



CASE
COMPREHENSIVE
CANCER CENTER



A Comprehensive Cancer
Center Designated by the
National Cancer Institute

Case Comprehensive Cancer Center Strategic Plan 2012-2018



Stan Gerson, MD
Director



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Strategic Plan 2012-2018

updated March 2014

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Reviewed by the Executive Committee and Program Leaders

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Overview

The Case Comprehensive Cancer Center is a consortium of cancer researchers who are members of the faculty of multiple schools across Case Western Reserve University and its clinical affiliates, the Seidman Cancer Center of University Hospitals Case Medical Center, the Taussig Cancer Institute and the Lerner Research Institute of Cleveland Clinic.

This strategic plan for the period 2012-2018, updated in March 2014, outlines the goals and aspirations of the cancer research community of the consortium and reflects the broadest approach to discovering the causes and testing strategies to prevent and cure malignancies of all types using the best innovative approaches possible. This document will provide guidance for cancer research within the Center and its partner institutions, and will be dynamic, responding rapidly to new discoveries, new needs, funding and scientific opportunities, and the underlying entrepreneurial strength of its members.

There are 367 members of the Cancer Center across these institutions. They are assembled in eight scientific programs and supported by 15 shared resources open to all members of the institutions with priority given to Cancer Center members. A robust clinical trials operation effort coordinates trials across the academic medical centers and community sites. Each of the institutions provides unrestricted support to the Cancer Center to conduct its research and to support recruitments, expenditures for shared resources, pilot initiatives, and clinical investigation. The Cancer Center is one of 41 comprehensive cancer centers supported by the National Cancer Institute, and it received an “Outstanding” merit rating at its last review in 2012.

Executive Summary of Strategic Priorities for 2014

Promote transdisciplinary research across the spectrum of basic and clinical sciences, with special emphasis on areas noted in our CCSG review including, for instance, therapeutics, imaging biology and biomedical engineering and clinical disciplines of radiation oncology, pediatric oncology, and surgical oncology.

Apply genomics and target discovery research into cancer etiology and progression, as well as prognostic and predictive markers, towards preventive and therapeutic clinical trials that improve our ability to predict therapeutic response and resistance.

Support drug discovery and development with the Center for High Throughput Drug Screening.

Continue to develop multi-investigator cancer research in brain tumors, immunotherapy of cancer, and the biology of adolescent and young adult cancers.

Enhance integration of basic and disease-based cancer research to positively impact our catchment area.

Advance efforts in population intervention studies.

Improve access to clinical trials for patients with cancer at our main campuses and community network sites.

Establish The Office of Minority Cancer Disparities Research within the Cancer Center and recruit its director.

Establish an Integrated Cancer Research Training Program.

Mission

To promote among our membership and institutions a coordinated, translational research-oriented culture of scientific discovery applied to human cancers culminating in dissemination to patients and populations in our catchment area. Our research efforts provide well-characterized, high-impact advances in cancer prevention, detection, treatment, cure, and survivorship. In this context, the Center provides a unique forum and academic network for cancer researchers across our campuses to accomplish more than they may individually. The Center embraces community oriented education and research to facilitate interventions that reduce the likelihood that our patient population will develop cancer and suffer from its consequences.

Vision

The Case Comprehensive Cancer Center links our medical institutions to enable innovative, cross-disciplinary research to understand the biology of cancer, leading to rapid deployment of new methods of cancer detection and treatment, to reduce the likelihood that our patient population will develop cancer and suffer from its consequences.

The Center:

- Advocates for cancer research across institutions
- Supports outstanding programs in cancer research
- Supports pilot grants, shared resource development, training programs, and recruitments
- Catalyzes multidisciplinary and transdisciplinary cancer research across institutions, emphasizing innovative discovery that impacts patients with cancer
- Develops clinical applications for recent discoveries and adroitly makes these available to Northern Ohio residents through the integrated efforts of the major health systems in the region
- Develops prevention and control initiatives to reduce cancer morbidity in Ohio and the nation

The overall approach taken by the Cancer Center is illustrated below. It catalyzes peer-reviewed cancer research that begins with basic discoveries into mechanisms of cancer initiation and progression and population risks; focuses these efforts on human cancers; identifies targets and biomarkers for prevention, detection, prognosis and treatment; develops novel therapeutics for these targets, tests new leads in clinical trials; and seeks to change the practice of medicine to reduce the impact of cancer on our patients and the population at large. Each scientific program encompasses this evolution.



Added Value

The value added by the Cancer Center is significant in a number of important ways that extend beyond its efforts coordinating cancer research.

- The Cancer Center strategically invests in scientific programs and clinical investigation to promote the most innovative and impactful research in cancer.
- The Cancer Center facilitates assembly of transdisciplinary investigative teams that develop new approaches to every aspect of cancer, from basic investigation, to translational and clinical applications, to population and epidemiologic research, and to research in cancer disparities due to particular risks, environmental factors, socioeconomic barriers to care, and race and ethnic origins.
- The Cancer Center seeks to challenge existing paradigms in basic research and clinical practice with the aspiration of improving every aspect of cancer research, from fundamental principles to prevention, early detection, and treatment applications.
- The Cancer Center assembles and maintains current leading edge shared resources that provide efficient and often unique capabilities and expertise that promote discovery and collaboration.

Strengths

The Cancer Center brings a number of strengths to a focus in cancer research.

- 9800 new cancer patients seen annually at Cleveland Clinic and University Hospitals with another 4000 seen at their network affiliates
- Coordinated clinical trial initiatives at all affiliate sites
- Inter-institutional collaborative research and training through scientific programs in these areas:
 - Cancer Genetics
 - Cancer Basic Sciences
 - Breast Cancer
 - Cancer Imaging
 - Hematopoietic Disorders
 - Developmental Therapeutics
 - GU Malignancies
 - Prevention and Control Research

Initiatives sponsored by the Cancer Center:

- GI SPORE – awarded September, 2011
 - Has identified an inhibitor of 15-PGDH, an enzyme which plays a key role in prostaglandin synthesis in both colon and esophageal cancers.
 - BETRnet – awarded September 2011
 - Identifying genes/mutations associated with familial Barrett’s Esophagus and markers of progression.
 - Breast cancer research program in development
 - Evolved into a full scientific program in 2013 (to be reviewed at the next NCI CCSG submission) with breadth in basic mechanisms of development, metastasis and progression, genomic analysis for treatment prediction, population risk assessment and survivorship research.
 - Brain tumor initiative
 - A multi-center SPORE group has assembled that focuses on angiogenesis, tumor migration, glioma stem cells, new therapeutic targets and trials, genetic factors in glioma, and pediatric brain tumors.
 - Biorepository system and review process
 - A rapidly evolving program for tumor and blood collection, clinical annotation, codified and secure data storage, and focused banks in brain tumors, colon, lung, prostate, kidney, CLL, AML, MDS, breast, and melanoma are available to promote human cancer-based research at both UHSCC and Cleveland Clinic. Access and biorepository support are being enhanced.
 - Hospital-based programs are developing patient-consented collections of blood and outcomes for longitudinal monitoring across cancer types.
 - An RFA has been released for the development of banks of tissue-specific patient-derived xenografts.
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- Cancer Genomics and Informatics.
 - HiSeq capabilities are offered in the Genomics Facility for basic and clinical investigators.
 - Genomic Tumor boards have been established at Cleveland Clinic and UHSCC, with outsourcing of clinical HiSeq genomics.
 - The Cancer Center has developed a clinical trial evaluating the feasibility and impact of using Foundation Medicine genomic diagnostics to influence treatment decision-making in patients with advanced cancers (Case 1Y13).
 - Population cohort research efforts in prevention, detection, energetics and cancer genetics in breast, brain, colon, prostate, and lung cancers; and Barrett's Esophagus
 - Development of cohorts of local patients undergoing colonoscopy, mammography, exercise, CT screening for lung cancer, and larger population-based studies in our patient populations and in Kentucky and Shanghai.
 - Core facility review and upgrades 2013.
 - A SOM-led review of core facilities established a working group oversight committee and efforts to facilitate upgrades, consolidate redundancies, improve concierge access, data sharing and documentation for billing.
 - Clinical trials infrastructure enhancements are designed to reduce the time between review and activation, and increase coordination between sites during protocol development, review, budget negotiations, audits and reporting. Oversight of non-accruing trials has led to a significant increase in protocol closures of these trials.
 - Institutional commitment supporting clinical trials infrastructure and protected faculty time is substantial.
 - The Minority Accrual Committee developed a clinical trials brochure and has implemented strategies to enhance accruals in the underserved.
 - Strong graduate training programs in Cancer Biology (renewed 2012), Computational Biology (renewed 2012), BME/Imaging (renewed 2012) and Cancer Pharmacology
 - K-12 Paul Calabrese Scholar Award in Clinical Oncology Research (renewed 2013)
 - Recruitment of clinical investigators and basic scientists to partner institutions benefit the Cancer Center and its research programs
 - RFA pilot grant competitions issued in 2013
 - A. [Opportunities for Developing Patient-Derived Xenografts](#)
This will support the development of patient-derived tumor xenografts (PDX) that will benefit collaborative, multi-investigator projects within the Cancer Center. Deadline: **November 15 2013**
 - B. [Use of Tumor Genomic Evaluation for Clinical Decision-Making](#)
This will provide seed money to foster collaborations and promote and increase institution-wide capacity and competitiveness in the use of tumor genomic evaluation for clinical decision-making. Research proposals must involve patients and/or their tissues. Deadline: **January 2014**
 - C. [Planning for Multi-Investigator Proposals](#)
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This will provide funding to further the important goal of facilitating successful applications for large multi-investigator grants (e.g., P01, P50, U54) in the current funding cycle. Applicants must demonstrate they are in communication with appropriate NIH administration, other structures within NIH, or other funding agencies (e.g., formal invitation, preparatory meeting, LOI and/or positive response to RFA or PA). Applicants must demonstrate intent to apply for national funding within a defined timeline, and describe new research that could not be achieved without the collaboration. Deadline: **Open**

