Green Radiochemistry
& Other Stories

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TRIUMF Science Week, August 2020

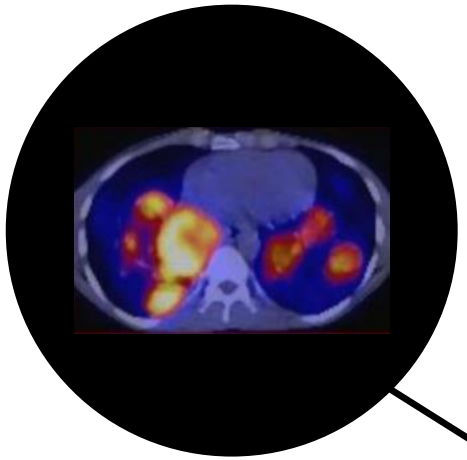
@Scott_LabUM

The University of Michigan PET Center

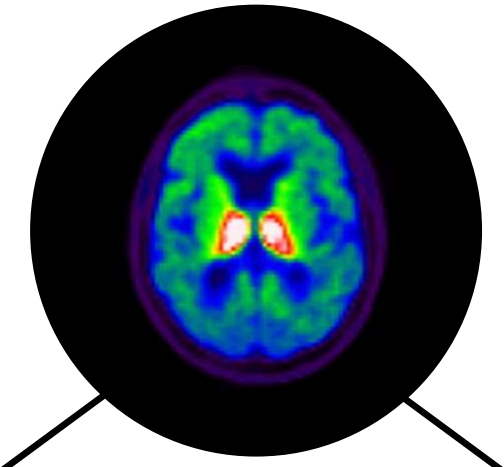
- New PET Center opened in 2006 and expanded in 2010
- 2 x GE PETTrace Cyclotrons
- 3 x Gallium-68 Generators
- 9 full-size hot-cells, 4 mini-cells and 1 dispensing hot-cell
- 10 GE TRACERlab & FASTLab 2 $^{18}F/^{11}C$ Synthesis Modules
- 2 x GE Irene modules (^{18}F / ^{68}Ga / ^{13}N)
- 3 clinical PET-CT, 7 SPECT-CT and 5 SPECT scanners
- Radiotherapy stations for ^{177}Lu, ^{131}I etc.
- Preclinical PET scanners for rodent, nonhuman primate etc.

Scott Lab Overview

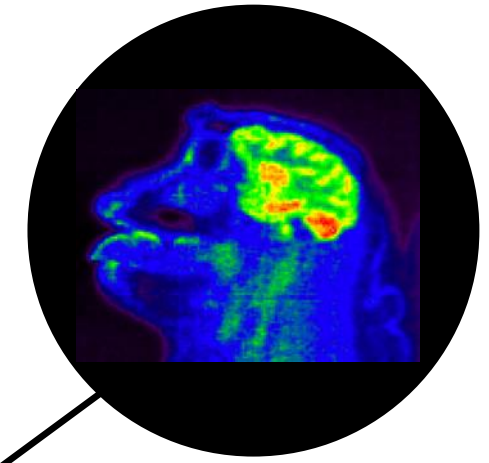
1. Clinical Operations

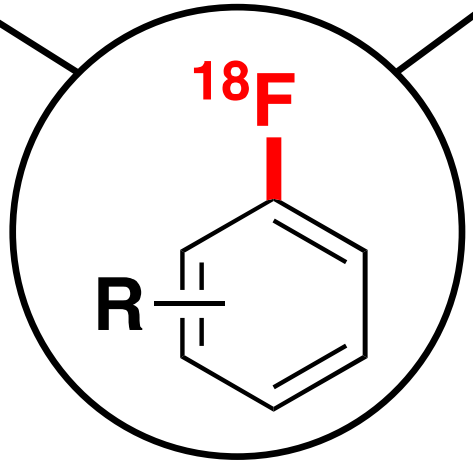


2. Clinical Research



3. Novel Tracer Discovery





4. New Radiochemistry

5. New Tech Development

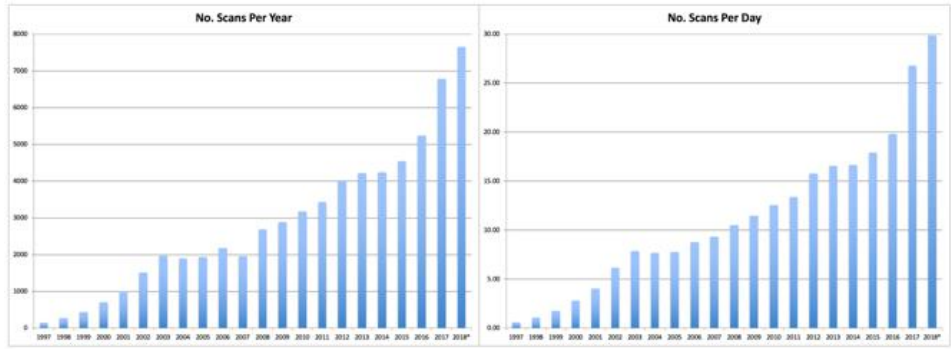
MICHIGAN MEDICINE
UNIVERSITY OF MICHIGAN

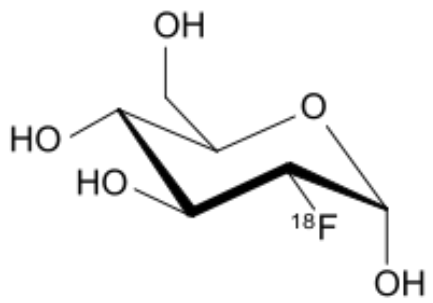
1. PET Utilization for Clinical Care @ UM

