The Intramural Clinical Research Program-CTAC Nov 2011

Lee J. Helman, M.D.
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 and Resource Planning Checklist

#### STUDY IDENTIFICATION

<table>
<thead>
<tr>
<th>Branch / Lab:</th>
<th>PI:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Title:</td>
<td></td>
</tr>
</tbody>
</table>

#### STUDY IMPACT

1. How is this study consequential to the field?
   - [ ] Success likely to lead to a significant change in paradigm in treatment and/or research
   - [ ] Study would rarely be done elsewhere
   - [ ] 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:

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):
     - [ ] Publication in high impact journal
     - [ ] 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
     - [ ] 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?
   - [ ] If this study is part of an existing clinical program at CCR, explain how the study fits within the existing program:
   - [ ] 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:

#### STUDY UTILIZATION OF UNIQUE NIH RESOURCES

- [ ] 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
- [ ] 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)
- [ ] Other:

#### 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
   - [ ] If YES, please identify:

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:

12. Does this study or its correlates take advantage of the unique resources that exist at the NIH?
    - [ ] Yes
    - [ ] No
    - [ ] If YES, please check all that apply:
      - [ ] 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
      - [ ] 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)
      - [ ] Other:
Strategic Alignment & Resource Planning Checklist (SARP)

13. Can this study be completed within your existing branch resources?
   - Yes
   - No

14. If No, how will you obtain additional resources?
   - Yes: Outside funding
   - No: Additional CCR Resources

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: Personnel (e.g., Research Nurse, Data manager, Physician Extender)
   - Yes: Clinical Trial Support Supplies & Services (e.g., assays)
   - Yes: Pharmaceutical Agents
   - Yes: Laboratory of Pathology
   - Yes: Monitoring of SINGLE-SITE study when IND is held by the CCR
   - Yes: Monitoring of MULTI-INSTITUTIONAL study when IND is held by the CCR
   - Yes: Patient Recruitment
   - Yes: Other

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

Principal Investigator Signature

Date

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Section 2: 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

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?
   • 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 long-term commitment and tolerance for a lack of significant early clinical impact?
   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:
### To Be Completed By The Branch Chief

#### Identify the Strategic Fit of This Study (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

#### Confirm the Resource Requirements (Select All That Apply)
- [ ] 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
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
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
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
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

• 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 Wiltzout, 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 your current clinical research direction?
  - How could your 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

Branch
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D
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H
I
J

Major Opportunity
A
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C
D
E
F
G
H
I
J

POB
MOB
LHC
Metabolism
LP
LTIB
CIP
LCMB
RBB
Surgery

Branch
A
B
C
D
E
F
G
H
I
J

Major Opportunity
A
B
C
D
E
F
G
H
I
J

Analysis of Cross-Collaboration

Branch
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D
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G
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J

Major Opportunity
A
B
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E
F
G
H
I
J

POB
MOB
LHC
Metabolism
LP
LTIB
CIP
LCMB
RBB
Surgery
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

- NIH 74% (23 other IRPs)
- NCI 14%
- IRP Clinical Taps 9%
- NCI Clinical Taps 3%

Outpatient Visits

- NIH
  - NCI 37%

Inpatient Days

- NIH
  - NCI 37%

New Patients

- NIH
  - NCI 22%

CCR is one of 24 Intramural Research Scientific Programs at NIH
Snapshot of where we are
<table>
<thead>
<tr>
<th>CCR Labs/Branches</th>
<th># protocols by L/B</th>
<th>% of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOB</td>
<td>108</td>
<td>25%</td>
</tr>
<tr>
<td>POB</td>
<td>64</td>
<td>16%</td>
</tr>
<tr>
<td>SB</td>
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</tr>
<tr>
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<tr>
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<tr>
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</tr>
<tr>
<td>LHC</td>
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<td>0%</td>
</tr>
</tbody>
</table>

