CTSI-Cancer Center Workshop

Future Directions & Opportunities

for Cancer-related Research Collaborations

CTSI – Cancer Center Workshop

Academic & Research Disciplines

- Medicine
- Biomedical Informatics
- Rehabilitation
- Psychology
- Economics
- Nursing
- Dentistry
- Public Health
- Computer Science
- Business
- Physical Therapy
- Exercise Science
- Biomedical Engineering
- Genetics
- Physics
- Chemistry
- Mechanical Engineering
- Psychiatry

CTSI – Cancer Center Workshop

Ming You, MD, PhD

- Dr. You received his medical degree from Peking University College of Medicine and his Ph.D. in Pathology from Medical College of Ohio
- He is the Joseph F. Heil Jr. Professor in Molecular Oncogenesis
- Dr. You is Professor of Pharmacology and Toxicology, Senior Associate Dean for Cancer Research, Education and Clinical Care and Director of the MCW Cancer Center
- Dr. You’s primary research interests are in the area of Genetics and Chemoprevention of Lung Cancer

MCW Cancer Center Director

Ming You, MD, PhD

Joseph F. Heil, Jr. Professor in Molecular Carcinogenesis

Sr. Associate Dean for Cancer Research, Education, and Clinical Care

Professor of Pharmacology & Toxicology

MEDICAL COLLEGE OF WISCONSIN

CANCER CENTER

Overview of the MCW Cancer Center

MCW Cancer Center

- Cancer is the TOP STRATEGIC PRIORITY of The Medical College of Wisconsin (MCW) because of its devastating effect on so many

- Our VISION:
  To become an NCI-designated Cancer Center as characterized by scientific excellence and the capability of integrating diverse MCW research programs to focus on the problem of cancer

Research Cures Cancer!

Location


300 mi
200 mi
100 mi
minnesota
michigan
WISCONSIN
Eau Claire
Green Bay
Appleton
Sheboygan
Madison
MCW
iowa
illinois

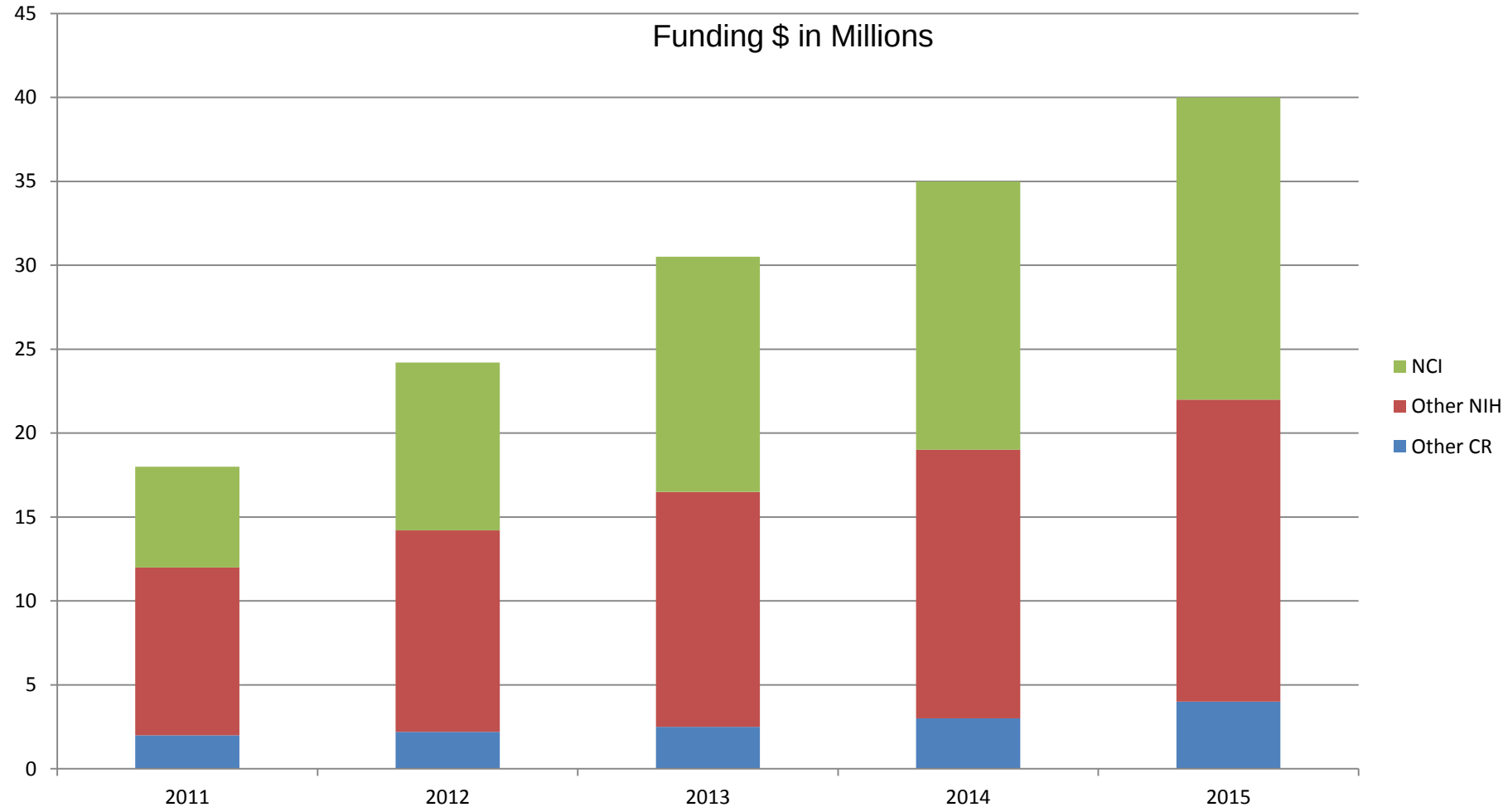
Why NCI-designation is Important

- Improves patient treatment, care, and prevention of cancer
- Attracts the best and brightest physicians and scientists to our region
- Brings more National Cancer Institute dollars to the region
- Promote scientific collaborations among the researchers in our region
- Lets industry know that we are ripe for a high tech environment and for economic development

NCI-Essential Characteristics

- Cancer Focus
- Institutional Commitment
- Organizational Capabilities
- Facilities
- Center Director
- Interdisciplinary Coordination and Collaboration

Growth Expected in MCW Cancer-related Research (total cost) in the Next 5 Years



NCI Funding Goals

Clinical

Basic

Translational

Experimental Therapeutics

Cancer Cell Biology

Prevention, Control, & Population Sciences

Pediatric Oncology/ Women's Cancers

Molecular Carcinogenesis & Chemoprevention

CIBMTR

Transplantation Biology & Immunotherapy

Cancer Imaging

Research Program Leaders

Ming You, MD, PhD
Director

Molecular Carcinogenesis & Chemoprevention
Gary Stoner, PhD
Ronald Hines, PhD

Cancer Cell Biology
Balaraman Kalyanaraman, PhD
Carol Williams, PhD

Transplantation Biology & Immunotherapy
William Drobyski, MD

Cancer Imaging
Kathleen Schmainda, PhD
James Hyde, PhD

Prevention, Control, & Population Science
Ann Nattinger, MD, MPH

Experimental Therapeutics
James Thomas, MD, PhD

Pediatrics
Michael Kelly, MD, PhD

Zablocki VA Hospital
Jeffrey Whittle, MD

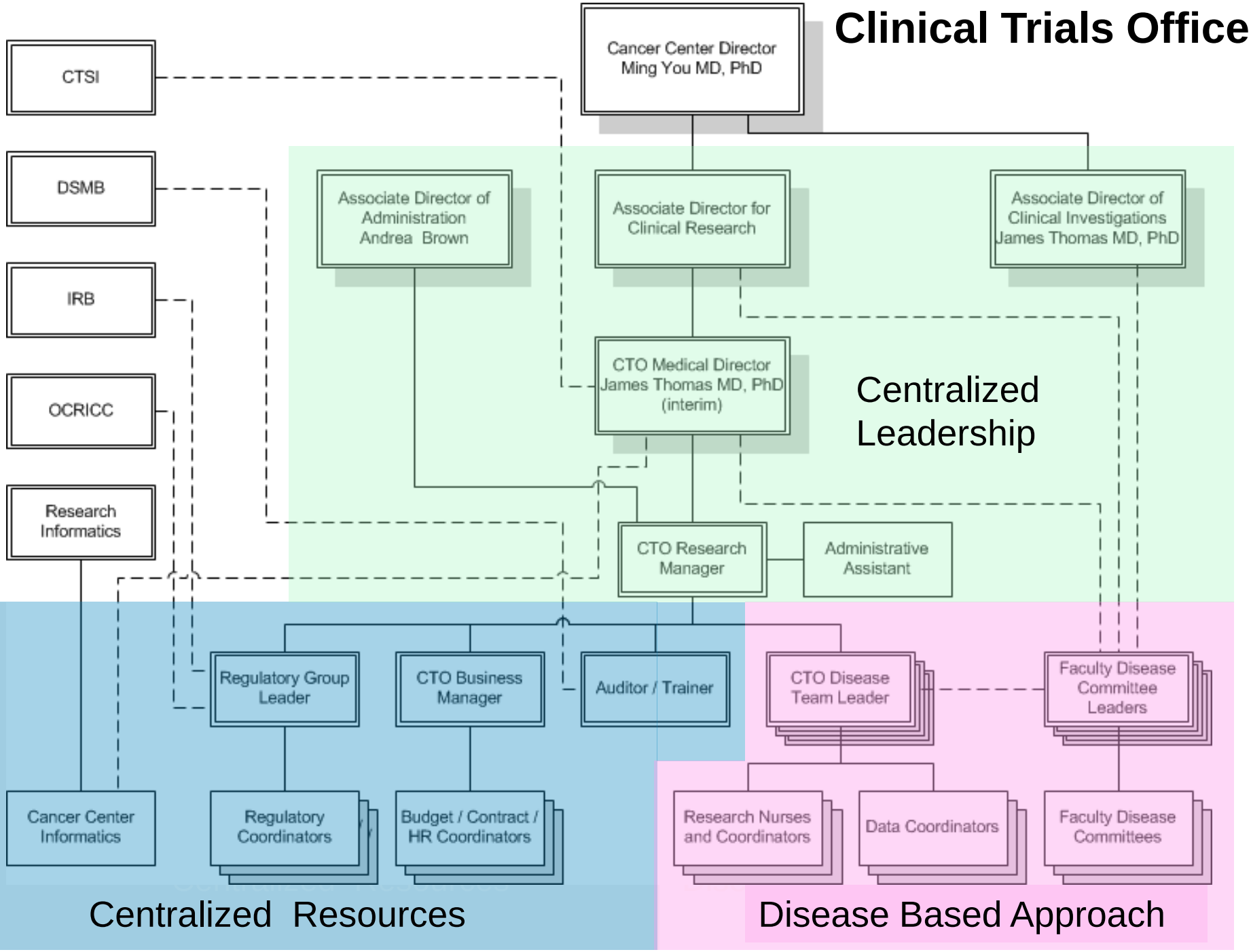
Pediatric Oncology

- Marcio Malogolowkin, MD, Assoc. Dir. of Pediatric Oncology
- MACC Fund Chair – Pediatric Oncology Research
- Increase interaction of physician and laboratory scientists to further our understanding of disease and to provide unique therapy options for children and young adults with cancer
  - Increase preclinical and translational capabilities for pediatric cancers
  - Increase early phase clinical trials
  - Increase NIH/NCI funding
  - Support training programs for pediatric cancer investigators

Shared Resources

- Biostatistics and Informatics Core – John P. Klein, PhD
- Clinical Trials Office – James P. Thomas, MD, PhD
- Tissue Procurement Core – Saul Suster, MD
- Immunological Monitoring Core – Jeffrey Woodliff, PhD, and Carolyn Taylor, PhD
- Small Animal Imaging Core – Jim Joers, PhD and Kimberly Pechman, PhD
- Bioenergetics Core – Balaraman Kalyanaraman, PhD
- Observational Methods – Tina Yen, MD, MPH
- Genomics Core – Howard Jacob, PhD

MEDICAL COLLEGE OF WISCONSIN
CANCER CENTER


Clinical Trials Office
CTSI
DSMB
IRB
OCRICC
Research Informatics
Cancer Center Director Ming You MD, PhD
Associate Director of Administration Andrea Brown
Associate Director for Clinical Research
Associate Director of Clinical Investigations James Thomas MD, PhD
CTO Medical Director James Thomas MD, PhD (interim)
Centralized Leadership
CTO Research Manager
Administrative Assistant
Regulatory Group Leader
CTO Business Manager
Auditor / Trainer
CTO Disease Team Leader
Faculty Disease Committee Leaders
Cancer Center Informatics
Regulatory Coordinators
Budget / Contract / HR Coordinators
Research Nurses and Coordinators
Data Coordinators
Faculty Disease Committees
Centralized Resources
Disease Based Approach

Faculty Disease Committees

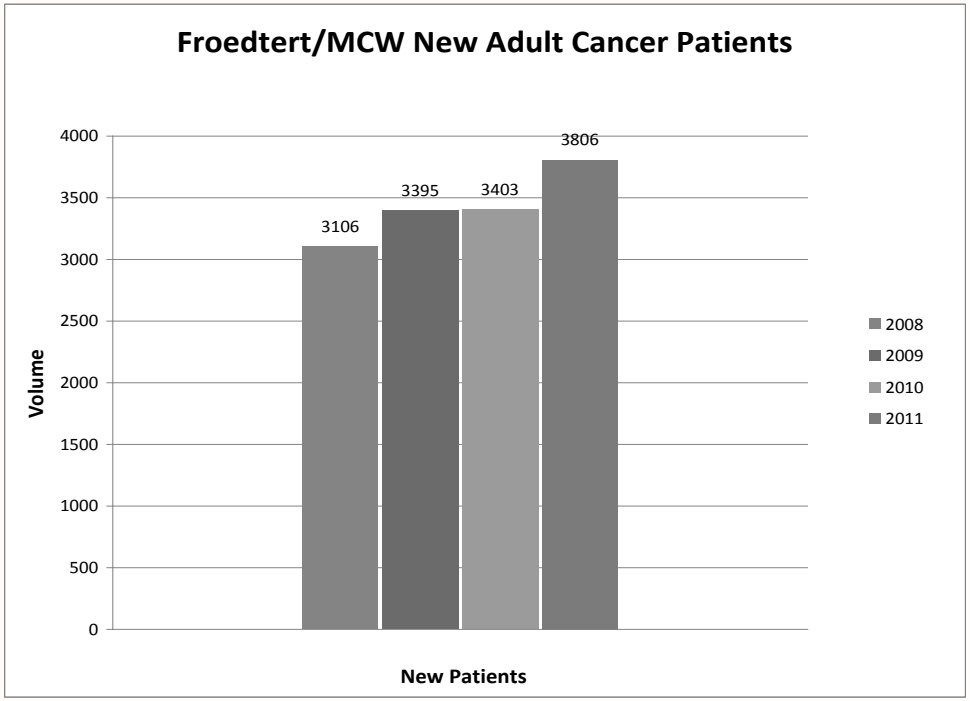
- Breast Cancer
- Genitourinary Cancers
- Endocrine Cancers
- Colorectal Cancers
- Liver, Pancreas and Bile Duct Cancers
- Blood and Lymph Node Cancers
- Bone Marrow Transplant
- Brain and Spine Tumors
- Bone and Connective Tissue Cancers
- Head and Neck Cancers
- Skin Cancers
- Lung Cancers
- Gynecologic Cancers
- Pediatric Cancers

- Faculty Disease Leaders
- Co-leaders selected from relative disciplines
  - e.g. surgery, med onc and rad onc
- Identified by the respective department and division leaders in conjunction with Cancer Center Leadership

Froedtert & Medical College of Wisconsin

Clinical Care at Froedtert Hospital

	2008	2009	2010	2011	Mean
Total New Cancer Patients per year	3106	3395	3403	3806	3,428
Solid Tumor per year	2609	2840	2886	3208	2,886
Hematologic/Lymphatic per year	563	505	470	556	499
Other/Ill defined per year	34	50	47	42	43
Adult Transplants per year	118	144	140	154	139

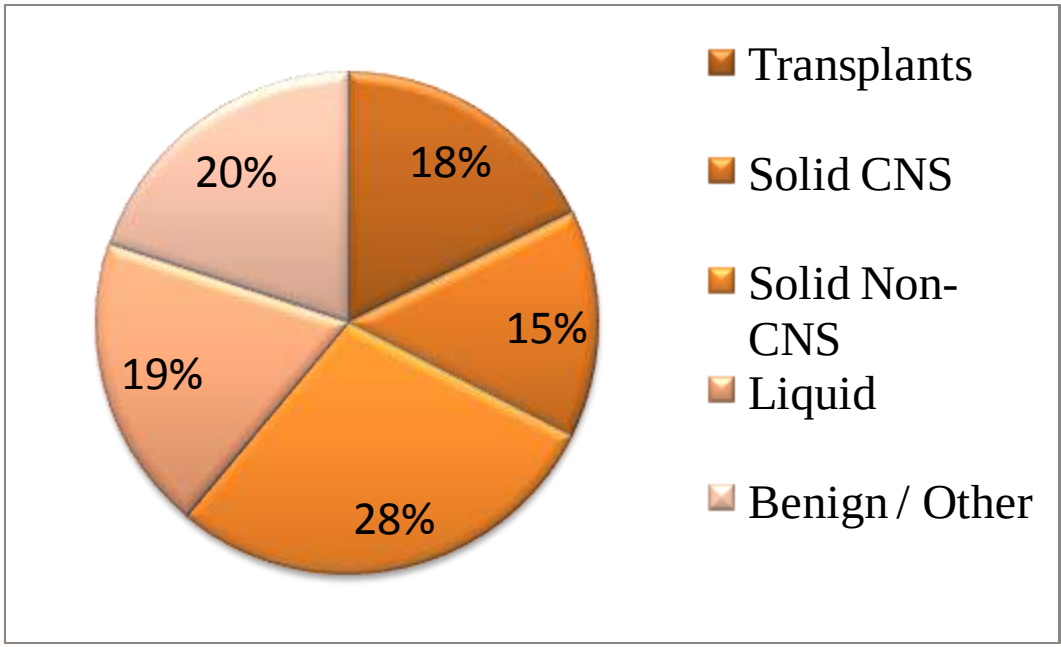


Clinical Care at Children's Hospital

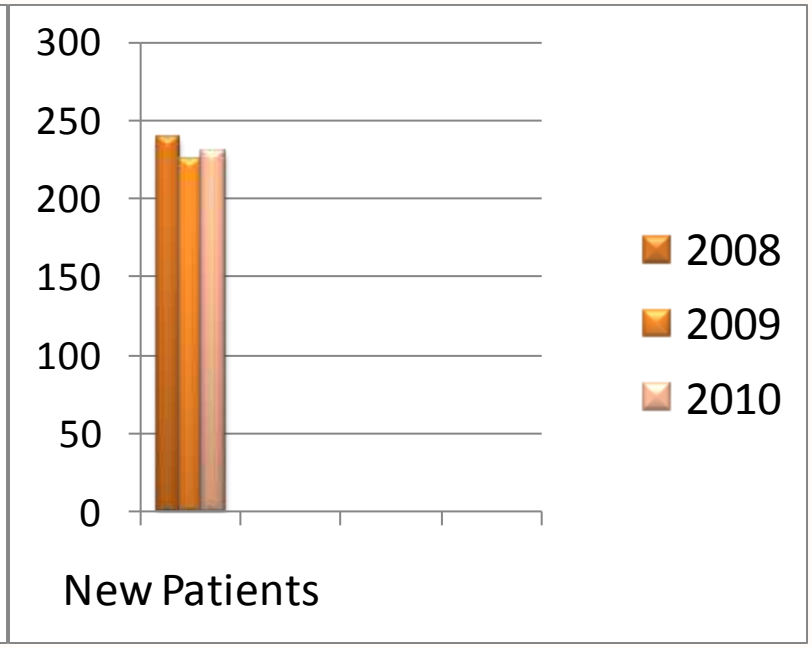
Average Number of New Patients per Year (2008-2010)

Total New Patients Per Year	232
Transplants	42
Solid Tumor CNS	34
Solid Tumor Non-CNS	66
Liquid	44
Benign / Other	46

Composition of Patient Population



New Patient Volume is Constant



MCW Tissue Bank

MCW TISSUE BANK:

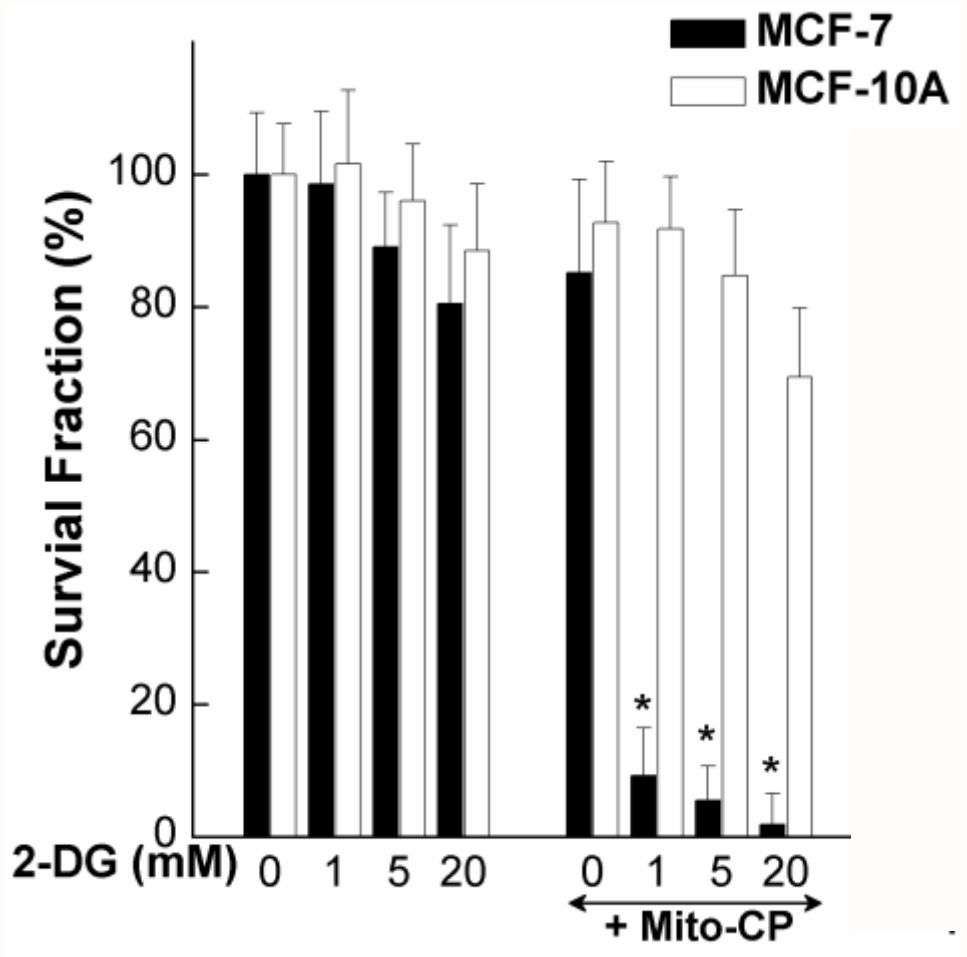
Location: Dynacare Lab Building, lower level, L-50
(next to Histology Lab)
Tissue Bank Manager:
Mary Rau
Director of Tissue Procurement:
Dr. Jian Huang
Director of Tissue Bank:
Saul Suster, M.D.

FUNCTIONS:

- To serve as the core facility at MCW for the prospective banking of specimens
- To serve as a link and “honest broker” between the banked specimens and the Clinical Data Warehouse (currently being developed by MCW Bioinformatics)
- To obtain informed consent from patients for the banking of specimens for research
- To facilitate research development and collaboration among researchers on campus
- To serve as a tissue/pathology core for future institutional core grants (PPG, SPORE, etc)
- To ensure uniform processing and handling of research specimens and the integrity and quality of the samples banked for research

Research Example

The mitochondria-targeted antioxidant Mito-CP enhances the effects of 2-deoxy-D-glucose (2-DG), and kills MCF-7 breast cancer cells but not MCF-10A mammary epithelial cells

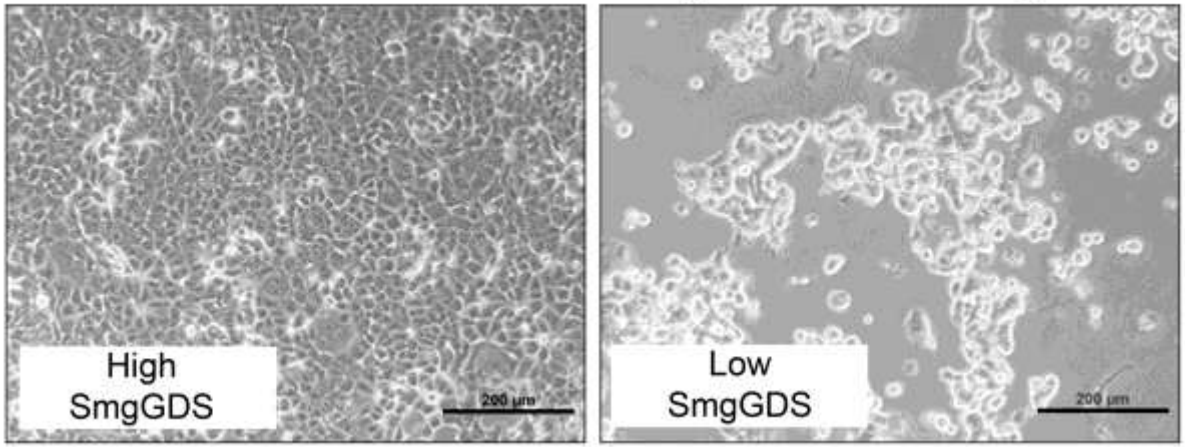


Identification of New Therapeutic Targets

Cancer cells make abnormally high amounts of the protein called SmgGDS.

