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Preclinical Modelling of in vivo Engineered CAR-T Products

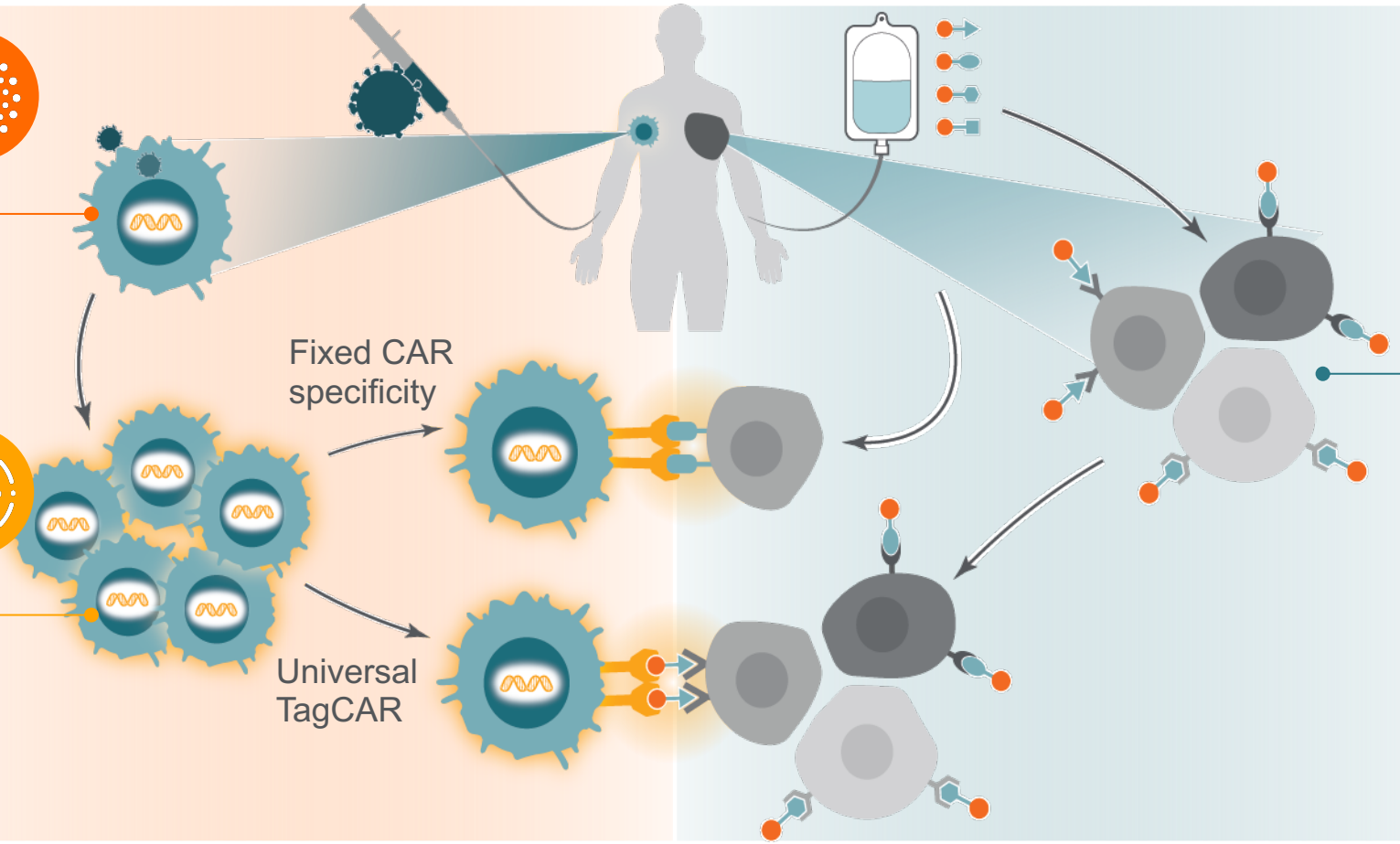
CAR-TCR Summit 2021

Shon Green

Umoja's integrated immunotherapy platform provides solutions to the challenges in both blood and solid tumor CAR-T therapies

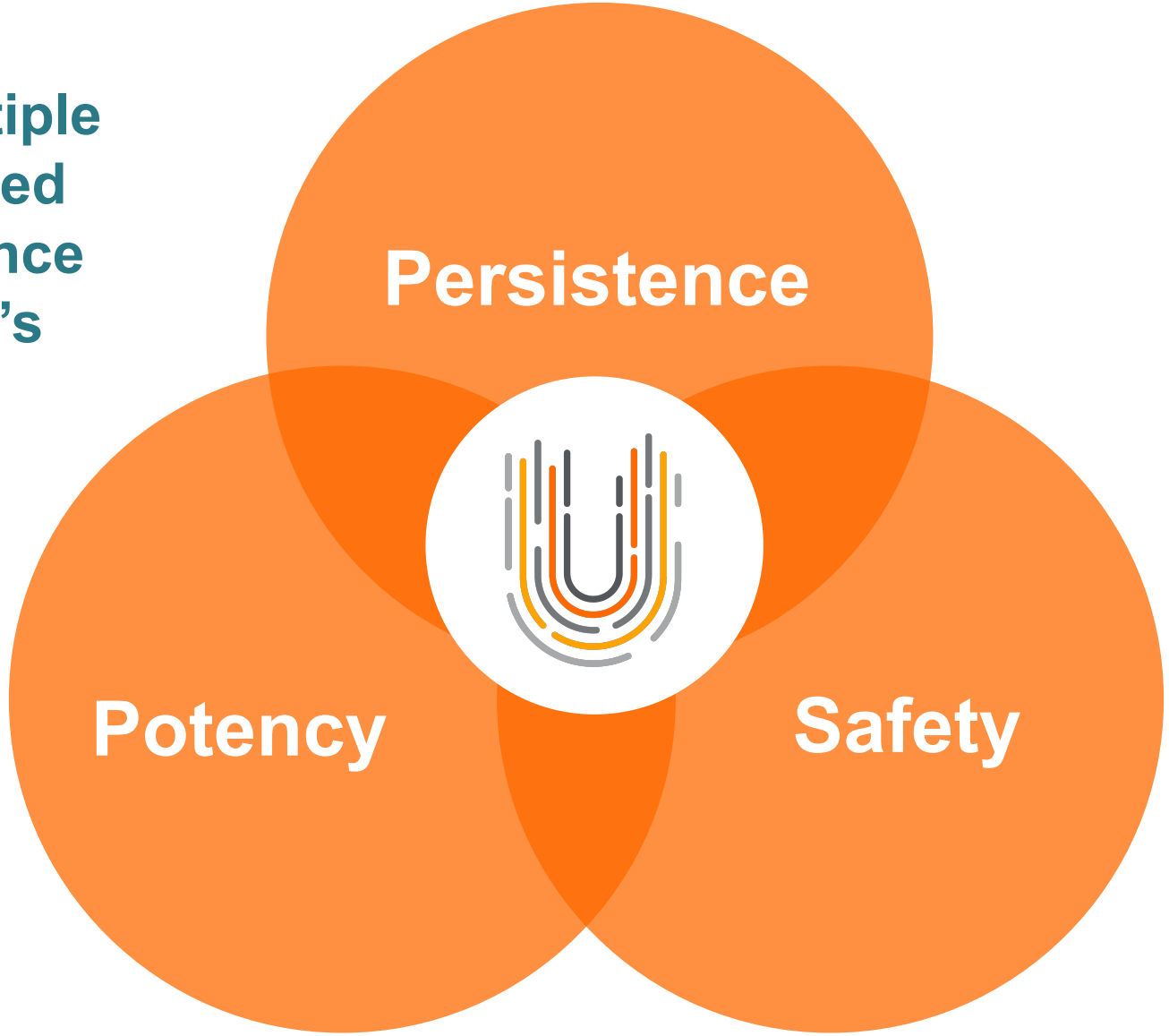
ARM:
VivoVec engineers cells in vivo
- surface engineered lentivirus-mediated in vivo transduction

EXPAND:
RACR preferentially expands engineered cells
- Rapamycin activated cytokine receptor (RACR)



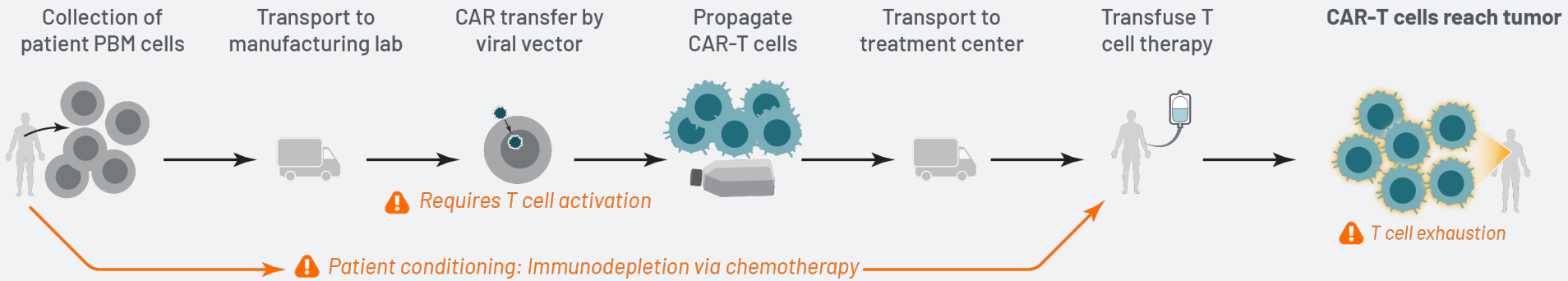
DESTROY:
TumorTag universally targets multiple tumor elements
- small molecule bi-specific adapters

Umoja's platform captures multiple key potency attributes associated with autologous CAR-T cells since it is compatible with the patient's own immune system…



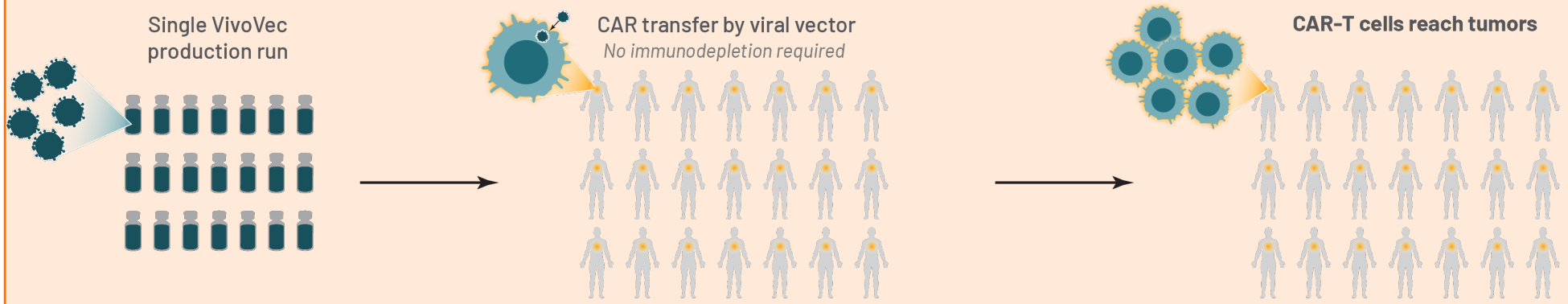
… while expanding convenience and scalability beyond allogeneic products

