



University of Bari "Aldo Moro"
Interdisciplinary Department of Medicine

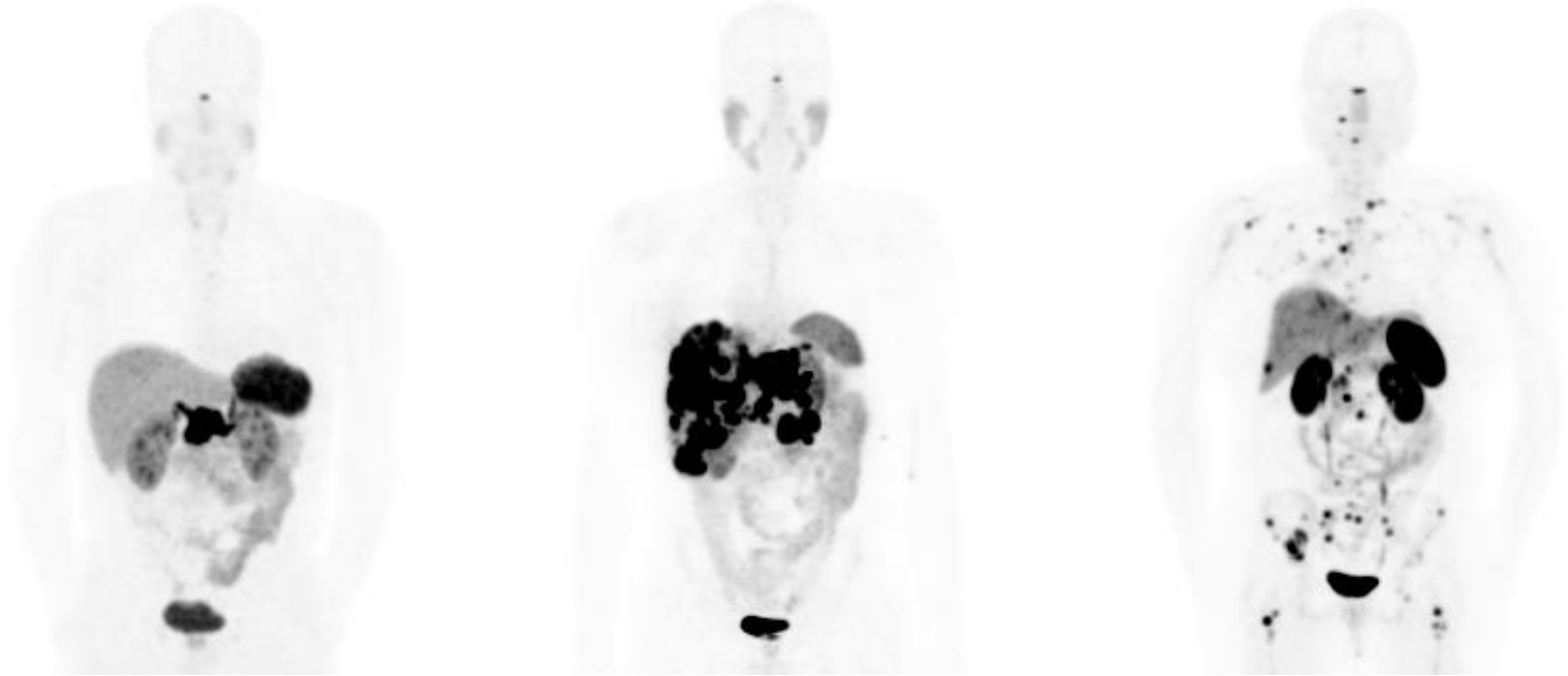
Medical Oncology Unit

SOMATOSTATIN ANALOGUES: KEY TO IMMUNOTHERAPY

Mauro Cives, MD

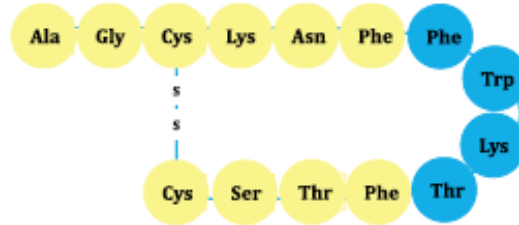
XX Symposium GETNE
November 14-15, 2024
Santiago de Compostela, Spain

WELL-DIFFERENTIATED NETs OVEREXPRESS SSTRs

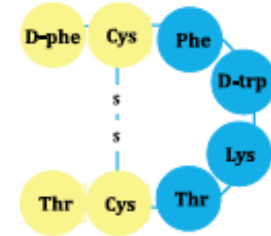


SSAs ARE CYCLIC STRUCTURE OCTAPEPTIDES

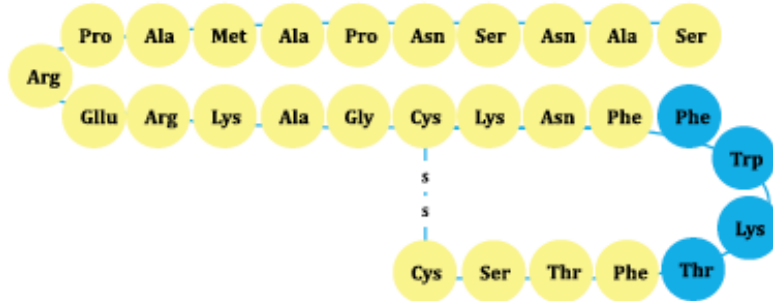
Human Somatostatin 14



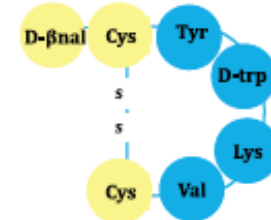
Octreotide



Human Somatostatin 28



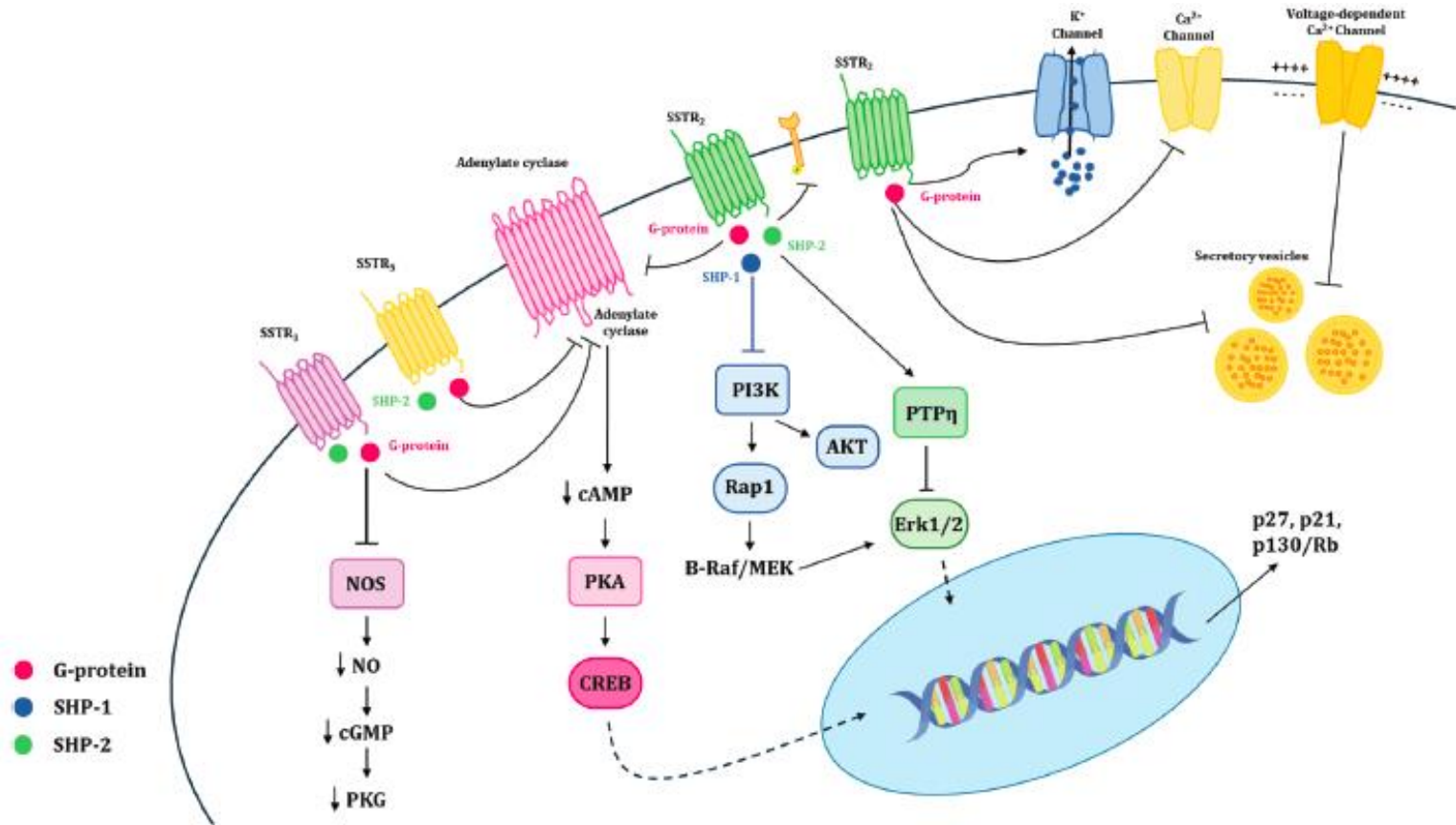
Lanreotide



Amino Acids Essential For Receptor Binding

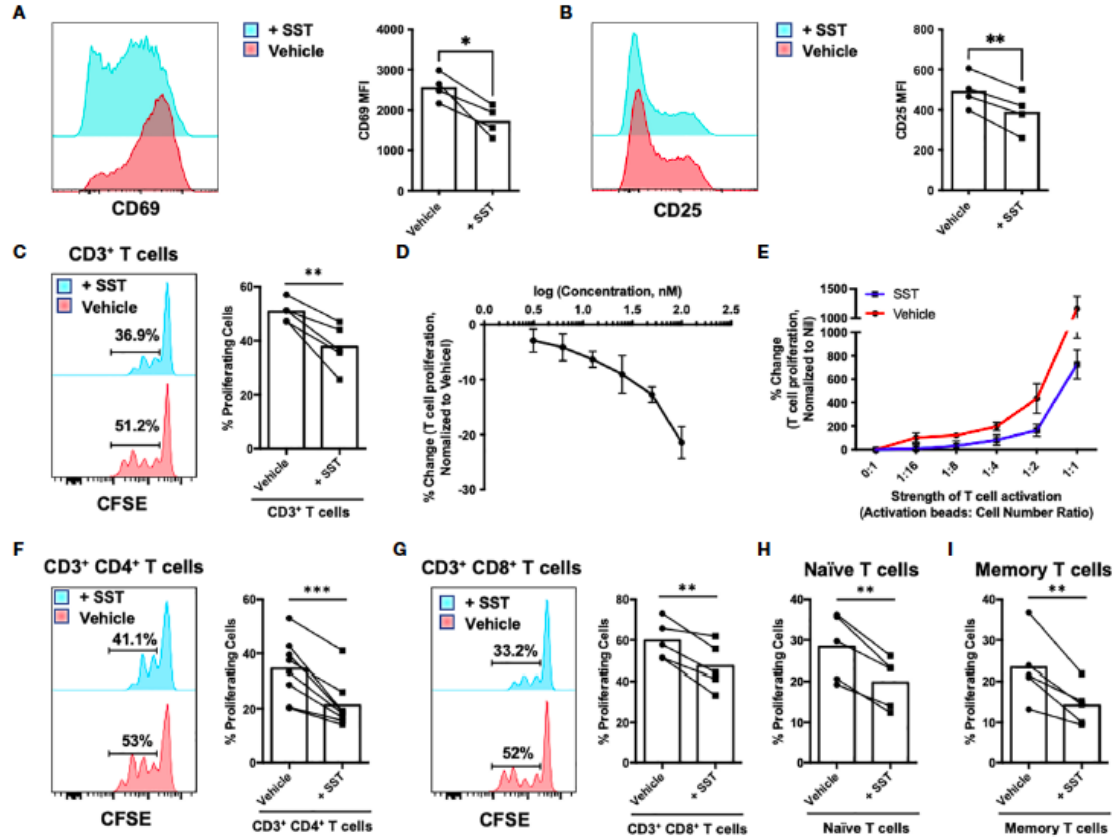


SSAs INHIBIT NET CELL PROLIFERATION

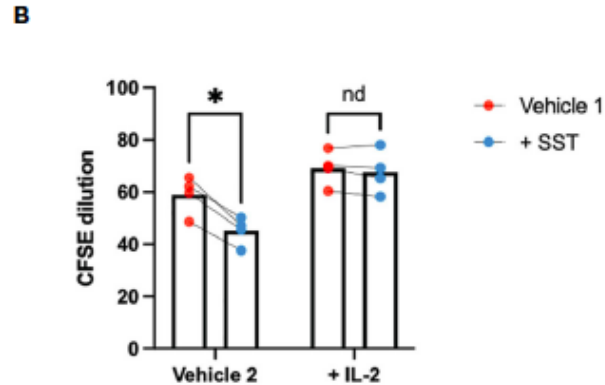
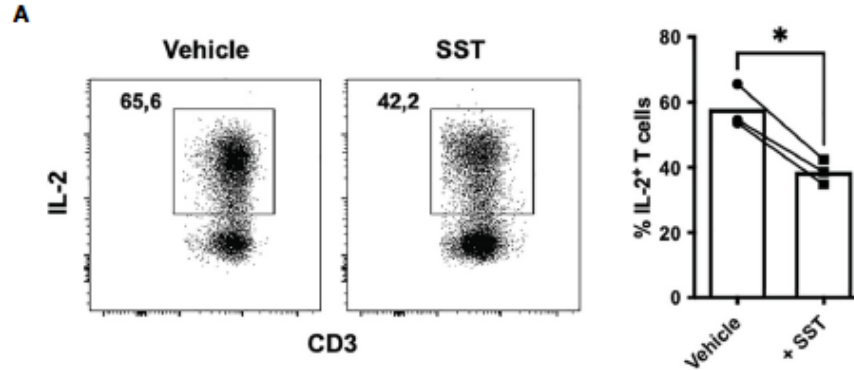


