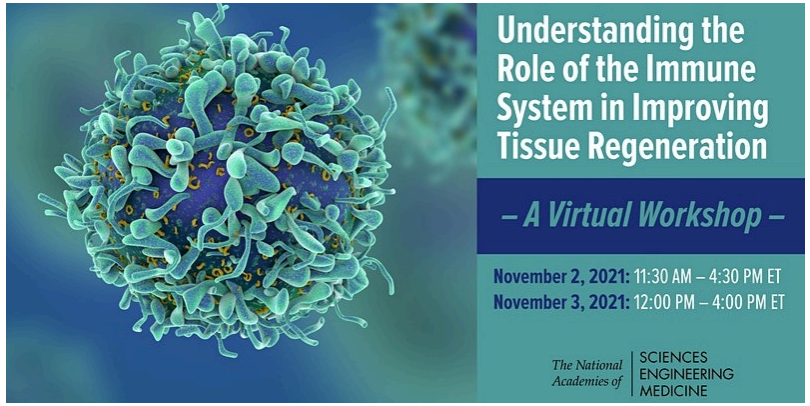


"Protecting transplanted cells from immune rejection is the key to unlocking the potential of regenerative medicine"

Sonja Schrepfer, MD, PhD

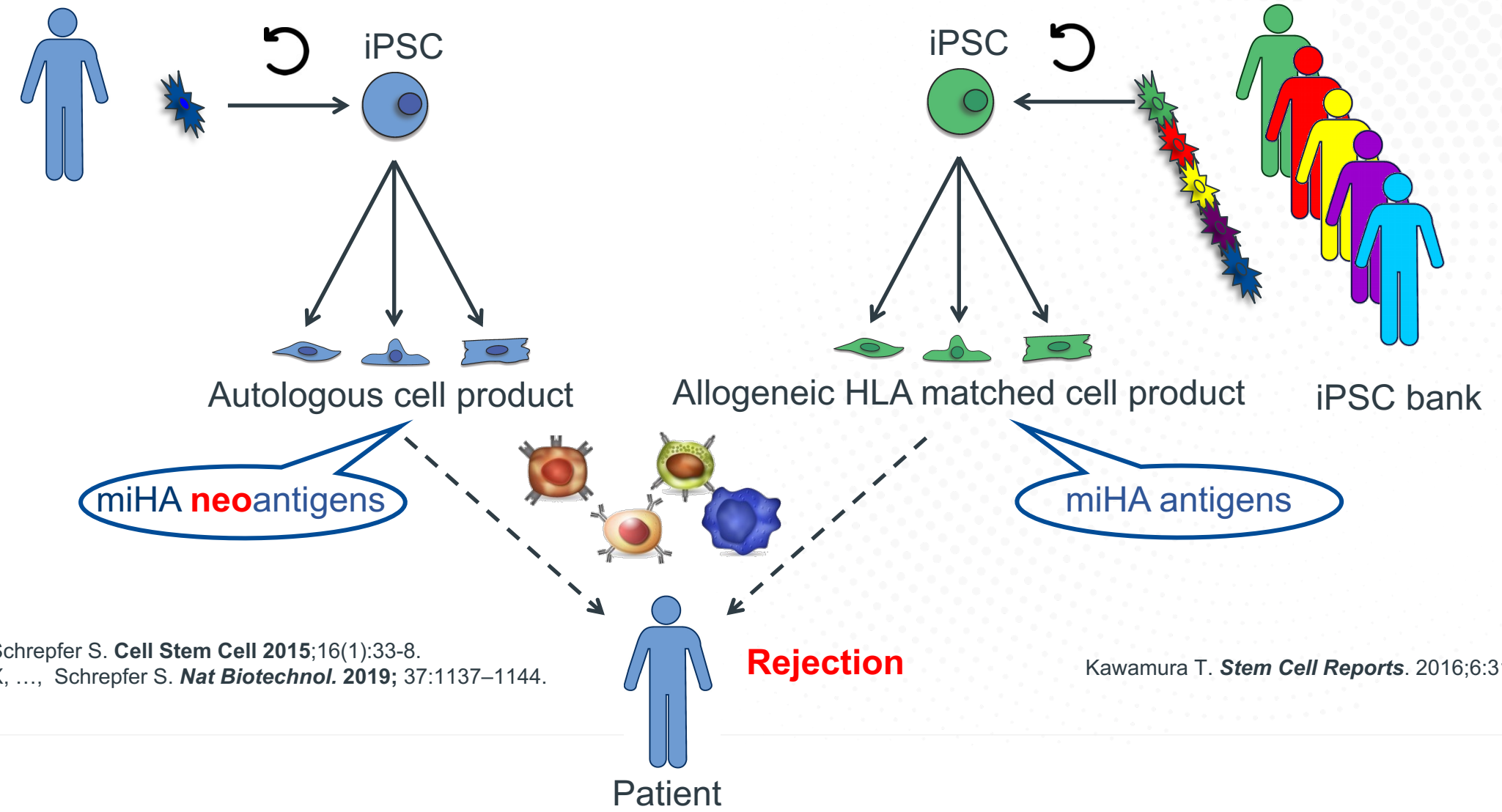
Sana
Biotechnology

Disclosure

- I am a scientific founder and stockholder of Sana Biotechnology, Inc. (“Sana”).
- Since Feb 2019, I have been an employee of Sana in South San Francisco, CA.
- Since 2015, I have been a Professor of Surgery at the University of California San Francisco (“UCSF”).

Regenerative stem cell therapy

Current concepts: Even recent advances in stem cell biology can be associated with immune recognition and rejection



Deuse T, …, Schrepfer S. **Cell Stem Cell 2015**;16(1):33-8.
Deuse T, Hu X, …, Schrepfer S. ***Nat Biotechnol.* 2019;** 37:1137–1144.

Kawamura T. ***Stem Cell Reports***. 2016;6:312-20.

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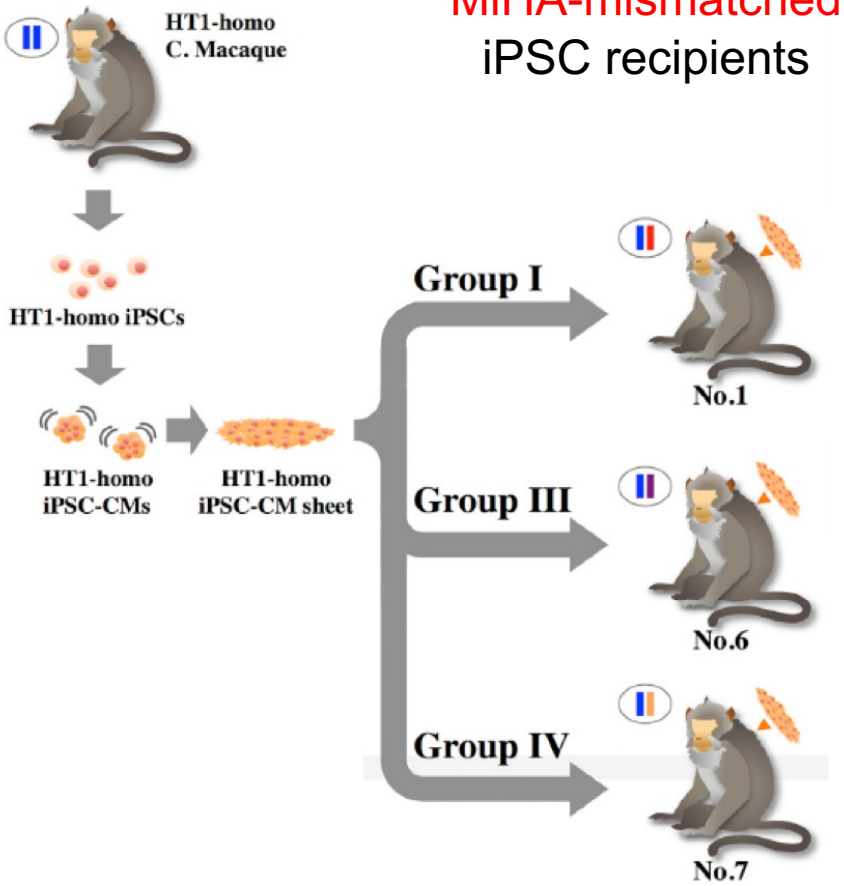
HLA banking for pluripotent stem cells

MHC homozygous
iPSC donor

MHC heterozygous
MiHA-mismatched
iPSC recipients



	Immunosuppression	Survival at 2 months
Group I	Prednisolone: 1mg/kg TAC: trough levels at >10 ng/ml MMF: 40mg/kg	100%
Group III	TAC: trough levels at >10 ng/ml	0%
Group IV	none	0%

Conclusion: *HLA banking does not avoid rejection and requires Immunosuppression.*

Kawamura T. ***Stem Cell Reports***. 2016;6:312-20.

