PDAC Stromal Reprogramming Consortium (PSRC)

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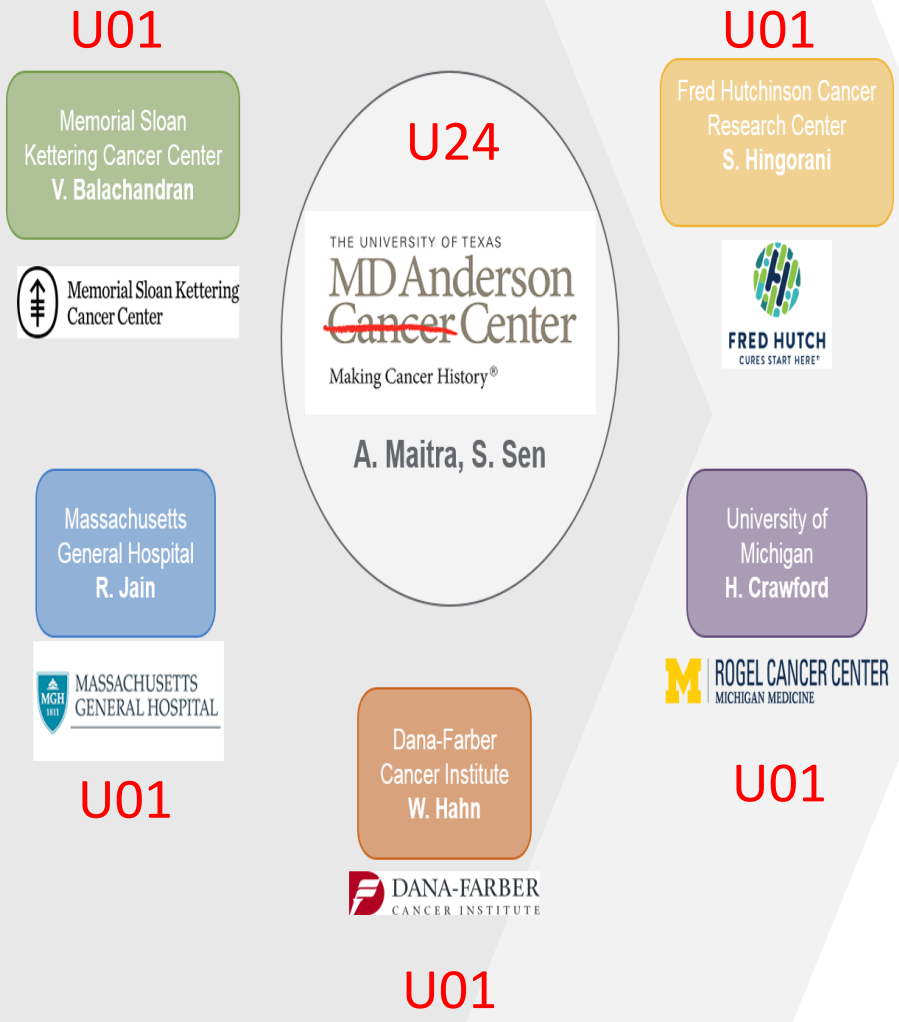
PDAC Clinical & Biological Challenges

- 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

PaCMEN
Pancreatic Cancer Microenvironment Network

CANCER MOONSHOT
RESEARCH INITIATIVES



- High productivity: 74 Cancer Moonshot funding-referenced publications cited 636x.
- Attracted 20+ additional investigators (Associate Members) from 12 US institutions.
- Several bi-and tri-lateral collaborative projects were already started.
- Resource Center (U24 PATReC) provides services that help to build and strengthen the ties between PaCMEN Full Members and Associate Members.
- Losartan studies (U01; Jain, PI) helped inform clinical testing in 2 trials (NCT03563248, NCT01821729) with promising results.
- Neoantigen vaccine studies (U01; Balachandran, PI) led to a clinical trial (NCT04161755).

