NCI Intramural Clinical Research Program

Lee J. Helman, SD for Clinical Research

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NATIONAL CANCER INSTITUTE

CCR's Clinical Vision

To improve outcomes of patients with cancer and related diseases and to be the world's leading oncology research organization by:

- Engaging outstanding researchers in consequential investigator-initiated clinical research in a translational research culture
- Providing the flexible funding necessary to support innovative, high- impact bench-to-bedside research through access to the largest publicly-funded research center in the world
- Collaborating with outstanding researchers across the NIH and throughout the extramural community

Clinical Research Priorities

- Take discoveries from within the CCR or other NIH laboratories to the point of first-in-human trials
- Foster the education and research of physician-scientists
- Design and execute novel, science-based clinical trials
- Focus on molecularly-based, tailored medicine
- Utilize technology and correlative science difficult to support elsewhere
- Study rare cancers that are not being adequately studied elsewhere

Training the Next Generation of Scientific Leaders

- **CCR maintains a robust core of scientists and physician scientists through active recruitment, technology-based training, and exceptional mentorship**

Clinical Fellowship Program

ACGME

- Anatomical Pathology
- Medical Oncology Fellowship
- Pediatric Hematology/Oncology

- Dermatology
- Gynecologic Cancer
- Hematopathology
- HIV and AIDS Malignancy
- Radiation Oncology
- Surgical Oncology
- Urologic Oncology
- Cytopathology
- Neuro-Oncology

CCR Clinical Alumni

- **A number of clinical trainees have launched successful careers**

- **36 Chairs, 48 Chiefs, 10 Directors, 2 VPs, 3 Deans (data from 4 branches)**

- **A few examples:**

Peter C. Adamson
Chair, Children's Oncology Group
Professor Univ of Pennsylvania
Clinical Fellow, POB 1987-90

Martha A. Zeiger
Chief, Section of Endocrine Surgery
Johns Hopkins
Medical Staff Fellow, SB, 1993-95

Deborah Powell
Executive Dean and Vice Chancellor for Clinical Affairs
University of Kansas
Medical Staff Fellow, LP, 1965-68

Gennady Bratslavsky
Chair, Department of Urology
University of Albany
Medical Staff Fellow, UOB, 2005-07

CCR's Vision for 2012 and Beyond

- Accelerate translational progress through flexible targeted approaches to solve difficult and complex problems

- Embrace new initiatives and programs that enable significant progress in alleviating the impact of human cancer

  - Use science-based knowledge about both the disease and its progression and intervene at the very earliest stages through early detection prior to invasion and metastasis

- By integrating advanced biomedical technologies into every clinical trial, we will make significant advances toward improving cancer therapy; treating each patient and each tumor based on the specific tumor and patient molecular characteristics

Distinctiveness of NCI's CCR Derives from a Convergence of Multiple Attributes

- **Sustained support for high-risk, high-impact research**
- **Highly interactive, multidisciplinary culture for basic and clinical scientists:**
  - generation of new knowledge
  - efficient bench to bedside to bench translation
  - development of new technologies and approaches
- **Access to the world's largest cancer-focused clinical research center**
- **Commitment to rare cancers and underserved patient populations**
- **Collaborations that facilitate joint ventures within NIH as well as partnerships in industry, pharma, academia**
- **Flexibility to rapidly redeploy resources**
- **Multi-faceted training for the next generation of scientific leaders**

Working Together With A Vision of Excellence

- **How can we be more efficient as costs increase and budgets grow tighter?**
- **How do we ensure that we fund the most important clinical research?**
  - Need maximize impact per dollar spent
- **How do we measure quality? How do we measure impact?**
- **Why should a study be done here instead of extramurally?**
- **Our protocols must:**
  - Support the mission of the CCR
  - Be scientifically exciting
  - Meet peer-reviewed standards of scientific design
  - Have a high likelihood of timely patient accrual

Strategic Alignment & Resource Planning Checklist (SARP)

- **A six section form:**
  1. **Study Identification**
  2. **Study Impact**
     - **<u>Why is this an important study for the CCR to do now?</u>**
  3. **Study Demographics**
  4. **Study utilization of unique CCR resources**
  5. **Study resource needs**
  6. **Any additional pertinent information**

The form will eventually be put into IRIS

Strategic Alignment & Resource Planning Checklist (SARP)

CENTER FOR CANCER RESEARCH

Strategic Alignment and Resource Planning Checklist

STUDY IDENTIFICATION

Branch / Lab: _____ PI: _____

Study Title: _____

STUDY IMPACT

1. How is this study consequential to the field?

2. Would leaders in this field consider this study to be of high impact? ○ Yes, Likely ○ No, Not Likely

If **YES**, please identify rationale (check all that apply)

- ☐ Success likely to lead to a significant change in paradigm in treatment and/or research
- ☐ Study would rarely be done elsewhere
- ☐ Incorporating new and/or novel approaches
- ☐ If negative results, likely no further study (productive failure)
- ☐ Publication in high impact journal
- ☐ Likely to lead to studies in a broader context both within and outside of your program
- ☐ Other

3. Why can't this study be **easily** conducted on the outside (i.e. at other institutions)?

4. Is this a direct translation of CCR laboratory research and/or an extension of a prior study phase completed at CCR? ○ Yes ○ No

If **YES**, briefly explain how this is a direct translation of prior research:

5. Is the study part of an **EXISTING** line of clinical investigation at CCR or is the study a **NEW** clinical area at CCR that requires long-term commitment and tolerance for a lack of significant early clinical impact?

5a. If this study is part of an **EXISTING** clinical program at CCR, explain how the study fits within the existing program:

5b. If the study is part of a **NEW** clinical program at CCR, explain why the new clinical area is important to be conducted at CCR:

Strategic Alignment and Resource Planning Checklist

Study Demographics

6. Is this a study of a rare cancer and/or under-studied population? ○ Yes ○ No

If **YES**, briefly describe this population:

7. Is this a CCR investigator-initiated clinical study? ○ Yes ○ No

8. Does the study use investigational drug(s) / device(s)? ○ Yes ○ No

If YES, please identify where the drugs/devices were developed (check all that apply)

- ☐ CCR
- ☐ CTEP
- ☐ Industry
- ☐ Other: _____

9. Is the study a multi-institutional study? ○ Yes ○ No

If **YES**, is the CCR PI the Lead Coordinator the study? ○ Yes ○ No

10. Is the study collaborative with other clinical research branches at the NIH/NCI? ○ Yes ○ No

If **YES**, please identify:

11. Is the study collaborative with others outside the NIH / NCI? ○ Yes ○ No

If **YES**, please identify:

STUDY UTILIZATION OF UNIQUE NIH RESOURCES

12. Does this study or its correlatives take advantage of the unique resources that exist at the NIH? ○ Yes ○ No

If **YES**, please check all that apply:

- ☐ Requires the use of resources not usually reimbursable at other institutions
- ☐ Intensive and/or comprehensive internal pharmacokinetic studies
- ☐ Intensive and/or comprehensive internal pharmacodynamic studies
- ☐ Use of existing or building of a new longitudinal tissue bank
- ☐ Manufacturing of investigational therapy requiring CCR resources (i.e. cell based treatments, generation of vaccines)
- ☐ Access to resource- intensive imaging studies
  - ___ Clinical Center Imaging
  - ___ Molecular Imaging Program
- ☐ Genomics, molecular profiling
  - ___ Laboratory of Pathology
  - ___ Clinical Molecular Profiling Core
- ☐ Unique & adaptive study design/methodologies
- ☐ Other

Strategic Alignment & Resource Planning Checklist (SARP)

Strategic Alignment and Resource Planning Checklist

STUDY RESOURCE NEEDS

13. Can this study be completed within your existing branch resources? ○ Yes (no further responses required) ○ No (Continue to question 14)

14. IF NO, how will you obtain additional Resources? ○ Outside Funding (Continue to question 14a) ○ Additional CCR Resources (Continue to question 15)

14a. Briefly describe potential outside source(s) of funding / resources that will be used:

15. The following resources will be required from CCR to support this study: (Check all that apply)

- ○ Yes ○ No Personnel (e.g. Research Nurse, Data manager, Physician Extender)
  List specific personnel required and estimated staffing level
- ○ Yes ○ No Clinical Trial Support Supplies & Services (e.g. assays)
  List the type of S&S and specific costs requested
- ○ Yes ○ No Pharmaceutical Agents
  List specific agent and estimated amount requested
- ○ Yes ○ No Laboratory of Pathology
  List specific requirements needed and estimated amount requested
- ○ Yes ○ No Monitoring of SINGLE-SITE study when IND is held by the CCR
  List specific monitoring requirements and estimated level of support
- ○ Yes ○ No Monitoring of MULTI-INSTITUTIONAL study when IND is held by the CCR
  List specific monitoring requirements and estimated level of support
- ○ Yes ○ No Patient Recruitment
  List specific patient recruitment activities and requested level of support
- ○ Yes ○ No Other
  List specific resource requirements and estimated level of support

16. Please add any additional comments regarding resource requirements for this study

Strategic Alignment and Resource Planning Checklist

Please add any additional comments regarding the strategic importance and/or resource requirements for this study:

Principal Investigator Signature _____ Date _____

Section 2: Study Impact

STUDY IMPACT

1. **How is this study consequential to the field?**
   - **i.e., why will this study change research paradigms, clinical practice or be a significant step in doing either?**

2. **Would leaders in this field consider this study to be of high impact?**
   - **If Yes**
     - **Success likely to lead to a significant change in paradigm in treatment and/or research**
     - **Publication in high impact journal**
     - **Study would rarely be done elsewhere**
     - **Incorporating new and/or novel approaches**
     - **Likely to lead to studies in a broader context both within and outside of your program**
     - **If negative results, likely no further study (productive failure)**
     - **Other**

Section 2: Study Impact

STUDY IMPACT

3. **Why can't this study be <u>easily</u> conducted on the outside (i.e. at other institutions)?**

4. **Is this a <u>direct translation</u> of CCR laboratory research and/or an extension of a prior study phase completed at CCR?**
   - **If YES, briefly explain**

5. **Is the study part of an EXISTING line of clinical investigation at CCR or is the study a NEW clinical area at CCR that requires <u>long-term commitment and tolerance for a lack of significant early clinical impact</u>?**
   a. **If this study is part of an EXISTING clinical program at CCR, explain how the study fits within the existing program**
   b. **If the study is part of a NEW clinical program at CCR, explain why the new clinical area is important to be conducted at CCR:**

Completed by Branch Chief

TO BE COMPLETED BY THE BRANCH CHIEF

IDENTIFY THE STRATEGIC FIT OF THIS STUDY (SELECT ALL THAT APPLY)	CONFIRM THE RESOURCE REQUIREMENTS (SELECT ALL THAT APPLY)
☐ This study fits within the branch strategy ☐ This study is a high priority within the branch ☐ This study is an important new area for the branch ☐ This study is important for programmatic support ☐ This study is in support of a junior investigator ☐ Further discussion with the PI is required	☐ This study has sufficient resources provided by the branch ☐ This study requests additional resources supported by CCR ☐ This study is dependent upon outside resource support ☐ This study requires re-evaluation of study resource requirements

Please add any additional comments regarding the strategic importance, branch priority, and resource requirements for this study:

Branch Chief Signature Date

Chief, Medical Oncology Branch* Date

* if protocol is scientifically reviewed through the MOB Branch

Scientific Director Signature Date

Formal Resource Allocation Process (in process)

- ***Goal: To, as optimally as possible, distribute CCR resources across the current and projected portfolio of clinical trials to maximize the likelihood of achieving the CCR missions***

- **Basic Principles:**
  - Transparency in decision making
  - Focus on impact & outcomes
    - When making the hard choices, do not concentrate on “entitlements” but on potential future impacts and outcomes for the entire CCR, the community of cancer researchers, and the community of current & future cancer patients
  - Acknowledge that some good research will not be funded now
    - There will not be sufficient resources for the foreseeable future

