Large Technologies
(Or More Accurately Big R&D)

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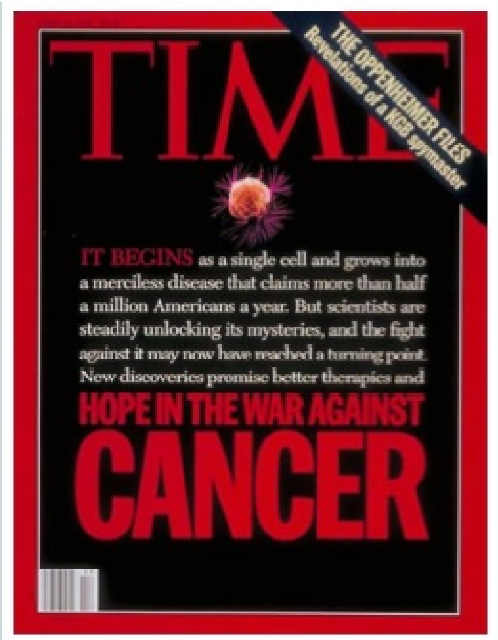
Madison WI

Horizons Meeting 2013

History of Hype about Hope



April 25, 1994

May 28, 2001

April 1, 2013

"The Truth in Small Doses: Why We're Losing the War on Cancer—and How to Win It," by Clifton Leaf (Simon and Schuster, 2013)

WORLD WAR CANCER, The New Yorker, July 1, 2013

Are we winning the war on cancer?
- NY Post, July 29, 2013

More Money Won't Win the War on Cancer – The Atlantic, Aug 28, 2013

Learning to Expect Less From the War on Cancer – Discover Magazine Blog, Sept 22, 2013

“We have managed to make cancer a huge business, and a national ‘terror,’ but the progress in reducing mortality is quite questionable.”

- Silvia Formenti, Chair of Radiation Oncologist, New York University, quoted in The New Yorker, July 1, 2013

Big R&D Must Be Goal-Directed

- Most research in the basic sciences is curiosity-directed
- Funding agencies primarily fund curiosity-driven research
- Goal-directed R&D requires a goal and scientific model development to drive the required <u>engineering</u>
- Goal-directed R&D in healthcare almost always requires corporate involvement in order to get sufficient investment for FDA clearance and other approvals

Scientific Paradigm

1. Hypothesis design based on curiosity
2. Use the hypothesis to design an experiment
3. Test the hypothesis experimentally
4. Refine the hypothesis

Clinical trials use the scientific paradigm

Engineering Paradigm

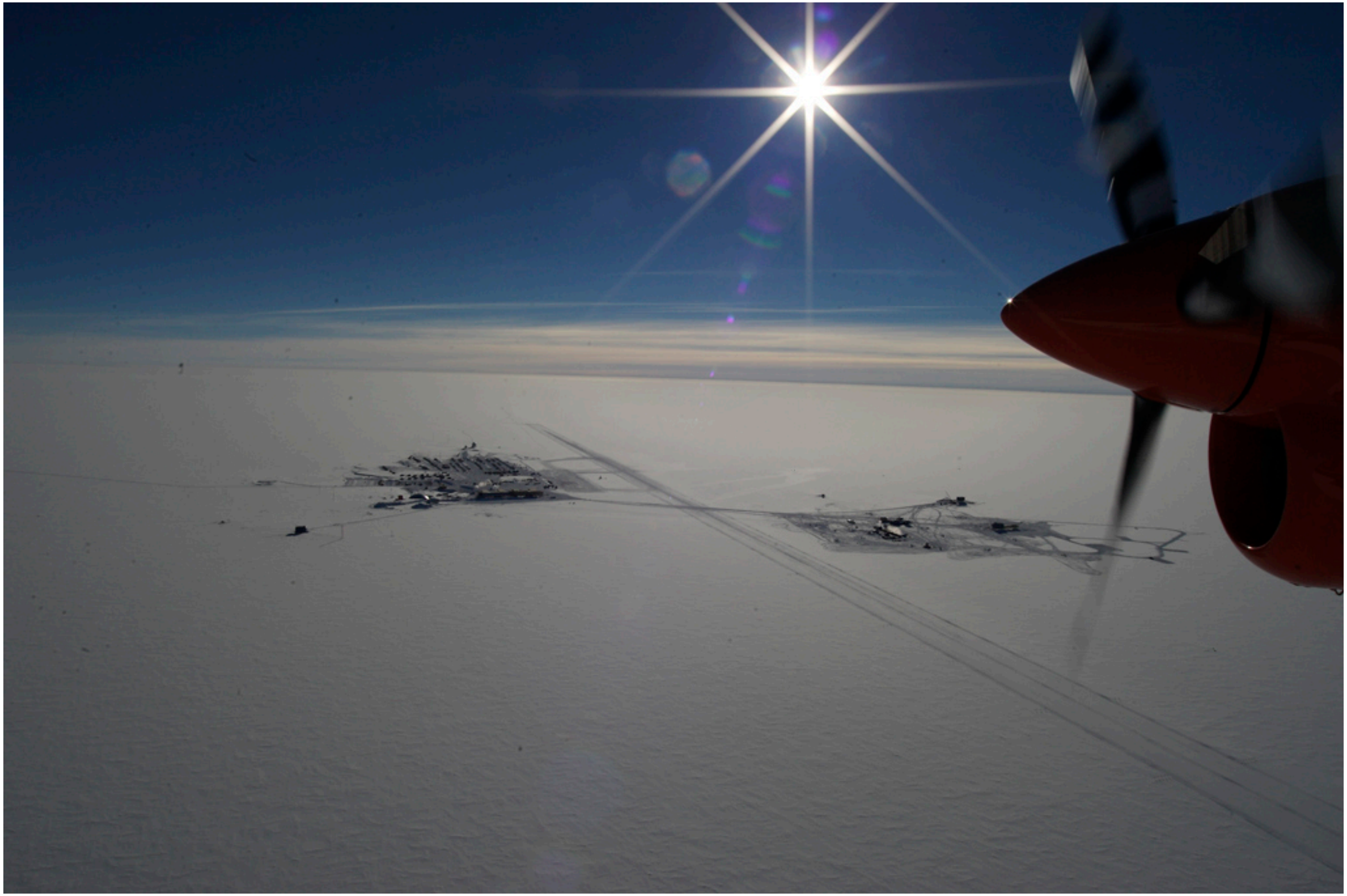
1. Model the science necessary to achieve the goal
2. Use the model to design a device, process, or even a drug
3. Test the device or process
4. Refine the device or process