Current Initiatives for 2014

- **Cancer bioinformatics**

- The SOM recruited Jonathan Haines to direct the Center for Computational Biology and chair the Department of Epidemiology and Biostatistics. These groups will provide the academic home for cancer researchers with expertise in bioinformatics and epidemiology and their team science collaborators.

- **Cancer Genomics Initiative**

- The SOM recruited Tony Wynshaw-Boris as Chair of Genetics and Genomics. He is rapidly building a department oriented towards human genomics, diagnosis of mutationally driven cancers and expanding HiSeq technology coupled with improved analytics. Strong genome sequencing efforts continue in hematologic malignancies, breast cancer, GI cancers, and high risk populations.

- **Cancer nanotechnology and imaging**

- The strong efforts in image and nanomedicine technology is ripe for clinical engagement and applications. The Cancer Center is facilitating clinical translation through development of clinically relevant models.

- **Drug discovery and development**

- Members of the Cancer Center are evaluating new drugs targeting novel key cancer pathways in the new CWRU Center for High Throughput Drug Screening.

- **Brain Tumor SPORE**

- Five projects with co-leaders investigating brain tumor angiogenesis, drug resistance, genomics, BRAF, and metabolism are included in this research team.

- **Immunotherapy of cancer**

- A group of investigators has formed a working group to develop molecule and cell-based approaches to immunotherapy

- **Biology of adolescent and young adult cancers**

- Pediatric cancer investigators are using biological, novel therapies, genomics, and imaging to understand the special attributes of AYA cancers.

- **Cancer Center Office of Minority Cancer Disparities Research will recruit an investigator to lead this research effort**

- The Community Advisory Board has active programs in lung cancer screening, cultural competency and education in screening and clinical trials.

Strategic Objectives 2014-2018

1. Enhance integration of basic and disease-based cancer research.

The Cancer Center strives to promote links between basic science discovery and application towards human cancers through collaborative efforts between basic science and population studies and disease-oriented investigators, as well as through early application in clinical investigation. Current examples include the new Breast Cancer Program, the brain tumor initiative, drug discovery leading to therapeutics, building genomics HiSeq capacity, and the new effort in cancer immunobiology.

2. Promote transdisciplinary research across the spectrum of cancer biology, bioinformatics and genomics with advanced disease models, therapeutics, imaging, and population sciences.

Institutional expertise in drug development, computational biology, bioinformatics, imaging, nanotechnology, and genomics are catalyzing cancer research across programs. The involvement of multiple clinical oncology groups in our research represents an expansion of our transdisciplinary research. Surgical oncology faculty participate in the GI SPORE, the Brain Tumor SPORE initiative, and the cancer immunology effort. Pediatric Oncology faculty participates in Developmental Therapeutics, cancer biology, the Brain Tumor SPORE, and Hematopoietic Disorders. Radiation Oncology faculty participates in Developmental Therapeutics, Imaging and Basic Biology.

3. Develop clinical and bioinformatics databases within CWRU IT that enable large database storage and sharing linked to clinical trials, genomics (HiSeq) and population studies.

The Cancer Center Informatics working group submitted a proposal accepted by CWRU for capital investment in a FISMA compliant environment for clinical informatics and the purchase and support for Labmatrix as the database platform. In 2014, this will be implemented with migration of cancer center databases including ONCORE, BSM and other clinical research efforts. The Center is also developing a modification to the patient informed consent to reflect the storage of these data in secure databases and their use by Cancer Center investigators.

4. Support drug discovery and development through the Center for High Throughput Drug Screening.

This joint departmental/center initiative will have the capacity for 8-12 screening projects a year. Cancer-related projects will be jointly funded through the SOM and the Cancer Center. Center members will identify 4-6 targets for screening per year.

5. Apply genomics and target discovery of disease and prognostic and predictive markers towards preventive and therapeutic clinical trials to create a platform for molecularly informed clinical decision-making.
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The cancer programs of both hospitals have begun to use HiSeq genomics on patient tumor samples to inform clinical decision-making. One protocol is specific to this, while others are developing research questions around HiSeq (DNA) and RNASeq evaluation of clinical tumor samples. Over 250 patient samples have been evaluated. In 2014, the Center expects over 600 patient samples to be evaluated for “actionable” changes that could lead to altered treatment. UH is also developing a CLIA lab for exom sequencing of human tumors.

6. Enhance integration of basic and disease-based cancer research to positively impact our catchment area.

Our institutions now have a number of emerging technologies that can be used for early detection as well as for cancer prevention through interventional efforts and screening. Examples include screening using novel DNA-based technologies for colon cancer or esophageal cancer; wellness efforts focused on behavioral and lifestyle changes (such as diet, exercise and smoking cessation); use of novel chemopreventive agents; and studies of survivorship to identify factors that can reduce recurrence rates and improve quality of life among those who have had cancer. Cohorts will be developed to test these markers and strategies for their ability to detect cancer early, identify patient-specific treatments and reduce the burden of cancer and its recurrence.

7. Improve access to clinical trials for patients with cancer.

Our partner academic medical centers are making major investments in clinical trials support, including investigator-initiated clinical trials. The 2013 accrual of 1008 patients is a 27 y highmark for the Case CCC. Our community sites are more engaged in clinical trials, which are now available at most of the 18 regional sites. Focus on high impact trials, cooperative group participation, efficiencies of trial monitoring, closure of non- accruing trials, and increased efforts to open trials in both clinical systems remain priorities. In 2014, new initiatives will include the Ohio Clinical Trials Consortium and the Ohio PBRN program.

8. Establish the Office of Minority Cancer Disparities Research within the Cancer Center.

The purpose of this office will be to support a multi-institutional initiative focused on the unique needs of the underserved, identify societal, behavioral, and biological risk factors within this population, and reduce disparities in cancer care including access and participation in clinical investigation. The recruitment is ongoing. We continue to expand the efforts of the Community Advisory Board in areas of lung cancer screening, education about clinical trials, and cultural competency training.

9. Establish an Integrated Cancer Training Program.

Increased coordination of cancer research training is a focus for the Center. We continue to support cancer research training programs funded by NIH. We have participated in developing a curriculum for expanded career opportunities for trainees (the DP7 RFA). In 2014, we will

review the cancer biology and oncology training offered to medical students, will develop a T32 in stem cell biology, and assist in the renewal of the cancer pharmacology training grant. We will promote stipend supplements for outstanding trainees, and fast-tracks to the best trainees. We will enhance course offerings in cancer biology, cancer genomics and cancer therapeutics.

10. Continue to develop multi-investigator cancer research in brain tumors, immunotherapy of cancer and the biology of adolescent and young adult cancers.

These initiatives represent the most recent priorities identified by Center members of worthy of additional investment, recruitment and emphasis. It is likely that as these scientific focus areas mature, they will require additional support from the institutions and the Cancer Center.