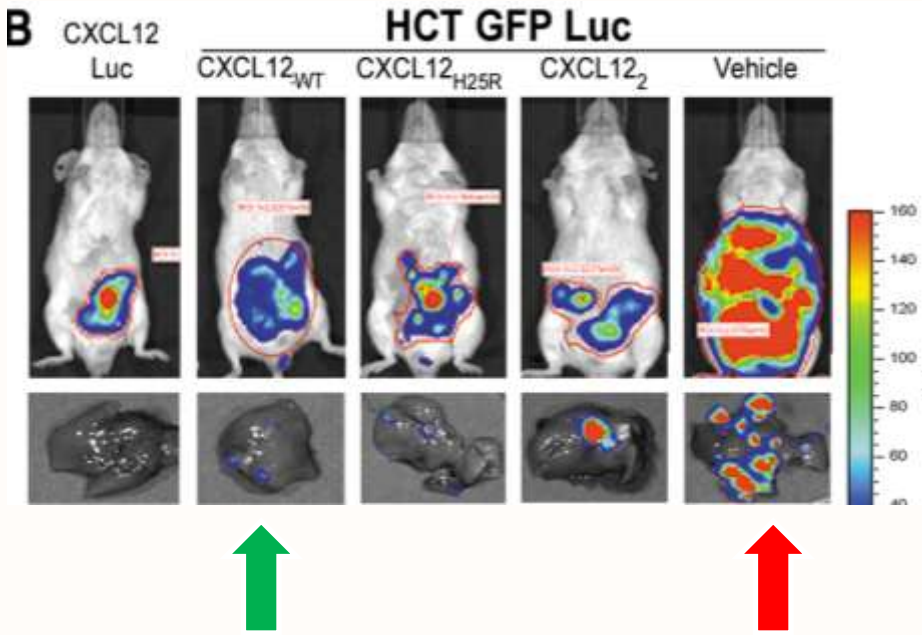
Cancer cells grow more slowly when we stop the cells from making SmgGDS.

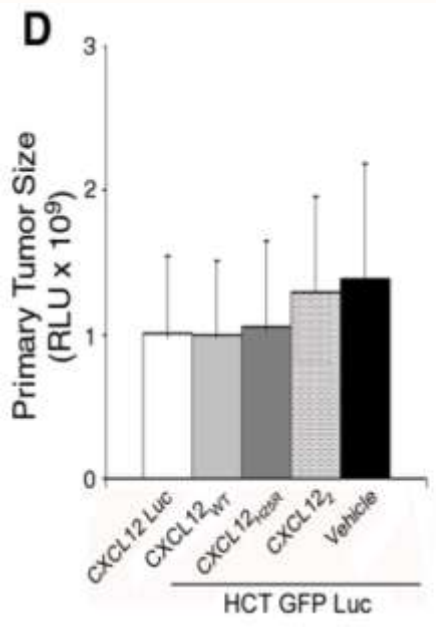
Breast Cancer Cells Growing in the Laboratory

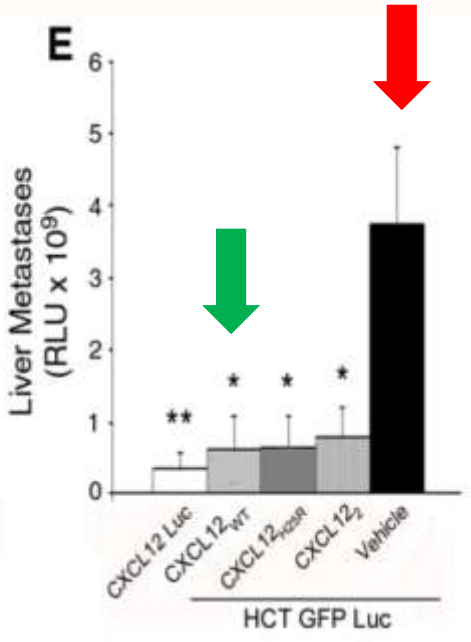


Therapeutic approaches to control SmgGDS and other newly identified molecules that promote cancer are being developed in collaboration with Cancer Center members and with scientific colleagues worldwide.

CXCL12 Treatment Inhibits Metastasis in a Preclinical Mouse Model

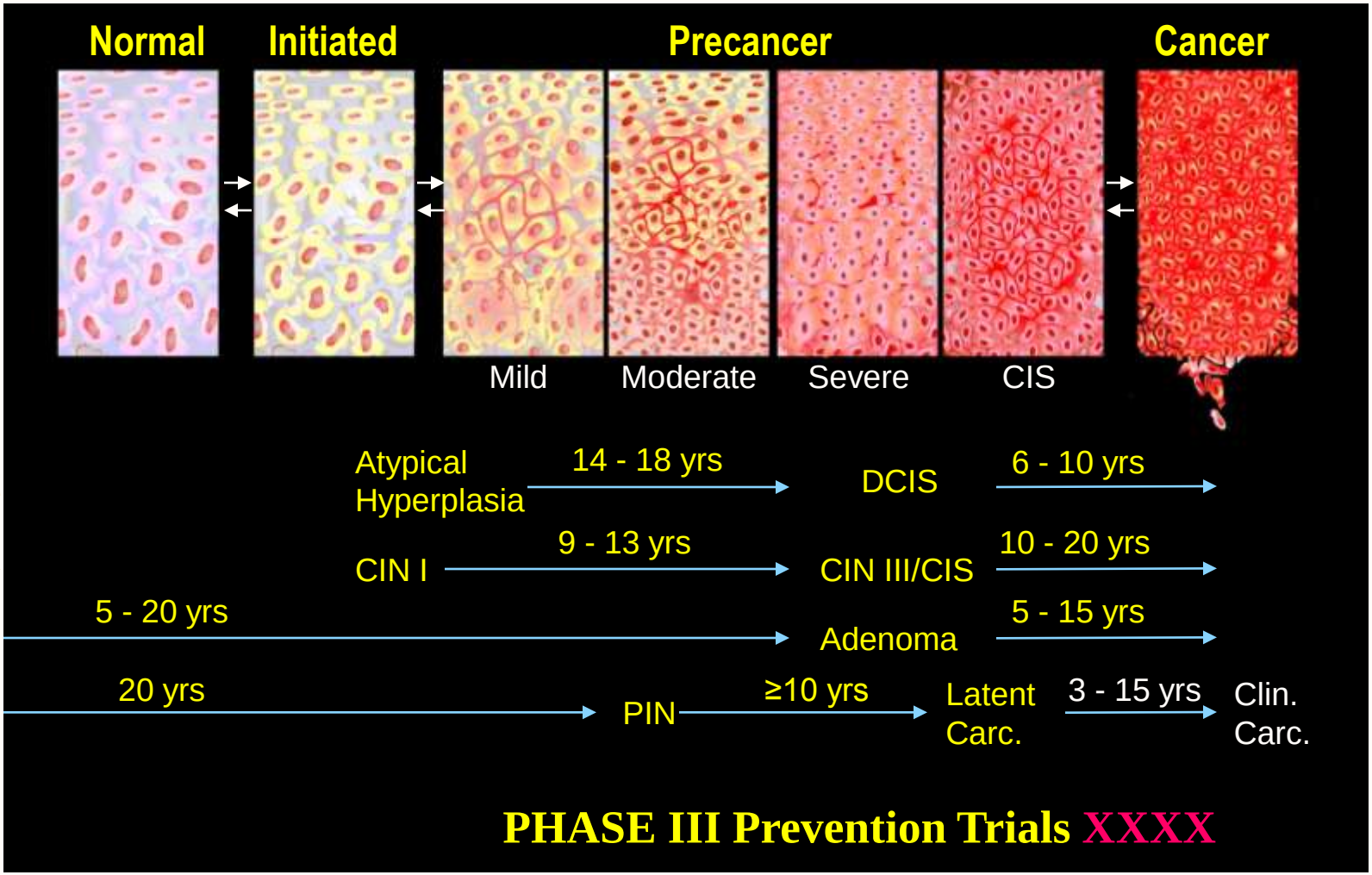






Drury et al., *PNAS*, 2011

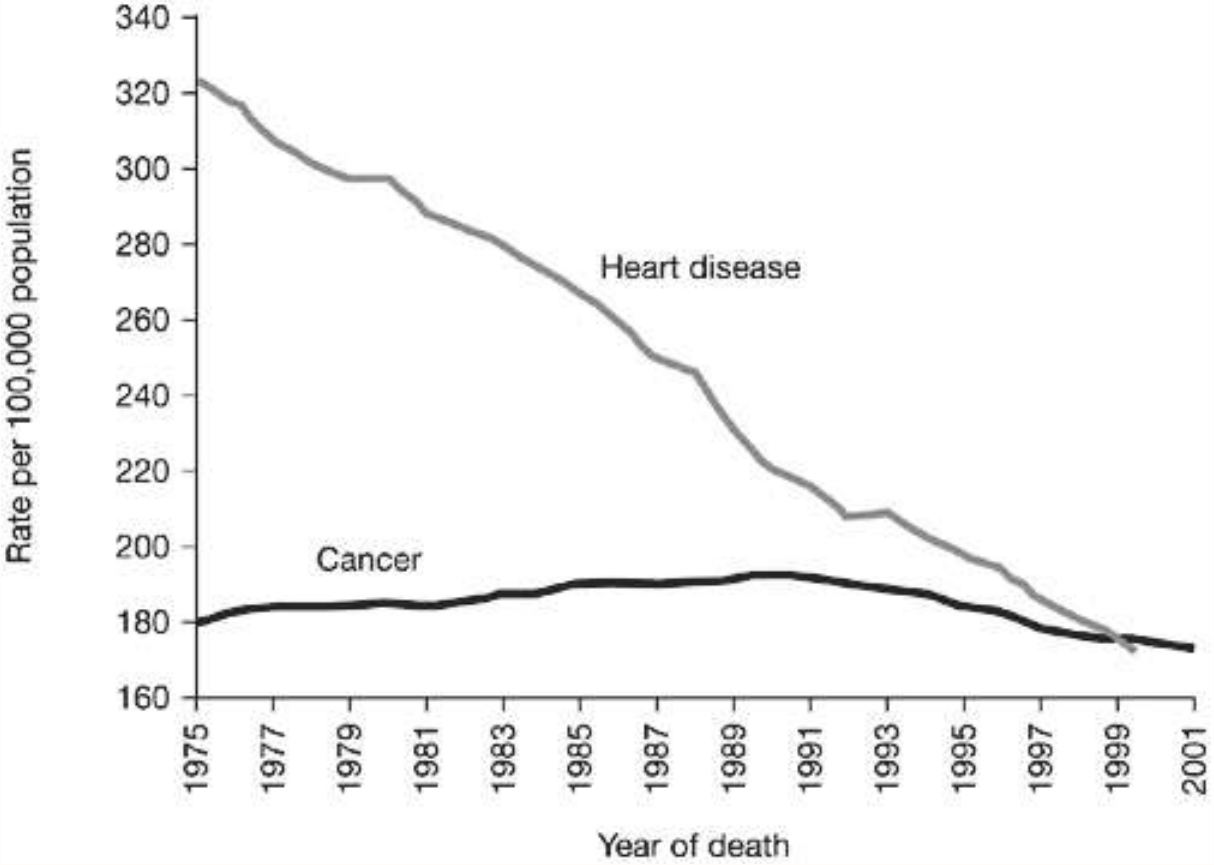
Cancer Prevention Opportunities
When To Do Animal Studies



Animal Experiments XXXXXXXXXXXXXXXXXXXXXX

Research Example: Cancer Chemoprevention

For men and women in the US, younger than 85 years, death rates from heart disease have dropped markedly since 1975, while overall death rates from cancer have shown relatively little change



Sporn MB and Liby KT (2005) Cancer chemoprevention: scientific promise, clinical uncertainty *Nat Clin Pract Oncol* **2:** 518–525 10.1038/ncponc0319

Research Example: Cancer Chemoprevention

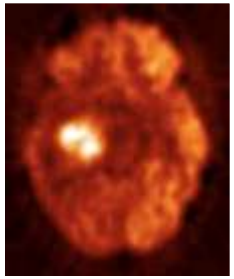
Use of Black Raspberry Powder
to Prevent Cancer

Freeze-dried powder

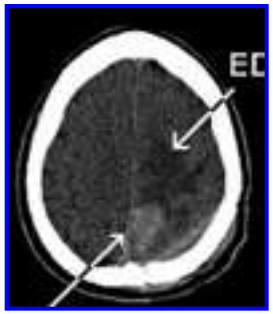
Medical Imaging

…….plays a central role in cancer care & research.

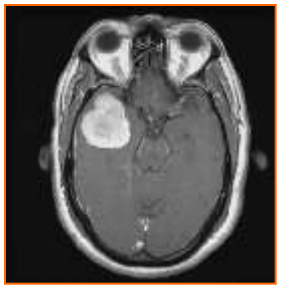
PET
(Positron Emission Tomography)



CT
(x-ray Computed Tomography)



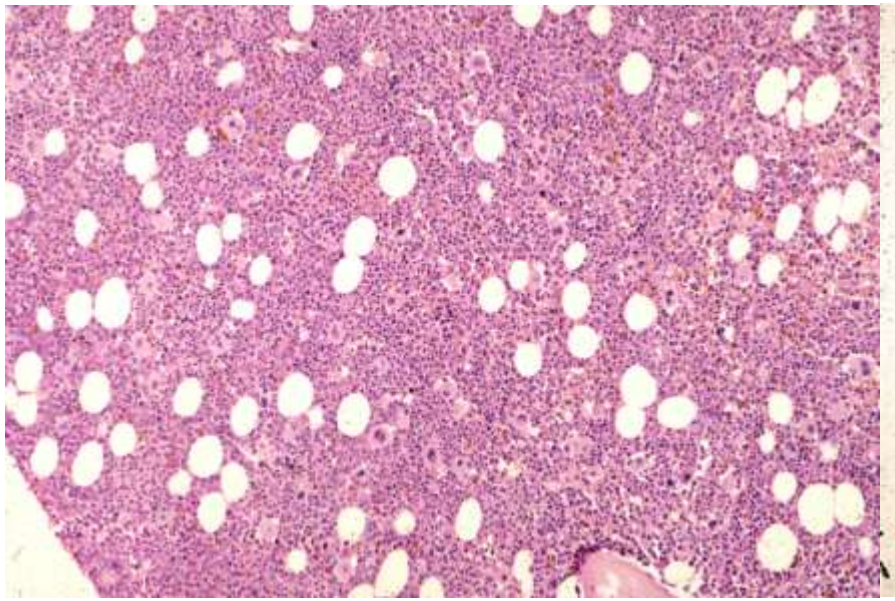
MRI
(Magnetic Resonance Imaging)

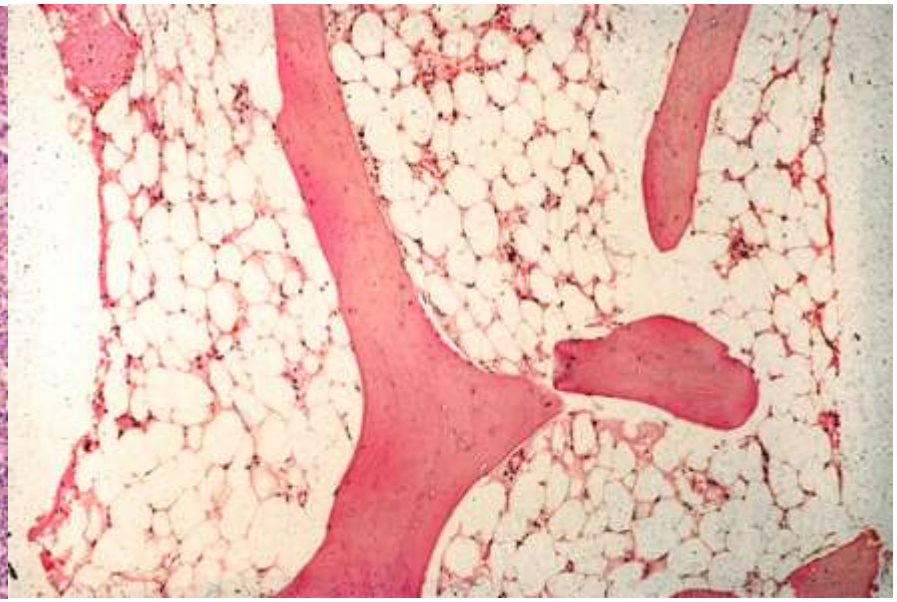


Truly Transformative Power Lies Ahead !!!!

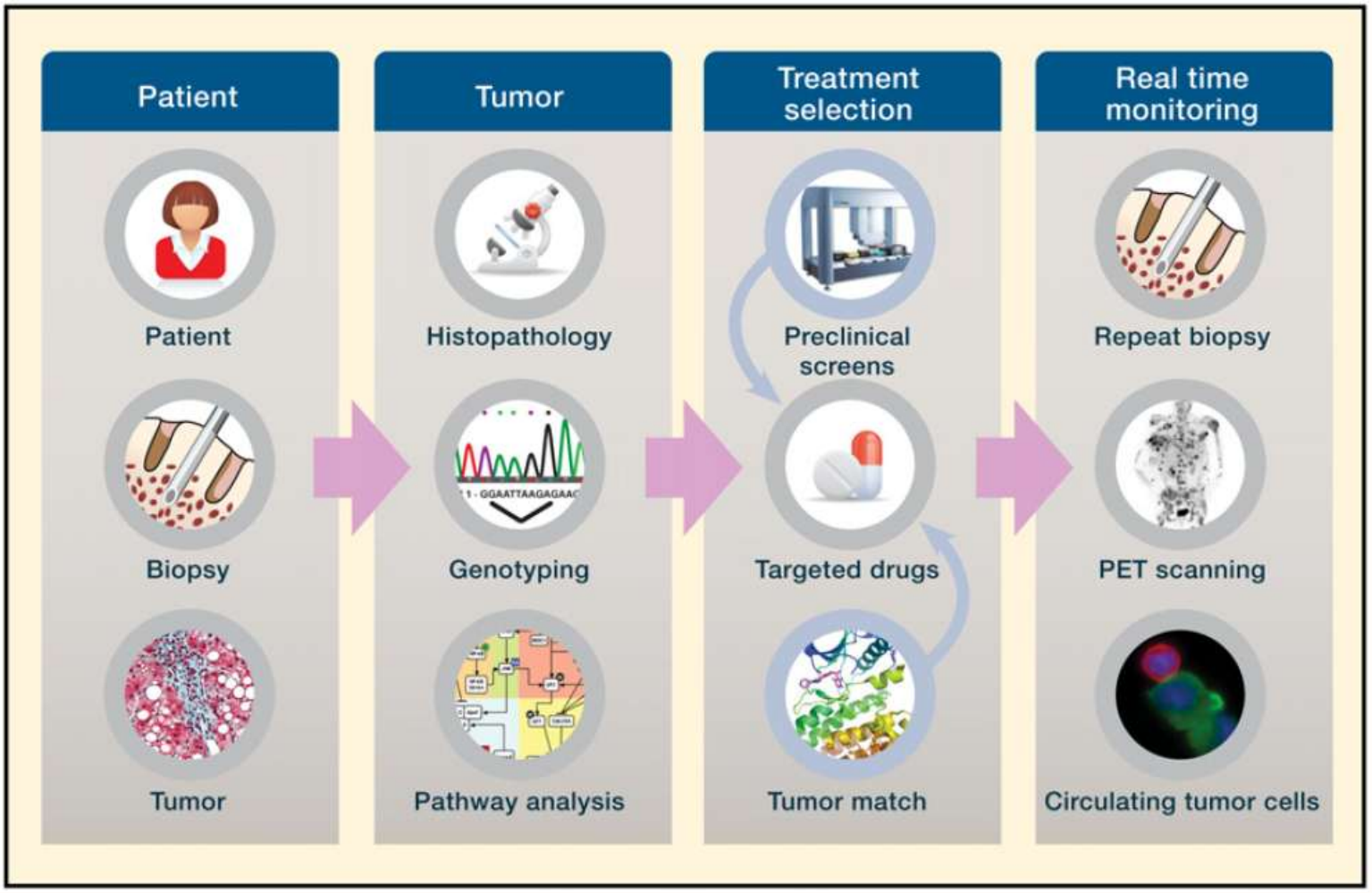
Untapped Power of the Immune System

Elimination of Leukemia in a
Transplant Patient by the Immune System



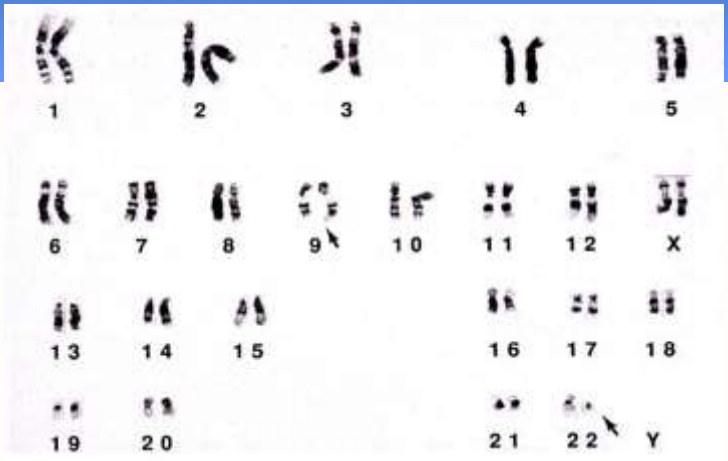


A New Initiative in Personalized Cancer Treatment

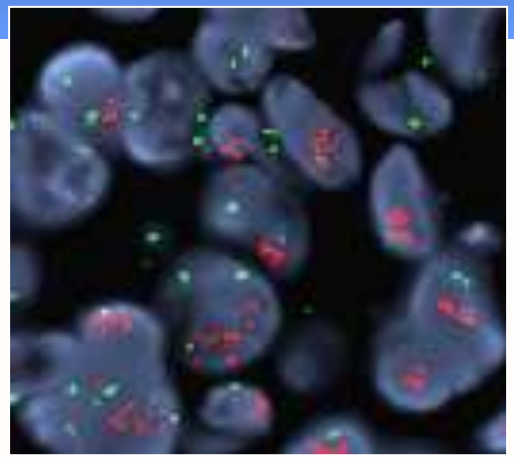


Haber, Gray, Baselga Cell 2011

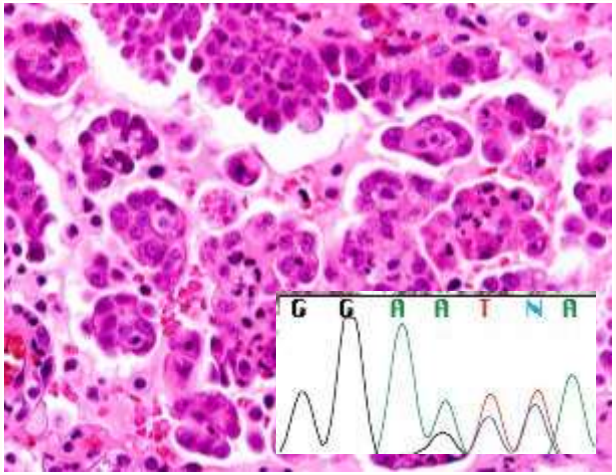
BCR-ABL Imatinib
100% Chronic myeloid leukemia



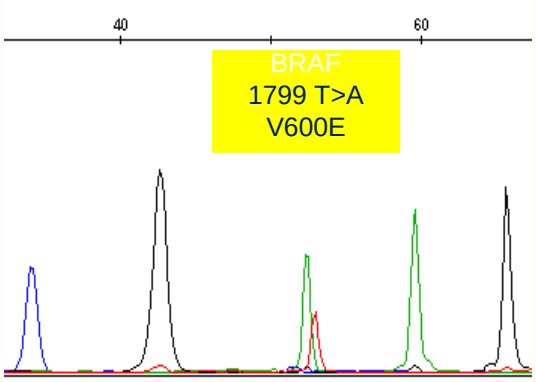
HER2 Trastuzumab
20-30% Invasive ductal carcinoma



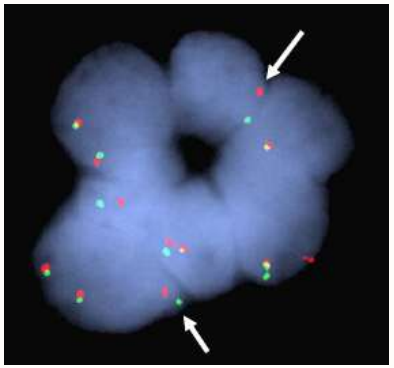
EGFR Erlotinib/ Gefitinib
20% Lung adenocarcinomas