Autologous or Allogeneic approaches require extensive ex vivo manipulations



Logistically complex and expensive, introduces less-than ideal activation and expansion conditions that may lead to unfavorable T cell health

VivoVec — one manufacturing process treats thousands of patients in vivo



One lot treats many patients who "manufacture" their own CAR-T cells with minimal manipulation and with potentially enhanced potency

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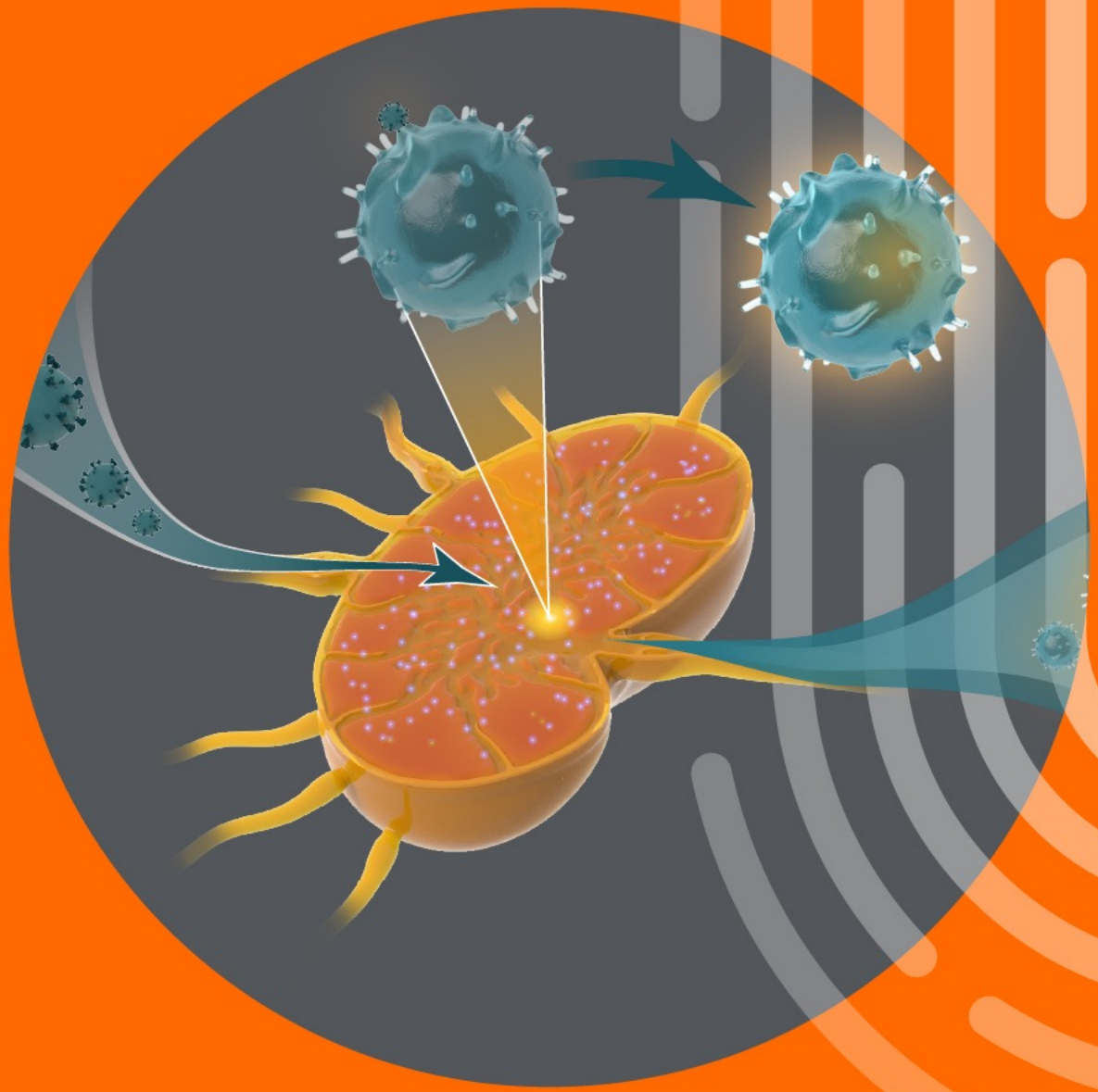
VivoVec

in vivo CAR T cell generation



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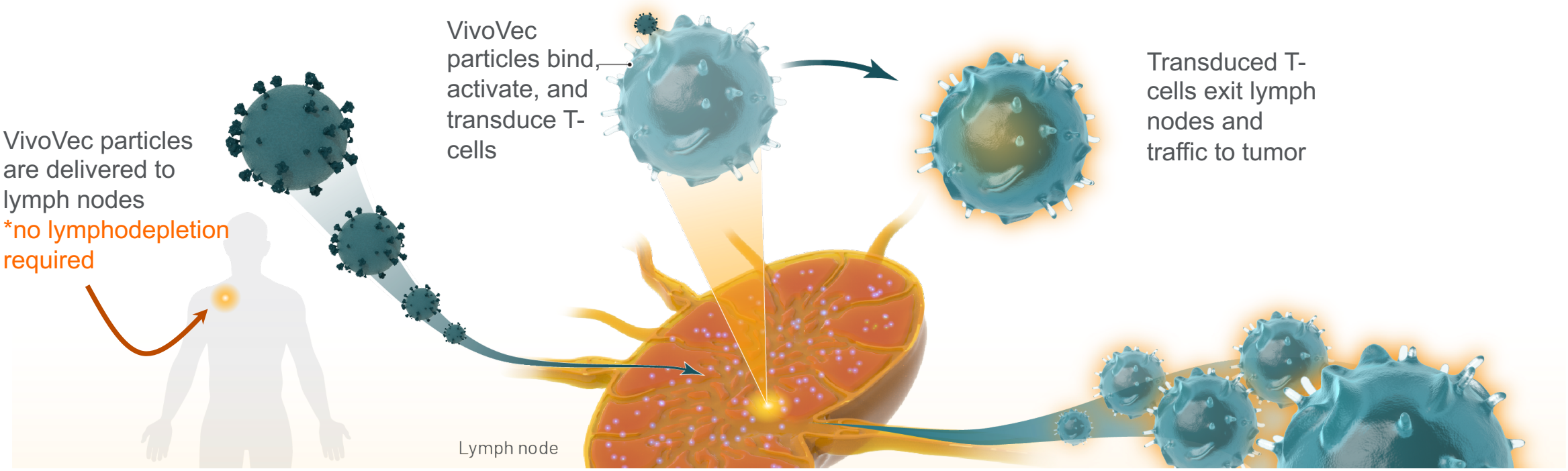
VivoVec platform solves the technical barriers to in vivo genetic engineering of T cells

Technical hurdles for *in vivo* genetic engineering	**VivoVec Solutions**
”Condition”/activate T cells for efficient transduction	**Lentivirus surface engineering for efficient T cell activation and transduction in vivo**
In vivo expansion of engineered T cells	**Drug-regulated cytokine receptor in the payload enables in vivo stimulation and expansion of transduced cells**
Avoid exhaustion during expansion	**“Natural” expansion process in the body maintains high potency**
VSV-G enveloped lenti particles are highly immunogenic and rapidly rejected	**Novel glycoprotein reduces potential for immunogenicity (relative to VSV-G)**

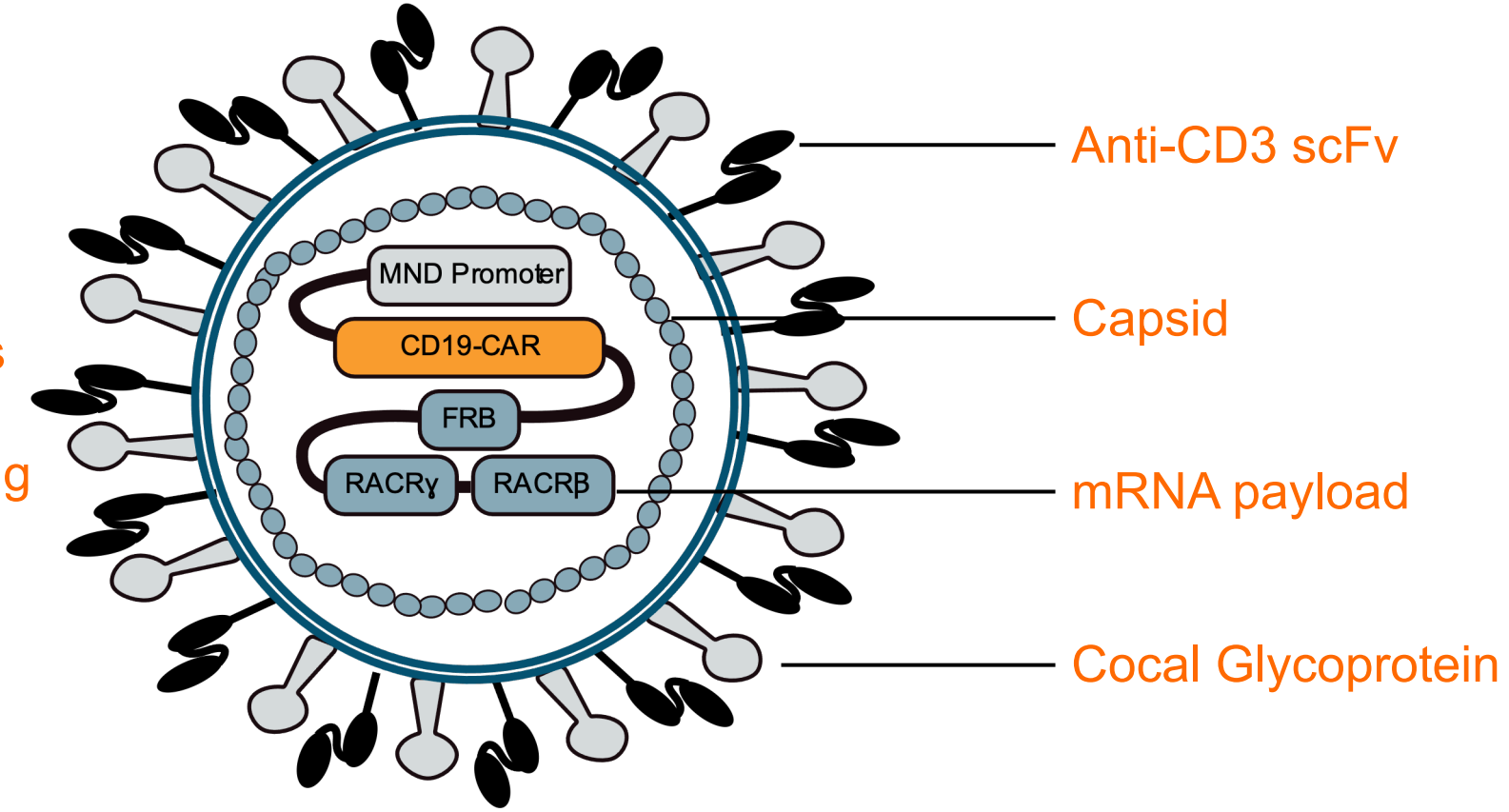
Foundational concept:
lymph nodes are nature's optimized T cell "manufactory"

