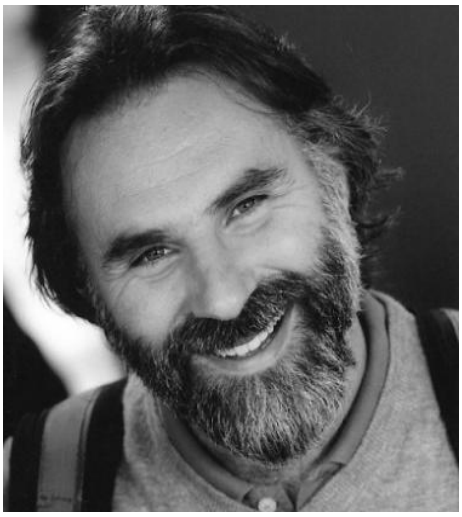
ImmunoTools *special* Award 2025



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Investigating AdCab-mediated modulation of monocytes and macrophages in pancreatic cancer

Need

Pancreatic ductal adenocarcinoma (PDAC) remains one of the deadliest cancers, with a median survival of less than 5 months and 5-year survival below 3%. Despite the remarkable success of cancer immunotherapies in other malignancies, none have been clinically approved for PDAC due to its highly immunosuppressive tumor microenvironment (TME). The TME is dominated by suppressive monocytes and macrophages, which shield tumor cells and suppress T cell activation, making conventional immunotherapies ineffective.

To overcome this, we have developed AdCab, a novel oncolytic adenovirus armed with a chimeric PD-L1 antibody featuring an Fc region that combines IgA and IgG properties. Once injected, AdCab selectively replicates in tumor cells, turning them into “biofactories” that both die through viral replication and release the therapeutic antibody directly into the TME.
This Fc design is key to AdCab’s mechanism of action. Standard IgG antibodies bind Fcγ receptors (such as CD16A on NK cells) but are limited by inhibitory Fcγ receptors (CD16B, CD32B) on myeloid cells, which dampen activity. Conversely, IgA antibodies bind FcαRI

(CD89), a potent activating receptor expressed on monocytes and macrophages, but they cannot recruit NK cells. By combining IgA and IgG into one chimeric Fc, AdCab uniquely:

1. Engages CD89 (FcαRI) on monocytes/macrophages, rewiring them into pro-inflammatory, anti-tumor effectors instead of suppressors.
2. Activates NK cells via IgG Fc interactions, enabling cytotoxic killing that IgA alone cannot provide.
3. Overcomes inhibitory Fcγ signaling that limits conventional IgG antibodies.
4. Broadly activates multiple immune cell subsets simultaneously (NK cells, macrophages, neutrophils, and T cells), minimizing exhaustion compared to antibodies that rely on a single effector population.

This dual IgA/IgG Fc strategy, combined with tumor-restricted viral delivery, makes AdCab fundamentally distinct from all clinically approved PD-L1 antibodies, which can block PD-L1 but cannot eliminate or reprogram suppressive myeloid cells.

Approach

We will study blood-derived leukocytes from PDAC patients in a mixed leukocyte reaction (MLR) system, comparing PBS versus AdCab treatment. Unlike isolated culture systems, MLR captures the complexity of immune–immune interactions, providing a more physiologically relevant context to study monocyte/macrophage function. Using ImmunoTools reagents, we will track surface markers that define monocyte/macrophage identity, polarization, and functional state, including:

• CD14, CD16: monocyte/macrophage lineage subsets.
• CD206: M2 macrophage polarization
• CD80: M1 macrophage polarization
• PD-1, CD47: inhibitory receptors mediating immune evasion.
• CD97, CD147: activation receptors linked to migration and inflammation.

In parallel, we will isolate monocytes from healthy volunteers and induce them into anti-inflammatory as well as M1 and M2 (a, b, c) phenotypes using a cocktail of specific cytokines. These polarized monocytes will then be co-cultured with PDAC cells to assess how AdCab modulates their functional state in a tumor context.

Materials and Methods

1. Sample collection: PBMCs will be isolated from fresh blood of PDAC patients.
2. MLR setup: PBMCs will be plated and treated with either PBS or AdCab.
3. staining: We will employ 19 ImmunoTools reagents for simultaneous detection of the above markers.
4. Data acquisition: Multiparametric flow cytometry will quantify expression patterns on circulating monocytes/macrophages in the presence of other immune subsets.

Read-outs

• Changes in monocyte subset distribution (CD14/CD16).
• Shifts in polarization balance: CD206 (M2) vs CD80 (M1).
• Expression of inhibitory versus activation receptors (PD-L1/CD47 vs CD97/CD147).
• Integration with T-cell responses in MLR (secondary read-out).

Expected Impact

This project will provide mechanistic proof-of-concept for how AdCab interacts with and rewires immunosuppressive monocytes/macrophages in PDAC patients. Demonstrating that AdCab reduces suppressive phenotypes while enhancing activation markers will substantiate its unique capacity to overcome the PDAC TME. Such insights will not only validate AdCab's mechanism of action but also guide rational combinations with existing immunotherapies. Importantly, a spin-out company is currently in development to advance AdCab toward clinical translation, and the data generated with ImmunoTools antibodies will directly strengthen its preclinical package.

ImmunoTools *special* AWARD for **Vincenzo Cerullo & Firas Hamdan**

includes 18 reagents

FITC - conjugated anti-human CD16, CD29, CD47

PE - conjugated anti-human CD80, CD86, PD1

PerCP-conjugated anti-human CD14

APC - conjugated anti-human CD147, CD36, CD66ade (CEACAM1/3/5)

Recombinant human cytokines: IFN-γ, GM-CSF, M-CSF, IL-4, IL-10, IL-13, TGF-β, IL-6

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