234 Tumor mitochondria vaccine for the treatment of cancer

Asset Overview

Product Type	Tumor mitochondria vaccine for the treatment of cancer
Indication	Oncology
Current Stage	Lead Identification/optimization
Target(MoA)	Dendritic cell–based RENCA mitochondrial lysate vaccine elicited a cytotoxic T cell response in vivo and conferred durable protection against challenge with RENCA cells.
Brief Description	Researchers at the Ohio State University, led by Dr. Chenglong Li, have designed novel, non-peptidomimetic molecules for use as anti-cancer inhibitors of STAT3, a protein involved in gene expression and associated with various cancers. The molecules were developed using Fragment-based Drug Design (FBDD) and tested for half maximal inhibitory concentration (IC50).
Organization	University of Pennsylvania

Differentiation

□ **Problem**

- Progression in cancer immunotherapy has been rapid with a number of products currently available and many others in late stage clinical development
- However, clinical response to immunotherapies is variable and dependent on cancer types as well as specific characteristics or genetic mutations within a patient's individual tumor
- There is a need for tumor-specific therapies with applicability to a range of cancer types

□ **Solution**

- The Facciabene lab at the University of Pennsylvania has developed a technology that uses Tumor Associated Mitochondria Antigens (TAMAs) extracted from the tumor as a cancer vaccine
- The technology involves pulsing dendritic cells with TAMAs. In an in vivo model of renal cell carcinoma (RCC) the vaccine elicits a cytotoxic T-cell response and provides long-term protection from tumor progression when used either prophylactically or therapeutically
- The Facciabene lab has established that TAMAs can produce an effective anti-tumor immune response in RCC (Future work will validate the data in human RCC and investigate additional cancer types and combinations with other immunotherapies)

□ **Advantages**

- Long-term protection from tumor progression demonstrated in RCC
- Potential use in other cancer types with mutations in mitochondrial proteins (e.g. kidney, colorectal, ovarian, breast, bladder, lung, pancreatic)
- Utilization of a dendritic cell platform validated in humans

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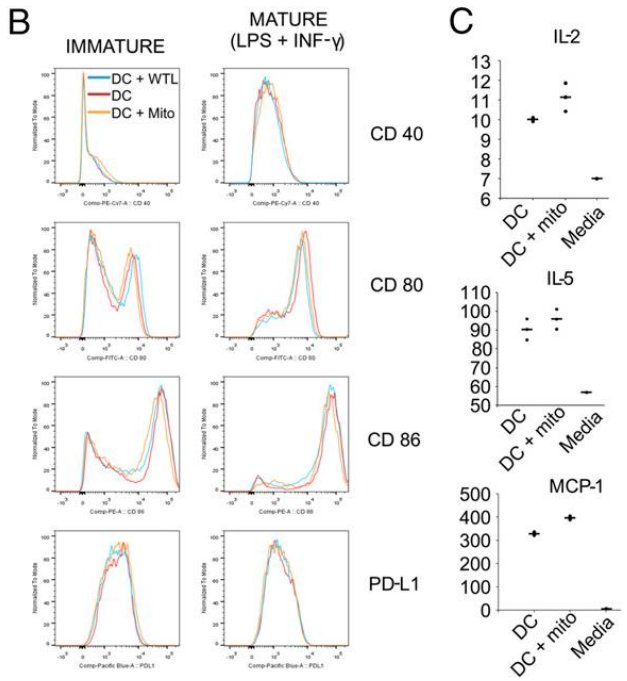
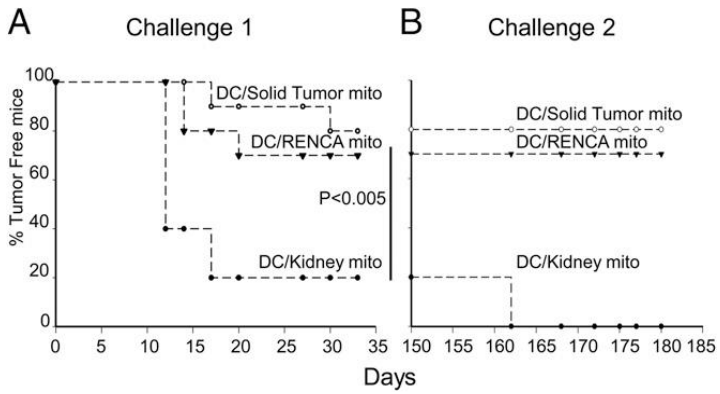
Key Data

Mitochondria lysate is engulfed by in vitro–derived bmDCs but does not induce maturation



B) Immature DCs were pulsed with mitochondrial preparation (Mito) or whole-tumor lysate (WTL) and then matured with IFN-g and LPS (right panels) or left untreated (left panels). CD11c, CD11b double-positive cells were analyzed for CD40, CD80, CD86, and PD-L1 markers by flow cytometry. (C) Cytokine production (IL-2, IL-5, and MCP1) was measured from supernatants of immature DCs cocultured with mitochondria (DC + mito) or immature unpulsed DCs (DC) (p = not significant between pulsed and unpulsed samples for all cytokines examined, all data pg/ml).

