Mechanisms for CCR Program Change at NCI-Frederick

Robert H. Wiltrout, Director, SD for Basic Science

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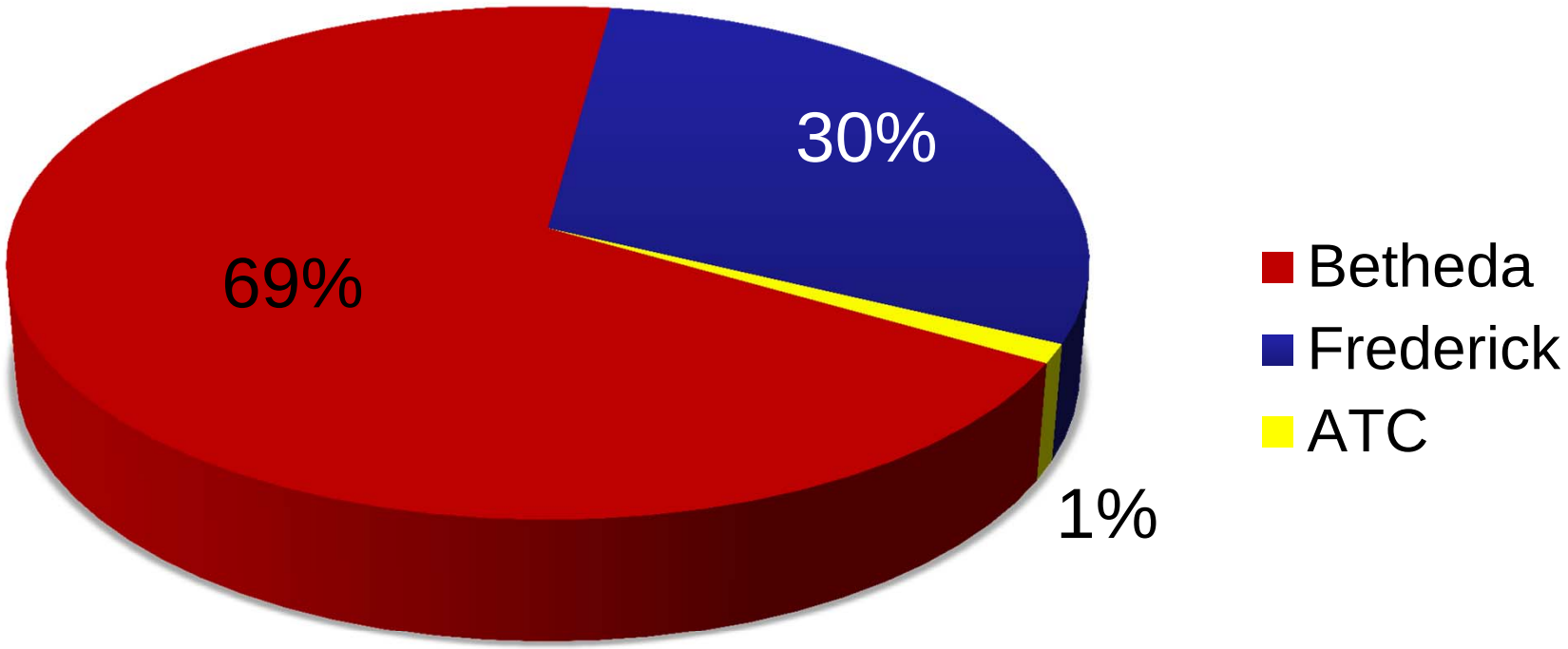
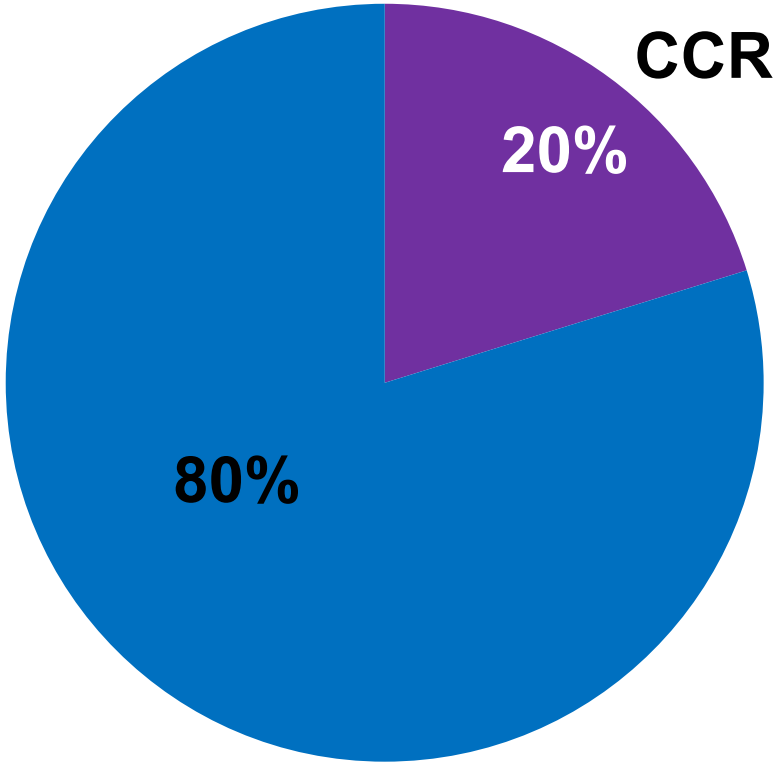
NATIONAL CANCER INSTITUTE

