



Overview of NCI/FNLCR Interactions

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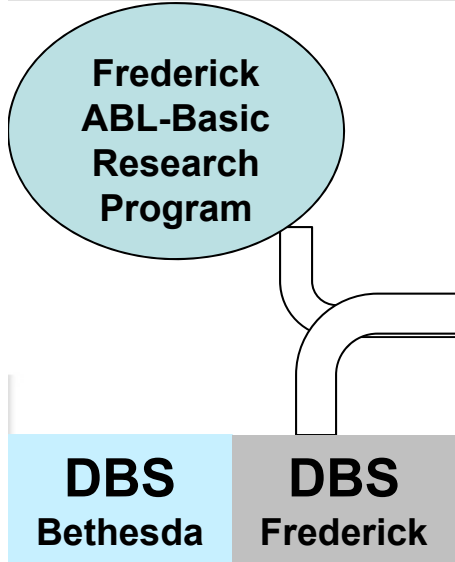
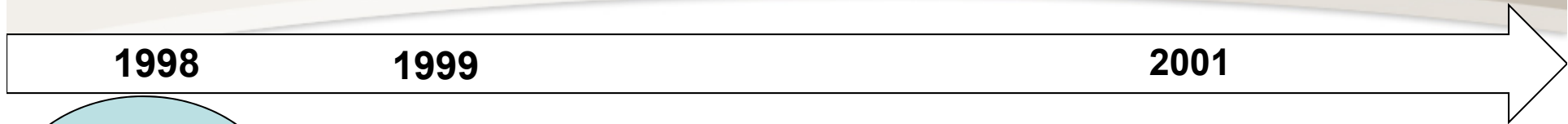
NFAC

