A DC-targeted nano-vaccine to overcome immune suppression and enhance chemotherapy efficacy for pancreatic cancer

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NEXT-GENERATION DELIVERY INNOVATIONS

Current PDAC therapies rely mostly on non-specific drugs, while immunotherapy is mostly ineffective

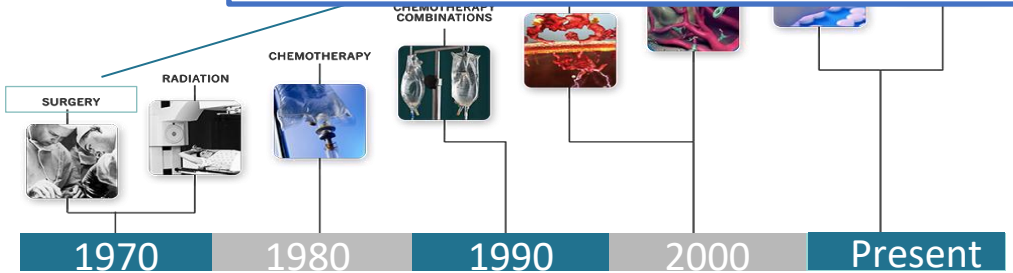
- PDAC (pancreatic ductal adenocarcinoma) is the **most common and aggressive** type of pancreatic cancer
- PDAC **5-year** survival is ~ **10%**
- **Non-specific drugs** for cancer cell destruction → **Severe adverse effects**
- **Anti-PD-1** was approved by the **FDA** in 2017 and **EMA**

in 2020 for tum

- Highly immunosuppressive microenvironment
- Highly dense stroma
- Low infiltration of immune cells

