NATIONAL CANCER INSTITUTE
CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE (CTAC)
PROGRESS IN PANCREATIC DUCTAL ADENOCARCINOMA (PDAC) RESEARCH WORKING GROUP
(PDAC PROGRESS WORKING GROUP)

WORKING GROUP REPORT, NOVEMBER 2015

INTRODUCTION

On September 19, 2012, the 112th Congress amended the Public Health Service Act by enacting the Recalcitrant Cancer Research Act (RCRA) of 2012 (Public Law 112-239, §1083). The legislation called upon the National Cancer Institute (NCI) to identify two or more recalcitrant cancers that have a five-year relative survival rate of less than 20% and cause more than 30,000 deaths per year in the United States and to develop scientific frameworks that will assist in making progress against these cancers. Pancreatic ductal adenocarcinoma (PDAC) is a recalcitrant cancer as defined with its five-year relative survival rate of less than 5 percent that translates into the loss of almost 40,000 lives per year. A report focused on the NCI's scientific framework for PDAC was submitted to Congress in 2014 and posted on NCI's website. Approximately a year later, the NCI convened the Progress in PDAC Research Working Group, chaired by Dr. James Abbruzzese, Associate Director Clinical Research, Duke Cancer Institute, to advise NCI on the research progress of the initiatives outlined in the scientific framework. Working Group members represent the broad clinical and translational research and advocacy communities (Appendix 1).

The Working Group's main objectives are to:

1. Assess the research progress of the scientific initiatives to date;
2. Provide recommendations for the process used for future annual assessments;
3. Review and provide recommendations for updating the scientific framework no later than 5 years after the initial development;
4. Advise NCI on the effectiveness of the scientific framework no later than 6 years after the initial development.

This report summarizes the initial deliberations of the Working Group which have focused on the first objective and ways to address the second objective. Future reports will address the other long-term objectives.

THE SCIENTIFIC INITIATIVES

The 2014 Scientific Framework for Pancreatic Ductal Adenocarcinoma provides the background, rationale and implementation plans for four initiatives proposed to expand PDAC research. These initiatives are summarized below:

1. Development of an in-depth understanding of the biological and clinical relationship between PDAC and diabetes mellitus (DM) of recent onset

   Twenty-five percent of PDAC patients have recent (within 3 years) onset of DM at the time of diagnosis and yet only a small percentage of patients with recent onset DM will develop PDAC. This fact requires a more detailed understanding of the clinical and biological characteristics of the population of patients who subsequently develop or have undiagnosed PDAC in the setting of newly diagnosed diabetes. This includes defining specific risk factors to make screening and early diagnosis efforts more efficient and cost-effective.

2. Evaluate longitudinal screening protocols for biomarkers for early detection of PDAC and its precursors

   The goal is to identify patients with the earliest stage PDAC who have the best chance of cure and those who have precursor lesions (PanIN-3 and cystic neoplasms of the pancreas) that are likely to evolve into PDAC. To accomplish this goal it is necessary to develop more accurate and sensitive methods of imaging and methods to identify the molecular alterations that characterize these early lesions and predict future malignant invasion. Research in this area would be enhanced by developing longitudinal screening protocols that collect specimens from early lesions from patients at high risk of developing PDAC because of their genetic background or the presence of mucinous pancreatic cysts.

3. New therapeutic approaches in immunotherapy

   Recent advances in understanding the induction and regulation of the immune response to cancer and the dynamic processes involved in the interaction of cancer cells and its microenvironment have provided opportunities to discover and validate new immunotherapeutic and stromal targets and to develop new interventions for clinical testing in PDAC patients.

4. Developing new treatment approaches that interfere with RAS oncogene-dependent signaling pathways

   Opportunities now exist—based upon technical advances in structural analyses, generation of genetically engineered mouse models, and new information on signaling pathways and networks, protein engineering, and use of RNA interference for target identification in synthetic lethality screens—to make progress in targeting mutant forms of RAS that is present in 95% of patients with PDAC and is thought to play a critical role in the initiation and maintenance of pancreatic carcinogenesis and resistance to therapy.

ASSESSMENT OF THE RESEARCH PROGRESS

In the spring of 2015 over the course of several months, the Working Group broke into subgroups that convened via teleconference and webinars to discuss current pancreatic cancer research being conducted in relation to each of the specific initiatives. A Working Group member was appointed to guide the assessment of the research progress for each specific initiative. Abstracts for FY 2013 NCI grant projects and subprojects coded to 25 percent or greater relevance to pancreatic cancer and NIH grant projects identified to be relevant to PDAC and one of the four initiatives in the scientific framework were reviewed. Related information from specific NCI programs and initiatives along with

other NIH projects with relevance to pancreatic cancer were retrieved from the NIH RePORTER database and provided to the subgroups. (Appendix 2)

The full Working Group convened via webinar in July 2015 to discuss the recommendations, progress and gaps within the current PDAC scientific framework portfolio. The Working Group's overall impression is that all of the initiatives in the scientific framework are still relevant, and that implementation progress is on target, but it is too early to assess scientific progress.

SUMMARY OF PROGRESS FOR THE SCIENTIFIC INITIATIVES

Initiative 1: Development of an in-depth understanding of the biological and clinical relationship between PDAC and diabetes mellitus (DM) of recent onset

Assessment: Implementation progress is on target; it is too early to assess scientific progress.

Activities to date:
The National Institute of Diabetes and Digestive and Kidney (NIDDK)-NCI held a Pancreatitis-Diabetes-Pancreatic Cancer Workshop in June 2013. The proceedings from the meeting were published in *Pancreas* (2013; 42(8): 1227-37). As a result of the Workshop NIDDK-NCI issued a joint Funding Opportunity Announcement (FOA)/Request for Applications (RFAs; RFA-DK-14-027 and RFA-DK-14-028) for a Consortium to Study Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CSCPDPC); and a Coordination and Data Management Center. Applications were due April 2015 with a scientific merit review July 2015. Ten Clinical Centers and a Data Management Center were selected and approved for funding September 2015.

NIDDK together with the National Institute of Biomedical Imaging and Bioengineering (NIBIB) sponsored a workshop, *Advances in Biomedical Imaging, Bioengineering, and Related Technologies for the Development of Biomarkers of Pancreatic Disease*, in July 2015. The workshop was designed to bring two divergent groups of clinicians and scientists together to facilitate the development of clinical studies and imaging research in diseases of the pancreas. This workshop is also pertinent to Initiative 2, early detection of PDAC and its precursors.

Recommendations:

- Follow the progress of the CSCPDPC awardees.
- Publish the proceedings of the NIDDK-NIBIB workshop and issue a joint FOA/RFA on areas of unmet Clinical/Imaging need and identified scientific gaps.
- Organize a joint NIDDK-NCI workshop with the DM and PDAC clinical/scientific communities on the utilization of animal models, to gain a better understanding of PDAC as it relates to DM subtypes and issue FOA/RFA on identified scientific gaps.
- Engage the DM community in scientific collaborations; negotiations are under way with the American Diabetes Association to hold a joint session in 2016.

Initiative 2: Evaluate longitudinal screening protocols for biomarkers for early detection of PDAC and its precursors

Assessment: Implementation progress is on target; although it is too early to assess scientific progress. There is consensus from the Working Group that advances and biospecimens are relatively sparse.

Activities to date:
NCI released a Program Announcement with Special Review (NCI-PAR 15-289) for a Pancreatic Cancer Detection Consortium (PCDC) in June 2015. The PAR has multiple receipt dates with the first receipt date of November 2015. The PCDC is intended to support research for the development and testing of new molecular and imaging biomarkers for identifying populations of high-risk individuals because of familial considerations or the presence of precursor lesions. Studies will be undertaken in the following areas: identification and testing of biomarkers measurable in bodily fluids for early detection of PDAC or its precursor lesions; determine which pancreatic cysts are likely to progress to cancer; develop molecular- and/or imaging-based approaches for screening populations at high risk of PDAC; conduct biomarker validation studies; and collect longitudinal biospecimens for the establishment of a biorepository.

As mentioned under activities of Initiative 1 NIDDK together with NIBIB sponsored a workshop, *Advances in Biomedical Imaging, Bioengineering, and Related Technologies for the Development of Biomarkers of Pancreatic Disease*, in July 2015. The workshop was designed to bring two divergent groups of clinicians and scientists together to facilitate the development of clinical studies and imaging research in diseases of the pancreas.

Recommendations:

- Follow release and funding of current and pending NCI PARs as they mature.
- Facilitate connections between programs at NIH (for example NCI's Specialized Programs of Research Excellence (SPOREs), Early Detection Research Network (EDRN), and the NIDDK-NCI consortium, CSCPDPC) to enable actions to identify high-risk populations, develop cohorts and collect specimens.
- Share biomarker validation information from EDRN.
- Improve coordination of validation of biomarkers, even of published candidates.
- Incorporate information from other NIH Institutes and Centers on imaging research with relevance to pancreatic cancer.
- Publish the proceedings of the NIDDK-NIBIB workshop and issue a joint FOA/RFA on areas of unmet Clinical/Imaging need and identified scientific gaps.

Initiative 3: New therapeutic approaches in immunotherapy

Assessment: Implementation progress has occurred as isolated efforts and would benefit from greater coordination within the NCI and greater access to new immunotherapy agents.

Activities to date:
The Cancer Immunotherapy Trials Network (CITN) has prioritized PDAC immunotherapy studies to address gaps left by industry. Additionally, NCI's funding of pancreatic cancer immunotherapy research through multiple mechanisms has increased over the past few years, delineated in the Scientific

Framework report. NCI is planning an immunotherapy meeting which will include a breakout session on PDAC research in early 2016.

Recommendations:

- Identify a "Champion" for immunotherapy to coordinate efforts at NCI and forge new collaborations to increase access to new agents.
- Collect additional information about immunotherapy reagents from other NCI programs such as NCI Experimental Therapeutics Program (NExT) and the Frederick National Laboratory for Cancer Research (FNLCR).
- Expand initiative to integrate research on tumor stoma and its relationship to immunotherapy.
- Increase availability of immunotherapy reagents for PDAC research and trials.
- Support development of immunocompetent preclinical animal models to test combination therapies.
- Develop scientific rationale for combination of immune modifiers, and other drugs in preclinical and clinical studies.
- Monitor the CITN progress in the design and conduct of therapy trials with promising immunotherapy agents.
- Monitor the Center for Cancer Research (CCR) clinical trials for conduct of PDAC therapy trials with promising immunotherapy agents.

Initiative 4: Developing new treatment approaches that interfere with RAS oncogene-dependent signaling pathways

Assessment: Implementation has started, but additional information is needed to assess progress. This initiative has had a lot of activity, particularly through the FNLCR RAS Program, but it is important to consider the larger NCI and community efforts in this area.

Activities to date:
The Working Group met with Dr. Frank McCormick and the FNLCR RAS project team leadership to discuss progress of the RAS Program and discuss potential joint opportunities relevant to PDAC.

Recommendations:

- Identify other NCI and non-NCI RAS therapeutics PDAC research efforts and map all efforts to a drug development pathway or continuum.
    - Consider NExT pipeline map as a basis for drug development steps
    - Drug development target is RAS and downstream pathway elements
    - Progress measured by moving from one step to next or being removed for scientifically validated reasons

CONCLUSIONS AND NEXT STEPS

The Working Group concluded that all of the initiatives in the scientific framework are still relevant. The overall impression is that implementation progress is on target, but it is too early to assess scientific progress.