BRAF V600E Vemurafenib
50-60% Melanoma



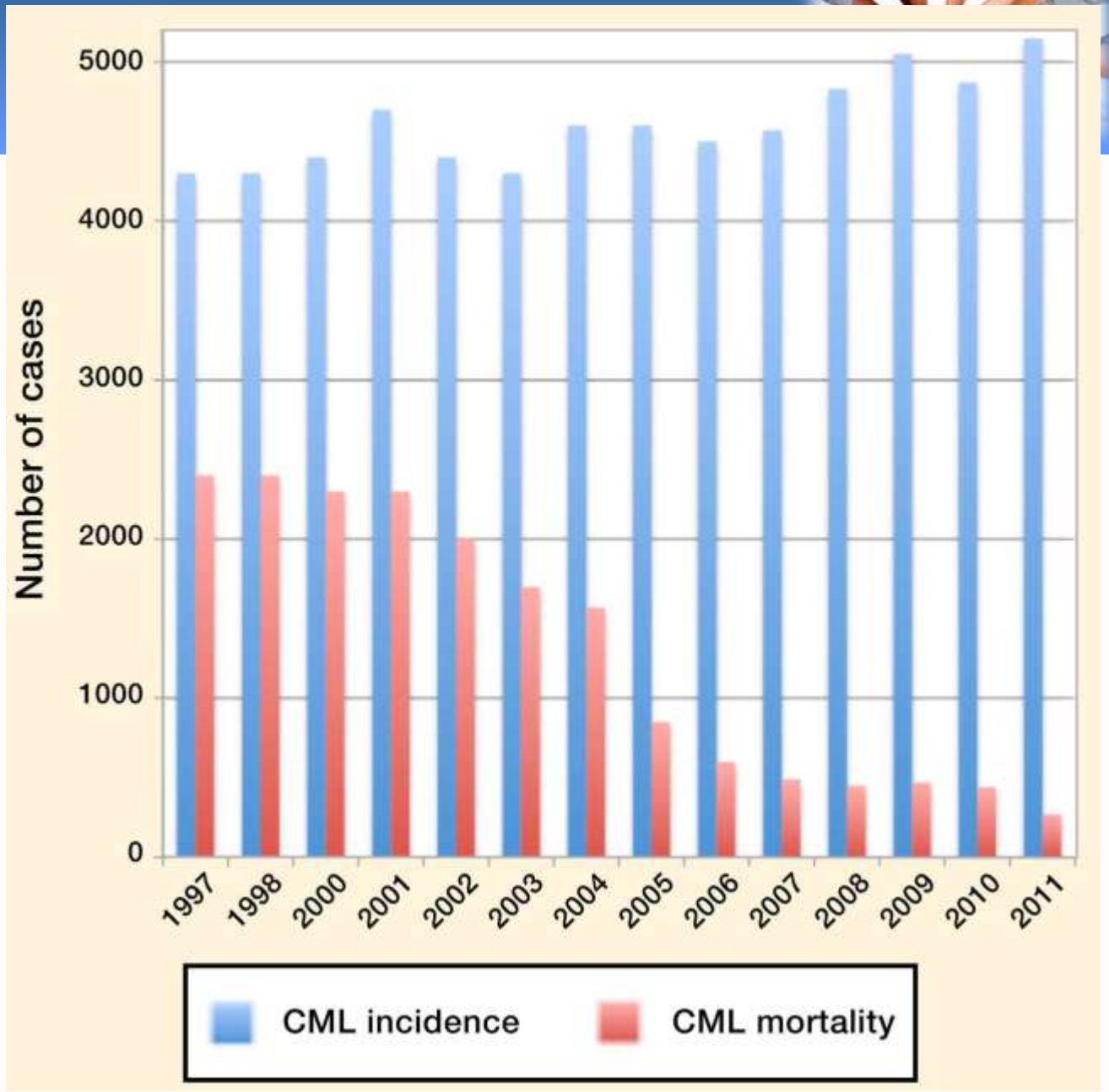
ALK Crizotinib
3-5% Lung adenocarcinoma



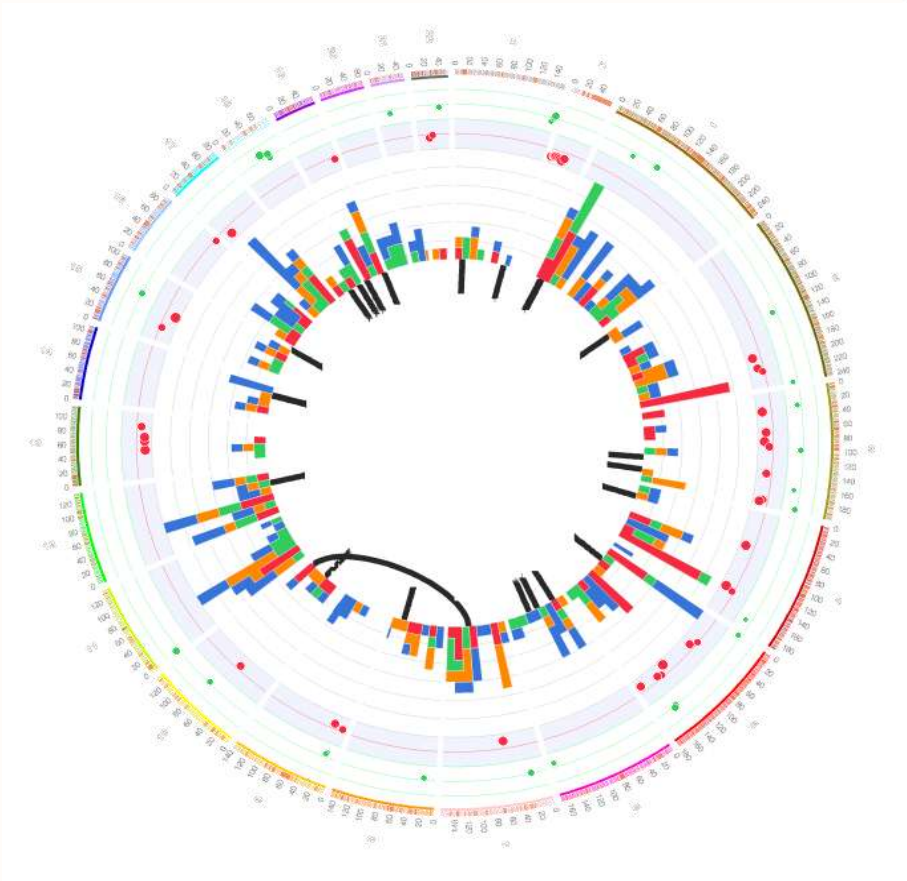
A. John Iafrate, 2010

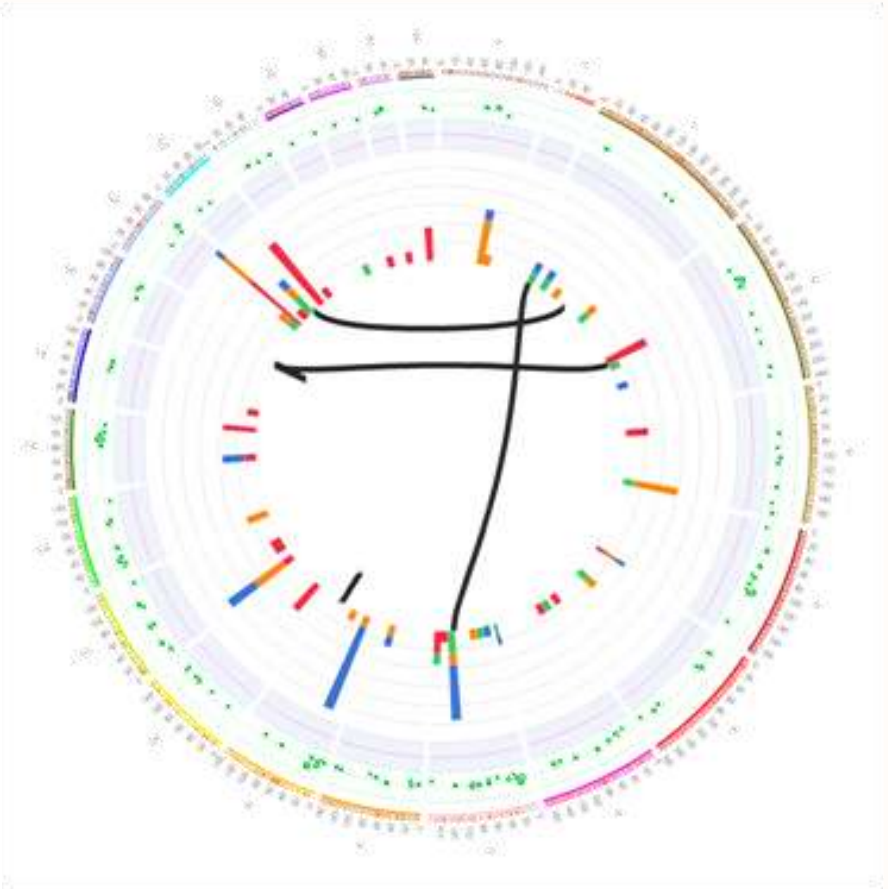
CML Mortality Has Declined in the United States, and the Annual Incidence Is Unchanged

Shown are the estimated US-based CML incidence and mortality rates for the years 1997, 1998, and 2000–2011. These data were abstracted from the annual cancer statistics publications published by *CA: A Cancer Journal for Clinicians*' in the years 1997, 1998, and 2000–2011 (Siegel et al., 2011).

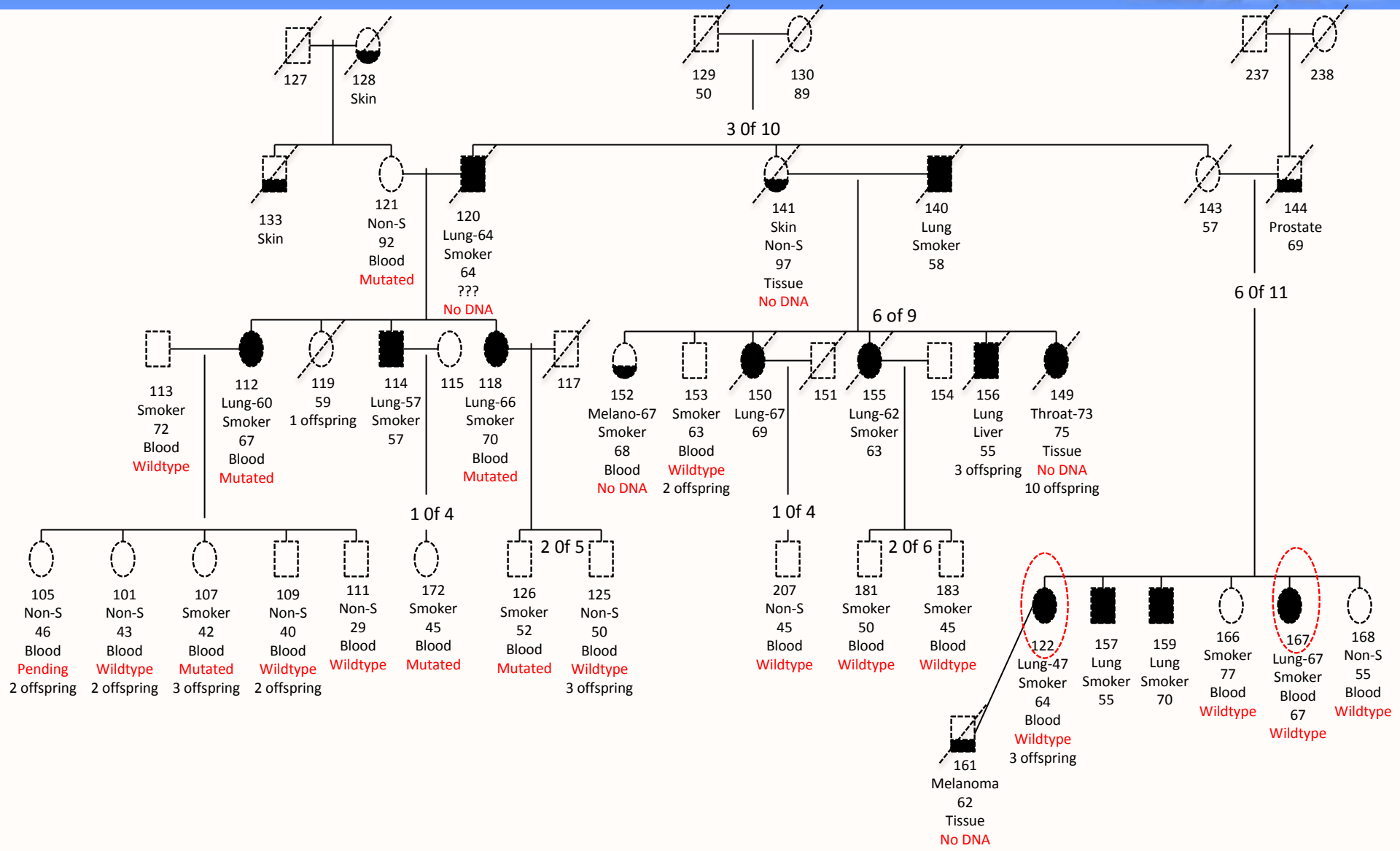


Lung Cancer Whole Genome Sequencing at MCW Cancer Center





Familial Lung Cancer Pedigree 504



Exome Sequencing Filtering Strategy

Patient 122: 56868 variants

Patient 167: 56440 variants

Filter 1: not present in both individuals → 34912 variants

Filter 2: present in dbSNP → 4555 variants

Filter 3: present in 1000 genomes or 200 exomes → 4018 variants

Filter 4: non-coding and synonymous variants → 234 variants

Filter 5: homozygous variants → 88 heterozygous SNPs, 12 heterozygous indels

Filter 6: predicted to be tolerated → 48 heterozygous SNPs, 12 heterozygous indels

Filter 7: LOD score → 17 heterozygous SNPs, 1 heterozygous indels

Filter 8: allele frequency → 17 heterozygous SNPs, 1 heterozygous indels

Family 504

Institutional Commitment

$100 million institutional commitment over 10 years (09/01/2010 – 08/31/2020)

$50 million capital fundraising campaign for MCW Cancer Center

(09/01/2010 – 08/31/2015)

$5 million from FH to support of MCW Cancer Clinical Trial Office

$5 million from AHW to support MCW Tissue Bank

Cancer-related Faculty Recruitments

- **Ming You, MD, PhD**
  Professor
  Washington University
- **Marshall Anderson, PhD**
  Professor
  University of Cincinnati
- **Michael Bishop, MD, FACP**
  Professor
  National Institutes of Health
- **Matthew Budde, PhD**
  Assistant Professor
  National Institutes of Health
- **Thomas Clark Gamblin, MD**
  Associate Professor
  University of Pittsburgh
- **Jian Huang, MD**
  Assistant Professor
  Baylor College of Medicine
- **Michael James, PhD**
  Assistant Professor
  Washington University
- **David Johnstone, MD**
  Professor
  Dartmouth Hitchcock Medical Center
- **Pengyuan Liu, PhD**
  Associate Professor
  Washington University
- **Yan Lu, PhD**
  Assistant Professor
  Washington University
- **Alexander Craig Mackinnon, Jr., MD, PhD**
  Assistant Professor
  University of Chicago/NorthShore
- **Marcio Malogolowkin, MD**
  Professor
  Assoc. Dir. of Pediatric Oncology
  University of Southern California
- **Tugan Lufti Muftuler, PhD**
  Assistant Professor
  University of California-Irvine
- **Roy Silverstein, MD**
  Chairman and Professor
  Cleveland Clinic
- **Gary Stoner, PhD**
  Professor
  The Ohio State University
- **James Thomas, MD, PhD**
  Professor
  The Ohio State University
- **Jay Tichelaar, PhD**
  Assistant Professor
  Washington University
- **Susan Tsai, MD**
  Assistant Professor
  Johns Hopkins Hospital
- H**aris Vikis, PhD**
  Assistant Professor
  Washington University
- **Liang Wang, MD, PhD**
  Associate Professor
  Mayo Clinic College of Medicine
- **Li-Shu Wang, PhD**
  Assistant Professor
  The Ohio State University
- **Donghai Xiong, PhD**
  Assistant Professor
  Washington University

Pending Recruitments

- CCB Recruitment
  - Hyeongnam Jeong, PhD, University of Southern California
- MCC Recruitment
  - Laura Kresty, PhD, University of Miami
- Joan A. Van Deuren Endowed Chair for Breast Cancer Research
  - George Somlo
- MACC Fund Chair
- Associate Director of Clinical Operations
- Associate Director of Basic Sciences
  - Michael Wargovich, PhD
- Associate Director of Prevention & Control

Organizational Capabilities

- Planning and Advisory Committees (ISAB, SLC & ESAB)
- Membership Review Process
- Research Development Awards (seed grants)

Internal Scientific Advisory Board

Ming You, MD, PhD
Director

Frank Wilson, MD
ISAB Chairman
Chairman and Professor
Radiation Oncology

Ellis Avner, MD
Assoc. Dean of Research
Pediatrics

Joseph Besharse, PhD
Chairman and Professor
Cell Biology,
Neurobiology & Anatomy

David Gutterman, MD
Senior Assoc. Dean
Office of Research

Sam Hwang, MD, PhD
Chairman and Professor
Dermatology

Howard Jacob, PhD
Director
Human & Molecular
Genetics Center

Joseph Kerschner, MD
Dean
Medical College of
Wisconsin

David Margolis, MD
Director, Pediatric Blood
& Marrow Transplant

Cheryl Maurana, PhD
Senior Assoc. Dean
Institutional &
Community Engagement

John Meurer, MD, MBA
Director
Institute for Health &
Society

Janet Rader, MD
Chairman and Professor
Obstetrics & Gynecology

William See, MD
Chairman and Professor
Urology

Gilbert White, MD
Exec. VP for Research
BloodCenter of Wisconsin

James Youker, MD
Chairman and Professor
Radiology

Sr. Leadership Committee

Ming You, MD, PhD
Director

Associate Director of Clinical Research
Roy L. Silverstein, MD

Associate Director of Translational Research
James Thomas, MD, PhD

Associate Director of Pediatric Oncology
Marcio Malogolowkin, MD

Associate Director of Prevention & Control
TBD

Associate Director of Basic Sciences
Paula Traktman, PhD

Associate Director of Administration
Andrea Brown, MBA

Sr. Leader
William Campbell, PhD

Sr. Leader
Sue Derus

Associate Director of Research Resources
Robert Truitt, PhD

Sr. Leader
Mary Horowitz, MD

Sr. Leader
Douglas Evans, MD

Membership Update

- Applications Received: 224
- Members
  - Research: 141
  - Clinical: 58
  - Affiliate: 25

Total	Program	Research	Clinical
15	MCC	14	1
42	CCB	41	1
27	TBI	22	5
31	CI	22	9
29	PCPS	19	10
55	ET	23	32
25	Affiliates	n/a	n/a
224	TOTAL	141	58

Facilities

- **Sixth floor of MACC Fund building**
- **Third and fourth floors of TBRC building**
- **Departmental space for cancer faculty**
- **Clinical Cancer Center of FH**
- **Children's hospital**

Center Director

- **To lead the cancer research and advancing cancer treatment at MCW**
- **To recruit the best and brightest faculty in cancer research**
- **To ensure cancer focus and to grow cancer research funding**
- **To develop multidisciplinary cancer research and care**
- **To increase translational cancer research and clinical trials**

Interdisciplinary Coordination

- Engaged and integrated leadership
- Targeted recruitment
- Shared resources (CTO, tissue banks, imaging, and genomics)
- Large grant (SPORE and PPG) planning seed grants
- Regular program and cancer center – wide meetings
- Multidisciplinary oncology clinical programs
- Collaborations with CTSI members

Areas for Growth

- Program Development Needs
  - Capital Campaign
  - Institutional Commitment
- Recruitment Efforts
  - NCI funded investigators
  - Fill in scientific expertise in growth areas
- Clinical Trials Office
  - Novel investigator initiated clinical trials
- Shared Resources identified and implemented
  - Collaboration with Clinical and Translational Science Institute (CTSI)
  - Includes 5 area institutions to extend scientific resources

Updates/Future of MCW Cancer Center

- AHW Full Program Funding
- Cores funded in Programs
- Establish the External Scientific Advisory Board
- Cancer Center Support Grant Submission Timeline
- Recruitment

Cancer Center Support Grant Timeline

2012	Jan/Feb - Full Funding	Feb/May -ISAB Retreats	Draft of Program Write-ups	Late Fall - 1st ESAB Meeting
2013	Summer - Executive Review ESAB	Finish Recruiting	Full Draft of CCSG	Fall - Endorsement of ESAB
2014	CCSG Submission			

Clinical

Basic

Translational

Cancer Cell Biology

Experimental Therapeutics

Molecular Carcinogenesis & Chemoprevention

Cancer Imaging

Transplantation Biology & Immunotherapy

CIBMTR

Prevention, Control, & Population Sciences

Pediatric Oncology/ Women's Cancers

Cancer Cell Biology Scientific Focus

Define the molecular mechanisms that promote malignancy, which is characterized by the uncontrolled proliferation, invasion, and metastasis of cancer cells.

Develop novel therapeutic agents and approaches to diagnose and treat cancer, while limiting toxicity in normal cells.

Cancer Cell Biology Program Vision

The Cancer Cell Biology program will

- bring together investigators from multiple institutions and disciplines to collaborate in innovative studies of cancer cell biology
- support new and ongoing studies in cancer cell biology led by investigators conducting basic, clinical, applied, and translational research
- provide access to advanced technical resources and equipment that facilitate cancer research

Cancer Cell Biology Program Vision

The Cancer Cell Biology program will

- build a comprehensive understanding of the molecular mechanisms that cause cancer

- develop more effective approaches to treat cancer

Cancer Cell Biology Program Goals

- Establish an interactive community of researchers investigating the mechanisms that regulate the survival, proliferation, invasion, and metastasis of cancer cells.
- Identify and validate new therapeutic targets that can be used for better detection and treatment of cancer.
- Test new approaches to sensitize cancer cells to chemotherapy and radiotherapy while diminishing the toxic side effects of these therapies in normal cells.

Cancer Cell Biology Program Goals

- Identify and optimize small molecular weight agents that selectively inhibit the malignant characteristics of cancer cells without harming normal cells.
- Develop animal models to test mechanisms of cancer development and progression, and to test the efficacies of new cancer treatments.
- Establish a Bioenergetics Core Facility that will provide advanced methods to define metabolic abnormalities in cancer cells.

Cancer Cell Biology Research Interests

The program promotes advanced research in multiple areas of cancer cell biology, including

- Signal transduction mechanisms in cancer cells
- Soluble mediators in tumorigenesis, invasion, and metastasis
- Cell cycle and genomic instability in cancer cells
- Cancer cell bioenergetics and redox signaling

Cancer Cell Biology Research Interests

Signal Transduction Mechanisms in Cancer Cells

Medical College of Wisconsin

Magdalena Chrzanowska-Wodnicka	*Small GTPases*
Andrew Chan	*Small GTPases, PTEN*
Guan Chen	*MAPK, p38, Small GTPases*
Michael Dwinell	*Chemokine Receptors*
Qing Robert Miao	*Small GTPases, Nogo-B*
Kasem Nithipatikom	*Eicosinoids, Small GTPases*
Jong-In Park	*MAPK, Small GTPases*
Ramani Ramchandran	*MAPK, Phosphatases*
Andrey Sorokin	*Eicosinoids*
Carol Williams	*Small GTPases, SmgGDS*
Gilbert White III	*Small GTPases, Integrins*

Cancer Cell Biology Research Interests

Signal Transduction Mechanisms in Cancer Cells

University of Wisconsin-Milwaukee

Douglas A. Steeber	*L-selectin signaling*
Valerica Raicu	*FRET analysis of GPCR signaling*

Marquette University

Allison Abbot	*Pathways regulated by miRNAs*

We hope to include your name and research interest

Cancer Cell Biology Research Interests

Soluble Mediators
In Tumorigenesis, Invasion, and Metastasis

<u>Medical College of Wisconsin</u>

Michael Dwinell	*Chemokine Receptor / Ligand Functions*
Samuel Hwang	*Chemokine Receptor / Ligand Functions*
Qing Robert Miao	*Nogo-B*
Sally Twining	*Maspin*
Brian Volkman	*Chemokine Receptor / Ligand Structure*

<u>University of Wisconsin-Milwaukee</u>

Douglas Steeber	*Chemokine receptors in T cell migration*

We hope to include your name and research interest

Cancer Cell Biology Research Interests

Cell Cycle and Genomic Instability in Cancer Cells

Medical College of Wisconsin:

Jonathan Bock	*Cyclins and p21*
Lisa Cirillo	*Chromatin Remodeling*
Vaughn Jackson	*Chromatin Structure*
Mark McNally	*Regulation of mRNA Splicing*
Vera Tarakanova	*Viral Proteins in Tumorigenesis*
Paula Traktman	*Cell Cycle Regulation*

University of Wisconsin-Milwaukee

Yi-Qing Cheng	*Histone Deacetylase Inhibitors*
Xiaohua Peng	*DNA replication mechanisms*

We hope to include your name and research interest

Cancer Cell Biology Research Interests

Cancer Cell Bioenergetics and Redox Signaling

Medical College of Wisconsin

Christopher Chitambar	*Iron Regulation*
Albert Girotti	*NO in Photodynamic Therapy*
Neil Hogg	*Redox Biology, Bioenergetics*
Joy Joseph	*Targeted Antioxidants*
Balaraman Kalyanaraman	*Redox Biology, Bioenergetics*
Jeannette Vasquez-Vivar	*Superoxide and eNOS*

University of Wisconsin-Milwaukee

Guilherme Indig	*Mitochondria in chemotherapy*
Xiaohua Peng	*Oxidative DNA damage*

We hope to include your name and research interest

Cancer Cell Biology Research Interests

- Signal transduction mechanisms
- Soluble mediators
- Cell cycle and genomic instability
- Bioenergetics and redox signaling
- *Additional areas of focus, arising from interactions with researchers from other institutions and disciplines*

Scientific Example

Many projects are identifying and validating
new therapeutic targets
that can be used for
better detection and treatment of cancer

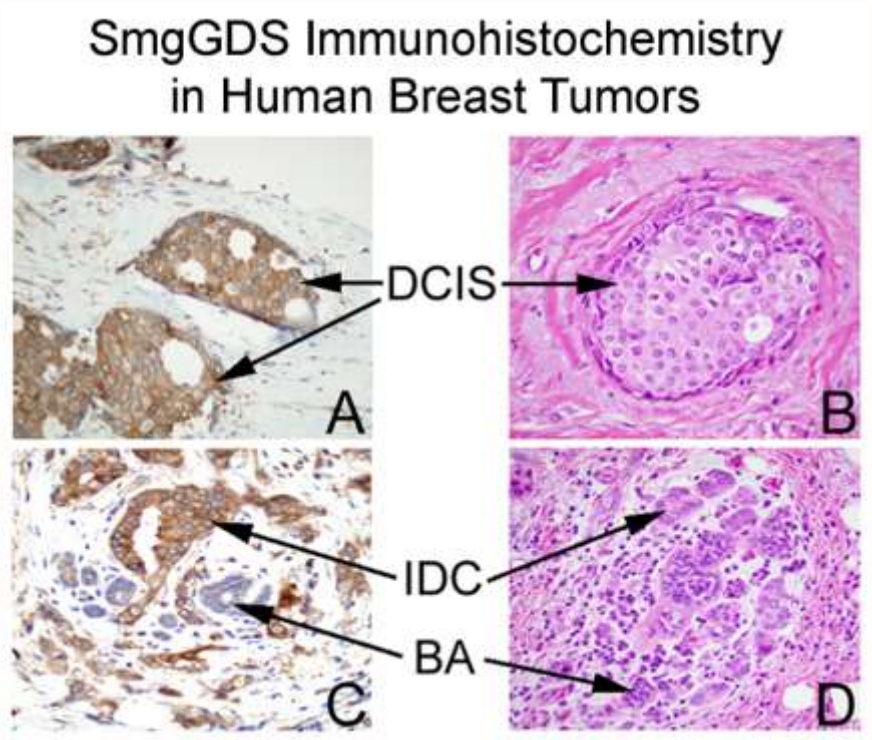
Scientific Example

Identify Therapeutic Targets	Identify potential targets (proteins, ROS, lipids, etc.) by detecting their abnormal expression or functions in cancer cells compared to normal cells.
↓	
Validate the Targets	Confirm that the identified targets actually contribute to malignancy, instead of being only a consequence of the malignant state.
↓	
Identify Lead Compounds	Identify small molecular weight agents or other compounds that suppress the abnormal function or expression of the identified therapeutic target.

Scientific Example

Identify Therapeutic Targets

SmgGDS is expressed more in lung, prostate, and breast tumors compared to normal tissues.



