Working Against Time: Designing and Synthesizing $^{18}$FDG for the First Human Studies in 1976

Joanna S. Fowler

Brookhaven National Laboratory
National Institutes of Health

The $^{14}$C-2-Deoxyglucose Method

Study from P. Hand, Penn) digitized by NIH
The $^{14}$C-2-Deoxyglucose (2-DG) Method

Goal was to label the 2-DG molecule with a radioisotope that would maintain its properties; could be imaged in humans.
December 19, 1973

Subject: Meeting to discuss collaboration between the Nuclear Medicine Programs at BNL and U. of Pennsylvania.

Participants:

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abass Alavi, M.D.</td>
<td>Nuclear Medicine</td>
<td>HUP</td>
</tr>
<tr>
<td>Harold Atkins, M.D.</td>
<td>Nuclear Medicine</td>
<td>BNL</td>
</tr>
<tr>
<td>David Christman, Ph.D.</td>
<td>Chemistry</td>
<td>BNL</td>
</tr>
<tr>
<td>Joanna Fowler, Ph.D.</td>
<td>Chemistry</td>
<td>BNL</td>
</tr>
<tr>
<td>David Kuhl, M.D.</td>
<td>Nuclear Medicine</td>
<td>HUP</td>
</tr>
<tr>
<td>Martin Reivich, M.D.</td>
<td>Neurology</td>
<td>HUP</td>
</tr>
<tr>
<td>Muni Staum, Ph.D.</td>
<td>Radiopharm. Chem.</td>
<td>HUP</td>
</tr>
<tr>
<td>Alfred Wolf, Ph.D.</td>
<td>Chemistry</td>
<td>BNL</td>
</tr>
<tr>
<td>Steven Nyary, M.D.</td>
<td>Neurology</td>
<td>HUP</td>
</tr>
</tbody>
</table>

Agenda:

- Lunch - Berkner Hall, conf. room C
- Discussion of programs of mutual interest with emphasis on labeled carbohydrates for brain function studies.
Top row: Brian Gallagher, David Christman, David Schlyer, Tony Guzikowski, Toshi Hara, Bob MacGregor, Al Wolf, Betty Crawford, David Tang, Hernan Vera Ruiz

Bottom row: Richard M. Lambrecht, Joanna Fowler, David Lloyd, Chyng Shiue, Richard Ehrenkaufner, Bob Lade, Karin Karlstrom
Brookhaven 60 inch cyclotron

Decommissioned in 2009

Ron Finn, 1973
### Short Lived PET Radioisotopes

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Half-life</th>
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</thead>
<tbody>
<tr>
<td>carbon-11</td>
<td>20.4 min</td>
</tr>
<tr>
<td>fluorine-18</td>
<td>110 min</td>
</tr>
<tr>
<td>nitrogen-13</td>
<td>10 min</td>
</tr>
<tr>
<td>oxygen-15</td>
<td>2 min</td>
</tr>
</tbody>
</table>

Fluorine-18’s half life was potentially long enough to be incorporated into a radiotracer and transported from Upton, NY to Philadelphia for imaging on Mark IV.
Where should we label the 2-DG molecule?

SUBSTRATE SPECIFICITY OF BRAIN HEXOKINASE*

BY ALBERTO SOLS† AND ROBERT K. CRANE

(From the Department of Biological Chemistry, Washington University School of Medicine, St. Louis, Missouri)

(Received for publication, February 8, 1954)
“2-Deoxy-glucose possesses certain advantages over glucose as a substrate for experimental studies with crude preparations of brain and other tissue hexokinases. The phosphate ester formed from 2-deoxy-glucose is not inhibitory and it is not a substrate for either phosphohexose isomerase or glucose-6-phosphate dehydrogenase. Thus the use of 2-deoxyglucose isolates the hexokinase reaction.” (J. Biological Chemistry 210: 581, 1954)
$^{18}$FDG: Design and Synthesis