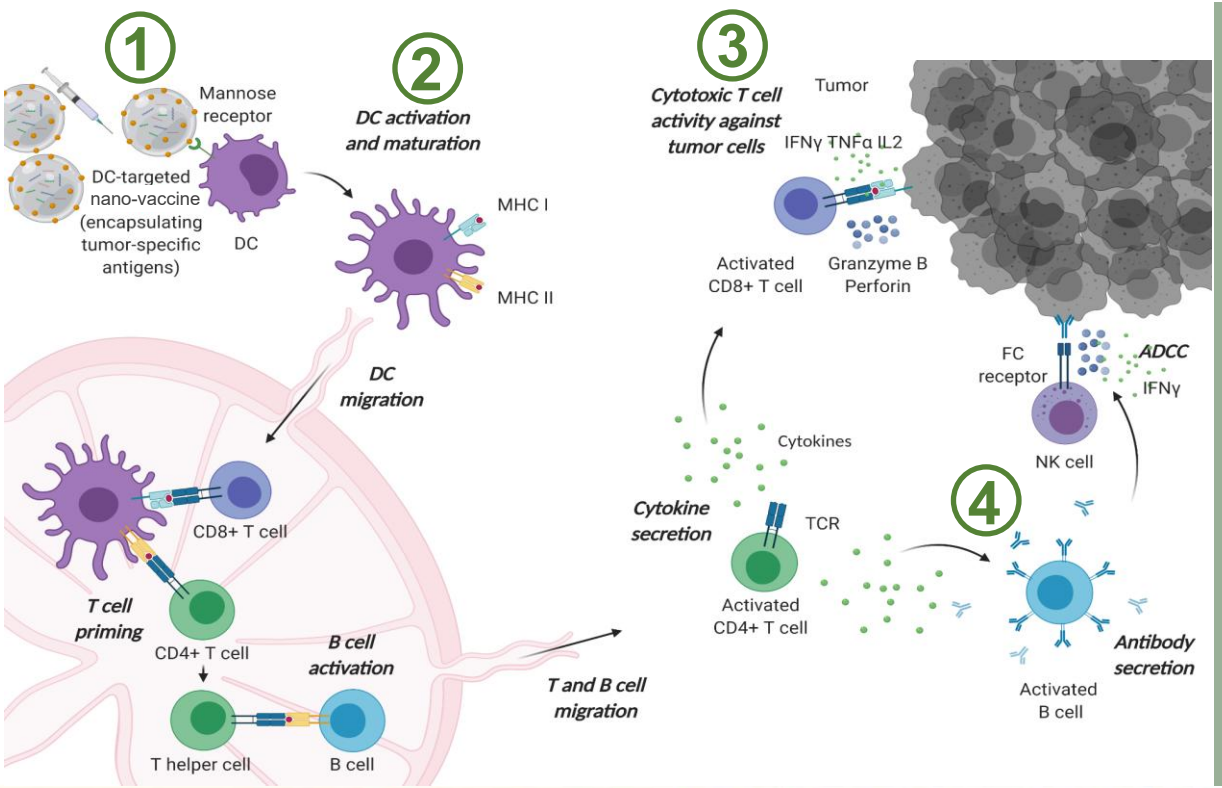
-MSI-H prevalence in only ~1-2%

-MSI-H advanced PDAC patients are treated with anti-PD-1 → no change in OS



Adapted from Luchini C. Et al. Gut. 2020 Jan; 70(1) 148:156.

The platform: DC-targeted NanoVaccine (NV)



1. DC-targeted NV delivers concomitantly TAA peptides and TLR ligands to DC.
2. The DC matures and activates while trafficking to lymph nodes, interacting with T and B cells.
3. Activation of specific cellular immunity against the tumor.