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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 (+Esophageal): 21
- Kidney/Bladder: 16
- Prostate cancer: 26
- Other Female: 12
- Breast Cancer: 24
- Neurological Cancers: 44
- Lymphatic/Hematologic: 68
- Multiple types of cancer: 72
Phase 0, 1%
Phase 1-2, 13%
Phase 1, 34%
Phase 2, 48%
Phase 3, 3%
N/A, 1%
Examples—where are we going
Pediatric Wild-Type GIST have SDH loss

<table>
<thead>
<tr>
<th>Pathologic Characteristics</th>
<th>Centrist n=18</th>
<th>Divergent n=34</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDHB IHC negative</td>
<td>0</td>
<td>34 (100%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SDH germline mutations</td>
<td>0/9</td>
<td>8/25 (32%*)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Keith Killian¹, Su Young Kim², Markku Miettinen³, Carly Smith², Maria Tsokos³, Martha Quezado³, William I. Smith, Jr.⁴, Mona Jahromi⁵, Robert L. Walker¹, Laura Jones¹, Joshua D. Schiffman⁵, Maureen J. O’Sullivan⁶, Constantine Stratakis⁷, Lee Helman², Paul Meltzer¹*, 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 hypermethylation
Fumarate Hydratase- and Succinate Dehydrogenase-Deficient Kidney Cancer: Warburg Model of Cancer

[Diagram showing metabolic pathways involving glucose, glycolysis, pyruvate, and the tricarboxylic acid cycle with annotations for HIF-α accumulation, VEGF, GLUT1, PHD, Fumarate, Succinate, FH, SDH, and 2-OG.]
Succinate Dehydrogenase
SDH-RCC

• Pheochromocytoma

• Paraganglioma

• Renal cell carcinoma

• Pediatric GIST- PNAS 2011
HIF1α

Fe²⁺

PHD2

Ascorbate

HIF1α

Fe²⁺

PHD2

Ascorbate

HIF1α

OH

2OG

2OG

2OG

2OG

α-ketoglutarate

Succinate

2OG

O₂

O₂

O₂

CO₂

Succinate
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 inhibit the disassociation of the PHD2 bound succinate and fumarate could then bind instead of \(\alpha\)-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 hydroxymethylcytosine, 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
The metabolic pathways of cells of endogenous/injected pyruvate. The metabolic products that can be imaged are shown in red.
<table>
<thead>
<tr>
<th>Site</th>
<th>Contact</th>
</tr>
</thead>
<tbody>
<tr>
<td>UCSF</td>
<td>Sarah Nelson</td>
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<td>George Radda</td>
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<td>Clermont-Ferrand</td>
<td>Betty Jean</td>
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**Academia**

**Industry**

**Government**

**National Institutes of Health**

**TRANSLATIONAL RESEARCH**

**Medical Imaging**

**NATURE**

**MRM**

**GE CONFIDENTIAL**

**Global Excitement**

**Open Innovation Leverage**

**Clinical**
Pyruvate conversion in human prostate/normal and malignant prostate tissue

Pyruvate is converted to lactate in malignant tissue.

First Human Data:
GE Healthcare Clinical Hyperpolarizer

- 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

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

<table>
<thead>
<tr>
<th>$^{13}$C labeled Tracer</th>
<th>Metabolic product</th>
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<tr>
<td>Pyruvate</td>
<td>lactate (aerobic glycolysis)</td>
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<tr>
<td></td>
<td>bicarbonate (ox phos)</td>
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<tr>
<td></td>
<td>alanine (transamination)</td>
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<td></td>
<td>oxaloacetate (carboxylation)</td>
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<tr>
<td>Fumarate</td>
<td>Malate</td>
</tr>
<tr>
<td>Succinate</td>
<td>Fumarate</td>
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<td>Glutamine</td>
<td>Glutamate</td>
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<tr>
<td>Glutamate</td>
<td>$\alpha$-Glutarate</td>
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<td>Acetyl-CoA</td>
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<tr>
<td></td>
<td>Acetyl carnitine</td>
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<tr>
<td>Choline ($^{15}$N)</td>
<td>Phosphocholine</td>
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THANK YOU