[14C]2-deoxyglucose

[18F]Fluorodeoxyglucose ($^{18}$FDG)

 autoradiography in animals  imaging in humans

$^{18}$F: $t_{1/2}$ 110 min; had a long enough half-life to make it at BNL and ship it to Philadelphia.
Synthesis of Unlabeled FDG

From **KHF$_2$** in 1969

*Chemical Communications, 1969*

**Synthesis of 2-Deoxy-2-fluoro-D-glucose**

By **Josef Pacák,** Zdeněk Točík, and Miloslav Černý

(University of Organic Chemistry, Charles University, Prague–Albertov, Czechoslovakia)

From **CF$_3$OF** in 1970

*Carbohydrate Research*

Elsevier Publishing Company, Amsterdam

Printed in Belgium

**FLUORINATED CARBOHYDRATES**

**PART III**

2-DEOXY-2-FLUORO-D-GLUCOSE AND 2-DEOXY-2-FLUORO-D-MANNOSE*

J. Adamson**, A. B. Foster,

Chester Beatty Research Institute, Institute of Cancer Research: Royal Cancer Hospital, Fulham Road, London, S. W. 3 (Great Britain)

L. D. Hall, R. N. Johnson†,

Department of Chemistry, University of British Columbia, Vancouver 8, B. C. (Canada)

and R. H. Hesse

Research Institute for Medicine and Chemistry, Cambridge, Mass., 02142 (U.S.A.)

(Received June 1st, 1970; accepted for publication, June 22nd, 1970)
2-FDG but not 3 or 4-FDG was a good substrate for hexokinase

**Biochem. J. (1972) 128, 199–204**

*Printed in Great Britain*

The Use of Deoxyfluoro-D-glucopyranoses and Related Compounds in a Study of Yeast Hexokinase Specificity

By E. M. BESSELL, A. B. FOSTER and J. H. WESTWOOD

*Chester Beatty Research Institute, Institute of Cancer Research; Royal Cancer Hospital, Fulham Road, London S.W.3, U.K.*

*(Received 20 December 1971)*

<table>
<thead>
<tr>
<th>Compound</th>
<th>$K_m$ (mm)</th>
<th>Relative $V_{max.}$</th>
<th>$K_m$ MgATP$^2$ (mm)</th>
<th>Calculated $K_m'$</th>
<th>Experimental $K_m'$</th>
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</thead>
<tbody>
<tr>
<td>D-Glucose</td>
<td>0.17</td>
<td>1.00</td>
<td>0.20</td>
<td>1</td>
<td>1</td>
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<tr>
<td>2-Deoxy-d-arabino-hexose</td>
<td>0.59 ± 0.11</td>
<td>0.85</td>
<td>0.36 ± 0.11</td>
<td>—</td>
<td>1.36 ± 0.37</td>
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<tr>
<td>2-Deoxy-2-fluoro-D-glucose</td>
<td>0.19 ± 0.03</td>
<td>0.50</td>
<td>0.26 ± 0.05</td>
<td>1.14</td>
<td>0.86 ± 0.75</td>
</tr>
<tr>
<td>2-Deoxy-2-fluoro-D-mannose</td>
<td>0.41 ± 0.05</td>
<td>0.85</td>
<td>0.66 ± 0.25</td>
<td>2.46</td>
<td>0.91 ± 0.47</td>
</tr>
<tr>
<td>2-Deoxy-2,2-difluoro-D-arabino-hexose</td>
<td>0.13 ± 0.02</td>
<td>0.53</td>
<td>0.21 ± 0.02</td>
<td>0.78</td>
<td>0.91 ± 0.47</td>
</tr>
<tr>
<td>3-Deoxy-3-fluoro-D-glucose</td>
<td>70 ± 30*</td>
<td>0.10</td>
<td>2.3 ± 0.3†</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>4-Deoxy-4-fluoro-D-glucose</td>
<td>84 ± 30*</td>
<td>0.10</td>
<td>1.9 ± 0.1†</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2-Chloro-2-deoxy-D-glucose</td>
<td>2.1 ± 0.6</td>
<td>0.54</td>
<td>0.97 ± 0.33</td>
<td>12.6</td>
<td>9 ± 10</td>
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</table>
Sokoloff: “Will F substitution change its behavior in vivo?”

