Current PI Distribution by Campus

- Betheda: 69%
- Frederick: 30%
- ATC: 1%
CCR Portion of the NCI’s Frederick Budget

- CCR: 20%
- Other: 80%

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
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
<table>
<thead>
<tr>
<th>Tenure Track</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
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<td>Ramamurthi</td>
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<td>Greten</td>
<td>Kaplan*</td>
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<td>Westlake</td>
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Red denotes Frederick
* Denotes Female

43% Female
Labs/Branches Created and Closed

New Labs/Branches
- CCRNP MOB
- LCDS LBMB LCBG CIP

Labs/Branches Closed
- LBC LB LMCB LCRC LCCTP LG
- Cytogenetics core Angio core Protein core
- Sequencing core Bioinformatics core
- LCC MBTL LPG LGD

Red denotes Frederick
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
• 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

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

Robert H. Wiltrout, Director, SD for Basic Science
Lee J. Helman, SD for Clinical Research

January 2012
**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

DATA

PERTURBATION

TIME

Computational Models (including human data)

Hypotheses

experimental evaluation

Clinical Research

Clinical Research

Center for Advanced Preclinical Research (CAPR)
Translational Development Pipeline

Investigator-Initiated Research

Molecular Discovery

Chemistry

Immunology

Genomics, Proteomics

Imaging

Molecular Targets

NExT Discovery/Development Committees

Early-Phase Clinical Trials

Drug Development Partnerships

Centers of Excellence

Biologics Review
Role of NCI-Frederick in NCI Therapeutics Development Program

Rapid translation of discoveries into public health benefits

Natural Products

Small Animal Imaging

Biopharmaceutical Development

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

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

Targets

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
- 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
**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*
- 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. At 17, in-10's passion need not inflame. Immunity. 2011
- Wiltrout RH. Macrophage-dependent nitric oxide expression regulates tumor cell detachment and metastasis after IL-2/antiCD40 immunotherapy. J. Exp. Med. 2010
HIV/AIDS and Cancer Virology
• Carrington M. The major genetic determinants of HIV-1 control affect HLA class I peptide presentation. Science. 2010

Proteomics

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

- 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

Projected Interactome
*a new paradigm for translational science*
• 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

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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<tbody>
<tr>
<td>1994</td>
<td>Marks-Castle Report</td>
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<tr>
<td>1995</td>
<td>Bishop-Calabresi Report</td>
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<tr>
<td>2001</td>
<td>CCR formed</td>
</tr>
<tr>
<td>2012</td>
<td>Emphasize multidisciplinary research to solve complex problems: Faculties, Working Groups, Centers of Excellence</td>
</tr>
</tbody>
</table>

**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