- **Focus of CCR clinical research: consequential, innovative and high-impact**

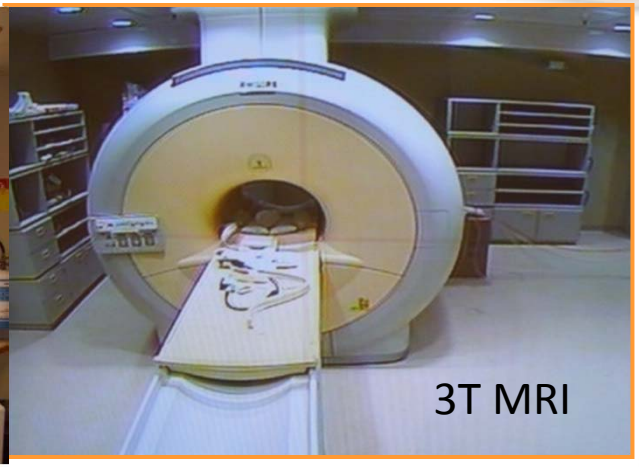
CCR Is Putting the Pieces in Place

- **Molecular Imaging Clinic**
- **Standardized biospecimen collection**
- **Genome-wide profiling of tumor/normal**
- **MicroRNA profiling of tumor/normal**
- **Genetic background profiling of patient**
- **Biomarker development to monitor targeted therapies**

Imaging is a CCR Priority

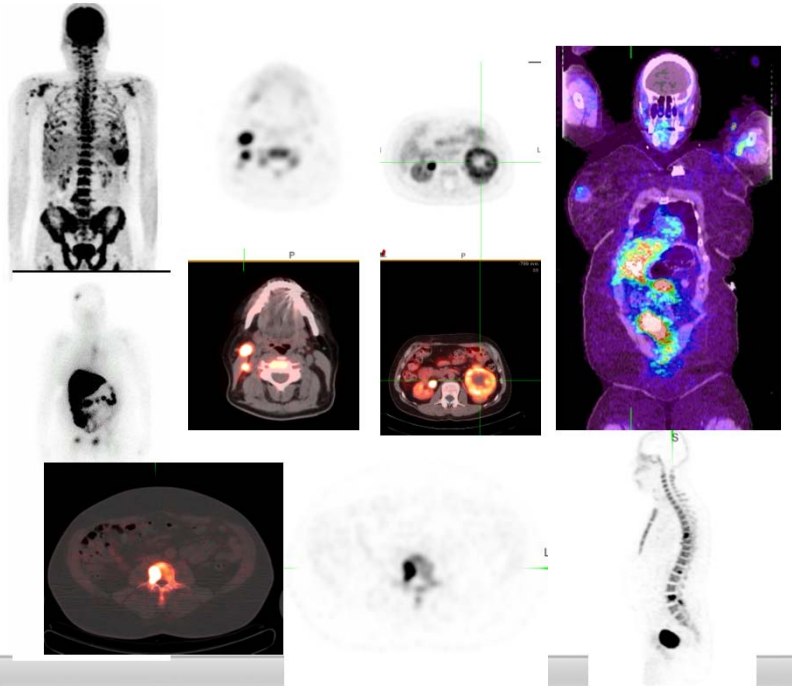
- **Blur the line between imaging and pathology**
- **Develop novel imaging approaches and technology:**
  - Basic discovery research
  - Translational applications
  - Non-invasive patient care
- **Improve imaging techniques to enhance early detection, diagnosis, and treatment**
  - Preclinical model testing and validation
  - Clinical trial design and implementation
- **Develop novel imaging instrumentation**
- **Preemptive medicine**
  - Detect lesion
  - Determine pathway
  - Monitor for reactivation
  - Intervene upon re-activation, before gross tumor recurrence

Molecular Imaging Clinic



Active Human Protocols:

^{18}F-FLT: DNA Proliferation
^{18}F-Fcytidine DNA Proliferation
^{18}F-Fluciclitide Integrin-angiogenesis
^{18}F-Paclitaxel Drug Delivery
^{18}F-FES Estadiol Imaging
^{18}F-ACBC Amino acid transport
^{18}F-Sodium Fluoride Bone Metastases
^{11}C-Acetate Fatty acid metabolism
^{111}In-Trastuzumab HER2 imaging
^{111}In-MorAb009 Anti-Mesothelin



NIH Center for Interventional Oncology

- Offers new and expanded opportunities to investigate cancer therapies that use imaging technology to diagnose and treat localized cancers in ways that are precisely targeted and minimally or non-invasive
  - Cutting edge technology
    - MRI, PET, CT
- Ideally and uniquely positioned to provide an interdisciplinary environment combining training, patient treatment, translational research and development in interventional oncology

Brad Wood

http://www.cc.nih.gov/centerio/index.html

Clinical Molecular Profiling Core

All CCR Clinical Protocols

↓

Tissue Procurement and Processing Facility
LCM, Annotation

↓

Intensive Clinical Characterization

↓

- **Profiling**
- **Sequencing**
- **Tissue Proteomics**
- **Experimental Imaging**
- **Pharmaco-genomics**

Clinical Molecular Profiling Core

CMPC Director: Paul Meltzer, M.D. Ph.D., CLIA Director: J. Keith Killian, M.D. Ph.D.,
Facility Head: Daniel Edelman, Ph.D.

CENTER FOR CANCER RESEARCH

The CMPC provides CCR clinical investigators with ready access to genome technologies for:

- Tumor classification and cancer gene discovery
- Discovery and validation of predictive and prognostic markers
- Hypothesis based exploration of genes and molecular pathways
- Clinical testing (under **CLIA**) for nucleic acid based tests incorporated into clinical trials

The CMPC operates on a collaborative model providing a fully integrated team with skills in genomics, oncology, pathology, bioinformatics and laboratory operation. Funding for assays is provided by collaborating investigators. Opportunities are sought which take advantage of unique NCI patient populations and expertise.

Assays:

- Expression microarrays (several platforms)
- CGH and SNP arrays
- DNA methylation by array and pyrosequencing
- DNA sequencing (Sanger and Illumina)
- Taqman and related multiplex assays for follow up of array data

CCR Sequencing Facility

BRINGS THE POWER OF NEXT GENERATION SEQUENCING TO THE INTRAMURAL PROGRAM

- DNA Sequencing is a broadly applicable technology which is beginning to displace older approaches to nucleic acid analysis for a large range of applications as well as enabling previously impossible investigations
- Supporting numerous investigators carrying out both large and small scale projects
- Illumina GAIIx and HiSeq instruments with capacity of several hundred samples per year
- Capable of all standard applications (mRNA, miRNA, DNA, ChIP-seq etc.)
- PacBio Sequencer installed and being tested (rapid single molecule sequencing for analysis of targeted regions in cancer and normal DNA, microbial genomes, development of scaffolds for whole genome assembly etc.)
- Work has led to publications in top journals including (Nature Genetics, Nature Methods, EMBO J)

Impact

- To ensure that the greatest amount of information can be derived from every patient participating in a clinical trial and to gain the types of detailed information that could serve as the foundation to rapidly accelerate the pace of translation of basic science to clinical application

- The integration of these technologies into every clinical trial will enable CCR to contribute greatly to creating an approach that will facilitate each patient receiving the most appropriate treatment

Major Opportunities

- **Should be high risk**
- **Should be a broad clinical effort that brings together numerous groups that results in a novel clinical trial**
- **Should take advantage of the unique environment of the CCR/CC**
- **Have milestones with the ultimate goal achievable within 5 years**

Exemplar MOs

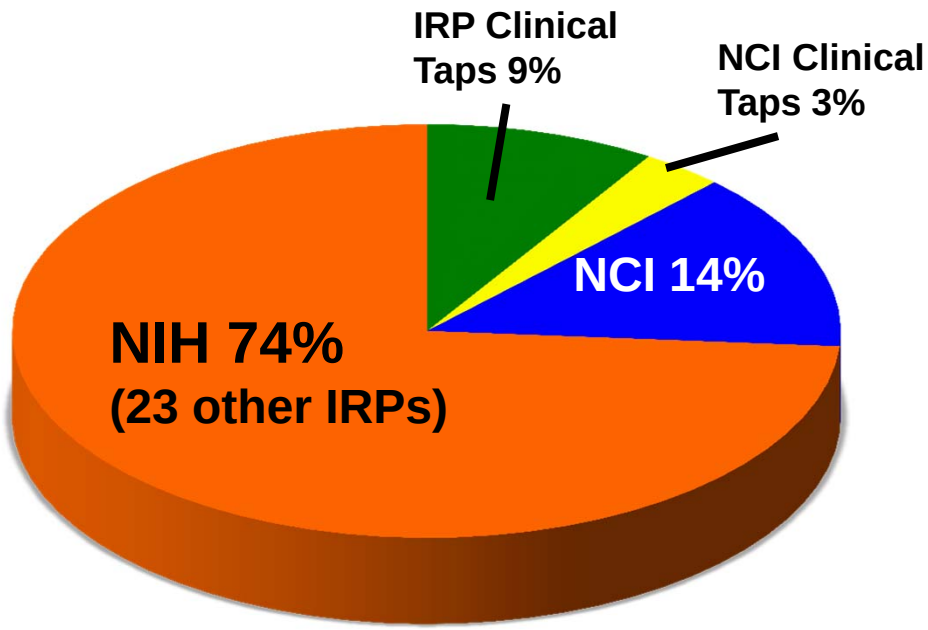
ID	Theme
A	Tailored immunotherapy for patients with metastatic cancer
B	Rare cancers and genetic tumor predisposition syndromes (GTPS)
C	Treatment of cancers based on drivers mutations independent of histology or site
D	Attacking Cancer Based on its Metabolic Basis
E	Improving molecularly targeted cancer treatment using synthetic lethality strategies focusing on DNA repair
F	Characterizing the transition from premalignant or smoldering cancers to malignant tumors to improve interventions between prevention and treatment

Next Steps

- **Input from broader CCR community, including basic and translational researchers**
- **Input from the BSC working group on the protocol reengineering process**
- **Finalize M.O.’s**
- **Operationalize M.O.’s including time line, logistics, champions and budget shifts**