Synthesis of $[^{14}C]$FDG for comparison to $[^{14}C]$2-DG

* * *

Will $^{18}$FDG behave like $[^{14}C]2$-DG in vivo?

This supported the development of a rapid radiosynthesis of $^{18}$FDG

The $[^{18}F]$fluorodeoxyglucose method for the measurement of local cerebral glucose utilization in man, M Reivich, D Kuhl, A Wolf, J Greenberg, M Phelps, T Ido, V Casella, J Fowler, E Hoffman, A Alavi, P Som and L Sokoloff Circulation Research 1979, 44:127-137
At the time Brookhaven’s only reliable source of $^{18}\text{F}$ for chemistry was as elemental fluorine ($^{18}\text{F}]\text{F}_2$) which Lambrecht and Finn had developed in 1973 (J. Nucl Med 14; 63-4, 1973).

$$^{20}\text{Ne}(d,\alpha)^{18}\text{F} \rightarrow^{18}\text{F} + \text{F}_2 (0.1\%)$$

$[^{18}\text{F}]\text{F}_2$
Tatsuo Ido, Chung Nan Wan and Vito Casella joined the Brookhaven group to work on $[^{18}\text{F}]\text{F}_2$ production and develop the $^{18}\text{FDG}$ synthesis.

By 1975, the target was producing 600-800 mCi of $[^{18}\text{F}]\text{F}_2$.

Tatsuo Ido’s report and notebook (July 14, 1975): developing the radiosynthesis of $^{18}$FDG
First $^{18}$FDG Synthesis for Humans (1976)

$^{20}$Ne (d, $\alpha$)$^{18}$F

Synthesis time 2 hr: prepared according to a protocol that had been shown to produce a sterile, pyrogen free product.
Tatsuo Ido mounts Ne/F\textsubscript{2} target

Tatsuo Ido   CN Wan   Al Wolf
Brookhaven National Laboratory; August 16, 1976

18FDG measurement

packaging

18FDG leaves hot lab

Brookhaven Calabro Airport

18FDG leaves BNL

Bob MacGregor
Philadelphia; August 16, 1976

Philadelphia International Airport

$^{18}$FDG arrives in Philadelphia

Arrival at Penn
Hospital University of Pennsylvania; August 16, 1976

Ed Hoffman (1944-2009)

Dave Kuhl  Mike Phelps  Martin Reivich

Joel Greenberg  Volunteer in Mark IV

Angela Sylvestro  Joel Greenberg
Hospital University of Pennsylvania; August 16, 1976

Vito Casella  Tatsuo Ido  Dave Kuhl  

Dave Kuhl  Martin Reivich  Mike Phelps
Hospital University of Pennsylvania; August 16, 1976

Vito Casella  Tatsuo Ido  Muni Staum
Hospital University of Pennsylvania; August 16, 1976

Martin Reivich

David Kuhl
First Brain images made on Kuhl’s Mark IV tomograph in August, 1976

Rates of glucose metabolism ranged from 10.27 mg/100 g/min in visual cortex to 3.80 mg/100 g/min in white matter.
The $[^{18}F]$ Fluorodeoxyglucose Method for the Measurement of Local Cerebral Glucose Utilization in Man

