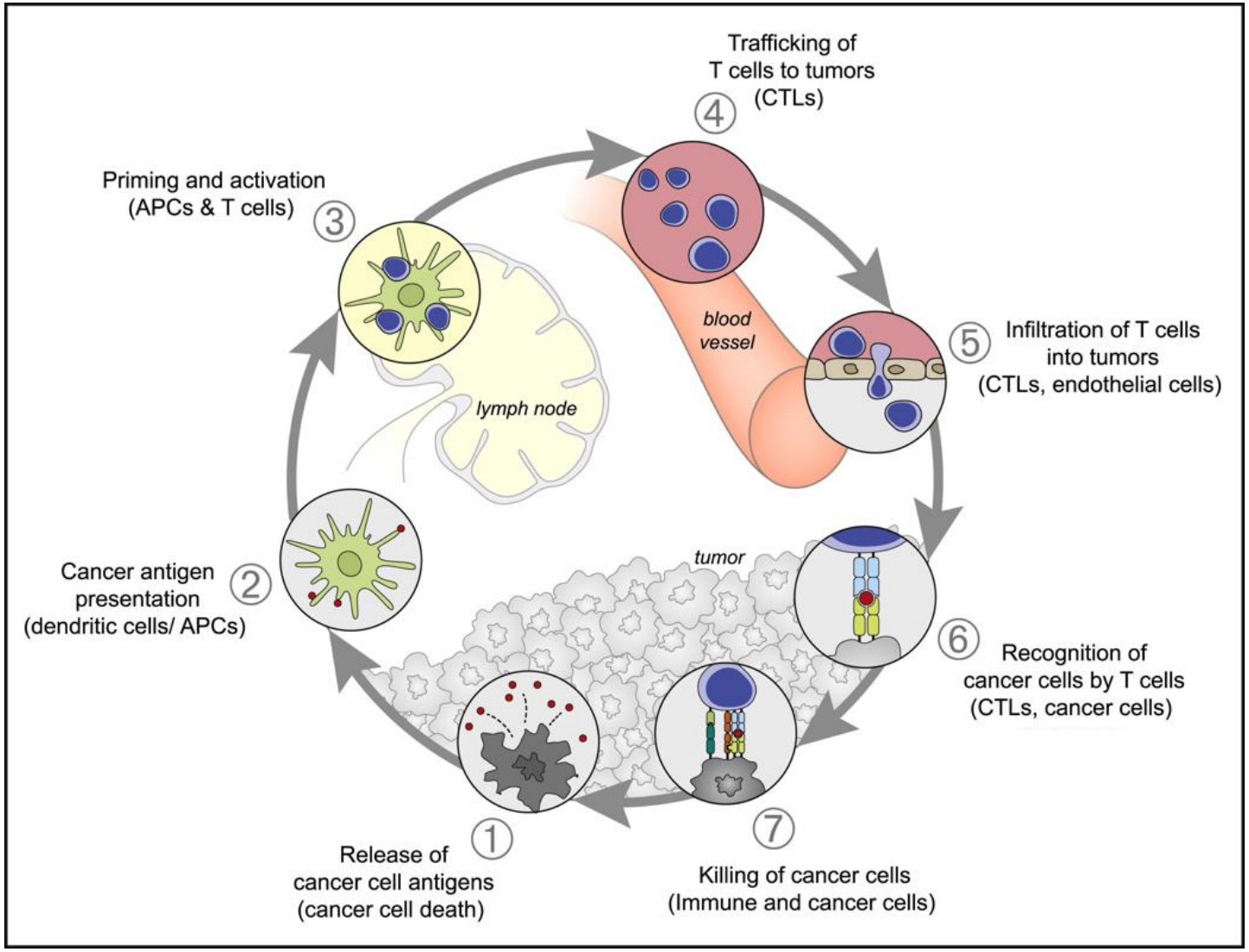
Pancreatic Cancer Immunology – Setting the Scene

Prof Jen Morton – CRUK Beatson / Glasgow Uni

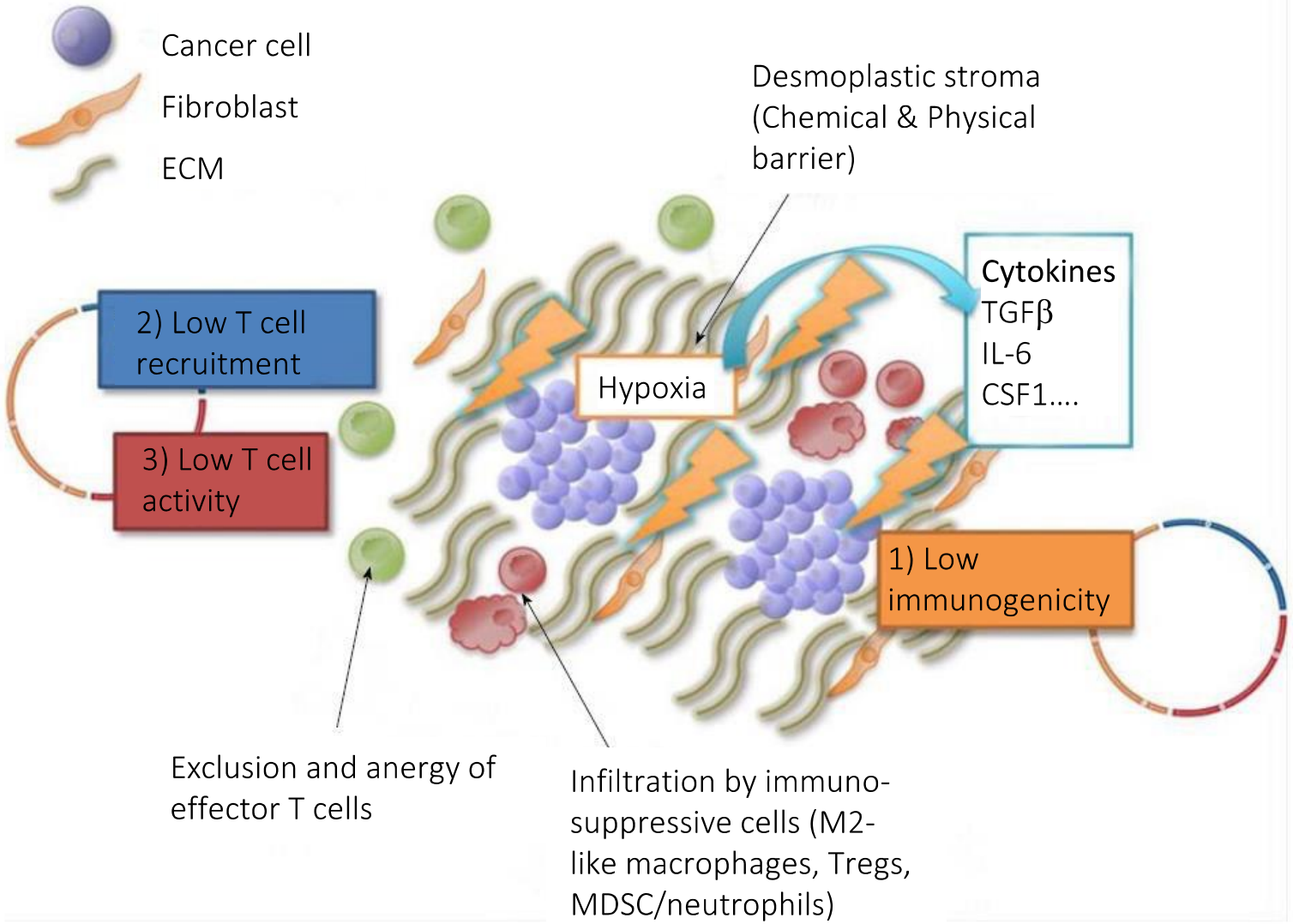
Disclosures:

Have received research funding from AstraZeneca, UCB Pharma, Redex Pharma, Bioven

Intro - Tumour Immunology 101



Intro – the PDAC immune landscape



Due to genetics and antigen presenting capacity

Current approaches

Targeting neutrophils/MDSCs

- In mice, neutrophil depletion or blocking trafficking (CXCR2) leads to reduction in tumour or metastatic burden and strongly synergize with PD-1 blockade.
- Mice treated with CCR2i show reduced PDAC tumour burden.
  - But, early trial data for CXCR2i + IO were disappointing
- FOLFIRINOX + CCR2i resulted in reductions in primary tumour burden, leading to downstaging and increased eligibility for surgery.
- Unfortunately, a similar trial of a CCR2i + Gem/nP in metastatic PDAC failed for both safety and efficacy.
- Neutrophil/MDSC blocking strategies cannot be maintained long term due to the critical importance of neutrophils for host defence?

Targeting neutrophils/MDSCs

CellPress

Cancer Cell

Article

CXCR2 Inhibition Profoundly Suppresses Metastases and Augments Immunotherapy in Pancreatic Ductal Adenocarcinoma

Colin W. Steele,[1] Saadia A. Karim,[1] Joshua D.G. Leach,[1] Peter Bailey,[2] Rosanna Upstill-Goddard,[2] Loveena Rishi,[2] Mona Foth,[1] Sheila Bryson,[1] Karen McDaid,[3] Zena Wilson,[3] Catherine Eberlein,[3] Juliana B. Candido,[4] Mairi Clarke,[5] Colin Nixon,[1] John Connelly,[1] Nigel Jamieson,[6] C. Ross Carter,[6] Frances Balkwill,[4] David K. Chang,[2] T.R. Jeffry Evans,[1,2] Douglas Strathdee,[1] Andrew V. Biankin,[2] Robert J.B. Nibbs,[5] Simon T. Barry,[3] Owen J. Sansom,[1,2,7,*] and Jennifer P. Morton[1,2,7]

Research Article

Cancer Immunology Research

CXCR2-Dependent Accumulation of Tumor-Associated Neutrophils Regulates T-cell Immunity in Pancreatic Ductal Adenocarcinoma

Timothy Chao[1], Emma E. Furth[1,2], and Robert H. Vonderheide[1,3]

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CANCER

Agonism of CD11b reprograms innate immunity to sensitize pancreatic cancer to immunotherapies

Roheena Z. Panni[1], John M. Herndon[2], Chong Zuo[2], Samarth Hegde[2], Graham D. Hogg[2], Brett L. Knolhoff[2], Marcus A. Breden[2], Xiaobo Li[3], Varintra E. Krisnawan[2], Samia Q. Khan[3], Julie K. Schwarz[4,5], Buck E. Rogers[4,5], Ryan C. Fields[1,4], William G. Hawkins[1,4], Vineet Gupta[3]*, David G. DeNardo[2,4,6]*†

Pancreas

OPEN ACCESS

ORIGINAL ARTICLE

Targeting both tumour-associated CXCR2$^+$ neutrophils and CCR2$^+$ macrophages disrupts myeloid recruitment and improves chemotherapeutic responses in pancreatic ductal adenocarcinoma

Timothy M Nywening,[1,2] Brian A Belt,[3,4,5] Darren R Cullinan,[1,2] Roheena Z Panni,[1,2] Booyeon J Han,[3,4,5] Dominic E Sanford,[1,2] Ryan C Jacobs,[1,2] Jian Ye,[3,4,5] Ankit A Patel,[3,4,5] William E Gillanders,[1,2] Ryan C Fields,[1,2] David G DeNardo,[2,6,7] William G Hawkins,[1,2] Peter Goedegebuure,[1,2] David C Linehan[3,4,5]

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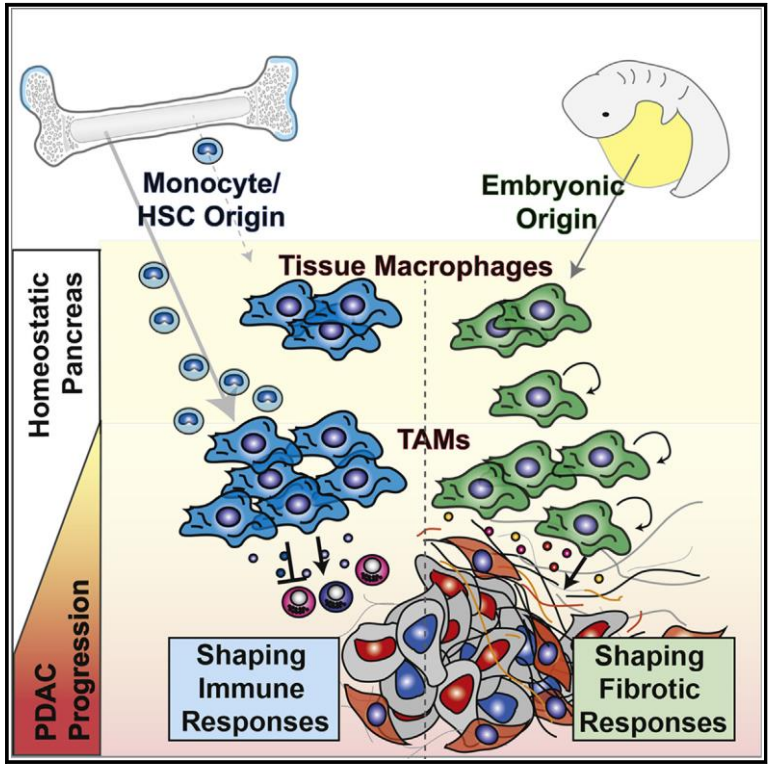
Targeting macrophages

- Macrophages are highly abundant and mostly tumor-promoting (?). Close proximity of alternatively activated TAMs to tumour cell nests correlates with poor prognosis
- Efficacy of macrophage depletion may be impacted by compensatory increases in other myeloid cell populations, however, there are alternative approaches, e.g.:
  - Reprogramming macrophages to phagocytose and kill live tumor cells
    - Via agonistic anti-CD40 which can activate the phagocytic program in macrophages.
    - Via NF-κB modulation which can induce lymphotoxin production from T cells to reprogramme macrophages to phagocytose.
    - Via activation of macrophages with the TLR9 ligand CpG which can induce phagocytosis
  - Blockade of the ‘don’t eat me’ ligand CD47 on tumor cells

Targeting macrophages – which ones??