J. Biol. Chem. 283:963-976, 2008; *J. Pathol*. 217:389-397, 2009;
J. Biol. Chem. 285:35255-35266, 2010; *J. Clin. Oncol*. 29s:225, 2011

Scientific Example

Identify Therapeutic Targets

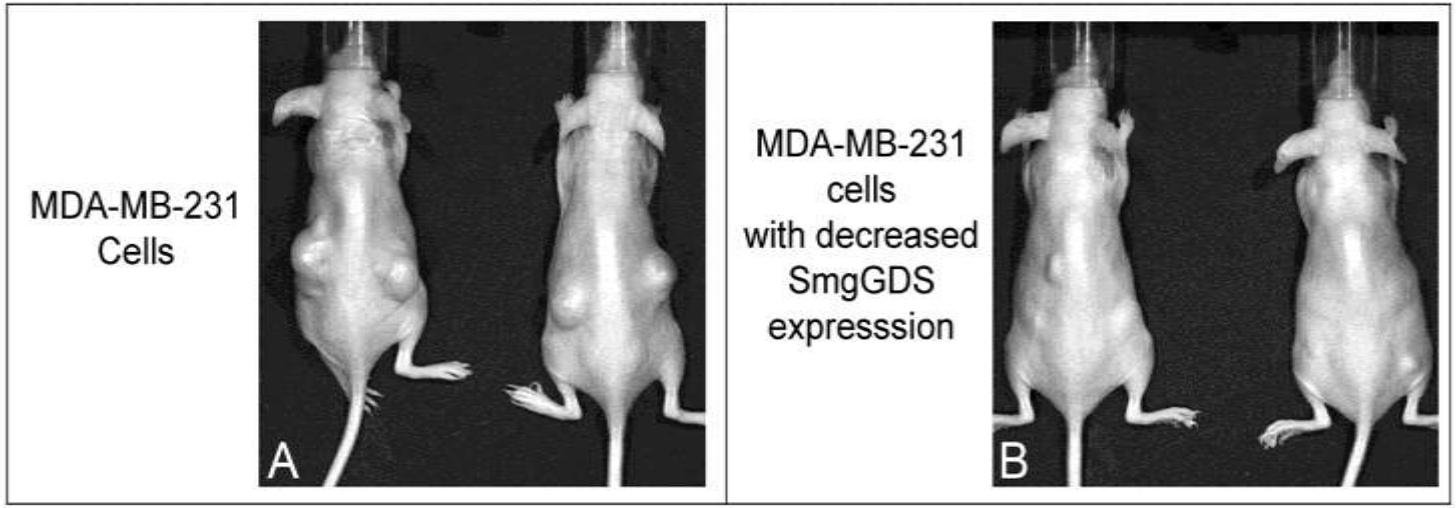
↓

Validate the Targets

SmgGDS is expressed more in lung, prostate, and breast tumors compared to normal tissues.

Decreasing SmgGDS diminishes the malignant features of lung, prostate, and breast cancer cells.

Tumor formation by MDA-MB-231 human breast cancer cells



Scientific Example

Identify Therapeutic Targets

SmgGDS is expressed more in lung, prostate, and breast tumors compared to normal tissues.

↓

Validate the Targets

Decreasing SmgGDS diminishes the malignant features of lung, prostate, and breast cancer cells.

↓

Identify Lead Compounds

Establish collaborative studies to identify small molecular weight compounds that suppress SmgGDS functions or expression in cancer cells.

Opportunities for Collaboration

Goal: Identify and validate new therapeutic targets

Existing assets:

- Access to patient samples through Froedtert Hospital and Children's Hospital
- Established research programs in basic cancer biology and cancer medicine

Opportunities for growth:

- Expansion into new areas of investigation

Opportunities for Collaboration

Goal: Develop new approaches to sensitize cancer cells to chemotherapy and radiotherapy

Existing assets:

- Access to equipment needed for radiation of cells and animals
- Strong biophysics, radiation oncology, and radiobiology programs

Opportunities for growth:

- Expansion into new areas of investigation
- Collaborative interactions with chemists to develop/optimize chemotherapeutic agents and radiosensitizers

Opportunities for Collaboration

Goal: Design and optimize small molecular weight agents that inhibit malignancy

Existing assets:

- Resources for crystallography and NMR spectroscopy

Opportunities for growth:

- In silico screening of targets that have a solved crystal structure
- High throughput analysis of compounds for targets that do not have a solved crystal structure
- Collaborative interactions with chemists to develop/optimize lead compounds

Opportunities for Collaboration

Goal: Develop animal models to examine mechanisms of cancer development and to test anticancer agents

Existing assets:

- Equipment to image luminescence and fluorescence in live animals
- Established research programs in mouse, rat, and zebrafish animal models
- Rat Genome Database

Opportunities for growth:

- Develop more sophisticated transgenic animal models for different types of cancer, and use more species.

Opportunities for Collaboration

Goal: Establish a Bioenergetics Core Facility to define metabolic abnormalities in cancer cells

Existing assets:

- State-of-the art equipment to analyze mitochondrial function and measure metabolism
- National Biomedical Electron Paramagnetic Resonance (EPR) Center
- Free Radical Research Center

Opportunities for growth:

- Expansion into new areas of investigation

Clinical

Basic

Experimental Therapeutics

Cancer Cell Biology

Prevention, Control, & Population Sciences

Pediatric Oncology/ Women's Cancers

Molecular Carcinogenesis & Chemoprevention

CIBMTR

Transplantation Biology & Immunotherapy

Cancer Imaging

Translational

Program Leadership

Molecular Carcinogenesis & Chemoprevention

Gary Stoner, PhD, Leader, Professor of Medicine, Hematology and Oncology

- Internationally recognized expert in the chemoprevention of esophageal and colon cancer using natural antioxidants.

Ron Hines, PhD, Co-Leader, Professor of Pediatrics and Pharmacology/Toxicology

- Internationally recognized expert in molecular mechanisms of carcinogenesis, developmental pharmacology, and environmental health

Program Vision

Molecular Carcinogenesis & Chemoprevention

- Better understand the molecular basis of neoplastic transformation and develop effective intervention strategies to prevent these diseases

Program Goals

Molecular Carcinogenesis & Chemoprevention

- To identify individuals at increased risk for cancer from exposure to environmental toxicants and carcinogens
- To further our understanding of key molecular events involved in the stepwise development of cancer at multiple organ sites.
- To develop effective cancer chemoprevention strategies using appropriate preclinical models and human trials in high-risk populations

Program Research Interests

Molecular Carcinogenesis & Chemoprevention

- Chemoprevention of a variety of cancer types, including leukemia, head and neck, esophageal, colon, pancreas, kidney, lung, skin, bladder, and prostate
- Identification and characterization of genetic risk factors for cancer
- Identification and characterization of pathways involved in the metabolic activation and detoxification of environmental carcinogens and the role of genetic variation and life stage in modifying risk

Scientific Story

Molecular Carcinogenesis & Chemoprevention

Use of Black Raspberry Powder to prevent cancer

Freeze-dried powder

Scientific Story

Molecular Carcinogenesis & Chemoprevention

Effects of 5% and 10% Black Raspberry Diets on Tumor Development

Species	Organ	Carcinogen	% Tumor Inhibition
Rat	esophagus	NMBA	50 – 75%
Rat	colon	AOM	50 – 80%
Mouse	small intestine		50%
Hamster	oral cavity	DMBA	50%

- Ongoing clinical trials of black raspberry powder as a chemopreventive agent for oral, esophageal, and colon cancer in high risk patients

Resource Needs/Areas of Collaboration

Molecular Carcinogenesis & Chemoprevention

- Expertise (areas for collaboration)
  - Pharmacokinetics and preclinical toxicology
  - Chemical synthesis and natural product isolation/characterization
  - Human chemoprevention clinical trials
- Capital resources
  - Instrumentation for pharmacokinetic analysis and natural product isolation

Potential Partners

Molecular Carcinogenesis & Chemoprevention

Xiaohua Peng, PhD

Assistant Professor of Chemistry, University of Wisconsin Milwaukee

Research focus: Understanding the chemical reactivity and function of DNA

- The chemistry of DNA damage with exogenous and endogenous carcinogens
- DNA-DNA and DNA-protein cross-linking by antitumor drugs and bi-functional carcinogens
- The use of modified nucleosides, nucleotides, and oligonucleotides as potential therapeutic agents
- Study of drug/nucleic acids interactions
- DNA/RNA recognition and DNA nanotechnology

Potential Partners

Molecular Carcinogenesis & Chemoprevention

Michael Laoisa, PhD

Assistant Professor, University of Wisconsin Milwaukee School of Public Health

Research focus: Translating how early life exposures adversely affect immune system development and function later in life

- Identifying developmental/early life environmental factors which influence cancer risks and autoimmune pathogenesis.
- Identifying pre- and early post-natal chemopreventative agents which may reduce risk for developing diseases such as leukemia, atopy, and autoimmune disease.
- Determine the impact of early life exposures to chemical mixtures on long term immunological health outcomes

Clinical

Basic

Experimental Therapeutics

Cancer Cell Biology

Prevention, Control, & Population Sciences

Pediatric Oncology/ Women's Cancers

Molecular Carcinogenesis & Chemoprevention

CIBMTR

Transplantation Biology & Immunotherapy

Cancer Imaging

Translational

Cancer Imaging Scientific Focus

- Perform cancer-related basic, translational, and clinical *research in imaging sciences and technology*.
- The research efforts undertaken will include *any imaging modalities* that can contribute to cancer-related discovery in either (or both) *pre-clinical or clinical research*.

Cancer Imaging Program Vision

The Cancer Imaging program will:

- bring together imaging scientists from multiple institutions to collaborate on innovative developments in imaging technology and its applications
- support ongoing studies and help develop new projects in cancer imaging led by investigators conducting basic, clinical, applied, and translational research
- provide access to advanced imaging resources and equipment that facilitate cancer research.

Cancer Imaging Program Vision

Research conducted by this multi-disciplinary and multi-institutional group of investigators will result in the development of a cancer imaging research program nationally renown for its innovative contributions to imaging technology, which result in new diagnostic and therapeutic approaches for cancer.

Cancer Imaging Program Goals

- Strengthen existing cancer imaging research efforts.
- Convert current imaging researchers into *cancer* imaging researchers.
- Develop key strengths in several imaging modalities (eg MRI, PET, SPECT/CT biophotonics, ultrasound, *add your favorite technology here*).
- Enable more cancer researchers to incorporate imaging into their research.
- Provide state-of-the art imaging for clinical trials.

Cancer Imaging Research Interests

The program promotes advanced research in multiple areas of cancer imaging:

- Technology development:
  - MRI technology (software, hardware, high-field (7T))
  - tracer development (ie Molecular Imaging)
  - new image acquisition or image processing strategies
- New Imaging applications (pediatric, non-neuro cancers)
- Preclinical / multi-modality imaging

Cancer Imaging Research Interests

Imaging Technology

James Hyde	*fcMRI, high-field MRI*
Kathleen Schmainda	*perfusion, diffusion*
Jim Joers	*pediatric, MRS, preclinical*
Shi-Jiang Li	*fcMRI*
Tugan Muftaler	*DTI, MRI coils*
Eric Paulson	*MRI acquisition / post-proc*
Robert Prost	*MRS / MRE*
Andrew Nenka	*high-field MRI*
Sarah Patch	*thermo-acoustic tomogr.*
Taly Gilat-Schmidt	*CT reconstruction*

We hope to include your name and research interest

Cancer Imaging Research Interests

Imaging Applications

James Hyde	*fcMRI in Cancer*
Kathleen Schmainda	*brain, breast, liver*
Alan Bloom	*fcMRI in breast cancer*
Eric Paulson	*pancreatic, liver, prostate*
Sarah White	*IR – liver cancer*
Sean Tutton	*IR – liver cancer*
Bill Rilling	*IR – liver cancer.*
Sarah Patch	*breast cancer*
Kim Pechman	*preclinical brain/br cancer*
Scott Rand	*brain cancer*
Mary Beth Gonyo	*breast cancer*

We hope to include your name and research interest

Cancer Imaging Research Interests

Pre-Clinical Multimodality

James Hyde	*fcMRI in Cancer*
Kathleen Schmainda	*brain, breast, liver*
Kim Pechman	*preclinical brain/br cancer*
Jim Joers	*MRI technology*
Bryon Johnson	*biophotonics*
Mike Dwinell	*biophotonics*
Balaraman Kalyanaraman	*MRI, tracer development*

We hope to include your name and research interest

Cancer Imaging Research Interests

The program promotes advanced research in multiple areas of cancer imaging:

- Technology development:
  - MRI technology (software, hardware, high-field (7T))
  - tracer development (ie Molecular Imaging)
  - new image acquisItion or image processing strategies
- New Imaging applications (pediatric, non-neuro cancers)
- Preclinical / multi-modality imaging
- *Additional areas of focus, arising from interactions with researchers from other institutions and disciplines*

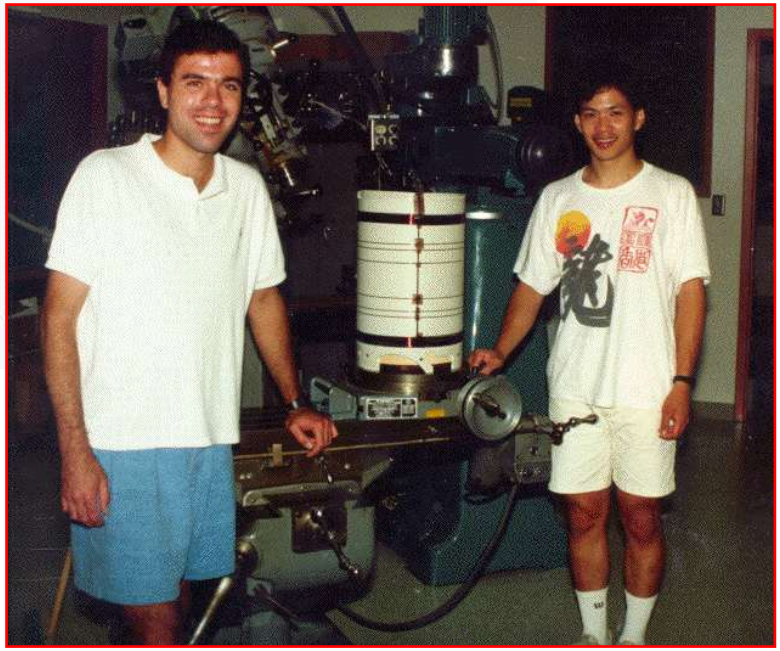
Scientific Story (fMRI)

1992: MCW Biophysics: Pioneers in fMRI

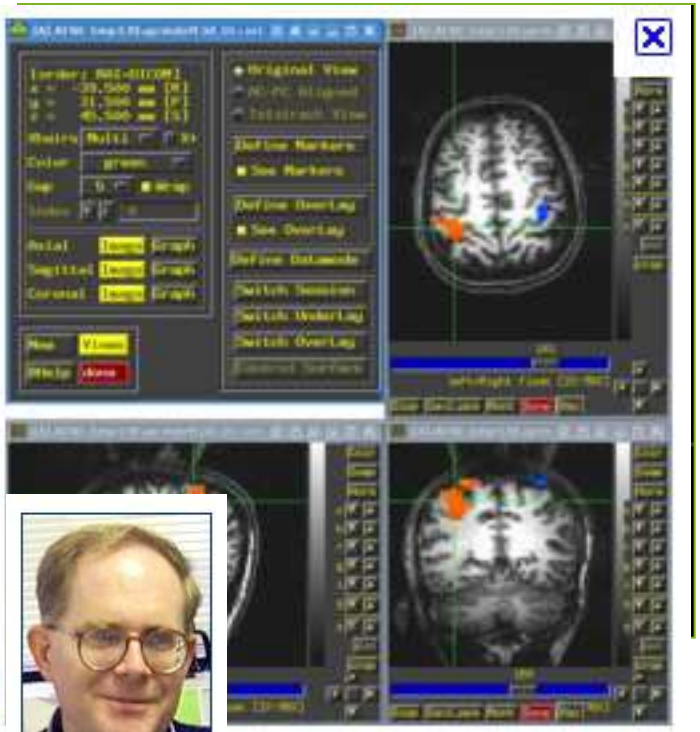
James Hyde

James S. Hyde, PhD

The James S. Hyde Professor of Biophysics
Director of the National Biomedical EPR Center



Peter Bandettini Eric Wong



Bob Cox

Scientific Story (fcMRI)

1995: MCW Biophysics: Pioneers in fcMRI (functional *connectivity* MRI)

Magn Reson Med. 1995 Oct;34(4):537-41.

Functional connectivity in the motor cortex of resting human brain using echo-planar MRI.

Biswal B, Yetkin FZ, Haughton VM, Hyde JS.

Biophysics Research Institute, Medical College of Wisconsin, Milwaukee 53226-0509, USA.

Abstract

An MRI time course of 512 echo-planar images (EPI) in resting human brain obtained every 250 ms reveals fluctuations in signal intensity in each pixel that have a physiologic origin. Regions of the sensorimotor cortex that were activated secondary to hand movement were identified using functional MRI methodology (FMRI). Time courses of low frequency (< 0.1 Hz) fluctuations in resting brain were observed to have a high degree of temporal correlation (P < 10(-3)) within these regions and also with time courses in several other regions that can be associated with motor functio It is concluded that correlation of low frequency fluctuations, which may arise from fluctuations in blood oxygenation or flow, is a manifestation of functional connectivity of the brain.

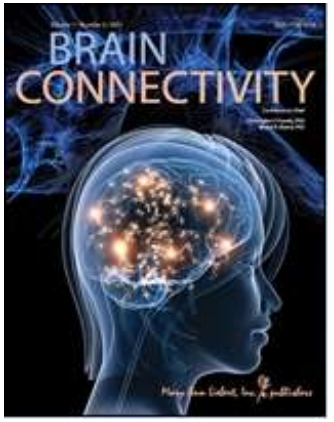
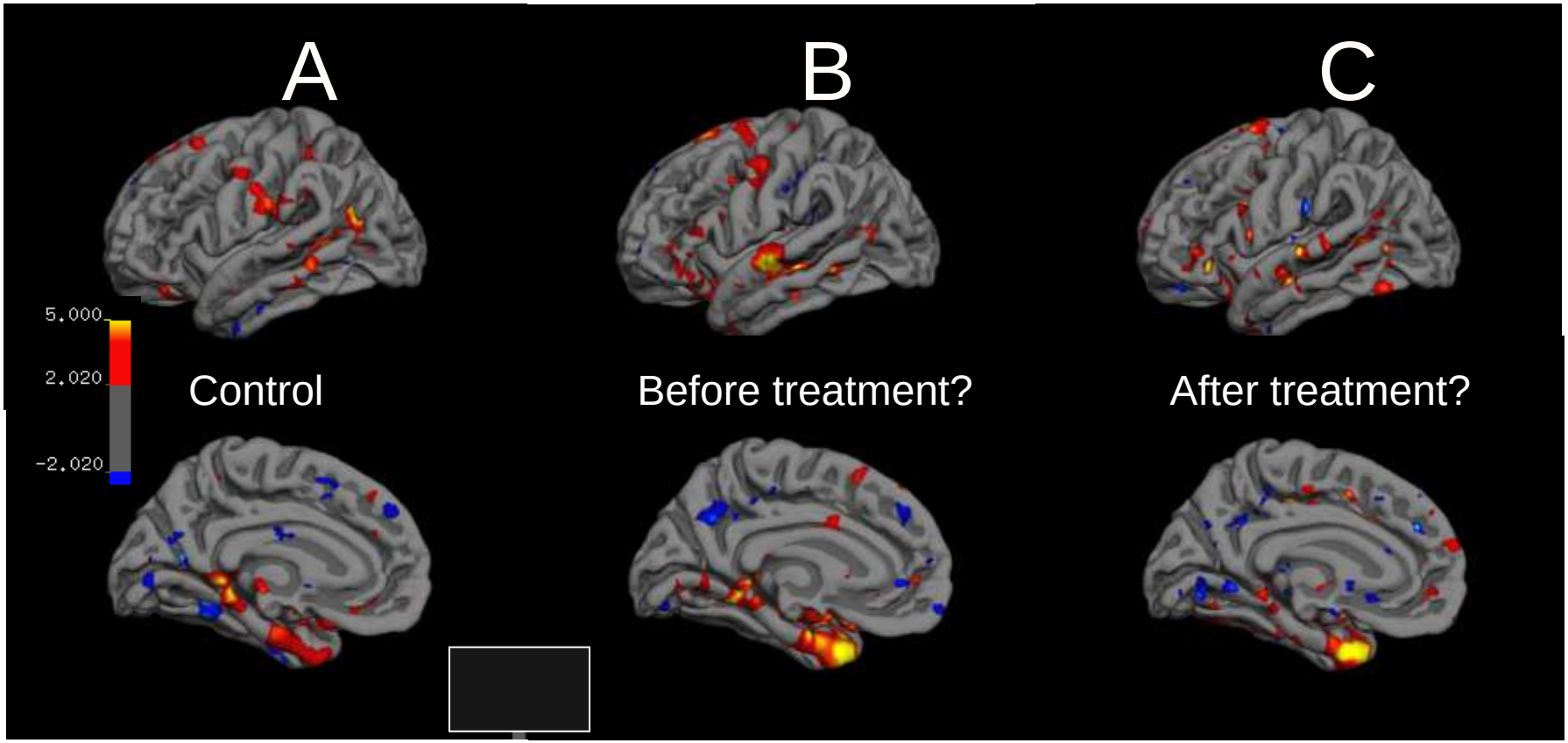


Figure 1. Journal on fcMRI started by MCW faculty.

Scientific *Story*
(fcMRI in Breast CA Patients)

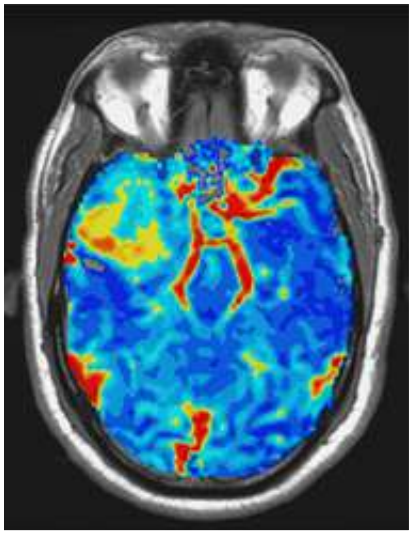


Correlation coefficients between the amygdala seed and all other voxels were transformed to normally distributed Fisher Z values for statistical comparisons. One-sample t-tests were performed and results are shown for the group of (A) control subjects, (B) breast cancer patients prior to treatment as well as (C) *patients following 4 cycles of chemotherapy.* All group maps are thresholded at $p<0.05$.

Scientific Story (Advanced MRI in Brain Tumors)

Perfusion-MRI (“rCBV”)

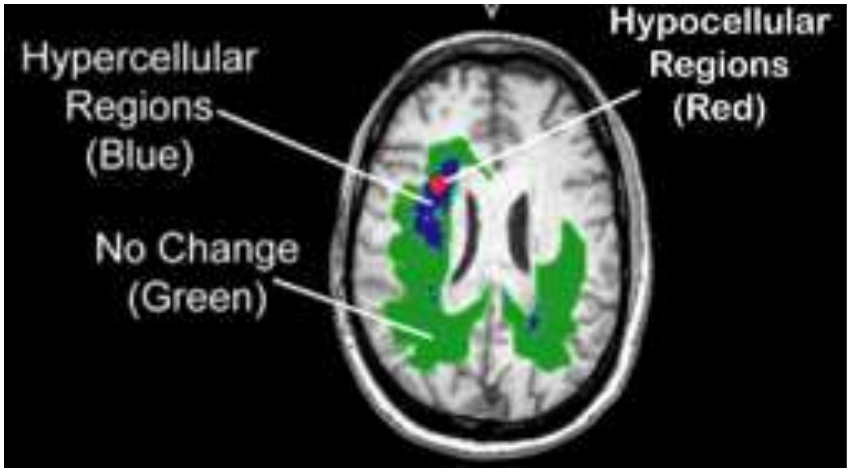
Angiogenesis



- NIH funding since 2000
- 5 Scientific Awards
- 3 U.S. Patents
- RTOG 0625/ACRIN 6677

Diffusion-MRI (“fDM”)

Tumor Invasion / Cell Density / Death



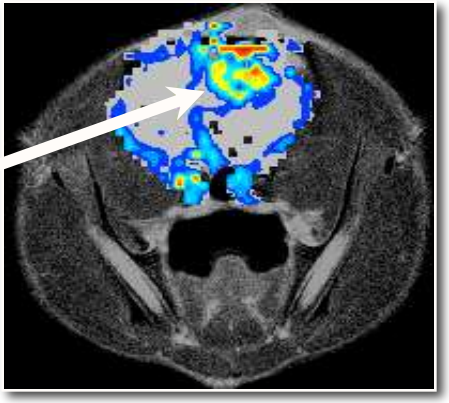
- NIH funding since 2007
- 2 Young Investigator Awards
- 1 Poster Award
- 1 U.S. Patent

Scientific Story (Preclinical MRI in Brain Tumors)

