# Supramolecular attack particles (SMAPs) for pancreatic cancer immunotherapy

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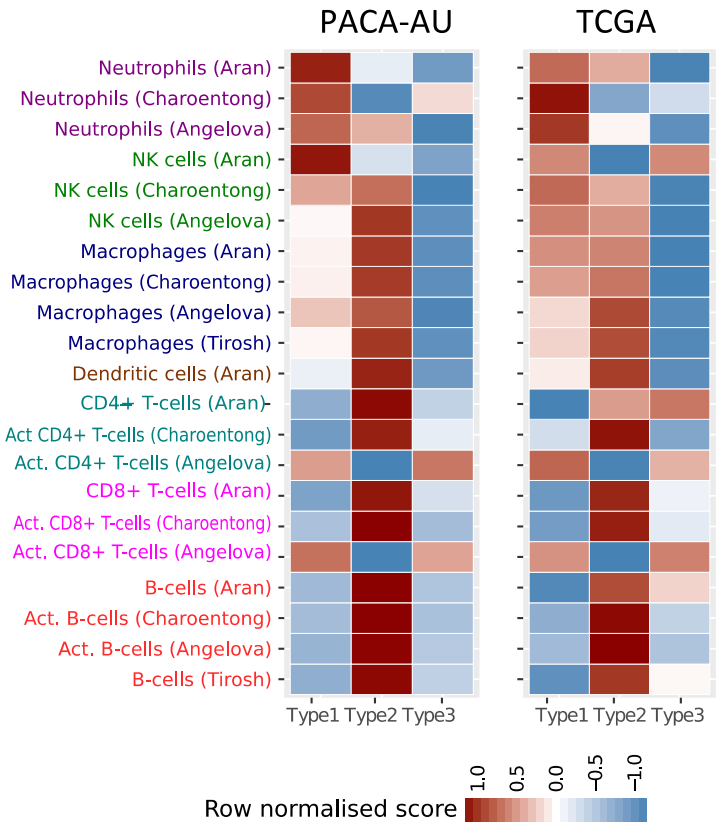
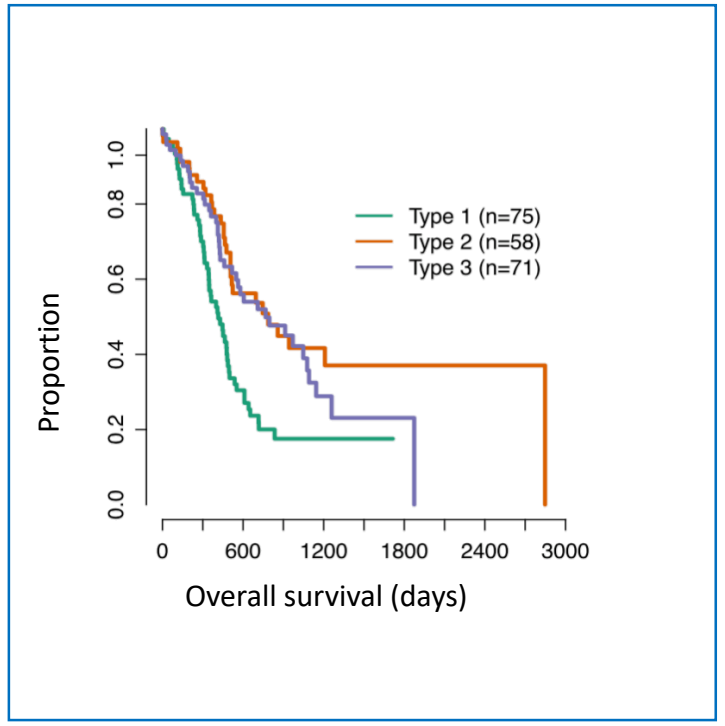
University of Oxford, University of Siena, Harvard Medical School

# Characterising the Pancreatic Cancer Microenvironment




Type 2 and 3, believed to be same phenotype,
Difference can be explained by cellularity

