Radiopharmaceutical and Radiotracer Sciences Institute at MU

Silvia Jurisson, Director
Richard Ferrieri, Co-Director

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Radiopharmaceuticals

- Drug containing a radioactive atom
- Emits particulate radiation (α or β⁻) for therapy
- Emits penetrating radiation (γ or β⁺ annihilation photons) for imaging

Examples
- $^{99m}$Tc: 140 keV γ for SPECT imaging
- $^{18}$F: β⁺ for PET imaging
- $^{177}$Lu: 0.497 MeV β⁻ for therapy
- $^{223}$Ra: 5.8 MeV α for therapy
Matched Pair Radionuclides

- Diagnostic/Therapeutic Pair
  - One radionuclide for imaging and one for therapy
  - Ideal if same element
    - $^{72}$As/$^{77}$As
    - $^{99m}$Tc/$^{188}$Re
Radiopharmaceutical Science is Multidisciplinary

- Biochemistry
- Chemistry
- Engineering
- Harry S Truman VA Hospital
- Medicine
- MURR
- Physics
- Radiology
- Veterinary Medicine & Surgery

Sustained long-term funding:
- NIH NIDA
- NIH NCI
- DOE
- NRC
- VA Merit
- American Heart Association
- Industry
Novel Radiotracer Development for PET Imaging

**Brain Imaging**

Adrenoceptor 2C ($\alpha_{2c}$)

Collaboration with NIAAA

Kun-Eek Kil

**Cardiovascular Imaging**

Small-molecule CXCR3 Radiotracers for Atherosclerosis

Collaboration with School of Medicine and VA Hospital

Funded by American Heart Association (07/2018-06/2020)
Small-molecule Radiotracers for PD-L1 Receptors on Cancer Cells

Novel Radiotracer Development for PET Imaging

Cancer Imaging

Somatostatin Receptors

Kun-Eek Kil
Hypothesis: Novel radioligands (FAN series) will display high $\sigma_2$ receptor affinity and selectivity, emerging as leading candidates for brain PET imaging of $\sigma_2$ receptors.

**FAN Series**: Variation in linker

$n = 2, 3, 4$

-CH$_2$- or heteroatom (N, O, S) substitution
FAN343F displays preferred Sigma 2 receptor binding properties compared to SIG343F; Radiolabeling studies underway at MURR

<table>
<thead>
<tr>
<th>Ligand</th>
<th>$\sigma_2$</th>
<th>$\sigma_1$</th>
<th>$\sigma_1 / \sigma_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAN343F</td>
<td>0.69 ± 0.16</td>
<td>564 ± 20</td>
<td>817</td>
</tr>
<tr>
<td>SIG343F</td>
<td>16.6 ± 0.93</td>
<td>527 ± 63</td>
<td>32</td>
</tr>
<tr>
<td>SIG343F $^b$</td>
<td>8</td>
<td>1600</td>
<td>200</td>
</tr>
</tbody>
</table>

$^a$ Means ± SEM, $n = 4 - 5$. $^b$ Values obtained using guinea pig brain membranes. $\sigma_2$: $[^3H]$DTG / 500 nM (+)-pentazocine; $\sigma_1$: $[^3H]$(+)-pentazocine. $^b$ Values reported by Nguyen et al. (EJNMMI Research 2013; 3:80) using the same radioligands and rat brain membranes.
**[177Lu]-DOTA-n-Hexylamido-Naltrindole for Delta Opioid Receptor Theranostics of Small Cell Lung Cancer**

$K_i^\delta = 0.15 \text{ nM}$  
$K_i^\mu = 46.1 \text{ nM}$  
$K_i^\kappa = 288 \text{ nM}$

**Control, 24 h** (saline; 1.05 mCi)  
**Blocked, 24 h** (NTI, 5 µmol/kg; 1.05 mCi)

**SPECT / CT**

**Radionuclide Therapy**

*Treatments vs. Controls*  
* $p < 0.05$; Day 21  
** $p < 0.01$; Day 24

- Controls  
- 1 x 0.8 mCi (20 Gy)  
- 2 x 0.8 mCi (2 x 20 Gy)  
- 1 x 1.6 mCi (40 Gy)

