



Overview of NCI/FNLCR Interactions

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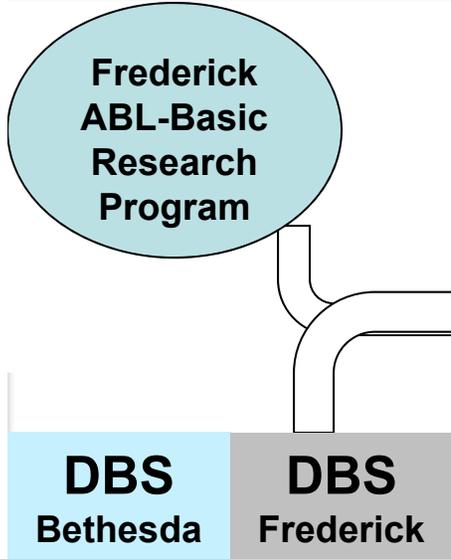
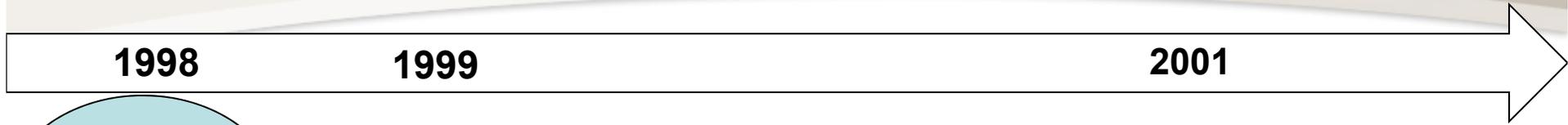
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NFAC

