Pancreas Cancer, Immunogenicity, and Checkpoint Resistance

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• Dr. Vonderheide reports research funding from Lilly and Janssen

• Will discuss investigational use of RO7009789, APX005M, and nivolumab
Cancer Immune Revolution

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Tumor Immunotherapy
CAR T cell FDA-approval Flash Mob
T cell immune surveillance of cancer

Vonderheide, Cancer Cell, 2018
T cell immune surveillance of cancer

Tumor response → Elimination → Immunoediting → Escape → Resistance to immune therapy

T cell response → Host/tumor immune suppression → Peripheral tolerance → Escape → Overcome with CTLA4 or PD-1 mAb, or both

Vonderheide, Cancer Cell, 2018
T cell immune surveillance of cancer

Tumor

T cell response
Elimination
Immuoediting
Escape
Resistance to immune therapy

HOT

T cell response
Host/tumor immune suppression
Peripheral tolerance
Escape
Overcome with CTLA4 or PD-1 mAb, or both

COLD

Host/tumor immune suppression
No T cell response in tumor
Immune privilege
No
Escape
Overcome by vaccination AND block immune suppression (either alone will not work)

Vonderheide, Cancer Cell, 2018
Pancreatic ductal adenocarcinoma (PDA)

*Projected cancer deaths for the leading cancer killers.* Projections of the number of deaths from the current top five cancer killers indicate that pancreatic cancer will become the second leading cause of cancer deaths as early as 2015. The estimated

*Rahib et al, Cancer Res, 2014*
Expression of GZMA and PRF1 in Pancreatic Adenocarcinoma

All primary tumors, untreated n=134

Balli et al, Clin Can Res, 2017
Immunobiology of pancreatic carcinoma

Mutant Kras
Loss of TS

Desmoplastic stroma

Gemcitabine
CD3+ T cell infiltration in pancreatic cancer

Clark et al, Cancer Res, 2007

PDA patient

KPC mouse

Kras^{G12D/+} Trp53^{R172H/+} Pdx-1 Cre

Melanoma patient

Melanoma patient

Clark et al, Cancer Res, 2007

Erdag et al, Cancer Res, 2012
Hypothesis: It’s not the *physical* barrier of the stroma but rather an acquired network of oncogene-driven immunosuppression that excludes effector T cells
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Implications:
• Immune surveillance in pancreatic carcinoma is more akin to “immune privilege” than “immunoediting”
Hypothesis:
It’s not the *physical* barrier of the stroma but rather an acquired network of oncogene-driven immunosuppression that excludes effector T cells

Implications:
• Immune surveillance in pancreatic carcinoma is more akin to “immune privilege” than “immunoediting”

• Without Darwinian-like pressure from T cells, the underlying pancreatic tumor cells remain highly susceptible to T cells…. if these can be provoked
Acquired immune privilege as a means of evasion

Vonderheide and Bayne, Curr Opin Immunol, 2013
Can we cut and paste single-agent CTLA-4 and PD-1 mAb from melanoma to PDA?

Mouse studies say ‘no’ (Winograd et al, Can Immunol Res, 2015)

Clinical results to date say ‘no’
- Single agent ipilimumab
  - no responses (Royal et al, Clin Can Res, 2010)
- Single agent PD-L1 mAb
  - Exception MSI-high (Le et al, Science, 2017)
T cell immunosurveillance in pancreatic cancer?

Young KPC (<5 weeks)  
*Kras^{G12D/+} Trp53^{R172H/+} Pdx-1 Cre*

Serial ultrasounds

• CD8 (2.43) + CD4 (GK1.5)  
• IgG2b isotype control (LTF-2)

Moribund or tumor >1000mm³

Endpoints:  
• Tumor burden (serial U/S)  
• Survival: age at sac

KPC tumor diagnosed at 15 wks, 8.9 mm³
No T cell immunosurveillance in pancreatic KPC model

- No difference in survival or time to diagnosis in T cell replete vs depleted mice
- KPC tumor cell lines from T cell replete or depleted mice grow same in T cell replete or depleted hosts (never rejected)

These observations are inconsistent with immunoediting

Evans et al, JCI Insight, 2016
Role of antigenic strength in KPC-OVA tumors

Subcutaneous growth of V6. Ova

Tumor Growth

Overall Survival

Tumor volume (mm³)

Days post-injection

S.C.