- PDAC TAMs originate from bone marrow-derived infiltrating monocytes *and* embryonic tissue resident macrophages (TRMs)
- TRMs exhibit pro-fibrotic activities (distinct from infiltrating monocytes) and only they promote PDAC progression
- Tissue-resident TAMs expand in PDAC via in situ proliferation
- However, during the early stages of tumorigenesis, TRMs could have tumor suppressive properties?
- Should we be specifically targeting the pro-tumorigenic, immunosuppressive signals, rather than the cells themselves?



Immunity
Article

Tissue-Resident Macrophages in Pancreatic Ductal Adenocarcinoma Originate from Embryonic Hematopoiesis and Promote Tumor Progression

Yu Zhu,[1,2] John M. Herndon,[1,2] Dorothy K. Sojka,[3] Ki-Wook Kim,[4] Brett L. Knolhoff,[1,2] Chong Zuo,[1,2] Darren R. Cullinan,[7] Jingqin Luo,[5] Audrey R. Bearden,[1,2] Kory J. Lavine,[1] Wayne M. Yokoyama,[3,5] William G. Hawkins,[6,7] Ryan C. Fields,[6,7] Gwendalyn J. Randolph,[1,4] and David G. DeNardo[1,2,4,6,8,*]

Article

Resident Macrophages Cloak Tissue Microlesions to Prevent Neutrophil-Driven Inflammatory Damage

Stefan Uderhardt,[1,4,*] Andrew J. Martins,[2] John S. Tsang,[2] Tim Lämmermann,[3] and Ronald N. Germain[1,*]
[1]Lymphocyte Biology Section, Laboratory of Immune System Biology, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD 20892, USA

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Targeting macrophages

Microenvironment and Immunology

Cancer Research

CSF1/CSF1R Blockade Reprograms Tumor-Infiltrating Macrophages and Improves Response to T-cell Checkpoint Immunotherapy in Pancreatic Cancer Models

Yu Zhu[1,2], Brett L. Knolhoff[1,2], Melissa A. Meyer[1,2], Timothy M. Nywening[3,4], Brian L. West[5], Jingqin Luo[4,6], Andrea Wang-Gillam[1], S. Peter Goedegebuure[3,4], David C. Linehan[3,4], and David G. DeNardo[1,2,4,7]

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CANCER

Agonism of CD11b reprograms innate immunity to sensitize pancreatic cancer to immunotherapies

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nature immunology

ARTICLES

https://doi.org/10.1038/s41590-018-0292-y

Metabolic rewiring of macrophages by CpG potentiates clearance of cancer cells and overcomes tumor-expressed CD47—mediated 'don't-eat-me' signal

Mingen Liu[1], Roddy S. O'Connor[2], Sophie Trefely[3,4], Kathleen Graham[1], Nathaniel W. Snyder[3] and Gregory L. Beatty[1,5]*

OPEN ACCESS CellPress

Cell Reports

Article

CSF1R+ Macrophages Sustain Pancreatic Tumor Growth through T Cell Suppression and Maintenance of Key Gene Programs that Define the Squamous Subtype

Juliana B. Candido,[1,8] Jennifer P. Morton,[2,3,8] Peter Bailey,[3] Andrew D. Campbell,[2] Saadia A. Karim,[2] Thomas Jamieson,[2] Laura Lapienyte,[2] Aarthi Gopinathan,[4] William Clark,[2] Ewan J. McGhee,[2] Jun Wang,[1] Monica Escorcio-Correia,[1] Raphael Zollinger,[1] Rozita Roshani,[1] Lisa Drew,[5] Loveena Rishi,[3] Rebecca Arkell,[1] T.R. Jeffry Evans,[2,3] Colin Nixon,[2] Duncan I. Jodrell,[4] Robert W. Wilkinson,[6] Andrew V. Biankin,[3] Simon T. Barry,[7] Frances R. Balkwill,[1] and Owen J. Sansom[2,3,9,*]

Pancreas

OPEN ACCESS

ORIGINAL ARTICLE

Targeting both tumour-associated CXCR2+ neutrophils and CCR2+ macrophages disrupts myeloid recruitment and improves chemotherapeutic responses in pancreatic ductal adenocarcinoma

Timothy M Nywening,[1,2] Brian A Belt,[3,4,5] Darren R Cullinan,[1,2] Roheena Z Panni,[1,2] Booyeon J Han,[3,4,5] Dominic E Sanford,[1,2] Ryan C Jacobs,[1,2] Jian Ye,[3,4,5] Ankit A Patel,[3,4,5] William E Gillanders,[1,2] Ryan C Fields,[1,2] David G DeNardo,[2,6,7] William G Hawkins,[1,2] Peter Goedegebuure,[1,2] David C Linehan[3,4,5]

Synergy or not with dual targeting???

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Targeting CAFs (to reprogramme the immune TME)

- Blanket CAF targeting has been unsuccessful, however, targeting CAF subsets or their secreted products (e.g. myeloid cell-recruiting chemokines) may be worthwhile, e.g.:
  - anti-TGFβ antibodies can decrease CAFs, reduce myeloid infiltration and relieve CTL suppression.
  - ATRA / PIN1 targeting have demonstrated efficacy in orthotopic mouse models by promoting CAF quiescence and reducing fibrosis and may synergize with chemo + ICB.
  - Blockade of IL-1β (which supports iCAFs to produce IL-6 and and reinforce the immunosuppressive PDAC TME) synergizes with ICB in preclinical models.
- Clinical trials of all of the above concepts are ongoing
- Whether any will be effective remains to be determined….