Umoja leverages a deep understanding of the human immune system's physiology for its proprietary approach to in vivo T cell engineering

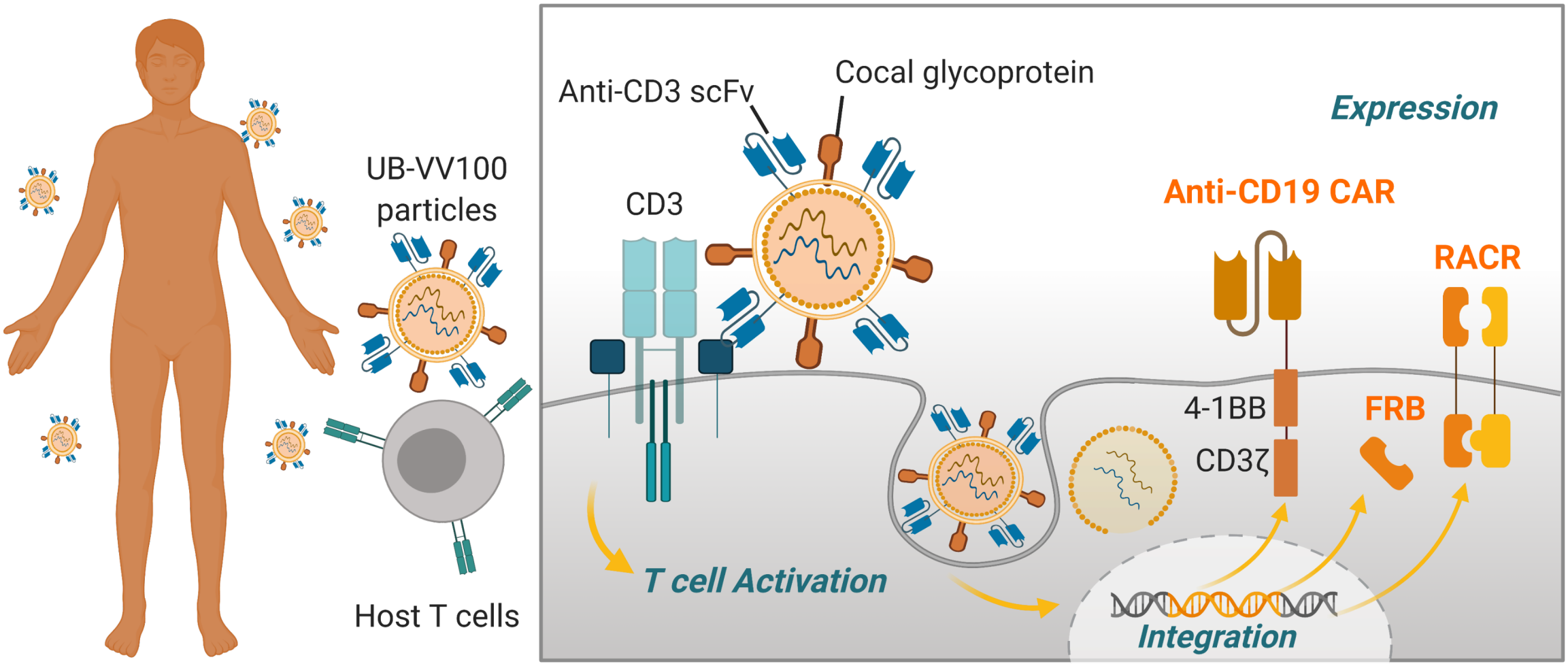


UB-VV100: Umoja's first in vivo CAR product for the treatment of B cell malignancies

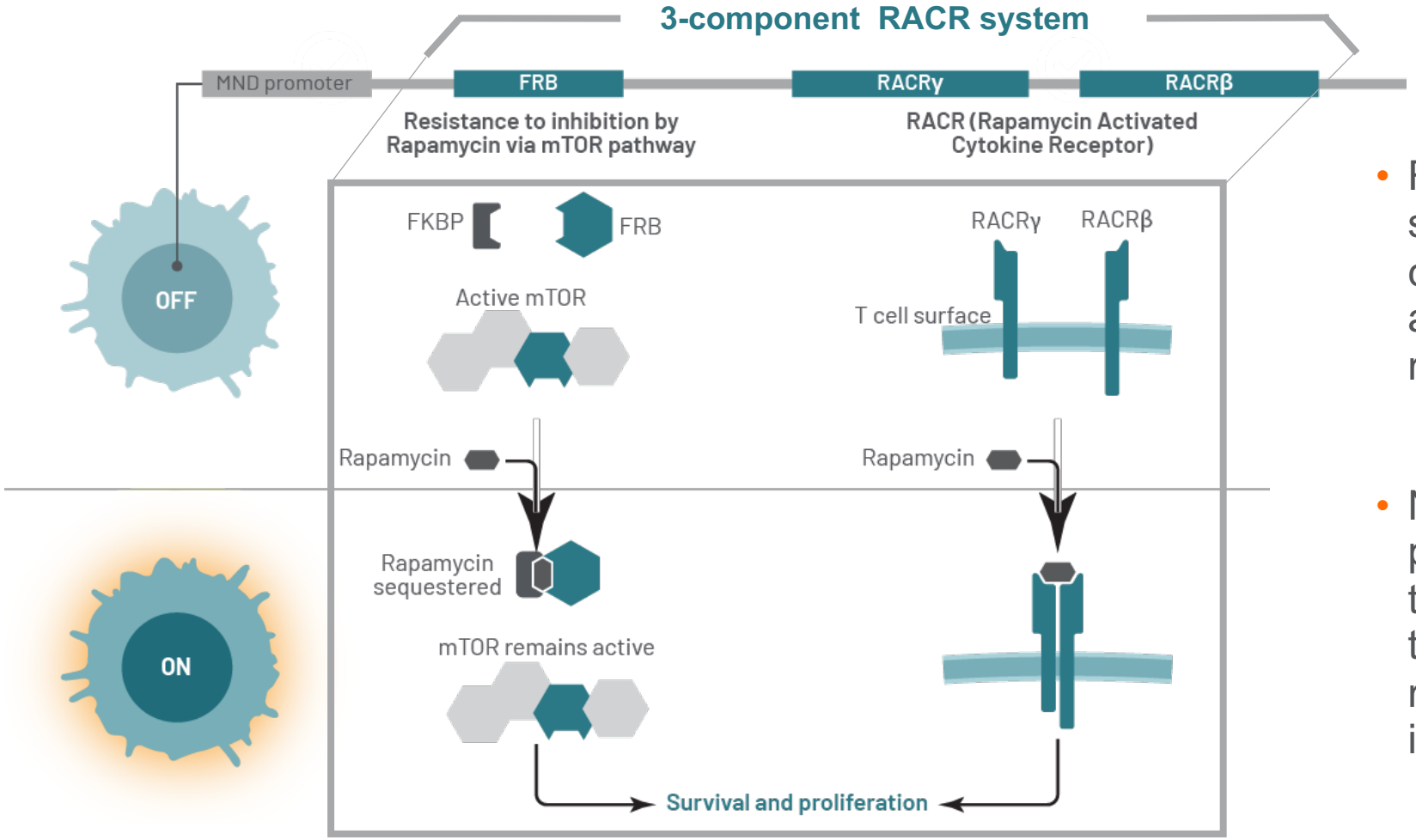
- A 3rd generation, self-inactivating, replication-incompetent lentivirus
- Designed for direct injection into patients to target T cells
- Delivers a payload consisting of a 2nd gen anti-CD19 CAR and a rapamycin-activated cytokine receptor (RACR) system.



UB-VV100's MOA has multiple steps



RACR: Rapamycin Activated Cytokine Receptor provides control over expansion



- Rapamycin activates the RACR system which replicates common γ chain cytokine activating STAT5 signaling for robust proliferation and survival
- Naked intracellular FRB domain provides rapamycin resistance to transduced cells while non transduced T and B cells are repressed through mTOR inhibition