Orthotopic

P < 0.0001

Percent survival

P < 0.0001

P < 0.0001

Evans et al, JCI Insight, 2016
## Burden of neo-epitopes in human cancer

<table>
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<th>Disease</th>
<th>Sample number</th>
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Rech et al, Can Immunol Res, 2018
A case for priming, not checkpoint

Prime

Checkpoint blockade

Vonderheide, Cancer Cell, 2018
Figure adapted from Chen and Mellman. Immunity, 2013.
CD40: Role in tumor immunity

Ott et al, Clin Can Res, 2013
Gemcitabine and agonist anti-CD40 mAb in chemo-naïve metastatic pancreatic carcinoma

- PR 24% (best response)
- mPFS 5.2 mo
- mOS 8.4 mo

FDG-PET response: 88%

Beatty et al, Science, 2011
Gemcitabine and agonist anti-CD40 mAb in chemo-naïve metastatic pancreatic carcinoma

FDG-PET response: 88%

PR 24% (best response)
mPFS 5.2 mo
mOS 8.4 mo

Beatty et al, Science, 2011
CD40/chemo in subcutaneous KPC model (no OVA)

- No regressions in T cell-depleted mice or IFNγ KO mice
- In the TME, marked change in T cell infiltration
  - Skewing toward IFNγ and TNFα secreting T cells and activated dendritic cells
  - Increased clonality of infiltrating T cells in tumor by TCR seq
  - Many tertiary lymphoid structures in TME in CD40/chemo mice
- Dependent on both nP and CD40 for maximal effect
  - Addition of nP to Gem/CD40 converts mechanism to T cell-dependent, macrophage-independent

Byrne et al, Cell Rep, 2016
CD40 with chemotherapy in spontaneous mouse model of pancreatic ductal adeno carcinoma

Gem – gemcitabine
nP – nab-paclitaxel (Abraxane)

Byrne et al, Cell Rep, 2016
CD40 as neoadjuvant therapy in pancreatic cancer

Phase I study of preoperative RO7009789 +/- chemo for patients with newly diagnosed resectable pancreatic carcinoma

**Arm A:** RO7009789 (CD40) \((n=10)\)
**Arm B:** Gem/nP then RO7009789 \((n=10)\)

**Safety**
**DFS**
**OS**

**Tissue and blood biomarkers**

IND sponsor, Robert Vonderheide
Sites: Penn, Hopkins, Case, U Wash, Wisconsin

Collaboration of PanCan, NCI’s CITN, SU2C
CD40/chemo plus checkpoint blockade in PDA

Gem – gemcitabine
nP – nab-paclitaxel (Abraxane)

PICI0002 Study Design

Gem/NP +/- CD40 +/- PD-1 for patients with first-line metastatic pancreatic carcinoma

**Phase Ib/Dose Escalation**

**Cohort C2:** 6 Subjects
Gem, NP + Nivo + APX005M
High dose

**Cohort C1:** 6 Subjects
Gem, NP + Nivo + APX005M
Low dose

**Cohort B2:** 6 Subjects
Gem, NP + APX005M
High dose

**Cohort B1:** 6 Subjects
Gem, NP + APX005M
Low dose

**Phase II**

**Arm A1:** 35 Subjects
Gem NP + Nivolumab

**Arm B1:** 29 Subjects
APX005M

**Arm B2:** 29 Subjects
APX005M

**Arm C1:** 29 Subjects
Nivo APX005M

**Arm C2:** 29 Subjects
Nivo APX005M

**Key Considerations:**
Histological or cytological documentation of metastatic pancreatic adenocarcinoma diagnosis:
- ECOG 0-1
- No prior treatment including prior CD40, PD-1, PD-L1, CTLA-4
- EP1/Ib: Feasibility and Safety + RP2D
- EP1/II: OS vs. 1-year OS historical for Gem/NP
- EP2/II: ORR, DCR. PFS and DOR in treatment arm

**IND Sponsor:** Parker Institute
Overall PI: Robert Vonderheide
Penn, MSKCC, MDACC, UCLA, UCSF, Stanford

**NCT03214250**
G: Gemcitabine  A: Nab-paclitaxel  F: αCD40  P: αPD-1  C: αCTLA-4

Li et al, Immunity, 2018
Opportunities beyond checkpoint

Cold tumor → Checkpoint blockade → No response

Checkpoint blockade + Adjuvant → Vaccine → New T cells → Hot tumor

Checkpoint blockade → Response

Checkpoint blockade:
- PD-1
- PD-L1
- CTLA-4

Adjuvant:
- Cytokines
- CD40
- STING
- TLR ligands
- Other

Radiation plus checkpoint blockade in pancreatic cancer

Summary

• There’s no immunoediting if there’s no immune response
  • Checkpoint blockade and ‘stacking’ combinations will be more likely to fail than succeed against tumors if the dominant biology is T cell exclusion, privilege, or ignorance

• Lack or deficient T cell priming represents a fundamental lesion in cancer immunity, but this can be fixed
  • CD40 activation of dendritic cells is one (among many) tractable ways to therapeutically repair deficient priming and trigger T cell immunity
  • Return of vaccines in all shapes and sizes
  • Once T cells primed, checkpoint blockade may enable – or even be necessary – for clinically significant T cell immunity
## Acknowledgements

<table>
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<td>Mark Diamond</td>
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<td>Ceire Hay</td>
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