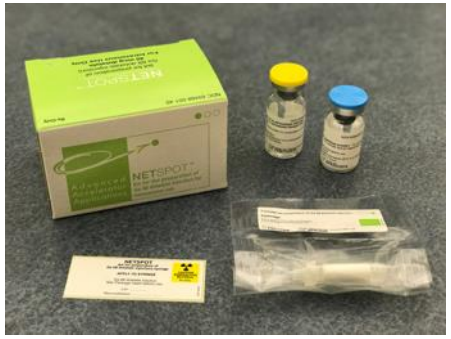
- Clinical PET utilization at Michigan Medicine doubled between 2014 and 2018 (8-10k patients get scanned per year). Driven by introduction of NETSPOT and ^{68}Ga-PSMA, growth in FDG utilization, and migration from cardiac SPECT to cardiac PET;

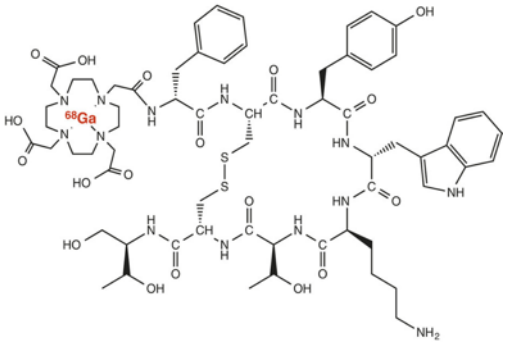
- Current scanner capacity is 2 x PET-CTs for clinical care and 1 PET-CT for clinical research. Two new clinical PET-CT scanners are being proposed to expand clinical bandwidth.

- Theranostics (e.g. Lu177 Lutathera (neuroendocrine) and Lu177 PSMA (prostate) taking Nuclear Medicine into a new age of theranostics)