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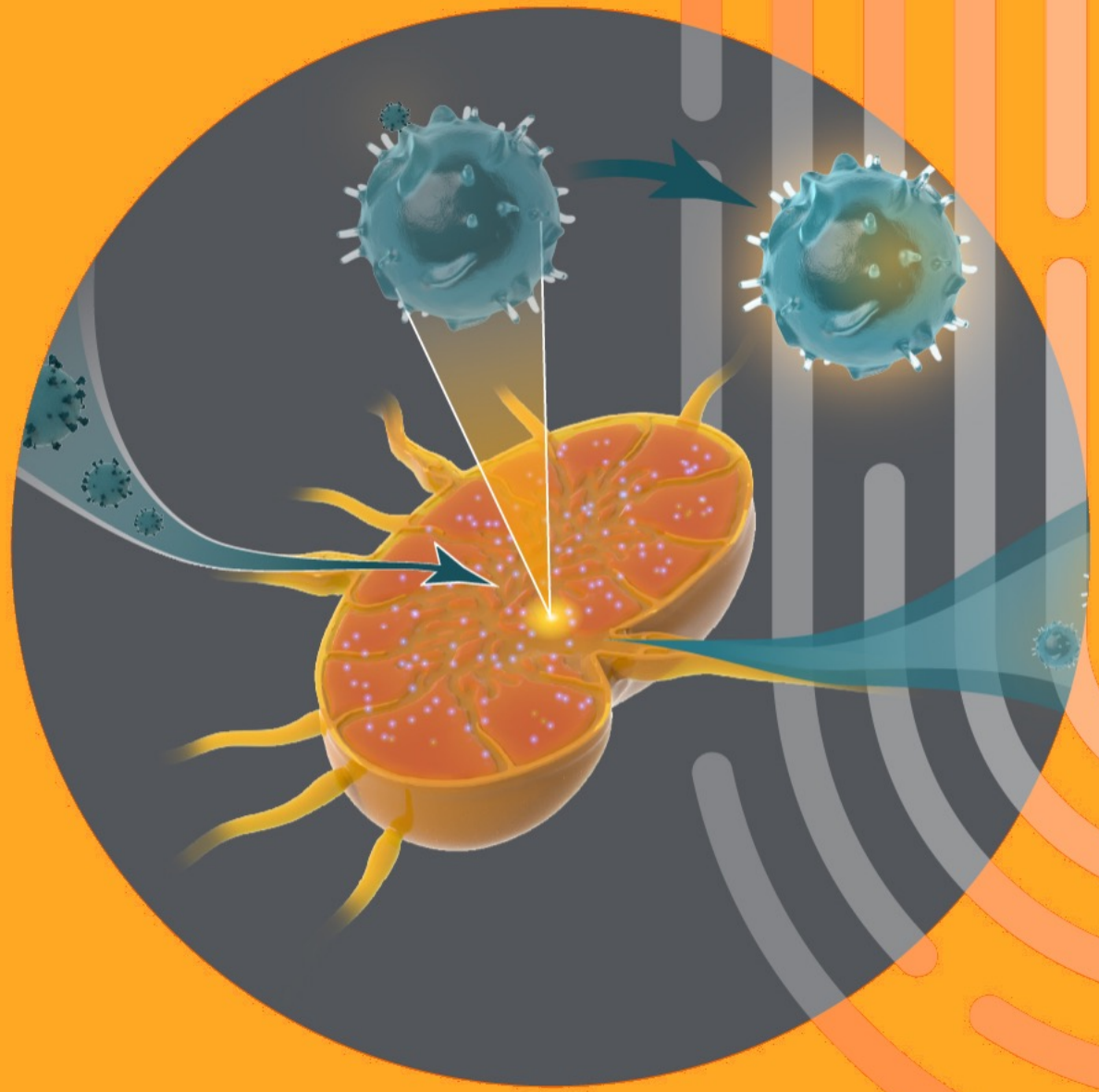
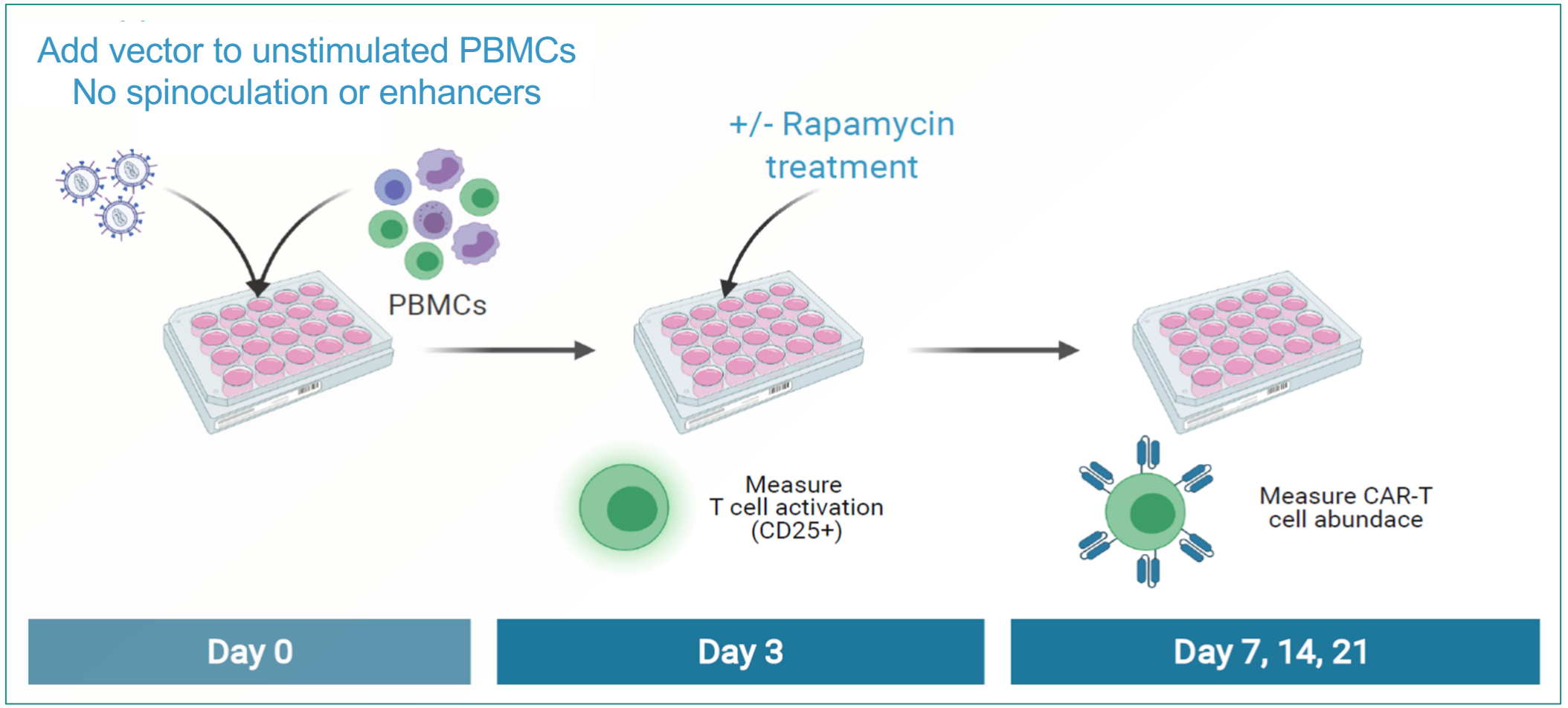
Preclinical models to evaluate in vivo-generated CAR T cells

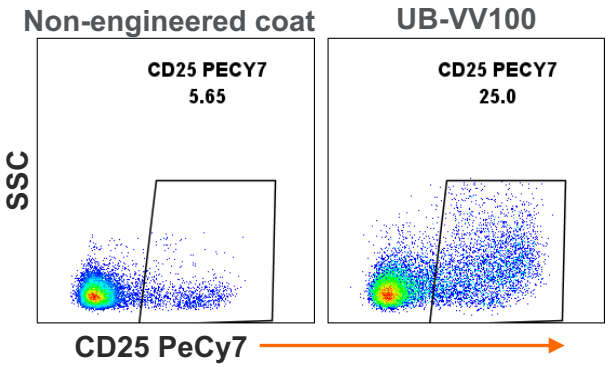


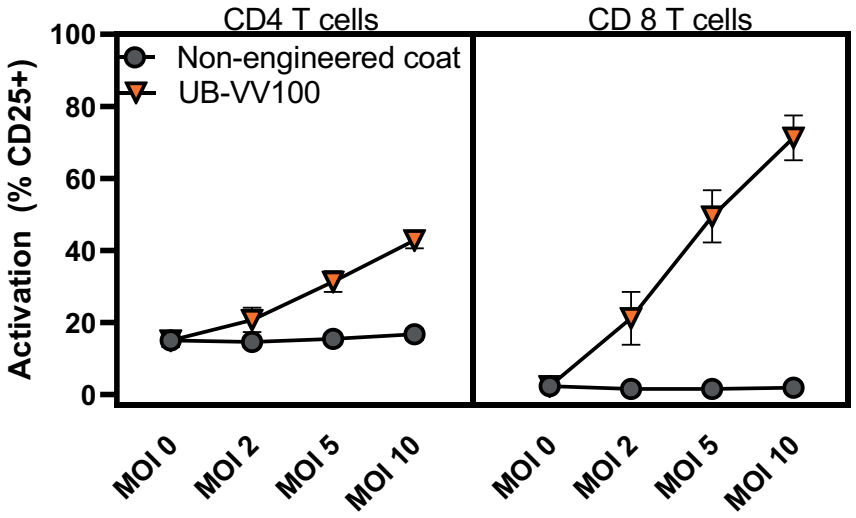
Methodology for testing UB-VV100 transduction efficiency in vitro



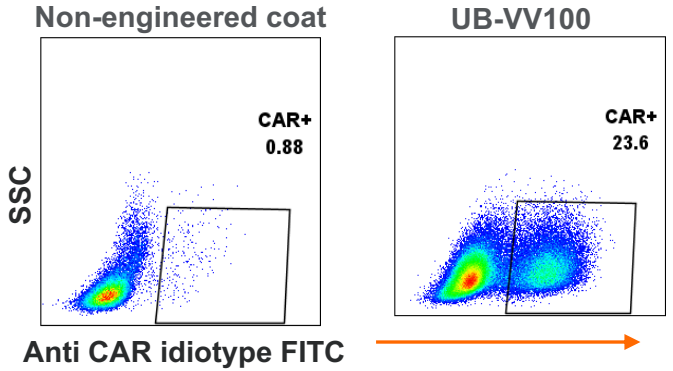
Anti-CD3 + Cocal viral envelope facilitates activation and transduction of T cells