TRANSLATIONAL RESEARCH: *preclinical* Brain Tumors

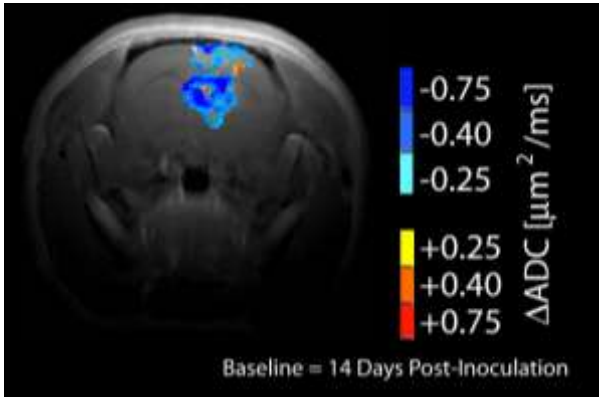
- **Perfusion MRI:**

rat

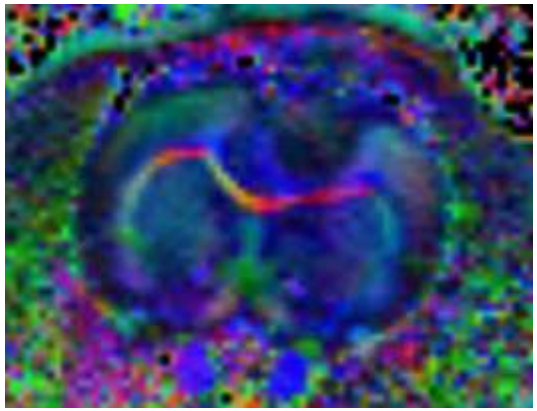


- **Diffusion MRI:**

fDM: **functional diffusion maps**

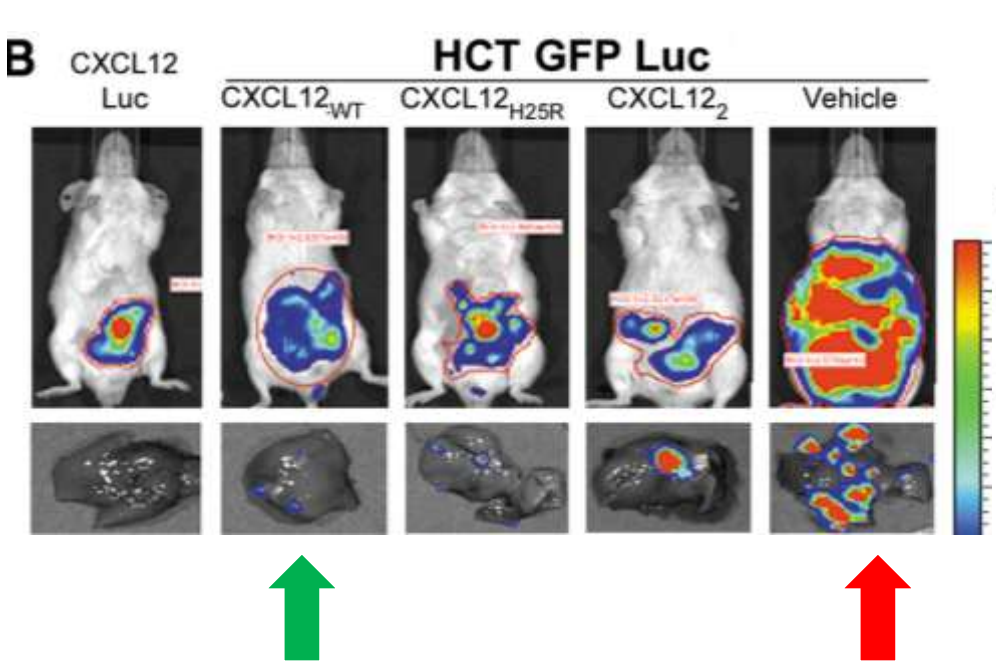


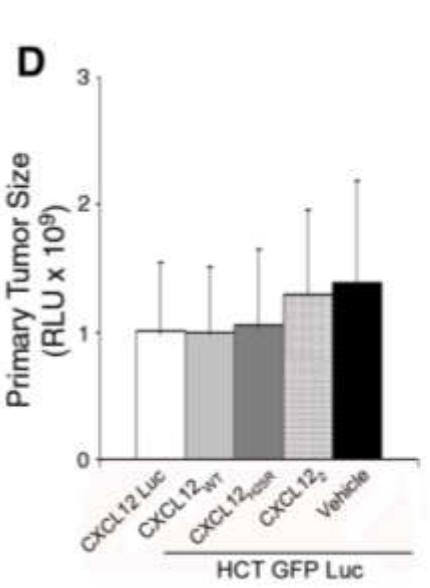
DTI: **diffusion tensor imaging**

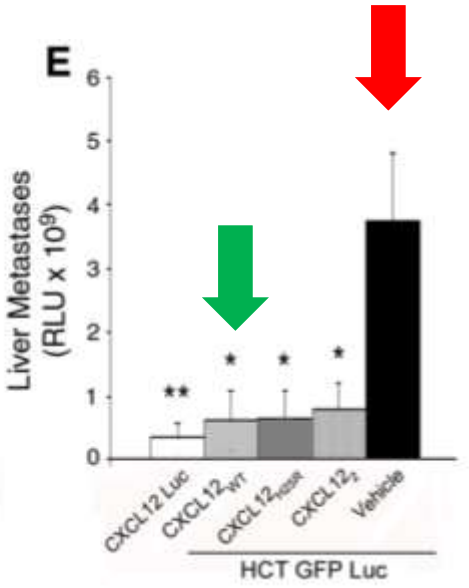


Scientific Story (Biophotonic Imaging)

CXCL12 treatment inhibits metastasis in a preclinical mouse model



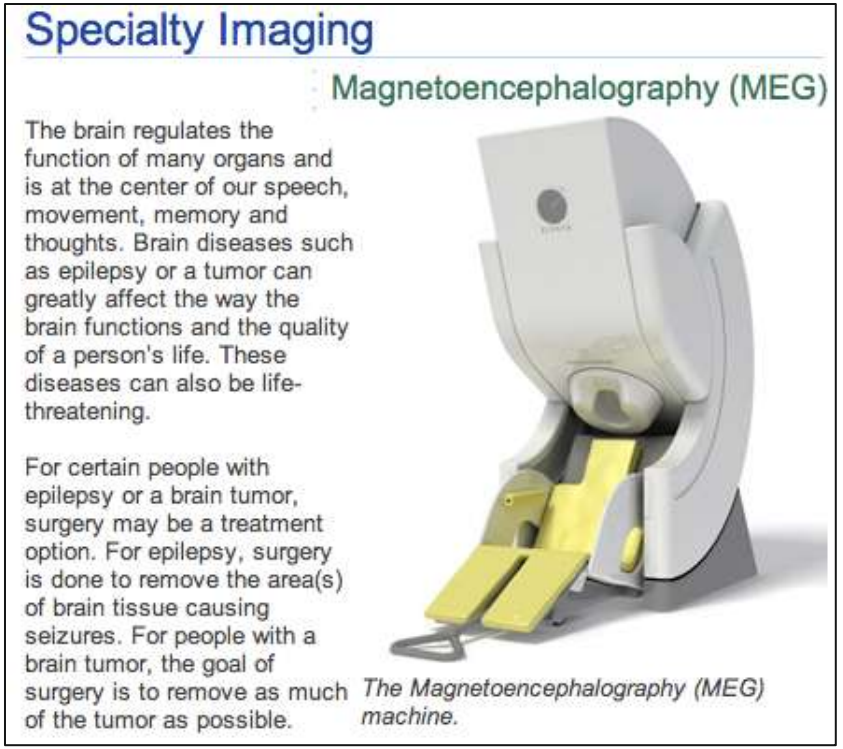




Drury et al., *PNAS*, 2011 (Mike Dwinell Laboratory)

Existing Assets

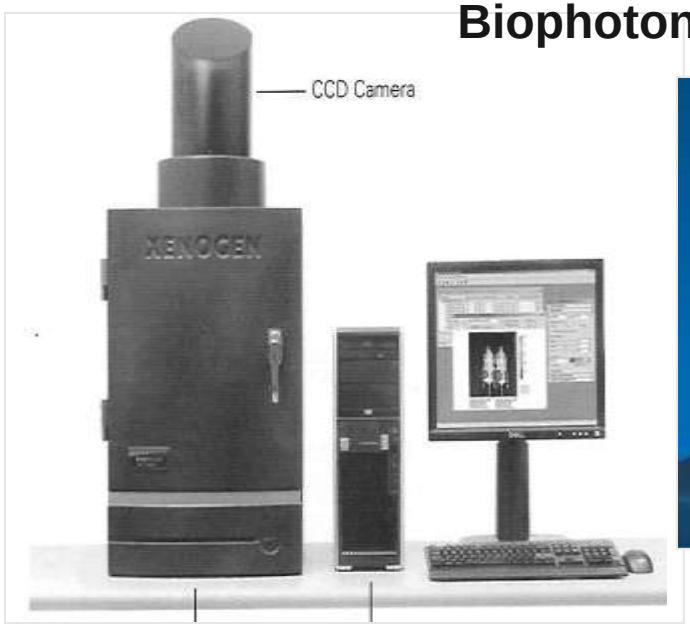
- MRI Facilities / Equipment
- Strong MRI research programs – MCW /MU / UWM
- Small Animal Imaging Core: MRI, SPECT/CT, biophotonics



1st in Wisconsin

Existing Assets: Small Animal Imaging Core

Biophotonics



Lumina IVIS from
Caliper LifeSciences
(formerly Xenogen)

- Bioluminescence
- Single bandwidth fluorescence

Maestro Multi-Spectral
Imaging System from CRI

- Multi-spectral fluorescence

MicroSPECT / MicroCT

Opportunities for Collaboration

- Expansion into new areas of investigation – both in terms of research focus and imaging modality
- Incorporation of imaging into other basic and clinical cancer initiatives
- Opportunities to develop larger multi-modality imaging programs focused on a particular cancer

Join the cancer imaging break-out session!

Clinical

Basic

Experimental Therapeutics

Cancer Cell Biology

Prevention, Control, & Population Sciences

Pediatric Oncology/ Women's Cancers

Molecular Carcinogenesis & Chemoprevention

CIBMTR

Transplantation Biology & Immunotherapy

Cancer Imaging

Translational

Program Leadership

Program Leader:

William R. Drobyski, MD, Professor of Medicine, Pediatrics and Microbiology

- Member of the Adult Bone Marrow Transplant Program in the Division of Hematology/Oncology, Department of Medicine
- Laboratory Research program in the MACC Fund Building focused on the area of transplantation immunology

Program Scientific Focus

The focus of the Transplantation Biology and Immunotherapy Program is to develop new approaches designed to augment the immune response against cancer and to reduce complications that are associated with bone marrow transplantation so that more patients may benefit from this life-saving therapy.

Program Vision

- Develop new approaches to enhance the ability of the immune system to eliminate cancer cells (e.g. cancer vaccines, gene therapy). Principles gained from these studies can be applied to many more cancers, not just cancers of the blood.
- Reduce complications from bone marrow transplantation so that patients have improved survival and an overall better quality of life.
- By reducing complications, expand the number of patients that can benefit from this therapy (i.e. older patients, patients who do not have good family donors, patients from diverse racial and ethnic groups).
- Use bone marrow transplantation as a platform to treat other diseases that are not due to cancer (e.g. sickle cell anemia, autoimmune diseases).

Program Goals

- To further our understanding of the processes which interfere with the restoration of normal immunity post transplantation and contribute to the deleterious pro inflammatory environment that arises as a consequence of graft versus host disease.
- To discover novel mechanisms by which cancer cells evade the immune system and develop strategies to overcome these inhibitory pathways.
- To translate preclinical findings into the clinical setting in order to decrease morbidity and mortality attendant to bone marrow transplantation and improve overall survival and patient quality of life.

Program Research Interests

- Hematological Malignancies (e.g. multiple myeloma, leukemia, lymphoma—preclinical and clinical)
- Immunological reconstitution (Adaptive and Innate arms)
- Graft versus host disease biology (pre-clinical and clinical studies)
- Immunotherapy-strategies to enhance the immune response against cancer
- Use of alternative donors (i.e. non-HLA-matched family donors) for transplantation
- Clinical outcomes-based research (Dr. Horowitz)

Current Membership

Adult BMT Program

William Drobyski, MD
Mary Horowitz, MD
Doug Rizzo, MD
Parameswaran Hari, MD
Jeanne Palmer, MD
Marcelo Pasquini, MD
Wael Saber, MD
Mary Eapen, MD
Michael Bishop, MD
Carolyn Taylor, PhD

Pediatric BMT Program

David Margolis, MD
James Casper, MD
Julie Talano, MD
Monica Thakar, MD

Basic Research

William Drobyski, MD
Bryon Johnson, PhD
Jack Routes, MD
S Malarkannan, PhD
Xiao Chen, MD PhD
Jill Gershan, PhD
Laurent Malherbe, PhD
Robert Truitt, PhD
Amy Hudson, PhD

Non-BMT Clinical

Richard Komorowski, MD (Pathology)
Horation Olteanu, MD (Pathology)
Eric Cohen, MD (Nephrology)
Marcy Neuberg, MD (Dermatology)

26 Members, 8 Departments/Divisions

What do we hope to accomplish?

- Develop new approaches to enhance the ability of the immune system to eliminate cancer cells (e.g. cancer vaccines, gene therapy). Principles gained from these studies can be applied to many more cancers, not just cancers of the blood.
- Reduce complications from bone marrow transplantation so that patients have improved survival and an overall better quality of life.
- By reducing complications, expand the number of patients that can benefit from this therapy (i.e. older patients, patients who do not have good family donors, patients from diverse racial and ethnic groups).
- Use bone marrow transplantation as a platform to treat other diseases that are not due to cancer (e.g. sickle cell anemia, autoimmune diseases).

Current Ongoing In-House Basic Science and Clinical Projects

Examples:

- Vaccine based-treatment post transplantation for the treatment of neuroblastoma/multiple myeloma
- Suicide gene-modified T cells for the therapy of recurrent hematological disease post allogeneic stem cell transplantation
- Blockade of inflammatory cytokine pathways for the treatment of corticosteroid refractory graft versus host disease.
- Treatment of Sickle Cell Anemia with Haploidentical Stem Cell Transplantation
- Use of Natural Killer Cells as Adoptive Immune Therapy in Hematological Malignancies
- Immunotherapy for relapsed lymphoproliferative disorders and viral diseases

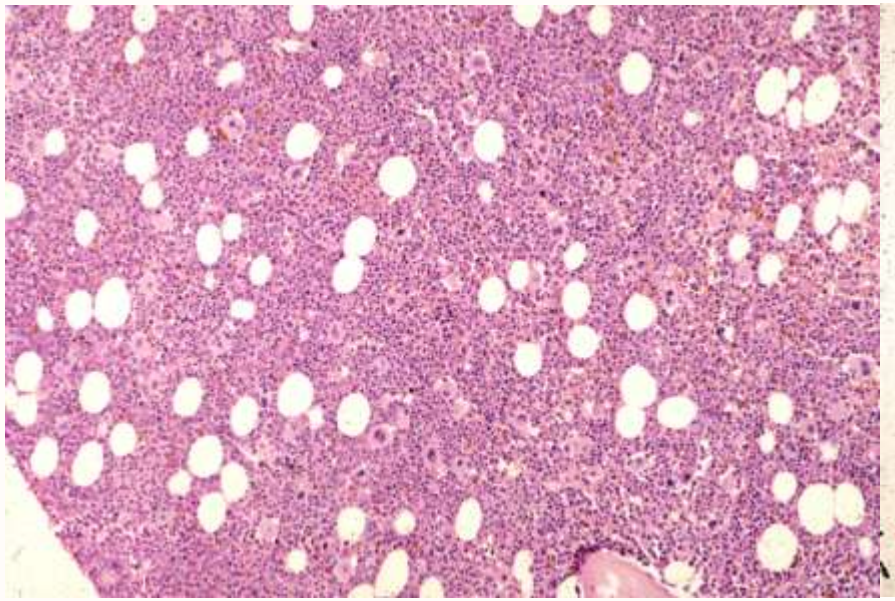
Current Resources

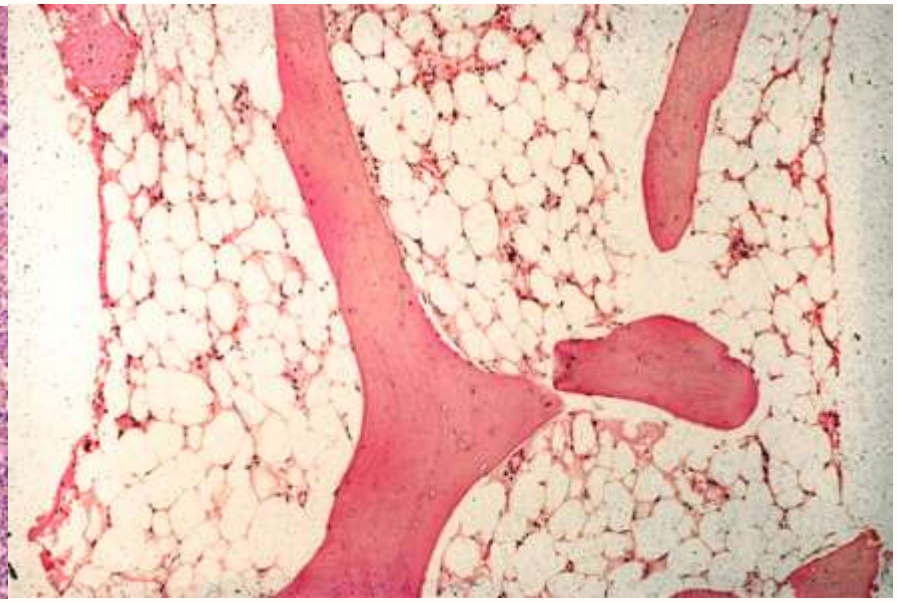
Available Resources within TBI Program:

- Small Animal Expertise
- Immunology (Adaptive and Innate Immunity)
- Cell Processing/Graft Engineering Laboratory (Dr. C. Taylor)
- Immune Monitoring Core
- Flow Cytometry Core
- Clinical Trials Design/Biostatistical Support
- Clinical Outcomes Analysis

Untapped Power of the Immune System

Elimination of Leukemia in a
Transplant Patient by the Immune System





Resource Needs/Areas of Colloboration

- Immunologists (Adaptive and Innate Immunity)
- Pharmacologists (Drug metabolism, pharmacogenomics)
- Microbiologists (Immune responses to pathogens, effect of the microbiome on immunity)
- Research Focus on disorders of the skin, gastrointestinal tract, liver (major target organs of graft versus host disease)
- Dentists (oral manifestations of GVHD)

Clinical

Basic

Experimental Therapeutics

Cancer Cell Biology

Prevention, Control, & Population Sciences

Pediatric Oncology/ Women's Cancers

Molecular Carcinogenesis & Chemoprevention

CIBMTR

splantation iology & unotherapy

Cancer Imaging

Translational

Program Scientific Focus

Transplantation Biology and Immunotherapy: To develop new approaches to augment immune response against cancer & reduce complications associated with BMT so that more patients may benefit from this life-saving therapy.

- CIBMTR: Assess new therapies and provide a platform for determining the biologic, clinical and socio-demographic factors that affect BMT outcomes

Prevention, Control and Population Sciences: To facilitate outstanding research to implement optimal preventive, screening, and therapeutic interventions for cancer, and reduce disparities in outcomes

- CIBMTR: Use BMT as a paradigm for delivery of high tech medical care in the US to understand socio-demographic and structural barriers to access and successful outcomes

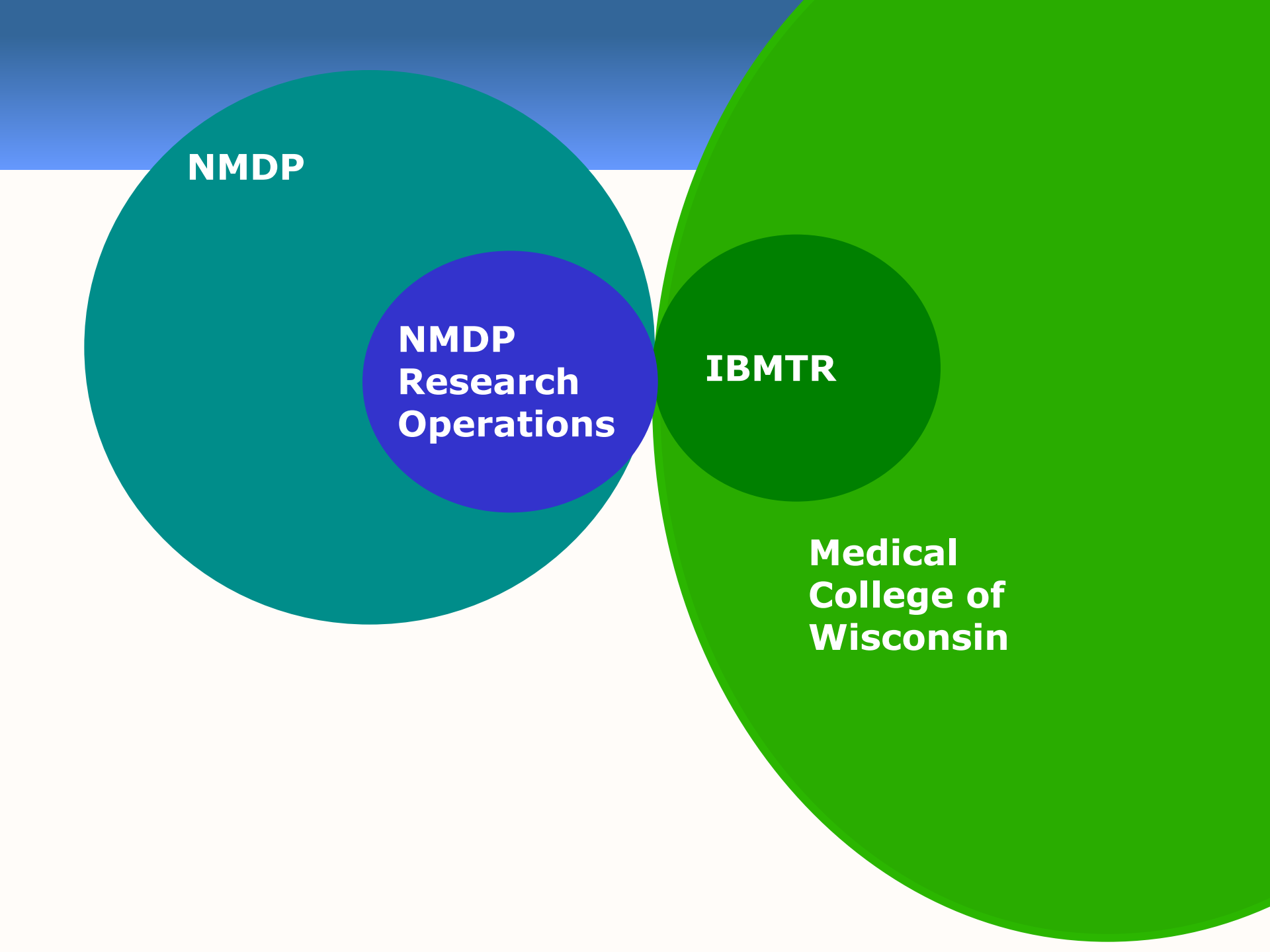
Center for International Blood and Marrow Transplant Research

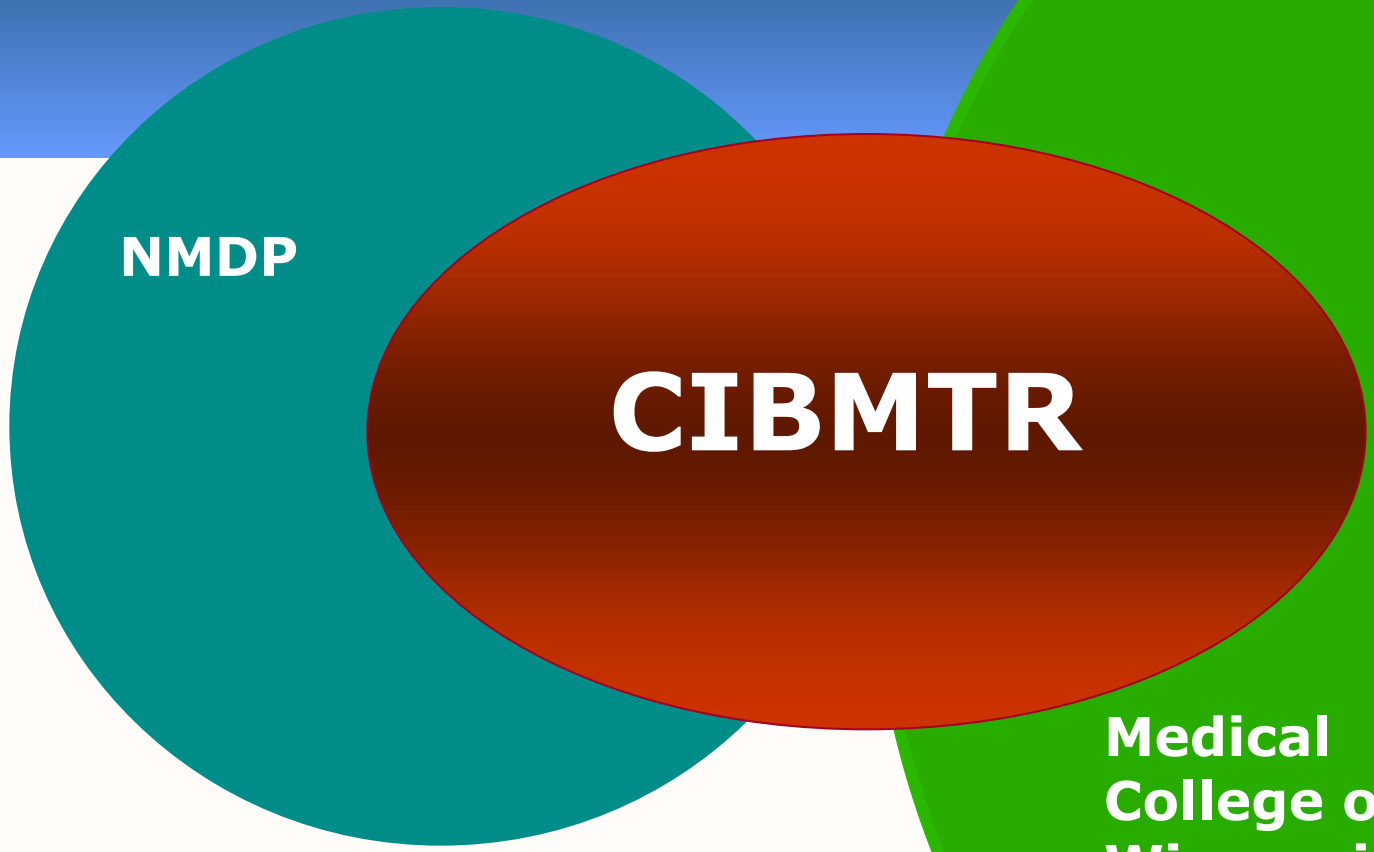
Sharing knowledge…..
…….Sharing hope

CIBMTR® CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

The CIBMTR Grew Out of Two Important Collaborative Efforts in BMT

- International Bone Marrow Transplant Registry (IBMTR): outcomes registry collecting data on BMT recipients since 1972; headquartered at MCW
- National Marrow Donor Program (NMDP): donor registry for unrelated donor BMT established 1987; also maintains large outcomes registry and biorepository of donor-recipient samples; headquartered in Minneapolis


NMDP
NMDP Research Operations
IBMTR
Medical College of Wisconsin



July 2004 Affiliation Agreement between MCW and the NMDP to support clinical research in BMT & related fields

