Richard Freifelder, PhD – Facility Director
Chin-Tu Chen, PhD – Faculty Director
Mohammed (Parvez) Bhuiyan, PhD – Radiochemist
Anna Kucharski, BS – Cyclotron Operator/Radiochemist
9,500 sf of space
6 m to the deck (ceiling)
Good work flow, sight lines, communications
Holistic, logical design – 5 clean rooms (pink) surrounding QC (white)
Radioisotope production space (left or west side)
Radiopharmaceutical production, QC/Pharmacy space (right or east side)
Vault

- Cyclotron in vault
- 8 possible targets
- 2 m thick walls, 7’ 2” thick
- 1.95 m thick ceiling, 6’ 5” thick
- Cyclotron weighs 27T
- Took 40 hrs to rig into vault
Vault door

- Big vault needs a big door!
- 4T empty, filled with 4 cu. yds. of concrete
- Total weight: 16T of shielding
Quality Control and Production

- GMP ready
- Redundant equipment
- 5 clean rooms
- 350 m² for radiochemistry
Power Supply Room
Approaching cGMP/FDA Compliance

Holistic facility designed to current regulatory standards
Not an “organic” growth out of old space with compromises in work flow, safety for workers, and safety for the produced drugs
Dispensing Area and Cell

Dispensing is a cleanroom! ISO Class 7 Cell combines ISO Class 6 pre-chamber and ISO Class 5 (sterile) drug dispensing area. Pass-throughs to non-classified QC area. Again, designed based on prior experience in clinical and research drug production.
More hot cells planned for other cleanrooms
amples of Available PET Radiotracers

- $^{18}$F-FDG, most commonly and routinely used in clinics
- $^{18}$F-NaF, an approved bone & plaque imaging agent
- $^{18}$F-MISO, a hypoxia imaging agent
- $^{18}$F-FLT, a cell proliferation imaging agent (IND)
- $^{18}$F-FAP (or $^{18}$F- 2FA) , a nicotinic receptor agent.
- $^{18}$F-Nifene, another nicotinic receptor agent
- $^{18}$F – NaBF$_4$, sodium/iodide symporter marker
- $^{11}$C-PIB, an Alzheimer’s amyloid plaque imaging (IND WIP)
- $^{13}$N-ammonia, an approved imaging agent for perfusion
- $^{15}$O-water, for imaging of blood-flow/perfusion
Samples of PET Radiotracer Research

- $^{18}\text{F} – \text{3F4AP}$, Imaging of multiple sclerosis (MS)
- $^{18}\text{F} – \text{JW199}$, Cancer imaging agent (with Chemistry)
- $^{18}\text{F} – \text{IGF-1}$, Brain imaging via intranasal drug delivery
- $^{48}\text{VO(}\text{acac)}\text{2}$, Cancer imaging agent for detection and staging potentially for PET/MRI
- $^{64}\text{Cu}/^{89}\text{Zr} – \text{NSC-MSN}$, for brain tumor tracking

Under Development for On-Site Production

- $^{18}\text{F} – \text{GR02}$, Imaging of glucocorticoid receptor in cancer
- $^{18}\text{F} – \text{FEPPA}$, Imaging of translocator protein TSPO
Critical Issues limiting growth

- Very new facility, opened in Feb. 2017
- Expensive facility, $8.4 for construction – need additional input of money for capital equipment
- Current staffing vs. Current project load – current staff of 4, need additional staff to handle projects
- Outreach (UC, NWU, UIC, Rush, IIT, Advocate)
- Education: Costs of drugs, time to develop, human vs. pre-clinical imaging
- Approach to cGMP (clinical production of FDG?)
- Contracts for clinical trials at and outside of UC
New and Expensive Facility

Original design cost was $10M but only $8.4M was available.
- Facility Value Engineered to fit budget
- Sacrificed additional hot cells and synthesis unit
- Somewhat limiting production capacity

Increased usage will require increased investment.
Cyclotron Facilities have historically run long-term deficits
Limited $^{11}$C capacity
Staff of only 3 FTEs in the lab (include Facility Director)
- Staffing is grossly undersized compared to other facilities
- Search for a Faculty radiochemist is ongoing but independent of production staff.
# Comparison to other Facilities

