Progress in Pancreatic Ductal Adenocarcinoma (PDAC) Research Working Group Update

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NIH NATIONAL CANCER INSTITUTE

Outline

- Primer on Pancreatic Ductal Adenocarcinoma (PDAC)
- Recent Scientific and Clinical Advances
- Brief History of Recalcitrant Cancer Research Act (RCRA)
- October 17, 2018 PDAC Progress Working Group Meeting
- Conclusions and Discussion of Next Steps

Pancreatic Cancer – Basic Statistics

- Highly lethal tumor
- 2% of All Cancer Cases
- 5% of All Cancer Deaths
- Currently the 4th Leading Cause of Cancer Death
  - Lung
  - Colorectal
  - Breast
  - Pancreas
- Projected to become the second leading cause of cancer deaths by 2030

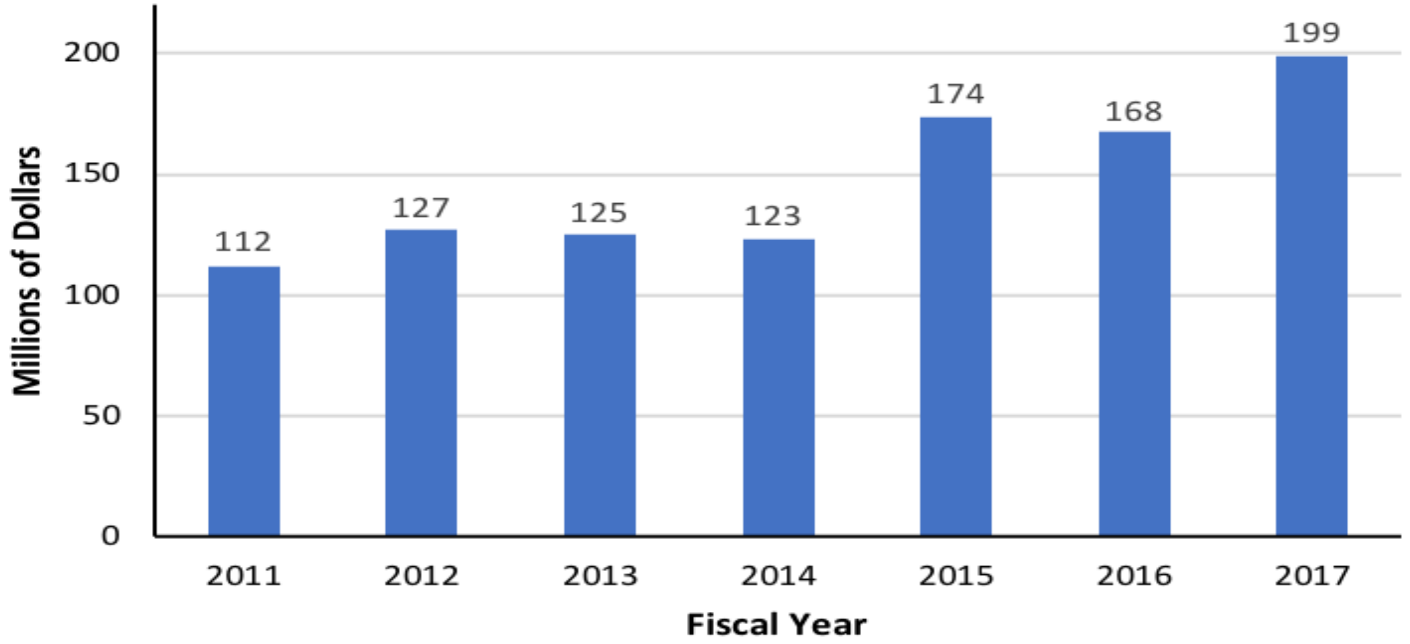
Pancreatic Cancer – Basic Statistics

- Cure is rare and only seen in resected patients.
- Five-year survival trends
  - 1989 – 4%
  - 2013 – 9%
- Clinical Presentation
  - 10% Resectable primary tumor
  - 30% Borderline resectable primary tumor
  - 20% Unresectable primary tumor
  - 40% Metastatic disease
- Tumors are resistant to chemotherapy, radiation, and immunotherapy
  - The mechanism(s) of resistance are diverse and not fully understood
- Survival for many patients is measured in months

