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Pete Gorycki, PhD
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Biotransformation & Drug Disposition
DMPK, RD Platform Technology & Science
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Upcoming ACS Webinars®

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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

#ACSWebinars

Co-produced by
ACS Division of Medicinal Chemistry
American Association of Pharmaceutical Scientists (AAPS)

Module 1: Improving Drug Design Efficiency and Efficacy		
Jan 29	Designing Better Drug Candidates	*Dr. Paul Leeson*
Feb 26	Strategies to Improve Solubility of Drug Candidates	*Dr. Michael Walker*
Module 2: Activity/Potency Screening for Drug Lead & Candidate Optimization		
Mar 19	Fragment-Based Drug Design Strategies	*Dr. Dan Erlanson*
April 30	Screening Strategies	*Dr. David Swinney*
May 28	PAINS (Pan-Assay Interference Compounds)	*Dr. Jonathan Baell*
June 25	Positron Emission Tomography (PET) Labeling in Drug Discovery & Development	*Dr. Lei Zhang*
July 30	X-Ray Crystallography in Drug Discovery	*Dr. Jon Mason & Dr. Miles Congreve*
Module 3: Enabling Drug Discovery		
Aug 27	Choices and Trends in Solid Dosage Form Section	*Dr. Scott Trzaska & Dr. Ron Smith*
Sept 24	Delivery Options to Support Dose Escalation in Preclinical Toxicology and Pharmacodynamic Activity Studies	*Dr. Evan Thackaberry*
Module 4: Pharmacokinetics		
Oct 29	Pharmacokinetic Considerations in Drug Design and Development	*Dr. Punit Marathe*
Nov 19	Prodrugs in Drug Discovery	*Dr. John Higgins*

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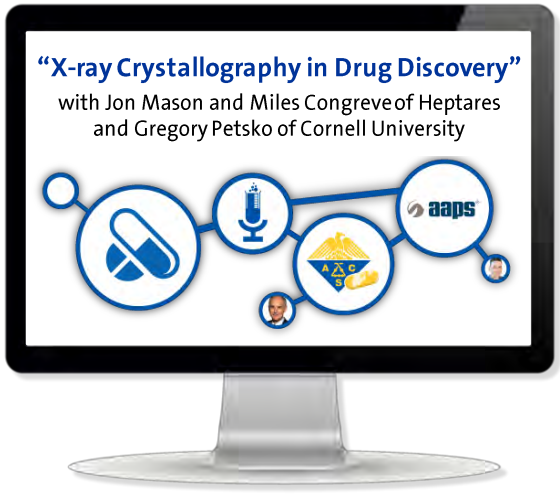
Join us July 30, 2015 for the 7th Session!



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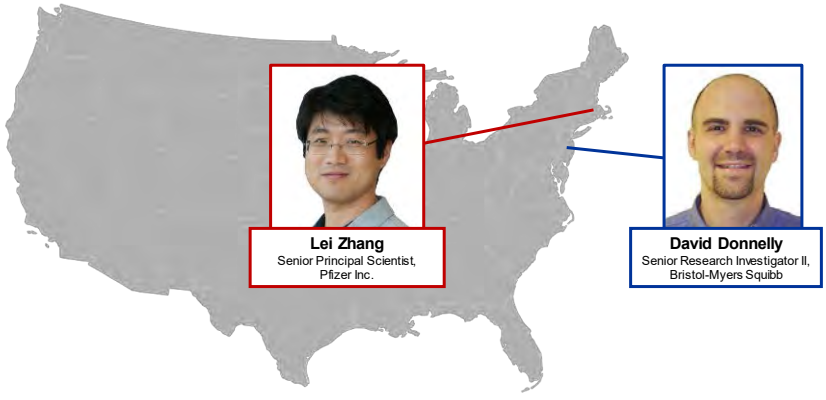
"2015 Drug Design and Delivery Symposium: Accelerating CNS Positron Emission Tomography Ligand Discovery"



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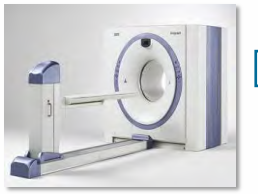
Strategies to Accelerate the Discovery of Novel CNS PET Ligands

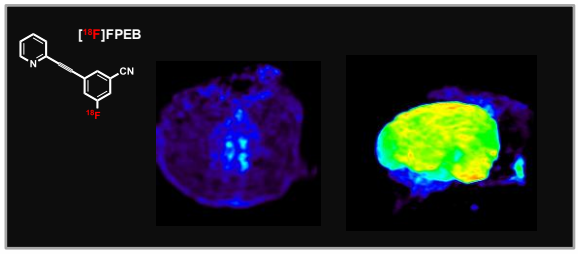
Lei Zhang
ACS Webinar
June 25th, 2015

Pfizer WORLDWIDE RESEARCH & DEVELOPMENT
Medicinal Chemistry

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)





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Medicinal Chemistry

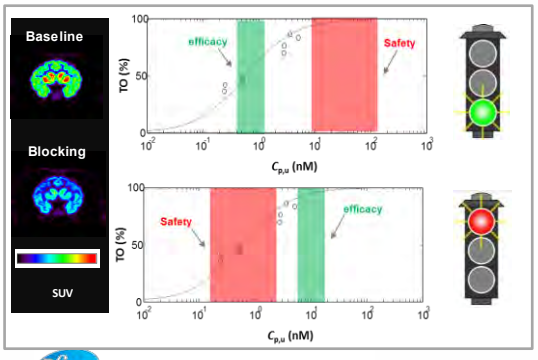
PET ligands play important roles in CNS drug discovery

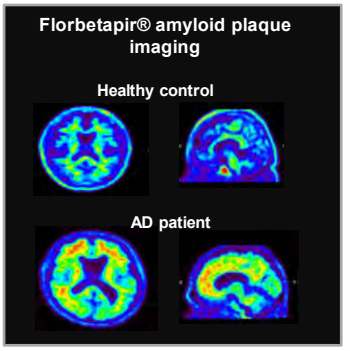
Measures target occupancy (TO):