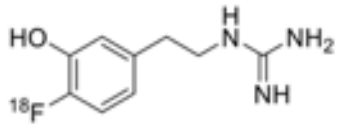




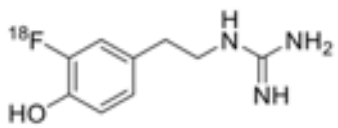
MICHIGAN MEDICINE
UNIVERSITY OF MICHIGAN

2. Clinical Research

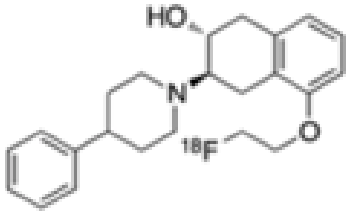
a) Translation of new tracers

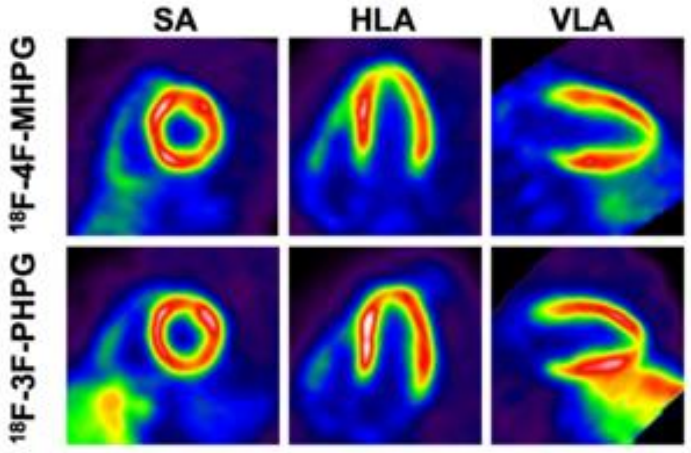


^{18}F-4F-MHPG



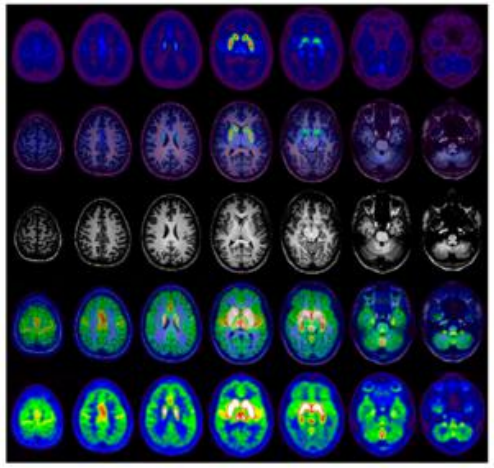
^{18}F-3F-PHPG





Circulation: Cardiovascular Imaging, 2019

IND: 122,511



J Nucl Med, 2014; 55 (3): 396

IND: 109,500

b) Menu of established tracers available to use

CARBON-11

- [^{11}C]Acetate (TCA Cycle – Cardiac, Oncology) -- RDRC
- [^{11}C]Butanol (Blood flow) -- RDRC
- [^{11}C]Carfentanil (Opioid) -- RDRC
- [^{11}C]Choline (Oncology) -- RDRC
- [^{11}C]DASB (SERT) -- RDRC
- [^{11}C]DTBZ (VMAT2) – IND / -- RDRC
- [^{11}C]FMZ (BZD) – IND / -- RDRC
- [^{11}C]HED (Adrenergic) -- RDRC
- [^{11}C]Methionine (Oncology) -- RDRC
- [^{11}C]Palmitate (Cardiac) -- RDRC
- [^{11}C]PBR28 (Neuro, Cardiac and Oncology) -- RDRC
- [^{11}C]PE2I (Dopamine transport) -- RDRC
- [^{11}C]PiB (Amyloid) -- RDRC
- [^{11}C]PMP (Acetylcholinesterase) -- RDRC
- [^{11}C]Raclopride (Dopamine) -- RDRC
- [^{11}C]Sarcosine (Prostate cancer) – IND

GALLIUM-68

- [^{68}Ga]NETSPOT (Neuroendocrine tumors) – Parent NDA
- [^{68}Ga]PSMA-11 (prostate cancer) – Cost-recovery IND

FLUORINE-18

- [^{18}F]FDG (Glucose metabolism) -- ANDA
- [^{18}F]NaF (Bone) -- RDRC
- [^{18}F]FLT (Cell proliferation) -- RDRC
- [^{18}F]FAZA (Hypoxia) -- RDRC
- [^{18}F]Flubatine (NAChRs) -- RDRC
- [^{18}F]Fluorocholine (Prostate cancer) -- RDRC
- [^{18}F]FEOBV (VAChT) -- RDRC
- [^{18}F]MPPF (5HT-1A) -- RDRC
- [^{18}F]ASEM (alpha 7) -- RDRC
- [^{18}F]MHPG / [^{18}F]PHPG (Cardiac NET) -- IND
- [^{18}F]N-Methyl Lansoprazole (Tau) -- RDRC
- [^{18}F]AV1451 (Tau) – RDRC

NITROGEN-13

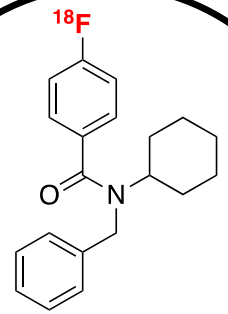
- [^{13}N]NH_3 (cardiac) – IND

RUBIDIUM-82

- $RbCl_2$ (Cardiac Rest/stress) – Parent NDA

3. Development of new PET radiotracers

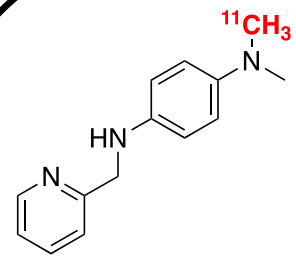
1. Neuroinflammation



JPA (2020)

RAGE, CSF1R

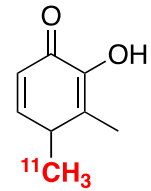
2. Metal/Protein Aggregates



ACS MCL (2015)

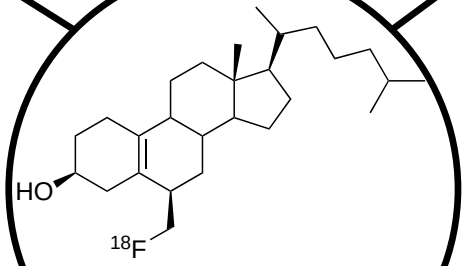
Aß, tau, TDP-43, α-Syn

3. Metal Homeostasis



J Nucl Med
(2020, S1)

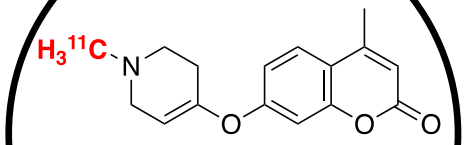
Iron dysregulation



SynOpen (2019)
ACS MCL (2020)

4. Cholesterol Metabolism

Cholesterol trafficking, ATR101



ACS CN (2015, 2018)
ACS MCL (2018)