Current PI Distribution by Campus



CCR Portion of the NCI's Frederick Budget



FY2010

Recommendations for Program Change Derive from Multiple Review Mechanisms

- **Ad hoc External Review**
  - **NCAB ad hoc review the IRP (Bishop-Calabresi)**
  - **NCI Divisions can convene special ad hoc review**

- **Quadrennial BSC Review of IRP Research**
  - **Fully extramural site visit teams and NCI's Board of Scientific Counselors review Labs/Branches and CCR core services**
  - **BSC subcommittees can be used for specific tasks**

- **NCI-Frederick Core Services Reviews**
  - **Intramural users and extramural experts review the core services to assure they are cutting-edge, cost-efficient, and aligned with NCI's research priorities**

NCI-Frederick Programmatic Changes Resulting From Bishop-Calabresi

- **Programs Realigned into Intramural and Extramural Divisions**
  - Frederick components of DBS and DCTD created
  - DTP split between DBS and DCTD
- **Biological Response Modifiers Program Split**
  - Clinical component aligned with DCS, moved to the Clinical Center
  - Basic Research Laboratories aligned with DBS
  - Biopharmaceutical Production Facility developed as contractor service, opened to extramural
- **Contract PIs**
  - SAIC PIs working in NCI Labs were recognized; retain SAIC affiliation, but reviewed directly by the BSC
  - ABL contract Labs were Federalized
- **Research Support Services**
  - Triennial reviewed process established
  - Services offered reconfigured to reflect NCI needs and research priorities
  - Opened to Extramural and Intramural

History of CCR in Frederick

1998 **1999** **2001**

Frederick ABL-Basic Research Program

DBS Bethesda | **DBS** Frederick

DCS

DBS Bethesda | **DBS** Frederick

DCS

CENTER FOR CANCER RESEARCH

A Rigorous BSC Process Drives Quality of Basic and Clinical Research

- Four-year cycle
- Retrospective/prospective review
  - Accomplishments
  - Future directions
  - Team science
  - Innovation
  - Mentoring and training
- Site visit teams and Board of Scientific Counselors
  - 100% Extramural participants
  - Evaluates the science being performed in light of its cost
  - Encourages high-risk approaches
- Recommendation
  - The site visit teams report their findings and provide recommendations to the BSC, which then advises the CCR Director whether research programs should continue to be supported, and at what level