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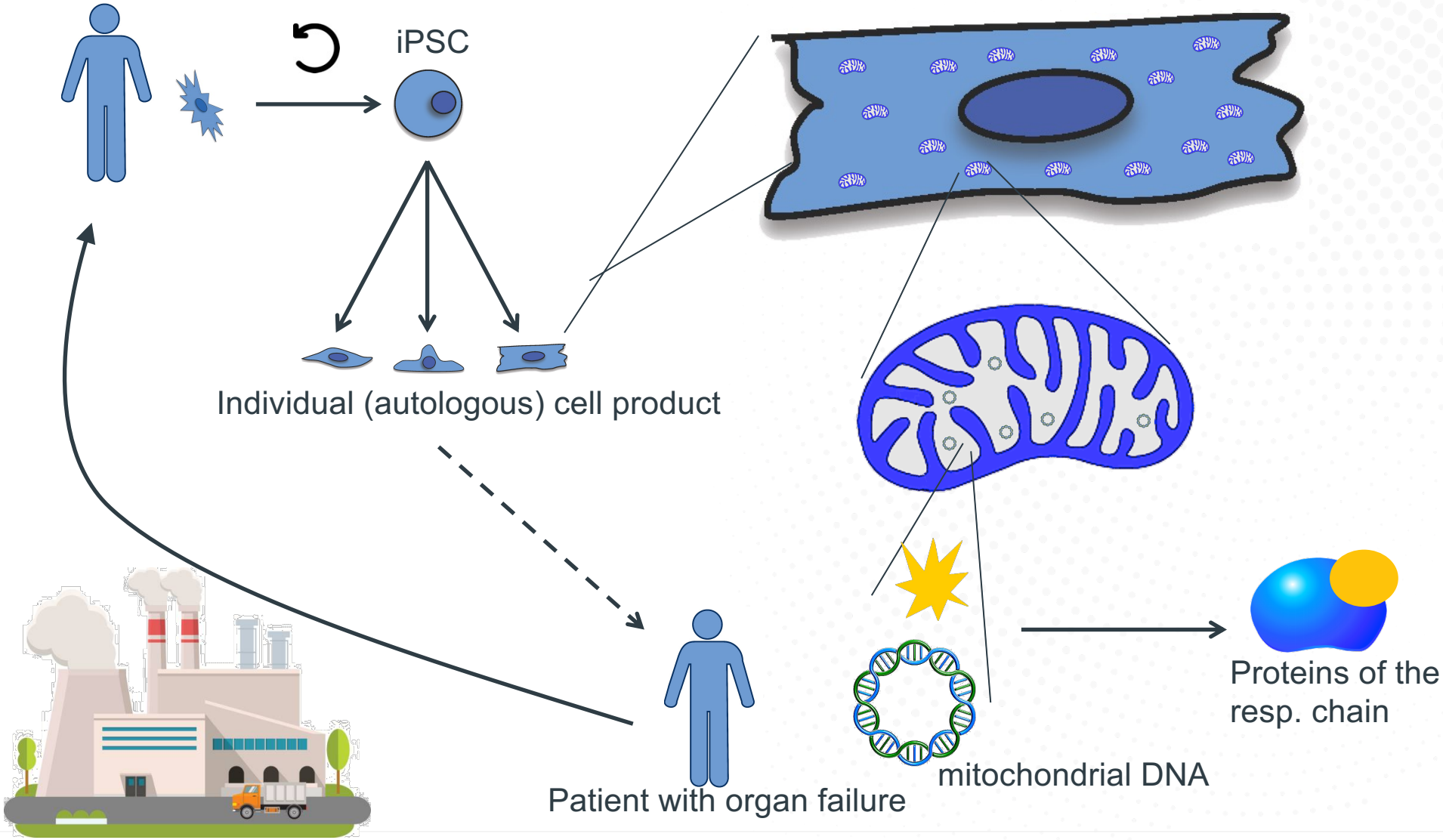
Immune barrier for autologous cell products



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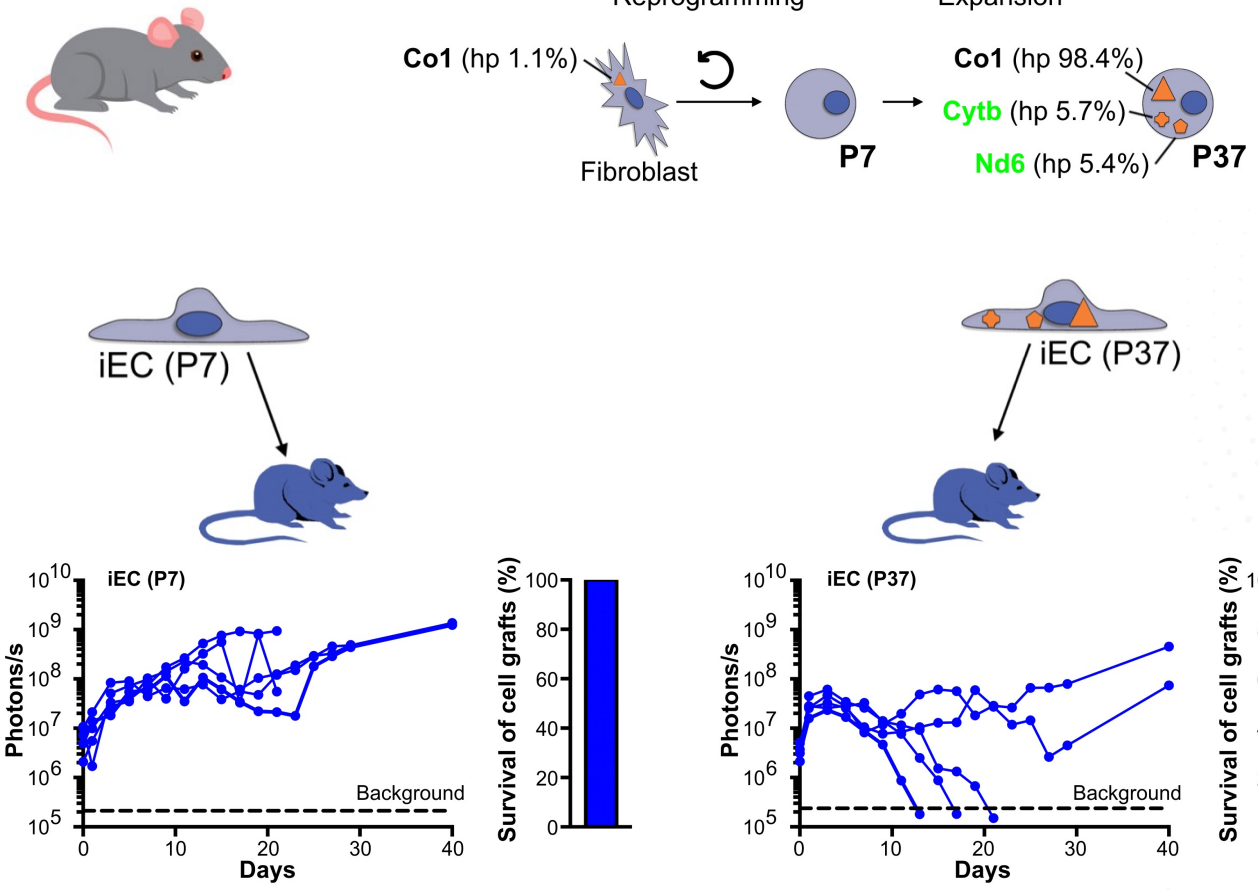
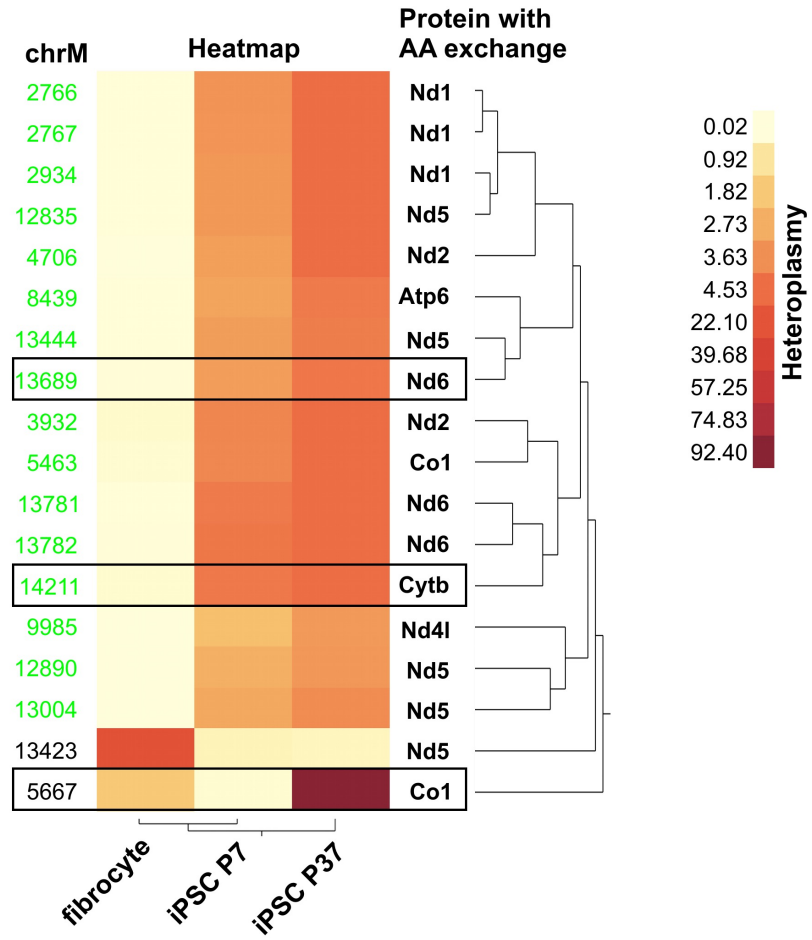
Deuse T, …, Schrepfer S. ***Nat Biotechnol. 2019****;37(10):1137-1144.*