February 4, 2014

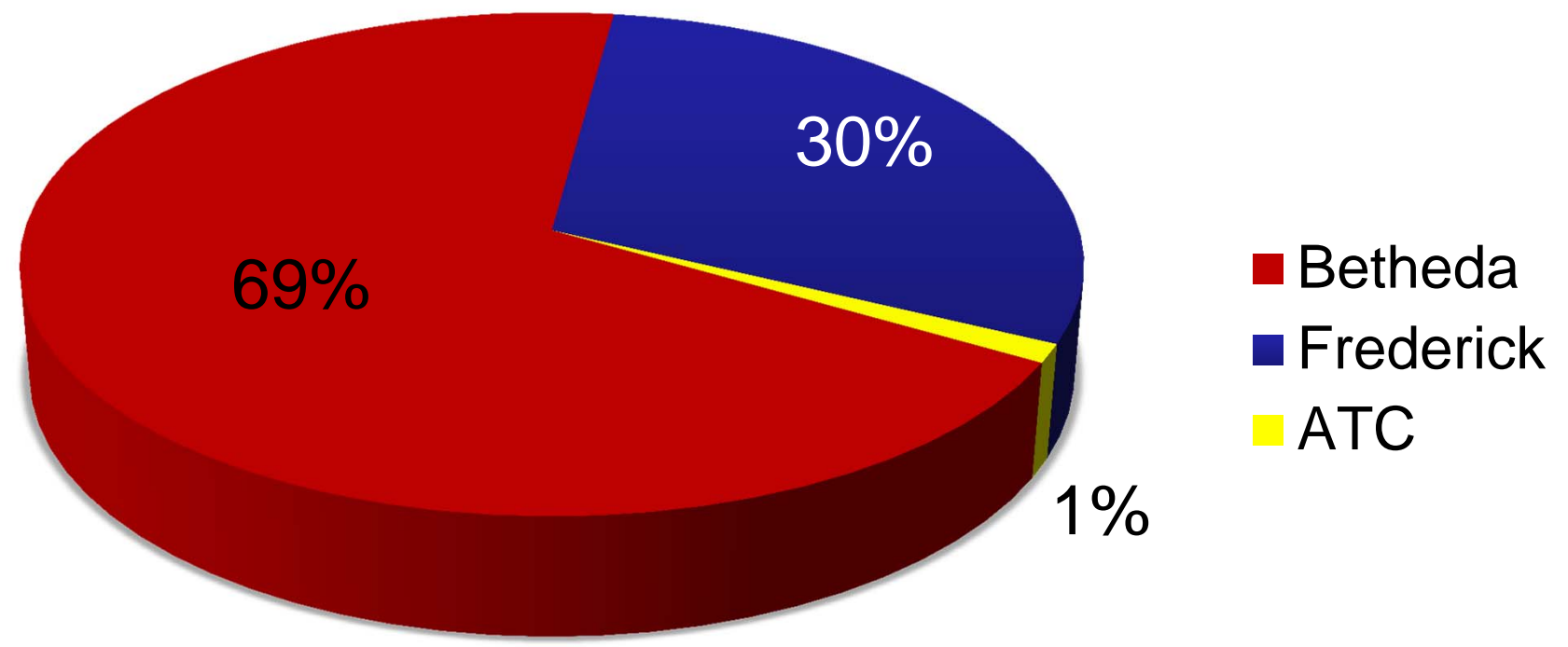




History of CCR in Frederick

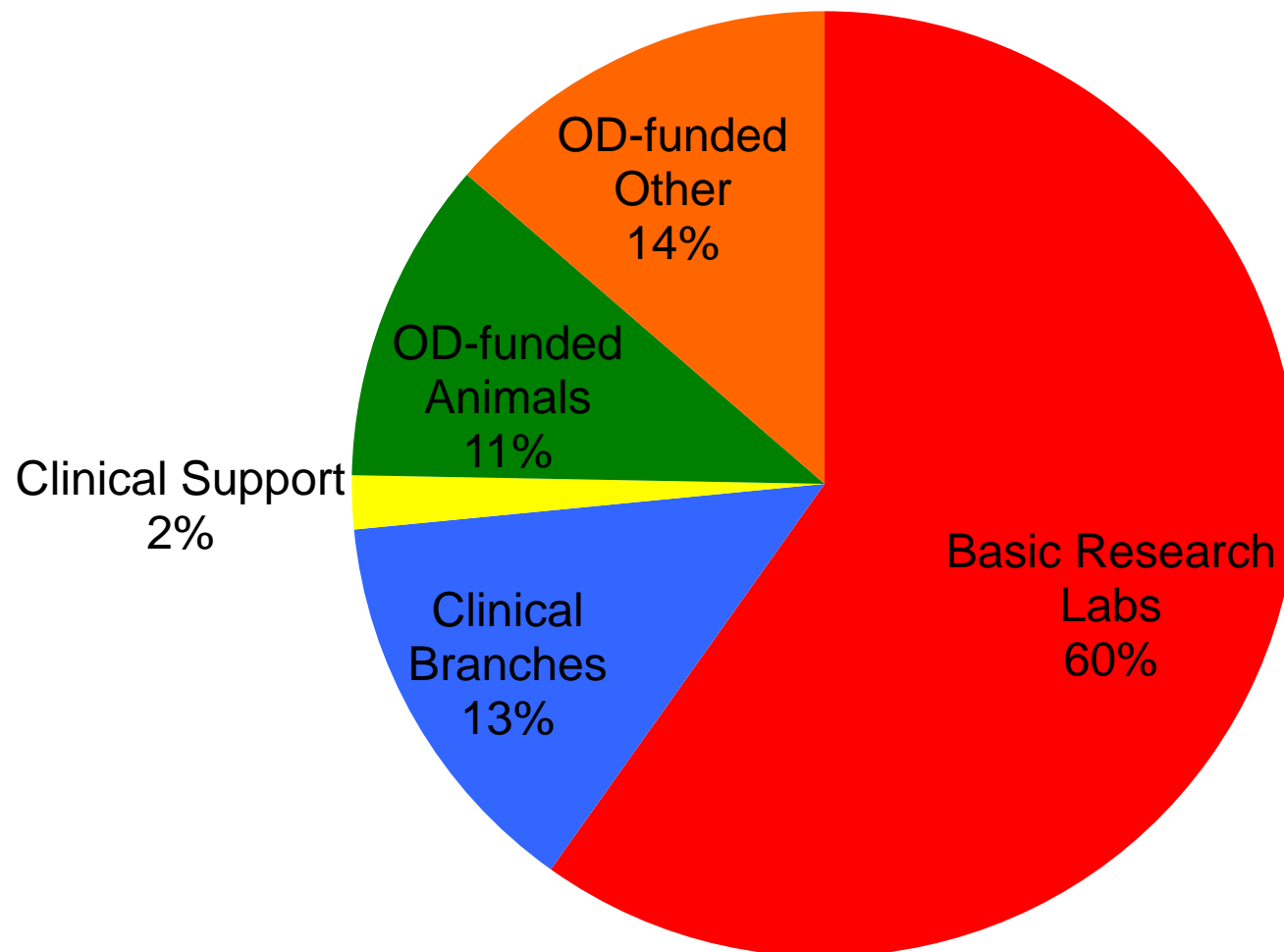


Current CCR Lab Distribution by Campus

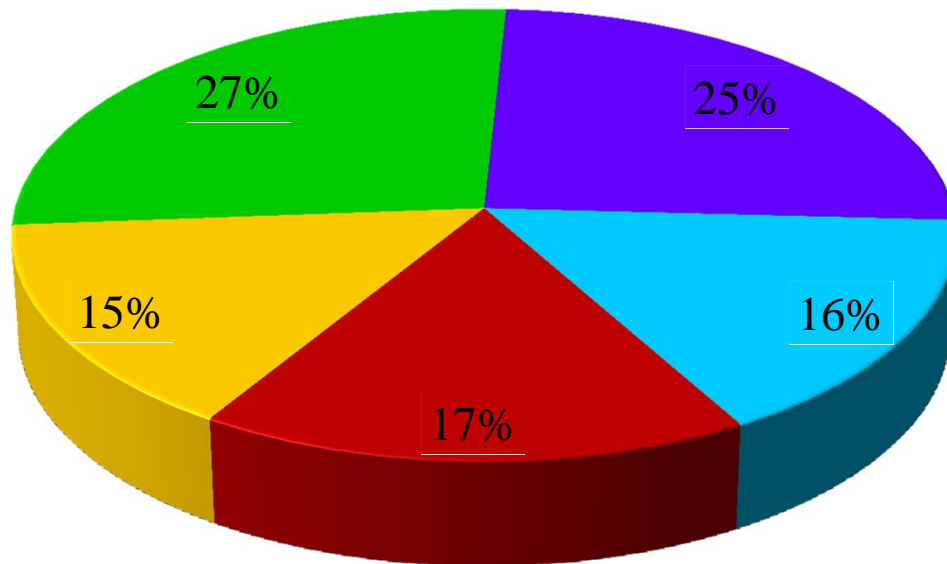




