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Dear Participants:

Thank you for your continued interest in the development of the NCI-CCR Major Opportunities and your participation in the upcoming Major Opportunities Retreat. In preparation for the retreat, the Clinical Strategic Planning Committee has put a packet of information together for your review.

Included in the packet are:

- The Clinical Research Mission of the Center for Cancer Research
- Definition of a Clinical Major Opportunity (MO)
- Agenda & Retreat Format
- Overview of CCR Protocol Reengineering Initiative
- Biosketches of Protocol Reengineering Collaborators
- CCR Clinical Strategic Planning Committee Membership
- Summary of the Eight (8) Clinical Major Opportunities to Be Presented
    - One evaluation form for each MO (please bring with you to the retreat)

Please complete the evaluation form for **each MO prior to the retreat**. Please print and bring the completed evaluation forms to the retreat as these will be collected to be given the respective MO teams. If you would like a Word version of the form or have any questions, please feel free to contact Steven Cheng (chengs@ohsu.edu).

We look forward to your valuable contributions on October 21.

# National Cancer Institute - Center for Cancer Research (CCR)

## CCR CLINICAL RESEARCH MISSION

- Engage outstanding researchers in consequential investigator-initiated clinical research in a culture of close interaction between basic and clinical science.
- Provide the flexible funding necessary to support innovative, high-impact bench-to-bedside research through access to the largest publically-funded research center in the world.
- Collaborate with world-leading researchers across the NIH and throughout the extramural community.

## WHAT IS A CLINICAL MAJOR OPPORTUNITY?

A Major Opportunity (MO) is a fundamental problem in oncology, with broad applications across multiple clinical and laboratory branches, the solution to which would lead to a fundamental paradigm shift in the treatment of patients. It should be something where the CCR has unique and enabling expertise, capabilities, and/or direct patient populations. Ideally, it should link a discovery from an NIH/NCI laboratory with the ability to evaluate it in the CCR clinical population.

The purpose of an MO is to focus clinical efforts over the next 3-5 years to achieve specified goals and deliverables that, when achieved, would be considered a major leap forward by the entire oncology community. Clinical MO's are designed to foster cross collaboration across branches and demonstrate that clinical research efforts are broader than any single group. Finally, they are meant to be "stretch-goals" in that there is a high likelihood of failure but the goal is worth the effort.

Clinical Major Opportunities to be discussed at the retreat:
Thirty MO's were submitted in addition to the six exemplars provided. These where reviewed by the CCR Clinical Strategic Planning Committee and eight were selected to be presented. They are:

1. *Inflammation-induced Therapy Effects In Cancer with Limited Therapeutic Options*
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. *Intersection of Immunotherapy and Molecularly Targeted Therapy*
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*

Important Note: There are not sufficient resources to support all proposed MOs. However, as each is an interesting concept, we encourage the MO teams to continue their cross-collaboration dialogue.

# OVERARCHING GOALS OF THE MAJOR OPPORTUNITY RETREAT

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

## AGENDA

| | | |
|---|---|---|
| 8:30 to 9:15 | Introduction,<br>Framework of the Retreat, General Questions | Helman /<br>Wiltrout / Dilts |
| | | |
| 11:25 to 11:50 | Review of the Process<br>Lunch and Q&A | |
| | | |
| 2:00 to 2:15 | Break | |
| | | |
| 4:25 to 5:00 | Presentation of the Evaluation / Q&A<br>Next Steps | Helman / Dilts |

### REVIEW SESSION FORMAT

| |
|---|
| |
| MO #1 (5 min Presentation of idea; 10 min Group Question & Clarifications) |
| |
| MO #3 (5 min Presentation of idea; 10 min Group Question & Clarifications) |
| |
| Table discussions of MOs (~15 min each)<br>• Perception<br>• Strength & Weakness<br>• Integration with Current Research |
| |
| • Reporting out |

## OVERVIEW OF THE PROTOCOL REENGINEERING INITIATIVE

Three years ago, the Center for Cancer Research (CCR) launched a broad effort to examine our clinical trials program, identifying and addressing challenges, both operational and strategic, with the goal of bringing the most promising research to the clinic faster and ultimately serving as a model in the conduct of clinical research for the national cancer program. Over this time, there have been many improvements across multiple aspects of the organization including:

- Unification of standard operating procedures (SOPs) for scientific review across all clinical branches
- Creation, implementation, and monitoring of measures and metrics that now allow real-time monitoring of our portfolio of clinical trials, including development time, accrual, and publication.
- Establishment of a centralized protocol support office
- Development of the CCR clinical vision and implementation of a process to strategically align every clinical trial to this vision
- Implementation of an annual survey of CCR clinical program staff.
- Engagement of the Board of Scientific Counselors in this process.
- Assessment and analysis of costs related to clinical trials across CCR

## NCI-CCR COLLABORATORS

**David Dilts, PhD, MBA, CMA**

Dr. Dilts is Director of Clinical Research for the Knight Cancer Institute and Professor of Management at the Oregon Health & Science University and Co-director of the Center for Management Research in Healthcare (cMRHc). cMRHc has as its mission the exchange of knowledge between the management research and healthcare to dramatically impact practice of medicine. One research stream, funded by the NCI, is to apply management principles to significantly reduce the time and steps required to open oncology clinical trials. This research has completed in-depth examinations of four NCI-designated comprehensive cancer centers, two major oncology cooperative groups, and the NCI Cancer Therapy Evaluation Program and the NCI CIRB.

His work has been published in nearly 200 articles, conference papers and presentations, book chapters, books and monographs, including in *Clin Cancer Res, J Clin Oncology, J of Med Info Assoc, Health Economics, Medical Decision Making,* and *Tissue & Cell*. He is an Associate Editor of two primary journals in Operations Management: *J of Ops Management* and *J of Supply Chain Management.* Next week he will receive an NIH Merit Group Award for his contribution to *AccrualNet* a novel tool that integrates knowledge on the problem of low accrual to oncology clinical trials.