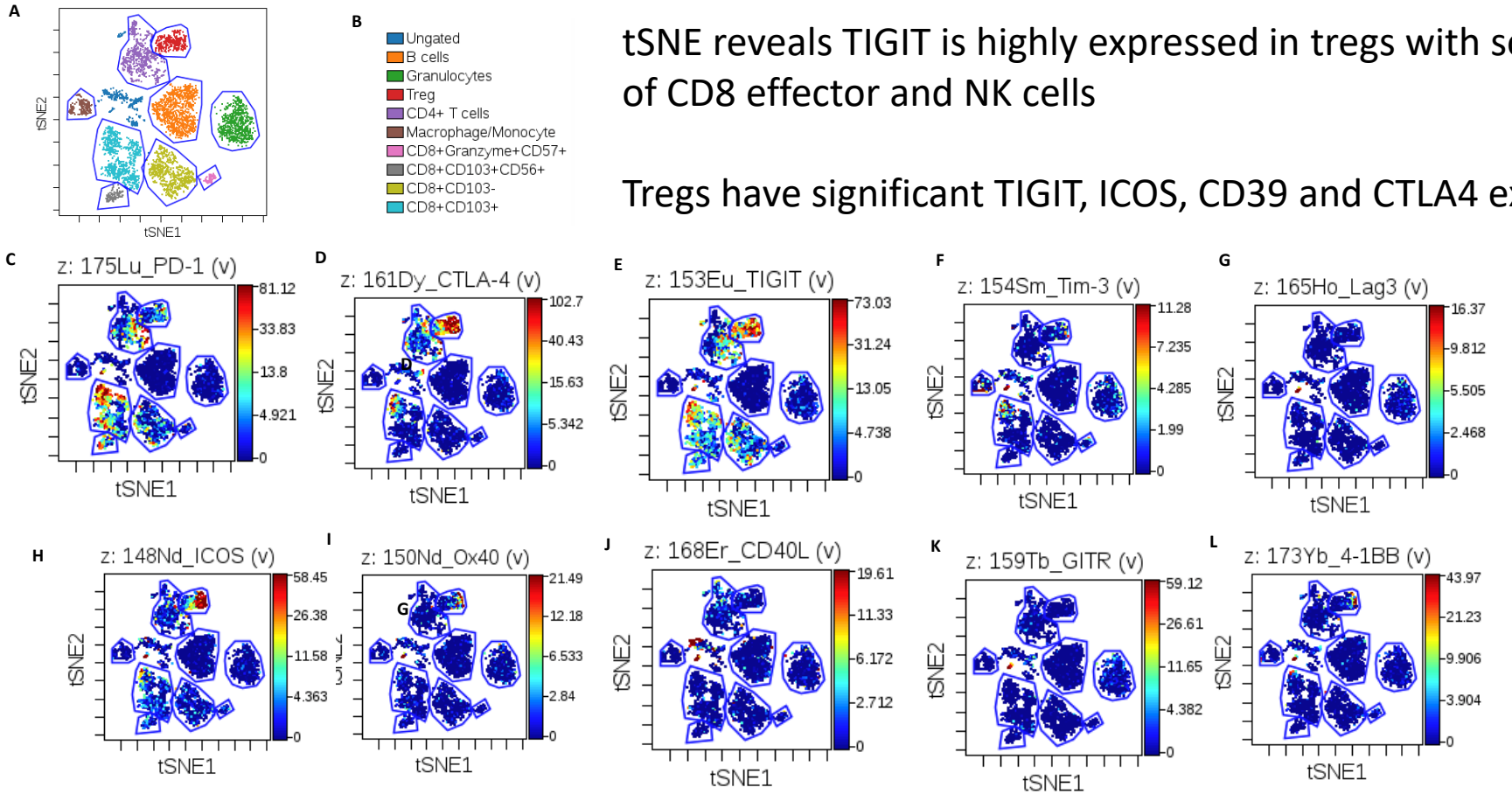
De Santiago, I.... Dustin, M., Sivakumar, S. 2019

# STATUS OF T-CELLS IN PANCREATIC CANCER by MASS CYTOMETRY

Majority of CD8 and CD4 are senescent

tSNE reveals TIGIT is highly expressed in tregs with some expression of CD8 effector and NK cells