<table>
<thead>
<tr>
<th>Institute</th>
<th>Staffing</th>
<th>Lead Radiochemst</th>
<th>Clinical Production</th>
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<tbody>
<tr>
<td>Duke University</td>
<td>5</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Kettering Health Network, Ohio (not MSKCC)</td>
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<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Massachusetts General Hospital (Harvard)</td>
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<tr>
<td>Memorial Sloan Kettering Cancer Center (NYC)</td>
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<td>Oregon Health and Science University (Portland)</td>
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<td>University of Chicago</td>
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<td>Washington University at St. Louis</td>
<td>25+</td>
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<tr>
<td>Yale University</td>
<td>25+</td>
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</tbody>
</table>
Outreach and Education

- Contacted/spoke with: NWU, Advocate, UIC
- Shipped drug products to NWU (Evanston), UIC
- Starting a joint project with UC and NWU (medical campus) on FEPPA
- Problem:
  - Start up costs range from $30,000 to $90,000 per drug
  - Start up time (assuming sufficient staffing) 4 – 6 months typically
  - Too expensive for most grants without explicitly budgeting for it in advance.
Education continued

• Pre-clinical use is easy after drug development
• Human clinical/research use is complicated after drug development
  • IND is required for human use.
• If used across academic sites multiple IRBs are needed
• IND submission can be relatively straightforward
  • If the drug has already been used in humans and IND information exists (toxicology, etc.)
  • Or very difficult where no prior IND/human use data is available
Approach to cGMP

Again, education: cGMP, continuing Good Manufacturing Practices is not a simple checklist of things to be done.

- It is subject to the interpretation of the FDA inspector
- Requires: training, environmental monitoring, paperwork, vendor inspection, precise documentation and record keeping
- In Pharma, Regulatory Affairs is at least as large as production in terms of staffing! Most radiochemists are not capable or educated in Regulatory and underestimate the manpower needed.
Approaching cGMP (not easy)

Facility Director directed Penn’s medium sized facility with two cyclotrons and a staff of 10 ½ (including himself), and supplied 25-30 clinical FDG doses/day. Regulatory group was 4½ (+1 substitute) FTEs of the 10. An ANDA for clinical production of FDG was submitted and upon FDA inspection received no 483 deficiencies.

- WashU for NaF received one 483
- Mass General for FDG received nine 483s.
- Penn received six 483s after the initial submission with 0 citations.
- Typical: a couple of citations
Approaching cGMP

Business plan for FDG production requires:

- cGMP compliance (1 year, 2 man-years of labor, > $1M investment in equipment).

- FDG is $100/dose. Requires tight coordination with PET center to limit no-shows. Requires buy-in from Hospital Admin so that a commercial pharmacy with a price of $85/dose doesn’t cause the hospital to give up in-house production for a savings of $15/dose.

Clinical production supports research activities!

- Requires more staffing for production and regulatory

- Shipping to other UC sites adds addn complications.
The Cyclotron and Animal Imaging Facilities: Our approach to a holistically unified Facility

Mechanical Space and infrastructure, 1,000 sq. ft.

Research Chemistry, 500 sq. ft.

Cyclotron Operations, 2,750 sq. ft.

Radiopharmaceutical Production and Quality Control, 3,250 sq. ft.

integrated Small Animal Imaging Research Resource, 2,000 sq. ft.
New Molecubes µPET/SPECT/CT

CUBE µSPECT  X-CUBE µCT  β-CUBE µPET

State-of-the-art
Mouse, rat capable
Philips Allegro PET – Large Animal Imaging

Dog
Pig
Rabbit
Monkey
etc.
• Nicotine Receptor Imaging

![Rat Brain Slice](image1.png)

![18F-Nifene](image2.png)

![18F-Nifrolene](image3.png)

![18F-Nifzetidine](image4.png)

<table>
<thead>
<tr>
<th>Nifene</th>
<th>AZAN, Flubatine, Nifrolene, XTRA</th>
<th>2-FA-85380, Nifzetidine</th>
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<tbody>
<tr>
<td>Fast PET kinetics</td>
<td>Intermediate PET Kinetics</td>
<td>Slow PET Kinetics</td>
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<tr>
<td>1</td>
<td>2</td>
<td>3</td>
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<tr>
<td>4</td>
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NIH/NIDA R01 DA044760
Nicotine Receptor Imaging
Green/Chen/Mukherjee
Imaging of Nicotine Receptor – 2FA (Slow) & Nifene (Rapid)