CCR Staffing in Frederick: Facts and Figures

- **In 2006 CCR Frederick had 95 PIs**
- **In 2012 CCR Frederick has 80 PIs**
- **Since 2006, 26 (31%) have departed**
  - 13 (50%) were directly or indirectly due to BSC
  - 5 (21%) departed for career advancement
  - 11 new hires-6 TT and 5 tenured (36% female)

  ** 10 (13%) received substantial reductions/re-review
- **Anticipated closures/departures**
  - FY2012= 1
  - FY2013= 1
  - FY2014= 1

CCR TT Hires 2007-2011

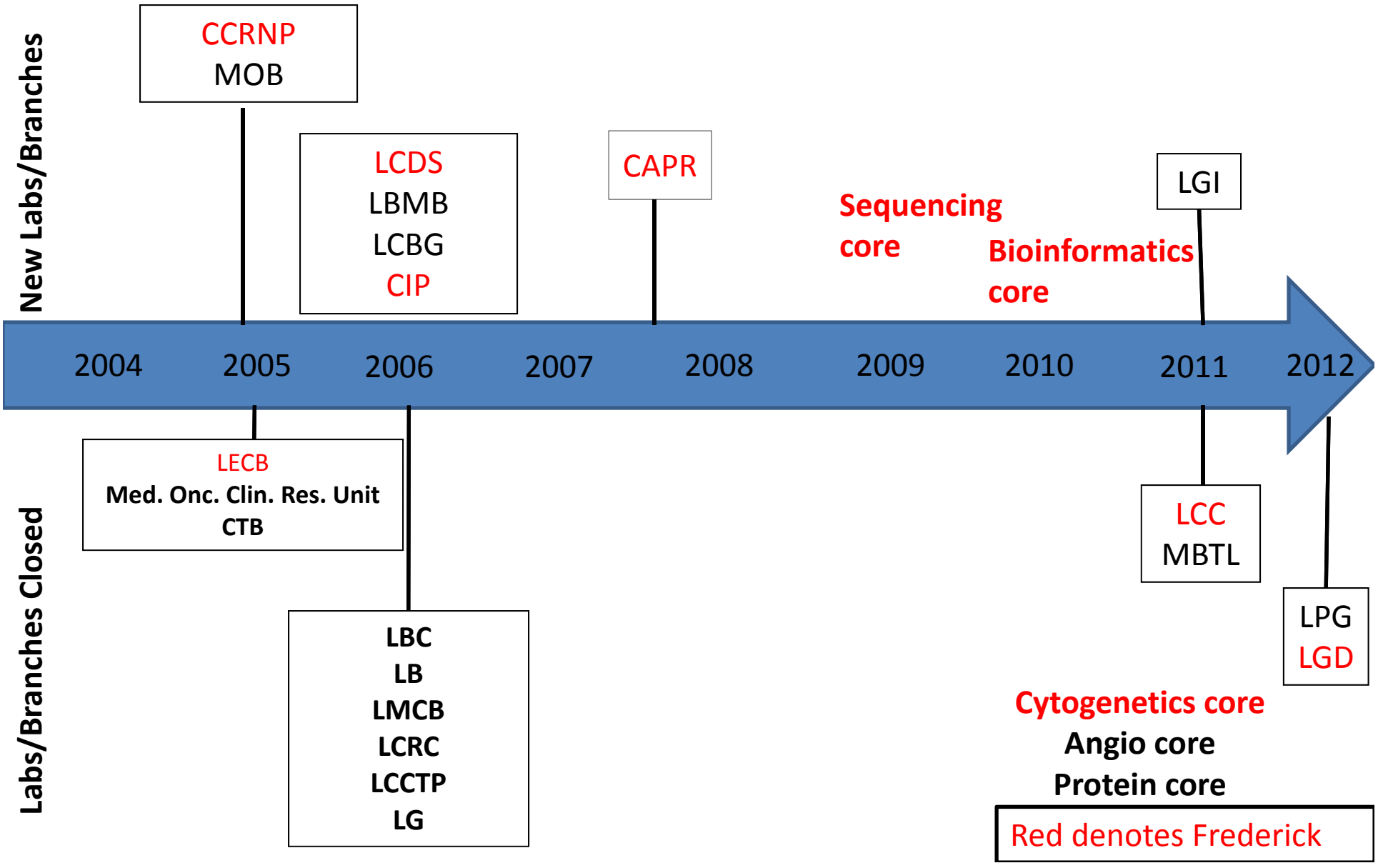
Tenure Track

2007	2008	2009	2010	2011
Buck	Avital	Hussain	Bernal	Annunziata
Kwong	Citrin*	Oberdoerffer	Fry	Batchelor
	Dalal*	Ramamurthi	Greten	Brownell
	Ho	Rudloff	Kaplan*	Guha
	Hu*	Yang*	Kreisl*	Hodge
	Huang		Lal	Kong*
	Kalab		Luo	Kovalovsky
	Kammal		Oberdoerffer*	Larson
	Lewis		Stommel*	Lazarevic*
	Park			Loncarek*
	Ziegelbauer			Palena*
				Schneekloth
				Tofilon
				Westlake

43% Female

Red denotes Frederick
* Denotes Female

Labs/Branches Created and Closed



Program Change: Capitalizing on Complementary Research Strengths

- **Cancer and Inflammation Program (CIP)-formed in 2005**

  -Recruited strong senior leader-Giorgio Trinchieri

  -Combined the Laboratory of Experimental Immunology with the Laboratory of Molecular Immunoregulation + additional cancer biology PIs

  -Provides leadership of CCR's inflammation and cancer initiative which melds NCI's expertise in inflammation and immunology with its broad-based cancer biology and carcinogenesis programs

- **Fostered closer collaborations among the 15 PIs in the Program and joint retreats and many collaborative studies on cancer and inflammation or cancer-related infections-very strong BSC review in 2010**
- **Stimulated Trans-CCR organization to propose and support a new Major Opportunity for Inflammation and Cancer associated with the re-engineering of CCR's clinical program**