Pancreatic Cancer – Risk Factors

- **Environmental**
  - Cigarette smoking (~25%)
  - Chronic pancreatitis
- **Metabolic (>25%)**
  - Obesity
  - Diabetes
- **Genetic**
  - Pancreatic cancer families
  - Hereditary syndromes (BRCA1/2, CDKN2A, PALB2, other)
- **Mucinous pancreatic cysts**
  - Mucinous Cystic Neoplasm
  - Intrapancreatic mucinous neoplasm (IPMN)

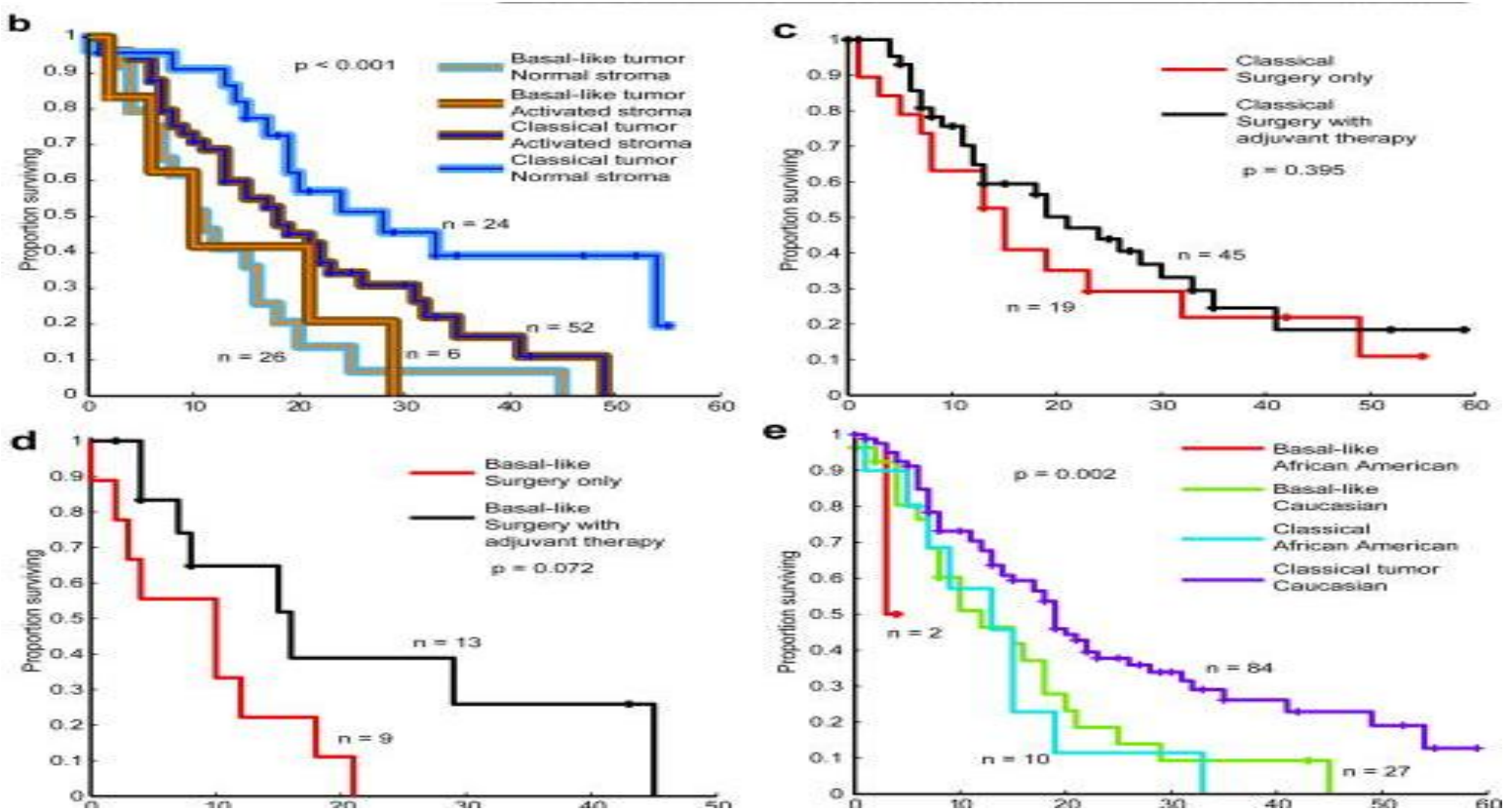
Trends in NIH Funding for Pancreatic Cancer FY2011 - FY2017



