0.5</td>
</tr>
<tr>
<td>6</td>
<td>4.55</td>
<td>21.7</td>
<td>1.57</td>
<td>0.12</td>
<td>2.0</td>
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<tr>
<td>7</td>
<td>4.83</td>
<td>28.4</td>
<td>1.12</td>
<td>0.07</td>
<td>1.7</td>
</tr>
</tbody>
</table>
Profile and F-18 labeling of PF-05270430

PF-05270430
- PDE2 IC$_{50}$: 0.5 nM
- > 1800x selective over other PDEs
- Clean in CEREP

- CNS PET MPO= 4.81
- RRCK = 21.0
- MDR BA/AB = 1.71
- Fu$_b$ = 0.08
- Fu$_p$ = 0.17

NHP PET imaging of $[^{18}F]$PF-05270430

Baseline
In vivo BP: Putamen 1.84; Caudate: 1.44

Blocking
With a selective PDE2 inhibitor (2.0 mg/kg sc)
Application of the PET design parameters in NOP opioid receptor *in vivo* radiotracer development

8

![Chemical Structure](8.png)

- **NOP Ki**: 0.59 nM
- **Mu-opioid**: 5.9 nM (10x)

9

![Chemical Structure](9.png)

- **NOP Ki**: 7 nM
- **Mu-opioid**: 735 nM (105x)

11 (PF-7191)

![Chemical Structure](11.png)

- **NOP Ki**: 0.1 nM
- **Mu-opioid**: 145.5 nM (1036x)

**Potency Handle**

**Selectivity Handle**

- **PET MPO**: 3.3
- **RRCK**: 13.9
- **MDR BA/AB**: 1.76
- **Fu_b**: 0.07
- **Fu_p**: 0.12

- **PET MPO**: 4.0
- **RRCK**: 8.0
- **MDR BA/AB**: 1.80
- **Fu_b**: 0.06
- **Fu_p**: 0.08


[3H]PF-7191 demonstrated high specific binding in vivo and enabled in vivo receptor occupancy study

![Chemical Structure](3HPF7191.png)

Biodistribution of [3H]PF-7191 in rat brain

- **Total Binding**
- **Non-specific Binding**

In vivo time course of [3H]PF-7191 in rat cortex

Dose response inhibition by PF-04926965

- % Inhibition
- **ED50**: 0.9 mg/kg
- **PF-04926965 (mg/kg)**
Our Strategy to improve the novel CNS PET ligand discovery process

- $B_{\text{max}}$ and Bio-distribution
- Lead Triaging and PET-specific SAR
- Assessing In vivo specific binding
- PET imaging in NHP
- GLP tox, dosimetry and eIND filing

*explore cost-effective alternatives for in vivo specific binding assessment

Explore cost-effective alternatives for in vivo specific binding assessment

**Assessing In vivo specific binding**

- LC-MS/MS “Cold-tracer”: Significant cost and time saving
  - No radioactivity involved: no need for precursor/labeling method validation; < 5 mg compound
  - 2-3 week turnaround; $10-12K for 5 tissues baseline/blocking

---

Application of LC-MS/MS cold tracer method in Enzyme Target 1

10 µg/kg, IV + 5-75 min Time Course

- Consistent with known target biodistribution
- High Level of specific binding

Pretreatment with a high dose of a selective inhibitor

Vehicle
Inhibitor

LC-MS/MS cold tracer outcome well-translated in NHP PET Imaging
Audience Survey Question #3

In which of the following Scenario one can apply LC-MS/MS Cold tracer method?

(A) Irreversible binder; similar potency in rat and human; aligned human and rat Bmax

(B) Reversible binder; similar potency in rat and human; aligned human and rat Bmax

(C) Reversible binder; potent in human, weak in rat; aligned human and rat Bmax

(D) Reversible binder; similar potency in rat and human; high Bmax in rats, 10x lower Bmax in human

A Streamlined and Resource-Sparing CNS PET Ligand Discovery Process

Early understanding of cross-species Bmax and biodistribution

PET design parameters to enable focused PET-specific SAR/lead prioritization

Future State 1-3 leads into in vivo assessment 1 successful PET ligand

LC-MS Tracer quantification
Acknowledgment

PET Discovery Core

Ellie Beck
Anabella Villalobos
Lei Zhang

Clinical Research Translational Imaging

Laigao Chen (cold tracer)
Timothy McCarthy
Kenneth Zasadny
Marc Scaddan

Project Team Members

Michael Brodney (NOP)
Chris Helal (PDE2)
Thomas Chappie (PDE2)
John Humphery (PDE2)
Jiemin Lu (PDE2)
Travis Wager (CNS PET MPO)
Xinjun Hou (CNS PET MPO)
Patrick Verhoest (CNS PET MPO)
Sarah Grimwood (NOP, PDE2)
Elena Drummond (NOP)

And many others teams...

Thank you for your attention!

Reference Guide

- Application of PET imaging in CNS drug discovery:

- Different approaches for novel CNS PET ligand discovery:

- CNS MPO and its application:

- Application of LC-MS/MS Cold tracer method:
“2015 Drug Design and Delivery Symposium: Accelerating CNS Positron Emission Tomography Ligand Discovery”

Lei Zhang
Senior Principal Scientist, Pfizer Inc.

David Donnelly
Senior Research Investigator II, Bristol Myers Squibb

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with Jon Mason and Miles Congreve of Heptares and Gregory Petsko of Cornell University

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Steven Isaacman, Founder and CEO, Biosciences

Thursday, July 16, 2015
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Anthony Rappè, Professor of Chemistry, Colorado State University
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Accelerating CNS Positron Emission Tomography Ligand Discovery”

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# 2015 Drug Design & Delivery Symposium

## Module 1: Improving Drug Design Efficiency and Efficacy

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<td>Designing Better Drug Candidates</td>
<td>Dr. Paul Leason</td>
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<td>Feb 26</td>
<td>Strategies to Improve Solubility of Drug Candidates</td>
<td>Dr. Michael Walker</td>
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## Module 2: Activity/Potency Screening for Drug Lead & Candidate Optimization

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<td>Fragment-Based Drug Design Strategies</td>
<td>Dr. Dan Eranson</td>
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<td>April 30</td>
<td>Screening Strategies</td>
<td>Dr. David Swinney</td>
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<td>May 28</td>
<td>PAINS (Pan-Assay Interference Compounds)</td>
<td>Dr. Jonathan Baell</td>
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<td>June 25</td>
<td>Positron Emission Tomography (PET) Labeling in Drug Discovery &amp; Development</td>
<td>Dr. Lei Zhang</td>
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<td>July 30</td>
<td>X-Ray Crystallography in Drug Discovery</td>
<td>Dr. Jon Mason &amp; Dr. Miles Congreve</td>
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## Module 3: Enabling Drug Discovery

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<td>Aug 27</td>
<td>Choices and Trends in Solid Dosage Form Section</td>
<td>Dr. Scott Trzaska &amp; Dr. Ron Smith</td>
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<td>Sept 24</td>
<td>Delivery Options to Support Dose Escalation in Preclinical Toxicology and Pharmacodynamic Activity Studies</td>
<td>Dr. Evan Thackaberry</td>
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## Module 4: Pharmacokinetics

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<td>Pharmacokinetic Considerations in Drug Design and Development</td>
<td>Dr. Punit Marathe</td>
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<td>Prodrugs in Drug Discovery</td>
<td>Dr. John Higgins</td>
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