M. Reivich,¹ D. Kuhl,² A. Wolf,³ J. Greenberg,¹ M. Phelps,² T. Ido,³ V. Casella,³
J. Fowler,³ E. Hoffman,² A. Alavi,² P. Som,³ and L. Sokoloff⁴

emission tomographic scanner. The method was used to measure local cerebral glucose consumption in two normal volunteers. The values in gray matter structures range from 5.79 mg/100 g per minute in the cerebellar cortex to 10.27 in the visual cortex, whereas, in white matter structures, the values range from 3.64 mg/100 g per minute in the corpus callosum to 4.22 in the occipital lobe. Average values for gray matter, white matter, and whole brain metabolic rates, calculated as a weighted average based on the approximate volume of each structure, are 8.05, 3.80, and 5.90 mg/100 g per minute, respectively. The value of 5.9 mg/100 g per minute compares favorably with values previously reported. Circ Res 44: 127–137, 1979
The $^{18}$FDG Method is quantitative

Operational equation for estimating glucose metabolic rate (mg$_{\text{glucose}}$/100 g$_{\text{brain}}$/min)

\[
R = \frac{\lambda \cdot V_{\text{max}} \cdot K_m}{\phi \cdot V_{\text{max}} \cdot K_m} \left[ \frac{\int_0^T (C_p^*/C_p)dt - e^{-(k_2+k_1)T} \int_0^T (C_p^*/C_p)e^{(k_2+k_1)t}dt}{\int_0^T C_p^*e^{(k_2+k_1)t}dt} \right]
\]

Lumped constant: takes into account differences between 2-DG or $^{18}$FDG and glucose
The first whole body human FDG scan was performed by Abass Alavi in August 1976 at University of Pennsylvania by employing a conventional rectilinear machine as the only option at the time.
HK and facilitated transport do not require -OH on C-2

glucose resorption (active transport) requires OH on C-2

The first whole body human FDG scan was performed by Abass Alavi in August 1976 at University of Pennsylvania by employing a conventional rectilinear machine as the only option at the time.
Metabolic Trapping as a Principle of Radiopharmaceutical Design: Some Factors Responsible for the Biodistribution of $[^{18}\text{F}] 2$-Deoxy-2-Fluoro-D-Glucose

Brian M. Gallagher, Joanna S. Fowler, Neal I. Gutterson, Robert R. MacGregor, Chung-Nan Wan, and Alfred P. Wolf

Brookhaven National Laboratory, Upton, New York
brain > heart ≅ kidney > lungs >> liver.
First Report of High $^{18}$FDG Uptake in Tumors

A Fluorinated Glucose Analog, 2-fluoro-2-deoxy-D-glucose (F-18): Nontoxic Tracer for Rapid Tumor Detection


Brookhaven National Laboratory, Upton, New York

Rapid uptake of F-18 FDG was observed in a variety of transplanted and spontaneous tumors in animals. The tumor uptake reached a peak by 30 min and remained relatively constant up to 60 min, with a very slow wash-out of F-18 activity from the tumor thereafter. Tumor-to-normal tissue and tumor-to-blood ratios ranged from 2.10–9.15 and 2.61–17.82, respectively, depending on the type of tumor. A scintiscan of a seminoma in a dog showed very high uptake in the viable part and lack of uptake in the necrotic mass. Toxicological studies in mice using 1000 times human tracer dose (HTD) per wk for 3 wk and in dogs using 50 times HTD per wk for 3 wk did not show any evidence of acute or chronic toxicity.


Prantika Som
1942-2011
First Report of High $^{18}$FDG Uptake in Tumors

A Fluorinated Glucose Analog, 2-fluoro-2-deoxy-D-glucose (F-18): Nontoxic Tracer for Rapid Tumor Detection


Prantika Som
1942-2011
In 1977 Brookhaven acquired PET III from Ter-Pogossian at Washington University and collaborations with Penn continued.

