Center for Cancer Research Update

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December 1, 2009

NCAB

NATIONAL CANCER INSTITUTE

CCR is the On-site Basic, Translational and Clinical Research Arm of the NCI

National Cancer Institute

Intramural Divisions

CENTER FOR CANCER RESEARCH

Division of Cancer Epidemiology and Genetics

Extramural Divisions

Division of Cancer Treatment and Diagnosis

Division of Cancer Control and Population Sciences

Division of Cancer Prevention

Division of Cancer Biology

Office of Centers, Training, and Resources

Center to Reduce Cancer Health Disparities

History and Evolving Culture Shift Continuum for CCR

1994 — 1995 — 2001 → → → → 2009

Marks-Castle Report

Bishop-Calabresi Report

DCS, DBS } CCR formed

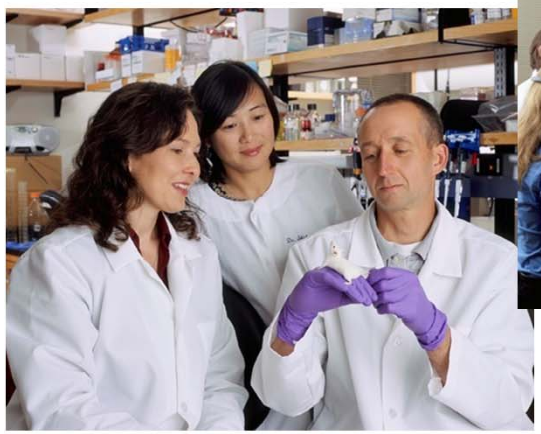
Emphasize multidisciplinary research to solve complex problems: Faculties, Working Groups, Centers of Excellence

Continue shifting the culture in CCR

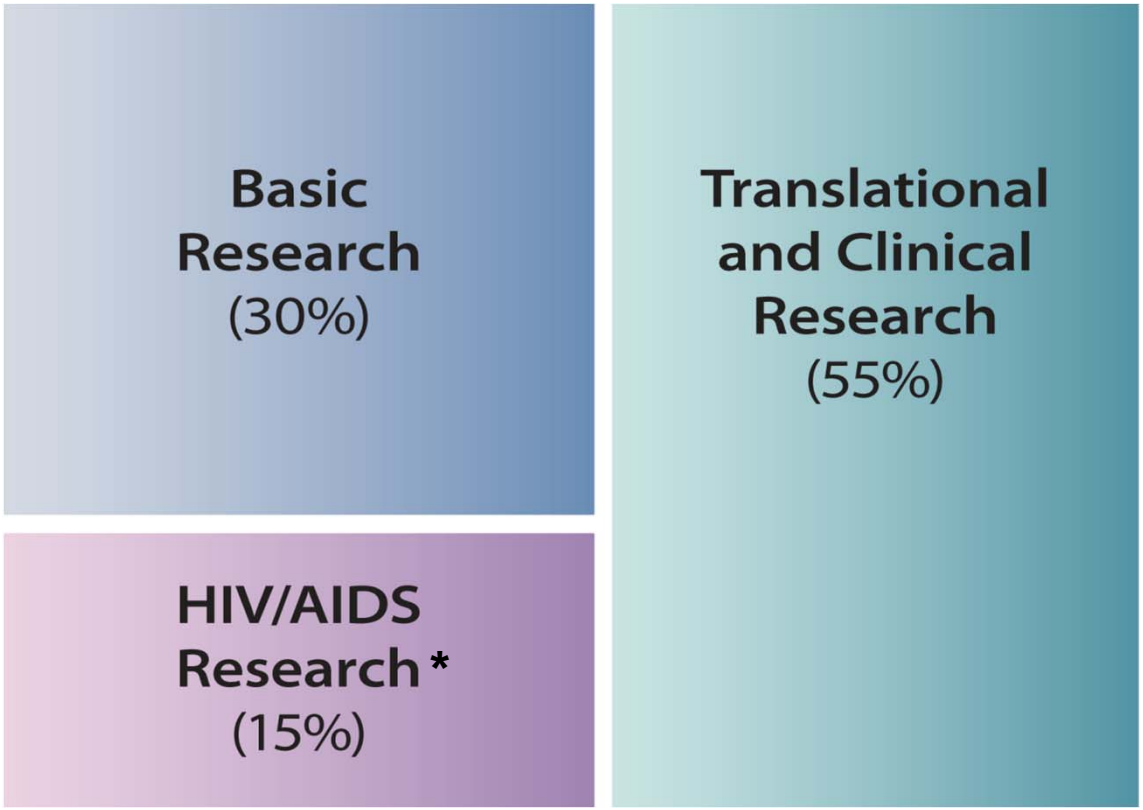
- Reengineering the IRP has been a dynamic process
- Encourage team science and collaboration while preserving and expanding outstanding PI-based research
- Strategies for rewarding team science have been implemented
- Faculty and working groups were formed, leading to the establishment of Centers of Excellence around areas of strength
- Closer ties between clinical and basic research have led directly to translational research advances and new opportunities