The implementation plan associated with Initiative 3 (New Therapeutic Immunotherapy Approaches) needs further assessment and a NCI "Champion" for immunotherapy is needed to coordinate efforts throughout the NCI in order to forge additional collaborations with outside interests and to increase access to new agents. The main objective of the NCI "Champion" would be to try to make more immunotherapy reagents available to investigators for PDAC research and trials in an effort to overcome some of the barriers put in place by the companies that share their reagents with NCI. Additionally, the Working Group concluded the implementation plan related to Initiative 4 (RAS Therapeutics) is on target; however, additional information to assess progress is needed. Increased efforts to track the progress made by the various PDAC related research activities along the drug development pathway could prove advantageous.

The Working Group will periodically review NIH/NCI information about related programs and initiatives, grants, projects, contracts, and clinical trials associated with each of the initiatives over the next year and possibility convene an in-person meeting sometime in 2016. The plan is to provide a progress report to CTAC on an annual basis with the focus on implementation and scientific progress for the short term. Longer term objectives would not be addressed for several years. These include: 1) Review and provide recommendations for updating the scientific framework no later than 5 years after the initial development; and 2) advise NCI on the effectiveness of the scientific framework no later than 6 years after the initial development.

Future activities and timelines for each of the initiatives were identified by the Working Group and are outlined below by calendar year quarter:

Initiative 1: Development of an in-depth understanding of the biological and clinical relationship between PDAC and diabetes mellitus (DM) of recent onset

- *Fourth quarter 2015*: Assess funded grants in response to the joint NCI/NIDDK FOA/RFAs for scientific relevance to this initiative and determination of gaps.
- *First quarter 2016*: Re-evaluate initiative following publication of NIDDK/NIBIB *Advances in Biomedical Imaging, Bioengineering, and Related Technologies for the Development of Biomarkers of Pancreatic Disease* workshop summary.
- *Second quarter 2016*: Potential joint symposium at the annual American Diabetes Association (ADA) meeting.
- *Fourth quarter 2016*: Assess progress of funded grants for scientific relevance.

Initiative 2: Evaluate longitudinal screening protocols for biomarkers for early detection of PDAC and its precursors

- *Second quarter 2015:* NCI PAR 15-289 entitled "The Pancreatic Cancer Detection Consortium (U01)" published.
    - *Fourth quarter 2015* initial receipt of applications.

    - *Third quarter 2016* funding of initial applications.
    - *Third quarter 2017*: Assess progress of funded grants for scientific relevance.
- *First quarter 2016*: Re-evaluate initiative following publication of NIDDK/NIBIB *Advances in Biomedical Imaging, Bioengineering, and Related Technologies for the Development of Biomarkers of Pancreatic Disease* workshop summary.

Initiative 3: New therapeutic approaches in immunotherapy

- *Third quarter 2015*: FNLCR RAS Immunotherapy meeting
- *First quarter 2016*: NCI immunotherapy meeting which will include a breakout session on PDAC research.
    - Discuss expanding the initiative to include tumor/stromal biology and the intersection with immunotherapy
- *Second quarter 2016:* Initiate trans-NCI (internal) Immunotherapy Working Group to closer coordinate NCI Programs.

Initiative 4: Developing new treatment approaches that interfere with RAS oncogene-dependent signaling pathways

- *Third quarter 2015:* Summarize the current progress of the FNLCR RAS project as it relates to PDAC
- *First quarter 2016:* Identify other NCI and non-NCI RAS therapeutics PDAC research and map efforts to a drug development pathway or continuum.
- *Third quarter 2016*: In-person meeting to discuss the following:
    - Potential relevance to PDAC of FNLCR RAS project, reagents in NCI's NExT program, and immunotherapy and trials being considered by NCI's CITN program.
    - Advances in PDAC immunotherapy; what resources or technical advances are needed to overcome obstacles and how can NCI facilitate the process.
    - Discuss expanding the initiative to include tumor/stromal biology and the intersection with immunotherapy.

APPENDICES - SUPPLEMENTAL RESOURCES

Appendix 1: Progress in Pancreatic Ductal Adenocarcinoma (PDAC) Research Working Group (PDAC Progress WG) Roster

Appendix 2: Funded Project Summary

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PROGRESS IN PANCREATIC DUCTAL ADENOCARCINOMA (PDAC) RESEARCH WORKING GROUP
(PDAC PROGRESS WORKING GROUP)
ROSTER

WORKING GROUP REPORT, NOVEMBER 2015

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RESEARCH WORKING GROUP
(PDAC PROGRESS WORKING GROUP)
FUNDED PROJECT SUMMARY

WORKING GROUP REPORT, NOVEMBER 2015

NCI PROGRESS IN PDAC RESEARCH

BY INITIATIVE ACCORDING TO THE SCIENTIFIC FRAMEWORK FOR PDAC

In February 2014, in accordance with the implementation of the Recalcitrant Cancer Act, the NCI delivered a Scientific Framework for Pancreatic Ductal Adenocarcinoma (PDAC) to Congress. The framework outlines recommendations for four research initiatives for PDAC research.

1. Understand the biological relationship between PDAC and diabetes mellitus (DM)
2. Evaluation of longitudinal screening protocols for biomarkers for early detection of PDAC and its precursors
3. Study new therapeutic approaches in immunotherapy
4. Development of new treatment approaches that interfere with RAS oncogene-dependent signaling pathways

The Clinical and Translational Research Advisory Committee (CTAC) has been tasked with monitoring progress in these four research initiatives. They will, at regular intervals, inform the public of progress in PDAC research. A CTAC Working Group was formed to discuss and monitor progress in PDAC research and provide recommendations to the NCI regarding the scientific framework and emerging areas of opportunity.

METHODS

For this analysis, NCI data were identified using the NCI Funded Research Portfolio (NFRP). These data include: FY2013 extramural grants and grant supplements, intramural projects, and research contracts. The NCI portfolio is coded to a variety of organ sites, including pancreatic cancer. Each project is assigned a "percent relevance" to the cancer site(s) to which it is coded.[1] NCI sub-projects with relevance to pancreatic cancer in FY13 pancreatic cancer grants were identified using the NIH RePORTER database.[2]

Projects with relevance to pancreatic cancer for non-NCI NIH were retrieved using the NIH RePORTER database. The database was queried for FY2013 projects (all institutes except NCI), and the "pancreatic cancer" NIH spending category. Abstracts of all projects were reviewed for relevance to PDAC. Projects without relevance, such as pancreatic neuroendocrine tumors, were excluded from this analysis.

Abstracts for each FY13 NCI project coded to 25 percent or greater relevance to pancreatic cancer, NCI sub-projects, and NIH projects identified through the spending category, were reviewed for relevance to PDAC and the four initiatives identified in the scientific framework. Note that research abstracts are not comprehensive, and the below reported projects might be an underrepresentation of the breath of relevant research taking place at NCI-funded laboratories.

Information about specific NCI programs and initiatives were identified by representatives from across the NCI Divisions, Offices and Centers. Note that this information was based on self-reported relevance to the initiatives outlined in the scientific framework for PDAC and might not be comprehensive.

[1] NCI grants, other extramural funding mechanisms, and intramural research projects are indexed for a variety of research categories and organ sites. Each category, such as pancreatic cancer research, is assigned, following a review of the entire application by professional staff, a "percent relevance" based on the portion of the funding relevant to the category. A funding mechanism may be 100 percent relevant to multiple categories, and the sum of the percent relevance assignments may exceed 100 percent. Dollars invested per year for pancreatic cancer research, was arrived at by multiplying the award for each grant, cooperative agreement, contract, and intramural project funded in that year by its percent relevance and then combining the numbers for a total.

[2] Research Portfolio Online Reporting Tools (RePORT)

INITIATIVE 1

UNDERSTAND THE BIOLOGICAL RELATIONSHIP BETWEEN PDAC AND DIABETES MELLITUS

Summary: Twenty-five percent of PDAC patients have a history of recent onset (within 3 years) of DM at the time of diagnosis and yet only a small percentage of patients with recent onset DM will develop PDAC. This fact requires a more detailed understanding of the clinical and biological characteristics of the population of patients who subsequently develop or have undiagnosed PDAC in the setting of newly diagnosed diabetes. This includes defining specific risk factors to make screening and early diagnosis efforts more efficient and cost-effective.

FY2013 RESEARCH PORTFOLIO

Based on manual abstract review four NCI funded projects have been identified in FY2013. An additional three sub-projects with relevance to initiative 1 were identified.

Table 1. NCI projects with Relevance to Initiative 1

PROJECT NUMBER	TITLE	PRINCIPAL INVESTIGATOR	INSTITUTION
1R21CA176337-01	DEVELOPMENT OF NEW THERAPEUTICS FOR PANCREATIC CANCER MANAGEMENT	PIETRAS, RICHARD	UNIVERSITY OF CALIFORNIA LOS ANGELES
3P50CA102701-10S1	MAYO CLINIC SPORE IN PANCREATIC CANCER	PETERSEN, GLORIA	MAYO CLINIC ROCHESTER
5P01CA163200-02	TARGETING DIET-INDUCED PROMOTION OF KRAS-INITIATED PANCREATIC ADENOCARCINOMA	EIBL, GUIDO	UNIVERSITY OF CALIFORNIA LOS ANGELES
ZIA CP010202-10378	PLCO PANCREAS CANCER	SOLOMON, RACHAEL	NCI

Table 2. NCI Subprojects with Relevance to Initiative 1

PROJECT NUMBER	TITLE	PRINCIPAL INVESTIGATOR	INSTITUTION
3P50CA102701-10S11 9007	CC: CLINICAL RESEARCH	PETERSEN, GLORIA M.	MAYO CLINIC ROCHESTER
3P50CA102701-10S1 0008	PANCREATIC CANCER-ASSOCIATED DIABETES: PATHOGENESIS AND BIOMARKERS	CHARI, SURESH T.	MAYO CLINIC ROCHESTER
5P50CA130810-04 6674	P2 - MARKERS OF PANCREATIC CANCER USING A GLYCOPROTEOMIC APPROACH	RUFFIN, MACK T.	UNIVERSITY OF MICHIGAN

FUNDING OPPORTUNITIES

There are currently two open funding announcements with relevance to initiative 1. These announcements are the result of collaboration between the NCI and NIDDK, following a meeting held in June 2013 to discuss the risk factors of chronic pancreatitis and diabetes mellitus and the development of PDAC. [3]

RFA-DK-14-027 Consortium for the Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer Clinical Centers (CSCDPC-CCs) (U01)

RFA-DK-14-028 Consortium for the Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer Coordination and Data Management Center (CSCPDPC-CDMC) (U01)

Applications for both RFAs were due April 2nd, 2015.

CURRENT NCI RESEARCH

There are currently four study cohorts that can provide insight into the risk factors between DM and PDAC.

Shanghai Men's Health Study (SMHS) – through the Division of Cancer Control and Population Sciences (DCCPS) at Vanderbilt University, CA082729

The SMHS was initiated in 2001 and now consists of 61,492 men aged 40-74 years living in Shanghai, China. The SMHS is the only large cohort of Chinese men with repeated measures of diet, physical activity, and other variables over an extended period of time. The SMHS is an important resource that has substantially enhanced understanding of how modifiable and genetic factors affect cancer etiology, prevention and survival in Chinese men. There are currently 280 PDAC cases in the SMHS. The SMHS has published a number of studies on PDAC since 2009. More recently, SMHS investigators have been collaborating with other cohorts to examine diabetes, as well as body mass index (BMI), as a risk factor for PDAC in Asians. In addition, SMHS investigators recently performed a comprehensive pathway analysis of the combined dataset of two pancreatic cancer genome-wide association studies (GWAS) to identify/confirm genetic variants involved in the development of PDAC.