**Under Review:** Delta Opioid Receptor Targeted Nuclear Imaging and Radionuclide Therapy of Small Cell Lung Cancer  
(NCI 1R01CA222143-01A1; 4/01/19 - 3/31/23; $2,213,595 Total Costs)  
Contact PI: John Lever (Radiology); Multiple Pis: Jussuf Kaifi and Guangfu Li (Surgery); Co-I, Amolak Singh (Radiology)
Synthesis of $^{18}\text{F}$-EAAT2 Tracer

- Cyclotron produced $^{18}\text{F}$ ($t_{1/2}=110$ min
- Automated radiochemistry system capable of utilizing up to 5 Ci $^{18}\text{F}$
- To date, 12 doses have been delivered to the VMC PET Center

Synthesis developed by Henry VanBroocklin, John Gerdes, and Joe Blecha at UCSF. Automation of process developed by Stacy Wilder, Mike Schueller, and Rich Ferrieri at MURR.
Development of “theranostic” agents for neuroendocrine cancer management using Tc-99m (diagnostic) and Re-186 (therapeutic) radiometals.

Excellent receptor-mediated tumor uptake (17% ID/g at 1 h)!

Fast clearance through kidneys!

One of the best 99mTc-labeled SSTR-targeting agents out there!

The best 99mTc(CO)₃ peptide complex out there!

Micro-SPECT/CT images of ⁹⁹mTc(CO)₃L-sst₂-ANT distribution at 1 h after administration to a live mouse bearing a somatostatin receptor-expressing tumor.
ROADMAP to CLINICAL TRANSLATION
C. Jeffrey Smith (Research Health Scientist/Professor of Radiology)

ROADMAP to TRANSLATION

[Monovalent Cell-targeting Agent]
2004 NIBIB
2005-2013 VA MERIT
2005 NCI

[Polyvalent Cell-targeting Agent]
TOXICITY STUDIES
2017-2021 VA MERIT

GRPR/PSMA TARGETING AGENTS for PROSTATE CANCER DIAGNOSIS, 1IO1BX003392

[Radiometal Complexing Agent]

[GRPR-targeting Agent]

[PSMA-targeting Agent]

[DUPA-6Ahx-DO3A-6-Ahx-RM2]


ONGOING VA-SPONSORED, UNFUNDED RESEARCH INVESTIGATIONS


48 year old, male had undergone radical prostatectomy in early 2016.
4 months prior, PSA increase observed.
Injected with 4mCi of $^{68}$Ga-tracer.
Whole-body PET/CT 60 min post-intravenous injection.
Intense tracer uptake in kidneys, pancreas, and urinary bladder.
Significant uptake in lymph node metastases equally superior to $^{18}$F-Choline.
Study is ongoing to recruit a diverse group of prostate cancer patients to continue studies with this bivalent agent. Unpublished Results.
Pretargeted *in vivo* click chemistry for targeted alpha and beta particle cancer therapy

Xiuli Zhang\(^1,2\), Manankumar Shah\(^1,2\), Raffaella Rossin\(^3\), Marc Robillard\(^3\), Thomas P Quinn\(^1,2\)

*University of Missouri\(^1\), Harry Truman VA\(^2\), Tagworks Pharmaceuticals\(^3\)*

**Pretargeted Approach**

**Step 1:**
Administer tumor binding antibody trans-cyclooctene TCO tag conjugate ( ). Slow in vivo kinetics. (Days).

Low molecular weight radiolabeled tetrazine probe.

**Step 2:**
Fast cycloaddition binding reaction between small radioactive tetrazine probe with high affinity for the TCO tag on antibody. Rapid in vivo kinetics. (Minutes)

**Pretargeted In-111 SPECT/CT Imaging:** LS-174T tumor bearing mouse injected with In-111-DOTA-TZ 24 h post administration of antibody-TCO. Efficient in vivo TCO-Tz reaction coupled with rapid whole body clearance resulted in high tumor to normal tissue uptake ratios.


