

Pancreatic Ductal Adenocarcinoma Progress Working Group

Dr. James Abbruzzese

November 4, 2015

Recalcitrant Cancer Research Act (RCRA)

- **September 2012 Congress amended the Public Health Service Act by passing the Recalcitrant Cancer Research Act (RCRA) of 2012**
- **Legislation required the National Cancer Institute (NCI) to develop a scientific framework for research of recalcitrant cancers (cancers with a 5 year survival rate of < 50%)**
 - **NCI identified two cancers with a 5 year survival rate of < 20% and more than 30,000 deaths/year in US**
- **February 2014 NCI submits the *Scientific Framework for Pancreatic Ductal Adenocarcinoma (PDAC)* to Congress**
- **June 2014 NCI submits the *Scientific Framework for Small Cell Lung Cancer (SCLC)* to Congress**
- **Scientific frameworks and meeting reports for PDAC and SCLC**

- **Initiative 1: Understanding the Biological Relationship between PDAC and DM**
 - Rachael Stolzenberg-Solomon*, Jim Abbruzzese, Dana Andersen, Jane Holt, Murray Korc, Gloria Petersen, Sudhir Srivastava
- **Initiative 2: Early Detection and Biomarkers**
 - Gloria Petersen*, James Abbruzzese, Tony Hollingsworth, Jane Holt, Alison Klein, Murray Korc, David Mankoff, Lynn Matrisian, Sheila Prindiville, Sudhir Srivastava
- **Initiative 3: New Therapeutic Strategies in Immunotherapies**
 - Elizabeth Jaffee*, Jim Abbruzzese, Christine Alewine, Toby Hecht, Tony Hollingsworth, Jane Holt, Andrew Lowy
- **Initiative 4: Development of RAS Therapeutics**
 - Lynn Matrisian*, Debbie Jaffe, Murray Korc, Andrew Lowy, Sudhir Srivastava, David Tuveson

* Subgroups' Facilitators

- **NIH Biennial reports:**
 - Information on research grants awarded by the NIH for research related to each cancer
 - Assessment of the progress made in improving outcomes for individuals diagnosed with each cancer, including survival rates
 - An update on the activities pertaining to each cancer related to the RCRA activities
- **Review and update the scientific frameworks no later than 5 years after initial development (2019)**
- **Review and update progress and submit a report to Congress on the effectiveness of the framework no later than 6 years after the initial development (2020)**

- **Extramural Working Groups**
 - Convened an external group of stakeholders for each disease (CTAC Working Groups)
 - Review of status of research
 - Identification of research questions that have not been adequately addressed
 - Recommendations for actions to advance research - initiatives
 - Members include scientific experts, clinicians, and patient advocates
 - Report implementation progress to CTAC at least annually beginning in 2015
- **NCI Action Planning Groups (APG)**
 - Internally track progress by a APG for each disease site
 - Provide data on grants and other projects to NCI leadership and extramural working groups

The primary purpose of the PDAC Progress WG is to monitor NCI's progress of the Scientific Framework sent to Congress in February of 2014.

The Working Group's main objectives are as follows:

- **Assess NCI progress to date**
- **Provide recommendations for process of future annual assessment reports to CTAC**
- **Review and update the scientific framework no later than 5 years after initial development**
- **Submit a report to Congress on the effectiveness of the scientific framework no later than 6 years after the initial development**

- **Provided PDAC Progress WG members with data**
 - FY13 extramural grants and grant supplements, intramural projects, and research contracts
 - Abstracts for each FY 2013 NCI and NIH project coded to 25 percent or greater relevance to pancreatic cancer were reviewed for relevance to PDAC and the four initiatives identified in the scientific framework
 - Information about specific NCI programs and initiatives were identified by representatives from across the NCI Divisions, Offices, and Centers
- **Initiative specific subgroup webinars to assess progress, identify any research gaps, and draft conclusions and recommendations**
- **PDAC Progress WG webinar to review subgroup findings prior to drafting written report**

Initiative 1

Development of an In-depth Understanding of the Biological and Clinical Relationship between PDAC and Recent Onset Diabetes Mellitus (DM)

- **Understand how PDAC mediates DM (T3cDM)**
- **Define specific risk factors to inform potential screening efforts**