Iowa Women's Health Study (IWHS) – through DCCPS, CA039742

The IWHS is a prospective, population-based cohort study of 41,836 women, mainly from rural areas, ages 55-69, who have been followed primarily for cancer incidence and mortality since study initiation in 1986. Because the IWHS is an older cohort, they have a large number of PDAC cases – nearly 350. The IWHS has participated in pooling projects looking at dietary factors and risk of pancreatic cancer. Specifically, the investigators have looked at intake of folate, coffee/tea/soft drinks, and fruit/vegetable and the risk of development of PDAC. More recently,

[3] Dana K. Andersen, et. al. Pancreatitis-Diabetes-Pancreatic Cancer. *Pancreas*: Volume 42, Number 8, November 2013. PMID: 24152948

the cohort investigators examined the duration of type-2 diabetes and pancreatic cancer risk in the Midwest.

Pancreatic Cancer Cohort Consortium (PanScan**)**– through DCCPS/Division of Cancer Epidemiology and Genetics (DCEG)

A multi-stage GWAS of pancreatic cancer is being conducted within the framework of the NCI Cohort Consortium. Researchers have completed three GWAS studies for pancreatic adenocarcinoma, which have led to the discovery of 10 novel regions in the genome associated with pancreatic cancer. Researchers are presently working on additional value-added studies, including a meta-analysis with PANC4, GWAS by phenotype, pathway and survival data.

Diabetes and Cancer Initiative **in the Cohort Consortium** – through DCCPS/DCEG

This project, initiated in 2013, seeks to understand the relationship between type-2 diabetes mellitus (T2DM) and cancer incidence and survival, both in terms of epidemiology and underlying molecular mechanisms. The project will investigate the association of T2DM with all major cancers and whether this association is modified by gender, ethnicity, body size, physical activity, smoking, diet, alcohol consumption or menopausal status. The study will also investigate the association of diabetes treatments with cancer incidence and survival. An additional aim will be to identify genetic and metabolic predictors of cancer risk among diabetics.

Studies of Potentially Modifiable Risk Factors for Pancreatic Cancer – through DCEG

The primary aim of this pancreatic cancer research is to identify potentially modifiable factors that may reduce the burden of this highly fatal disease by primarily utilizing cohort studies. Exposures examined include adiposity in both early and later life, diet, dietary patterns, biomarkers related to insulin resistance, and other biomarkers.

Specialized Programs of Research Excellence (SPORE**)** – through the Division of Cancer Treatment and Diagnosis (DCTD)

SPOREs are a cornerstone of NCI's efforts to promote collaborative, interdisciplinary translational cancer research. SPORE grants involve both basic and clinical/applied scientists and support projects that will result in new and diverse approaches to the prevention, early detection, diagnosis, and treatment of human cancers. Each SPORE is focused on a specific organ site (or a group of highly related cancers) and designed to enable the rapid and efficient movement of basic scientific findings into clinical settings. Individual SPOREs also aim to determine the biological basis for observations made in individuals with cancer or in populations at risk for cancer. SPOREs, in addition to four subprojects, can also support a pilot or career enhancement projects. In FY13 there was one subproject with relevance to initiative 1.

Table 3. SPORE Project with Relevance to Initiative 1

TITLE	PRINCIPLE INVESTIGATOR	INSTITUTION
CC: CLINICAL RESEARCH	PETERSEN, GLORIA	MAYO CLINIC ROCHESTER

INITIATIVE 2

EVALUATE LONGITUDINAL SCREENING PROTOCOLS FOR BIOMARKERS AND EARLY DETECTION OF PDAC AND ITS PRECURSORS

Summary: The goal is to identify patients with the earliest stage of PDAC who have the best chance of cure, as well as those who have precursor lesions (PanIN-3 and cystic neoplasms of the pancreas) that are likely to evolve into PDAC. To achieve this, it is necessary to develop more accurate and sensitive methods of imaging and methods to identify the molecular alterations that characterize these early lesions. In addition, development of longitudinal screening protocols are needed – these protocols will collect specimens from early lesions in patients at high risk of developing PDAC because of their genetic background or the presence of mucinous pancreatic cysts.

FY2013 RESEARCH PORTFOLIO

Based on manual abstract review 42 NCI-funded projects have been identified in FY2013. An additional 11 NCI subprojects and nine NIH projects with relevance to initiative 2 were identified.

Table 4. NCI Projects with Relevance to Initiative 2

PROJECT NUMBER	TITLE	PRINCIPAL INVESTIGATOR	INSTITUTION
1R01CA169134-01A1	HLTF GENE SILENCING: A NOVEL DETERMINANT OF SENSITIVITY TO AUTOPHAGY INHIBITION	AMARAVADI, RAVI	UNIVERSITY OF PENNSYLVANIA
5R21CA164593-02	MUTATION-SPECIFIC P53 ANTIBODIES AS BIOMARKERS OF PANCREATIC CANCER	ANDERSON, KAREN	ARIZONA STATE UNIVERSITY-TEMPE CAMPUS
5R21CA158640-02	SIMULTANEOUS ATTACK OF EPITHELIAL AND STROMAL COMPARTMENTS IN PANCREATIC CANCER	BEACHY, PHILIP	STANFORD UNIVERSITY
5R01CA132971-05	COLOR-CODED IMAGING OF PANCREATIC CANCER MICROENVIRONMENT FOR DRUG DISCOVERY	BOUVET, MICHAEL	UNIVERSITY OF CALIFORNIA SAN DIEGO
5R01CA142669-04	FLUOROPHORE-CONJUGATED ANTIBODIES FOR IMAGING AND RESECTION OF GI TUMORS	BOUVET, MICHAEL	UNIVERSITY OF CALIFORNIA SAN DIEGO
3P50CA130810-04S1	TRANSLATIONAL RESEARCH IN GI CANCER	BRENNER, DEAN	UNIVERSITY OF MICHIGAN
5P50CA130810-04	TRANSLATIONAL RESEARCH IN GI CANCER	BRENNER, DEAN	UNIVERSITY OF MICHIGAN
5P50CA101955-09	UAB / UMN SPORE IN PANCREATIC CANCER	BUCHSBAUM, DONALD	UNIVERSITY OF ALABAMA AT BIRMINGHAM
1R21CA174594-01A1	SINGLE MOLECULE MICROARRAYS FOR THE DETECTION OF MUTANT DNA IN BODY FLUIDS	CELEDON, ALFREDO	TWISTNOSTICS, LLC

PROJECT NUMBER	TITLE	PRINCIPAL INVESTIGATOR	INSTITUTION
5R21CA164592-02	IDENTIFYING FAMILIAL PANCREATIC CANCER PREDISPOSITION GENES	ESHLEMAN, JAMES	JOHNS HOPKINS UNIVERSITY
1R01CA176828-01A1	USING MARKERS TO IMPROVE PANCREATIC CANCER SCREENING	GOGGINS, MICHAEL	JOHNS HOPKINS UNIVERSITY
5R01CA096924-08	DETECTION AND DIAGNOSIS OF PANCREATIC CARCINOMA	GOLD, DAVID	CTR FOR MOLECULAR MEDICINE/IMMUNOLOGY
5U54CA151668-04	TEXAS CENTER FOR CANCER NANOMEDICINE	GORENSTEIN, DAVID	UNIVERSITY OF TEXAS HLTH SCI CTR HOUSTON
5U01CA152653-04	DETECTION OF PRE-INVASIVE PANCREATIC CYSTS USING PROTEIN AND GLYCAN BIOMARKERS	HAAB, BRIAN	VAN ANDEL RESEARCH INSTITUTE
5U01CA168896-02	TARGETED GLYCOMICS AND AFFINITY REAGENTS FOR CANCER BIOMARKER DEVELOPMENT	HAAB, BRIAN	VAN ANDEL RESEARCH INSTITUTE
5R21CA159240-02	PERIPHERAL BLOOD BIOPSY FOR MOLECULAR DIAGNOSIS OF PANCREATIC CANCER	HINGORANI, SUNIL	FRED HUTCHINSON CAN RES CTR
5U01CA111294-09	EARLY DIAGNOSIS OF PANCREATIC CANCER	HOLLINGSWORTH, MICHAEL	UNIVERSITY OF NEBRASKA MEDICAL CENTER
N44CO130071-000	SBIR PHASE II: LOW-COST MICROFLUIDIC SYSTEM FOR DETECTION OF CTC'S.	HUPERT, MATEUSZ	BIOFLUIDICA MICROTECHNOLOGIES LLC
ZIA BC 011162	INTEGRATIVE MOLECULAR PROFILING OF HUMAN PANCREATIC CANCER	HUSSAIN, S. PERWEZ	NCI
1R01CA172880-01A1	ADVANCED GLYCATION END-PRODUCTS AND RISK OF PANCREATIC CANCER	JIAO, LI	BAYLOR COLLEGE OF MEDICINE
5P50CA062924-20	SPORE IN GASTROINTESTINAL CANCER	KERN, SCOTT	JOHNS HOPKINS UNIVERSITY
5U01CA111302-09	BIOMARKERS FOR THE EARLY DETECTION OF PANCREATIC CANCER	KILLARY, ANN	UT MD ANDERSON CANCER CTR
2R01CA097022-11	SURVIVAL MECHANISMS OF INVASIVE CARCINOMA CELLS	KLEMKE, RICHARD	UNIVERSITY OF CALIFORNIA SAN DIEGO
5R01CA155198-02	DESIGN OF MEK INHIBITOR REGIMENS FOR THE TREATMENT OF PANCREATIC CANCER	LEOPOLD, JUDITH	UNIVERSITY OF MICHIGAN
7U01CA151455-04	NANOSCALE METAL-ORGANIC FRAMEWORKS FOR IMAGING AND THERAPY OF PANCREATIC CANCER	LIN, WENBIN	UNIVERSITY OF CHICAGO
5R21CA164880-02	NON-INVASIVE SAMPLING OF DNA MARKERS FOR PANCREATIC CANCER SCREENING	LIU, YU-TSUENG	UNIVERSITY OF CALIFORNIA SAN DIEGO
5R01CA154455-03	SERUM GLYCOPROTEIN MARKERS OF CANCER USING AN ION MOBILITY/MASS SPEC APPROACH	LUBMAN, DAVID	UNIVERSITY OF MICHIGAN