- **Benefits by close proximity to NCI-F's animal models expertise**

Program Change: New Initiatives

- **The Center for Advanced Preclinical Research (CAPR) -**
  - **-formed in 2008 as a new initiative with the goals of:**
  - **- using genetically engineered mouse models and gene expression profiling to accelerate cancer drug and biomarker development**
  - **- more accurately assessing the potential of candidate drugs to succeed in clinical trials.**
- **Built out in less than a year using SAIC staffing**
- **Envisioned as a national resource for the comprehensive preclinical testing of early stage candidate drugs. Candidate compounds will be primarily assessed for anti-tumor efficacy and selectivity in genetically engineered animal models.**
- **Program review mechanism: NFAC or BSC?**

Summary of Current CAPR Out-Reach Activities/Partnership Leads

Partnership Lead	Project Concept	Contract Vehicl	% Complete	Projected Timeline	Expected Funds
Foundation A/University Partner B/ Non-Profit Partner C	Fund raising: support an integrated preclinical/clinical drug development platform in NSCLC	MOU/Consortium	80%	Foundation Board approval (exp. February)	$15M in total funds for three years
Pharma Partner D (recent IPO)	Testing novel RTKi's in EGFR-driven GEM models	Full CRADA	70%	NCI CRADA Subcommittee (exp. February)	$100K-$200K (first milestone)
Pharma Partner E	Testing two classes of compounds in ovarian cancer GEMs	Full CRADA	60%	Filing with NCI CRADA Subcommittee (exp. March-April)	$150K-$200K
Foundation F	Goal: Establish a cancer preclinical trial consortium based on GEM models	TBD/Consortium concept discussed	50%	White Papers/concept documents exchanged	Option 1: $150K-$200K Option 2: up to $3.1M
Pharma Partner G	Multiple candidate drugs to be tested in GEM models for NSCLC, ovarian cancer and melanoma	Full CRADA	30%	Opportunities for joint projects identified	up to $200K per compound tested

