Organiza:

Chiesi

HIGHLIGHTS

AMERICAN TRANSPLANT CONGRESS

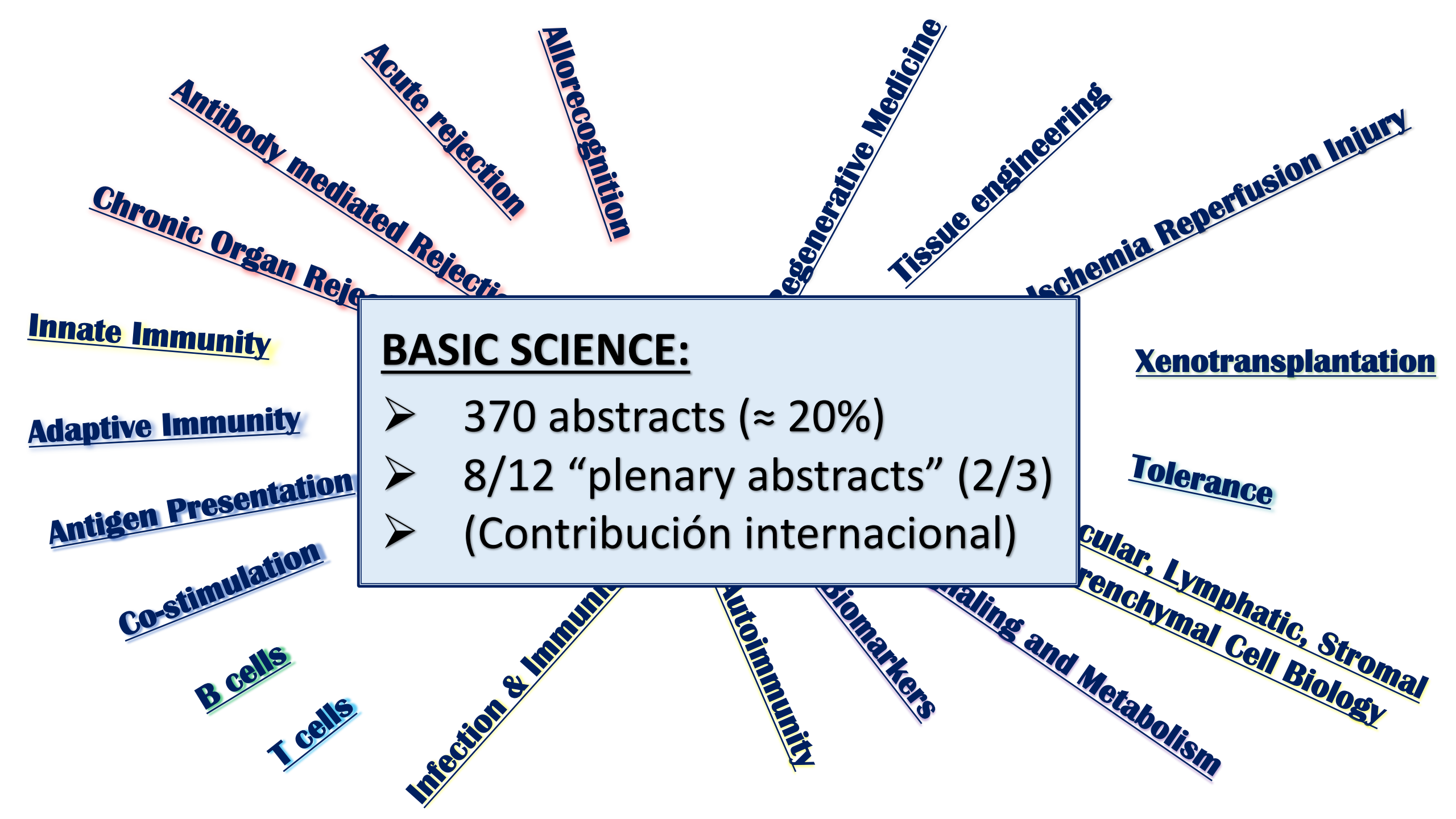
ATC2023

JUNIO 3-7, 2023

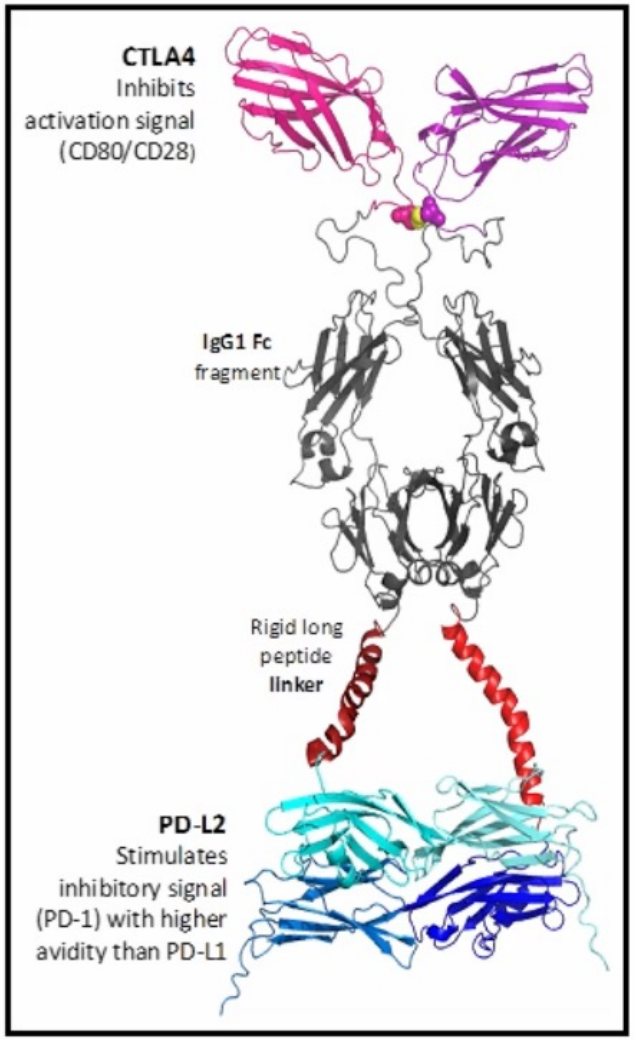
En esta presentación puede haber mención a datos científicos que no están aprobados en el registro. Por favor, consulte la ficha técnica. Las opiniones expresadas en esta presentación corresponden únicamente a quienes las emiten y no representan necesariamente las opiniones de Chiesi España S.A.U.

Highlights ATC 2023

– BASIC SCIENCE –

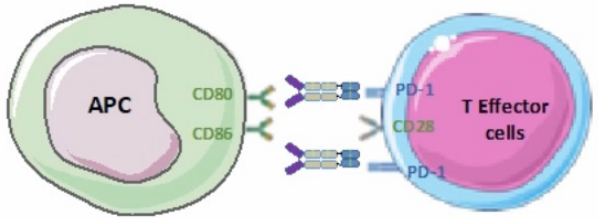

Allorecognition
Acute rejection
Antibody mediated Rejecti
Chronic Organ Reje
egenerative Medicine
Tissue engineering
schemia Reperfusion Injury
Innate Immunity
Adaptive Immunity
Antigen Presentation
Co-stimulation
B cells
T cells
Infection & Immuni
Autoimmunity
Biomarkers
aling and Metabolism
Xenotransplantation
Tolerance
cular, Lymphatic, Stromal
renchymal Cell Biology
BASIC SCIENCE:
370 abstracts (≈ 20%)
8/12 “plenary abstracts” (2/3)
(Contribución internacional)

A novel Bi-specific Fusion Protein With CTLA4-Ig/PD-L2 as a New Immunosuppressive Molecule (Duacept) Modulating Alloimmune Responses

