CENTER FOR CANCER RESEARCH

Connecting the Cancer Community

The Intramural Clinical Research Program-CTAC Nov 2011

Lee J. Helman, M.D.

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

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**
     - **Why is this an important study for the CCR to do now?**
  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)

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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
- ☐ 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

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
- ☐ Industry
- ☐ CTEP
- ☐ 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)

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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**

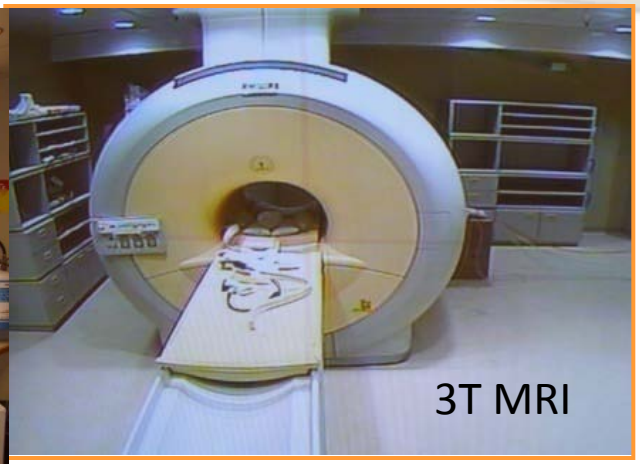
CCR Is Putting the Pieces in Place

- **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

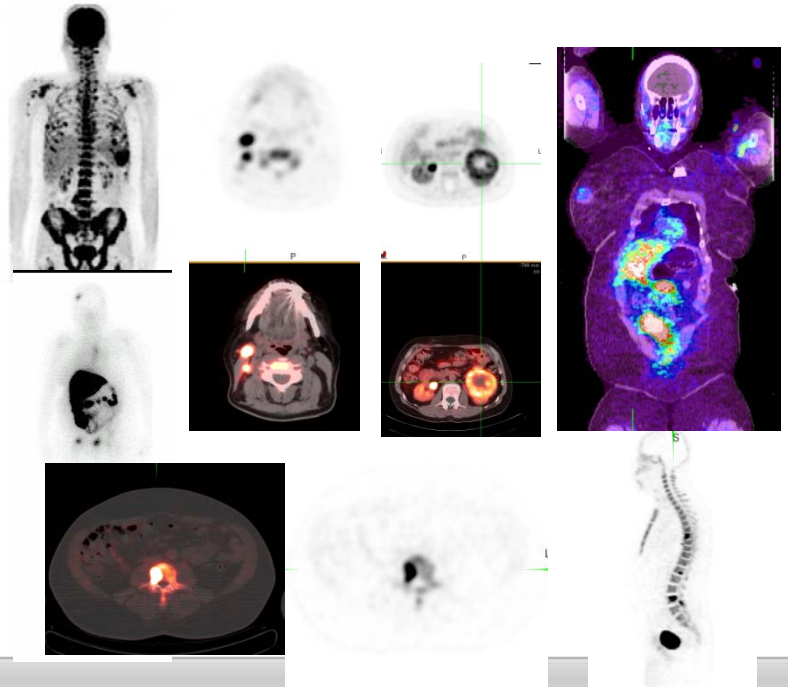
- **Blur the line between imaging and pathology**
- **Develop novel imaging approaches and technology:**
  - Basic discovery research
  - Translational applications
  - Non-invasive patient care
- **Improve imaging techniques to enhance early detection, diagnosis, and treatment**
  - Preclinical model 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.

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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

What is a Major Opportunity?

- **A Clinical Major Opportunity:**
  - Addresses a fundamental problem in oncology, with broad applications across multiple clinical and laboratory branches, where the CCR has rare enabling expertise, capabilities, and/or direct patient populations.
  - Focuses efforts over the next 3-5 years to achieve specified goals & deliverables that, when achieved, would be considered a major leap forward by the entire oncology community.
  - By definition, are not permanent organizational units, but are focused groups with a time sensitive deliverable
    - i.e., they are not a branch, faculty, Center of Excellence, or working group
    - Managed with a new level of leadership
  - Must have the following elements:
    - Major thematic
    - Paradigm shifting scientific and clinical goal
    - Rational why this is unique and feasible area at CCR
    - Collaborative across multiple branches

Goals of the Major Opportunity Retreat

- **Increasing communication among CCR members on clinical and basic activities**
- **Understanding the importance of the Major Opportunities to the CCR**
- **Improving the Major Opportunities presented and identifying opportunities for cross-branch collaborations**
- **Providing transparency of the Major Opportunities selection process**

Strategic Visioning Committee Members

Committee Members

- Lee Helman, MD (chair)
- Deborah Citrin, MD
- William Dahut, MD
- Giuseppe Giaccone, MD, PhD
- Ronald Gress, MD
- Ola Landgren, MD, PhD
- Marston Linehan, MD
- Steven Rosenberg, MD, PhD
- Briggite Widemann, MD

External & Ancillary Members

- Bob Wiltrout, PhD
- James Doroshow, MD
- Mel Bronez, MPH
- Caryn Steakley, RN
- David Dilts, PhD, MBA
- Steven Cheng, PhD

Process of Identifying and Creating Major Opportunities for the Retreat

- **Developed 6 exemplar Major Opportunities (April – August 2011)**
- **Created the dimensions to best capture the framework of the Major Opportunities**
  - Lay Summary
  - Uniqueness to the Cancer Community
  - Overarching Strategy
  - Anticipated Timeline
  - Targeted Population / Pathway
  - Scientific and Therapeutic Goals
  - Current CCR laboratory and/or clinical research
  - Potential level of scientific and clinical impact
- **Refined each MO with input from CCR members, extramural community, and Board of Scientific Counselors**
- **Multiple iterations to generate the exemplar MOs**
- **Distributed 6 exemplars and asked for other potential MOs**

Major Opportunities Presented at the Retreat

1. Targeting Inflammation in Cancer
2. Matrix Drug Screening for Combination Therapies in Cancer
3. Treatment of Cancers based on Drivers Mutations Independent of Histology or Site
4. Monitoring and Manipulating the Epigenome In Human Cancer
5. Targeted Therapy Combining Immunotherapy and Pharmacotherapy
6. Attacking Cancer Based on its Metabolic Basis
7. Rare cancers and Genetic Tumor Predisposition Syndromes
8. Characterizing the Transition from Premalignant or Smoldering Cancers to Malignant Tumors to Improve Interventions between Prevention and Treatment

Structured Discussions

- **Perceptions from external and internal oncology communities**
  - Assuming the scientific objectives are met in year 5, how would this MO "change the face of cancer", i.e., novel, impactful, paradigm shifting, stretch goal?
  - Why should the MO be done at CCR and not by other cancer centers or by industry? (Do you know of similar activities outside of the CCR that would fit within or compete with this MO)?
- **MO strengths and areas for improvement**
  - In what ways could this MO be strengthened?
- **Integration of current research direction with the MO**
  - Could this MO be integrated with <u>your</u> current clinical research direction
  - How could <u>your</u> research stream improve this MO?