**CAN SOMATOSTATIN ANALOGS
EXERT IMMUNE-MODULATORY ACTIVITIES?**

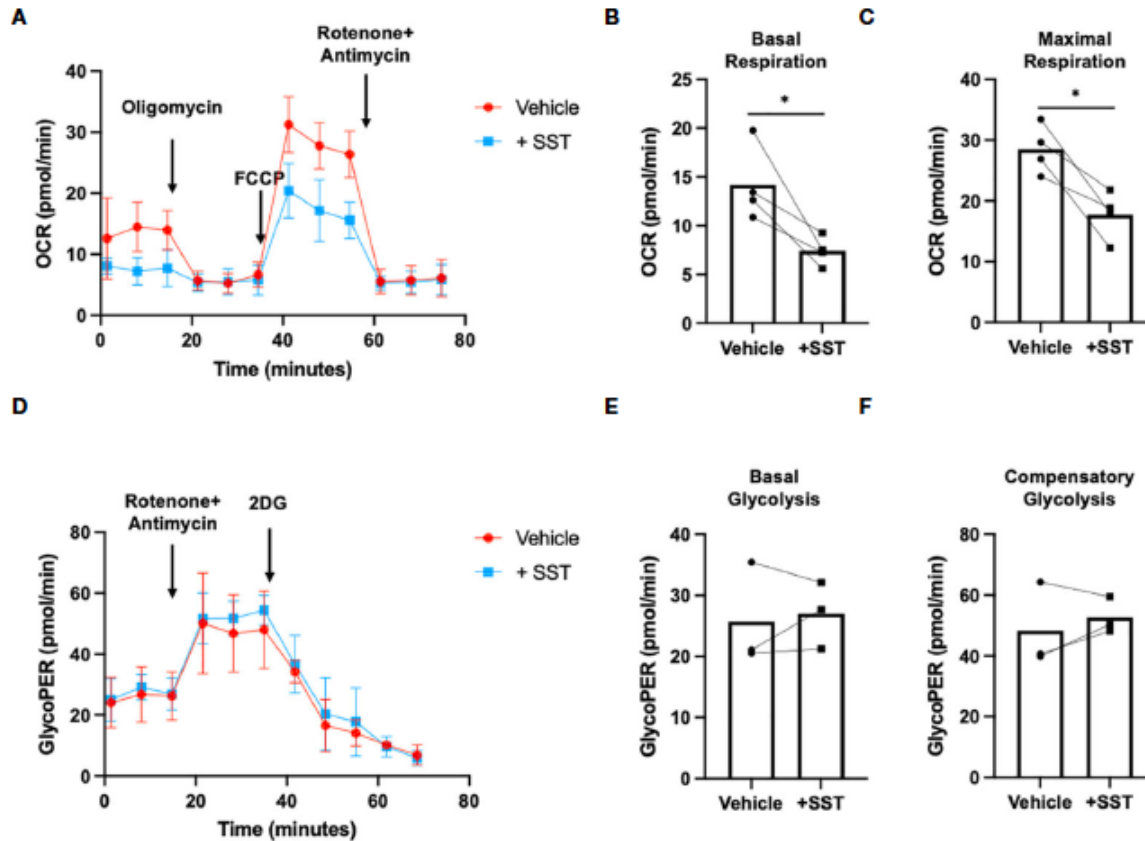
SOMATOSTATIN INHIBITS PROLIFERATION AND ACTIVATION OF T CELLS



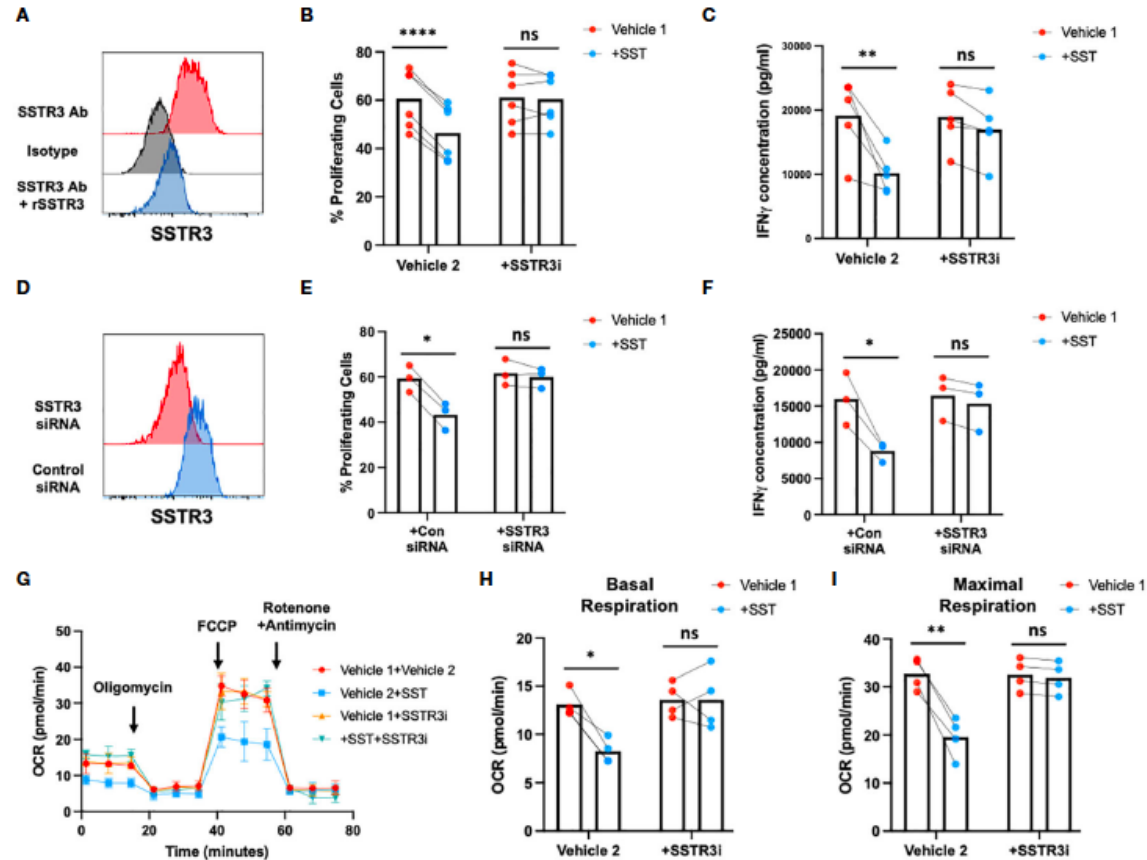
SOMATOSTATIN MODULATES PRODUCTION OF PRO-INFLAMMATORY CYTOKINES



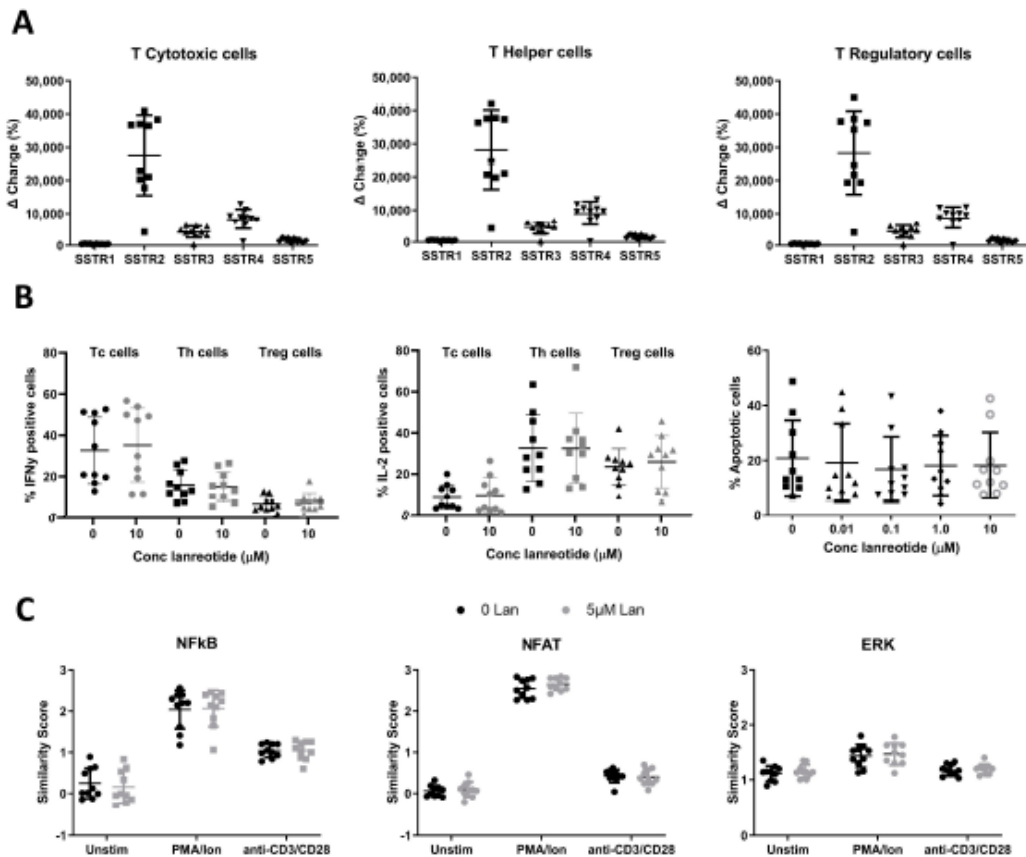
SOMATOSTATIN MODULATES T CELL METABOLISM



SOMATOSTATIN MODULATES T CELL RESPONSES THROUGH SSTR3

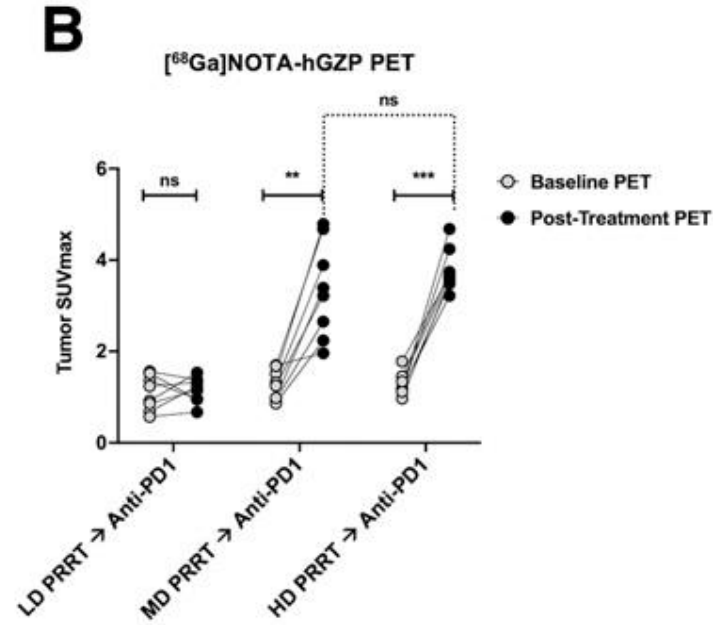
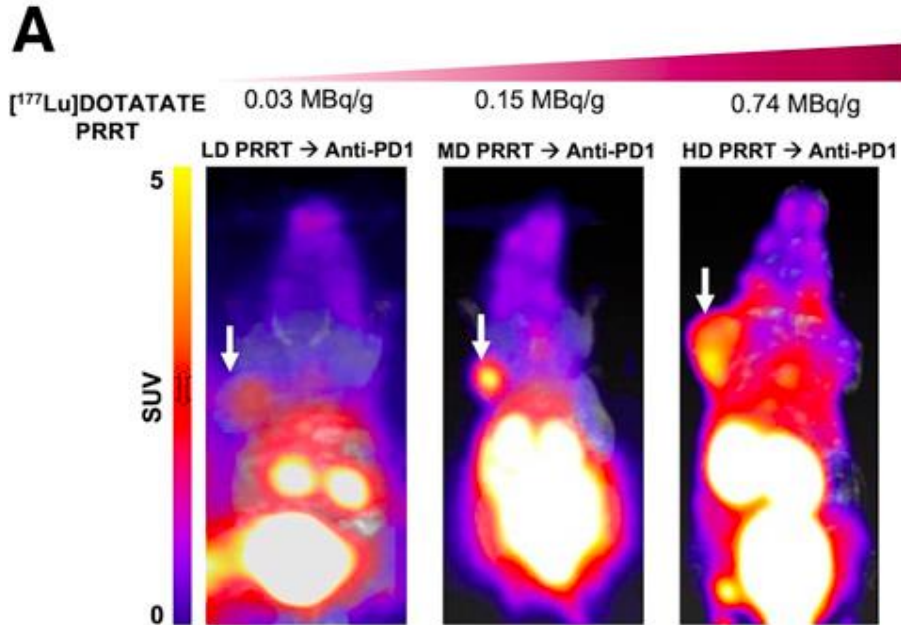


LANREOTIDE IS INERT OF T CELL PROLIFERATION AND ACTIVATION

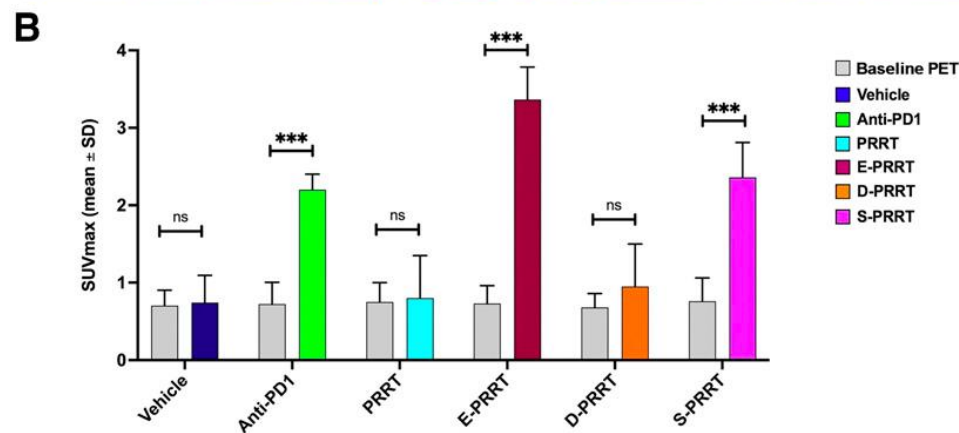
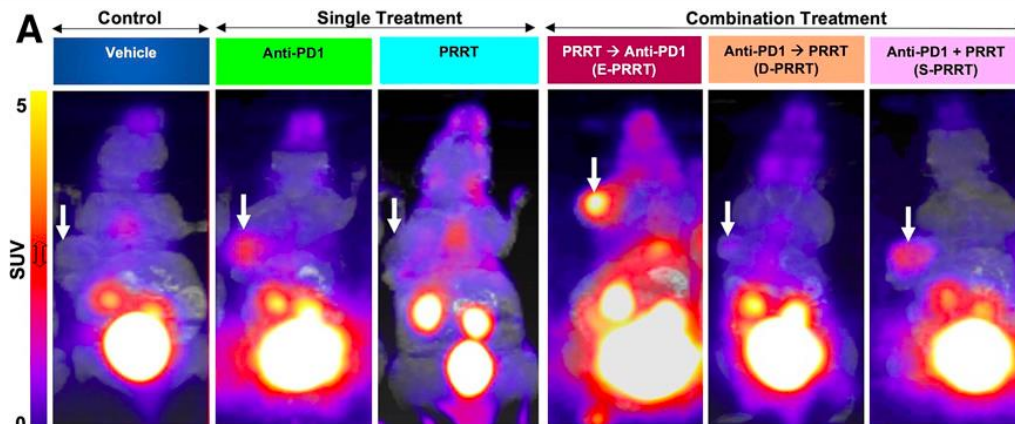