**Steven Cheng, PhD**

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# CCR CLINICAL RESEARCH STRATEGIC PLANNING COMMITTEE MEMBERSHIP

## Committee Membership

Lee Helman, MD
Deborah Citrin, MD
William Dahut MD
Giuseppe Giaccone, MD, PhD
Ronald Gress, MD
Ola Landgren, MD, PhD
Marston Linehan, MD
Steven Rosenberg, MD, PhD
Brigitte Widemann, MD

## External and Ancillary Members

Robert Wiltrout, PhD
James Doroshow, MD
David Dilts, PhD, MBA
Steven Cheng, PhD
Melissa Bronez, MPH
Caryn Steakley. RN

# MO 1: INFLAMMATION-INDUCED THERAPY EFFECTS AND CANCER WITH LIMITED THERAPEUTIC OPTIONS

**Lay Summary:** Inflammation is known to impact the therapeutic effects of cancer treatment. Research conducted at the NCI has also demonstrated that inflammation shapes the tumor microenvironment, activating processes that are a common root cause of disease progression in solid human tumors. This proposed research targets cancers with limited therapeutic options by aligning the existing expertise and synergy across multiple NCI CCR research and clinical groups, to seek a three-armed program of impact that will bring inflammation and stress modulators into clinical trials, build a novel systems biology-based platform to advance early cancer detection markers and immunotherapeutics into clinical application, and target cancer induced co-morbidities that deprive patients of optimal care, quality of life, and clinical trial opportunities. NCI researchers have made landmark discoveries describing the deleterious role of inflammation in human cancer (e.g., liver and lung), linking inflammatory processes to metastasis, cancer stem cell biology and therapy effectiveness, and pre-mature deaths among cancer patients.

**Uniqueness (to the cancer community; why should it be attempted at CCR?):** The proposal is a rare opportunity because NCI, unlike other institutions, has extensive expertise in leading transdisciplinary and translational research covering inflammation and cancer, having made landmark discoveries in this field by integrating cancer biology, immunology, chemistry and biochemistry with novel omics-based approaches and innovative imaging technologies, and also applying pioneering pre-clinical models. Also, CCR branches have demonstrated experience and expertise in clinical trials that incorporate sophisticated biomarkers and innovative biological concepts derived from pre-clinical studies. Implementation of these trials will leverage existing collaborations between experimental and clinical groups with the rapid translation of novel biological concepts from the bench to the bedsite.

**Overarching Strategy:** Create a new inter-disciplinary community with expertise in pre-clinical models and patient care to advance inflammation and stress modulators into human studies, to validate models in patients and to bring them into clinical assessment, and to establish excellence in systems biology and imaging technology to advance predictive biomarkers and novel targets for guidance of inflammation-regulated therapy.

**Anticipated Timeline:**

**Year 1-3:** Characterization and testing of inflammation and stress modulators in pre-clinical models of lung and ovarian cancer and in human clinical material. Extension to renal and liver cancer at a later timepoint, or when liver cancer patients can be recruited into clinical trials. Development of a systems biology platform to identify predictive biomarkers and therapy targets with the recruitment into the project of the relevant expertise of CCR, intramural, and extramural investigators.

**Year 3-5:** Development of clinical trials to evaluate inflammation and stress modulators in cancer therapy and predictive biomarkers to guide patient selection/therapeutic intervention. Initial trials in lung and ovarian cancer will use available inflammatory modulators. Trials in subsequent years can also include renal cancer patients and will utilize compounds/drugs that are at earlier stages of development or capitalize on knowledge gained in first trial to guide choice of drug in second trial. Scientific goal should reflect improvement in clinical outcomes as well as decreased morbidity due to decreased cachexia.

**Targeted populations:** Cancers with limited therapeutic options (lung, kidney, ovarian, liver), with rare patient subsets (a NCI unique opportunity), targeting both systemic and tumor-microenvironmental inflammation.

**Scientific and Therapeutic Goals:** Dissect immune microenvironment; identify early disease biomarkers and predictive biomarkers of therapy response with our systems biology platform; characterize inflammation and

stress modulators and their targets for cancer therapy; validate models in patients and bring them into clinical assessment.

**Sample of activities on-going within CCR/NIH:** The NCI Cancer and Inflammation Program (CIP) is spearheading research defining how local and systemic inflammation influences therapy effectiveness and cancer co-morbidities and is affected by the interaction of the organism with the commensal flora. CCR basic science and clinical laboratories (e.g., LHC, LEC, LCBG, Radiation Biology Branch) are examining the influence of inflammatory processes on disease progression and outcome. These efforts will partner with the Trans-NIH Center for Human Immunology that has established a system biology infrastructure to bring markers of local and systemic inflammation/immunity into clinical development.

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## MO 1: INFLAMMATION-INDUCED THERAPY EFFECTS AND CANCER WITH

**Perceptions from the external and internal oncology community**

Assuming the scientific objectives are met, 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)?

**Major Opportunities Strengths and Potential Improvements**

In what ways could this MO be strengthened to foster cross-collaboration across branches?

**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?

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# MO 2:MATRIX DRUG SCREENING FOR COMBINATION THERAPIES IN CANCER

**Lay Summary:** Many therapeutic agents targeting signaling pathway components exhibit single agent activity in molecularly defined cancers. However, relapse from single agent therapy is common, and might be circumvented by combination therapies aimed at more than one essential pathway in a cancer cell. Moreover, a single agent may evoke compensatory pathways that mitigate its effect, and concurrent blockade of these compensatory pathways may prove synergistic. High-throughput screening of small molecules remains a primary mechanism for the discovery of novel pharmacological agents. The same screening technologies are being put to task in the screening of approved drug libraries and matrix screening for synergistic combination therapies. The screening of agents for synergism, however, requires the ability to screen agents at a range of concentrations. The NIH Chemical Genomics Center (NCGC), NHGRI has developed "quantitative high throughput screening" (qHTS) , in which all compound library members are screened in a dose-response fashion. Screening in matrix format requires that each individual compound be tested in a concentration range that will identify potency shifts as well as efficacy enhancements. Informatics methods have been developed that differentiate between antagonistic, additive and synergistic effects in an automated fashion. Promising synergistic drug combinations would form the basis of new clinical trial proposals in the CCR.