Strategic Resources (Updated 2014)

Our large patient populations, which as of 2014 will encompass approximately 70% of the individuals in NE Ohio, can be further engaged in cancer investigation, through implementation of and access to cancer prevention strategies, high-risk for cancer assessment, genomics, clinically annotated tissue banks and development of clinical trials to which they can accrue, both at the academic sites and throughout the networks.

Our research can flourish through support for collaborative research efforts across institutions of the Center. Areas of targeted efforts that will benefit from focused development include cancer imaging, prevention, community outreach and research, and cancer immunobiology and therapy.

The ability of our basic scientists to perform disease-relevant research benefits from strong interactions with our population and clinical investigators. Cross links between investigator groups can be encouraged with pilot project support and protected time for clinical investigators to participate in collaborations.

We continue to recruit outstanding laboratory-based cancer researchers across departments and campuses who contribute to the scientific programs.

Each campus has strengthened interest in converting pathway discoveries to therapeutic targets and is assisting in compound and eventually drug development through the CAAH at CWRU, Harrington Project at University Hospitals, and the Center for Innovations at Cleveland Clinic.

Center investigators are developing more large multi-investigator grants. To date efforts have resulted in a cancer-focused program project grant, "Inflammation and Tumorigenesis", the GI SPORE, the Barrett's Esophagus consortium, the UM10 and N01 grants for clinical investigation, and the U10 for the NCTN. Additional areas of multi investigator collaborative research developing applications are the Brain tumor SPORE, and the breast cancer research group.

The high impact of our science can be published in equally high impact journals by encouraging authors to seek pre-submission review and advice from our most accomplished senior investigators.

Our prevention and control research efforts are achieving greater recognition by implementing population interventional and observational studies.

Our clinical trial support infrastructure facilitates investigator-initiated and high impact clinical trials with increased rates of patient accrual to therapeutic, other interventional, and behavioral clinical trials. The affiliate institutions are developing a network strategy for clinical trial access across the region.

Our clinical trials program has substantially benefited from institutional support for clinical trials activities -- with a target of 50% of costs, based on the median observed at other NCI designated cancer centers. Therapeutic Clinical Trials accrual in 2013 was 1008 patients, the highest in our 27 year history. We plan to leverage the institutional commitment for funding 50% of the clinical trials infrastructure costs, by aggressively seeking extramural support for investigator-initiated studies.

Our minority populations are a target for navigation, education, and community engagement programs including the Community Advisory Board and the Minority Accrual Committee. Current focus areas are in lung cancer and prostate cancer screening, development of a brochure about clinical trials, cultural competency training and navigation. These will improve access, community understanding and interest in clinical trial participation.

Our population sciences efforts have developed strong cohorts for ongoing research and are now poised to focus on cancer research with minority and underserved populations & community outreach. This effort will be coordinated with the recruitment of an investigator in this area who will also direct the Office for Minority Cancer Disparities Research.

Training programs for pre- & post-docs are an important asset for a major research institution. We will increase efforts to recruit the best and brightest researchers. The Cancer Center will maintain its K12, R25, T32 and R32 training grants. It will support highly promising trainees through special awards and stipend supplements. We will also increase the quality and number of post-doctoral fellows by forming a post-doctoral training program that focuses on joint recruitment and career development activities, including pathways towards broad careers while supporting early academic career development.

Our expertise in cancer genomics has spurred development of broad reaching training of basic and clinical trainees in cancer genomics to increase the effort in genomics research across disciplines.

Institutional Request for Support

The following were identified in 2012 as part of the interinstitutional MOU. As we enter 2014, institutional commitments have all been met in these areas.

1. Annual support for new initiatives, core facilities, and center operations.
2. Clinical Trials support at a rate of 50% of total CTU costs at both UHSCC and CCTCI.
3. Protected time for clinical investigation at a rate of approximately 1% cFTE per accrual.
4. Support for clinical investigator recruitments to both SCC and TCI; with a focus in breast, lung, hematologic malignancies, GI cancers, and GU cancers. UH has recruited 5 clinical investigators and CCF recruited 10 clinical investigators.
5. Support for cancer research investigator recruitment at the rate of 2 faculty per year at UH/CWRU and 1-2 researchers per year at CC LRI. In 2012-2013, 5 laboratory investigators were recruited, 3 to CCF and 2 to CWRU.
6. Recruitment of a population scientist with an expressed focus on disparities research.

Strategic Initiative Investments

7. Support for bioinformatics within the expanded Biostatistics and Bioinformatics Shared Resource. Faculty and staff with expertise in analysis and interpretation of high throughput genomics and proteomics data with an anticipated recruitment need of 3 faculty and 5 support staff over the next 4 years.
8. Support for informatics software for clinical annotation, consolidation of databases, HIPAA compliant data storage and retrieval, database management, and informatics analysis and queries. Servers to manage large databases.
9. Equipment purchases: Next generation high throughput sequencers, as needed to support investigators; other equipment will be placed in the Center for High Throughput Drug Screening.
10. Development of Animal Pharmacokinetics, Pathology, and Pharmacodynamics Shared Resources to evaluate the therapeutic potential of new lead compounds.
11. Support for promising, highly competitive post-doc junior investigators with supplemental special funding at the rate of 1-2/y per institution.

Discipline Strategic Plans

Clinical Research

Clinical trials are the basis for improving the prevention, detection, and treatment of patients with cancer, and represent high quality cancer care for those who participate. The next six years are a critical opportunity to leverage recent advances in biology and technology to benefit population health. Recent enhancements in the clinical trials infrastructure of the Case CCC have streamlined our ability to activate trials rapidly, prioritize resource allocation, monitor ongoing studies, and make studies available to patients treated at community sites. We are thus poised to develop and conduct the next generation of high-impact clinical research. Priorities include:

- Accelerate the preclinical development of new drugs developed at the Case CCC and available through NCI CTEP
- Incorporate genomics analysis into clinical practice through a genomics review board and clinical trials that evaluate the utility of genomics based decision making in treatment choices
- Recognize cancers based upon molecular characterization and not solely site of origin. Direct therapy based upon biology and not histology. This will involve integrated and integral biomarker studies to identify and validate predictive classifiers. Interrogation of local and national annotated tissue banks for biomarker discovery can form the basis for future prospective clinical trials
- Conduct early phase investigations of new targeted therapeutics, often in phenotypically and genomically-defined populations. In addition, continue to pursue mechanism-based studies of resistance modulating agents
- Conduct studies to more precisely define risk in “at risk” populations, and pursue tailored approaches to prevention and treatment. This will involve platforms that measure components of blood, and other body fluids, in addition to tissue biopsies
- Pursue non-invasive methods to assess treatment effect in vivo, including imaging and microfluidic technologies and circulating cells
- Employ study designs that minimize the patient resource required to address specific questions. Adaptive statistical designs will be more common
- Pursue the science of clinical trial accrual to overcome barriers to patient participation
- Continue to build a clinical investigator workforce that develops home-grown concepts and leverages local strength in laboratory science and technology
- Expand sites of clinical trial access to include community network sites and other major cancer centers such as the OSU James CCC

Population Research

Population research cuts across all aspects of translational cancer research ranging from epidemiology, psychosocial and behavioral sciences, genomics, biomarker discovery and validation, to the application of novel discoveries from both wet and dry laboratories to screening and early detection, prevention and intervention. It also includes dissemination of effective strategies in the community and population at large for health promotion and disease prevention. The Case CCC has significant strengths in psychosocial and behavioral research, practice-based network research, community-based lifestyle intervention, and cancer

epidemiology. Recent establishment and expansion of several cohorts and population/community resources have enhanced our ability to conduct multidisciplinary and transdisciplinary population cancer research. The following areas are of high priority over the next five years:

- Promoting disease-focused transdisciplinary, population-based prevention/ intervention studies that link expertise in psychosocial and behavioral intervention, epidemiology, biology and genomics.
- Developing capacities to conduct community outreach, participatory, and cancer disparities research, leveraging the CDC funded Case Prevention Research Center which has strong community involvement. Recruitment of a middle- to senior-level cancer investigator to champion and catalyze these efforts is needed.
- Enhancing capacities in energy imbalance-cancer research, with a focus on lifestyle intervention studies in high-risk population and cancer survivors. This programmatic emphasis needs recruitment of cancer survivorship investigator with expertise in exercise physiology and intervention.
- Establishing a body composition and exercise laboratory for both population intervention studies and clinical trials.
- Extending the Cancer Center's well-recognized expertise in risk prediction modeling into identification of high-risk individuals for prevention and intervention studies in community outreach and disparities research.
- Expanding support for assembling cohorts and disease-specific population resources. Well-established and characterized populations provide the basis for long term, multi-faceted large-scale collaborative programs.
- Promoting chemoprevention and non-therapeutic intervention population trials to reduce cancer risk. This will entail increased interactions among population investigators, basic scientists, and clinicians.