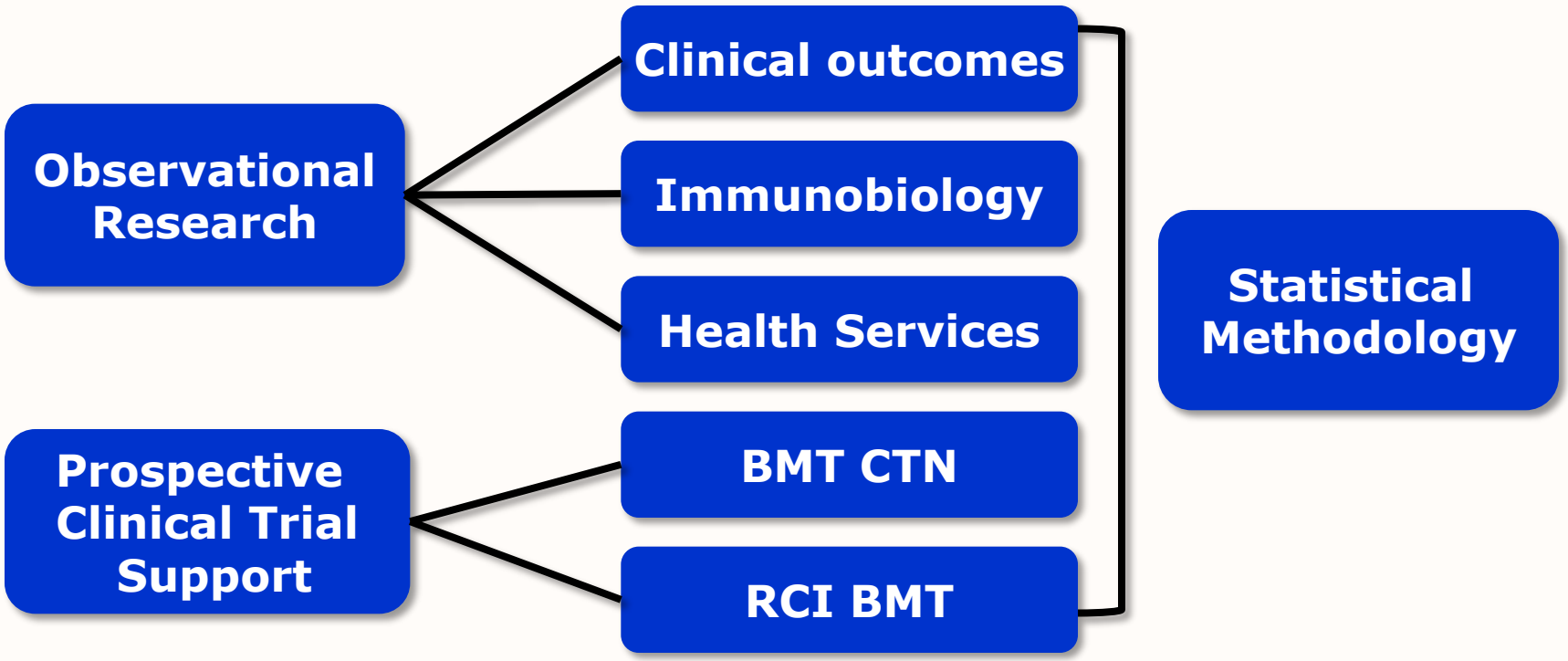
CIBMTR, 2011

180 staff including, 6 PhD statisticians, 14 MS statisticians, 11 MD-MS faculty;
Active program of statistical methodology research specifically focused on transplant outcomes in addition to supporting clinical studies

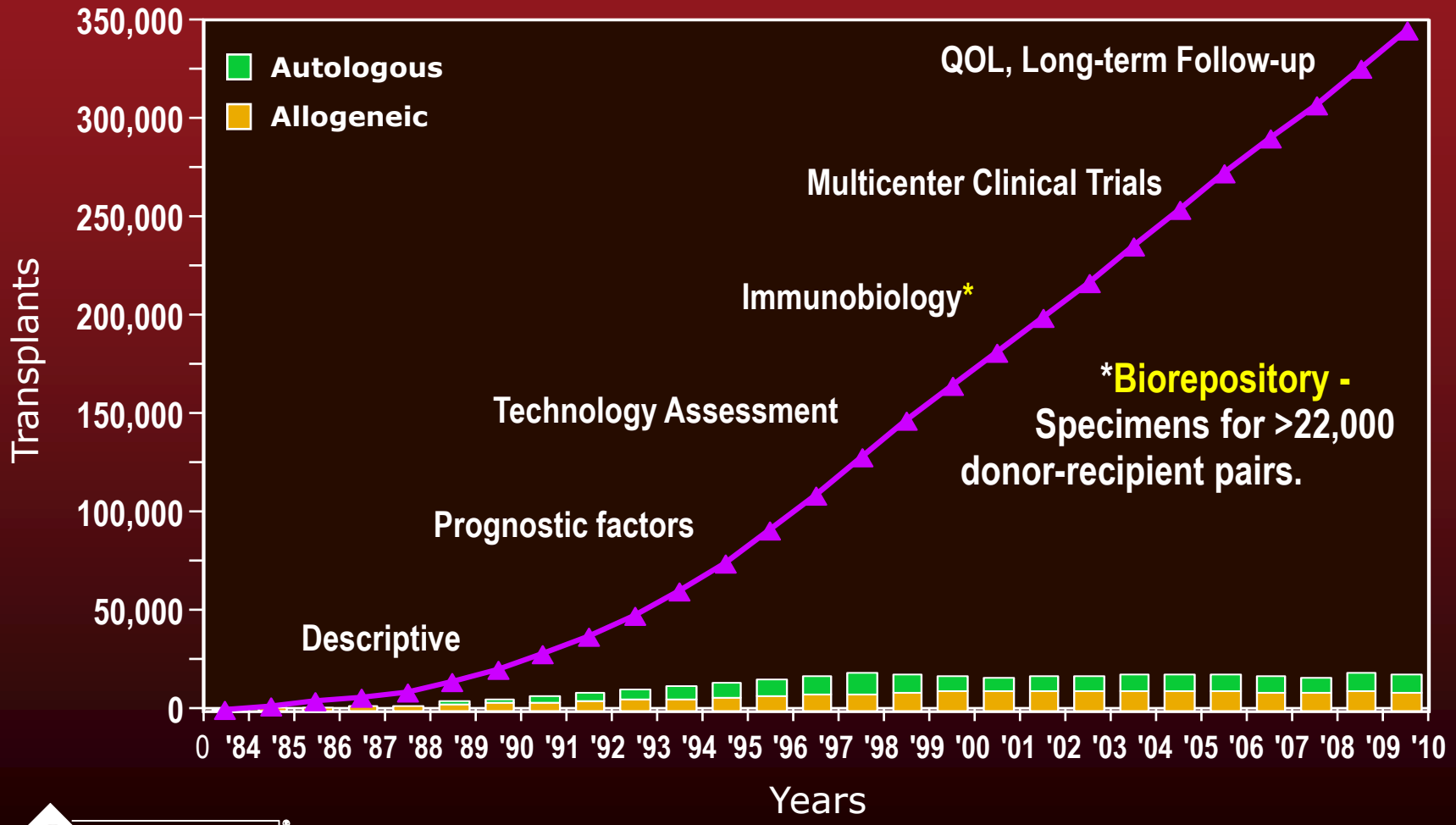
Some Key Features of CIBMTR Data

- Participation Mandatory for US Centers since 2007
  - Voluntary for non-US Centers *but* all participating centers must report all consecutive transplants
- Two levels of data detail:
  - Basic (transplant essential data)
  - Comprehensive (research data) – selected by weighted randomization
- Longitudinal: 100 days, 6 months, 1, 2, 3 years, then every other year
- Data provided by transplant centers (no direct communication with patients) - electronic data entry
- Centers audited on four-year cycle

CIBMTR Scientific Activities



CIBMTR
>350,000 Cases Registered,1984-2011
>650 Publications



CIBMTR®

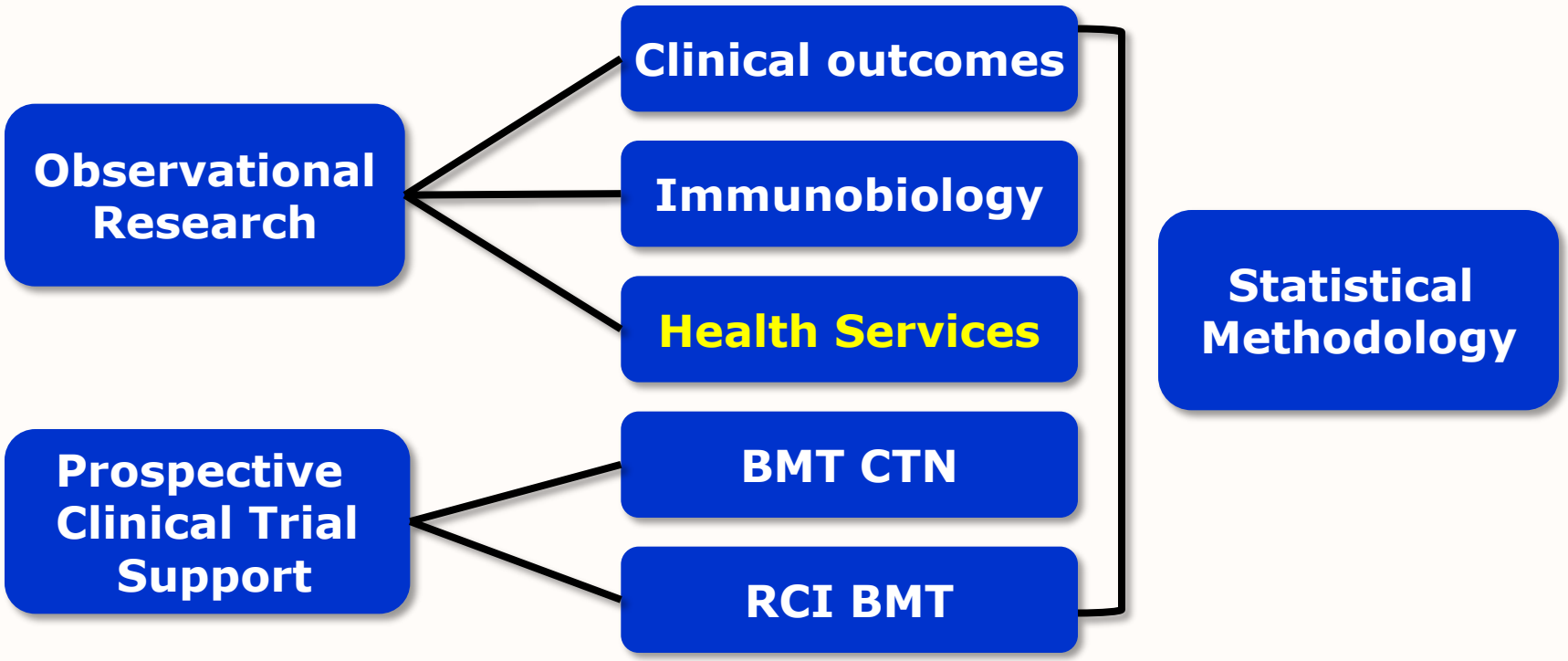
NMDP Research Sample Repository Inventory as of October 2011

Unique Unrelated Donors:	40,344
Unique Unrelated Recipients:	40,065
Unique Umbilical Cord Grafts:	5,114
Unique Related Donors:	1,180
Unique Related Recipients:	1,294
Unrelated Donor/Recipient pairs:	22,805
Related Donor/Recipient Pairs:	1,047

Sample Types

- Whole blood
- Plasma and serum
- Blood spotted on filter paper
- Peripheral blood mononuclear cells (PBMC) viable and non-viable
- B-Lymphoblastoid cell lines (B-LCL) viable and non-viable
- Granulocytes
- DNA

CIBMTR Scientific Activities



Health Services Research Issues Related to BMT

- Characteristics of BMT that are relevant to HSR
  - Highly specialized – good paradigm for high-tech care
  - Limited to few centers/hospitals – issues of access; assessing a large fraction of the population is feasible
  - Expensive/Resource-intense – financial issues for both provider and patient
  - Lack of RCTs/many competing technologies – technology dissemination/decision analysis
  - Practice variation – mandatory center-specific analysis
  - High morbidity/mortality – patient utilities/decision making

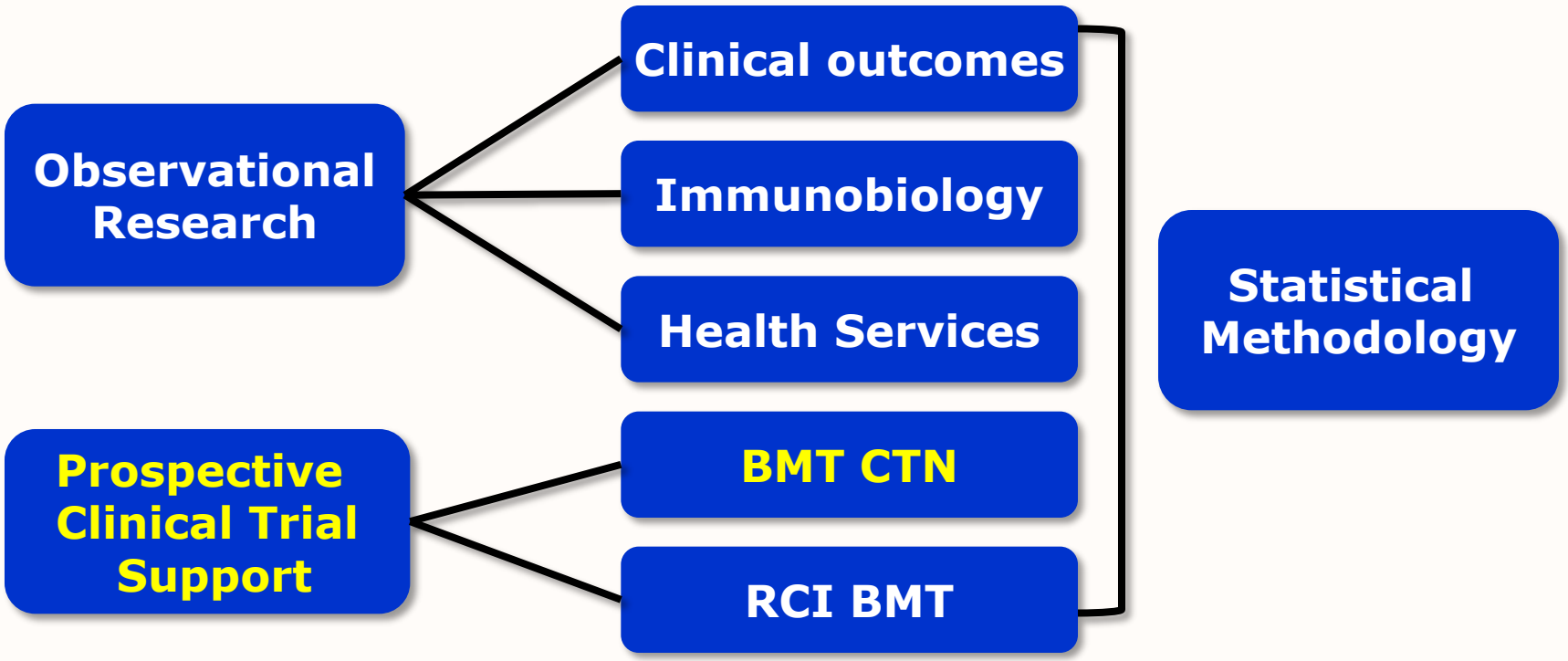
CIBMTR Health Services Research

- HSR conducted using available observational data
  - Constrained by data availability
- Examples of completed projects
  - Race and gender and access to HCT
  - Race and socio-economic status and outcomes of unrelated donor HCT
  - Rural-urban disparities in outcomes
  - Race and outcomes of autologous HCT for myeloma
  - Center effects in HCT
  - Physician practice and supportive care variation

CIBMTR-NMDP Office of Patient Advocacy Collaborations

- Main areas of interest:
  - Barriers to access: income, referral patterns, etc.
  - Workforce and infrastructure issues; international comparisons
  - Economic analyses
  - Practice variation and quality of care
  - Long-term quality of life and health behaviors
- Requires supplementing standard CIBMTR data with data available in public databases, or collected directly from centers, patients, families
- *Would benefit from input from experts in health economics, social sciences, access to other databases*

CIBMTR Scientific Activities



- Established: Sept. 2001; renewed Oct. 2006 and 2011
  - 20 Core Centers/>75 affiliate centers
  - Data and Coordinating Center:
    CIBMTR with subcontracts to NMDP & EMMES
- Goal of the Program:
  - Provide the infrastructure needed to allow promising HCT therapies to be developed/evaluated in high quality multicenter studies

2000 State of Science Symposium #1 sets scientific agenda for 2001-2007 ⇨ 7 focus areas for HCT trials

1. Expanding donor/graft source
2. Reduce regimen related toxicity
3. GVHD prevention/therapy
4. Decrease relapse
5. Decrease infections
6. Improve late effects/QOL
7. Rare diseases (added by Steering Committee and 2005 RFA

2007 State of Science Symposium #2 sets scientific agenda for 2008-2012+ ⇨ 12 Working Committees

11 high priority trials – 6 in development ; 1 anticipated for release in 2011

Chemo + Dasatinib vs. Allo HCT for Ph+ ALL – 0805/SWOG lead

Note: See July 2011 Progress Report for list of all high-priority trials

Collectively Administer DCC

CIBMTR

EMMES

NMDP

BMT CTN Foundation

2001

2002

- Governance and leadership
- Established 16 Core Centers
- Manual of Policies/procedures
- Electronic data capture system
- Per patient reimbursement model
- Websites for members & public

Early and ongoing collaboration with cooperative groups to synergize and avoid duplication (intensified since 2005)

N of pts = 440 1,058 1,615 2,090 2,700 3,000 4,000 [5,200]

2003 2004 2005 2006 2007 2008 2009 2010 2011 2012

Other trials to be opened in 2011 or later:
- 0903 Allo-HCT in HIV+ Patients
- 1101 Haplo vs. Double Cord UCB with RIC
- 1102: Hypomethylating Therapy vs. RIC BMT for MDS

ECOG

CALBG

BMT CTN Steering Committee

SWOG

COG

= Enrollment complete

= Enrollment on-going

= Cumulative actual [projected] accrual

= Coop group collaboration (see color key above)

0901 Full vs. RIC in MDS/AML

0804 High Risk CLL

0902 Post Tx Stress Mgmt

0803 HIV+ Lymphoma

0702 PIII Myeloma Follow-on

0801 P II/III CGVHD Treatment

0802 PIII AGVHD Treatment

0701 PII NST for NHL

0604 PII Double CB in Adults

0603 PII Haplo in Adults

0601 PII Sickle Cell NST

0703 PII Hodgkin Disease

0403 PIII Etanercept for IPS

0704 PIII MM maintenance

0502 PII NST for AML >60y

0402 PIII GVHD prophylaxis

0501 III Single vs Double CBT

0301 PII Unrelated Tx for aplastic anemia

0401 PIII BEAM vs BEAM-Bexxar for Lymphoma

0302 PII AGVHD therapy

0303 PII T-depleted HCT for AML

0202 PIII follicular NHL (closed early)

0201 PIII Unrelated PBSC vs. Marrow

0101 PIII Vori vs. Fluconazole

0102 PIII Myeloma Tandem HCT

TRIALS OPEN FOR ENROLLMENT 2001-2011

Blood and Marrow Transplant Clinical Trials Network

- Ancillary Studies
  - Biomarkers for Transplant Complications and Response to Therapy
  - Pharmacokinetics of High-Dose Therapies
  - Evaluation of minimal residual disease
  - Cost-effectiveness of Transplant Drugs/Strategies
  - Symptom Burden of Various Therapies

Summary – Opportunities for Research Partnerships

- Large database capturing almost all BMTs in the US and many BMTs in other countries
  - Opportunity to study delivery, accessibility and outcomes of high tech care
- Biospecimens for patients in observational database and on prospective trials
- Opportunities for ancillary studies in prospective trials

Resource Needs/Areas of Collaboration

- Immunologists (Adaptive and Innate Immunity)
- Pharmacologists (Drug metabolism, pharmacogenomics)
- Geneticists (Candidate gene, gene-wide association studies)
- Health economists (Cost-effectiveness)
- Social scientists
  - Health care infrastructure
  - Health disparities
  - Patient-reported outcomes/quality of life

Clinical

Basic

Translational

Experimental Therapeutics

Cancer Cell Biology

Prevention, Control, & Population Sciences

Pediatric Oncology/ Women's Cancers

Molecular Carcinogenesis & Chemoprevention

IBMTR

Transplantation Biology & Immunotherapy

Cancer Imaging

Program Scientific Focus

Prevention, Control, & Population Science

Laboratory Research Settings → T1 → Clinical Trial Setting (Efficacy) → T2 → Patient Care & Community Settings (Effectiveness) (Outcomes Assessment)

IOM Clinical Research Roundtable, JAMA 2008;299:211-213

Program Vision

Prevention, Control, & Population Science

To facilitate the conduct of outstanding research to implement optimal preventive, screening, and therapeutic interventions for cancer, as well as to reduce disparities in outcomes

Program Goals

Prevention, Control, & Population Science

- Study adoption of cancer-related discoveries into clinical practice, as well as barriers to or disparities in that adoption
- Test new approaches to cancer implementation science, i.e., the fielding and/or evaluating of interventions in real world settings
- Identify novel methods to improve cancer outcomes by influencing human behavior, organizational inertia and/or public policies

Mission: To conduct cutting-edge research on the provision of effective and efficient patient care services and on related health outcomes.

PCOR

Center for **Patient Care and Outcomes Research**

Scientific Story: Survey and Claims Data

Patient's Predisposing Characteristics (e.g., age, race, ethnicity, education)

Patient's Need (e.g., extent of disease, presence and severity of health conditions)

Patient's Enabling Resources (SES, medical insurance)

Systematic use of Quality Processes

Hospital and Surgeon Volume of Cases

Overall Mortality

Breast Cancer Mortality

Improving the Care and Outcomes of Women Undergoing Breast Surgery

- 3,083 women aged 65-89 years at time of breast cancer in 2003, residing in California, Florida, Illinois, New York. Identified using Medicare claims.
- Opt-out recruitment procedures resulted in 70% initial participation; wave 2-4 participation was >90% of eligibles
- Telephone surveys at median of 30, 36, 48, 60 months after surgery
- Information available includes sociodemographic, treatment, adherence to HT, QOL, ADL; Medicare claims, tumor registry

Am J Epidem 2010;172:637-44

Methods Papers

- Nattinger AB, Pezzin LE, Sparapani RA, Neuner JM, King TK, Laud PW. Heightened attention to medical privacy: Challenges for unbiased sample recruitment, and one solution. *Am J Epidemiol* 2010;172:637-44.

- Yen T, Sparapani RA, Guo C, Neuner JM, Laud PW, Nattinger AB. Elderly breast cancer survivors accurately self-report key treatment information. *J Am Geriatr Soc* 2010;58:410-412.

Lymphedema Risk Factors

- Yen T, Fan X, Sparapani R, Laud PW, Walker AP, Nattinger AB. A Contemporary, population-based study of lymphedema risk factors in older breast cancer women. *Ann Surg Oncol* 2009;16:979-988.

Adoption of Newer Hormone Agents

- Yen TW, Czypinski LK, Sparapani RA, Guo C, Laud PW, Pezzin LE, Nattinger AB. Socioeconomic factors associated with adjuvant hormone therapy use in older breast cancer survivors. *Cancer* 2011;117:398-405. Sep 7 (Epub ahead of print; available 1/1/12).

- Pezzin LE, O'Niel M, Nattinger AB. The economic consequences of newer breast cancer adjuvant hormonal treatments. *J Gen Int Med* 2009;24(4):S446-50.

Comparative Effectiveness of Hormonal Agents

- Neuner JM, Yen TW, Sparapani RA, Laud PW, Nattinger AB. Fracture risk and adjuvant hormonal therapy among a population-based cohort of older female breast cancer patients. *Osteoporos Int* 2011;22(11):2847-55.

Volume of Cases and Breast Cancer Outcomes

- Kong AL, Yen TWF, Pezzin LE, Miao H, Sparapani RA, Laud PW, Nattinger AB. Socioeconomic and racial differences in treatment for breast cancer at a low volume hospital. *Ann Surg Oncol* 2011 DOI 10.1245/s10434-011-2011-z.