Regenerative stem cell therapy

Immunological hurdles of autologous cell products





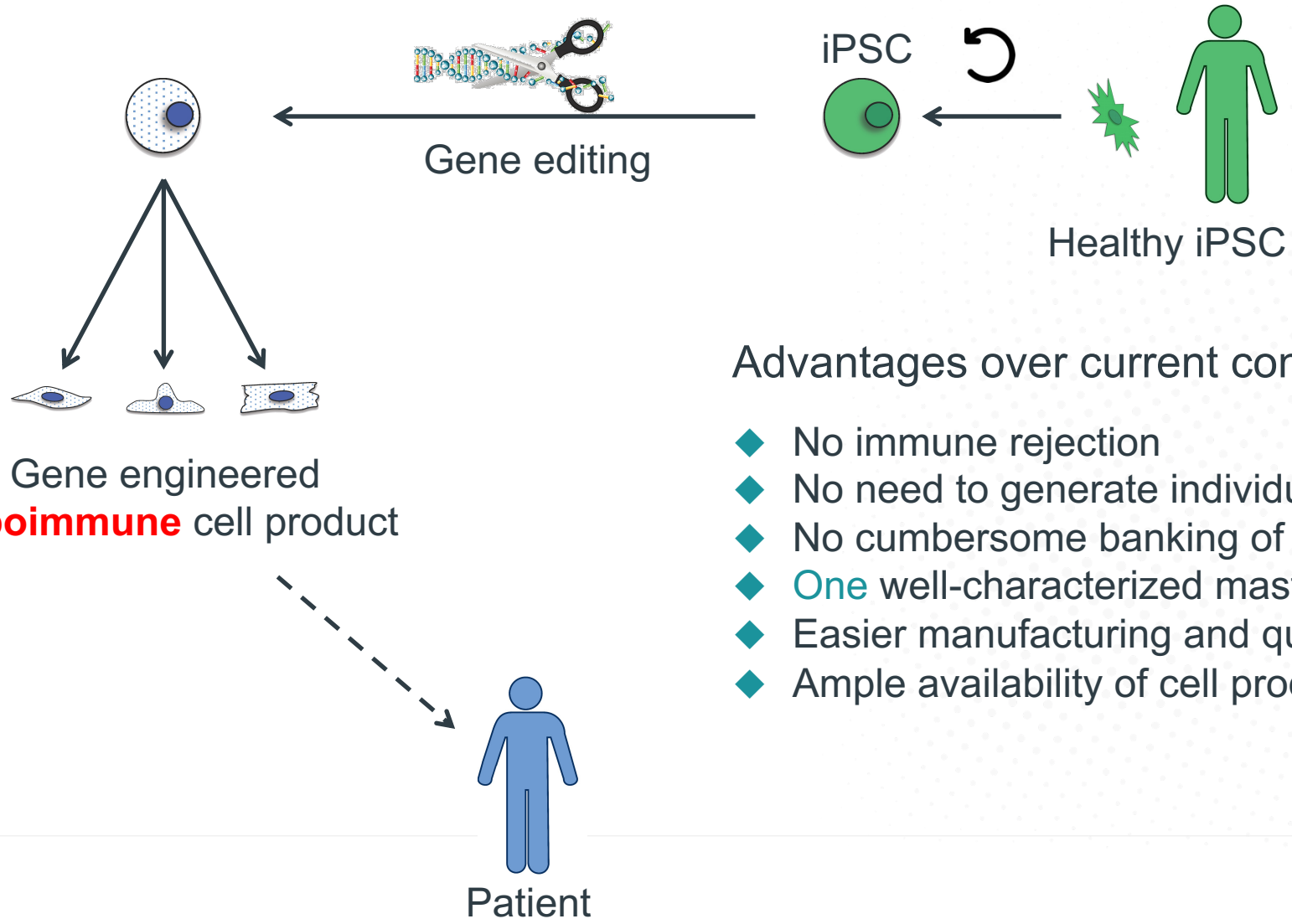
Conclusion: *Autologous HLA can present neo-antigens leading to rejection of autologous iPSCs.*

Deuse T, …, Schrepfer S. ***Cell Stem Cell.* 2015**;16:33-8.

Deuse T, …, Schrepfer S. ***Nat Biotechnol. Sept.* 2019;** doi:10.1038/s41587-019-0227-7

Protecting allogeneic cells from immune destruction is the key to unlocking the potential of regenerative medicine

New concept: Hypoimmune cell products



Advantages over current concepts:

- No immune rejection
- No need to generate individualized cell products
- No cumbersome banking of huge amounts of cell lines
- One well-characterized master cell line
- Easier manufacturing and quality control
- Ample availability of cell products

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Protecting allogeneic cells from immune destruction is the key to unlocking the potential of regenerative medicine

Fetomaternal tolerance during pregnancy

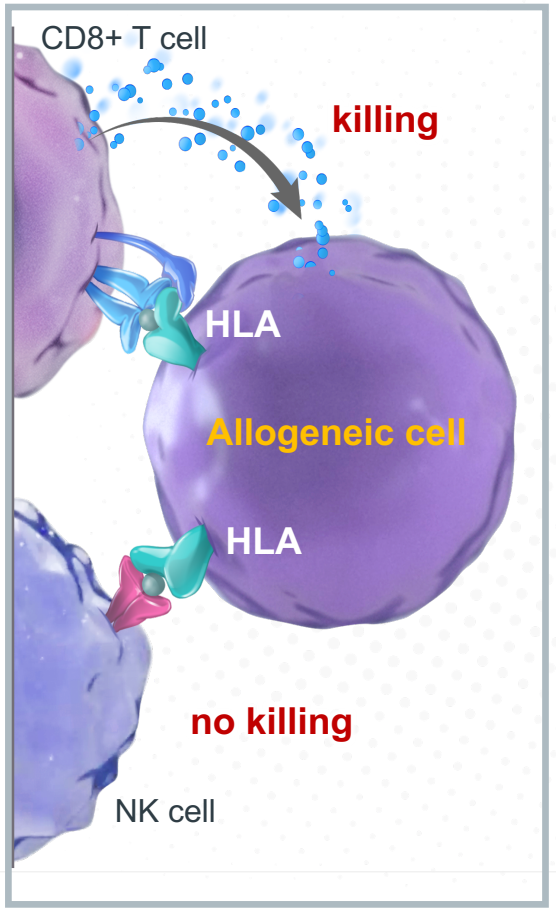
"Allogeneic" fetus:

- Half of fetal proteins are from the father, not the mother.
- However, the fetus is not rejected by the mother.