CAPR Center for Advanced Preclinical Research

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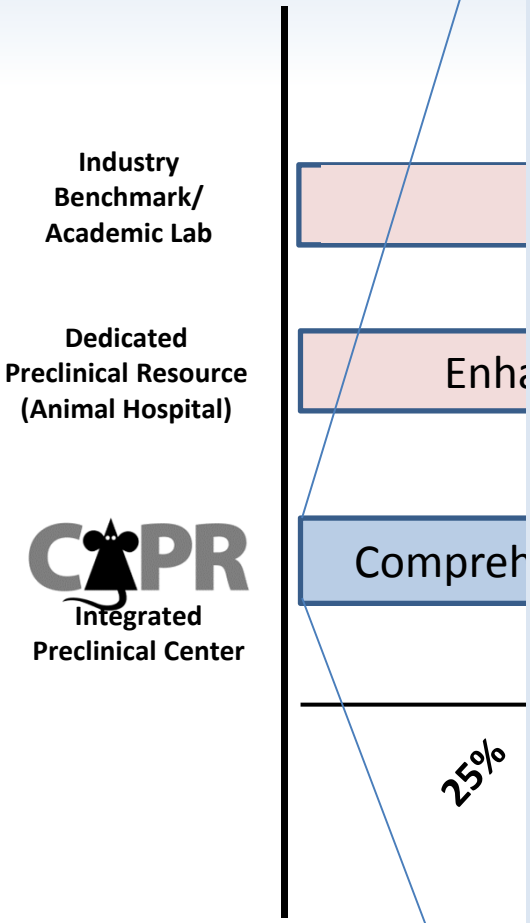
Resource I

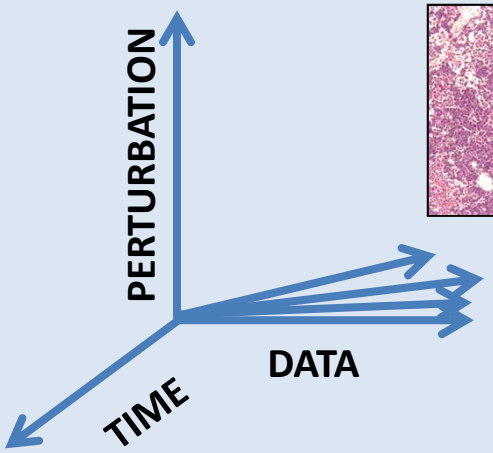


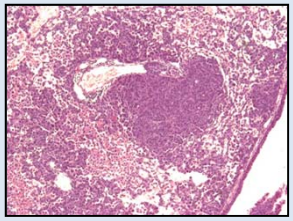
Value Added

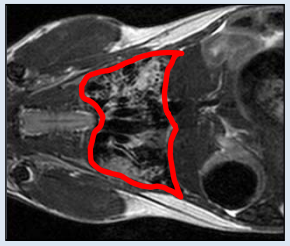
- Dedicated stable infrastructure and technology expertise
- Expert external scientific oversight maintained
- Statistically powered unbiased temporal evaluation (8-parameter systems biology)
  feedback/resistance → combination and relapse therapies
  hypothesis generation for human research
  therapeutic and disease biomarker prediction
- Integrated studies for
  imaging endpoints
  molecular pathology/heterogeneity
- Optimized model/cohort generation
- Standard of care comparisons
- Establishment and export of:
  SOPs
  retooled models
  cross model predictive value
- Visiting scientists/training
- Frees resources for strong basic science/translational iteration

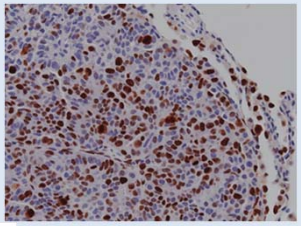
Systems Analysis of Disease and Treatment Response