**CAN RADIOLABELED SSAs
EXERT IMMUNE-MODULATORY ACTIVITIES?**

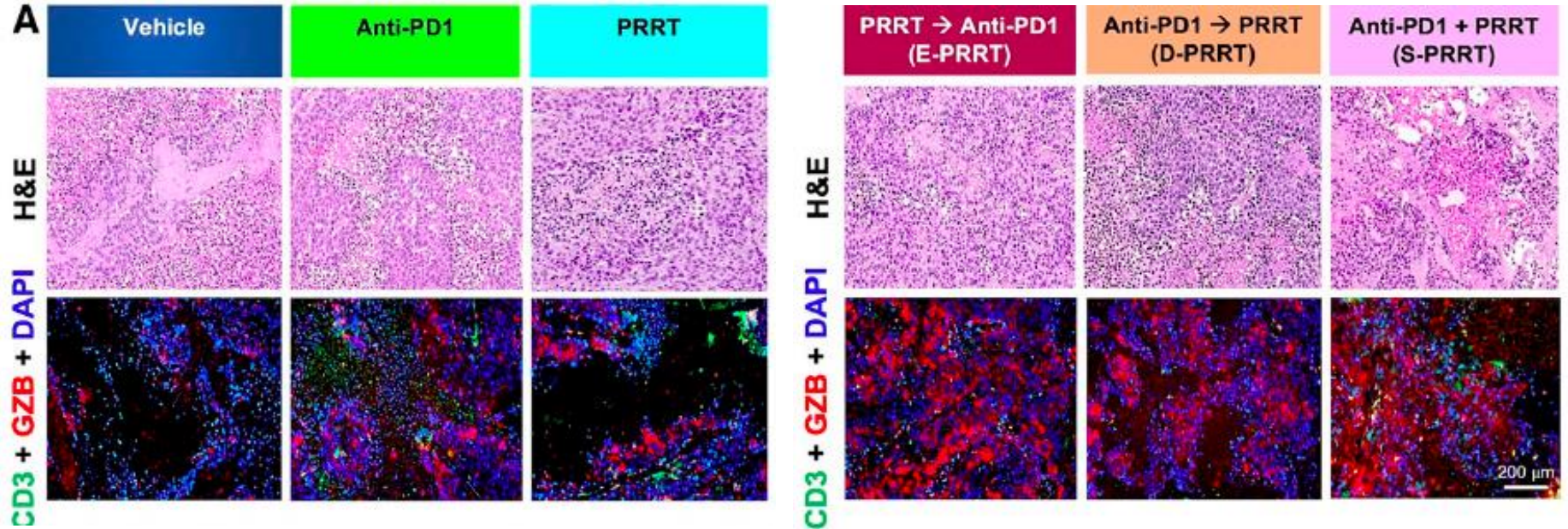
PRRT DOSE AFFECTS INTRATUMORAL T CELL ACTIVITY



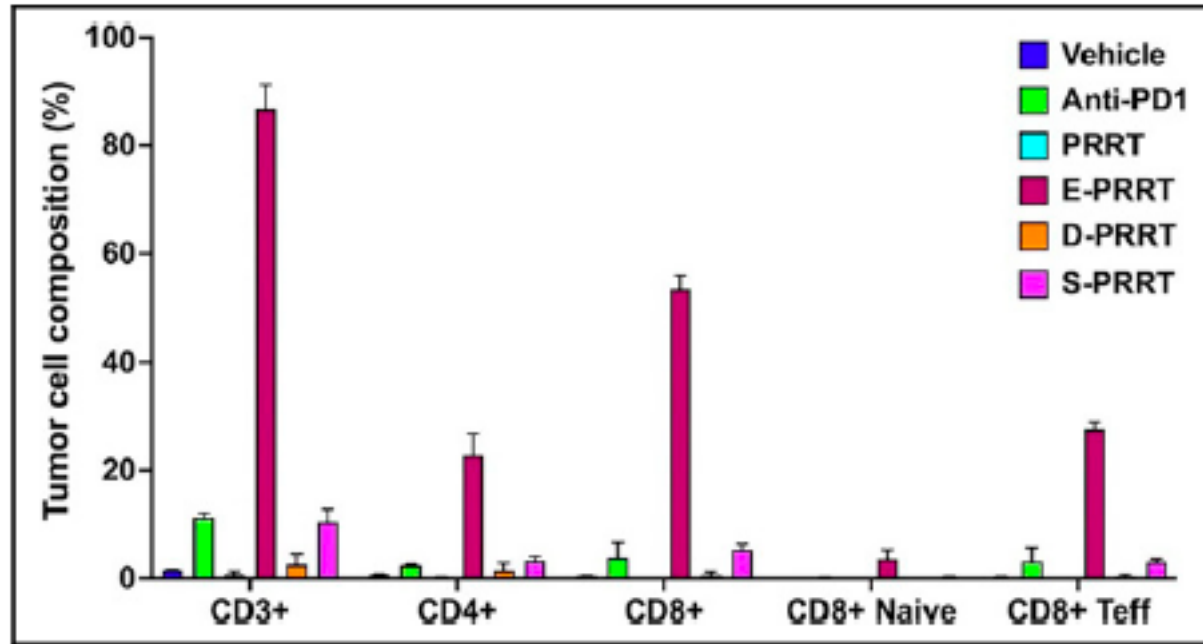
TIMING OF PRRT ADMINISTRATION AFFECTS INTRATUMORAL T CELL ACTIVITY



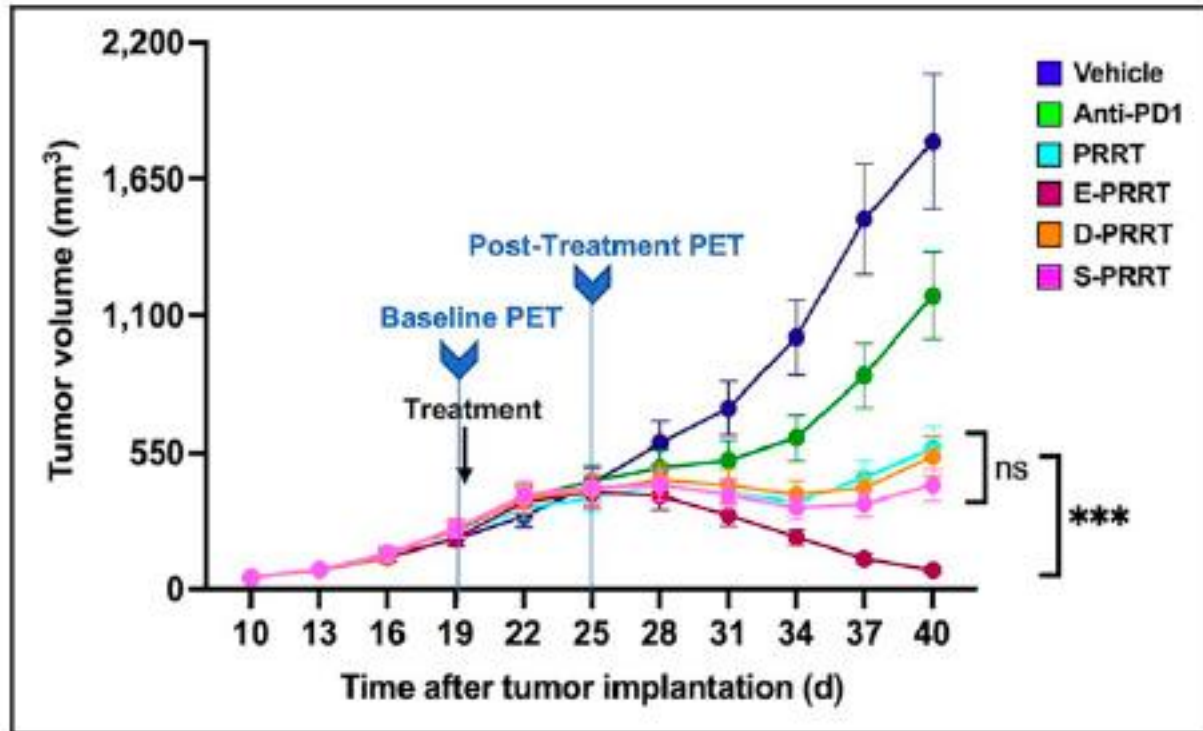
TIMING OF PRRT ADMINISTRATION AFFECTS INTRATUMORAL T CELL ACTIVITY



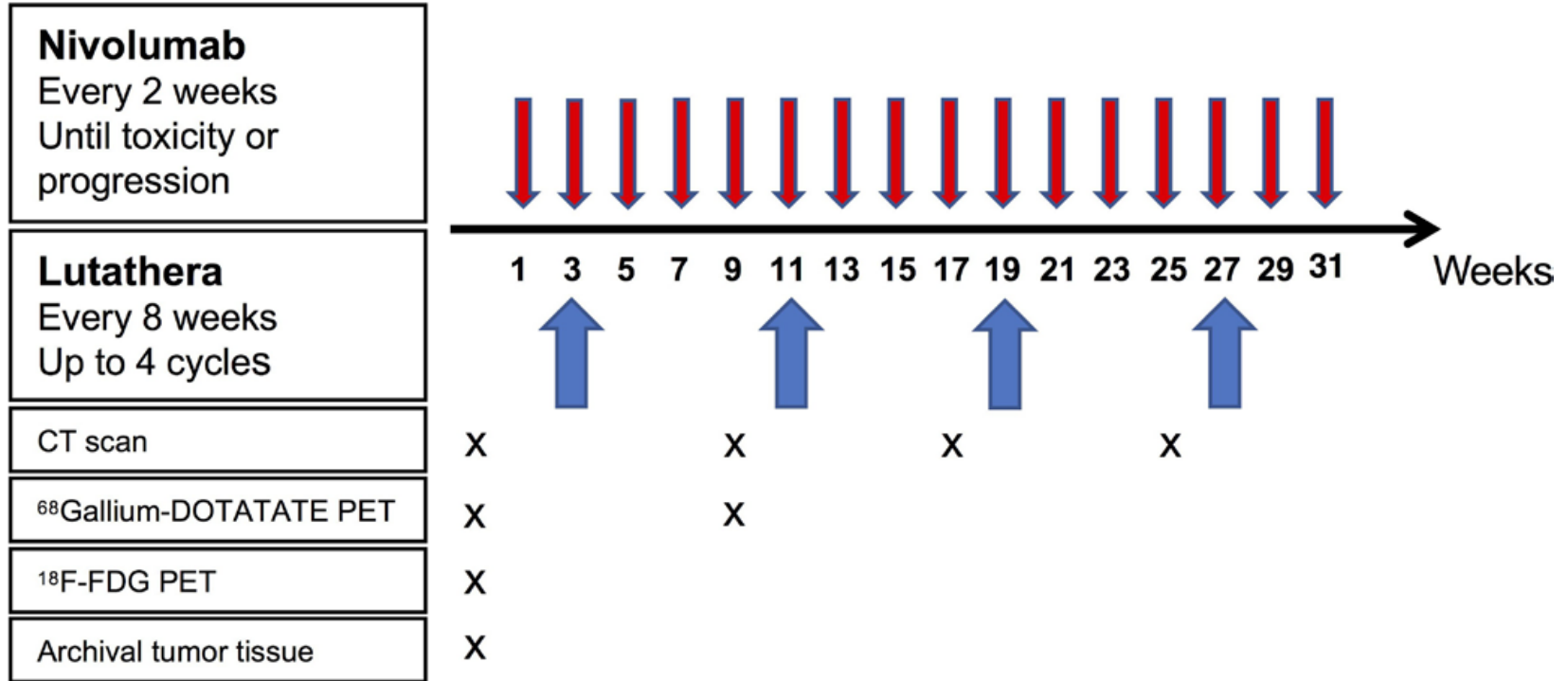
TIMING OF PRRT ADMINISTRATION AFFECTS INTRATUMORAL T CELL ACTIVITY



COMBINING PRRT AND ICIs HAS SYNERGISTIC EFFECTS



PHASE I STUDY PRRT PLUS NIVOLUMAB IN PATIENTS WITH PULMONARY NENS



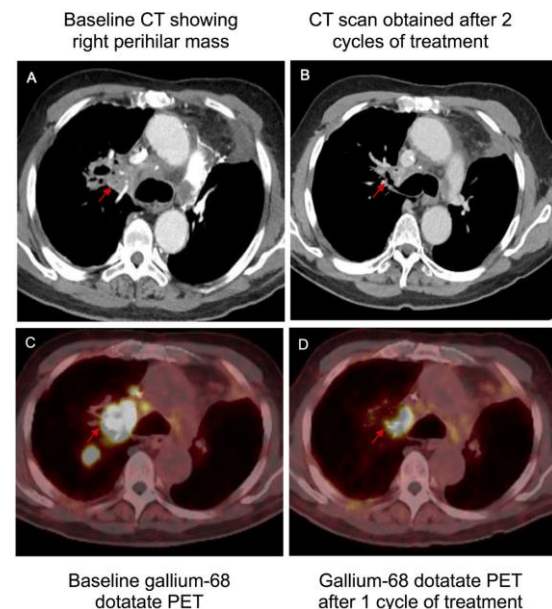
PHASE I STUDY PRRT PLUS NIVOLUMAB IN PATIENTS WITH PULMONARY NENS

Table 4 Summary of response to study treatment

Patient ID	Dose level	Disease at study entry	Prior therapy	Response to prior systemic treatment	Cycles of lutathera, n	Best response to study treatment
1	1	ES-SCLC	Carboplatin/etoposide/RT	PD	2	PD
2	1	ES-SCLC	Carboplatin/etoposide	SD	2	PR
3	1	ES-SCLC	Carboplatin/etoposide	PD	1	PD
4	2	Atypical carcinoid	1. Cisplatin/etoposide 3. Carboplatin/paclitaxel/bevacizumabNintedanib 4. Everolimus/lanreotide	NA	3	SD
5	2	ES-SCLC	1. Cisplatin/etoposide/RT 2. Carboplatin/irinotecan	SD	4	NE*
6	2	ES-SCLC	1. Carboplatin/irinotecan 2. Cisplatin/etoposide	PD	1	PD
7	2	Atypical carcinoid	Carboplatin/etoposide/lanreotide	PD	3	SD
8	2	High-grade neuroendocrine carcinoma	1. Carboplatin/etoposide 2. Everolimus/octreotide	PD	1	PD
9	2	ES-SCLC	Carboplatin and etoposide followed by thoracic RT	PR	2	NE*

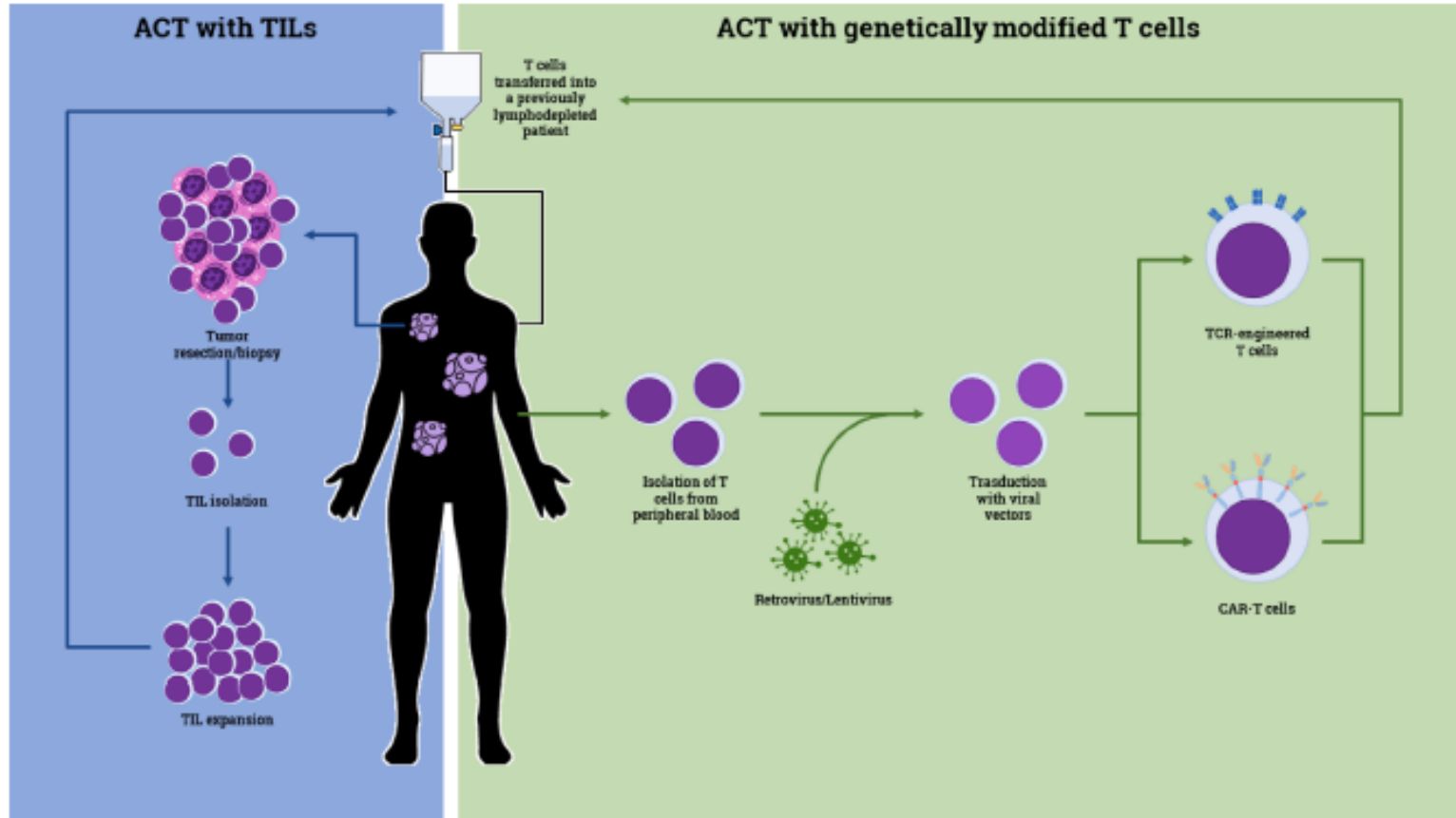
*Not evaluable due to no measurable disease.

ES-SCLC, extensive-stage small-cell lung cancer; NA, not available; NE, not evaluable; PD, progressive disease; PR, partial response; RT, radiotherapy; SD, stable disease.

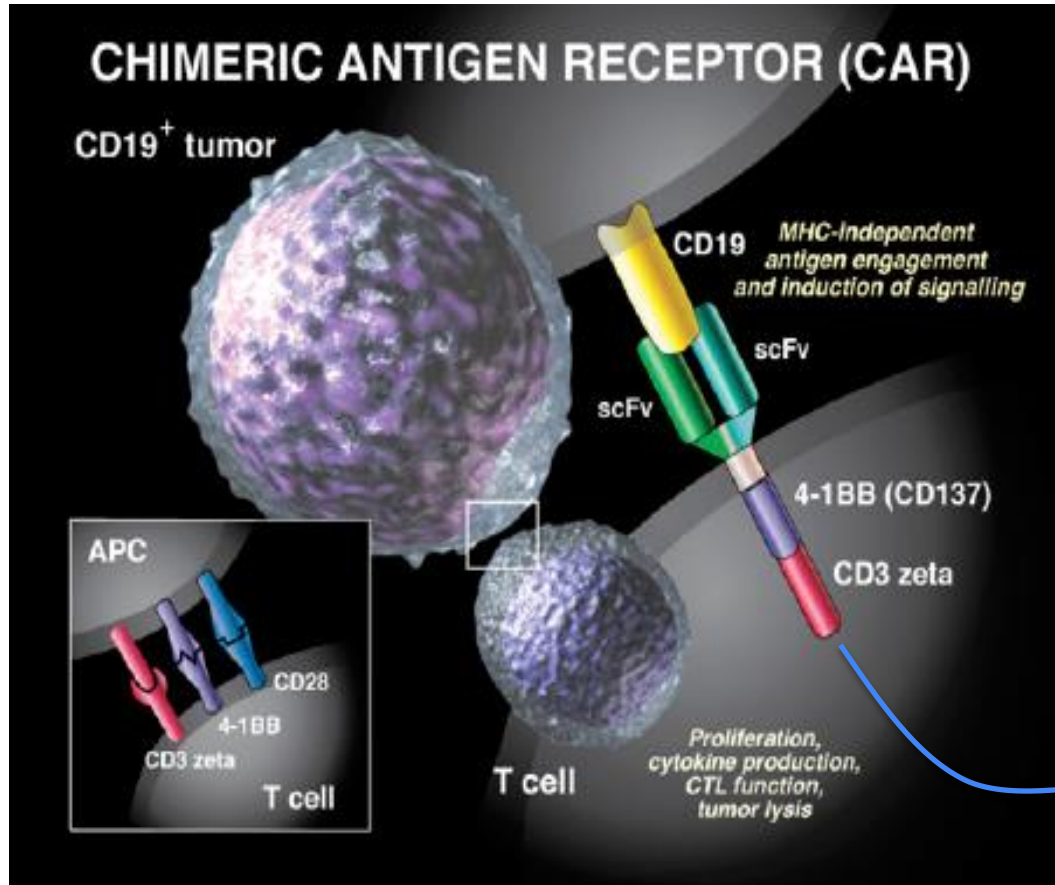


**CAN SSTRs BE EXPLOITED AS AN AGNOSTIC
IMMUNOTHERAPEUTIC TARGET?**

ADOPTIVE T CELL THERAPY FOR CANCER TREATMENT



ENGINEERING T CELLS TO TREAT CANCER



Ectodomain

- ❖ Antigen recognition
- ❖ Usually an Ab single-chain variable fragment

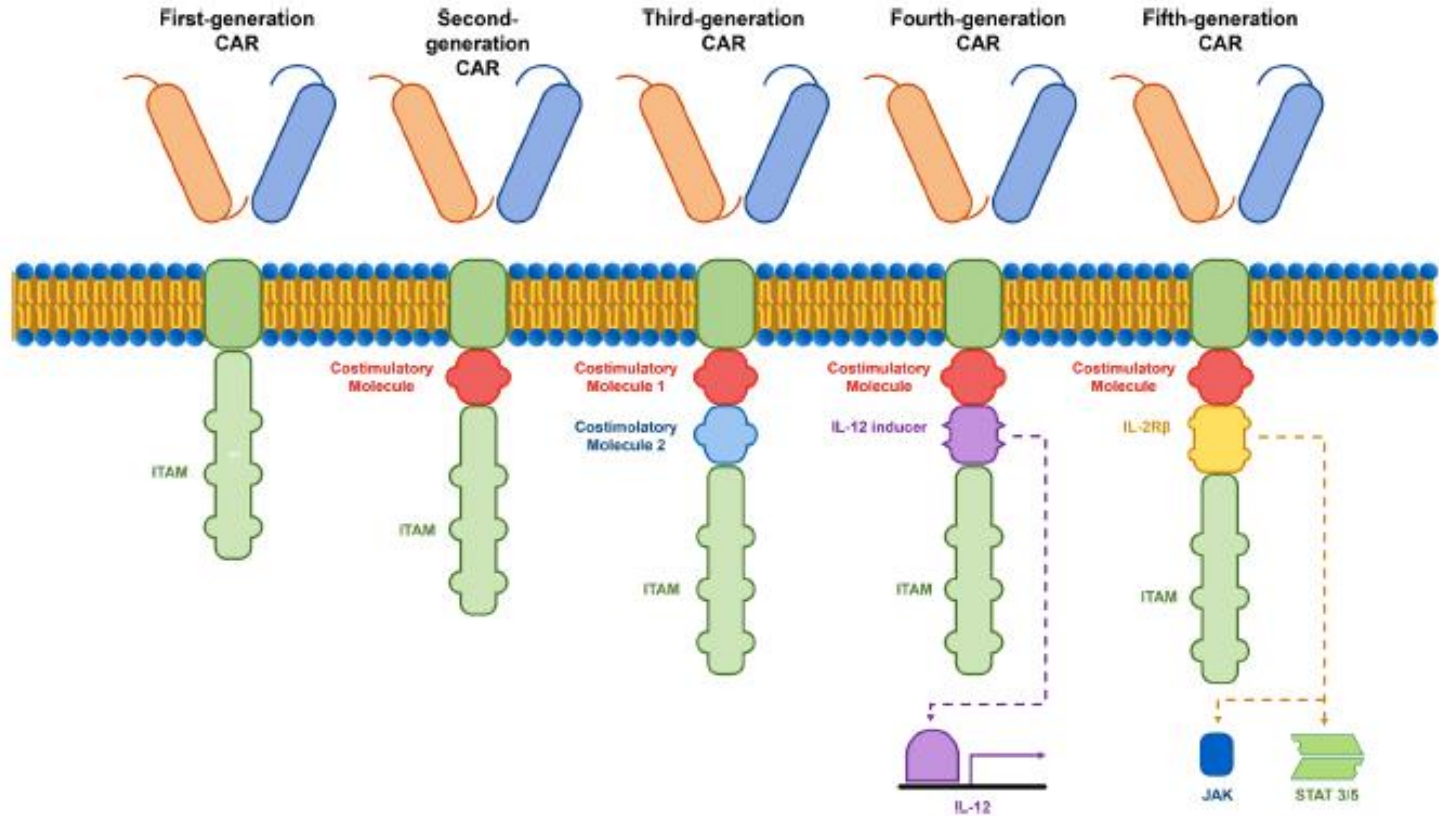
Endodomain

- ❖ Intracellular signaling
- ❖ Costimulatory domains (usually CD28 and 4-1BB)
- ❖ Stimulatory domain (usually the CD3zeta chain of the T-cell receptor)