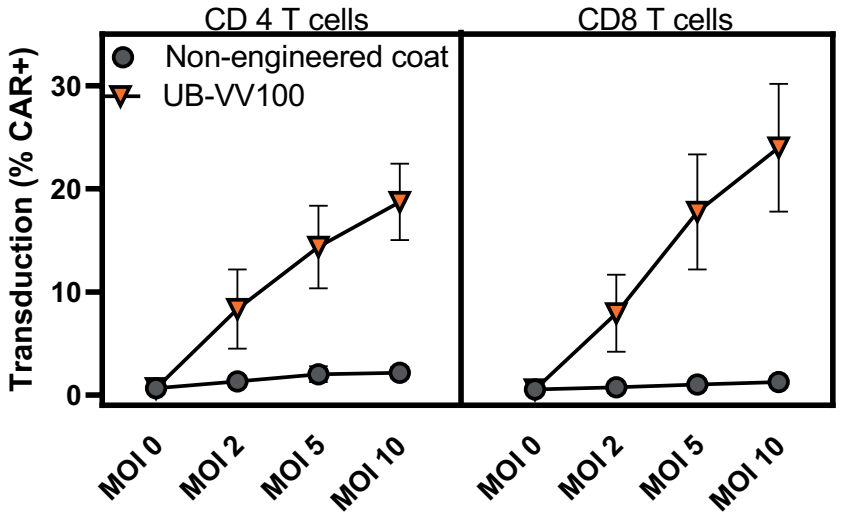
Day 3 Activation





Day 7 Transduction

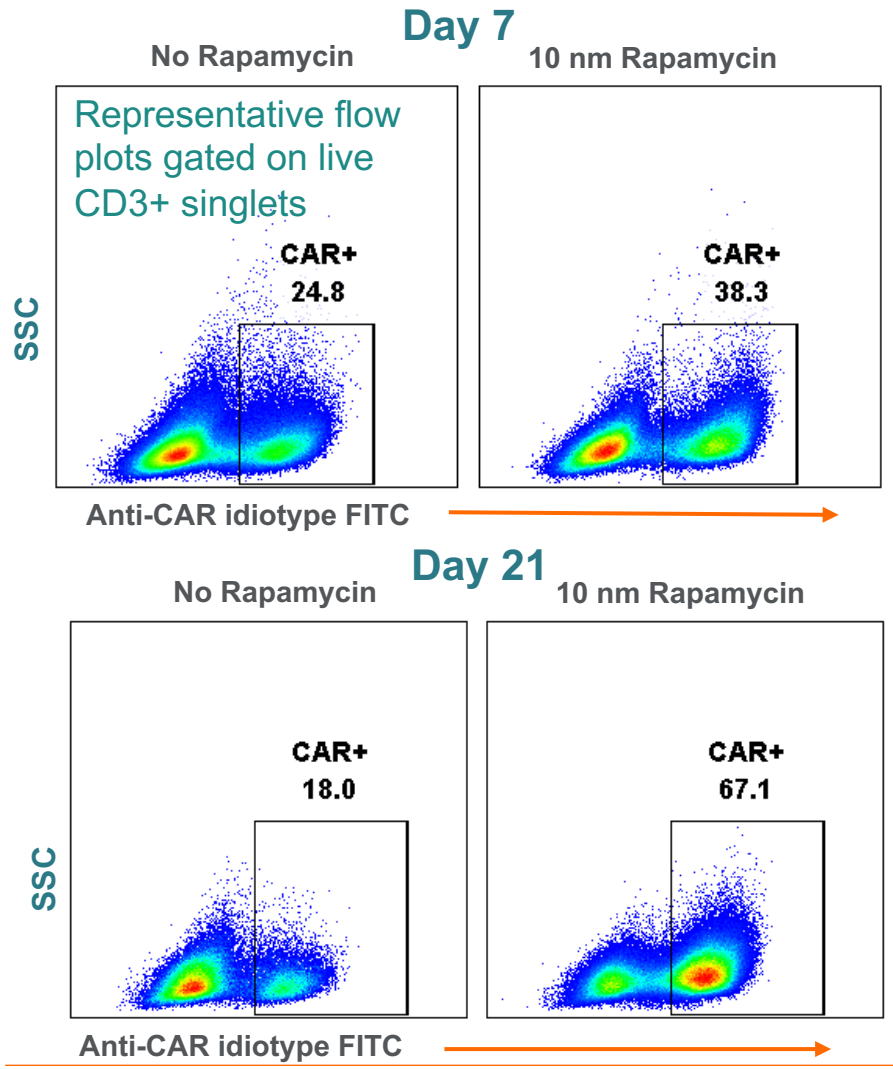


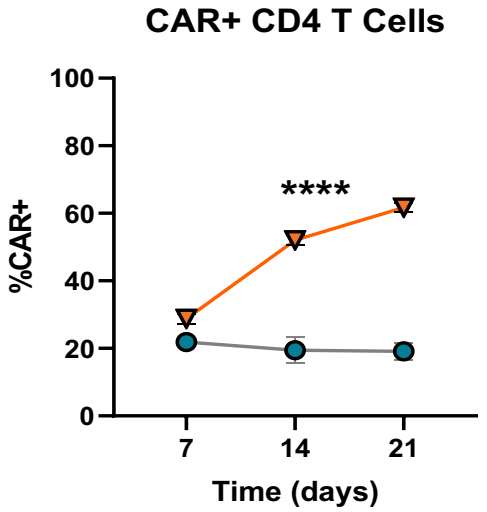


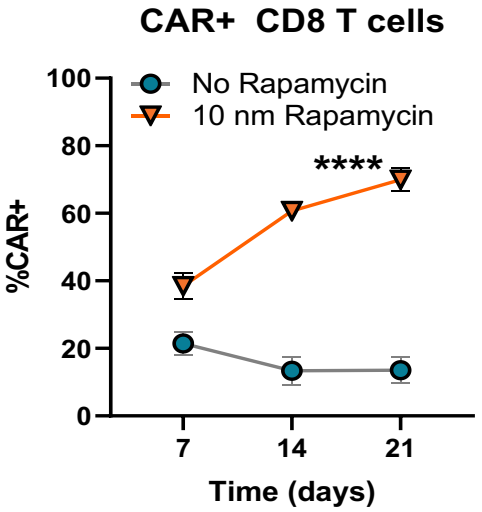
N= 3 PBMC donors

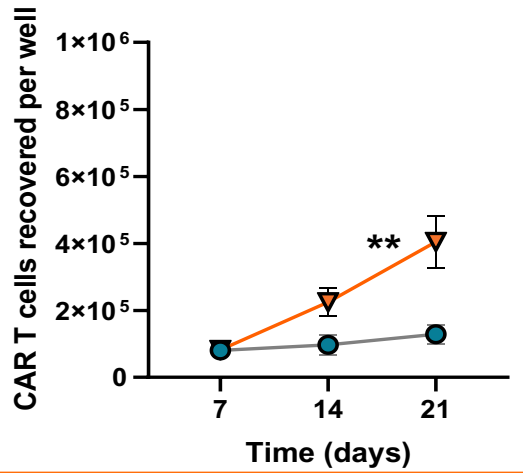
Error bars represent ± 1 SEM

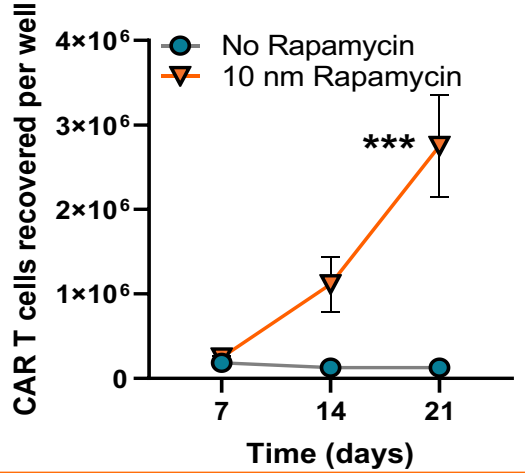
RACR engine drives enrichment and proliferation of CAR T cells in vitro











Error bars indicate ± 1 SEM. **, ***, and **** indicate p values of <0.01, <0.001, and <0.0001, 2-way ANOVA multiple comparisons for rapamycin treatment over time.

Choosing the Right Animal Model for the Right Question

Key Challenges:

- To understand the pharmacology and the toxicology of a proposed drug, non-clinical models in which your drug is pharmacologically active are highly desired (and often required).
- Human specific, autologous, immune-modulating and/or immune activating therapies present a unique challenge to model in non-human species.
- Engineered T cell therapies and immunotherapies in general have a complex MOA and require complex systems to model.

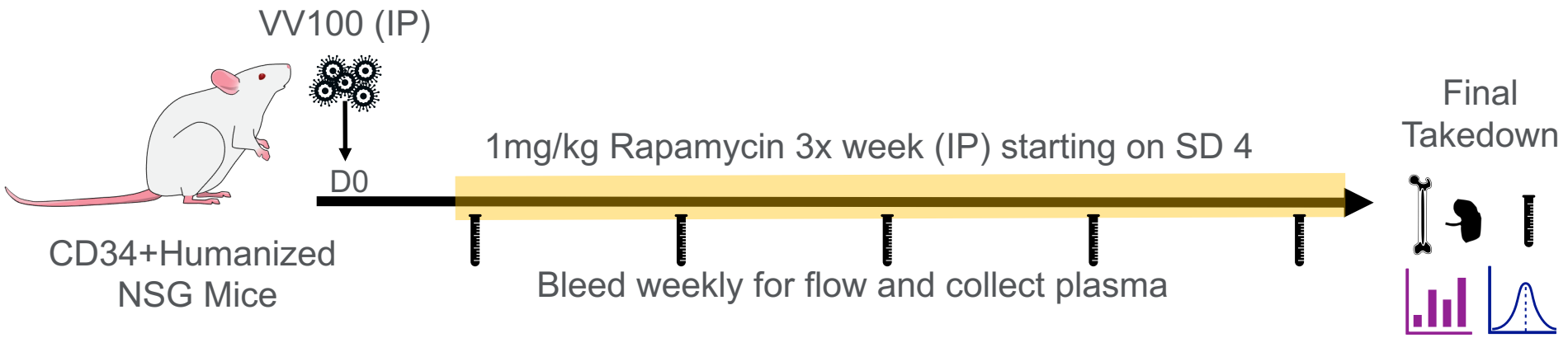
Umoja's approach requires overcoming additional challenges:

- To model in vivo transduction of T cells we must use humanized mice
- To more closely mimic the environment in a patient we must limit allo and xeno activation of PBMCs/T cells

Humanized Mouse Models for in vivo Pharmacology

	Humanized CD34+ HSC-engrafted NSG	Humanized PBMC-engrafted NSG
Pros	• Better resemblance of human IS dependent on model variant used • Supports limited tumor cells/PDX growth (only SC) • No/low GvHD • Can include huBLT engraftment for T cell education on human MHC	• Less cost than CD34-humanized • Supports tumor cells/PDX growth with limitations • Greater control of donor material and cohort size
Cons	• Cost and time • Allo-response to tumor • Low numbers of NK cells (improved with SRG-15) and low myeloid (improved with NSG-SM3) • hHSC donor & engraftment variability	• Allo-response to tumor • Incomplete IS (>95% T cells, no real B cells or myeloid) • Rapid GvHD limiting duration and confounding results (**unless use NSG MHCI/II KO**) • Low numbers of NK cells (improved with SRG-15) • hPBMC donor and engraftment variability

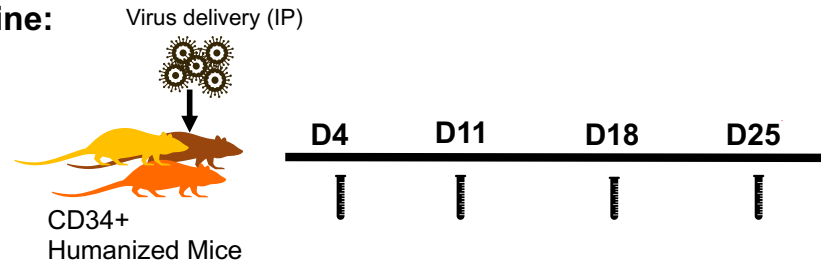
Mouse models used for evaluating VV100 activity: CD34+ HuNSG