Solving problems requires a goal and uses the engineering paradigm

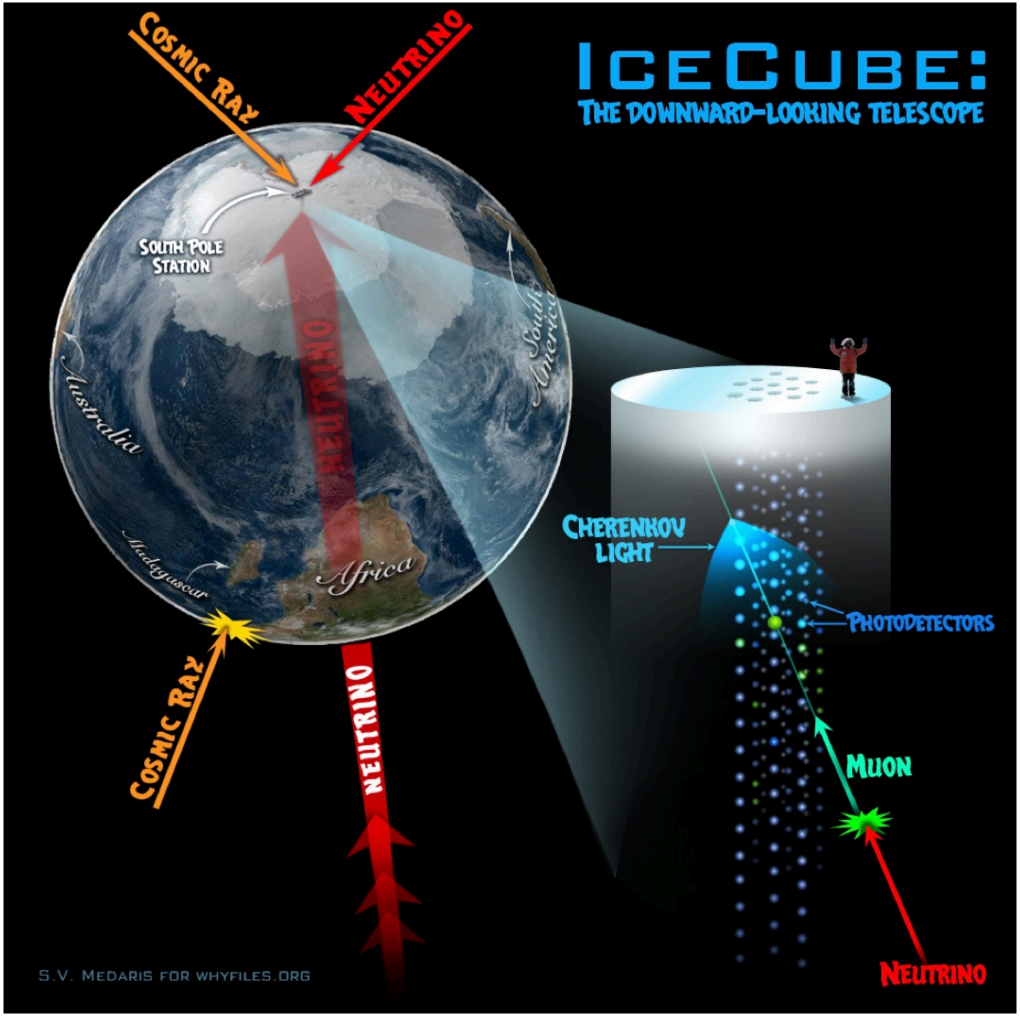
Engineering Paradigm Requires Scientific Models

- Make models of existing knowledge
- Model building is modern scholarship
- Most efficient time in history to be a scholar
- Where data does not exist for a model refine the model or do research to get the data it requires
- Use simulation to test the model and design experiments
- Sharing models is more important than publishing papers