Output

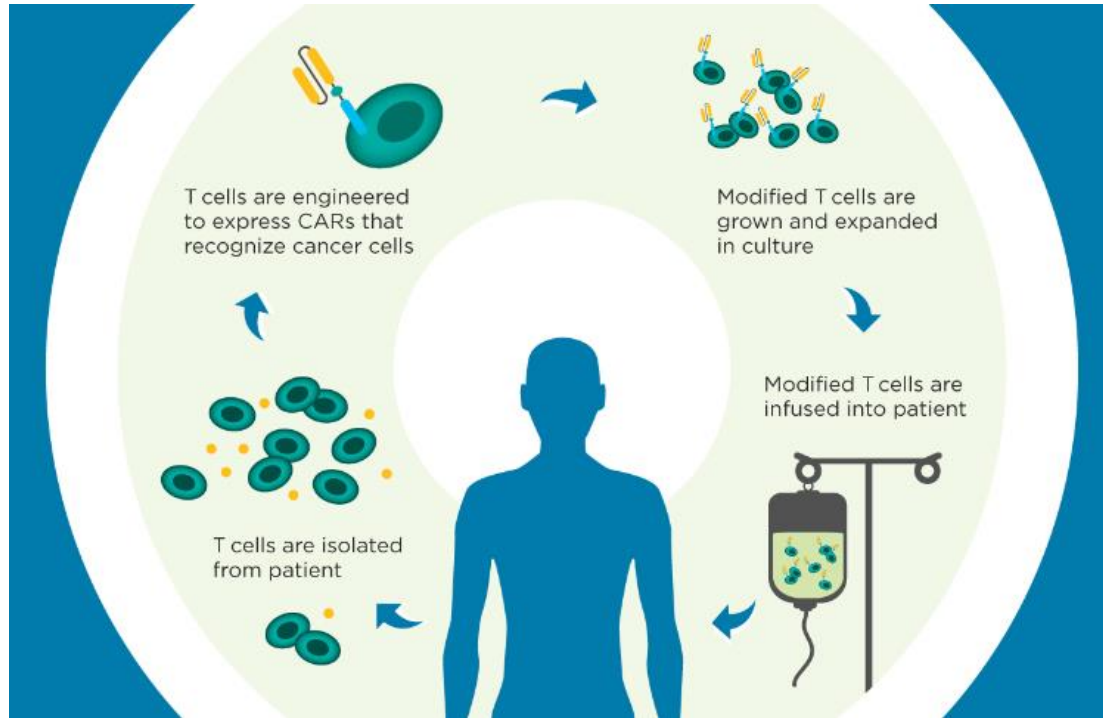
- ❖ T cell proliferation
- ❖ Cytokine production
- ❖ Tumor cell killing

CAR MODELING



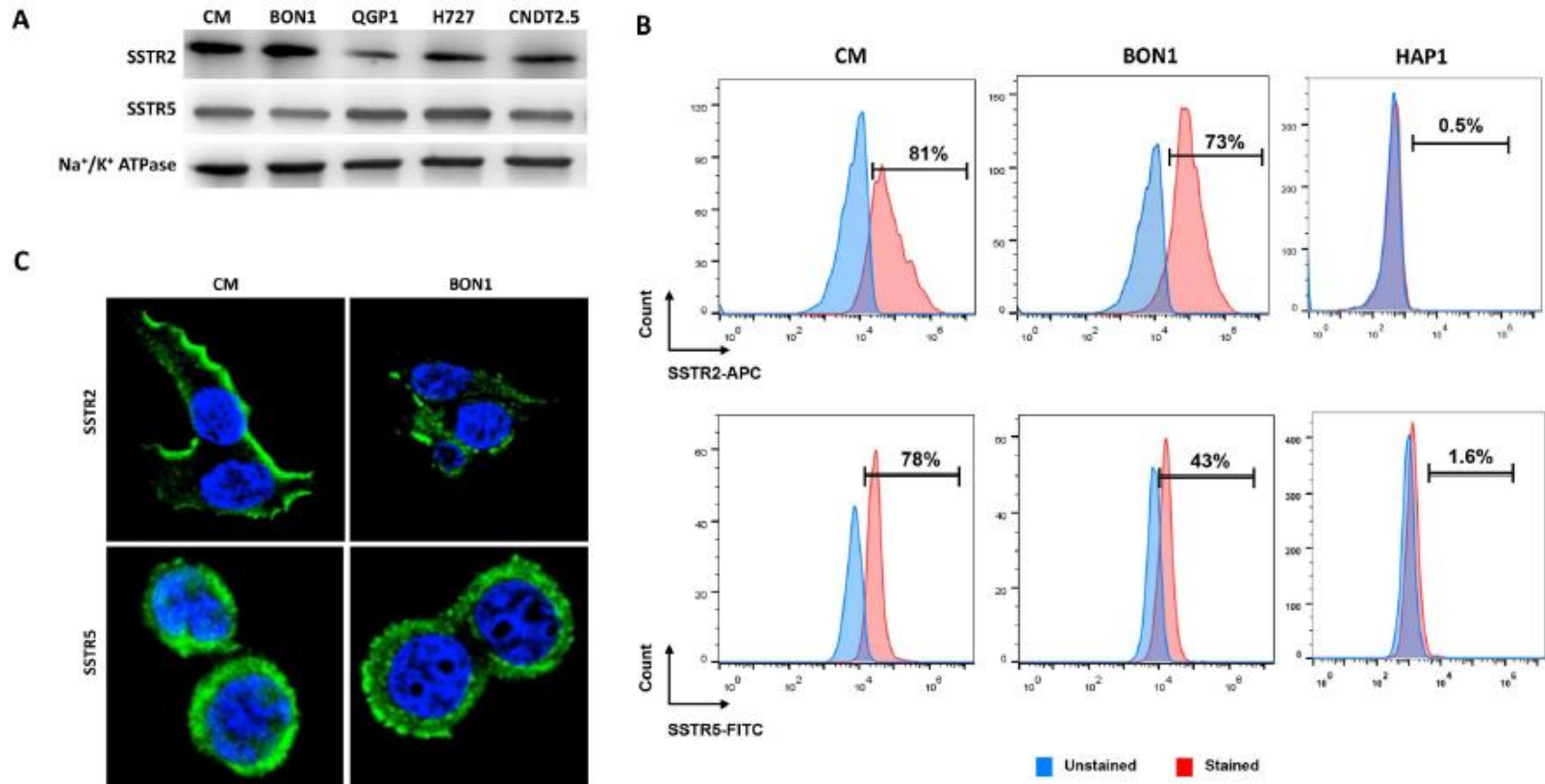
ADOPTIVE TRANSFER OF CAR T CELLS

After intravenous infusion, CAR T cells circulate, traffic into the tumor, and accumulate locally where they recognize their cognate ligand and are stimulated to proliferate and produce their effector functions.

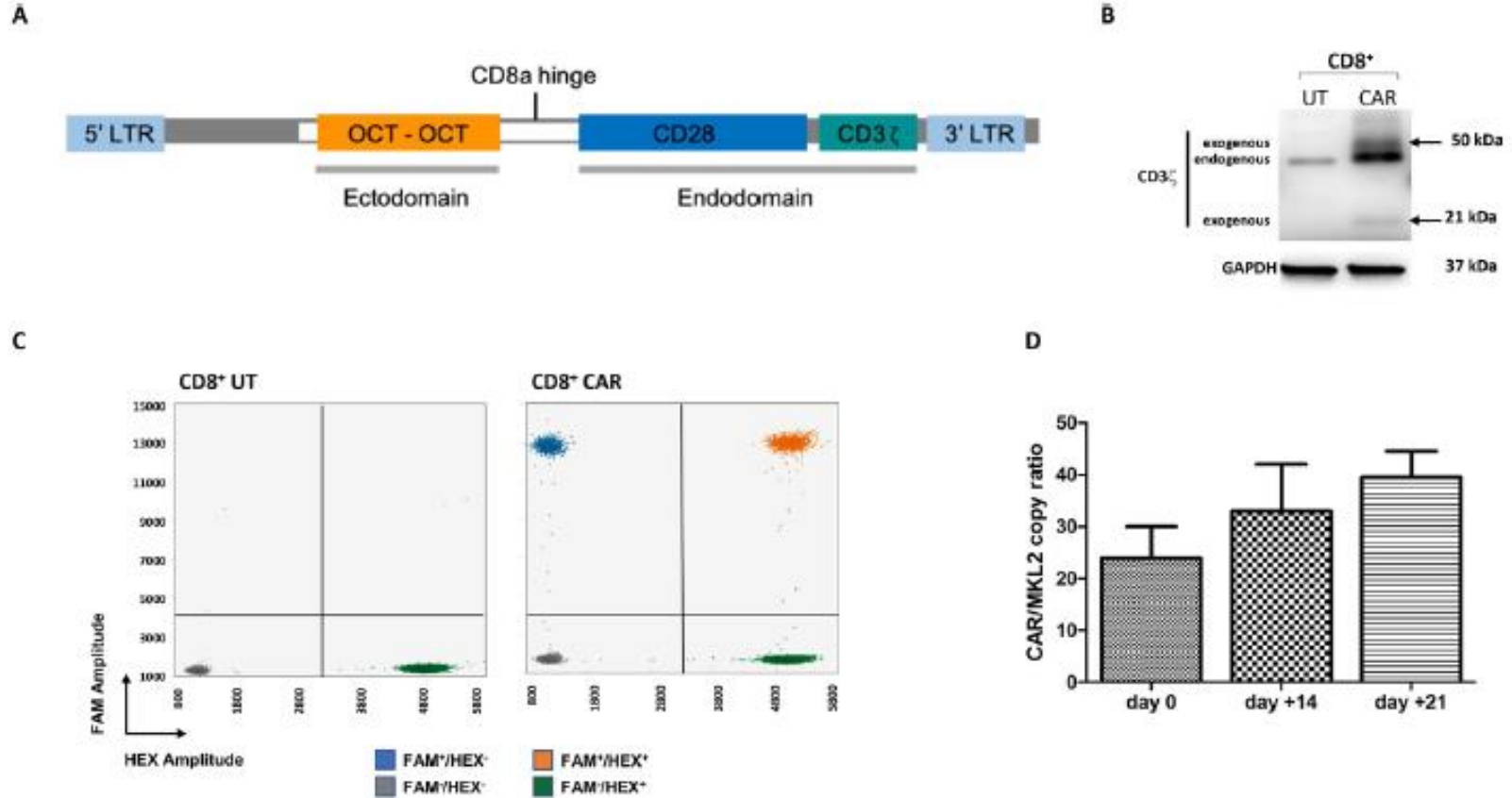


The T cells must avoid inhibitory signals and suppression from the tumor and the tumor microenvironment and must persist until elimination of all malignant cells.

