



2017 CST-Astellas Canadian Transplant Fellows Symposium

The Future of Transplantation

Atul Humar, MD

Atul Humar is a Professor in the Department of Medicine, University of Toronto. Dr. Humar received his medical degree from the University of Ottawa. He completed his residency and did further training in Transplant Infectious Diseases in Toronto and Boston. Dr. Humar's research interests are in virology with a focus on the pathogenesis of herpesvirus infections post-transplant. He is involved in both basic and clinical research assessing immunologic and virologic determinants of infection. Dr. Humar is the Director of Multi Organ Transplant Program at the University Health Network and the University of Toronto Transplant Institute. He is also active in the Canadian Society of Transplantation as a President and has been very active in both the AST and TTS. Dr. Humar operates a joint research lab with his wife, Dr. Deepali Kumar, who is also a faculty member at the University of Toronto.



The Future of Transplantation

Atul Humar, MD

Dangers of predictions



Too optimistic

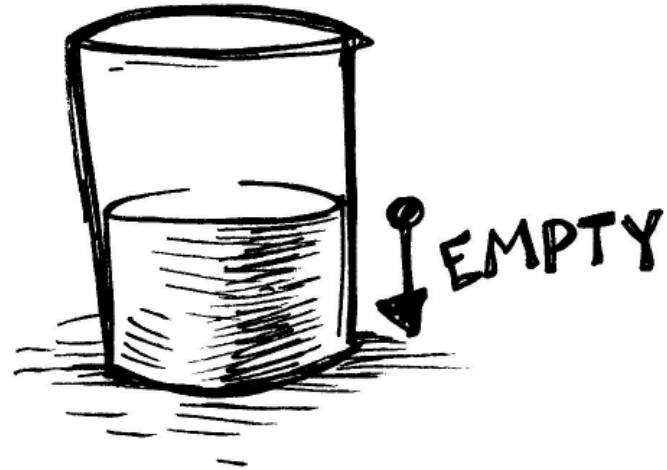
- "In 2000, tolerance enables transplants without antirejection drugs"
- "In 2003, xenografts made possible"
- "In 2008, kidneys and livers coated with recipients' genetic code purchased over the counter"

Rx 2000: Breakthroughs in Health, Medicine, and Longevity by the Year 2000 and Beyond. JH Fisher, MD, Simon & Schuster, 1992.

Dangers of predictions

Too pessimistic

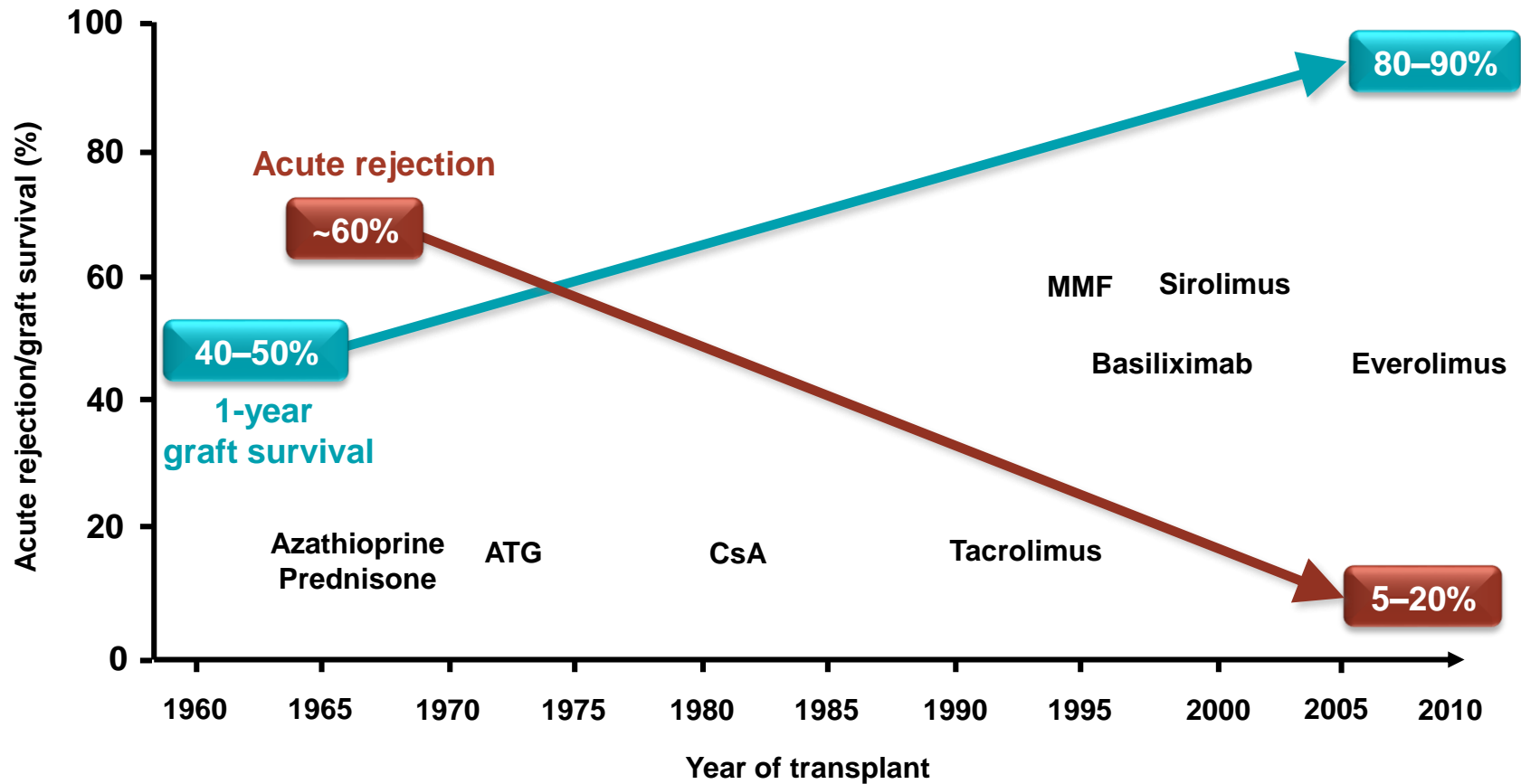
- "I think there is a world market for maybe five computers." Thomas Watson, IBM Chairman, 1943
- "There is no reason anyone would want a computer in their home." Ken Olsen, Digital Equipment CEO, 1977
- "The Internet will collapse within a year." Bob Metcalf, founder of 3M Corp., 1995



Herrick twins 1954



Amazing Accomplishments Who would have believed it?...



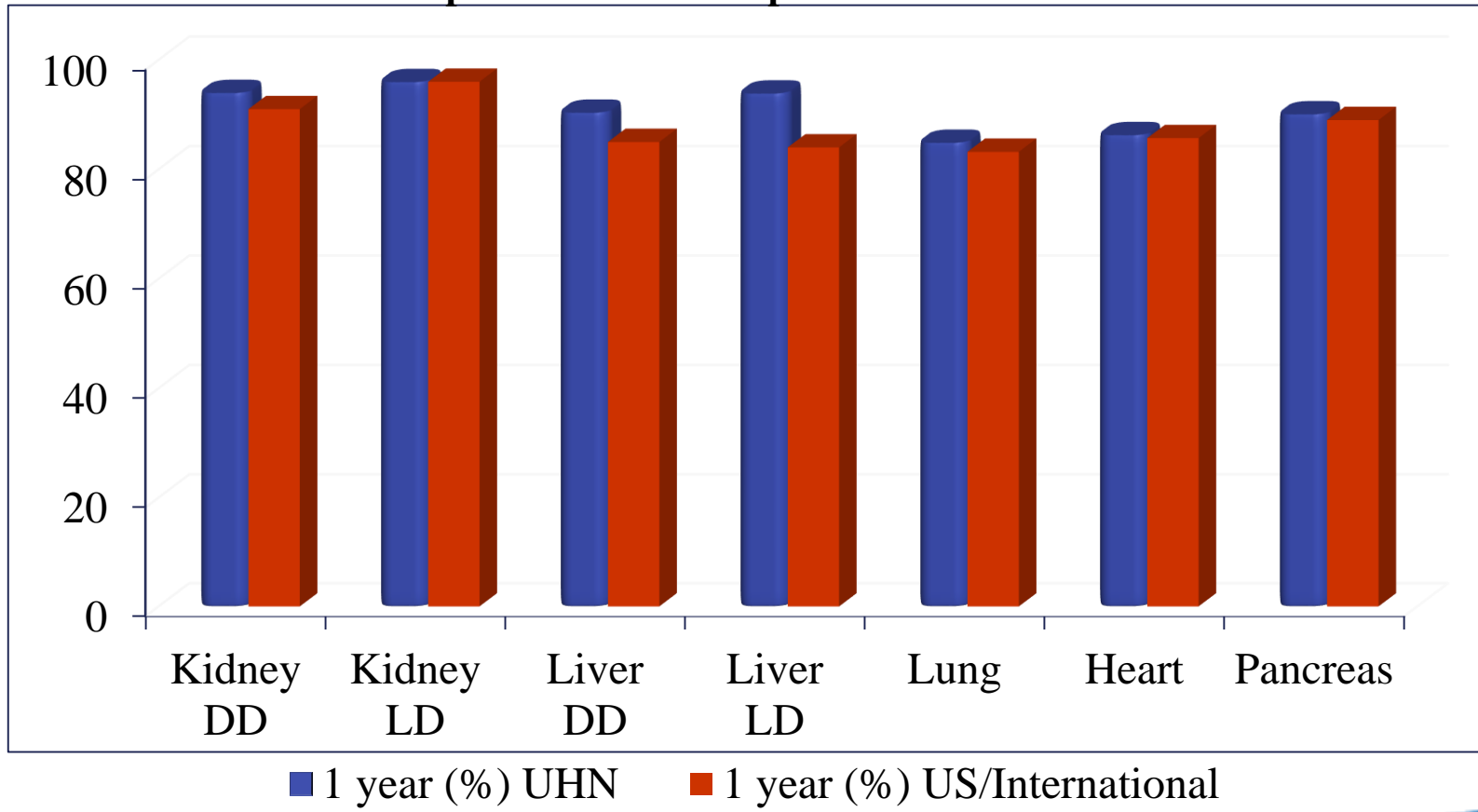
CsA, ciclosporin; ATG, anti-thymocyte globulin; MMF, mycophenolate mofetil

