Reprogramming the Tumor Microenvironment to Improve Responses to Therapy

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AACR National
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Washington University in St. Louis

SITEMAN CANCER CENTER
BARNES-JEWISH HOSPITAL • WASHINGTON UNIVERSITY SCHOOL OF MEDICINE
Related:
### Pancreas Cancer Outcomes

<table>
<thead>
<tr>
<th>Type</th>
<th>Deaths/year</th>
<th>% 5 year Survival</th>
<th>All</th>
<th>Local</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>158,040</td>
<td>17%</td>
<td>45%</td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>49,700</td>
<td>65%</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>40,730</td>
<td>89%</td>
<td>99%</td>
<td></td>
</tr>
<tr>
<td><strong>Pancreas</strong></td>
<td><strong>40,560</strong></td>
<td><strong>7%</strong></td>
<td><strong>26%</strong></td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>27,540</td>
<td>99%</td>
<td>&gt;99%</td>
<td></td>
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</tbody>
</table>

### Immunotherapy

<table>
<thead>
<tr>
<th></th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>0% (SD responses only)</td>
</tr>
<tr>
<td>Ipilimumab + GVAX</td>
<td>0% (SD responses only)</td>
</tr>
<tr>
<td>Anti-PD1 (Pembro)</td>
<td>unpublished .... (+ MSI^Hi )</td>
</tr>
</tbody>
</table>
Pancreatic cancer is poorly responsive to T cell-directed immunotherapy for reasons not completely understood.


Have responded to T cell immunotherapy
Has not responded to T cell immunotherapy

Pancreas Cancer Is Not Melanoma
Targeting PDAC Microenvironment

- CCR2i
- CSF1Ri
- αCD40
- CXCR2i
- PI3Kγi
- Myeloid Cells
- PDAC Tumor
- Anti-Tumor CTLs Responses
- CAF and Fibrosis
- CXCR4i
- Shh/Notchi
- VitD
- PEGPH20
Targeting PDAC Microenvironment

Myeloid Cells → PDAC Tumor

Anti-Tumor

CTLs Responses

CAF and Fibrosis

Target
Adopted from Nat Rev Cancer Sulzmaier et al 2014,
Adopted from Nat Rev Cancer Sulzmaier et al 2014,
FAK1 Hyper-activated in Human PDAC

**Human PDAC**

<table>
<thead>
<tr>
<th>A</th>
<th>Human PDAC</th>
<th>Human PDAC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>total FAK1</td>
<td>pFAK1</td>
</tr>
<tr>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDAC</td>
<td>Overexpressed in 80%</td>
<td>Hyper-activated in 86%</td>
</tr>
</tbody>
</table>

*(N=56)*

![Image showing overexpression and hyper-activation of FAK1 in PDAC tissues.](image)

**Bar Graph**

- **CD8α+ CTLs**: 80 ± 40
- **CD15+ Granulocytes**: 70 ± 35
- **NE+ Granulocytes**: 70 ± 35

*Significant differences indicated by *.*

- **pFAK Low (n=27)**
- **pFAK High (n=23)**
FAK1 is Overexpressed in Highly-Fibrotic PDAC

[Images of tissue sections showing immunostaining for pFAK and Sirius Red in adjacent “Normal” tissue and PDAC, with quantitative analyses of Sirius Red and Collagen I intensity.]
FAK1 Hyperactivated in Human PDAC

Myeloid Cells

Anti-Tumor CTLs Responses

PDAC Tumor

CAF and Fibrosis
Pre-clinical Models

KPC Mice
C57/B6(wt) | p48-CRE⁺/Kras⁰¹²D/p53́floxed

Normal | PanIN >1mo | PDAC >3.5mo

KP cells
(Fibroblasts; Tumor Cells)

Fibrotic (collagen)

% Survival

Untreated (n=25)

+αPD1/
αCTLA4 (n=6)

OS (months)
FAK Inhibition Dramatically Extends Survival

KPC (FAKi VS-4718)
FAKi 50 mg/kg, Bid
↑
Gemcitabine, 50 mg/kg

Early Treatment
PDAC 3.5 months

Late Treatment
US Diagnosis / Monitoring

KPC GEMM Survival
%-Survival
0 20 40 60 80 100
Survival from treatment start (in days)
0 60 120 180 240

Vehicle early n=16
FAKi early n=11
GEM early n=4
FAKi late n=10
Alive at study end

p<0.001
p<0.01

Gross Estimated Tumor Diameter
0.0 0.5 1.0 1.5 2.0
Days from treatment start
0 60 120 180 240

Vehicle early
FAKi early

NCT-00787033 Phase I Single Agent FAKi (VS-6063)

- 11/27 (41%) of patients enrolled experienced SD (>100mg)
- 1 of these patients had metastatic PDAC and had SD for > 6 months

(ASCO 2011)

Targeting PDAC Microenvironment

Myeloid Cells

Anti-Tumor CTLs Responses

PDAC Tumor

CAF and Fibrosis

FAK

P
FAK Inhibition Reduces PDAC Fibrosis

KPC PDAC Tumors

**Sirus Red**

- **Vehicle**
- **FAKi**

**Collagen Level**

<table>
<thead>
<tr>
<th></th>
<th>Vehicle</th>
<th>FAKi</th>
<th>Vehicle</th>
<th>FAKi</th>
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</table>