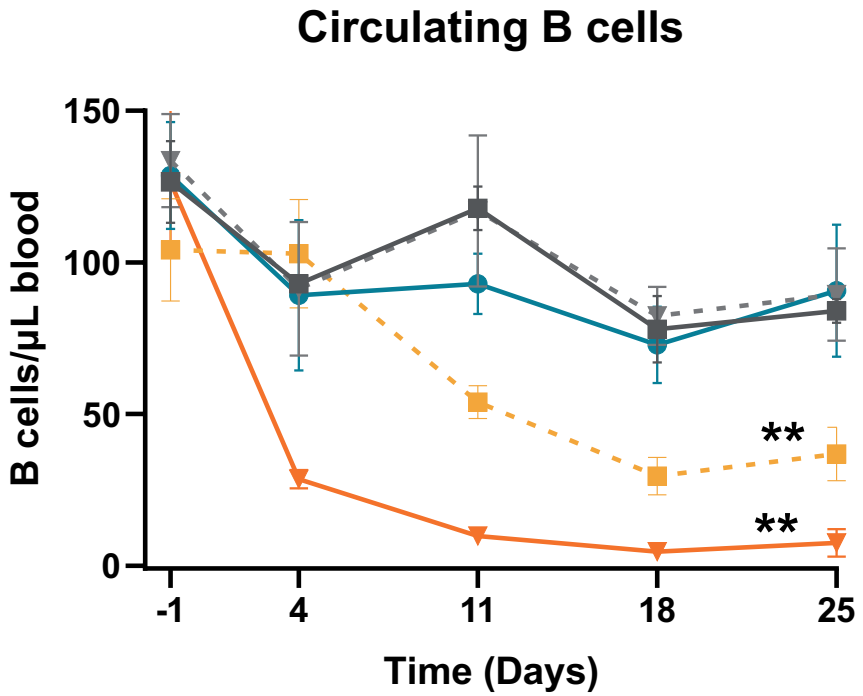


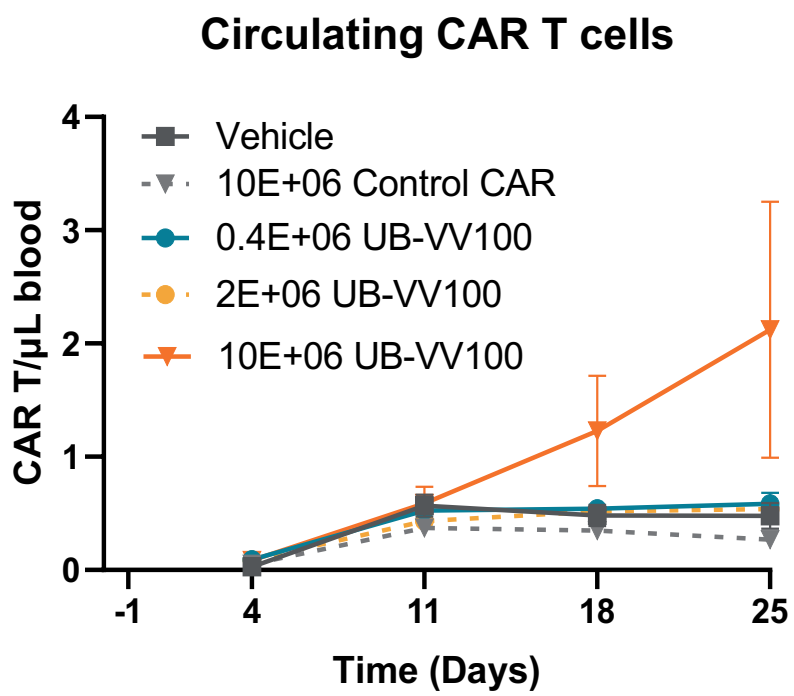
Feature	
Appropriate primary target cell population exists? (i.e. human T cells)	✓
Appropriate CAR target exists? (i.e. CD19-expressing cells)	✓
Does model mimic disease state in humans?	X
Does model mimic baseline activation state of T cells in humans	✓

UB-VV100 injection into CD34-humanized mice results in dose-dependent B cell depletion and CAR T expansion

Timeline:







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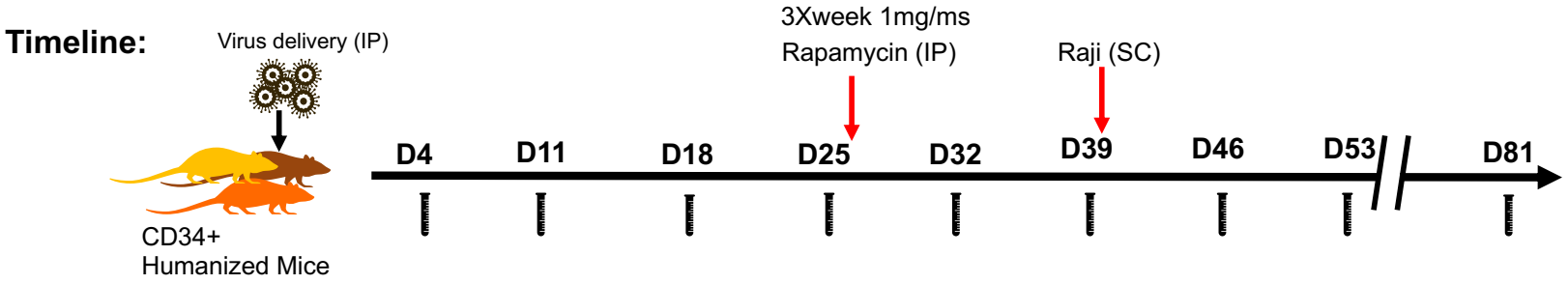
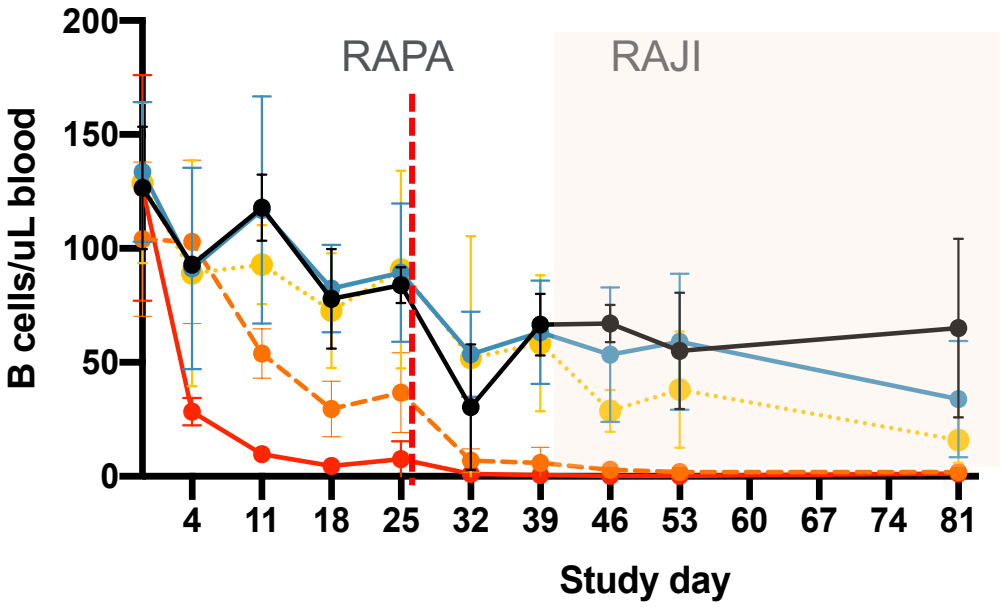
Onset of rapamycin dosing on D26 correlated with more complete and lasting B cell depletion in the 2 million TU dose level

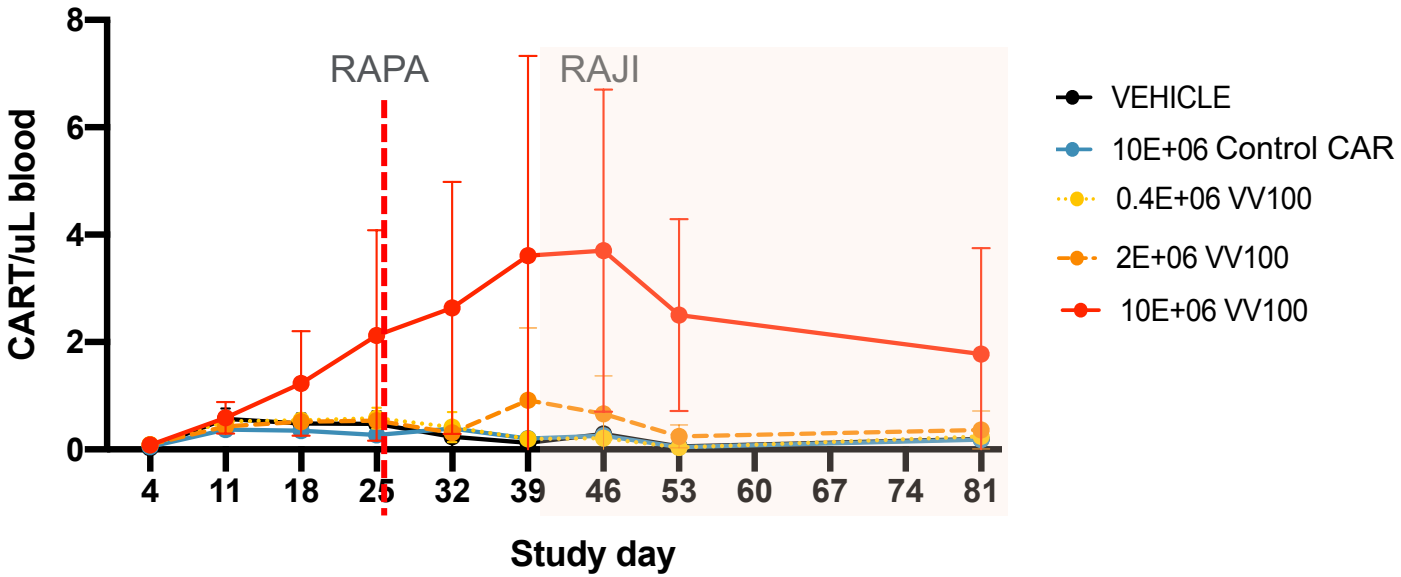


- A sharp decrease in B cells was detected in the 2 million TU group one week after onset of rapa dosing
- This corresponded with a detectable expansion of CAR+ T cells in the blood that began prior to Raji implantation

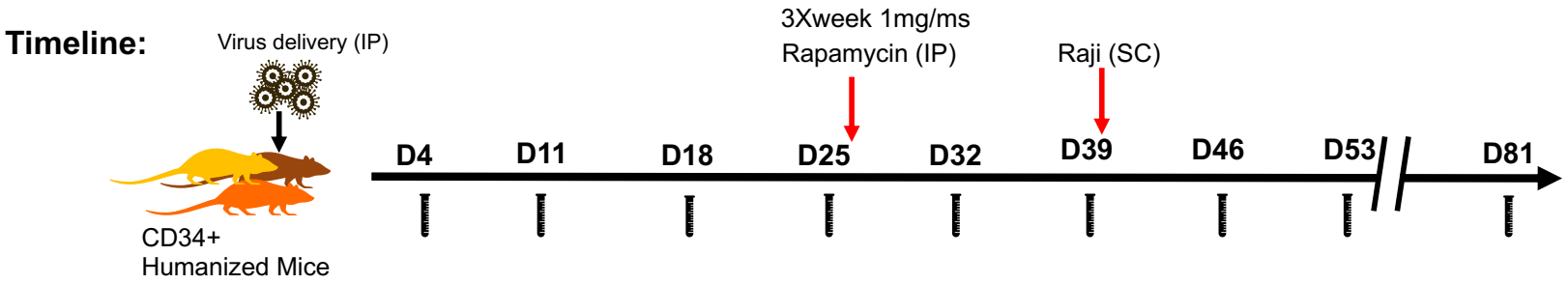
Circulating B cells (by flow cytometry)