CCR-Frederick FY13 Spending



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

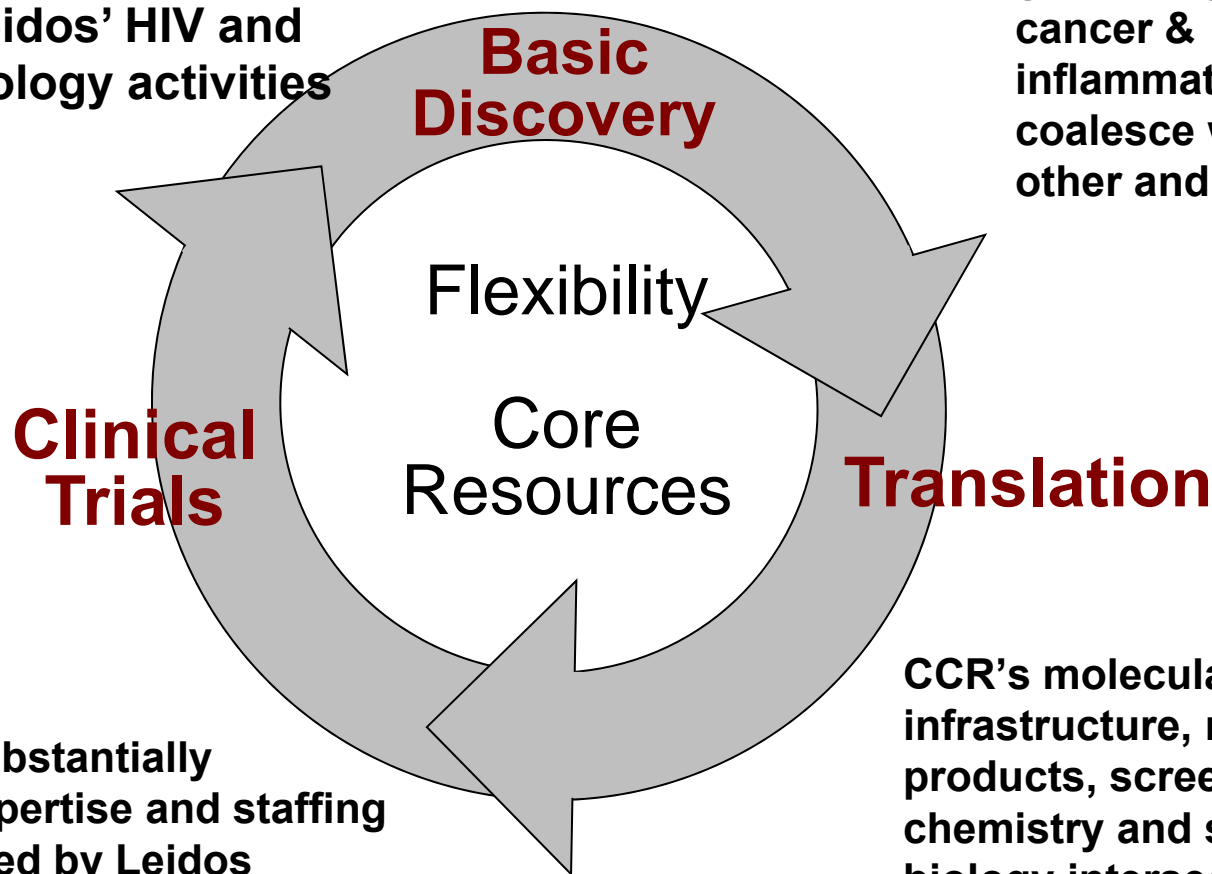
■ Gene Regulation, Cell Signaling, RNA Biology, Cell and Cancer Biology ↑