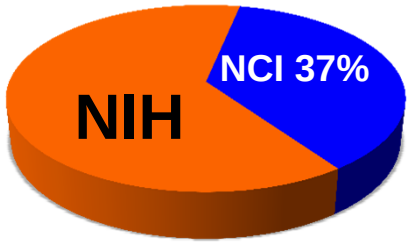
CCR Clinical Activity at the NIH

NIH IRP vs CCR Budget

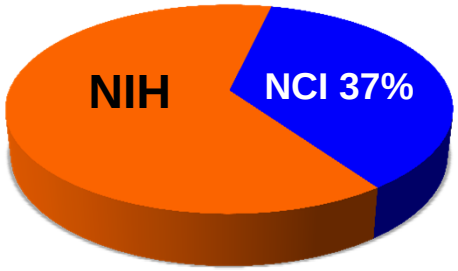


CCR is one of 24 Intramural Research Scientific Programs at NIH

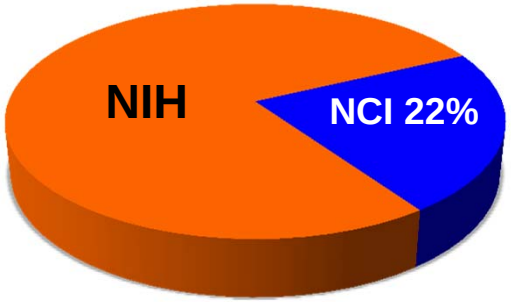
Outpatient Visits



Inpatient Days



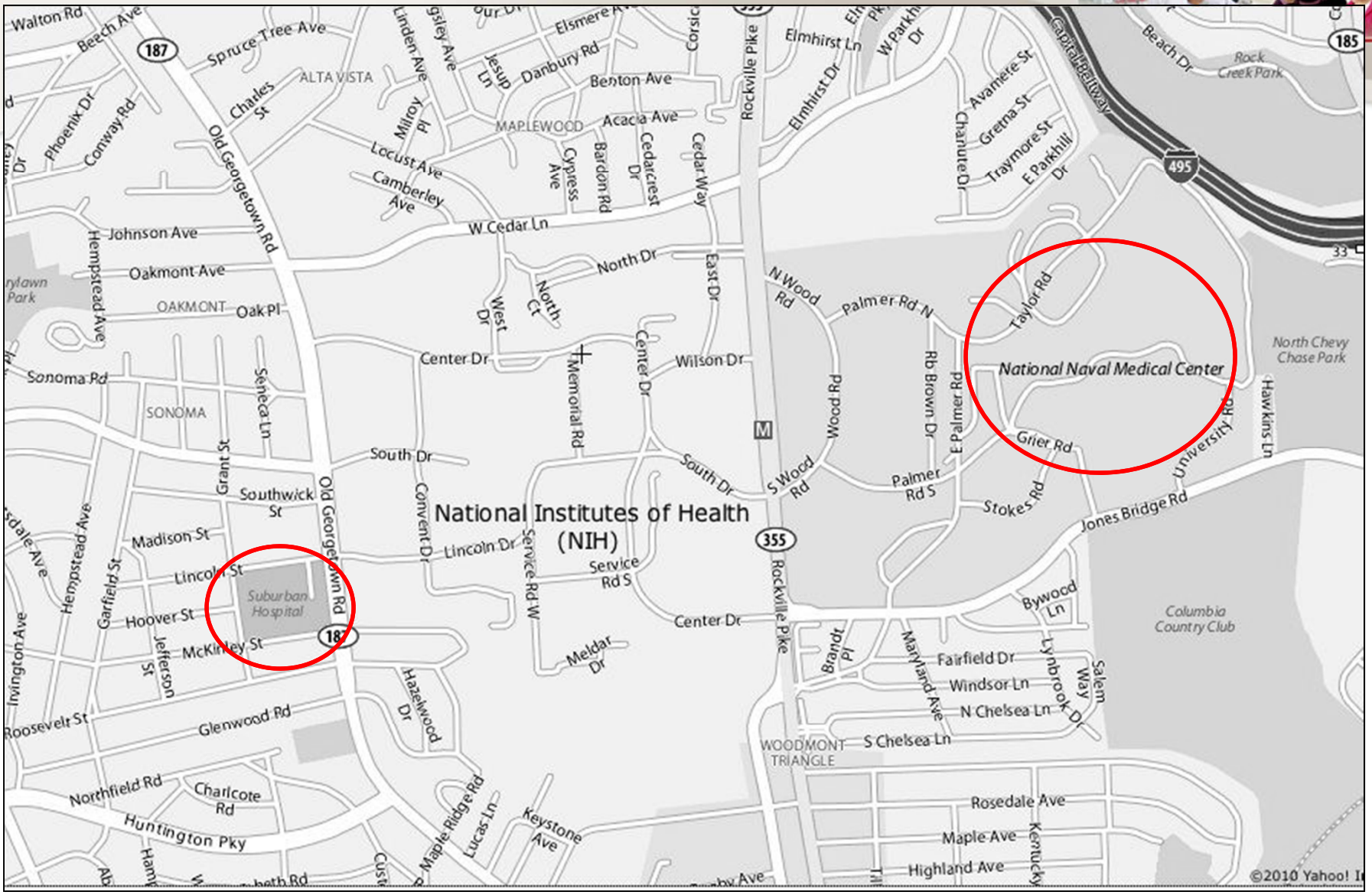
New Patients



Collaborative Vision

A nexus for the integration of three institutions to leverage the strengths and resources of each for clinical cancer care and research

- **National Cancer Institute/Clinical Center**
- **Walter Reed National Military Medical Center**
- **Johns Hopkins Suburban Community Hospital**


National Institutes of Health (NIH)
National Naval Medical Center
Suburban Hospital
Columbia Country Club
North Chevy Chase Park
Rock Creek Park
WOODMONT TRIANGLE
Walton Rd
Beech Ave
Spruce Tree Ave
ALTA VISTA
Danbury Rd
Benton Ave
MAPLEWOOD
Acacia Ave
Rockville Pike
Elmhirst Ln
Elmhirst Dr
Avamere St
Gretna St
Traymore St
E Parkhill Dr
Beach Dr
Capital Beltway
Phoenix Dr
Conway Rd
Old Georgetown Rd
Charles St
Linden Ave
Jesup Ln
Millroy Pl
Locust Ave
Camberley Ave
Cypress Ave
Bardon Rd
Cedarcrest Dr
Cedar Way
W Cedar Ln
Johnson Ave
Oakmont Ave
OAKMONT
Oak Pl
Hempstead Ave
North Dr
West Dr
North Ct
East Dr
Center Dr
Memorial Rd
Wilson Dr
N Wood Rd
Palmer Rd N
Taylor Rd
Sonoma Rd
SONOMA
Seneca Ln
Grant St
South Dr
Southwick St
Madison St
Lincoln Dr
Service Rd S
Service Rd W
Convent Dr
S Wood Rd
Wood Rd
Rb Brown Dr
E Palmer Rd
Palmer Rd S
Grier Rd
Stokes Rd
University Rd
Hawkins Ln
Jones Bridge Rd
Lincoln St
Hoover St
McKinley St
Garfield St
Jefferson St
Irvington Ave
Roosevelt St
Glenwood Rd
Hazelwood Dr
Meldar Dr
Center Dr
Bywood Ln
Brandt Pl
Maryland Ave
Fairfield Dr
Windsor Ln
N Chelsea Ln
S Chelsea Ln
Lynbrook Dr
Salem Way
Northfield Rd
Charlcote Rd
Huntington Pky
Maple Ridge Rd
Lucas Ln
Keystone Ave
Rosedale Ave
Maple Ave
Highland Ave
Kentucky
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Opportunity Presented by BRAC

- **As a result of base realignment and closure (BRAC), Walter Reed Army Medical Center has relocated all tertiary (sub-specialty and complex care) medical services to National Naval Medical Center, Bethesda, MD, establishing it as the Walter Reed National Military Medical Center (WRNMMC)**

Opportunities for New and Expanded Collaborations with Military

Radiation Oncology

- Integration of Radiation Oncology Departments at Walter Reed and NCI including joint protocol development and NCI staff on site at WRMI
- Discussions on-going about developing new technology at WRNMMC

Centers of Excellence

- Lung Cancer, Breast Cancer, Gynecological Oncology, and Genitourinary Oncology Centers of Excellence would be established with both NCI researchers and WRNMMC staff
- Would leverage current expertise and integrate world-class translational research programs combining state of the art laboratory research and support with cutting-edge clinical trials in these diseases
- Collaboration would further improve the care of the military patients and other eligible beneficiaries who are diagnosed with cancer

Current Collaborations With Suburban and JHU

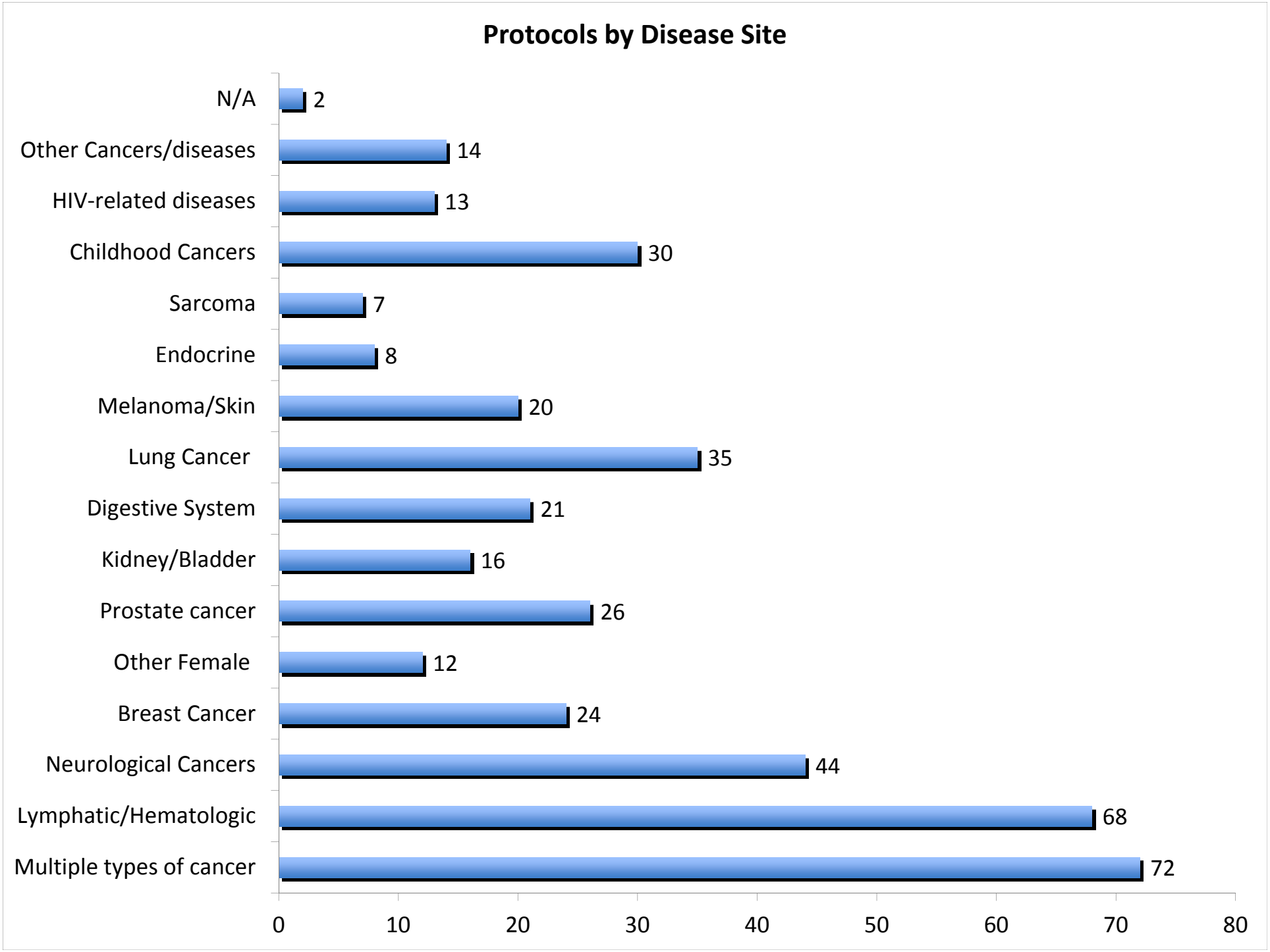
Patient Referral Through Collaboration

- NCI physicians participating in Suburban GI and Prostate Tumor Boards
- Collaboration for Treatment with Radiation Oncology (Brachytherapy Trial)
- Long standing successful joint fellowship program between JHU/NCI in Pediatric Hematology/Oncology

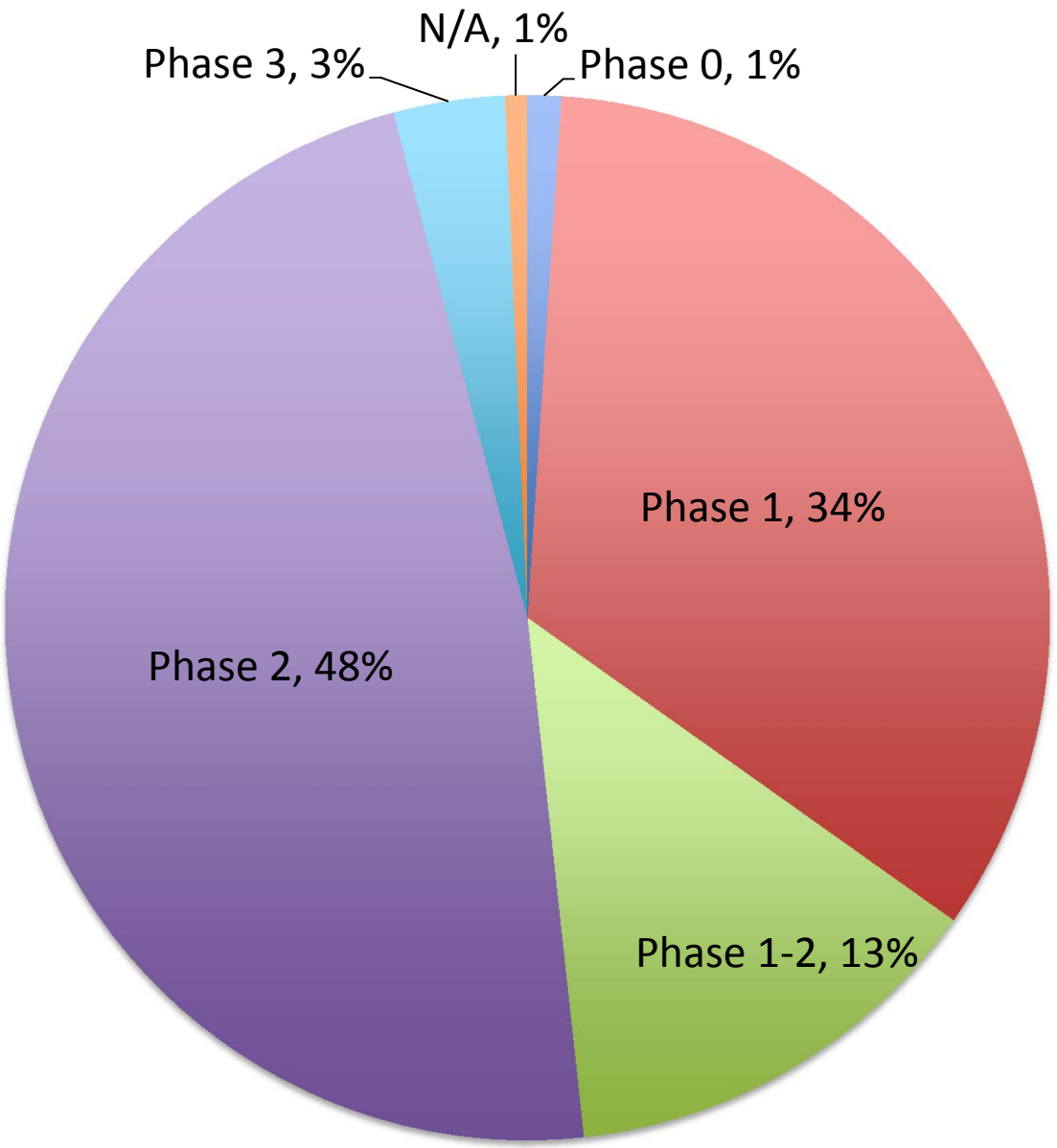
Snapshot of where we are

NATIONAL CANCER INSTITUTE

CCR Labs/Branches	# protocols by L/B	% of total
MOB	108	25%
POB	64	16%
SB	49	12%
MTB	31	8%
ETIB	24	6%
ROB	20	5%
NOB	19	5%
LMB	17	4%
LTIB	12	3%
HAMB	11	3%
MIP	10	2%
Derm	9	2%
UOB	9	2%
VB	7	2%
LGD	6	1%
LP	4	1%
CC	3	1%
OCD	3	1%
LEI	3	1%
CCR-OD	1	0%
GB	1	0%
LHC	1	0%
412		


