PET: Positron Emission Tomography
# Positron-emitting Radioisotopes

## Standard PET Radioisotopes

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Half-life</th>
<th>$E_{\beta^{+}\text{max}}$ (MeV)</th>
<th>Mode of Decay ($\beta^+%$)</th>
<th>Nuclear Reaction</th>
<th>Target Media</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{15}\text{O}$</td>
<td>2 min</td>
<td>1.74</td>
<td>100</td>
<td>$^{14}\text{N}(d,n)^{15}\text{O}$</td>
<td>$\text{N}_2 + 1 %\text{O}_2$</td>
</tr>
<tr>
<td>$^{13}\text{N}$</td>
<td>10 min</td>
<td>1.19</td>
<td>100</td>
<td>$^{16}\text{O}(p,\alpha)^{13}\text{N}$</td>
<td>$[^{16}\text{O}]\text{H}_2\text{O}/\text{EtOH}$</td>
</tr>
<tr>
<td>$^{11}\text{C}$</td>
<td>20.3 min</td>
<td>0.96</td>
<td>99</td>
<td>$^{14}\text{N}(p,\alpha)^{11}\text{C}$</td>
<td>$[^{11}\text{C}]\text{CO}_2$: $\text{N}_2 + 0.5 %\text{O}_2$ $[^{11}\text{C}]\text{CH}_4$: $\text{N}_2 + 10 %\text{H}_2$</td>
</tr>
<tr>
<td>$^{18}\text{F}$</td>
<td>110 min</td>
<td>0.64</td>
<td>97</td>
<td>$^{18}\text{O}(p,n)^{18}\text{F}$</td>
<td>$[^{18}\text{F}]\text{F}^{-}$: $^{18}\text{O}$-enriched $\text{H}_2\text{O}$ $[^{18}\text{F}]\text{F}_2$: $^{18}\text{O}$-enriched $\text{O}_2 + \text{O}_2/\text{Ar}$</td>
</tr>
</tbody>
</table>

## Non-Standard PET Radioisotopes

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Half-life</th>
<th>$E_{\beta^{+}\text{max}}$ (MeV)</th>
<th>Mode of Decay ($\beta^+%$)</th>
<th>Nuclear Reaction</th>
<th>Target Media</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{64}\text{Cu}$</td>
<td>12.7 h</td>
<td>0.653</td>
<td>17.6</td>
<td>$^{64}\text{Ni}(p,n)^{64}\text{Cu}$</td>
<td>Electroplated $^{64}\text{Ni}$ Metal</td>
</tr>
<tr>
<td>$^{55}\text{Co}$</td>
<td>17.5 h</td>
<td>1.598</td>
<td>76%</td>
<td>$^{58}\text{Ni}(p,\alpha)^{55}\text{Co}$</td>
<td>Electroplated $^{58}\text{Ni}$ Metal</td>
</tr>
<tr>
<td>$^{89}\text{Zr}$</td>
<td>3.27 d</td>
<td>0.902</td>
<td>22.7%</td>
<td>$^{89}\text{Y}(p,n)^{89}\text{Zr}$</td>
<td>Yttrium foil</td>
</tr>
<tr>
<td>$^{86}\text{Y}$</td>
<td>14.74 h</td>
<td>3.141</td>
<td>31.9%</td>
<td>$^{86}\text{Sr}(p,n)^{86}\text{Y}$</td>
<td>$^{86}\text{SrCO}_3/^{86}\text{SrO}$ powder</td>
</tr>
</tbody>
</table>
Strategic Siting of the Cyclotron Facility

Moncrief Radiation Oncology Building (NF)  Clements Imaging Building (NE)
Cyclotron and Radiochemistry Operation Flow Chart
Regulatory Requirements prior to Clinical Production

Equipment Installation & Validation
- cGMP
  - QC equipment
  - Radiosynthesis modules
- non-cGMP
  - Cyclotron

Facility Validation
- Critical Areas
  - Clean Room for production
  - Ante room
- Non-Critical Areas
  - Non-Clinical Production Areas

Production Validation
- Regulatory Filings to FDA for Clinical use of PET Drugs
  - $^{18}$F-FDG
  - $^{18}$F-NaF
  - $^{13}$N-NH$_3$
  - $^{11}$C-Choline