1. Morris PJ. *N Engl J Med.* 2004;351:2678-80; 2. Sayegh MH, et al. *N Engl J Med.* 2004;351:2761-6;

3. Khurana A, Brennan D. Current concepts of immunosuppression and side effects in *Pathology of Solid Organ Transplantation*, 2011

Benchmarking: One year Graft Survival Rate

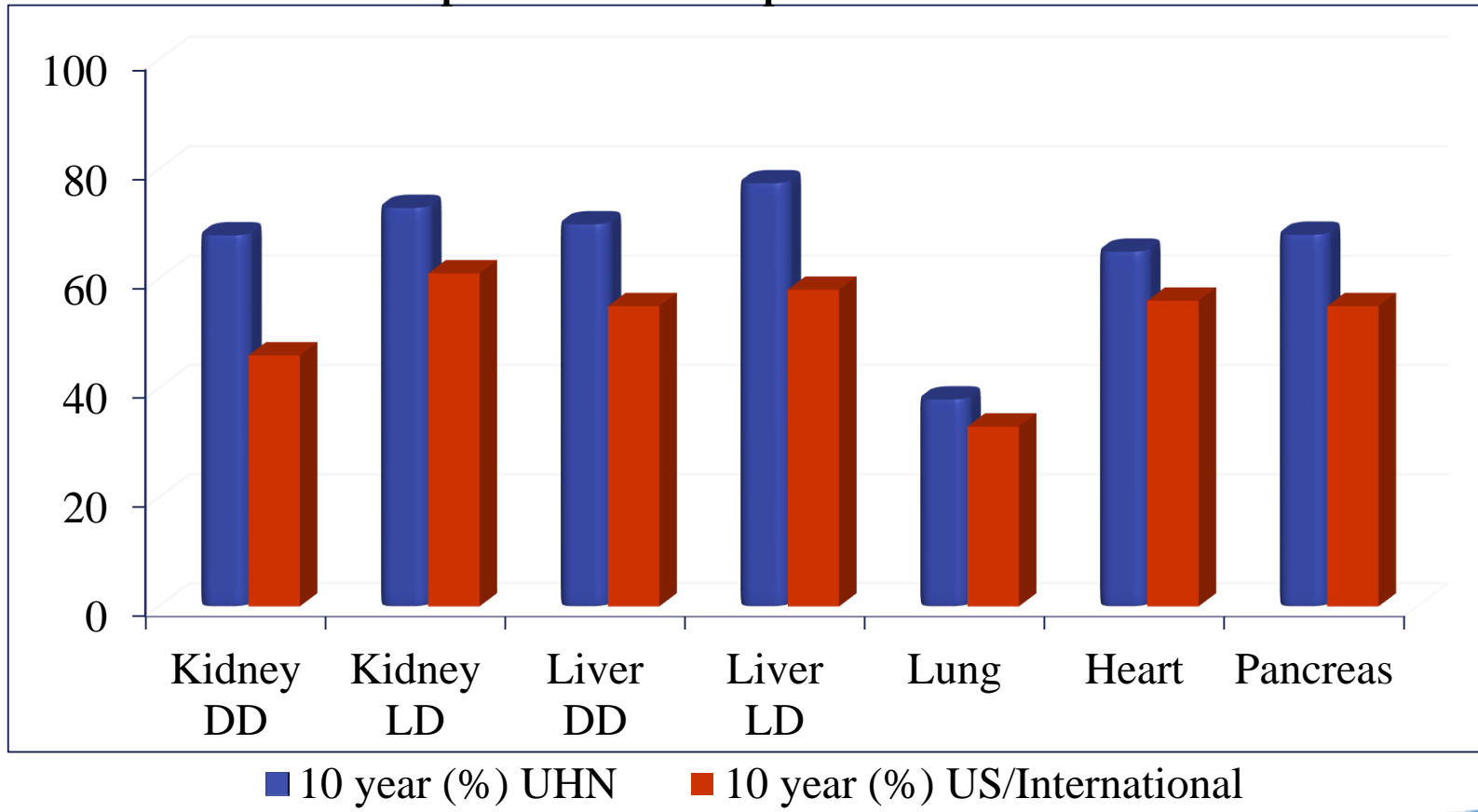
One Year Transplant Survival comparison to available benchmark



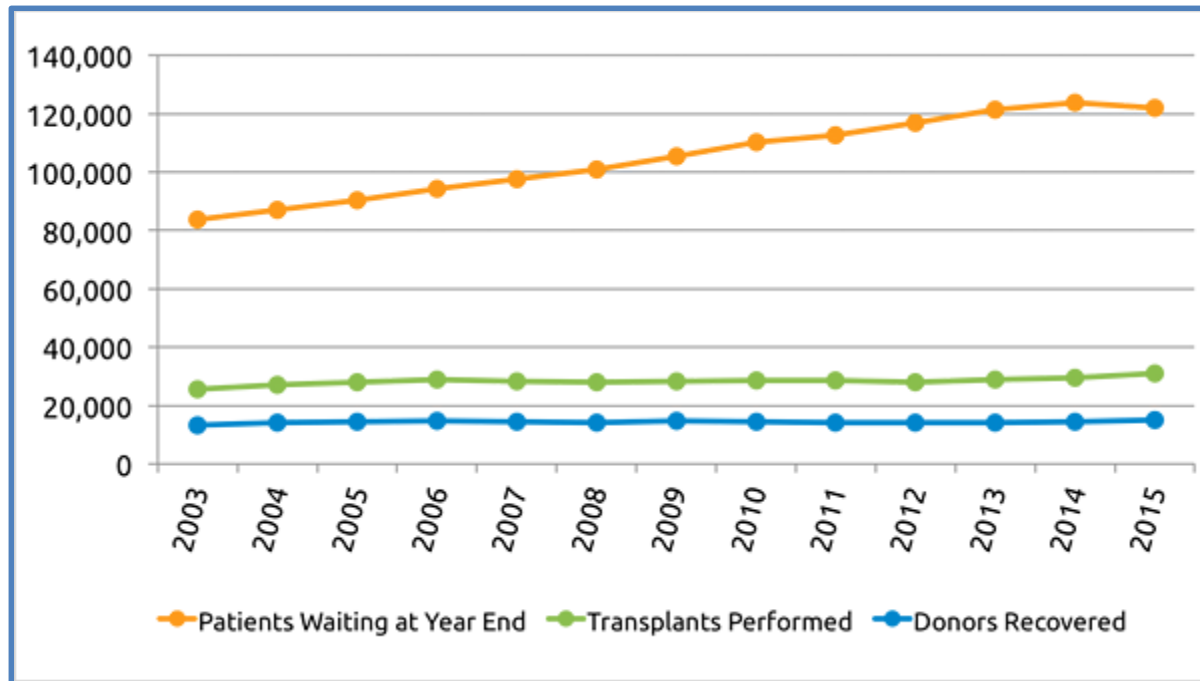
Data source: OTTR, UNOS (SRTR) and ISHLT