- Support Proof of Mechanism
- Optimize clinical dose selection
- Facilitate clinical go/no go decision

Disease state biomarker:

- Diagnostic tools, e.g. Florbetapir®
- Patient enrichment





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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

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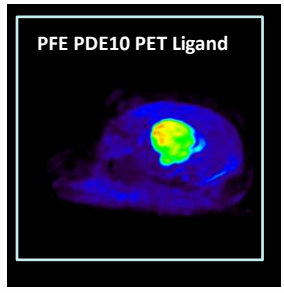
Desired attributes of CNS PET Ligands

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

GLP Tox: single acute IV in rats + 14d observation



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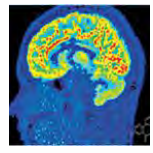
PET ligand discovery process historically suffered from high attrition rates

- *Med Chem Publications*
- *Close-in analogs of Clinical Candiate*

→ *NHP PET imaging* → *GLP tox, dosimetry and eIND filing*

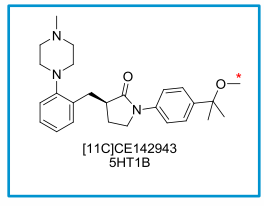


Clinical PET Imaging

5HT1B

(Pfizer/Washington University)

→ 12 analogs



- Average cost: ~ $80-120K /ligand for PET assessment in NHPs
- ~$1-1.5 million to identify a PET lead prior to GLP safety studies

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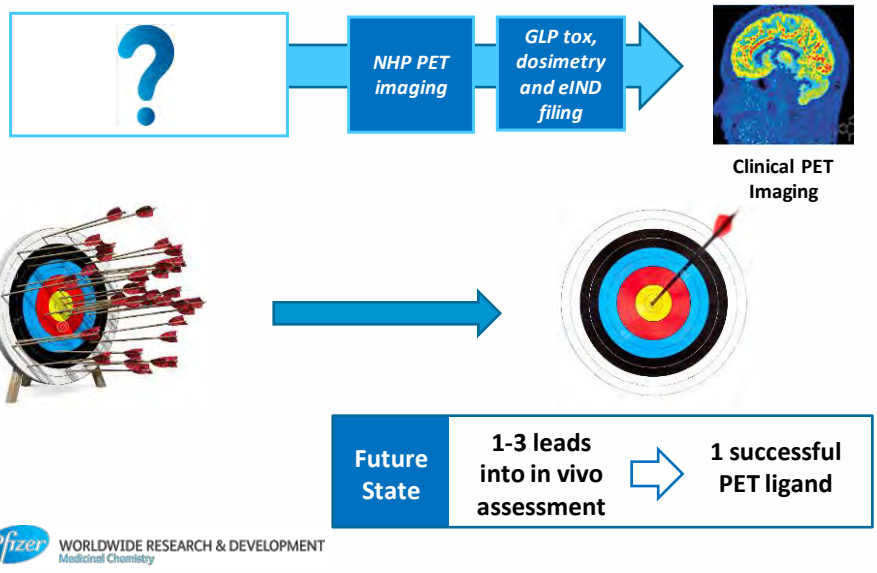
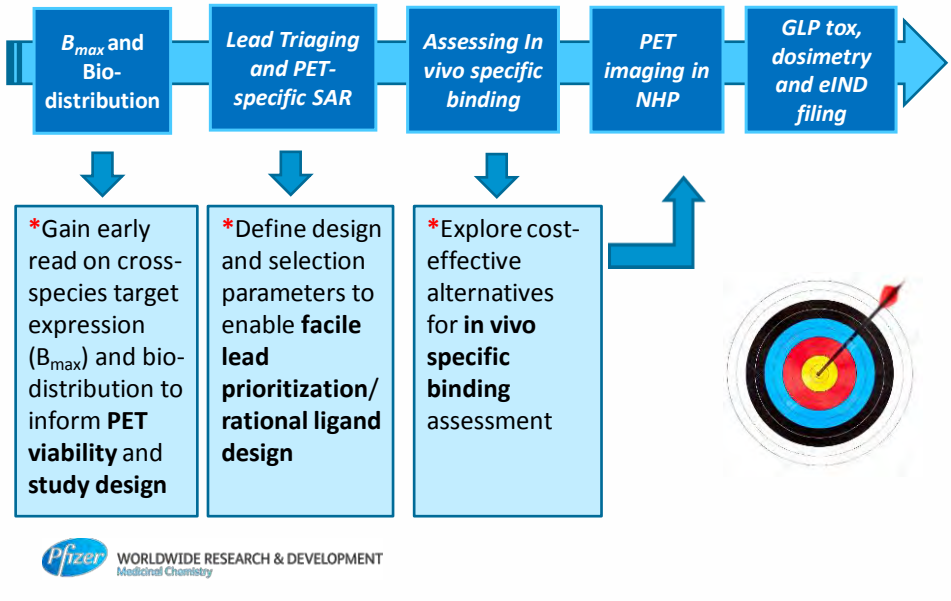
There is a clear need in a more efficient and resource-sparing PET ligand discovery process



Our Strategy to improve the CNS PET ligand discovery process



Our Strategy to improve the novel CNS PET ligand discovery process

*Gain early read on cross-species target expression (B_{max}) and bio-distribution to inform **PET viability** and **study design**

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Gain an early understanding on B_{max} to inform PET viability

