

Scholars Trained in Advanced Radiochemistry Technologies

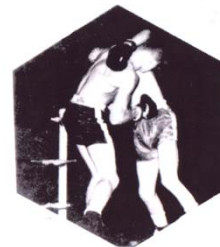
Crump Institute for Molecular Imaging

Dr. Michael E. Phelps
Norton Simon Professor
Chair, Department of Molecular & Medical Pharmacology
Director, Crump Institute for Molecular Imaging

My Unusual Career Path

10 yrs as a boxer
(Golden Gloves title as a
Welterweight)

Coma (car accident)



♣ MICHAEL PHELPS
vs.
JIM COHEN

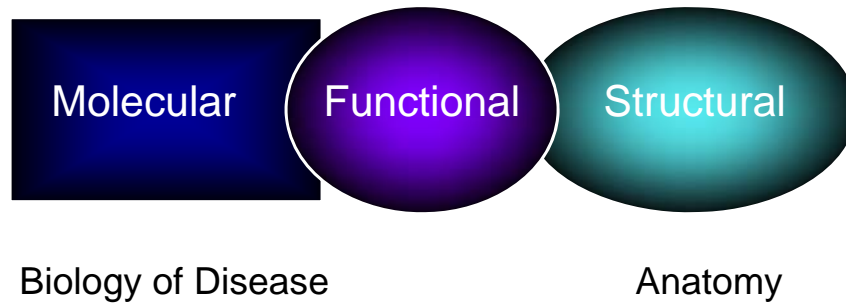
BS degrees in math & chemistry

PhD in chemistry

Faculty in Medical schools
(Wash. Univ., Penn. & UCLA)

With 2 others, started a company, CTI, to deliver molecular imaging with
PET to research & medicine; sold to Siemens in 2005 for \$1.1 Billion.

Classes of *In Vivo* Imaging



Molecular Imaging with In vivo Bioluminescence

Gene Expression - Reporter Gene (Luciferase) & Reporter Probe (Luciferin)

Molecular Imaging with PET

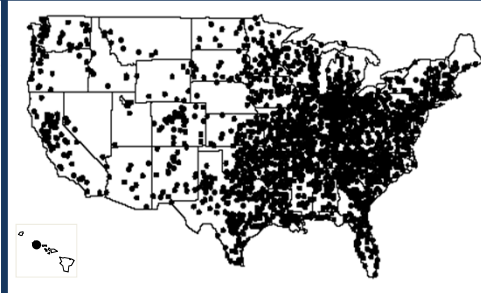
- In vivo metabolic pathway assays
- In vivo enzyme activity assays
- In vivo protein binding assays
- In vivo Quantitative pharmacokinetics & pharmacodynamics
- In vivo kinetic modeling
- In vivo DNA synthesis and expression
- In vivo tumor and stem cell tracking
- In vivo phenotypic studies

Clinical PET Centers in the USA – **how did this happen?** (~4 million studies in 2010; growing ~30%/yr)

In 1974 when the PET scanner was invented



In 2010 (In 1990 PET went from research to medicine)



Begin with an Invention - the PET Scanner



First PET Scanner: Phantom & animal studies
Date started - 12/73; Date Completed - 2/74
Washington University



First whole body clinical PET system
Date Started - 6/74; Date Completed - 12/74
Washington University



First commercial PET scanner
Date Started - 6/76; Date Completed - 12/76; UCLA

Question: What is PET? **Answer: A Molecular Camera**

2-[F-18]Fluoro-2-Deoxy-D-Glucose (FDG)

511 keV photon
180°
511 keV photon
 $E = mc^2$
UCLA

1,600 PET Probes
Probes for metabolism, receptors, enzymes, DNA replication, gene expression, immune activation, antibodies, hormones, drugs, etc. **in nmole amounts** - labeled with F-18, C-11, N-13, O-15, I-124, Cu-64, etc.