**Uniqueness (to the cancer community; why should it be attempted at CCR?):** This opportunity brings together three strengths within the CCR and NIH. First, the CCR has expertise in several cancer types, both in the laboratory and the clinic. Second, the NIH Chemical Genomics Center has exceptional capability in high-throughput screening, involving robotic infrastructure for the delivery of compounds in miniaturized cell cultures in 1586 well plate format. This capability is not available in most academic centers. Finally, the CCR is ideally positioned to exploit the results of these matrix drug screens by initiating phase I/II trials with particularly synergistic drug combinations in the NIH Clinical Center. A particular strength of the Clinical Center is to perform pre-treatment and on-treatment biopsies to assess molecular parameters that are relevant to drug mechanism of action as well as to image tumors to assess response.

**Overarching Strategy:**

**Phase 1** - Complete pilot screening project involving selected cancer subtypes using existing library of ~100 drugs that are clinically available. Follow up synergistic combinations with RNA interference and secondary assays of cellular signaling, gene expression profiling changes and activity in xenograft models.
**Phase 2** - Expand the NIH Chemical Genomics Center compound library to include ~300 drugs that are approved for clinical use, are in early phase clinical trials, or that target key signaling/regulatory pathways.
**Phase 3** - Search for synergistic drug combinations with expanded compound library in cell line panels that represent the major tumor types of interest to CCR researchers.
**Phase 4** - Initiate phase I/II clinical trials of selected synergistic drug combinations in the NIH Clinical Center

**Anticipated Timeline:**

**Phase 1** - 6 months. Pilot matrix drug screening complete in lymphoma cell lines. Follow-up studies underway.
**Phase 2** - 6 months. Expand compound panel - requires acquisition of drugs from commercial vendors and/or contract synthesis
**Phase 3** - 1-2 years. Test multiple cancer types for which well validated cell line models exist that bear known recurrent mutations and/or are phenotypically good models of the in vivo cancer.
**Phase 4** - 5 years. Pursue agreements with companies to initiate phase I/II trials of drug

**Targeted populations:** Combinatorial matrix drug screening is an enabling technology that will cross virtually all CCR Laboratories and Branches

**Scientific and Therapeutic Goals:**

1. Identify compounds targeting signaling/regulatory pathways that exhibit synergistic toxicity for particular molecular subtypes of cancer.
2. Understand the molecular basis of observed pathway synergism with respect to underlying oncogenic abnormalities that initiate pathway dependence.
3. Evaluate synergistic drug combinations in phase I/II clinical trials

**Sample of activities on-going within CCR/NIH:** The Staudt laboratory has initiated a pilot matrix screening test of cell line models of the ABC subtype of diffuse large B cell lymphoma. A panel of ~100 drugs has been screened in all pairwise combinations. Highly synergistic drug combinations have been discovered that are now being validated. This constitutes part of the phase I testing of the NCGC platform.

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## MO 2: MATRIX DRUG SCREENING FOR COMBINATION THERAPIES IN CANCER

**Perceptions from the external and internal oncology community**

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(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)?

**Major Opportunities Strengths and Potential Improvements**

In what ways could this MO be strengthened to foster cross-collaboration across branches?

**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?

## MO 3: TREATMENT OF CANCERS BASED ON DRIVERS MUTATIONS INDEPENDENT OF HISTOLOGY OR SITE

**Lay Summary:** Traditionally cancer is treated based upon the site where the tumor occurs, for example, prostate cancer is treated by prostate treatment, lung cancer by lung treatments, etc. However, recent research has shown that there are molecular similarities with the cancers that are independent of the site of the tumor. For example, the P53 tumor suppressor is mutated in 50% of human cancers and HER2, BRAF, and RAS gene mutations are observed across multiple tumor types. This Major Opportunity seeks identify mutual mutations in pathways with the goal of discovering individual treatment alternatives that are applicable irrespective of disease site If successful, this research will result in a major paradigm shift in treating patients based on common therapeutic treatments based on specific pathways that transverse across disease types.

**Uniqueness (to the cancer community; why should it be attempted at CCR?):** There are multiple reasons for why the CCR can uniquely undertake this research. These include:

- The ability to recruit patients from across the country to participate in clinical trials.
    - This allows us to study efficiently rare populations based upon biomarker driven classifications
- Molecular imaging facility to develop treatment-specific probes for real-time monitoring of therapy.
- Close collaboration with DCTD tumor characterization core in Frederick that will allow us to develop clinically relevant biomarker assays, critical for these proposed studies
- Strong interactions between basic and clinical scientists developing biomarkers across tumor histologies

**Overarching Strategy and Anticipated Timeline:**

Year 1: Prioritize the top 3 driving pathways to study

- Consider expertise of CCR-IRP basic and clinical investigators; Availability of targeted agents, imaging agents
- Develop and refine critical biomarker signatures predictive of response to specific agents across tumor types
- Profile pathway dysregulation: gene expression, DNA copy number variation, and exome sequencing for mutational analysis

Year 2: Develop clinical trial design and clinical process flows that coordinate tissue acquisition and analysis across multiple tumor types

- Assure that biomarker assays developed will perform in a clinically relevant timeframe
- Work with multiple clinic directors to coordinate and harmonize sample collection