Post Retreat Survey

98 Responses to Post-Retreat Survey

18 did not attend retreat

80 attended retreat

19 Clinical

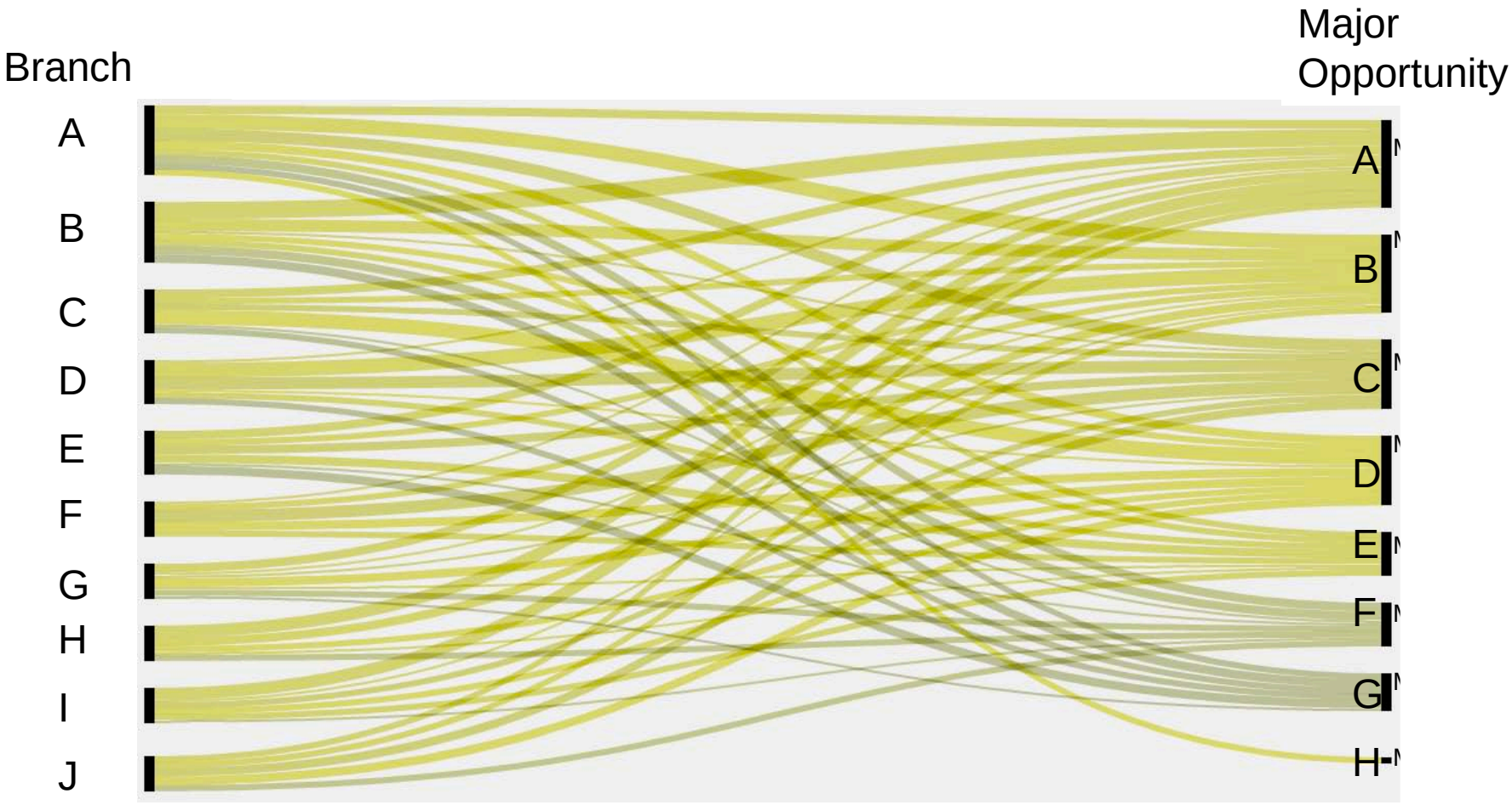
49 Both

31 Basic

Major Opportunities Retreat Feedback

- **"Good exercise for CCR. Good way to potentially get people to work together."**
- **"I like the transfer of effective strategies to NIH and biology from other disciplines where effectiveness and progress can be accurately measured. Applying these measures or processes to biomedical research is exciting and progressive!"**
- **"I ranked those opportunities that bridge many cancer disciplines."**
- **"A difficult decision, all were excellent."**

Analysis of Cross-Collaboration

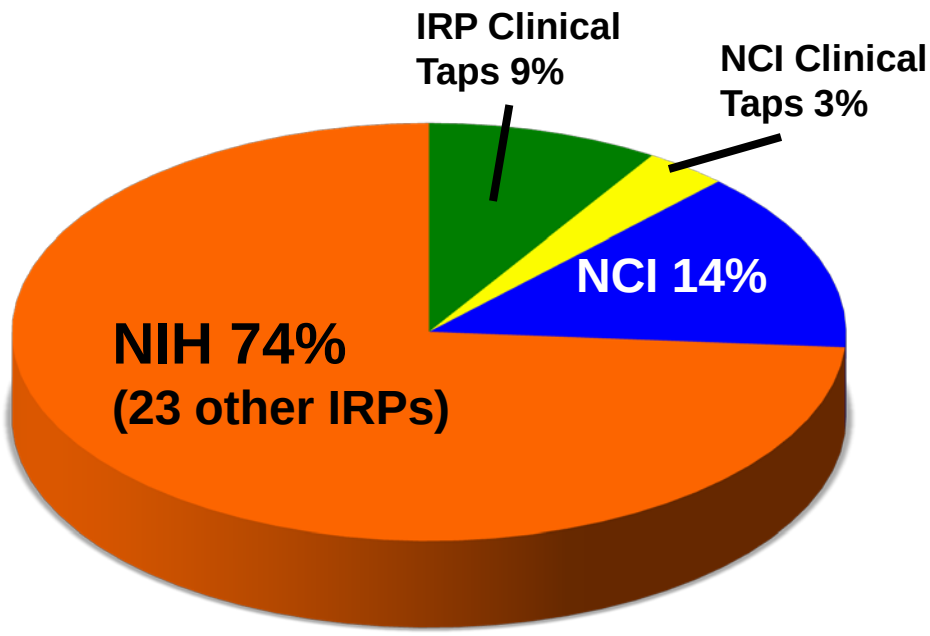


Next Steps

- **MO Input given to all MO Leaders**
- **Post-retreat survey to all participants for additional input**
- **Presentation to BSC meeting in November for additional information**
- **All input collected and provided to Bob & Lee for initial prioritization**
- **Initial priorities reviewed with NCI Director and Deputy Directors**
- **Specific MOs contacted to create a detailed schedule, budget, and resource list**
- **Final selection by Bob & Lee**
- **Announcement: January 2012**

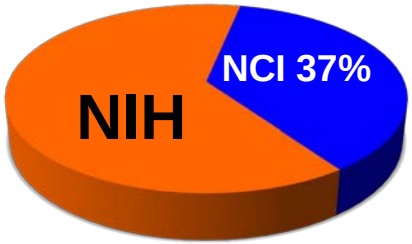
CCR Clinical Activity at the NIH

NIH IRP vs CCR Budget

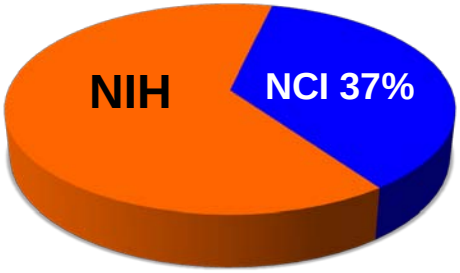


CCR is one of 24 Intramural Research Scientific Programs at NIH

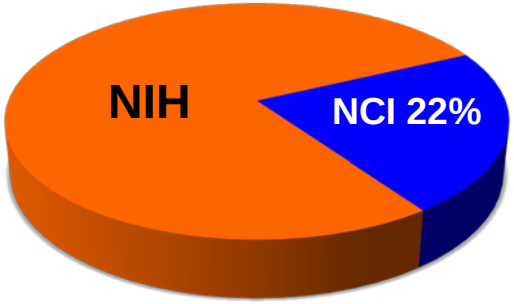
Outpatient Visits



Inpatient Days



New Patients



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Connecting the Cancer Community