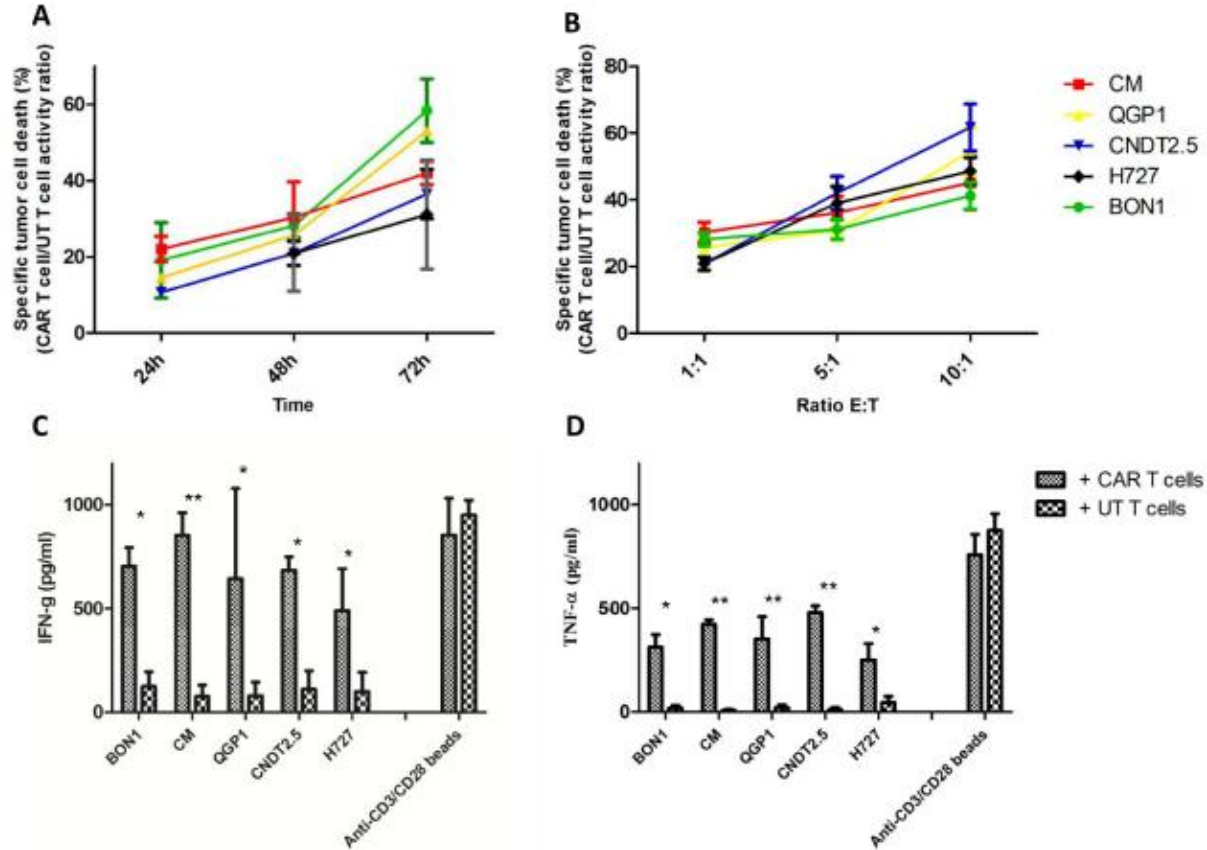
NETs OVEREXPRESS SSTRs



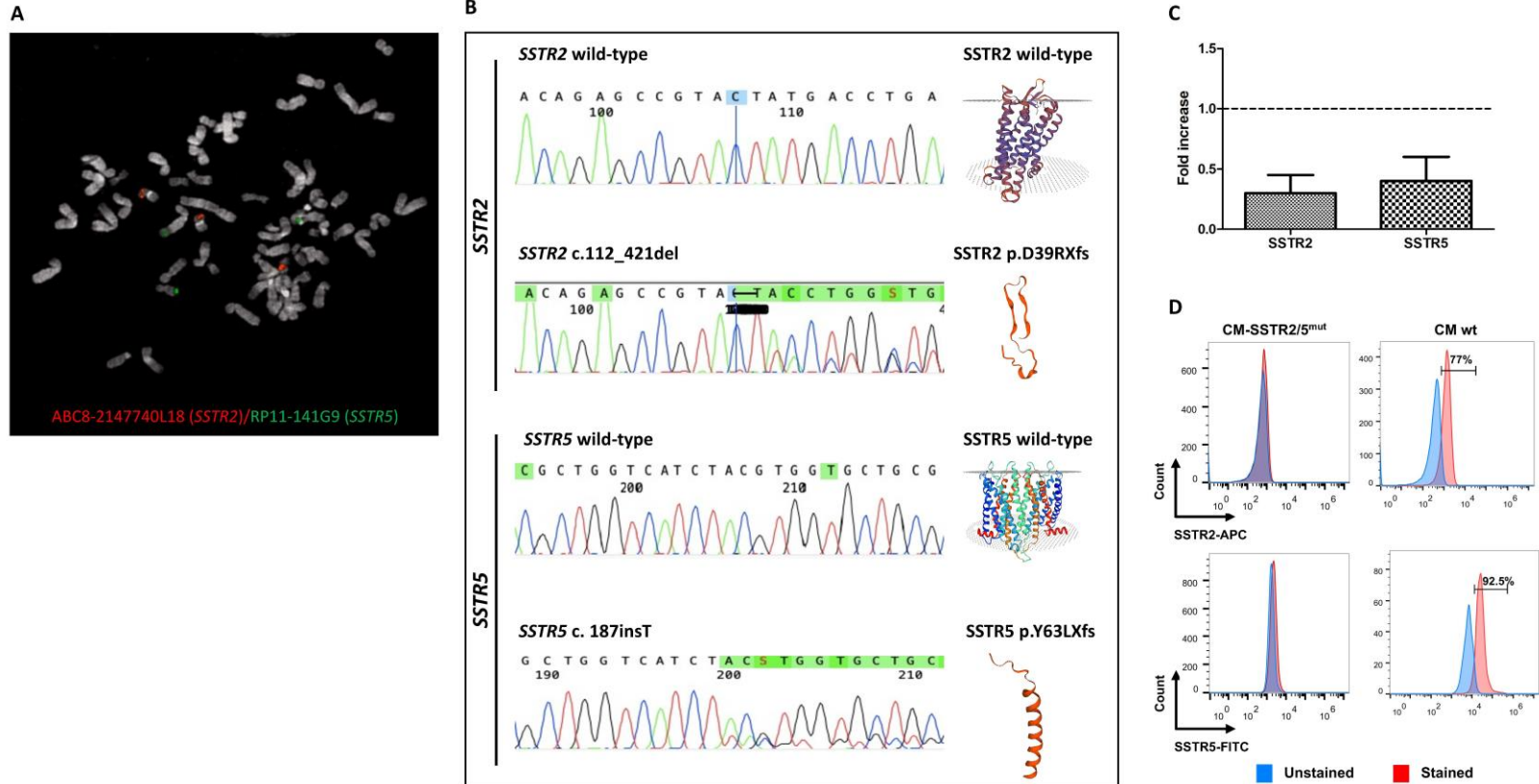
ANTI-SSTR CAR DESIGN



ANTI-SSTR CAR T CELLS EXERT CYTOLYTIC ACTIVITY AGAINST SSTR⁺ NET CELLS

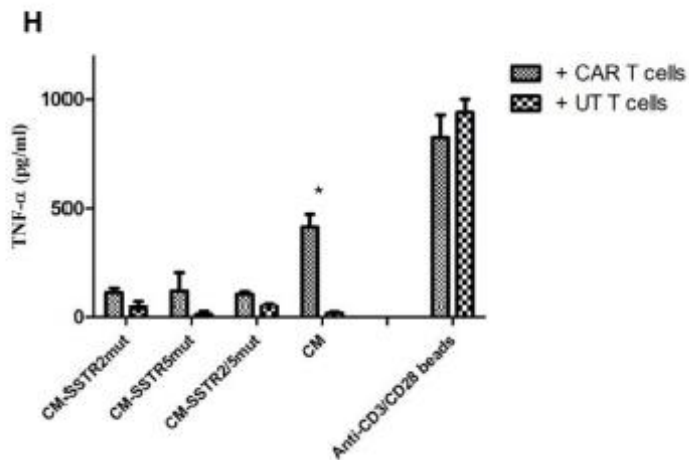
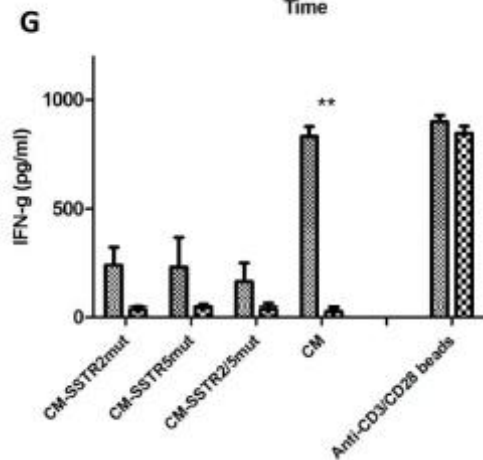
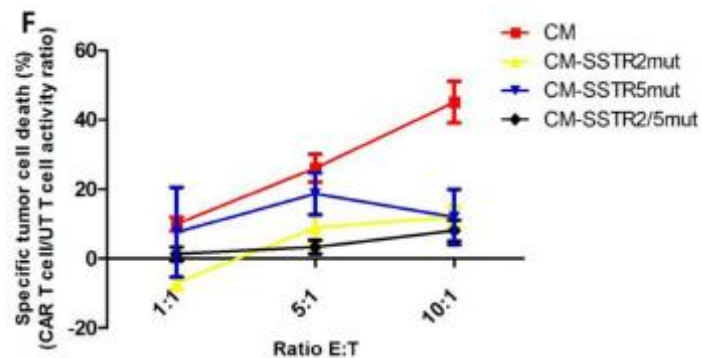
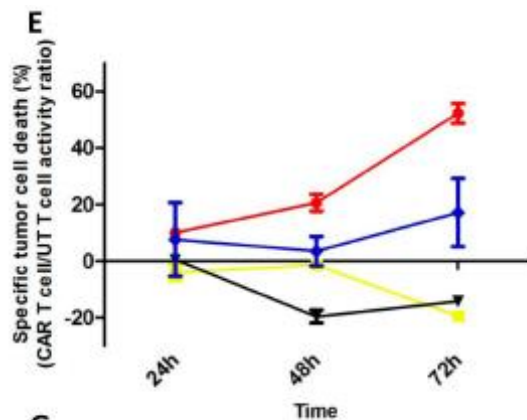


