Consortium for Pancreatic Ductal Adenocarcinoma (PDAC) Translational Studies on the Tumor Microenvironment (RFA)

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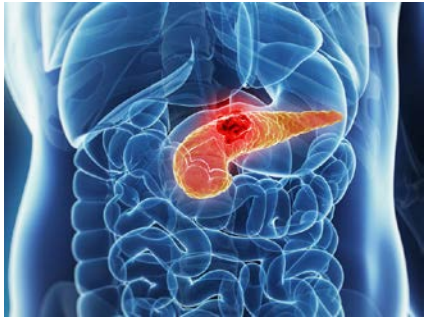
NIH NATIONAL CANCER INSTITUTE

Introduction

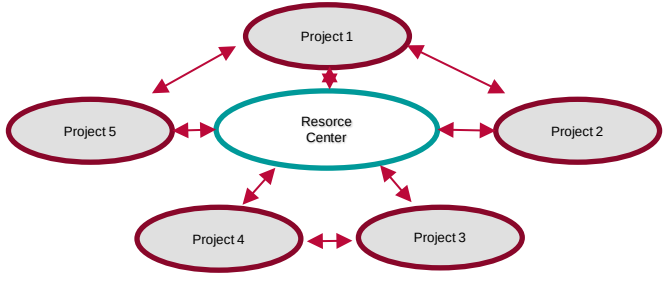


- Congress-driven initiative in recalcitrant cancers
- DCTD Workshop recommends to create opportunities in research of PDAC to increase success of immunotherapy
- Blue Ribbon Panel Cancer Immunology Working Group recommendation 2: The Cancer Immunity Atlas

Purpose of the RFA

- To stimulate research in the area of PDAC microenvironment with the ultimate goal of understanding the interaction between tumors and the microenvironment in order to design new immunotherapy and other treatment interventions

Plan: To Create a PDAC Microenvironment Consortium

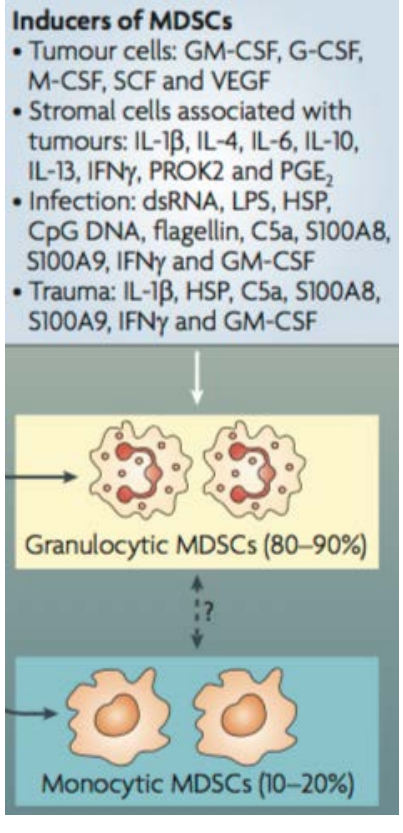


Background

- Immunotherapy achieved recently major advances in liquid and solid cancers (antibodies, checkpoint inhibitors, cellular therapy)
- Pancreatic cancer is considered a “immunologically cold tumor” due to:
  - Absence of effector T cells in the tumor microenvironment
  - Complex immunosuppressive tumor infiltrate (T-regs, MDSC, regulatory B cells)
  - Desmoplastic tumor stroma that can support tumor growth

However:

- New evidence suggests ways to reprogram PDAC microenvironment by:
  - normalizing structural proteins (hyaluronan, collagen, osteonectin)
  - normalizing an immunologically pro-tumor environment to a less growth-supportive environment
  - reversing epithelial-to-mesenchymal transition



Reprogramming tumor microenvironment: Peg-Hu-Hyaluronidase in combination with Nab-Paclitaxel and Gemcitabine in PDAC

(Phase 2, NCT 01839487)

Endpoint/Population	HPG	PG	P-value
ORR			
N = 135	25/74 (34%)	14/61 (23%)	0.17
HA^{High} N = 34	12/17 (71%)	5/17 (29%)	0.02
HA^{Low} N = 28	9/18 (50%)	5/10 (50%)	0.94
PFS			
N = 135	42/74; 5.7 months	39/61; 5.2 months	0.10
HA^{High} N = 48	12/25; 9.2 months	15/23; 4.3 months	0.03
HA^{Low} N = 58	22/36; 4.8 months	15/22; 5.6 months	0.81