CCR Vision

Integrate basic, translational, and clinical research to make cancer preventable, curable, or chronically manageable.



Distribution of Research Emphasis Across CCR



* About 50/50 Basic/Translational

Centers of Excellence serve as Focal Points for Bench to Bedside Translation

- Centers of Excellence serve to support the IRPs dedication to long-term, high-risk, innovative basic, and clinical research
  - Immunology - *Robert Wiltrout, Head*
  - Chromosome Biology – *Gordon Hager, Head*
  - HIV and Cancer Virology - *Stuart LeGrice, Head*
  - Molecular Oncology - *Guiseppe Giaccone, Head*
  - Integrated Cancer Biology and Genomics - *Snorri Thorgeirsson, Head*
  - **Genitourinary Malignancies- *Marston Linehan and William Dahut, Co-Heads*

***Currently under development*

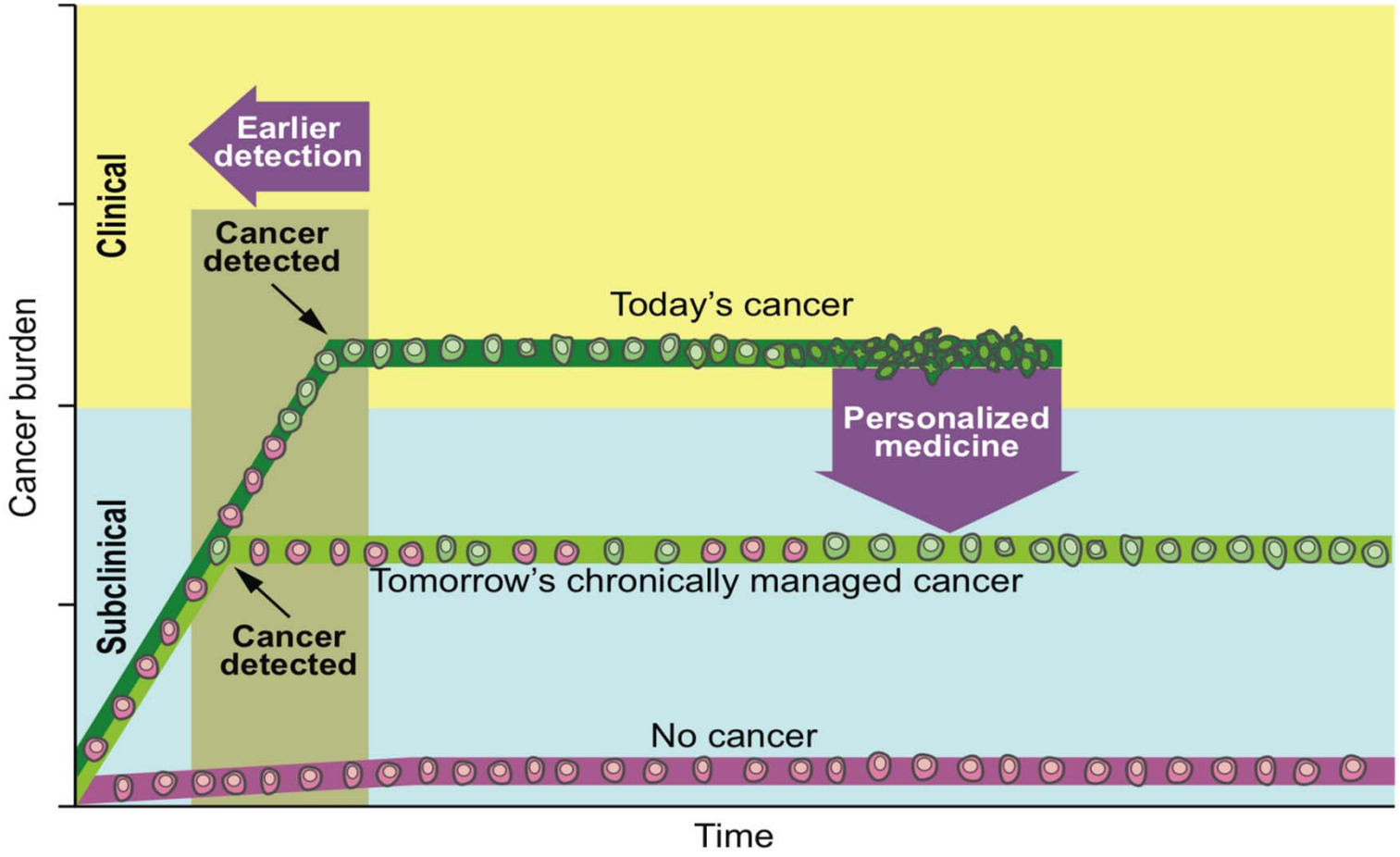
Distinctive Attributes of CCR's Clinical Research Program