5. Trapped Metabolite Imaging

MAO

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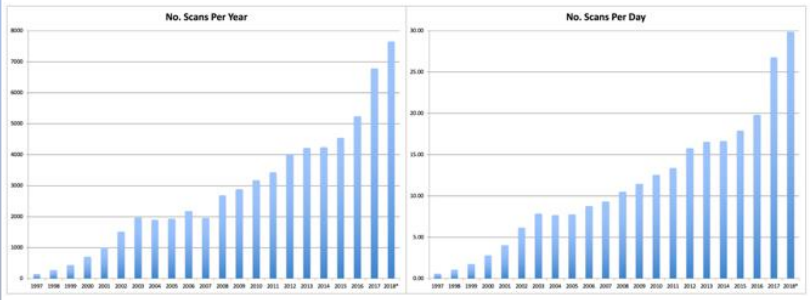
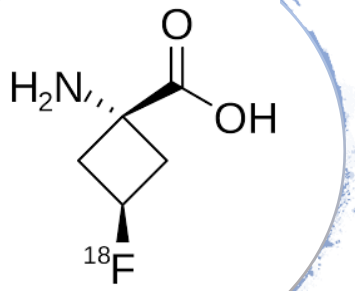
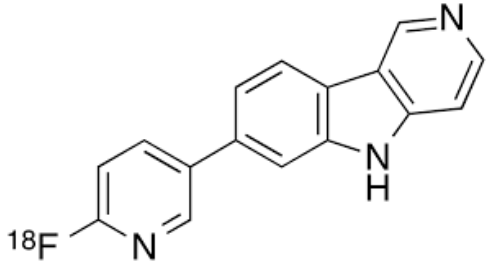
4. Basic Science Research

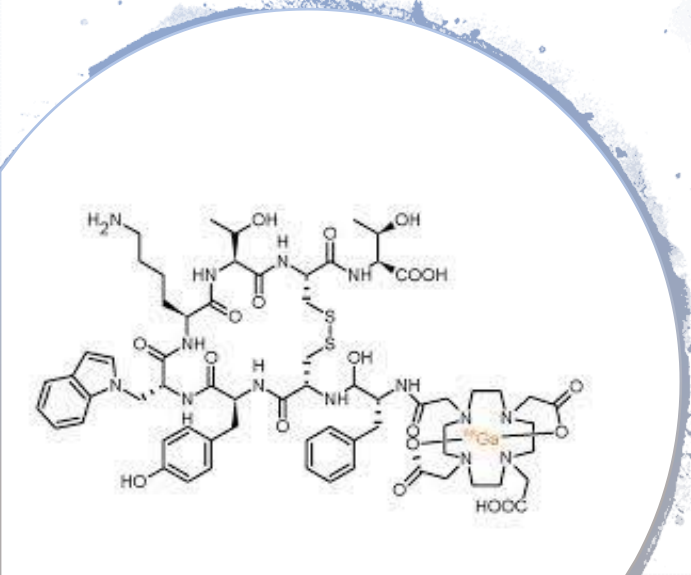
Radiochemistry
Methodology

Simplifying Radiotracer Production









There are a number of challenges facing PET drug manufacturers in 2020:

1. More tracers are garnering FDA approval, including ^{11}C, ^{18}F and ^{68}Ga tracers, mandating increased numbers of more diverse radiosyntheses per day;

2. Demand for PET drugs is increasing overall (clinical throughput has doubled at UM since 2014);

3. There is a need to label more complex molecules (e.g. labeling tracers for new imaging targets or labeling complex pharmaceutical assets);

4. cGMP is increasing regulatory burden (and cost) associated with PET drug manufacture.

My lab is therefore motivated to simplify the synthesis and quality control of PET drugs

Basic Science A: Green Radiochemistry

Peter's Methodology Philosophy

- Develop general, mild, high-yielding, and user-friendly labeling procedures;
- We're starting to better understand fluorine-18 and carbon-11, as well as their behavior
- Our chemistry must work with diverse substrates – long term goal of our program is to be able to label any molecule!
- Our methods must be suitable for clinical production;
- Our chemistry must be easy to use, work in different labs and be compatible with many different synthesis modules or manual set-ups - **Simple is always better!**

Residual Solvents

- Solvents assigned Class by ICH Guidelines based upon toxicity:
  - Class III (EtOH, DMSO, Acetone, MEK etc.)
  - Class II (MeCN, DMF, DCM, 2-Pentanone etc.)
  - Class I (Benzene, CCl_4) – **NOT ALLOWED IN THE LAB!**
- Syntheses employing Class II solvents represent an element of risk to the patient, and thus require daily residual solvent testing. This is time consuming, especially for short-lived ^{11}C doses, and difficult to schedule 8 x 20-30 min GC runs (typically includes blank – 3 x standards – blank – 3 x doses – blank) and is particularly challenging on days with high volume of syntheses;
- In the cGMP age, all solvents, reagents etc. require management through an inventory system;
- All waste requires disposal as HAZMAT (expensive, especially for waste containing methyl ethyl ketone (MEK) due to regulations stemming from its use in the dry-cleaning industry);
- USP<823> gives a provision that for syntheses employing Class III solvents ONLY (for cleaning, synthesis, HPLC, reformulation etc.), then daily residual solvent analysis **is not required** and the test can be reduced to a periodic QC test (e.g. quarterly like RNP, Osmolality etc.)
- **Therefore, we have an interest in eliminating Class II solvents from the synthesis of clinical PET drugs**

This is Green chemistry…

- The invention, design and application of chemical products and processes to reduce or to eliminate the use and generation of hazardous substances.

Anastas, P. T.; Warner, J. C. Green Chemistry: Theory and Practice, Oxford University Press, 1998, p.30

and Pharmaceutical QbD

- Quality should be designed into a product, recognizing that most quality crises and problems relate to the way in which a product was designed in the first place. A high-quality drug product Is a product free of contamination and reliably delivering the benefit promised in the label to the consumer.