B_{max} and Bio-distribution

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

Important to be highly selective; brain permeability not necessary

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

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

Target 1

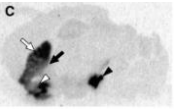
Species	Bmax
Mice	0.3 nM
Human	0.2 nM

Target 2

Species	Bmax
Mice	98 nM
NHP	75 nM
Human	TBD

Target 3

Target 4



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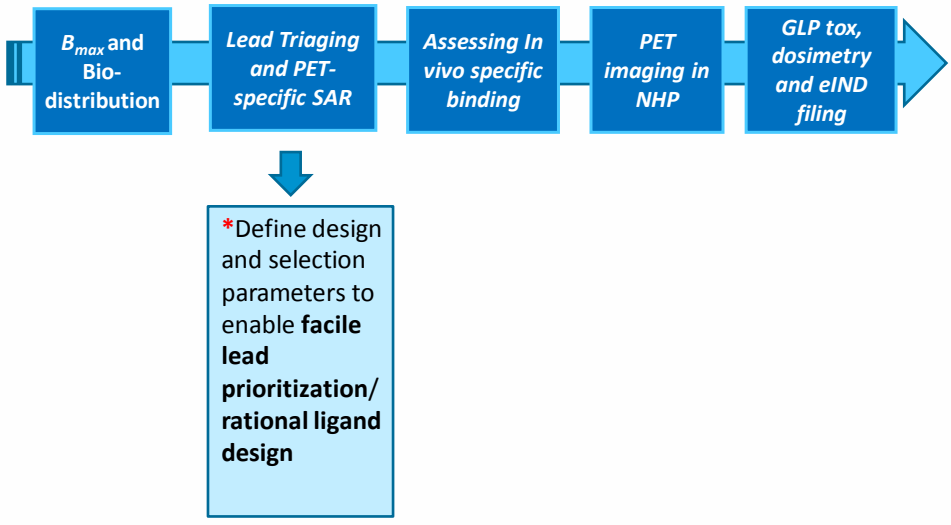
Patel, S.; Gibson, R. In vivo site-directed radiotracers: a mini-review. *Nucl. Med. Biol.* 2008, *35*, 805-815.

Our Strategy to improve the novel CNS PET ligand discovery process



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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

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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

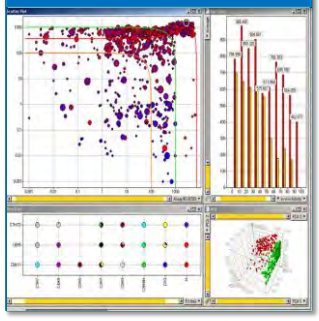
62 Validated PET ligands ("**Yes**" category)

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



Zhang, L.; Villalobos, A.; Beck, E. M.; Chappie, T. A.; Heck, S. D.; Helal, C. J.; Hou, X.; Skaddan, M. B.; McCarthy, T. J.; Verhoest, P. R.; Wager, T. T.; Zasadny, K. *J. Med. Chem.* **2013**, *56*, 4568.

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

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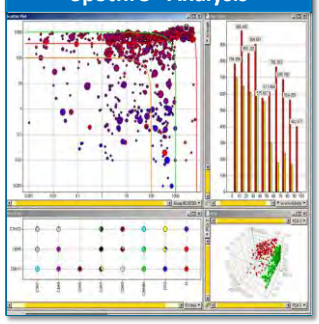

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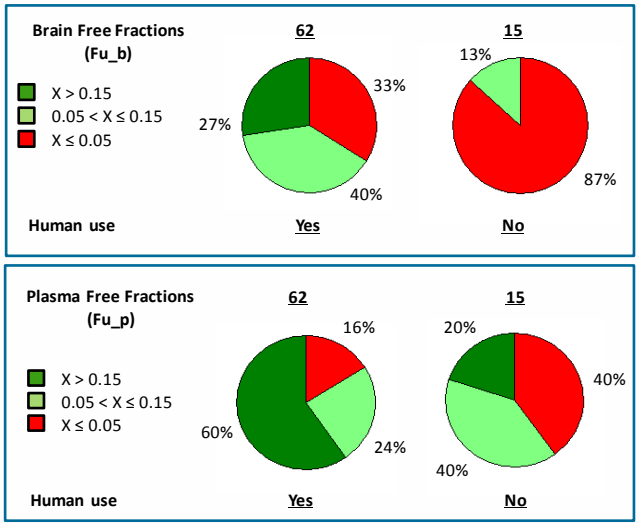
In vitro ADME properties: Brain Free Fraction (Fu_b) can serve as a useful predictor for NSB



Low non-specific binding

Fu_b > 0.05

High risk of NSB If both Fu_b and Fu_p < 0.05,

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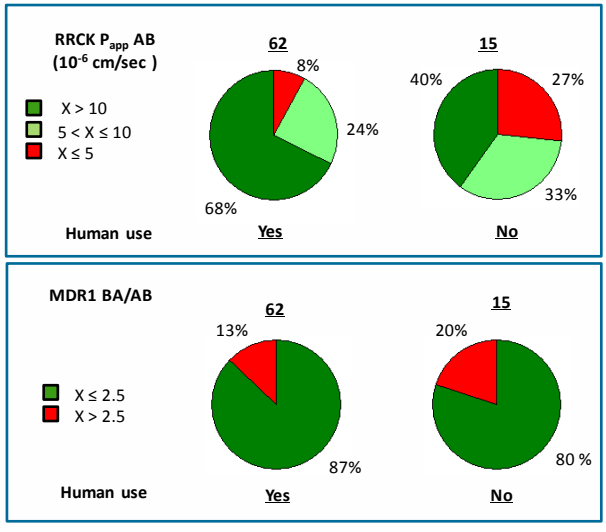
Moderate to high passive permeability and low Pgp liability are preferred for brain permeability



Brain Permeability

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

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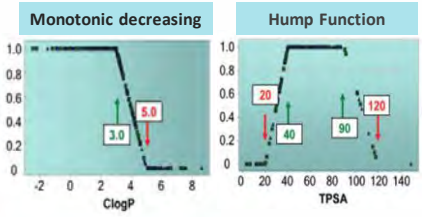
CNS MPO (Multi-parameter Optimization)

Properties	Function	Weight	CNS MPO	
			More desirable range (T0 = 1.0)	Less desirable range (T0 = 0.0)
ClogP	Monotonic decreasing	1.0	ClogP ≤ 3	ClogP > 5
ClogD	Monotonic decreasing	1.0	ClogD ≤ 2	ClogD > 4
MW	Monotonic decreasing	1.0	MW ≤ 360	MW > 500
TPSA	Hump Function	1.0	40 < TPSA ≤ 90	TPSA ≤ 20; TPSA > 120
HBD	Monotonic decreasing	1.0	HBD ≤ 0.5	HBD > 3.5
pK_a	Monotonic decreasing	1.0	pK_a ≤ 8	pK_a > 10