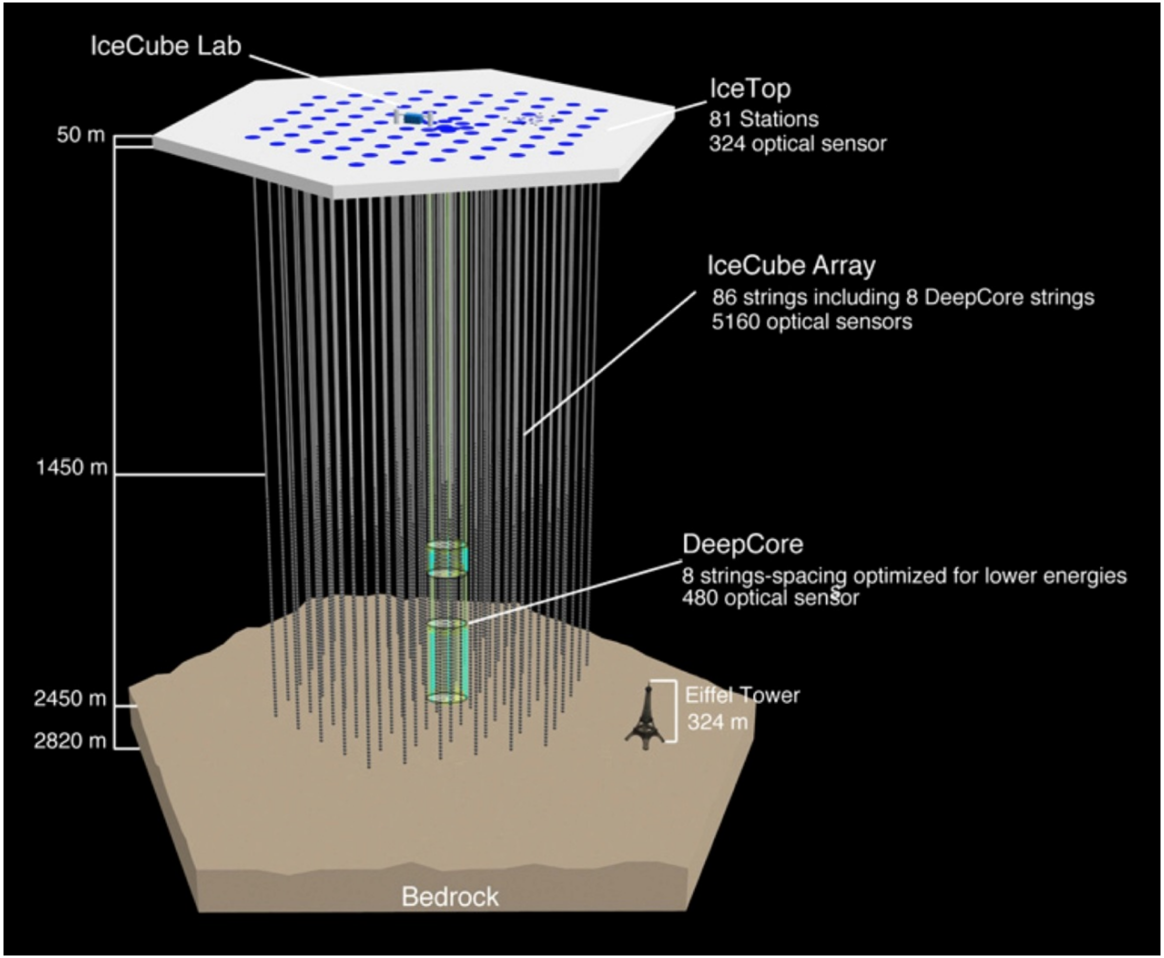
Examples of Big R&D: Ice Cube



Goal to Detect Direction of Cosmic Neutrinos



Hexagonal Array of Cables Carrying Photomultiplier Tubes Embedded in Ice

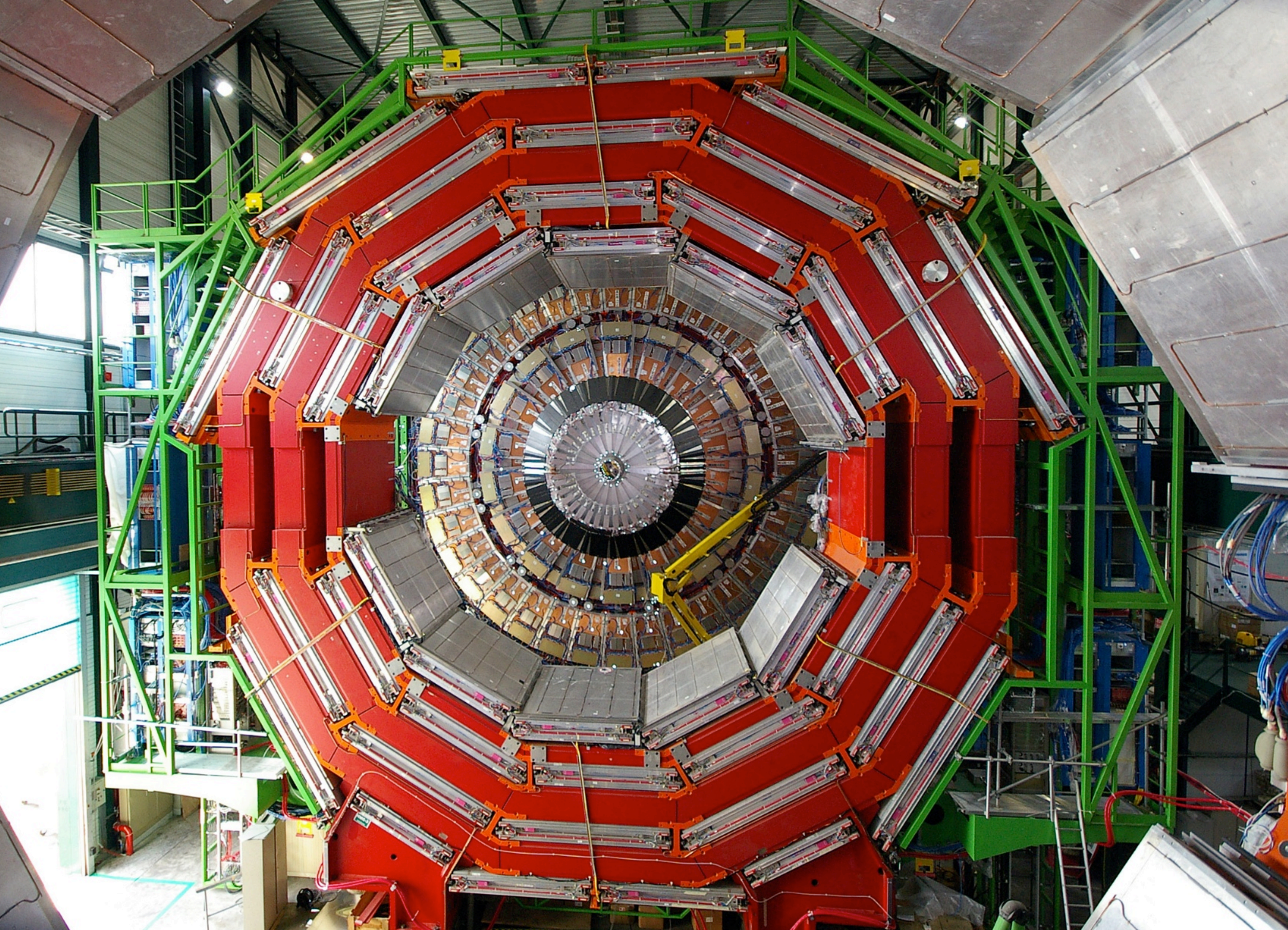


Data and Models Needed for Ice Cube

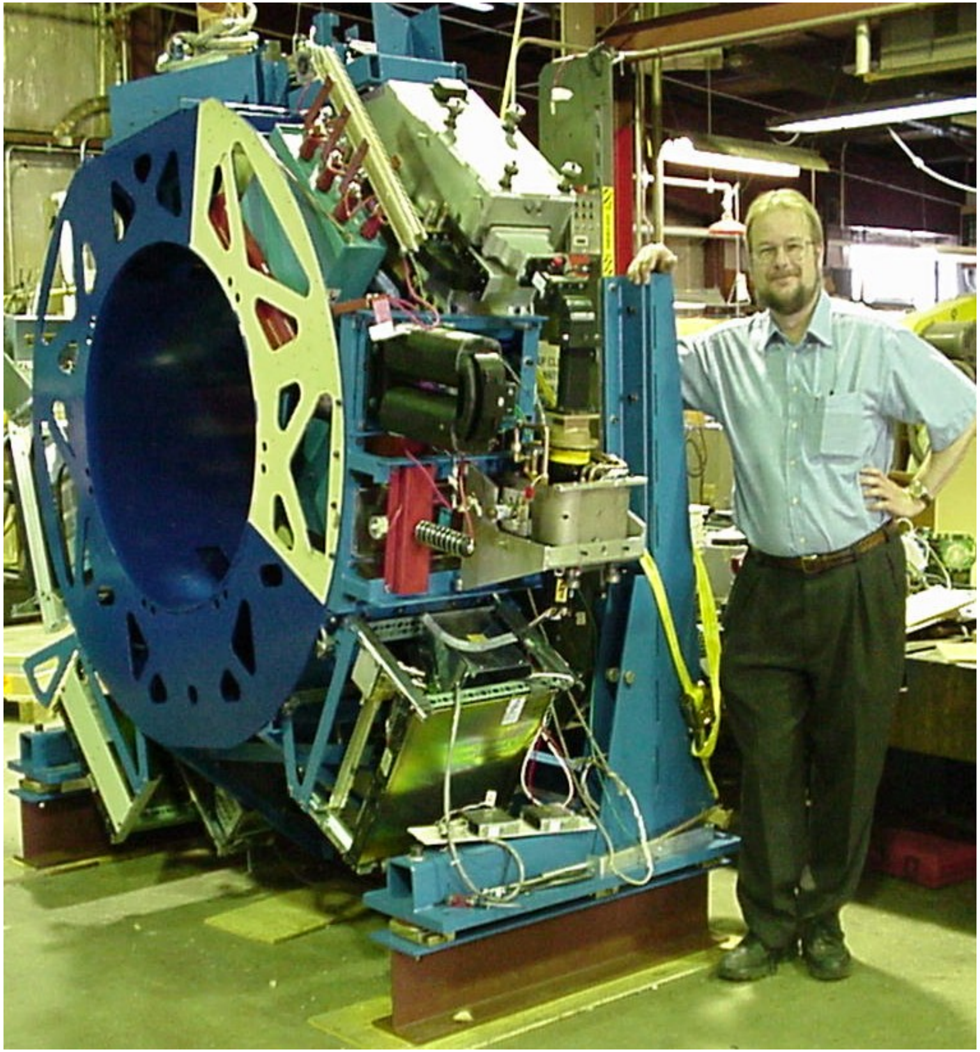
- Where is ice thick enough?
- How clear (attenuation and scattering) is the ice?
- How will the data be reconstructed to obtain the neutrino direction with as much angular resolution as possible?