4. Generation of humoral immunity, which leads to immunological memory.

The selected tumor associated antigen: CEACAM5 (CEA5)

CEACAM5 (CEA5)

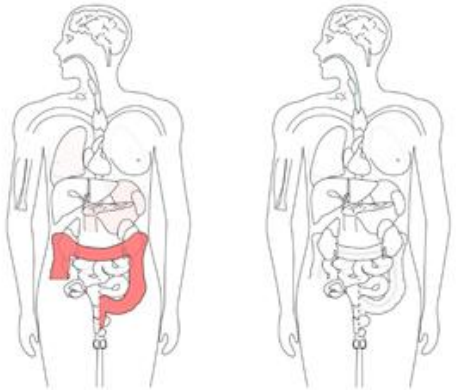
Carcinoembryonic antigen-related cell adhesion molecule 5

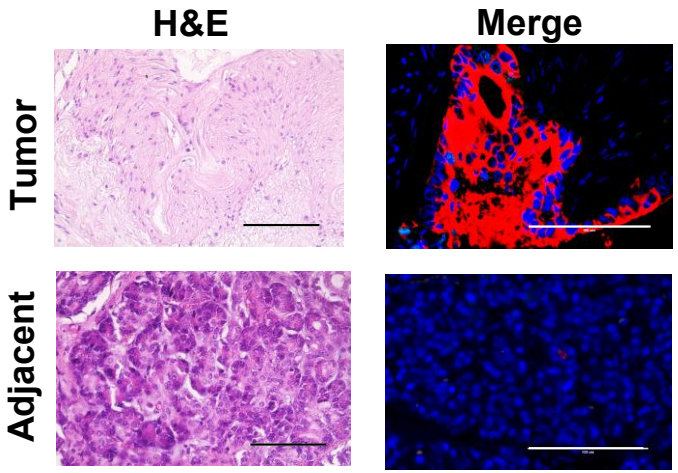
Highly expressed in >70% of PDAC

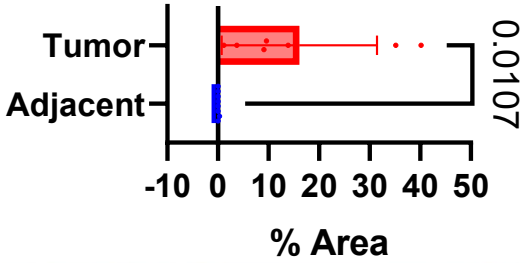
Correlates with poor prognosis

CEA5 expression in PDAC/Normal: 1918

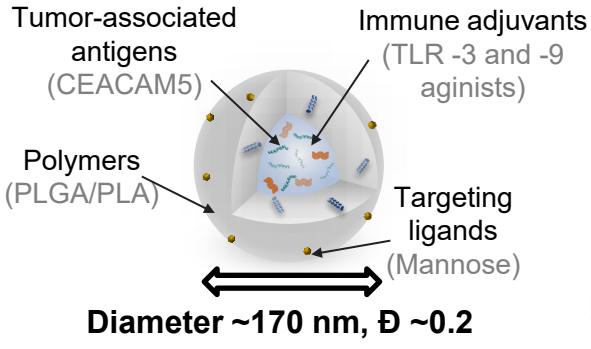
GEPIA
Gene Expression Profiling Interactive Analysis

