PDAC Stromal Reprogramming Consortium (PSRC)
RFA-CA-21-041/-042
Webinar

Peter Ujhazy (DCTD)
Jeff Hildesheim (DCB)

August 31 & September 3, 2021

https://www.cancer.gov/about-nci/organization/dcb/funding/resources
PDAC Clinical & Biological Challenges

• Standard of care for advanced PDAC remains highly ineffective and involves combinations of surgery, chemotherapy and radiation that primarily target the tumor mass

• Systemic palliative gemcitabine treatment did little to address the bleak 5% survival rate of PDAC patients

• FOLFIRINOX (combined 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin) only modestly extended the median overall survival from 6.8 to 11.1 months; other drugs (olaparib, sunitinib) have limited use

• Recent attempts to enhance drug delivery and modulate the vascular & immune microenvironment (TiME) only resulted in partial clinical successes

• The ongoing disconnect between basic and translational research have precluded comprehensive mechanistic characterization of stromal targets

• Further exacerbated by insufficient biological studies on the role of stroma as a co-organizer of tumor fate
PSRC Overarching Objectives

To address the outstanding challenges and gaps by:

• Developing a community of PDAC researchers that will expand upon traditional tumor-centric studies and ongoing immuno-oncology efforts by emphasizing additional TME elements driving PDAC progression and response to therapy

• Adopting a comprehensive “Tumor-TME Co-Organizer” research model in the pursuit of novel biology-backed targets that disrupt these multi-dimensional tumor sustaining dynamics

• Informing the design and testing of more effective combinatorial approaches in pre-clinical platforms and near future clinical trials

And more broadly:

• Using PDAC (and the PSRC program) as a model system to stimulate further studies of TME as a co-organizer in other cancer platforms
PSRC Scientific Areas of Interest

• Build upon and replace the Moonshot Pancreatic Cancer Microenvironment Network (PaCMEN) – primarily focused on immuno-oncology

• Bridge basic/mechanistic science with preclinical/translational science by
  • Study of non-immune cellular microenvironment drivers of tumor progression and response to therapy
  • Investigation of extracellular matrix/stromal modulators of epithelial cell behavior
  • In depth characterization of human PDAC TME pre-post SOC therapy
  • Preclinical testing new/repurposed combinatorial interventions

• Complement other ongoing NCI-sponsored programs (SPOREs, RAS Initiative, Pancreatic Cancer Cohort Consortium, and Pancreatic Cancer Detection Consortium)

• PSRC program intends to further cultivate and support tumor cell intrinsic and immuno-oncology studies, but they must also triangulate with the key basic and translational areas highlighted here
Cancer-Associated Fibroblast influence (CAF):

- Activated CAFs are the primary source of desmoplasia and creation of tissue stiffness, vascular collapse, and immunologically cold TiME, however
- Disruption of ECM and interstitial pressure or elimination of $\alpha$SMA$^+$ CAFs and/or blockade of associated Shh and TGF$\beta$ signaling has disastrous effects

PDAC non-Immune Stromal Dynamics: role of numerous other stromal cell types remain poorly understood and understudied:

- Neural-tumor interactions in tumorigenesis and progression
- Endothelial-tumor interactions in aggressiveness
- Infiltrating adipocyte/adipose tissue-mediated therapy resistance

PDAC Microbiome: an often-overlooked TME component
PSRC Network Framework

**Structure:**
- 6x U01 Research Programs, with each U01
  - Complementary Multi-PI & integrated Basic + Translational Research Areas
  - Access to clinical specimens/derivatives (PDXs, organoids, lines) & computational/systems biology infrastructure
- 1x U24 Coordinating & Data Management Center

**Networking and Synergy:**
- **Restricted funds** for inter-U01 collaborations (15%)
- **Working group** activities to address common goals, challenges and opportunities
- **Sharing** of tools, reagents and resources
- **Required** Steering Committee-led meetings
- **Inclusion of Associate Members** (from relevant NCI programs)
Non-Responsive Applications

Research Projects will be considered non-responsive to the PSRC RFA if applications:

- **Do not propose a combination** of basic/mechanistic areas and preclinical/translational areas of study – refer to RFA Part 2/Section IC (Areas of Scientific Priority and Interest) for examples

- **Are not hypothesis testing**

- **Do not propose to study** PDAC across the tumor-TME continuum, or

- **Focus solely on tumor cell intrinsic and/or immune-oncology** studies that fail to triangulate with non-immune stromal elements
Read the PSRC RFA carefully:

• In initial planning, look for the “must” have components
• When writing, look for the “Describe the…” prompts within each sub-section
• Place emphasis on what the reviewers are looking for in the Scored Review Criteria section
  • “Specific to this FOA: How will…”
  • “Specific to this FOA: How well does…”
Data Sharing and Consortium Integration

New awardees are expected to adhere to PSRC data use and sharing policies:

- Deposition of data, protocols and SOPs with the PSRC Coordinating & Data Management Center (CDMC)
- Standard NIH Public Access, Data Sharing and Unique Resource Sharing policies

New awardees are also expected to participate in PSRC Working Groups, monthly Steering Committee Meetings and bi-annual Face-to-Face Meetings