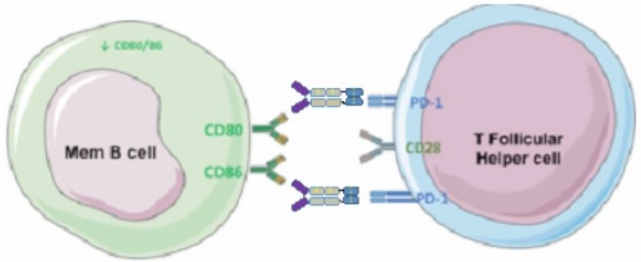


Dual and opposite costimulatory targeting

- Inhibits a T-cell activation signal (CTLA4-CD80)
- Stimulates a T-cell Inactivation signal (PD-L2-PD-1)



↓ T Effector responses

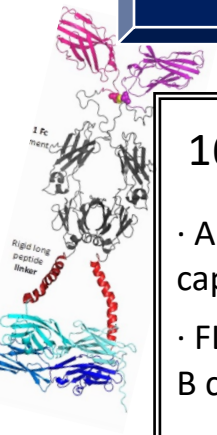


↓ IgG Ab production

Vall d'Hebron Institut de Recerca

Bestard O et al., Barcelona, Spain

A novel Bi-specific Fusion Protein With CTLA4-Ig/PD-L2 as a New Immunosuppressive Molecule (Duacept) Modulating Alloimmune Responses



16 Sensitized kidney transplant candidates

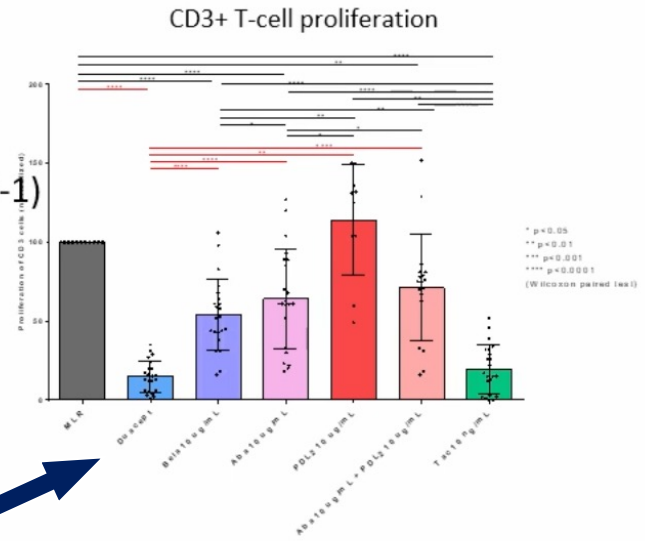
· Allogenic mixed lymphocyte reactions (MLR) to assess the capacity to inhibit T-cell proliferation *in vitro*

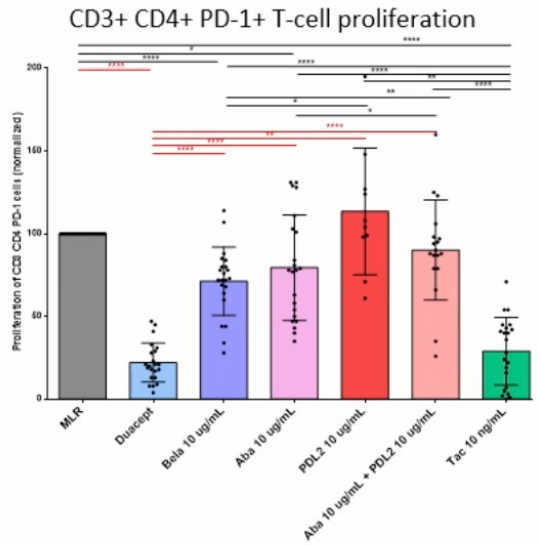
· FLuorSpot assay to assess Its capacity to hinder memory B cell differentiation to IgG-secreting plasmablasts.

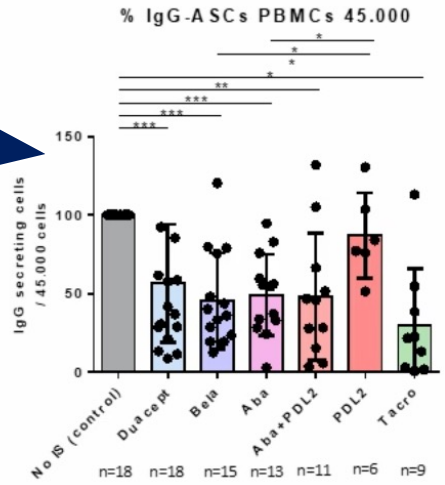
(**Duacept** – **Bela** – **Aba** – **ABA+PDL2** – **PDL2** – **Tacro**)

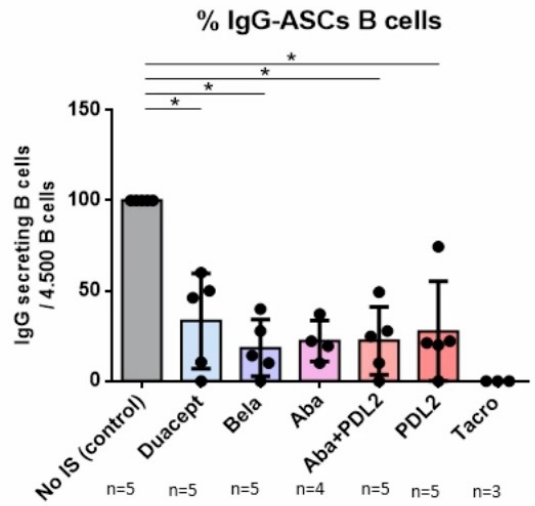
* Abrogates T cell proliferation in allogeneic MLR (more potently than CTLA4-Ig)

* Reduces allogeneic memory B cells activation and IgG producing plasma cell frequencies









CONCLUSION: (CTLA4Ig/PDL2) shows high potential to effectively abrogate T and B alloimmune responses.