Hingorani et al, ASCO 2015

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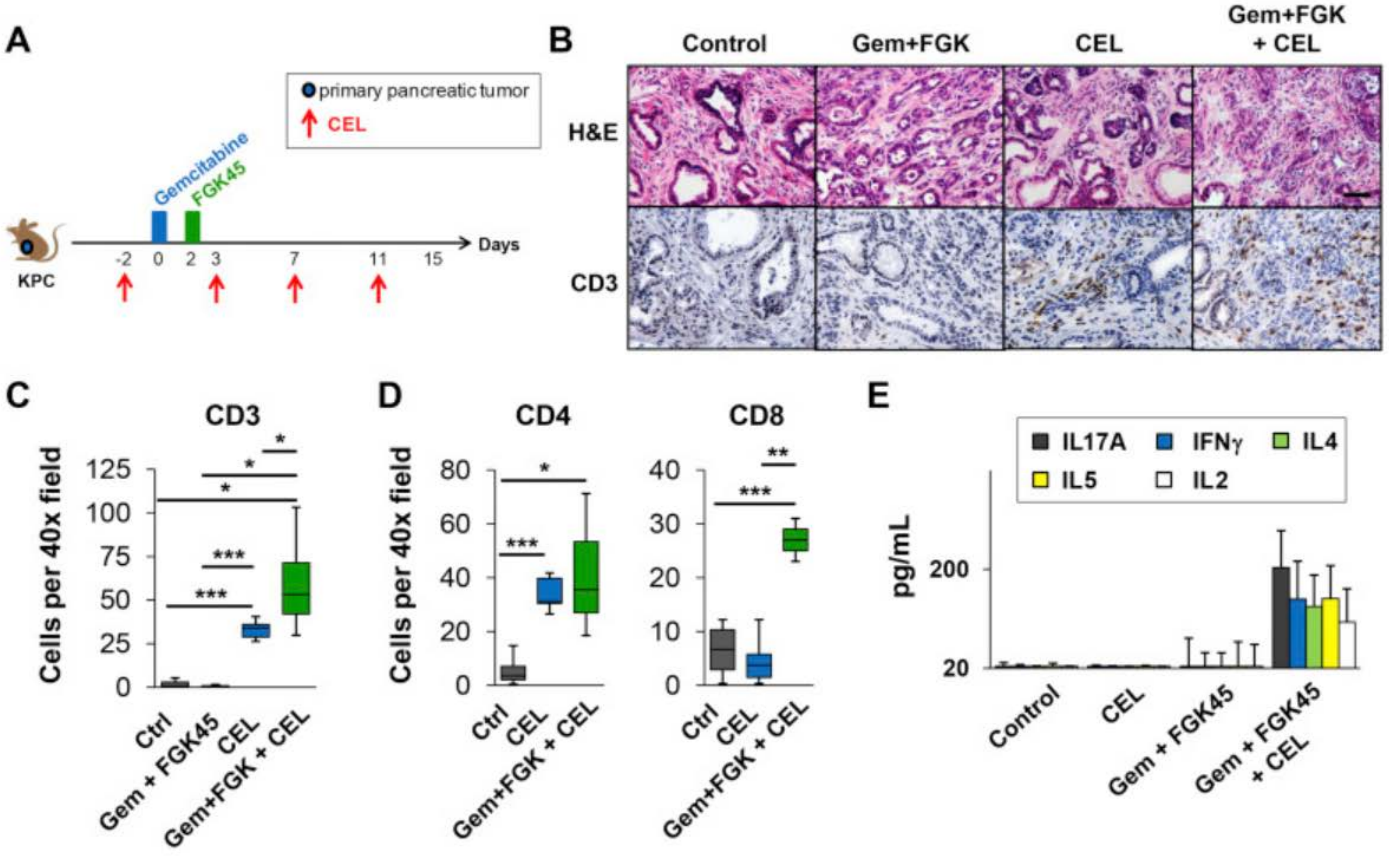