Snapshot of where we are

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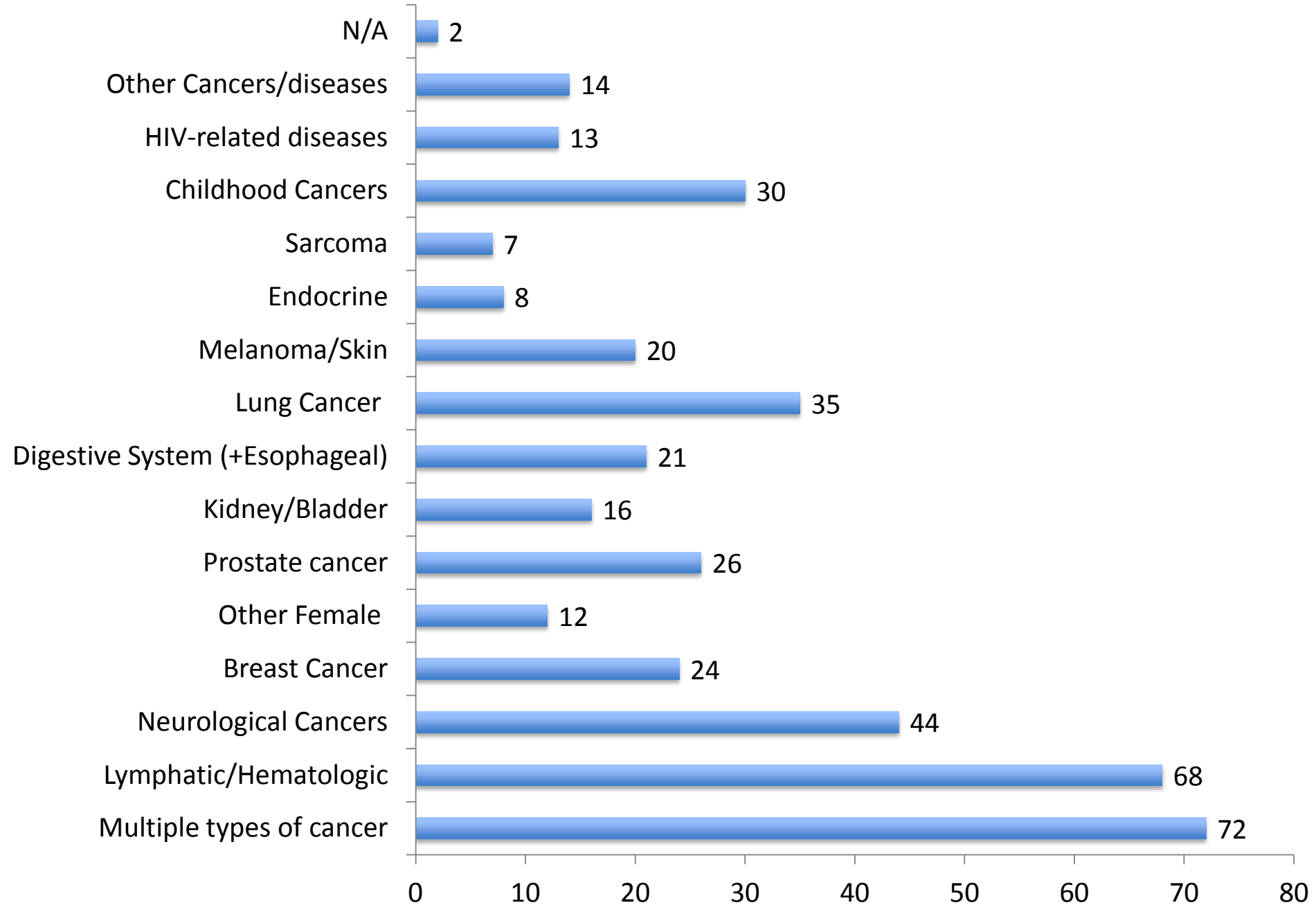
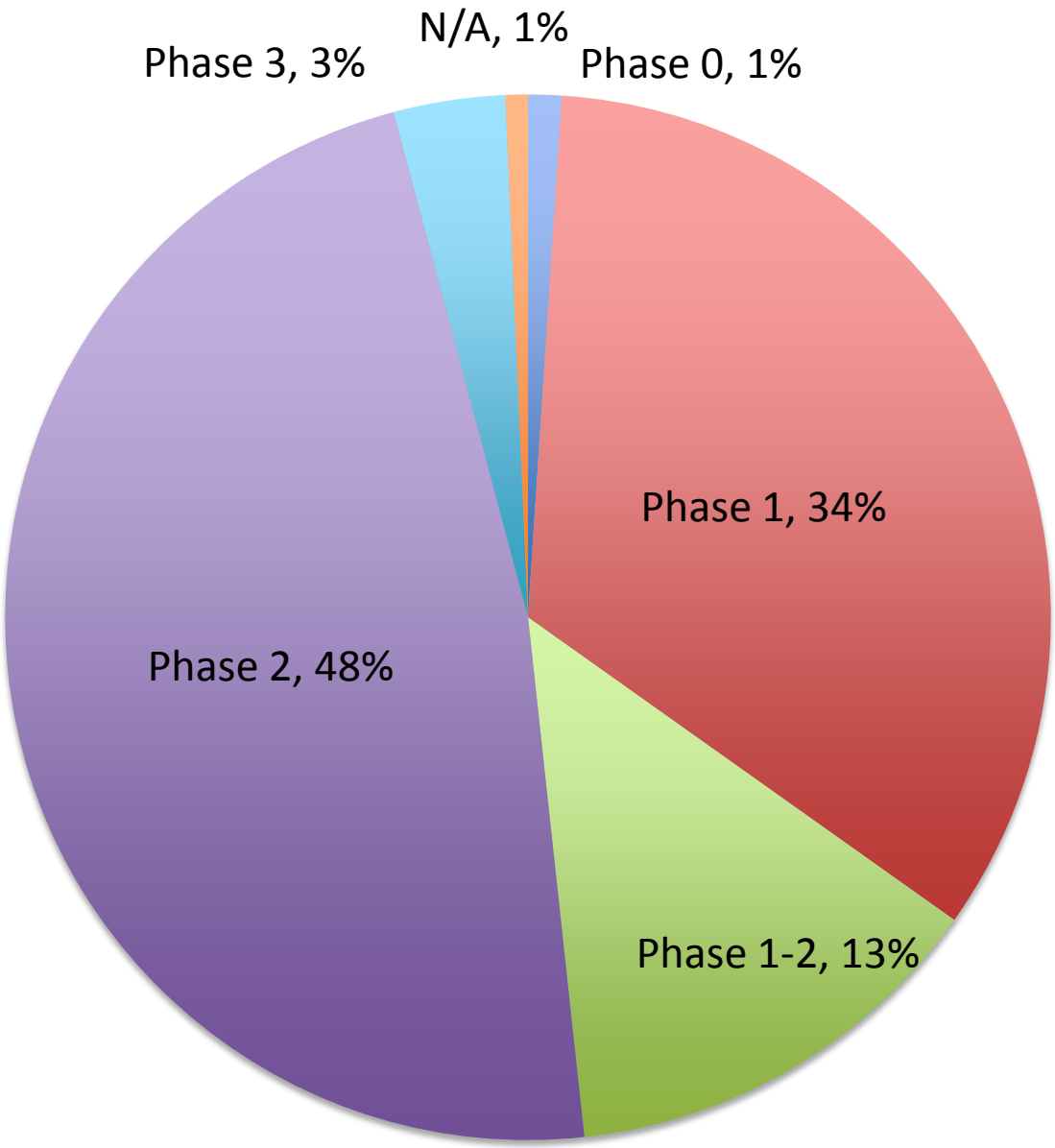
CCR Labs/Branches	# protocols by L/B	% of total
MOB	108	25%
POB	64	16%
SB	49	12%
MTB	31	8%
ETIB	24	6%
ROB	20	5%
NOB	19	5%
LMB	17	4%
LTIB	12	3%
HAMB	11	3%
MIP	10	2%
Derm	9	2%
UOB	9	2%
VB	7	2%
LGD	6	1%
LP	4	1%
CC	3	1%
OCD	3	1%
LEI	3	1%
CCR-OD	1	0%
GB	1	0%
LHC	1	0%
412		