Prophylactic vaccination using DCs loaded with RENCA mitochondria lysate



(A) BALB/c lysate derived from RENCA solid tumors (DC/Solid Tumor mito) resected from 20-d-old tumor-bearing mice, from RENCA cells grown in vitro (DC/RENCA mito), or from kidneys (DC/Kidney mito) of healthy mice. Two weeks after the last immunization, animals were injected (s.c.) with 1 3 106 RENCA cells and monitored for tumor growth. Data are mean (n = 10 mice/group for each experiment). p , 0.05, Tumor mito or RENCA mito versus Kidney mito, log-rank test. (B) Animals that rejected tumors after the first challenge in (A) were rechallenged with RENCA cells 3 mo later. All of the animals previously immunized with DC/RENCA mito and DC/Solid Tumor mito were protected after a second challenge.

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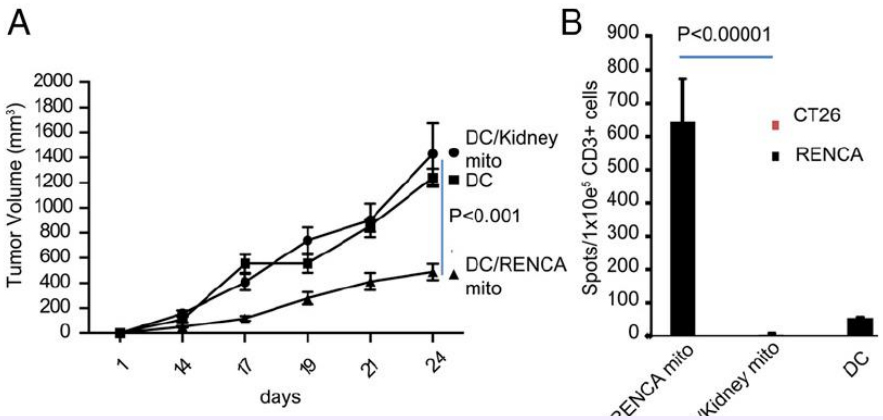
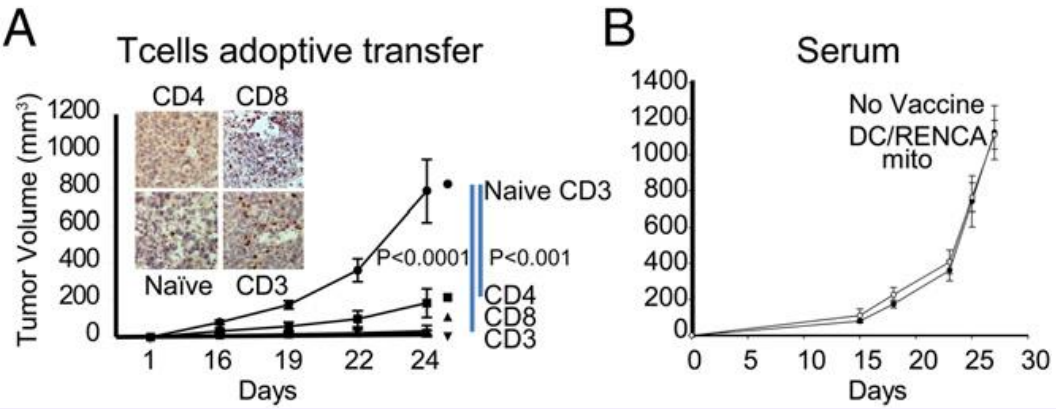
Therapeutic vaccination with DCs loaded with RENCA mitochondria lysate controls tumor progression.



(A) In a therapeutic setting, mice were challenged s.c. with 1 3 106 RENCA cells and were vaccinated 1 wk later with bmDCs pulsed with DC/RENCA mito, DC/Kidney mito, or DCs alone (DC). Data are mean 6 SEM (n = 10 mice/group for each experiment, except DC group [n = 5]). (B) T cells isolated from DC/RENCA mito–vaccinated mice are reactive against RENCA cells. Purified T cells (1 3 105) from DC/RENCA mito–vaccinated mice were cocultured with stimulator RENCA cells or control CT26 cells (10:1 ratio), and IFN-g ELISPOT was performed.

Adoptive transfer demonstrates a T cell–mediated antitumor effect upon vaccination using DCs loaded with RENCA mitochondria



Isolated CD3+, CD4+, and CD8+ T cells and naive CD3+ T cells were injected i.v. into RENCA tumor–bearing mice (challenged 1 wk before the adoptive transfer) that were sublethally irradiated (4–5 Gy) 8 d before adoptive transfer. Data are mean 6 SEM (n = 10 mice/group for each experiment). Adoptively transferred CD3+, CD4+, or CD8+ T cells control tumor progression and result in CD3+ T cell infiltration. p , 0.0001, CD8 and CD3 versus naive CD3; p , 0.001, CD4 versus naive CD3. (B) Serum, injected i.p. into another group of mice, did not control tumor progression (p = not significant).

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Intellectual Property

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