Protocols by Disease Site
N/A
2
Other Cancers/diseases
14
HIV-related diseases
13
Childhood Cancers
30
Sarcoma
7
Endocrine
8
Melanoma/Skin
20
Lung Cancer
35
Digestive System
21
Kidney/Bladder
16
Prostate cancer
26
Other Female
12
Breast Cancer
24
Neurological Cancers
44
Lymphatic/Hematologic
68
Multiple types of cancer
72
0
10
20
30
40
50
60
70
80

Treatment Protocols



Examples-where are we going

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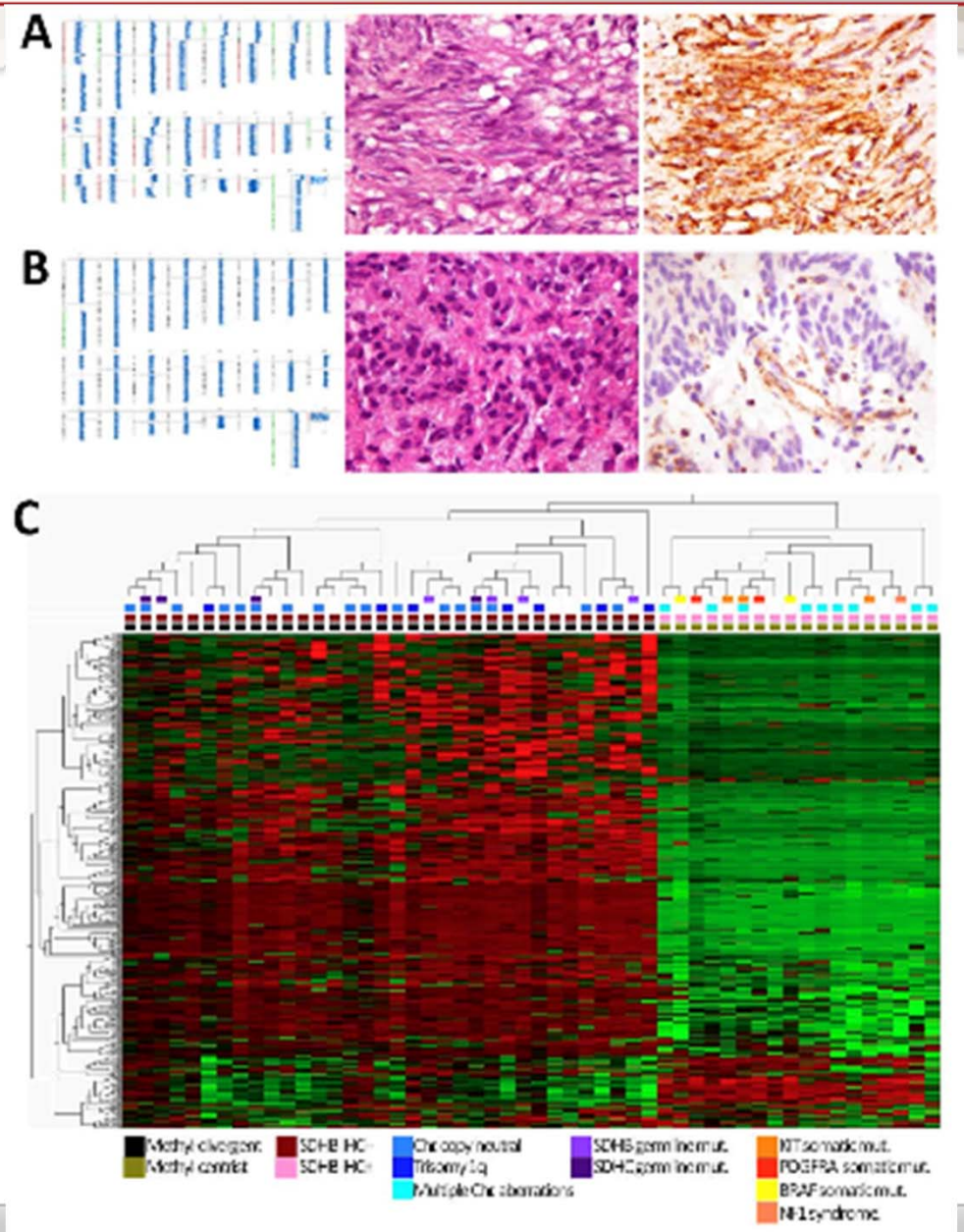
Pediatric Wild-Type GIST have SDH Loss

Pathologic Characteristics	Centrist n=18	Divergent n=34	p-value
SDHB IHC negative	0	34 (100%)	<0.0001
SDH germline mutations	0/9	8/25 (32%*)	0.07

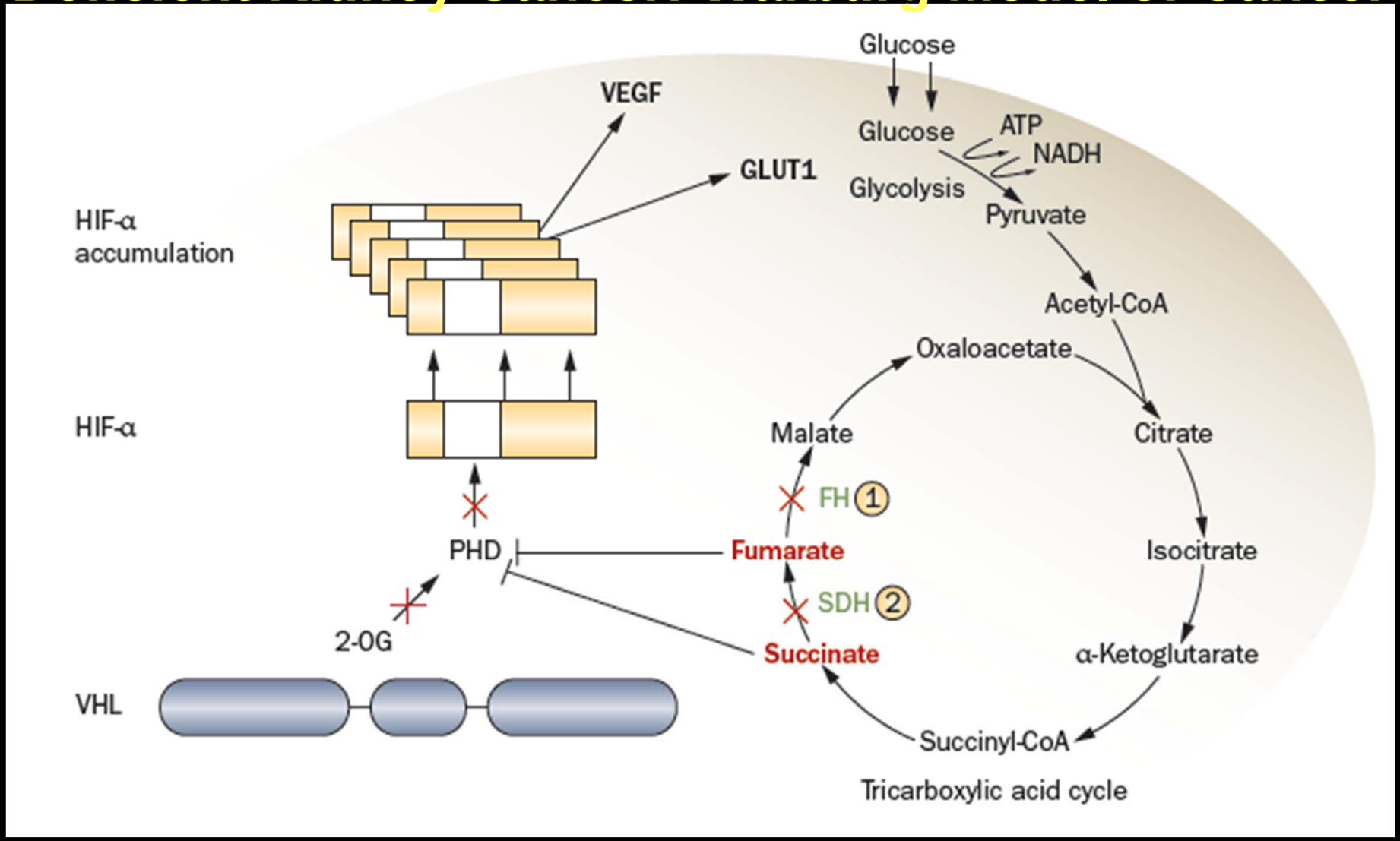
Keith Killian[1], Su Young Kim[2], Markku Miettinen[3], Carly Smith[2], Maria Tsokos[3], Martha Quezado[3], William I. Smith, Jr.[4], Mona Jahromi[5], Robert L. Walker[1], Laura Jones[1], Joshua D. Schiffman[5], Maureen J. O'Sullivan[6], Constantine Stratakis[7], Lee Helman[2], Paul Meltzer[1*], presenting for the NIH Pediatric and wildtype GIST Clinic

Cristina Antonescu, Memorial Sloan Kettering Cancer Center
George Demetri, Dana Farber Cancer Institute
Anette Duensing, University of Pittsburgh Cancer Institute
Suzanne George, Dana Farber Cancer Institute
Katherine Janeway, Children's Hospital Boston
Joe Marie Jose-Dizon, McLaren Regional Medical Center
Shivaani Kummar, National Cancer Institute
Michael LaQuaglia, Memorial Sloan Kettering Cancer Center
Maya Lodish, National Institute of Child Health and Human Development
Grant MacArthur, Peter MacCallum Cancer Centre
Pamela Merola, Memorial Sloan Kettering Cancer Center
Alberto Pappo, St. Jude Children's Research Hospital
Mark Raffeld, National Cancer Institute
Margarita Raygada, National Institute of Child Health and Human Development
Jonathan Trent, M.D. Anderson Cancer Center
Margaret von Mehren, Fox Chase Cancer Center
Christopher Weldon, Children's Hospital Boston
Jennifer Wright, University of Utah