Benchmarking: Ten year Graft Survival Rate

Ten Year Transplant Survival comparison to available benchmark



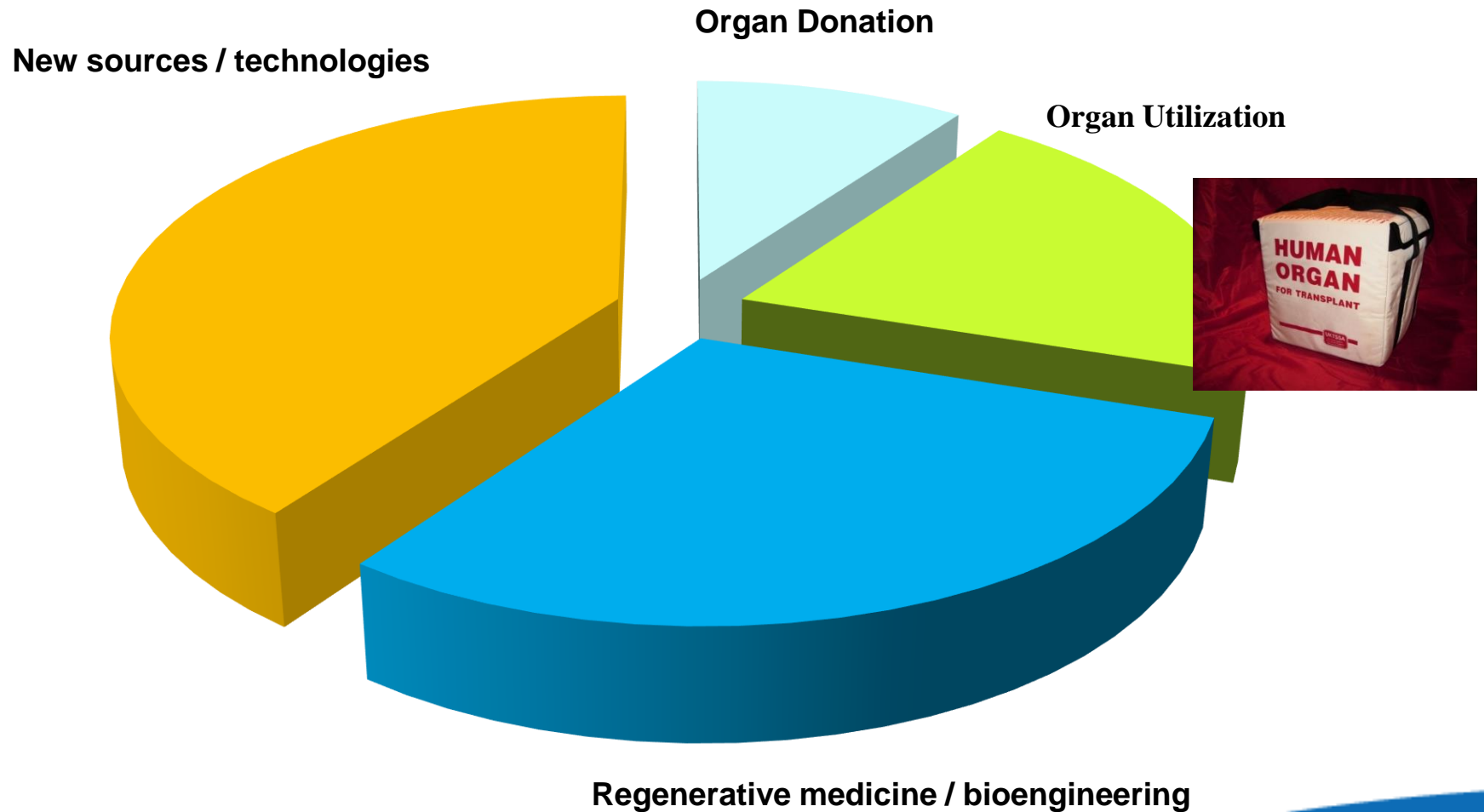
Transplant Waiting List



Will the waiting list go down with new treatments for disease?

The FUTURE OF TRANSPLANTATION

Solving organ failure



Increased availability of acceptable substitutes for failing organs to meet the demand?

Selected solutions for the future

Human organ donors

- Ex vivo normothermic perfusion
- Treatments to decrease delayed graft function

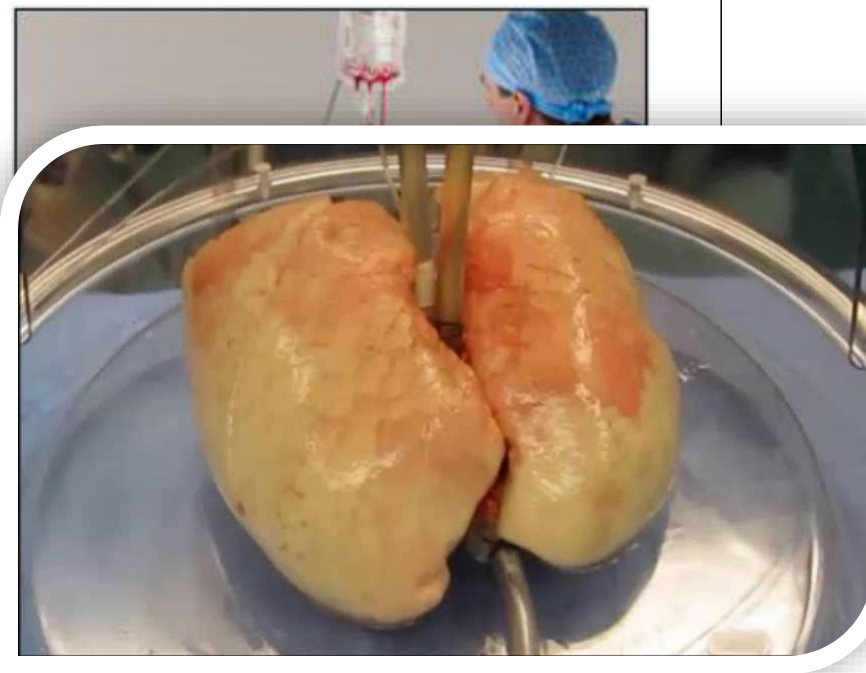
Stem cells

- Regenerate marginal organs
- Create new organs

Non-human organ donors

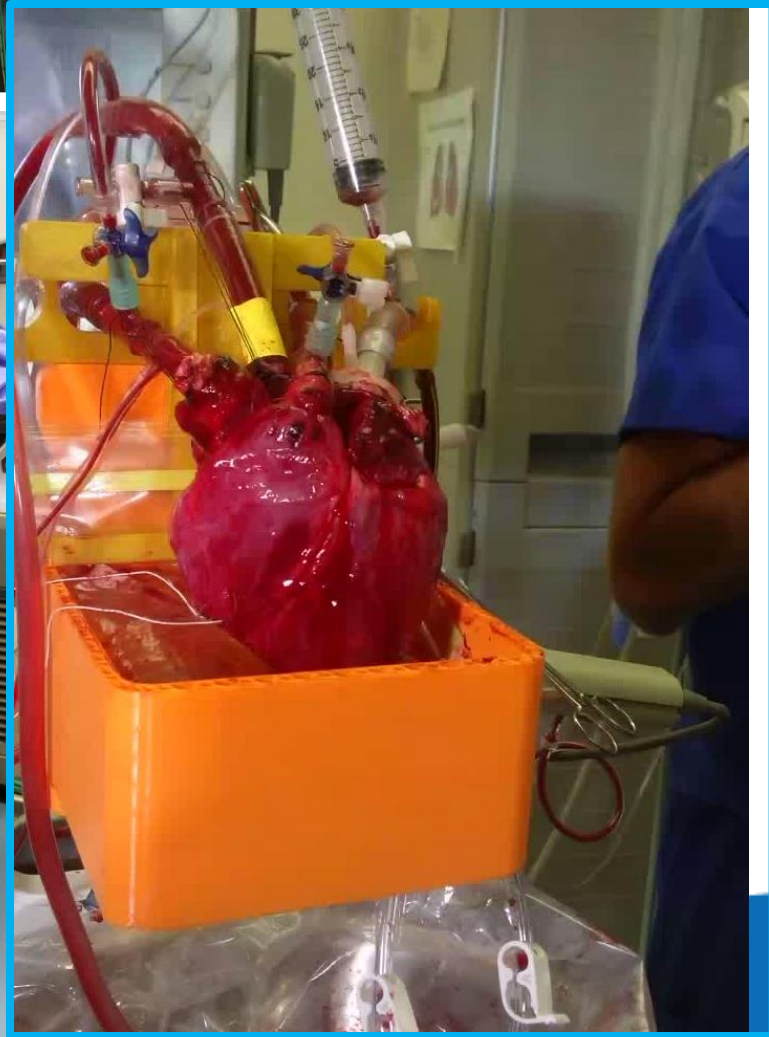
Increased availability of organs from humans: ex vivo normothermic liver perfusion (EVNP)?

- Potential advantages of EVNP:
 - Avoiding ischemia/reperfusion injury
 - Avoiding cold injury
 - Allowing viability assessment
 - Deliver other therapeutic interventions during preservation to modulate and optimize the graft before transplantation
 - Restoring function in marginal donor organs and enabling the clinician to appraise its viability, expand the donor pool

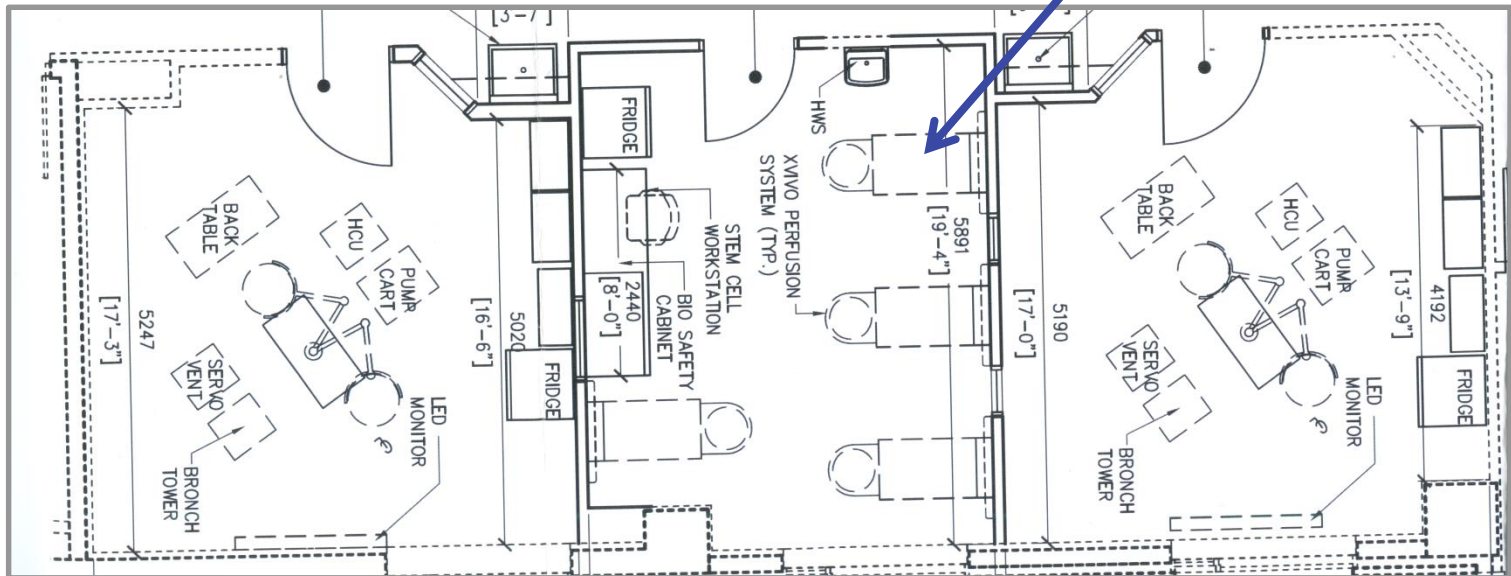


Vogel T, et al. *Transplant Rev* . 2012;26:156–162.