Basic Research

Identification of novel pathways and targets for prevention, detection, prognosis and treatment of cancer typically stem from discoveries in laboratories that study basic molecular mechanisms underlying aberrant cell biology associated with disease. Novel findings can then be confirmed in animal models of disease and ultimately translated to evaluation of clinical samples and development of new interventions. We have significant strengths in basic cancer research that extend from atomic resolution of drugs/drug targets to integration of gene/protein networks and ultimately to therapeutic targeting and molecular imaging of tumors. To capitalize on these strengths and extend our capabilities in disease-based research, we have identified areas of high priority for the next five years. These are listed below.

- Promoting discovery research into the fundamental mechanisms of cell survival, proliferation, migration, invasion, inflammation, and therapeutic response, with particular emphasis on pathway cross-talk to increase synergies among basic, translational, and clinical investigators
 - Encourage basic scientists to link their research to human disease and develop strategies to address key provocative questions in human cancers
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- Acquiring high-throughput approaches for functional discovery of key regulators of disease such as RNAi and chemical library screening
- Expanding our considerable strengths in genomics and proteomics to discover epigenetic, genetic, and protein changes associated with disease initiation, progression, and therapeutic response; this will involve use of cell and animal models in addition to well-annotated biorepository samples
- Collecting biorepository samples that are associated with long-term patient follow-up to permit evaluation of novel mechanisms of therapeutic response/resistance and disease progression in diseases that are associated with late recurrence; develop tissue microarrays for these diseases.
 - Increasing interactions between investigators focused on systems biology, imaging and nanodrug delivery and nanotechnology with cancer biologists and clinical investigators to develop disease-relevant technologies
 - Adding clinical expertise to multi-disciplinary research programs to ensure a disease oriented focus and increased competitiveness of cancer oriented grant applications
 - Leveraging strength in tumor-initiating/stem cells to identify targetable mechanisms of dissemination and metastatic progression, including modulators of stem cell niches
 - Recruiting individuals with expertise in recalcitrant cancers such as ovarian and pancreatic that are understudied, and have limited treatment options due to the lack of a detailed understanding of their unique molecular characteristics
 - Developing a shared resource for animal pharmacokinetics and pharmacodynamics that can be utilized to evaluate the therapeutic potential of new lead compounds

Cancer Center Scientific Program Priorities

Each scientific program has been asked to develop priorities for scientific development, needs for shared resources, recruitment priorities, and ties to disease based research. The following is a short summary of each program priorities. This section is followed by a description in greater detail of the needs and aspirations of each program.

Program 1: Cancer Genetics

Sanford D. Markowitz, MD, PhD & Robert C. Elston, PhD

Scientific Focus Areas

- To discover and elucidate the role of tumor suppressor genes and oncogenes in human cancers
- To identify cancer susceptibility genes active in the human population, and to develop molecular assays for detection of cancer risk and molecular assays for early cancer diagnosis
- To develop new methods for the discovery of cancer causing genes

Strategic Initiatives

- Pursue research under the GI SPORE Center grant with an emphasis on applying Next-Generation Sequencing technologies to colon and esophageal cancers to identify informative gene sets for prognosis and metastasis
- Pursue research under the Barrett's and Esophageal Cancers Center grant
- Expand the Cancer Center core to support NextGen Sequencing and the associated informatics requirements to process NextGen Sequencing and whole genome sequencing data
- Expand the GI cancers biorepository, including consented patient tumor tissues, blood, and medical records, to support development of molecular methods for diagnostics, early detection, prognostics, and new cancer therapeutic and cancer prevention strategies
- Bring to multicenter clinical trials through the EDRN, two novel tests developed within the Program – a stool DNA-based method for early detection of GI cancers and the blood DNA-based method for post-operative surveillance of GI cancers

Program Needs

- Upgraded instrumentation for high throughput sequencing (HiSeq 2500)
 - Expanded informatics development to support analysis of whole genome and NextGen Sequencing data generated both internally and available in public databases
 - Capability in functional genomics (including methods such as whole genome siRNA screening)
 - Support for comprehensive collection of consented patient samples (tissue, blood, and medical records) for cancer research at the time of diagnosis
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- Philanthropic support to further enable building a nationally competitive GI SPORE Center program

Recruitment Priorities

- Cancer genetics faculty with expertise in high throughput sequencing and other genomics technologies
- Cancer genetics faculty with expertise in informatics for cancer genomics and sequencing
- New physician-scientist pathology faculty to build strength of investigator group in GI Pathology
- New senior and junior faculty recruitment to maintain expertise and leadership in Computational Genetics

Program 2: Basic Science

Clark W. Distelhorst, MD & Alexandru Almasan, PhD

Themes

- Understanding and targeting cancer's resistance to cell death
- Understanding and targeting cancer's replicative immortality
- Understanding and targeting cancer's cell signaling
- Understanding and targeting the role the tumor microenvironment including endothelial cells, and angiogenesis in tumor formation

Focus Areas

- Bcl-2 protein family
- DNA damage responses including cell cycle checkpoints
- Oxidative stress
- Mutations induced by DNA damage
- Microenvironment
- Cell Signaling
- Brain tumor biology
- Renal cell cancer
- Lymphoid malignancy

Strategic Initiatives

- Develop the Program to be greater than the sum of its Focus Groups
 - Orient discovery research towards translational cancer impact across all focus areas
 - Encourage involvement of Focus Groups in the disease-related initiatives
 - Foster multi-investigator grant applications through targeted discussions in each of the focus groups. The availability of designated seed funding from the Cancer Center will continue to facilitate the gathering of key preliminary data
 - Foster new translational initiatives. Of note are ongoing strong interactions with disease-specific initiatives in glioma, lymphoid malignancy, prostate, lung and renal cancer
 - Target autophagy and DNA repair abnormalities of cancer to establish new diagnostics and therapeutics
 - Recruit clinical investigators to the program to facilitate translational initiatives and provide mentoring in clinical investigation
 - Make multi-investigator initiatives, such as the Ohio Brain Tumor SPORE, a goal for the entire program membership
 - Explore novel mechanism-based interactions of established and experimental radio- and chemo-therapeutics to develop enhanced treatment of cancer
 - Explore synthetic lethal interactions between front-line clinical therapeutics and new agents that target autophagy, DNA repair abnormalities, and signaling abnormalities in genetically-defined cancer subsets
 - Encourage wider use and sharing of animal models and genomic approaches including
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the new patient derived xenografts

Program Needs

- A major need is for Case CCC support for collaborative interactions fostered through focus group meetings, funds to initiate collaborative interactions and the translation of findings into clinical research protocols, and support for clinical investigators as members of the program and collaborators

Recruitment Priorities

- Targeted faculty recruitments to fill current voids in the program, such as cancer metabolism and autophagy
- Joint recruitment with Program 5 in lymphoid malignancies research as well as Program 4 to support renal cell cancer research

Program 3: Breast Cancer

Lyndsay N. Harris, MD & William P. Schieman, PhD

Overview

The Breast Cancer Program (BCP) comprises 40 basic, translational, and clinical researchers housed at three adjacent institutions: CWRU (18), UH/SCC (8), and CCF (14). Members are organized into 4 Scientific Focus Areas – namely, TME & Metastasis (Schieman); Transcription & Gene Regulation (Kao); Mammary Gland Development & Transformation (Jackson); and Biomarkers, Genomics & Epidemiology (Thompson), with an emerging focus group in clinical trials – and utilize multidisciplinary and team-based approaches to address the BCP's overarching goals:

- To understand breast cancer pathogenesis from initiation to metastasis to disease recurrence
- To translate these findings into novel diagnostic platforms and therapeutic strategies

Strategy Forward and Strategic Initiatives

- Cultivate Multi-Investigator Initiatives Leading to New PPG and SPORE Grants: Efforts will be supported by (i) focus groups activities, (ii) mini- and annual program retreats; and (iii) developing pilot grant initiatives and promoting collaborative, multi-investigator R01 level grant applications.
- Strengthen Internal and External Breast Cancer-specific Seminar Series.
- Strengthen Interprogrammatic Efforts in Imaging, Genomics, and Developmental Therapeutics: Efforts will be supported by (i) convening joint retreats with other CCCC Programs, as well as developing interprogrammatic pilot grant award opportunities; (ii) enhancing and streamlining bench-to-bedside clinical trials; and (iii) strengthening ongoing interdisciplinary working groups, including the imaging breast cancer metastasis working group, the TNBC working group, the breast cancer genomics working group, and the PDX model working group.
- Enhance Collaborative Interactions and Communication: Efforts will provide streamlined and improved BCP member access to experimental resources, data and technique sharing, and clinically annotated tissue samples.
- Advocate Junior Investigator and Translational Pilot Grants to Promote Junior Trainee Involvement: Efforts will provide grant proposal and career development mentoring, particularly by enrollment of junior trainees in the BCP's Research Incubator Program.