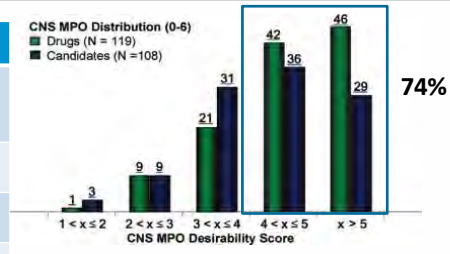
- **Functions set to favor CNS drug space**
- **Score each property ranging from 0 to 1**
- **Total CNS MPO = 0 (low) – 6 (high); A single parameter to track all 6 physicochemical properties**



Wager, T. T.; Hou, X.; Verhoest, P. R.; Villalobos, A. Moving beyond Rules: The Development of a Central Nervous System Multiparameter Optimization (CNS MPO) Approach to Enable Alignment of Druglike Properties. *ACS Chem. Neurosci.* 2010, *1*, 435-449.

CNS MPO (Multi-parameter Optimization)

Properties	Function	Weight	CNS MPO	
			More desirable range (T0 = 1.0)	Less desirable range (T0 = 0.0)
ClogP	Monotonic decreasing	1.0	ClogP ≤ 3	ClogP > 5
ClogD	Monotonic decreasing	1.0	ClogD ≤ 2	ClogD > 4
MW	Monotonic decreasing	1.0	MW ≤ 360	MW > 500
TPSA	Hump Function	1.0	40 < TPSA ≤ 9	
HBD	Monotonic decreasing	1.0	HBD ≤ 0.5	
pK_a	Monotonic decreasing	1.0	pK_a ≤ 8	



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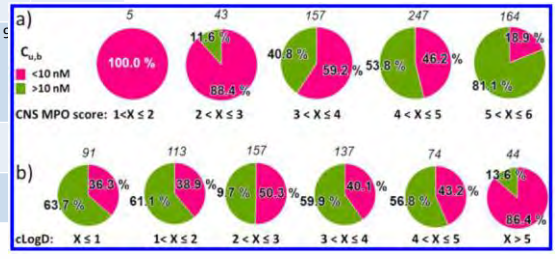

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Rankovic, Z. CNS Drug Design: balancing physicochemical properties for optimal brain exposure. *J. Med. Chem.* **2015**, *58*, 2584-2608.

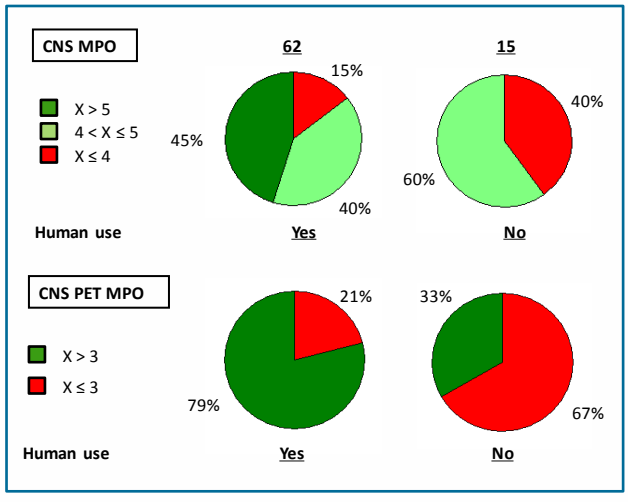
Definition of CNS PET MPO

Properties	Function	Weight	CNS MPO		CNS PET MPO	
			More desirable range (T0 = 1.0)	Less desirable range (T0 = 0.0)	More desirable range (T0 = 1.0)	Less desirable range (T0 = 0.0)
ClogP	Monotonic decreasing	1.0	ClogP ≤ 3	ClogP > 5	ClogP ≤ 2.8	ClogP > 4.0
ClogD	Monotonic decreasing	1.0	ClogD ≤ 2	ClogD > 4	ClogD ≤ 1.7	ClogD > 2.8
MW	Monotonic decreasing	1.0	MW ≤ 360	MW > 500	MW ≤ 305.3	MW > 350.5
TPSA	Hump Function	1.0	40 < TPSA ≤ 90	TPSA ≤ 20; TPSA > 120	44.8 < TPSA ≤ 63.3	TPSA ≤ 32.3; TPSA > 86.2
HBD	Monotonic decreasing	1.0	HBD ≤ 0.5	HBD > 3.5	HBD ≤ 1	HBD > 2
pK_a	Monotonic decreasing	1.0	pK_a ≤ 8	pK_a > 10	pK_a ≤ 7.2	pK_a > 9.5

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

Wager, T. T.; Hou, X.; Verhoest, P. R.; Villalobos, A. Moving beyond Rules: The Development of a Central Nervous System Multiparameter Optimization (CNS MPO) Approach to Enable Alignment of Druglike Properties. *ACS Chem. Neurosci.* 2010, *1*, 435-449.

Physicochemical properties: CNS PET MPO shows differentiation between two categories



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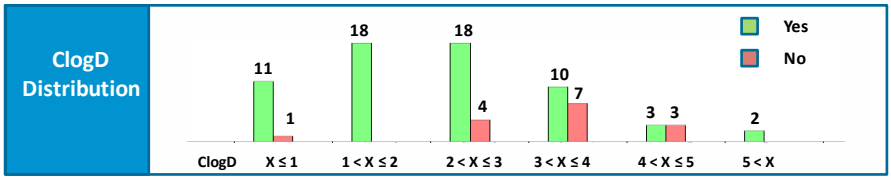
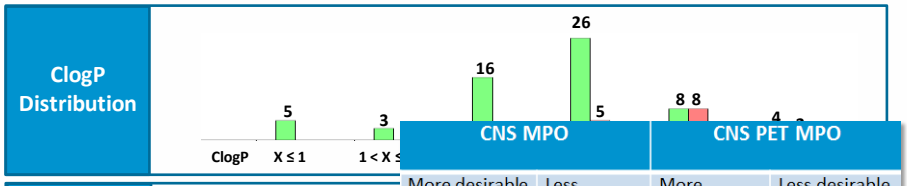
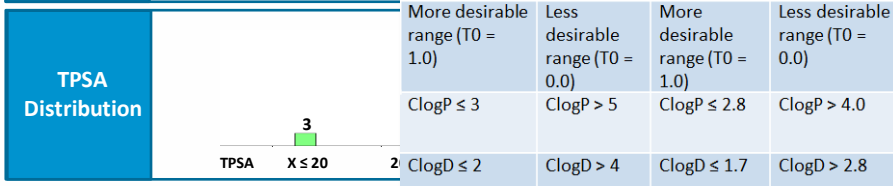
Majority of the successful PET ligands have ClogD ≤ 3 (47 out of 62) and ClogP ≤ 4 (50 out of 62)