Targeting CAFs (to reprogramme the immune TME)

CellPress

Cancer Cell
Article

Cancer-Associated Fibroblasts Neutralize the Anti-tumor Effect of CSF1 Receptor Blockade by Inducing PMN-MDSC Infiltration of Tumors

Vinit Kumar,[1] Laxminarasimha Donthireddy,[1] Douglas Marvel,[1,10] Thomas Condamine,[1,11] Fang Wang,[1] Sergio Lavilla-Alonso,[1,12] Ayumi Hashimoto,[1] Prashanthi Vonteddu,[1] Reeti Behera,[1] Marlee A. Goins,[6] Charles Mulligan,[6] Brian Nam,[6] Neil Hockstein,[6] Fred Denstman,[6] Shanti Shakamuri,[6] David W. Speicher,[2] Ashani T. Weeraratna,[1] Timothy Chao,[4] Robert H. Vonderheide,[4] Lucia R. Languino,[8] Peter Ordentlich,[3] Qin Liu,[1] Xiaowei Xu,[4] Albert Lo,[5,13] Ellen Puré,[5] Chunsheng Zhang,[9] Andrey Loboda,[9] Manuel A. Sepulveda,[7] Linda A. Snyder,[7] and Dmitry I. Gabrilovich[1,14,*]

CellPress

Cancer Cell

Article

Type I collagen deletion in αSMA$^+$ myofibroblasts augments immune suppression and accelerates progression of pancreatic cancer

Yang Chen,[1] Jiha Kim,[1] Sujuan Yang,[1] Huamin Wang,[2] Chang-Jiun Wu,[3] Hikaru Sugimoto,[1] Valerie S. LeBleu,[1] and Raghu Kalluri[1,4,*]

Cancer Cell

CellPress
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Article

Mesothelial cell-derived antigen-presenting cancer-associated fibroblasts induce expansion of regulatory T cells in pancreatic cancer

Huocong Huang,[1,2,11,*] Zhaoning Wang,[7] Yuqing Zhang,[2,3,9] Rachana N. Pradhan,[8] Debolina Ganguly,[2,3] Raghav Chandra,[1,2] Gilbert Murimwa,[1,2] Steven Wright,[2] Xiaowu Gu,[4,10] Ravikanth Maddipati,[2,5] Sören Müller,[8] Shannon J. Turley,[8] and Rolf A. Brekken[1,2,3,6,*]

CXCR4 inhibition in human pancreatic and colorectal cancers induces an integrated immune response

Daniele Biasci[a,b,c,1], Martin Smoragiewicz[a,b,1,2], Claire M. Connell[a,b,d,1], Zhikai Wang[e,1], Ya Gao[e], James E. D. Thaventhiran[a,b,c], Bristi Basu[d,f], Lukasz Magiera[a,b,3], T. Isaac Johnson[a,b], Lisa Bax[d], Aarthi Gopinathan[a,b], Christopher Isherwood[a,b], Ferdia A. Gallagher[g], Maria Pawula[a,b], Irena Hudecova[a,b], Davina Gale[a,b], Nitzan Rosenfeld[a,b], Petros Barmpounakis[h], Elizabeta Cristina Popa[i], Rebecca Brais[i], Edmund Godfrey[g], Fraz Mir[k], Frances M. Richards[a,b], Douglas T. Fearon[a,e,i,4,5], Tobias Janowitz[a,b,e,l,4,5], and Duncan I. Jodrell[a,b,4]

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Targeting / reprogramming DCs

- Is T cell exhaustion the problem in PDAC or is it a lack of T cell priming?
- In mice, there is a dearth of cross-presenting type 1 conventional dendritic cells (cDC1s) in pancreatic tumours
- Anti-CD40 (agonistic) antibodies can activate DCs and enhance T cell priming.
- FLT3L treatment increases intratumoral cDC1s and restores sensitivity to CD40 agonist antibody and RT in PDAC mouse models.
- Ongoing trials to determine tolerability & efficacy of CD40 agonist + FLT3L in human.
- Other approaches include targeted agents that affect DDR pathways, to activate the STING pathway and IFN production, to promote DC activation.

Targeting / reprogramming DCs

Sufficiency of
blockade for

Alexander H. Morrison[a], Marl

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Perelman School of Medicine, Universit
Pennsylvania, Philadelphia, PA 19104

nature medicine

ARTICLES

https://doi.org/10.1038/s41591-022-01829-9

Check for updates

OPEN

Sotigalimab and/or nivolumab with chemotherapy in first-line metastatic pancreatic cancer: clinical and immunologic analyses from the randomized phase 2 PRINCE trial

Lacey J. Padrón[1,17] ✉, Deena M. Maurer[1,17], Mark H. O'Hara[2,17], Eileen M. O'Reilly[3], Robert A. Wolff[4], Zev A. Wainberg[5], Andrew H. Ko[6], George Fisher[7], Osama Rahma[8], Jaclyn P. Lyman[1], Christopher R. Cabanski[1], Jia Xin Yu[1], Shannon M. Pfeiffer[1], Marko Spasic[1], Jingying Xu[1], Pier Federico Gherardini[1], Joyson Karakunnel[1], Rosemarie Mick[2], Cécile Alanio[2,9,10,11], Katelyn T. Byrne[2,9], Travis J. Hollmann[3], Jonni S. Moore[2], Derek D. Jones[2], Marco Tognetti[12], Richard O. Chen[13], Xiaodong Yang[14], Lisa Salvador[15], E. John Wherry[2,9,10,11], Ute Dugan[1], Jill O'Donnell-Tormey[16], Lisa H. Butterfield[1], Vanessa M. Hubbard-Lucey[16], Ramy Ibrahim[1], Justin Fairchild[1], Samantha Bucktrout[1], Theresa M. LaVallee[1] and Robert H. Vonderheide[2,9,11] ✉

ne evasion of
ing MHC-I

Julian Yano[2], Douglas E. Biancur[1],
S. W. Sohn[1], Subhadip Mukhopadhyay[1],
[1], Joao A. Paulo[5], Kwun Wah Wen[6], Jayanta Debnath[6,7],
as T. Fearon[9,10,11], Rushika M. Perera[2,6,7] ✉ &

Cancer Cell
Article

Dendritic Cell
to Dysfunction
Surveillance in

Samarth Hegde,[1] Varintra E. Kri
Graham D. Hogg,[1] Jack P. Tang
Buck E. Rogers,[3,7] Kenneth M. M
and David G. DeNardo[1,4,7,8,*]

JEM Journal of Experimental Medicine

re systemically
:inogenesis

vid M. Feldser[3,6], Gregory L. Beatty[5,6],

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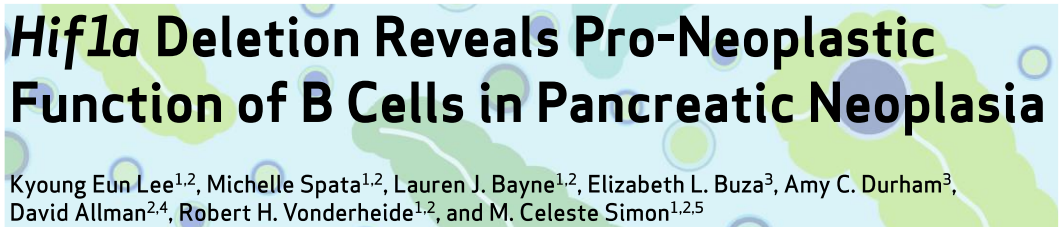
Targeting B cells

