Regenerative Medicine: Challenges and Opportunities in Nephrology

The National Academies of Sciences, Engineering and Medicine

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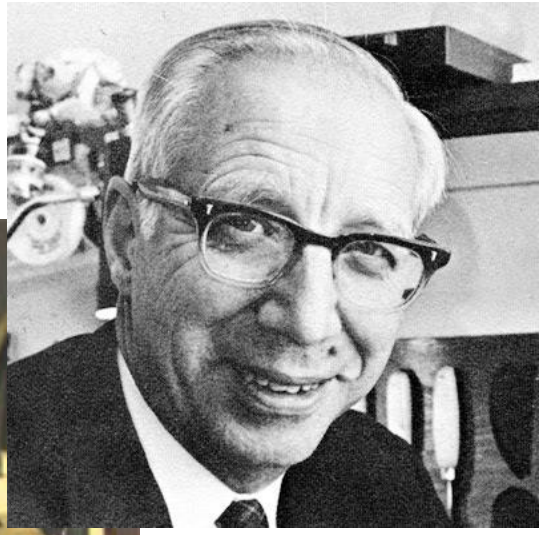
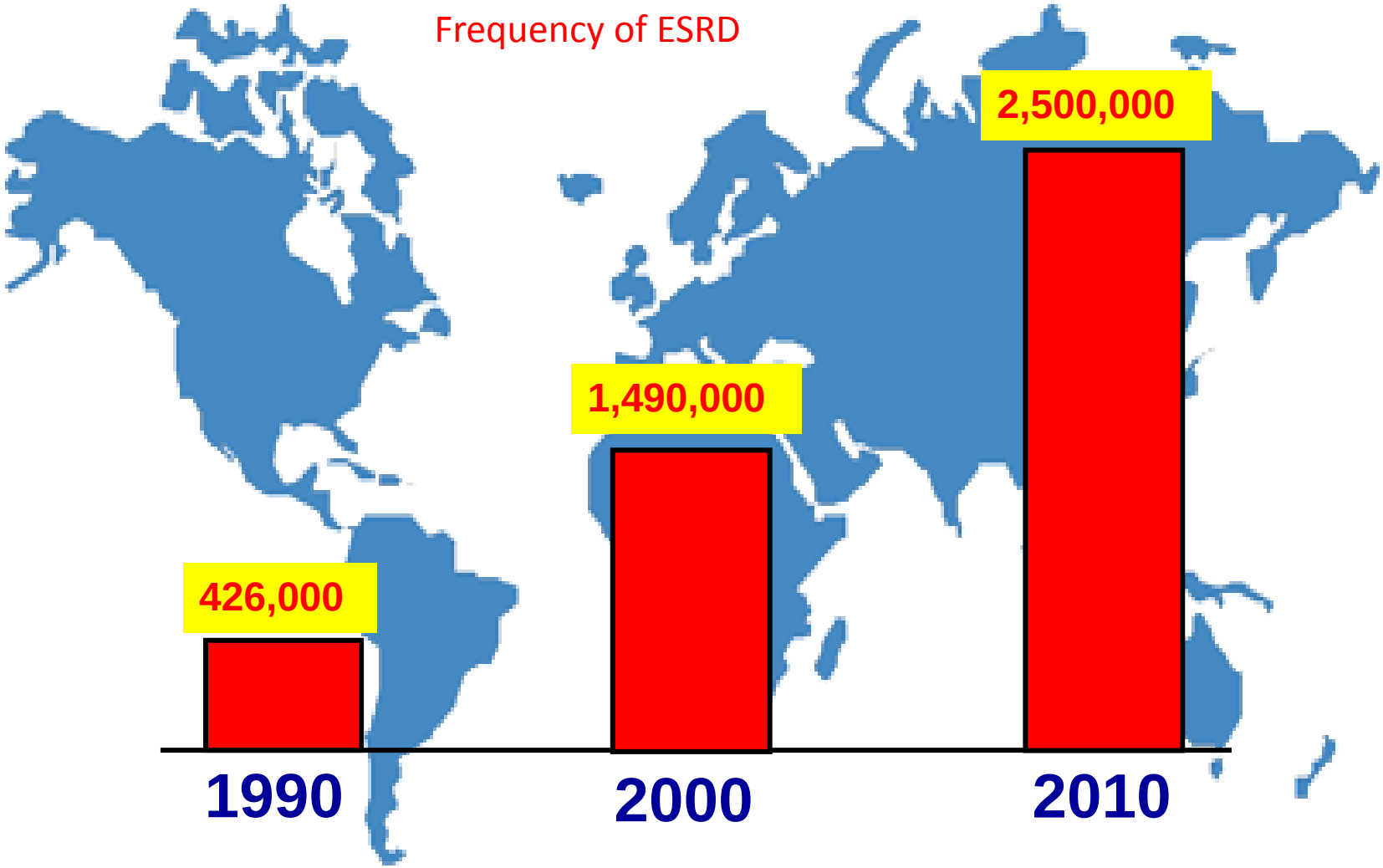
The First Artificial Organ: 1945