Protocols by Disease Site



Treatment Protocols



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Examples-where are we going

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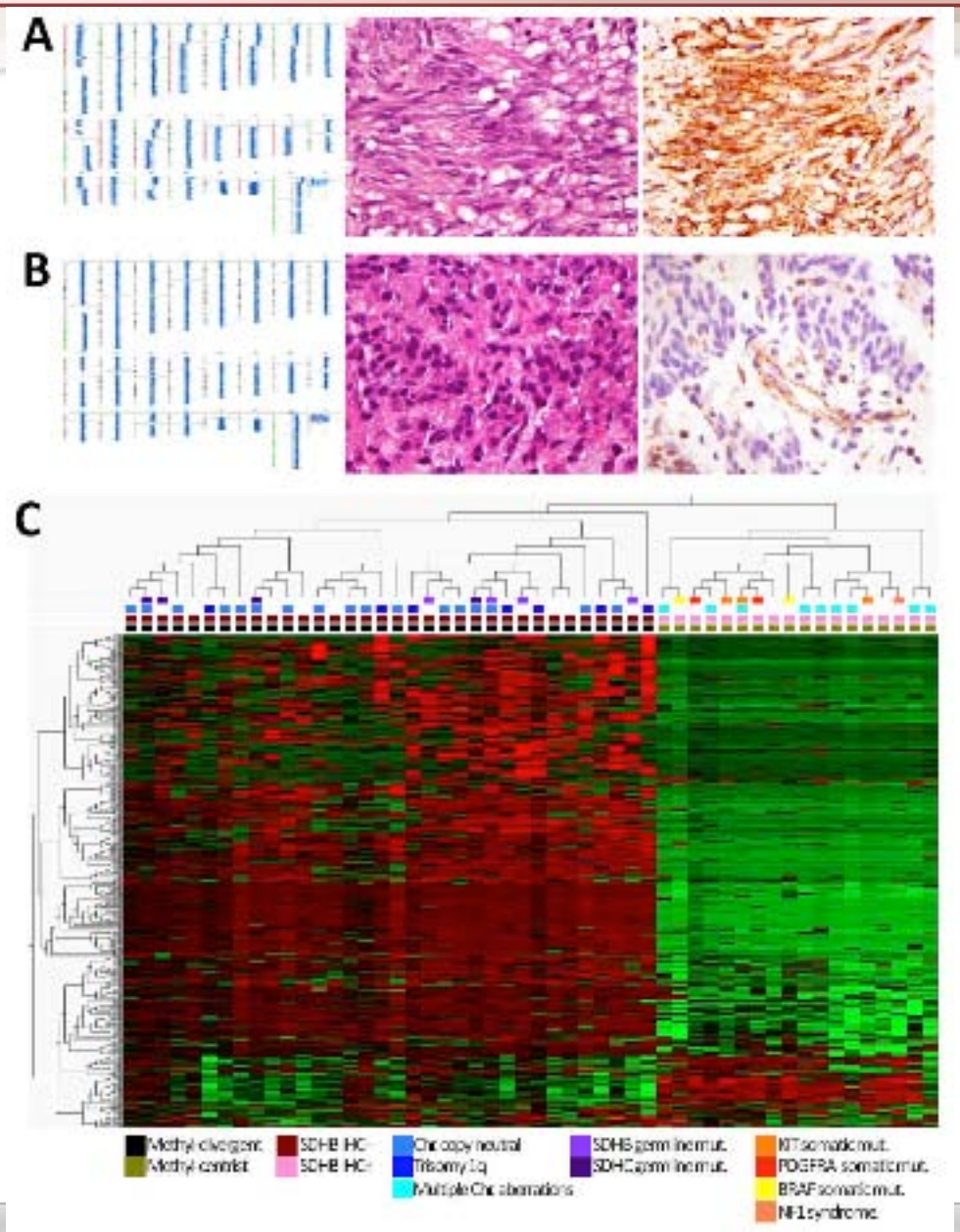
Pediatric Wild-Type GIST have SDH loss

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

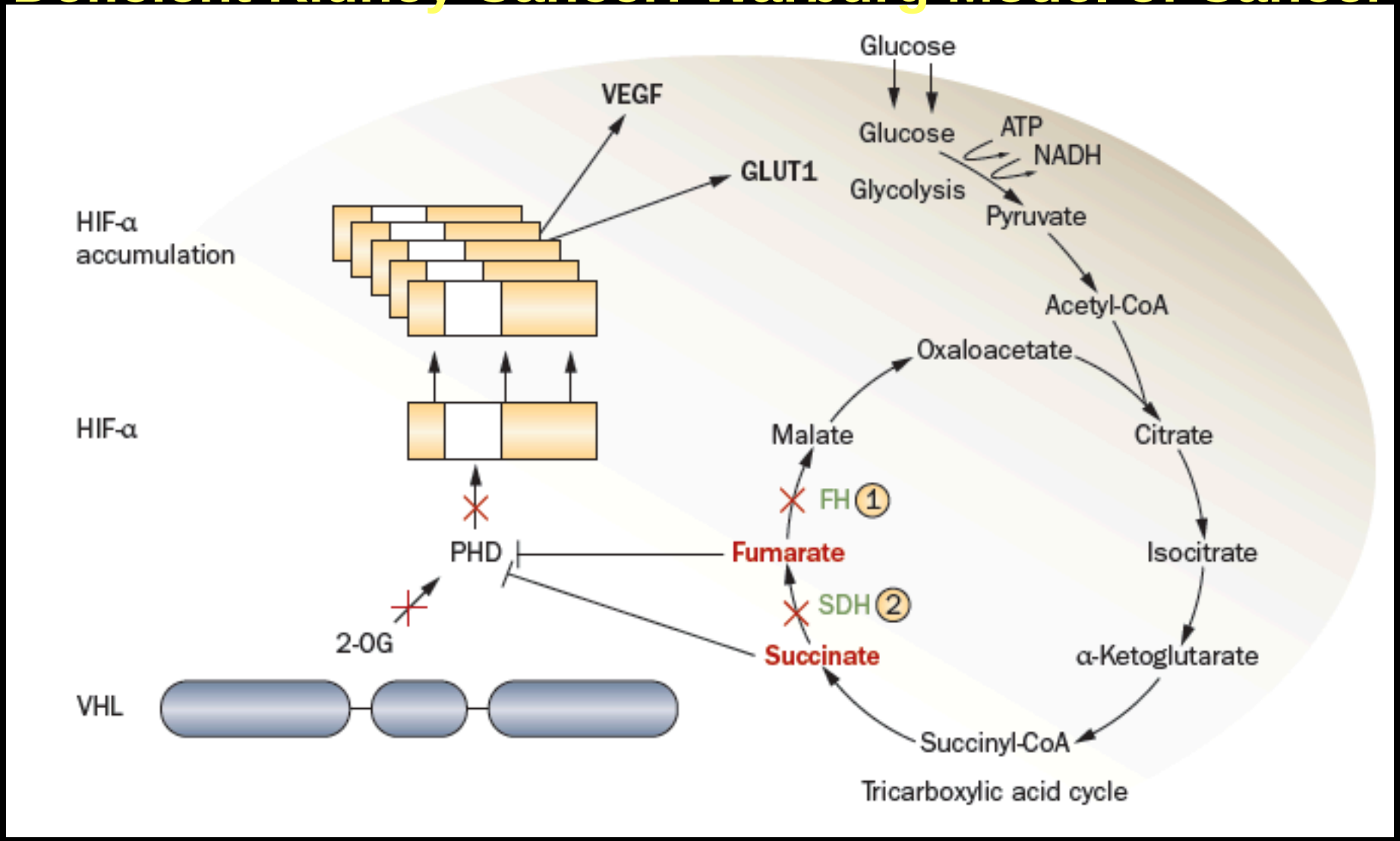
Keith Killian[1], Su Young Kim[2], Markku Miettinen[3], Carly Smith[2], Maria Tsokos[3], Martha Quezado[3], William I. Smith, Jr.[4], Mona Jahromi[5], Robert L. Walker[1], Laura Jones[1], Joshua D. Schiffman[5], Maureen J. O'Sullivan[6], Constantine Stratakis[7], Lee Helman[2], Paul Meltzer[1]*, presenting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