- **Rx 1.5mo**
- **End Stage**

**FAP**

- **Vehicle**
- **FAKi**

**DAPI**

10x

**FAP+ Fibroblasts**

- **Vehicle**
- **FAKi**

**End Stage**

*Jiang et al Nature Medicine 2016*
Targeting PDAC Tumor Microenvironment

Suppressive Myeloid Cells

Fibrosis

PDAC Cells

FAKi
Inhibiting FAK Decreases Immunosuppressive Myeloid Cells

Same results in KPPC GEMMs and Syngeneic KP and KI models
Working Model

Myeloid Cells

Anti-Tumor CTLs Responses

PDAC

CAF and Fibrosis

CSF1
CCL2
CXCL2

FAK1

STAT3
P

CXCL12
FGF-1

Does FAK inhibition create a permissive microenvironment for immunotherapy?

SIDEBAR

Does this improve the efficacy of chemotherapy.
FAK Inhibition Improves Response to Chemotherapy

**KPPC Survival**

- **FAKi + GEM-75**
- **Vehicle**
- **FAKi**
- **GEM-75**

**Days from Treatment Start**

<table>
<thead>
<tr>
<th>% Survival</th>
</tr>
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<tbody>
<tr>
<td>100</td>
</tr>
<tr>
<td>50</td>
</tr>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

**KPPC End Stage**

- **CC3 DAPI**
- **H&E**

NCT02651727 VS-4718 + GEM/Abraxane in PDAC
(Industry Sponsored, WUSTL Site)

*Jiang et al Nature Medicine 2016*
Does FAK inhibition create a permissive microenvironment for immunotherapy?

Does it do so by allowing more T cell to traffic into PDAC tumors?
Back to the point!

Myeloid Cells

Anti-Tumor CTLs Responses

PDAC

CAF and Fibrosis

FAK

CXCL12 FGF-1

CSF1 CCL2 CXCL2
FAK Inhibition Improves Response to Adoptive T cell Therapy

KP-OVA cells → Luc⁺ OT1 T cells → BLI

FAKi 7 days

Luc⁺ CD8⁺ Infiltration Into PDAC Tumors

Bli (photons sec⁻¹/mm³)

- Vehicle
- FAKi

KP-OVA Transplantable

Days from Treatment Start

Tumor volume (mm³)

- Vehicle
- ACT
- FAKi
- FAKi+ACT

R2 = 1.777 ± 0.05
FAK Inhibition Improves Response to Adoptive T cell Therapy

FAK inhibition improves T cell recruitment into PDAC tumors.

What about endogenous T cell responses?
FAK Inhibition Improves Responses to Checkpoint Immunotherapy

KPPC Survival

Rx Start → PD1/CTLA4 → FAKi

% Survival

Days from Treatment Start

- Vehicle (n=12)
- Immuno (n=11) αPD1/CTLA4
- FAKi (n=10)
- FAKi+Immuno (n=15)

FAK Inhibition Improves Responses to Checkpoint Immunotherapy

KPPC PDAC Model
CD8+ CTL Tumor cell DAPI

Checkpoint Immunotherapy

FAKi + Checkpoint Immunotherapy
FAK Inhibition Improves Responses to Checkpoint Immunotherapy

KP Transplantable Survival

Days from Treatment Start

% Survival

GEM²⁵
GEM²⁵ + FAKi
GEM²⁵ + αPD-1
GEM²⁵ + FAKi + αPD-1

KP Transplantable
CD8a CK19 DAPI

FAKi + GEM²⁵ + αPD1
Investigator Initiated Phase Ib Study Design
NCT02546531 (now open)

Defactinib (FAKi) + Pembro (αPD1) + Gemcitabine in Advanced PDAC

Andrea Wang-Gilliam MD

Funded by PRMA and BJCIH Foundations
Early Biomarker Results

Data from PDAC tissue biopsies (metastasis) Pre-Treatment and Post Cycle 2

Proliferating CD8+ T cells (CD3+ CD8+ Ki67+ DR+)

Macrophages (CD11b+ CD15-CD16- CD14+ CCR2 low DR+)

Proliferating CTL to TAM Ratio

Pre-Rx Post-Rx

% of CD8+ CTLs

% of Total Cells

Relative Ratio

Patient 04
Patient 09
Patient 10
Patient 13
Targeting PDAC Microenvironment

Myeloid Cells

Anti-Tumor CTLs Responses

PDAC Tumor

Target

CAF and Fibrosis
FAK Inhibition + Immunotherapy

Cell Death

anti-PD1

FAKi (VS-4718)
Currently Looking for Qualified Postdocs

Contributors/Collaborators

**WashU Collaborators**
Andrea Wang-Gillam, MD, PhD
William Hawkins, MD
Greg Longmoore, MD
Timothy Nywening, MD

**Outside Collaborators**
David Linehan, MD (URMC)
Jonathan Pachter (Verastem)
David Weaver (Verastem)

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- AACR/PANCAN
- DOD
- PRMA/BJCIH
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Target