Willem Kolff, MD

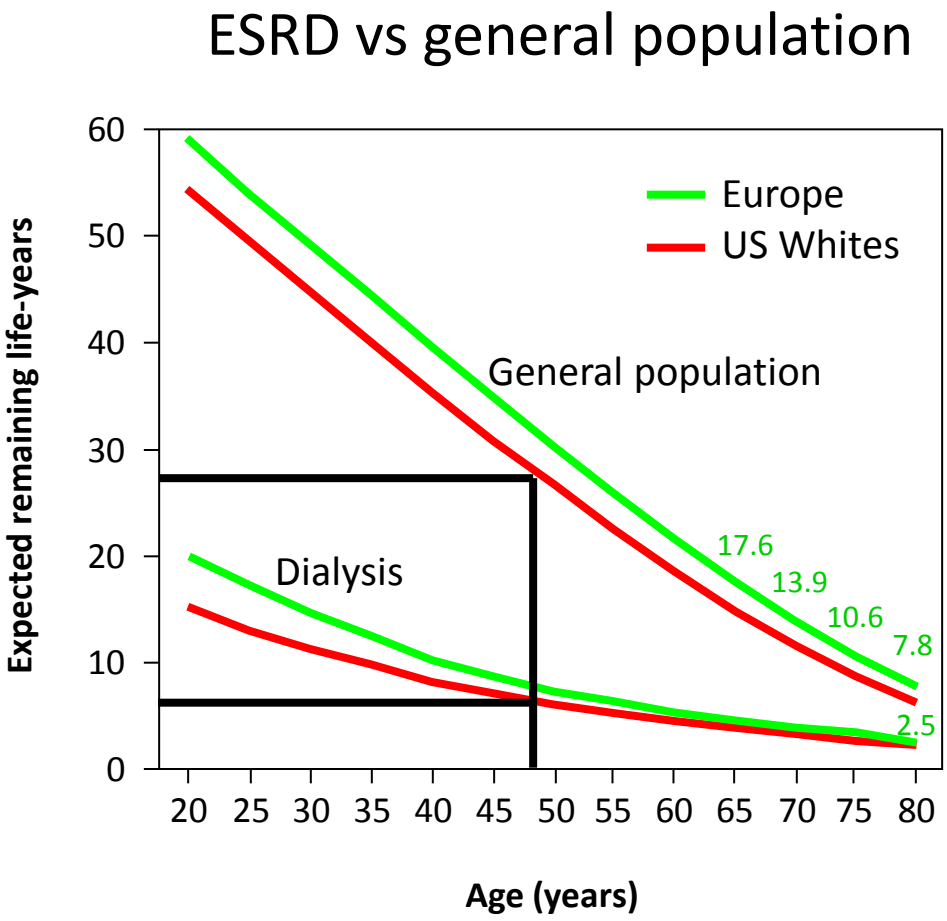
Hemodialysis Today

ESRD is increasingly common worldwide



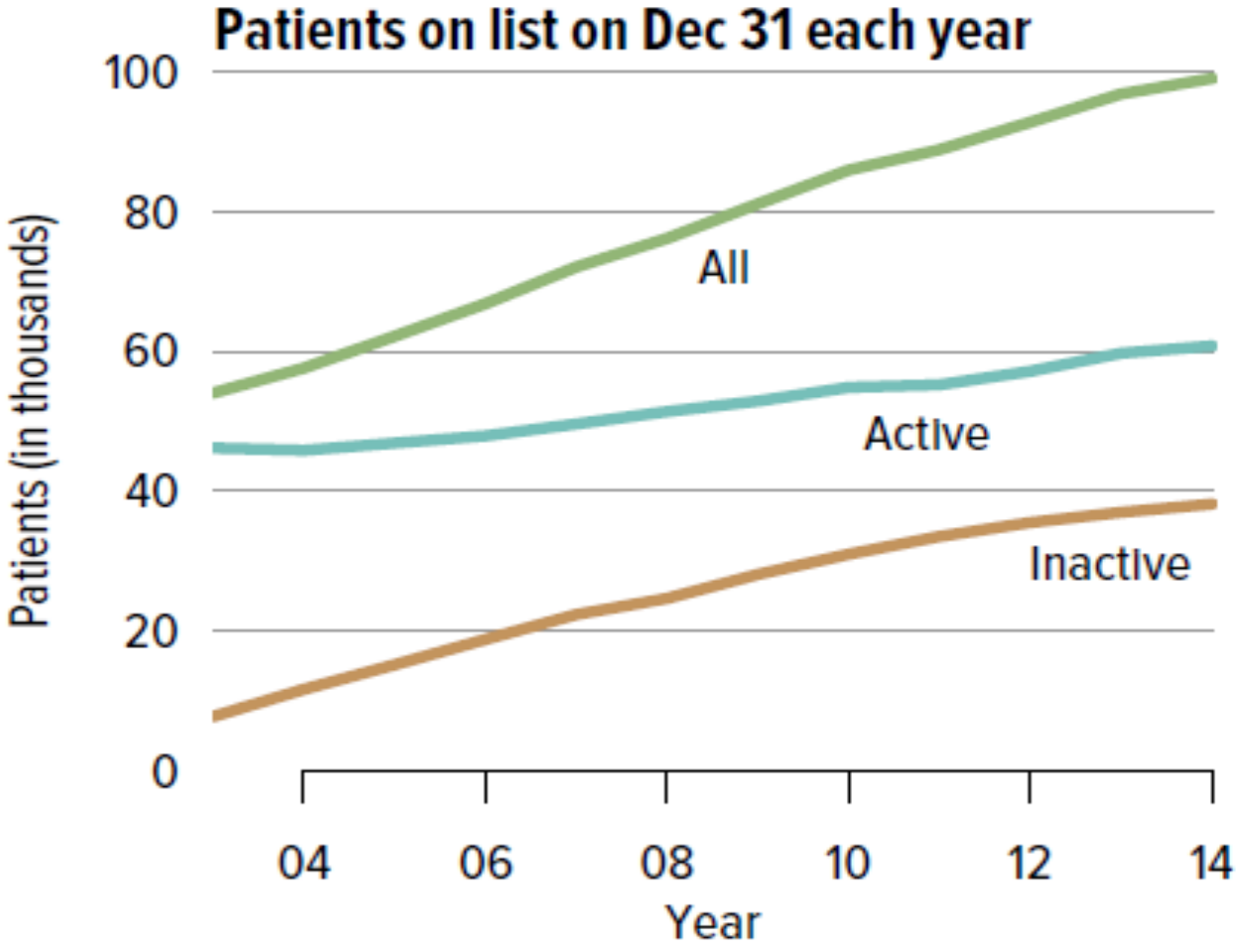
Lysaght, J Am Soc Nephrol, 2002

ESRD: Exceedingly high mortality



Jager, from ERA-EDTA and USRDS data
Alberta Kidney Disease Network, unpublished data