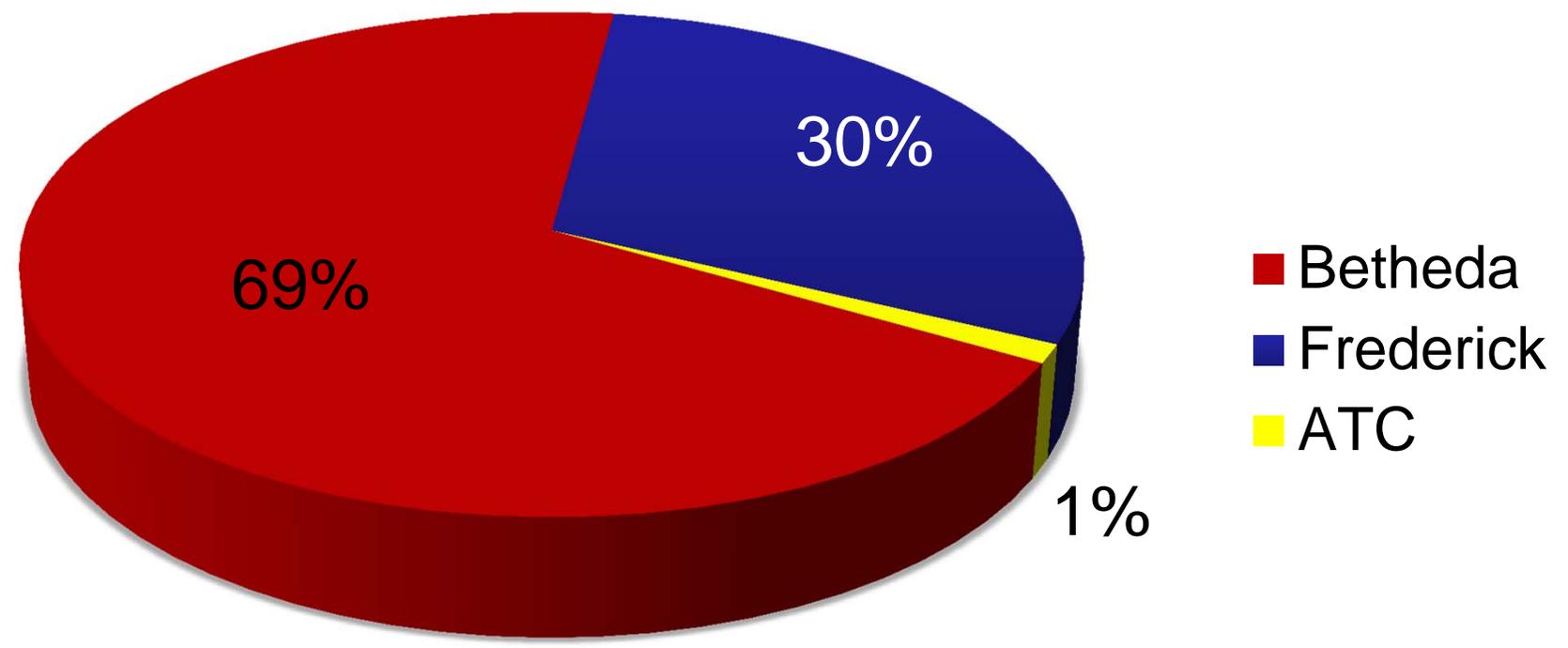
February 4, 2014



History of CCR in Frederick

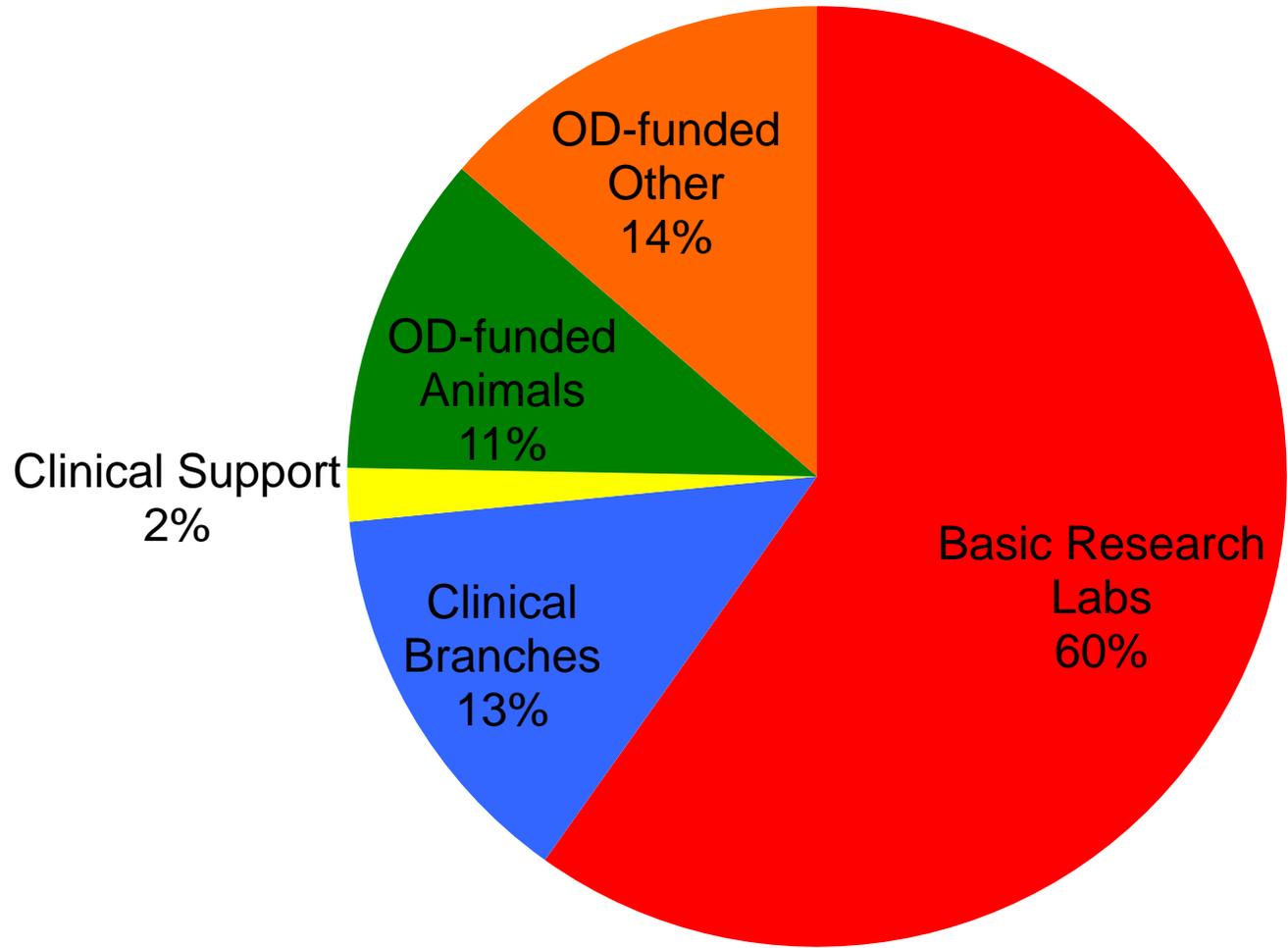


Current CCR Lab Distribution by Campus

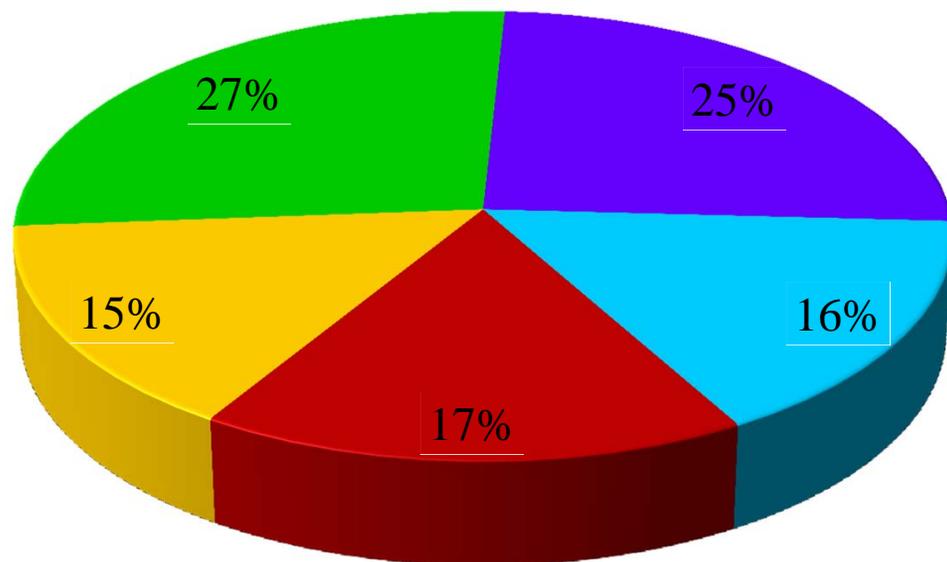




CCR-Frederick FY13 Spending



Current CCR-Frederick Labs Research Portfolio



■ Chemistry, Structural Biology, and Drug Development



■ Mouse Models of Cancer and other Diseases



■ Inflammation and Immunology

■ HIV/AIDS & Cancer Virology

■ Gene Regulation, Cell Signaling, RNA Biology, Cell and Cancer Biology

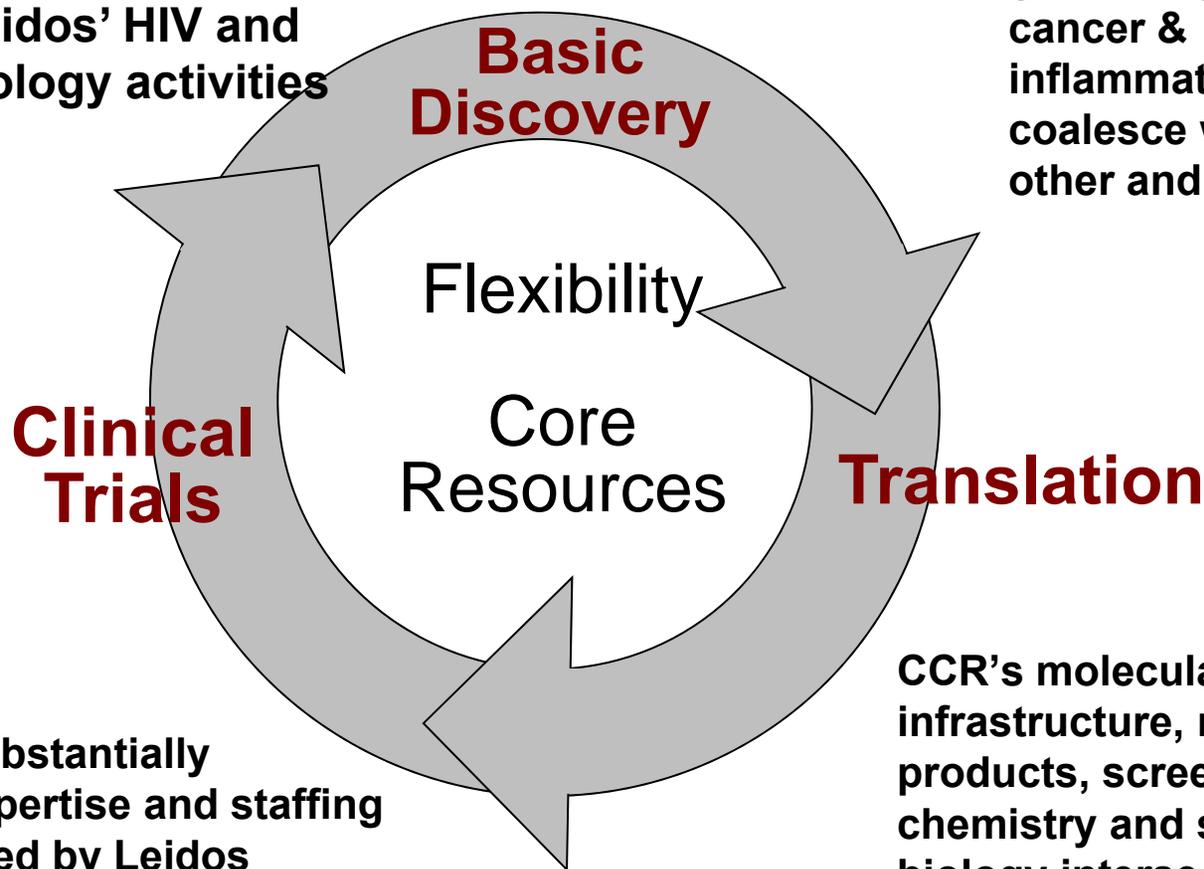




Benefits to CCR of Having Some Programs at FNLCCR

CCR's HIV, chemistry and structural biology efforts intersect with Leidos' HIV and advanced technology activities

CCR's mouse models development, CAPR, genetics/genomics, cancer & inflammation coalesce with each other and with LASP