PET: Positron Emission Tomography
## Preclinical Radiotracer Production

<table>
<thead>
<tr>
<th>18F tracer</th>
<th>Application/Target</th>
<th>Precursor</th>
</tr>
</thead>
<tbody>
<tr>
<td>18F-FLT</td>
<td>Cellular proliferation imaging via Thymidine kinase-1</td>
<td></td>
</tr>
<tr>
<td>18F-FMISO</td>
<td>Hypoxia imaging</td>
<td></td>
</tr>
<tr>
<td>18F-FHBG</td>
<td>Herpes simplex virus thymidine kinase (HSV-tk)</td>
<td></td>
</tr>
<tr>
<td>18F-FDOPA</td>
<td>Neuroimaging via dopamine receptor; cancer imaging via amino acid uptake and metabolism</td>
<td></td>
</tr>
<tr>
<td>18F-FET</td>
<td>Cancer imaging via amino acid transport system</td>
<td></td>
</tr>
<tr>
<td>18F-FES</td>
<td>Cancer imaging via estrogen receptor</td>
<td></td>
</tr>
<tr>
<td>18F-FDHT</td>
<td>Cancer imaging via androgen receptor</td>
<td></td>
</tr>
<tr>
<td>18F-FACBC</td>
<td>Cancer imaging via L-type amino acid transporter</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>11C tracer</th>
<th>Application/Target</th>
<th>Precursor</th>
</tr>
</thead>
<tbody>
<tr>
<td>11C-acetate</td>
<td>TCA cycle, fatty acid synthetase</td>
<td>Br-Mg</td>
</tr>
<tr>
<td>11C-choline</td>
<td>Cancer imaging via the choline kinase</td>
<td></td>
</tr>
<tr>
<td>11C-methionine</td>
<td>Cancer imaging via amino acid uptake and protein synthesis</td>
<td></td>
</tr>
<tr>
<td>11C-PIB</td>
<td>AD imaging via binding to amyloid plagues</td>
<td></td>
</tr>
<tr>
<td>(+)-11C-DTBZ</td>
<td>Neuroimaging via targeting VMAT2</td>
<td></td>
</tr>
<tr>
<td>11C-ACBC</td>
<td>Cancer imaging via amino acid uptake</td>
<td></td>
</tr>
<tr>
<td>11C-Lactatic acid</td>
<td>Lactate metabolism</td>
<td></td>
</tr>
<tr>
<td>11C-Pyruvic acid</td>
<td>Pyruvate metabolism</td>
<td></td>
</tr>
</tbody>
</table>

**Goal:** Five preclinical radiotracers per year starting in 2015

Validated tracers not included: [18F]FDG, [15O]H₂O, and [13N]NH₃
FDA Regulations on PET Drugs & Regulatory Filings

Preclinical R&D

RDRC/eIND/IND

Clinical Research

ANDA/NDA

New Drug Application

**Timeliness** | **# patients** | **Scope** | **Clinical Trial**
--- | --- | --- | ---
√ √ √ | 30 | √ | Phase 0
√ √ | 30 | √ | Phase 0 – I
√ √ | unlimited | √ √ | Phase I – III
√ | unlimited | √ √ √ | FDA-approved

**RDRC:** Radioactive Drug Research Committee

**eIND:** Exploratory Investigational New Drug

**IND:** Investigational New Drug

**ANDA:** Abbreviated New Drug Application

ANDA is required for commercial dose distribution of $[^{18}F]FDG$, $[^{18}F]NaF$, $[^{13}N]NH_3$, and $[^{11}C]Choline$.

Goal: To file one RDRC and one IND applications in 2015
## Planned Radiotracer Production (Clinical)

<table>
<thead>
<tr>
<th>Radiotracer</th>
<th>Precursor</th>
<th>Target</th>
<th>Radiotracer</th>
<th>Precursor</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>18F-Fluorothymidine</strong> <em>(18F-FLT)</em></td>
<td><img src="image1.png" alt="Structure" /></td>
<td>Cellular proliferation/Thymidine kinase 1</td>
<td><strong>11C-Acetate</strong></td>
<td><img src="image2.png" alt="Structure" /></td>
<td>Acetate metabolism</td>
</tr>
<tr>
<td><strong>18F-Fluoromisonidazole</strong> <em>(18F-FMISO)</em></td>
<td><img src="image3.png" alt="Structure" /></td>
<td>Tumor hypoxia/Tissue oxygenation</td>
<td><strong>11C-Choline</strong></td>
<td><img src="image4.png" alt="Structure" /></td>
<td>Synthesis of phospholipids in recurrent prostate cancer</td>
</tr>
<tr>
<td><strong>18F-ISO-1</strong></td>
<td><img src="image5.png" alt="Structure" /></td>
<td>Cellular proliferation (Ki-67) α2 receptor</td>
<td><strong>11C-Methionine</strong></td>
<td><img src="image6.png" alt="Structure" /></td>
<td>Amino acid transporters</td>
</tr>
<tr>
<td><strong>[18]fluoroestriadol</strong> <em>(18F-FES)</em></td>
<td><img src="image7.png" alt="Structure" /></td>
<td>Estrogen receptor</td>
<td><strong>11C-Palmitic acid</strong></td>
<td><img src="image8.png" alt="Structure" /></td>
<td>Fatty acid Metabolism</td>
</tr>
<tr>
<td><strong>18F-Fluorodihydrotestosterone</strong> <em>(18F-FDHT)</em></td>
<td><img src="image9.png" alt="Structure" /></td>
<td>Androgen receptor</td>
<td><strong>α-11C-methyl-L-tryptophan</strong> <em>(11C-AMT)</em></td>
<td><img src="image10.png" alt="Structure" /></td>
<td>Tryptophan metabolism</td>
</tr>
</tbody>
</table>