Infrastructure Necessary to Support Initiatives

- Breast Cancer Patient-derived XenoBank Core to Bolster Basic, Translational, and Predictive Biomarker Development.
 - CCCC Breast TMA: Enhance member access to TMA and promote data sharing.
 - CNS Metastasis Cohort: 80 archival breast cancer brain metastases have been identified, 40 of which have matched primary tumors. Cohort needs additional expansion and completion of clinical annotation, tissue microarray and gene expression microarray analyses.
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- TNBC Cohorts: 176 TNBCs have been identified and arrayed, all of which contain complete clinical and race annotation. Cohort needs additional expansion and implementation to support multi-investigator initiatives.
- CCCC Breast Cancer Genomics Database: Develop a novel database of all CCCC gene expression, copy number and mutation analysis data from in-house and publicly available cohorts with clinical annotation for target mining.
- Support for Clinical Trials Nurse/Technician to Assist in Investigator-initiated Trials and Tissue Collection.
- Support for Pilot Grant Funding
- Complete Gene Expression and DNA Sequencing Analyses on Over 400 Primary Breast Tumors with Clinical Annotation: Enhance member access and data development.
- Support to Link Broad-based Clinical and Population Annotations to Breast Cancer Biorepository.
- Enhance Minority Inclusion and Access to Clinical Trials Through Cancer Prevention & Control Programs.

Program 4: GU Malignancies

Brian Rini, MD & Bing-Cheng Wang, PhD

Strategic Initiatives

- Develop multi-investigator research in microenvironment, immunomodulation, targeting PI3K, mTOR, and AKT
- Develop research effort in bladder cancer
- Work toward horizontal integration across the three disease foci of GU
- Develop a coordinated biorepository
- Increase the number of investigator initiated clinical trials linked to laboratory investigation
- Encourage biomarker linked clinical trials, including genomics based decision making
- Expand clinical research in the use of radiation treatments

Recruitment Priorities

- Investigators with expertise in tumor progression/metastatic disease, microenvironment, angiogenesis, and inflammation / oncolytic viruses
- An endowed chair in prostate cancer research
- Clinical investigators to develop investigator initiated clinical trials

Strategies Forward

- Multi-PI Opportunities
 - Build multi-investigator team science in basic mechanisms of androgen metabolism, AR signaling, AR regulators and effectors, and their roles in the development of CRPC and therapeutic resistance.
 - Guided by the fundamental mechanistic research above, discover and develop novel therapeutic agents for CRPC, which will fully engage the new Center for High Throughput Drug Screening and take advantage of the strong existing collaborations between GU and DT Programs.
 - Expand the scope and collaborations around the IRDS (interferon-related DNA damage resistance signature) project recently funded by the Prostate Cancer Foundation. Promote possible new multi-PI project(s) around the theme of IRDS, which will have important impact on the catchment area, because of the association of IRDS with African American PCa patients.
 - Investigate possible AR-IRDS link.
 - Capitalizing on Klein Genomic Health data, investigate the functions and druggability of 12 gene products that differentiate indolent vs. aggressive prostate cancer.
 - Administrative
 - Proactively respond to new scientific themes, new resources, or new recruitments by hosting more irregular small and focused interest group meetings and mini-retreats (physicians and basic researchers) to promote emerging ideas and collaborations. This will be in addition to larger retreats for program-wide interactions and evaluations.
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- Integration of basic research, imaging and clinical data.
- Clinical Studies
 - E.g. Drs. Silverman and Rini are currently collaborating with Jennerex to bring the sunitinib/oncolytic virus strategy to clinical trials for renal cell carcinoma.
 - Recruitment of physician scientists to the program, e.g. Norbert Avril
 - Use these initiatives to drive development of MPI grants and program grants
 - UO1 Grants (MPIs: Drs. Lee, Gulani, Matabushi-Rutgers University)
 - BRP Grants (MPIs: Drs. Griswold, Von Recum, and Exner)
- Recruitments
 - One more PhD, or MD/PhD researcher in AR signaling and prostate cancer
 - One or 2 RCC basic researchers

Program 5: Hematopoietic Disorders

Jaroslaw P. Maciejewski, MD, PhD & Marcos de Lima, MD

Future goals of the Heme Disorders Program align with the Case CCC Strategic Plan 2012-2018 and are directed toward enhancing several general strategic areas:

- Building of new Focus Areas
- Promotion of multi-investigator research applications

Establishment of a Lymphoid Malignancy Scientific Focus Area

To complement growing scientific and translational research strengths, the Heme Disorders Program plans to work toward creation of a new Focus Area in Lymphoid Malignancies. Towards that end the new members of the program include Dr. Mitchel Smith, Director of Lymphoma Section at the Taussig Cancer Center and Dr. Qing Yi, Chair of the Department of Cancer Biology at Lerner Research Institute with expertise in B cell lymphoma biology and myeloma therapeutics, respectively. Mechanisms of apoptosis in B cells in general (Clark Distelhorst, and CLL specifically (Alex Almasan and Paolo Caimi) are a clinical strength that will be incorporated the Heme Disorders Program. The Lymphoma focus area will establish an early clinical trials program in CLL and other indolent B-cell malignancies, led by Dr. Caimi, Dr. Reu and colleagues. In addition, Lan Zhou and Stan Gerson have mouse models of lymphoma.

Multi-investigator grant applications

Heme Disorders Program members have been invited by NHLBI to submit a PPG1 application entitled "Epigenetic Dysfunction and Targeting in MDS". Other multi-investigator grants will be forthcoming based on Focus Area research.

To achieve these 2 strategic goals Program 5 will engage in:

- **Targeted recruitment initiatives** in areas of need with synergistic potential. The Cancer Center Strategic Plan 2012-2018 indicates that 5-8 recruitments in hematologic malignancies will take place at both clinical sites over the next 5 years. Some will have laboratory programs. The institutions plan "physician-scientist" recruitments in the following areas: 1) Epigenetics of histone modification: methylation/deacetylation, 2) Genomics of lymphoma and/or multiple myeloma, 3) Stem optimization of graft-vs.-tumor effects/tumor surveillance. 4) HSC biology/cellular therapy "graft engineering"
- **Strategic initiative in Cancer Genomics.** The Case CCC has implemented a plan to coordinate cancer genomics efforts across the institutions. Program 5 will take advantage of these developments and introduce clinical multimutational testing platforms for somatic mutations in myeloid neoplasms, multimutational panel in lymphoma and bone marrow failure hereditary mutational panel. Heme Disorders Program members propose to utilize NGS for the development of a cost-efficient multi-mutational diagnostic tool, providing a tremendous amount of information about molecular defects. In the first part of this genomic initiative whole genome sequencing has been applied to 200 MDS cases (200 MDS exome project), supported by institutional and philanthropic funds including the Scott Hamilton Fund. Based on the results of this project a targeted exome-

enrichment panel has been designed to sequence relevant exons in 80 genes harboring mutations important for the pathogenesis of the most common cancers.

- **Expansion of cell therapy approaches in hematologic malignancies** (with or without transplantation) is planned. We are developing a pre-clinical model of human NK ex-vivo expansion, and investigating pharmacologic approaches to increase NK cell activity, aiming at treating hematologic malignancies. In addition, we are investigating the use of mesenchymal stromal cells to enhance cord blood engraftment in adults, using an intra-osseous co-transplantation model. Improving engraftment of cord blood in adults will involve investigators with interest in bone marrow niche and imaging, for example (Dr. Zhang, Dr. Huang).