SDH Deficient GIST Have Global Hypermethalyation



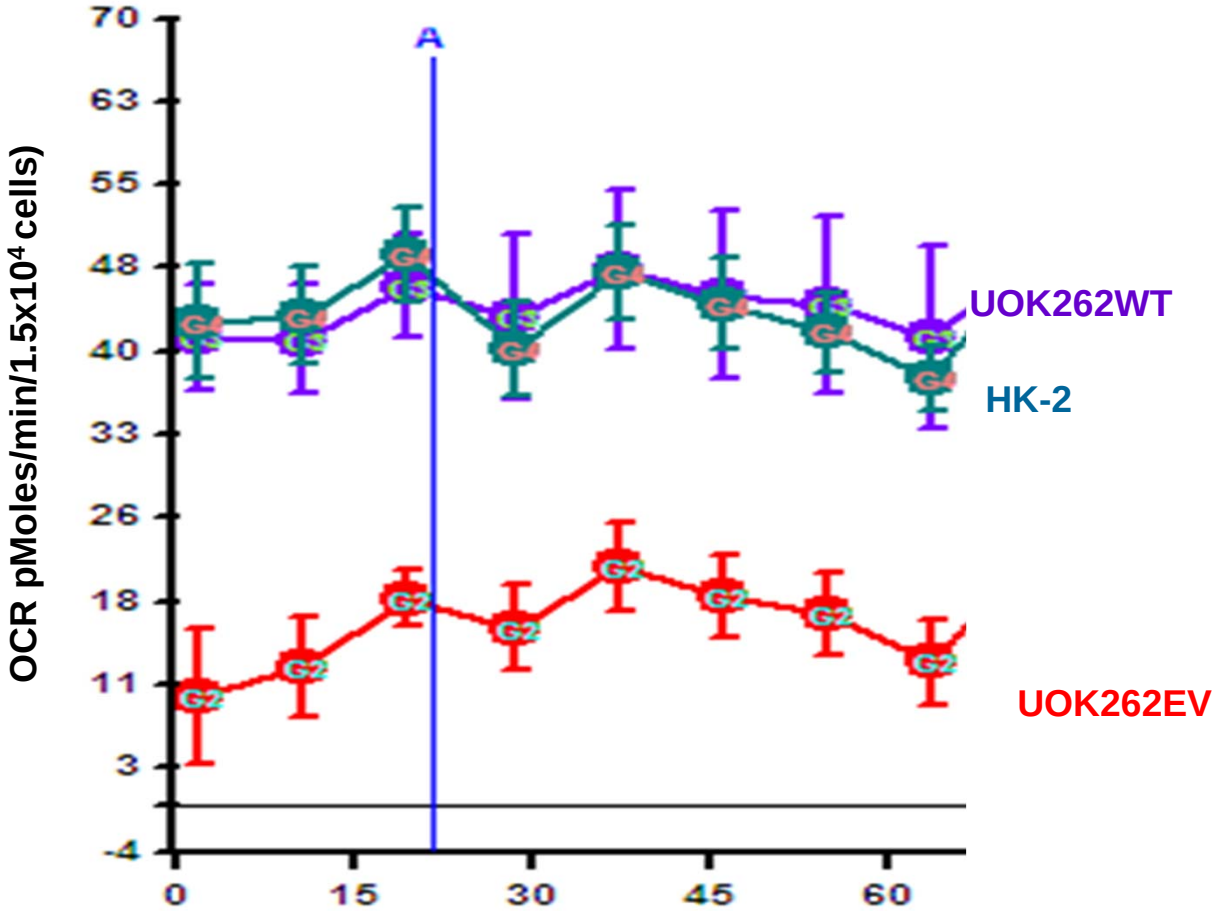
Fumarate Hydratase- and Succinate Dehydrogenase-Deficient Kidney Cancer: Warburg Model of Cancer



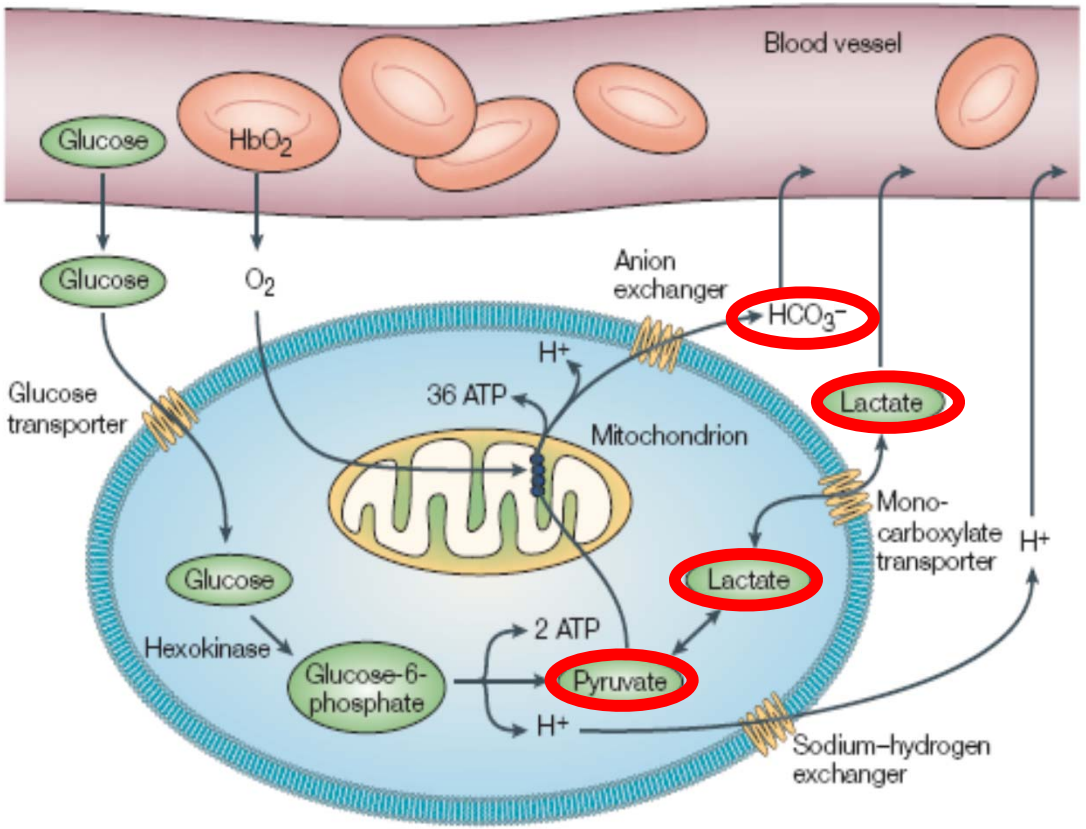
Succinate Dehydrogenase SDH-RCC

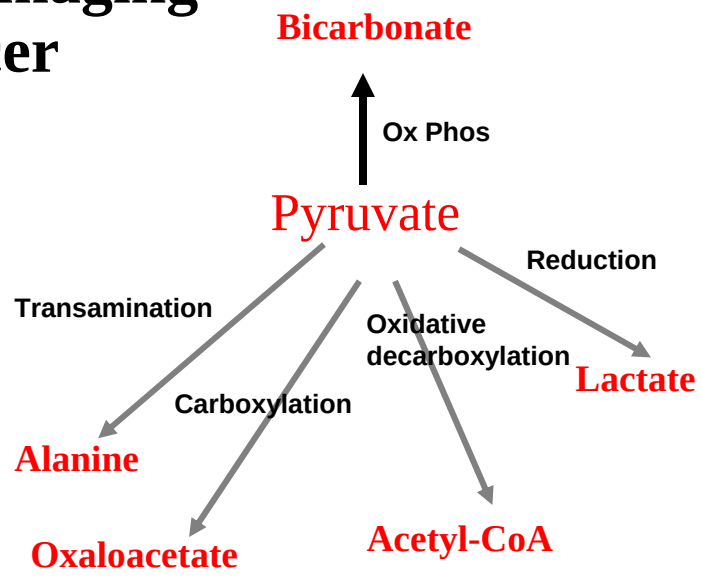
- Pheochromocytoma
- Paraganglioma
- Renal cell carcinoma
- Pediatric GIST

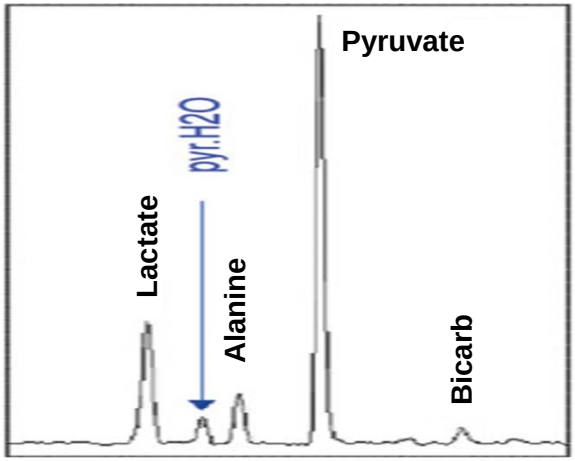
Oxygen Consumption Rate (OCR)



Hyperpolarized MRI Metabolic Imaging With ^{13}C-Pyruvate as a Tracer







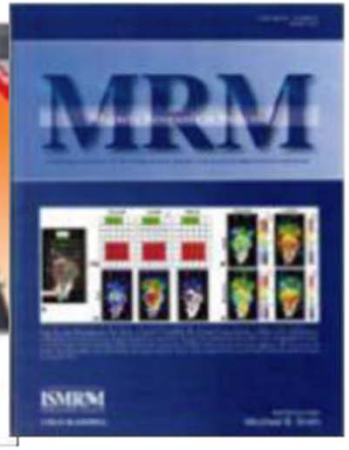
The metabolic pathways of cells of endogenous/injected pyruvate.
The metabolic products that can be imaged are shown in red

Global Excitement

GE CONFIDENTIAL

Open Innovation Leverage

Clinical ➡



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BRAINWATCH Neurochemical Imaging

Research Hyperpolarizer at NIH/MIF

Pre-clinical Today

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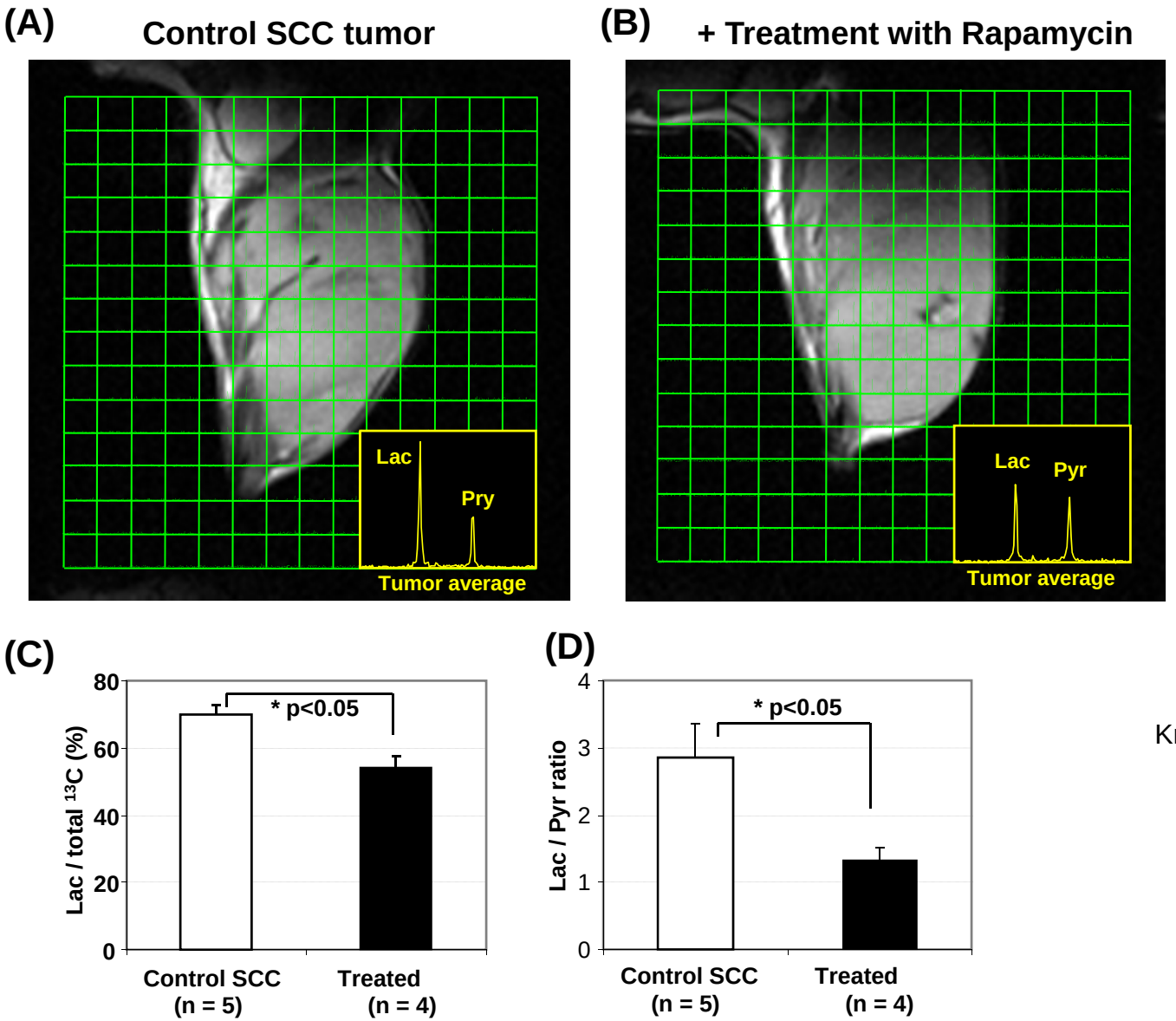
- 100L LHe/week, $40k/year*
- One dose every 2 hours
- 3-10 mL dose size – *in vitro*
- Partially automated
- Requires skilled technicians
- No quality control
- Preclinical