Relationships Between Diabetes and Pancreatic Cancer

Pancreatogenic (T3cDM) DM
Islet cell loss

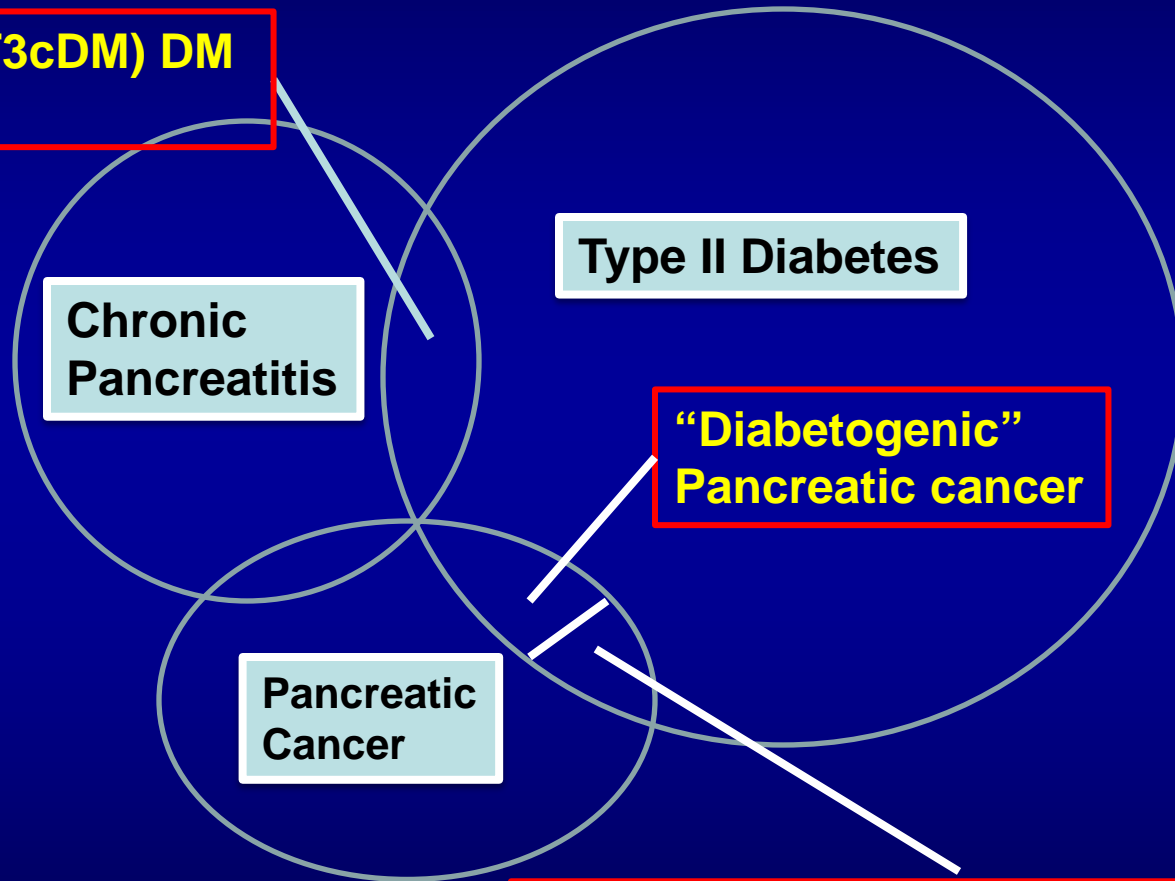
Chronic
Pancreatitis

Type II Diabetes

**“Diabetogenic”
Pancreatic cancer**

Pancreatic
Cancer

Pancreatogenic (T3cDM) DM (PC-DM)
? paraneoplastic



Initiative 1

Summary of Progress

Development of an In-depth Understanding of the Biological and Clinical Relationship between PDAC and Recent Onset DM

Implementation Progress:

- June 2013 National Institute of Diabetes and Digestive and Kidney (NIDDK)-NCI Pancreatitis-Diabetes-Pancreatic Cancer Workshop
 - Recommended NIDDK-NCI develop a funding opportunity announcement for expanding research in the critical areas identified by the workshop
- October 2014 NIDDK-NCI issued joint RFAs for a Consortium to Study Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CSCPDPCC) and a Coordination and Data Management Center
 - Ten Clinical Centers and a Data Management Center were selected and approved for funding September 2015
- July 2015 NIDDK-National Institute of Biomedical Imaging and Bioengineering (NIBIB) sponsored the “Advances in Biomedical Imaging, Bioengineering, and Related Technologies for the Development of Biomarkers of Pancreatic Disease” designed to facilitate the development of clinical studies and imaging research

Initiative 1 Subgroup Update



October 2014 NIDDK-NCI issued joint RFAs for a Consortium to Study Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CSCPDPCC) and a Coordination and Data Management Center

Ten Clinical Centers and a Data Management Center were selected and approved for funding September 2015

The Clinical Centers:

- UC, ALIYE (University of Iowa)
- PANDOL, STEPHEN J (Cedars Sinai LA)
- CHARI, SURESH T. (Mayo Clinic)
- PARK, WALYTER GWANG-UP (Stanford University)
- FISHER, WILLIAM E (Baylor University)
- FOGEL, EVANS (Indiana University)
- FORSMARK, CHRISTOPHER E (University of Florida)
- VAN DEN EEDEN, STEHPEHEN (Kaiser Foundation)
- CONWELL, DARWIN LEWIS (Ohio State University)
- WHITCOMB, DAVID Clement (University of Pittsburgh)