Year 3: Implement clinical trials to test three pathways identified above

Year 4-5: Analyze conditions under which treating molecular drivers across tumor sites is more or less effective than traditional methods

- Identify mechanisms of *de novo* or acquired resistance to targeted treatment
- Using results of clinical studies, re-evaluate predictive biomarkers

**Targeted populations:** Cancer patients with common molecular biological drivers irrespective of tumor site.

**Scientific and Therapeutic Goals:**

- Overarching hypothesis: Constitutively deregulated signaling pathways define unique treatable subsets across histological cancer subtypes
- Problem: What is the minimal information necessary to determine equivalence of pathway dependency across tumor types
- Overarching strategy: Identify testing strategies that would allow us to assign disparate histological tumor types to similar or identical pathway dependency
    - Survey the known pathway dependencies already discovered by CCR investigators, associated with specific tumor types
    - Apply this knowledge in the clinic to evaluate its performance across recurrent tumor subtypes

**Sample of activities on-going within CCR/NIH:**

- Biomarker/signature development, pathway, tissue specificity:
    - Ji Luo (MOB) – RAS pathway, colorectal cancer
    - Lou Staudt (MB) – NF-kB pathway, lymphoma
    - Christina Annunziata (MOB)– NF-kB pathway, ovarian/uterine cancer
    - Phil Dennis (MOB) – PTEN/PI3K/AKT/mTOR, lung cancer
    - (others for discussion)
- Molecular imaging development:
    - Pete Choyke (Molecular Imaging Program)
- Molecular profiling:
    - Paul Meltzer (Genetics Branch)
- Pathway/signature/molecular network development:
    - George Wright (Biometrics Research Branch)
- Proteomics development:
    - Elise Kohn (MOB), Liang Cao (GB), Paul Goldsmith (OD?)
- Investigational New Drugs:
    - J. Wright, N. Takebe, P Ivy, etc. (CTEP)

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## MO 3: TREATMENT OF CANCERS BASED ON DRIVERS MUTATIONS INDEPENDENT OF

**Perceptions from the external and internal oncology community**

Assuming the scientific objectives are met, how would this MO "change the face of cancer"?
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**Major Opportunities Strengths and Potential Improvements**

In what ways could this MO be strengthened to foster cross-collaboration across branches?

**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?

# MO 4: MONITORING AND MANIPULATING THE EPIGENOME IN HUMAN CANCER

**Lay Summary:** Cancer therapy fails in as much as 90% of patients for several tumor types largely due to metastasis and treatment resistance. A surprisingly high fraction of genetic variants associated with several cancers have recently been identified in gene families encoding enzymes or complexes with chromatin modifying activities, and epigenetic instability has been shown to contribute significantly to cancer. Cancer population studies increasingly demonstrate that many cancer associated genetic loci occur in regulatory elements critical to cell growth control. Our approach encompasses the entire landscape of the expressed genome in humans using recent advances developed at CCR. A two-pronged approach will be used: (1) the new methods recently developed by CCR will be used to characterize the genome sequence and global chromatin landscape in tumors and cell lines which will allow a genome wide understanding of the impact from high frequency cancer lesions in chromatin and DNA modifiers. By coordinating these analyses with studies on the impact of existing, or newly developed, drugs targeted to epigenetics, this will allow an understanding of the global impact of a given drug, and the development of improved compounds. (2) the entire spectrum of chromatin and DNA modifications will be examined in patient tumors. This novel approach has never been attempted, and offers the possibility of identifying aberrant regulatory networks not previously suspected, therefore identifying the root causes of cancer and therapy failure. This approach is likely to enable a radically more effective way of understanding and treating a patient's cancer.

**Uniqueness (to the cancer community; why should it be attempted at CCR?):** The CCR has a unique opportunity as it can have a coordinated activity between clinical and basic science groups in the CCR which includes adult and pediatric cancers. Several groups existing CCR groups, including Dean/Nickerson, Thiele, Khan, Apolo, Bates, Wayne, Gottesman, and Ambudkar, have large scale data sets on multiple tumor systems, and thus can provide patient material, cell lines, and access to patients in clinical trials for both standard agents and agents targeting epigenetic modifications. The Hager group has pioneered the genome wide analysis of DNase I hypersensitivity sites (DHS) by deep sequencing (DHS-seq). This technique provides a robust genome-wide description of chromatin structure, and active regulatory elements. The unprecedented power of this approach has yet to be therapeutically exploited. The Dean group is actively involved in sequencing tumor exomes, identifying mutations in chromatin remodeling genes, and functionally characterizing these lesions. The Thiele group studies epigenetic dysregulation in pediatric neuroectodermal tumors and its normalization by retinoids, HDACs and inhibitors of EZH2 (Histone 3K27 methylase). In addition the clinical center carries out a number of clinical trials on cancers with chromatin remodeling gene mutations (Apolo-Bladder; Wayne-pediatric ALL) and has been a leader in Phase I trials of epigenetic modifiers (Bates–Romidepsin, MS-275; Pediatric PET section-retinoids) The unique investigatory nature of the Clinical Center, in combination with world class molecular biology, informatics and chromatin biology in CCR makes this proposal uniquely suited to the CCR.

**Overarching Strategy:** The strategy to understand the epigenome of cancer and apply this to therapy will involve:

1. Establish the digital-DHS landscapes in tumor cell lines and normal tissue and upon experimental manipulation including siRNA knockdown and re-expression of wild type genes. Apply this characterization to tumors of patients in clinical trials of standard and new agents to understand treatment response/failure.
2. Characterization of the chromatin and DNA modifying genes mutated in selected cancers.
3. Analysis of changes in digital-DHS landscape following treatment of the cell lines with therapeutic agents in clinical use or by new molecules identified in chemical screens.
4. Establish the cohort of critical DHS elements active in a given tumor type. Develop an array capture set targeted to these elements to limit future sequencing in to the relevant regulatory subsets strategy for applying to clinical materials.
5. Apply targeted sequencing and digital-DHS to biopsy samples to allow the strategy to be applied to *real life clinical situations* where tumor material is scarce or primary tumor is heterogeneous. Focus on patients that respond to therapy vs. failures to obtain signatures of response for individualized therapy.