- How will the ice be bored?
- How long will the components last without service?
- What is the architecture of data processing and transfer.
- What is the organization and management of the construction effort at the South Pole?

Ice Cube Was Built by UW Physical Sciences Lab (PSL) Engineering and Physics Services

Large Hadron Collider: End Caps



First Tomotherapy Unit – Built at PSL

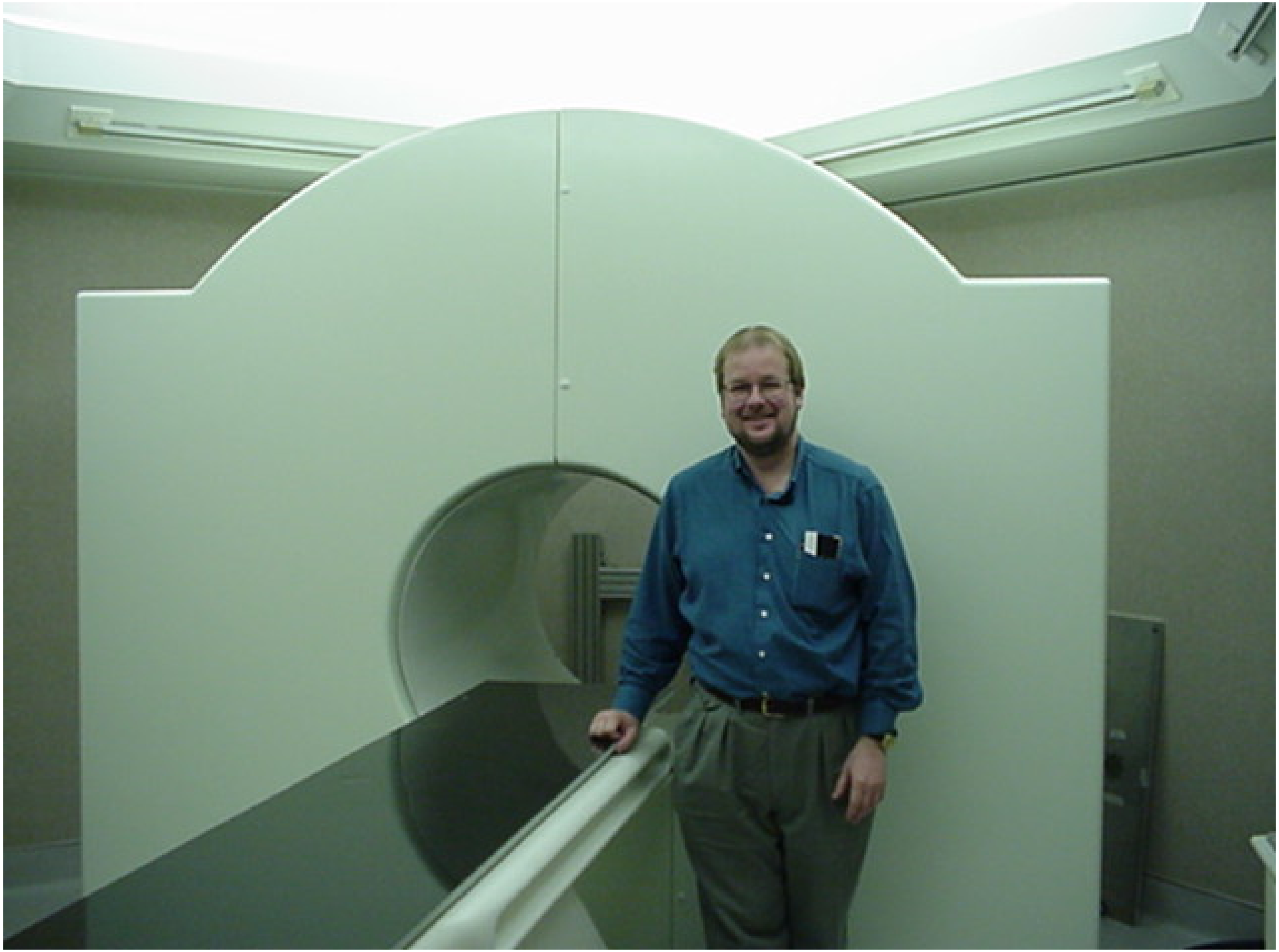


Goal: to build a combined IMRT unit and CT scanner

Questions:

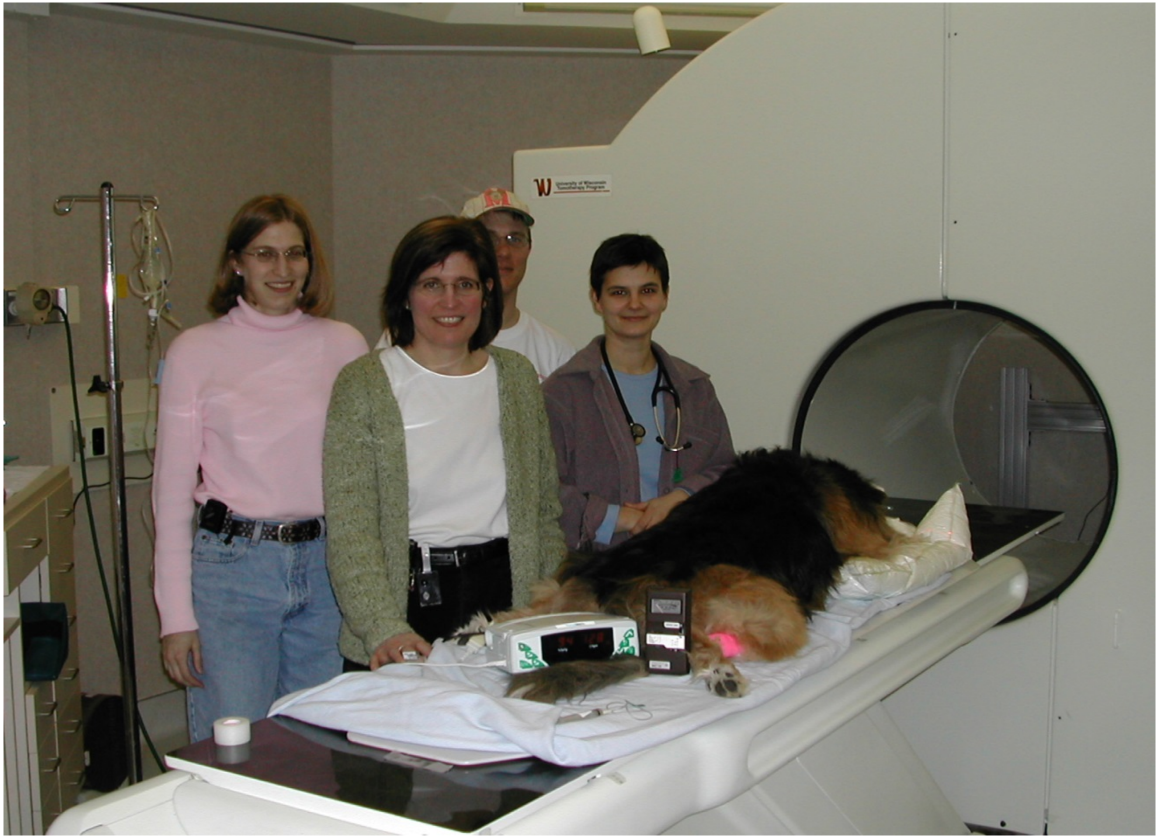
- How will the intensity modulation be optimized?
- How will the intensity modulation be achieved?
- Will the RF system for the linac interfere with the on-board CT scanner?
- How reliably can you send power for a linac across a slip ring system?

UW Clinical Helical Tomotherapy Unit - 2001

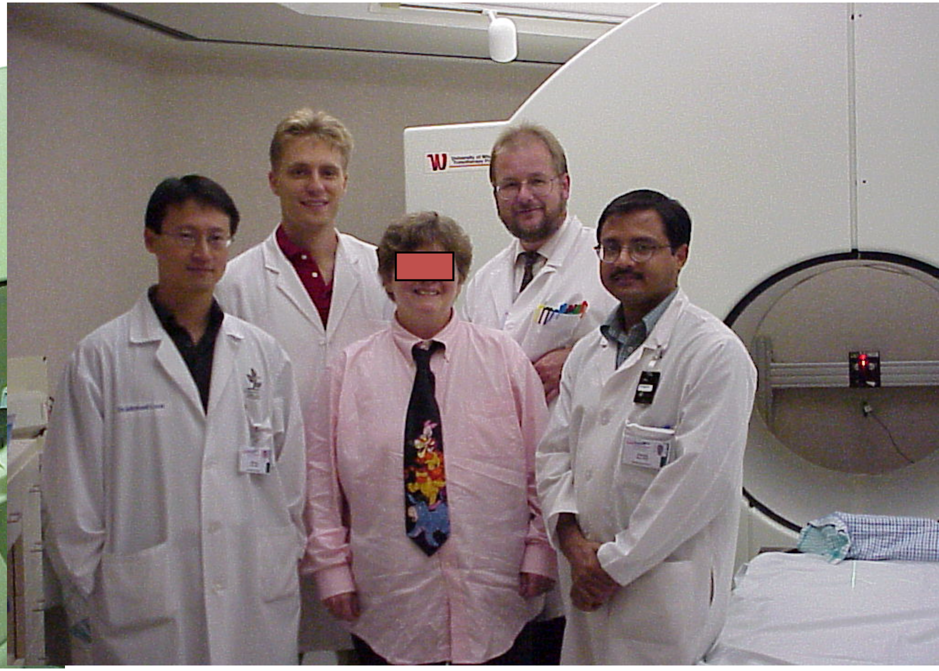


FDA Clearance Celebrations - 2002

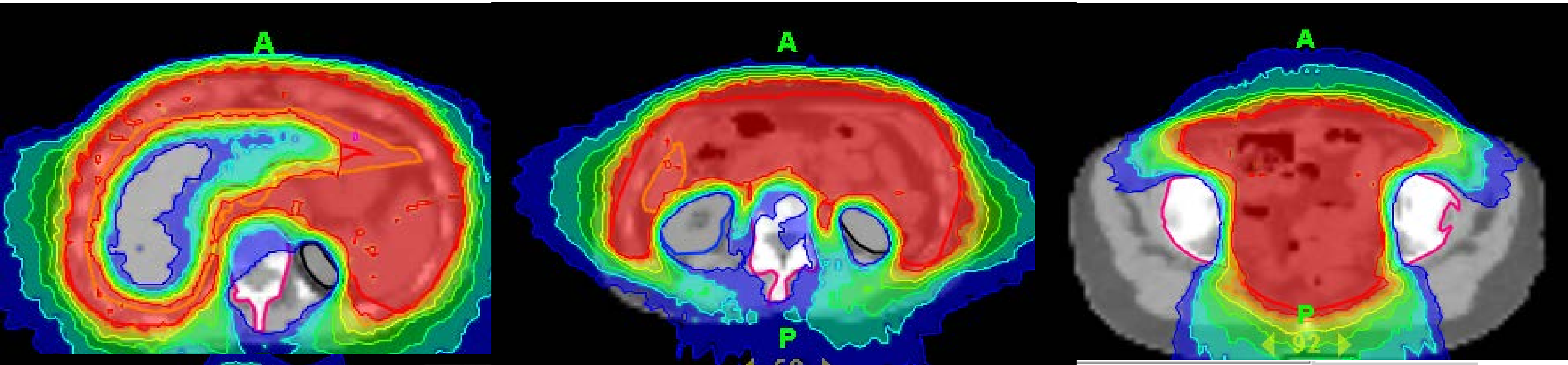
Lisa Forrest and Her Vet Radiation Oncology Team