Poverty is a carcinogen

- *Samuel Broder, NCI Director, 1990*

Emerging Program Research Interests

- Implementation Science
  - Association between neighborhood disadvantage factors and colon cancer screening *PI Kirsten Beyer, PhD, MPH*
  - Improving racial and socioeconomic disparities in breast cancer mortality and adverse events *PI Joan Neuner MD, MPH*

Methodologic Expertise

- Analysis of complex databases
  - Cancer registries, Administrative databases (e.g., Medicare)
- Survey research
- Community-based participatory research
- Knowledge synthesis
  - Decision and cost-effectiveness analysis, Meta-analysis
- Comparative effectiveness research

Areas of Potential Collaboration

- Health psychology
- Sociology
- Communication
- Decision Sciences
- Biostatistics
- Economics
- Operations Research/Human Factors
- Public Policy

Clinical

Basic

Experimental Therapeutics

Cancer Cell Biology

Prevention, Control, & Population Sciences

Pediatric Oncology/ Women's Cancers

Molecular Carcinogenesis & Chemoprevention

CIBMTR

Transplantation Biology & Immunotherapy

Cancer Imaging

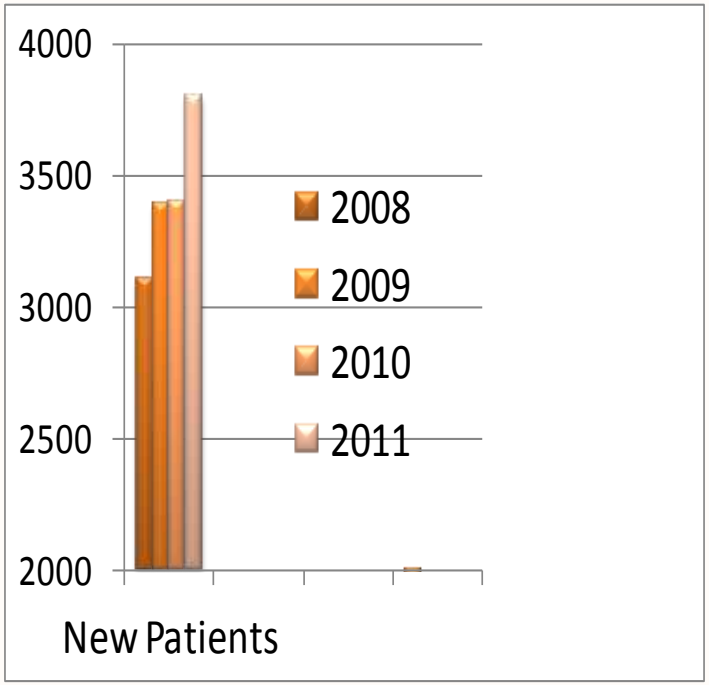
Translational

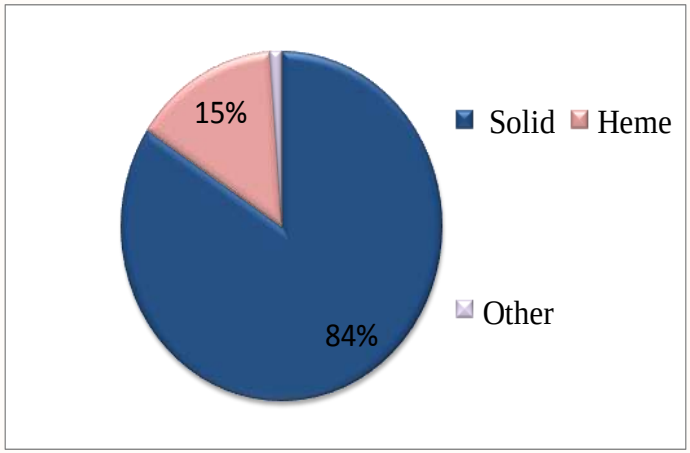
Program Goals

Experimental Therapeutics

- To be a major source of innovative cancer clinical trials and advance the treatment of cancer
- To increase early phase clinical trials
- To foster translational cancer research
- To provide efficient, compliant clinical cancer research
- To increase NCI/NIH funding
- To provide state of the art patient-centered cancer care through interdisciplinary clinical programs
- To educate patients, trainees and community physicians

Scope of Clinical Operation



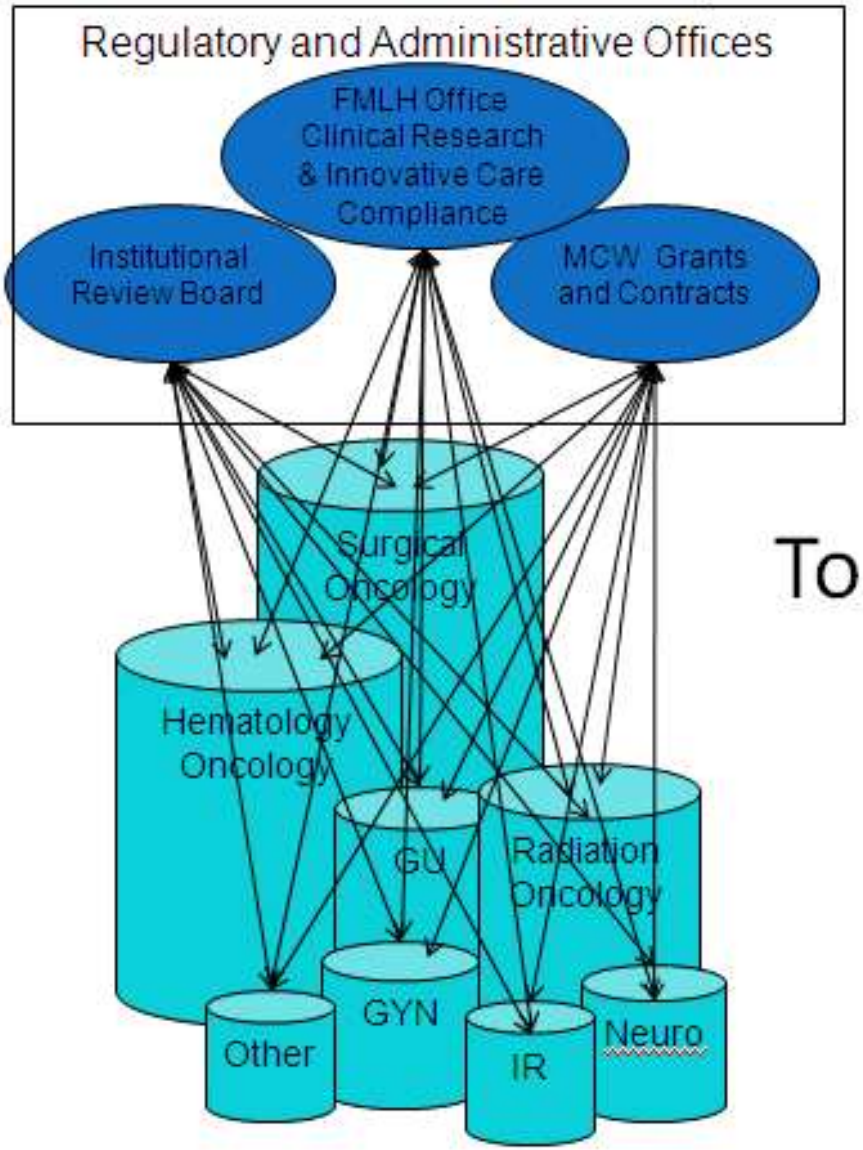


Faculty Disease Committees

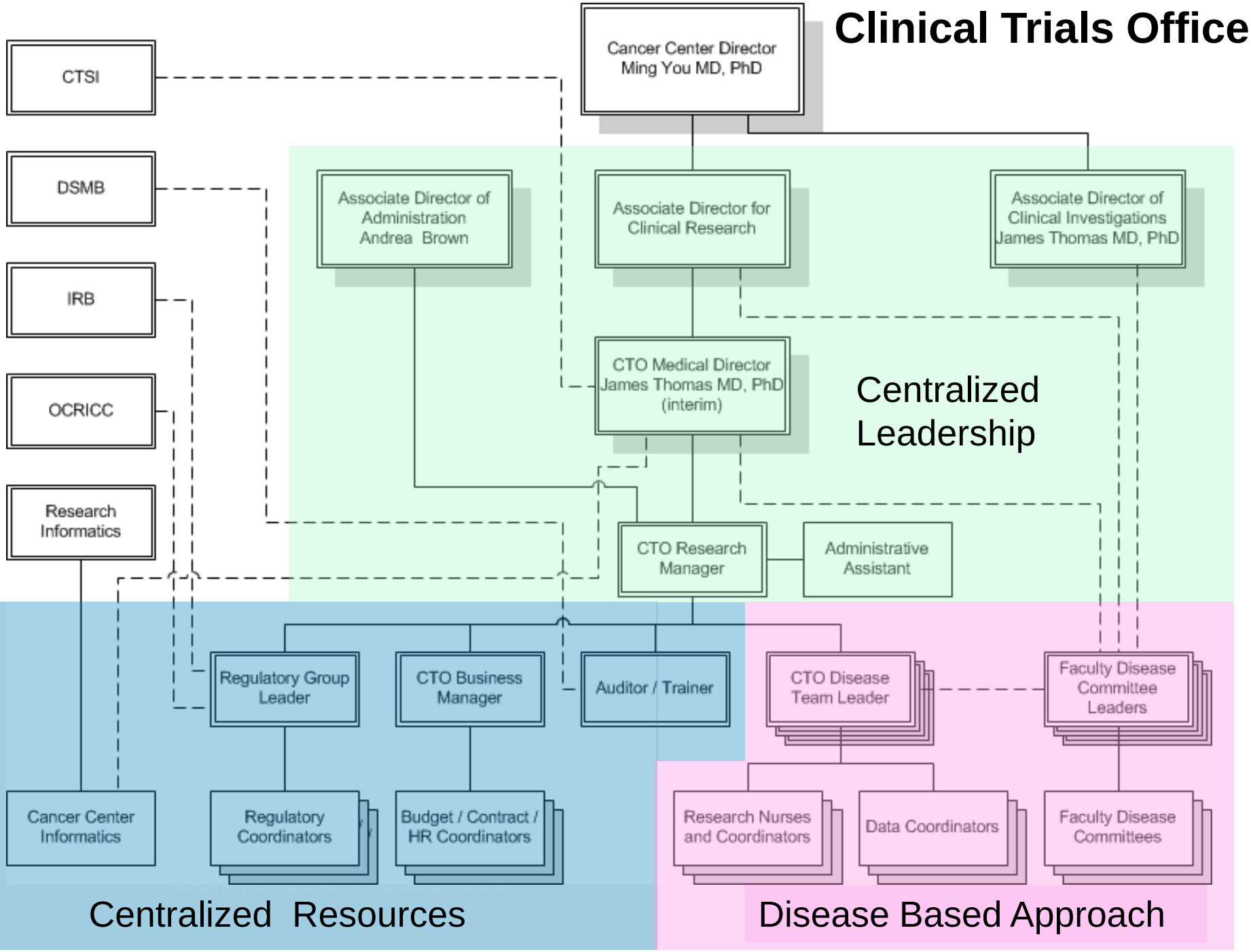
- **Breast Cancer**
- **Genitourinary Cancers**
- **Endocrine Cancers**
- **Colorectal Cancers**
- **Liver, Pancreas and Bile Duct Cancers**
- **Blood and Lymph Node Cancers**
- **Bone Marrow Transplant**
- **Brain and Spine Tumors**
- **Bone and Connective Tissue Cancers**
- **Head and Neck Cancers**
- **Skin Cancers**
- **Lung Cancers**
- **Gynecologic Cancers**

- Faculty Disease Leaders
- Co-leaders selected from relative disciplines
  - e.g. surgery, med onc and rad onc
- Identified by the respective department and division leaders in conjunction with Cancer Center Leadership

Clinical Trials Office



To…


Clinical Trials Office
CTSI
DSMB
IRB
OCRICC
Research Informatics
Cancer Center Director Ming You MD, PhD
Associate Director of Administration Andrea Brown
Associate Director for Clinical Research
Associate Director of Clinical Investigations James Thomas MD, PhD
CTO Medical Director James Thomas MD, PhD (interim)
Centralized Leadership
CTO Research Manager
Administrative Assistant
Regulatory Group Leader
CTO Business Manager
Auditor / Trainer
CTO Disease Team Leader
Faculty Disease Committee Leaders
Cancer Center Informatics
Regulatory Coordinators
Budget / Contract / HR Coordinators
Research Nurses and Coordinators
Data Coordinators
Faculty Disease Committees
Centralized Resources
Disease Based Approach

Clinical Trial Management Software

Cancer Registries/ Biospecimens

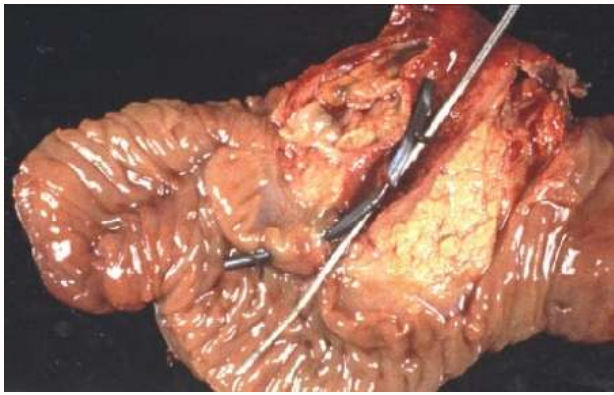
- Cancer Registries
  - Recruiting patients
  - Tracking treatment plans
  - Determining study feasibility
  - Retrospective chart reviews
  - Oncore URM to provide a uniform, scalable, flexible solution
- Biospecimen management
  - Tissue banking
  - Correlative specimens
  - Integration with clinical trial management system and electronic medical record

Cancer Translational Research Unit

- ***Cancer Phase I Unit***
  - Formation of a specialized cancer treatment area for the delivery of early phase, investigational agents
  - A facility that will allow investigators to conduct Phase I and Phase II clinical translational research in a methodologically sound, expedient and cost-effective manner.
  - A discrete approximately 8-station unit encompassing both infusion beds and chairs that would be utilized primarily for patients receiving protocol-directed therapy.
  - Dedicated Senior Nursing staff experienced in administering investigational agents, who will be involved in the development and evaluation of research protocols.
  - A facility that can accommodate the collection, processing, storage and shipping of research related samples such as plasma for pharmacokinetics.

Program Scientific Focus
Experimental Therapeutics

- **Personalized Medicine**
  - Providing cutting edge regimens tailored to the individual patient



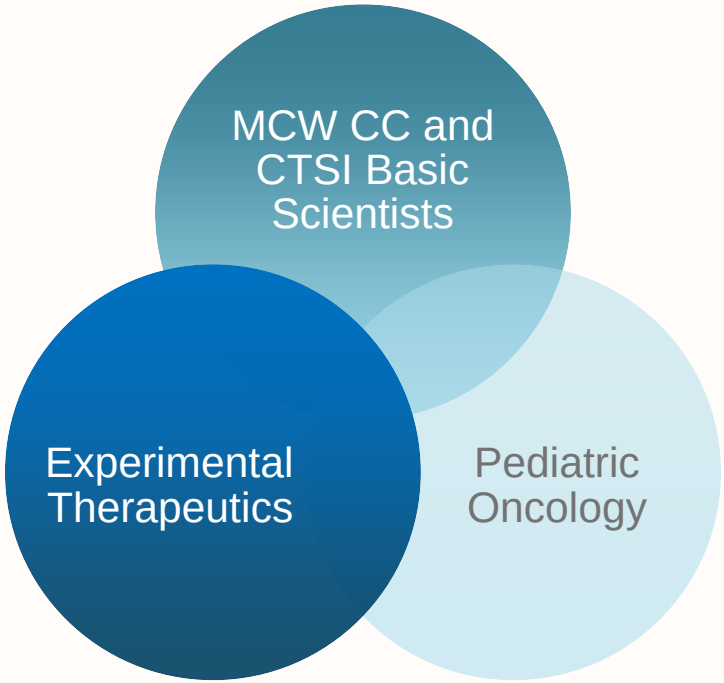
  - Neoadjuvant Pancreatic Cancer Trial
    - Biopsy taken prior to surgery for phenotypic and genotypic analysis
      - IHC
      - mRNA
      - Sequencing
    - Preoperative chemotherapy determined by tumor profiling

Program Strengths
Experimental Therapeutics

- Large adult cancer population
- Institutional Commitment
  - State of the art cancer treatment facility
- Successful recruitment of key translational research faculty
- Active Participation in Cooperative Groups
  - RTOG
  - BMT CTN
  - ACOSOG
  - ECOG
  - NSABP
  - ACRIN
  - Wisconsin Oncology Network

Experimental Therapeutics

Collaborations



- Development of correlative assays to improve the therapeutic delivery of anti-cancer agents
- Translate discoveries from CTSI laboratories into the clinic through novel clinical trials

MCW Cancer Center
Experimental Therapeutics

- ***Future Directions***
  - Increase accrual to clinical trials
  - Increase the number of clinical trial opportunities for our patients
  - Increase investment in investigator-initiated cancer trials
    - Therapeutic Cancer Trials Grant Program
  - Increase the number of Therapeutic Phase I Clinical Trials
    - Cancer Translational Research Unit
  - Leverage the unique resources of the Medical College of Wisconsin and the CTSI to improve the treatment of cancer patients

Clinical

Basic

Translational

Pediatric Oncology

Experimental Therapeutics

Cancer Cell Biology

Molecular Carcinogenesis & Chemoprevention

Cancer Imaging

Transplantation Biology & Immunotherapy

CIBMTR

Prevention, Contr & Population Sciences

CTSI-Cancer Center Workshop

Future Directions & Opportunities for Cancer-related Research Collaborations:

MCW Cancer Center Pediatric Oncology-Developing

Pediatric Oncology

Program Leadership

Marcio Malogolowkin, MD

- Section Chief, Pediatric HOT

Michael Kelly, MD, PhD

- Director, Pediatric Cancer Program

David Margolis, MD

- Director, Pediatric Hematopoietic Stem Cell Transplantation

Clinical

Basic

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Pediatric Oncology

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Cancer Imaging

Transplantation Biology & Immunotherapy

CIBMTR

Prevention, Contr & Population Sciences

Children Are Not Little Adults

Unique Cancers

Dynamic developmental physiology

- Impacts drug metabolism
- Unique susceptibilities to environmental exposures

Neurocognitive and Psychosocial development

- Spectrum of understanding and coping
- Different and unique exposures

Longer life expectancy of survivors

Goals

Increase interaction of physician and laboratory scientists to further our understanding of disease and to provide unique therapy options for children and young adults with cancer

- Increase preclinical and translational capabilities for pediatric cancers
- Increase early phase clinical trials
- Increase NIH/NCI funding
- Support training programs for pediatric cancer investigators

Program Research Interests

Investigators

Clinical/Translational

Oncology
Michael Kelly, MD, PhD
Meghen Browning, MD
Bruce Camitta, MD
Sachin Jogal, MD
Richard Tower, MD

HSCT
David Margolis, MD
James Casper, MD
Julie Talano, MD
Monica Thakar, MD

Psychology
Kristin Bingen, PhD
Mary Jo Kupst, PhD

Pathology
Paula North
Jason Jarzembowski
Gabriela Gheorghe
Annette Segura

Dermatology
Beth Drolet
Dawn Siegel
Valerie Lyons

Genetics
David Dimmock

Surgery
David Lal
Sean Lew

Basic

HOT
Bryon Johnson +
Gill Gershan
Carolyn Taylor
Andrew Chan*
Fritz Sieber
Sid Rao+

Cell biology
Ramani Ramchandran +

Immunology
Jack Routes *

Surgery
Quing Robert Miao +

+ Current NIH
* Current NCI

Areas of focus

Tumor Immunology

Cellular therapies

Signal transduction mechanisms in cancer cells

Mediators of tumorigenesis and metastasis

Leukemia stem cells

Mitigation of therapy related toxicities

Strengths

Large pediatric cancer population

MACC Fund

CTO

CIBMTR, CTSI

Key CRI cores for basic and translational research:

- Tissue and Serum Bank
- Pharmacokinetic/genomics core
- Genomics, GWA
- Zebrafish facility (Zebrafish drug screening core)
- Histology and Imaging
- Flow Cytometry
- Transgenic Facility

Scope of Clinical Operation

Average Number of New Patients per Year (2008-2010)

Total New Patients Per Year	232
Transplants	42
Solid Tumor CNS	34
Solid Tumor Non-CNS	66
Liquid	44
Benign / Other	46

Interventional Trial Accruals: Pediatric Cancer

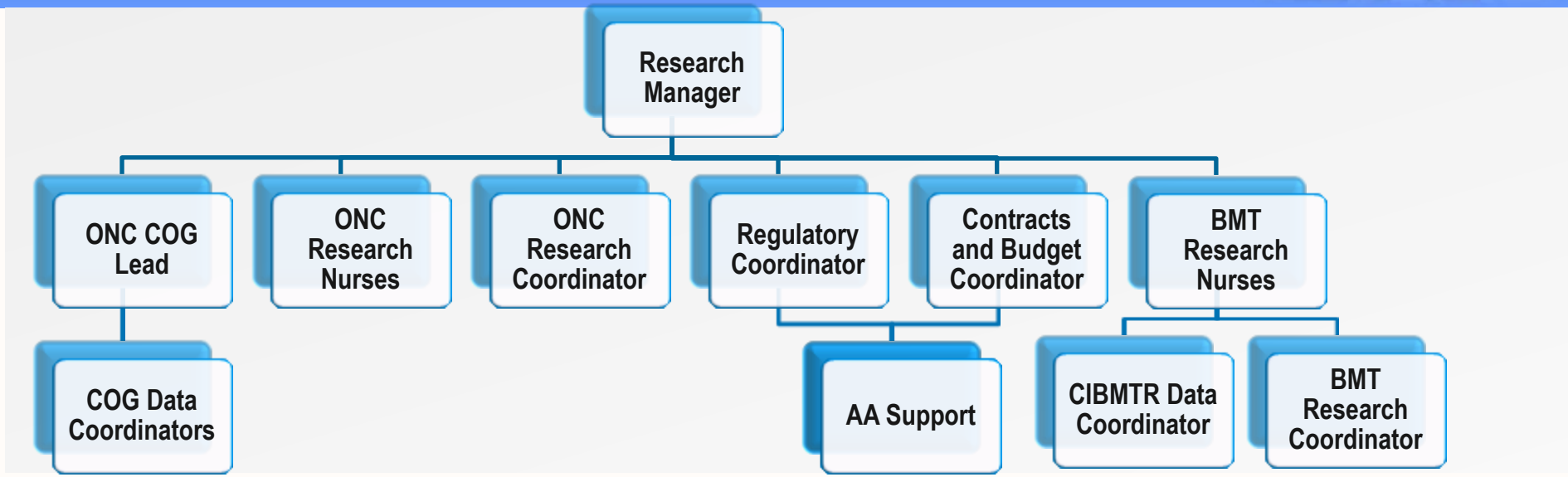
	Industry	Investigator Initiated	Cooperative	Total
2008	1	7	58	66
2009	9	5	88	102
2010	7	11	55	73
Average	5	8	67	80*

Currently a Member of the COG Phase 1 Consortium

***95% of pediatric cancer centers**

Clinical Research Staff

People



Services

Provide support from study design to publication for:

- **Phase I – III interventional trials**
- **Prospective observational studies**
- **Retrospective reviews**

Coordination Services

- **Pre-study feasibility analyses**
- **Grants & contracts applications**
- **Budget negotiations**
- **Human Research Review Board Submissions**
- **FDA Investigational New Drug applications**
- **Logistics and project coordination**

Current State

Current Studies

- **Consortium trials (Phase I/II-III)**
- **Pharma-sponsored drug trials (Phase I-III)**
- **Expanded / Compassionate Use**
- **Investigator initiated studies**
- **Translational studies**

Pediatric Tissue and Serum Bank

Bio-Bank

Capture, store, analyze and distribute tissue, bone marrow, and blood products

Technical Services

- Biospecimen accessioning and storage
- High-resolution digital microscope slide scanning and image post-processing and analysis
- DNA Extraction from tissue and blood samples
- Tissue Micro Array
- Laser Scanning Cytometry

Logistical Services

- Pre-identification of relevant cases
- Obtain informed consent
- Timely sample procurement
- Linkage to relevant clinical data
- Recurring acquisition of specimens from same patient
- Disbursement of correct materials and data to investigators

Laboratory Research

1. **Cancer Immunotherapy**
2. **Signal transduction mechanisms in cancer cells**
3. **Mediators of tumorigenesis and metastasis**
4. **Leukemia stem cells**
5. **Mitigation of therapy related toxicities**

Education


Patients and families
Health Care Professionals
• Nurses
• Residents
• Fellows
• Psychologists
Community

Areas of Future Growth/Collaboration

1. Preclinical models of pediatric cancer
2. Outcomes research pediatric cancer and bone marrow transplantation
3. Cancer Immunotherapies
4. AYA Program
5. Cancer Imaging
6. Tumor and Host genetics to individualize therapy
7. Biomarkers

Clinical

Basic

Translational

Women's Cancers

Experimental Therapeutics

Cancer Cell Biology

Molecular Carcinogenesis & Chemoprevention

Cancer Imaging

Transplantation Biology & Immunotherapy

CIBMTR

Prevention, Contr & Population Sciences

Women's Reproductive Cancers

- Uterine Cancer – endometrium
- Ovarian Cancer
- Cervical Cancer

Women's Reproductive Cancers

Cervical Cancer

99.7% of cervical cancer patients have a persistent human papillomavirus infection (HPV)

- 6 million people become infected with HPV each year
- Over 7% of all cancers are caused by HPV
- A vaccination is available for prevention of HPV 16/18
  - vaccine not therapeutic
  - present vaccine only covers 70% viral types and screening still needed
  - 45% of females 13-17 in Milwaukee have received at least 1 dose - completion of all 3 doses much lower
  - poor and minority teens less likely to finish the vaccine series

Utilizing peer teen advocates to increase HPV vaccination rates in adolescents

- Increase intention to vaccinate among parents/guardians and adolescents
- Expand efforts to include other STDs and reduction of high risk sexual behavior

- Development of a practical curriculum based on information regarding HPV infection and vaccination created in conjunction with:
  - Boys and Girls Club of Greater Milwaukee
  - Milwaukee Health Department
  - MCW

Disseminate this information to the larger community served by the Boys and Girls Club through social media channels such as YouTube, Facebook and Twitter web pages

HWPP: Denise Uyar, MD; Staci Young, PhD; Angela Hagy, Jeanette Kowalik

Genetic Epidemiology study to identify viral and host factors of disease progression (CerGE)

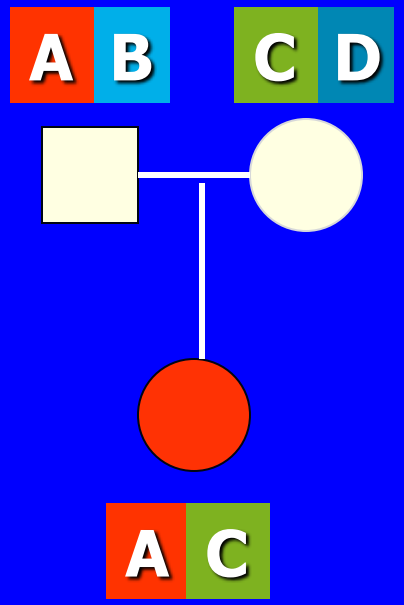
Genetic polymorphisms in genes involved in the host cellular response to HPV enhances the progression of cervical carcinogenesis

Candidate gene approach

1. Keratinocyte response to viral infection
2. Merged data from analysis of tumors
3. Immune cell response to viral infection

Janet S. Rader, MD

Family-based Tests
Transmission Disequilibrium Test (TDT)