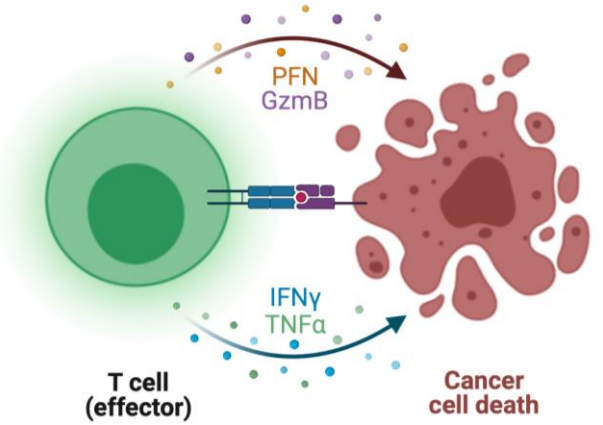
Tregs have significant TIGIT, ICOS, CD39 and CTLA4 expression

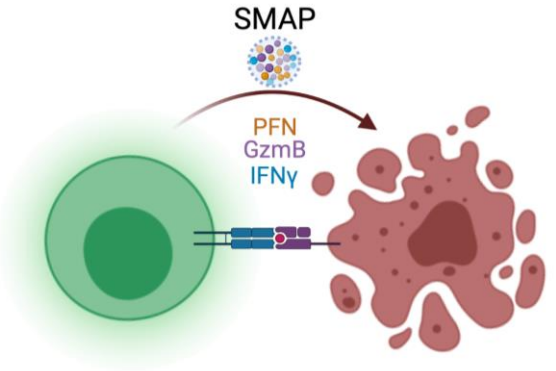



Sivakumar, Abu Shah…. Dustin. Cancers 2021

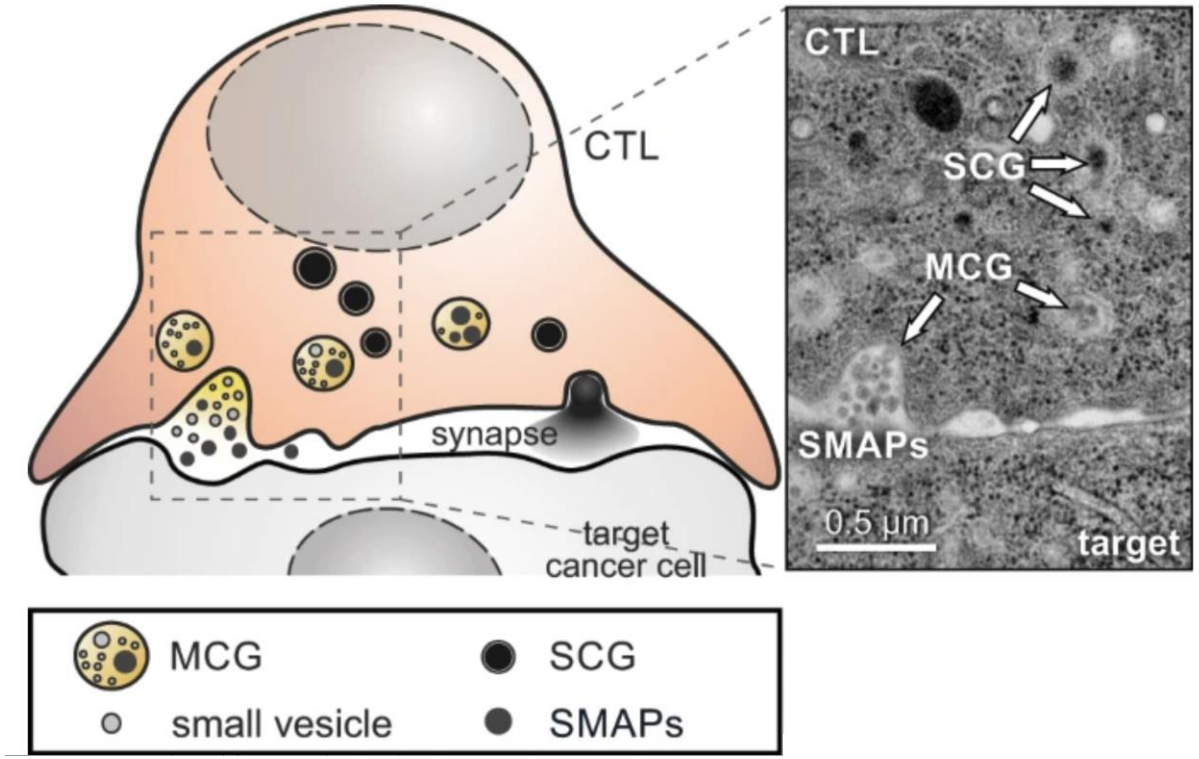
# Supramolecular attack particles (SMAPs)