PROJECT NUMBER	TITLE	PRINCIPAL INVESTIGATOR	INSTITUTION
7R01CA151374-04	EVALUATION OF IN VIVO OPTICAL IMAGING IN PANCREATIC AND OVARIAN CANCER PATIENTS	MARTIN, LAINIE	RESEARCH INST OF FOX CHASE CAN CTR
5R01CA140211-05	DISTINCTIVE GLYCAN FINGERPRINTS OF PANCREATIC CANCER FOR PLASMA DETECTION	MISEK, DAVID	UNIVERSITY OF MICHIGAN
ZIA CP010197-10542	METABOLOMICS OF ENERGY BALANCE, NUTRITIONAL STATUS, AND CANCER	MOORE, STEVEN	NCI
5R01CA169774-02	DETECTION OF IN VIVO ENZYME ACTIVITIES WITH CEST MRI	PAGEL, MARK	UNIVERSITY OF ARIZONA
5K25CA137222-04	QUANTITATIVE GLYCOPROTEOMICS FOR PANCREATIC CANCER STUDIES	PAN, SHENG	UNIVERSITY OF WASHINGTON
3P50CA102701-10S1	MAYO CLINIC SPORE IN PANCREATIC CANCER	PETERSEN, GLORIA	MAYO CLINIC ROCHESTER
5U01CA128454-07	DISCOVERY AND DEVELOPMENT OF CANCER GLYCOMARKERS	PIERCE, JAMES	UNIVERSITY OF GEORGIA
5R33CA155586-03	ADVANCED DEVELOPMENT OF A MULTIPLEXED SERS-BASED BIOMARKER DETECTION PLATFORM: A	PORTER, MARC	UNIVERSITY OF UTAH
5U01CA151650-04	MAGNETORESISTIVE SENSOR PLATFORM FOR PARALLEL CANCER MARKER DETECTION	PORTER, MARC	UNIVERSITY OF UTAH
N43CO130060-000	SBIR PHASE I TOPIC 324: DEVELOPMENT OF AN IMAGING AGENT TARGETING SIALYL LEWIS A	SCHOLZ, WOLFGANG	MABVAX THERAPEUTICS, INC.
1R43CA171744-01A1	LOCALIZATION OF PANCREATIC CANCER BY A PRETARGETED 18F-HAPTEN-PEPTIDE	WEGENER, WILLIAM	IMMUNOMEDICS, INC.
1R01CA174294-01A1	MULTIFUNCTIONAL IMMUNOPET TRACERS FOR PANCREATIC AND PROSTATE CANCER	WU, ANNA	UNIVERSITY OF CALIFORNIA LOS ANGELES
5R01CA152309-04	FUNCTIONAL VALIDATION OF PANCREATIC CANCER PROGRESSION BIOMARKER	XIE, KEPING	UT MD ANDERSON CANCER CTR
5U01CA151810-04	THERANOSTIC NANO PARTICLES FOR TARGETTED TREATMENT OF PANCREATIC CANCER	YANG, LILY	EMORY UNIVERSITY
5U01CA151886-04	PRECLINICAL PLATFORM FOR THERANOSTIC NANOPARTICLES IN PANCREATIC CANCER	HALAS, NANCY J	RICE UNIVERSITY

Table 5. NCI Subprojects with Relevance to Initiative 2

PROJECT NUMBER	TITLE	PRINCIPAL INVESTIGATOR	INSTITUTION
5P50CA086355-14 5171	BIND CHEMISTRY FOR IMAGING INTRACELLULAR TARGETS	WEISSLEDER, RALPH	MASSACHUSETTS GENERAL HOSPITAL
5P01CA084203-10 7855	BIOLOGICAL MODELS, MOLECULAR PATHOLOGY AND BIOSTATISTICS	TEARNEY, GUILLERMO J.	MASSACHUSETTS GENERAL HOSPITAL

PROJECT NUMBER	TITLE	PRINCIPAL INVESTIGATOR	INSTITUTION
5P50CA101955-09 7893	BIOMARKER DISCOVERY FOR EARLY DETECTION OF PANCREATIC DUCTAL ADENOCARCINOMA	KLUG, CHRISTOPHER A	UNIVERSITY OF ALABAMA AT BIRMINGHAM
5P01CA130821-06 5800	CELLULAR INTERACTIONS B/T TGF-B PATHWAY MEMBERS AND TERT AND C-MYC IN GASTRO CAN	MISHRA, BIBHUTI B	UNIVERSITY OF TX MD ANDERSON CAN CTR
5P50CA062924-20 5540	DIAGNOSTIC STRATEGY AND RISK ASSESSMENT OF CYSTS	KINZLER, KENNETH W.	JOHNS HOPKINS UNIVERSITY
5P50CA062924-20 5538	FAMILIAL MARKERS OF RISK	KLEIN, ALISON P	JOHNS HOPKINS UNIVERSITY
5P30CA046592-25 6463	GASTROINTESTINAL ONCOLOGY	WICHA, MAX S.	UNIVERSITY OF MICHIGAN
5P50CA062924-20 5539	MARKERS FOR SCREENING AND PROGNOSIS	GOGGINS, MICHAEL G.	JOHNS HOPKINS UNIVERSITY
5U54CA151668-04 8846	NANOTECHNOLOGY PLATFORMS FOR THE PREVENTION AND PERSONALIZED THERAPY OF PANCREATI	LOGSDON, CRAIG D	UNIVERSITY OF TEXAS HLTH SCI CTR HOUSTON
5P50CA130810-04 6674	P2 - MARKERS OF PANCREATIC CANCER USING A GLYCOPROTEOMIC APPROACH	RUFFIN, MACK T.	UNIVERSITY OF MICHIGAN
5U54CA151881-04 5126	DEVELOP AND HIGH-THROUGHPUT SCREENING OF TARGETED ANTICANCER NANOMEDICINES	PETRENKO, VALERY A	AUBURN UNIVERSITY AT AUBURN

Table 6. NIH Projects with Relevance to Initiative 2

PROJECT NUMBER	TITLE	PRINCIPAL INVESTIGATOR	INSTITUTION	INSTITUTE
1R21EB017317-01	SOLID-PHASE PLATFORM FOR THE PREPARATION OF DUAL-RECEPTOR TARGETED PET AGENTS	ZENG, DEXING	UNIVERSITY OF PITTSBURGH AT PITTSBURGH	NIBIB
1R43TR001010-01	PANCREATIC CANCER:ASSAY FOR EARLY DETECTION	NISHIOKA, GARY M	H AND N INSTRUMENTS, INC.	NCATS
1S10OD016316-01	LEICA LMD 7000 LASER CAPTURE MICRODISSECTION MICROSCOPE	JANZ, SIEGFRIED	UNIVERSITY OF IOWA	OD
3R01EB002568-09S1	HIGH-PERFORMANCE HIGH-FIELD PARALLEL MRI	SODICKSON, DANIEL K	NEW YORK UNIVERSITY SCHOOL OF MEDICINE	OD
5K08EB012859-03	VALIDATION OF MRI MICROVASCULAR BIOMARKERS IN PANCREATIC CANCER WITH MAGNETIC NAN	GUIMARAES, ALEXANDER RAMOS	MASSACHUSETTS GENERAL HOSPITAL	NIBIB

PROJECT NUMBER	TITLE	PRINCIPAL INVESTIGATOR	INSTITUTION	INSTITUTE
5K08ES019615-03	BIOMARKERS OF EXPOSURE AND RESPONSE TO ENVIRONMENTAL TOBACCO SMOKE IN THE PANCREA	YU, KENNETH H	SLOAN-KETTERING INST CAN RESEARCH	NIEHS
5R01EB002568-09	HIGH-PERFORMANCE HIGH-FIELD PARALLEL MRI.	SODICKSON, DANIEL K	NEW YORK UNIVERSITY SCHOOL OF MEDICINE	NIBIB
5R01EB006432-08	INTEGRATED FMT APPROACHES FOR BIOMOLECULAR MEASUREMENTS	WEISSLEDER, RALPH	MASSACHUSETTS GENERAL HOSPITAL	NIBIB
5R01EB010023-04	DEVELOPMENT OF MOLECULARLY TARGETED IMAGING AGENTS FOR KRAS ACTIVITY IN VIVO	KELLY, KIMBERLY A.	UNIVERSITY OF VIRGINIA	NIBIB

FUNDING OPPORTUNITIES

Applications are currently under review from four funding opportunity announcements with relevance to initiative 2.

PA-11-297 Pilot Studies in Pancreatic Cancer (R21)

PA-11-298 Pilot Studies in Pancreatic Cancer (R03)

RFA-CA-14-010 Molecular and Cellular Characterization of Screen-Detected Lesions (U01)

RFA-CA-14-011 Molecular and Cellular Characterization of Screen-Detected Lesions – Coordination Center and Data Management Group (U01)

Under Development: In addition to these four funding opportunity announcements, the NCI Division of Cancer Prevention (DCP) is planning on developing an announcement that would focus on the development of novel methods to obtain and interrogate pancreatic tissues containing pre-neoplastic lesions.

CURRENT NCI RESEARCH

Pancreatic Cancer Cohort Consortium (PanScan)– through DCCPS

The Pancreatic Cancer Cohort Consortium consists of more than a dozen prospective epidemiologic cohort studies within the NCI Cohort Consortium whose leaders work together to investigate the etiology and natural history of pancreatic cancer. PanScanIII is a collaboration between NCI extramural and intramural investigators. A joint analysis of newly GWAS-scanned cases will be conducted with cases from PanScan I and II to identify novel regions of the genome associated with pancreatic cancer susceptibility. With the larger sample size (about 6,200 cases and 13,900 controls), the PanScan III investigators anticipate that they will identify new genetic

risk variants for etiology. It is notable that this study will include about 3,200 incident cases from the Cohort Consortium, which are more likely to represent the diversity of pancreatic cancers at presentation.

Pancreatic Case-Control Consortium (PANC4) Consortium – through DCCPS/DCEG
PANC4 is a collaboration of investigators leading eight hospital-based case-control studies to identify genetic factors, environmental exposures, and gene-environment interactions that contribute to the development of PDAC. These investigators also seek to identify and develop methods of surveillance and diagnosis for early detection of the disease.

Early Detection Research Network (EDRN)– through DCP

The EDRN brings together dozens of institutions to help accelerate the translation of biomarker information into clinical applications and to evaluate new ways of testing for cancer in its earliest stages and for cancer risk. Currently, EDRN is working to establish a reference set for PDAC that consists of serum and plasma from patients with pancreatic cancer, chronic pancreatitis, acute benign biliary obstruction, and healthy controls. The set is available to the scientific community for the validation of promising biomarkers for pancreatic cancer. EDRN investigators have also identified seven putative biomarkers for PDAC. These biomarkers are currently being annotated and are under review.

The presence of mucinous pancreatic cysts, such as intrapancreatic mucinous neoplasm (IPMN), is a risk factor for PDAC. IPMNs are detected incidentally on high quality CT scans of the abdomen. The PDAC risk factor study includes cystic fluid from IPMNs and concomitant histopathological confirmation of the IPMN (benign or high grade dysplasia). This study will provide a unique reference set to be used in ongoing EDRN-associated biomarker discovery and validation studies for the early detection of PDAC.

Alliance of Glycobiologists – through DCP

The major objective of the Alliance of Glycobiologists is to discover and develop molecular markers for early detection of cancer by conducting innovative, translational research in the field of complex carbohydrates. An important factor in biomarker discovery is understanding the biological mechanisms by which changes in glycosylation promote cancer progression. Taking this biologically informed approach, Alliance investigators focus their efforts on specific classes of glycan markers that are likely to play important roles in oncogenesis.

There are two teams of investigators in the Alliance with projects with relevance to PDAC.

1. Van Andel Research Institute/Emory University – Research on low CA19-9 antigen subgroup (20% of pancreatic cancers) to discover complementary glycan biomarkers for early detection and diagnosis of pancreatic cancer.
2. University of Georgia – Research to determine precise structure of glycan epitopes and development of glycomarkers for pancreatic cancer for diagnostic tests.