The Data Coordination and Management center:

- FENG, ZIDING (University of Texas-MD Anderson)

Initiative 1 Subgroup

Conclusions and Recommendations



Conclusions

- Initiative implementation on target, too early to assess scientific progress

Recommendations

- Follow the progress of the CSCPDPC awardees
- Publish the proceedings of the NIDDK-NIBIB workshop and consider issuing a joint FOA/RFA on areas of unmet Clinical/Imaging need and identified scientific gaps
- Consider organizing 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

Initiative 2

Summary of Scientific Framework

Develop New Molecular and Imaging Biomarkers for Early Detection of PDAC and its Precursors

- **Issued a Funding Opportunity Announcement (FOA) to support the formation of a Pancreatic Cancer Early Detection Consortium and the formation of a Biospecimen Resource Center**
 - Applications to focus on the development of novel methods to obtain and interrogate pancreatic tissues containing pre-neoplastic lesions
- **Leverage resources from other NCI funded programs**
 - Build strong alliances with other NCI-supported programs:
 - GI and Pancreatic SPORES
 - Early Detection Research Network (EDRN)
 - Consortium for the Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer Clinical Centers (CSCPDPCCs)

Initiative 2

Summary of Progress

Implementation Progress:

- **NCI PAR 15-289, “The Pancreatic Cancer Detection Consortium (U01) published June 30, 2015;**
<http://grants.nih.gov/grants/guide/pa-files/PAR-15-289.html>
 - Multiple receipt dates, first receipt date November 25, 2015
 - Earliest start date, July 2016
- **July 2015 NIDDK-NIBIB sponsored the “Advances in Biomedical Imaging, Bioengineering, and Related Technologies for the Development of Biomarkers of Pancreatic Disease” meeting designed to facilitate the development of clinical studies and imaging research**

Initiative 2 Subgroup

Conclusions and Recommendations

Conclusions

- Initiative implementation on target, too early to assess scientific progress

Recommendations

- Follow release and funding of current and pending NCI PARs as they mature
- Facilitate connections between programs at NIH (e.g., 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 consider issuing a joint FOA/RFA on areas of unmet Clinical/Imaging need and identified scientific gaps

Initiative 3

Implementation of New Immunotherapy Approaches Based on a Deeper Understanding of how PDAC Interacts with its Potentially Immunosuppressive Microenvironment

- **Utilize recent advances in cancer immunology to reverse immunosuppression, and in the use of immune checkpoint blockade agents, vaccines, and T cell-based immunotherapies – to develop new immunotherapies**
- **Support grants dealing with the discovery and validation of new immunotherapy targets with a focus on the combination of immune modifiers in preclinical and clinical studies, and the production of immune-modulatory molecules at Frederick National Laboratory for Cancer Research (FNLCR) to facilitate the initiation of early phase PDAC immunotherapy trials**

Initiative 3

Summary of Progress

Implementation Progress:

- The *Cancer Immunotherapy Trials Network (CITN)* has prioritized pancreatic cancer immunotherapy studies

Initiative 3 Subgroup

Conclusions and Recommendations

Conclusions

- Progress would benefit from a NCI “champion” of immunotherapy

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 stroma 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

Summary of Scientific Framework

Development of New Treatment Strategies that Interfere with *RAS* Oncogene-Dependent Signaling Pathways

- **Five high priority projects for the focus of the NCI's large-scale program on *RAS* at the FNLCR have been identified:**
 1. Pursuing allele specific compounds for those *RAS* alleles most prevalent in human cancer (e.g., *KRAS* G12D and G12V in pancreatic cancer)
 2. Developing *KRAS* selective binding compounds for *KRAS* ablation without allele specificity
 3. Developing imaging methods and screens to identify and disrupt *KRAS* complexes in cells and to monitor their disruption
 4. Mapping the surface of *KRAS* cancer cells
 - identifying epitopes that could be targeted by immunotherapy
 - Identifying proteins that could be targeted for drug delivery by nanoparticles
 5. Developing and conducting next-generation synthetic lethality screens and engineering mice to facilitate these screens

Initiative 4

Summary of Progress

Implementation plan is launched

FNLCR provides oversight for overall RAS project

- CTAC Working Group met with the FNLCR RAS project team to identify joint opportunities relevant to PDAC