Image **Scanner**
UCLA

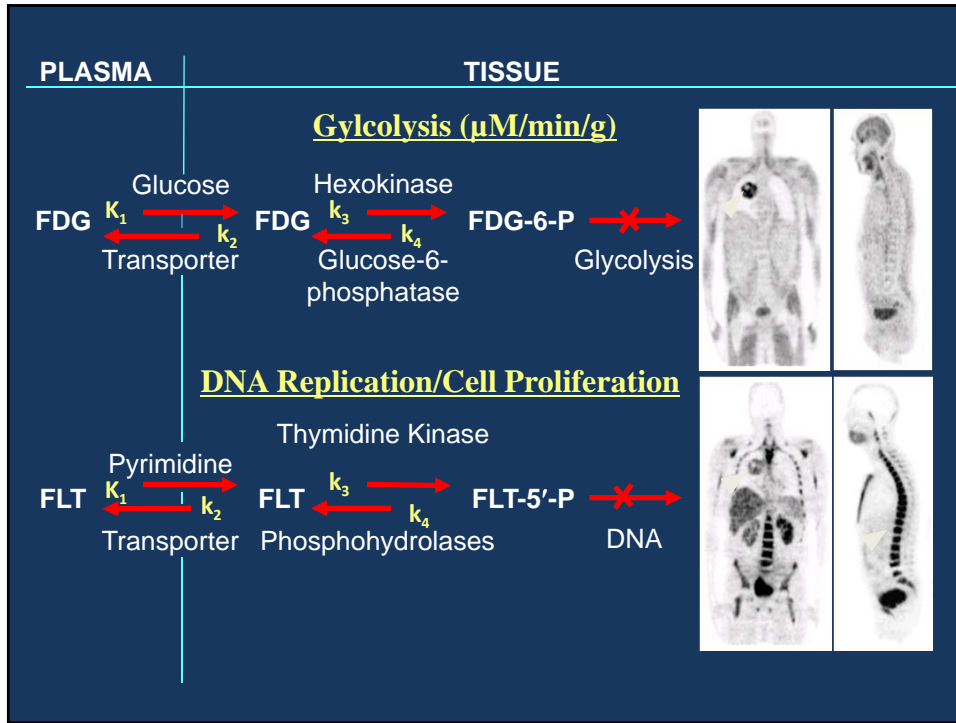
Thymidine Analogs

Thymidine
Substrate for DNA replication: [³H]thymidine used for replication & cell proliferation *in vitro*

AZT
Drug- block DNA replication & cell proliferation

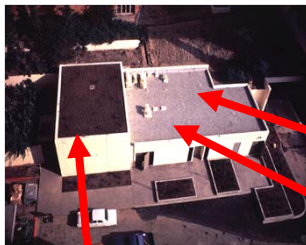
FLT
Probe - Image DNA replication & cell proliferation *in vivo*

Shields, et. al. Nature Med 4:1334-1336, 1998

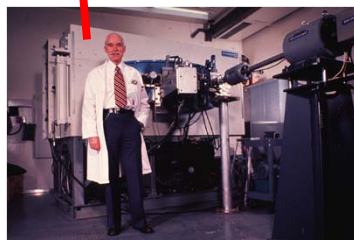


Original UCLA Biomedical Cyclotron for producing PET imaging Probes

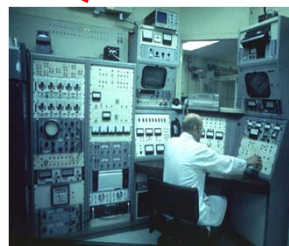
An impossible Task: Convert this bldg & everything in it into a small electronic device controlled and operated by a PC



Radiochemistry labs



Cyclotron



Cyclotron Control room



PET Radiopharmacies

PET Radiopharmacies with "Electronic Generators"

PET Radiopharmacy Inc.

Shield

Miniature Cyclotron

Automated Radiochem. Modules

PC Control

PET/CT: Integration of Biology & Structure in single scanner
Why do this?

PET Scanner
Biology & biochemistry

PET/CT Scanner
Biology, biochem./Structure

From 2000 to 2007, PET/CT went from 0% to 100% of sales of PET scanners
Commercial PET/MRI was introduced in 2009

PET/CT scan in Ovarian Cancer

Case: 54 y/o female: ovarian CA previously treated with surgery & chemo
Now with negative CT scans but rising CA125 levels.