- Integrate basic and clinical research to accelerate translation of advances to benefit patients
- Integrate genetically engineered mouse models and methods with early drug development
- Discover and develop molecularly targeted agents and combinations of agents
- Conduct concept-based (science-driven) clinical trials to evaluate new therapies rather than test existing ones
- Develop and deliver novel technologies
- Study rare diseases and underserved cancers
- Provide translational research training
- Integrate personalized medicine into all clinical trials

A Shift Is Under Way

Previous Approach	New Practices
Descriptive medicine	Understanding of disease mechanisms
Empirical diagnosis	Mechanism-based diagnosis/treatment
Grouped by organ	Sub-grouped by molecular/biological classification
Uniform treatment	Individualized treatment
Retrospectively diagnose disease	Prospectively evaluate relative disease risk
Acute care	Early detection and intervention

Envisioning Personalized Care



Reengineering the Clinical Trials Process at the NCI

April 2008
Round 2 of Interviews with clinical Branches and Staff which began in Dec 2007

Aug 2008
Presentation of Key Findings to subset of Clinical Branch Chiefs: Discuss Retreat Agenda

September 2008
Retreat to discuss results and recommendations with
Focus group discussions

October 2008
Begin Implementation

July 2009
Subcommittees Completed Work
Action items identified

Sept 2009
Clinical Research Strategic Placement committee holds first meeting

Dec 2009
Clinical Staff Trained; SOP's finalized; Metrics Collection begins

Current NCI IRP clinical trials process evaluated based on data (2000-09)

- Recommendations were developed
- Presented to NCAB and BSC
- CCR implementing changes now including:
  - Developed Standard Operating Procedure for Scientific Review Groups (now at Lab/Branch level)
  - Identified 86 initial metrics for collection and completed necessary IT system changes
  - Establishing a central protocol support office
  - Established a CCR Clinical Research Strategic Planning & Monitoring Committee
  - Conducting visioning exercises

Investing in Programs to Bolster Discovery and Accelerate Translation

- Clinical Molecular Profiling Core
- Deep Sequencing Facility
- Trans-NIH program of large-scale RNAi screening based (NCGC)
- High-Resolution Imaging Facility
- NIH Mouse Imaging Facility -Bethesda Campus
- Small Animal Imaging Program –Frederick Campus
- Integrated Oncology Imaging Clinic
- NIH Center for Interventional Oncology
- Comparative Oncology Program
- Comparative Molecular Pathology Research Training Program
- Molecular Pathology
- Molecular Discovery Program
- Center for Advanced Preclinical Research
- NIH-Systems Biology
- Chemical Biology Consortium in Partnership with DCTD
- Centers of Excellence

Additions to Senior Leadership

- Joel Schneider, Chief, CBL (2009)
- J. Carl Oberholtzer, Chief, LP (2008)
- Crystal Mackall, Chief, POB (2008)
- Terry Van Dyke, Chief, MCGP (2007)
- Kevin Camphausen, Chief, ROB
- Giuseppe Giaccone, Chief, MOB (2007)
- Giorgio Trinchieri, Chief, LEI (2006)
- Paul Meltzer, Chief, GB (2006)