CCR's clinical program benefits substantially from **flexibility** in expertise and staffing mechanisms provided by Leidos

- protocol review office
- clinical trials re-engineering initiatives
- clinical monitoring labs

CCR's molecular targets infrastructure, natural products, screening, chemistry and structural biology intersect with DCTD's NExT Program activities



Past Contributions of CCR to FNLCR

- **CCR labs provide a strong scientific culture for the FNLCR campus and serve as an intellectual resource for many NCI activities of the FFRDC**
 - **Heavy emphasis on programs to encourage interactions**
 - **Mouse Cancer Genetics**
 - **Cancer & Inflammation**
 - **Molecular Targets**
 - **HIV Drug Resistance**
 - **Physical Sciences – Chemistry and Structural Biology**
- **CCR labs have historically assisted with development and β -testing of new technologies by the Advanced Technology Program and Lab Animal Sciences Program that are then made available more broadly across NIH**
- **CCR contributes to NCI's broader efforts in drug development by close co-location of PIs with components of DCTD's NExT Program**
- **Development of IL-15 and IL-7 with BDP**
- **Natural products for drug development**



Product Development: Immunotherapy

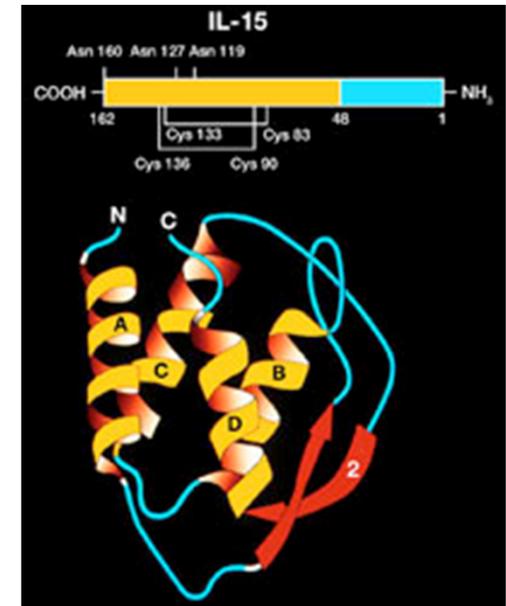
- IL-15 and IL-7 were two of the top 5 agents select for development at the BDP during the 2007 Immunotherapy Agent Workshop
- BDP developed these agents and made them available to the intramural and extramural community
- Both are being used in several investigational studies for cancer therapy
 - First clinical trials of IL-15 for the treatment of patients with metastatic malignant melanoma and metastatic renal cell cancer
 - First clinical trials of IL-7 in humans