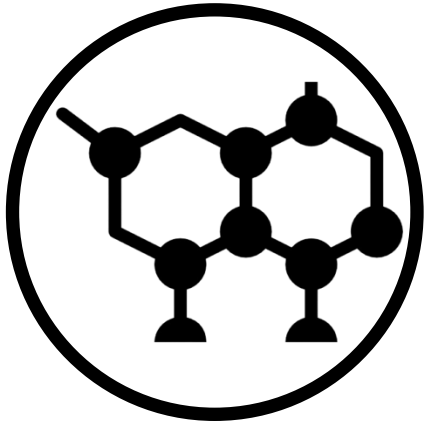
- It quickly became apparent that using ethanol as the only organic solvent would be advantageous – Class III, GC methods in place;
- However, perfluoroalkanesulfonate esters ‘known’ to be prone to solvolysis;
- But, many ‘standard practices’ in organic synthesis do not translate to radiochemistry because of the tracer concept;
- We have explored elimination of Class II solvents from the synthesis of ^{11}C and ^{18}F-labeled tracers.

Principles of Green Radiochemistry

Synthesis Module Cleaning

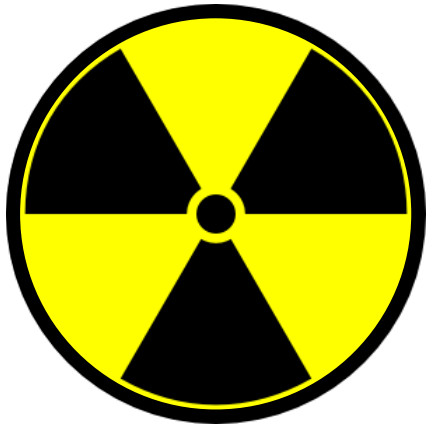
Use EtOH for cleaning (acetone is also green and Class III)

Reagent Preparation



Use EtOH for preparing reagents (e.g. azeotropic drying of ^{18}F)

Radiolabeling



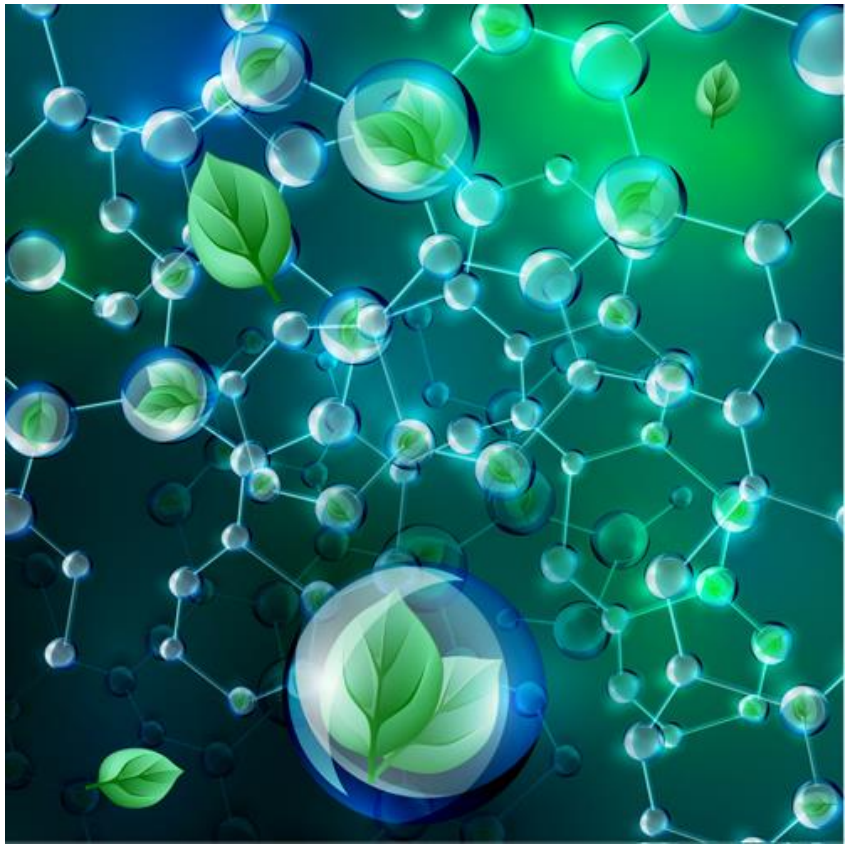
Use EtOH as reaction media (DMSO is also Class III, but less green)