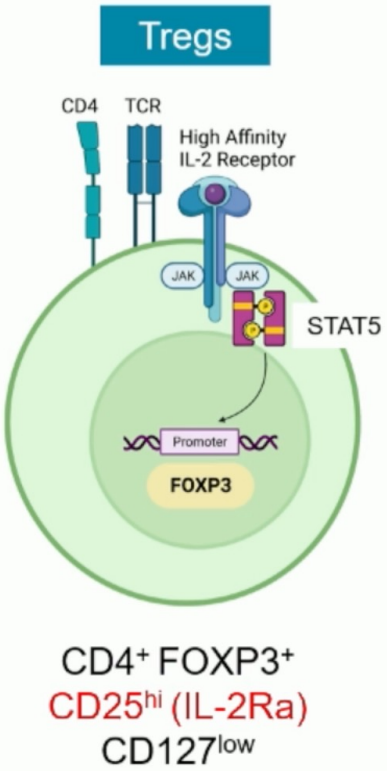
Bestard O et al., Barcelona, Spain

Vall d'Hebron Institut de Recerca

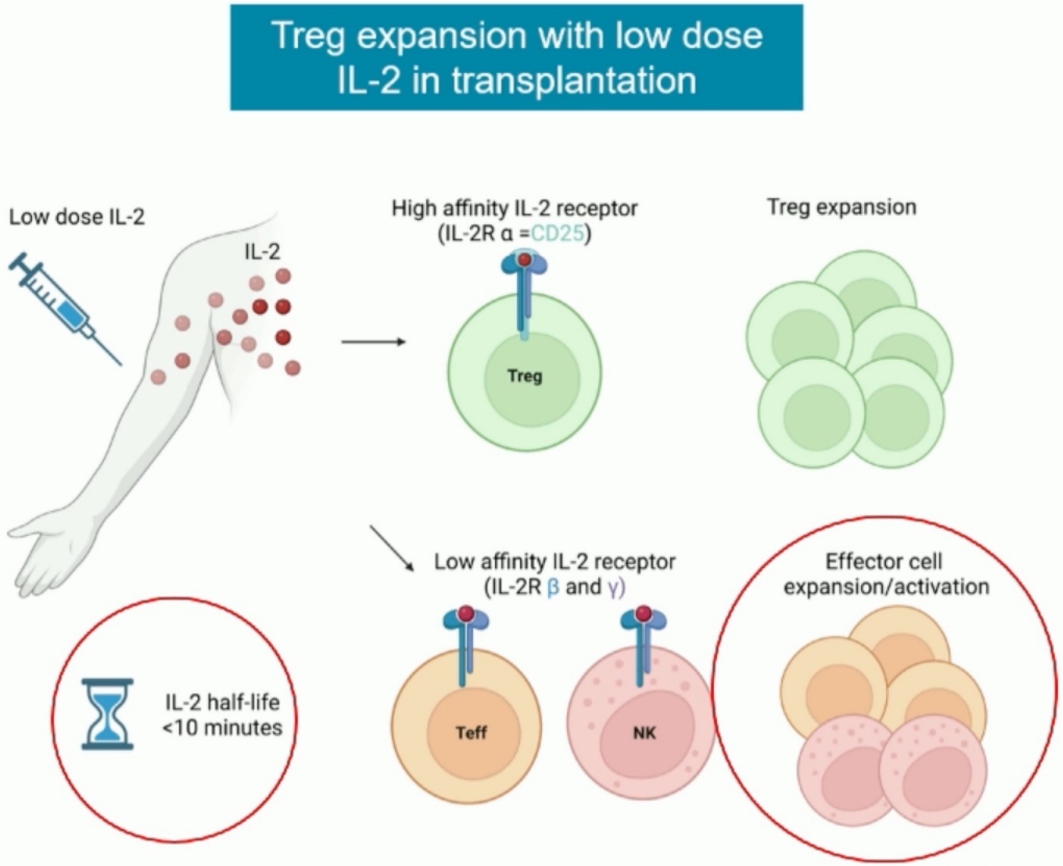
Tolerance

Selective Regulatory T-cell Expansion By A Novel IL-2 Mutein In Murine Transplant And Humanized NSG Model

Regulatory T cells (Treg) Expansion in Transplantation



$CD4^{+}$ $FOXP3^{+}$
$CD25^{hi}$ (IL-2Ra)
$CD127^{low}$



Murakami, Borges et al. AJT 2023

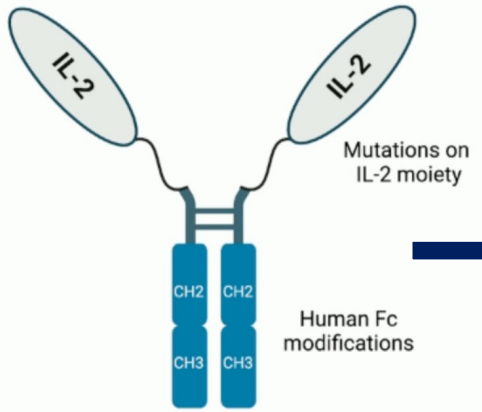
MASSACHUSETTS GENERAL HOSPITAL
TRANSPLANT CENTER

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Tolerance

Selective Regulatory T-cell Expansion By A Novel IL-2 Mutein In Murine Transplant And Humanized NSG Model

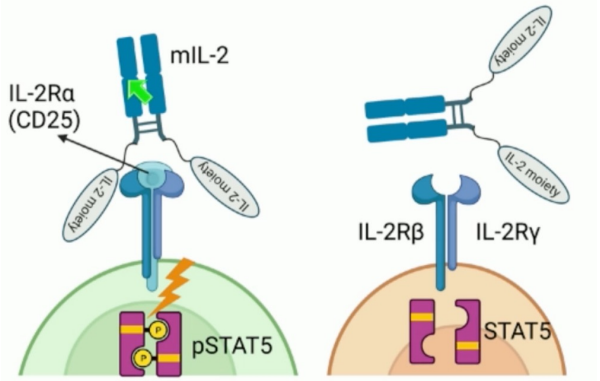
Novel IL-2 Mutein (mIL-2)



- Decreased IL-2Rβ and IL-2Rγ but maintained IL-2Rα affinity
- Engineered for molecular stability and developability
- Fusion of human IgG1 Fc

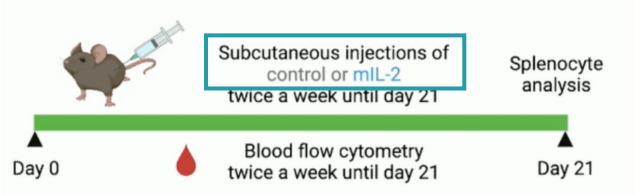
MASSACHUSETTS GENERAL HOSPITAL
TRANSPLANT CENTER

- Selective for Tregs
- Longer plasma half-life



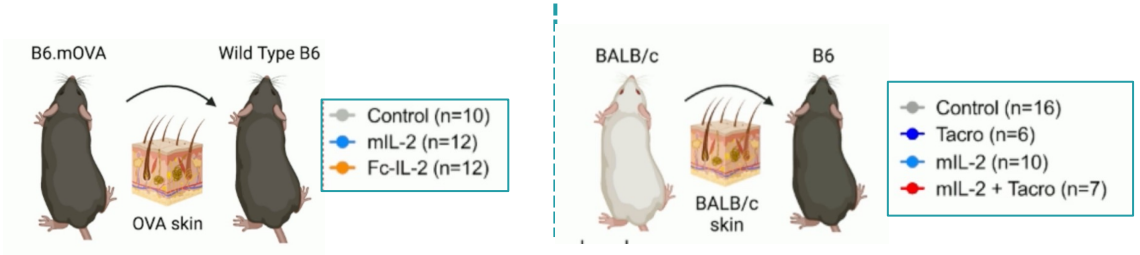
1

Mouse splenocytes and human PBMCs <u>in vitro</u>



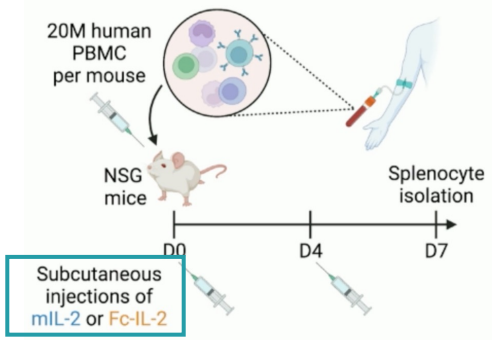
2

Minor mismatched (OVA to B6) and Major mismatched (BALB/c to B6) <u>Skin Transplant models</u>



<u>NSG mouse model</u> (human PBMCs transferred to NSG recipients)

3



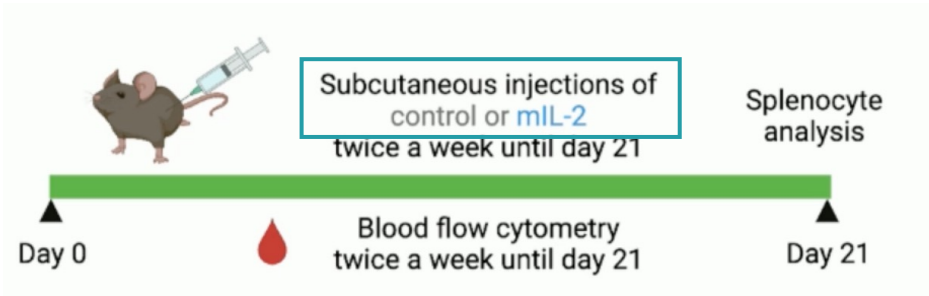
Efe et al.
Massachusetts General Hospital
RIELLA LAB