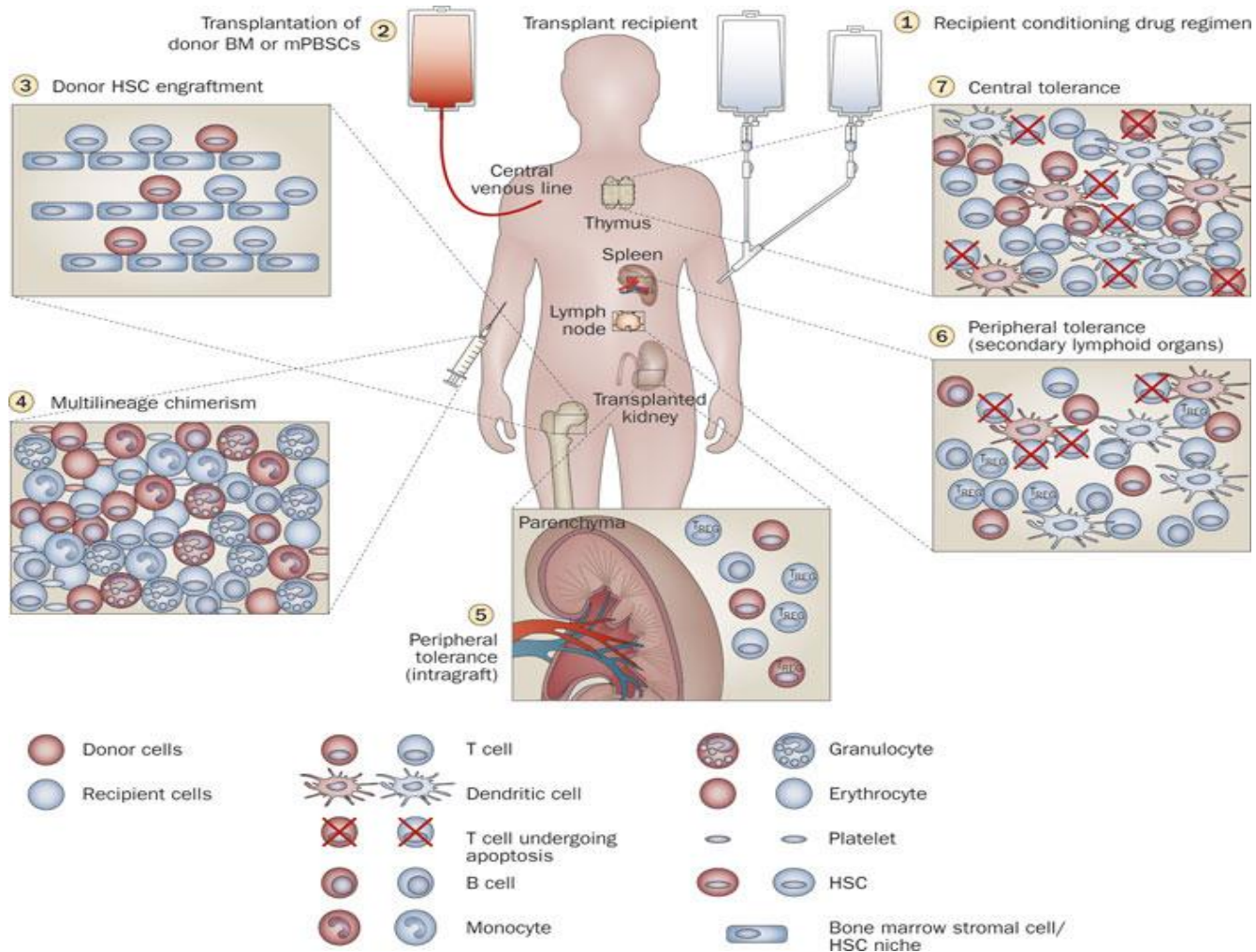
<http://www.organox.com/products/organ-perfusion/> Accessed 12 April 2014.



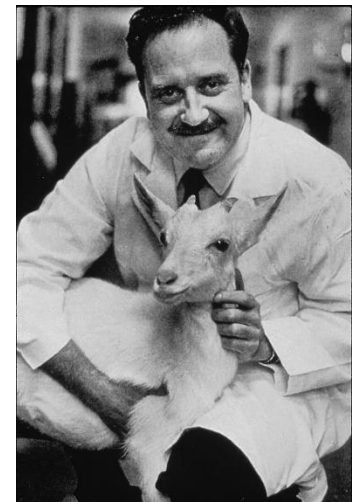
Organ Repair Lab



The Holy Grail..Immune Tolerance

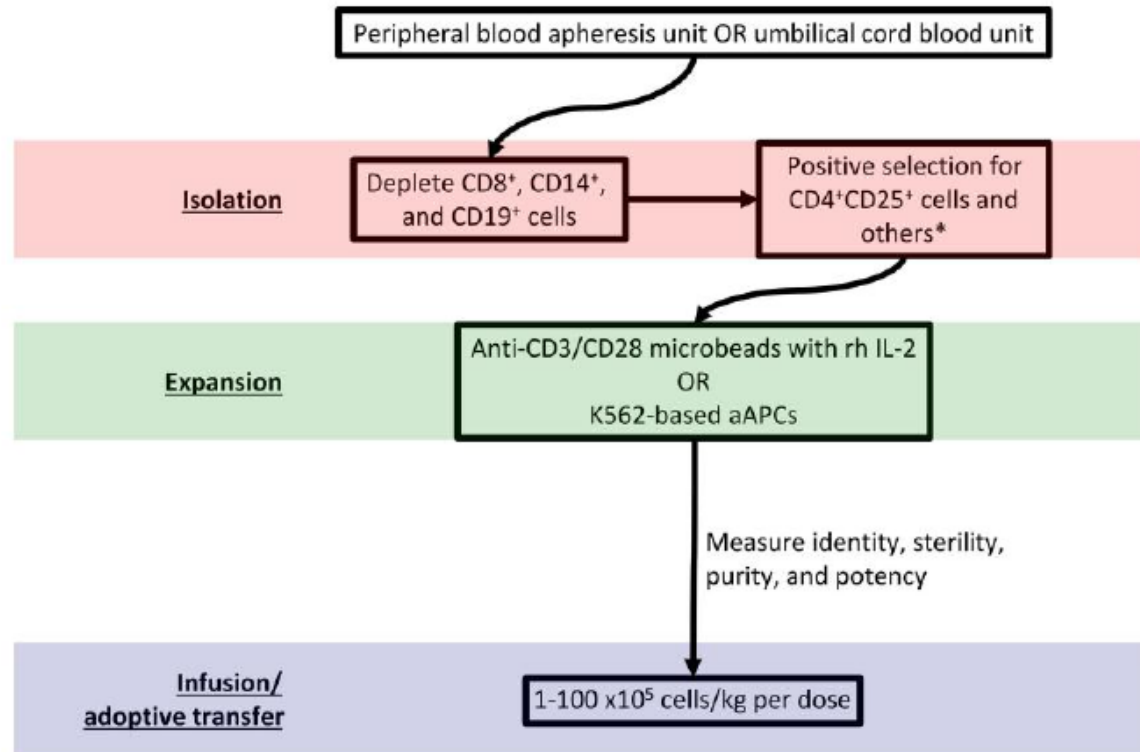


Ray Owen



More effective, safer, and less complex therapies to extend organ and recipient transplant survival times: regulatory T cells?

Schematic of a strategy to isolate, expand, and infuse Tregs¹



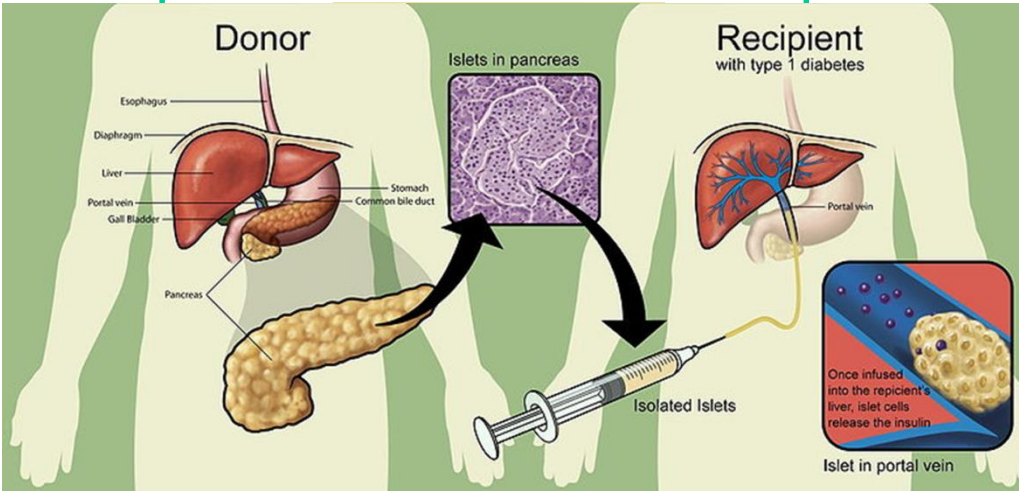
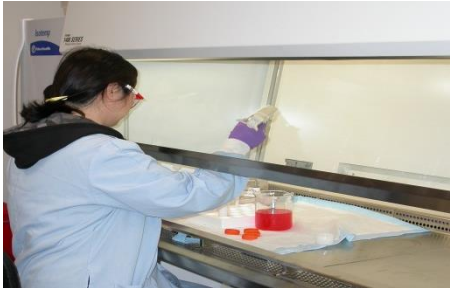
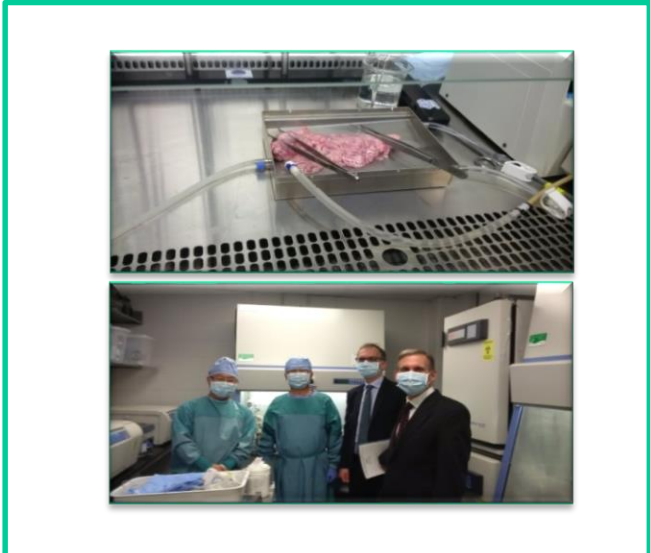
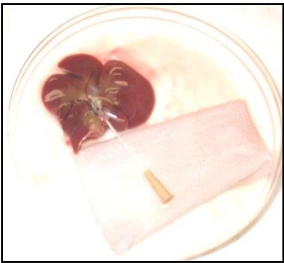
- Tregs suppress acute GVHD in HLA-identical HSCT²