Purification

Use EtOH for HPLC mobile phase and/or SPE processing

Formulation

Formulate doses in EtOH

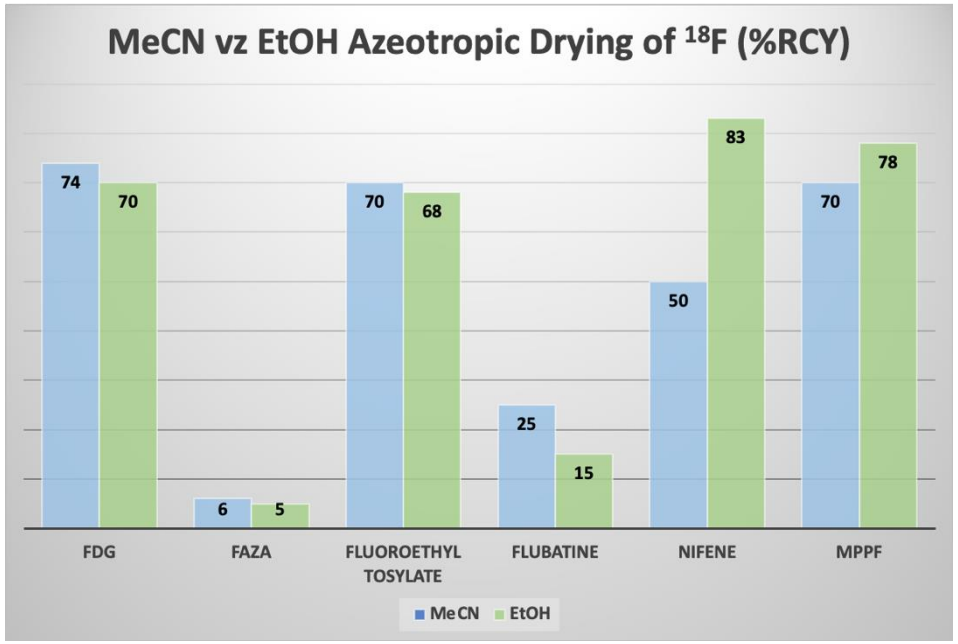


		CFN	CHO	DASB	DTBZ	FMZ	HED	MET	OMAR	PBR28	PIB	PMP	RAC
Clean	Old	Acetone											
Synth		DMSO	EtOH	MEK	DMF	MeCN	DMF	Acetone	DMSO	MeCN	3-Pen	DMF	MEK
Purif		PrOH	EtOH	MeCN	EtOH				MeCN/MeOH	MeCN	MeCN	EtOH	
Clean	Green	Ethanol											
Synth													
Purif													

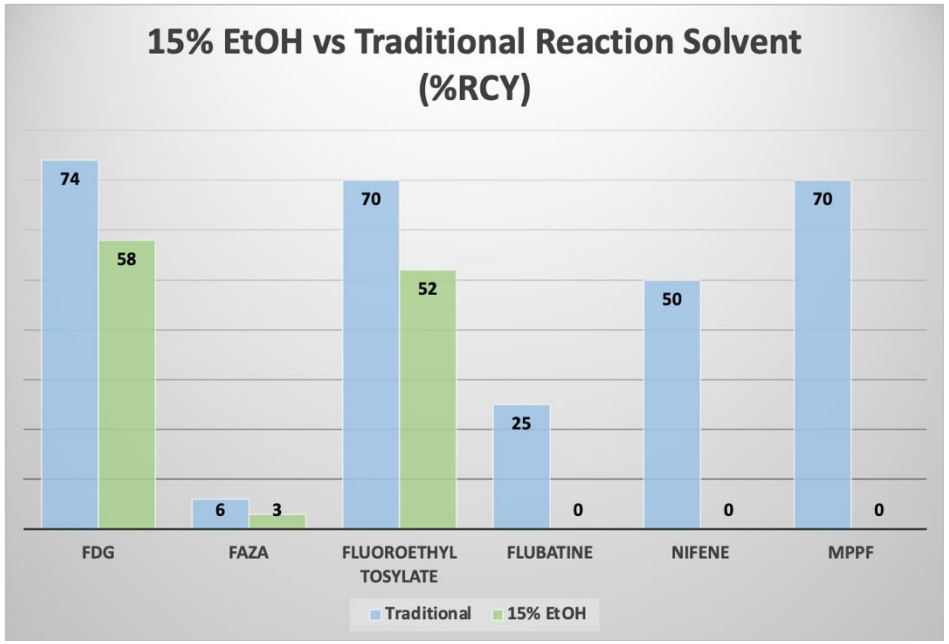
Carbon-11 radiochemistry can be conducted using ethanol as the only organic solvent for module cleaning, synthesis, HPLC, and reformulation!

See: Shao *et al*., NMB (2012), ARI (2015)

Green Carbon-11 Radiochemistry



MeCN is a class II solvent used to azeotropically dry fluoride. Due to the similar BPs of the azeotropes (MeCN=76.5°C; EtOH=78.2°C), switching to EtOH is straightforward and does not impact RCY.

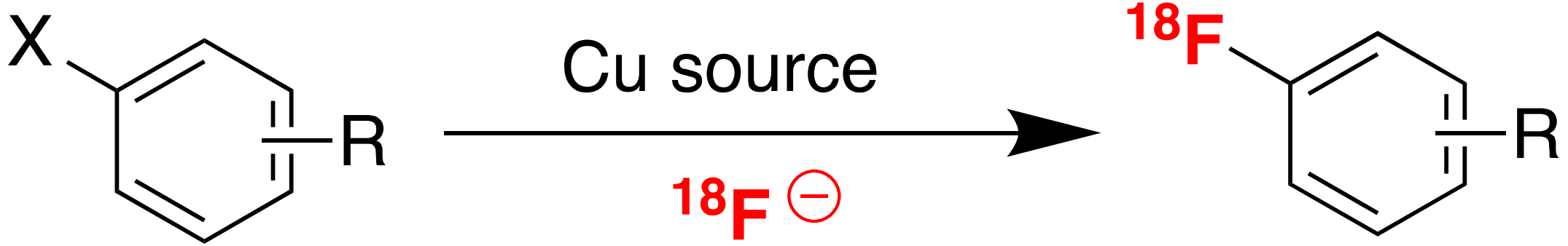


Remarkably, aliphatic fluorination reactions could be conducted using 15% EtOH in H_2O as reaction solvent, with some reduction in RCY compared to traditional solvents (DMSO, MeCN); arene substrates were unreactive in EtOH.

