PDAC Stromal Reprogramming Consortium (PSRC)

RFA-CA-21-041/-042

Webinar

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NIH NATIONAL CANCER INSTITUTE

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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)

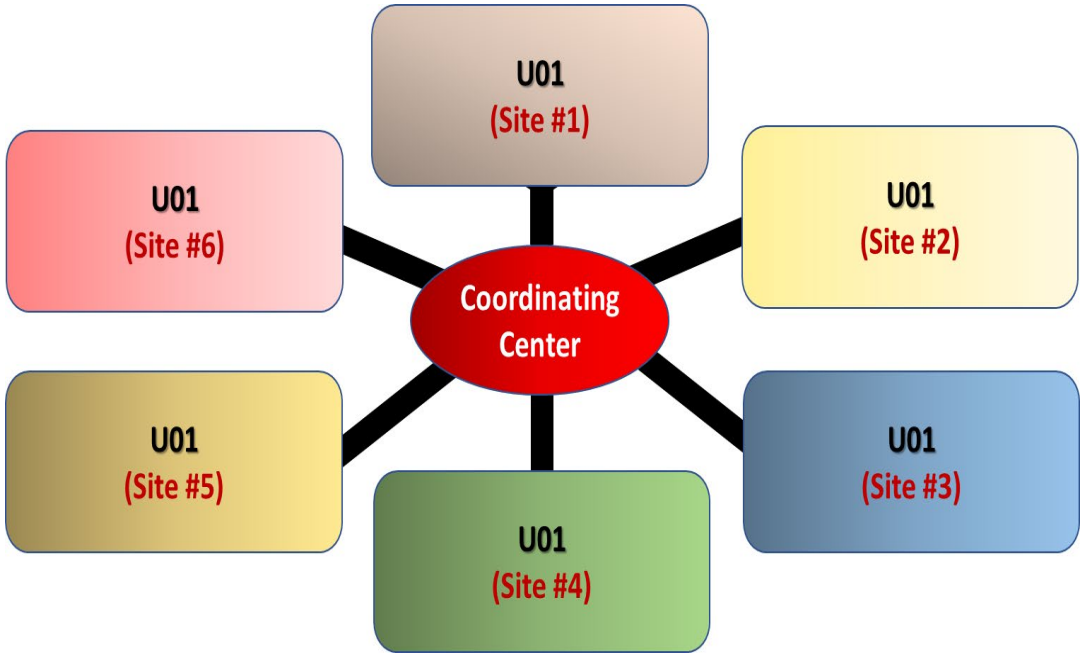
- PSRC program intends to further cultivate and support tumor cell intrinsic and immuno-oncology studies, but they must also triangulate with the key basic and translational areas highlighted here

Stroma-Derived Influence on PDAC Recalcitrance
(Understudied and Underdeveloped Areas)

- **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 αSMA^+ CAFs and/or blockade of associated Shh and TGFβ 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

Disparities Research

PSRC Network Framework



NCI Programs/Resources

CTEP
SPOREs
PDMC

ETCTN
PDXNet
ROBIN

ARTNet,
CSBC
PSON

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

Non-Responsive Applications

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

PHS 398 Research Plan: 12 Page Limit

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

PHS 398 Research Plan: 12 Page Limit

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.

Review Information (continued)

- 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

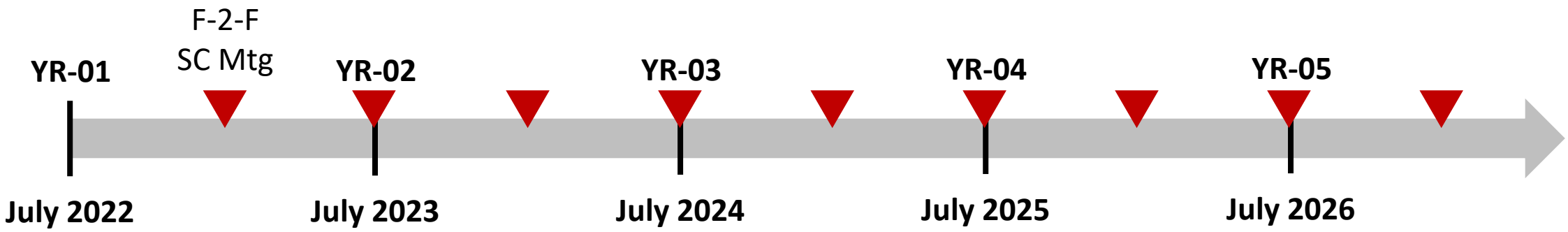
- Applications will compete for available funds with all other recommended applications submitted in response to these FOAs.

- 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

LOI Due Date	Application due Date	Review Date	Earliest Anticipated Start Date
October 1, 2021	November 1, 2021	March - May 2022	July 2022



- PSRC Charter Implem
- Working Groups Dev

(15% Restricted Funds/YR for Collaborative Efforts)

Agency Contacts

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THANK YOU!

QUESTIONS?

www.cancer.gov www.cancer.gov/espanol