From Bench to Bedside: A History of Fluciclovine from Discovery to FDA Approval

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Target Audience: Pharmacists
ACPE#: 0202-0000-18-078-L04-P
Activity Type: Knowledge-based
Disclosures

None to Note

The American Pharmacists Association is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.
Learning Objectives

• Understand why amino acids were targeted and developed for tumor imaging
• Learn about the discovery of fluciclovine at Emory University, including the different synthesis platforms used during development
• The Emory University roadmap to the current FDA approved clinical indication will be discussed
1. The first PET drug, $[^{18}\text{F}]\text{NaF}$, was approved by the FDA in what year?

A. 1965  
B. 1994  
C. 1972  
D. 2010
2. Fluorine-18 is an ideal isotope for PET tracers because

A. F-18 has a 110 minute half-life
B. F-18 is a high energy \( \alpha \)-emitter
C. F-18 is rapidly metabolized to other radio-labeled species
D. F-18 cannot form a stable bond with carbon
3. Why are Amino Acids useful in tumor imaging?

A. Amino Acids have greater uptake in inflammatory tissue as compared to $[^{18}\text{F}]$FDG.
B. High uptake of Amino Acids in the kidney and bladder yields better and more definitive imaging of the prostate.
C. Many tumor cells have increased Amino Acid transport and protein synthesis as compared to normal cells.
D. Amino Acids are useful only for therapy and do not have diagnostic or prognostic use.
4. The typical “First Step” on The Road to FDA Approval is

A. Discovery of the drug/lead compound
B. Toxicity study of the drug/lead compound
C. Clinical Phase 1: drug safety and dosimetry
D. Identification of a clinical need
“Half the story has never been told”

- Robert Nesta Marley
By 1994 the FDA had approved only three PET drugs:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Year</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>F-18 Sodium Fluoride</td>
<td>1972</td>
<td>Osteogenic Activity</td>
</tr>
<tr>
<td>Rb-82 RbCl</td>
<td>1989</td>
<td>Myocardial Infarction</td>
</tr>
<tr>
<td>F-18 2-FDG</td>
<td>1994</td>
<td>Epilepsy/Myocardial Glucose Metabolism</td>
</tr>
</tbody>
</table>
Goals of Clinical PET Tumor Imaging

1) Diagnosis and anatomic localization
2) Evaluating the extent of disease in known malignancies (staging/restaging)
3) Detection of tumor recurrence, in the presence of elevated tumor markers with no clinical evidence of disease
4) Treatment planning
5) Response to therapy
FDG has been shown to be useful in several cancer types

- Lymphoma - staging/restaging, response therapy
- Breast - recurrence/metastasis
- Lung - initial staging
- Colorectal - recurrence, response to therapy
- Head and Neck - new diagnosis, response to therapy
- Cervical - preoperative staging and restaging
FDG has certain tumor imaging limitations, however...

- FDG images confounded by factors that increase glycolysis
  - Tissue hypoxia
  - Infiltration of inflammatory cells - BPH

- FDG images of brain tumors are difficult to interpret
  - High metabolic activity brain tissue results in relatively “low” tumor to brain ratios (contrast)

- High levels of urinary excretion makes very difficult tumor visualization of the
  - Prostate
  - FDG uptake in primary PCA is modest
  - Bladder
...and FDG has unmet clinical needs

- Not accurate in the imaging of gliomas
  - No solid ability for grading
  - Difficult to determine the extent of disease
  - Unable to determine response to radiation and chemotherapy

- Not useful in the imaging of prostate cancer
  - Primary
  - Metastasis
  - Recurrence
  - except for aggressive metastatic cancer
Some alternative PET agents for glioma and PCA did exist in the mid-90’s

- **Metabolism based agents**
  - amino acids: L-$^{11}$Cmethionine, L-$^{18}$FDOPA, L-$^{11}$Cleucine, L-$^{11}$Ctryptophan
  - lipid metabolism: $[^{11}$C]Choline
  - carboxylic acids: $[^{11}$C]acetate, $[^{18}$F]Fluoroacetate

- **Receptor based agents**
  - androgen receptors: $[^{18}$F]FDHT
So, why develop amino acids for use in tumor imaging?