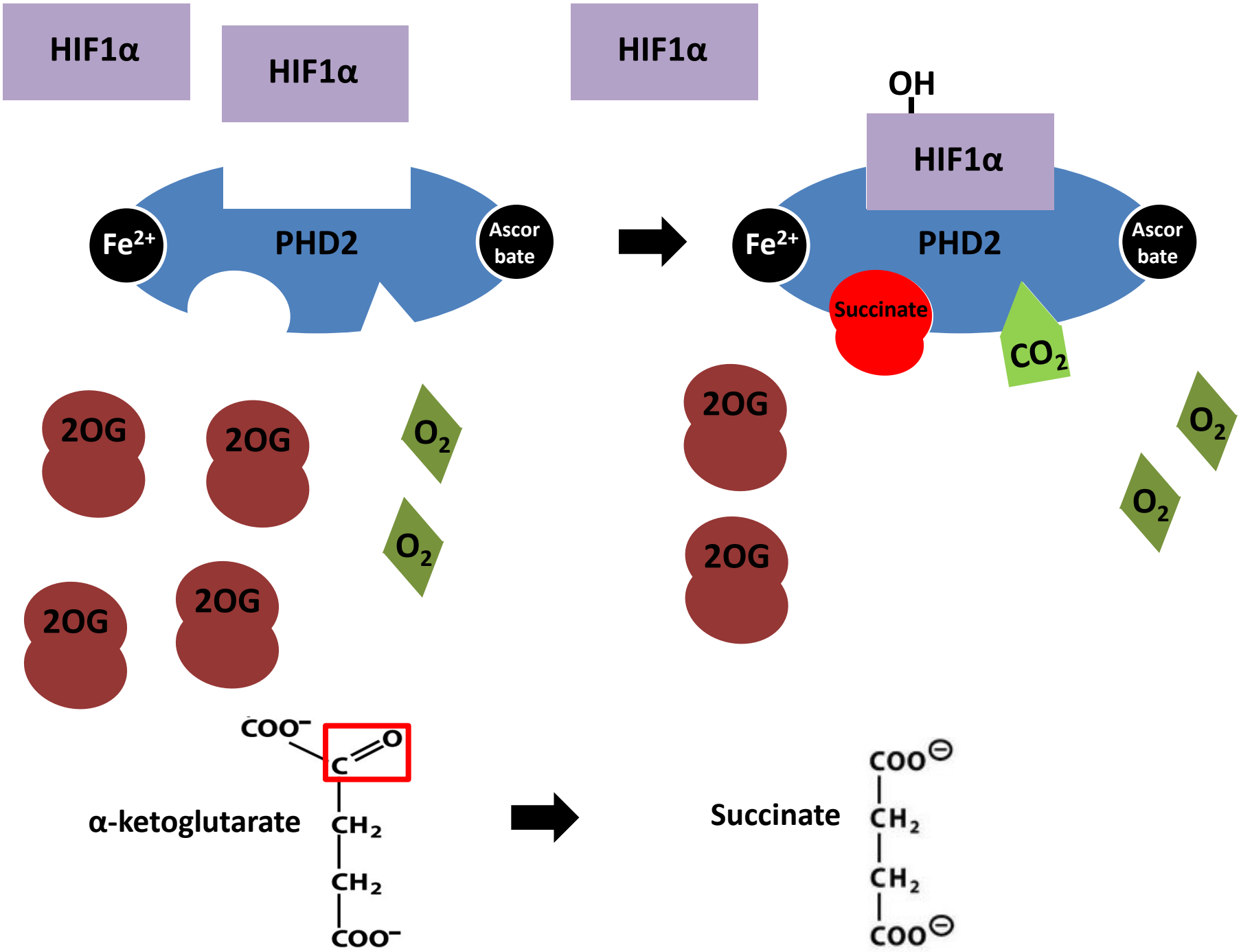


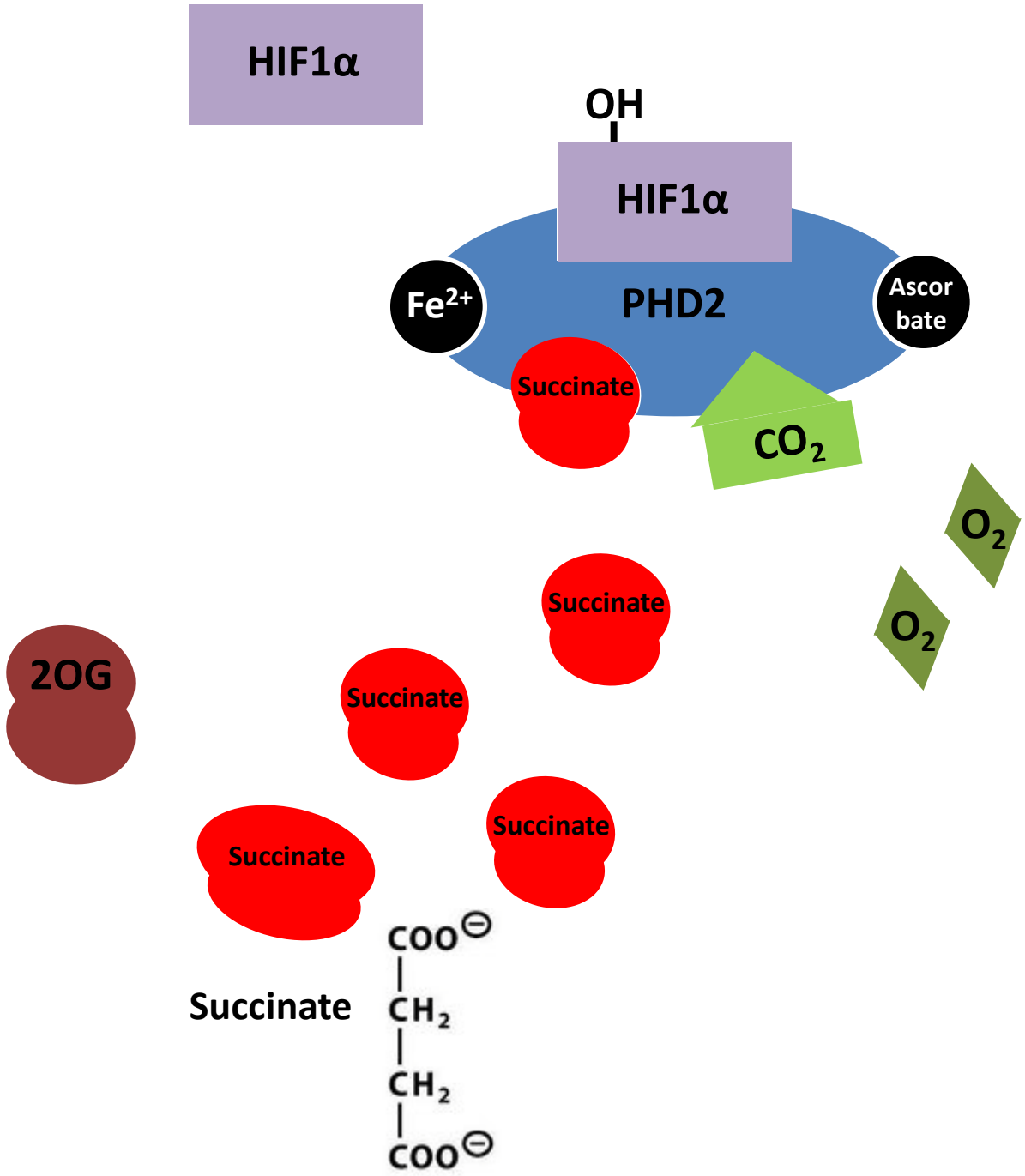
Fumarate Hydratase- and Succinate Dehydrogenase-Deficient Kidney Cancer: Warburg Model of Cancer