CNS MPO		CNS PET MPO	
More desirable range (T0 = 1.0)	Less desirable range (T0 = 0.0)	More desirable range (T0 = 1.0)	Less desirable range (T0 = 0.0)
ClogP ≤ 3	ClogP > 5	ClogP ≤ 2.8	ClogP > 4.0
ClogD ≤ 2	ClogD > 4	ClogD ≤ 1.7	ClogD > 2.8

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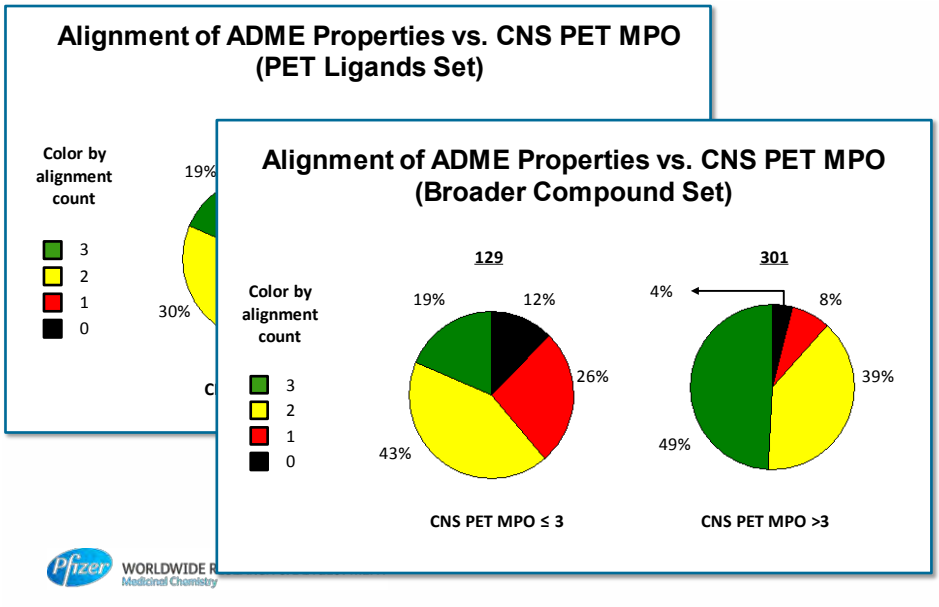
CNS PET MPO: Better probability to align all three in vitro ADME properties



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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	Low non-specific binding
CNS PET MPO > 3	Fu_b > 0.05
Brain Permeability	
RRCK > 5 x 10^{-6} cm/s; MDR BA/AB ≤ 2.5	High risk of NSB If both Fu_b and Fu_p < 0.05,

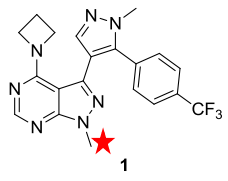
Prospective PET ligand design

(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

Rank order by potency

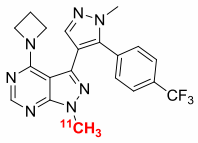


1

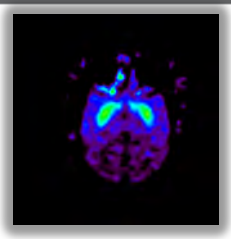
PDE2 IC_{50}: 2.3 nM
>600x selective over other PDEs
Clean in CEREP

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

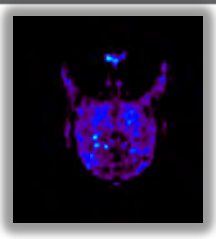
NHP PET images of Compound 1 and optimization strategy



[^{11}C]-1



Baseline
In vivo BP 0.6



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

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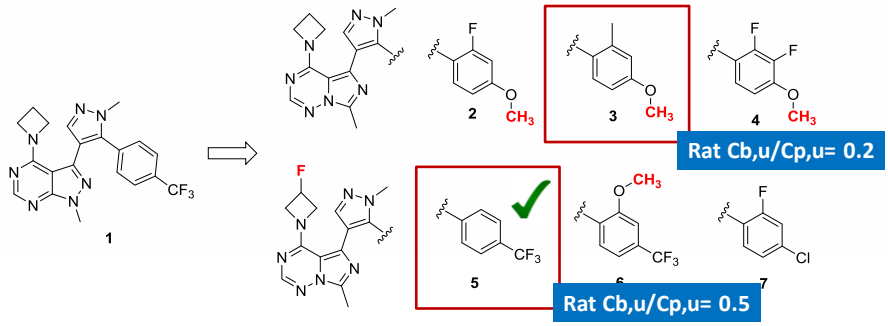
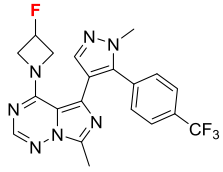
PET specific SAR guided by the Design Parameters



Compound #	CNS PET MPO	cRRCK (x 10^{-6} cm/sec)	cMDR1 BA/AB	cFu_b	Human PDE2 IC_{50} (nM)	
2	4.55	25.5	1.36	0.21	0.8	
3	4.55	23.5	1.87	0.21	0.6	←
4	4.55	23.9	1.48	0.18	1.1	
5	4.81	21.5	1.32	0.10	0.5	←
6	4.55	21.7	1.57	0.12	2.0	
7	4.83	28.4	1.12	0.07	1.7	