Pancreatic Cancer – Recent Scientific Accomplishments

- Initial genomic/transcriptional profiles of pancreatic cancer
  - Moffitt et al. Nature Genetics 47:1168-1178, 2015
    - Tumor specific: Basal vs. Classical
    - Tumor-related stroma: Activated vs. Normal
- Development of GEMMs, patient-derived xenografts (PDX) and organoids
- Importance of tumor-related stroma, stellate cells, & immunocytes
  - Role in mediating resistance to chemotherapy and immunotherapy
- Recognition of the role of diabetes and obesity in pancreatic cancer risk and survival
  - Mechanistic understanding is a major focus of current NCI/NIH efforts

Prognostic Impact of Major Pancreatic Cancer Sub-types

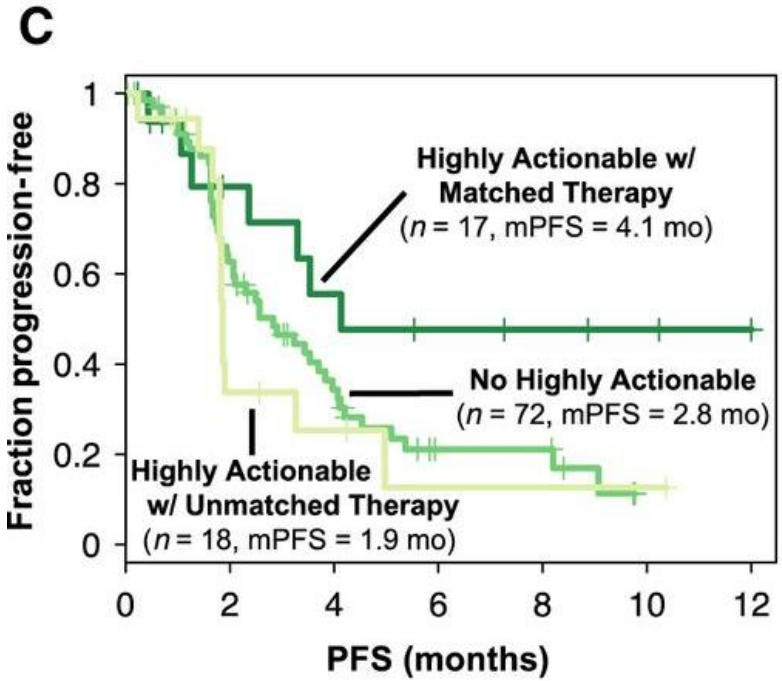


Moffitt et al., *Nature Genetics* 47:1168-1178, 2015

Pancreatic Cancer – Recent Clinical Advancements

- Initial screening efforts for high-risk patients (CAPS Trials)
- Elucidating the natural history of mucinous cystic neoplasms/IPMN
- NGS testing identifies patients with HRD (BRCA1/2, PALB2, etc) but limited targetable mutations with high therapeutic impact
- FDA approval of nab-paclitaxel + gemcitabine (first line) and 5FU + liposomal irinotecan (second line). FOLFIRINOX in the adjuvant setting
- Integration of currently available modalities; neo-adjuvant and adjuvant options that improve resectability and improve survival
- Improved management of local obstructive complications