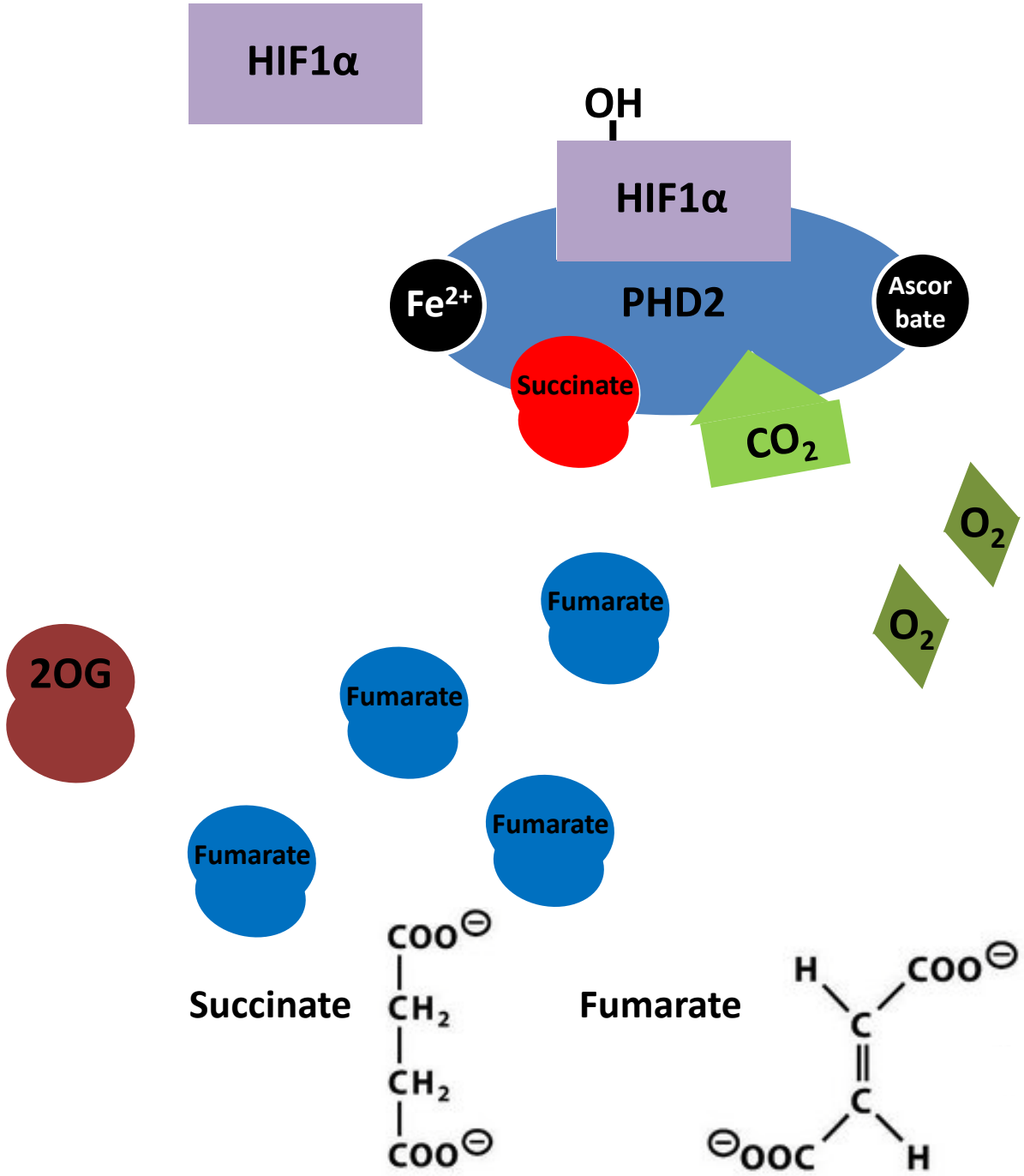
Succinate Dehydrogenase SDH-RCC

- Pheochromocytoma
- Paraganglioma
- Renal cell carcinoma
- Pediatric GIST-PNAS 2011


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
α-ketoglutarate
COO⁻
C
O
CH2
CH2
COO⁻
Succinate
COO⊖
CH2
CH2
COO⊖