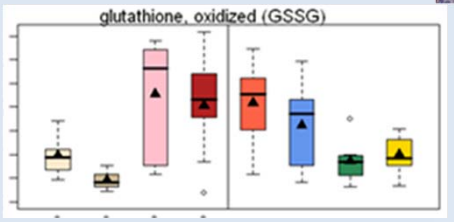
Preclinical Research

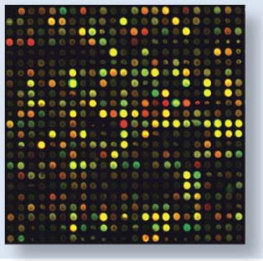












Computational Models (including human data)

Hypotheses

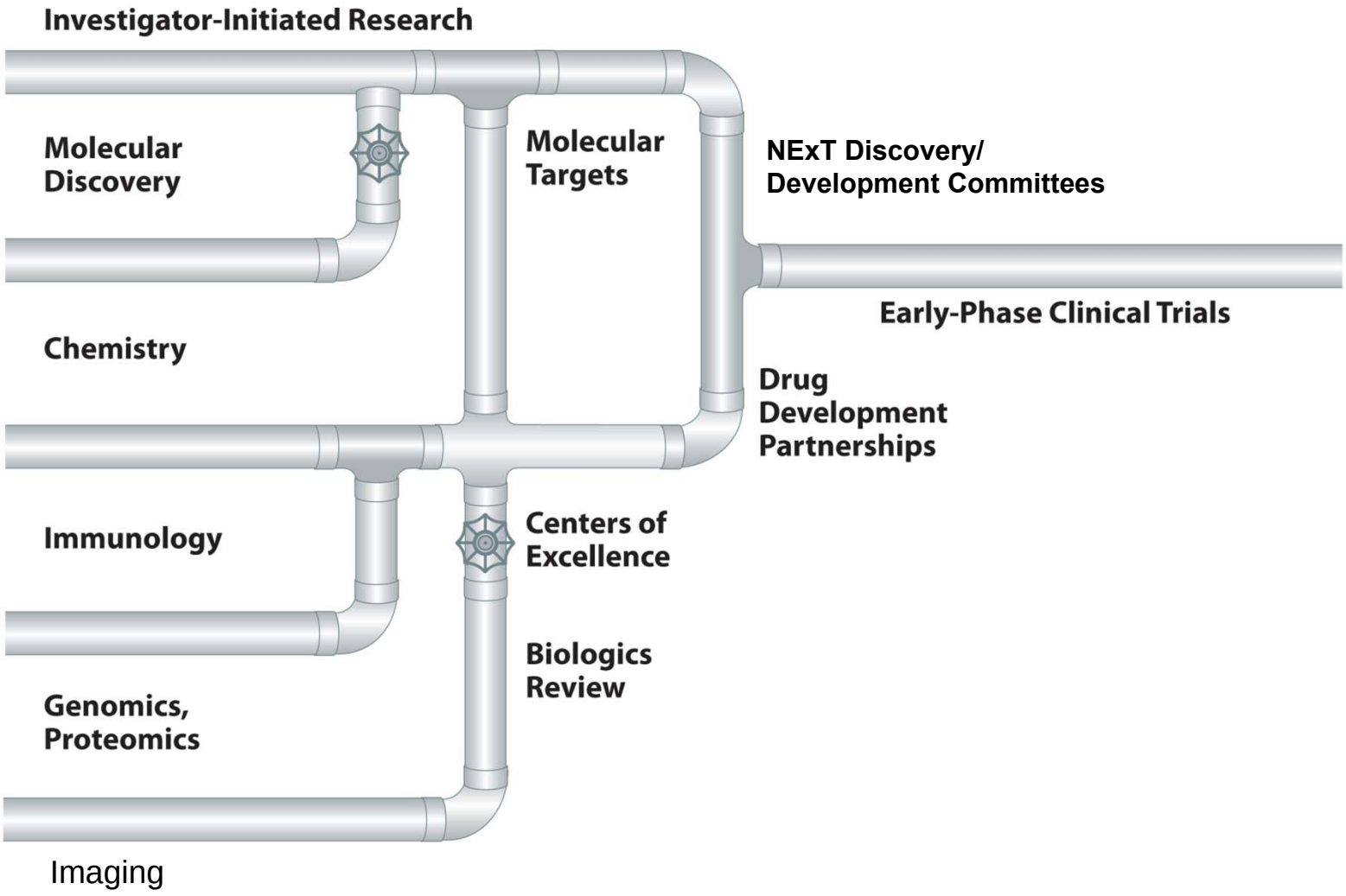
experimental evaluation

Clinical Research

Clinical Research

CAPR Center for Advanced Preclinical Research

Translational Development Pipeline



Role of NCI-Frederick in NCI Therapeutics Development Program

Rapid translation of discoveries into public health benefits

Natural Products

Biopharmaceutical Development

Small Animal Imaging

Pharmacodynamics

Target Identification and Validation	Hit Finding	Lead Optimization	Early Clinical Safety and Efficacy	PoC/Phase I Trials	Phase II Trials	Phase III Trials	Registration	Post-launch Activities

Drug Discovery **Early Development** **Full Development**

Targets

Includes:

- Investigational drugs and biologics
- Investigational imaging agents
- Academic, biotech, pharma projects
- Includes Phase 0, I, II programs

Therapeutics

Commercial Successes in Fighting Cancer and HIV

Vaccines and Therapeutics

2-F-Ara-Fludara (1991) Berlex
Videx® (1991) Berlex
Hivid® (1992) BMS
Paclitaxel® (1992) BMS
Trimetrexate- Neu Trexin (1993) US Bioscience
Zenapax® (1997) Hoffman La Roche
Vitravene® (1998) Isis Pharma
Zevalin® (2002) IDEC Pharma
Kepivance® (2004) Amgen
Gardasil® (2006) Merck
Prezista® (2006) Tibotec Pharma
Cervarix® (2009) GSK

Diagnostics

Serological Detection of Antibodies to HIV-1 (1985)
Serological Detection of Antibodies to HTLV-1 (1988)
DNA Probe for Breast Cancer Diagnosis (1998)