Case genotype - A C

Constructed control genotype - B D

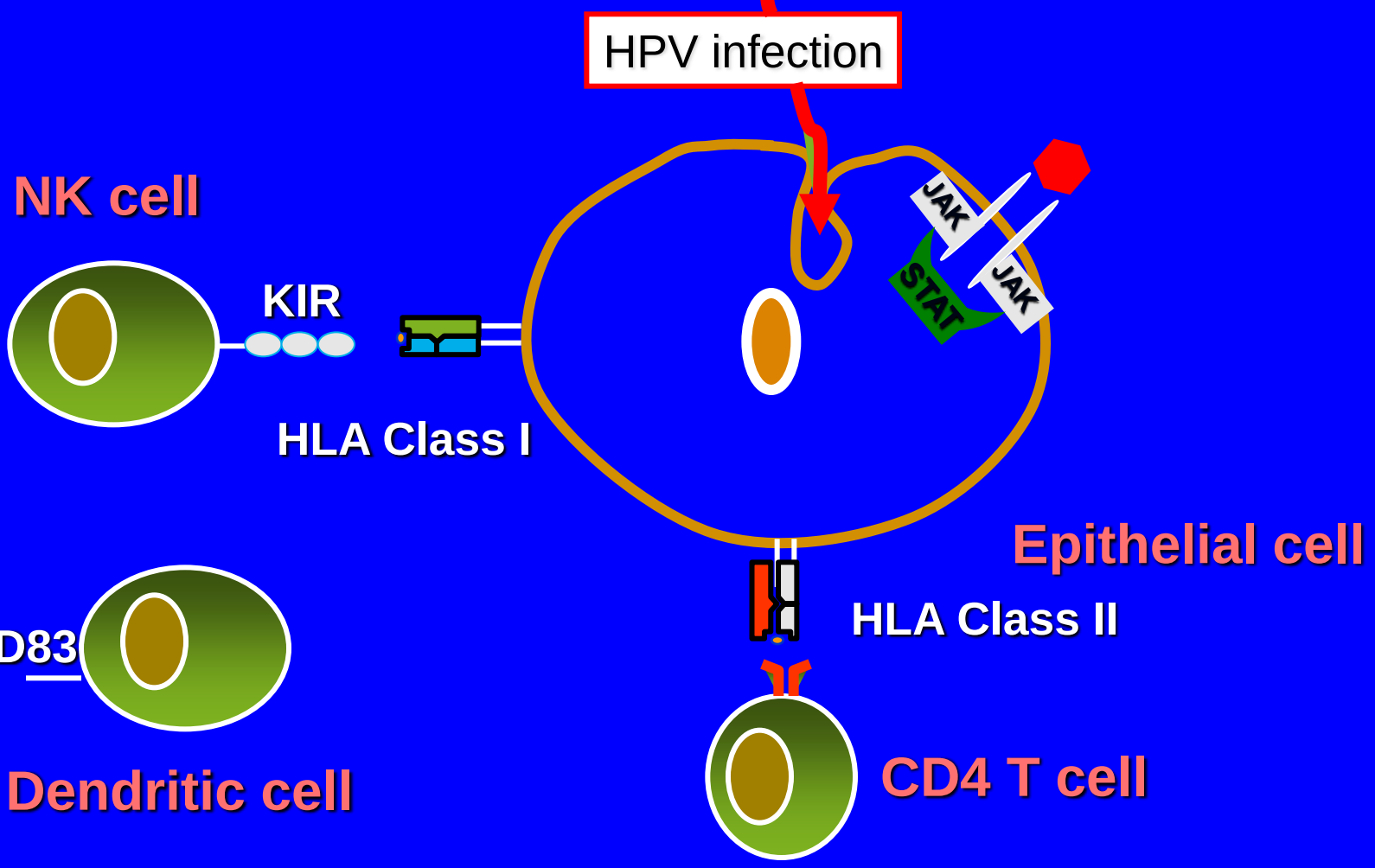
1500 affected subjects

3400 family member

70 multiple affected families

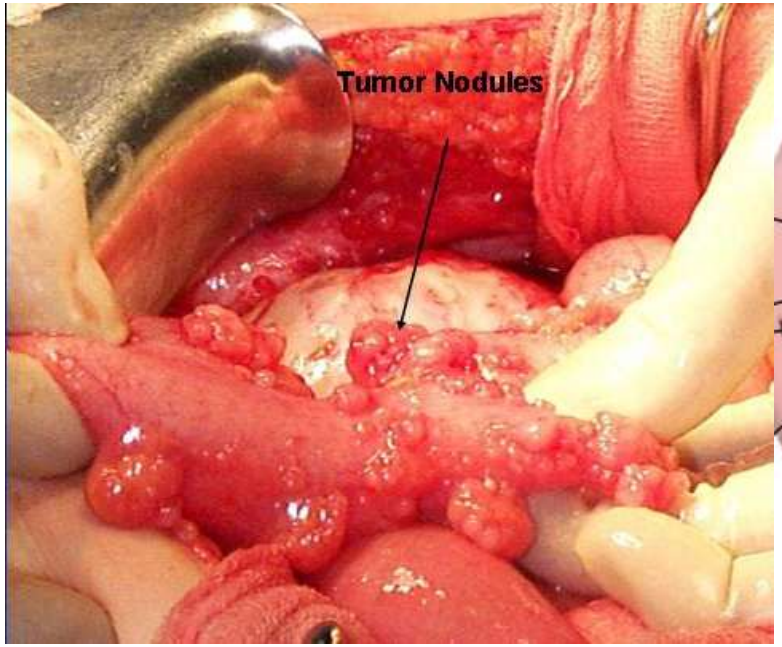
1200 tumors (in situ, invasive)

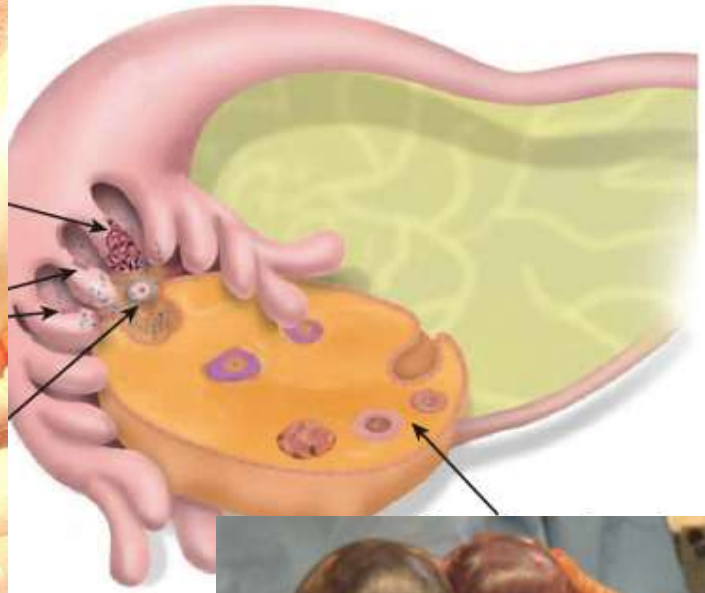
HPV sequence data on 700 samples

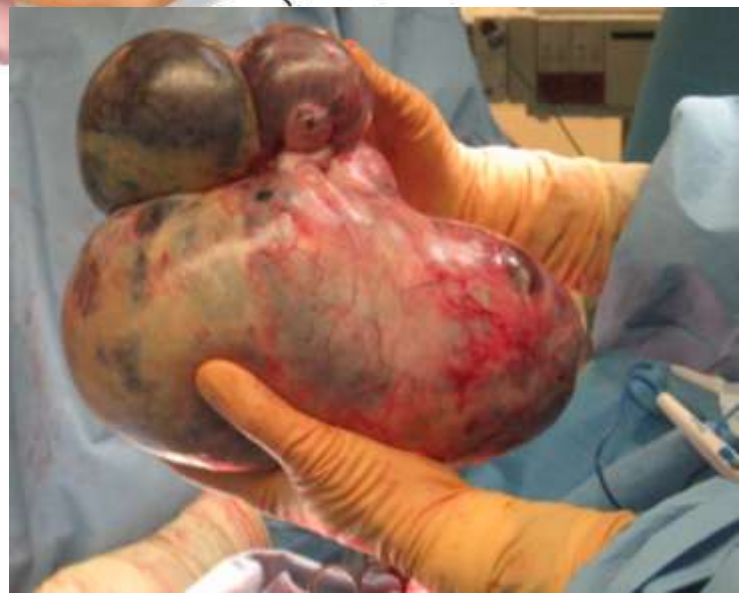

HPV infection
NK cell
KIR
HLA Class I
JAK
STAT
JAK
Epithelial cell
HLA Class II
CD83
Dendritic cell
CD4 T cell

Women's Reproductive Cancers

Ovarian Cancer

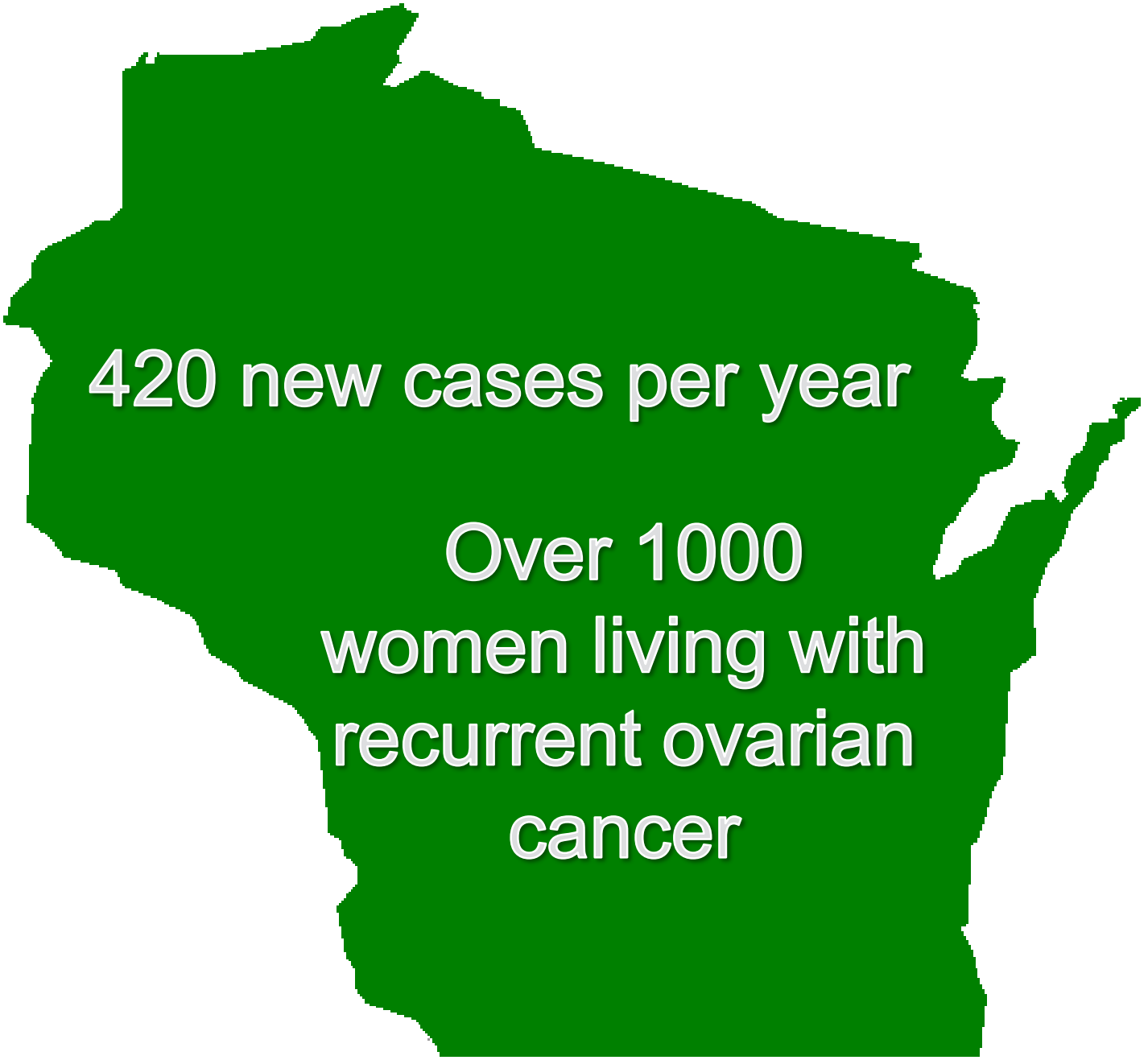




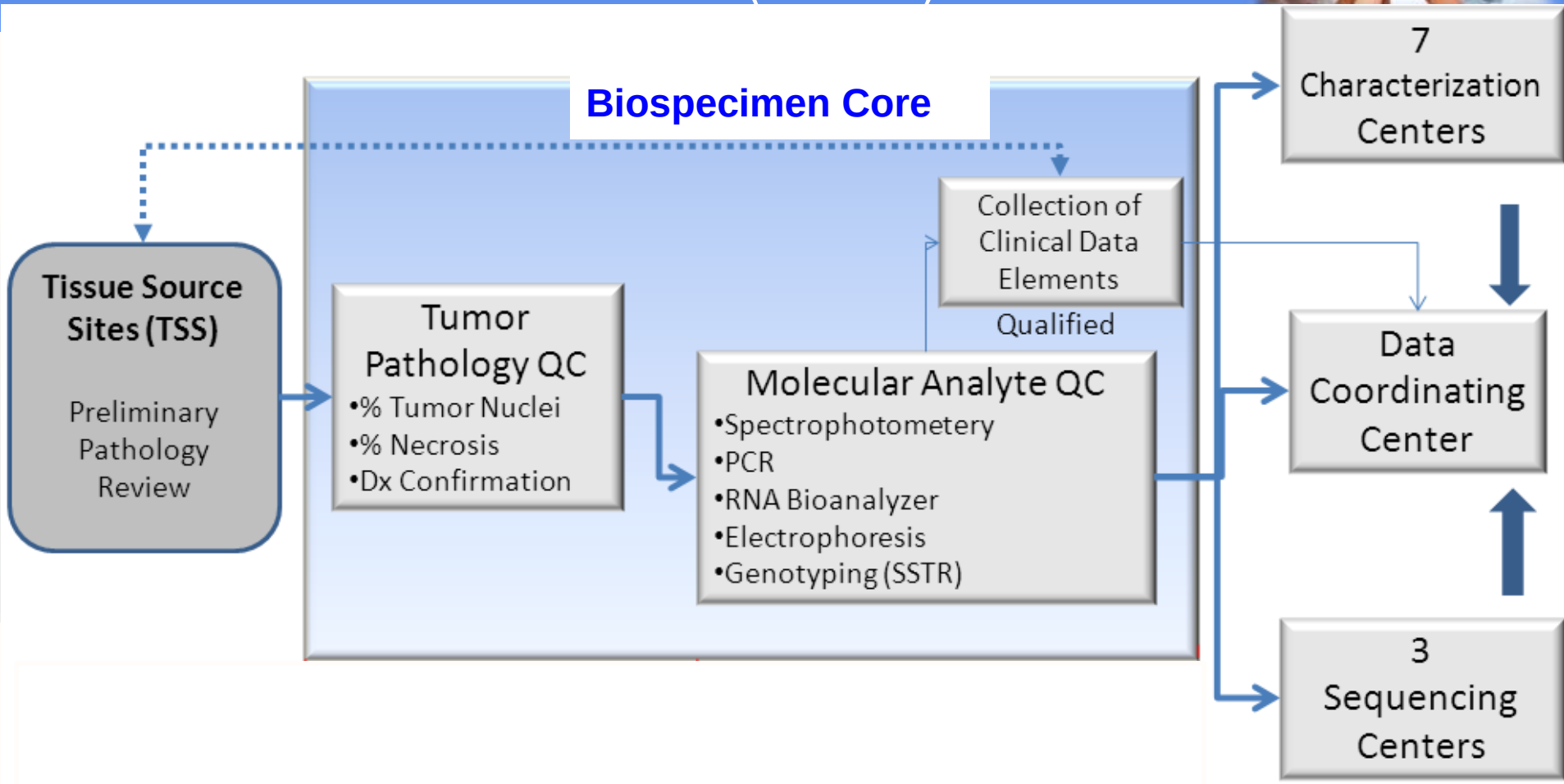


Risk factors:

- ↑ Age
  Genetic – BRCA1, BRCA2
- ↓ Ovarian suppression - OCP


420 new cases per year
Over 1000
women living with
recurrent ovarian
cancer

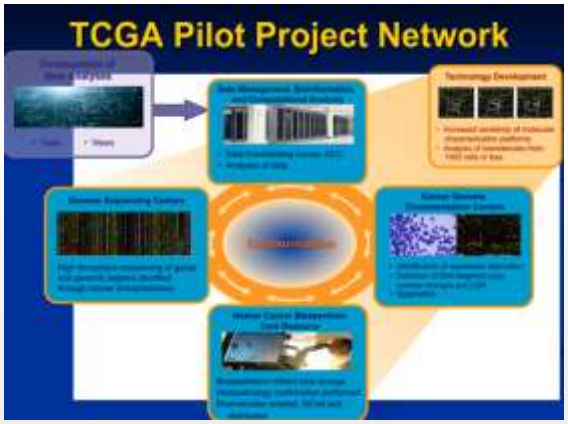
Ovarian Cancer
The Cancer Genome Atlas (TCGA) Network



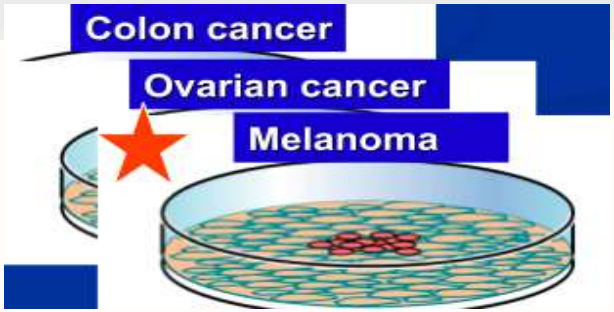
Ovarian cancer paper:The Cancer Genome Atlas Research Network. Integrated Genomic Analyses of Ovarian Carcinoma. Nature 2011;474:609-615

Janet S. Rader, MD

Personalized treatment for patients with recurrent ovarian cancer

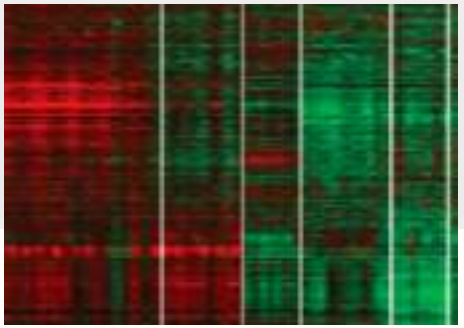


575 ovarian ca patient samples



NCI 60

Available chemotherapy



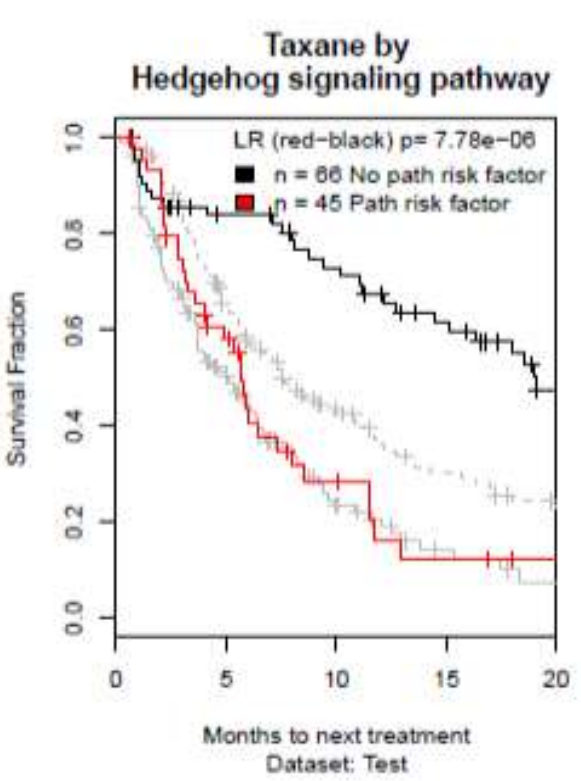
Medical College of Wisconsin
William Bradley
Oleg Moskin
Janet Rader

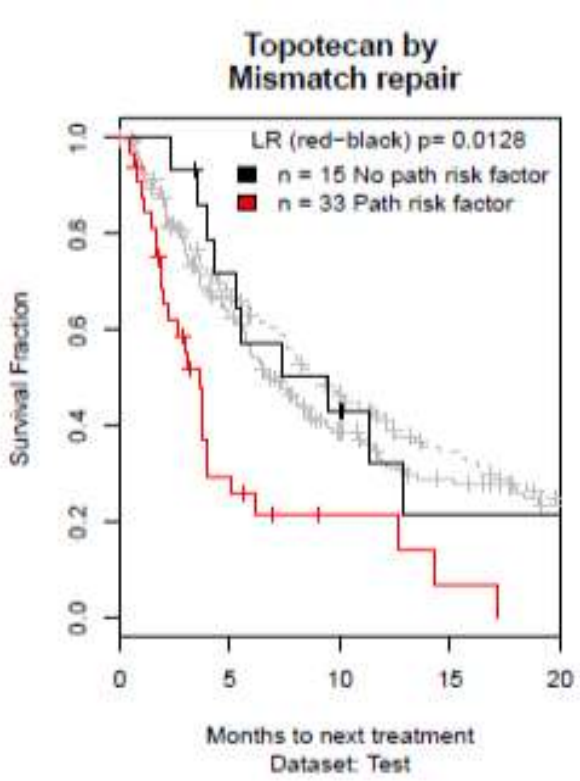
University of Wisconsin
Christina Kendziorski
Kevin Eng

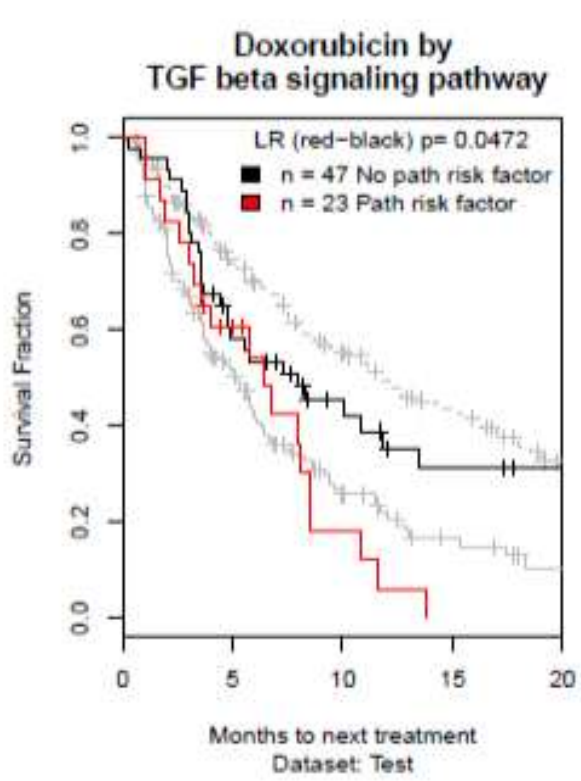
Risk Profiles and Core Signaling Pathways

Subgroups pick treatments for recurrences

Time to next event







Cancer predisposition DNA-based signature

Women's Reproductive Cancers

Endometrial Cancer

- Risk factors
  - Estrogen excess
  - Obesity
    - Incidence (risk ratio, per 5kg/m^2 increase: 1.59
    - Mortality (risk ratio, normal vs. obese, BMI>40) : 6.25
  - Polycystic ovarian syndrome
  - Family History - HNPCC

Women's Reproductive Cancers

Endometrial Cancer - Biomarkers

- Proteomic biomarkers for screening and response to therapy
- To further study the role of these protein in carcinogenesis of endometrial cancer
- Resource: collection of serum samples from patients before and after hysterectomy for their cancer

Denise Uyar, MD; Shama Mirza, PhD

Women's Reproductive Cancers

TOPS – Take Off Pounds Sensibly Club, Inc.

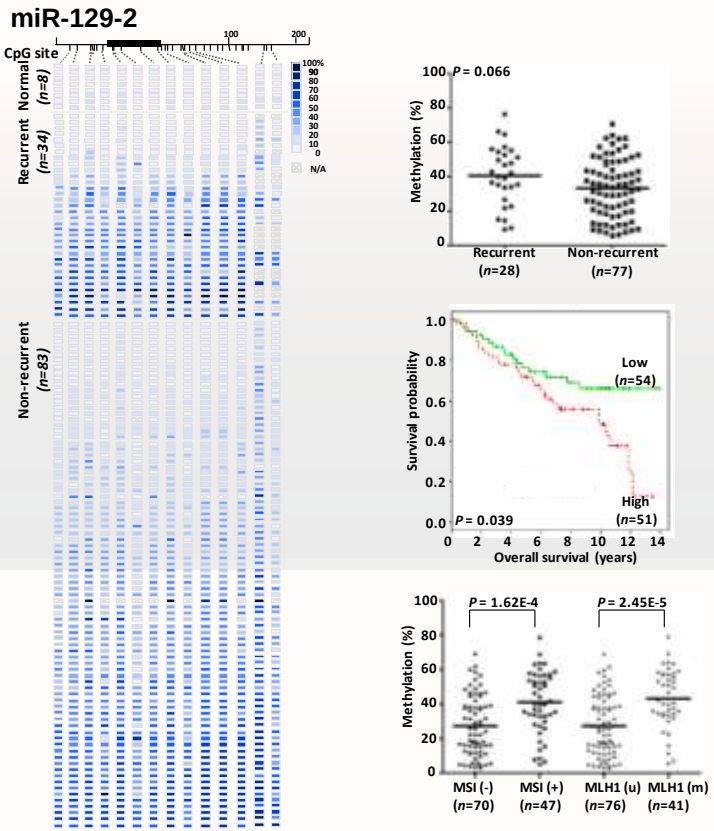
- Membership 175,000
- Phase I: 1993-1997 Genetics of Obesity
  - 55,000 questionnaire – health, weight history and family structure
  - 620 families (3007 individuals) & 183 diabetics DNA/serum/plasma, anthropometrics, biochemical measurements
- Phase II: 1998-2003
  - 503 subjects from 39 families – extensive testing, sample collection
- Genotyping: ~3000-4000 adults genome wide SNP typing
- Resource for cancer questionnaire – for studying obesity and cancer (uterine, breast, colon, others)

Ahmed Kissebah, MD, PhD,
Michael Olivier, PhD, Omar Ali, MD

Endometrial cancer

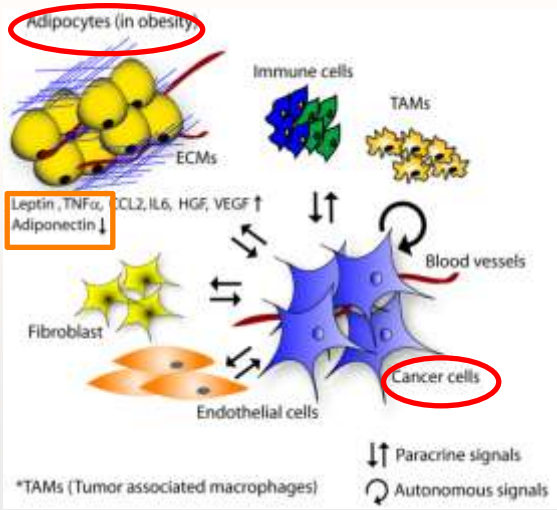
Hypermethylated loci can be prognosis/diagnosis and therapies.

Example

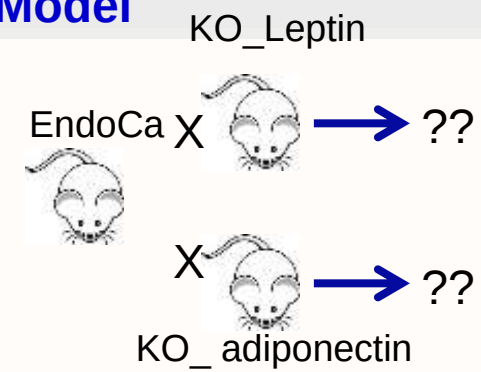


Obesity, DNA methylation and endometrial cancer

Promotion adipokine: leptin
Inhibition adipokine: adiponectin



Model



Yi-Wen Huang, PhD