6. Develop tools to examine histone modifications altered by somatic mutations identified in tumors and examine functional implications on gene expression and cell physiology.

Development of targeted agents against mutated or dis-regulated genes or pathways involved in epigenetic regulation.

**Anticipated Timeline:** A timeline is given for bladder cancer, but similar studies are in place and will follow in neuroblastoma, kidney and/or pediatric ALL and breast cancer. Additional cancers would be selected to initiate in year 2.

**Year one**: Perform digital-DHS on normal bladder tissue and bladder cancer cell lines with existing exome sequence, gene expression and drug sensitivity data. Repeat digital-DHS on selected cell lines with high-frequency mutations (UTX and MLL family) before and after gene replacement or knock down. Correlate DHS patterns with specific epigenetic modifications predicted to be dysregulated by genetic alterations. Initiate assay development to detect and quantitated specific chromatin modifications predicted to be altered by somatic mutations. Perform exome sequencing/digital-DHS on a set of patient tumors and develop protocols for serial biopsy of patients with recurrent disease. Use pharmaceutical company or internally developed agents (DZNep) to evaluate activity and normalization or alterations in tumor associated digital-DHS.

**Year two:** Expand sequencing and digital-DHS on bladder cancer and normal tissue to compare results to cell lines. Develop a targeted selection array to pull down and sequence the loci subject to DHS in bladder and test methods for using frozen tissue and clinical material. Continue pre-clinical development and testing of EZH2 targeted agents and develop pro-drugs to find compounds with improved pharmacokinetics. Develop targeted resequencing of frequently mutated bladder cancer genes. Develop clinical protocol to collect serial biopsies for digital-DHS. Perform digital-DHS on serial biopsies of bladder cancers in NCI clinical center patients using methods in common use in cancer diagnostics. Expand gene resequencing and targeted digital-DHS to large cohort of bladder cancer patients. Develop clinical protocols on 2 other cancers with chromatin remodeling defects (neuroblastoma, kidney, ALL, APL, liver, ovarian, breast or prostate) depending on availability of patients and biopsy/tumor samples and epigenetic therapy.

**Year three-four:** Initiate clinical studies of cancers 2 and 3 with emphasis on response to therapy, metastasis and relapse or therapy failure. Design trial to prospectively apply sequencing/digital-DHS. Correlated gene sequence, DHS profile, clinical parameters and outcomes. Move existing and new therapeutic agents into pre-phase 1 and phase 1 clinical trials. Examine chemical agents that restore or target specific chromatin modifications in tumor cell lines Sequence genes of interest in patient tumors to match somatic mutations to therapeutic response.

**Year five:** Launch prospective clinical trial using sequencing and landscapes to select most likely effective therapy for patient. Design prospective trials for cancers 2 and 3. Expand characterization of chemical agents identified in small molecule screens to multiple tumor systems.

**Targeted populations:** Bladder cancer-6 known chromatin genes mutated (UTX, ARID1A, CREBBBP, EP300, MLL, MLL3), EZH2, known drugable target; Kidney cancer-PBRM1, a known sensor of histone modification; Pediatric ALL-ARID5B association; Neuroblastoma- EZH2 dysregulation/retinoid therapy; Triple Negative breast cancer (from Jackson Labs xenografts)/BRCA2 (recently shown to be involved in chromatin remodeling.

**Scientific and Therapeutic Goals:** To characterize the gene mutations and active sites of chromatin across the genomes of cancer cells and generate a digital-DHS map of cancer to develop root cause biomarkers. Understand how these genome maps change with tumor subtype, evolution, therapy exposure and correlate with mutations in specific chromatin modifying genes. To apply these chromatin patterns to clinical trials and determine biomarkers for therapy response/resistance and better understand the mechanisms of action of epigenetic therapies (demethylation, HDAC inhibition) and targeted epigenetic agents. Identify therapeutics that will return the cancer chromatin landscape to a more normal profile, or which sensitize the tumor cell to therapy, eliminating cancer metastasis and treatment failure.

**Sample of activities on-going within CCR/NIH:** See description in the uniqueness section

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## MO 4: MONITORING AND MANIPULATING THE EPIGENOME IN HUMAN

**Perceptions from the external and internal oncology community**

Assuming the scientific objectives are met, 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)?

**Major Opportunities Strengths and Potential Improvements**

In what ways could this MO be strengthened to foster cross-collaboration across branches?

**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?

## MO 5: INTERSECTION BETWEEN IMMUNOTHERAPY AND MOLECULARLY-TARGETED THERAPY

**Lay Summary:** Burgeoning data from sequencing the genomes of cancers opens new opportunities to fashion unique and personalized treatments based on this information. Although most current efforts are seeking drugs to target specific "driver mutations", the existence of such aberrant proteins in cancers opens up potent strategies to target them immunologically, using the same data being generated by sequencing. Sharing this information and developing ways to mount immune responses to these mutated proteins, as well as exploring the interaction between drug-oriented strategies and immunotherapy is the main theme of this initiative.