<u>Other Appointments:</u>

- R. Andrew Byrd, Acting Director, MDP
- William Dahut, Clinical Director
- Robert Yarchoan, Director for the NCI Office of HIV and AIDS Malignancies
- Michelle Bennett, Deputy Director

NCI's IRP can rapidly redirect research efforts and resources to address encouraging public health issues; Xenotropic Murine Leukemia like Retrovirus (XMRV)

- Found in approximately two-thirds of chronic fatigue syndrome (CFS) patients and 4% of controls in clusters of cases in Nevada and Florida-South Carolina
  - *Science, 2009 Oct 8 online*

- The NCI IRP was able to rapidly assemble a multidisciplinary team to approach this public health concern. Experts in retrovirology, oncogenesis, cancer biology, epidemiology, and clinical research as well as others are actively engaged in advancing scientific knowledge of XMRV and the question of its possible impact on human health

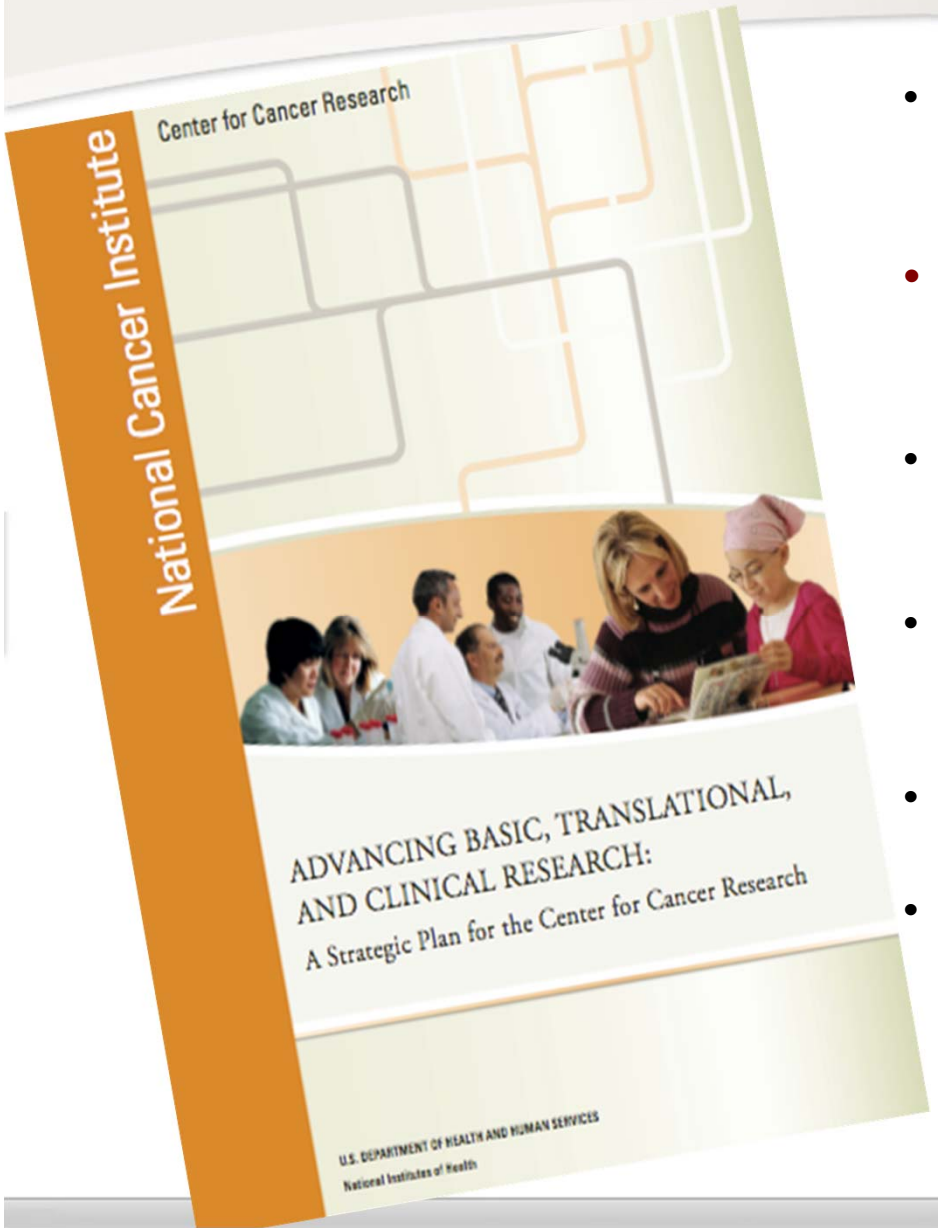
- An intramural/extramural working group has been assembled to communicate findings and collaborate