Treatment outcomes in patients with identified highly actionable biomarkers



Pishvaian, MJ et al., *Clin. Cancer Res.* 2018;24:5018-5027

Brief History RCRA

- Public Health Service Act amended through Recalcitrant Cancer Research Act (RCRA) of 2012
- Legislation requires NCI to develop scientific frameworks for research of two recalcitrant cancers (cancers with a 5 year survival rate of < 50%)
- NCI identifies two recalcitrant cancers – pancreatic ductal adenocarcinoma (PDAC) and small cell lung cancer (SCLC) in 2013
- NCI submits Scientific Frameworks for PDAC (March 2014) and SCLC (June 2014)
- **5-year updates on the Scientific Framework due to Congress in 2019**
- Effectiveness report on the Scientific Frameworks due to Congress in 2020

2014 Scientific Framework for PDAC

Summarized the Literature and Recent Advances in:

- Biology and Genetics
- Risk, Prevention, Screening, & Diagnosis
- Animal Models
- Therapy and Resistance

Proposed Four Scientific Initiatives

1. Development of an in depth understanding of the biological and clinical relationship between PDAC and DM of recent onset
2. Evaluate longitudinal screening protocols for biomarkers for early detection of PDAC and its precursors
3. New therapeutic approaches in immunotherapy
4. Developing new treatment approaches that interfere with RAS oncogene dependent signaling pathways

2019 Scientific Framework Update Process

- PDAC Progress WG reconvened on October 17, 2018 to review the Scientific Framework
  - Provide update of key scientific advances and determine if the initiatives are still scientifically relevant, if they need to be modified, and if there are new opportunities
  - Discuss if they think the NCI is on track in terms of research direction
- Portfolio analyses provided by NCI
  - FY15 - FY17 extramural grants and grant supplements, intramural projects, and research contracts
  - Clinical trials
- Working Group report will inform NCI's 5-year update of Scientific Framework
  - Due to Congress March 2019

PDAC Progress WG Meeting – Oct 2018

- Working Group Chair(s) – James Abbruzzese/Tony Hollingsworth

- Meeting Planning Chairs (based on the 2014 Scientific Framework)
  - Biology (Genomics-Metabolomics-Tumor Biology): Tony Hollingsworth
  - Animal and Human Tissue Models: David Tuveson
  - Risk-Prevention-Screening-Diagnosis: Alison Klein
  - Treatment: James Abbruzzese

PDAC Progress WG Meeting – Oct 2018

Session 1:

NIH Updates

- Sudhir Srivastava: Biomarkers, Early Detection, Screening
- Dana Anderson: Consortium for the Study of Pancreatitis, Diabetes and Pancreatic Cancer (CPDPC)
- Peter Ujhazy- Moonshot (Immunotherapy and Microenvironment)
- Dwight Nissley: RAS Initiative

Session 2-5:

Highlights from Planning Webinars

- Focus on Scientific Progress, Gap & New Opportunities

Session 6:

General Discussion

Progress on the Scientific Initiatives

- **Development of an in depth understanding of the biological and clinical relationship between PDAC and DM of recent onset**
- **Evaluate longitudinal screening protocols for biomarkers for early detection of PDAC and its precursors**
  - Engagement of the EDRN
    - Validation of diagnostic/prognostic biomarkers
  - Consortium for the Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer (CPDPC)
    - DM-PDAC WG; T3cDM DETECT; Chronic Pancreatitis WG; Pediatric INSPIRE2
  - Consortium for Molecular Cellular Characterization of Screen-Detected Lesions

Progress on the Scientific Initiatives

New Therapeutic Approaches - Immunotherapy

- Moonshot Initiative – Immunotherapy and Microenvironment
- Pancreatic Cancer Microenvironment Network (PaCMEN)
  - Dissect microenvironment cellular heterogeneity
  - Disrupt immune/drug privileged microenvironment
  - Disrupt cellular cross talk
  - Reprogram PDAC microenvironment toward immunoresponsiveness