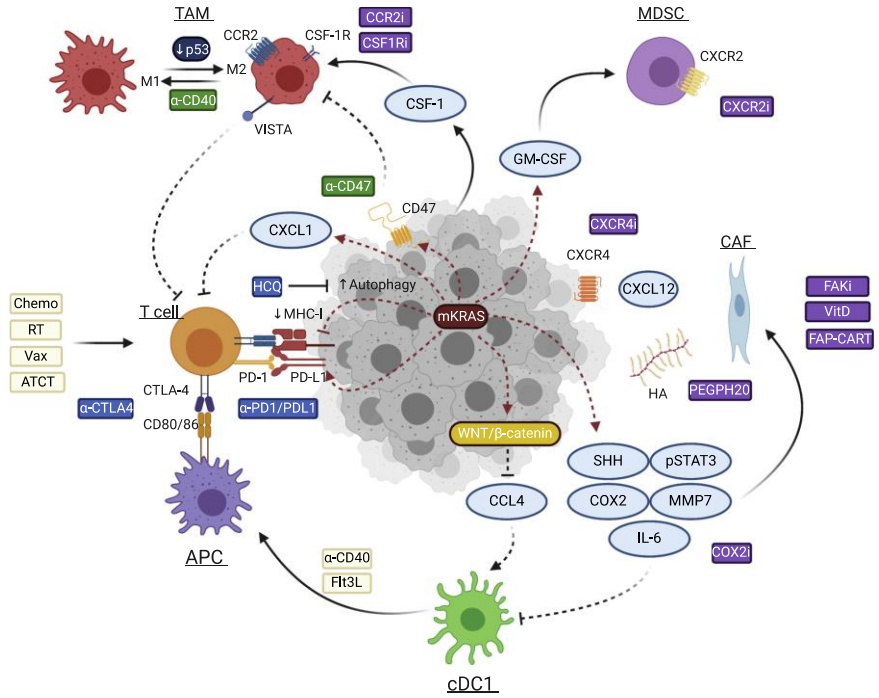
- Several high impact papers reported a tumour promoting role in PDAC
- My lab have a lot of evidence that this isn't true…. If nothing else, the conflicting data show that model and context are very important!



Aside: Do we know what tertiary lymphoid structures are doing???

Tumour-Intrinsic immune resistance

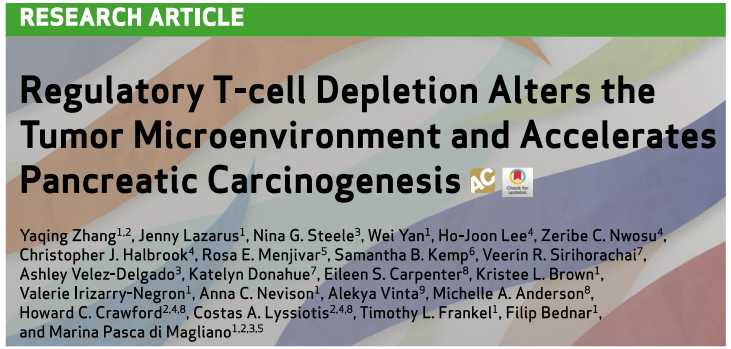
- mKRAS orchestrates a network of immunosuppression
  - enhances autophagocytosis to modulate cell surface MHC-I
  - regulates expression of CD47 & PD-L1
  - drives GM-CSF & CXCL1 expression
  - downregulates CCL4 to impede DC recruitment
  - promotes SHH signalling & expression of COX2, IL-6, pSTAT3, and MMP7 tc drive chronic inflammation & fibrosis.
- p53 deficiency promotes M2-like TAM polarization.
- $p53^{R172H}$ mutation drives neutrophil accumulation
- *Cdkn2a*, *Pten*, *Lkb1* mutations all associated with IO resistance



Should we consider genetic/transcriptomic subtype when thinking about immune-targeting strategies?

Targeting T cell function

- ICB (typically targeting PD-1/PD-L1 or CTLA-4) has been been largely unsuccessful, beyond the ~1% of patients with MSI high tumors
- Although T cell numbers can vary, they're rarely located adjacent to tumor cell nests. Thus, efforts have focused on increasing T cell numbers more than targeting function
- But, do we understand T cells well enough???
  - e.g. Are Tregs good or bad???
  - What ICB should we use?? (e.g. TIGIT – Pasca di Magliano, Jacks)



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What about the 'other' T cells?

- γδ T cells
  - γδT cells constitute ~40% of infiltrating T cells in PDAC???

- Innate lymphoid cells – do they do anything??

Article

Cell

γδ T Cells Support Pancreatic Oncogenesis by Restraining αβ T Cell Activation

Donnele Daley,[1,6,7] Constantinos Pantelis Zambirinis,[1,6,7] Lena Seifert,[1,6,7] Neha Akkad,[1] Navyatha Mohan,[1] Gregor Werba,[1] Rocky Barilla,[1] Alejandro Torres-Hernandez,[1] Mautin Hundeyin,[1] Vishnu Raj Kumar Mani,[1] Antonina Avanzi,[1] Daniel Tippens,[1] Rajkishen Narayanan,[1] Jung-Eun Jang,[2,3] Elliot Newman,[1] Venu Gopal Pillarisetty,[4] Michael Loran Dustin,[3,5] Dafna Bar-Sagi,[2] Cristina Hajdu,[3] and George Miller[1,6,8,*]

Article

ILC2s amplify PD-1 blockade by activating tissue-specific cancer immunity

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John Alec Moral[1,2,3], Joanne Leung[1,2,3,17], Luis A. Rojas[1,2,3,17], Jennifer Ruan[1,2,3,17], Julia Zhao[1,2,3], Zachary Sethna[1,2,3], Anita Ramnarain[1,2,3], Billel Gasmi[4], Murali Gururajan[5], David Redmond[6], Gokce Askan[7], Umesh Bhanot[7], Ela Elyada[8,9], Youngkyu Park[8,9], David A. Tuveson[8,9], Mithat Gönen[10], Steven D. Leach[11], Jedd D. Wolchok[2,4,12,13,14,15], Ronald P. DeMatteo[16], Taha Merghoub[2,4,13,14,15]✉ & Vinod P. Balachandran[1,2,3,13]✉

Hot topics

- Neoantigen quality, not quantity?