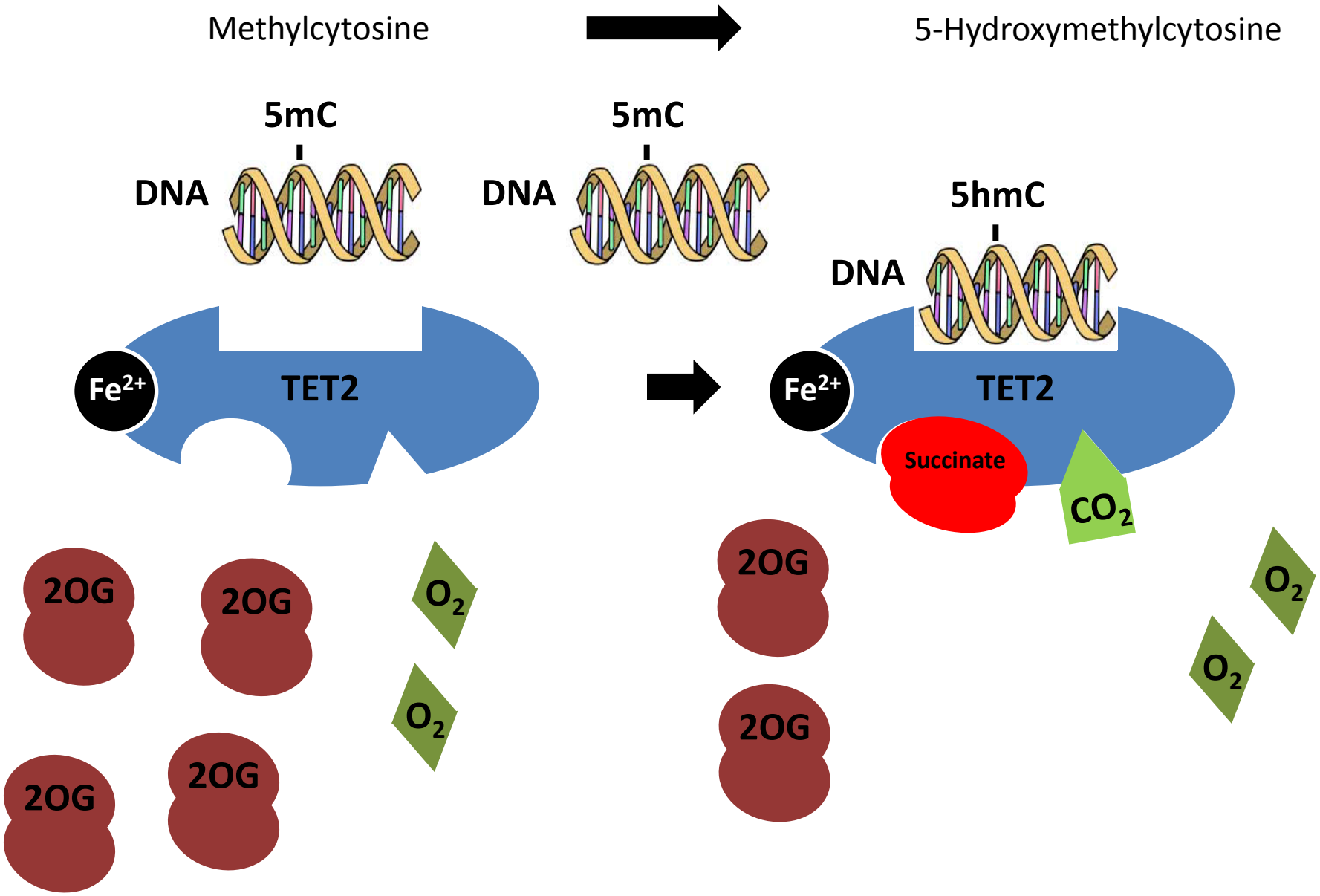


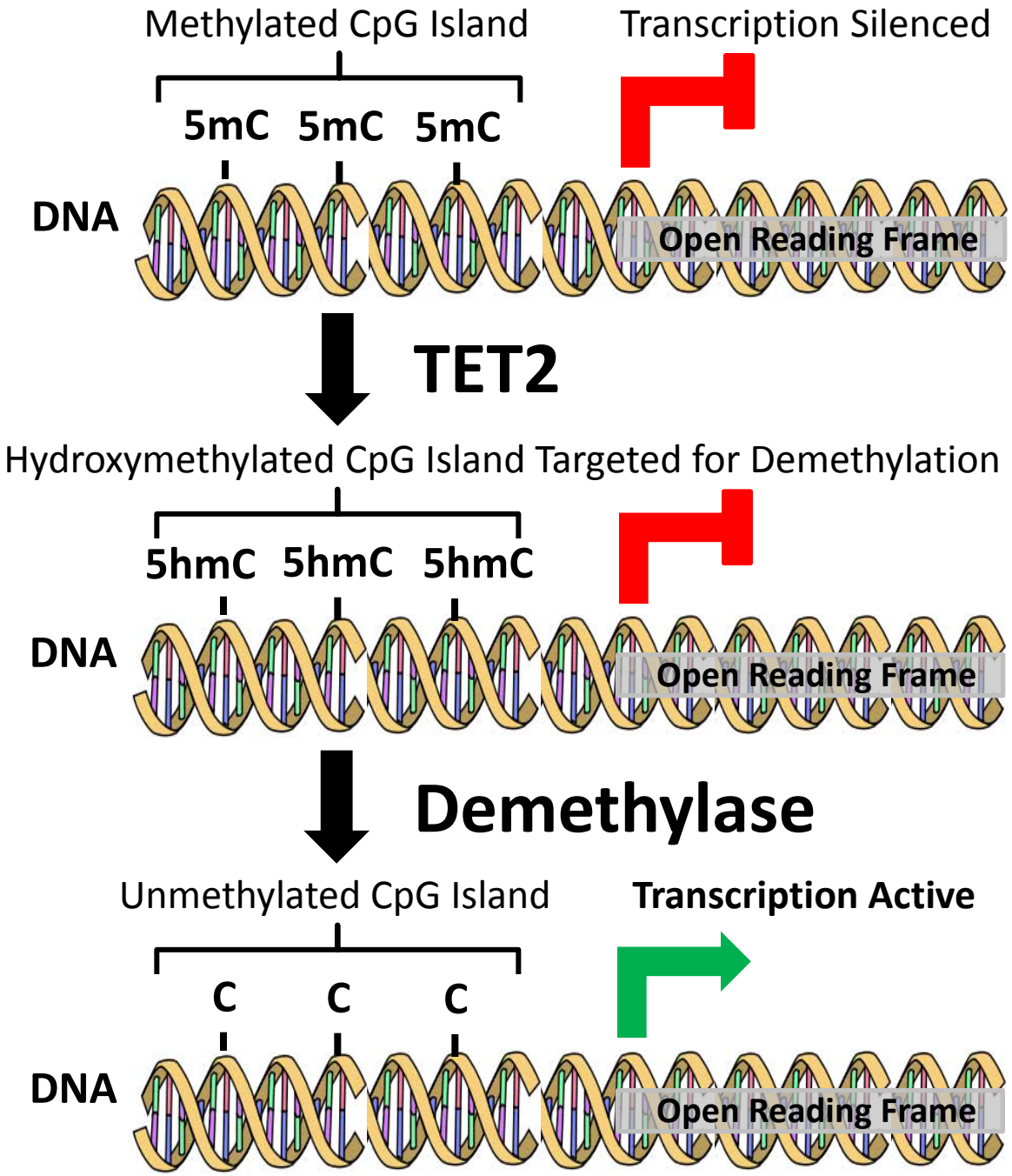
Increased succinate levels inhibits the disassociation of the PHD2 bound succinate (hence the animated wiggling) and increase the chances of succinate binding again instead of α-ketoglutarate, but the succinate will still keep disassociating and some α-ketoglutarate will bind



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



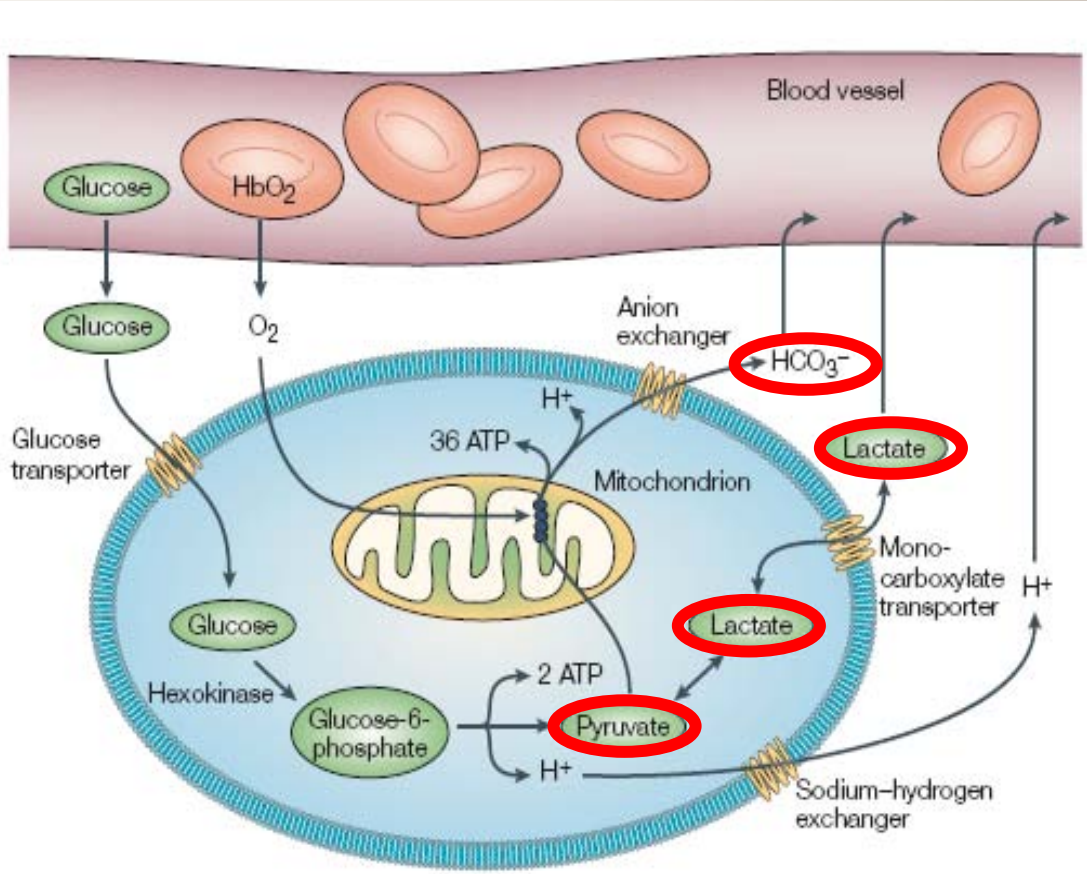


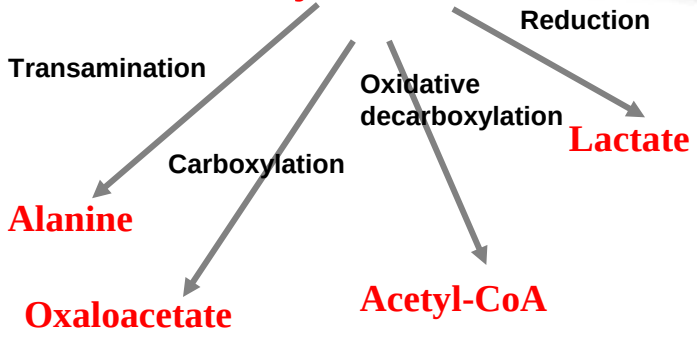
TET2 converts methylcytosine to hydroxmethylcytosine, which is thought to target it for complete demethylation. This is important for differentiating cells that are altering gene expression, but also in the removal of aberrant methylation from the promoters of important genes. Inactivation would inhibit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