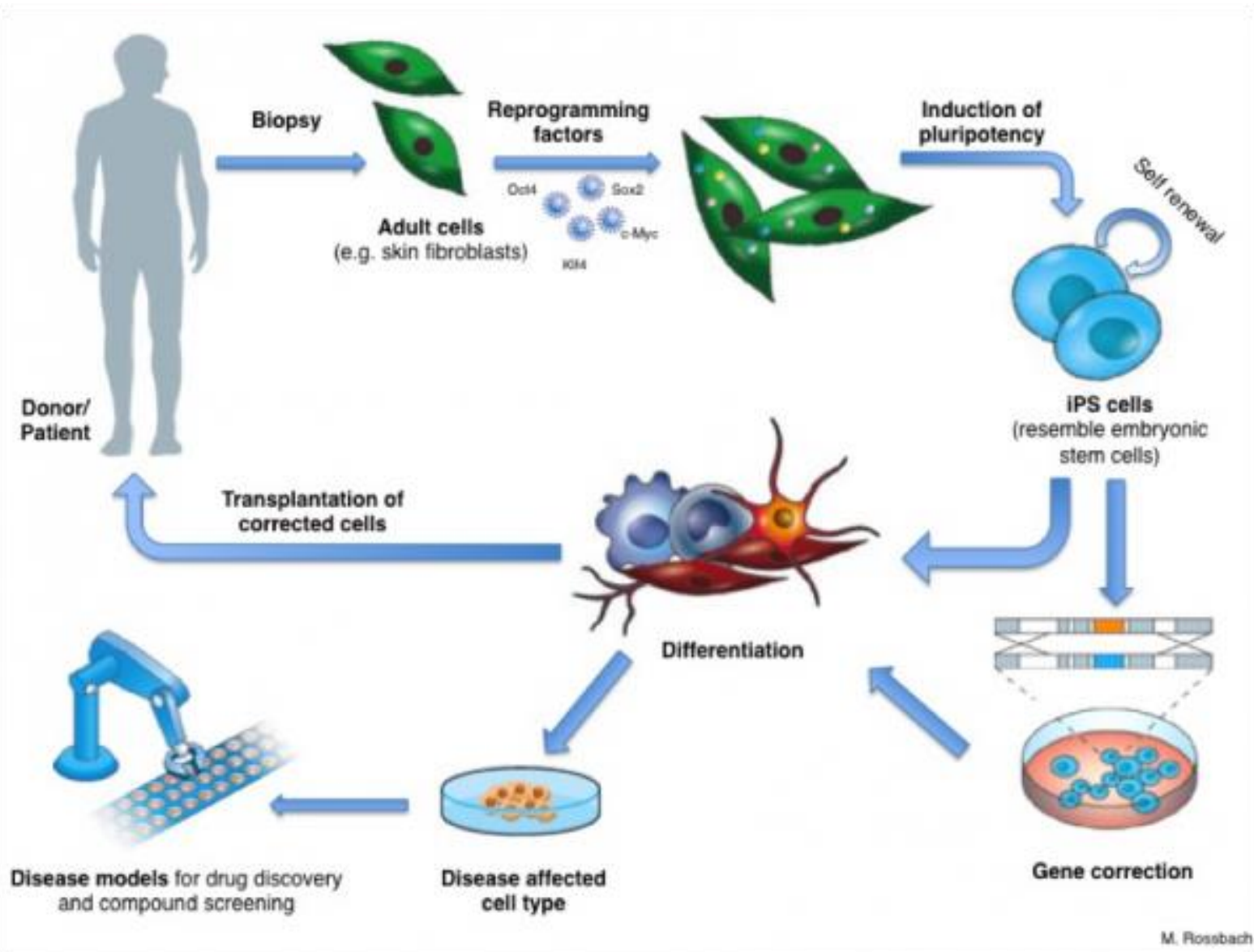
GVHD, graft versus host disease; HSCT, hematopoietic stem cell transplantation.

1. Singer BD, et al. *Front Immunol*. 2014 Feb 11;5:46; 2. Di Ianni M, et al. *Blood*. 2011;117:3921–3928.

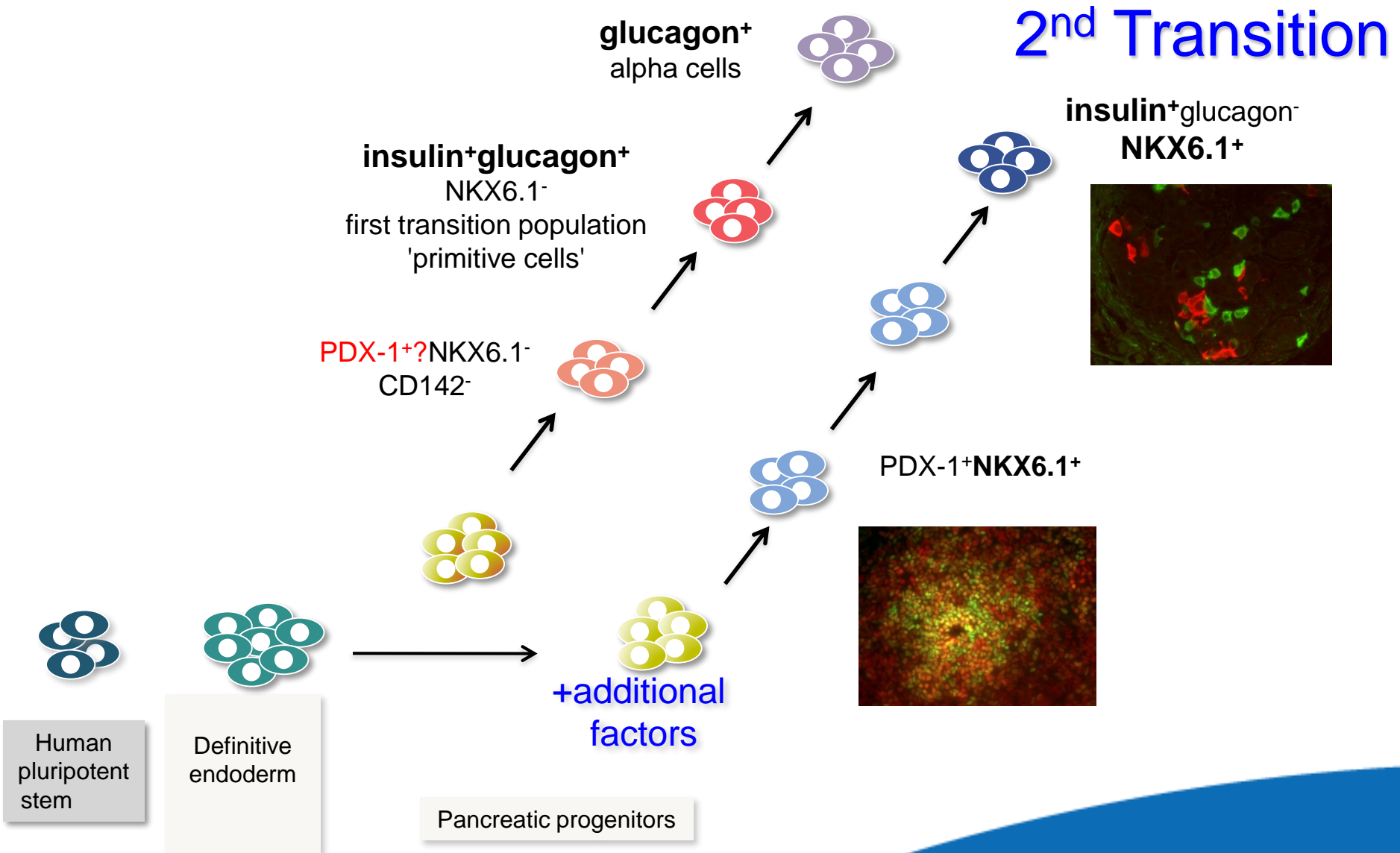
Regenerative medicine:

Cellular Transplantation, stem cells, bioengineering

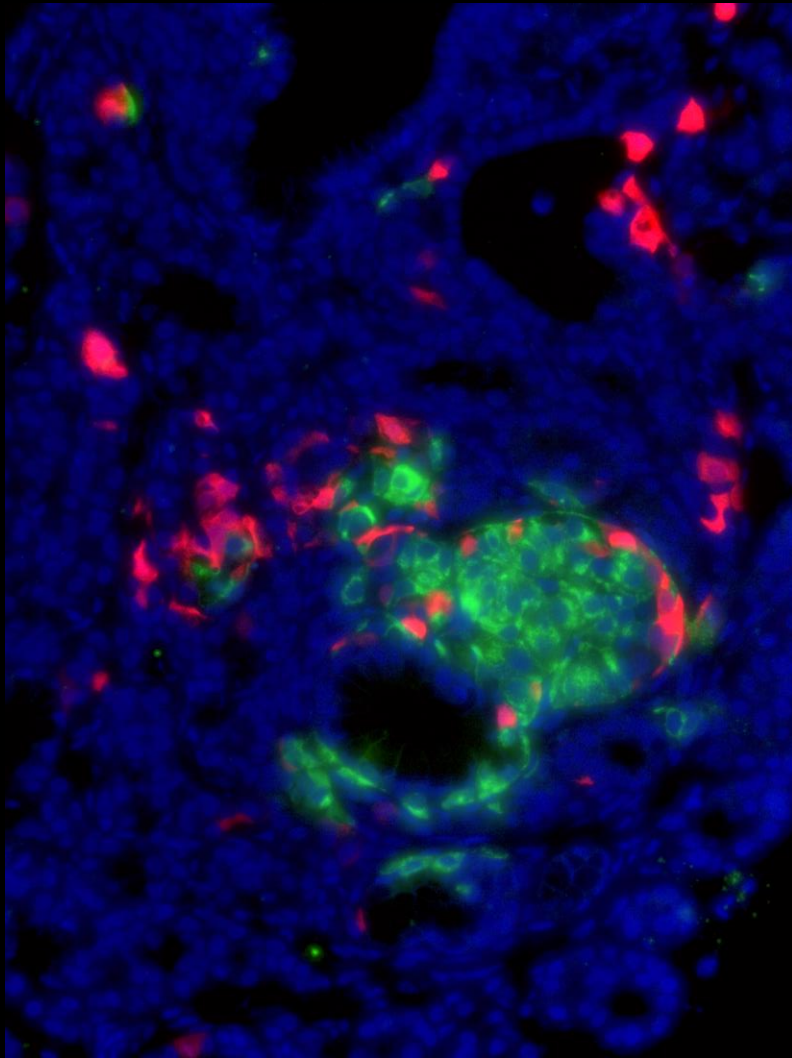




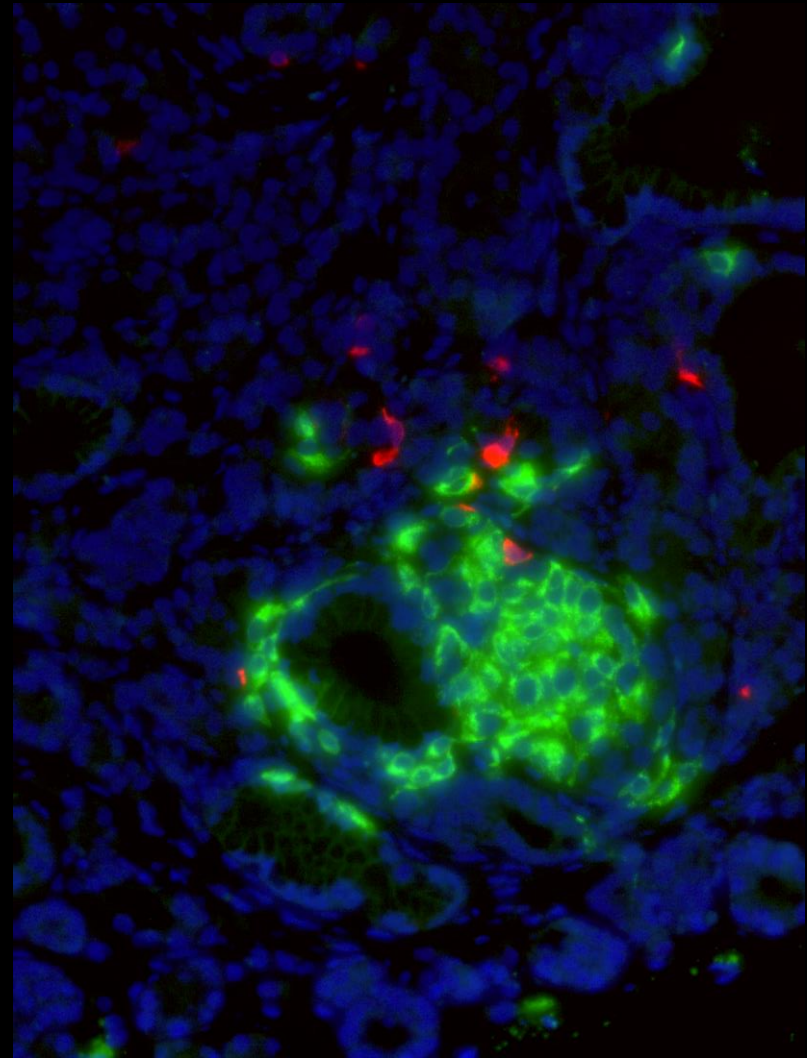
Scheme of beta cell development



Islet structures derived from human ESCs



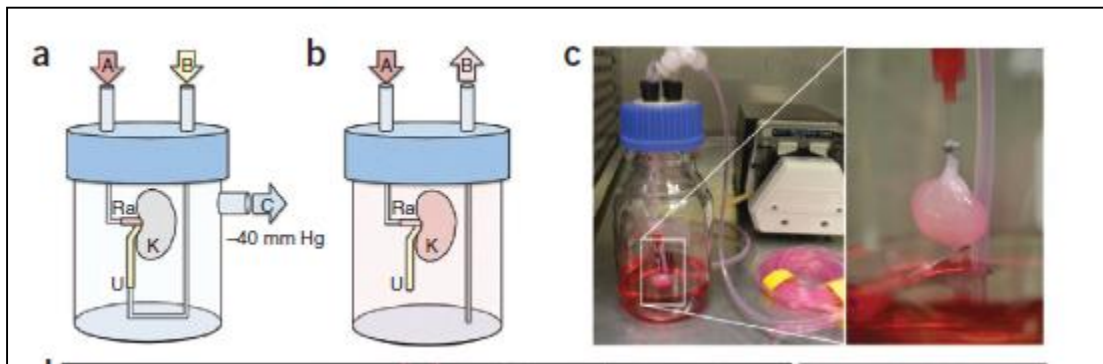
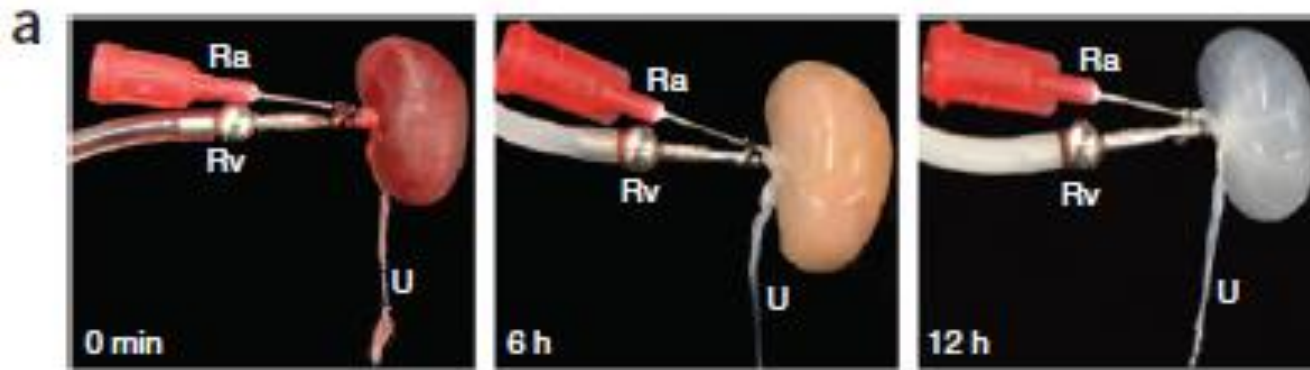
INS GCG DAPI



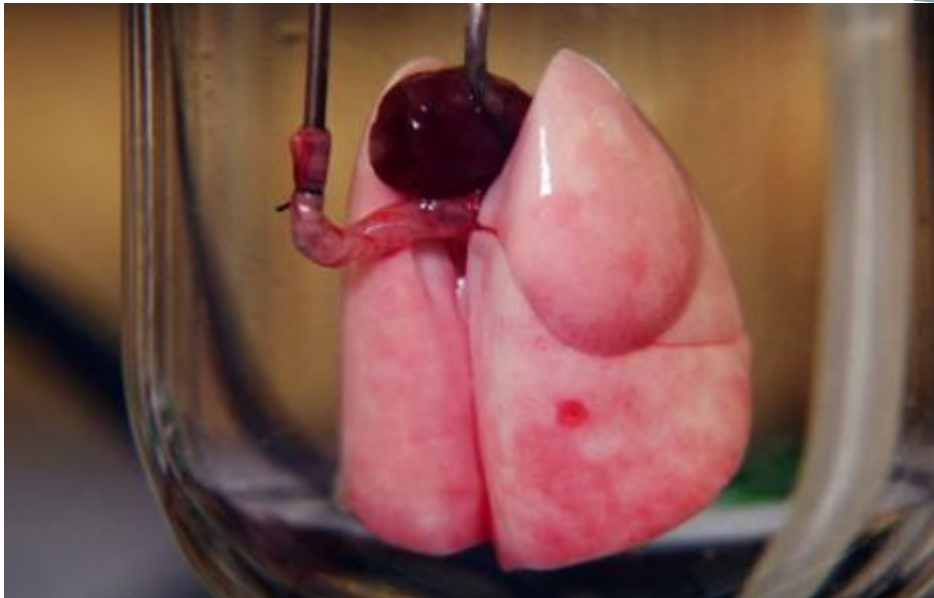
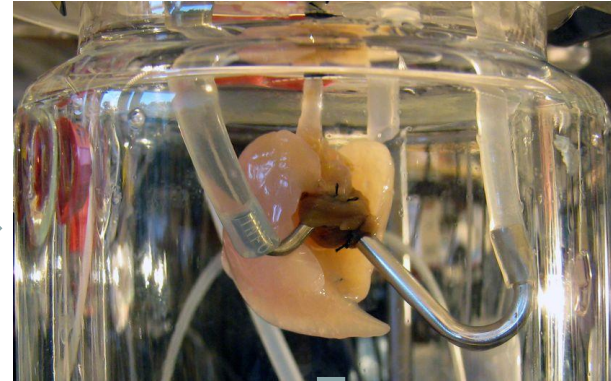
INS SST DAPI