Article

Neoantigen quality predicts immunoediting in survivors of pancreatic cancer

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Published online: 19 May 2022
Open access
Check for updates

Marta Łuksza[1,16], Zachary M. Sethna[2,3,4,16], Luis A. Rojas[3,4,16], Jayon Lihm[2], Barbara Bravi[5,6], Yuval Elhanati[2], Kevin Soares[4,7], Masataka Amisaki[3,4], Anton Dobrin[8,9], David Hoyos[2], Pablo Guasp[3,4], Abderezak Zebboudj[3,4], Rebecca Yu[3,4], Adrienne Kaya Chandra[3,4], Theresa Waters[3,4], Zagaa Odgerel[3,4], Joanne Leung[4], Rajya Kappagantula[7,10], Alvin Makohon-Moore[7,10], Amber Johns[11], Anthony Gill[11,12], Mathieu Gigoux[3,13], Jedd Wolchok[3,13], Taha Merghoub[3,13], Michel Sadelain[8,9], Erin Patterson[4], Remi Monasson[5], Thierry Mora[5], Aleksandra M. Walczak[5], Simona Cocco[5], Christine Iacobuzio-Donahue[7,10], Benjamin D. Greenbaum[2,14] & Vinod P. Balachandran[3,4,7,15]

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Neoantigen T-Cell Receptor Gene Therapy in Pancreatic Cancer

Rom Leidner, M.D., Nelson Sanjuan Silva, B.S., Huayu Huang, M.S., David Sprott, B.S., Chunhong Zheng, Ph.D., Yi-Ping Shih, Ph.D., Amy Leung, B.S., Roxanne Payne, M.N., Kim Sutcliffe, B.S.N., Julie Cramer, M.A., Steven A. Rosenberg, M.D., Ph.D., Bernard A. Fox, Ph.D., Walter J. Urba, M.D., Ph.D., and Eric Tran, Ph.D.

CellPress

Immunity
Article

Tumor Cell-Intrinsic Factors Underlie Heterogeneity of Immune Cell Infiltration and Response to Immunotherapy

Jinyang Li,[1,14] Katelyn T. Byrne,[2,5,14,*] Fangxue Yan,[1] Taiji Yamazoe,[1] Zeyu Chen,[6] Timour Baslan,[9] Lee P. Richman,[1] Jeffrey H. Lin,[1] Yu H. Sun,[11] Andrew J. Rech,[1,5] David Balli,[1] Ceire A. Hay,[2] Yogev Sela,[1] Allyson J. Merrell,[1] Shannon M. Liudahl,[12] Naomi Gordon,[1] Robert J. Norgard,[1] Salina Yuan,[1] Sixiang Yu,[1] Timothy Chao,[1] Shuai Ye,[1] T.S. Karin Eisinger-Mathason,[1] Robert B. Faryabi,[1,6,7] John W. Tobias,[8] Scott W. Lowe,[9,10] Lisa M. Coussens,[12] E. John Wherry,[4,5,6] Robert H. Vonderheide,[1,2,4,5,6,*] and Ben Z. Stanger[1,2,3,4,5,13,*]

LETTER

doi:10.1038/nature24462

Identification of unique neoantigen qualities in long-term survivors of pancreatic cancer

Vinod P. Balachandran[1,2,3], Marta Łuksza[4], Julia N. Zhao[1,2,3], Vladimir Makarov[5,6], John Alec Moral[1,2,3], Romain Remark[7], Brian Herbst[2], Gokce Askan[2,8], Umesh Bhanot[8], Yasin Senbabaoglu[9], Daniel K. Wells[10], Charles Ian Ormsby Cary[10], Olivera Grbovic-Huezo[2], Marc Attiyeh[1,2], Benjamin Medina[1], Jennifer Zhang[1], Jennifer Loo[1], Joseph Saglimbeni[2], Mohsen Abu-Akeel[9], Roberta Zappasodi[9], Nadeem Riaz[6,11], Martin Smoragiewicz[12], Z. Larkin Kelley[13,14], Olca Basturk[8], Australian Pancreatic Cancer Genome Initiative*, Mithat Gönen[15], Arnold J. Levine[4], Peter J. Allen[1,2], Douglas T. Fearon[13,14], Miriam Merad[7], Sacha Gnjatic[7], Christine A. Iacobuzio-Donahue[2,5,8], Jedd D. Wolchok[3,9,16,17,18], Ronald P. DeMatteo[1,2], Timothy A. Chan[3,5,6,11], Benjamin D. Greenbaum[19], Taha Merghoub[3,9,18]§ & Steven D. Leach[1,2,5,20]§

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Hot topics - microbiome

Bacterial ablation protects against PDAC, associated with reduced MDSCs, M1-like TAM polarisation, increased TH1 CD4 T cells, and CTL activation. The PDA microbiome generates a tolerogenic immune program by activating select TLRs in monocytes?

Tumor Microbiome Diversity and Composition Influence Pancreatic Cancer Outcomes

Erick Riquelme,[1,2,18] Yu Zhang,[1,18] Liangliang Zhang,[3,4] Maria Montiel,[1] Michelle Zoltan,[1] Wenli Dong,[3] Pompeyo Quesada,[1] Ismet Sahin,[5] Vidhi Chandra,[1] Anthony San Lucas,[6] Paul Scheet,[6] Hanwen Xu,[1] Samir M. Hanash,[1,7] Lei Feng,[3] Jared K. Burks,[8] Kim-Anh Do,[3] Christine B. Peterson,[3] Deborah Nejman,[9] Ching-Wei D. Tzeng,[10] Michael P. Kim,[10] Cynthia L. Sears,[11] Nadim Ajami,[12] Joseph Petrosino,[12] Laura D. Wood,[13] Anirban Maitra,[14] Ravid Straussman,[9] Matthew Katz,[10] James Robert White,[15] Robert Jenq,[4] Jennifer Wargo,[4,10] and Florencia McAllister[1,16,17,19,*]

The gut microbiome modulates the PDAC tumor microbiome landscape. A high diversity PDAC tumoral microbiome signature predicts long- term survival, with fecal microbial transplants able to modulate tumour growth and the immune TME.

LETTER

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The fungal mycobiome promotes pancreatic oncogenesis via activation of MBL

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Antifungals limited PDAC progression and improved chemo efficacy. A glycan on the wall of a yeast prevalent in mouse and human PDAC is recognized by mannose binding lectin which activates C3 and the complement cascade?

or…

Article

Fungal mycobiome drives IL-33 secretion and type 2 immunity in pancreatic cancer

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Pancreatic Cancer UK TAKE IT ON

CANCER RESEARCH UK | BEATSON INSTITUTE

Hot topics - radiation

- Can figuring out what's going on in the TME in terms of immune landscape help to improve utility of RT?