- Natural glycoprotein shell-cytotoxic core nanoparticles discovered in Dustin lab (patent/publication 2020).
- Combines the key cytotoxic agents from CTL in a 110 nm particle that can kill target cells autonomously.
- T cells deliver SMAPs to tumors, but this process fails in PDAC.
- We propose to directly target SMAPs to tumors through the blood and circumvent PDAC defences.



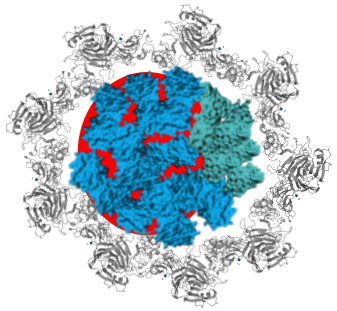



# SMAP biology and composition



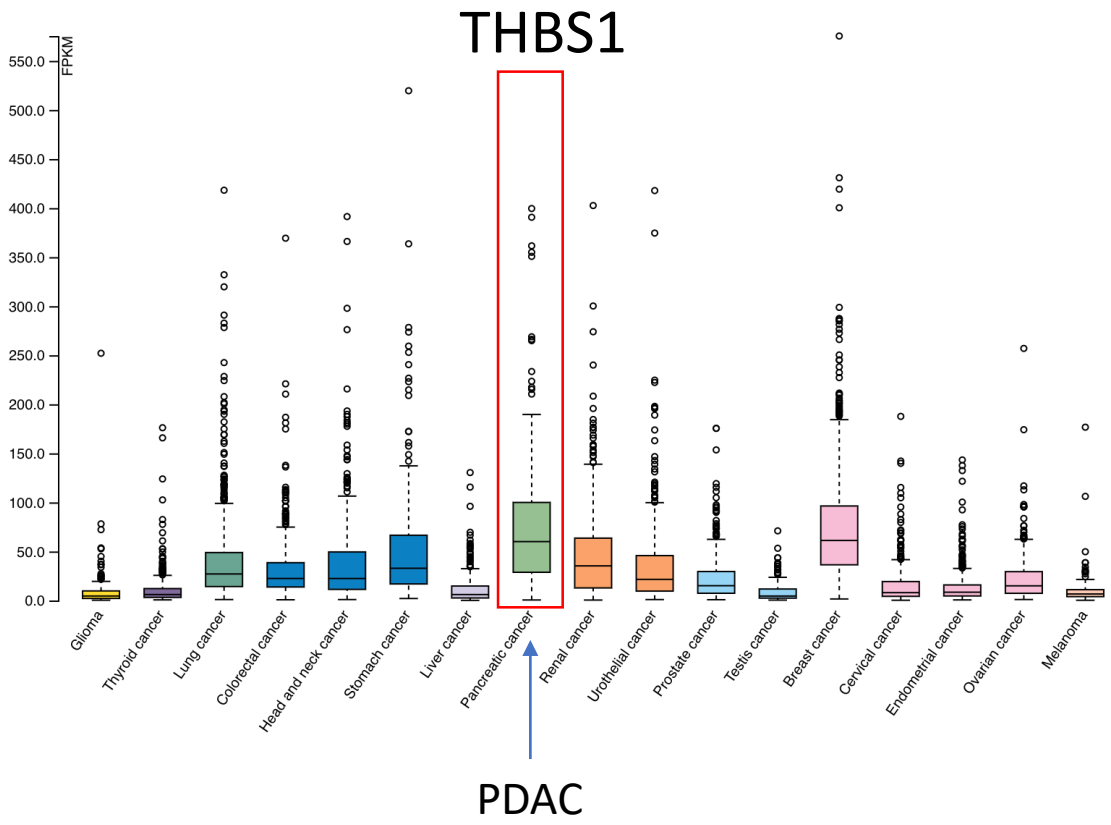

Balint et al, *Science* 2020
Chang et al, *Nature Comms* 2022
50% of degranulation events release SMAPs.
50% of GZMB and 100% of THBS1 is in SMAPs.