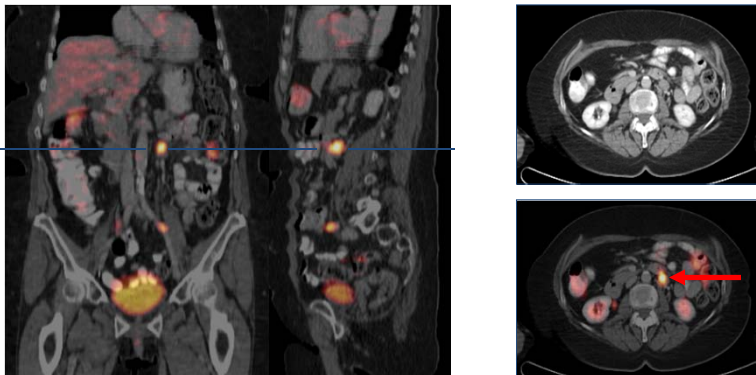
Findings: PET/CT reveals two foci with intense glucose metabolism (FDG) localized to L iliac node and L periaortic node.



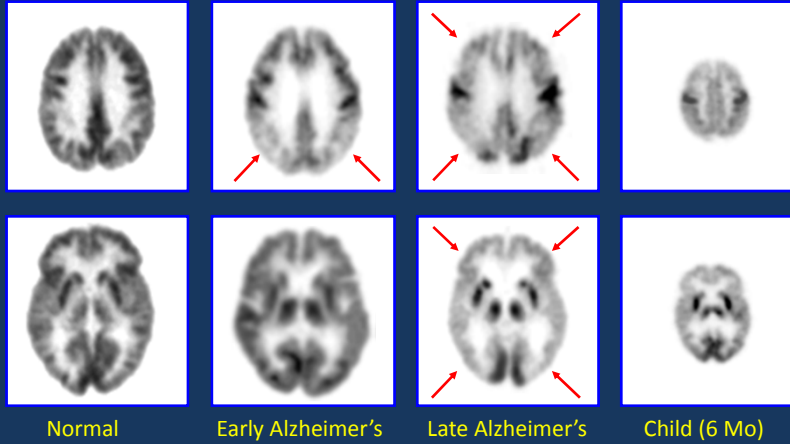
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PET Images of Early and Late Stage Alzheimer's



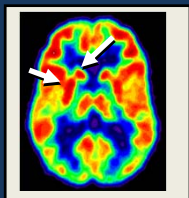
PET is 93% accurate in detecting Alzheimer's 3 yrs before diagnosis of "Probable Alzheimer's"



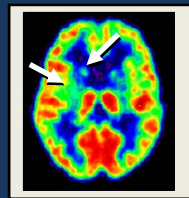
Detection of Asymptomatic Genetic Diseases

Huntington's Disease - New England J. Med. - 7 yrs before symptoms

Normal PET Scan



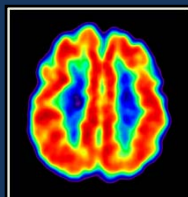
Abnormal PET Scan



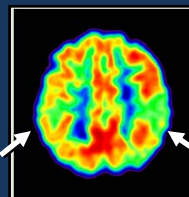
Normal MRI



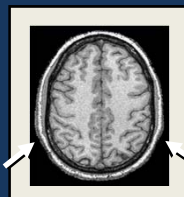
Familial Alzheimer's - New Eng J Med & JAMA - 5 to 8 yrs before symptoms



No APOE-4



APOE-4




Institute for Molecular Medicine (IMED)
UCLA School of Medicine

Two Patients Diagnosed with Gastrointestinal Stromal Tumor (GIST)

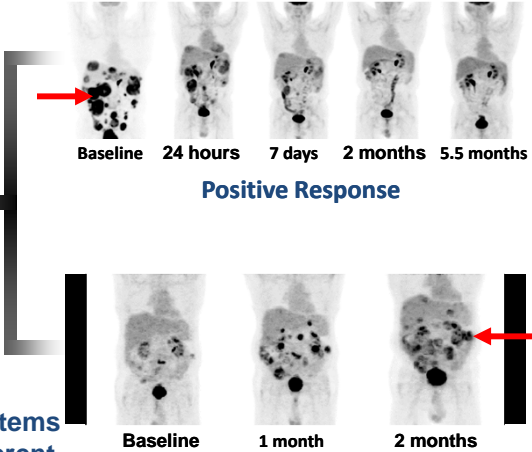
Both patients diagnosed by tissue pathology to have GIST

Both treated with Gleevec



PET Scanner

Glucose metabolism (FDG)



Positive Response

Refractory

Each patient had a different Systems Biology of cancer requiring different treatments