JEM Journal of Experimental Medicine

ARTICLE

CCR2/CCR5 inhibitor permits the radiation-induced effector T cell infiltration in pancreatic adenocarcinoma

Jianxin Wang[1,4,5*], May Tun Saung[1,4,5*], Keyu Li[1,4,5], Juan Fu[1,4,5], Kenji Fujiwara[1,4,5], Nan Niu[1,4,5], Stephen Muth[1,4], Junke Wang[1,4,5], Yao Xu[1,2,4,5], Noah Rozich[1,2,4,5], Haley Zlomke[1,2,4,5], Sophia Chen[1,2,4,5], Birginia Espinoza[1,4,5], MacKenzie Henderson[1,4,5], Vanessa Funes[1,4,5], Brian Herbst[1,4,5], Ding Ding[1,2,4,5], Christina Twyman-Saint Victor[6], Qihong Zhao[6], Amol Narang[1,3,4], Jin He[1,2,4], and Lei Zheng[1,2,4,5]

CLINICAL CANCER RESEARCH | TRANSLATIONAL CANCER MECHANISMS AND THERAPY

Modulation of the Human Pancreatic Ductal Adenocarcinoma Immune Microenvironment by Stereotactic Body Radiotherapy

Bradley N. Mills[1], Haoming Qiu[2,3], Michael G. Drage[4], Chunmo Chen[4], Jocelyn S. Mathew[1], Jesse Garrett-Larsen[1], Jian Ye[1], Taylor P. Uccello[5], Joseph D. Murphy[5], Brian A. Belt[1], Edith M. Lord[3,5], Alan W. Katz[2,3], David C. Linehan[1,3], and Scott A. Gerber[1,3,5]

Tumor Biology and Immunology

Cancer Research

Radiotherapy and CD40 Activation Separately Augment Immunity to Checkpoint Blockade in Cancer

Andrew J. Rech[1], Hannah Dada[2], Jonathan J. Kotzin[3,4], Jorge Henao-Mejia[3,4,5], Andy J. Minn[1,4,6,7], Christina Twyman-Saint Victor[2,4,6,7], and Robert H. Vonderheide[1,2,4,7]

LETTER

doi:10.1038/nature14292

Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer

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Hot topics – vaccines

- Therapeutic cancer vaccines have historically been unsuccessful; however, recent developments have reignited interest.
- Mutant KRAS epitopes can be presented on multiple human HLA alleles and can elicit antitumor T cell responses, suggesting T cell recognition of mKRAS is possible.
- Analysis of blood from healthy donors with diverse HLA haplotypes revealed that mutant KRAS-specific T cells could be readily expanded.
- Given the early emergence of KRAS mutations, mKRAS-specific T cells may acquire tolerance?
- The development of better tools for candidate neoantigen prioritization, improved vaccine delivery platforms, and innate immune adjuvants or microbial products to engage TLR signalling and support DC activation/function could drive development?

SCIENCE IMMUNOLOGY | RESEARCH ARTICLE

IMMUNOTHERAPY

Bispecific antibodies targeting mutant *RAS* neoantigens

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Where are we going?

- Probably, more and more combos?
- Combination approaches to target tumour cells, CAFs/ECM, immune system, but also the myeloid cell mediated resistance to maximize response.
- Cancer vaccines????
- Adoptive T cell therapies????
- ???

Ongoing IO Trials

Strategy	Molecular target	Cell targets	Active clinical trial(s)
Removing short-lived immunosuppressive myeloid cells	CCR2	Infiltrating monocytic immunosuppressive cells	NCT03496662: BMS-813160 with nivolumab and Gem/Abraxane in borderline resectable and locally advanced PDAC
	CXCR2	Infiltrating granulocytic immunosuppressive cells	NCT04477343: SX-682 with nivolumab as a maintenance therapy in metastatic PDAC
Reprogramming DCs to better prime tumor-specific T cell responses	FLT3L and CD40 (agonism)	Mobilization of conventional DCs from bone marrow and activation in the TME	NCT04536077: Immunologic effects of CDX-301 and CDX-1140 in resectable PDAC NCT03329950: A study of CDX-1140 (CD40) as monotherapy or in combination in patients with advanced malignancies
Reprogramming PDAC-associated fibroblasts	Vitamin D receptor	PDAC-associated fibroblasts	NCT03520790: Paricalcitol plus Gem/Abraxane in previously-untreated metastatic PDAC NCT02754726: Phase II Pilot of Paricalcitol + Gem/Abraxane + Nivolumab + Cisplatin in first-line metastatic PDAC
Blocking immunosuppressive TGFβ signaling	Angiotensin II receptor	PDAC-associated fibroblasts	NCT03563248: Losartan and nivolumab in combination with FOLFIRINOX and SBRT in localized PDAC.
Blocking immunosuppressive TGFβ signaling	TGFβ	PDAC-associated fibroblasts	NCT04390763: NIS793 (+/- spartalizumab) in combination Gem/Abraxane in first-line metastatic PDAC
Blocking immunosuppressive IL-1β signaling	IL-1β	PDAC-associated fibroblasts	NCT04581343: Phase 1B study of canakinumab, spartalizumab, and Gem/Abraxane in metastatic PDAC

Vaccine Trials in PDAC

Vaccine candidate	Molecular targets	Mechanism	Phase	Trial design	Population	Primary endpoints
mRNA-5671/V941	KRASG12D, KRASG12V, KRASG13D, KRASG12C	mRNA against KRAS elicits T cell response	1	Two-arm trial: drug alone and drug plus pembrolizumab	Basket trial with KRAS-mutated PDAC, NSCLC, or CRC	Safety
ELI-002	KRASG12D, KRASG12R	Lipid-conjugated immune-stimulatory oligo + mix of lipid-conjugated peptide-based antigens	2	90 patients with PDAC randomized to vaccine or observation	Basket trial with KRAS-mutated PDAC, CRC, NSCLC, OvCa, CCa.	relapse-free survival
KRAS peptide vaccine + poly-ICLC		Targeted long peptide vaccine elicits immune response against mutant KRAS	1	Single-arm, sequential assignment of individuals	Individuals with high risk of PDAC by family history or germline mutation	Safety, IFN-producing mutant KRAS-specific CD4+ & CD8+ T cells
KRAS peptide vaccine plus poly-ICLC	KRASG12C, KRASG12V, KRASG12D, KRASG12A, KRASG13D, KRASG12R	Targeted vaccine elicits immune response against mKRAS, enhanced with ICB	1	Single-arm study of vaccine candidate + anti-PD-1 + anti-CTLA-4	Resected PDAC patients after neoadjuvant and/or adjuvant chemo and/or RT	Safety, IFN-producing mutant KRAS-specific CD8+ & CD4+ T cells
Neoantigen peptide vaccine plus poly-ICLC	Prioritized neoantigens and personalized mesothelin epitopes	Neoantigen peptide vaccine will generate neoantigen-specific CD4 & CD8 T cell responses	1	Single-arm study of PDAC patients	Resected PDAC patients after adjuvant chemotherapy	Safety
RO7198457 (mRNA-based personalized tumor vaccine)	Tumor-associated antigens	APCs take up vaccine and express antigens, leading to CTL and memory responses	1	Single-arm study in resected PDAC + vaccine + FOLFIRINOX + atezolizumab.	Resected PDAC patients	Safety
Synthetic personalized tumor-associated peptide vaccine therapy	Tumor-associated antigens	APCs take up vaccine and express antigens, leading to CTL and memory responses	I	Single-arm study of imiquimod (TLR7 agonist), pembrolizumab + vaccine	Patients with advanced PDAC or CRC	Demonstrate feasibility & safety of vaccine + pembrolizumab

Where should we be going?