GENERATION OF SSTR^{mut} CM CELL LINE

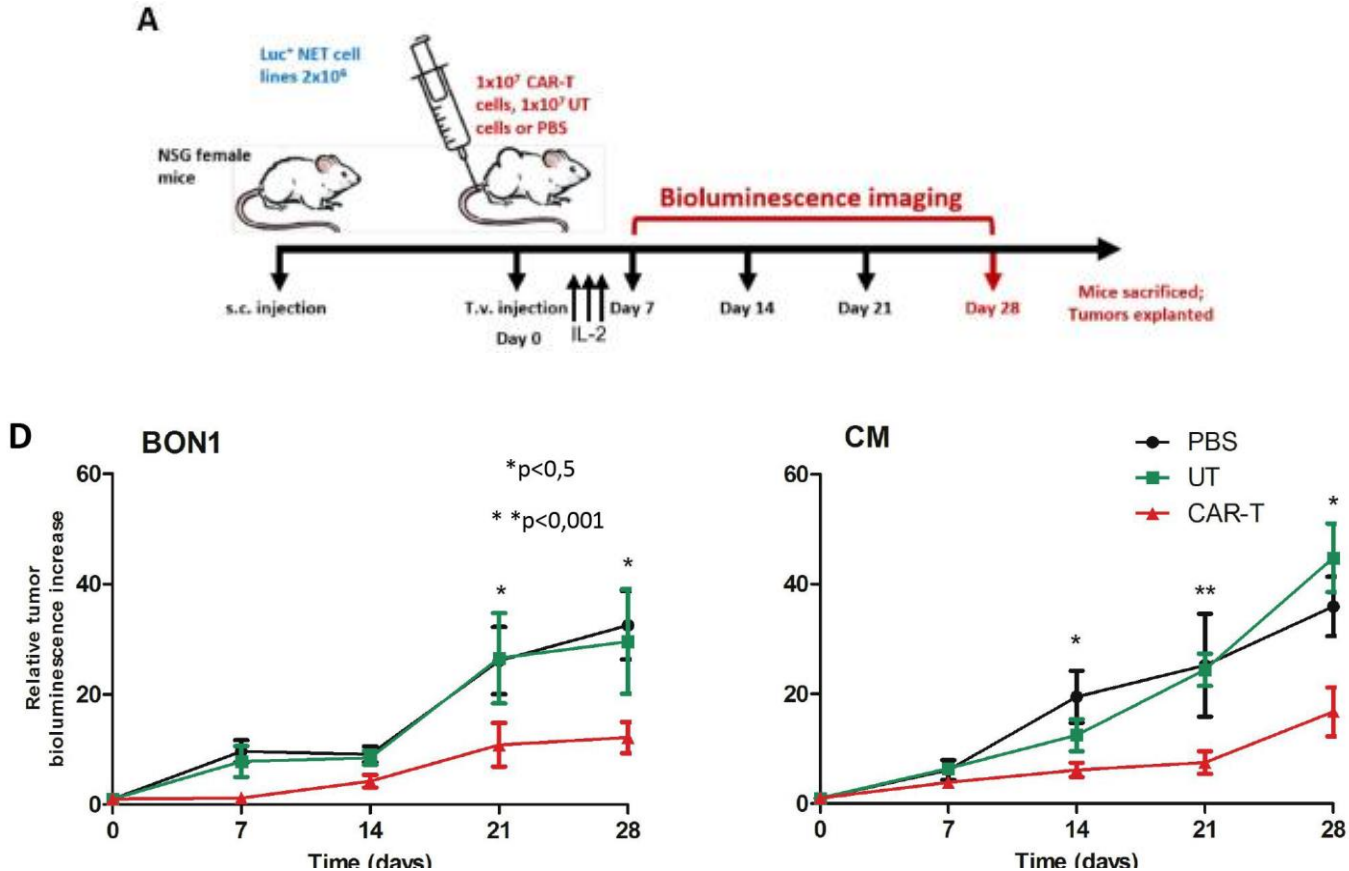


Supplementary Figure 3

THE TUMORICIDAL ACTIVITY OF ANTI-SSTR CAR T CELLS IS ANTIGEN-SPECIFIC

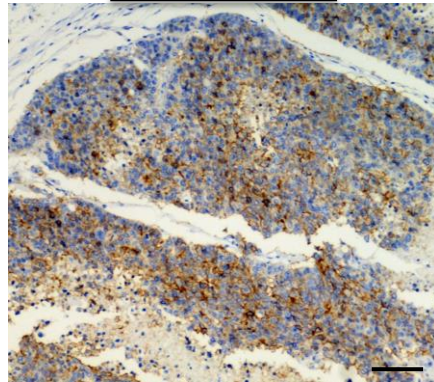


ANTI-SSTR CAR T CELLS EFFECTIVELY INHIBIT THE GROWTH OF NET XENOGRRAFTS

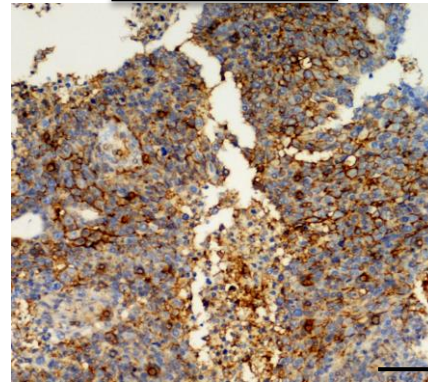


EXPLANTED HUMAN XENOGRAFTS RETAIN SSTR EXPRESSION

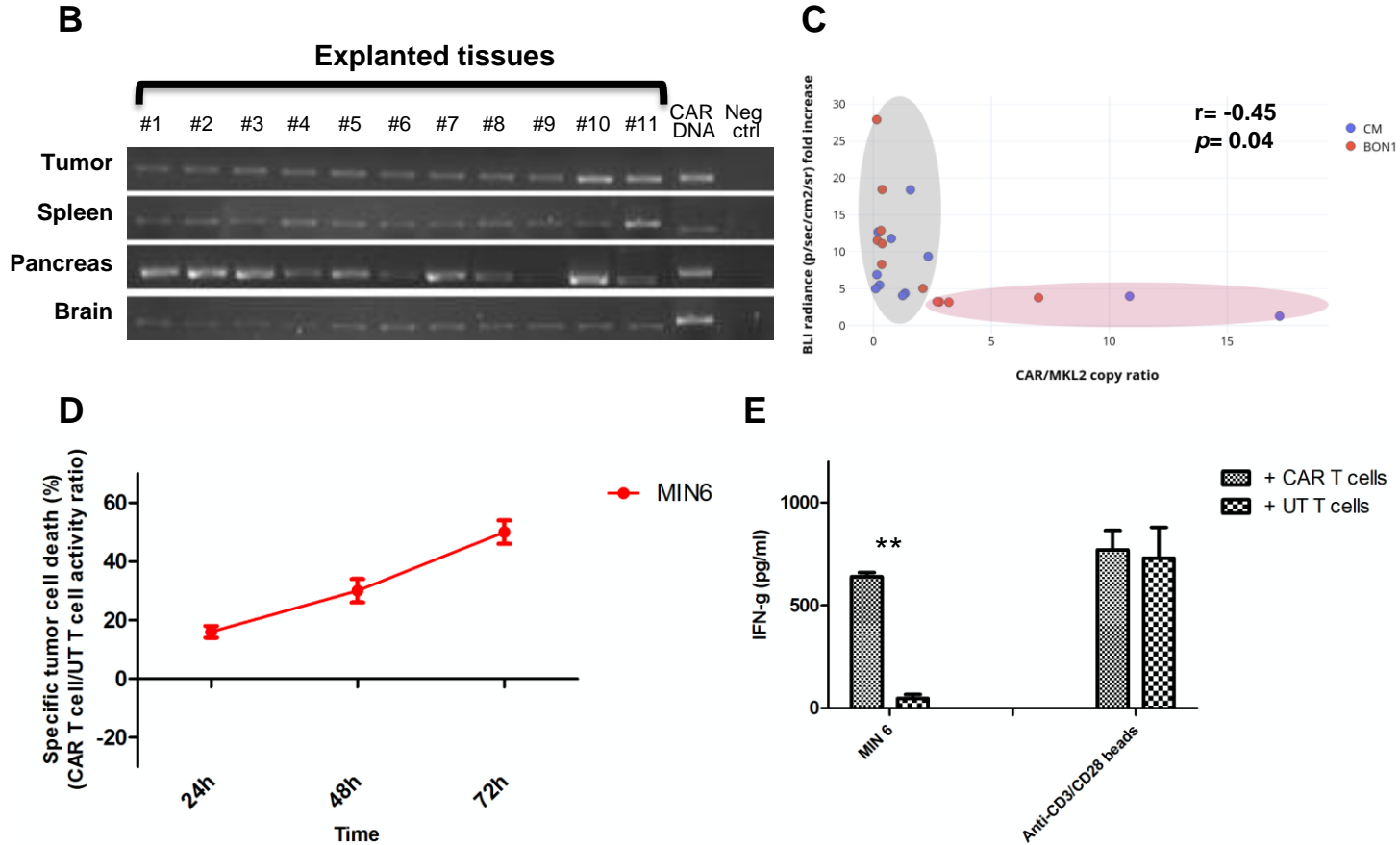
SSTR2



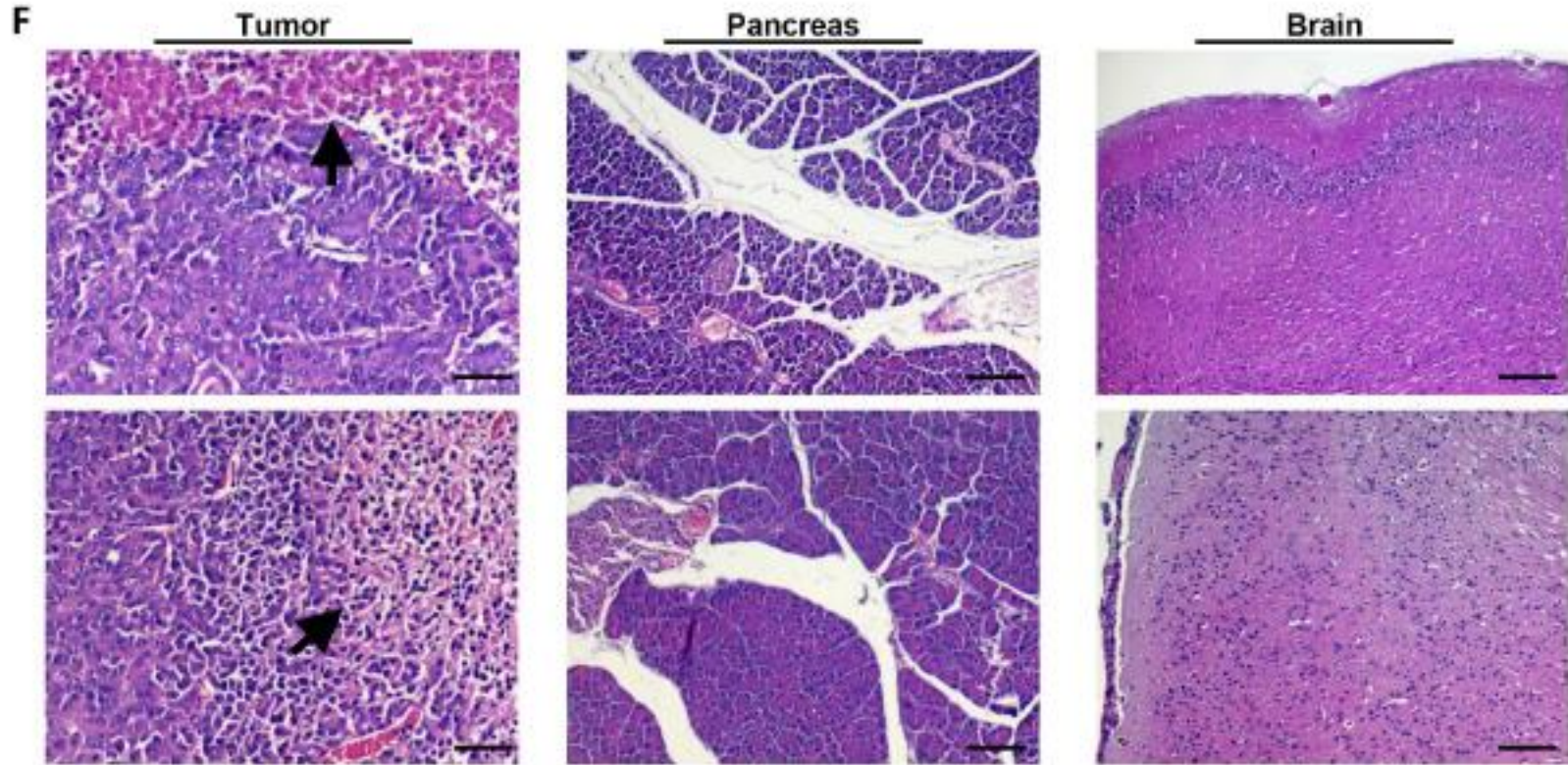
SSTR5



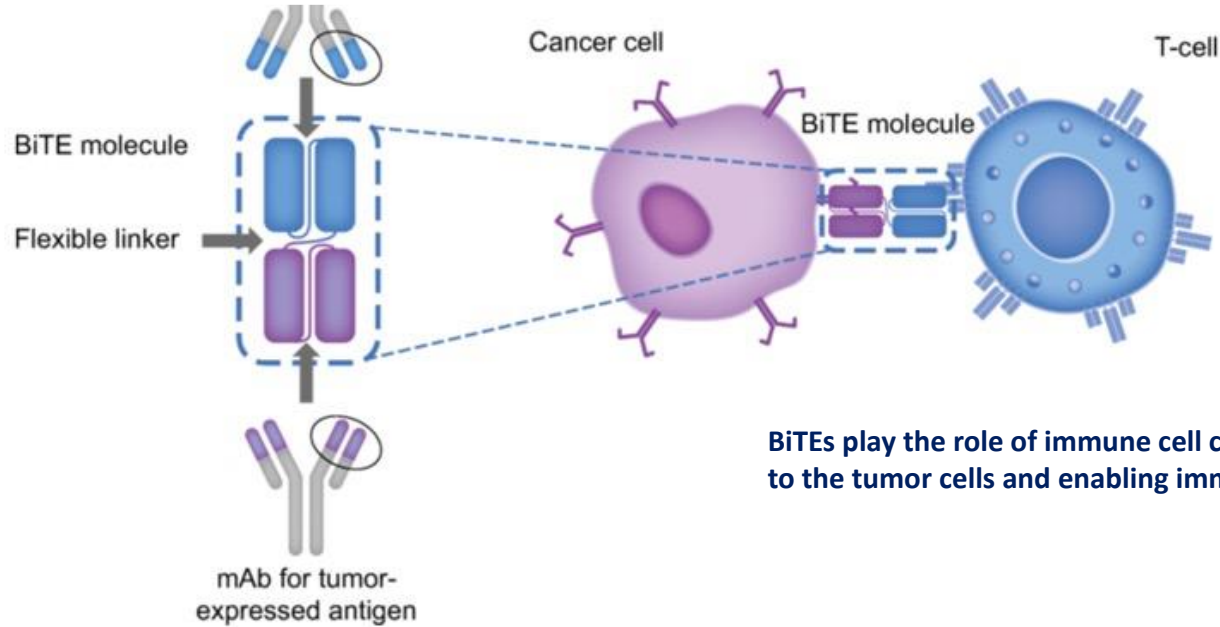
ANTI-SSTR CAR T CELLS INFILTRATE SSTR-EXPRESSING ORGANS



ANTI-SSTR CAR T CELLS DO NOT DAMAGE SSTR-EXPRESSING ORGANS IN MICE



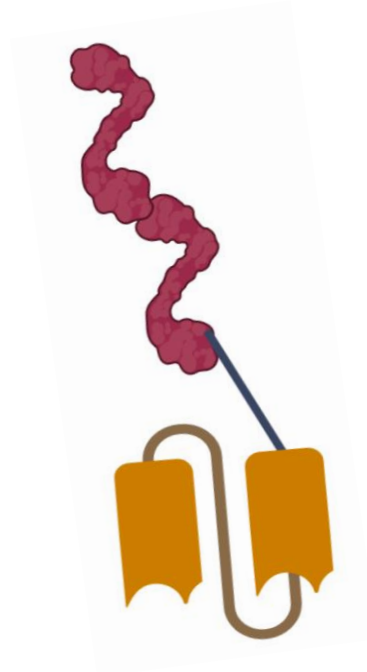
T CELL REDIRECTION THROUGH BiTEs



BiTEs play the role of immune cell connector, connecting the immune cells to the tumor cells and enabling immune cells to exert their killing effect

ANTI-SSTR BiTE DESIGN

Somatostatin – Somatostatin — anti CD3 Ab

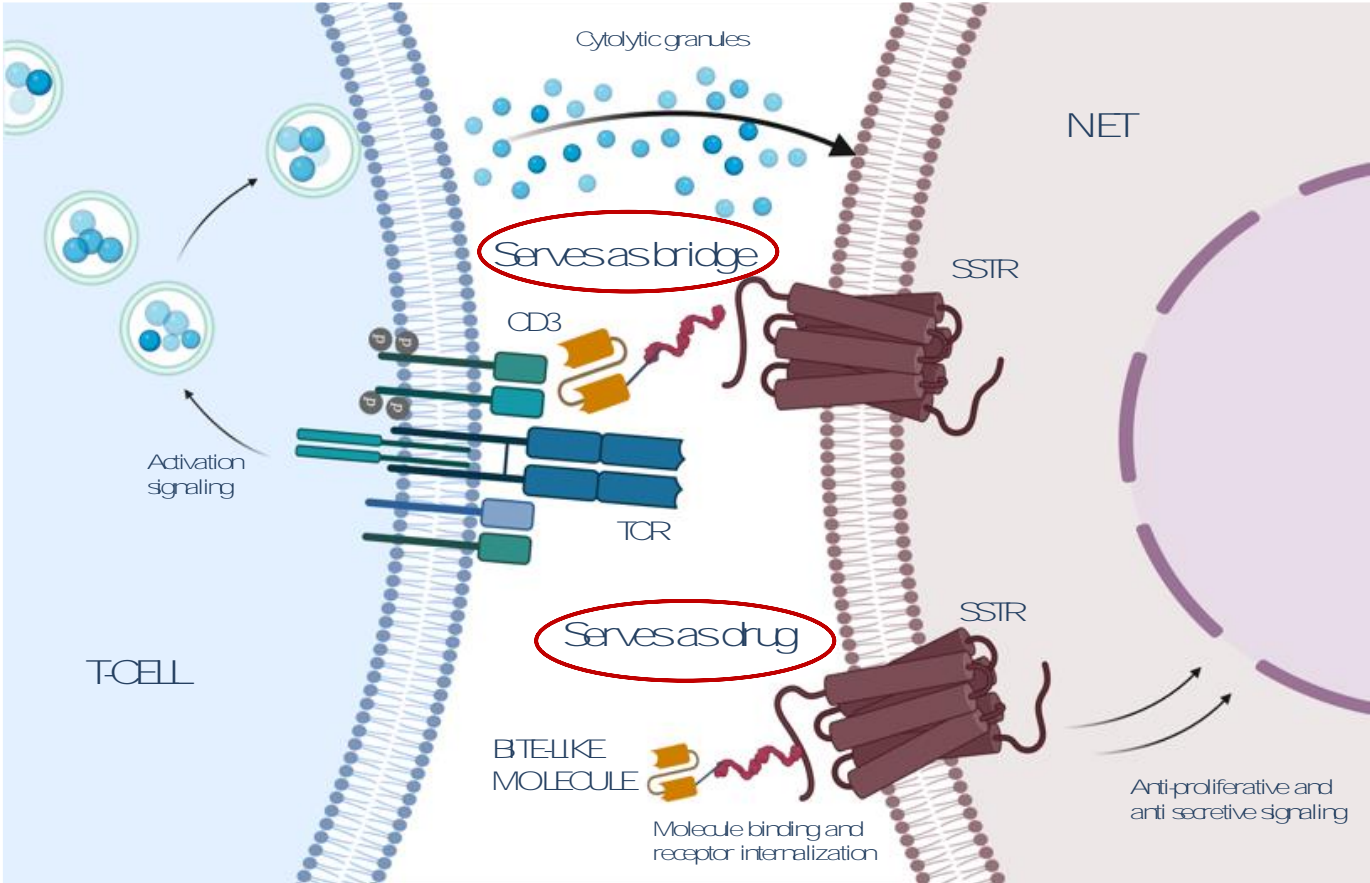


HORMONE
TARGETING
SSTR ON NET
CELLS

scFv
TARGETING
CD3 ON T-CELL

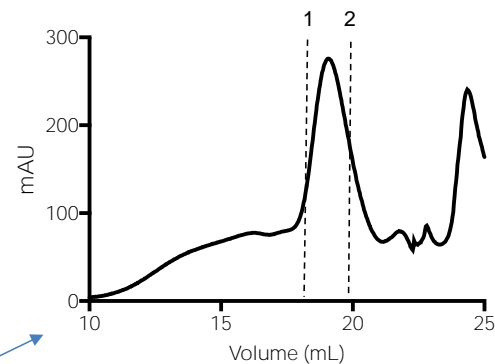
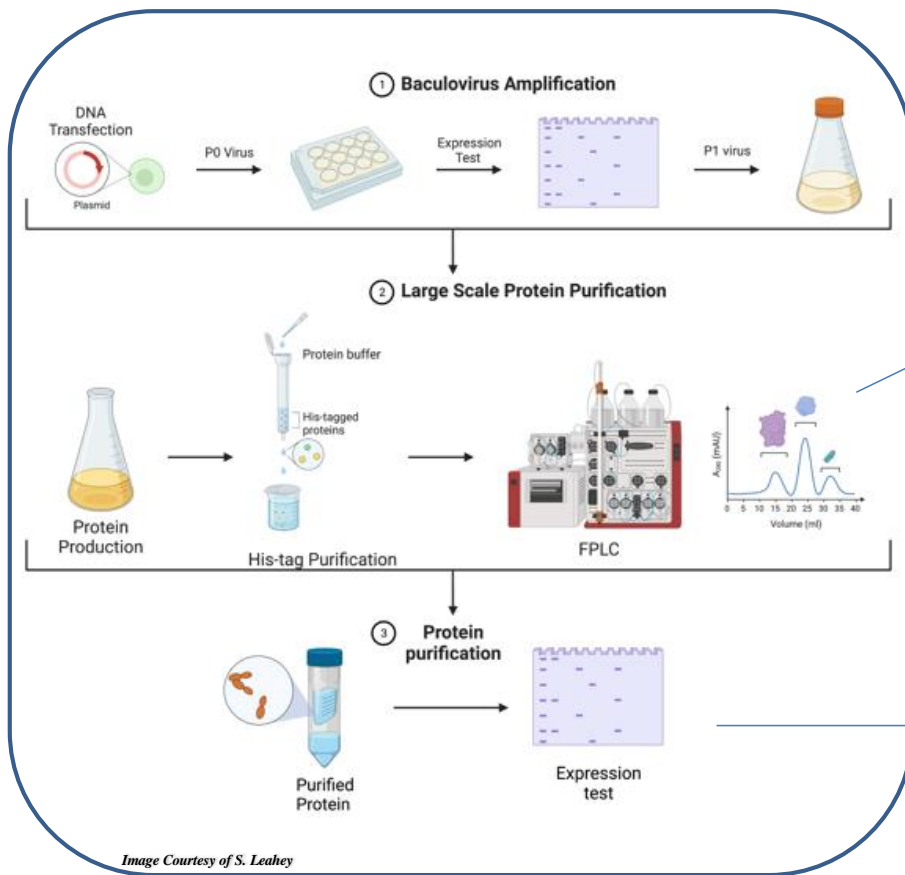
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ANTI-SSTR BiTE MAY HAVE A DUAL MECHANISM OF ACTION



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EXPRESSION AND PURIFICATION OF THE ANTI-SSTR BiTE



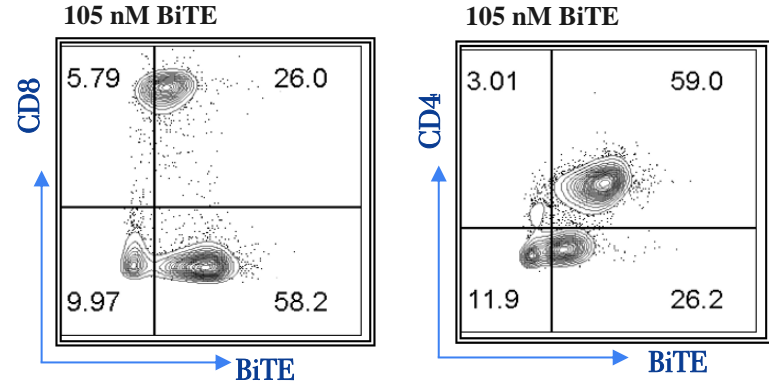
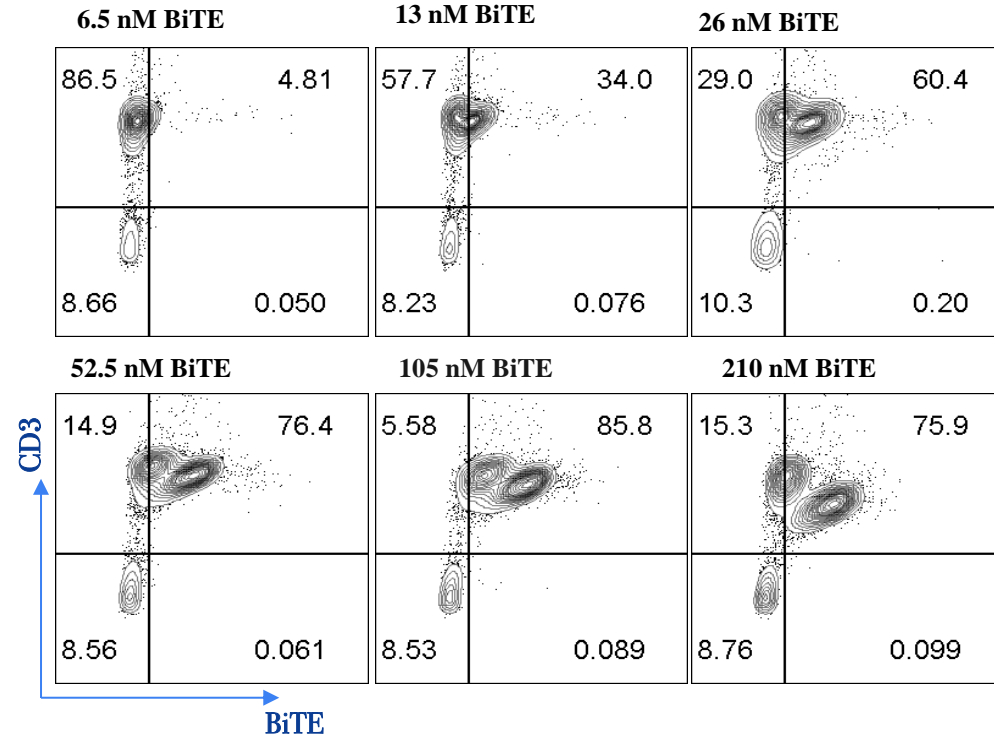
Nonreduced		Boiled and reduced	
1	2	1	2



Image Courtesy of S. Leahy

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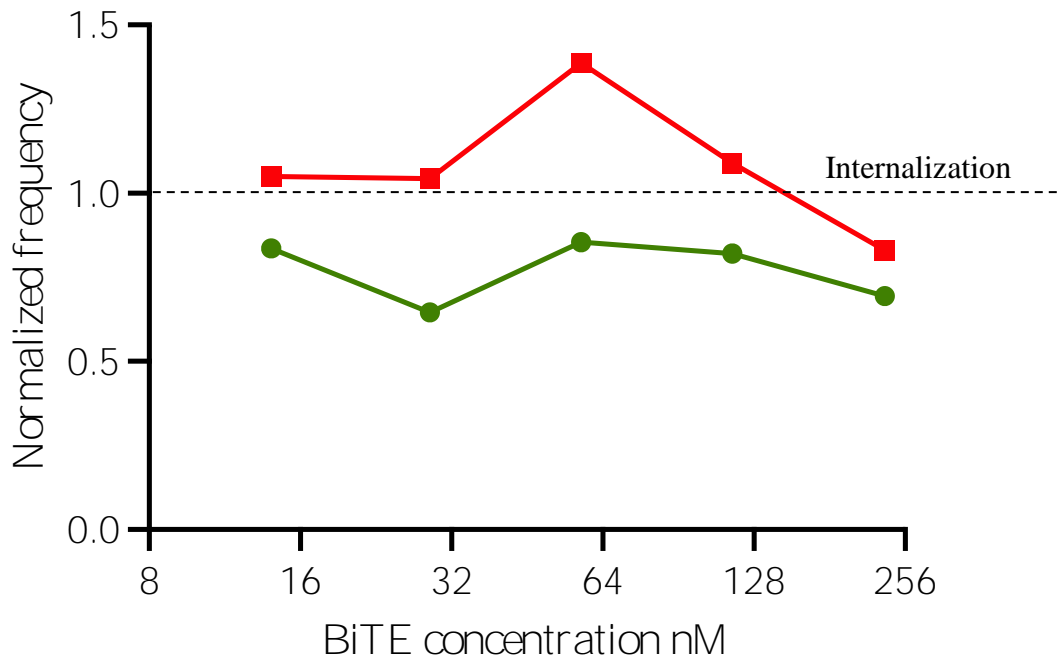
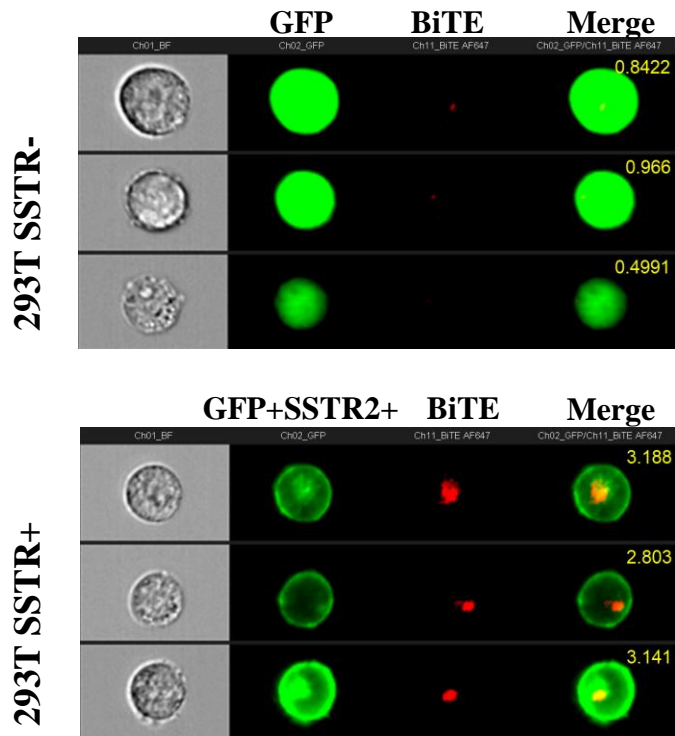
ANTI-SSTR BiTE BINDS CD3 ON T CELLS