Regeneration and experimental orthotopic transplantation of a bioengineered kidney

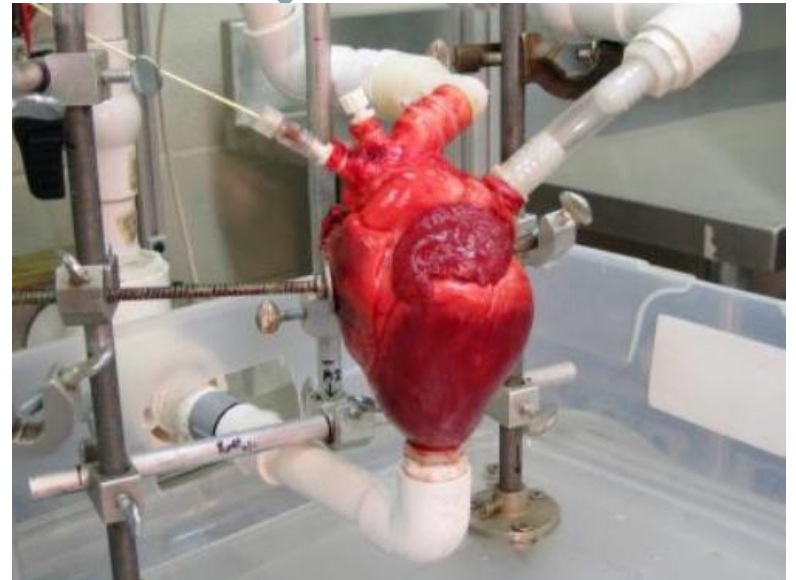
Jeremy J Song^{1,2}, Jacques P Guyette^{1,2}, Sarah E Gilpin^{1,2}, Gabriel Gonzalez^{1,2}, Joseph P Vacanti¹⁻³ & Harald C Ott^{1,2,4}



Decellularize: perfusion with detergents and phosphate buffered saline
Recellularize: epithelial and endothelial cell seeding followed by transplantation



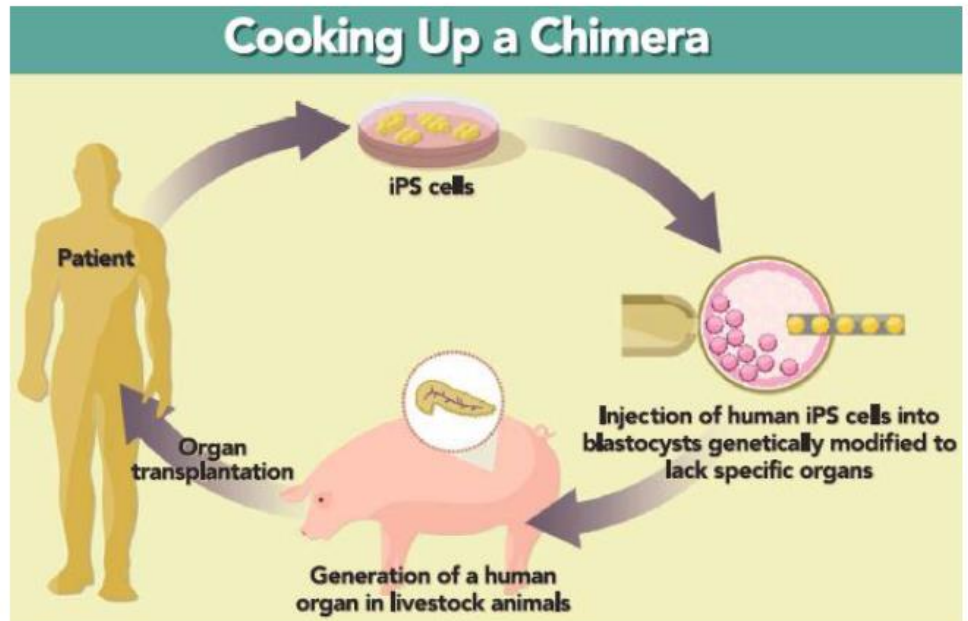
Ott, H. Nature Medicine, 2010



Ott, H. Nature Medicine, 2008

BLASTOCYST COMPLEMENTATION: INTERSPECIES ORGANOGENESIS

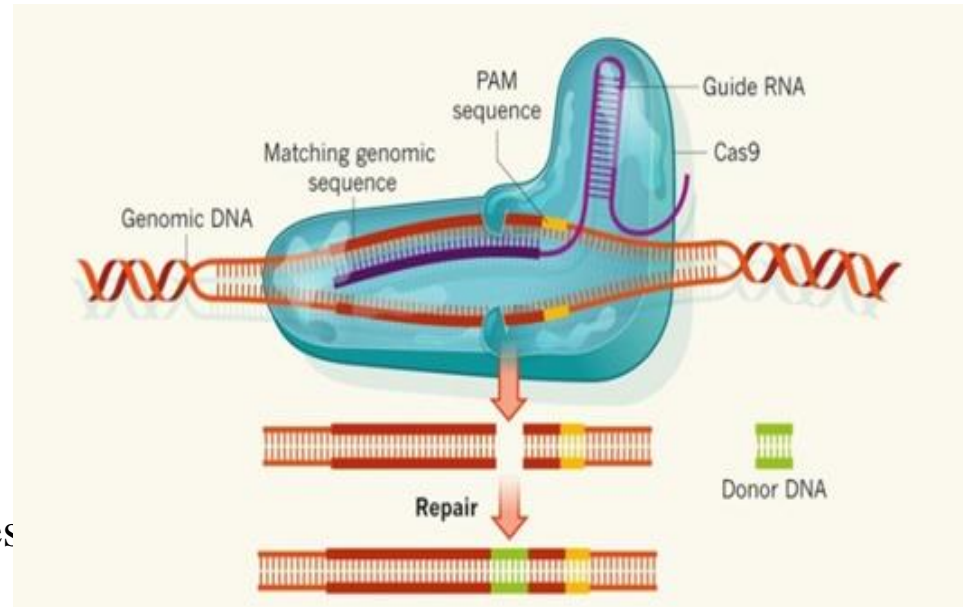
- Implant human induced pluripotent stem (iPS) cells from prospective transplant recipients in pig embryos incapable of developing a pancreas¹
- Human pancreas could be developed and used as source of islets for diabetic recipient²
- However, even autologous stem cells are immunogenic and can be rejected without immunosuppression³



1. Normile D. *Science*. 2013;340:1509; 2. Matsunari H, et al. *Proc Natl Acad Sci U S A*. 2013;110:4557–4562; 3. de Almeida PE et al. *Circulation Research*. 2013;112:549–561.

What is CRISPR?

- Genome-editing tool originally discovered in prokaryotes
- Consist of specialized guide RNAs (crRNAs) that are linked to a nuclease (cas9)
- crRNAs are complimentary to target regions of the genome
- If annealing takes place, nuclease causes double stranded breaks in DNA
- Gene inactivation



Cite as: D. Niu *et al.*, *Science*
10.1126/science.aan4187 (2017).

Inactivation of porcine endogenous retrovirus in pigs using CRISPR-Cas9

Dong Niu,^{1,2*} Hong-Jiang Wei,^{3,4*} Lin Lin,^{5*} Haydy George,^{1*} Tao Wang,^{1*} I-Hsiu Lee,^{1*} Hong-Ye Zhao,³ Yong Wang,⁶ Yinan Kan,¹ Ellen Shrock,⁷ Emal Lesha,¹ Gang Wang,¹ Yonglun Luo,⁵ Yubo Qing,^{3,4} Deling Jiao,^{3,4} Heng Zhao,^{3,4} Xiaoyang Zhou,⁶ Shouqi Wang,⁸ Hong Wei,⁶ Marc Güell,^{1,7,9,†} George M. Church,^{1,7,9,†} Luhan Yang^{1,†,‡}

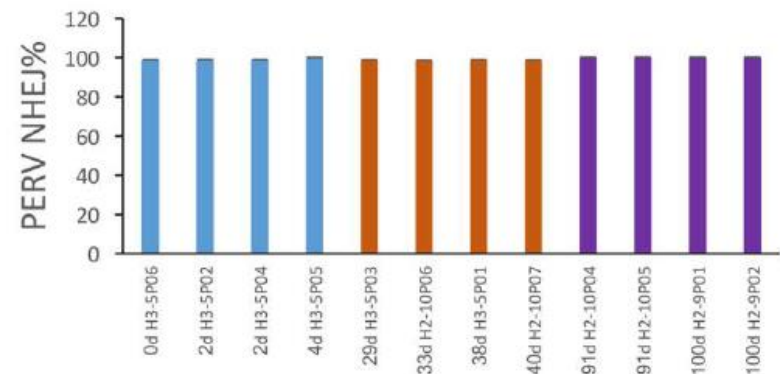
¹eGenesis, Inc., Cambridge, MA 02139, USA. ²College of Animal Sciences, Zhejiang University, Hangzhou 310058, China. ³State Key Laboratory for Conservation and Utilization of Bio-Resources in Yunnan, Yunnan Agricultural University, Kunming 650201, China. ⁴College of Animal Science and Technology, Yunnan Agricultural University, Kunming, 650201, China. ⁵Department of Biomedicine, Aarhus University, 8000 Aarhus C, Denmark. ⁶Department of Laboratory Animal Science, College of Basic Medical Sciences, Third Military Medical University, Chongqing, 400038, P. R. China. ⁷Department of Genetics, Harvard Medical School, Boston, MA 02115, USA. ⁸Research Institute of Shenzhen Jinxinnong Technology CO., LTD., Shenzhen 518106, China. ⁹Wyss Institute for Biologically Inspired Engineering, Harvard University, Cambridge, MA 02138, USA.