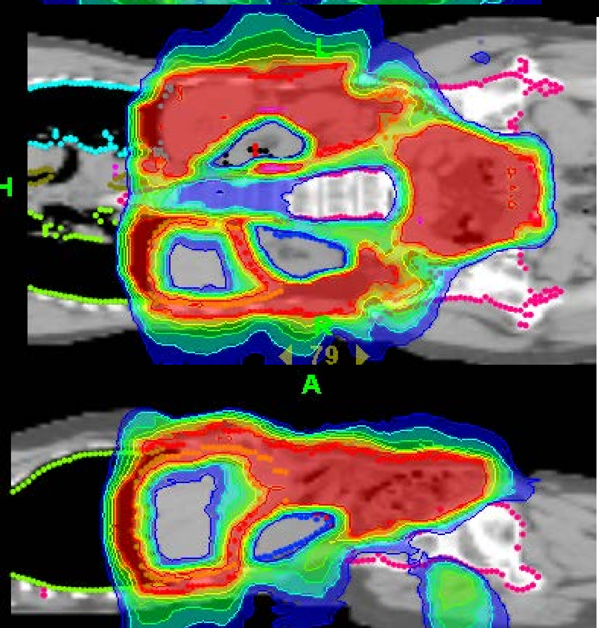


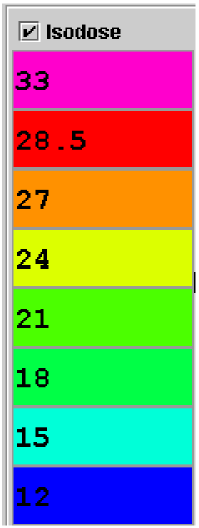
First Patients Treated - 2002

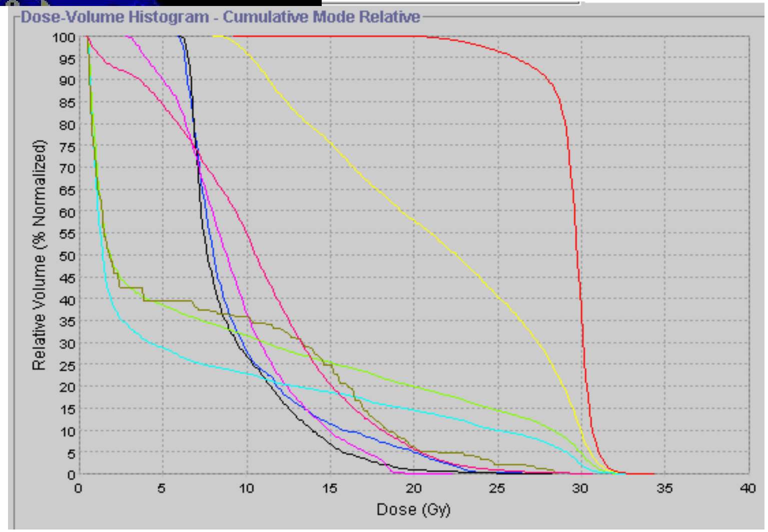


Complex Abdominal/Pelvic Treatment





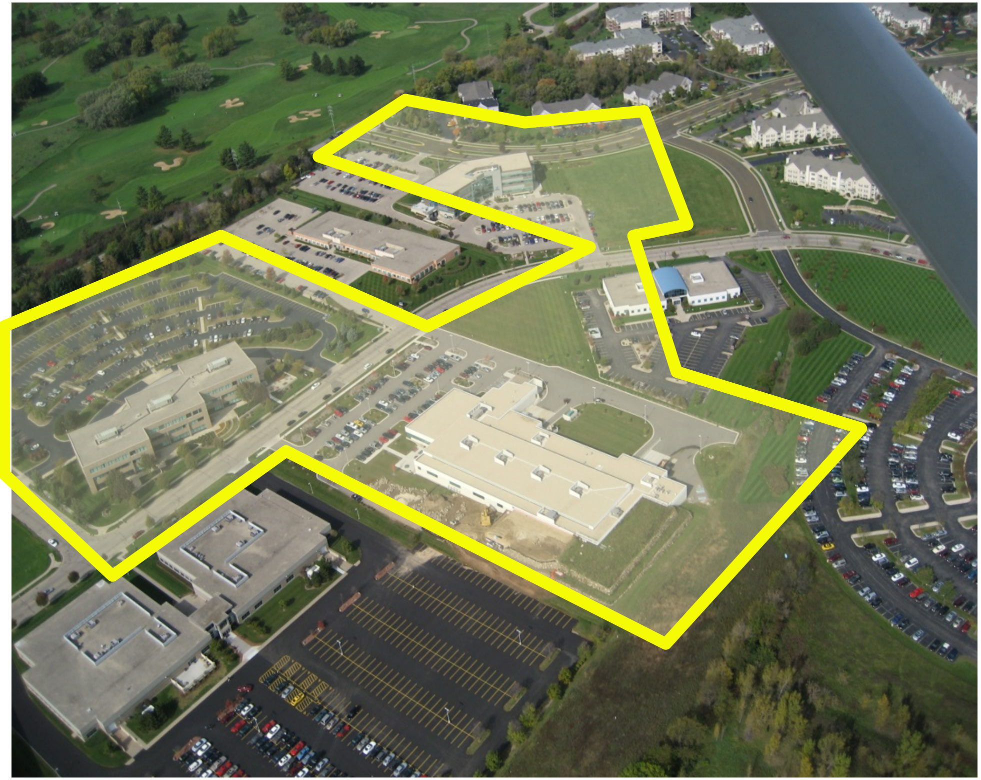




Dr. Jürgan Debus, Heidelberg University Clinic

Commercial TomoTherapy Unit

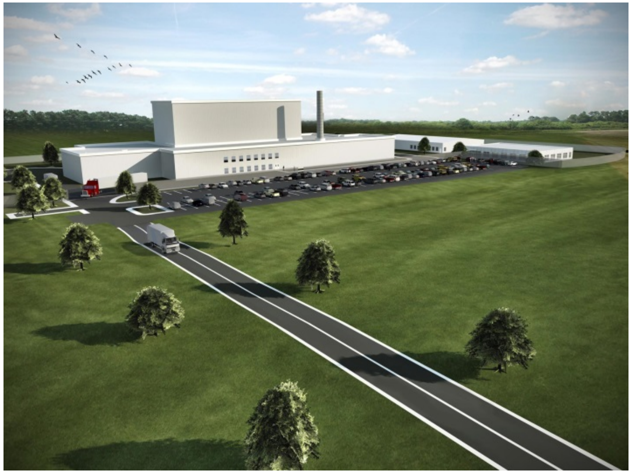
TomoTherapy Campus



Now Product Line for Accuray
Up to 650 Employees
~500 Clinical Systems
Operating in > 25 Countries
> $1.5 B in Revenue Since 2003