IL-15: Bench to Bedside

Much progress has been made in basic, translational, and preclinical research on IL-15, a cytokine of enormous promise in treating cancer, HIV, and autoimmune disease. This includes:

- Co-discovery of IL-15, discovery of two of the three subunits of the IL-15 receptor, and demonstration that IL-2 and IL-15 share receptor components
- Development of mice transgenic for IL-15 and subsequent demonstration of distinct and contrasting functions of IL-2 and IL-15
- Increased understanding of the biological effects and mechanisms of action of IL-15
- IL-15 is a broad stimulant for both innate and adaptive immune lymphocytes
- Demonstration that IL-15 enhances effectiveness of therapeutic cancer vaccines and increases survival in some murine models of cancer



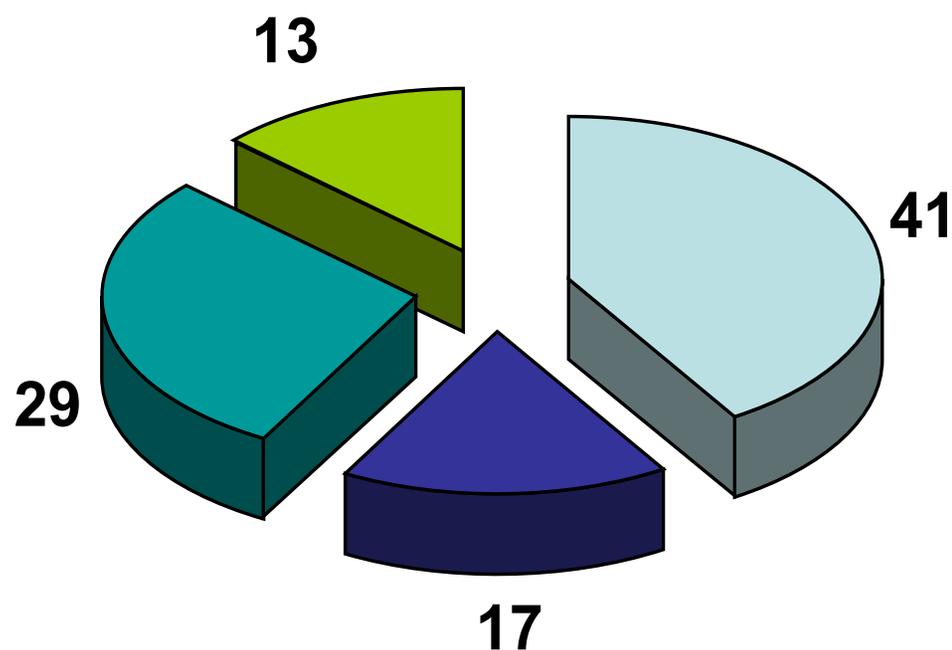


Biological Properties of IL-7 Are Attractive for Clinical Translation

- IL-7 is a master regulator of T cell homeostasis and potent immunorestorative
 - IL-7 therapy enhances immune reconstitution in mice
 - IL-7 therapy enhances vaccine responses in mice
 - Circulating IL-7 levels rise in response to lymphopenia (humans and mice)

- rhIL-7 under study in > 15 trials in US, Europe and Asia. Studies ongoing or planned include:
 - Immunodeficiency following chemotherapy for cancer
 - Immunodeficiency following allogeneic stem cell transplantation
 - Idiopathic CD4 lymphopenia
 - Some congenital immunodeficiencies (*planned*)
 - Glioblastoma (*planned*)
 - Vaccine adjuvant in aged individuals
 - Tumor vaccine adjuvant
 - Support for adoptive immunotherapy (*planned*)

Approved Anticancer Drugs as of 2012



- Natural products & derivatives
- Natural product pharmacophores
- Synthetics
- Biologics & vaccines