Green Fluorine-18 Radiochemistry

See: Stewart *et al*., Chem Commun (2015)

4. Basic Science B: Development of New Radiolabeling Reactions



X = I, B, Sn, H etc.

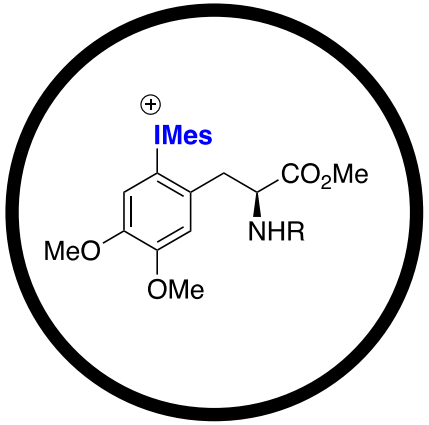
Copper-mediated Radiofluorination (CMRF)

NIBIB Funded to develop new radiochemistry (R01EB021155)

[For recent work, see: ACIE 2019, JACS 2020, Nature Prot 2020]

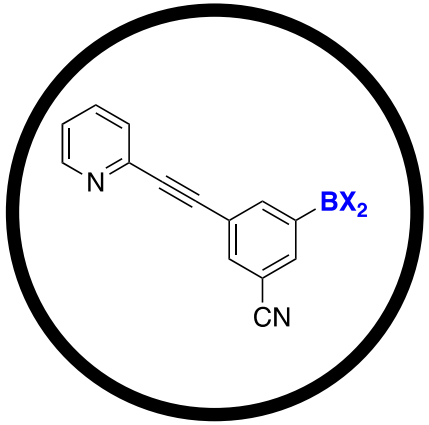
Application of Green Radiochemistry to CMRF

Iodonium Salts



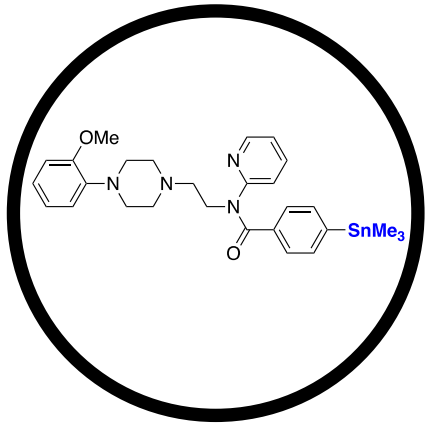
Org Lett (2014)

Organoborons



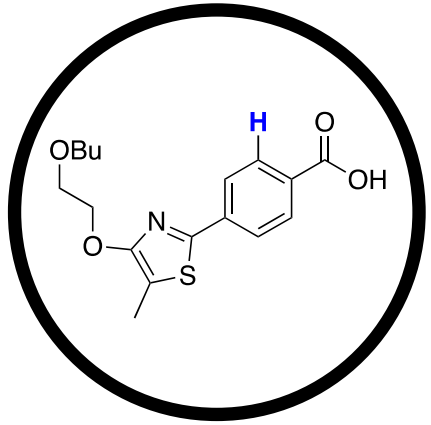
Org Lett (2015)
Sci Rep (2017)
JLCR (2018), OBC (2019)
Nat Prot (2020)

Organostannanes



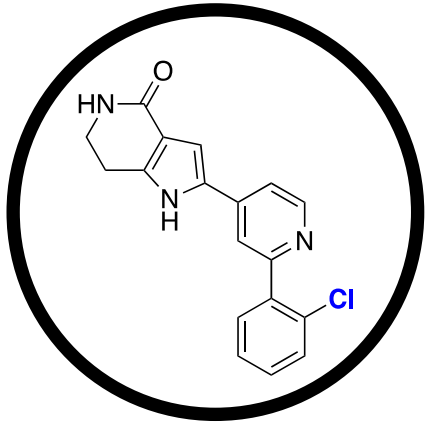
Org Lett (2016)
ACS Med Chem Lett (2020)

C-H Fluorination



ACIE (2019)

Aryl Halides



JACS (2020)

- Our CMRF methods have been rapidly adopted by the radiochemistry community and used to prepare >100 radiotracers for preclinical and clinical PET imaging [for a review, see: Wright et al., Clin Trans Imaging (2020)];
- Green chemistry and QbD principles have informed our method development from day 1;
- For example, QbD and green chem informed our decision to use Cu-mediated reactions. It is both a green choice for a catalyst, and has amongst the lowest toxicity of available catalysts.