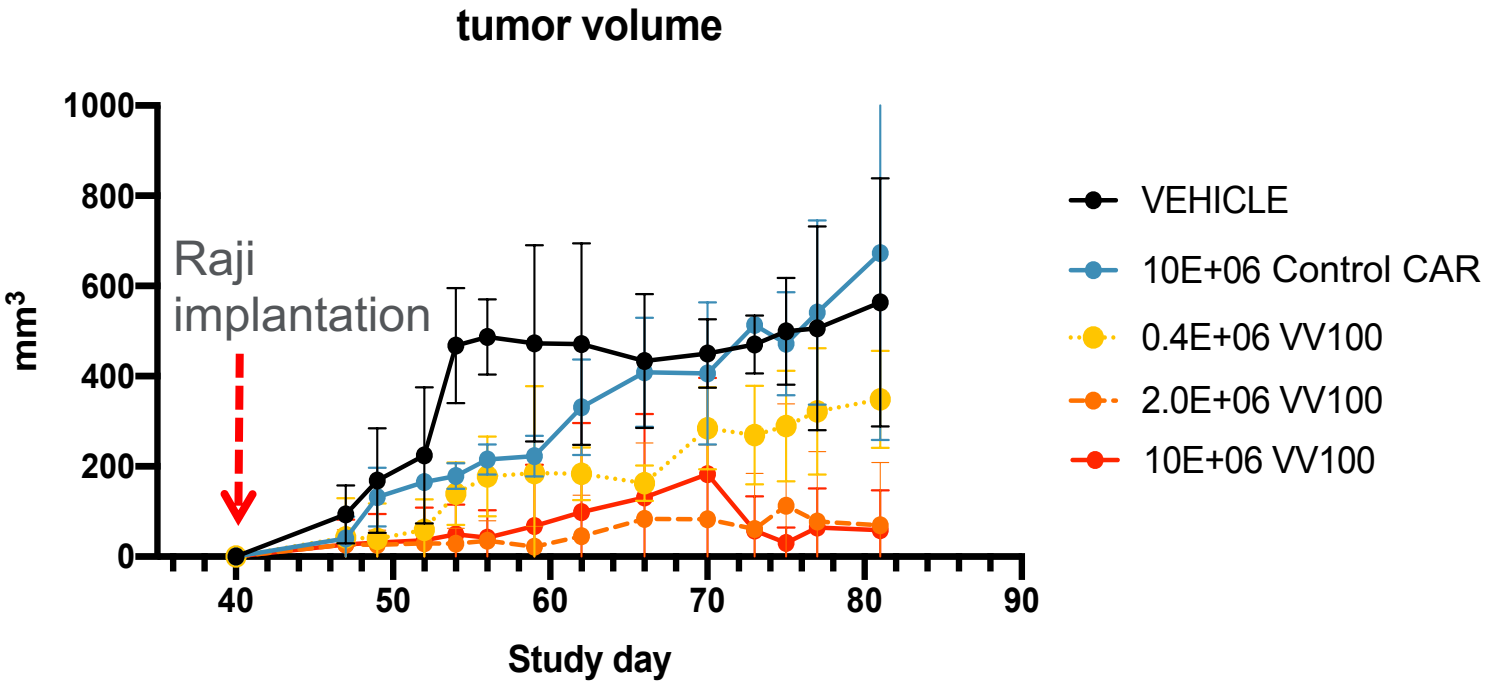


Circulating CAR-T cells (by flow cytometry)



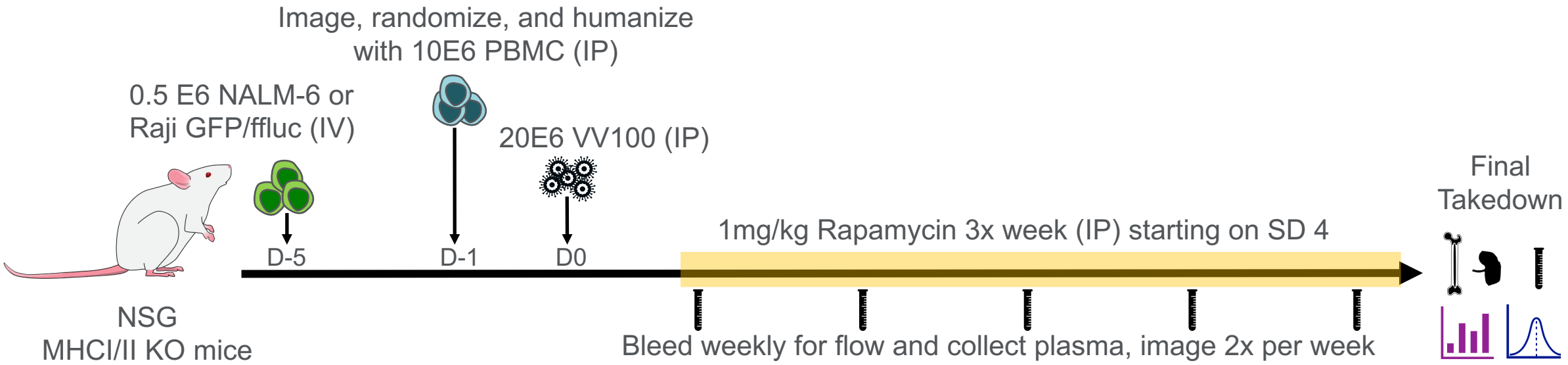
Previous treatment with UB-VV100 inhibits Raji solid tumor growth in a dose-dependent manner





Tumors failed to develop or grew to a very small size in the 10 million and 2 million dose groups

Mouse models used for evaluating VV100 activity: PBMC NSG MHCI/II KO



Feature	
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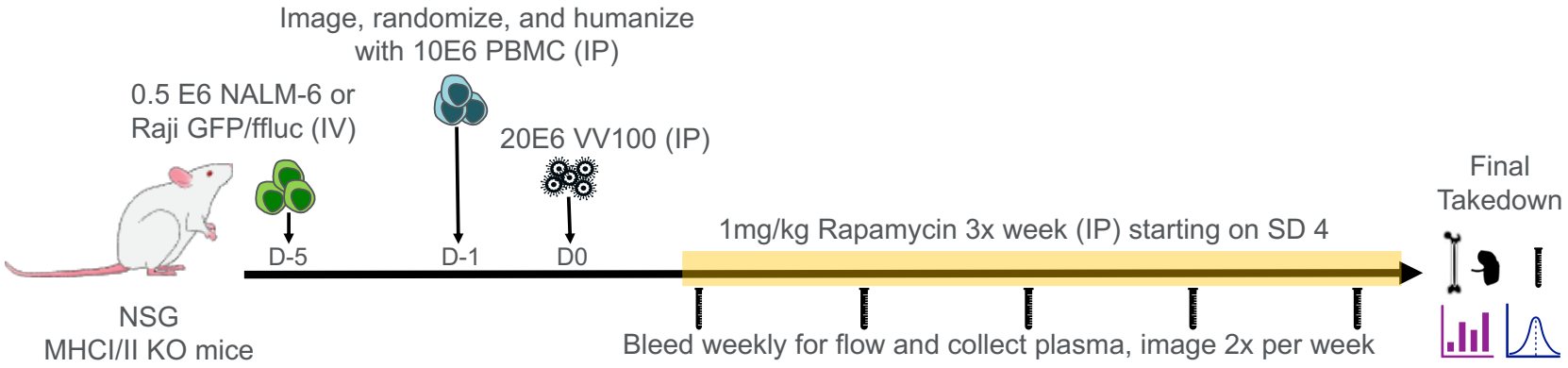
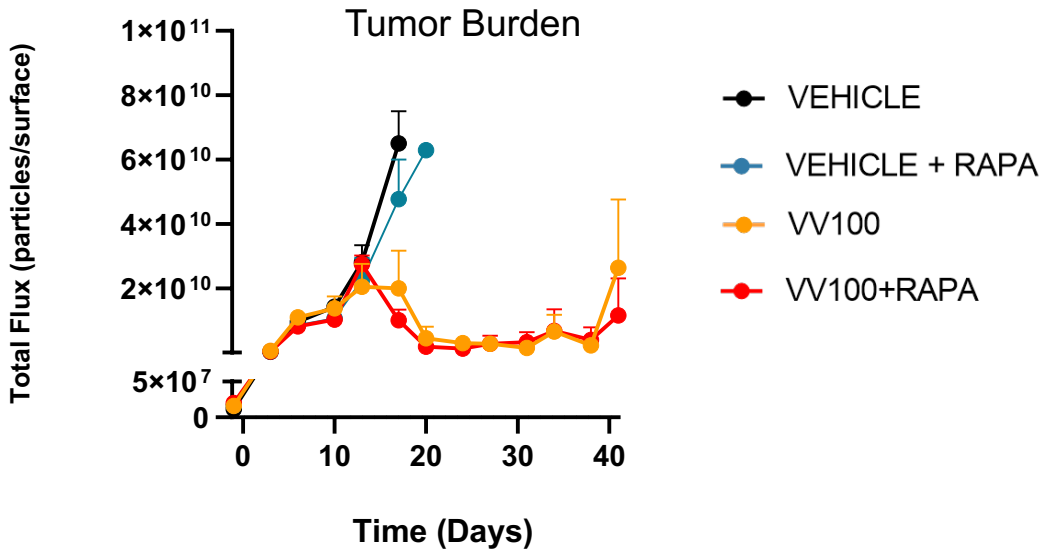
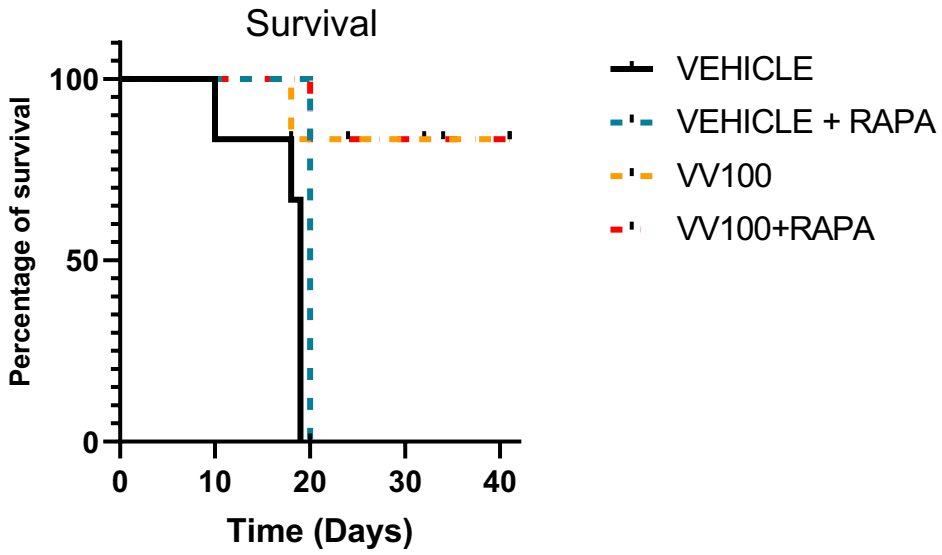
Appropriate CAR target exists? (i.e. CD19-expressing cells)	✓
Does model mimic disease state in humans?	✓
Does model mimic baseline activation state of T cells in humans	X