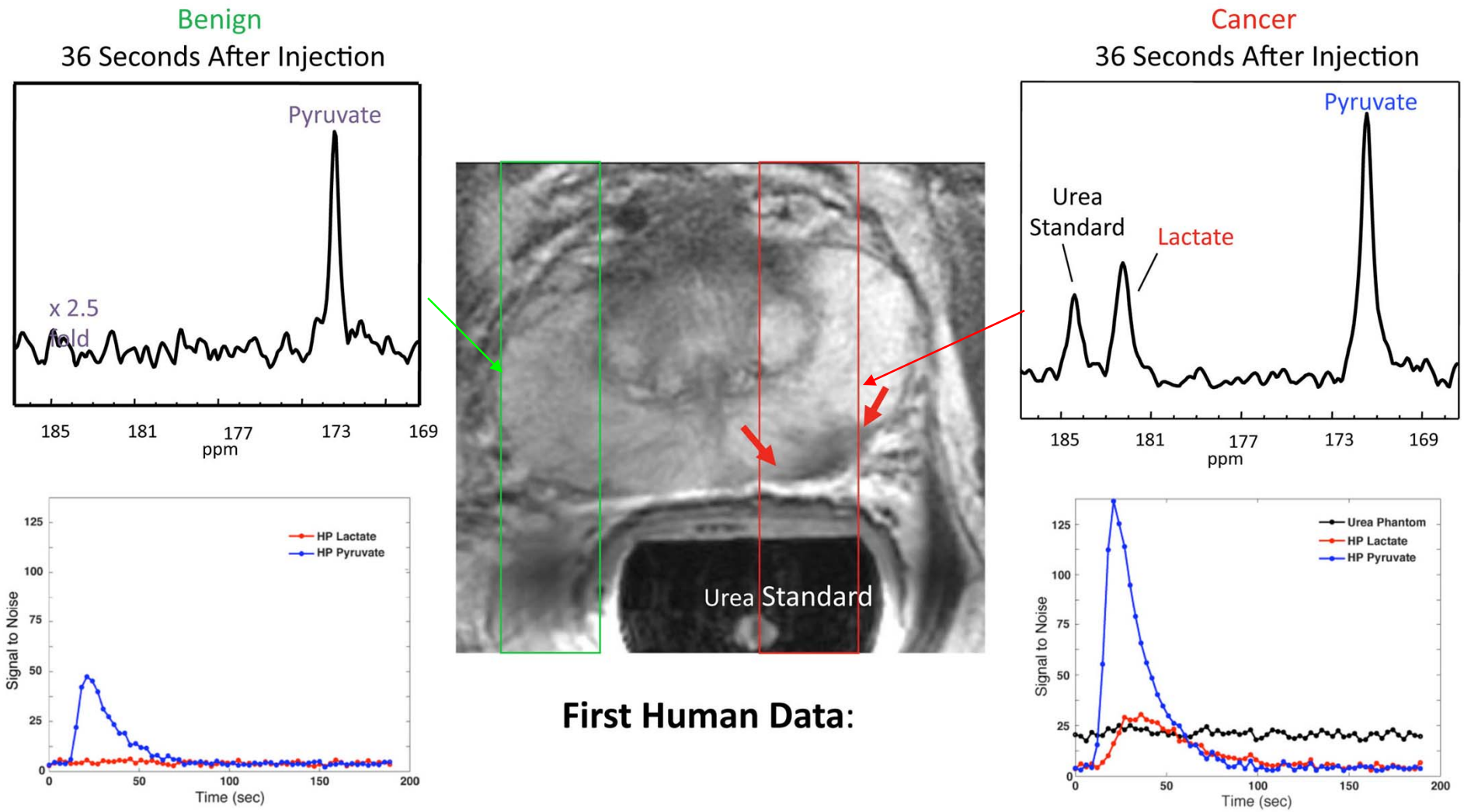
Molecular Imaging Biomarker to Monitor Treatment Response
SCC VII implant in C3H mouse. Treated with rapamycin.
Injected with ^{13}C labeled Pyruvic acid as tracer. Ratio of lactate/pyruvate monitored before and after treatment with MRI.



Krishna M RBB

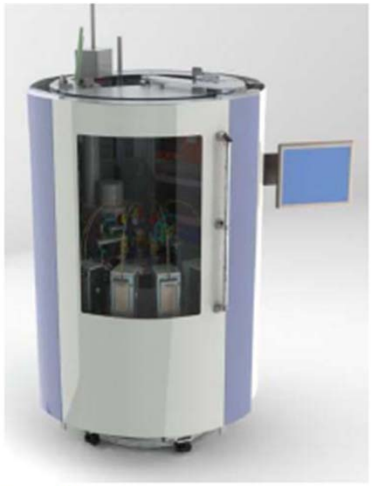
Lactate/pyruvate ratio determined by MRI can serve as a biomarker for malignancy and response to treatment

Pyruvate conversion in human prostate/ normal and malignant prostate tissue



Pyruvate is converted to lactate in malignant tissue

GE Healthcare Clinical Hyperpolarizer



Sterile Tomorrow

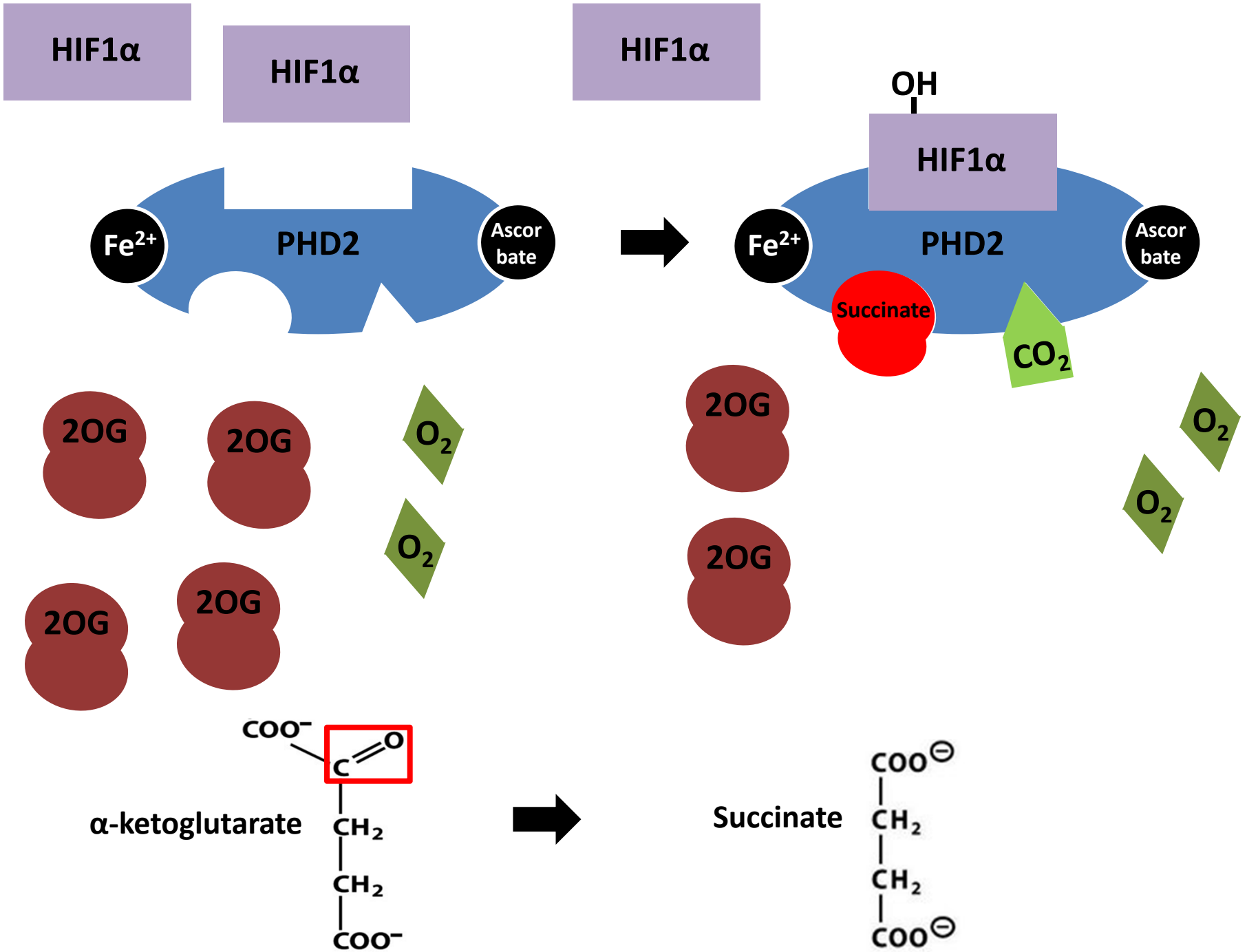
GE SpinLab™

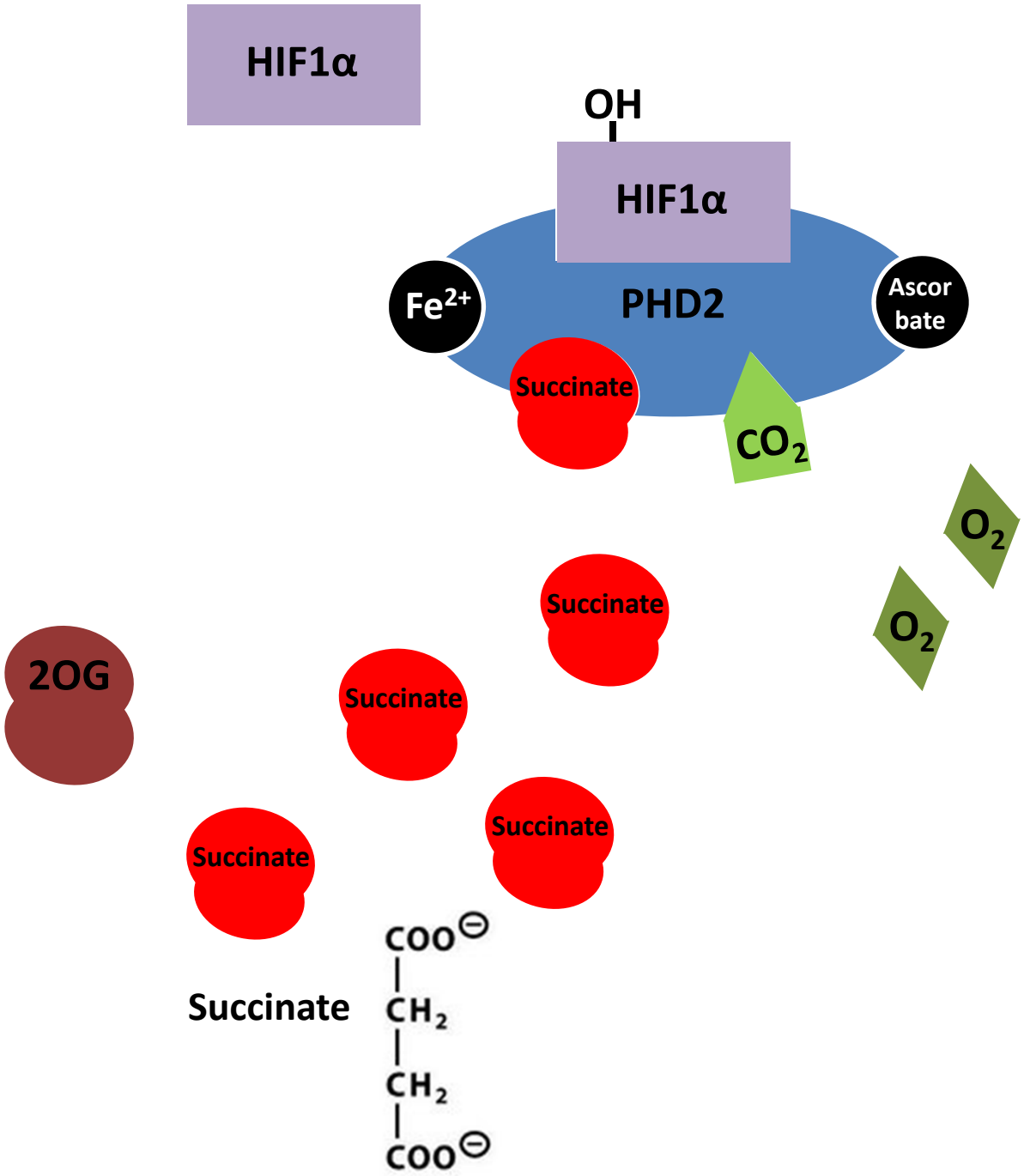
- Zero boil-off, 1 cyl./mon- $500/yr
- 4 doses per hour - Sterile
- 10-100 mL dose size
- Fully automated
- Non-technical operator
- QC ensures safety and efficacy
- (Pre) clinical (w/ Pharmacist oversight)