At ~100nM, the BiTE binds more than 85% of the T-cells, both CD4+ and CD8+

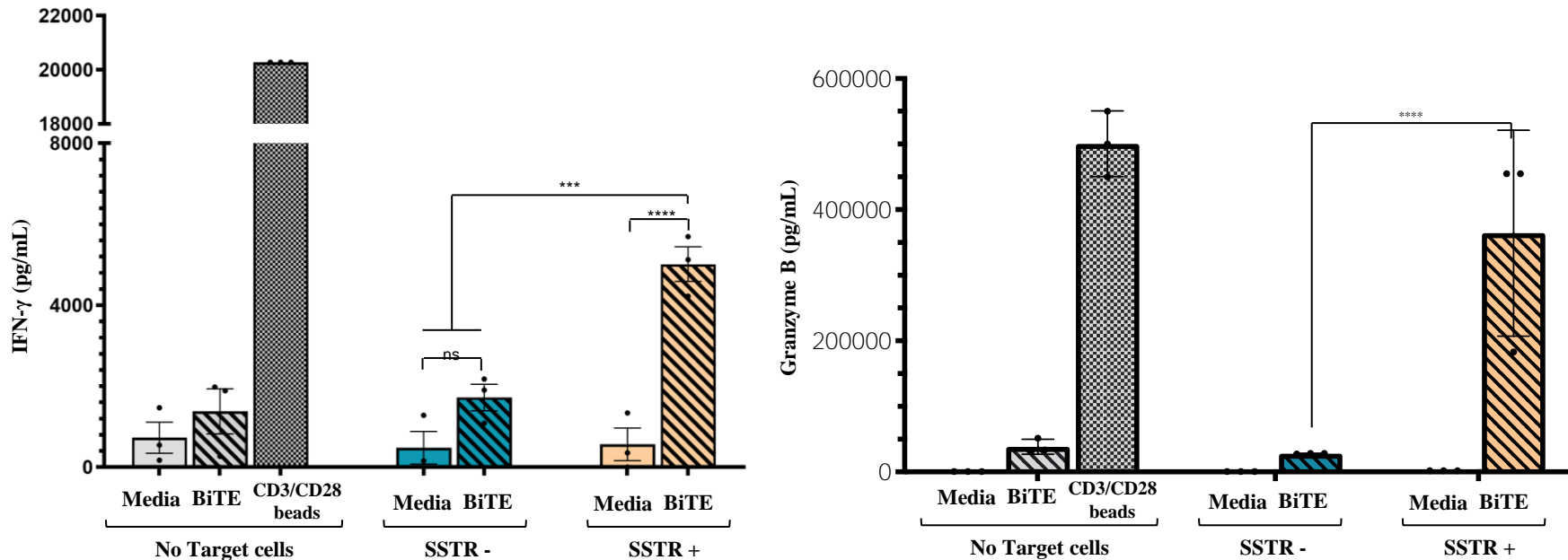
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ANTI-SSTR BiTE BINDS SSTRs ON SSTR-TRANSDUCED CELLS



The BiTE binds the SSTR2, and it is internalized between 30 and 120 nM, with higher internalization around 60 nM.

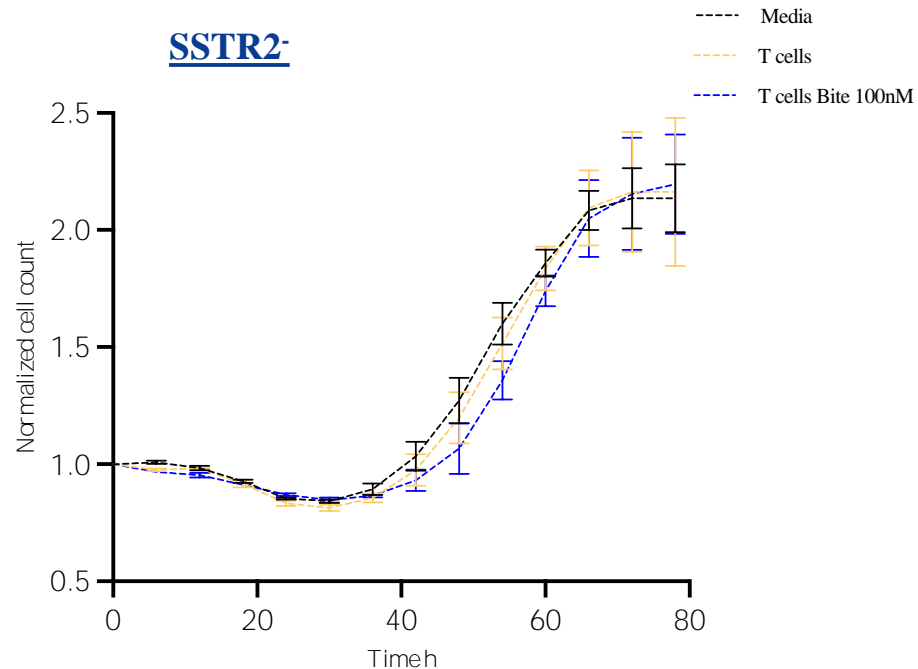
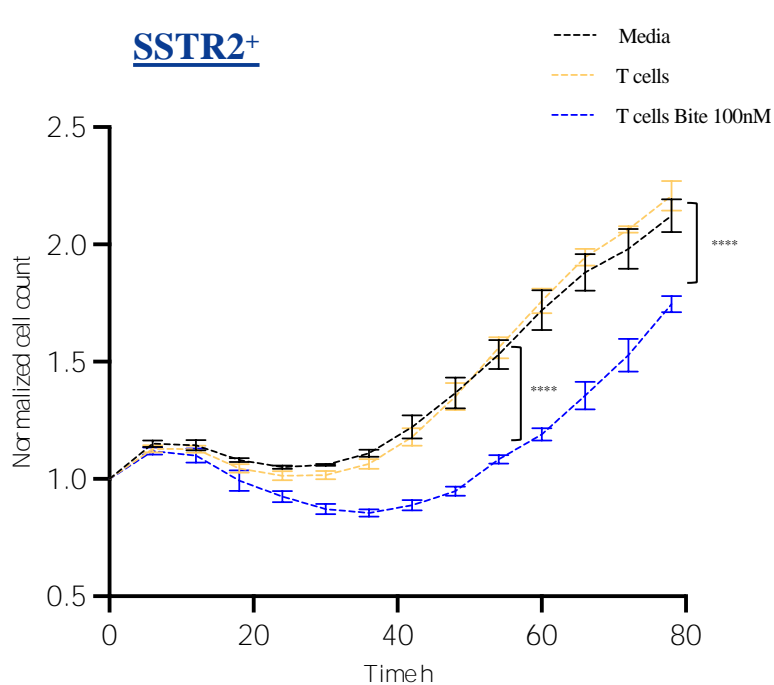
ANTI-SSTR BiTE MEDIATES SSTR-SPECIFIC T CELL ACTIVATION



IFN- γ and Granzyme B secretion significantly increases when the T cells are cocultured with SSTR⁺ 293T and 100 nM BiTE

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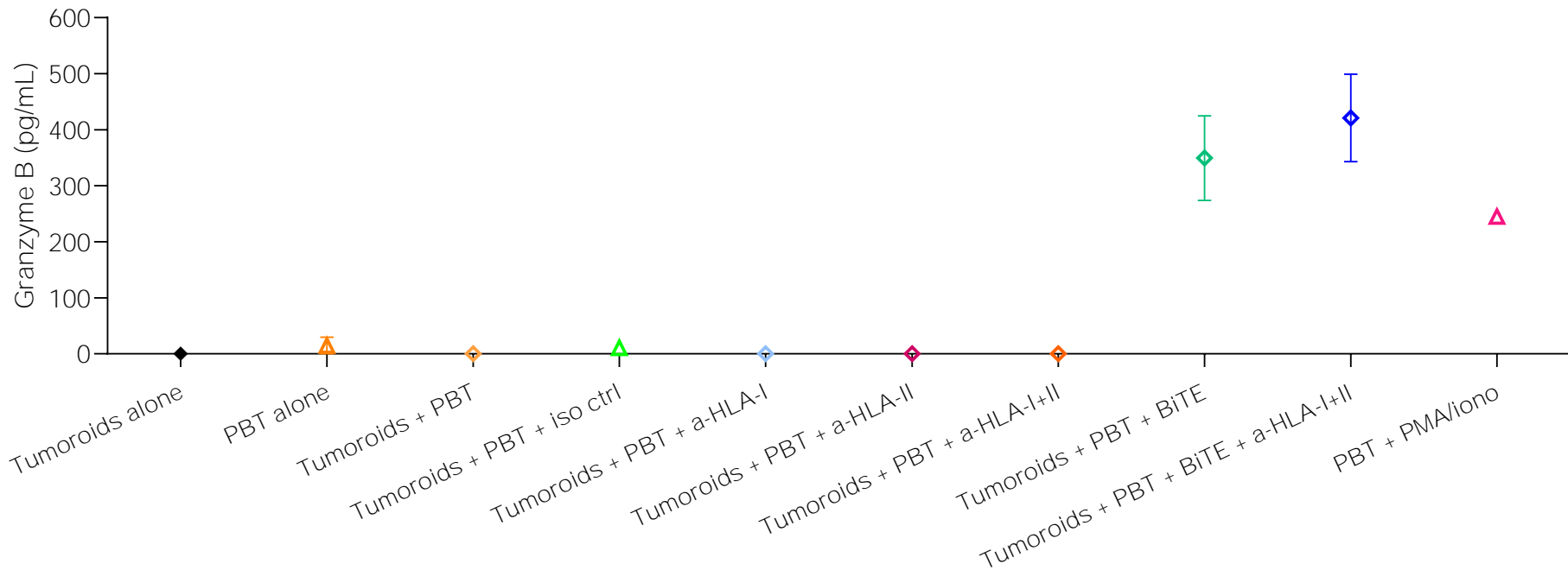
ANTI-SSTR BiTE MEDIATES SSTR-SPECIFIC T CELL KILLING



T cells control tumor growth of SSTR2 expressing target cells in presence of the BiTE

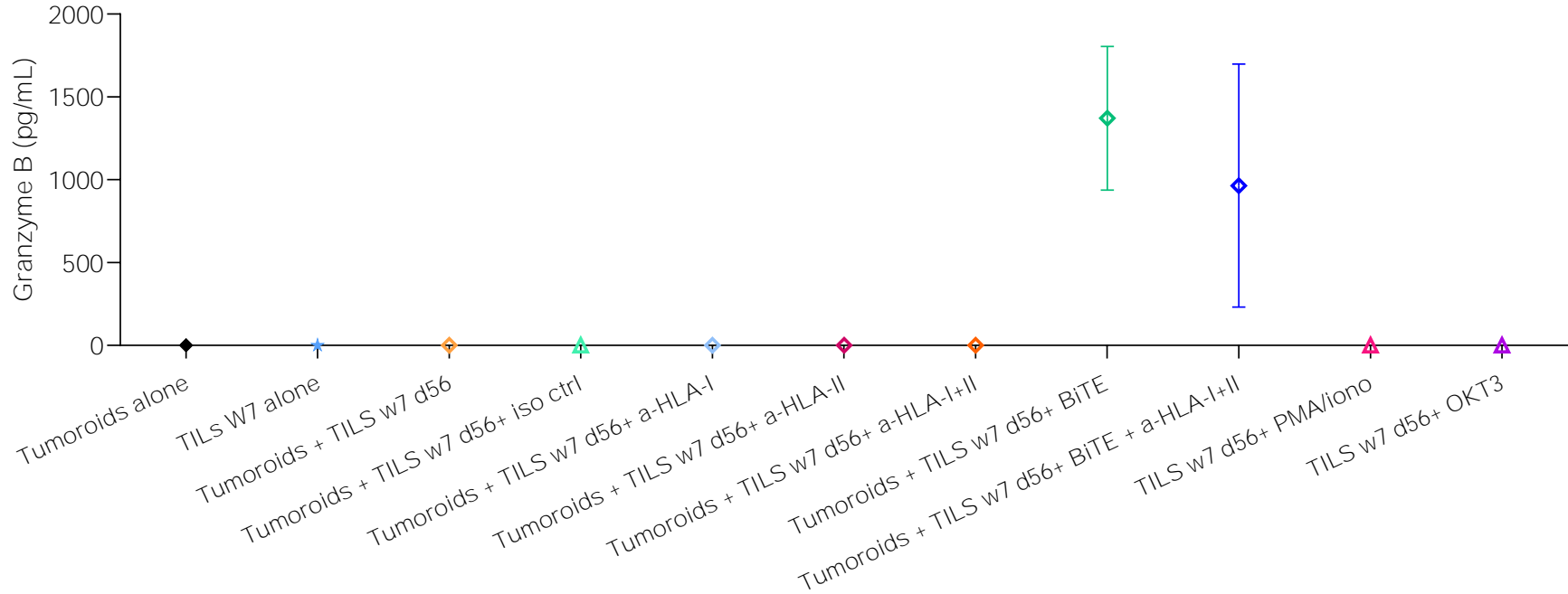
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ANTI-SSTR BiTE ACTIVATES PERIPHERAL BLOOD T CELLS AGAINST AUTOLOGOUS NET TUMOROIDS



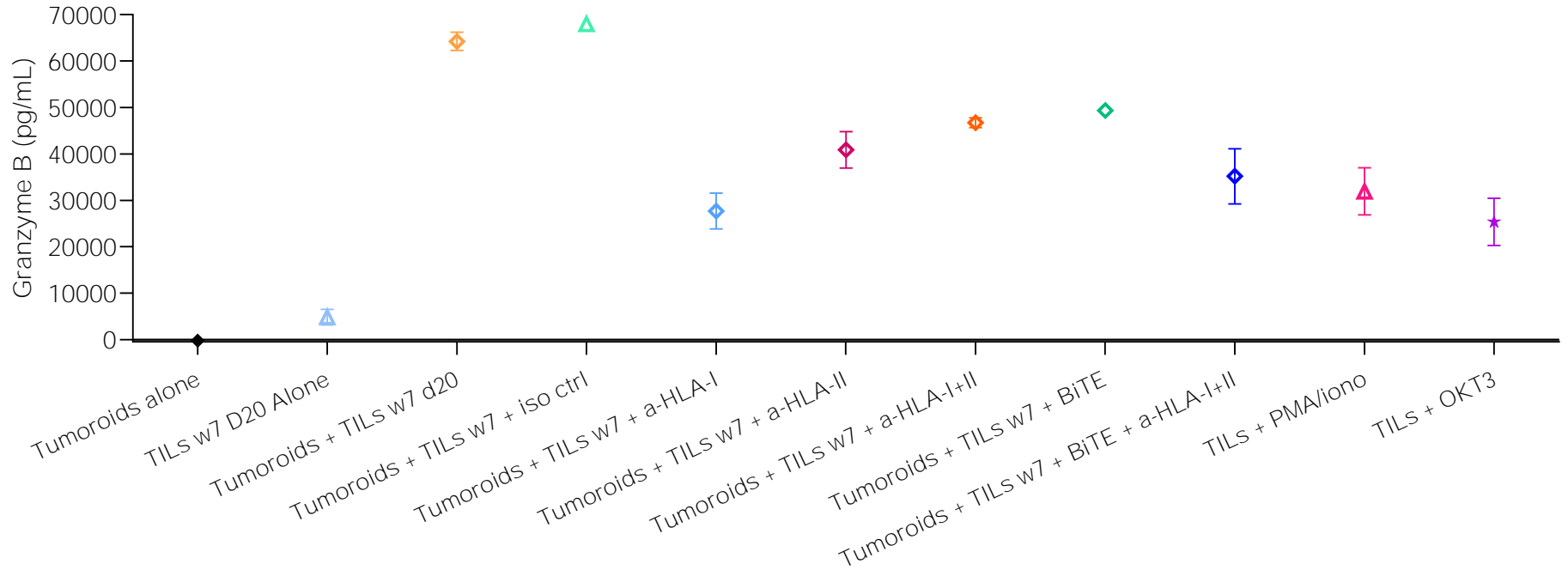
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ANTI-SSTR BiTE ACTIVATES TILs AGAINST AUTOLOGOUS NET TUMOROIDS



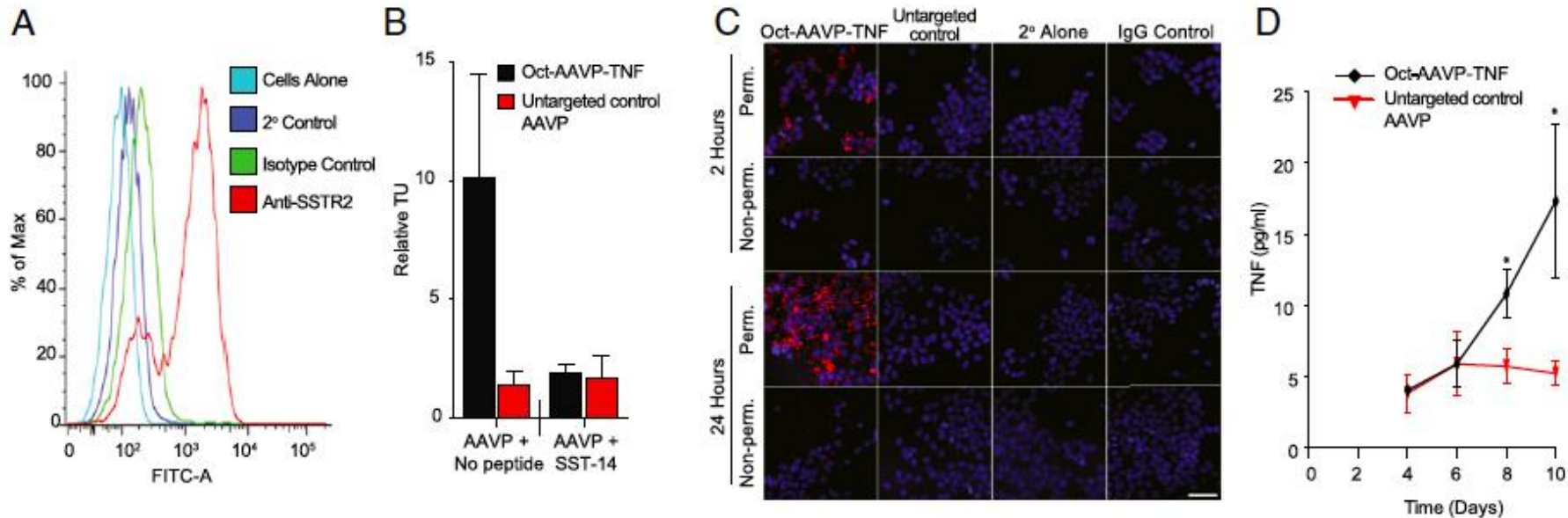
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ANTI-SSTR BiTE ACTIVATES TILs AGAINST AUTOLOGOUS NET TUMOROIDS