PREVENT Cancer Preclinical Drug Program – through DCP

PREVENT functions as a pipeline to bring new cancer-preventing interventions and biomarkers through preclinical development to clinical trials. Currently (FY15), there are two funded projects with relevance to pancreatic cancer.

NCI Alliance for Nanotechnology in Cancer – through Center for Strategic Scientific Initiatives (CSSI)

The NCI Alliance for Nanotechnology in Cancer is engaged in efforts to harness the power of nanotechnology to radically change the way we diagnose, treat, and prevent cancer. The Alliance for Nanotechnology in Cancer seeks to generate new preventative, diagnostic and therapeutic approaches to cancer in areas where improvements cannot be realized using existing technologies. In FY13 and FY14 there were seven awards with relevance to pancreatic cancer, six of which had direct relevance to initiative 2.

Table 7. NCI Alliance for Nanotechnology in Cancer Projects Relevant to Initiative 2

TITLE	PRINCIPAL INVESTIGATOR	INSTITUTION
NANOSCALE METAL-ORGANIC FRAMEWORKS FOR IMAGING AND THERAPY OF PANCREATIC CANCER	LIN, WENBIN	UNIVERSITY OF CHICAGO
MAGNETORESISTIVE SENSOR PLATFORM FOR PARALLEL CANCER MARKER DETECTION	PORTER, MARC D	UNIVERSITY OF UTAH
THERANOSTIC NANO PARTICLES FOR TARGETTED TREATMENT OF PANCREATIC CANCER	YANG, LILY	EMORY UNIVERSITY
PRECLINICAL PLATFORM FOR THERANOSTIC NANOPARTICLES IN PANCREATIC CANCER	HALAS, NANCY J	RICE UNIVERSITY
TEXAS CENTER FOR CANCER NANOMEDICINE	GORENSTEIN, DAVID G	UNIVERSITY OF TEXAS HLTH SCI CTR HOUSTON
DEVELOP AND HIGH-THROUGHPUT SCREENING OF TARGETED ANTICANCER NANOMEDICINES	PETRENKO, VALERY A	AUBURN UNIVERSITY AT AUBURN

Innovative Molecular Analysis Technologies (IMAT) – through CSSI

The Innovative Molecular Analysis Technologies (IMAT) program was established to support the development, technical maturation, and dissemination of novel and potentially transformative next-generation technologies through an approach of balanced but targeted innovation. The program utilizes a variety of investigator-initiated research project grant mechanisms while retaining a strong commitment to diversity and to the training of scientists and clinicians in crosscutting, research-enabling disciplines. In FY13 and FY14, there were seven awards with relevance to PDAC, including three FY13 projects with relevance to initiative 2.

Table 8. IMAT Projects with Relevance to Initiative 2

TITLE	PRINCIPAL INVESTIGATOR	INSTITUTION
SINGLE MOLECULE MICROARRAYS FOR THE DETECTION OF MUTANT DNA IN BODY FLUIDS	CELEDON, ALFREDO ANDRES	SCANOGEN, INC.
TECHNOLOGY FOR SENSITIVE AND RELIABLE MUTATIONAL PROFILING IN PANCREATIC CANCER	MAKRIGIORGOS, G. M	DANA-FARBER CANCER INST
ADVANCED DEVELOPMENT OF A MULTIPLEXED SERS-BASED BIOMARKER DETECTION PLATFORM	PORTER, MARC D	UNIVERSITY OF UTAH

Vitamin D Pooling Project (VDPP) – through DCEG

Vitamin D-binding protein (DBP) is the primary carrier of 25-hydroxyvitamin D [25(OH)D] in circulation. One prospective study of male smokers found a protective association between DBP and pancreatic cancer, particularly among men with higher 25(OH)D concentrations. Researchers examined the association between genes involved in endogenous vitamin D synthesis, transport, and catabolism within the PanScan GWAS studies. The vitamin D pathway was not association with pancreatic cancer. CYP24A1 gene was nominally associated with pancreatic cancer. Ongoing studies of vitamin D binding protein and 25(OH)D are underway in the prostate, lung, colorectal and ovarian cancer screening trial (PLCO) cohort.

Specialized Programs of Research Excellence (SPORE) – Division of Cancer Treatment and Diagnosis (DCTD)

SPOREs are a cornerstone of NCI's efforts to promote collaborative, interdisciplinary translational cancer research. SPORE grants involve both basic and clinical/applied scientists and support projects that will result in new and diverse approaches to the prevention, early detection, diagnosis, and treatment of human cancers. Each SPORE is focused on a specific organ site (or a group of highly related cancers) and designed to enable the rapid and efficient movement of basic scientific findings into clinical settings. Individual SPOREs also aim to determine the biological basis for observations made in individuals with cancer or in populations at risk for cancer.

There were a total of five SPOREs conducting PDAC research in FY2013 and FY2014. Each SPORE has four sub-projects, in addition they can support a number of pilot or career enhancement projects. Within those SPOREs there were seven projects with relevance to initiative 2.

Table 9. SPORE Projects with Relevance to Initiative 2

TITLE	PRINCIPAL INVESTIGATOR	INSTITUTION
BIOMARKER DISCOVERY FOR EARLY DETECTION OF PANCREATIC DUCTAL ADENOCARCINOMA	KLUG, CHRISTOPHER	UNIVERSITY OF ALABAMA AT BIRMINGHAM
BIOMARKERS IN PANCREATIC CANCER	CHUGH, ROHIT	UNIVERSITY OF ALABAMA AT BIRMINGHAM
A NON-INVASIVE HIGH THROUGHPUT LABEL FREE MICROFLUIDIC APPROACH FOR DETECTION AND CHARACTERIZATION OF CIRCULATING TUMOR CELLS IN PANCREATIC CANCER	NAGRATH, SUNITA	UNIVERSITY OF MICHIGAN
FAMILIAL MARKERS OF RISK	KLEIN, ALISON	JOHNS HOPKINS UNIVERSITY
MARKERS FOR SCREENING AND PROGNOSIS	KINZLER, KENNETH	JOHNS HOPKINS UNIVERSITY
DIAGNOSTIC STRATEGY AND RISK ASSESSMENT OF CYSTS	KINZLER, KENNETH	JOHNS HOPKINS UNIVERSITY

Intramural Research Program – Center for Cancer Research (CCR)

Within the intramural research program at CCR, there were three projects with relevance to initiative 2.

Integrative Molecular Profiling of Human Pancreatic Cancer: A large sample set of PDAC (N>200) was examined using global strategies. These strategies included transcriptomics and metabolomics for molecular characterization of potential subgroups defined by inflammatory gene-expression, and to identify sub-group specific novel candidate therapeutic targets. Next prognostically significant genes and metabolites, and their interactive role in disease progression were identified. Molecular characterization of early stage PDAC tumors with extreme prognoses were examined for inflammatory mediators, and their interactive pathways, linked to disease progression and patient's outcome.

Forkhead-box (FOX) Transcription Factors in the Progression of Pancreatic Cancer: Our overall objective is to examine the interactive role of prognostically significant FOX transcription factors and inflammatory mediators in pancreatic cancer progression and disease aggressiveness.

Development of ES/iPSC approach for non-germline GEM modeling: This project is aimed at establishing a new approach in generation of non-germline GEM cohorts for the purposes of preclinical anti-cancer drug evaluation, biomarker discovery for disease progression and drug response, and basic mechanistic studies of carcinogenesis. This research involves:

1. Adopt and possibly improve current technologies for derivation of ES and iPSC cell lines from differentiated mouse cells using non-integrating reagents, such as adenoviral and episomal plasmid vectors, and mRNAs.
2. Generate a collection of ES/iPSC clones from clinically relevant GEM models of high-grade astrocytoma, serous epithelium ovarian cancer, pancreatic carcinoma, and melanoma.
3. During the validation phase of this novel approach, develop experimental cohorts of chimeric animals employing ES and iPSC cells generated from the pancreatic cancer model and test the efficiency and the time course of tumor progression upon pharmacological induction.
4. Compare the course of carcinogenesis in such non-germline animals with that of observed in experimental animals obtained through conventional breeding, conducting both histopathologic and disease-associated molecular signatures analyses.
5. Once this modeling strategy proves itself successful, design and perform a series of drug studies that employ cohorts of chimeric "non-germline" GEM animals.

MEETINGS

NIDDK is in the process of developing a meeting entitled: “Imaging and Biomarkers for Screening and Early Detection of Pancreas Disease, Including PDAC.” Tentative date of the meeting is July 22nd, 2015.

INITIATIVE 3

STUDY NEW THERAPEUTIC APPROACHES IN IMMUNOTHERAPY

Summary: Recent advances in understanding the induction and regulation of the immune response to cancer, and the dynamic processes involved in the interaction of tumor and its microenvironment, have provided opportunities to discover and validate new immunotherapeutic targets and to develop new interventions for clinical testing for progress against PDAC.

FY2013 RESEARCH PORTFOLIO

Based on manual abstract review, 36 FY13 NCI-funded projects have been identified as relevant to initiative 3. An additional five NCI subprojects and one NIH project were identified as relevant to initiative 3.

Table 10. NCI Projects with Relevance to Initiative 3

PROJECT NUMBER	TITLE	PRINCIPAL INVESTIGATOR	INSTITUTION
1R01CA168863-01A1	CCR2 BLOCKADE IN HUMAN PANCREATIC CANCER	LINEHAN, DAVID	WASHINGTON UNIVERSITY
1R03CA173223-01	FLT3L TREATMENT OF PANCREATIC CANCER	SOLHEIM, JOYCE	UNIVERSITY OF NEBRASKA MEDICAL CENTER
1R15CA173668-01	MUC1 ENHANCES NEUROPILIN-1 SIGNALING IN PANCREATIC DUCTAL ADENOCARCINOMA	MUKHERJEE, PINKU	UNIVERSITY OF NORTH CAROLINA CHARLOTTE
1R21CA164756-01A1	GRP94 TARGETED THERAPY FOR PANCREATIC DUCTAL ADENOCARCINOMA	FERRONE, SOLDANO	MASSACHUSETTS GENERAL HOSPITAL
1R21CA167329-01A1	NMDA RECEPTORS IN THE DIAGNOSIS AND TREATMENT OF PANCREATIC CANCER	NORTH, WILLIAM	DARTMOUTH COLLEGE
1R21CA169720-01A1	NOVEL ANTI-HER3 STRATEGY FOR PANCREATIC CANCER	ZHOU, TONG	UNIVERSITY OF ALABAMA AT BIRMINGHAM
1R21CA172983-01A1	ANTI-PV1 THERAPY FOR PANCREATIC CANCER	STAN, RADU	DARTMOUTH COLLEGE
1R21CA173518-01A1	BREAKDOWN OF DESMOPLASIA IN PANCREATIC CANCER TO ENHANCE DRUG EFFECTIVENESS	BOUCHER, YVES	MASSACHUSETTS GENERAL HOSPITAL
1R21CA174306-01A1	IDO-SILENCING SALMONELLA THERAPY FOR THE TREATMENT OF PRIMARY AND METASTATIC PDAC	DIAMOND, DON	CITY OF HOPE/BECKMAN RESEARCH INSTITUTE
1R43CA174025-01A1	DEVELOPMENT OF MONOCLONAL ANTIBODIES TO TREAT PANCREATIC CANCER	PANTAZIS, PANAYOTIS	COARE BIOTECHNOLOGY, INC.
1R43CA176957-01	SLEEPING BEAUTY MEDIATED THERAPY FOR ALPHA V BETA 6-	HYLAND, KENDRA	DISCOVERY GENOMICS, INC.