Transplantation is Wonderful – But Not Entire Answer



Hart et al. OPTN/SRTR 2014 ANNUAL DATA REPORT, 2016, AJT

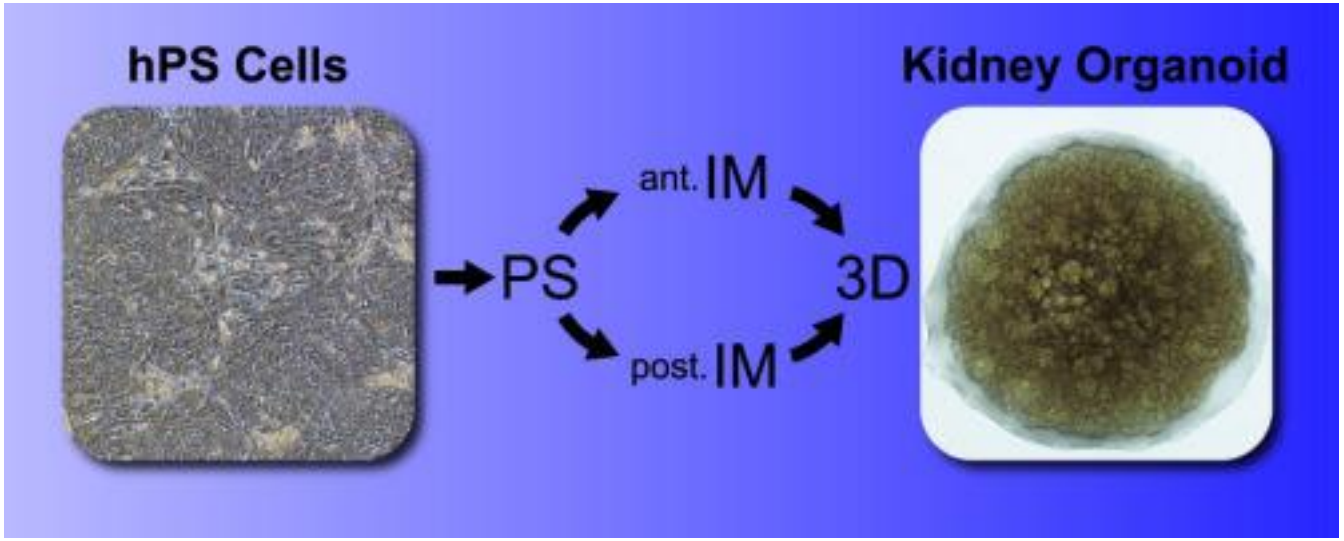
Why do we lack therapies to prevent ESRD?

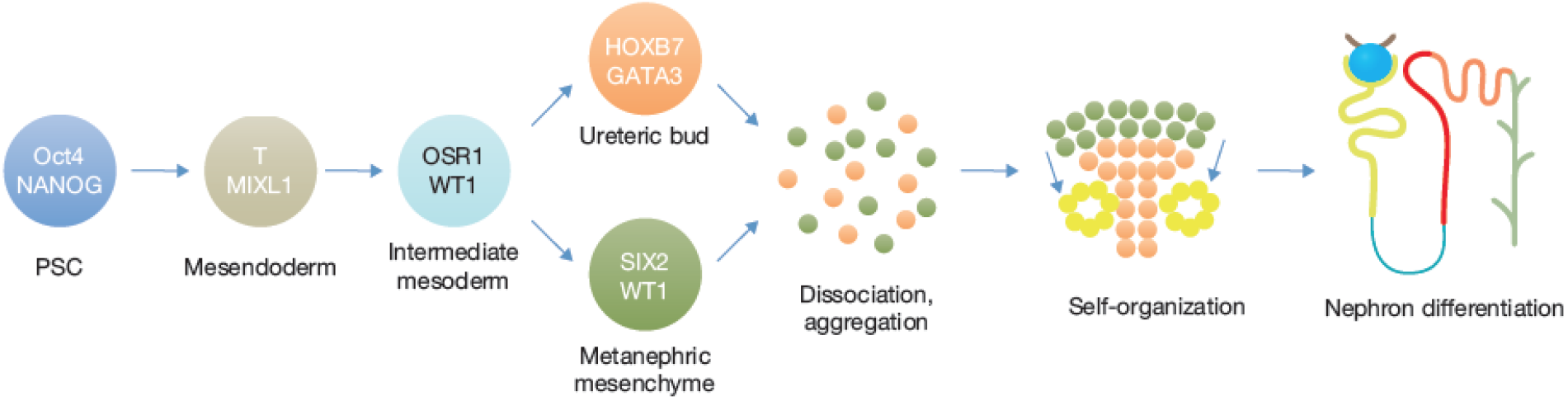
Underinvestment?

Disease (US Prevalence)	2013 Budget	% of 2013 NIH Budget	NIH Spending per Patient
HIV/AIDS (1 million)	$2,898,000,000	10%	$2,898
Cancer (14 million)	$7,477,000,000	26%	$534
Alzheimer's (5 million)	$504,000,000	2%	$101
Heart Disease (27 million)	$1,634,000,000	6%	$61
Diabetes (26 million)	$1,007,000,000	3%	$39
Kidney Disease (20 million)	$591,000,000	2%	$30