Demetri GD, et. al., N Engl J Med: 347:472-480, 2002

GIST patient non-responsive to Gleevec

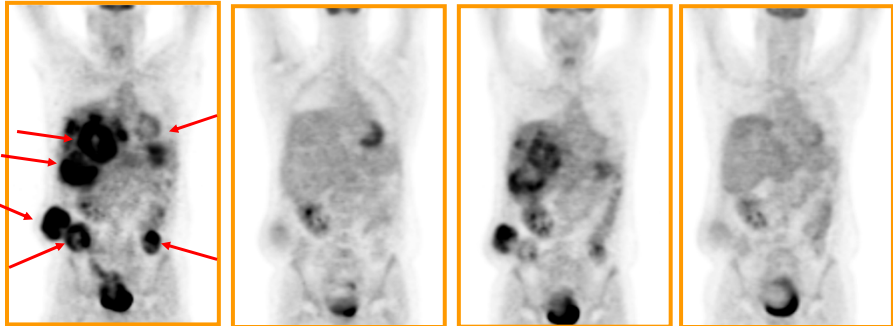
Switch drug from Gleevec to target inhibition with SU11248

Baseline
Cycle 1, day 0

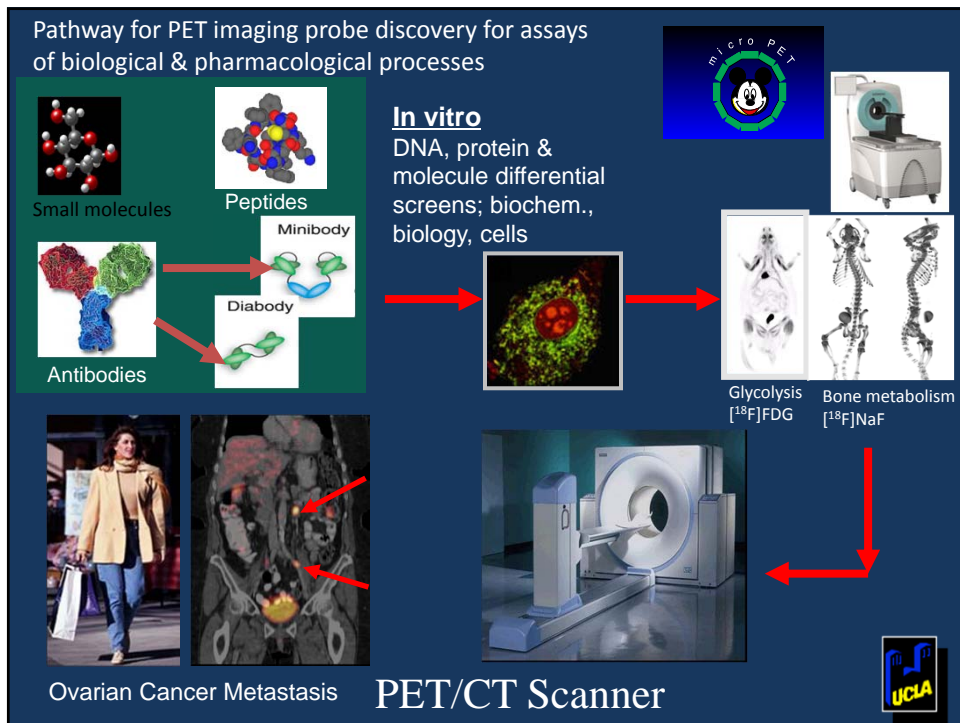
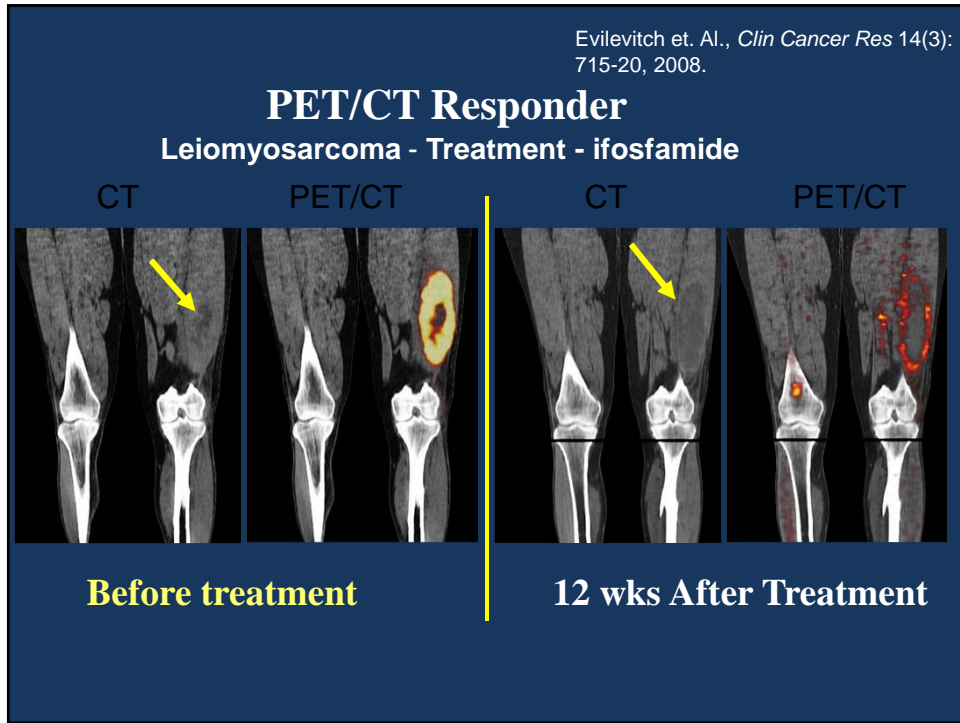
On SU11248
Cycle 1, day 7