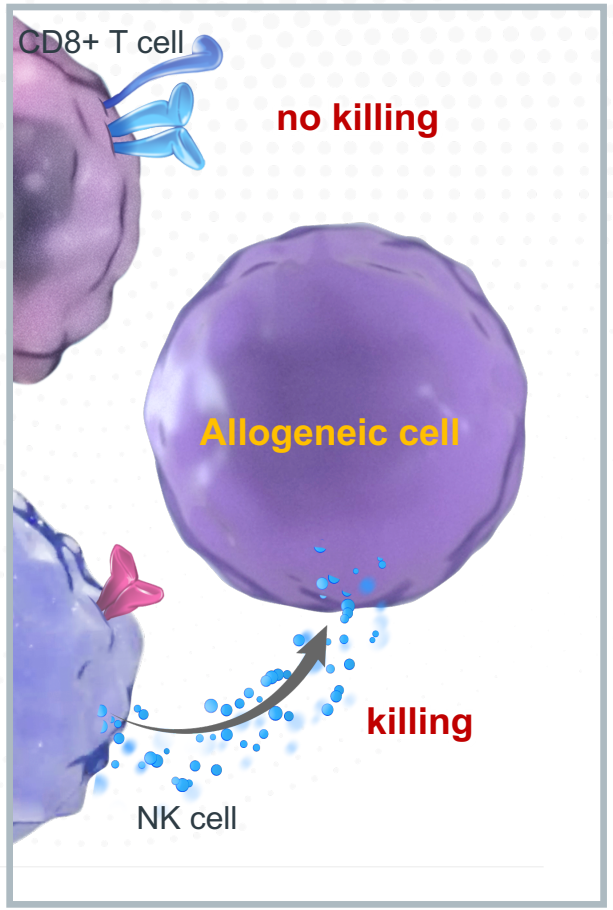
How can we protect our engineered cells from getting attacked from the recipient's immune system?

The adaptive and innate immune system

Adaptive response to HLA:



Innate response to "missing-self":



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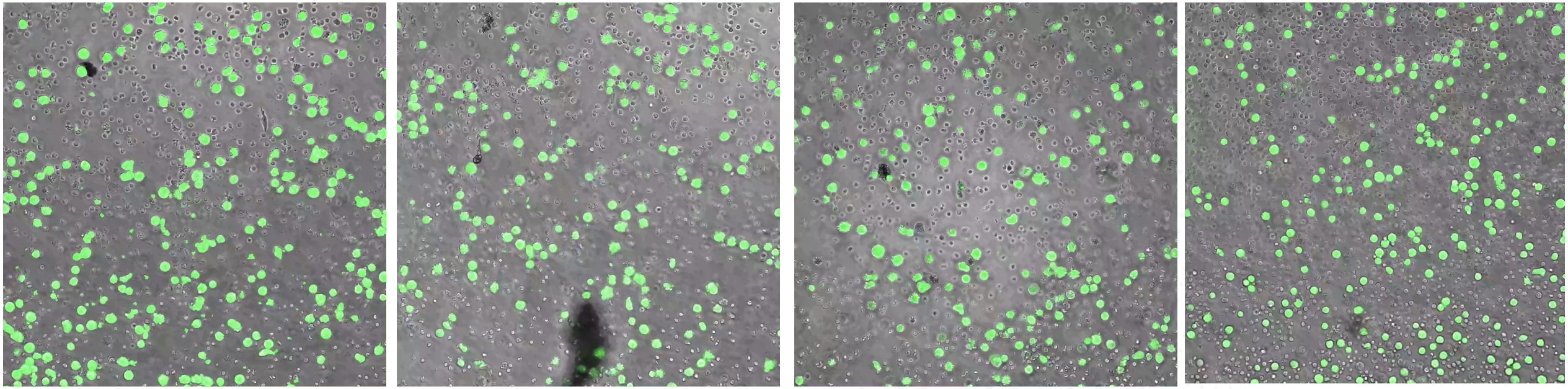
Molecules to prevent killing of HLA-knockout target cells by innate immune response

HLA-E_{KI}	HLA-G_{KI}	PD-$L1_{KI}$	$CD47_{KI}$



Allogeneic cell without HLA (triggering innate immune response through “missing-self”)

NK cells

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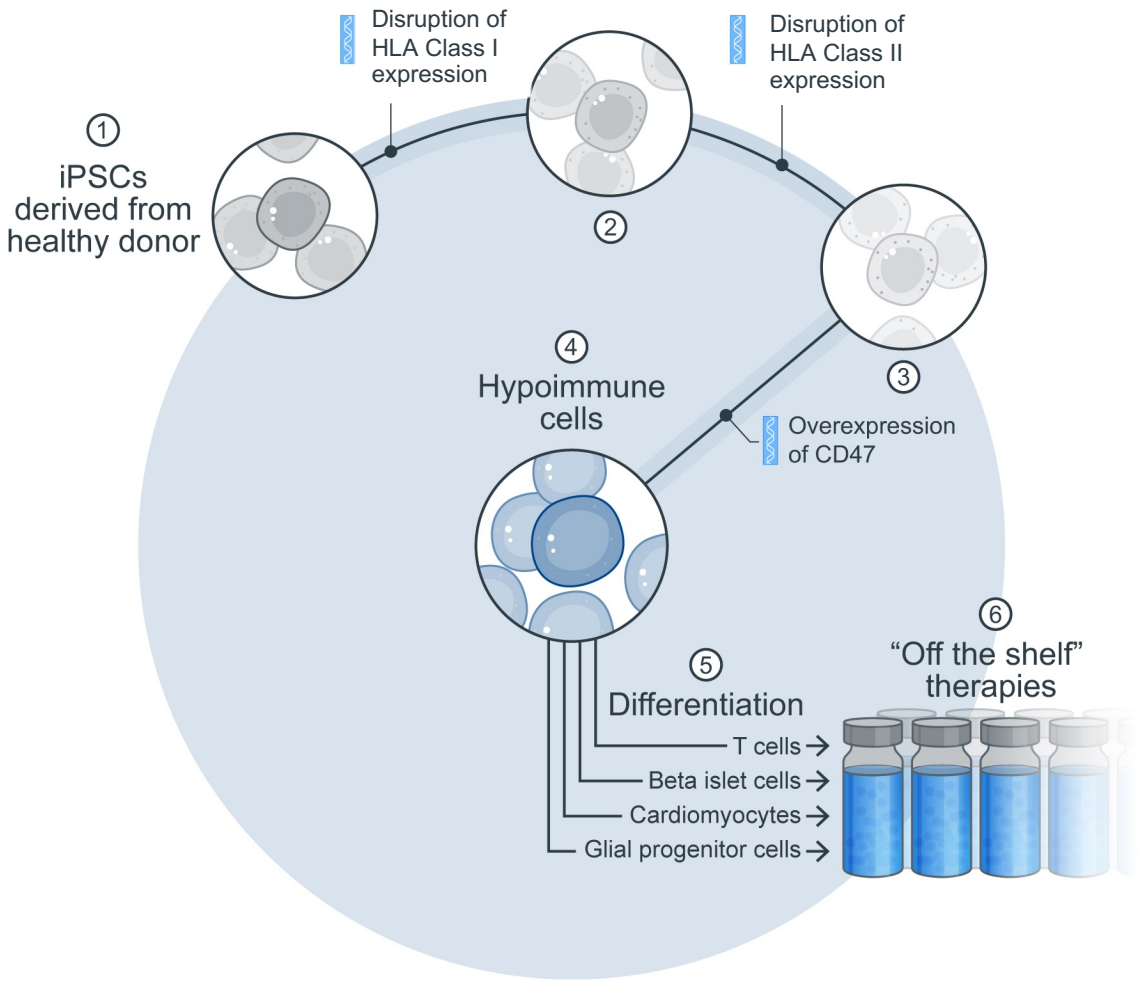
Protecting cells from immune destruction is the key to unlocking the potential of regenerative medicine

The engineering approach



"Off the shelf" therapies without the need for immunosuppression for anyone, anytime, anywhere

Deuse T, …, Schrepfer S. ***Nat Biotechnol.*** **2019**;37:252-258.
Deuse T, …, Schrepfer S. **J Exp Med 2021**;218(3):e20200839.
Hu X, …., Schrepfer S. **AACR 2021** (Sana Biotechnology, Inc.)
Deuse T, …, **Proc Natl Acad Sci U S A.2021**;118(28):e2022091118.