Elemental Impurities for Drug Products

Element	Oral Daily Dose PDE[a] (µg/day)	Parenteral Daily Dose PDE (µg/day)
Cadmium	5	2
Lead	5	5
Inorganic arsenic[a]	15	15
Inorganic mercury[a]	30	3
Iridium	100	10
Osmium	100	10
Palladium	100	10
Platinum	100	10
Rhodium	100	10
Ruthenium	100	10
Chromium	11000	1100
Molybdenum	3000	1500
Nickel	200	20
Vanadium	100	10
Copper	3000	300

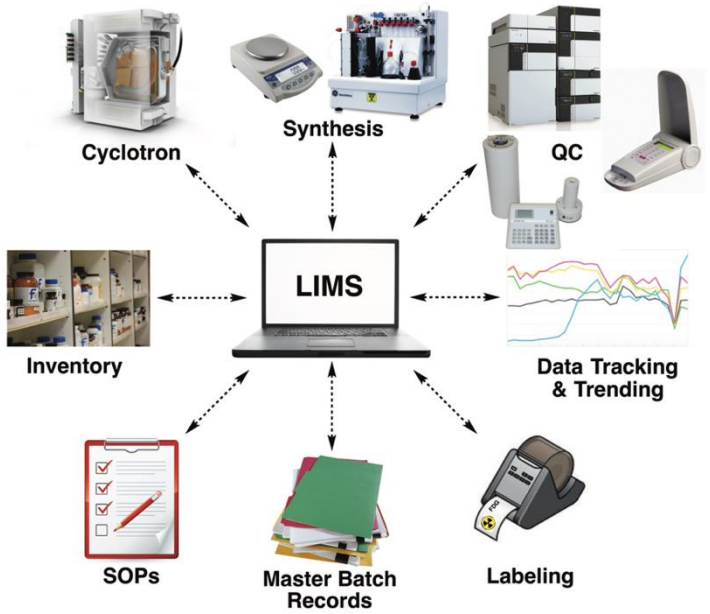
^{68}Ga Targetry
Rodnick *et al*. (2020)
EJNMMI R&C, Accepted

New automation
Frank *et al*. (2019)
EJNMMI R&C, 4:24

IoT, big data, AI
Thompson *et al*. (2016)
ACS Cent Sci, 2:497

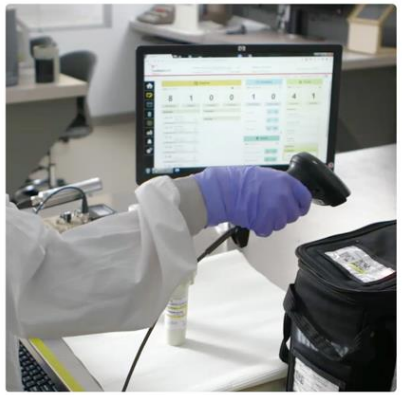
5. New Technology

Radiochemistry



Thompson, ACS Cental *Science,* 2016.

Nuclear Pharmacy



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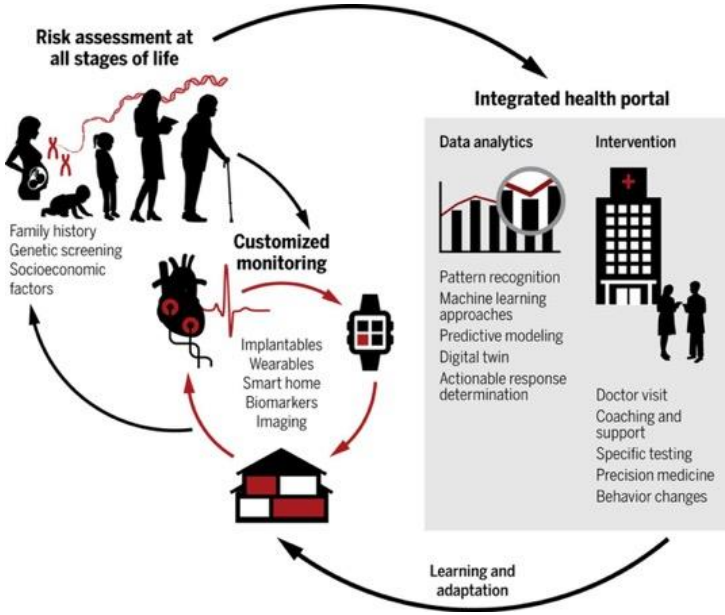

Gambhir, *Science Transl. Med.* 2018: 10, eaao3612.

IoT and Precision Health

Summary

- Nuclear medicine (PET, SPECT and Radiotherapy) are very active areas of research and clinical growth in radiology departments;
- A lot of developments have occurred in the community over the last few years that have pushed nuclear medicine into a new era, including FDA approval of new diagnostic PET drugs and radiotherapeutics;
- Much of this innovation presents new challenges to the community (cGMP, challenging targets, the transition from getting products FDA-approved to meeting routine delivery etc.), but new developments continue to facilitate this (green radiochemistry, late-stage radiofluorination, IoT, targetry etc.) that will be the exciting future of the field.

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