Product Development: Natural Products

**DTP
Natural Products
Branch**

**CCR
Molecular Targets
Lab**



**CCR Basic Science
Discoveries**

**Expertise in
Natural
Products
Chemistry**

**Expertise in Assay
Design and High
Throughput
Screening**

World's largest storehouse of natural products collected from 25 countries

- 170,000 extracts from samples
 - 70,000 plants
 - 10,000 marine organisms
- 230,000 diverse bacteria and fungi
- FNL dedicated service to DCTD



Areas of Potential Interaction for CCR with FNL

- **Co-located Cores at ATRF**
- **Computational Support from ABCC to address common needs**
- **Center for Advanced Preclinical Research**
- **Collaboration on FNL project areas or needed technologies, if requested**



ATRF Co-Located Cores

Pre-Pivot

ATP Shared Services: CCR Usage

	CCR Effort (FTEs)	CCR Cost
Microarrays (LMT)	4	771 K
Mass Spec (LPAT)	8	468 K
Protein Chemistry (PCL)	2	48 K
Protein Expr/Purif (PEL)	9	260 K
Light Microscopy (OMAL)	7	450 K
Electron Microscopy (EML)	4	202 K

34 FTEs 2.2 M CCR

+ Support from NCI-OD for campus-wide technology infrastructure and development (4.4M)

CCR Dedicated Cores

CCR Sequencing Core

Post-Pivot

ATP Shared Services: CCR Usage

Microarrays (LMT) ~771 K?

CCR Dedicated Cores

	FTEs	Cost
Mass Spec	4	680 K
Protein Chemistry	0.5	75 K
Protein Production	4	610 K
Light Microscopy	4.25	612 K
*Electron Microscopy	2	300 K
	15 FTEs	2.3 M + Equipment

CCR Sequencing Core

*Located in part at NCI-Frederick



Advantages of Co-located Cores

- Shared instrumentation, less duplication
- Access to additional bandwidth in urgent situations
- Critical mass of highly specialized expertise



Lessons Learned and Best Practices for FNL Core Support to CCR and DCEG

- **Strengths**: Leidos has done well when responding to specific, directed tasks or dedicated labs and where efforts are guided by oversight groups
 - NCI drives the science and technology development, while taking maximum advantage of Leidos expertise
 - These partnerships often are lead by very competent, mission-dedicated Leidos staff, resulting in sustained results of high value

- **Challenges**: Undedicated core labs have tended to suffer mission drift and/or reduced efficiency/customer satisfaction
 - Management sometimes does not understand the scientific changes at the cutting edge and takes directions not needed or wanted
 - Core leaders redirect time and effort in support of areas of their interest which may not coincide with NCI's needs



Computational Resources

- Translating genomics and proteomics insights into therapeutics requires computational resources to support structural biology, imaging, chemistry, and drug development activities
- ABCC's Simulation, Analysis, and Modeling (SAM) group currently provides computational support in several areas (4 FTEs)
- Expanded capabilities in SAM would be highly relevant to CCR's portfolio and potentially highly relevant to the Ras project
- ABCC also provides services to CCR in related areas, such as informatics

Center for Advanced Preclinical Research



- Partnering with the Lustgarten Foundation on preclinical development of therapeutics for pancreatic cancers (95% of which are driven by RAS)
- Numerous Technical Service Agreements (TSAs) with outside entities on preclinical development of therapeutics using the pancreatic and lung models



Collaboration on Special Projects

Progress on Ras Collaborations:

- Initial meets were held with CCR staff working on Ras biology and the FNL Ras project team
- CCR is hosting a Ras forum during the SS/SC retreat in April 2014, with participation from Drs McCormick and Heimbrock
- Laboratory of Cancer Biology and Genetics/FNL collaboration on siRNA interrogation of downstream Ras signaling pathways
- Cancer and Inflammation Program/FNL collaboration on Ras inhibitors
- CCR structural biology expertise has been offered

Arising issues:

- Lack of clarity about whether communication and collaborations between ATRF Ras and IRP PIs is desirable on areas of common interests
- Lack of clarity about ability to share reagents or technologies may lead to some redundancy



Areas of Strategic Emphasis

- Mouse models-partnership with Leidos
- Screening for natural products and drug development-partnership with DCTD/Leidos
- Structural biology and chemistry – CCR emphasis
- Improve communications and interactions on Ras-related projects and reagents?