- **Establishment of a new cancer drug development center to include drug screening** (Drs. Abazeed, Reu), molecular target selection (Drs. Maciejewski, Makishima) and medicinal chemistry (Dr. Phillips) and systems biology (Dr. Radivoyevitch). This group will integrate and collaborate with the drug-discovery effort by Dr. Wald. This new initiative is highly collaborative with the Developmental Therapeutics Program.

Developmental Therapeutics

Afshin Dowlati, MD & Yogen Sauntharajah, MD

Overall Goals

- Academic drug development towards commercialization
- Companion biomarker development to enable individual optimization of current and novel therapeutics

Scientific Focus Areas/Strategic Initiatives

The overall goals are pursued via a number of broad thematic areas or fronts. These are:

(i) New drugs to target the most common and important genetic alterations in cancer

The most common genetic alterations in cancer inactivate master apoptosis genes (e.g., TP53 or p16/CDKN2A etc.). There are limited or no treatment to target these most common alterations. Developmental Therapeutics will promote and facilitate research, discovery and evaluation of novel anti-cancer agents to address this problem, and to promote translation of novel cancer biology discoveries.

(ii) New assays to enable individualization of therapy

Cancer therapeutics are applied as if one size fits all, when inter-individual differences in disease genetics, pharmacogenetics and even gender may influence pharmacodynamic and biologic effects. Developmental Therapeutics will promote development of assays to facilitate patient selection and on-therapy optimization of treatments.

(iii) New drug delivery systems to improve therapeutic index

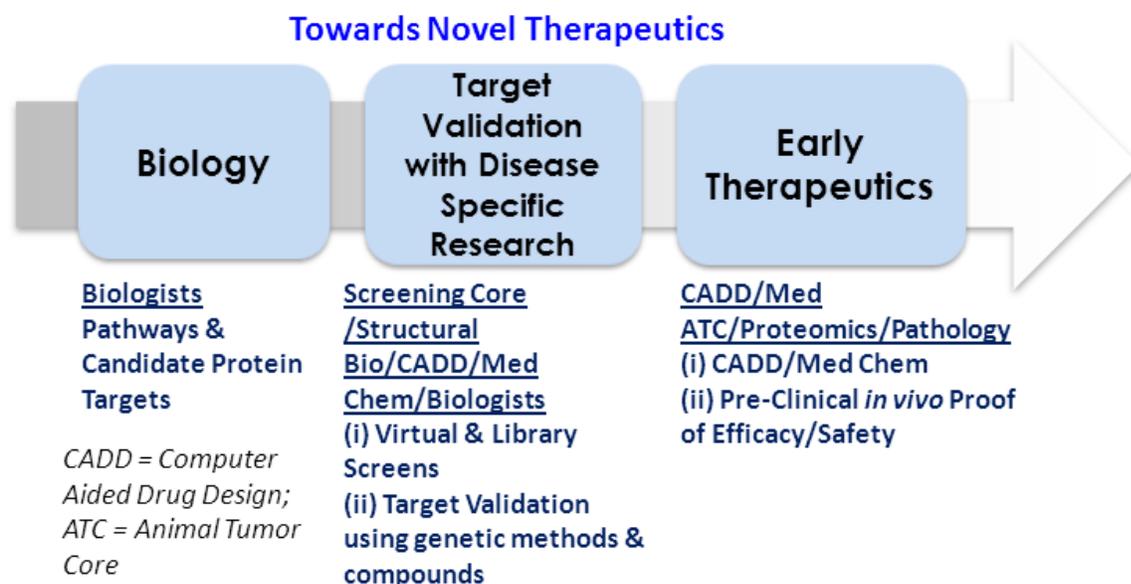
Novel drug delivery systems, e.g., based on new nanotechnologies, may facilitate more selective delivery of therapeutics to cancer cells. Developmental Therapeutics will facilitate interactions between Biomedical Engineering groups and cancer researchers to accelerate development of such systems.

(iv) Better pre-clinical in vivo models for more valid pre-clinical in vivo proof of concept experiments

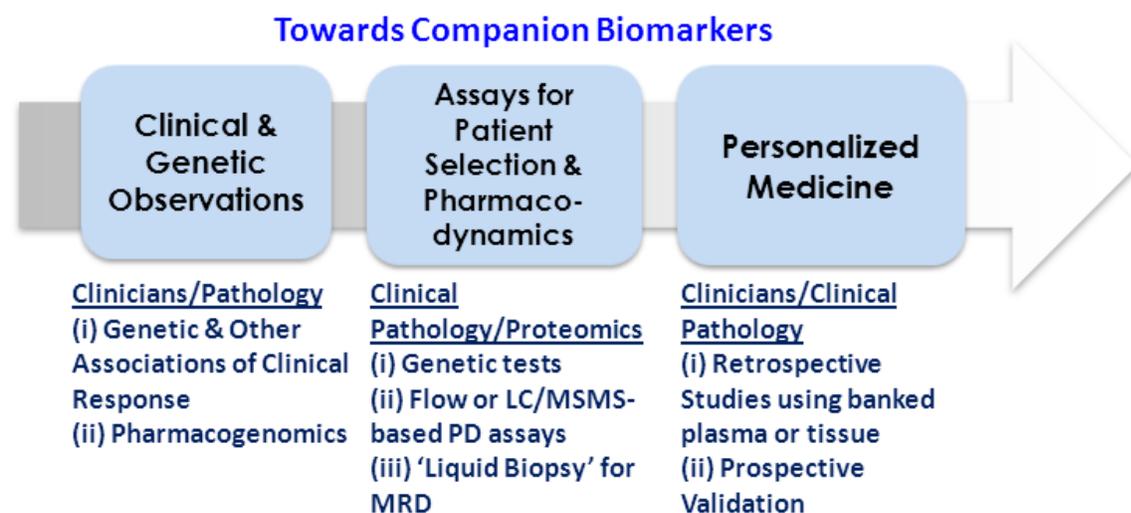
A crucial step in any therapeutic development effort is pre-clinical in vivo proof of principle, to justify the investments needed for IND-enabling studies. To improve the validity and impact of such studies, better pre-clinical in vivo models, that more faithfully recapitulate the biology and phenotype of human disease, are needed. Developmental Therapeutics will work with the Animal Tumor Core to develop these models and make them available to investigators.

Execution

Execution of these Strategic Initiatives requires fostering of relationships and interactions between different disciplines. The overall premise is that solutions to the problem of cancer lie in understanding its biology. Big pharmaceutical companies are not designed to understand biology, we are:



Scheme for Goal#1: Progress towards novel therapeutics requires close collaboration between multiple disciplines and infrastructure resources: biologists, structural biologists, computer-aided drug design experts, medicinal chemistry, screening core, proteomics experts and cores, animal tumor core and pathology, and finally, commercialization experts.



Scheme for Goal#2: Progress towards companion biomarkers requires close collaboration between multiple disciplines and infrastructure resources: clinicians, pathologists, genomics/flow cytometry/proteomic cores and clinical pathologists.

Developmental therapeutics will facilitate and engender these inter-disciplinary relationships and collaboration through inventory and advertising of available resources and expertise, development of needed additional assets, Academic Drug Development Seminars, and fostering of relationships with other internal organizations: Harrington Institute, Council for Advancement of Human Health, SPOREs, UO1 or NO1 consortiums, Case Western Reserve University Technology Transfer, Cleveland Clinic Innovations.

Program Needs

- Institutional pilot funds to facilitate early clinical trials and biomarker assessments of inter-institutional UH and CCF studies of CCCC pipeline molecules and NIH endorsed new therapeutics through NCI-CTEP and NCI-CAN.
- Development and support for essential preclinical studies of animal pharmacology, pathology and toxicology through the Drug Development Core Collective to bring CCCC molecules into an IND ready phase for productive dialogue with regulatory authorities, industry, and the NCI. While the transition through this critical development phase is complex, a platform technology for animal assessment will facilitate grant applications and discussion of novel compounds with NCI and industry partners.
- Expand the core resource for structure-activity studies and synthetic and computational chemistry, the composite of which will intensify efforts in drug discovery and early lead compound screening. Collaborative efforts underway with the Department of Chemistry at CWRU and at Cleveland State, and the drug screening program supported by the SOM with the University of Cincinnati have brought credible support for drug identification and evaluation and would benefit from compound synthesis capabilities.
- Develop, with the CTSA's in the state of Ohio, the new Ohio Network for Early Phase Clinical Trials in Oncology, designed to enhance cross institution and cancer center development and accrual of phase II clinical trials.
- New faculty in clinical pathology for CLIA certified biomarker validation and clinical testing of enzyme, pathway, DNA damage, tumor DNA and RNA biomarkers and similar profiles for therapeutic and observational clinical trials aimed at lining biomarker changes with drug effect, efficacy, prognosis and selecting therapies specific to the tumor.