TomoTherapy Campus Occupied Three Buildings in Madison WI

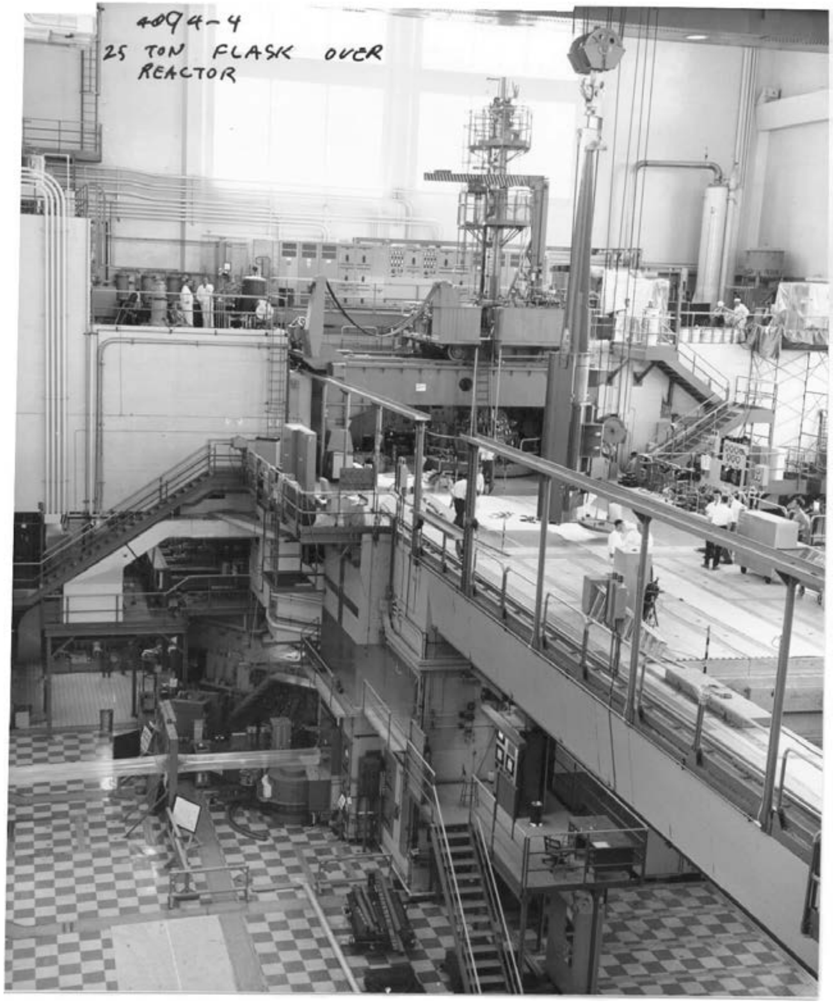
Medical Isotope Production Using a Sub-Critical Assembly



Proposed Janesville WI Production Facility

- ^{99m}Tc is an essential ingredient in over 30 important diagnostic radiopharmaceuticals
- ^{99m}Tc is made in a generator from the decay of ^{99}Mo
- Worldwide > 40 million scan procedures performed each year
  - Stress tests to detect heart disease
  - Cancer screening
- ^{99}Mo represents ~ $1 billion market at current prices
  - World wide unit demand growing at 5% annually