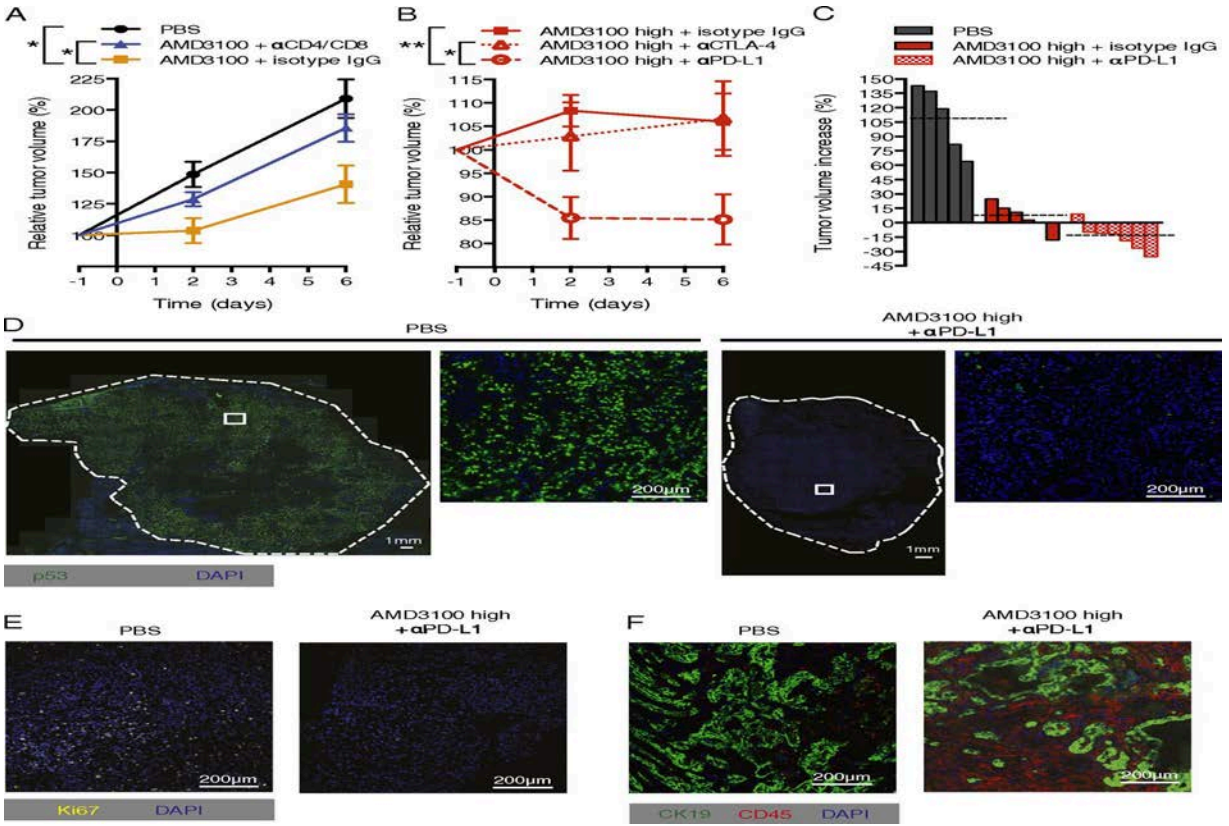
Reprogramming tumor microenvironment: Macrophage depletion renews CD8 T-cell infiltration