- Many tumor cells have increased amino acid transport, cell membrane transporter expression and protein synthesis to support the malignant cell growth as compared to normal cells.
- Specific amino acid metabolic pathways are important in tumor biology and therefore are good therapeutic targets.
- The activity of certain amino acid transporters may have prognostic and therapeutic implications.
- AA may have < uptake in inflammatory tissue vs FDG.
- AA may have < uptake in kidney and bladder vs FDG, and therefore higher tumor to kidney and prostate contrast.
Amino acid transport basics

- Three transport systems have been the major focus of amino acid-based tumor imaging
  - System L (prefers Leucine)
  - System A (prefers Alanine)
  - System ASC (prefers Glutamine)

- Transport is generally more important than protein synthesis when imaging tumors with amino acids
Systems A and ASC transport requires Na ions for co-transport while System L concentrates amino acids through efflux of intracellular amino acids.
Aromatic Synthetic Non-Natural Amino Acids $[^{18}\text{F}]$Fluoroethyl-L-tyrosine (L-FET) and $[^{18}\text{F}]$Fluoro-a-methyl Tyrosine (L-FMT): Not Suitable for Prostate Cancer Imaging

Kaira K et al. Chest 2007
L-[\textsuperscript{11}C]\text{Methionine} studied previously for evaluation of glioma tumor volume

L-[\textsuperscript{11}C]Methionine biodistribution exhibits low excretion in kidney, abdominal, and pelvic lymphadenopathy and therefore better detection of abdominal and pelvic lymph node mets vs. FDG.
L-$^{[11}\text{C}]$Methionine for Glioma and Prostate PET Imaging

- **Advantages**
  - Low brain grey matter uptake
  - Low bladder accumulation
  - Greater uptake vs FDG in glioma
  - Greater uptake vs FDG in primary and metastatic prostate cancer

- **Disadvantages**
  - Rapid metabolism to other radiolabeled species
  - Metabolism rate and metabolites varies
  - Short half-life of [C-11] not good for commercial distribution
[¹¹C]ACBC

- [¹¹C] 1-Aminocyclobutane-1-Carboxylic Acid
- Prepared with 12 MeV cyclotron
- Synthesized using Bucherer-Strecker method

Goodman MM et al, 1989
Evaluation of a 64 Year Old With Grade 2 Astrocytoma Who Received Prior Radiation Therapy Shows High $^{11}$C ACBC Uptake In Area Poorly Identified by $^{18}$F FDG.
The Cyclobutane Ring outperforms $^{18}$FFDG, but what about the shortcomings of $^{11}$C?
Thus the search begins for a new and better imaging tracer......
Fluorine-18 is the answer...

- Radionuclidic and Chemical properties make F-18 ideal for PET tracers
  - 110 minute half-life: good for kinetics and commercial distribution
  - Low energy $\beta^+$-emitter (2-4mm range)
  - Metabolically stable carbon fluorine bond
  - Production available in curie amounts from low energy cyclotrons (11MeV)
- Fluorine is a bioisotere for H or OH
Cyclobutane ring is the question...?

- Substitution of \(^{18}\text{F}\)F or \(^{18}\text{F}\)CH\(_2\) for H at 3-position may lead to an Amino Acid with high tumor uptake

- [\(^{11}\text{C}\)]ACBC
- Anti-3-[\(^{18}\text{F}\)]FACBC
- Syn-3-[\(^{18}\text{F}\)]FACBC
- Anti-3-[\(^{18}\text{F}\)]FMACBC
- Syn-3-[\(^{18}\text{F}\)]FMACBC
Cyclobutane ring question...

- Substitution of $[^{18}\text{F}]$ for H at 2-position would lead to stereoisomers

2-$[^{18}\text{F}]$FACBC

Syn-$[^{18}\text{F}]$FACBC

Anti-$[^{18}\text{F}]$FACBC (Fluciclovine)

Non-natural amino acid; MW=132
Anti-3-[18F]FACBC synthesis is a nine-step reaction sequence.