- Is there a role for XMRV in either prostate cancer and/or lymphoma?

Presidential Visit

President Obama toured the NIH campus on September 30th. During his visit he stopped in the laboratory of Dr. Marston Linehan, Chief of the Urologic Oncology Branch, to talk about hereditary kidney cancer and advances being made in CCR.

CCR Labs and Branches Are Woven Together Around Strategic Priorities



- Understand the Cancer Process from Initiation to Metastasis
- **Interrogate the Molecular Genetics of Cancer**
- Improve Cancer Prevention, Early Detection, and Diagnostic Approaches
- Develop and Validate Novel Molecularly Targeted Interventions
- Harness the Immune System to Combat Cancer
- Discover and Develop Approaches to Combat HIV/AIDS and AIDS-associated Malignancies

CCR Scientific Presentations to the NCAB

- **Shiv Grewal - RNAi-mediated epigenetic control of the genome**
- **Shyam Sharan - Understanding the functional significance of variants identified in human breast cancer susceptibility genes**
- **Pat Steeg - Brain metastasis of breast cancer: Molecular and preclinical advances**
- **Louis Staudt - RNA interference screens and cancer gene resequencing to discover the Achilles heel of cancer**
- **Marston Linehan - Genetic Basis of Kidney Cancer: Opportunity for Disease Specific Targeted Therapy**

- What clinical initiatives are required to test emerging preclinical strategies?
- How do we get bench discoveries to the bedside more efficiently/effectively as well as address the "personalized aspect”?
- What clinical initiatives are required to test emerging preclinical strategies for brain metastases of breast cancer?

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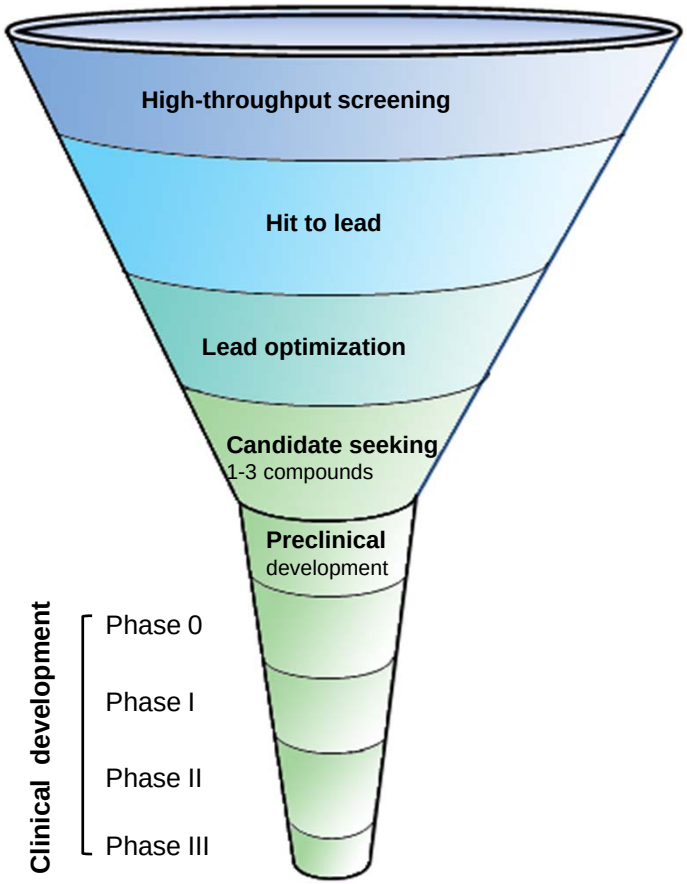
Scientific Advances