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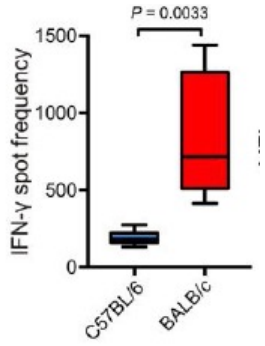
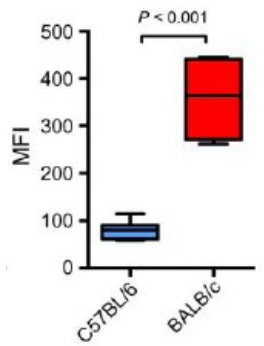
Hypoimmune iPSC-derived endothelial cells survive and evade rejection in allogeneic mice

Evade the adaptive immune system

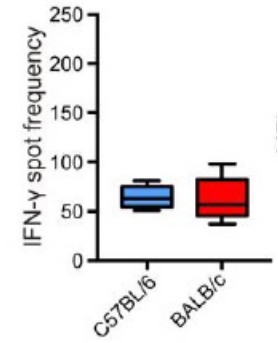
	T Cell Activation (ELISPOT)	IgM Binding (FACS)
	No systemic T cell activation with HIP cell transplantation	*No binding of donor specific antibodies against HIP cells*

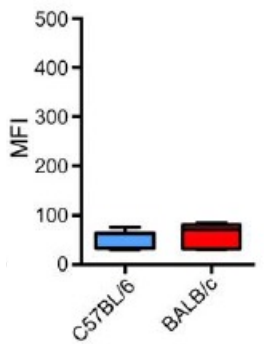
Unmodified endothelial cells





HIP endothelial cells





Deuse T, Hu X, …, Schrepfer S. *Nat Biotechnology*. 2019; 37:252-258

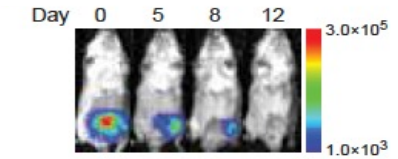
Survival in allogeneic recipients

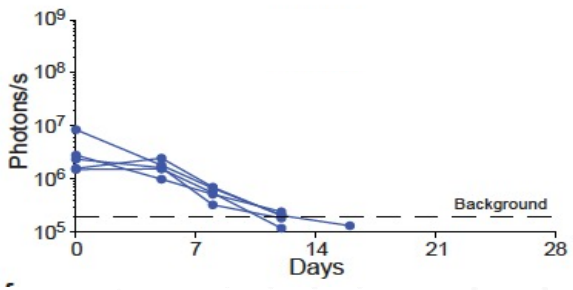
Survival

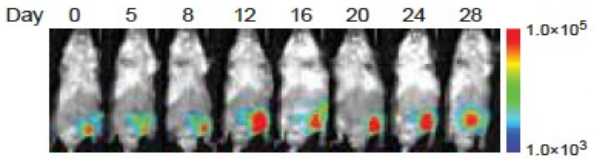
No survival of unmodified allogeneic iPSC-derived endothelial cells	*Survival of HIP iPSC-derived endothelial cells in allogeneic recipients*

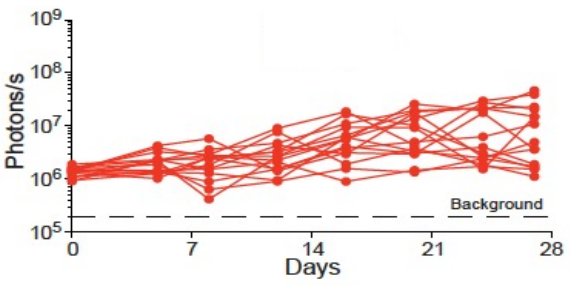
Hypoimmune induced pluripotent stem cell–derived cell therapeutics treat cardiovascular and pulmonary diseases in immunocompetent allogeneic mice

Tobias Deuse[a,1], Grigol Tediashvili[a,b,1], Xiaomeng Hu[a,b,c,d,1], Alessia Gravina[a], Annika Tamenang[a,b], Dong Wang[a], Andrew Connolly[e], Christian Mueller[f,g], Beñat Mallavia[h], Mark R. Looney[h,i], Malik Alawi[j], Lewis L. Lanier[k,2,3], and Sonja Schrepfer[a,d,2,3]









Unmodified endothelial cells | **HIP endothelial cells**

Deuse T, …, Schrepfer S. Proc Natl Acad Sci USA.2021;118(28):e2022091118.

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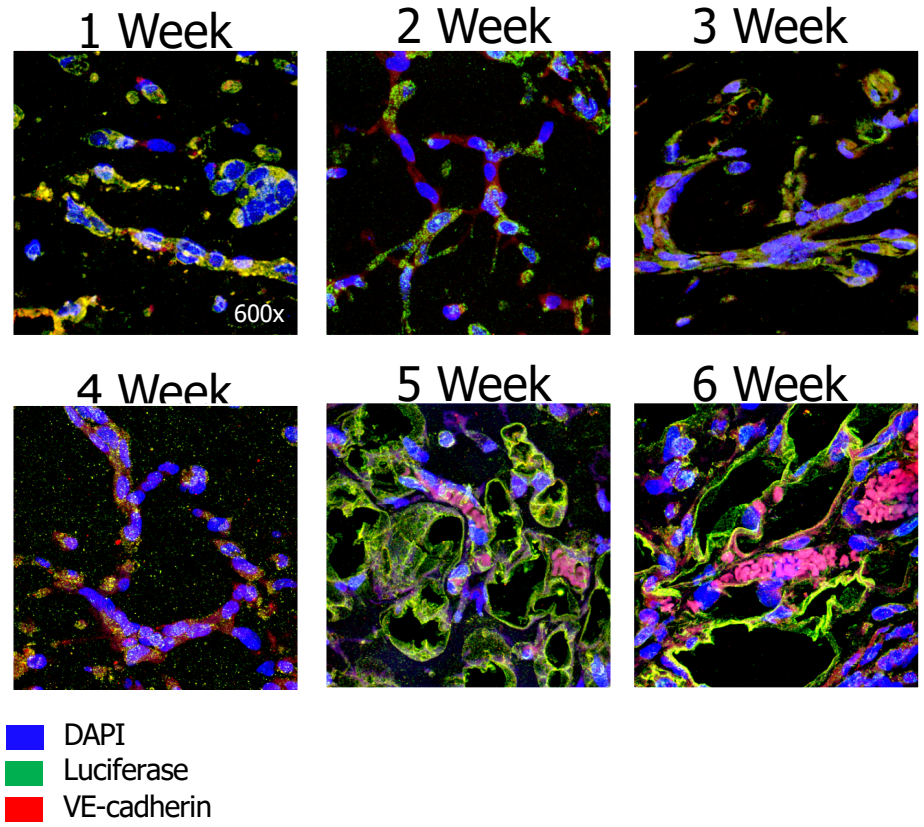
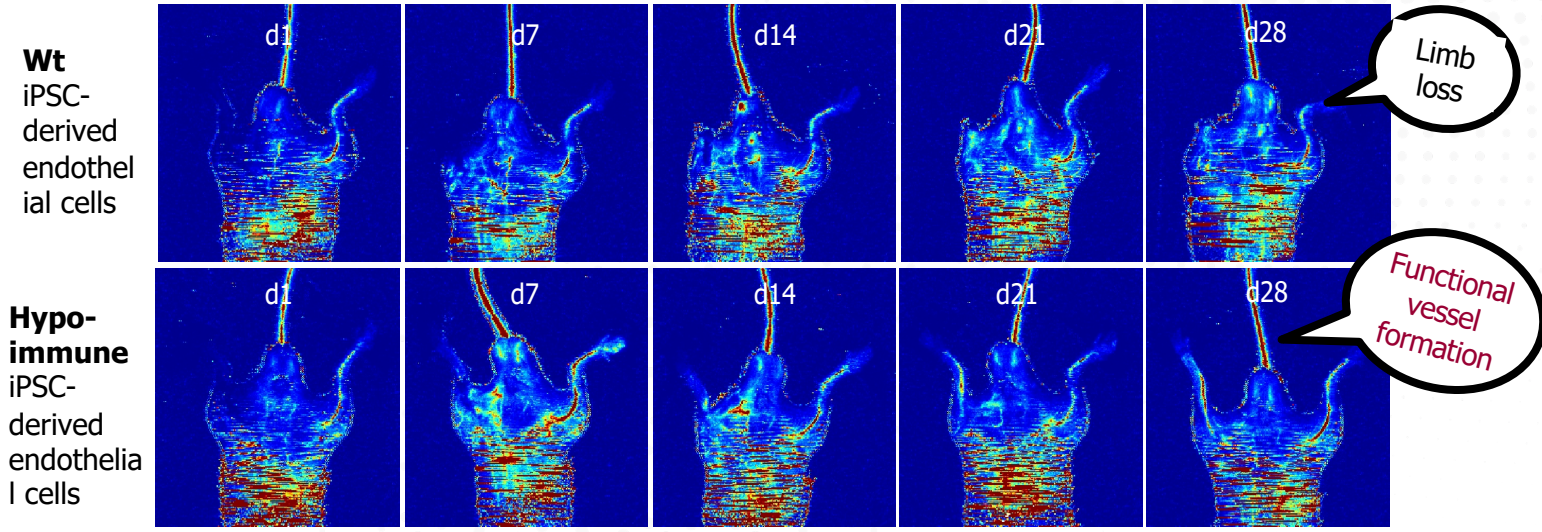
Hypoimmune edits (HLA-I knockout, HLA-II knockout, CD47tg) do not affect differentiation capacity nor intrinsic cell function