Progress on the Scientific Initiatives

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

- (K)RAS Targeted
  - Discover small molecules that bind/inhibit (K)RAS directly
  - Disrupt (K)RAS/effector molecule interactions
  - Delineate (K)RAS/RAF signaling complexes at the cellular membrane
- Synthetic Lethality
  - RAS Synthetic Lethality Network developed
    - Current focus: Target discovery and validation

October 17, 2018 PDAC Progress Working Group Meeting

Horizon Questions and Opportunities

Tumor Biology

- Continued understanding of microenvironment and contribution to drug resistance and immunosuppression
  - Biomechanical/biophysical properties
  - Basic mechanisms of metastasis; role for in vivo imaging
- Continued focus on (K)RAS signaling with pharma collaborations to efficiently move basic observations to the clinic
- Understand systemic and local metabolic perturbations
  - Pathophysiology of cachexia and sarcopenia
- Role of the microbiome
- Enable correlative science in clinical trials

Animal Model Systems

- Ongoing refinement of existing GEMMs
  - Cellular precursor targeted induction approaches, role of permissive insults: pancreatitis, diabetes, obesity
  - Expanded study of high risk precursor lesions: PanIN3, IPMN
  - Models for metastasis and cachexia/sarcopenia
  - Models that facilitate study of immunotherapy
  - Expand use of imaging in assessment of model systems
- Develop additional models including stromal elements

Risk, Prevention, Screening, Diagnosis

- Expansion of research on PDAC and DM
  - Role of glucose intolerance
  - Role of insulin in pathophysiology
- Research into the mechanism(s) of increased risk conferred by obesity
- Greater understanding of the natural history of IPMN and MCN
  - Expanded research into novel imaging strategies - detection of early invasive disease
- Continued research into heritable causes of pancreatic cancer and expansion of germline testing for both patients and families
- More minority representation in studies of pancreatic cancer risk and prevention
- Broaden efforts directed at early detection of PDAC in high risk and average risk patients

Treatment

- Continue efforts to directly or indirectly target KRAS
- Enhance precision medicine efforts to allow more rapid turn-around of NGS data
- Develop strategies to reverse cachexia and sarcopenia
  - Targeting metabolic alterations in PDAC for diagnosis and therapy
- Improve tissue acquisition methods to facilitate conduct of correlative science within clinical trials
- Increase access of patients to trials; include minority populations
- Novel immunotherapy strategies as the understanding of the tumor suppressive microenvironment increases
- Expand understanding of tumor and microenvironment heterogeneity

PDAC Progress WG Meeting: Overall Summary

- There have been scientific advances in PDAC biology; risk, prevention, screening, & diagnosis; and therapy to varying degrees
- The NCI has been responsive to the research directions outlined in the 2014 Scientific Framework
- The 2014 Scientific Framework is still scientifically relevant
- The 2014 initiatives have not been completed, they need to be updated. There are additional scientific opportunities that should be prioritized and targeted

Next Steps

- Finalize report of WG and circulate to CTAC members for acceptance (December 2018)

- NCI updates Scientific Framework for submission to Congress by March 1, 2019

2018 PDAC Progress WG Members

Chair: James Abbruzzese/Michael (Tony) Hollingsworth

Members:

Christine Alewine
Sunil R. Hingorani
Tony Hollingsworth
Jane M. Holt
Alison Klein
Murray Korc
Theodore S. Lawrence
Andrew Lowy
Anirban Maitra
David Mankoff
Lynn Matrisian
Gloria Petersen
Rachel Stolzenberg-Solomon
David Tuveson
Robert Vonderheide

NIH Liaisons:

Carmen Allegra, Dana Anderson, James Doroshow, Toby Hecht, Deborah Jaffe, Grace Liou, Margaret Mooney, Dwight Nissley, Sheila Prindiville, Sudhir Srivastava, Peter Ujhazy, Amy Williams

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