a) benzyl bromide, Hg\textsubscript{2}Cl\textsubscript{2}, 150°C; b) nBuLi, CH\textsubscript{3}S(O)CH\textsubscript{2}SCH\textsubscript{3}, THF then 35% HClO\textsubscript{4}/Et\textsubscript{2}O; c) NH\textsubscript{4}(CO\textsubscript{3})\textsubscript{2}, NH\textsubscript{4}Cl, KCN, 1:1 EtOH:H\textsubscript{2}O, 60°C d) 3N NaOH, 180°C then Boc\textsubscript{2}O, 9:1 CH\textsubscript{3}OH:Et\textsubscript{3}N; e) (CH\textsubscript{3})\textsubscript{3}SiCHN\textsubscript{2}, 1:1 CH\textsubscript{3}OH:THF; f) 10% Pd/C, H\textsubscript{2}, CH\textsubscript{3}OH.
anti-3-[¹⁸F]FACBC synthesis cont’d

McConathy J et al. Applied radiation and isotopes, 203
**[¹⁸F]FACBC: CPCU Synthesis**

- Initial few productions of [¹⁸F]FACBC done completely manually (!)
- Chemistry Process Control Module (Unit)
- General nucleophillic chemistry module designed by CTI, Knoxville, TN
- Dual vertically adjustable “open” glass reaction vessels with dual moveable heated oil baths
- Additions, transfers, and evaporations/heating carried out by timed O/C of gas pressure valves.
- Silicone stoppers with poly lines provide addition and transfer of solvent/reagents and reaction mixture
- Programming language iRMX 386
Yes! Still in use today!
CPCU [¹⁸F]FACBC production

Batch Production Record

QC Summary & Release
First Animal work in Fischer rats

- Used as a model for human glioblastoma multiforme
- 9L cells implanted intracranially develop into solid tumors
- \(^{18}\text{F}-\text{labeled amino acid injected i.v. ~ 16 days after tumor implantation}\)
- Data normalized as percent of injected dose per gram of tissue
Anti-[\textsuperscript{18}F]FACBC showed greater in vivo uptake ratio of tumor-to-contralateral normal brain than 2-[\textsuperscript{18}F]FDG at 60 minutes P.I.
Next step... Human subject

Under the auspices of the Emory University Radioactive Drug Research Committee (RDRC), Radiation Safety Committee 1, and Institutional Review Board (IRB), a study involving a total of 24 human Subjects with Brain Tumors was approved.
Images in a Volunteer with Glioblastoma Multiforme; \([^{18}\text{F}]\text{FACBC}\) Superior to \([^{18}\text{F}]\text{FDG}\)


- Left frontal lesion biopsied 1 month later, metastatic adenocarcinoma

- Lesions are isointense or slight ‘cold’ on FDG, ‘hot’ on FACBC
Anti-[¹⁸F]FACBC uptake in various in-vitro human cancer cell lines by an “L” but not “A” transport inhibitor, suggesting that there is an active amino-acid transport mechanism involved in tumor uptake.

<table>
<thead>
<tr>
<th></th>
<th>Anti-FACBC H125 (Lung)</th>
<th>Anti-FACBC DU145 (Prostate)</th>
<th>Anti-FACBC SKOV3 (Ovarian)</th>
<th>Anti-FACBC A549 (Lung)</th>
<th>Anti-FACBC MDA MB468 (Breast)</th>
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<tbody>
<tr>
<td>Control</td>
<td>7.1</td>
<td>16.5</td>
<td>6.9</td>
<td>15.9</td>
<td>20.2</td>
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<tr>
<td>ACS¹</td>
<td>0.29</td>
<td>0.29</td>
<td>0.06</td>
<td>0.17</td>
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<tr>
<td>BCH²</td>
<td>4.4</td>
<td>4.2</td>
<td>1.17</td>
<td>3.5</td>
<td>5.8</td>
</tr>
<tr>
<td>MeAIB³</td>
<td>5.6</td>
<td>13.9</td>
<td>6.6</td>
<td>18.4</td>
<td>19.3</td>
</tr>
</tbody>
</table>

¹ 10 mM
² 10 mM “L” amino acid transport inhibitor
³ 10 mM “A” amino acid transport inhibitor
FACBC began to attract some attention...