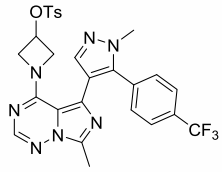
Profile and F-18 labeling of PF-05270430



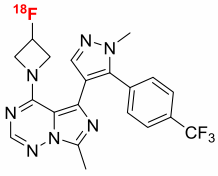
PF-05270430

- **PDE2 IC_{50}: 0.5 nM**
- > 1800x selective over other PDEs
- Clean in CEREP

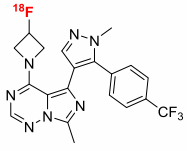
- CNS PET MPO= 4.81
- RRCK = 21.0
- MDR BA/AB = 1.71
- Fu_b= 0.08
- Fu_p= 0.17



TBA[^{18}F], *t*-amyl alcohol, 110°C, 30 min.
99.5% radiochemical purity,
14592 ± 4095 Ci/mmol
specific activity.



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



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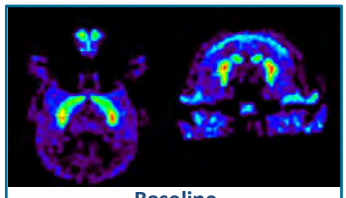
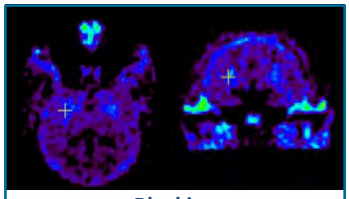
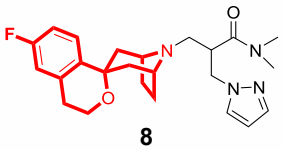


Baseline
In vivo BP: Putamen 1.84;
Caudate: 1.44



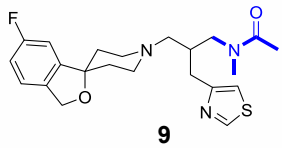
Blocking
With a selective PDE2 inhibitor
(2.0 mg/kg sc)

Application of the PET design parameters in NOP opioid receptor *in vivo* radiotracer development



8

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

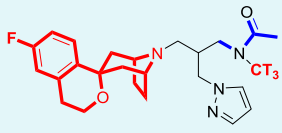


9

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

- **Potency Handle**
- **Selectivity Handle**

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

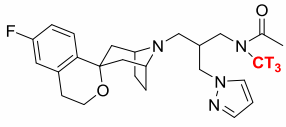


11 (PF-7191)

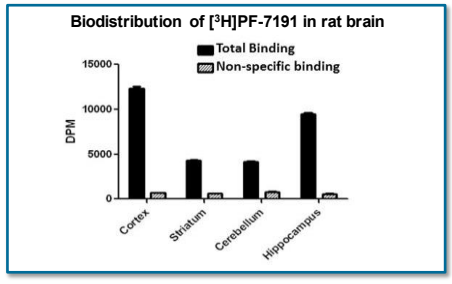
- NOP Ki= 0.1 nM
- Mu-opioid= 145.5 nM (1036x)
- PET MPO= 4.0
- RRCK = 8.0
- MDR BA/AB = 1.80
- Fu_b= 0.06
- Fu_p= 0.08

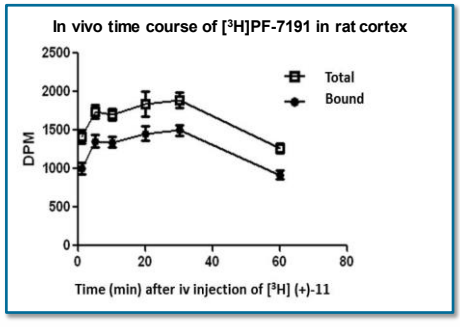
Zhang, L.; Drummond, E.; Brodney, M. A.; Cianfrogna, J.; Drozda, S.; Grimwood, S.; Villalobos, A. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 5219.

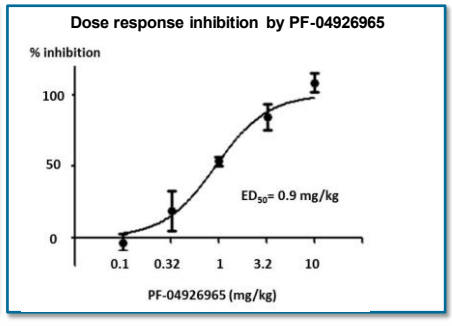
[3H]PF-7191 demonstrated high specific binding in vivo and enabled in vivo receptor occupancy study