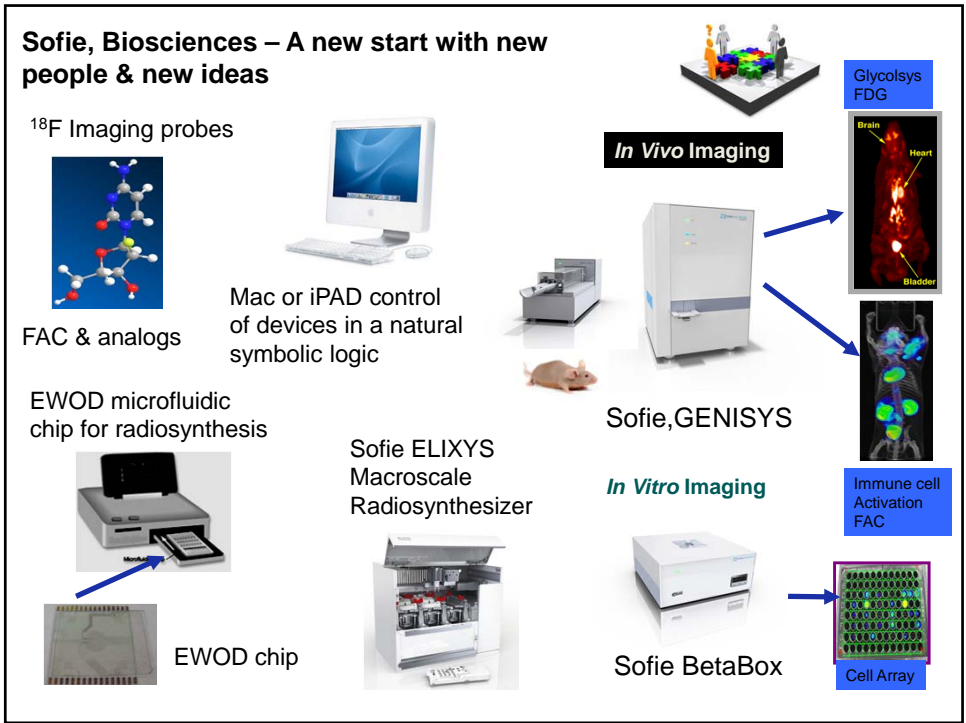
Off treatment
Cycle 1, day 28

On SU11248
Cycle 2, day 14



Demetri GD, et. al., N Engl J Med: 347:472-480, 2002

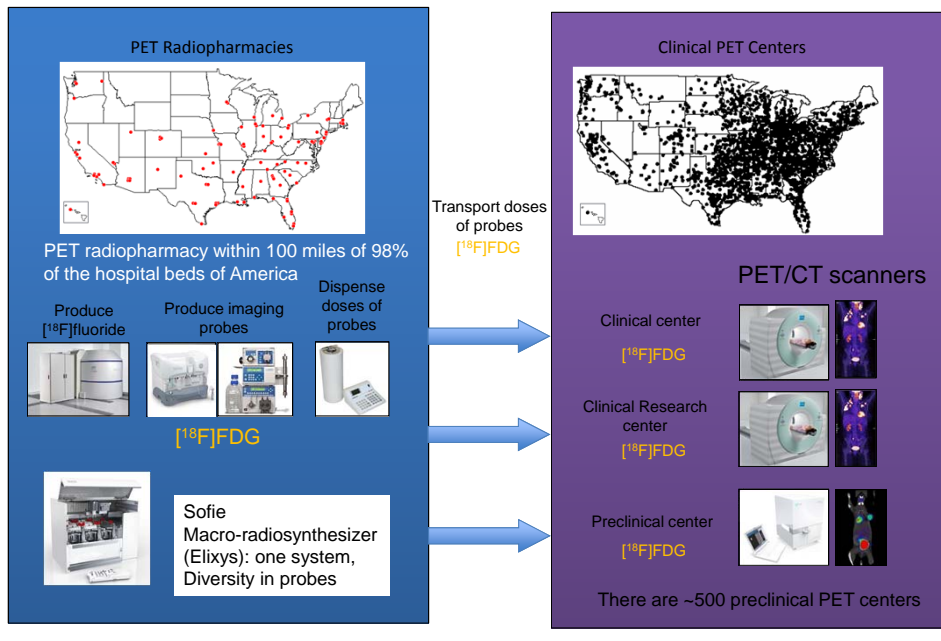




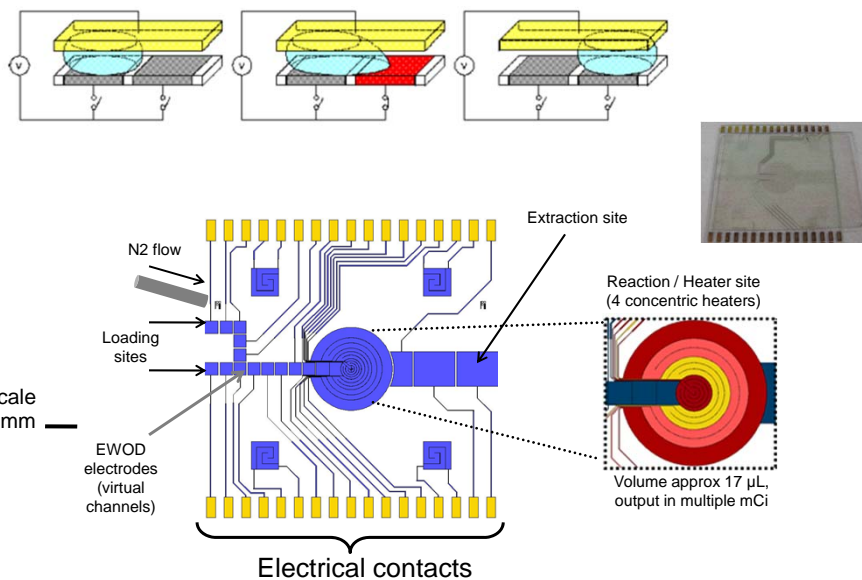
SMOOTH INSTALLATION