- The PD/PI (or MPI) is required to serve as a voting member of the PSRC Steering Committee
The Coordinating and Data Management Center (CDMC) U24

Key Roles

• Provide a **centralized administrative infrastructure** to support and coordinate the activities of the PSRC Steering Committee and U01 research projects;

• **Facilitate and strengthen collaborations** within the PSRC, and promote PSRC interaction and collaboration with NCI-sponsored programs and resources;

• Provide multidisciplinary **analytic expertise** and application of statistical and computational tools in support of U01 research projects when appropriate;

• Develop **data integration and management** methods to enhance PSRC research capacity;

• Ensure PSRC **compliance with NIH and NCI policies**;

• Assist the PSRC in **identifying and developing collaborative opportunities**;

• Develop **outreach activities** to promote the exchange of scientific outcomes both within PSRC and between PSRC and the public
The Coordinating and Data Management Center (CDMC) U24

Expertise needed

• Network coordination and collaboration
• Data Management and Analytical support
• Basic and translational and clinical research expertise
Mechanisms of Support & Funding

**Mechanism of support:** U01 / U24 – Cooperative Agreement

*Used to accommodate substantive programmatic involvement to facilitate integration between U01 and U24 grants*

**Application Type:** All submissions will be Type 1 (new applications) and Multi-PI (U01s). *No resubmissions are allowed; a Leadership Plan is required; and each PI/MPI must have a minimum of 1.2 CM Effort throughout the life of the grant.*

**Budget:** Application budgets are limited to $600,000 / year in direct cost. *Applicants must budget for travel to biannual PSRC face-to-face meetings*

**Project Period:** Up to 5 years.

**Note on Eligible Applicants:** Foreign (non-U.S.) institutions, non-domestic (non-U.S.) components of U.S. Organizations, and foreign components are eligible to apply.

**Anticipated Number of Awards:** Up to six U01 awards and one U24 award *Contingent upon submission of a sufficient number of meritorious applications.*
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Letter of Intent (LOI)

Highly encouraged, but not required. Not binding and does not enter into review.

Standard elements:
• Descriptive title of proposed activity
• Name(s), address(es), telephone number(s) of the PD(s)/PI(s)
• Names of other key personnel
• Participating Institution(s)
• Number and title of funding opportunity (RFA-CA-21-041 or -042)

Additional recommended information:
• Provide a brief summary of the Research Project.
• Include relevant expertise and Keywords

Email LOI to Peter Ujhazy: pu5s@nih.gov
Significance:
• How does the proposed U01 Research Project help address significant challenges in identification, integration and mechanistic evaluation of tumor and TME elements as co-drivers of PDAC progression and response to therapy; and how might it enhance our understanding of cancer progression and inform future therapeutic strategies?

Approach:
• Rationale for the tumor-TME targets, pathways, etc that will be studied
• Strength and complementarity of multidisciplinary team design and approaches to iteratively bridge basic and translational research across the tumor-TME continuum in each U01 Research Project
Approach (continued):

- Does Project involve hypothesis-driven approaches that bridge basic/mechanistic and preclinical/translational research to address unresolved PDAC challenges within the tumor-microenvironment continuum?
- How well matched are the Built-In Capabilities to the needs of the overall Research Project? Are they essential to the goals of bridging the basic/mechanistic and preclinical/translational aspects of the U01 Research Project?

Environment

- How well does the scientific environment at the participating site(s) stimulate trans-disciplinary research collaborations; and the iterative flow between basic/mechanistic and preclinical/translational researchers?
- Are the Resource Sharing plans conducive for the sharing of data, model organisms, human and non-human specimens, tools, reagents, therapeutics, genomic data, IP, know-how and proprietary techniques and inventions within and outside the institution, especially with other members of the PSRC?
Review Information

• Applications will be evaluated for scientific and technical merit by an appropriate Scientific Review Group convened by the NCI, using the stated review criteria.

• As part of the scientific peer review, all applications:
  - May undergo a selection process in which only those applications deemed to have the highest scientific and technical merit will be discussed and assigned an overall impact score – applications will not be percentiled.
  - Will receive a written critique.
• The following will be considered in making funding decisions:
  ➢ Scientific and technical merit of the proposed project as determined by scientific peer review
  ➢ Relevance of the proposed project to program priorities

• Applications will compete for available funds with all other recommended applications submitted in response to these FOAs.

• Following initial peer review, recommended applications will receive a second level of review by the NCAB/NCI

• The review panel roster will be available in eRA Commons **30 days prior to review.** Applicants may contact the Scientific Review Officer with concerns prior to review.
### Key Dates

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<tr>
<th>LOI Due Date</th>
<th>Application due Date</th>
<th>Review Date</th>
<th>Earliest Anticipated Start Date</th>
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<tbody>
<tr>
<td>October 1, 2021</td>
<td>November 1, 2021</td>
<td>March - May 2022</td>
<td>July 2022</td>
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#### Timeline:

- **YR-01**: July 2022
- **YR-02**: July 2023
- **YR-03**: July 2024
- **YR-04**: July 2025
- **YR-05**: July 2026

- PSRC Charter Implem
- Working Groups Dev

(15% Restricted Funds/YR for Collaborative Efforts)
Agency Contacts

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THANK YOU!
QUESTIONS?