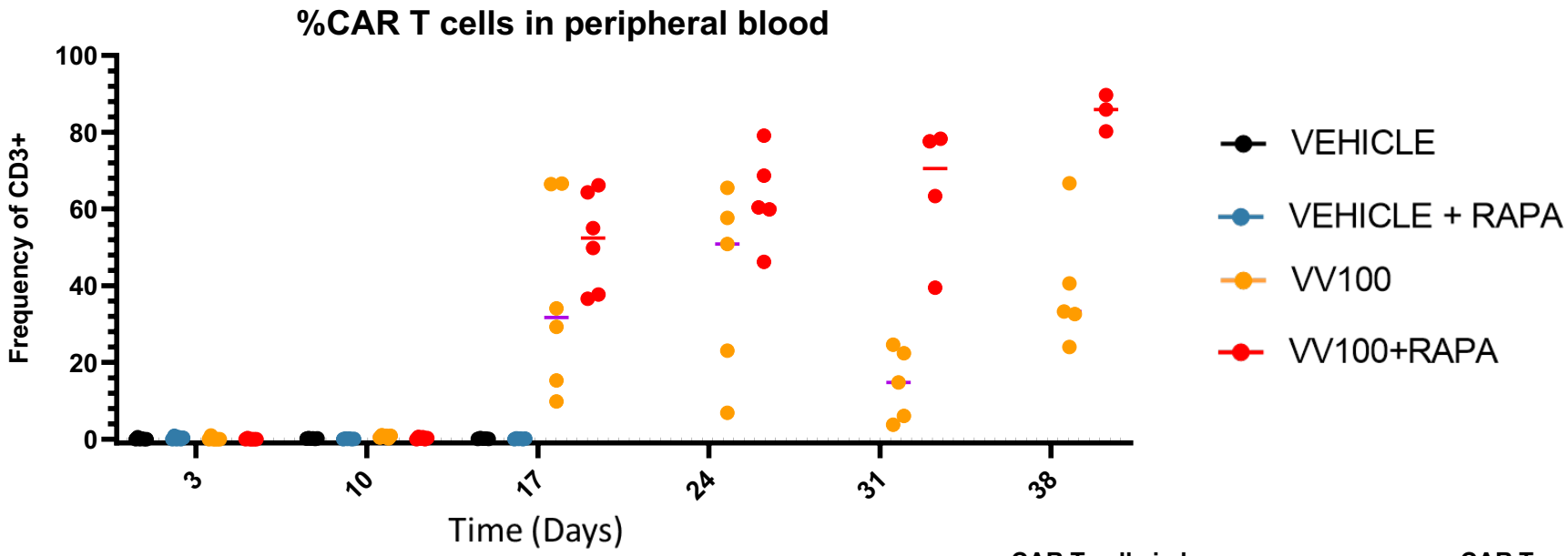
UB-VV100 prolongs survival and slows tumor progression in a NALM6 systemic tumor model in PBMC-humanized NSG DKO mice

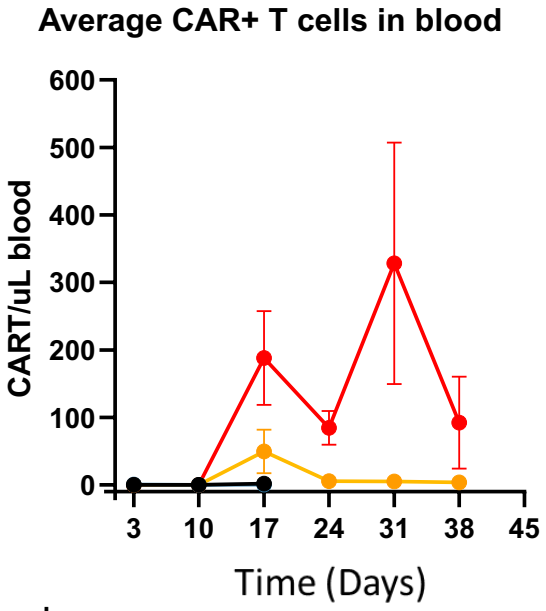




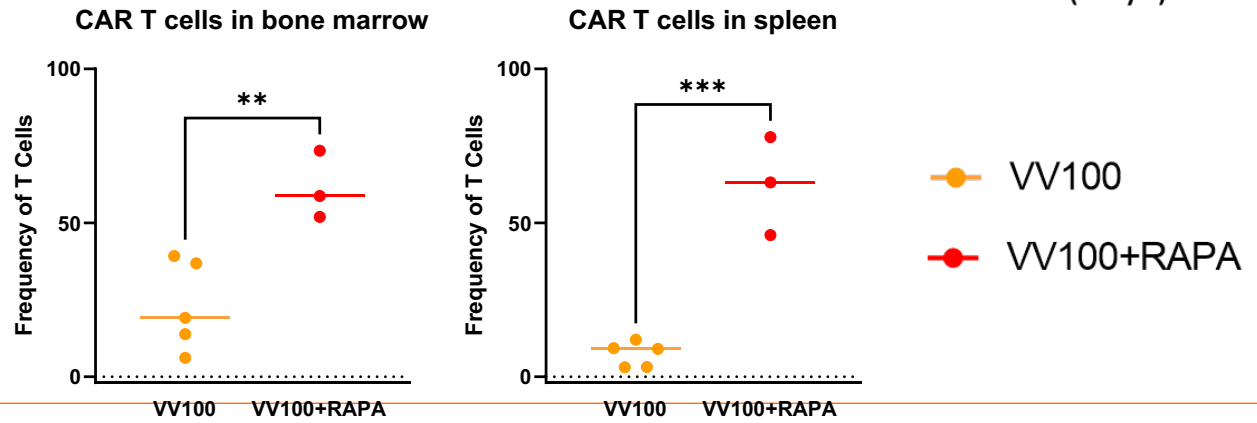


Rapamycin treatment enhances CAR T cell expansion in blood, bone marrow, and spleen





At study completion (Day 41), bone marrow and spleen show enrichment for CAR T cells in the rapamycin treatment group



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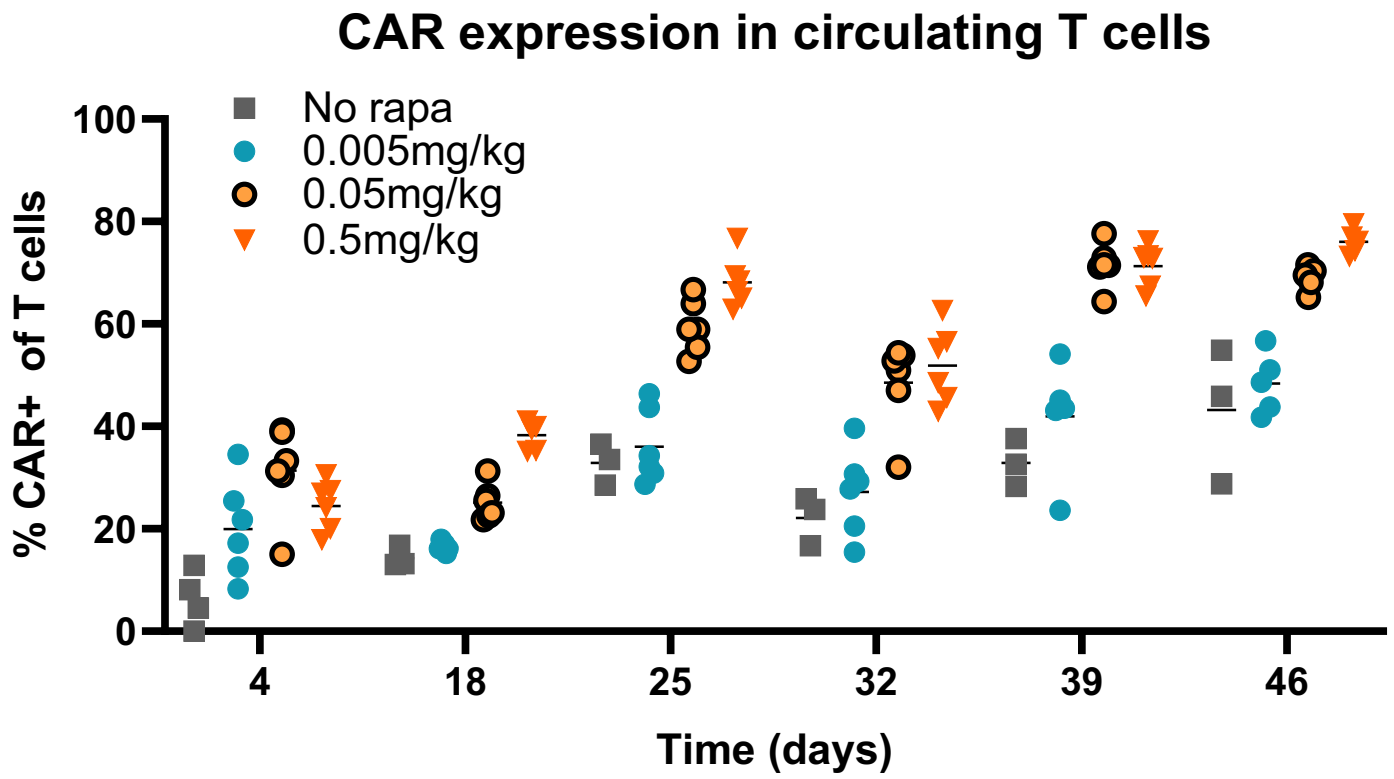
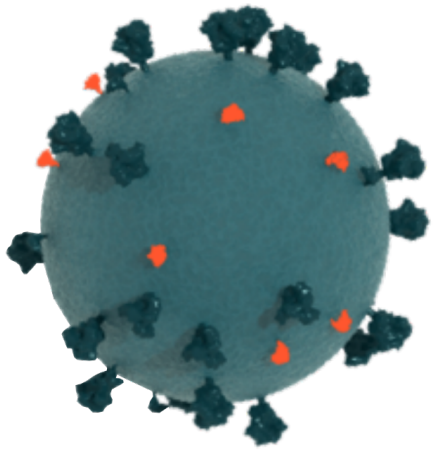
Mouse models used for evaluating RACR activity:

NSG MHCI/II KO mice systemically implanted with Raji tumor cells and treated with ex-vivo manufactured CAR T cells, followed by rapamycin 5X week (IP)



Rapamycin promotes enrichment (and expansion) of CAR T cells in vivo in a dose-dependent manner

Our preliminary data using PBMC cultures and humanized NSG mice demonstrates that UB-VV100 can:



ARM T cells in vitro and in vivo using only its surface engineering without other additives or stimulants

EXPAND transduced cells in vitro and in vivo using rapamycin to engage the RACR system

TARGET and destroy normal and malignant B cells in vitro and in vivo

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Thank you

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