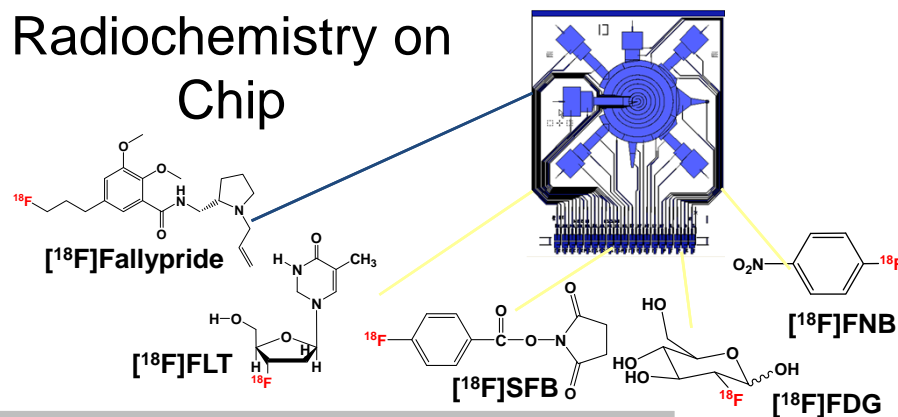
Existing Centralized Model of clinical & pre-clinical PET Centers in America



ElectroWetting-On-Dielectric (EWOD) Chip Radiosynthesizer



Radiochemistry on Chip



P Natl Acad Sci USA, 109(3): 690-695, 2012.