Investigation of trapping in acidic vesicles for explaining different kinetics of various PET radiotracers for imaging of nicotine receptors

Figure 2: Representative cross sections of whole in images of nicotine receptor binding by 2-[F]A85380 and (B) [F]Nifene in wild type and β2-subunit knockout mice.
Multimodality Investigation of Tumor Hypoxia to Improve Radiotherapy – To Make FMISO-PET Clinically Useful for Dose-Painting in Radiotherapy of Hypoxic Tumors

- EPRI: Electron Paramagnetic Resonance Imaging
  - Directly measures oxygen levels to 1 torr
- MRI: T2w and Dynamic Contrast Enhanced (DCE)
  - T2w to contour anatomy
  - DCE-MRI images vascular permeability ($k_{\text{trans}}$) and washout ($k_{\text{ep}}$)
- PET: Positron Emission Tomography (F-Miso)
  - Radiotracer made in-house at our cyclotron facility
  - F-Miso targets hypoxic cells

CCC Team Science Award
/NCI R01 CA236385 Multimodality Imaging of Hypoxic Tumors Chen/Halpern

Yellow/Red = Hypoxia
PET – $^{18}$F-Miso of Hypoxia in Stroke

Transmission (Cs137) and emission fused image

Ears

Eyes

Image orientation

Region scanned

180mm

NIH/NINDS R01 NS093908
MRI & PET Imaging of Stroke
Carroll & Christoforidis
Left Brain Hypoxia in Stroke Induced $^{18}$F-Miso PET + MRI

- Image positions as indicated by cross hairs

Color: PET

Gray: transmission image ($^{137}$Cs)

20min scan @ 204 minutes Post-injection

MRI not shown

NIH/NINDS R01 NS093908

MRI & PET Imaging of Stroke Carroll & Christoforidis
Development of a Novel PET Tracer for K⁺ Channels to Image CNS Demyelination (Multiple Sclerosis)

Initial radiochemistry, autoradiography, and in vivo rodent imaging at UChicago

Improvements in radio-synthesis, in vivo Non-Human Primate Imaging and Bio-distribution at NIH

First-in-Human & Clinical Studies
Funded by an Innovation Award from UChicago Polsky Center, to be Conducted at MGH, UChicago, & Other Medical Centers

NIH/NIBIB K99/R00 EB020075
Imaging of MS
Brugarolas
Examples of New Projects in Progress

• Cell Proliferation in response to therapy
• Nasal delivery of Insulin Growth Factor-1
• Glucocorticoid Receptor Imaging
• Benzodiazepine receptors (traumatic brain injury, neuroinflammation)
• Amyloid imaging for Alzheimer’s
• Tau imaging for Alzheimer’s
• $^{48}\text{V}$ Vanadyl for PET/MRI
Clinical Trials and Pharma/Biotech

In 2 years of operations, Facility has been approached by several pharma & biotech companies. Facility is the only academic cyclotron-based radiotracer production facility within the state of Illinois. Pharma/biotech demands cGMP compliance. Facility has encountered much difficulty in contract negotiations for trials both on and off site. But many other academic sites produce for “For profit” entities and participate in trials: MSK, Mass General, Wisconsin, WashU, etc.
Clinical Human Research Trials

No dedicated PET/CT or PET/MRI research scanner
Only a single PET/CT scanner in the NM clinic
Routine clinical PET scans reaching capacity
Clinical research protocols often VERY different from the routine clinical PET imaging procedures
Skills, expertise, and experience required for a clinical research imaging technologist also somewhat different from those for a regular NM PET technologist
Ideally, dedicated research PET/CT scanners
Ideally, dedicated research PET imaging tech(s)
EXPLORER: Total-Body (TB) PET

- x40 gain NEC!
- Higher statistics
  - Support higher spatial resolution
- Lower radiation dose
  - Whole body scans at ~ 100 μSv
- Higher dynamic range
  - Late imaging, 5 more \( T_{1/2} \)
- Whole-body kinetics
  - Better temporal resolution
  - All tissues/organs simultaneously

From http://explorer.ucdavis.edu