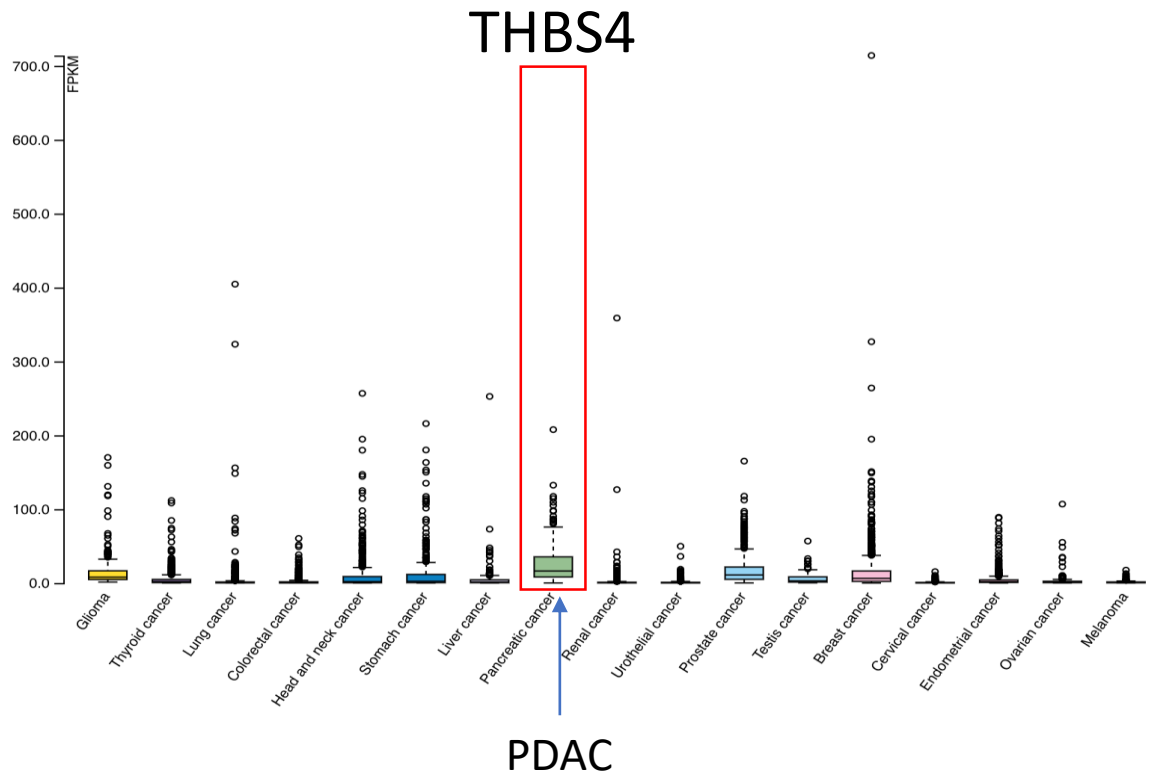
- Supramolecular attack particle
  - Glycoprotein shell
    - Thrombospondin-1 (gray)
    - Thrombospondin-4
    - Galectin-1
    - Others components- proteomics
  - Cytotoxic core
    - Granzyme B (blue)
    - Granzyme A
    - Perforin-1 (green)
    - Interferon gamma
    - Chemokines
    - Serglycin (red)



Proteomics by Benedikt Kessler (Oxford).