Micro-chemical synthesis of molecular probes on an electronic microfluidic device

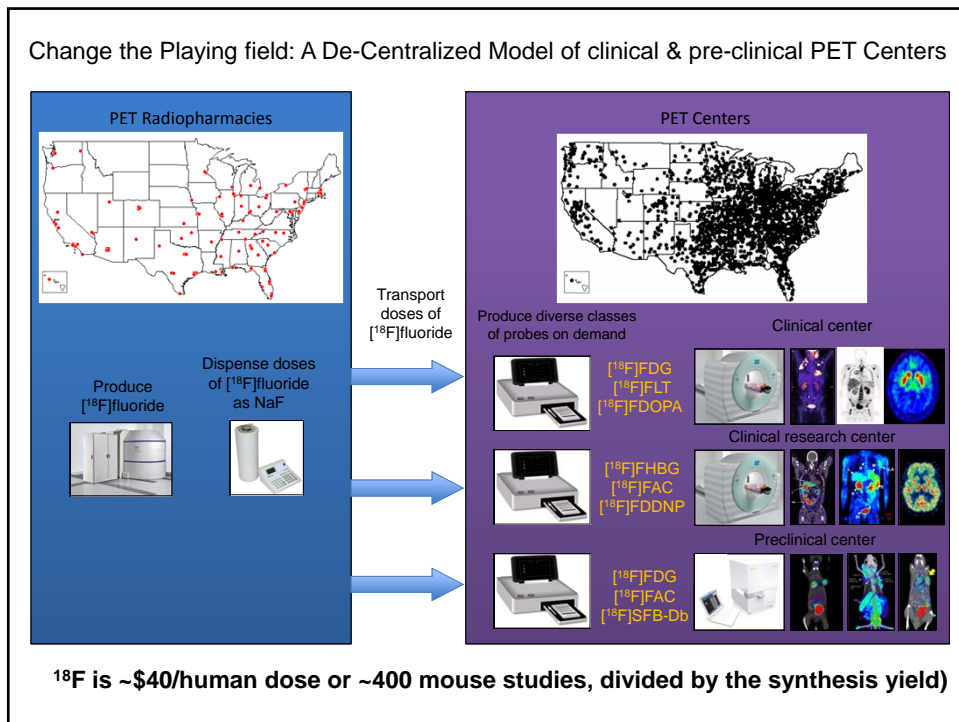
Pei Yuán Keng^{1,2}, Supin Chen¹, Huijing Ding^{1,2}, Saman Sadeghi^{1,2}, Gaurav J. Shah¹, Alex Dooraghi¹, Michael E. Phelps^{1,2}, Nagichettiar Satyamurthy^{1,2}, Arion F. Chatzigeorgidis^{1,2,3}, Chang-Jin "CJ" Kim¹, and R. Michael van Dam^{1,2,4,5}

¹Crump Institute for Molecular Imaging; ²Department of Molecular and Medical Pharmacology, David Geffen School of Medicine; ³Biomedical Engineering Department; ⁴Biomedical Physics Interdepartmental Program; ⁵Mechanical and Aerospace Engineering Department, University of California (UCLA), Los Angeles, CA 90095; and ⁶Sofie Biosciences, Inc., Culver City, CA 90230

Edited by Nicholas J. Turro, Columbia University, New York, NY, and approved December 8, 2011 (received for review December 7, 2011)

We have developed an all-electronic digital microfluidic device for microscale chemical synthesis in organic solvents, operated by electro-wetting-on-dielectric (EWOD). As an example of the principles,

batches of reagents within a chamber. Solvents can be evaporated while solutes remain in the chamber (6), permitting multistep organic synthesis in nanoliter volumes.



Here are two boxing lessons I learned during that period of my life:

1. "All the world is about training and fighting. Training is a way of Becoming and fighting is about standing and delivering when the time comes".
2. Boxers are trained to not focus on winning fights. They focus on winning rounds. They win fights, round by round - win some & loose some but when they lose one they are trained to build the will & courage to not lose the next one.
3. Boxers are also trained that they must be willing to get hurt to have the opportunity of winning