PROJECT NUMBER	TITLE	PRINCIPAL INVESTIGATOR	INSTITUTION
	EXPRESSING PANCREATIC CANCER		
2R01CA033084-30A1	MECHANISMS OF MURINE TURMOR ERADICATION BY IMMUNOTHERAPY	GREENBERG, PHILIP	UNIVERSITY OF WASHINGTON
2R01CA135274-06A1	OVERCOMING PANCREATIC TUMOR RESISTANCE TO GEMCITABINE	CUI, ZHENGRONG	UNIVERSITY OF TEXAS, AUSTIN
3P50CA102701-10S1	MAYO CLINIC SPORE IN PANCREATIC CANCER	PETERSEN, GLORIA	MAYO CLINIC ROCHESTER
3R01CA105412-10S1	TRANSMEMBRANE PROTEINS INVOLVED IN HUMAN TUMOR EXPANSION	QUIGLEY, JAMES	SCRIPPS RESEARCH INSTITUTE
3U54CA132384-05S2	COMPREHENSIVE SDSU/UCSD CANCER CENTER PARTNERSHIP 1 OF 2	KLONOFF, ELIZABETH	SAN DIEGO STATE UNIVERSITY
5K08CA138907-03	CD40 PATHWAY IN PANCREATIC ADENOCARCINOMA	BEATTY, GREGORY	UNIVERSITY OF PENNSYLVANIA
5K23CA148964-04	DISSECTING THE MECHANISMS OF IMMUNE TOLERANCE WITHIN THE PANCREATIC TUMOR'S MICRO	ZHENG, LEI	JOHNS HOPKINS UNIVERSITY
5K23CA163672-02	CYCLOPHOSPHAMIDE MODIFIED GM-CSF PANCREATIC TUMOR VACCINE + LISTERIA-MESOTHELIN	LE, DUNG	JOHNS HOPKINS UNIVERSITY
5P01CA080124-12	INTEGRATIVE PATHOPHYSIOLOGY OF SOLID TUMORS	JAIN, RAKESH	MASSACHUSETTS GENERAL HOSPITAL
5P50CA062924-20	SPORE IN GASTROINTESTINAL CANCER	KERN, SCOTT	JOHNS HOPKINS UNIVERSITY
5P50CA101955-09	UAB / UMN SPORE IN PANCREATIC CANCER	BUCHSBAUM, DONALD	UNIVERSITY OF ALABAMA AT BIRMINGHAM
5R01CA095137-10	NK CELL BIOLOGY	LANIER, LEWIS	UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
5R01CA105412-10	TRANSMEMBRANE PROTEINS INVOLVED IN HUMAN TUMOR EXPANSION	QUIGLEY, JAMES	SCRIPPS RESEARCH INSTITUTE
5R01CA120409-07	IMMUNOTHERAPY WITH CAR T CELLS	JUNE, CARL	UNIVERSITY OF PENNSYLVANIA
5R01CA142637-04	CD147 AS A NOVEL TARGET IN HEAD AND NECK CANCER	ROSENTHAL, EBEN	UNIVERSITY OF ALABAMA AT BIRMINGHAM
5R01CA155620-03	RON RECEPTOR IN PANCREATIC CANCER BIOLOGY AND THERAPY	LOWY, ANDREW	UNIVERSITY OF CALIFORNIA SAN DIEGO
5R01CA163441-02	RADIOTHERAPY AS IMMUNOTHERAPY OF TUMORS	STROBER, SAMUEL	STANFORD UNIVERSITY

PROJECT NUMBER	TITLE	PRINCIPAL INVESTIGATOR	INSTITUTION
5R01CA163649-02	TARGETING MUC1-INDUCED TUMOR-STROMAL METABOLIC CROSS-TALK IN PANCREATIC CANCER	SINGH, PANKAJ	UNIVERSITY OF NEBRASKA MEDICAL CENTER
5R01CA169123-02	IMMUNOBIOLOGY AND IMMUNOTHERAPY OF PANCREATIC CANCER	VONDERHEIDE, ROBERT	UNIVERSITY OF PENNSYLVANIA
5R03CA159383-02	OMEGA-3 FATTY ACID EFFECTS ON PANCREATITIS AND ADENOCARCINOMA DEVELOPMENT	JOLLY, CHRISTOPHER	UNIVERSITY OF TEXAS, AUSTIN
5U01CA141468-05	BIOLOGY AND IMMUNOLOGY OF PANCREATIC CANCER STEM CELLS IN A NOVEL MOUSE MODEL	ENGLEMAN, EDGAR G.	STANFORD UNIVERSITY
ZIA BC 010451	CARBOHYDRATE ANTIGEN-BEARING NANOPARTICLES FOR ANTI-ADHESIVES AND TUMOR VACCINES	BARCHI, JOSEPH	NCI
ZIA BC 010649	IMMUNOTHERAPY STRATEGIES FOR GASTROINTESTINAL AND HEPATOCELLULAR CANCER	KAMMULA, UDAI	NCI
ZIA BC 011343	CLINICAL PROTOCOLS FOR THE TREATMENT OF GASTROINTESTINAL CANCER	GRETEN, TIM	NCI
ZIA BC 011344	IMMUNE SUPPRESSOR MECHANISMS IN PATIENTS WITH GI CANCER	GRETEN, TIM	NCI

Table 11. NCI Subprojects with Relevance to Initiative 3

PROJECT NUMBER	TITLE	PRINCIPAL INVESTIGATOR	INSTITUTION
5P50CA101955-09 7894	COMBINED MODALITY TARGETED THERAPY OF PANCREATIC CANCER WITH DEATH RECEPTOR	BUCHSBAUM, DONALD J.	UNIVERSITY OF ALABAMA AT BIRMINGHAM
5P50CA101955-09 7916	DEVELOPMENTAL RESEARCH PROGRAM	BUCHSBAUM, DONALD J.	UNIVERSITY OF ALABAMA AT BIRMINGHAM
2P30CA013330-40 6910	EXPERIMENTAL THERAPEUTICS	GOLDMAN, ISRAEL DAVID	ALBERT EINSTEIN COLLEGE OF MEDICINE
3P50CA102701-10S1 0010	P-4: DIRECT DELIVERY OF IMMUNE-MODULATING THERAPIES TO THE PANCREATIC TUMOR SITE	MUKHERJEE, PINKU	MAYO CLINIC ROCHESTER

PROJECT NUMBER	TITLE	PRINCIPAL INVESTIGATOR	INSTITUTION
5P50CA062924-20 5541	TUMOR ANTIGENS FOR INDIVIDUAL SIGNATURES AND THERAPY	JAFFEE, ELIZABETH M	JOHNS HOPKINS UNIVERSITY

Table 12. NIH Projects with Relevance to Initiative 3

PROJECT NUMBER	TITLE	PRINCIPAL INVESTIGATOR	INSTITUTION	INSTITUTE
5R21AI099128-02	A NEW ANTI-CD27 MONOCLONAL ANTIBODY ADJUVANT FOR PANCREATIC CANCER VACCINES	SCHLESINGER, SARAH JANE	ROCKEFELLER UNIVERSITY	NIAID

FUNDING OPPORTUNITIES

Applications are currently under review from two funding opportunity announcements with relevance to initiative 3.

PA-11-297 Pilot Studies in Pancreatic Cancer (R21)

PA-11-298 Pilot Studies in Pancreatic Cancer (R03)

CURRENT NCI RESEARCH

PREVENT Cancer Preclinical Drug Program – DCP

PREVENT functions as a pipeline to bring new cancer preventing interventions and biomarkers through preclinical development towards clinical trials. Currently (FY15), there are two funded projects with relevance to pancreatic cancer.

Specialized Programs of Research Excellence (SPORE) – through DCTD

SPOREs are a cornerstone of NCI's efforts to promote collaborative, interdisciplinary translational cancer research. SPORE grants involve both basic and clinical/applied scientists and support projects that will result in new and diverse approaches to the prevention, early detection, diagnosis, and treatment of human cancers. Each SPORE is focused on a specific organ site (or a group of highly related cancers) and designed to enable the rapid and efficient movement of basic scientific findings into clinical settings. Individual SPOREs also aim to determine the biological basis for observations made in individuals with cancer or in populations at risk for cancer.

There were a total of five SPOREs conducting PDAC research in FY2013 and FY2014. Each SPORE has four sub-projects, in addition they can support a number of pilot or career enhancement projects. Within those SPOREs there were seven projects with relevance to initiative 3.

Table 13. SPORE Projects with Relevance to Initiative 3

TITLE	PRINCIPAL INVESTIGATOR	INSTITUTION
COMBINED MODALITY TARGETED THERAPY OF PANCREATIC CANCER WITH DEATH RECEPTOR MONOCLONAL ANTIBODIES	BUCHSBAUM, DAVID	UNIVERSITY OF ALABAMA AT BIRMINGHAM
DEVELOPMENT OF ONCOLYTIC ADENOVIRUS TARGETING PANCREATIC CANCER STEM CELLS	CURIEL, DAVID	UNIVERSITY OF ALABAMA AT BIRMINGHAM
AD-MEDIATED INF THERAPY IN COMBINATION WITH CHEMORADIATION FOR PANCREATIC CANCER	DAVYDOVA, JULIA	UNIVERSITY OF ALABAMA AT BIRMINGHAM
BACTERIALLY DELIVERED TUMOR-TARGETED IMMUNOTHERAPY FOR PANCREATIC CANCER	SALTZMAN, DAVID	UNIVERSITY OF ALABAMA AT BIRMINGHAM
OPTIMAL PAIRING OF CHEMOTHERAPY WITH IMMUNOTHERAPY FOR PANCREATIC CANCER	GENDLER, SANDRA	MAYO CLINIC
MECHANISM-BASED USE OF CHK1 (CHECKPOINT PROTEINS) INHIBITORS IN PANCREAS CANCER	MAYBAUM, JONATHAN	UNIVERSITY OF MICHIGAN
TUMOR ANTIGENS FOR INDIVIDUAL SIGNATURES AND THERAPY	KERN, SCOTT	JOHNS HOPKINS UNIVERSITY

Cancer Immunotherapy Trials Network (CITN) – through DCTD

The CITN conducts multicenter research on immunotherapy agents. It is designed to conduct early phase clinical trials using agents with known and proven biologic function and to provide high quality immunogenicity. There are no current, ongoing trials with relevance to PDAC but a study using anti-CD40 for resectable pancreatic cancer is planned.

Intramural Research Program – CCR

Immune Suppressor Mechanisms in Patients with GI Cancer: The aim of this project is to study myeloid derived suppressor cells (MDSC) and other cells with immune suppressor function in patients with cancer. Better understanding of the biology of MDSC cells will help identify novel approaches to eliminate these cells and thereby enhance anti-tumor immunity.