**Uniqueness (to the cancer community; why should it be attempted at CCR?):**

- The CCR has world-class expertise in cytokine discovery and therapy, tumor immunology and T-cell therapy and vaccine development and translation—all of the major areas of clinical immunotherapy
- CCR investigators have been instrumental in identifying critical mutations and pathways important to tumor growth and metastasis
- CCR investigators are also active in the development and application of small molecules targeting genetically-identified critical tumor pathways
- CCR collaborators are already actively sequencing cancer genomes for mutations and biomarkers relevant to immunotherapy

**Overarching Strategy:** Several lines of study, in particular rapid sequencing of cancer genomes, are identifying pathways critical to the behavior of an individual's cancer. Once identified, these can be targeted by pharmacological interventions or by immunotherapy (especially mutations seen as 'foreign' proteins). The rapid and rational coordination of these three components, target identification, drug selection and immunological attack could result in personalized therapies of the greatest efficacy

**Anticipated Timeline:**

**Year 1-3:** Defining and optimizing approaches to target identification, particularly limited genetic sequencing of cancers. Develop methodologies to sensitize or immunize patients against multiple candidate peptides/antigens. Preclinical studies on interactions of small molecules and immune cells.

**Year 2-3:** Pre-clinical and initial clinical testing of concept using selected patients with widely-shared known tumor-specific mutations or pathways crucial to metastases or tumor survival.

**Year 4-5:** Phase I and II studies of personalized therapies using immunological, pharmacological or combined modalities.

**Targeted populations:** This approach could be applicable to any patient population with advanced cancer. Initial efforts would concentrate on cancers with a limited number of known driver mutations to test the concept.

**Scientific and Therapeutic Goals:** We wish to exploit new individualized information about critical tumor pathways by applying and integrating tailored pharmacological and immunological interventions with the goal of complete tumor eradication.

**Sample of activities on-going within CCR/NIH:** Surgery Branch is collaborating with NHGRI to sequence the genome of multiple melanoma samples to identify important mutations and biomarkers relevant to immunotherapy. Vaccine Branch and LTIB have been identifying target antigens and developing vaccine platforms now in clinical testing. MOB, UOB and SB have experience in the use of small molecules and antibodies to target pathways known to be active in several malignancies. Surgery Branch has multiple active protocols targeting specific antigens with adoptive cell transfer using genetically re-targeted T-cells. ETIB has immunotherapy and combined modality experience in the context of allotransplantation.

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## MO 5: INTERSECTION BETWEEN IMMUNOTHERAPY AND MOLECULARLY-

**Perceptions from the external and internal oncology community**

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Could this MO be integrated with **your** current clinical research direction?

How could **your** research stream improve this MO?

## MO 6: ATTACKING CANCER BASED ON ITS METABOLIC BASIS

**Lay Summary:** Certain tumor cells are known to have a fundamentally altered metabolism compared to normal cells. If this change, termed aerobic glycolysis, can be better characterized, it will provide a unique opportunity to develop novel therapies for such cancers, which include GIST, Kidney, Prostate, CNS, and other tumors characterized by aerobic glycolysis

**Uniqueness (to the cancer community; why should it be attempted at CCR?):** The NCI has expertise in the pre-clinical as well as clinical studies for the development of novel imaging technology to evaluate the metabolic basis of cancer as well as for identifying new targets for therapy and monitoring effect of therapy. The fundamental basis for C13 Hyperpolarized Pyruvate imaging was developed in CCR's Radiation Biology Branch. This expertise spans multiple branches and programs, including Urologic Oncology, Molecular Imaging, Radiation Biology, Pediatric Oncology, and Neuro Oncology. This collection of pre-clinical, clinical and imaging expertise is unique in comparison to research communities across the United States.

**Overarching Strategy:** The overarching strategic approach is to combine and share the knowledge of intramural investigators with expertise in target diseases (genetics, molecular biology, imaging, tumor models, clinical trial development). At a more detailed level the strategy is composed of 3 elements:

**Pre-clinical evaluation** Detailed understanding of the presentation, phenotype, natural history, molecular biology, and genetics of cancers characterized by aerobic glycolysis. Evaluation of the metabolic profiles of tumors characterized by aerobic glycolysis as well as those with mutations of succinate dehydrogenase and fumarate hydratase as well as isocitrate dehydrogenase will lead to the identification of targets for treatment and development of effective therapies.

Characterizing the metabolic abnormalities in cancer can be best and most efficiently answered using stable isotope tracers coupled with metabolomics technologies, e.g. Stable Isotope Resolved Metabolomics or SIRM. Metabolic characterization of human tumor cell lines has identified new paradigms in metabolic reprogramming that may account for unusually aggressive tumor behavior. In particular, using $^{13}C$ glucose and $^{13}C/^{15}N$ glutamine as tracers, the sources of carbon and nitrogen and their transformation pathways for energy production and biosynthesis of glycogen, nucleotides, and both the glycerol and fatty acyl chains of a large number of lipids have been identified. This type analysis is leading to the design of anticancer agents that target the metabolic growth susceptibilities of cancer cells, which can be tested readily in cell culture and animal models. Furthermore, we expect that SIRM analysis of "Warburg" slices of resected primary tumors at the Clinical Center should provide the most direct translational information about the influence of the cancer microenvironment and target tissue response to anticancer agents without the complications from whole body interactions.

**Imaging** Conventional MRI provides high-resolution anatomic images utilizing NMR signals from water protons, which are abundant in tissue. Until recently, it was not possible to provide metabolic images using MRI by mapping organic molecules because of their lower concentrations, which are below the detection limits. However, with the recent development of novel hyperpolarization methods of $^{13}C$ to significantly enhance sensitivity of detecting organic molecules, MRI can now be used to map tissue metabolic processes such as oxidative phosphorylation and aerobic glycolysis. Pyruvate is a tracer most suitable for enhanced sensitivity using the hyperpolarization procedure. The majority of the pre-clinical and clinical studies have utilized $^{13}C$ labeled pyruvic acid. $^{13}C$-labeled pyruvic acid tracers can be used to monitor tumor lactate levels prior to, during, and after treatment. Using pyruvic acid as a tracer, its conversion to bicarbonate (oxidative phosphorylation), lactate (aerobic glycolysis), alanine (transamination), oxaloacetic acid (carboxylation), and acetyl CoA (oxidative decarboxylation) can be individually mapped in one a single scan along with pyruvate levels using their characteristic NMR spectra from the $^{13}C$-based MR images. Likewise, the rates of conversion of the $^{13}C$-labeled injected tracer to its various metabolites can be acquired enabling metabolic profiles to be overlaid on high-resolution anatomic images. Given that many tumors have known mutations that result in compromised enzymatic activity of key metabolic pathways, $^{13}C$-MRI can be used non-invasively to identify tumors harboring mutations in metabolic