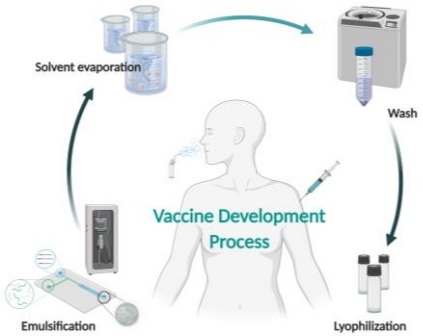




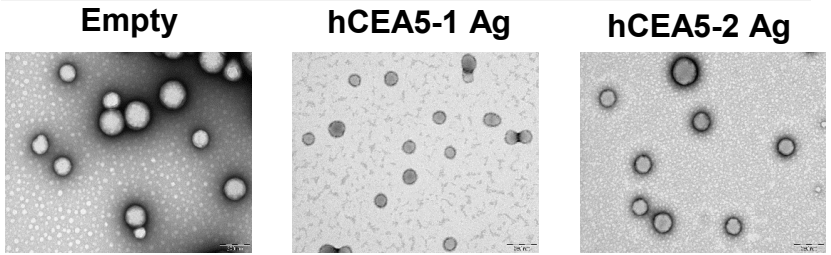


NanoVaccine (NV) physico-chemical characterization

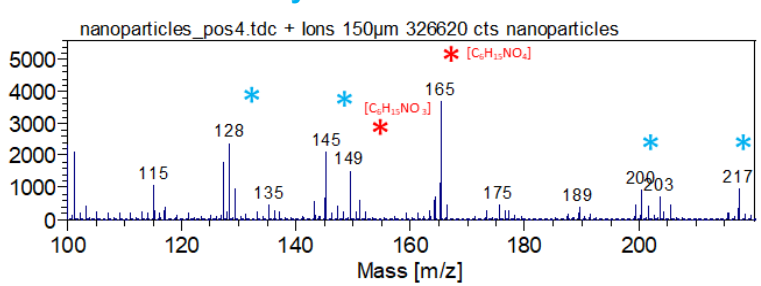




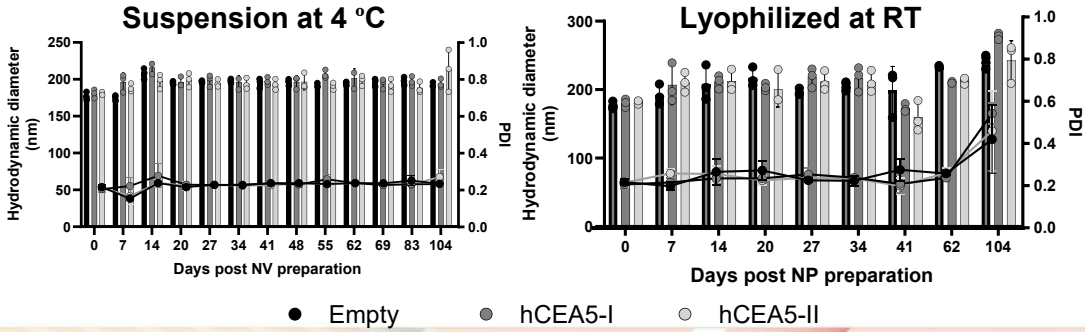
TEM



Detection of mannose on the NV surface

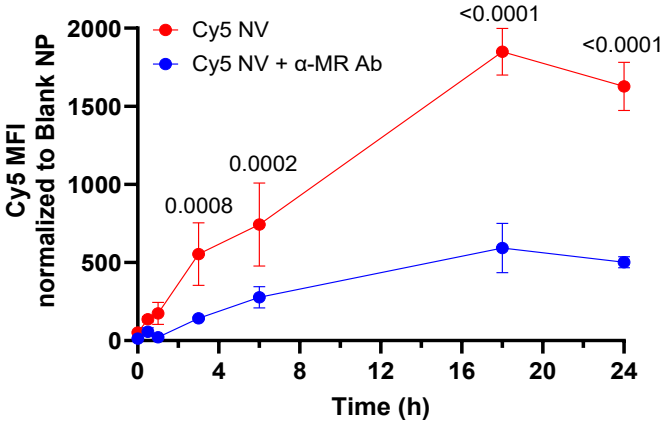


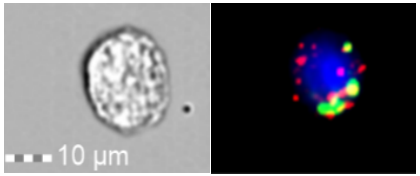
Stability over time (size and PDI)



NV is highly internalized into DCs via mannose receptor mediation

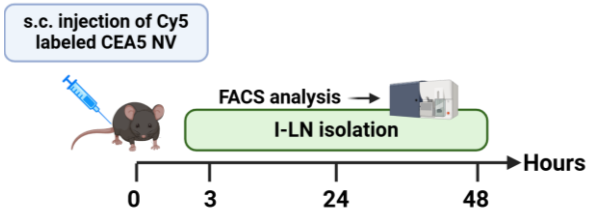
Ex vivo internalization into mouse BMDC



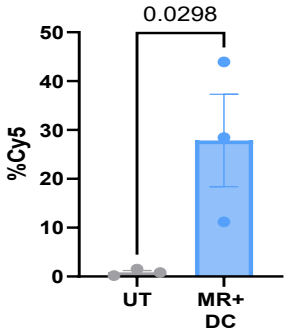


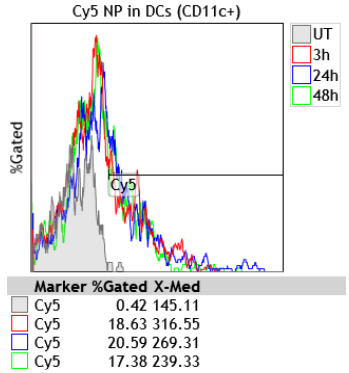
Nucleus
Cy5 NV
Lysotracker

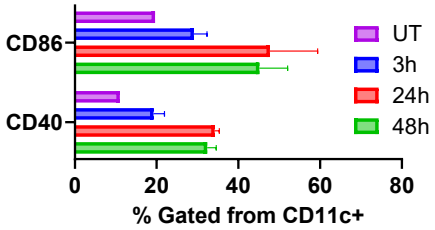
In vivo internalization into lymph nodes (LN)