Am J Public Health 2016

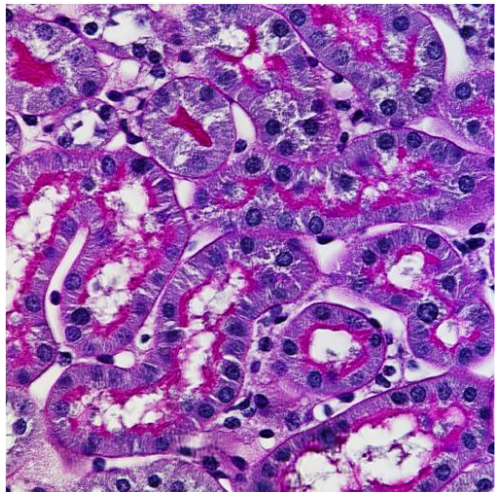
Re-Building a Kidney from hPS

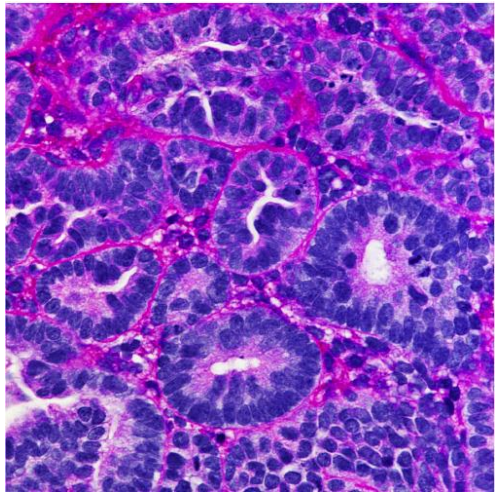


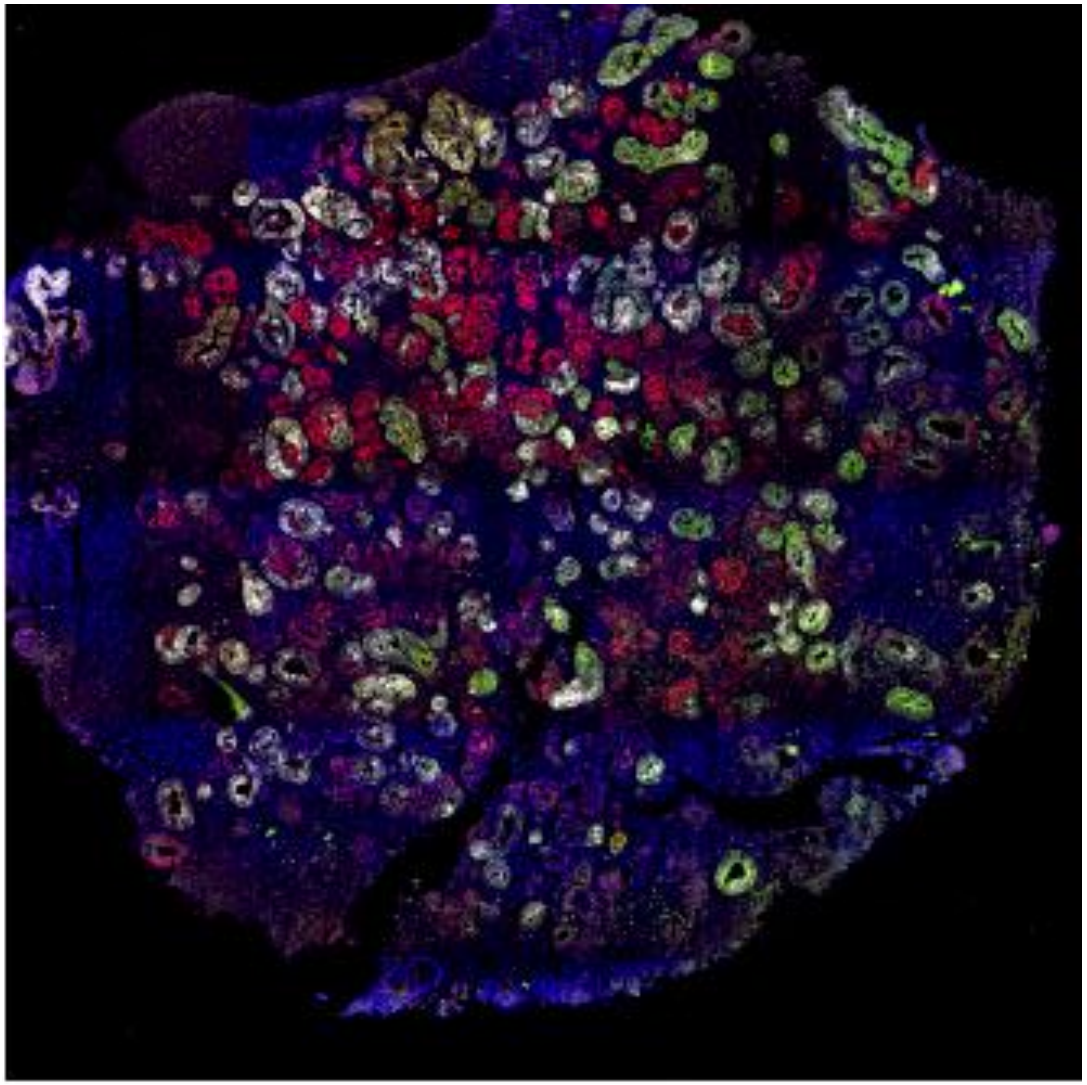


Little, MH. Developmental Biology, 2016, Humphreys 2014

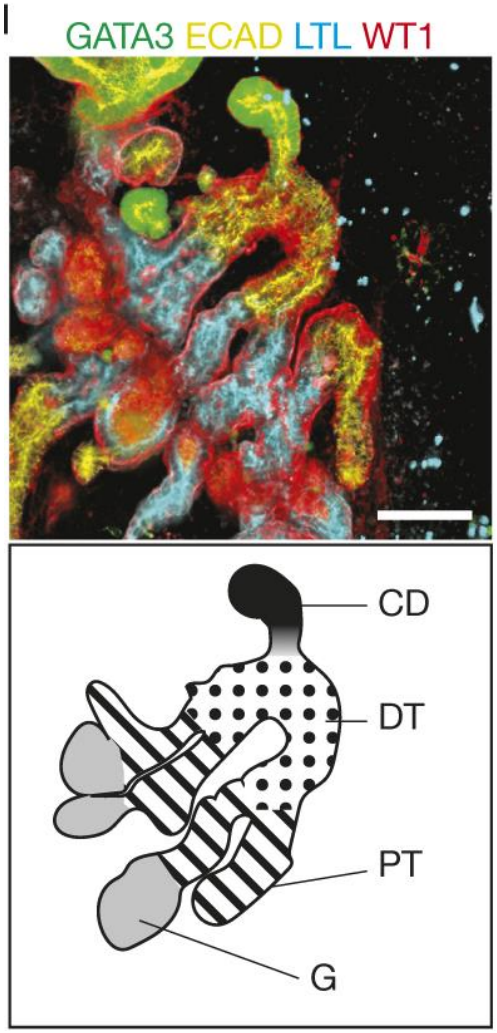
Kidney Organoids Recapitulate Nephrogeneisis