Multi-Replica Blotting Kit for Proteins

Instrumentation/Devices

Laser Capture Microdissection

Knowledge Generation by CCR-Frederick PIs: FYs 10/11

Signaling and Gene Regulation

- **Yamaguchi TP. Regulation of angiogenesis by a non-canonical Wnt-Flt1 pathway in myeloid cells. Nature. 2011**
- **Sharan S. Tumor Suppressor BRCA1 epigenetically controls oncogenic miRNA-155. Nat. Medicine. *In press***
- **Burke Jr TR. Serendipitous alkylation of a Plk1 ligand uncovers a new binding channel. Nat. Chem. Biol. 2011**
- **Hurwitz AA. FOXO3 Programs Tumor-Associated DCs To Become Tolerogenic in Human and Murine Prostate Cancer. J. Clin Invest. 2011**

Immunology and Inflammation

- **Trinchieri G. Plasmacytoid dendritic cells: one-trick ponies or workhorses of the immune system? Nat. Rev. Immunol.**
- **Trinchieri G. Innate immune mechanisms of colitis and colitis-associated colorectal cancer. Nat. Rev. Immunol. 2011**
- **Tessarollo L, Klinman D, Wiltrout R, and Young H. IFN- gamma ARE-deleted mice reveal a role for chronic IFN-gamma in autoimmune disease. Nat. Immunol. *In press***
- **Young H. and Trinchieri G. Interferon-γ links ultraviolet radiation to melanomagenesis in mice. Nature. 2011**
- **Trinchieri G. At 17, in-10's passion need not inflame. Immunity. 2011**
- **Trinchieri G. MyD88-mediated signaling prevents development of adenocarcinomas of the colon: role of interleukin 18. J. Exp. Med. 2010**
- **Wiltrout RH. Macrophage-dependent nitric oxide expression regulates tumor cell detachment and metastasis after IL-2/antiCD40 immunotherapy. J. Exp. Med. 2010**