A rapid synthesis of $[^{11}\text{C}]2$-DG was developed in 1980 by Bob MacGregor (1944-2009), Chyng Shiue and Robert Lade for serial studies on PET III using a subject as his/her own control.
Increased Accumulation of 2-Deoxy-2-\textsuperscript{18}F]Fluoro-d-Glucose in Liver Metastases from Colon Carcinoma


Brookhaven National Laboratory, Upton, New York, and Memorial Sloan-Kettering Cancer Center, New York, New York
Glucose utilization of cerebral gliomas measured by $[^{18}\text{F}]$ fluorodeoxyglucose and positron emission tomography

Giovanni Di Chiro, M.D., Robert L. DeLaPaz, M.D., Rodney A. Brooks, Ph.D., Louis Sokoloff, M.D., Paul L. Kornblith, M.D., Barry H. Smith, M.D., Ph.D., Nicholas J. Patronas, M.D., Conrad V. Kufta, M.D., Robert M. Kessler, M.D., Gerald S. Johnston, M.D., Ronald G. Manning, Ph.D., and Alfred P. Wolf, Ph.D.
Some Early Human Studies with $^{18}$FDG

- Normal Aging
- Neurologic disorders
- Psychiatric disorders
- Mapping brain activity
- Cerebrovascular disorders
- Brain development
- Myocardial viability
- Cancer
- Inflammation
The Active Human Brain

PET Images of glucose metabolism (FDG) in performing tasks

Looking

Remembering

Listening

Thinking

Working

Phelps, Kuhl, Mazziotta, Science, 1981
18FDG and Cancer

- Whole body $^{18}$FDG-PET scan showing lung metastases from ovarian cancer (Phelps, UCLA)

- PET scans like this stimulated need for a high yield production of F-18 and $^{18}$FDG for distribution to institutions without a cyclotron and chemists.
Ruth and Wolf publish high yield of $^{18}$F via the $^{18}$O(p,n)$^{18}$F reaction (1979)

Ruth TJ, Wolf AP: Absolute cross sections for the production of $^{18}$F via the $^{18}$O(p,n)$^{18}$F reaction. Radiochim Acta 26:21-24, 1979
Small volume enriched water targets yielded large quantities of $[^{18}\text{F}]$fluoride via the $^{18}\text{O}(p,n)^{18}\text{F}$ reaction

- Small volume (1 mL), 95% enriched water target ($\text{H}_2^{18}\text{O}$) ($\sim$ $100$/mL) (Wieland)
- $\text{H}_2^{18}\text{O}$ could be recovered by anion exchange and reused

Schlyer DJ, Bastos MAV, Alexoff D, Wolf AP. Separation of $[^{18}\text{F}]$fluoride from $[^{18}\text{O}]$water using anion exchange resin, IJARA. Part A. Applied Radiation and Isotopes 41: 531, 1990)
Hamacher’s rapid synthesis of $^{18}$FDG from $[^{18}$F$]$Fluoride in 1986 was a major milestone.

Tatsuo Ido first suggested FDG black boxes in 1980, Lake of the Ozarks meeting.

David Alexoff

Alexoff $^{18}$FDG Box (~1986)

Siemens Explora FDG

GE FASTlab

MicroCHIP- UCLA
There is a Commercial PET Radiopharmacy within a 100 miles of >98% of the patient beds of America (Slide from M. Phelps)
Spearheaded efforts to require the FDA to approve reimbursement for \(^{18}\)FDG scans.
In 2012, the NY Chapter of the American Chemical Society designated the Chemistry Department at Brookhaven National Laboratory as a Historic Chemical Landmark for the development of $^{18}$FDG.

Why a rich country should support science

Louis Sokoloff: 1921-2015
Acknowledgments

• Office of Science, U. S. DOE (1977-2016) and predecessor offices, ERDA (1974-1977) and AEC (1946-1974)
• National Institutes of Health
• SNMMI for providing a home for radiotracer chemistry
1981 LASKER AWARDS:

1981 Albert Lasker Clinical Medical Research Award

[14C]Deoxyglucose method for measuring brain function

“This is an unprecedented achievement that contributes to the basic understanding and diagnosis of brain diseases.

Dr. Sokoloff’s brilliant contributions constitute a prime example of a bridge that leads from basic laboratory research to clinical application that can benefit literally millions of people everywhere.”

Louis Sokoloff
National Institute of Mental Health