miECs for vascular regeneration



Hindlimb ischemia model in BALB/c: Removal of the A. femoralis and endothelial cell injections; perfusion assessed by Doppler



Deuse T, …, Schrepfer S. Proc Natl Acad Sci USA.2021;118(28):e2022091118.

Conclusion: Hypoimmunogenic iPSC-derived endothelial cells survive and spontaneously form new vessels in allogeneic hosts without immunosuppression.

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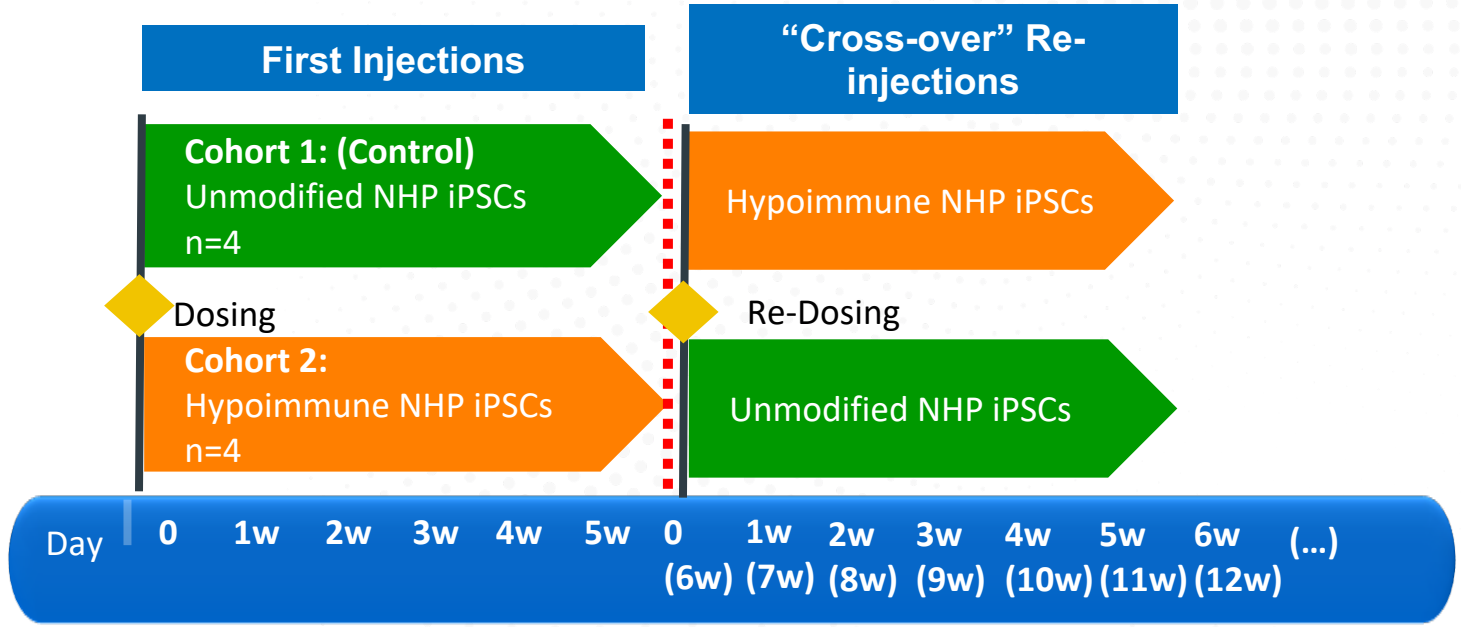
Vision of the Future – Immunosuppression free!

Vision

Don't only cure mice – cure patients!

NHP Study Design – a high bar translational model

NHP iPSCs were transplanted intramuscularly into allogeneic NHPs without immunosuppression (n=8 NHP)

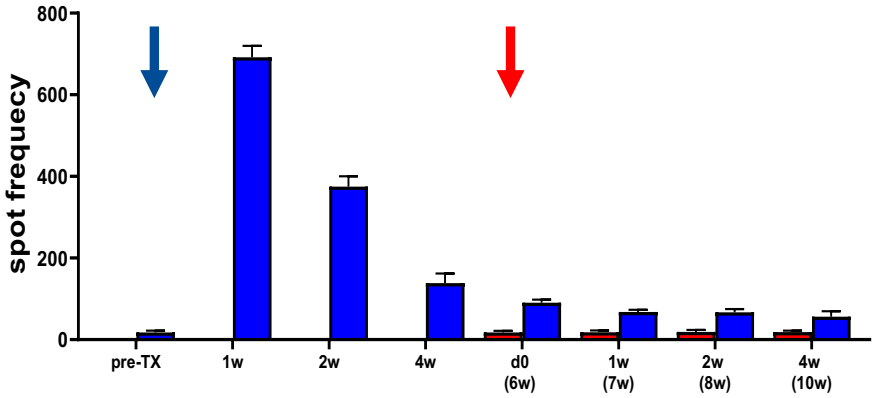


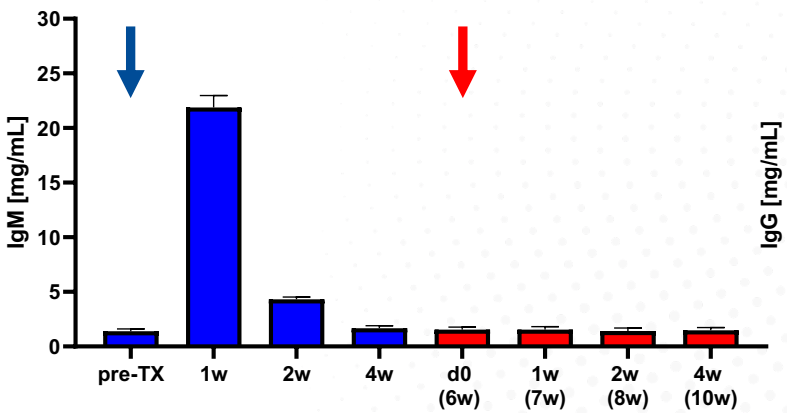
Hypoimmune NHP iPSCs do not elicit an adaptive immune response in allogeneic NHP recipients

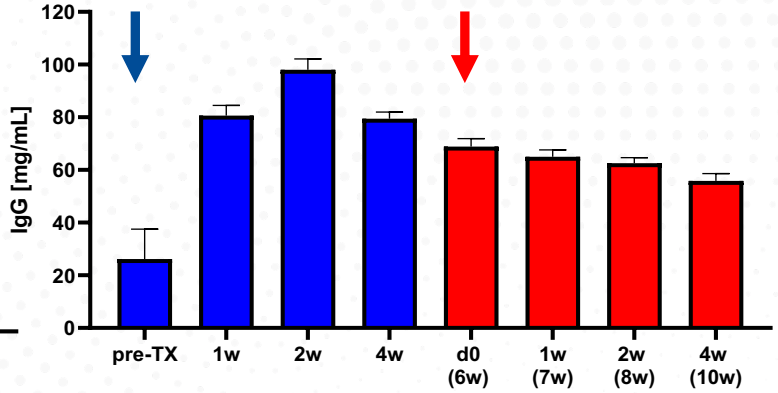
Transplantation of NHP iPSCs into allogeneic NHPs: Immune evasion is achieved even after prior sensitization