A




(A) Image of the first born PERV-inactivated pig (B) PERV inactivation at genomic DNA level

B

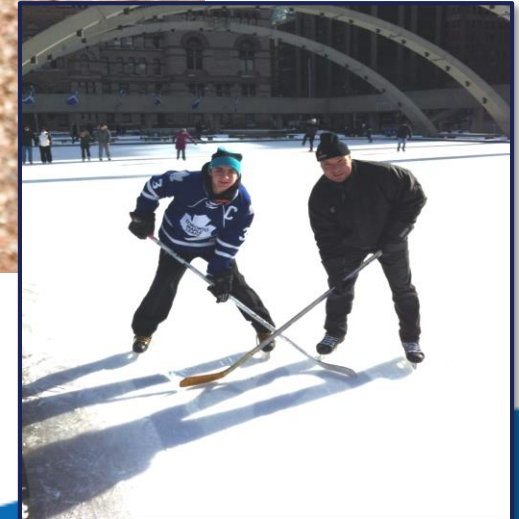
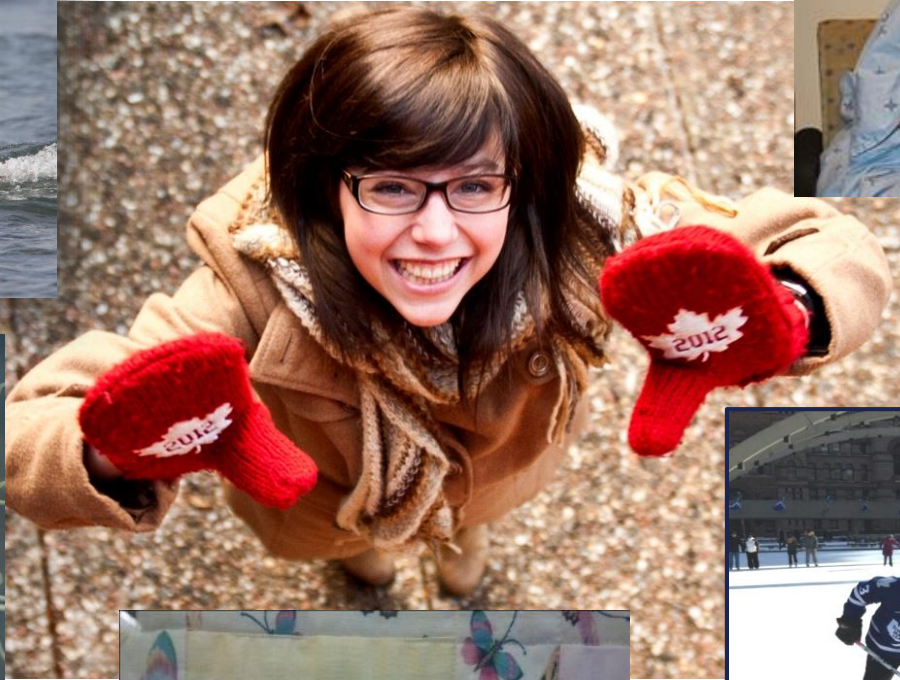


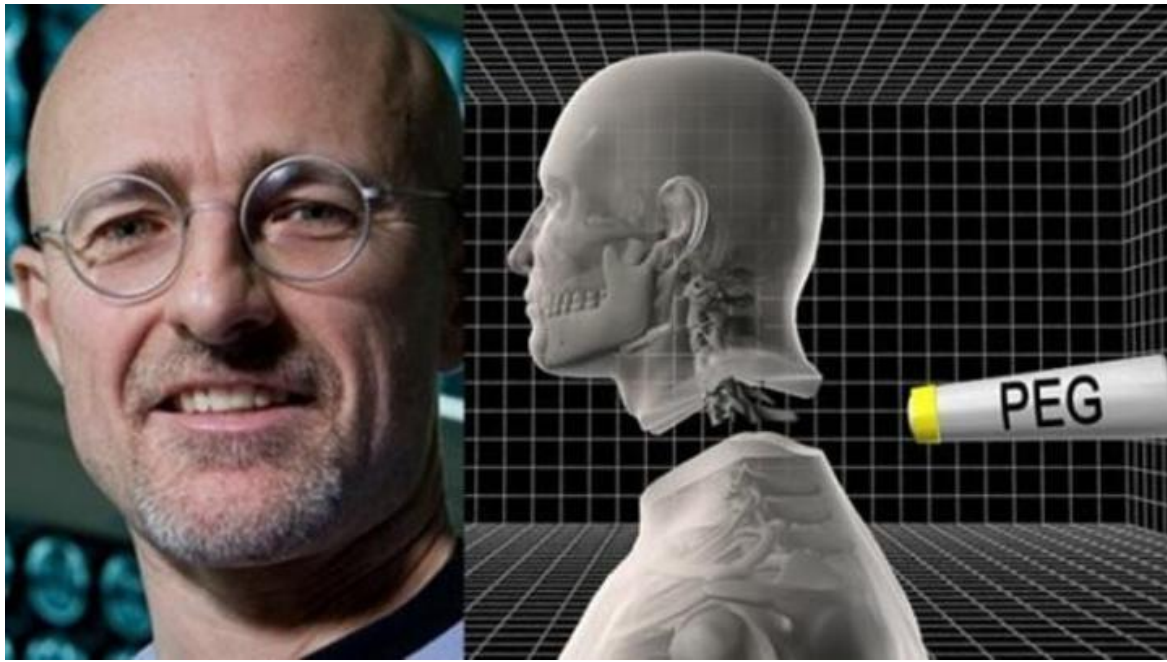
Transplantation-The Future

- **First 50 years of Transplantation (1960-2010)**
 - Solid organ transplantation (SOT) is now recognized as a highly effective therapy for patients with end stage organ injury.
 - **The next 50 years in Transplantation**
 - Opportunities to solve organ donor shortage
 - Tolerance is achievable..at least in some
 - New Technologies offer unparalleled opportunities... specifically the Regenerative Medicine field is poised to revolutionize all aspects of medicine
 - Research Funding is now improving both for basic and translational research programs
- 

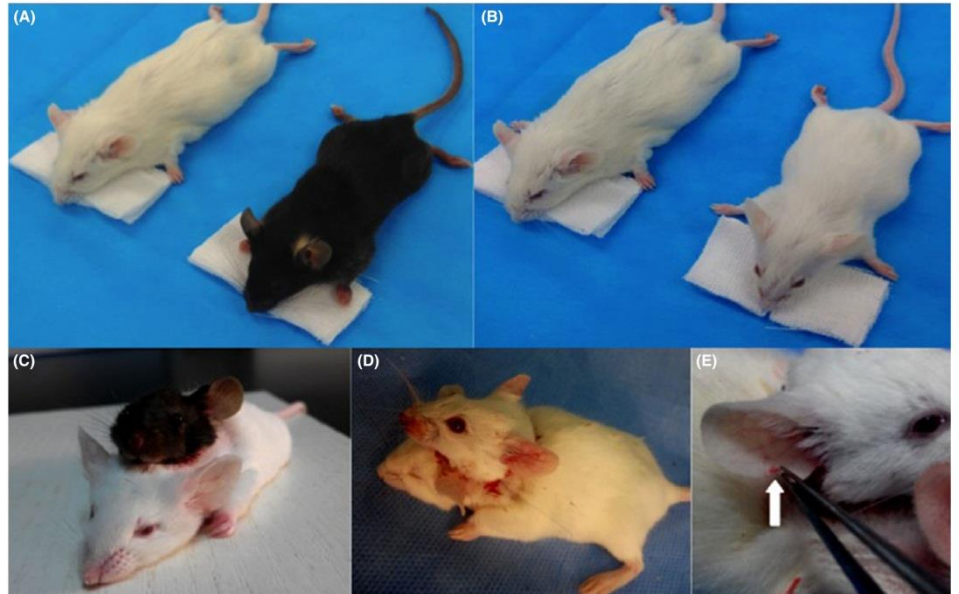
Thanks you!

Questions?





<http://hqgrandeprairie.com/health/human-head-transplant-crazy-gamble/024939>



ORIGINAL ARTICLE

CNS Neuroscience & Therapeutics

Head Transplantation in Mouse Model

Xiao-Ping Ren,^{1,2,3} Yi-Jie Ye,^{1,2} Peng-Wei Li,^{1,2} Zi-Long Shen,^{1,2} Ke-Cheng Han^{1,2} & Yang Song^{1,2}

¹ Hand and Microsurgical Center, The Second Affiliated Hospital of Harbin Medical University, Harbin, China
² State-Province Key Laboratories of Biomedicine-Pharmaceutics, Harbin Medical University, Harbin, China
³ Department of Molecular Pharmacology & Therapeutics, Stritch School of Medicine, Loyola University Chicago, Chicago, IL, USA