- In 2000, Nihon Medi-Physics, LTD., Japan licensed the intellectual property of [F-18]FACBC from Emory University

- Decision was made to apply for the National Cancer Institute DCIDE program to determine pharmacokinetics, dosimetry, toxicology, etc. for a potential IND filing
DCIDE will make available to investigators, on a competitive basis, the preclinical development contract resources of NCI. The goal of DCIDE is the development of promising imaging molecular probes or enhancers (contrast agents) that are otherwise unlikely to undergo further development leading to Investigational New Drug (IND) application. DCIDE will assist the selected investigators by providing or facilitating any (or all) of the preclinical development requirements, including, for example, pharmacokinetics, dosimetry, and IND-directed toxicology.
Then something unexpected happened...

“Luck is What Happens When Preparedness Meets Opportunity”

- Roman Philosopher Seneca
During a study (n=6) of renal masses sponsored by a SNMMI pilot grant of Dr. David Schuster’s, one patient had uptake in retroperitoneal lymph nodes which turned out to be unexpected metastatic prostate carcinoma.

This lead to further study for prostate carcinoma.
But there was already interest in using $^{11}$C-Methionine for prostate imaging

Macapinlac HA et al. Clinical Positron Imaging 1999
However, Emory requested priority by NCI for $^{18}$F]-FACBC due to its uniqueness and advantages for tumor imaging:

1) $^{18}$F]-FACBC has better tumor imaging characteristics compared to $^{11}$C]-methionine, due to better transport, tumor accumulation and lower background activity in surrounding tissues.

2) $^{18}$F]-FACBC is not metabolized, and radiolabeled metabolites will not confound the interpretation of the images as can be the case with $^{11}$C]-methionine.

3) Imaging brain tumors is enhanced by the lower brain (background) activity observed with $^{18}$F]-FACBC as compared to $^{11}$C]-methionine and to $^{18}$F]-FDG.

4) Imaging systemic tumors is enhanced by the lower abdominal (e.g., liver and pancreas) background activity observed with $^{18}$F]-FACBC as compared to $^{11}$C]-methionine.
5) $[^{18}\text{F}]\text{FACBC}$ and $[^{11}\text{C}]-\text{methionine}$ imaging provides different information (up-regulation of amino acid carrier-mediated transport across endothelial and tumor cell membranes) compared to that obtained with contrast-enhanced MR imaging (passive vascular permeability), or with $[^{18}\text{F}]-\text{FDG}$ (glucose metabolism).

6) $[^{18}\text{F}]\text{FACBC}$ provides substantial logistical and cost-effective benefits for tumor imaging in a busy nuclear medicine department as compared to $[^{11}\text{C}]-\text{methionine}$, due to the longer half-life of $[^{18}\text{F}]$ ($t_{1/2}=110\ \text{min}$) compared to $[^{11}\text{C}]$ ($t_{1/2}=20\ \text{min}$).

7) A 370 MBq (10 mCi) dose of $[^{18}\text{F}]\text{FACBC}$ is sufficient for imaging brain and prostate tumors in a clinical setting, and a 370 MBq (10 mCi) dose is likely to be safe and within FDA guidelines.
October 30, 2002

Dr. Mark M. Goodman
Professor of Radiology and Psychiatry
Emory School of Medicine
1364 Clifton Road NE
Atlanta, GA 30322

Re: "IF-18/FACBC - A Novel Agent for Tumor Imaging by PET"

Dear Dr. Goodman:

Both the external and internal evaluations of your DCIDE request have been completed. The evaluation panels feel that you responded to the critiques of your previous submission in a very positive manner. Overall, your submission was scored very favorably. A copy of the comments from the external evaluation panel is included for your information.

Based on both evaluations, we propose to provide the data required for your IND application. The exact nature of the resources will be determined following consultation with NCI toxicologists. The first issue to be addressed is determination of the most appropriate source of bulk material, which we are in the process of evaluating. As we make decisions, we will be in touch with you to discuss our decisions prior to taking any action.

We look forward to working with you in the coming months to bring this exciting compound to a successful IND application. If you have any questions regarding this evaluation, or any other issues regarding the DCIDE program, please contact us at your convenience.