T Cell Activation (ELISPOT)	IgM Production (ELISA)	IgG Production (ELISA)
No systemic T cell activation by hypoimmune cells	*Implantation of hypoimmune cells does not cause activation of antibody production*	

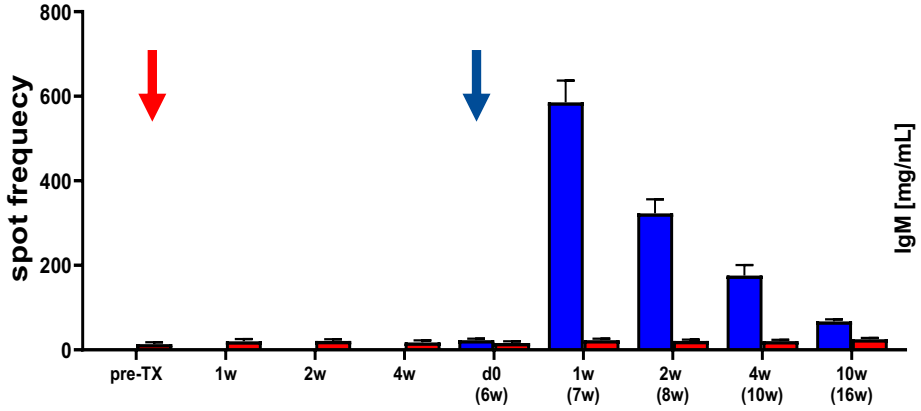
Unmodified iPSC

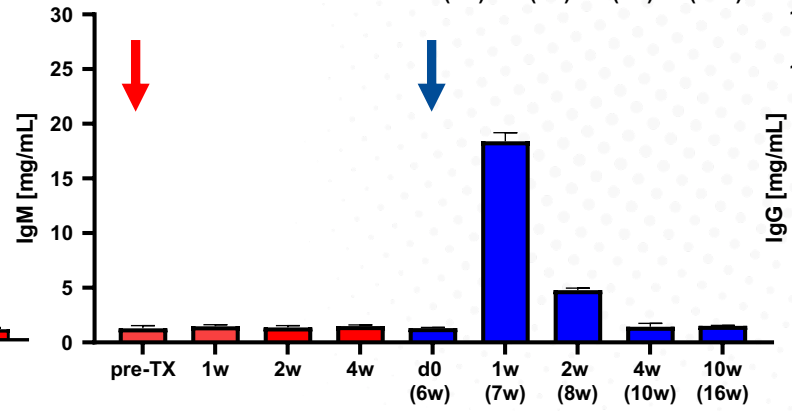


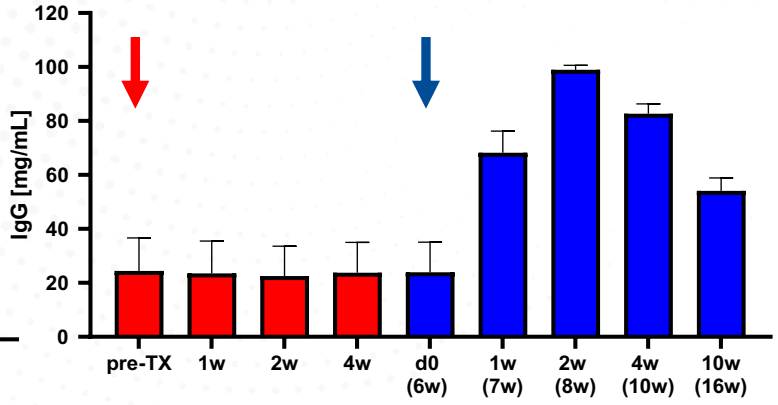




Hypoimmune iPSC







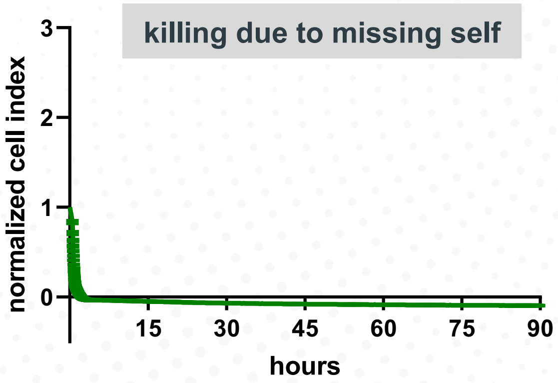
WT HIP

Hypoimmune NHP iPSCs do not elicit an innate immune response in allogeneic NHP recipients

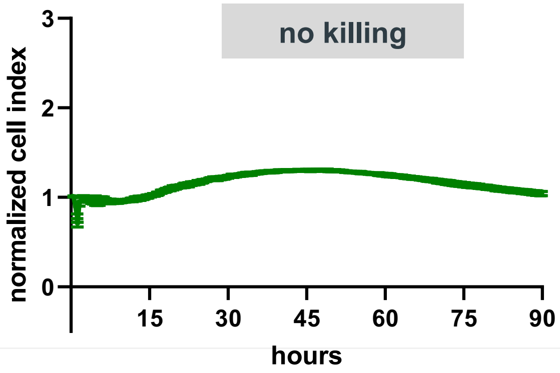
Transplantation of NHP iPSCs into allogeneic NHPs (n=4/group)

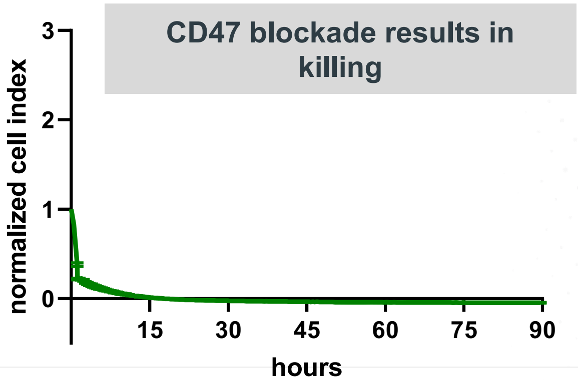
Killing by macrophages		Killing by NK cells	
Hypoimmune cells do not activate the "missing self" response from the macrophages	*Anti-CD47 blockade*	*Hypoimmune cells do not activate the "missing self" response from the NK cells*	*Anti-CD47 blockade*