- Gene Therapy Method Slows Tumor Growth in Mice (Trinchieri/ Blumenthal) *Cancer Gene Therapy online October 9, 2009*
- Short Strand of RNA May Help Predict Survival and Response to Treatment for Patients with Liver Cancer (Wang) *New England Journal of Medicine. No. 361, Vol. 15 Oct 2009*
- Gene Mutation Linked to Type of Childhood Cancer (Khan) *J Clin Invest Online October 5, 2009*
- Hormone Cycling Found to Affect Gene Activity (Hager) *Nat. Cell Biol. Sept 2009. Vol. 11, No. 9*
- NIH Study Reveals New Genetic Culprit in Deadly Skin Cancer (Rosenberg) *Nature Genetics online: 30 August 2009*
- Immunity to murine prostatic tumors: continuous provision of T-cell help prevents CD8 T-cell tolerance and activates tumor-infiltrating dendritic cells (Hurwitz) *Cancer Res. 2009 Aug 1;69(15):6256-64*
- Researchers Identify a Novel Mechanism that Could be Targeted to Prevent Cancer Spread (Weissman/ Byrd) *Molecular Cell. Vol. 34, No. 6. June 26, 2009*
- Cancer Immunotherapy Can Use Small Numbers of Stem-Like Immune Cells to Destroy Large Tumors in Mice (Restifo) *Nature Medicine. Online June 14, 2009*

Chemical Biology Consortium (CBC)