**Pretargeted Pb-212 Alpha Therapy:** Pretargeted treatment groups with increasing doses ( , , ) of radiolabeled tetrazine had significantly improved survival over traditional direct labeled antibodies, antibody alone and vehicle ( , , ).


1 R21 CA177526
Encapsulation of Mangiferin Phytochemical Around Radioactive $^{198}$Au Nanoparticles Provides Prostate and Breast Tumors Receptor Specificity

Kattesh Katti et.al Patent Pending (2018)
Licensed to DNA

Mangiferin from Mango peel
Antioxidant...sensitizer..

Cell Internalization of Mangiferin Gold Nanoparticles (M-AuNPs) into Prostate Cancer (PC-3) cells

25 µg/ml; 4 h incubation
25 µg/ml; 8 h incubation
**In vivo** tumor retention of MGF-\(^{198}\)AuNPs
(Katti, Amal and Menka et al: 2018 Patent Pending)

Biodistribution results in mice

![Graph showing biodistribution of MGF-\(^{198}\)AuNPs in various organs at different time points]
**In vivo** T1-weighted MRI in mice bearing PC-3 tumor, acquired at 7 T MRI (gadolinium dose of 0.02 mmol/kg).

Ma, et al
The concept of *One Medicine One Science* embraces scientific approaches that unify health-related research at the intersection of humans, animals, plants and the ecosystems they form.

*Nutrition is at the core of human health.* Chronic malnutrition causes the death of 2 children every minute worldwide.
Boron deficiency in plants can lead to crop yield losses...

Boron deficient ear

Collaboration between Paula McSteen (MU, Div. of Biological Sciences USDA-NIFA award to McSteen), Rich Ferrieri (MURR) and Kun-eek Kil (MU VMC).

Understanding the effects of boron limitation may help to sustain crop yields under environmental change.
Boron is assimilated by plants as boric acid...

PET Imaging Agent

\[
\begin{align*}
&\text{K}^{18}\text{F}/\text{K(OTf)}, \ K_2\text{CO}_3 \\
&\text{5 eq Cu(OTf)}_2 \\
&\text{125 eq Pyridine} \\
&\text{DMF} \\
&\text{110°C, 20 min}
\end{align*}
\]

Improving crop nutritional value by leveraging soil microorganisms…

**USDA-NIFA Award to Ferrieri in Crop Physiology**

Recognizing that micronutrients are essential in the human diet, researchers at MURR are harnessing the power of certain soil microbes to increase iron and zinc nutritional value in corn, promising a solution to a pressing global challenge on human nutrition and health.
Improving crop nutritional value by leveraging soil microorganisms...

Plant Assimilation

Plant Iron Assimilation

Study Conditions

- Control: No treatment
- Hm053: Azospirillum brasilense (high N\textsubscript{2} fixer and high auxin producer)
- ipdC: Azospirillum brasilense (high N\textsubscript{2} fixer but low auxin producer)
- FP-10: Azospirillum brasilense (low N\textsubscript{2} fixer but high auxin producer)
- SmR1: Herbaspirillum seropedicae (high N\textsubscript{2} fixer and high auxin producer)
- Auxin: 30 \mu M indole-3-acetic acid
First C-11 Metabolic Flux Studies at MURR

The search for signature biomarkers...

Mapping the $^{11}$C-metabolic landscape

Uninoculated Control

- Other and Small Organic Acids: 45%
- Structural: 18%
- Amino Acids: 4%
- Sugars: 33%

HM053 Inoculated

- Other: 12%
- Structural: 27%
- Amino Acids: 16%
- Small Organic Acids: 11%
- Sugars: 34%

Tracer Flux Aids in Identifying Signature Biomarkers

- HM053
- Control

$\text{Aspartate} \quad \text{Glutamate} \quad \text{Asparagine} \quad \text{Serine} \quad \text{Glutamine} \quad \text{Histidine} \quad \text{Glycine} \quad \text{Arginine} \quad \text{Alanine}$

$\text{H}^+ + \text{H}^+ \iff \text{H}^+_2 \text{O}$

University of Missouri Research Reactor Center

Interdisciplinary Plant Group
First C-11 Plant Physiology Studies at MURR

Does the presence of *Azospirillum brasilense* bacteria growing on maize roots promote increased root exudation of iron chelating substrates?