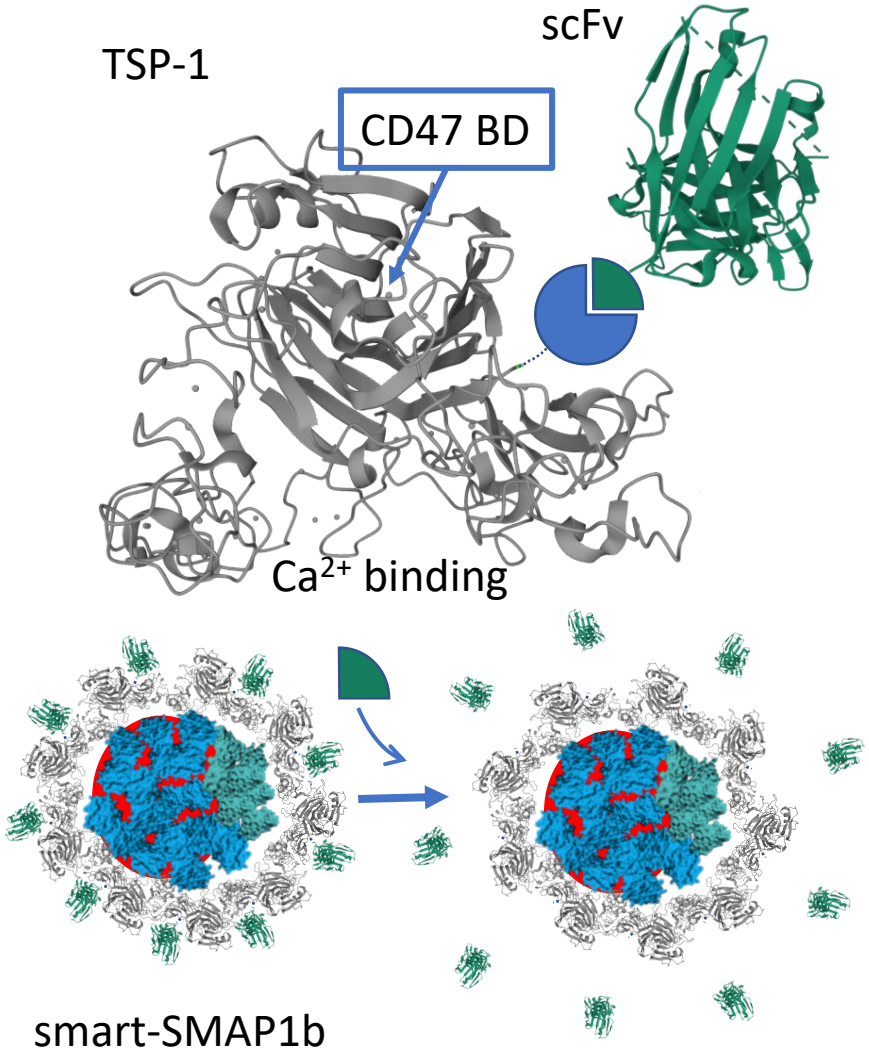
# PDAC expresses high levels of thrombospondins 1 and 4, part of SMAP shell.




TCGA data mined by Ashwin Jainarayanan

# smart-SMAP1




- SMAPs are cytotoxic particles generated by cytotoxic T cells (50% of GZMB).
- Pancreatic cancer cell lines produce SMAP-like particles containing same form of THBS1.
- We propose to develop Smart-SMAP – CAR-like cytotoxic particles to target pancreatic cancer.

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Lina Chen- protein infrastructure
Ewoud Compeer- ATTACK- Treg SMAPs
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Elke Kurz- SMAPCAN
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Alex Mørch- RIFINs and Coreceptors
Shivan Sivakumar- BMS- PANCAN
Oskar Staufer (Marie Curie)- Synthetic cells
Salvatore Valvo- bilayer infrastructure

Recent Alumni

James Felce (ONI)- Chemokine Receptors
Viveka Mayya (Century)- T cell search
Philippos Demetriou (Cyprus)- CD2 corolla
David Depoil (Evotech)- CD2 corolla
Enas Abu Shah (Adaptimmune)- T cell eng.
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http://www.ibiology.org/ibioseminars/michael-dustin-part-1.html