Beatty et al, Gastroenterology, 2015

Reprogramming tumor microenvironment: Inhibition of CXCR4 by AMD3100 and immune elimination of PDA cells.



Christine Feig et al. PNAS 2013;110:20212-20217

What is needed?

- A deeper understanding of the complex PDAC microenvironment including
  - its individual components
  - their interactions with tumor
  - their potential role in facilitating immunotherapeutic and other interventions
- DCTD Precision Medicine initiative 2016:

Administrative Supplements to Support Studies of How the Microenvironment of Pancreatic Ductal Adenocarcinoma (PDAC) Affects Immunotherapy

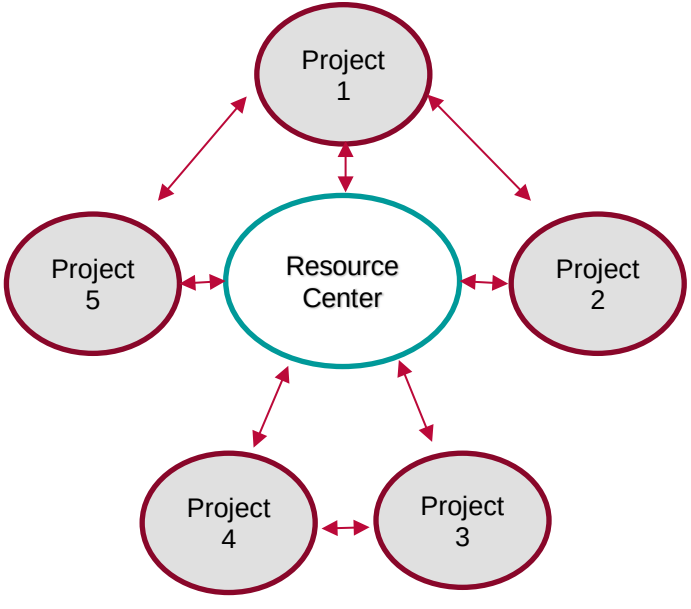
  - 1 year pre-clinical supplements solicited, 36 appl. received
  - 9 were funded (all had priority scores of ≤18)

Selected administrative supplement titles

- Targeting the granulocyte/fibroblast axis to overcome immunosuppression in pancreatic ductal adenocarcinoma *(Columbia University)*
- Modifying the tumor microenvironment to enhance engineered T cell therapy for PDAC *(Fred Hutchinson Cancer Research Center)*
- Effects of pancreatic cancer microenvironment on tumor immune responses *(University of Nebraska)*
- Genetic and transcriptional identification of immunogenic human pancreatic cancer subtypes *(Sloan Kettering Institute for Cancer Research)*
- Therapeutic modulation of immune microenvironment in pancreatic cancer *(University of Michigan)*
- Extracellular matrix-targeted immunocytokines for pancreatic cancer treatment *(Massachusetts Institute of Technology)*
- The tumor micro-environment in early metastasis of pancreatic ductal adenocarcinoma *(Einstein College of Medicine)*
- How the microenvironment of pancreatic ductal adenocarcinoma affects immunotherapy *(Washington University)*
- Differences of microenvironment characteristics between PDAC primary tumor and its metastases *(University of Pennsylvania)*

Consortium

- 5 Translational Single Project Grants (U01):
  - Translational research leading to early phase testing of interventions developed by project
  - Utilization and sharing of specimens from ongoing clinical trials
  - Pre-clinical models and correlative studies
- 1 Resource Center (U24)
  - Administrative support of the consortium including monthly conference calls, annual meetings, communication and oversight
  - Bioinformatics support that would allow centralization of data resources generated by the consortium (GDC)
  - Coordinating the sharing of specimens and models; distribution of consortium-generated resources
  - Creation and maintenance of the consortium website
  - Assistance with the collection of data for the NCI



Evaluation Criteria

- **For the U01 projects:**
- Scientific output of pre-clinical studies and their impact on state of science through publications and spin-off of new funded projects
- Discoveries that lead to the development of predictive, and response monitoring assays
- Successful initiation of early phase clinical trials (if proposed) with adequate accrual and potential to move to higher stage clinical testing
- Number and quality of collaborative studies among members of the consortium
- Number of resources produced by the consortium (models, shared genomic data)
- Overall novelty of interventions designed

- **For the Resource Center U24**
- Fulfillment of specific aims delineated by the needs of the consortium
- Quality and efficient distribution of resources to the consortium
- Successful management of data generated by U01 sites
- Assistance with publications and with NCI's periodic evaluation of the consortium

Current portfolio

Search of current grants relevant to RFA:

- 37 grants:
  - 1 U01
  - 1 R33
  - 6 R21
  - 1 R03
  - 15 R01
  - 1 R00
  - 1 K99
  - 1 K23
  - 4 F31
  - 2 F30
  - 1 U54
  - 3 P50 (only partial relevance)

Budget

Consortium Component	Number of Sites	Total Cost/ Year/Site ($)	Total Cost/ Year ($)	Total Cost/ 5 Years ($)
U01	up to 5	0.5 M	2.5 M	12.5 M
U24	1	0.5 M	0.5 M	2.5 M
		Total	3.0 M	15.0 M

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