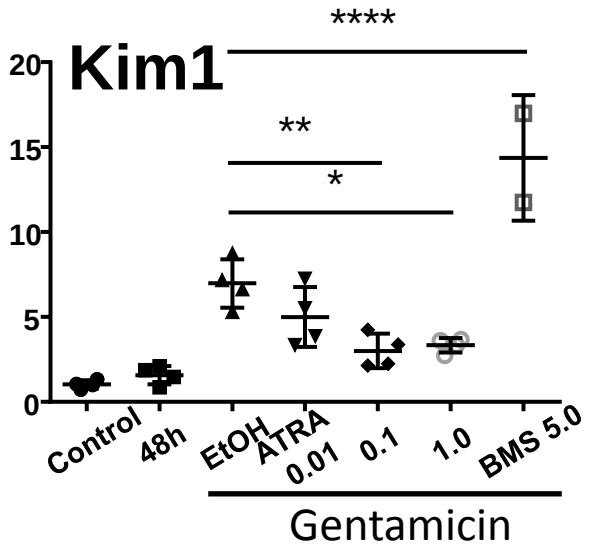


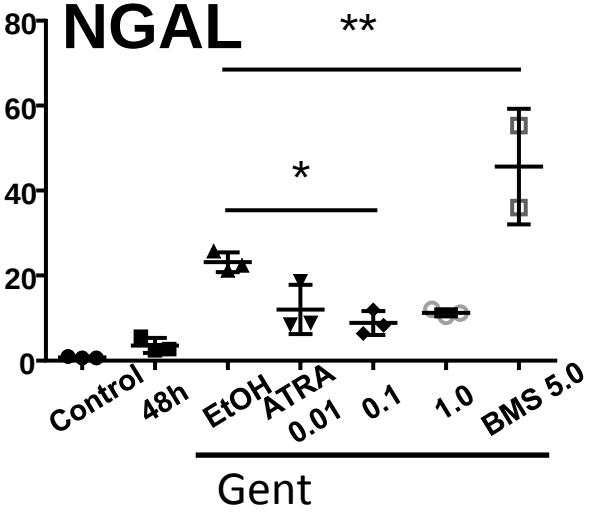
Organoids Respond to Injury



M Takasato *et al. Nature 2014*

mRNA





Uchimura unpublished

hPS-derived Organoids: Obstacles

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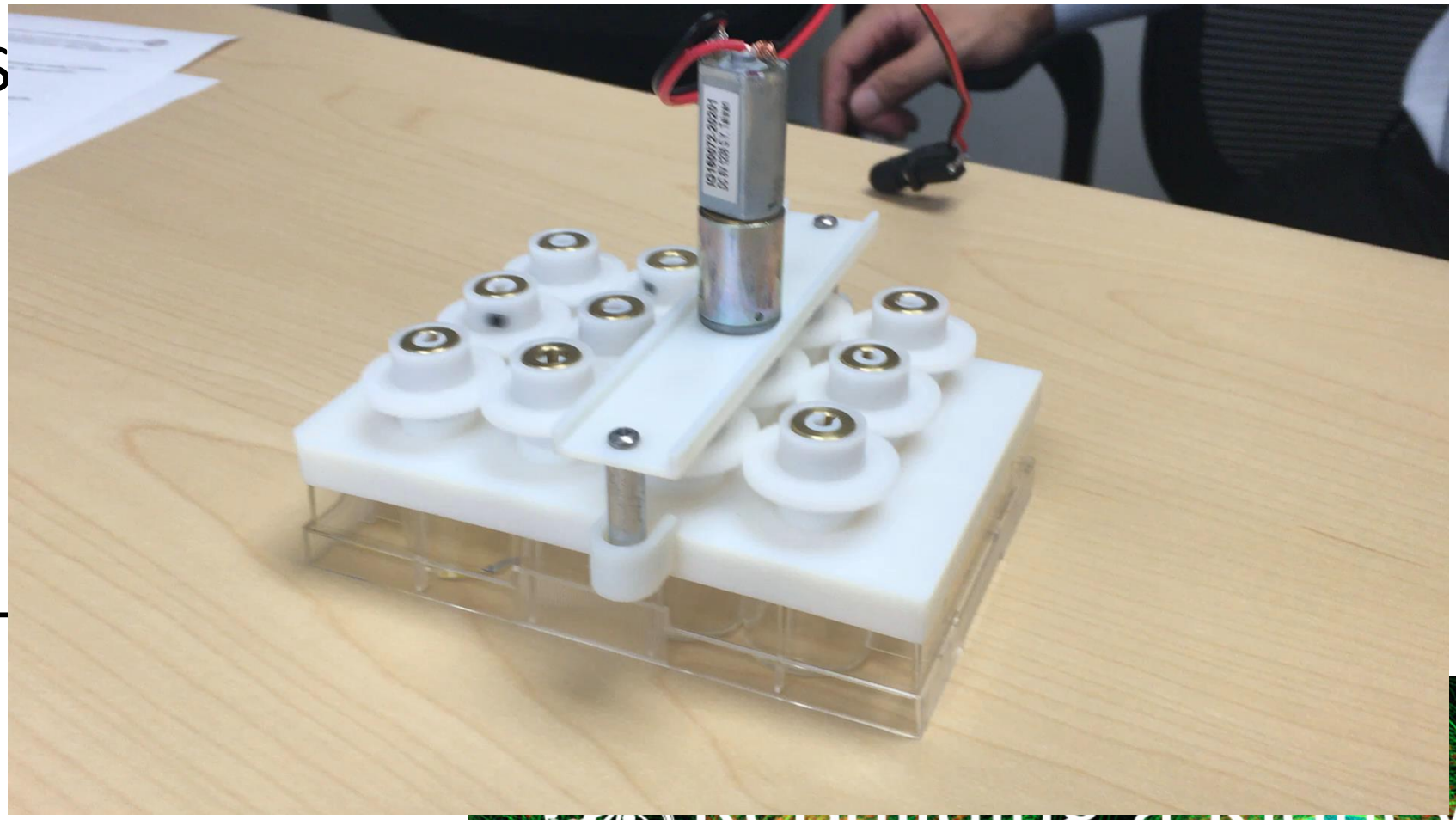


www.rebuildingakidney.org

Xenotransplantation: Back to the Future?

1996:

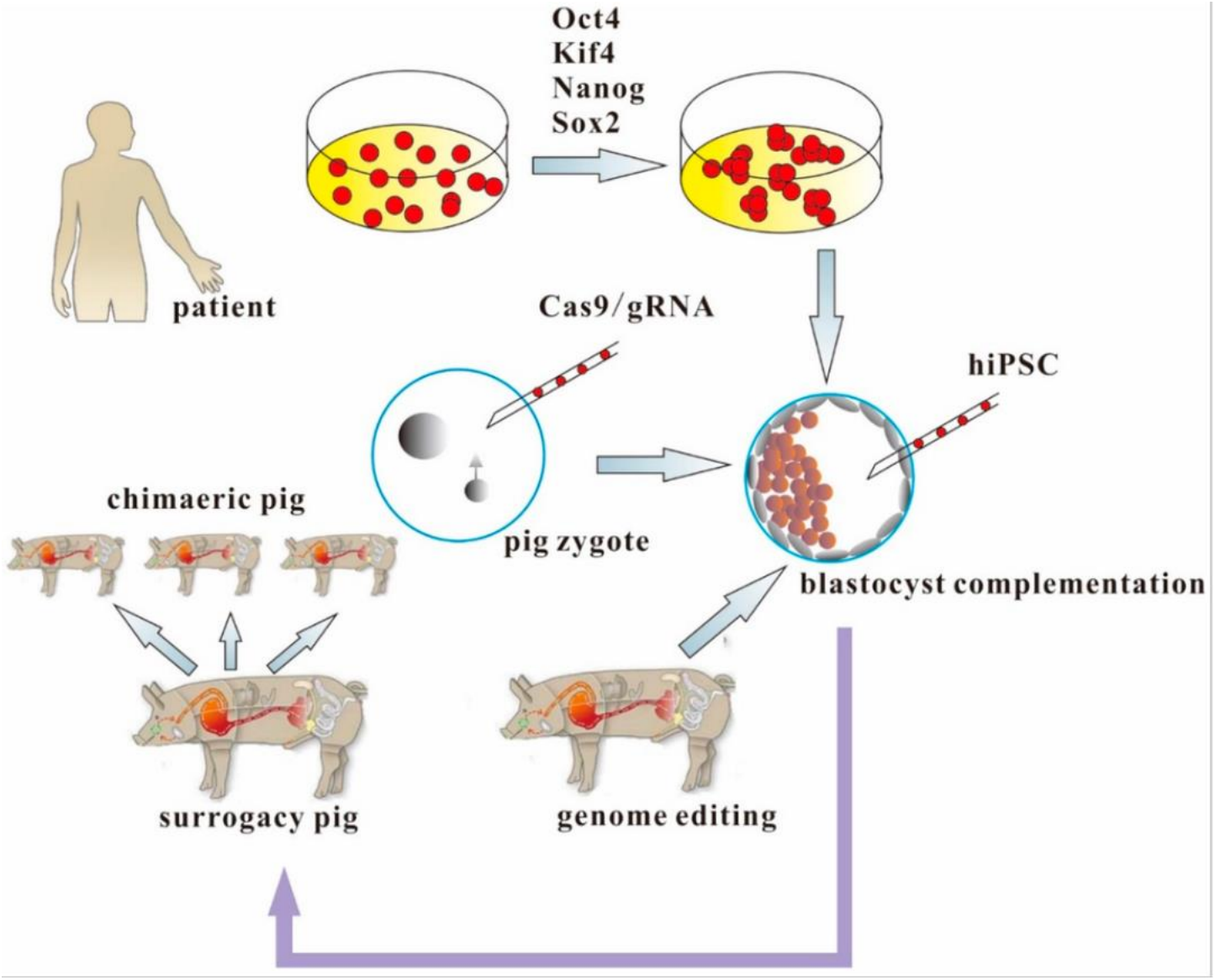
- Pfizer invests $1b to investigate pig organ xenotransplantation
- 2 major hurdles:
  - Rejection (largely from one sugar molecule)
  - Infection: Concern over porcine retroviruses
- Plug pulled in early 2000s
- But:

REPORT

Genome-wide inactivation of porcine endogenous retroviruses (PERVs)

Luhan Yang[1,2,3,*,†], Marc Güell[1,2,3,†], Dong Niu[1,4,†], Haydy George[1,†], Emal Lesha[1], Dennis Grishin[1], John Aach[1], Ellen Shrock[1], Weihong Xu[6], Jürgen Poci[1], Rebeca Cortazio[1], Robert A. Wilkinson[5], Jay A. Fishman[5], George Church[1,2,3,*]

Blastocyst Complementation: Moonshot



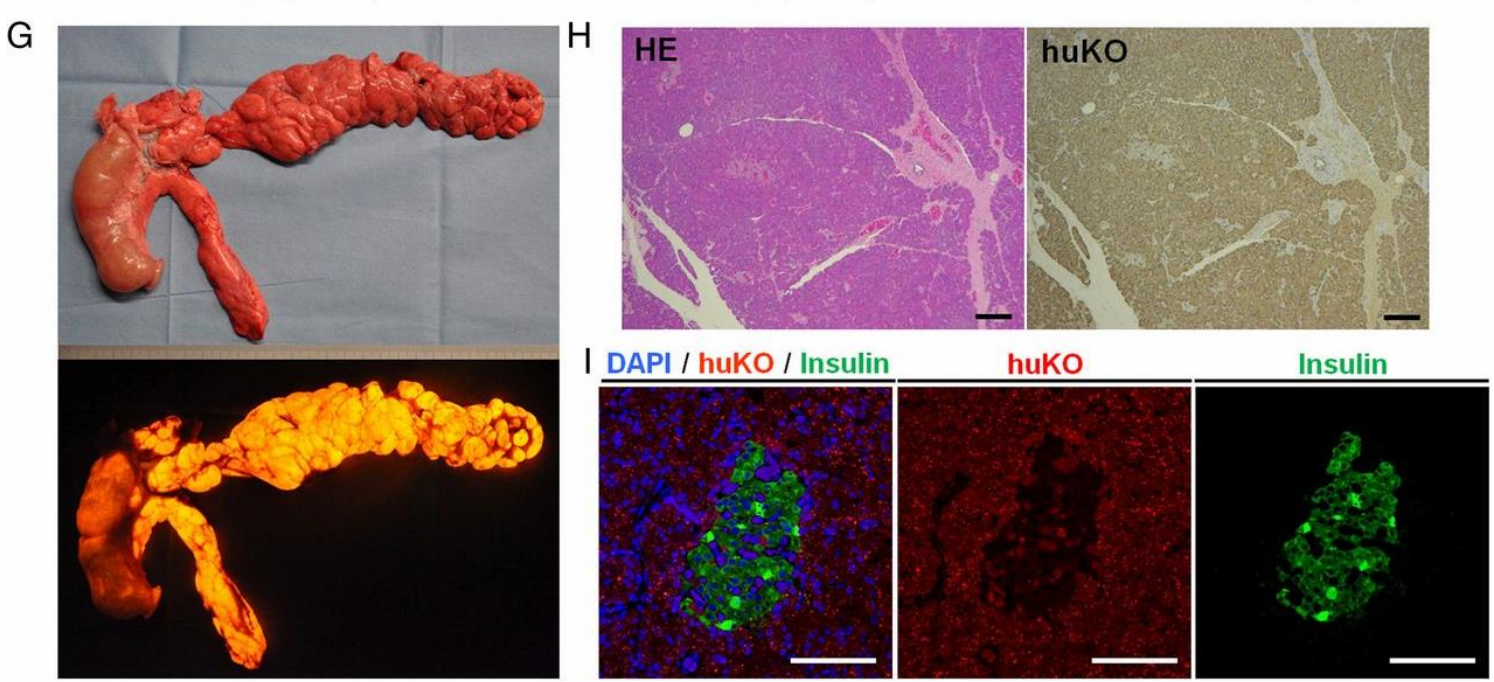
Ethics…

Int. J. Mol. Sci. 2015, 16(3), 6545-6556

Blastocyst Complementation: Moonshot

Blastocyst complementation generates exogenic pancreas in vivo in apancreatic cloned pigs