HM053 increases:
- Carbon input
- Leaf export
- Root allocation
- Root exudation of organic acids
New radiotracers using C-11 to examine bacteria carbon metabolism...

Collaboration between Rich Ferrieri (MURR) and Kun-ee Kil (MU VMC)

\[
\begin{align*}
\text{MeCOOME} & \xrightarrow{\text{NBS, p-TsOH}} \text{BrCOOME} \\
\text{Ph} \xrightarrow{\text{KOH, DMF, } ^{11}\text{CH}_3} & \xrightarrow{80^\circ\text{C, 2 min}} \text{H}_2\text{N} \xrightarrow{6 \text{ M HCl, } 130^\circ\text{C, 5 min}} \text{HOO}^{\text{11C}} \xrightarrow{45^\circ\text{C, 2.5 min}} \text{HO}^{\text{11C}}
\end{align*}
\]
Building New Capabilities at MURR in Plant Ionomics

Collaboration between Rich Ferrieri and Mike Schueller (MURR)

Production and chemical separation of radioactive Zn-63

Isotope Excitation Function

Ion Exchange Chromatography

Copper Elution Profile

Zn-65 Elution Profile
Collaborative MU partnerships – Mapping root nodule metabolism using C-11…

Dedicated PET Imager for Plants at MURR

Quantification of Image Data

Partnership with SynchroPET
Future Plant PET Imaging at the Large Animal PET-CT Suite...

Transporting $^{11}\text{CO}_2$ from MURR to VMC

$^{11}\text{CO}_2$ Battery
Building new MU-Danforth partnerships in plant science...

Can we breed plants for enhanced memory?

Plateau in Genetic Gain

![Graph showing wheat grain yield from 1970 to 2010 for The Netherlands, United Kingdom, and France.](image)
Building new MU-Danforth partnerships in plant science...

RadioMetabolite Flux Analysis shows evidence of memory imprinting...

Blake Meyers (Danforth-MU Joint Faculty - small RNA profiling)
Ron Mittler (MU Plant Sciences - ROS wave propagation)
Rich Ferrieri (MURR - plant metabolic flux and imaging)
Keith Slotkin (Danforth-MU Joint Faculty - plant cell biology)
Bing Yang (MU-Danforth Joint Faculty – plant genetics)
Establishing partnerships outside of MU...


*Can we produce soybeans with higher protein content without compensatory loss of seed oil content?*

Pivot Bio, Inc. and Rich Ferrieri (MURR) – maize research using soil *nitrogen fixing* microorganisms.

*Can we produce a nitrogen fixing corn in the next 5 years?*
Building New International Partnerships - Thermal Neutron Radiography at MURR…

Collaboration between Rich Ferrieri & John Brockman (MURR), Bruce Hibbard (MU, USDA ARS) and Emil Hallin (GIFS, U. Saskatchewan)…

*CAFNR International Collaboration Program Award with additional travel subsidy through GIFS*…

Thermal neutron radiograph of switchgrass (left) and maize (right) seedlings revealing detail of the plant and soil structure based principally on neutron scattering of hydrogen (as H₂O) – *image courtesy of E. Hallin (Chalk River Reactor)*

Western Corn Rootworm
Plants are natures biofactories – since the realization that plants can be bred to produce artemisinin, an anti-malaria drug at lower cost than chemical synthesis, there is renewed interest in plant natural product synthesis.

Ian Graham (Director, Centre for Novel Agricultural Products at the University of York), 2018 ASPB Keynote – presented his work on the discovery of a 10 gene cluster in poppy plants enabling their biosynthesis of noscapine, a benzyl isoquinoline alkaloid compound that has interesting anti-cancer properties.