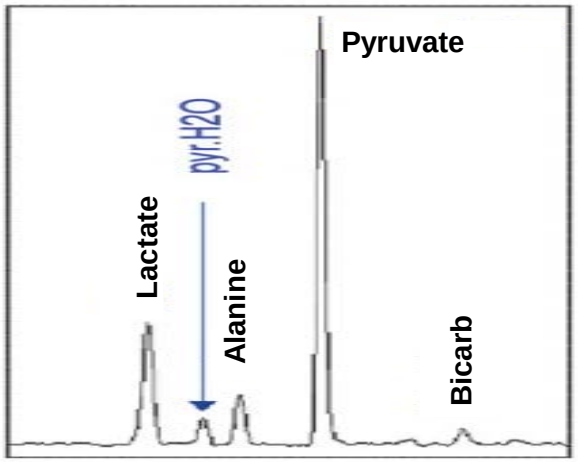
Conclusion

- 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

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



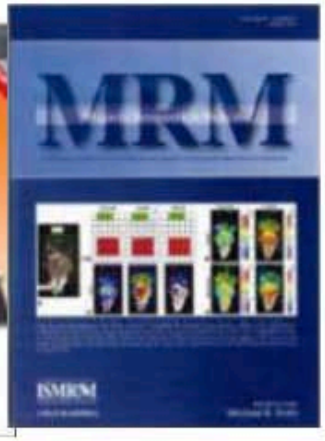




The metabolic pathways of cells of endogenous/injected pyruvate.
The metabolic products that can be imaged are shown in red

Global Excitement
Open Innovation Leverage

GE CONFIDENTIAL



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Clermont-Ferrand	Betty Jean

Clinical

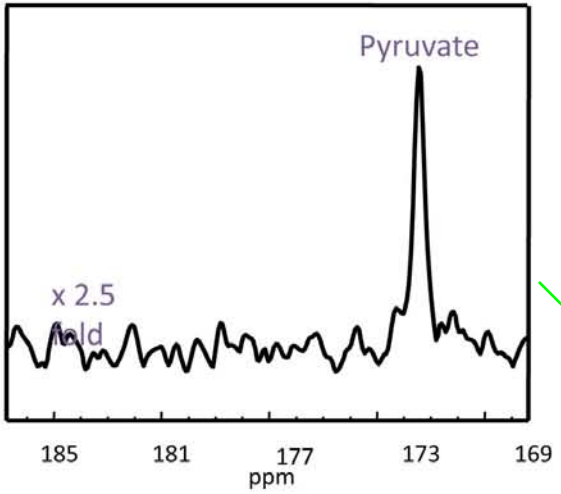
MERCK

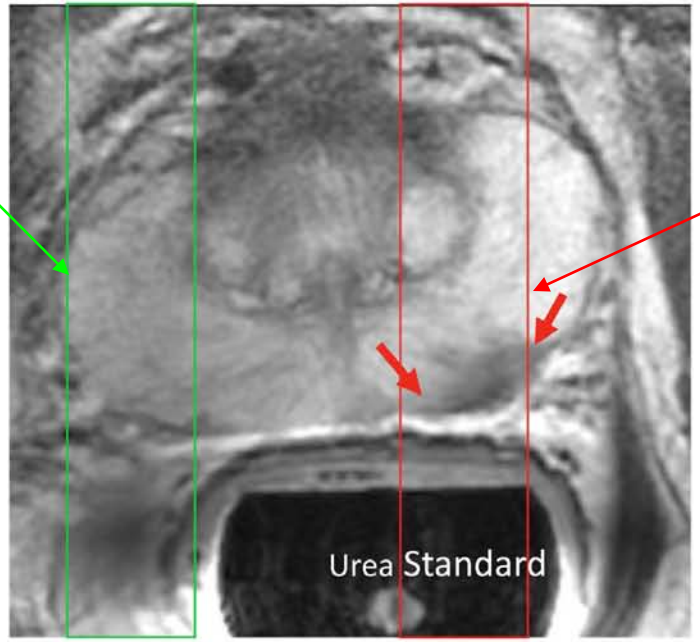
BRAINWATCH
Neurochemical Imaging

Pyruvate conversion in human prostate/ normal and malignant prostate tissue

Benign

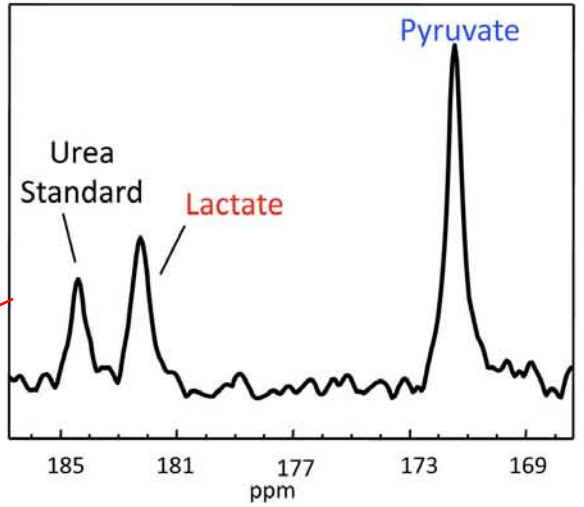
36 Seconds After Injection

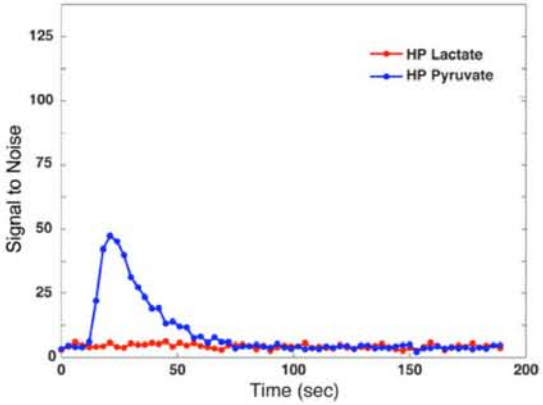




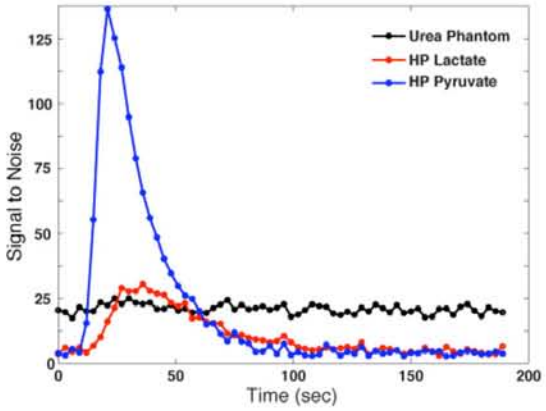
Cancer

36 Seconds After Injection



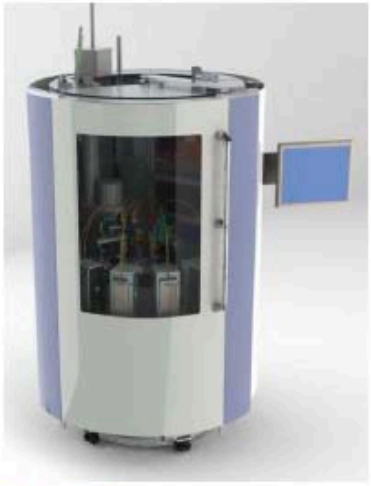


First Human Data:



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

THANK YOU