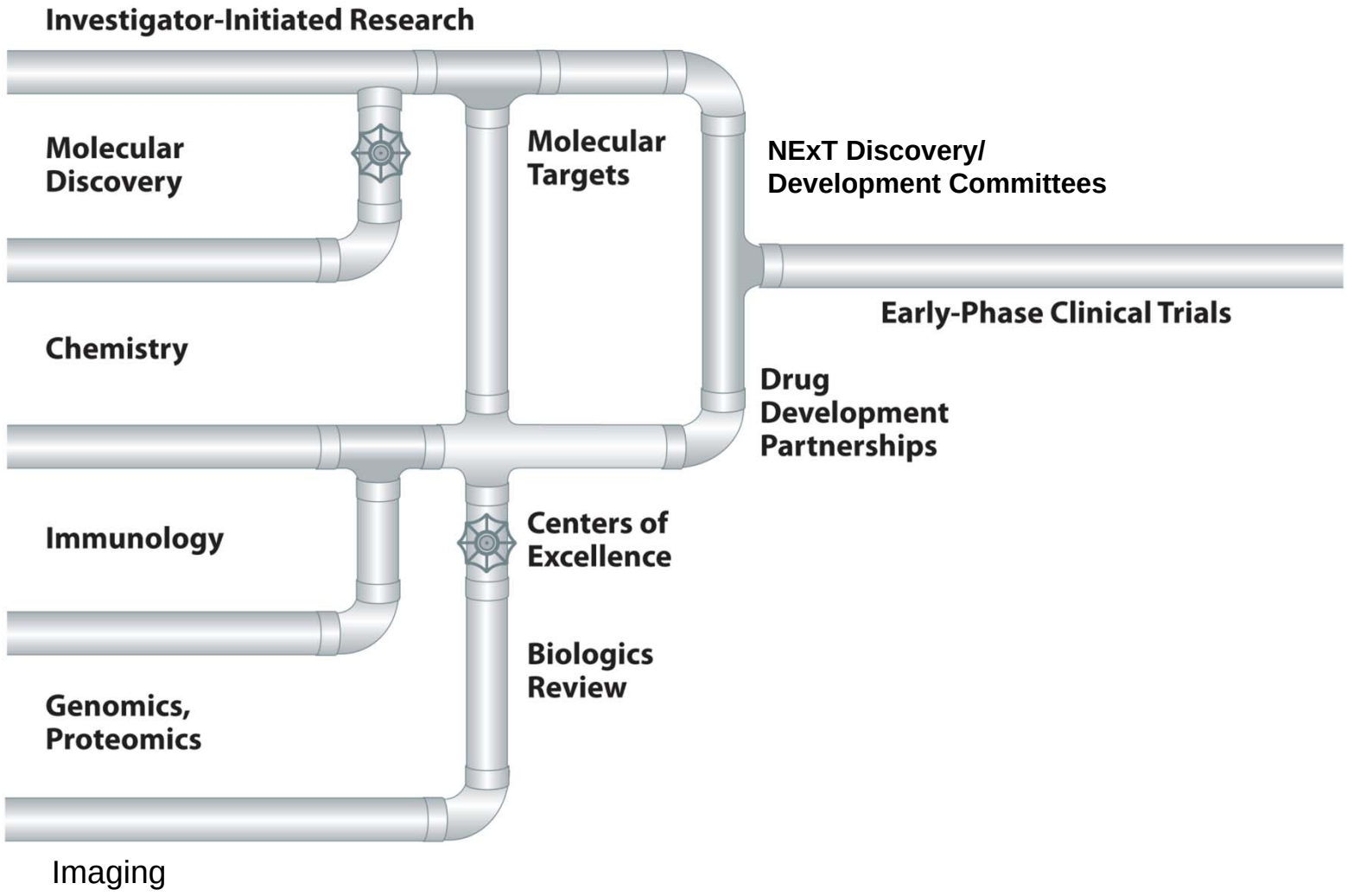
Vision

- Develop an integrated network of chemists, biologists, and molecular oncologists, with synthetic chemistry support.
  - Active project management by NCI and external advisory boards.
  - Unified discovery with NCI preclinical and clinical development.
  - Link to other NCI initiatives with CCR as an integral partner.
  - Ongoing grant portfolio analysis.

- Focus on unmet needs in therapeutics such as “undruggable” targets and under-represented “orphan” malignancies.

- Enable a clear, robust pipeline from target discovery through clinical trials for academic, small biotech, and pharma investigators.