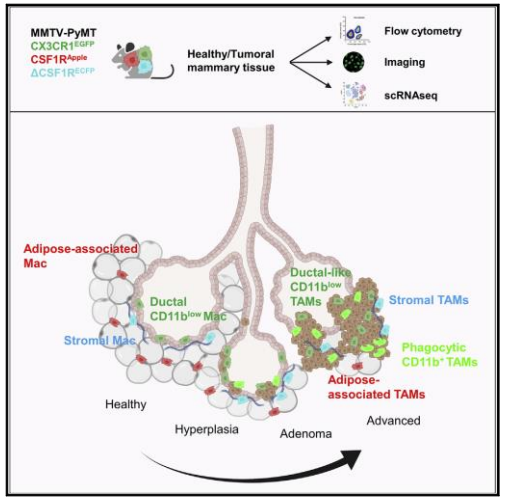
- Better models (cell of origin!)
  - Do we need germ-free facilities???
- Consideration of tumour genetics?
  - e.g. mutations linked to intrinsic resistance to ICB
- Predictive biomarkers (e.g. NLR)
- Spatial analysis – transcriptomic, multiplex IF
  - Can we target subsets of cells or aberrant signalling, to 'normalize' rather than wiping out whole cell populations
- Intravital imaging of transient interactions

Article

Cell Reports

Tumor-associated macrophage heterogeneity is driven by tissue territories in breast cancer

Graphical abstract



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In brief

The origin of tumor-associated macrophage (TAM) heterogeneity is unclear. Laviron et al. show that TAM diversity is driven by the various tissue territories existing prior to tumor apparition and by the state of tumor malignancy. This provides a definition of TAM heterogeneity according to their spatial distribution *in situ*.

Highlights

- TAMs differentiate according to their localization *in situ*
- TAM heterogeneity is associated with resident TAM diversity prior to tumor development
- Orthotopic tumor models negate TAM diversity
- Similar heterogeneity is found in human breast TAMs

Where should we be going?

- Pancreatitis – why is the relative risk of PDAC not much higher?
- Investigation of cachexia and other systemic changes
  - Interplay between tumor and host ‘normal’ cells can have effects in the tumour and systemically. In turn, systemic signals may impact tumour biology.
  - Cancer-associated cachexia likely depends on specific tumour-related mechanisms including pro-inflammatory signals.
  - Does altered systemic inflammation/metabolism affect the tumour immune microenvironment?

Cancer Cell

CellPress

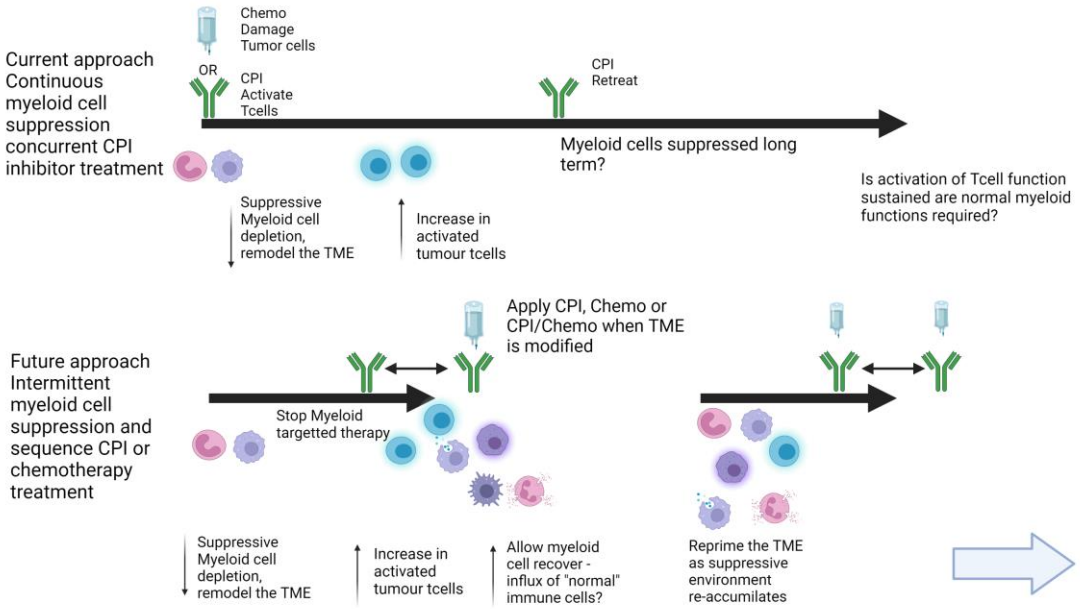
Article

Exercise-induced engagement of the IL-15/IL-15Rα axis promotes anti-tumor immunity in pancreatic cancer

Emma Kurz,[1] Carolina Alcantara Hirsch,[1,2] Tanner Dalton,[3] Sorin Alberto Shadaloey,[1] Alireza Khodadadi-Jamayran,[4] George Miller,[5] Sumedha Pareek,[6] Hajar Rajaei,[7] Chirayu Mohindroo,[7] Seyda Baydogan,[7] An Ngo-Huang,[8] Nathan Parker,[9] Matthew H.G. Katz,[10] Maria Petzel,[11] Emily Vucic,[2] Florencia McAllister,[7,12] Keri Schadler,[6] Rafael Winograd,[13] and Dafna Bar-Sagi[2,14,*]

Where should we be going?

- Scheduling / priming studies?
  - Priming the immune system by targeting suppressive cells prior to chemo + ICB?
  - Intermittent dosing could allow “normalised” myeloid cells to repopulate tumours and support anti-tumour immune responses (and manage tox?)
- Personalized IO strategies for individual patients or patient subgroups
- Better trials (not set up to fail!)



Conclusions

- There's a lot we don't know
- The immune TME appears, on the whole, to be tumour-promoting.
  - Is is too late to re-educate the tumour-promoting immune cells in PDAC patients? Can we only target it in terms of immunosuppression?
- There are many potential ways to transform the PDAC TME from ''cold'' to ''hot'' but we don't know which might be effective or in what combination
  - Targeting Myeloid cells / Targeting CAFs and/or ECM / Anti-CD47 to re-activate "eat me" signalling?? / Priming innate immunity - via cGAS-STING, TLRs, etc - Good or bad idea? / CD40 agonists to restore cDC1 function / novel ICB targets: TIGIT, TIM3, VISTA / Cancer vaccines, Can mKRAS be harnessed as a tumour antigen? / Adoptive T cell therapies?
- Personalized immunotherapy strategies might be appropriate for individual patients or subgroups of patients ???

Points for discussion

- What are we genuinely confident that we know?!
- What don't we know that we need to?
- Can we address this? What do we need for that to happen? (tools, tech, teamwork?)
- Is this something we do well as a UK community?
  - Should we be doing this??
- Can we work better together?