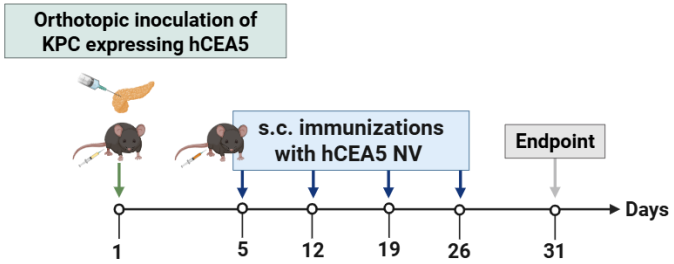
3h post administration

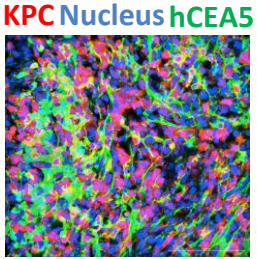






NV induces pro-inflammatory cell phenotype and reduces T cell exhaustion





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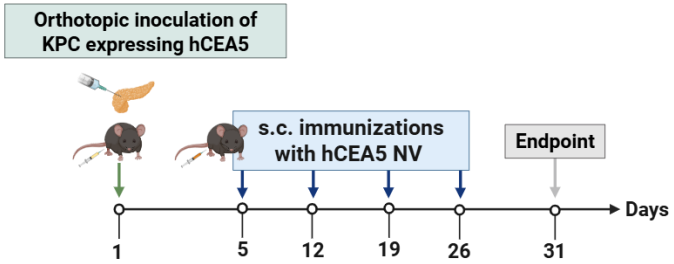
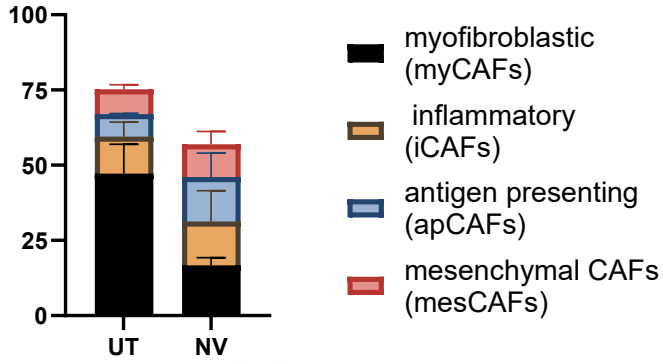
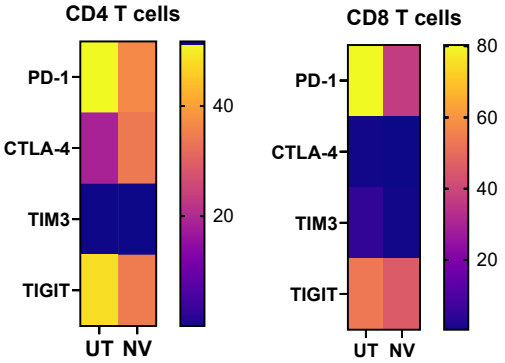


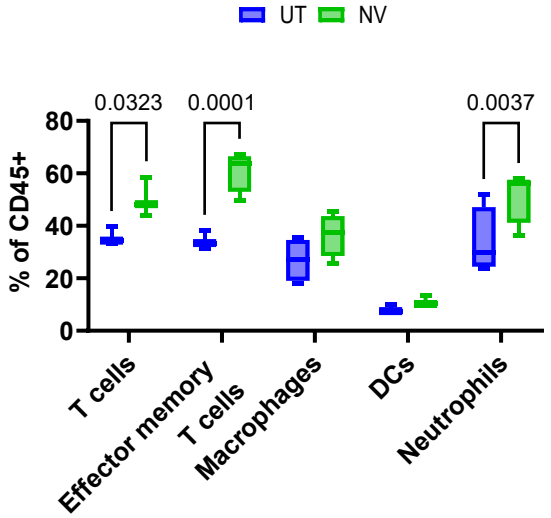
Cancer Associated Fibroblasts (CAFs)