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

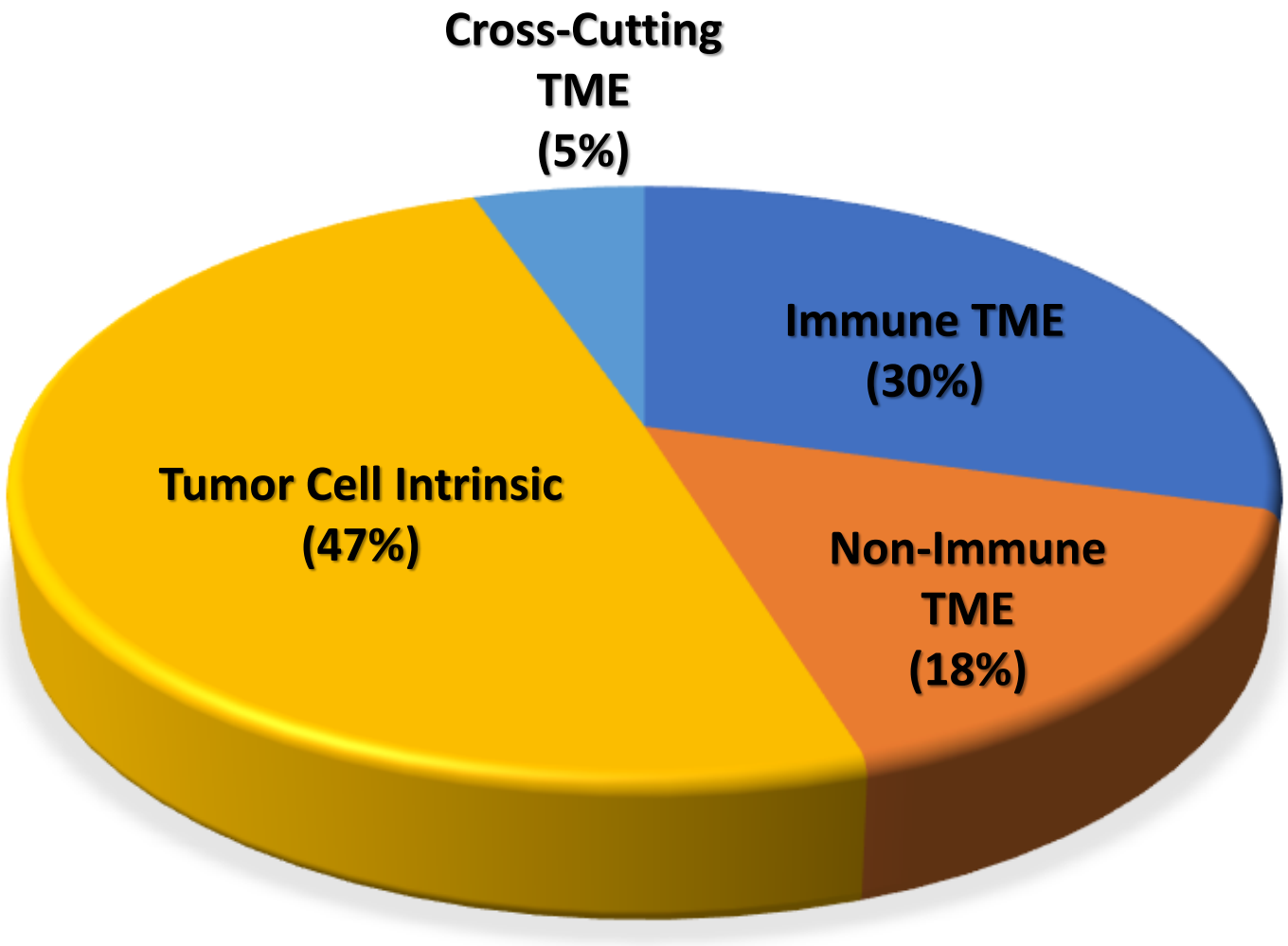
- Build upon and replace the Moonshot Pancreatic Cancer Microenvironment Network (PaCMEN) – primarily focused on immuno-oncology
- Complement other ongoing NCI-sponsored programs (SPOREs, RAS Initiative, Pancreatic Cancer Cohort Consortium, and Pancreatic Cancer Detection Consortium)
- Bridge basic/mechanistic 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
- 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