Sincerely,

John M. Hoffman, M.D.
Chief, Molecular Imaging Branch
Biomedical Imaging Program
Division of Cancer Treatment and Diagnosis

Enclosures
There existed unmet clinical needs with regards to Prostate Carcinoma imaging

- ~180,000 cases of prostate cancer diagnosed per year
  - 30% of treated PC subjects have biochemical failure
  - 20,000 deaths each year
- No definitive technique for prostate cancer imaging
  - Primary
  - Metastasis
  - Recurrence
  - FDG not useful except for aggressive cancer
Emory Investigators began to think more about filing an IND:

- At this time an IND was required for clinical trials involving greater than 30 subjects and the IND must also include:
  - Preclinical Data
  - Human Protocol
  - Chemistry, Manufacturing, and Control Data
  - Pharmacology and Toxicology Data - ~$500k??

- And will require:
  - $, $, and more $$!
  - Time, in years!
  - Effort and focus to meet challenges...
FDA Drug Approval, typically a 15+ year process
The potential of FACBC was getting exciting so in 2004 I decided to submit an abstract to the APhA 2004 Annual Meeting in Seattle

APhA 2004 Abstract #117

QUALITY CONTROL OF [F-18]FACBC: A NON-NATURAL AMINO ACID TUMOR IMAGING AGENT

Ronald J. Crowe, Weiping Yu, Mark M. Goodman

Department of Radiology, EUH, Emory University
1364 Clifton Road NE, Atlanta, GA 30322

Objective:

FACBC, anti-1-amino-3-[F-18]fluorocyclobutyl-1-carboxylic acid, is a non-natural amino acid that has shown promise for PET tumor imaging. An improved method of synthesis has been reported that demonstrates high stereoselectivity and possible suitability for larger scale preparation. Determine and develop potential QC methods to insure safe intravenous administration and begin data collection in anticipation of IND submission.
And my Abstract was accepted as a poster!

From: apha@cos.com
To: <ronald_crowe@Emory.ORG>
Date: 12/18/03 7:54AM
Subject: APhA Contributed Papers Notification

Congratulations! Your abstract, 95800: QUALITY CONTROL OF [F-18]FACBC: A NON-NATURAL AMINO ACID TUMOR IMAGING AGENT, has been accepted as part of the APhA-APPM and APhA-APRS Contributed Papers Poster Session at the APhA2004 Annual Meeting & Exposition, March 26-30, 2004, in Seattle, Washington. Comments from the evaluators who reviewed your abstract are below and may provide useful feedback for creating your poster.

In addition to your participation in the Poster Session, your abstract will be published in the March/April 2004 issue of the Journal of the American Pharmacists Association (JPhA).

Your abstract number (which must be affixed to your poster) will be provided to you in early January, along with other meeting details. All poster presenters must be paid registrants of the APhA Annual Meeting & Exposition. For registration information, please visit www.aphameeting.org. Please be aware that Wednesday, February 25, 2004, is the deadline to receive early registration rates.

Thank you for your support of this important educational activity. If you have any questions, please do not hesitate to contact me. Although I am out of the office, I am checking email frequently.

Jo Pumphrey
APhA Education Department
aphacontributedpapers@aphanet.org
Then, in 2005 Mark Goodman, PhD, David Schuster, MD, & Ronald Crowe, RPh, BCNP, wrote, submitted and received FDA IND 72437

- Enabled the study of 39 human subjects with high and low grade gliomas
  - 1RO1CA121320: PI- Mark Goodman

- Enabled the study of > 100 subjects with prostate cancer
  - 1RO1CA129356: PI- David Schuster
  - P50CA128301 Project 1: PI- David Schuster
Then to make things interesting, we moved into a new Radiopharmacy and upgraded our antiquated synthesis system to a newer and better(?) “closed” synthesis system:
GE Tracerlab FXFN
But the FXFN was not designed specifically to replace a two vessel CPCU and was not ideal for our purpose:

- FXFN designed for single vessel reactions with prep-HPLC purification
- But we needed two vessels for our complete reaction, and we didn’t need prep-HPLC
- Resulted in major revamping of the plumbing, used prep-HPLC valve to return crude FACBC mixture to vessel for de-protection step
- Complete synthesis programming required
- Design of FXFN valves and lack of prep-HPLC purification resulted in residual MeCN breakthrough in some production batches
FXFN $^{18}$F]FACBC production woes, cont.:

- To combat the MeCN breakthrough we instituted a very lengthy custom post-production cleaning program
  - Some help but occasional batches still not released
  - Physician and patients not happy, nor Radiopharmacy
- Quality Control release criteria revisited for MeCN in final production batch.
  - Original release ("old days") based upon administration of entire production batch to patient
  - New criteria based upon actual dose volume
  - Drafted new document, approved and signed by concerned parties
Human Pilot (Phase 2a) Study


- 15 prostate patients
  - initial staging for 9
  - Restaging for 6

1RO1CA129356: PI-DM Schuster
[\textsuperscript{18}F]FACBC: Clinical data

- 9 patients with newly diagnosed prostate cancer
- 300 - 380 MBq anti-[\textsuperscript{18}F]FACBC
- 65 min dynamic imaging of pelvis + static whole body images
- Uptake evaluated quantitatively and qualitatively
- Max SUV and peak SUV measured in R and L lobes (and sextants) and in lymph nodes
- Imaging findings correlated with clinical history, imaging findings and pathology

Subject with pathologically proven bilateral prostate carcinoma
[¹⁸F]FACBC: Clinical Data

- Transrectal sextant biopsy indicated bilateral prostate carcinoma

- Focal intense uptake of [¹⁸F]FACBC only in left lobe

- Final pathology on prostatectomy: Carcinoma involving only the left lobe
[18F]FACBC: Prostate Bed Recurrence, Clinical Data

[\textsuperscript{18}F]FACBC Shows Recurrent Prostate Cancer to Metastatic to Bone and Lymph Nodes

Tc\textsubscript{99m} MDP  [In-111] Prostacint  [F-18]FACBC
Human Prostate Cancer (DU-145) Cells Orthotopically Implanted Into Prostate of Nude Rats

- Orthotopic Prostate Cancer DU145 Transplantation (OPCT) Model
- Autoradiography, conspicuity of FACBC in cancer implant vs FDG
- GE takes notice...

FACBC showed higher relative uptake compared to FDG in prostate carcinoma vs. normal or inflamed prostate or nodes.

Also relatively low urinary excretion

Uptake ratio of tumor to bladder 30 times higher than with FDG.

General Electric takes over...

- GE sub-licenses \(^{18}\text{F}\)FACBC from Nihon Medi-Physics in 2008
- GE begins trials in Europe to determine the utility of \([\text{F-18}]\)FACBC
- Emory researchers are excited about the future possibilities now that GE is involved
- However, not much happens as it pertains to moving towards a possible NDA filing
- Emory continues producing \(^{18}\text{F}\)FACBC, imaging patients and collecting data
In 2011, an important study was published:

Detection of Recurrent Prostate Carcinoma with anti-1-Amino-3-18 F-Fluorocyclobutane-1-Carboxylic Acid PET/CT and 111 In–Capromab Pendetide SPECT/CT

David M. Schuster, MD, Bital Savir-Baruch, MD., Peter T. Nieh, MD, Viraj A. Master, MD, PhD, Raghuveer K. Halkar, MD, Peter J. Rossi, MD, Melinda M. Lewis, MD, Jonathon A. Nye, PhD, Weiping Yu, PhD, F. DuBois Bowman, PhD, Mark M. Goodman, PhD

Radiology, 2011
Anti-3-[^{18}F]FACBC diagnostic performance in the prostate bed, sensitivity is 88.9%, specificity 66.7% and accuracy 83.3%. \(^{111}\)Indium-capromab-pendetide with sensitivity 69.4%, specificity 58.3%, and accuracy 66.7%.

<table>
<thead>
<tr>
<th>Prostatic Bed</th>
<th>(anti-3-[^{18}F]FACBC) (n=50)</th>
<th>(^{111})Indium-capromab-pendetide (n=50)</th>
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<tbody>
<tr>
<td></td>
<td>Positive (n=37)</td>
<td>Negative (n=13)</td>
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<tr>
<td>Biopsy (+)</td>
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<td>2</td>
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<tr>
<td>Biopsy (-)</td>
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<td>8</td>
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<td>Biopsy (-)</td>
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<tr>
<td>Definitive follow-up pending</td>
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</tbody>
</table>

PSA nadir(+): Proven local disease by PSA nadir after local therapy only

Schuster DM et al. Radiology, 2011
Post radical prostatectomy PSA 1.1 - \textit{anti}-3-\textsuperscript{[\textit{18}F]}FACBC (a and b) shows intense uptake in 5 mm left obturator lymph node biopsy proven recurrence. No uptake in same region on \textsuperscript{111}Indium-capromab-pendetide (c and d) images.