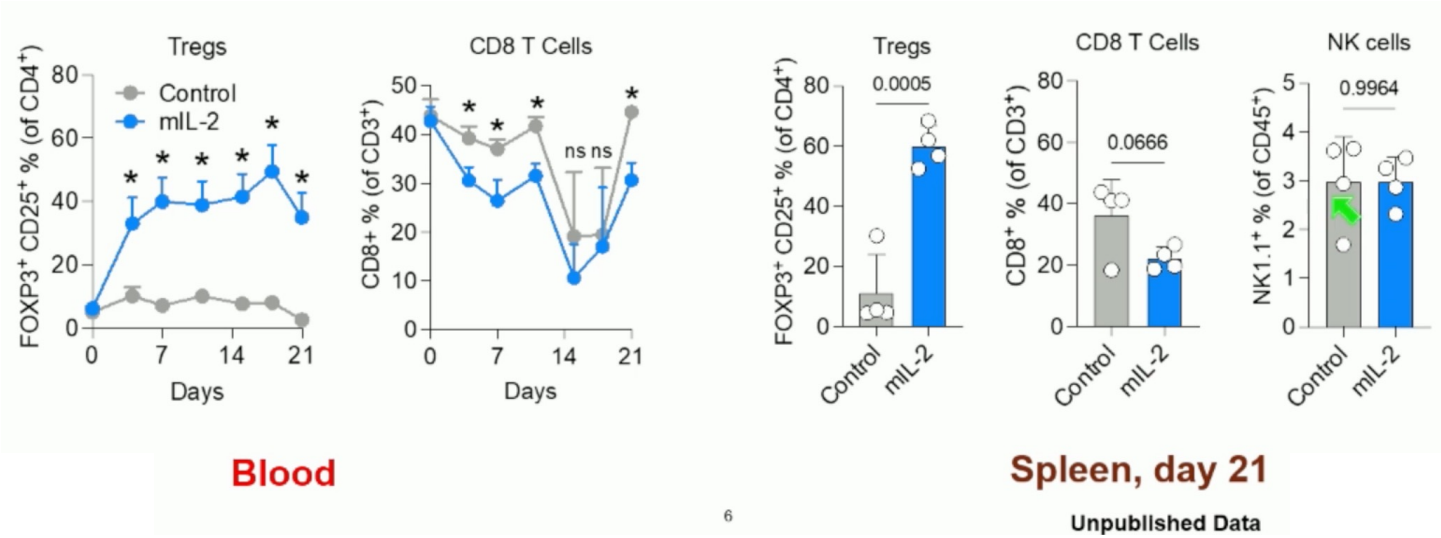
Tolerance

Selective Regulatory T-cell Expansion By A Novel IL-2 Mutein In Murine Transplant And Humanized NSG Model

1

Mouse splenocytes and human PBMCs <u>in vitro</u>





* mIL-2 induces selective and sustainable Treg expansion and has a prolonged half life

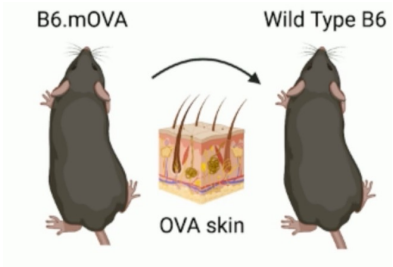
Efe et al.
Massachusetts General Hospital
RIELLA LAB

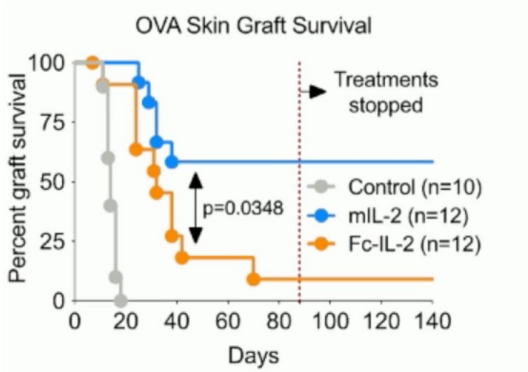
Tolerance

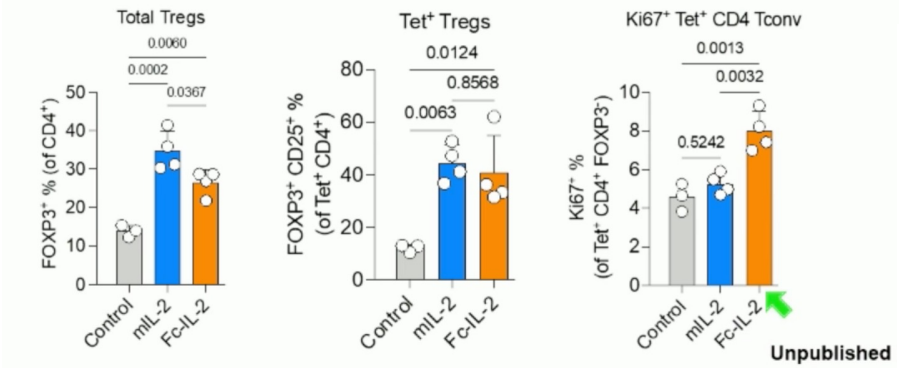
Selective Regulatory T-cell Expansion By A Novel IL-2 Mutein In Murine Transplant And Humanized NSG Model

2 *Skin transplant models*

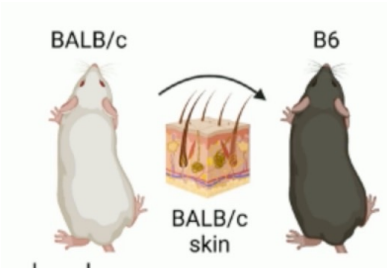
Minor mismatched (OVA to B6)

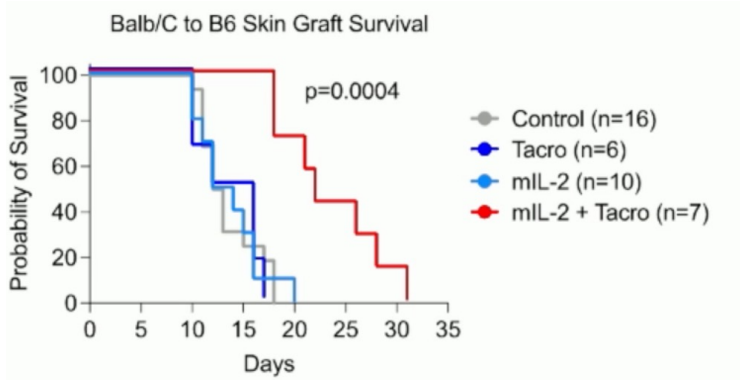


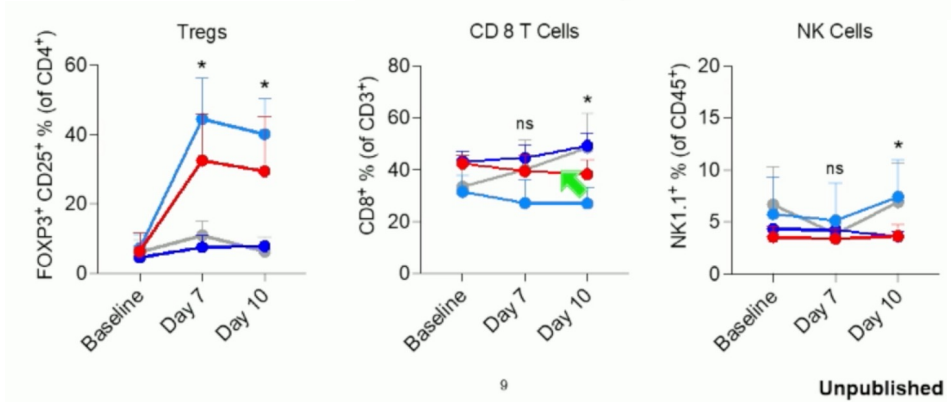




Major mismatched (BALB/c to B6)







* mIL-2 prolongs survival in both (minor & major mismatched) skin transplantation