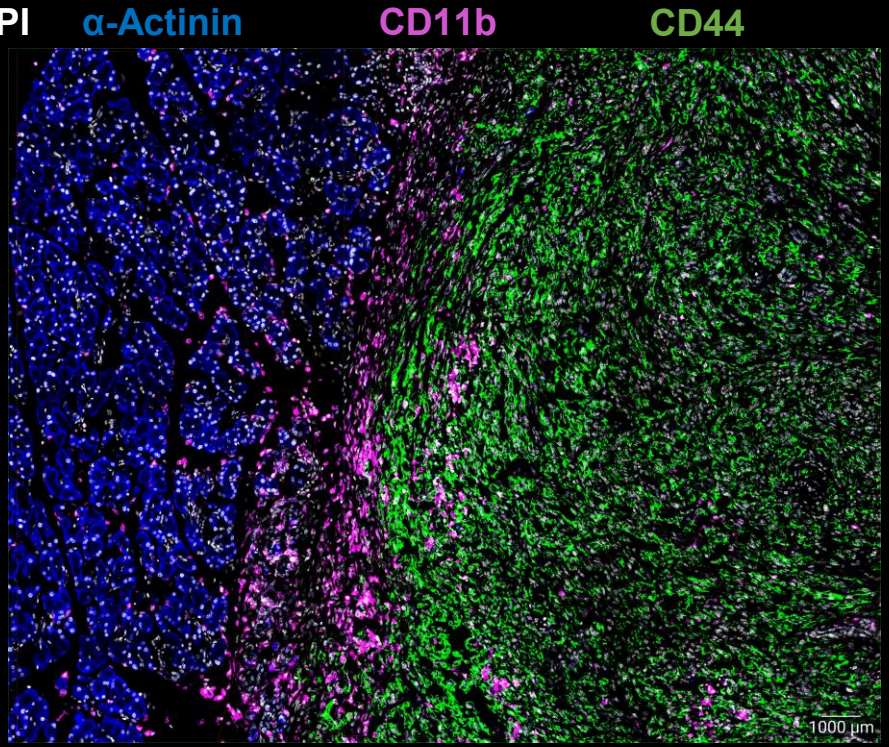
Reduced T cell exhaustion phenotype

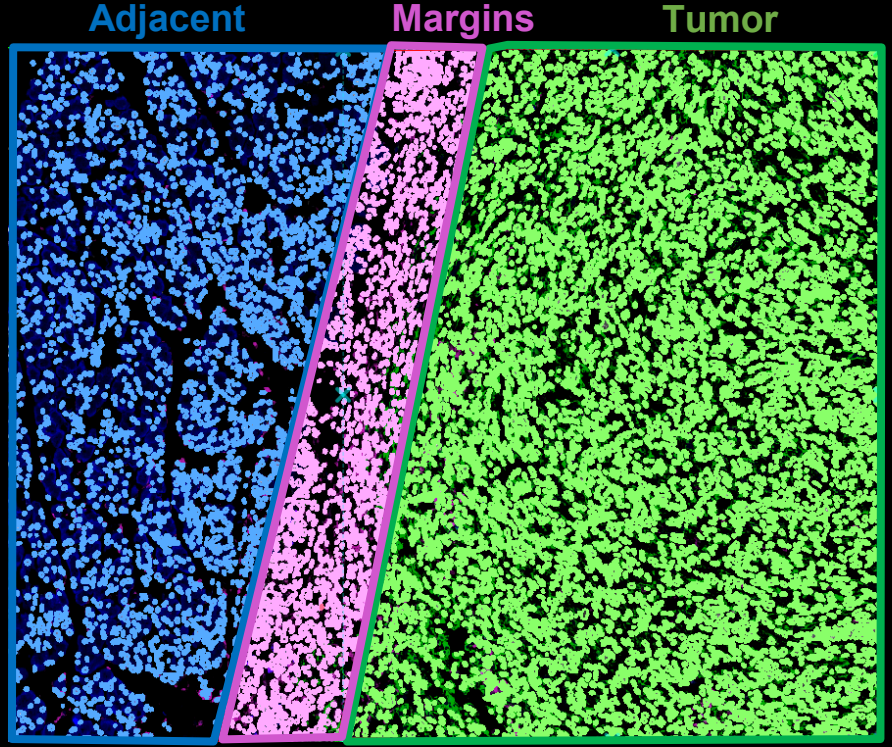


Increase in circulating lymphocytes

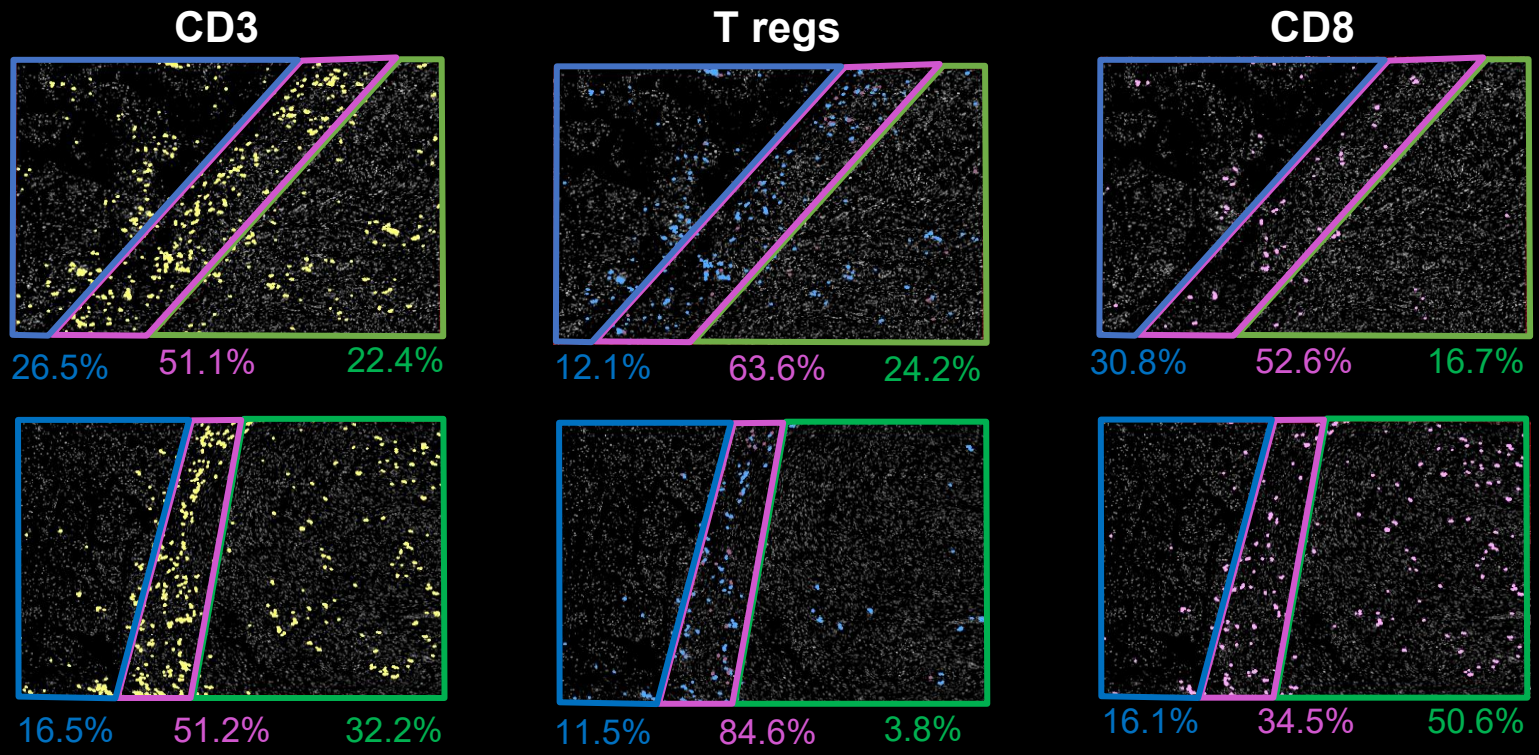


Lymphocyte infiltration into the tumor site using spatial biology

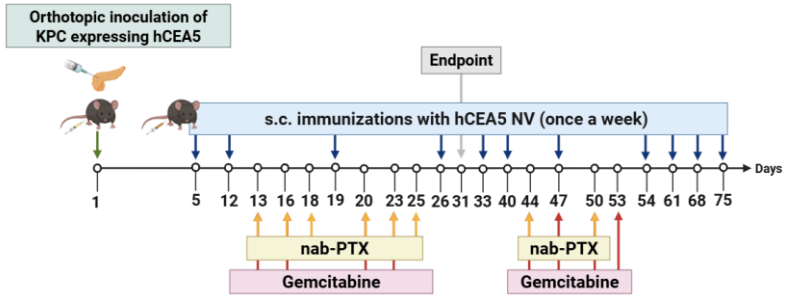


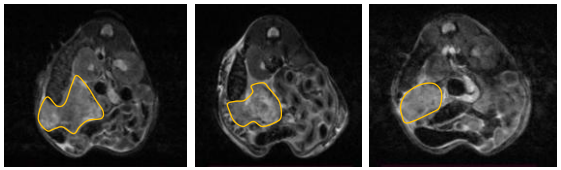


Increased infiltration of lymphocytes and decreased regulatory cells

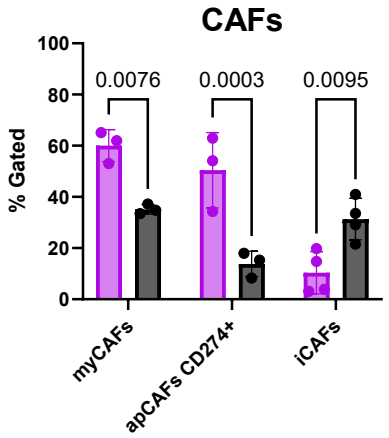


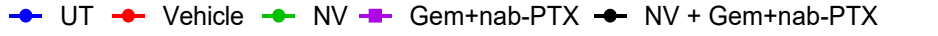
NV improved the therapeutic efficacy of the standard of care (SoC) chemotherapy