Schuster DM et al. Radiology, 2011
Post radical prostatectomy PSA 16.9 \textit{anti}-3-\textsuperscript{18}F]FACBC (a & b) shows intense uptake corresponding to biopsy proven recurrence. No uptake with \textsuperscript{111}Indium-capromab-pendetide (c & d) with bladder and rectal activity arrowheads (c & d) .

\textbf{Schuster DM et al. Radiology, 2011}
Post radical prostatectomy PSA 2.97 - *anti-3-[^18F]FACBC* (a & b) shows intense uptake in subtle lytic bone lesion in right pubic ramus at biopsy proven recurrence. No uptake in same region on $[^{111}]$Indium-capromab-pendetide images (arrows in c & d).

Schuster DM et al. Radiology, 2011
Another synthesis platform?

GE FastLab
GE FASTlab™

- Robust, automated reliable production of Fluciclovine
- Closed synthesis system, cGMP friendly
- Utilizes disposable single-use cassette
- ~45 minute synthesis time
- Synthesis yield 45-50% (non decay corrected)
- Easily and routinely make > 1 Ci of product
- Radiochemical purity typically > 98%
- Love it!

Wickstrom et al J Nucl Med 2011
New Drug Application! (yeah!)

- Blue Earth Diagnostics sub-licensed $^{18}$F]FACBC from General Electric in 2014
- Blue Earth correlated the results from European trials and the extensive data from Emory University and submitted NDA in 2015
- $^{18}$F]Fluciclovine, trade name Axumin™, received FDA Priority Review, ~6 months
The Road to FDA Approval is a 10 Step Process

1. Identify Clinical Need
2. Drug Discovery
3. Preclinical Research and Validation for Lead Compound
4. Toxicity for Lead Compound
5. Submit IND to FDA for Approval
6. Clinical Phase 1: safety and dosimetry (n=6)
7. Clinical Phase 2a: safety and efficacy (n=50)
8. Clinical Phase 2b: safety and efficacy (n=150)
9. Clinical Phase 3: efficacy (n=500)
10. NDA Filing to FDA
Axumin™ Roadmap

<table>
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<tr>
<th>Step</th>
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<tbody>
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<td>Identify Clinical Need - Gliomas and Prostate Cancer</td>
<td>1994 and 2000</td>
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<td>Drug Discovery</td>
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<td>Preclinical Research and Validation For Lead Compound</td>
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<td>IRB Approval For First in Humans</td>
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<tr>
<td>Toxicity Studies For IND Submission-NIH DCIDE</td>
<td>2001-2004</td>
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<td>IND Preparation, Submission and IND FDA Approval</td>
<td>2004-2005</td>
</tr>
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<td>Clinical Phase 1 Safety and Radiation Dosimetry</td>
<td>2006</td>
</tr>
<tr>
<td>Clinical Phase 2a</td>
<td>2007-2010</td>
</tr>
<tr>
<td>Clinical Phase 2b</td>
<td>2007-2012</td>
</tr>
<tr>
<td>Clinical Phase 3</td>
<td>2012-2015</td>
</tr>
<tr>
<td>NDA Filing</td>
<td>November 2015</td>
</tr>
</tbody>
</table>
NDA Approval May 27, 2016!

IDENTIFYING RECURRENT PROSTATE CANCER

AXUMIN™
Fluciclovine F 18 Injection
IS FDA APPROVED

To learn more, visit Axumin.com
Axumin™: Approved Indication

- INDICATION Axumin™ (fluciclovine F 18) injection is indicated for positron emission tomography (PET) imaging in men with suspected prostate cancer recurrence based on elevated blood prostate specific antigen (PSA) levels following prior treatment.
**Anti-[^18F]FACBC Readily Visualizes High-grade Brain Tumors, With A Significantly Higher Tumor To Brain Activity Ratio Than [^11C]Methionine.**

Tumor and Normal Brain uptake of FACBC and C-11 Methionine (n=15)

<table>
<thead>
<tr>
<th>Amino Acid</th>
<th>Tumor (SUV)</th>
<th>Cortex (SUV)</th>
<th>Tumor/Cortex ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-[^18F]FACBC</td>
<td>4.7 ± 2.2</td>
<td>0.5 ± 0.1</td>
<td>10.1 ± 3.9</td>
</tr>
<tr>
<td>[^11C]Methionine</td>
<td>5.2 ± 2.3</td>
<td>1.3 ± 0.4</td>
<td>3.6 ± 1.1</td>
</tr>
</tbody>
</table>

Akhurst T et al., J Nucl Med, 2006
Potential Future Axumin™ Indications?