* mIL-2 promotes antigen-specific tolerance

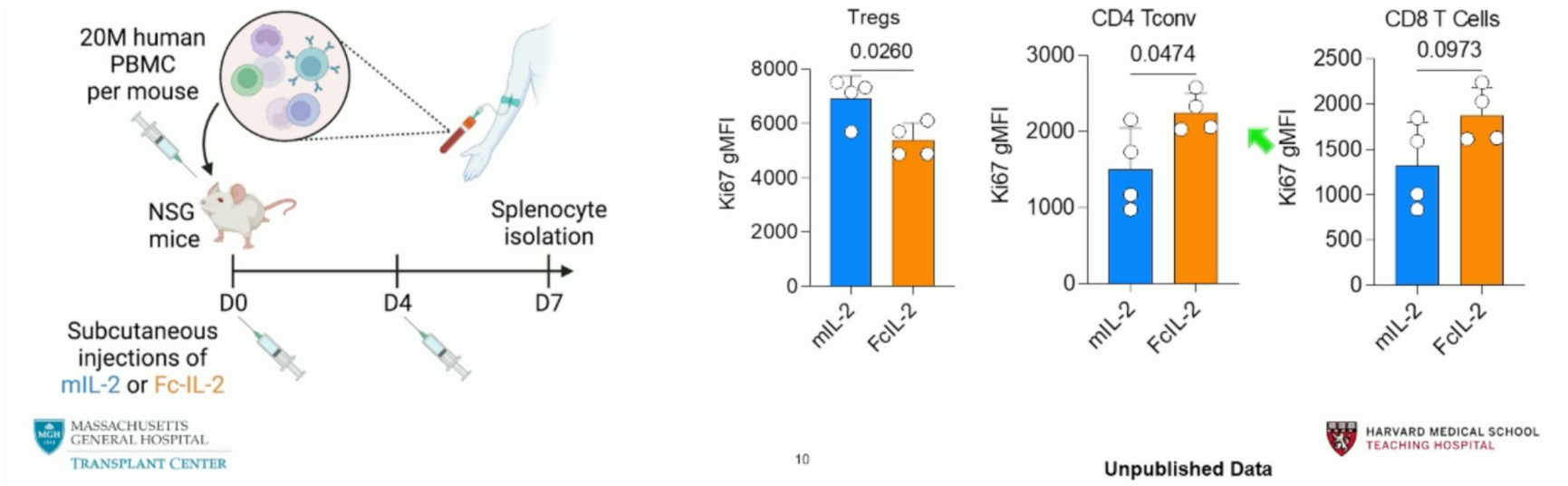
Efe et al.
Massachusetts General Hospital
RIELLA LAB

Tolerance

Selective Regulatory T-cell Expansion By A Novel IL-2 Mutein In Murine Transplant And Humanized NSG Model

3 *NSG mouse model*

(human PBMCs transferred to NSG recipients)



* mIL-2 selectively expands human Tregs

CONCLUSION: mIL-2 selectively expands both mouse and human Tregs and prolongs skin graft survival, inducing antigen-specific tolerance.

Innate Immunity

AXL Inhibition Suppresses Monocyte-to Macrophage Differentiation and Prolongs Allograft Survival

BACKGROUND

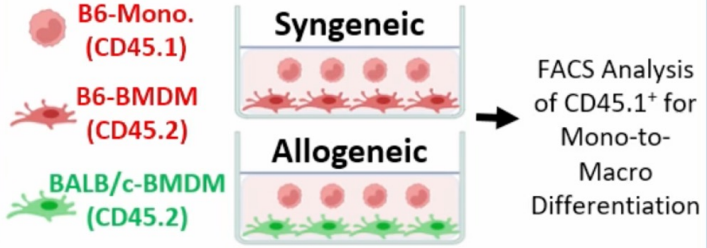
Early intragraft monocyte and macrophage accumulation, and subsequent inflammation correlates with poor transplantation outcomes. *(Kirk, AJT 2008)*

Single cell transcriptomic data implicates **AXL kinase** as a unique molecule of interest in trajectory analysis of intragraft monocyte-derived macrophage differentiation. (L*uo, JCI Insight 2020)*

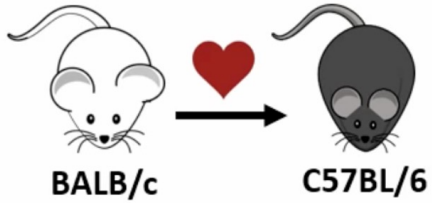
Bemcentinib (**small molecule AXL inhibitor**) would serve as a novel therapeutic approach in transplantation to selectively target the monocyte-macrophage lineage.

METHODS

Model 1: D/R in-vitro innate cell co-culture



Model 2: Mouse heterotopic heart transplant

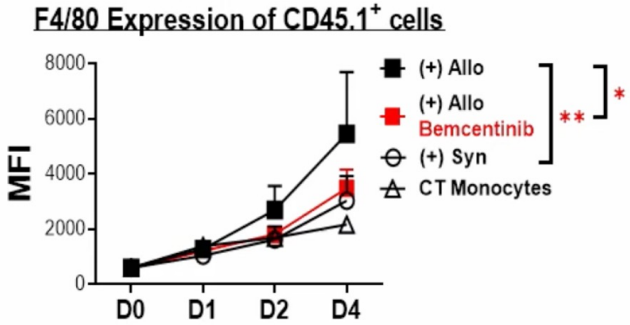


"CT" Group: Untreated

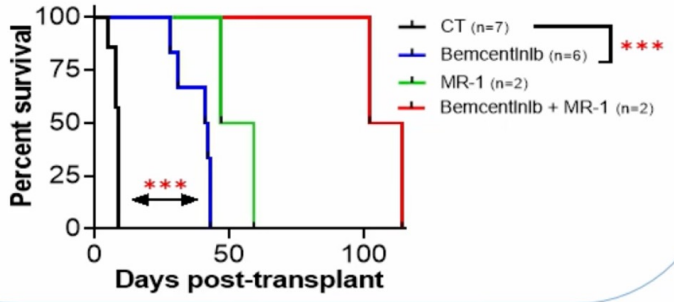
"Bemcentinib" Group: D-1 to D+10; 100mg/kg

FINDINGS

Result 1: AXL inhibition attenuates monocyte-derived macrophage differentiation.



Result 2: Bemcentinib therapy prolongs cardiac allograft survival.



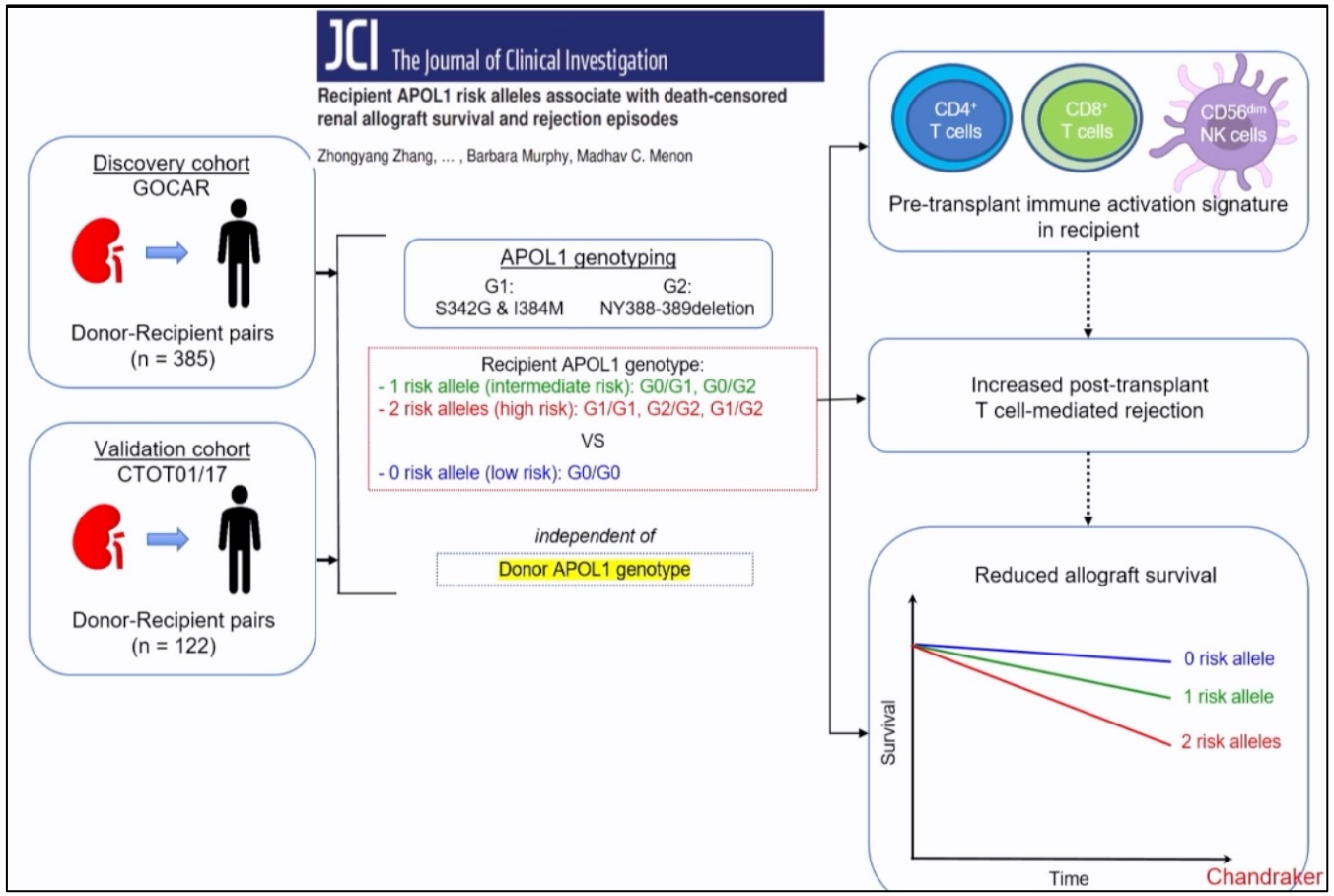
CONCLUSION:

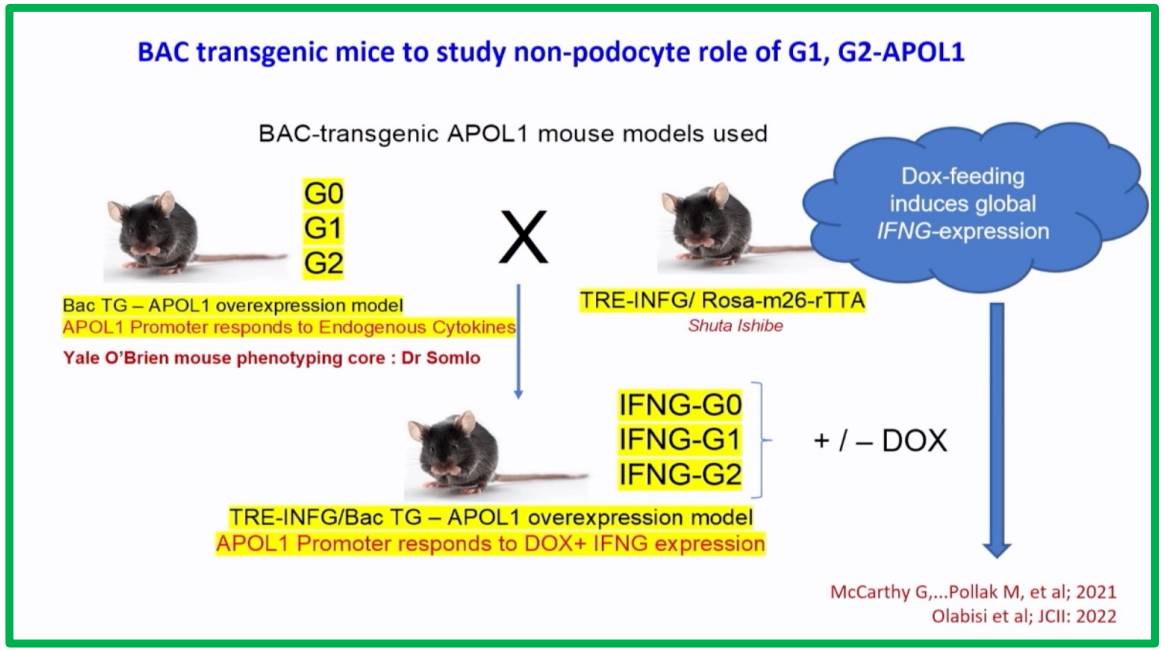
- **AXL kinase: master regulator of intragraft monocyte-derived macrophage differentiation.**
- **Blockade of AXL kinase with bemcentinib prolongs cardiac allograft survival.**

Collin Z. Jordan (Xunrong Luo Lab)
Duke University School of Medicine, Durham, NC

Bac-Transgenic Mice Show a Novel T-Cell Intrinsic Excitatory Role for Apol1 Risk-Alleles

Systems Biology – Biomarkers

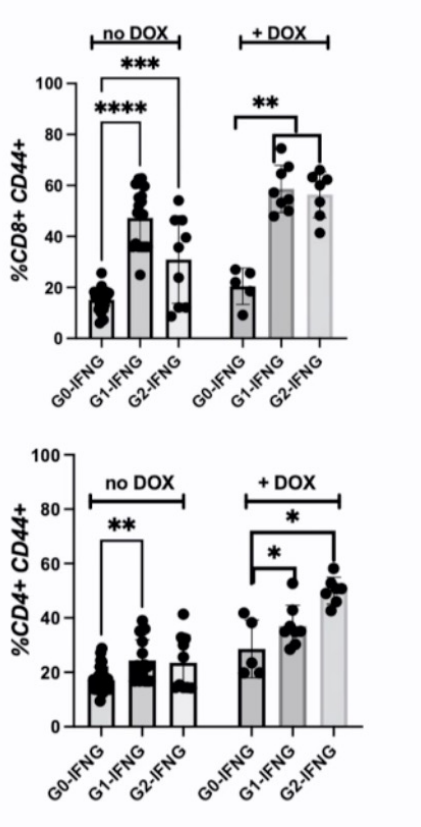




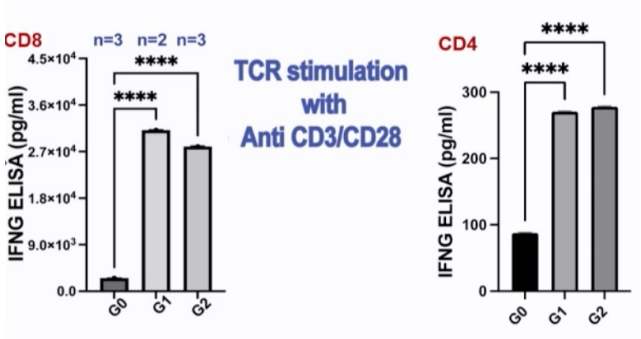
Bac-Transgenic Mice Show a Novel T-Cell Intrinsic Excitatory Role for Apol1 Risk-Alleles

Systems Biology – Biomarkers

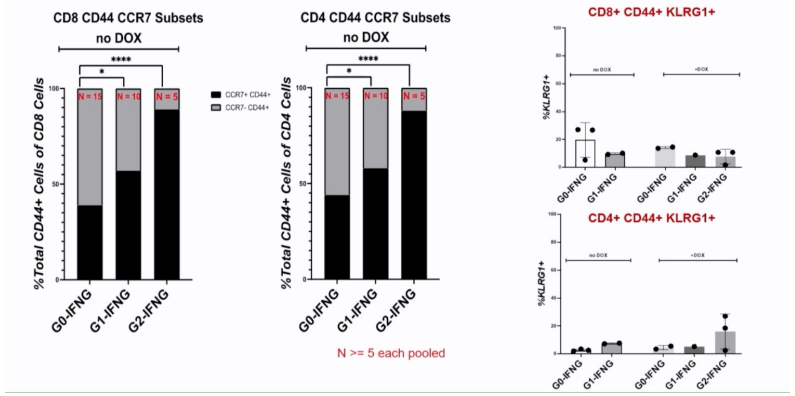
CD8+ and CD4+ Activation in G1, G2



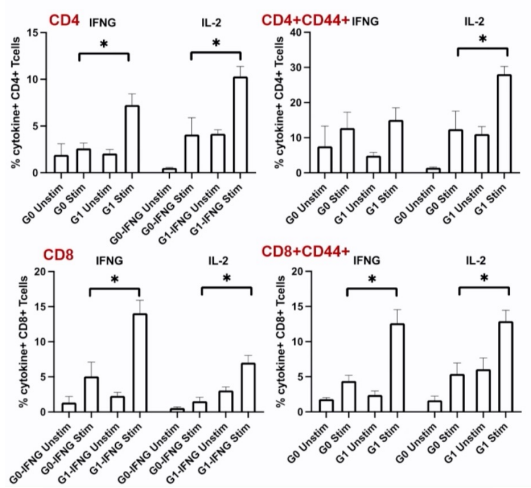
G1-CD8+ T cells: increased proliferation/IFNg production

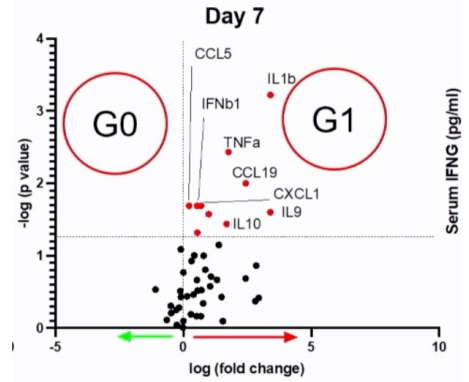


APOL1 variant CD44+ T cell phenotype: increased CCR7+ expression



Cytokine production after Poly (I:C) in Bac-Tg mice





CONCLUSION: A novel T-cell intrinsic role for APOL1-exonic variants increasing activation, proliferation and cytokine production.