Hitomi Matsunari[a,b,c,1], Hiroshi Nagashima[a,b,c,1,2], Masahito Watanabe[b,c], Kazuhiro Umeyama[b,c], Kazuaki Nakano[c], Masaki Nagaya[b,c], Toshihiro Kobayashi[a], Tomoyuki Yamaguchi[a], Ryo Sumazaki[d], Leonard A. Herzenberg[e,2], and Hiromitsu Nakauchi[a,f,2]



Hitomi Matsunari et al. PNAS 2013;110:4557-4562

Xenotransplantation, Blastocyst Complementation: Obstacles

Xenotransplantation:

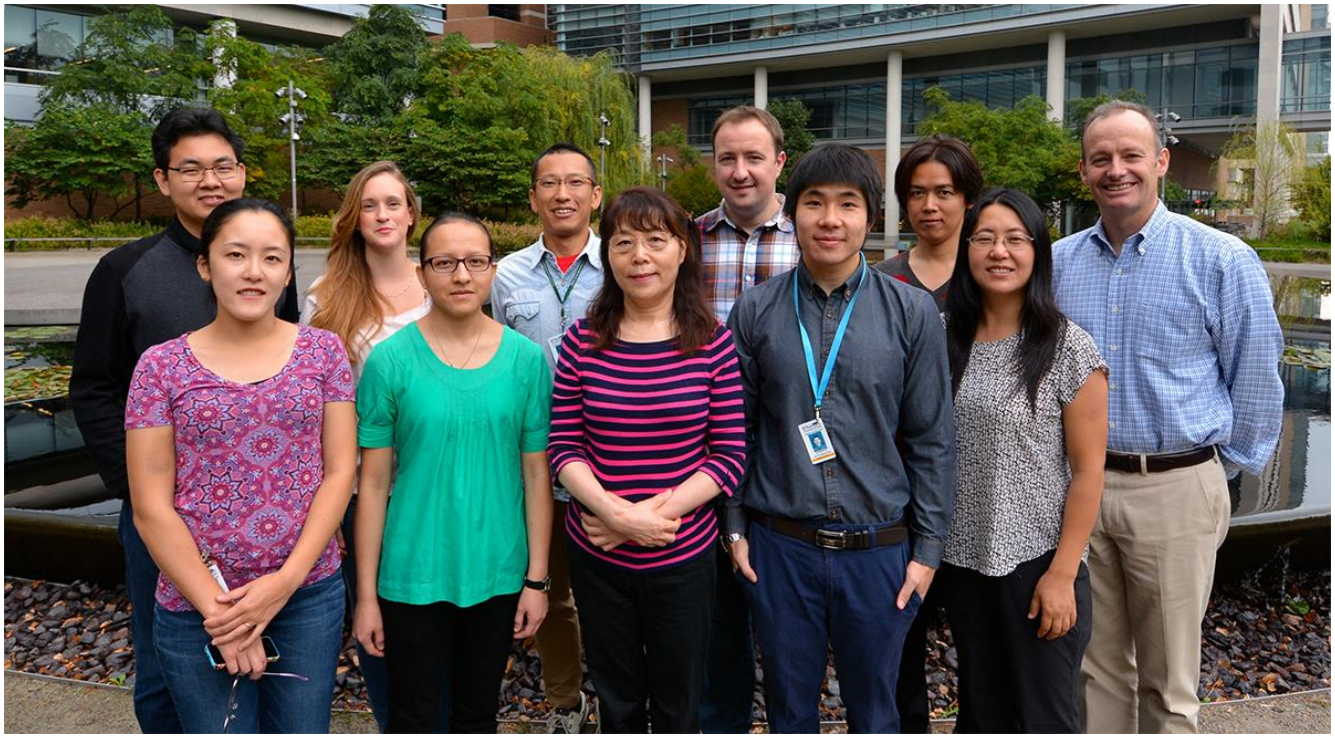
- Rejection is not limited to a-Gal
- Immunosuppression still be required

Blastocyst Complementation:

- Very early days!
- Efficiency unclear
- What pig derived cells would carryover (graft vs. recipient)

Conclusions

- Kidney failure: tremendous clinical need
- No major new therapies in *many decades*
- Human kidney organoids: Promising
  - Immediate application: toxicity testing, screening
  - Need for scale: engineers, industry collaborators
- Recent progress: surprising and remarkable
  - Reason for cautious optimism
  - Inter-disciplinary collaboration needed