**Goal:** Two clinical radiotracers per year starting in 2015  
**Validated tracers not included:** *[18F]FDG, [15O]H2O, and [13N]NH3*
CRP: Governance and Operation

First-in-Human & Human Clinical Trials
- Toxicology & Pharmacology
- IRB Applications
- RDRC/eIND/IND/ANDA Filings
- Subject Enrollment
- Clinical coordination
- Clinical Imaging Protocols
- Medical Imaging Physics
- Diagnostic Radiology
- Biostatistics
- Clinical Trial Outcome
- Technology Dissemination

CRP’s Responsibility
- Production & delivery of radiotracers for clinical or research use
- Novel imaging probe development
- Collaborative research (academic or industry)
- FDA regulatory filings as the sponsor or a participant

Regulatory Affairs Officer
CRP Facility Manager
CRP Chief Radiochemist
CRP Research Radiochemist
Radiochemistry
Production
Research with Radiotracers
Radiotracer & Isotopes R&D

CRP Facility Records & Maintenance
CRP Production Clinical Tracers
Postdocs & Students

Dean’s Office
Steering Committee
Clinical Advisory Committee
Governance Committee

CRP - Director
Administrative assistant

Affiliated Entities
External Consultants
Business Partner

Budget & Accounting
Radiation Safety
Physics & Engineering

Clinical PET Facility Radiology, Nuclear Medicine Division
UTSW Small Animal Imaging Resources

UTSouthwestern Medical Center
Industry-sponsored Clinical Trial Consortium

PET Companion Diagnostics for Hypoxia-Targeted Lung Cancer Therapy

Industry Sponsor: Threshold Pharmaceuticals
Participant Physicians: David Gerber and Orhan K. Öz

cGMP Production of Radiotracers: The Cyclotron Team

TH-302, an anti-cancer prodrug
HX-4, a hypoxia imaging agent
Requests for Unlisted Clinical Radiotracers

Technically, the radiochemical synthesis of the radiotracers is not an issue. However, how should we handle such requests of preliminary experiments for future grant opportunities?

1) Impact on the current work priority of the cyclotron team?
2) Impact on the current work load of the Clinical PET Facility?
3) Regulatory workload sharing?
4) Upfront cost sharing with the PI and/or the PI’s department or center?
Tryptophan Metabolism/Kynurenine Pathway

[Diagram of the kynurenine pathway]

α-[\(^{11}\)C]methyl-L-tryptophan – [\(^{11}\)C]AMT

[\(^{11}\)C]AMT was developed initially as a radiotracer for noninvasive assessment of brain serotonin synthesis. To date, clinical studies have shown that it can be used to trace the kynurenine pathway.
Examples of $^{[11}\text{C}]$-AMT PET Imaging

- **FDG**
- **AMT**

- **Epileptogenic lesion in Tuberous sclerosis**

- **Pre-Surgery**
- **Post-Surgery**

- **AMT-PET/CT of Breast Cancers**
  - SR 60 yo.
  - SA 50 yo.
  - VS 59 yo.

- **Non-small-cell lung cancer AMT-PET**

- **AMT-PET in patients with failed epilepsy surgery**

- **AMT-PET image of Brain Tumor**

Imaging Depression with \([^{11}\text{C}]\text{AMT}\)?

A Without exercise

- Stress
  - TDO and IDO
  - Liver
  - Spleen
  - Monocytes

B With exercise

- Stress
  - TDO and IDO
  - Liver
  - Spleen
  - Monocytes

Active skeletal muscle

Blood-brain barrier

Kynurenine converted to neuroactive metabolites

↓ Neurotrophins
↑ Inflammation
↑ Reactive oxygen species production
↑ Glutamate transmission

Increased stress resilience due to reduced exposure to kynurenine

The Cyclotron & Radiochemistry Team

Cyclotron Working Group

Neil Rofsky, MD
Dean Sherry, PhD
Robert Lenkinski, PhD
Dana Mathews, PhD, MD
Orhan K. Öz, MD, PhD
Jon Anderson, PhD
Dan Crawley, MBA
Michael Medina, MBA
Randy Kirchmeier, MBA
Sylvia Revell, RSO

Administrative Support

Sonia Hill
Jocelyn Chafouleas
Emily Mayer
Dan Crawley

UT Southwestern Medical Center
Acknowledgements

Financial Support
CPRIT RP110771
UT Southwestern – Dr. Fitz
Department of Radiology – Dr. Rofsky
Simmons Cancer Center– Dr. Willson

For more information:
http://www.utsouthwestern.edu/research/cyclotron/index.html

Contact us:
Cyclotron@UTSouthwestern.edu

Cyclotron Pilot Awards (RFP issued on 2/19/2015):
$50K each year for three years
Submission deadline: April 1, annually
Submission to: Sonia.Hill@UTSouthwestern.edu