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

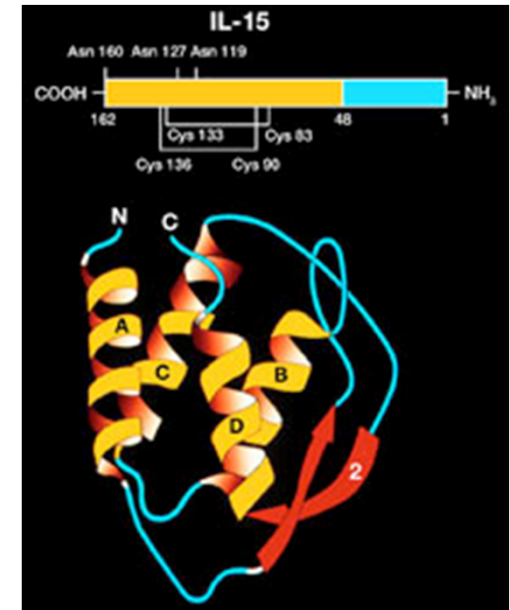
- IL-15 and IL-7 were two of the top 5 agents select for development at the BDP during the 2007 Immunotherapy Agent Workshop
- BDP developed these agents and made them available to the intramural and extramural community
- Both are being used in several investigational studies for cancer therapy
 - First 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



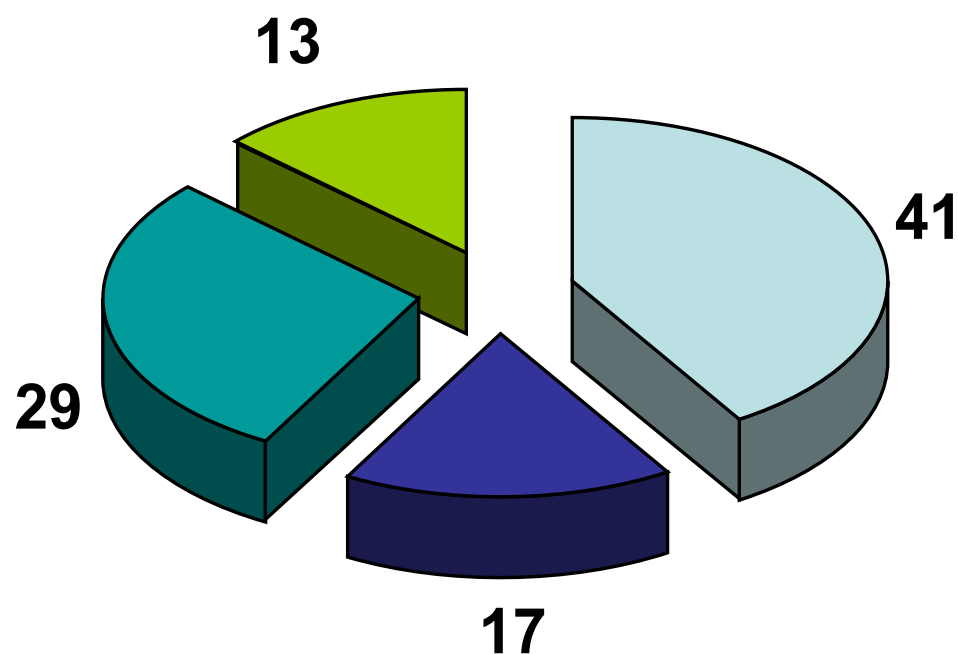


Biological Properties of IL-7 Are Attractive for Clinical Translation

- 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?