pathways. Additionally, since many tumors undergo aerobic glycolysis (Warburg effect). Pre-clinical studies at UCSF, Cambridge, and CCR/NCI have documented changes in tumor lactate levels (reduction) following treatment. In the first human studies (UCSF), this technique was able to identify aerobic glycolysis processes in prostate carcinoma (elevated lactate levels).

**Clinical Trials** Based on the preclinical studies, novel therapeutic approaches to targeting the metabolic abnormalities in cancer will be developed. These approaches will be evaluated in patients in tumors characterized by aerobic glycolysis as well as those in patients with germline mutation of genes that involve metabolic pathways (PTEN, fumarate hydratase, succinate dehydrogenase, isocitrate dehydrogenase, etc.) Patients will undergo C13 Hyperpolarized Pyruvate imaging to 1) evaluate their metabolic characteristics as well as 2) to evaluate response to therapy. Findings made in these tumors, characterized by Krebs cycle mutations and aerobic glycolysis, will be applied to understand gene pathways that also affect non-hereditary, common cancers that are characterized by aerobic glycolysis.

**Anticipated Timeline:**

- Year 1-2: Characterize metabolic pathways of tumors characterized by aerobic glycolysis as well as Krebs cycle mutations (FH, SDH, IDH) with metabolic evaluation as well as C13glucose and C13 glutamine metabolite profiling.
- Year 2: Perform metabolic imaging in xenograft and human models to characterize the metabolic basis of these cancers
- Year 3: Analysis of initial trials and development of additional trials with agents targeting metabolic pathways in cancer

**Targeted populations:** GIST, Kidney tumors, Prostate tumors, CNS tumors, or any tumor characterized by aerobic glycolysis

**Scientific and Therapeutic Goals:** There are two sets of goals for this theme, learning and treatment. Learning goals include:

- Characterize the phenotypic and genotypic characteristics of tumors characterized by aerobic glycolysis using novel C13 glucose and C13 glutamine metabolic tracing and imaging approaches
- Development of trial designs specifically applicable to cancers characterized by aerobic glycolysis
- Application of new knowledge about common cancers (e.g., prostate cancer, CNS cancers, etc).

The primary treatment goals are to development of effective, targeted therapies, which improve survival and quality of life for patients affected with cancers characterized by altered metabolism.

**Sample of activities on-going within CCR/NIH:** Numerous activities are currently underway that could be combined, including: metabolic imaging for characterization and response to therapy of CNS tumors (UOB, MIP, ROB, NOB), metabolic imaging and assessment of response to targeted therapeutic approaches to novel small molecule inhibitors of epithelial NADPH oxidase gene family (Doroshow), succinate dehydrogenase-deficient GIST tumors (POB) and metabolic evaluation and imaging of prostate cancer characterized by aerobic glycolysis (ongoing and future) (UOB & CCBB)

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## MO 6: ATTACKING CANCER BASED ON ITS METABOLIC BASIS

**Perceptions from the external and internal oncology community**

Assuming the scientific objectives are met, 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)?

**Major Opportunities Strengths and Potential Improvements**

In what ways could this MO be strengthened to foster cross-collaboration across branches?

**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?

## MO 7: RARE CANCERS AND GENETIC TUMOR PREDISPOSITION SYNDROMES

**Lay Summary:** Rare cancers and genetic tumor predisposition syndromes (GTPS) in children and adults are not well understood, but several of them have been associated with germline alterations in tumor suppressors or oncogenes that drive common cancers. Thus, there is an urgent need to study these diseases and develop effective treatments, not only for people who have these syndromes but also because treatments for these rare syndromes could impact treatment for people with common cancers that bear these same mutations. The Center for Cancer Research is uniquely qualified to implement this research, because several investigators have expertise in rare cancers and GTPS, and travel subsidies facilitate accrual of these rare patients onto clinical trials that would be impossible elsewhere. The goal of this major opportunity is to provide better characterization of rare cancers and GTPS, and facilitate development of therapeutic approaches that could be applied to these syndromes that often lack effective therapies, as well as common cancers that have the same molecular alterations.

**Uniqueness (to the cancer community; why should it be attempted at CCR?):** CCR is in a unique position to address this problem because investigators in multiple Branches and Laboratories have longstanding experience and expertise in the study of rare diseases. This, combined with the NIH Clinical Center infrastructure and the ability to simultaneously conduct a comprehensive analysis of pediatric and adult tumors will greatly accelerate this process. These resources will be used to develop a detailed understanding of the presentation, phenotype, natural history, molecular biology, and genetics of rare pediatric and adult cancers to identify of targets for treatment and prevention of cancer.

**Overarching Strategy:** The overarching strategy is to combine and leverage the expertise of intramural investigators with expertise in genetics, genomics, molecular biology, imaging, tumor models, pharmacokinetics, pharmacodynamics, biomarkers, and clinical trial development and execution:

**Anticipated Timeline:** A timeline for this Major Opportunity is:

**Year 1-2:** Identify initial target diseases and syndromes, establish collaborations, and prioritize syndromes for future therapeutic trials based on drug availability. Implement natural history trials for target diseases/syndromes to enhance knowledge and establish patient relationships.

**Year 1-3:** Develop, initiate, and successfully complete treatment trials for prioritized rare syndromes

**Year 3-5:** Analysis of initial trials and development of subsequent trials in same syndromes or expansion into additional syndromes.