Development Pipeline for DCTD/CCR Early Phase Clinical Trials Initiative

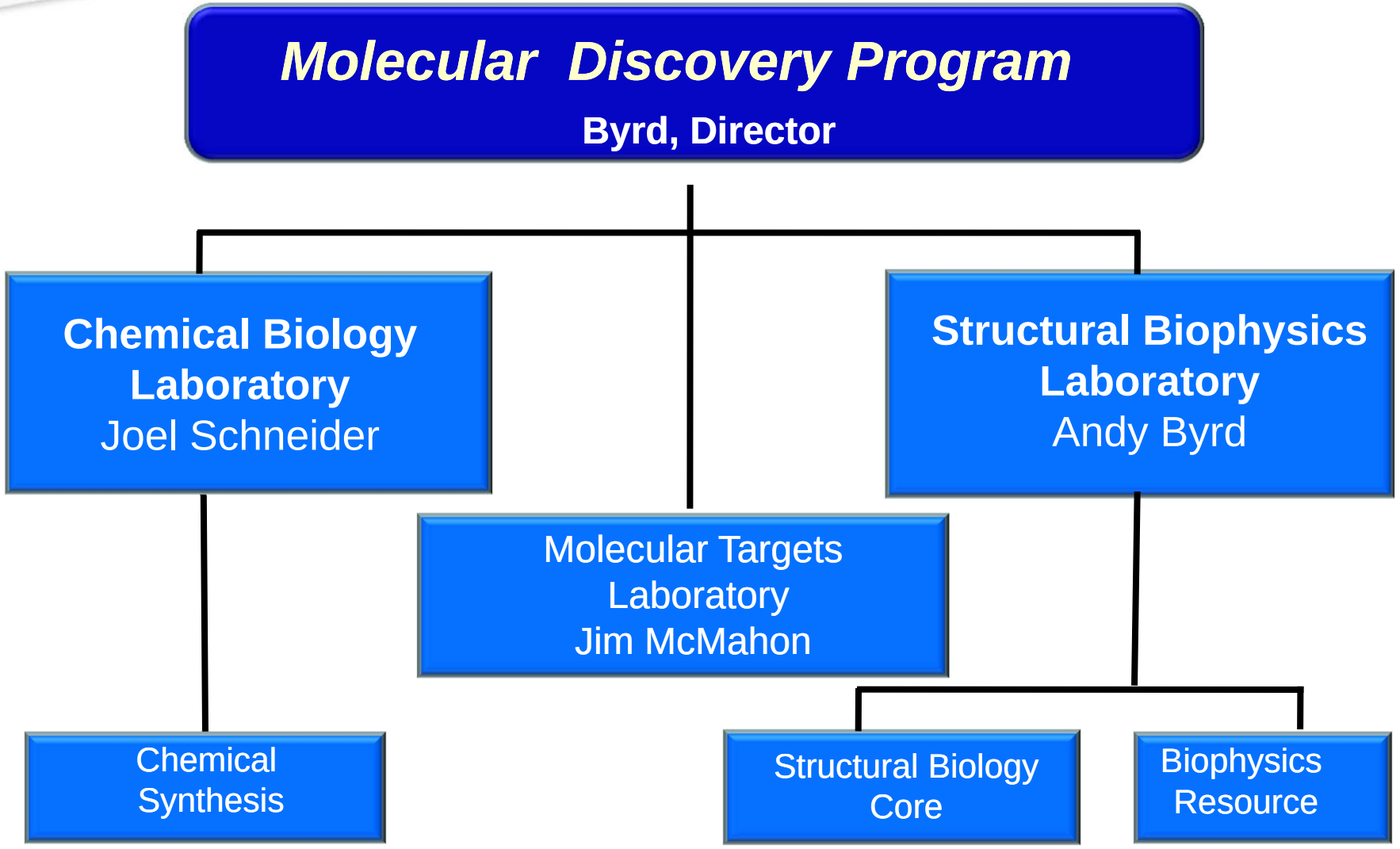


DCTD/CCR Phase 0/ Early Phase I Clinic

- Clinical trials performed using an exploratory investigational new drug (IND) will facilitate targeted therapies entering early phase evaluation where the target can be carefully monitored. The goal of this new guidance is to safely shorten the timeline for drug development. As part of the DCTD-CCR collaboration, novel agents for high-priority targets originating from academic and other extramural researchers will be eligible to take advantage of intramural resources.

- Kummar et al, Phase 0 clinical trial of the poly (ADP-ribose) polymerase inhibitor ABT-888 in patients with advanced malignancies. J Clin Oncol. 2009 Jun 1;27(16):2705-11.

Molecular Discovery Program

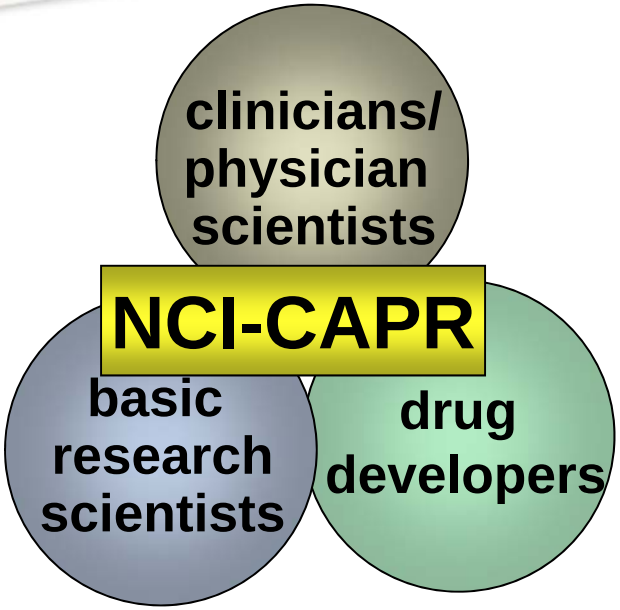


Molecular Discovery Program

Build on the Strength of Biology in the CCR Mission / Founding Principles

- Enable collaborative, multi-disciplinary, basic research to advance mechanistic understanding
- Re-invigorate chemistry and chemical biology
- Facilitate the combinations of biological, chemical, and structural approaches to understanding human biology
- Enable the discovery of biological modulators and the verification of such modulators *in vitro* and *in vivo*
- Establish partnerships with the CBC and NCGC to share expertise and resources in areas such as Chemical Synthesis, Natural Products and Structure-based discovery
- Facilitate the transition of discoveries to the CBC development engine of DCTD and to Phase 0/1 trials

CAPR Center for Advanced Preclinical Research



Projected Interactome

a new paradigm for translational science

To facilitate the improvement of preclinical assessment and clinical trial design for effective cancer diagnosis and treatment

Terry van Dyke