- Attaches to any MRI (3T and higher)
- Pharmaceutical Cost ~$500/injection
- Maintenance ~$50-100,000/year
- Cost: ~$1.8 million (to be negotiated)
- Personnel: MR physicist, Radiologist, Pharmacy, NCI-dedicated MRI facility, ^{13}C Radiofrequency channel for MRI

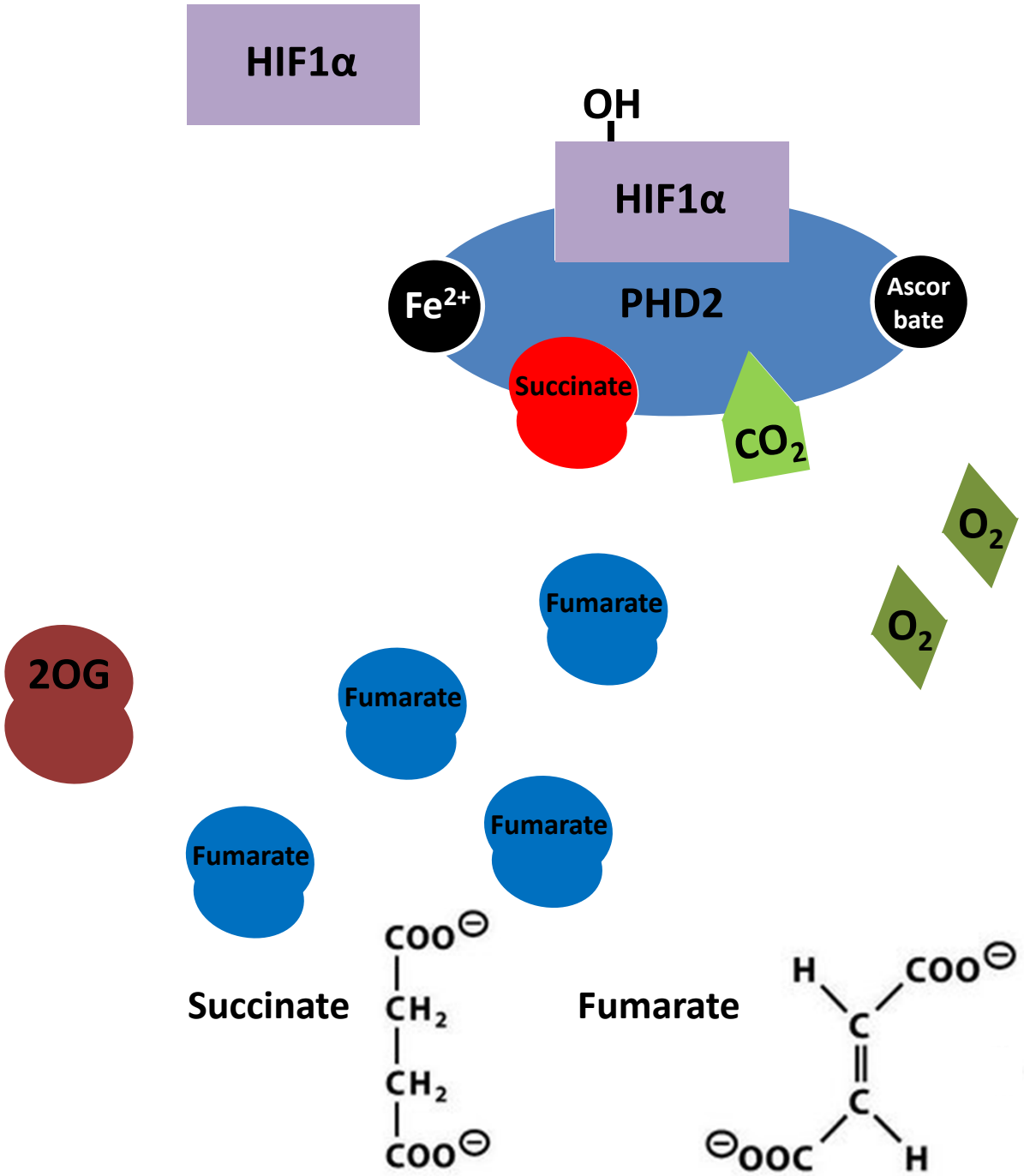
A few endogenous molecules which can be polarized for use as tracers in ^{13}C MRI based metabolic imaging:

^{13}C labeled Tracer	**Metabolic product**
Pyruvate	lactate (aerobic glycolysis) bicarbonate (ox phos) alanine (transamination) oxaloacetate (carboxylation)
Fumarate	Malate
Succinate	Fumarate
Glutamine	Glutamate
Glutamate	α-Glutarate
Acetate	Acetyl-CoA Acetyl carnitine
Choline (^{15}N)	Phosphocholine


HIF1α
HIF1α
HIF1α
OH
HIF1α
Fe2+
PHD2
Ascor bate
Fe2+
PHD2
Ascor bate
Succinate
CO2
2OG
2OG
2OG
2OG
2OG
2OG
O2
O2
O2
O2
COO−
C
O
α-ketoglutarate
CH2
CH2
COO−
Succinate
COO⊖
CH2
CH2
COO⊖

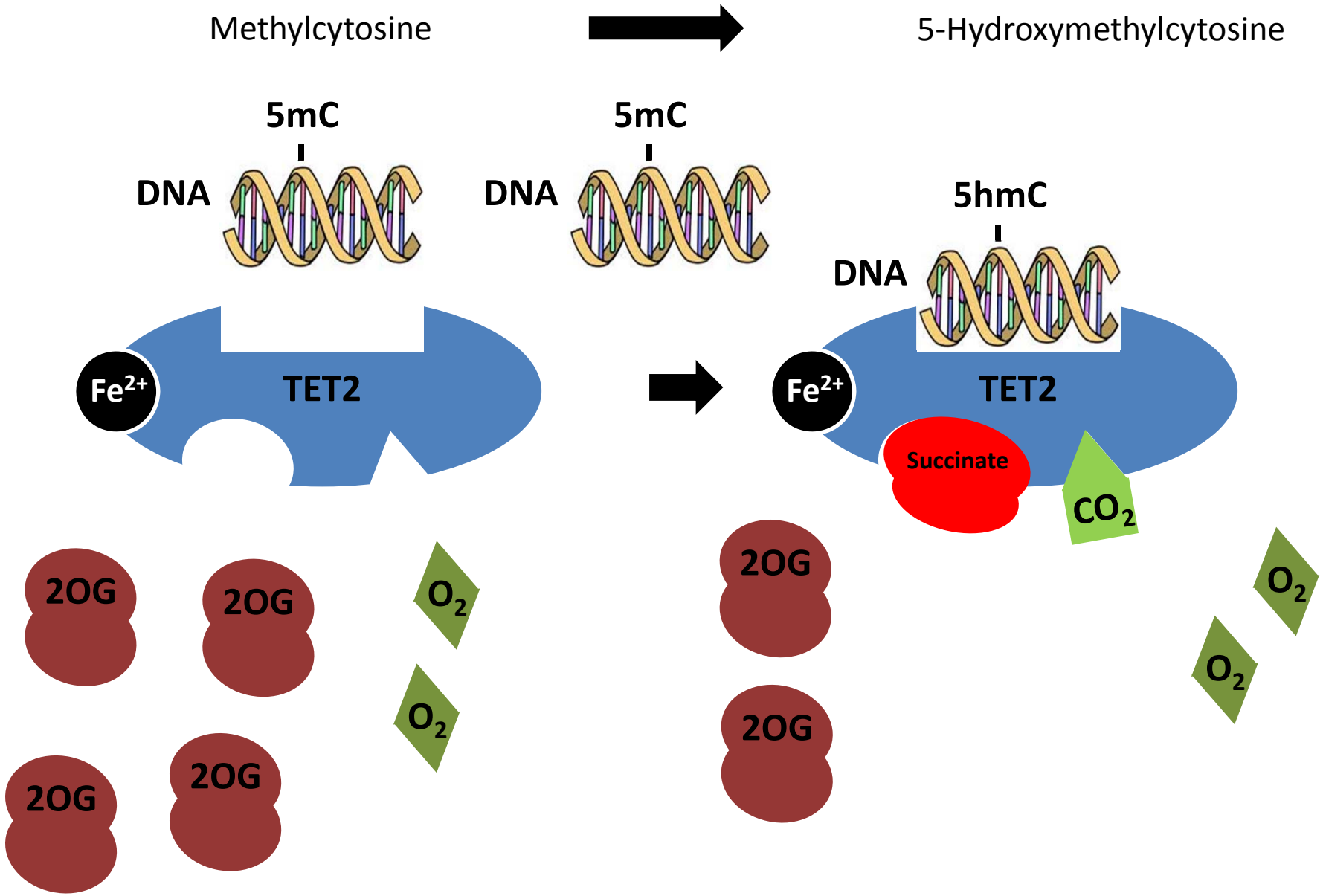


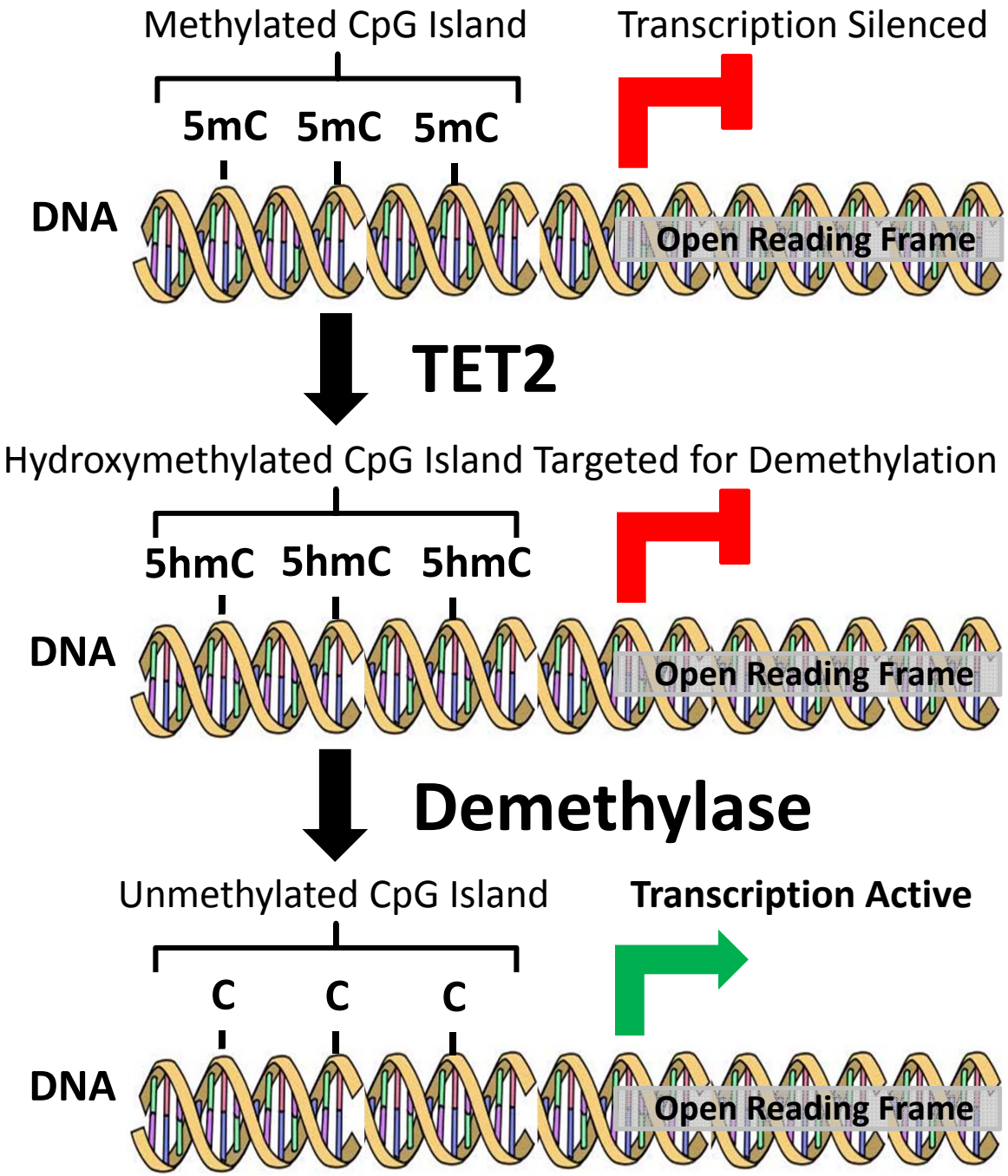
Increased succinate levels inhibits the disassociation of the PHD2 bound succinate (hence the animated wiggling) and increase the chances of succinate binding again instead of α-ketoglutarate, but the succinate will still keep disassociating and some α-ketoglutarate will bind



Increased fumarate levels may also inhibits the disassociation of the PHD2 bound succinate and fumarate could then bind instead of α-ketoglutarate. Fumarate is thought to bind with a much better affinity and is a more rigid molecule making it likely it would be much harder for disassociation to occur. This could explain why fumarate is more effective than succinate, but this would only be true for enzymes with a higher affinity for fumarate.