Mo-99 Made in Aging Reactors, None in the US



NRU Reactor, Chalk River, Canada

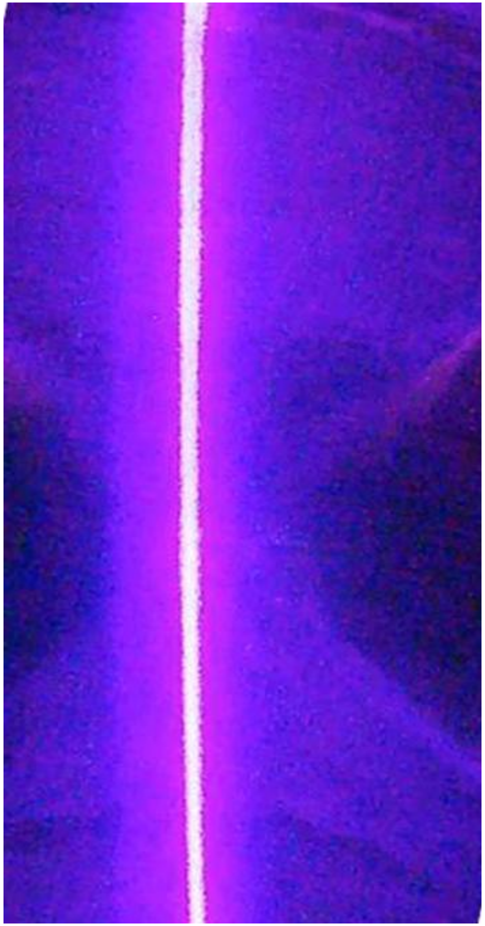
Both reactors are ~50 years old

HFR Petton Reactor, Holland

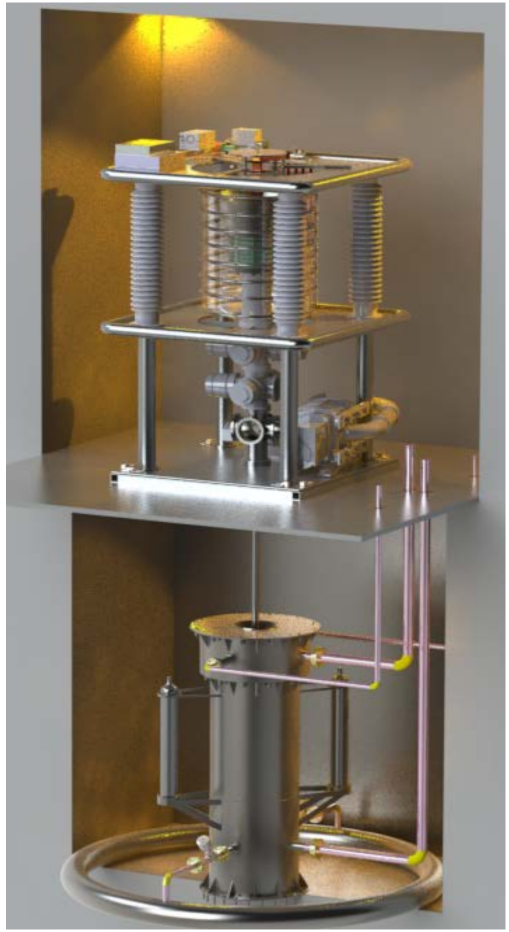
Status Quo is Not Tenable

- Reactor problems have led to severe ^{99}Mo shortages
- A significant negative impact on public health
- Present use of highly enriched uranium (HEU) creates a nuclear proliferation threat
- US Congressional response:
  - AMIPA bill wants to abolish the use of HEU in 7 years
  - Offered four $25 million cooperative agreements to U.S. suppliers who can develop a source without HEU
  - Goal Set By DOE: 3000 6-day curies/wk (half US demand) with LEU

Deuterium – Tritium Source Driving an Aqueous Sub-Critical Assembly



Phoenix Nuclear Deuteron Accelerator



Production Assembly

Modeling the Processes

- **Neutronics and isotope production and decay in an aqueous sub-critical assembly**
- **Modeling the production and recombining of hydrogen gas**
- **Modeling the separation of Mo-99 and volatile long-lived isotopes**
- **Modeling the clean-up of the uranium solution so that uranium can be reused**
- **Modeling the decay of long-lived non-commercial isotopes (waste)**

Complex Distributed Projects Requires Project Management

Partners:

- **Morgridge Institute for Research (Original Lead)**
- **SHINE Medical Technologies (Commercial Partner)**
- **Phoenix Nuclear Labs (Commercial Supplier)**
- **University of Wisconsin**
- **Los Alamos National Lab (LANL)**
- **Argonne National Lab (ANL)**
- **Savannah River National Lab (SRNL)**
- **TechSource (Engineering Consultants)**

Are We Ready for Goal-Driven Research?

Nixon declares War on Cancer, Dec 23, 1971

Regan declares War on Drugs, Sept 14, 1986

Bush declares War on Terror, Sept 20, 2001

Why Our "Wars on X" Don't Work

- The "Wars On X" have brought the wrong solutions to complex distributed problems.
- War on **X** brings **A** to what amounts to a heterogeneous **B** that is empowered by **C.**

X	A	B	C
Drugs	Military Solution	Gorilla War	Gradient Between Drug Production Cost and Street Revenue
Terror	Military Solution	Gorilla War	Social Injustice
Cancer	Costly Drugs	Often Incurable Disease	Biological Entropy

The Goals Might be Set Top-Down But the Solutions Need to Be Bottom-Up

How Was R&D for the Space Race Different than for the War on Cancer?

- Space race science was goal-driven
- Corporations collaborated with public research institutions and universities
- R&D projects were closely managed
- Missing scientific models were fashioned and new science was generated to extend and test the models
- The solutions were really risky

Remains After Apollo 1 Fire

Investigator and Project Manager

Robert Oppenheimer and Leslie Groves at Trinity Site

Most Academic Science Is Like an Easter Egg Hunt

- It feels good
- It is safe
- It is ritualistic

Goal-driven researchers should not be satisfied with just collecting publications or grants – they are way-markers and provisions for the journey, not the destination itself

Ensuring Relevant Projects

- We need to establish an adaptive evolution-mimicking system of funding support that can respond effectively and efficiently to test and propel big ideas and solutions to problems
- High reward, high risk projects require risk reduction strategies that requires close attention to detail and honest goal-driven analytics
- Close project management of process, scope, budget and schedule should be borrowed from industry practice in order to reduce or retire risk

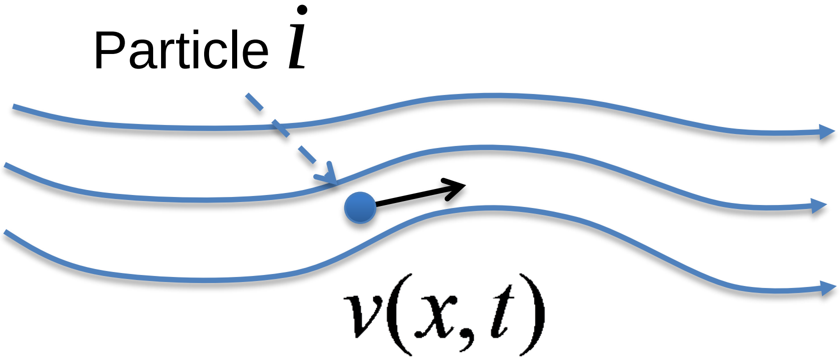
Use Principles of Evolution

- Need a broad distribution of ideas (almost exclusively from the bottom-up) from which to select
- Need to allow “natural selection” of ideas that are supported
- The “evolution” is driven by success in meeting goals
- Realistic analytics of progress on goals provides the test of fitness
- Evolution also favors cooperation not just competition

Summary of Problem/Opportunity

- We are moving too slowly to solve large medical problems, especially cancer
- We have not spent enough effort on modeling the science so that we can turn our efforts to finding out what science is missing and applying the knowledge
- Part of the problem is cultural:
  - Incremental hypothesis-driven science is safe
  - Project management is not science and therefore thought not worthy of support
  - Funding process encourages competition not cooperation
- Goal-driven research and development has been successful before and perhaps can be cautiously applied to cancer

Researchers Should Go With the Flow



Eulerian Reference Frame $v(x,t)$

Lagrangian Reference Frame $X(i,t)$

$$v(X(i,t),t) = \frac{\partial X}{\partial t}(i,t)$$

Adapted from Dr. Sang Kim

What Does Going With the Flow Mean?

This might not be true for NSF grants.

- Researchers should be engaged in getting to the goal
- Investigators should collaborate with others moving along with them
- Academics should spend time in industry and national labs advancing their goals and translating their work to practice
- Most NCI investigators should be judged on how they close they are leading us to their goal

Goal: Virtual Understanding of Cancer
Need: Cellular Models

- **Biological Pathways Exchange (BioPAX) ontology:**
  http://biopax.org
- **Systems Biology Markup Language (SBML) format:**
  http://sbml.org
- **Rule-based Description of Molecular Interaction (BioNetGen):**
  http://bionetgen.lanl.gov
- **Virtual Cell (VCell) Modeling and Simulation Software Framework:**
  http://vcell.org