- Glioblastoma Imaging
- Single Pulmonary Lung Nodule Imaging
- Systemic Tumor Imaging
- Breast Cancer Imaging
- Cancer Staging
- Others?
In Summary:

- Fluciclovine is an exciting and useful imaging tool with reliable production chemistry.
- Developing production and quality assurance methods and routinely and successfully preparing fluciclovine for patients was challenging, frustrating and rewarding.
- Current generations of nuclear pharmacists only move forward on the advances and contributions of those dedicated nuclear pharmacists who proceeded us: We stand on the shoulders of giants!
- I was also very fortunate to work with a very diverse and talented group of collaborators dedicated to the mission.
- Unfortunately I did not get rich off the approval of fluciclovine, but I did and do get a nice paycheck each month!
Collaborators

Chemistry/Radiochemistry
Mark Goodman, PhD, Timothy Shoup, PhD
Weiping Yu, Ph.D., Jon McConathy, M.D., Ph.D., Ron Voll, Ph.D.

Preclinical Studies
Dennis Eshima, Ph.D., Weiping Yu, Ph.D., Zhaobin Zhang, B.S., Eugene Malveaux, B.S., Vernon M. Camp, CNMT, Larry Williams, B.S.

Radiopharmacy
Ronald Crowe, BCNP, Karen Dolph, NP, Michael Waldrep, B.S.

Human Studies
David Schuster, M.D., Jeffrey Olson M.D., John Hoffman, M.D. Peter Nieh, M.D., Viraj A. Master, M.D., Ph.D., Ragu Halkar, M.D., Bital Baruch Savir, M.D., Delicia Votaw, CNMT, Margie Jones, CNMT, Angie Williams, R.N, Leah Bellamy, R.N.

Transport Mechanism Studies
Shuntaro Oka, Ph.D., D.V.M., Vernon M. Camp, CNMT, Hiroyuki Okudaira, Ph.D., Takeo Nakanishi, Ph.D., Masato Kobayashi, Ph.D., Hiroshi Tamagami, Shirakami, Ph.D., Ikumi Tamai, Ph.D., Keiichi Kawai, Ph.D.

Graphical Methods of Analysis
Jonathan Nye, Ph.D. John R. Votaw, Ph.D.
Acknowledgements

Mark M. Goodman, PhD and David Schuster, MD for the use of some of their slides and images

This presentation is dedicated to Michael Mosley, RPh, BCNP, and Eric Weiner, RPh. Two mentors who patiently showed a young whippersnapper pharmacy graduate the ropes in Nuclear Pharmacy
Thank You!

Lead, follow, or get out of the way!
1. The first PET drug, $[^{18}\text{F}]\text{NaF}$, was approved by the FDA in what year?

A. 1965  
B. 1994  
C. 1972  
D. 2010
2. Fluorine-18 is an ideal isotope for PET tracers because

A. F-18 has a 110 minute half-life
B. F-18 is a high energy α-emitter
C. F-18 is rapidly metabolized to other radio-labeled species
D. F-18 cannot form a stable bond with carbon
3. Why are Amino Acids useful in tumor imaging?

A. Amino Acids have greater uptake in inflammatory tissue as compared to $^{18}\text{F}$FDG.
B. High uptake of Amino Acids in the kidney and bladder yields better and more definitive imaging of the prostate.
C. Many tumor cells have increased Amino Acid transport and protein synthesis as compared to normal cells.
D. Amino Acids are useful only for therapy and do not have diagnostic or prognostic use.
4. The typical “First Step” on The Road to FDA Approval is

A. Discovery of the drug/lead compound
B. Toxicity study of the drug/lead compound
C. Clinical Phase 1: drug safety and dosimetry
D. Identification of a clinical need