TET2 (and TET1) is an enzyme that works in a similar manner to PHD2 but within a different substrate – methylated cytosines within the genomic DNA





TET2 converts methylcytosine to hydroxmethylcytosine, which is thought to target it for complete demethylation. This is important for differentiating cells that are altering gene expression, but also in the removal of aberrant methylation from the promoters of important genes. Inactivation would inhibit the removal of aberrant methylation occurring within a tumor cell and thus would lead to a susceptibility to gene inactivation via promoter methylation

Conclusion

- Discovery of metabolic pathway mutations (SDH and FH) in two rare tumors studied taking advantage of unique resources of the Hatfield CRC
- Identification of novel mechanism (global hypermethylation) and potential treatment (metformin or other AMPK activators, antiangiogenic etc)
- Use of both genomics and imaging to develop new approaches to Dx and to monitor therapy in real time
- Likely to inform subsets of common diseases

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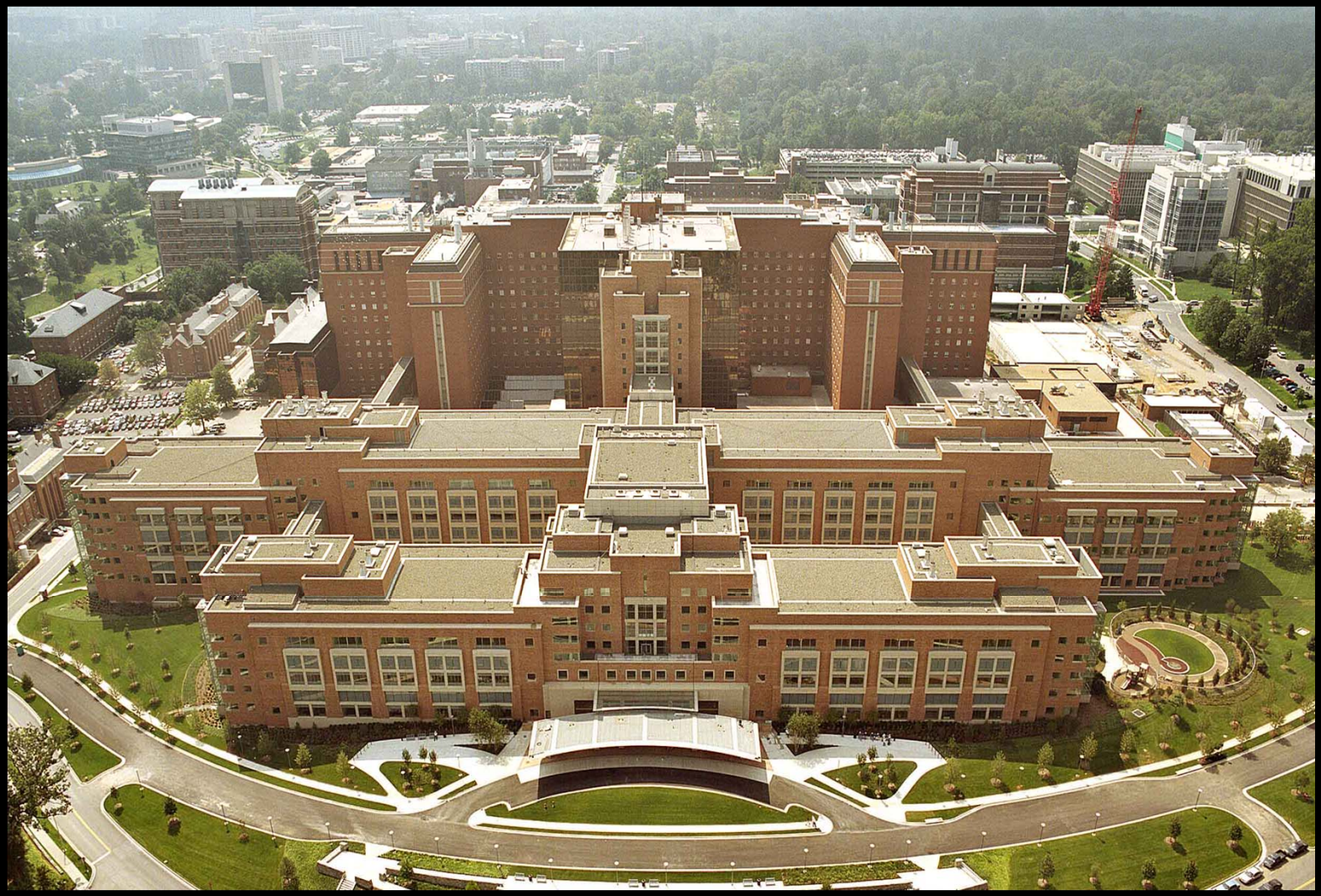

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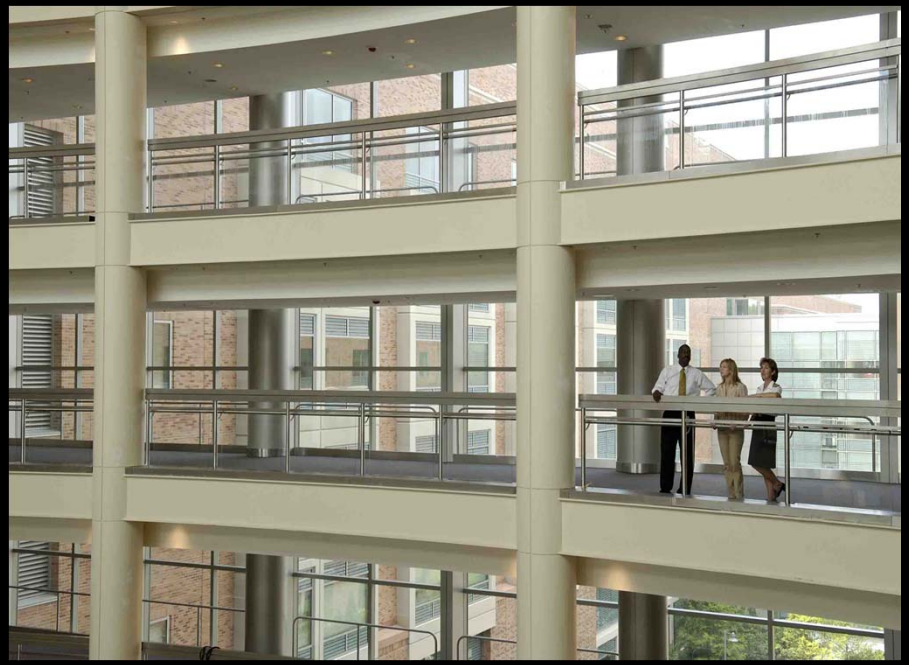

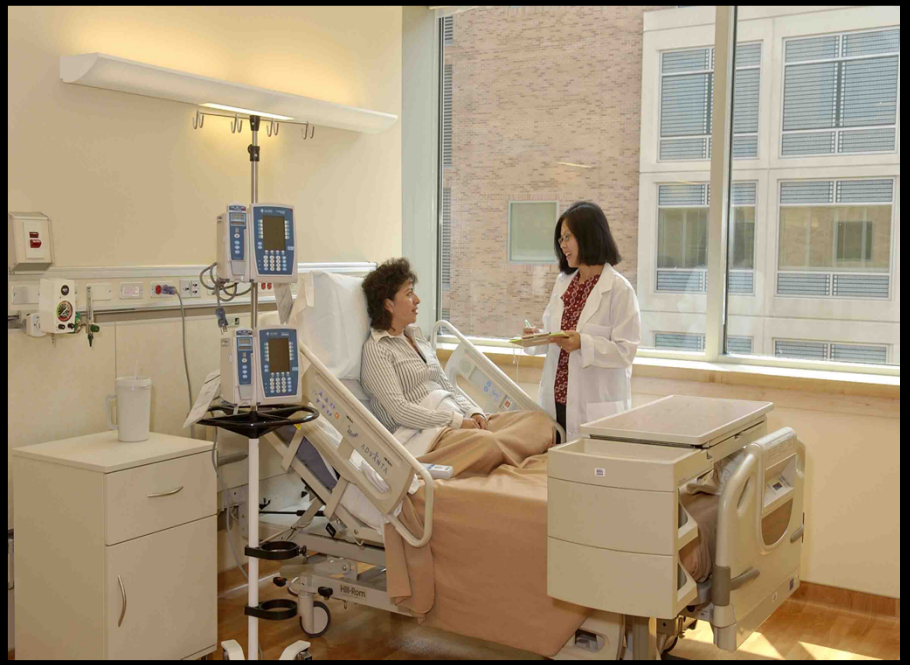

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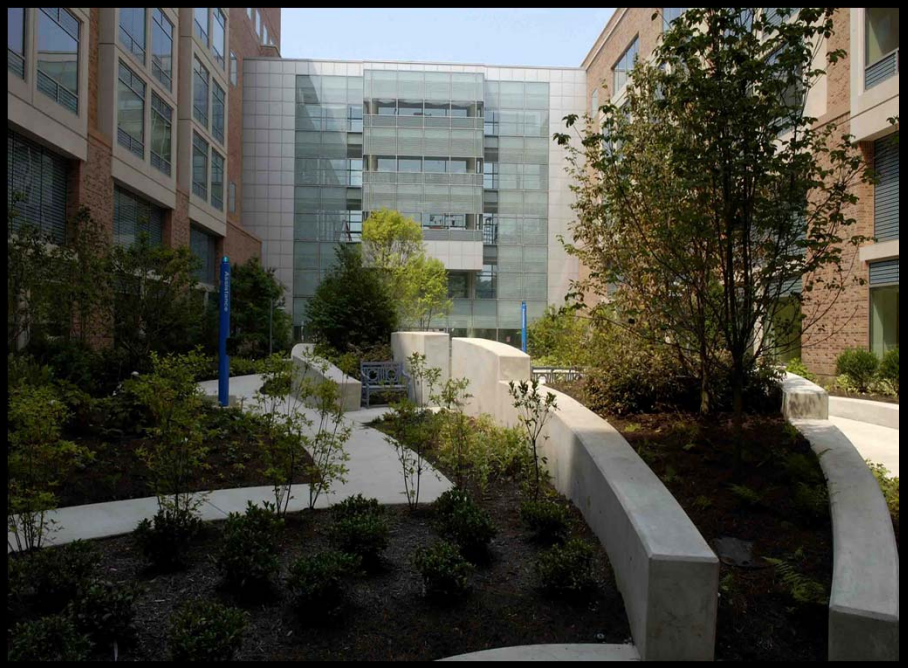

^{13}C-Glucose and ^{13}C-Glutamine Tracer Data Highlights Both Novel and Known Targets Within The Metabolic Pathways For Targeted Therapy