**Targeted populations:** Examples of some targeted pathways include:

- Related to PI3K/Akt/mTOR pathway (Cowden Syndrome, Peutz Jaegher Syndrome, Tuberous Sclerosis, Proteus Syndrome)
- Medullary thyroid carcinoma
- Pediatric malignant melanoma
- Multiple types of renal tumors, GIST
- Rare lymphomas
- Thymoma
- NF1 and NF2 tumors
- Li Fraumeni Syndrome

**Scientific and Therapeutic Goals:** There are two types of goals for this theme, discovery and treatment. Discovery goals include:

- Develop a detailed understanding of the presentation, phenotype, natural history, molecular biology, and genetics of a given syndrome
- Compare genotypic and phenotypic features in pediatric and adult cases
- Develop clinical trial designs and endpoints specifically applicable to rare cancers

The primary treatment goals are to develop effective targeted therapies that improve quality of life and disease free and overall survival and to apply lessons learned to common cancers.

**Sample of activities on-going within CCR/NIH:** Activities in this opportunity span both pediatric and adult cancers. In pediatrics, ongoing areas of research include wildtype (non KIT/PDFGRA mutated) GIST, hereditary medullary thyroid carcinoma, and neurofibromatosis type 1 and 2 related tumors. In adult cancers examples include renal tumors (Von Hippel-Lindau, Hereditary Papillary Renal Cell Carcinoma, Birt-Hogg-Dubé syndrome, Hereditary Leiomyomatosis Renal Cell Carcinoma, SDH-renal cell carcinoma, TFE3 kidney cancer), rare lymphomas, Cowden Syndrome, Proteus Syndrome and Li Fraumeni Syndrome.

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## MO 7: RARE CANCERS AND GENETIC TUMOR PREDISPOSITION SYNDROMES

**Perceptions from the external and internal oncology community**

Assuming the scientific objectives are met, 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)?

**Major Opportunities Strengths and Potential Improvements**

In what ways could this MO be strengthened to foster cross-collaboration across branches?

**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?

## MO 8: CHARACTERIZING THE TRANSITION FROM PREMALIGNANT OR SMOLDERING CANCERS TO MALIGNANT TUMORS TO IMPROVE INTERVENTIONS BETWEEN PREVENTION AND TREATMENT

**Lay Summary:** Rapid identification of pre-malignant and smoldering (i.e., slow growing) cancers offers a unique opportunity, particularly in cancers that involve long and complicated courses of treatment. In pre-malignant cancers, the identification of precursor states across multiple cancer types will lead to improved interventions aimed at delaying or preventing cancer progression. In smoldering cancers, with the understanding when to treat and when to wait, treatment can be optimized over time. By combining world-class molecular-imaging technologies with biomarker identification via laboratory analysis of blood and tissue specimens that are collected sequentially and longitudinally over the progression of disease, critical disease change states can be identified. This allows for treatment timing and options to be tailored specifically to each patient either through new discoveries for initial treatments beyond active surveillance or through the optimization of gradation of aggressive treatments over time. This profiling of tumors between the pre-malignant and lethal malignant states allows for more individualized risk stratification and counseling to patients.

**Uniqueness (to the cancer community; why should it be attempted at CCR):** This research requires both highly intensive core capabilities and the requirement of long-term sustained funding over a long period of time, both unique competencies of the CCR. This research requires the intensive collection of blood and tissue specimens, laboratory, and unique molecular imaging evaluations across a longitudinal cross-section of patients. The requirement of extensive, regular follow-up of patients to collect sequential samples and conduct molecular imaging would be beyond the budget of most academic institutions. Additionally, the CCR Molecular Imaging Program (MIP) has leading-edge experimental imaging capabilities, dedicated to research, and commitment required to maintain this capability at the leading-edge of imaging. Finally, there are vibrant clinical programs in cancers known to have pre-cancerous or smoldering states, namely: multiple myeloma, GU malignancies, lymphoma and malignant melanoma.

**Overarching Strategy & Timeline:** The overarching strategy is to link basic and applied imaging, biomarker, and laboratory research with long-term patient outcomes over time to understand the nature of disease progression. The timeline for this Major Opportunity is:

- Year 1: Identify prospective cohorts of patients with premalignant and early stage disease, intensely characterizes these patients with molecular imaging studies, biomarker collection, and analyses of urine/blood/tissue specimens including circulating tumor cells. Design tracking plan for each patient.
- Year 2-3: Continual tracking of patients characterizing the progression (or nonprogression) of disease from premalignant and early-stage patient through laboratory analyses of urine/blood/tissue specimens and molecular imaging studies
- Year 4-5: Correlation of clinical laboratory and molecular data with molecular imaging data to develop a focused clinical trial targeted against molecular drivers of progression.

**Targeted Population:** Focus on cancers with known pre-malignant or smoldering states such as multiple myeloma, GU malignancies, lymphoma, malignant melanoma

**Goal:** Identify patients with high-risk early stage or pre-malignant disease and develop tailored therapy pathways designed to prevent progression or potentially cure the disease. Develop individualized risk stratification to optimize therapeutic options that correspond both with the molecular profiling of the tumor and the state of progression of the disease.

**Sample of activities on-going within CCR/NIH**: Numerous branches/labs have ongoing research in this area including MIP (Choyke), Laboratory of Metabolism (Gonzalez), Genetics Branch (Cao), familial kidney cancer (Linehan), prostate cancer (UOB,MOB,ROB), lymphoma (Wilson, Staudt) malignant melanoma (Rosenberg) and multiple myeloma (Landgren).

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## MO 8: CHARACTERIZING THE TRANSITION FROM PREMALIGNANT OR

**Perceptions from the external and internal oncology community**

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Could this MO be integrated with **your** current clinical research direction?

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