Initiative 4 Subgroup

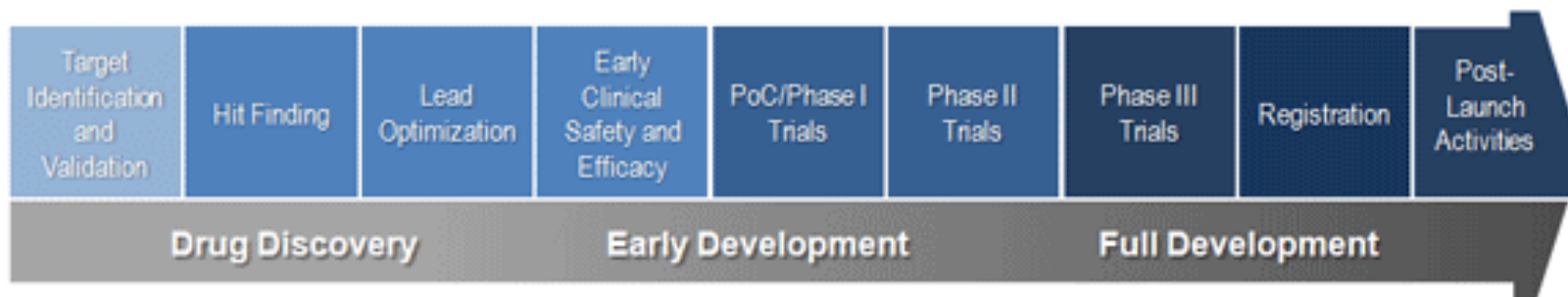
Conclusions and Recommendations

Conclusions

- Implementation plan is launched, but additional information is required to assess scientific progress

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



DRAFT CONCLUSIONS and NEXT STEPS

Draft Conclusions

All of the initiatives within the Scientific Framework are still relevant

- **Initiative 1 (Relationship between PDAC and DM):**

Implementation progress on target

- NIDDK/NCI RFA for a Consortium for the Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer released, grants submitted, review scheduled for Summer 2015, funding FY 2016
- NIDDK/NIBIB meeting, “Advances in Biomedical Imaging, Bioengineering, and Related Technologies for the Development of Biomarkers of Pancreatic Disease” July 22, 2015
- Organize a workshop with the DM community on the utilization of animals and better understand PDAC as it relates to DM subtypes and issue FOA on identified scientific gaps

- **Initiative 2 (Early Detection and Biomarkers):**

Implementation progress on target

- NCI PAR 15-289, “The Pancreatic Cancer Detection Consortium (U01) published June 30, 2015; <http://grants.nih.gov/grants/guide/pa-files/PAR-15-289.html>
- NIDDK/NIBIB meeting “Advances in Biomedical Imaging, Bioengineering, and Related Technologies for the Development of Biomarkers of Pancreatic Disease” on July 22, 2015

- **Initiative 3 (Immunotherapy):**

- **Implementation plan needs further assessment**

- Consideration of a ‘Champion’ of immunotherapy to coordinate efforts within the NCI
- Initiative would benefit from an additional meeting and closer coordination among NCI Programs as well as additional information
- Meeting to address the following areas:
 - FNLCR RAS project and potential relevance to PDAC immunotherapy
 - NCI’s NExT program and potential relevance to PDAC immunotherapy
 - NCI’s CITN and CCR Clinical Trials programs and potential relevance to PDAC immunotherapy and trials being considered
 - Parse out grant information about immunotherapy reagents under development
- Expand initiative to include stromal components

- **Initiative 4 (Development of Ras Therapeutics):**

- **Implementation plan is launched, but need additional information to assess progress**

- Learn more about FNLCR RAS project and relevance to PDAC
- Identify other NCI and non-NCI RAS in PDAC-related research activities
- Track progress on a drug development pathway

Additional information requested

- **RAS Project at FNLCR**
 - FNLCR leadership and the PDAC Progress WG met in September
- **NExT Program potential PDAC agents**
 - Arrange for a survey of the Next Program potential PDAC agents, immunotherapeutic agents and small molecules, to be presented to the PDAC Progress WG
- **Follow release and funding of current and pending RFAs/PAs as they mature**
- **Incorporate information on pancreatic research projects supported across NIH Institutes and Centers**

Next Steps

- **Initiative 1 (Relationship between PDAC and DM):**

- *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 (Early Detection and Biomarkers):**

- *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 (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 (Development of RAS Therapeutics):**

- *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
 - Discuss expanding the initiative to include tumor/stromal biology and the intersection with immunotherapy

PDAC Progress WG Members

Chair: James Abbruzzese

Members:

Christine Alewine

Dana Andersen

Michael (Tony) Hollingsworth

Jane M. Holt

Elizabeth Jaffee

Alison Klein

Murray Korc

Andrew Lowy

David Mankoff

Lynn Matrisian

Gloria Petersen

Rachel Stolzenberg-Solomon

David Tuveson

NIH Liaisons:

Jeffrey Abrams

Dana Andersen

Amy Bulman

James Doroshow

Toby Hecht

Deborah Jaffe

Bhupinder Mann

Sheila Prindiville

Sudhir Srivastava

Questions