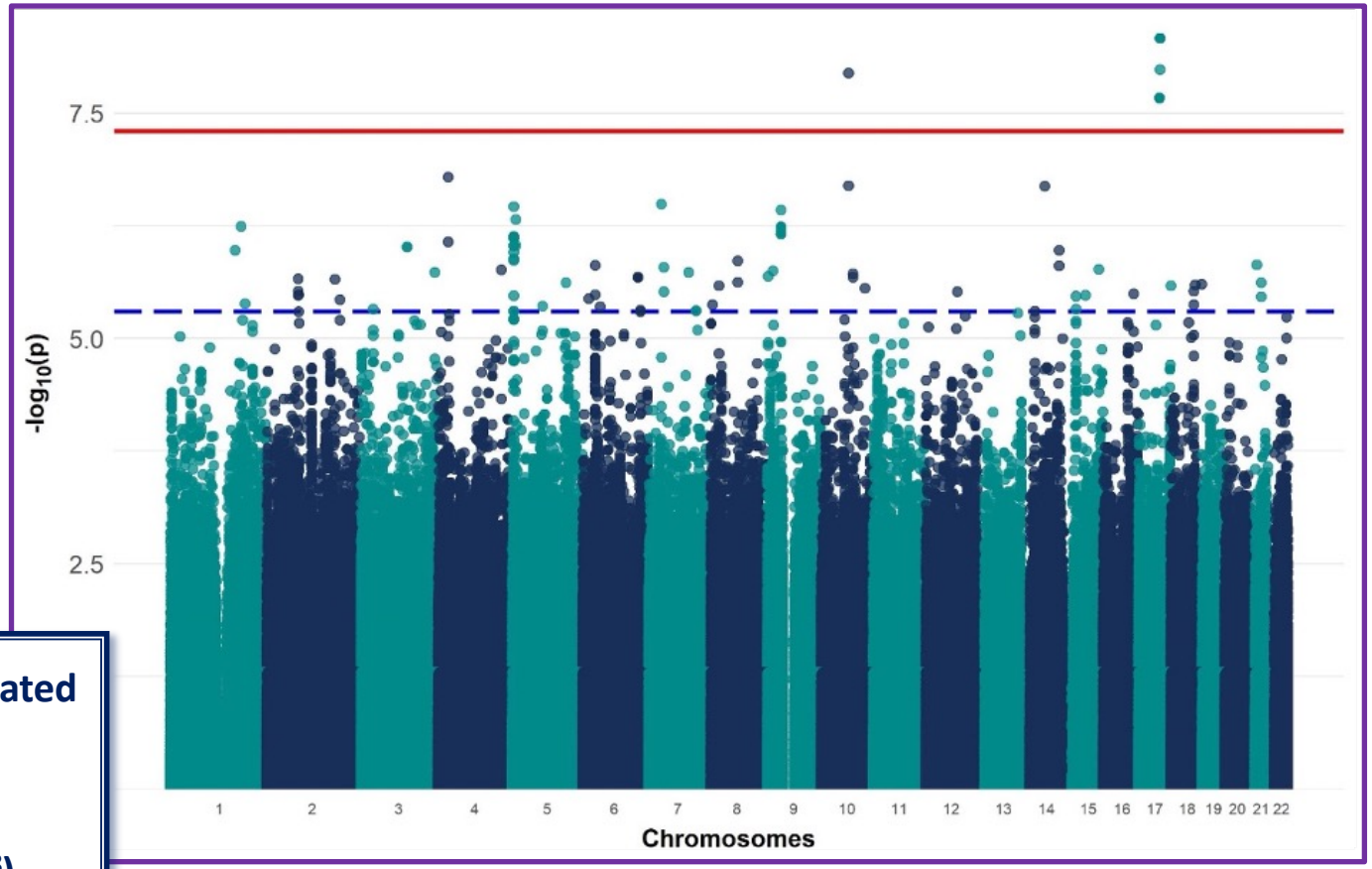
Histocompatibility & Immunogenetics

Genome-Wide Survival Study Identifies Three Novel Associations between Non-HLA Donor-Recipient Mismatches and Kidney Graft Failure

Non-HLA donor-recipient mismatches could be associated with kidney graft survival.

Analysis using genome-wide data in a large French monocentric cohort (KiT-GENIE):

- Transplanted in Nantes 2002-2018
- 1,482 complete European pairs
- Mean follow-up = 6,7 years
- 303 graft failure events



GWSS results for D-R mismatches in European pairs for time-to-Kidney graft failure (significance threshold in red)

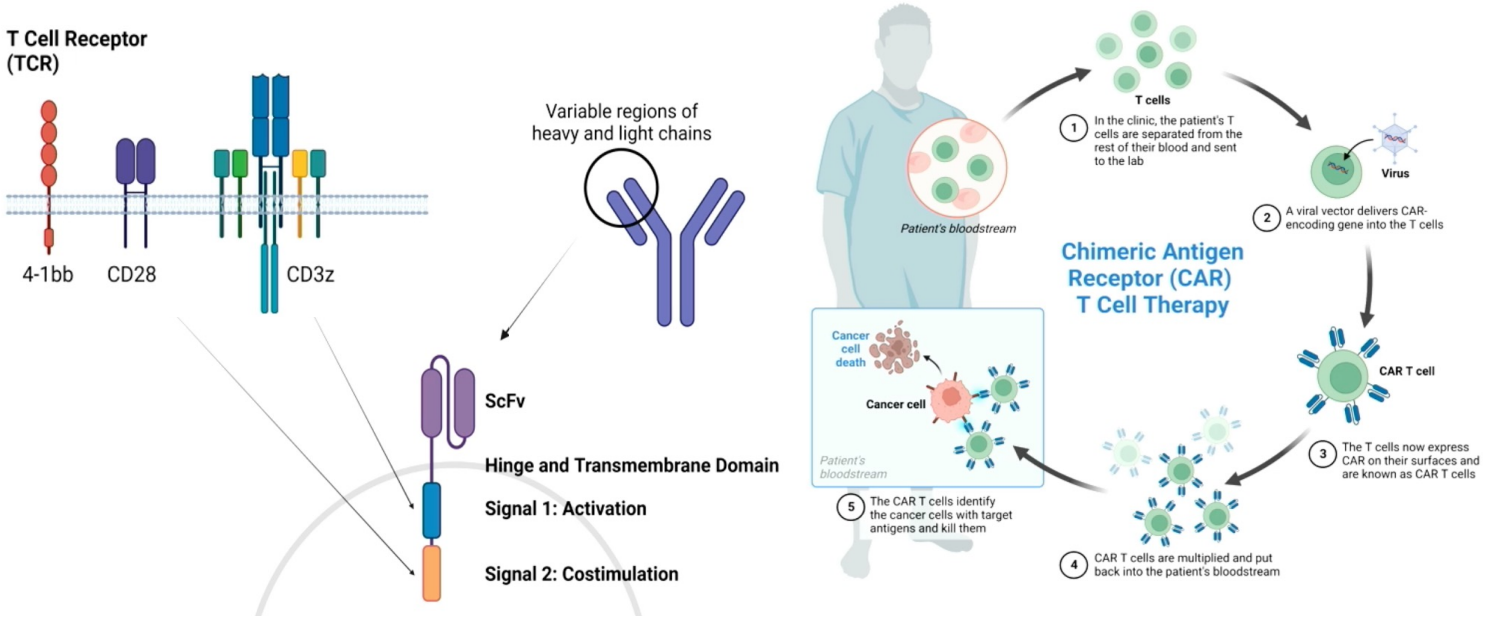
(External validation pending)