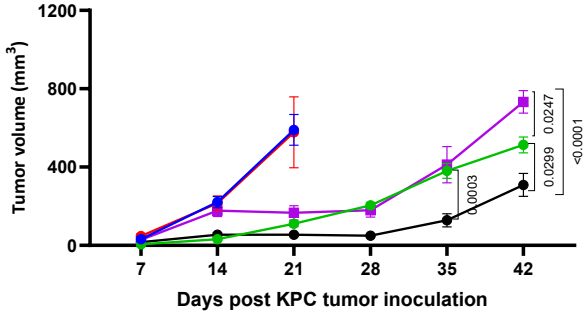


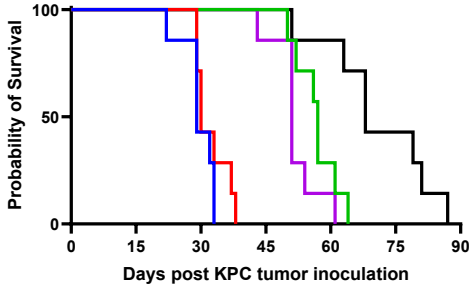


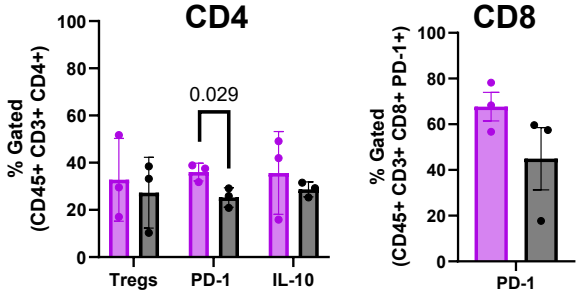
Gem+ nab-PTX | NV | Gem+ nabPTX+ NV











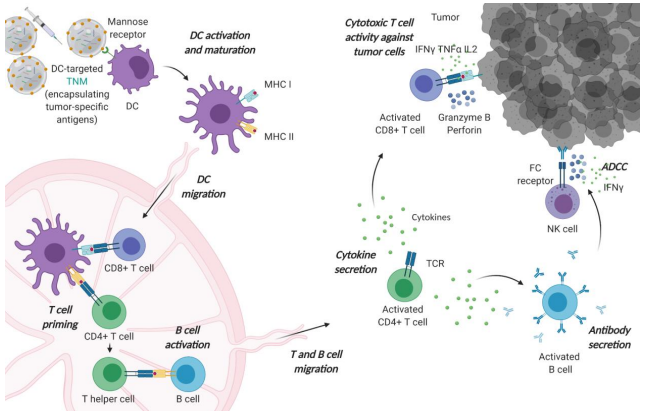
Conclusions

- **Stable and safe NV formulation** retains physico-chemical properties for over a 100 days at RT and 4 °C and was found safe *in vivo*.
- **Efficient DC uptake and activation** via mannose receptor targeting *ex vivo* and *in vivo*.

***In vivo* model:**

- NV alters PDAC's TME into a **less immune suppressive** phenotype. Decrease ECM-secreting CAFs and increase tumor-infiltrating lymphocytes.

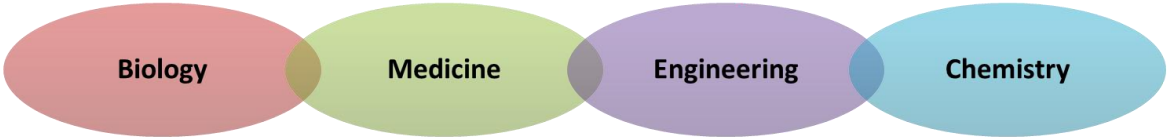
- Combination with chemotherapy further **delays tumor growth and prolongs the mice's survival.**



The NV has a promising translational potential for combination therapy in PDAC

RSF's Multidisciplinary research team

The whole is greater than the sum of its parts …



Establishment and molecular characterization of dormant vs fast-growing, primary vs metastatic, resistant vs drug-sensitive orthotopic tumor models

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Patient-derived tumor models

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3D-Bioprinted tumor models

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Design, synthesis and characterization of novel nanomedicines

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