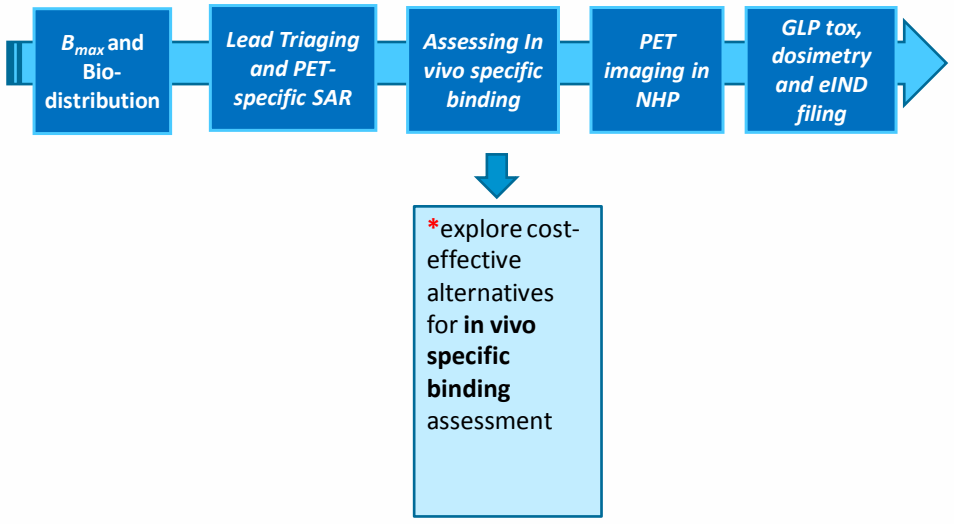
[^{3}H]**PF-7191**







Our Strategy to improve the novel CNS PET ligand discovery process



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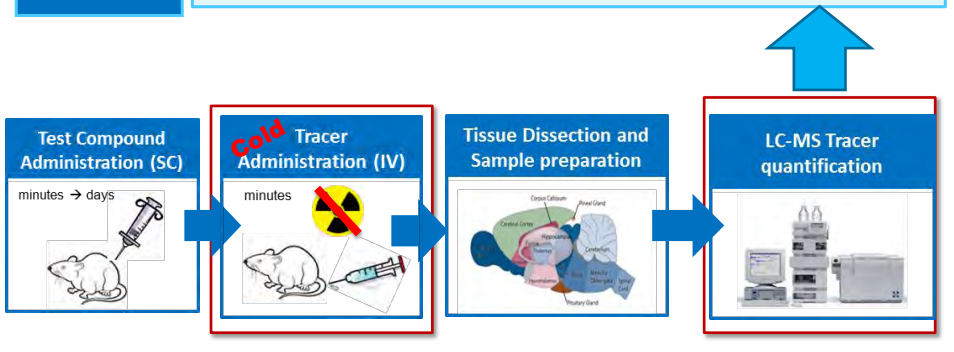
Explore cost-effective alternatives for in vivo specific binding assessment

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**



Chernet, E.; Martin, L. J.; Li, D.; Need, A. B.; ***Barth, V. N.***; Rash, K. S.; Phebus, L. A. Use of LC/MS to assess brain tracer distribution in preclinical in vivo receptor occupancy studies: dopamine D2, serotonin 2A and NK-1 receptors as examples. *Life Sci.* **2005**, *78*, 340-346.

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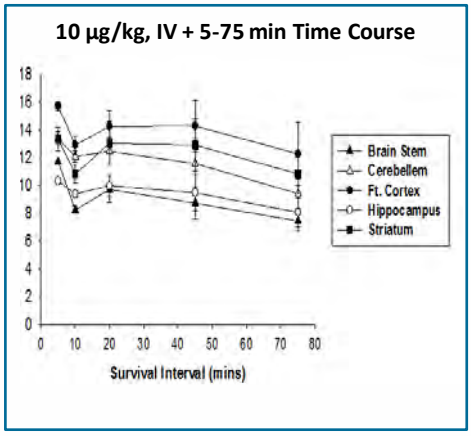
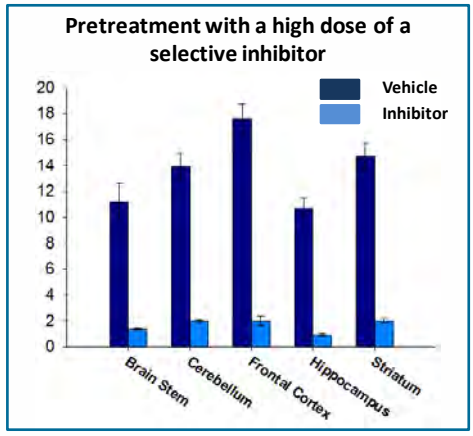
Application of LC-MS/MS cold tracer method in Enzyme Target 1





- Consistent with known target bio-distribution
- High Level of specific binding

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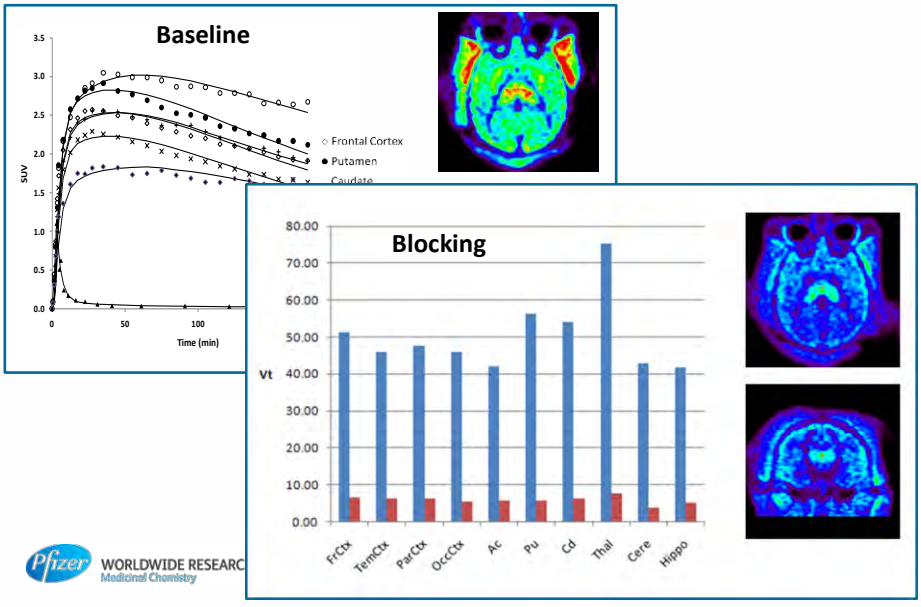
LC-MS/MS cold tracer outcome well-translated in NHP PET Imaging



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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