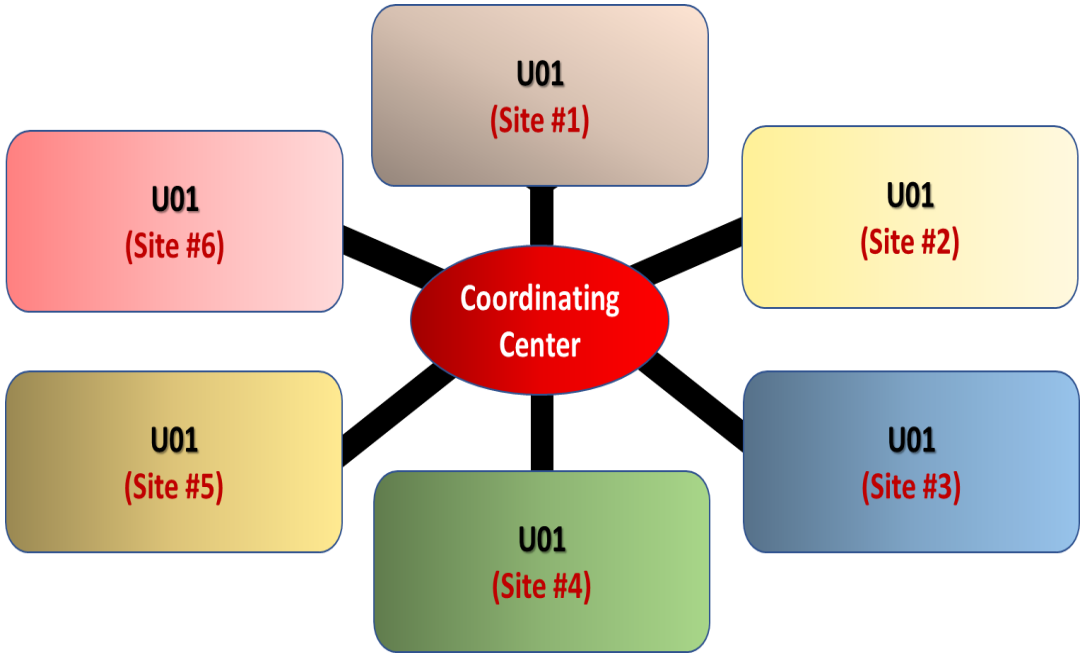
Disparities Research

Portfolio Analysis (Combined Basic & Translational)



Research Focus	Count	Stromal Drivers
Tumor Cell Intrinsic	70	N/A
Immune TME	45	7
Non-Immune TME	26	
Cross-Cutting TME	8	
TOTAL	**149**	**7**

PSRC Network Framework



NCI Resources

CTEP Agents

NExT

ARTNet, etc

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)

PSRC Evaluation Criteria

- Publication of center-specific & collaborative research findings
- Collaboration & participation in new pilot study development within and outside the network
- Sharing of human specimens, data and technologies/knowhow between centers to answer collaborative research questions
- New grant applications generated by cross-PSRC studies
- Novel models and resources to be shared with the broader scientific community
- Development of research tools & applications for patient management

PSRC Initiative: Proposed Budget

Funding Mechanism	No. of Awards	Funding Level Direct Costs (DC)	Recommended Total Costs (TC)
U01	6	Each award max. $600 K DC	$6.93 M (First year TC)
U24	1	$600 K DC	
			Total for the Program $34.65 M (5 years TC)

THANK YOU!

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