Recruitment Priorities

Critical to the success of this program are recruitment of medicinal chemists, structural biologists and computer-aided drug design specialists.

Program 7: Cancer Imaging

James P. Basilion, PhD & Zhenghong Lee, PhD

The overall theme of this program is to provide an enhanced understanding of cancer biology via imaging resulting in new and improved approaches to cancer diagnosis and therapy. Translational research is stimulated in the program through formation of interprogrammatic collaborative groups interested in organ-specific cancer issues. Significantly, members remain closely associated with the Developmental Therapeutics Program (DTP) interacting by having a Cancer Imaging Program member attend each of the DTP monthly meetings to assess synergistic research potential. There is strong advocacy between clinicians and cancer biologists to incorporate proteomic and genomic approaches to inform imaging technology development, including the use of imagable tumor signatures to create virtual biopsies.

Scientific Focus Areas

- Nanotechnology and nanotherapeutics
- Image Guided Drug Delivery
- Stem Cell Imaging
- Tumor Microenvironment

Strategic Initiatives

- Expand research of imaging brain tumors. We have defined an area of opportunity in imaging the underlying biology of brain tumors with particular interest into the microenvironment, metabolic dysregulation, and dispersive brain cancer models. The program is developing strong cross-departmental and cross institutional teams focused on specific collaborative projects. Topics include nanotherapeutics and imaging, glioma cell migration and therapeutics, and radionuclide imaging.
- Encourage development of more and novel cross-disciplinary research efforts leading to multi investigator grant submissions such as initiatives linking breast cancer imaging to genomic changes.
- Support development of more clinical trials that focus on imaging including novel nuclear PET imaging tagged drugs and related agents to define tumor margins and location, and drug effects. The endpoint will be true quantitative acquisition of multiple tissue properties simultaneously, i.e., MRI fingerprinting. *Specific effort to support Developmental Therapeutics with imaging biomarkers are a priority.*
- Prepare novel imaging probes that identify hypoxia, DNA damage, pH, etc. that are selective in cancers for preclinical assessment and clinical use.
- Encourage Nanotechnology development around imaging and therapeutics.

Program Needs

- Infrastructure/equipment needs to support initiatives:
 - Partial support to establish cassette-based radiochemistry to facilitate translation studies
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- New Bioluminescent Imaging Instrumentation (Shared equipment grant submitted)
- Technical person to provide two-photon imaging
- Retreat and Pilot program funding

Recruitment Priorities

- Ongoing recruitment in BME should provide ample additional faculty expertise
- Increase clinical radiology participation in cancer clinical research projects across institutions
- Recruitment and funding for radiology research fellows

Program 8: Cancer Prevention, Control & Population Research

Gregory S. Cooper, MD & Susan A. Flocke, PhD

Scientific Focus Areas

- Risk prediction and decision making to inform cancer prevention and control
- Cancer epidemiology and gene-environment interaction, including international cancer health initiatives
- Health promotion and interventions to decrease cancer risk
- Quality of life and survivorship in cancer patients

Strategic Initiatives

- Tobacco Control Research: Program members are expanding their focus on tobacco with an emphasis on cigarillos/little cigars from a prevalence and regulatory perspective, and cessation assistance, particularly the intersection between primary care and public health. Both focal areas emphasize assisting economically disadvantaged populations. Surveillance work of the CDC funded Prevention Research Center for Healthy Neighborhoods and methods expertise from the Behavioral Measurement Core have facilitated these initiatives. The efforts have led to an inter-institutional P01 application and several new NCI and PCORI grant applications.
- Risk Prediction and Decision Making: Based on the expertise and research programs of members, this area has emerged as a new focus area within the program. Areas of emphasis include simulation modeling and development and application of clinical decision aids to facilitate cancer prevention and prognostic decision making.
- Cohorts: Program members have developed several study populations/cohorts for cancer epidemiology/prevention research, with a focus on gene-environment interaction. These cohorts add significant value to the Case CCC program by creating opportunities for secondary data analysis and opportunities for prospective data collection because of the ability to collect and store biomaterials. Initiatives that have recently begun or are planned for the near future include studies of the fecal microbiome in subjects with colon adenomas and colonoscopy controls, studies of 15-PDGH in a population-based cohort of patients with colorectal cancer and advanced colon adenomas, the interaction of sleep quality and genetics in breast cancer risk, and creation of a biobank in high risk patients undergoing spiral chest computerized tomography scans for lung cancer screening.

Recruitment

- Integrative Oncology: The University has received private funds to endow a Professor of Integrative Oncology who will develop a research program in the use of holistic and natural approaches as complementary therapy to more traditional disease management. A search for this individual is currently ongoing and it is anticipated that this individual's research program will contribute to and potentially bridge chemoprevention and survivorship research within the Prevention Program and will serve as a lead collaborator with other disease-focused programs.
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- **Cancer Disparities Research:** Racial and socioeconomic disparities in cancer screening receipt, stage at cancer diagnosis and prognosis following initial cancer treatment have been well recognized by the Case CCC. The Case CCC has initiated the Office of Minority Cancer Disparities Research to champion the Cancer Center's efforts to reduce or eliminate disparities in our community through orchestrated efforts in research, education and outreach. The Center is actively recruiting an established cancer investigator with a track record in cancer disparities research to lead this high priority research area. He or she will then be charged with recruitment of additional faculty to further develop this program, which will span the focus areas of the prevention program.
- **Biostatistical Support:** Given the expanding program in community-based and practice-based research, there is an urgent need for recruitment of a biostatistician with expertise in methods that are relevant to community based and practice based research, specifically, multilevel modeling, structural equation modeling, complex sampling, analyses of social network data, time series analyses. The funding of recent grant applications was hindered by the lack of CWRU-based personnel with these skills.
- **Programmer Support:** The use of large datasets for studying oncology-based clinical, epidemiological and health policy research has traditionally been a strength in the Prevention Program. However, due to uncertainties in grant funding in the current climate, we have been unable to retain analysts who have trained at CWRU. In addition, there are an increased number of cancer-related projects proposed by trainees and faculty that cannot be performed because of lack of programmer support. We propose a position with a base of intramural support which will likely be supplemented by grant support.

Initiatives

Cancer Genomics and Bioinformatics Initiative

The Case CCC recognizes that major cross-institutional investment is needed in a coordinated fashion to develop an innovative, productive and responsive capability in cancer genomics. This need is pervasive in cancer research and cancer care. Furthermore, cancer genomics will transform clinical decision-making and population health. We now have the opportunity to understand our risks and take measures to accurately reduce those risks and treat cancer with precision. A multi institutional and community investment is needed. The bioinformatics effort will catalyze interactive databases that link annotated samples of results with analytical techniques for all “omics” platforms – genomics, proteomics, RNAseq and noncoding RNAs.

Themes

Recognizing these needs, the Director tasked several working groups to identify needs in the Case CCC to define the scope and structure of this initiative. The following working groups were convened:

- Bio-Informatics: Jill Barnholtz-Sloan, Nick Beckloff, Sheldon Bai, Kishore Guda, John Barnard, Angela Ting, Patrick Mergler, Bob Lanese, Mike Warfe, Dan Clark, Tom LaFramboise, Mike Kattan, Charis Eng, Sandy Markowitz, Mark Chance, Kristin Waite, Yingli Wolinsky
- High risk population identification and analysis: Charis Eng, Goutham Narla, Lyndsay Harris
- Tumor analysis: Joe Willis, Jaroslaw Maciejewski, Angen Liu
- Platforms and infrastructure: Cliff Harding, Mark Chance, Sandy Markowitz, Peter Scacheri, Tom LaFramboise, Nick Beckloff, Charis Eng, Eric Hsi;
- Clinical research and decision making: Neal Meropol, Lyndsay Harris, Afshin Dowlati, Ernie Borden, Brian Rini

The working groups developed strategic reports outlining the current state of the art in the field and a brief outline of institutional support and Case CCC priorities. The groups concluded that infrastructure development would advance the use of genomics, including germline analysis across diseases and disciplines but that cancer represented the focal point given the potential for broad clinical impact. The initial recommendations were presented to the Case CCC Institutional Board of Governors in June 2012. They requested further refinement of the request by the fall of 2012.