Three D-R mismatches outside of the HLA region were associated with kidney graft survival:

- **Chromosome 10 intronic mismatch (HR=3.5, $p=3.1x10^{-8}$)**
- **Chromosome 17 intergenic mismatch (HR=4.0, $p=1.0x10^{-8}$)**
- **Chromosome 21 intronic mismatch (HR=5.2, $p=2.0x10^{-8}$)**

Chimeric HLA Antibody Receptor T Cells for Targeted Therapy of Antibody Mediated Rejection in Transplantation

Chimeric Antigen Receptor (CAR) structure and CAR-T cell therapy

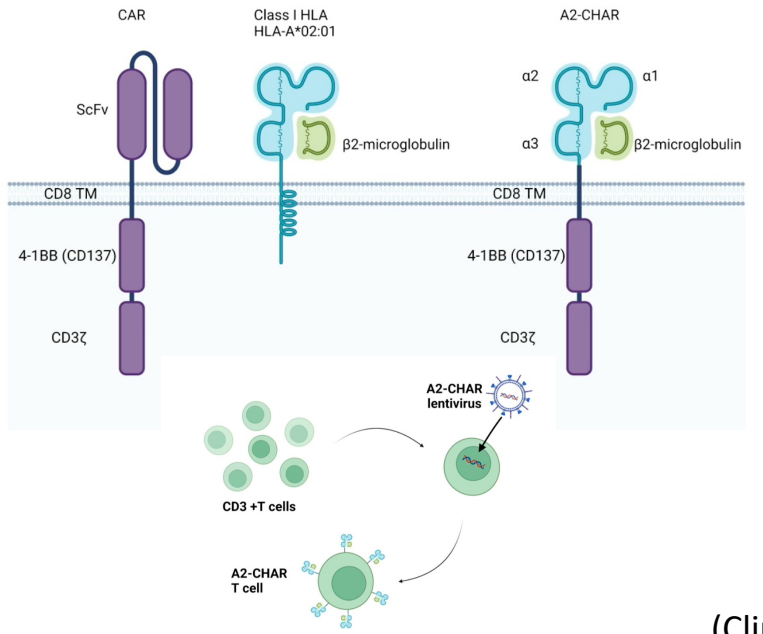


Huang, E. (2022) BioRender.

<u>Hypothesis:</u> Transduction of cytotoxic T cells with a CAR may be used to develop a targeted therapy for DSA desensitization and ABMR.

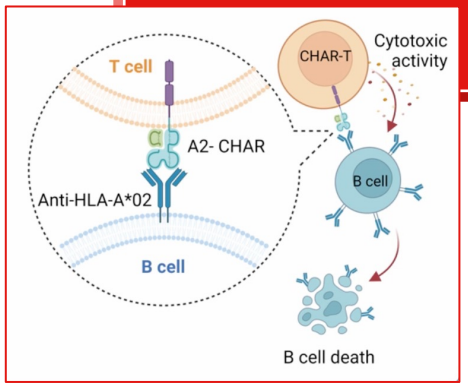
<u>Objective:</u> To generate T cells with chimeric anti-HLA antibody receptor (CHAR-T cells) that specifically eliminate donor-specific HLA class I antibody-producing B cells.

Chimeric HLA Antibody Receptor (CHAR) design



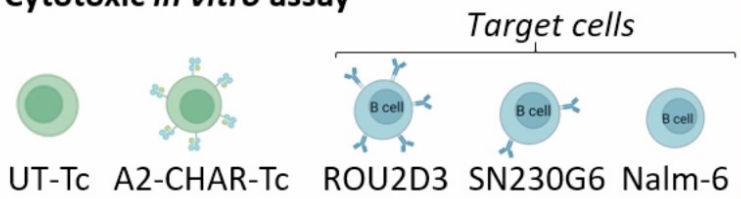
Betriu S
(Clinic Barcelona)

Chimeric HLA Antibody Receptor T Cells for Targeted Therapy of Antibody Mediated Rejection in Transplantation

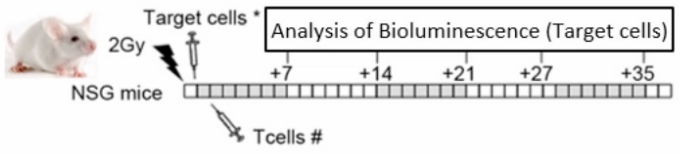


ROU2D3 *and* ***SN230G6****: B cells that express antibodies against HLA-A2 on their membrane*

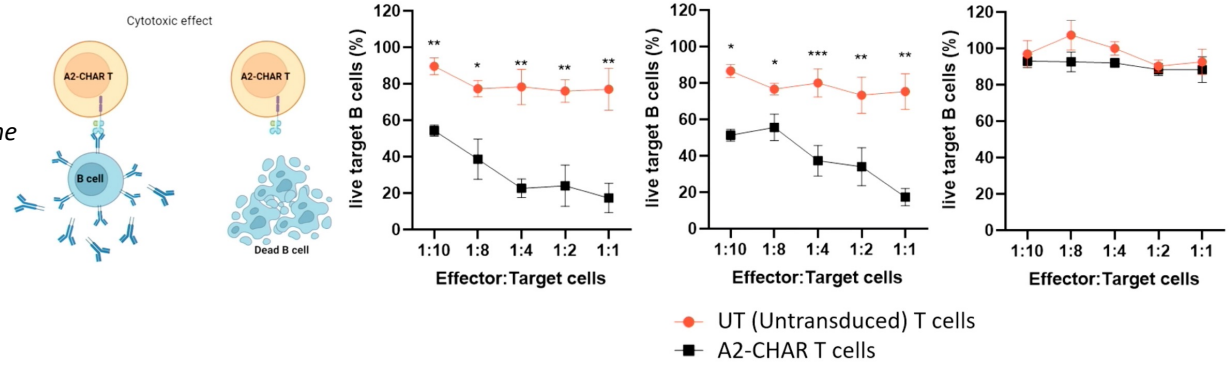
Cytotoxic *in vitro* assay



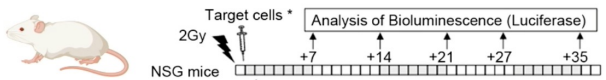
Cytotoxic *in vivo* assay

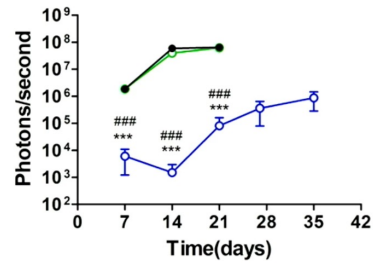


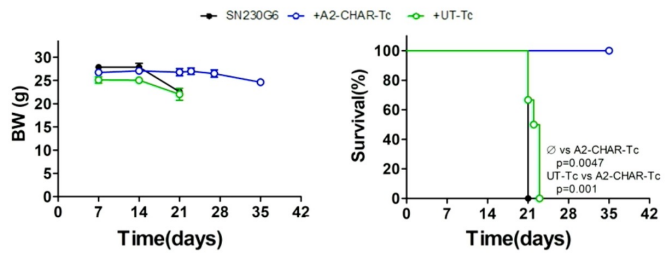
A2-CHAR-T Lymphocytes: *in vitro* cytotoxic activity



A2-CHAR-T Lymphocytes: *in vivo* cytotoxic activity







CONCLUSION:

· CHAR technology can kill, *in vitro* and *in vivo*, anti-HLA antibody producing B cells.

· CHAR-T cells could be useful in DSA desensitization protocols and ABMR therapy, by selectively eliminating donor-specific anti-HLA antibody producing B cells.

Betriu S