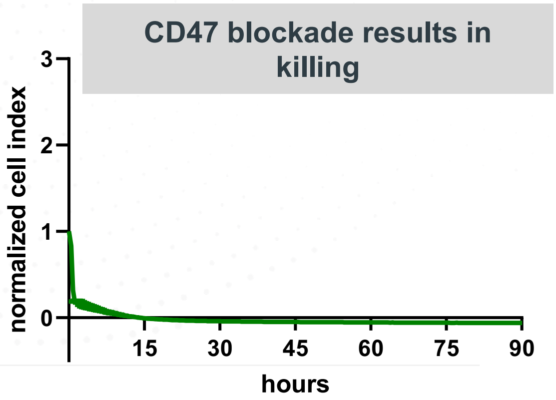
MHC-I/II KO iPSC



Hypoimmune iPSC



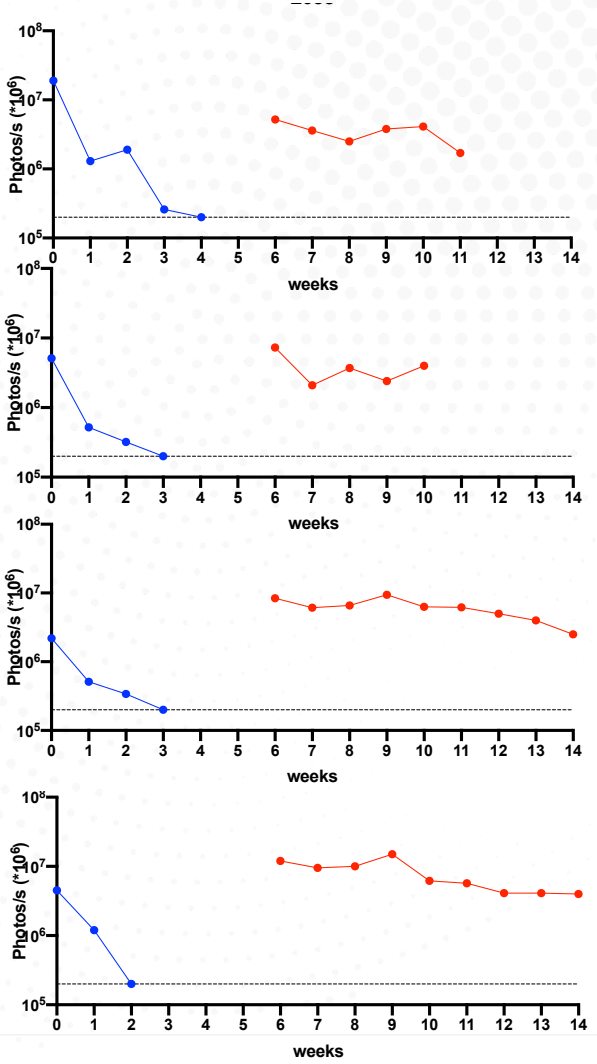




Allogeneic NHP hypoimmune iPSCs survive *in vivo* in sensitized recipients

	unmodified rhesus iPSC		hypoimmune rhesus iPSC			
	D0 (day of transplant)	3 wks (after transplant)	D0 (cross over)	3 wks (after crossover transplant)	4 wks (after crossover transplant)	8 wks (after crossover transplant)
NHP 1						
NHP 2						
NHP 3						
NHP 4						

Summary



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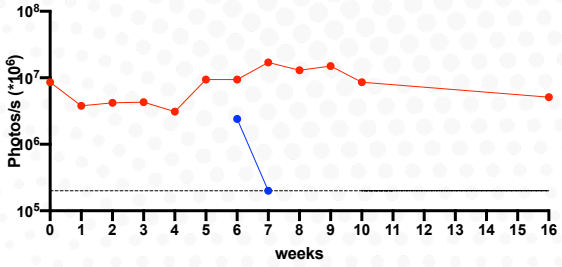
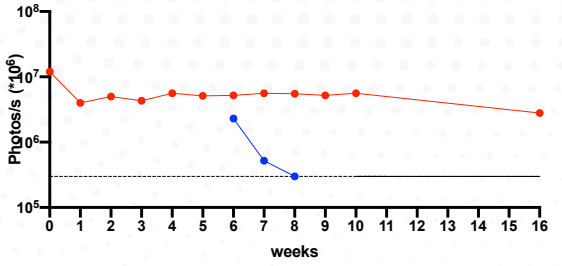
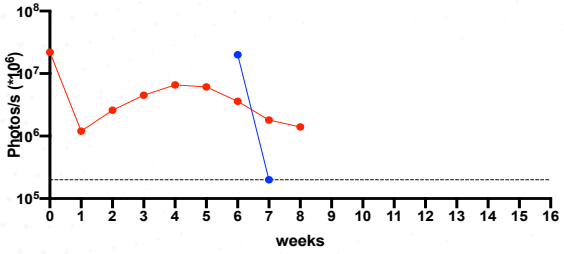
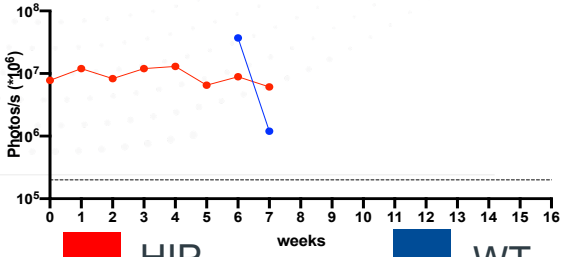
Allogeneic NHP hypoimmune iPSCs survive *in vivo* in NHP while unmodified iPSC get rejected

	hypoimmune rhesus iPSC					unmodified rhesus iPSC		Summary
	D0 (day of transplant)	2 wks (after transplant)	5 wks (after transplant)	10 wks (after transplant)	4 months/16wks (after transplant)	D0 (cross over)	2wks (after crossover transplant)	
NHP 5								
NHP 6					moved			
NHP 7								
NHP 8								









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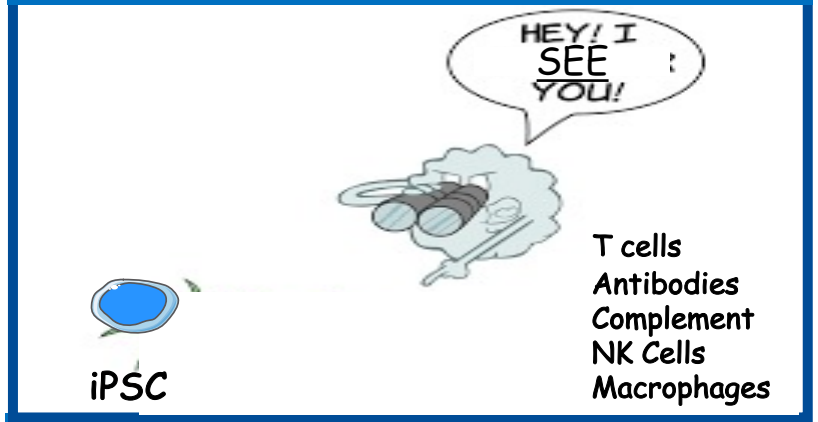
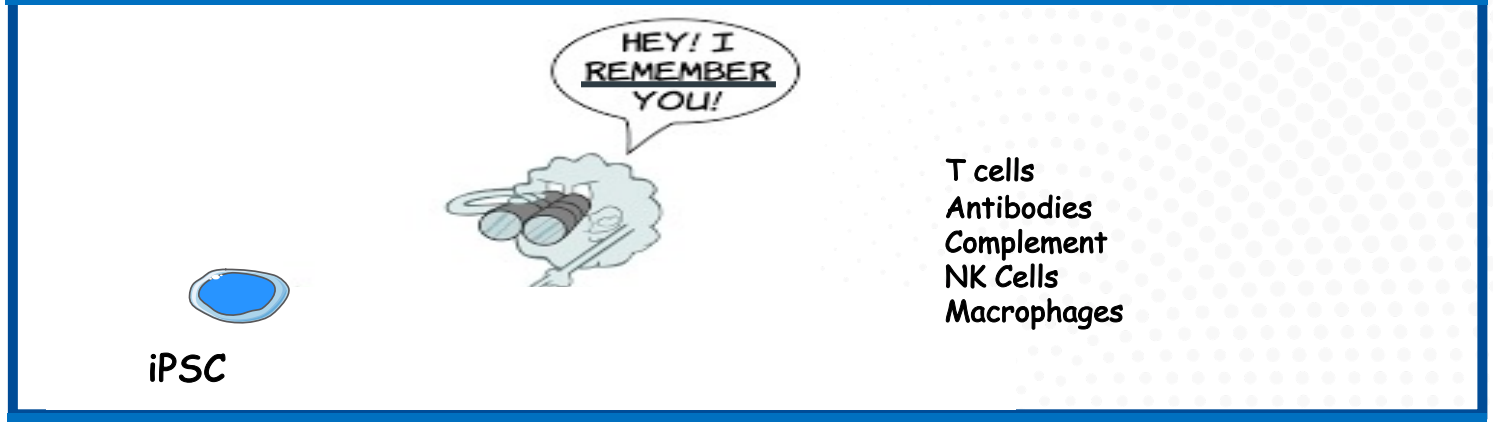
Key Immunological Findings

First transplantation



HIP demonstrates NO immune activation in mice, humanized mice, and NHP.

Re-Injection "cross-over"



Immune evasion: HIP demonstrates NO de-novo immune activation when injected into sensitized NHPs with memory immune cells from previous unmodified iPSC injection.

Summary

These findings show that hypoimmune cells:

- evade allogeneic immune rejection,
- do not activate the "missing self" response from NK cells and macrophages,
- can be transplanted into sensitized recipients (which opens the possibility of redosing),
- are not altering the recipients' immune system.

This hasn't been achieved before in NHP-a robust immunologic model.

Thus, cellular transplantation without immunosuppression appears to be an achievable goal using hypoimmune cells.

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Acknowledgements

HIP Research Team
Tech Science Team
HIP Core Team
Developmental Sciences Team
Cell Therapy Team

Thank You

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