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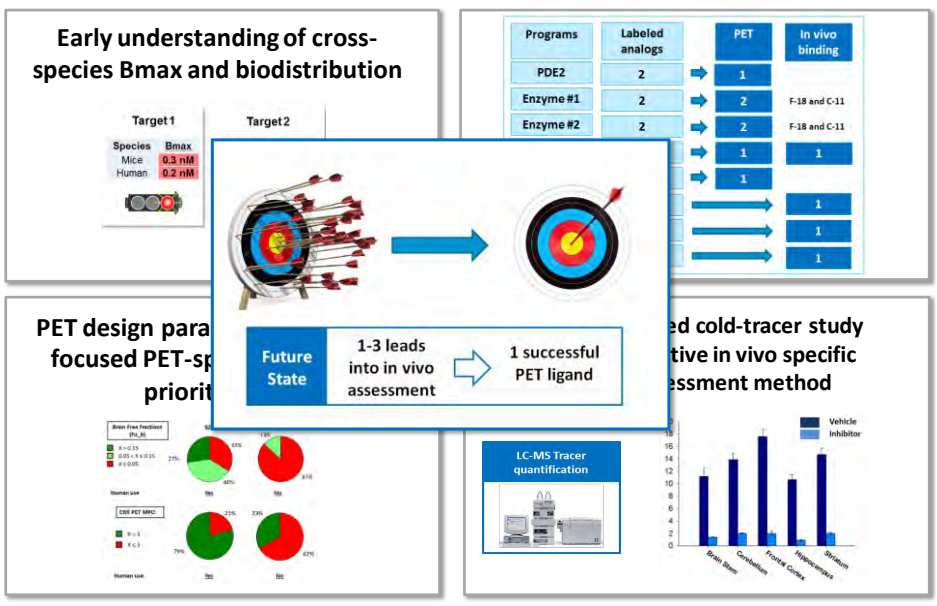
A Streamlined and Resource-Sparing CNS PET Ligand Discovery Process



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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…

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Thank you for your attention!

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Reference Guide

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  - Rankovic, Z. CNS Drug Design: balancing physicochemical properties for optimal brain exposure. *J. Med. Chem.* **2015**, *58*, 2584-2608.
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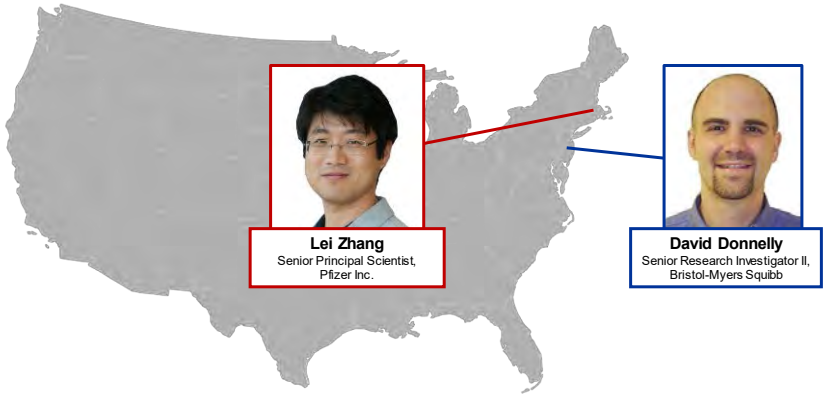

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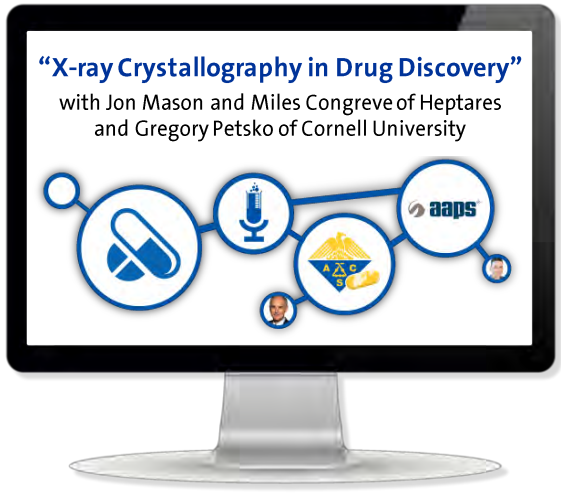

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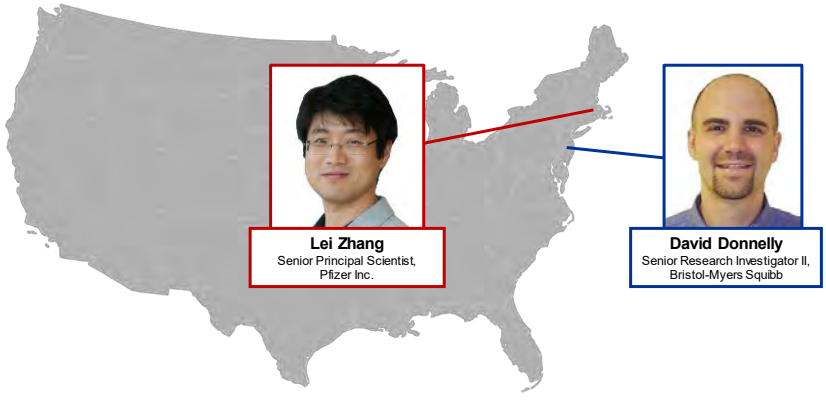

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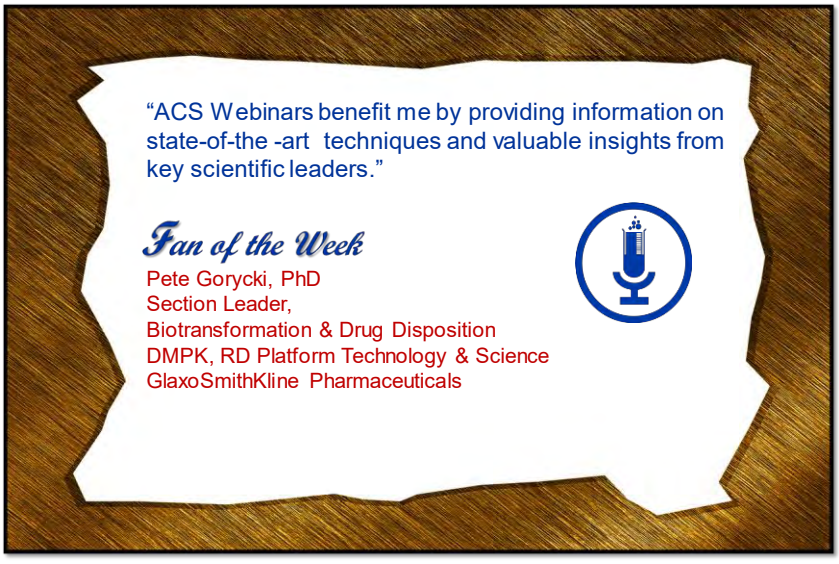

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