T Cell Alternative p38 Activation Pathway: p38 Mitogen Activated Protein Kinase (MAPK) is a key mediator of inflammatory responses and drugs that target its activity are currently in clinical trials. We have found that T cells possess a unique mechanism for activating p38 downstream of physiologic T cell receptor (TCR) signaling (named the T cell alternative p38 activation pathway). The goal of this project is to understand in detail how p38 is activated in T cells and how this

differs from the mechanism used in most cells, how the alternative pathway is regulated *in vivo*, and how p38 activity may relate to inflammation and autoimmunity. An understanding of these facets of p38 activation may allow it to be targeted specifically in T cells in disorders of immunity and inflammation. Intra-tumor injection of the p38 inhibitor SB203580 into Panc02 pancreatic tumors halts tumor growth and inhibits proinflammatory cytokine production by tumor infiltrating CD4+ T cells (TIL). Intravenous injection of the peptide into KPC mice (a mouse model of human pancreatic cancer) inhibits the progression of pre-neoplastic to neoplastic lesions. Just as with Panc02, proinflammatory cytokine production by TIL is reduced. Examination of 193 human pancreatic cancers revealed that all have CD4+ TIL with alternatively activated p38. Furthermore, there was a highly statistically significant correlation between the percent of TIL with alternatively activated p38 and disease severity. These T cells secreted TNF and IL-17, just like their murine counterparts. High throughput screens have identified a family of small molecules that are cell permeable, non-toxic, and inhibit the alternative p38 activation pathway. Studies in animal models of inflammation will be performed. Our observations establish the alternative p38 pathway as the only mechanism for the activation of this important kinase upon TCR-mediated stimulation, and show that TCR-activated p38 plays a critical role in several mouse models of human disease, and is highly active in human pancreatic cancer. The data support the importance of the alternative p38 activation pathway as a molecular target.

Role of Immune and Inflammation Mediators in Progression of Pancreatic Cancer: The goal of this study is to understand the underlying mechanism of disease aggressiveness with a focus on the role of two interconnected immune and inflammatory mediators - macrophage migration inhibitory factor (MIF) and nitric oxide (NO) - and evaluating their potential as candidate therapeutic targets in PDAC. The following specific aims are pursued in this project:

a) Investigate the association of MIF expression in pancreatic tumors with patient survival
b) Define the mechanistic role of MIF in pancreatic tumor progression
c) Investigate the effect of MIF on tumor growth and metastasis in an orthotopic and genetically engineered mouse model of pancreatic cancer
d) Examine the effect of small molecule MIF inhibitor on pancreatic cancer progression
e) Investigate the association of inducible nitric oxide synthase (NOS_2) expression with survival in resected patients
f) Investigate the role of NO in tumor progression by using NOS_2-deficient mouse model of pancreatic cancer
g) Examine the effect of NOS2-inhibitor on the progression of pancreatic cancer

Clinical Trials

Table 14. CCR Clinical Trials with Relevance to Initiative 3

CLINICAL TRIAL IDENTIFIER	PRINCIPAL INVESTIGATOR	TITLE
NCI-12-C-0111	STEVEN A. ROSENBERG, M.D., PH.D.	PHASE I/II STUDY OF METASTATIC CANCER USING LYMPHODEPLETING CONDITIONING FOLLOWED BY INFUSION OF ANTI-MESOTHELIN GENE ENGINEERED LYMPHOCYTES
NCI-10-C-0166	STEVEN A. ROSENBERG, M.D., PH.D.	A PHASE II STUDY USING SHORT-TERM CULTURED, AUTOLOGOUS TUMOR-INFILTRATING LYMPHOCYTES FOLLOWING A LYMPHOCYTE DEPLETING REGIMEN IN METASTATIC CANCERS
NCI-12-C-0008	RAFFIT HASSAN, M.D.	AN OPEN LABEL PHASE I DOSE ESCALATION STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, PHARMACODYNAMICS, AND MAXIMUM TOLERATED DOSE OF THE ANTI-MESOTHELIN ANTIBODY DRUG CONJUGATE BAY94-9343 IN SUBJECTS WITH ADVANCED SOLID TUMORS
NCI-14-C-0142	CHRISTOPHER R. HEERY, M.D.	AN OPEN-LABEL PHASE I STUDY TO EVALUATE THE SAFETY AND TOLERABILITY OF A MODIFIED VACCINIA ANKARA (MVA)-BASED VACCINE MODIFIED TO EXPRESS BRACHYURY AND T-CELL COSTIMULATORY MOLECULES (MVA-BRACHYURY-TRICOM)
NCI-12-C-0056	JAMES L. GULLEY, M.D., PH.D.	AN OPEN LABEL PHASE I STUDY TO EVALUATE THE SAFETY AND TOLERABILITY OF GI-6301 VACCINE CONSISTING OF WHOLE, HEAT-KILLED RECOMBINANT SACCHAROMYCES CEREVISIAE (YEAST) GENETICALLY MODIFIED TO EXPRESS BRACHYURY PROTEIN IN ADULTS WITH SOLID TUMORS
15-C-0027	AUSTIN G. DUFFY, M.D.	IMMUNE CHECKPOINT INHIBITION (TREMELIMUMAB AND/OR MEDI4736) IN COMBINATION WITH RADIATION THERAPY IN PATIENTS WITH UNRESECTABLE PANCREATIC CANCER

INITIATIVE 4

DEVELOPMENT OF NEW TREATMENT APPROACHES THAT INTERFERE WITH RAS ONCOGENE-DEPENDENT SIGNALING PATHWAYS

Summary: Opportunities now exist—based upon technical advances in structural analyses, generation of genetically engineered mouse models, and new information on signaling pathways and networks, protein engineering, and use of RNA interference for target identification in synthetic lethality screens—to make progress in targeting mutant forms of RAS which drive 95% of PDAC.

FY2013 RESEARCH PORTFOLIO

A total of 36 NCI projects, nine NCI subprojects and two NIH projects following manual review of abstracts have been identified as relevant to initiative 4.

Table 15. NCI Projects with Relevance to Initiative 4

PROJECT NUMBER	TITLE	PRINCIPAL INVESTIGATOR	INSTITUTION
1F31CA180693-01	TARGETING K-RAS EFFECTOR SIGNALING FOR PANCREATIC CANCER TREATMENT	HAYES, TIKVAH	UNIV OF NORTH CAROLINA CHAPEL HILL
1R01CA172431-01A1	INHIBITION OF PANCREATIC CARCINOGENESIS VIA TARGETING C-RAF AND SEH	YANG, GUANG-YU	NORTHWESTERN UNIVERSITY AT CHICAGO
1R21CA164245-01A1	NON-ONCOGENE ADDICTION AS A TARGETED THERAPY FOR PANCREATIC CANCER	FALLER, DOUGLAS	BOSTON UNIVERSITY MEDICAL CAMPUS
1R21CA170995-01A1	ANTI-PANCREATIC TUMORIGENESIS BY INACTIVATION OF SAG/RBX2 E3 UBIQUITIN LIGASE	SUN, YI	UNIVERSITY OF MICHIGAN
1R21CA172997-01A1	TARGETING RAS SIGNALING WITH CDK AND AKT INHIBITION IN PANCREATIC CANCER	AZAD, NILOFER	JOHNS HOPKINS UNIVERSITY
1R21CA175974-01	DIFFERENTIAL NETWORK INTERROGATIONS OF EPITHELIAL TO MESENCHYMAL TRANSITION	MOHAMMAD, RAMZI	WAYNE STATE UNIVERSITY
1R21CA178651-01	A RAS-FAM83A REGULATORY LOOP AS A NOVEL THERAPEUTIC TARGET FOR PANCREATIC CANCER	JACKSON, MARK	CASE WESTERN RESERVE UNIVERSITY
1R21CA179453-01	AN EPIGENETIC SWITCH CONTROLLING PANCREATIC CANCER SUSCEPTIBILITY	MURTAUGH, LEWIS	UNIVERSITY OF UTAH
1R43CA180398-01	PRE-CLINICAL DEVELOPMENT OF A NOVEL PANCREATIC CANCER CHEMOTHERAPEUTIC	CHAN, KYLE	BIOTHERYX, INC.

PROJECT NUMBER	TITLE	PRINCIPAL INVESTIGATOR	INSTITUTION
2R01CA045726-26A1	INTEGRIN ALPHA V BETA 3 PROMOTES RESISTANCE TO EGF RECEPTOR INHIBITORS	CHERESH, DAVID	UNIVERSITY OF CALIFORNIA SAN DIEGO
2R01CA097061-10A1	CHEMICAL GENETIC PROFILING OF ENGINEERED TUMOR CELLS	STOCKWELL, BRENT	COLUMBIA UNIV NEW YORK MORNINGSIDE
2R01CA124586-06A1	KRAS-INDUCED CELLULAR PLASTICITY IN PANCREATIC CANCER	KONIECZNY, STEPHEN	PURDUE UNIVERSITY WEST LAFAYETTE
2R44CA168158-02	DEVELOPMENT OF SEPHB4-HSA AS NOVEL THERAPEUTIC IN CANCER	KRASNOPEROV, VALERY	VASGENE THERAPEUTICS, INC
3P50CA102701-10S1	MAYO CLINIC SPORE IN PANCREATIC CANCER	PETERSEN, GLORIA	MAYO CLINIC ROCHESTER
3R01CA136754-05S1	PHOSPHATIDYLINOSITOL 3-KINASE AND PREVENTION OF PANCREATIC CANCER	LIN, RICHARD	STATE UNIVERSITY NEW YORK STONY BROOK
5F30CA167910-02	K-RAS4A TRAFFICKING AND SIGNALING	TSAI, FREDERICK	NEW YORK UNIVERSITY SCHOOL OF MEDICINE
5F30CA167963-02	DEFINING PI3K P110ALPHA AS A THERAPEUTIC TARGET IN PANCREATIC CANCER	CARPENTER, EILEEN	STATE UNIVERSITY NEW YORK STONY BROOK
5F30CA168063-02	ROLES OF MIR-17-92 CLUSTER MICRORNAS IN K-RAS-INDUCED PANCREATIC TUMORIGENESIS	QUATTROCHI, BRIAN	UNIV OF MASSACHUSETTS MED SCH WORCESTER
5K08CA137153-04	A MODEL FOR PRECLINICAL BIOMARKER DISCOVERY IN PANCREATIC DUCTAL ADENOCARCINOMA	COLLISSON, ERIC	UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
5P01CA117969-08	GENETICS AND BIOLOGY OF PANCREATIC DUCTAL ADENOCARCINOMA	DEPINHO, RONALD	UT MD ANDERSON CANCER CTR
5P50CA101955-09	UAB / UMN SPORE IN PANCREATIC CANCER	BUCHSBAUM, DONALD	UNIVERSITY OF ALABAMA AT BIRMINGHAM
5R00CA149169-04	DEFINING LINEAGE-SPECIFIC DETERMINANTS OF K-RAS "ADDICTION" IN HUMAN CANCERS	SINGH, ANURAG	BOSTON UNIVERSITY MEDICAL CAMPUS