Scope

The treatment of cancer has been largely empiric, with all patients with a particular organ-specific diagnosis (eg. lung cancer, breast cancer) treated in a fairly uniform fashion. Discovery of specific driving mechanisms for cancer development along pathways defined by genetic mutations and altered gene expression linked to the recent capability of sequencing individual patient tumors has led to new paradigm shifts in our understanding of the diagnosis and treatment of cancer. Success is linked to viewing cancer as an individual disease – each patient has a unique cancer affected by specific genetic changes that coalesce into a unique – “personal” abnormality that can now be mapped. This fingerprint gives rise in some but not all

cases to recognizable “actionable” abnormalities with which physicians can ascribe prognosis, effective treatments and survival predictions.

Some genetic changes have given rise to successful precision medicines that are now the mainstay of cancer diagnosis and treatment. Examples include imatinib for CML and GI stromal tumors, EGFR targeted therapies in lung and colorectal cancers, EGFR/EML4-ALK testing for lung adenocarcinomas and HER2 for breast and gastric cancers. Insofar as the variability in cancer can be defined at the molecular level, and treatment can be selected based upon the unique characteristics of each patient and tumor, the personalization of cancer care can be realized. This variability may be somatic, i.e. a feature of the tumor cell, or germline, a feature of the host. Whereas the former may impact tumor response to a particular treatment, the latter may be most closely associated with drug disposition (i.e. pharmacokinetics, pharmacodynamics), and hence treatment toxicity as well as response to particular therapies. The complexity of cancer dictates sophisticated leading edge solutions that coalesce the latest technology, therapeutic agents and informatics into improve clinical outcomes. This effort is termed “precision medicine”.

Strategic Initiatives

The field of cancer genomics represents a critical opportunity in current and future cancer research, and establishing capability in this area is the highest priority for the Case CCC and its scientific and clinical programs. The opportunities in this area are broad, ranging from basic research to translational/clinical research. In addition, clinical application to patient care will develop, establishing the need for clinical programs to anticipate and plan development of cancer genetic/genomic testing in clinical diagnostic laboratories. Given the expertise within the Case CCC (e.g. discovery and cancer drug development), the coordination across institutions within our consortium, and the large patient population served, the Case CCC is in an ideal situation to achieve leadership nationally in our approach to clinical cancer research and cancer care.

There is an inseparable link between discovery genomic research and clinical practice. While these efforts take place in research labs and in clinical spaces segregated between clinical practice and research investigation across three institutions, building three separate efforts within the Case CCC consortium institutions would be inefficient. The Case CCC proposes that the three institutions build complementary efforts that align with their primary mission and in so doing, establish a comprehensive program for cancer genomics and personalized diagnosis and evaluation of cancer patients leading to precision medical diagnosis and decision making. These efforts will share platforms, bioinformatics and genomic data across institutions under the appropriate privacy and security contingencies and guidelines, compliant with federal laws and IRB, HIPAA regulations.

Program Needs

We have the unique opportunity to link cancer genomic discovery in our scientific programs with direct cancer care and clinical decision making that will define how patients select their provider and how we provide the best care to the community. Given our expertise and clinical cancer

volume, we intend to be national leaders in the field of genomic medicine. We propose five areas of investment:

- NextGen Sequencing capabilities for discovery research, including whole genome sequencing, RNASeq, exon sequencing
- Clinical genomic sequencing in a time sensitive and CLIA-approved fashion focused on actionable changes that impact treatment and prognosis
- Appropriate infrastructure to support linked clinical data systems and research databases, biospecimen handling, and bioinformatic pipelines to support genomics needs for real-time clinical applications
- Protocols and workflow for the study and ultimate application of genomic information to genetic predisposition and therapeutic decision-making
- Clinical support tools to allow medical providers to deliver actionable genomic information, starting with clinical trials, but including a genomics tumor board review panel for clinical utility

For optimal cost-effectiveness, we propose that the institutions coordinate these activities through complementary investments to support collaborative efforts.

Aging and Energetics Initiative

Nathan A. Berger, MD

Scientific Focus Areas

The 24 members of this initiative study the basic mechanisms and biobehavioral aspects of the linkages between aging, energetics, obesity and cancer. Investigators use animal models, psychosocial research, and the study of patient cohorts.

The investigator groups coalesce around:

- Genetics, energy balance and environment in aging, age related cancers and survivorship
- Psychosocial and Health Services research
- Therapeutic and non-therapeutic interventions that evaluate the impact of energy balance, weight loss, sleep, and support interventions on outcomes
- Interactions of obesity, aging and cancer in model systems

Members have developed expansive cohorts to study these interactions in patients with and at risk for colon, breast and brain tumors and have developed longitudinal observation cohorts such as the Kentucky and Shanghai cohorts.

Strategic Initiatives

- To expand efforts in survivorship research particularly focused on the impact of aging and obesity on recurrence
- To study the impact of age and comorbidities on tolerance to cancer treatments
- Translate model system discoveries into patient based research and interventions

Recruitment Priorities

- Recruit faculty in cancer metabolism that would develop collaborative efforts in human energy metabolism and cancer etiology and recurrence
- Recruit cancer disparity researcher to assess the issues of aging and energetics in underserved populations
- Develop an exercise physiology/nutrition lab and the scientists needed to run it (including a DEXA scanner to assess body composition)

Brain Tumor Initiative

Jill S. Barnholtz-Sloan, PhD & Steven S. Rosenfeld, MD, PhD

Themes

The Case CCC Brain Tumor Initiative will utilize the strengths already available throughout Case CCC and its respective academic institutions to foster cutting-edge neuro-oncology research. The Case CCC has assembled over 65 investigators with an interest in the basic biology of brain tumors, use of tissues and genomics, development of novel therapeutics, and use of marker driven therapeutics for these recalcitrant malignancies. The initiative is linked to biorepository and genomics efforts, and has an active clinical trials group.

Scientific Focus Areas

- Brain Tumor Stem Cells and Tumor Models: Investigators are examining the defining properties of brain tumor stem cells and are developing novel tumor models based on these insights. Gene expression patterns that define this unique tumor cell population, the microenvironmental requirements for tumor stem cell maintenance, and the critical gene products that can serve as targets for translational strategies to eliminate this chemo- and radio-resistant cell population are aspects of the research focus.
- Engineering Applications to Neuro-Oncology: Brain tumor imaging, nanotechnology, and polymer science forms the basis of collaborative efforts to translate the therapeutic potential through pre-clinical tumor models.
- Population Science and Genomics/Proteomics: This group evaluates associations between somatic genomics and clinical outcomes in individuals with brain tumors. The goal of this work is to develop models that predict treatment response, based on:
 - associations between germline and somatic genomics that look for risk or prognostic markers;
 - molecular pathology-based classifications of brain tumor subgroups;
 - proteomic targets for risk and prognostic prediction for neuro-oncology.
- Brain Tumor Angiogenesis and Dispersion: Pre-clinical studies of several angiogenesis inhibitors are already underway. A similar research focus on glioma dispersion is currently being formed.

Strategic Initiatives

- Continue to develop and build a rigorous clinical neuro-oncology investigational base by developing new Phase I or Phase II trials available through the Ohio Neuro-Oncology Consortium or a variety of NCI clinical consortia such as ABTC, RTOG, and ECOG
 - Discover new prognostics and diagnostics for brain tumors using genomics, proteomics, epigenomics, and transcriptomics by continuing to implement comprehensive and integrated informed consent, collection of biospecimens, clinical annotation and active follow-up for all brain tumor patients via the Ohio Brain Tumor Study
 - Expand in vitro and in vivo model systems for basic and translational research for brain tumors
 - Development of a clinical/translational career development program in neuro-oncology
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- Coordinate efforts towards PPG or a Brain Tumor SPORE application within the next two years

Program Needs

- Expand biorepository functions to include SOPs for tissue collection, processing and storage; extraction of analytes from tissue and blood; implementation of a biorepository and database for brain tumors. Personnel to manage this biorepository
- Support brain tumor animal models core and coordinate pre-clinical trials in a variety of animal models of glioma
- Support for pilot studies in brain tumors leading to NIH grant funding

Recruitment Priorities

- Faculty recruitments with research interests in priority areas such as immunotherapy, oncolytic viral therapy