Knowledge Generation by CCR-Frederick PIs: FYs 10/11

HIV/AIDS and Cancer Virology

- Carrington M. HLA-A*3101 and carbamazepine-induced hypersensitivity reactions in Europeans. New Eng. J. Med. 2011
- Carrington M. Differential microRNA regulation of HLA-C expression and its association with HIV control. Nature. 2011
- Carrington M. The major genetic determinants of HIV-1 control affect HLA class I peptide presentation. Science. 2010
- Carrington M. Maternal activating KIR protect against human reproductive failure mediated by fetal HLA-C2. J. Clin. Invest. 2010

Proteomics

- Weissman AM. The predator becomes the prey: regulating the ubiquitin system by ubiquitylation and degradation. Nat. Rev. Mol. Cell. Bio. *In press.*
- Lipkowitz S and Weissman AM. RINGs of Good and Evil: RING finger ubiquitin-protein ligases at the crossroads of tumor suppression and oncogenesis. Nat. Rev. Cancer. *In press*.
- Weissman AM. Working on a chain: E3s ganging up for ubiquitylation. Nature Cell Biol. 2010

Genomics

- Hou SX. Kidney stem cells found in adult zebrafish. Cell Stem Cell. 2011

Developmental Biology

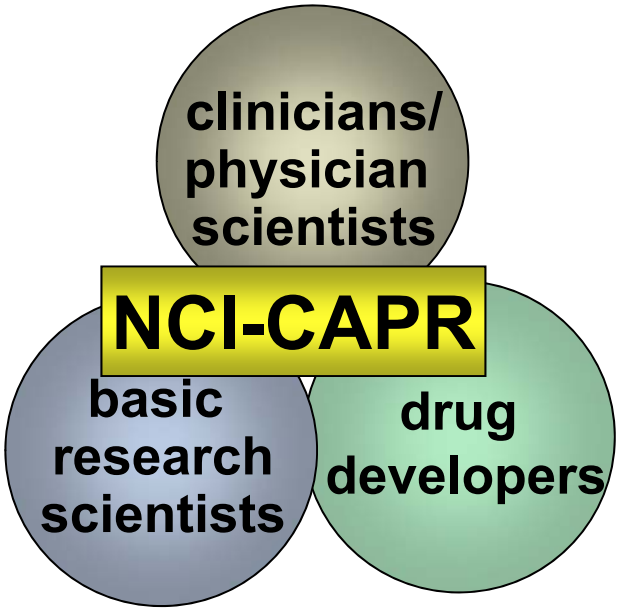
- Mackem S and Lewandoski M. Development: Limb cells don't tell time. Science. 2011

Chromosomal Biology

- Oberdoerffer, S. CTCF promotes pol II pausing and links DNA methylation to alternative splicing. Nature. *In press*

Program Changes: Center for Advanced Preclinical Research(CAPR)

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



Projected Interactome

a new paradigm for translational science

- **To accelerate the development of therapeutics and diagnostics for human diseases by providing state-of-the-art animal models genetically programmed to develop diseases in the same way they arise in humans for preclinical studies**
- **Genetically engineered mouse models will significantly reduce the time to identify promising candidate drugs and will provide improved systems for target discovery and validation, and biomarker discovery for early detection and treatment assessment**

CCR Staffing:
Facts and Figures

- **In 2003 CCR had 307 PIs**
- **In 2011 CCR has 252 PIs**
- **Since 2003, 110 (34%) have departed**
  - 57 (53%) were directly or indirectly due to BSC
  - 22 (20%) departed for career advancement
  - 55 new hires (25% female)
- **Anticipated closures/departures**
  - FY2012 =12
  - FY2013= 4
  - FY2014=3

History and Evolving Culture Shift Continuum for CCR

1994 — 1995 — **2001** → → → → 2012

Marks-Castle Report

Bishop-Calabresi Report

CCR formed

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

Shifting the culture in CCR

- **Reengineering the IRP has been a dynamic process**
- **Preserving and expanding outstanding PI-based research**
- **Encourage team science and collaboration**
- **Strategies for rewarding team science have been implemented**
- **Formation of Faculty and Working Groups and creation 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**