PROJECT NUMBER	TITLE	PRINCIPAL INVESTIGATOR	INSTITUTION
5R01CA042978-27	BIOLOGICAL ACTIVITY OF RAS ONCOGENES	DER, CHANNING	UNIV OF NORTH CAROLINA CHAPEL HILL
5R01CA055360-22	MECHANISMS OF SIGNAL TRANSDUCTION BY RAS PROTEINS	BAR-SAGI, DAFNA	NEW YORK UNIVERSITY SCHOOL OF MEDICINE
5R01CA109525-09	MOUSE MODEL FOR HUMAN PANCREATIC DUCTAL ADENOCARCINOMA	SU, GLORIA	COLUMBIA UNIVERSITY HEALTH SCIENCES
5R01CA116034-08	REGULATION OF K-RAS BY A FARNESYL-ELECTROSTATIC SWITCH	PHILIPS, MARK	NEW YORK UNIVERSITY SCHOOL OF MEDICINE
5R01CA133557-06	TGF-BETA SIGNALING IN PANCREATIC CANCER	BARDEESY, NABEEL	MASSACHUSETTS GENERAL HOSPITAL
5R01CA136754-05	PHOSPHATIDYLINOSITOL 3-KINASE AND PREVENTION OF PANCREATIC CANCER	LIN, RICHARD	STATE UNIVERSITY NEW YORK STONY BROOK
5R01CA140424-04	TARGETING RAS-RAL GEF-RAL EFFECTOR SIGNALING FOR PANCREATIC CANCER TREATMENT	YEH, JEN JEN	UNIV OF NORTH CAROLINA CHAPEL HILL
5R01CA155198-02	DESIGN OF MEK INHIBITOR REGIMENS FOR THE TREATMENT OF PANCREATIC CANCER	LEOPOLD, JUDITH	UNIVERSITY OF MICHIGAN
5R01CA155784-03	DISSECTING HEDGEHOG, TGF BETA AND BMP SIGNALING DURING PANCREATIC TUMORIGENESIS	LEWIS, BRIAN	UNIV OF MASSACHUSETTS MED SCH WORCESTER
5R01CA161112-03	OVERCOMING STROMAL BARRIERS TO THERAPEUTICS IN PANCREAS CANCER	HINGORANI, SUNIL	FRED HUTCHINSON CAN RES CTR
5R01CA163489-02	CHARACTERIZATION OF LCMT IN ANIMAL MODELS OF CANCER	PHILIPS, MARK	NEW YORK UNIVERSITY SCHOOL OF MEDICINE
5R01CA168692-02	TARGETING A NON-CANONICAL RAS-DRIVEN PATHWAY IN PANCREATIC CANCER	CHERESH, DAVID	UNIVERSITY OF CALIFORNIA SAN DIEGO

PROJECT NUMBER	TITLE	PRINCIPAL INVESTIGATOR	INSTITUTION
5R21CA155736-02	ROLE OF CELL CYCLE WITHDRAWAL IN RESTRICTING PANCREATIC CANCER PROGRESSION.	DAVID, GREGORY	NEW YORK UNIVERSITY SCHOOL OF MEDICINE
5R21CA158640-02	SIMULTANEOUS ATTACK OF EPITHELIAL AND STROMAL COMPARTMENTS IN PANCREATIC CANCER	BEACHY, PHILIP	STANFORD UNIVERSITY

Table 16. NCI Subprojects with Relevance to Initiative 4

PROJECT NUMBER	TITLE	PRINCIPAL INVESTIGATOR	INSTITUTION
5P01CA130821-06 5798	CELLULAR INTERATIONS OF TGS-B PATHYWAY MEMBERS AND REGULATORS OF FOREGUT CANCERS	MISHRA, LOPA	UNIVERSITY OF TX MD ANDERSON CAN CTR
5P01CA117969-08 8697	FUNCTIONAL GENOMIC IDENTIFICATION AND CHARACTERIZATION OF THERAPEUTIC TARGETS	DEPINHO, RONALD ANTHONY	UNIVERSITY OF TX MD ANDERSON CAN CTR
3P50CA102701-10S1 0009	HEDGEHOG EGF PATHWAY INTERACTION: NOVEL MULTI-TARGET THERAPY PANCREATIC CANCER	FERNANDEZ-ZAPICO, MARTIN ERNESTO	MAYO CLINIC ROCHESTER
5P50CA101955-09 7896	IDENTIFYING AND TARGETING PATHWAYS OF PANCREATIC CANCER PROGRESSION	LARGAESPADA, DAVID ANDREW	UNIVERSITY OF ALABAMA AT BIRMINGHAM
3U54CA151880-04S1 5058	IMAGE-GUIDED NANOEMBOLIZATION FOR THE TREATMENT OF PANCREATIC CANCER	OMARY, REED A.	NORTHWESTERN UNIVERSITY AT CHICAGO
5U54CA151880-04 5058	IMAGE-GUIDED NANOEMBOLIZATION FOR THE TREATMENT OF PANCREATIC CANCER	OMARY, REED A.	NORTHWESTERN UNIVERSITY AT CHICAGO
5P01CA117969-08 8698	MEK AND PI3K INHIBITION IN THE REGULATION OF PANCREATIC CANCER METABOLISM	CANTLEY, LEWIS C.	UNIVERSITY OF TX MD ANDERSON CAN CTR
5P01CA117969-08 8699	MODELS FOR GENETIC ASSESSMENT OF TUMOR MAINTENANCE GENES IN PDAC	JACKS, TYLER E.	UNIVERSITY OF TX MD ANDERSON CAN CTR
3P50CA102701-10S1 0007	P-1: REGULATION OF PANCREATIC CANCER CELL PRODUCTION AND SURVIVAL BY GSK-3B	BILLADEAU, DANIEL D	MAYO CLINIC ROCHESTER

Table 17 NIH Projects with Relevance to Initiative 4

PROJECT NUMBER	TITLE	PRINCIPAL INVESTIGATOR	INSTITUTION	NIH IC
5R01EB010023-04	DEVELOPMENT OF MOLECULARLY TARGETED IMAGING AGENTS FOR KRAS ACTIVITY IN VIVO	KELLY, KIMBERLY A.	UNIVERSITY OF VIRGINIA	NIBIB
1F32HL117581-01A1	MECHANISMS OF LKB1 FUNCTION IN LYMPHOCYTES IN THE CONTEXT OF KRAS ACTIVATION	SOUROULLAS, GEORGE	UNIV OF NORTH CAROLINA CHAPEL HILL	NHLBI

Funding Opportunities

Currently, there are two open funding announcements with relevance to initiative 4. An additional two funding announcements have closed, and applications are currently under review.

PAR-14-314 New Approaches to Synthetic Lethality for Mutant KRas-Dependent Cancers (U01)

NOT-CA-15-012 NCI Announcement of Interest in Supporting KRAS-Related Research through NIH Parent Program Announcement PA-14-149 "Ruth L. Kirschstein National Research Service Award (NRSA) Individual Postdoctoral Fellowship (Parent F32)

PA-11-297 Pilot Studies in Pancreatic Cancer (R21)

PA-11-298 Pilot Studies in Pancreatic Cancer (R03)

Current NCI Research

RAS Initiative – Frederick National Laboratory for Cancer Research (FNLCR)

Launched in 2013 by NCI Director Dr. Harold Varmus, in conjunction with the Frederick National Lab Advisory Committee (FNLAC), the RAS Initiative is operated as a research hub based at the Frederick National Laboratory for Cancer Research (FNLCR) in Frederick, MD. This research hub functions as a "hub and spokes model", with spokes reaching into all corners of the extramural research community. Intended to deepen knowledge of several aspects of RAS genes, their protein products, role in cell signaling, and functions in health and disease with the explicit goals of improving treatment, diagnosis, and prevention of the many human cancers driven by mutant RAS genes. This initiative involves all sectors of the NCI research community.

The research hub at the Frederick National Laboratory has been able to produce a panel of the most common forms of mutant KRAS proteins. Structural studies of these forms of KRAS are aimed at identifying unique drug pockets, as well interfaces where protein effectors bind are

ongoing. Several drug screening assays have been developed using engineered proteins, imaging platforms in cells, and mouse embryo fibroblasts that each have only one form of RAS. The best assays will be utilized by the National Center for Accelerating Translation to screen large compound libraries to identify drugs that inhibit RAS signaling. Large-scale screens in pancreatic cancer cell lines have been done to abrogate various components in the RAS signaling network in order to identify potential therapeutic targets, and understand the genotypes of pancreatic cancer cells that might be treated with drugs to these targets. A number of potential targets for cell surface epitopes that could be targeted on the surface of KRAS-dependent cancer cells have been identified and are being validated for effectiveness.

Clinical Proteomic Tumor Analysis Consortium (CPTAC) – through CSSI

In cooperation with the RAS Initiative, the NCI's Clinical Proteomic Tumor Analysis Consortium (CPTAC) launched a project to develop quantitative assays for proteins and phosphopeptides involved in RAS signaling. Within the next 1-2 years these assays should allow the amounts and phosphorylation states of tens of RAS and RAS-related proteins to be determined in tumor samples, cell lines, or cancer models in a single run.

Intramural Research Program – CCR

Adoption and Retooling of GEM model for Pancreatic Cancer: There are five main goals of the retooling project involving the GEM model for PDAC.

1. Import and expand, via optimized breeding strategies, a tri-allelic model of PDAC. This model is composed of a PdxCre driver allele (specifically expressing Cre-recombinase in a subset of precursors of pancreatic cells, including ductal epithelium cells of the pancreas), an inducible dominant-activating Kras-G12D allele, and a conditionally expressed mutant p53 allele (p53-R172H).
2. Development of supporting molecular diagnostics tools for animal genotyping.
3. In cooperation with the SAIC Small Animal Imaging Program, set of anatomical criteria (including tumor size/volume, anatomic location, etc.) will be identified to qualify PDAC tumor-bearing animals for enrollment to preclinical cohorts, as well as designing more robust approaches to longitudinal *in vivo* imaging of PDAC lesions and associated metastasis.
4. Following model validation by monitoring the disease time course and reported histopathologic/biomarker features, a pilot multi-arm drug evaluation project will be designed. This project will include placebo, standard-of-care treatments (e.g. gemcitabine), and two experimental arms with candidate therapeutics currently in early stages of clinical development.
5. In partnership with a private Foundation interested in the development of pancreatic cancer diagnostics and therapies, the KPC model will be completed, and applicable workflows will be documented to enable projects for preclinical development with the Foundation's grantee organizations.

Specialized Programs of Research Excellence (SPORE) – through DCTD

SPOREs are a cornerstone of NCI's efforts to promote collaborative, interdisciplinary translational cancer research. SPORE grants involve both basic and clinical/applied scientists and support projects that will result in new and diverse approaches to the prevention, early detection, diagnosis, and treatment of human cancers. Each SPORE is focused on a specific organ site (or a group of highly related cancers) and designed to enable the rapid and efficient movement of basic scientific findings into clinical settings. Individual SPOREs also aim to determine the biological basis for observations made in individuals with cancer or in populations at risk for cancer.

There were a total of five SPOREs conducting PDAC research in FY2013 and FY2014. Each SPORE has four sub-projects, in addition they can support a number of pilot or career enhancement projects. Within those SPOREs there were four projects with relevance to initiative 4.

Table 18. SPORE Projects with Relevance to Initiative 4

TITLE	PRINCIPAL INVESTIGATOR	INSTITUTION
ROLE OF ST6GAL-I-MEDIATED SIALYATION IN THE PANCREATIC TUMOR CELL PHENOTYPE	BELLIS, SUSAN	UNIVERSITY OF ALABAMA AT BIRMINGHAM
ATDC AS A THERAPEUTIC TARGET IN PANCREATIC CANCER	LJUNGMAN, MATS	UNIVERSITY OF MICHIGAN
NFAT TRANSCRIPTION FACTORS AS THERAPEUTIC TARGETS IN PANCREATIC CANCER	BILLADEAU, DANIEL	MAYO CLINIC
INHIBITION OF CDK5 AS A TREATMENT FOR PANCREATIC CANCER	HOLLINGSWORTH, TONY	UNIVERSITY OF NEBRASKA