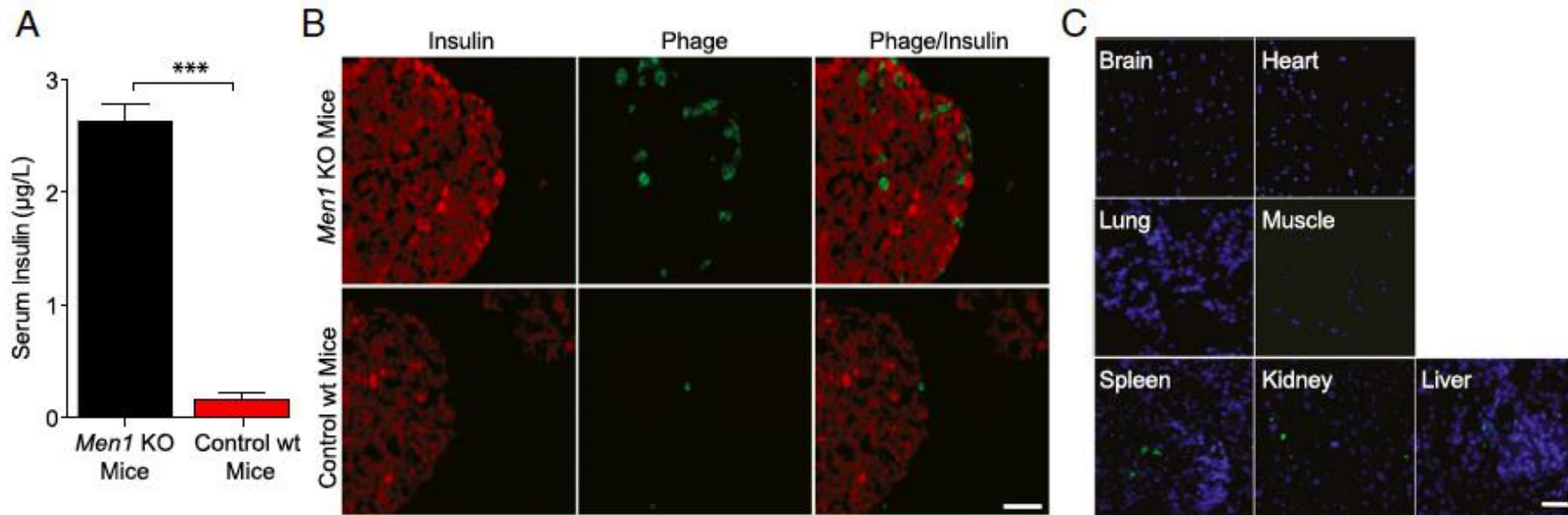


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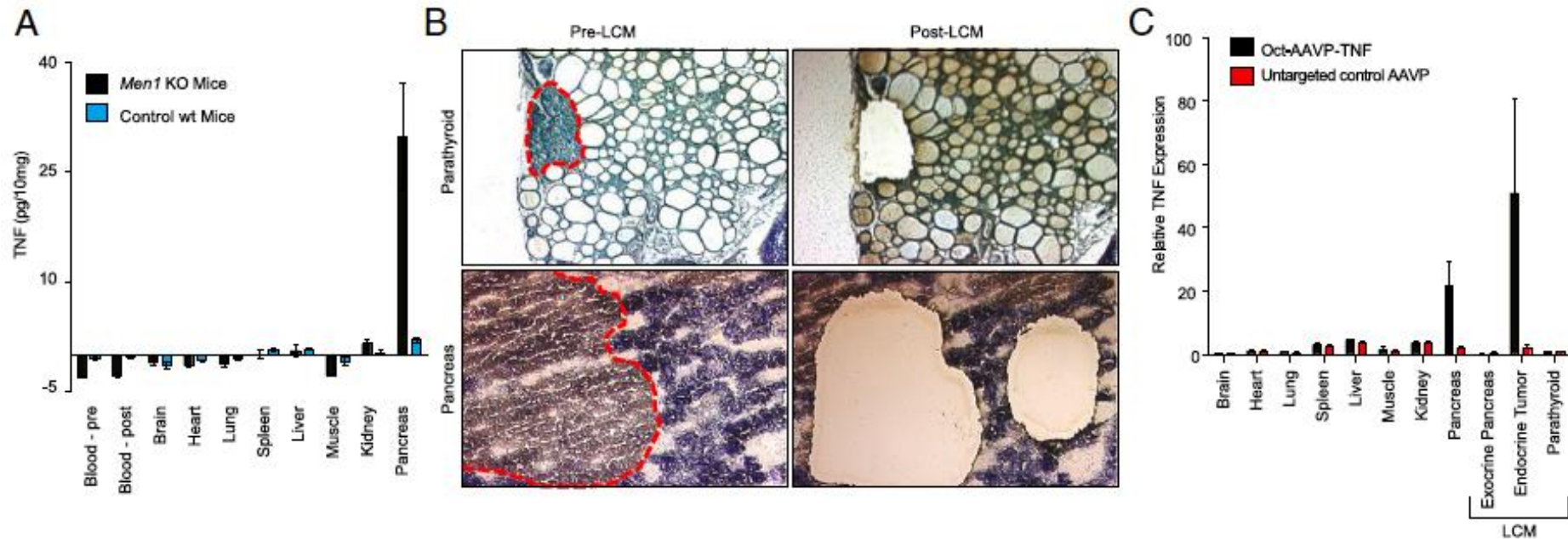
ADENO-ASSOCIATED VIRUS AND PHAGE DISPLAYING OCTREOTIDE FOR LIGAND-DIRECTED THERAPY OF NETs



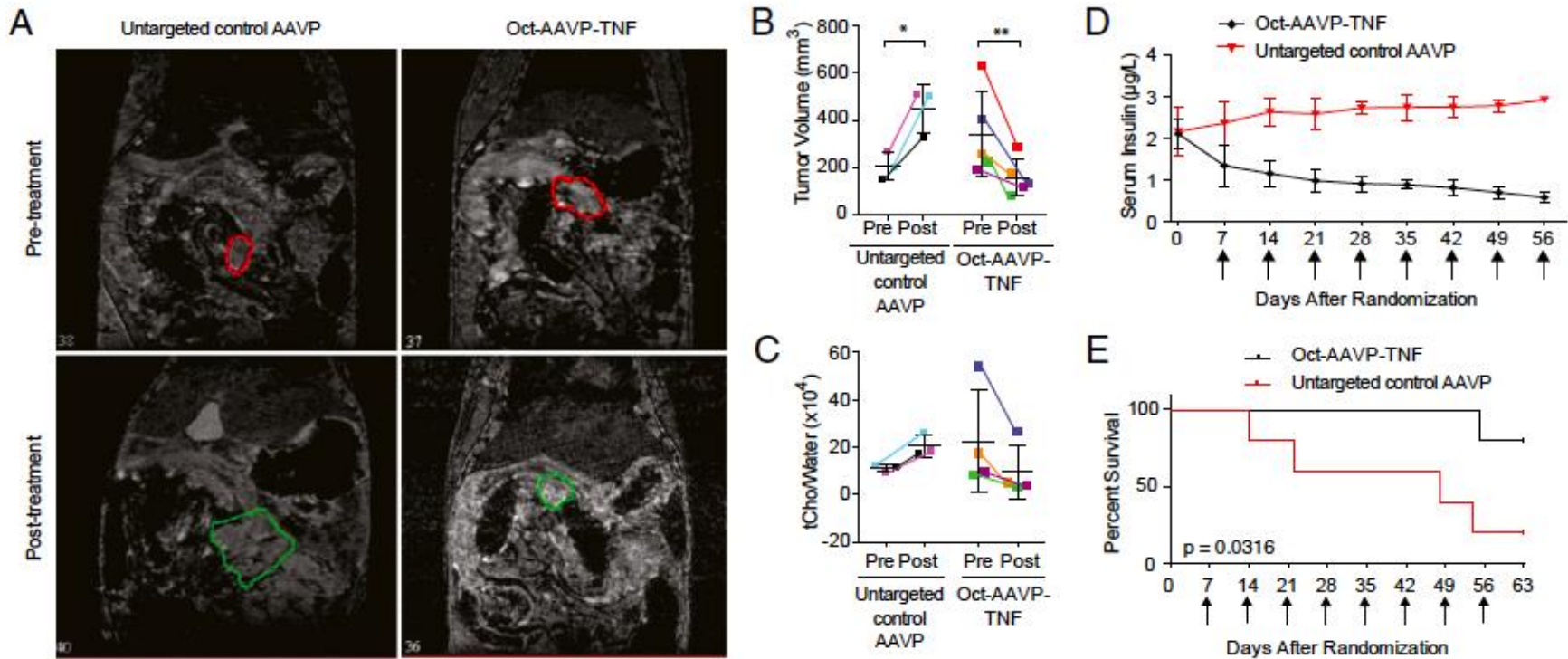
ADENO-ASSOCIATED VIRUS AND PHAGE DISPLAYING OCTREOTIDE FOR LIGAND-DIRECTED THERAPY OF NETs



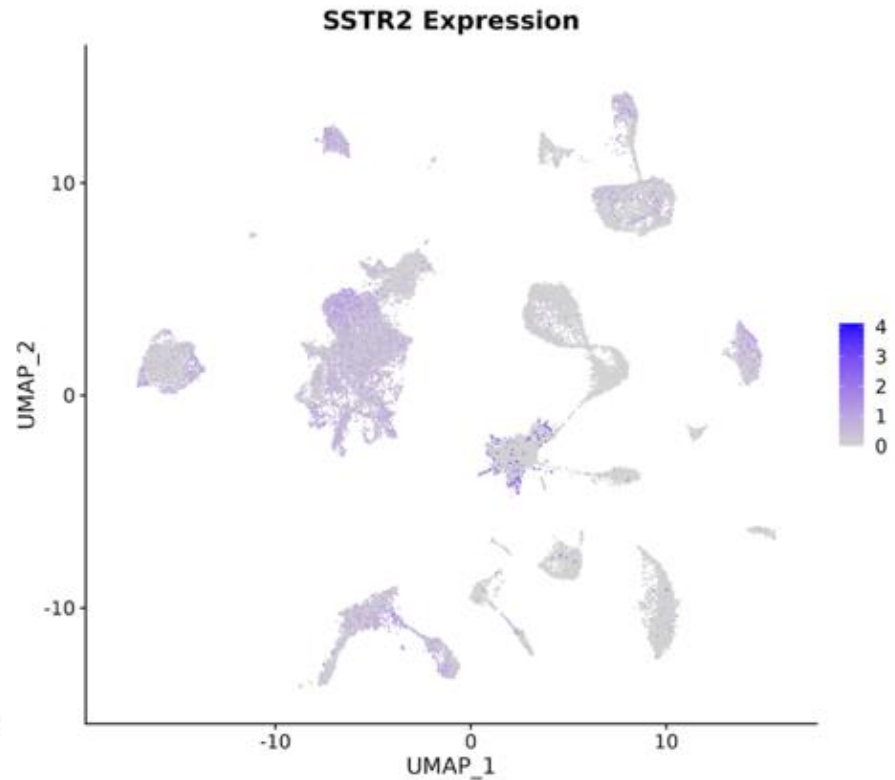
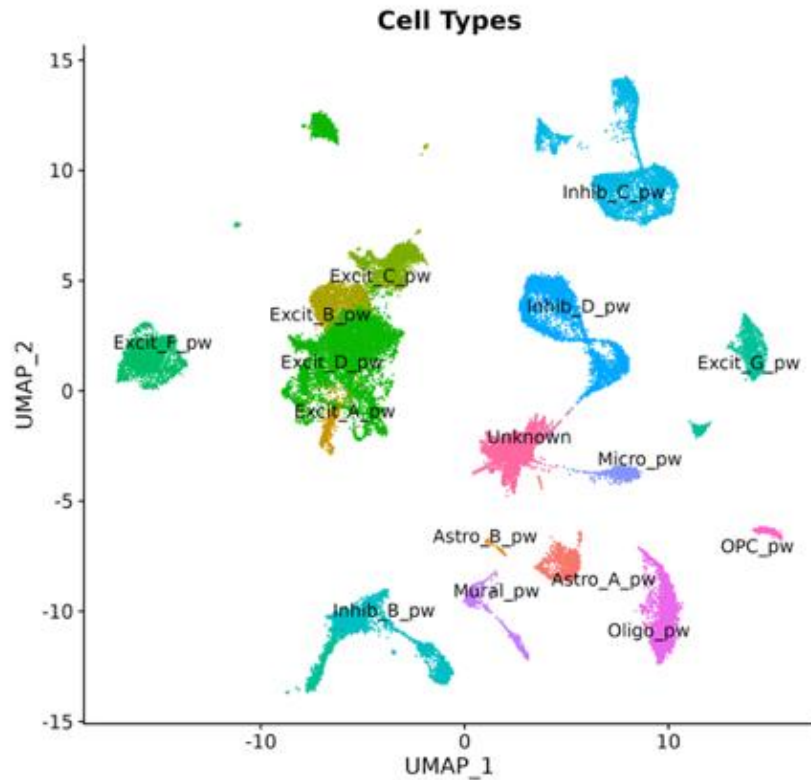
ADENO-ASSOCIATED VIRUS AND PHAGE DISPLAYING OCTREOTIDE FOR LIGAND-DIRECTED THERAPY OF NETs



ADENO-ASSOCIATED VIRUS AND PHAGE DISPLAYING OCTREOTIDE FOR LIGAND-DIRECTED THERAPY OF NETs



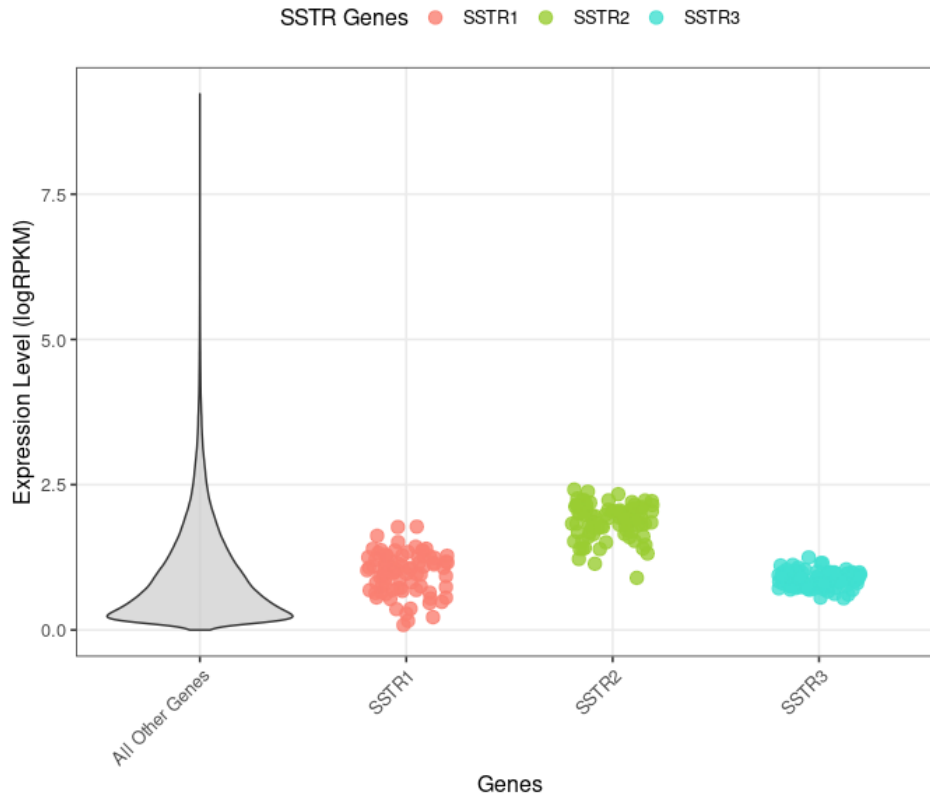
SSTR2 EXPRESSION IN BRAIN BY scRNAseq



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SSTR2 EXPRESSION IN BRAIN BY MASS SPECTROMETRY

SSTR Gene Expression Compared to All Genes in LCM Dentate (Control)



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CONCLUSIONS

- 1. The effects of SST/SSAs on the immune compartment are largely unexplored/not fully understood**
 - 2. PRRT might sensitize tumors to immune-checkpoint blockade through antigen spreading**
 - 3. Anti-SSTR CAR T cells are a potential candidate for early phase clinical investigations**
 - **Are anti-SSTR CAR T cells safe? (potential for on-target off-tumor toxicities)**
 - **Suicide gene safety switches may render this therapeutic approach safer**
 - 4. Anti-SSTR BiTE exerts antitumor activity by eliciting an immune synapsis between T cells and NET cells**
 - 5. Biologically active drugs can be successfully used as a displayed ligand to impart target specificity to CAR T cells, BiTEs, viruses, etc.**
-

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ENETS
Neuroendocrine Tumor Society**



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