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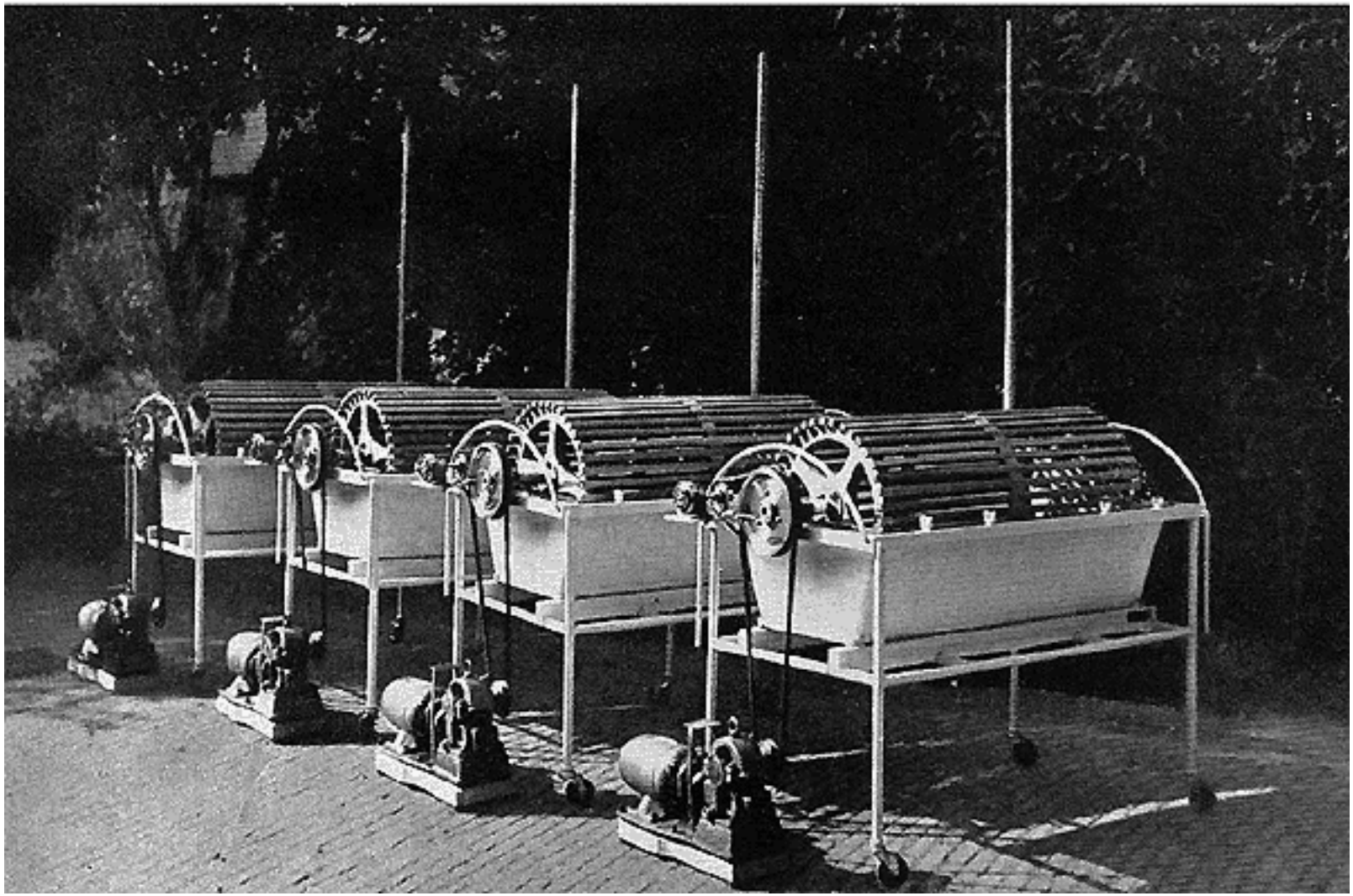
Lucy Fan, PhD
Jeff Lai, MD

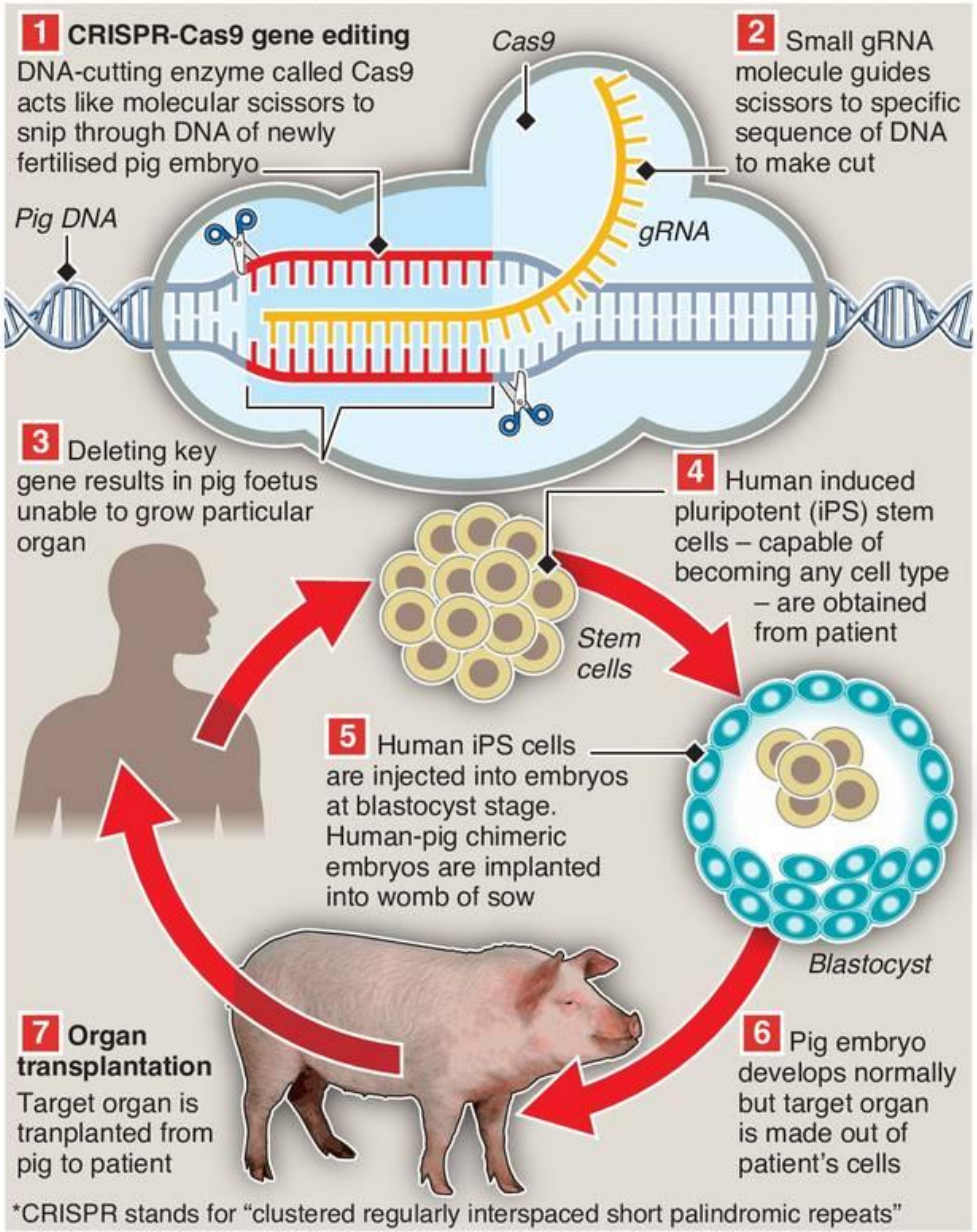
Washington University in St. Louis



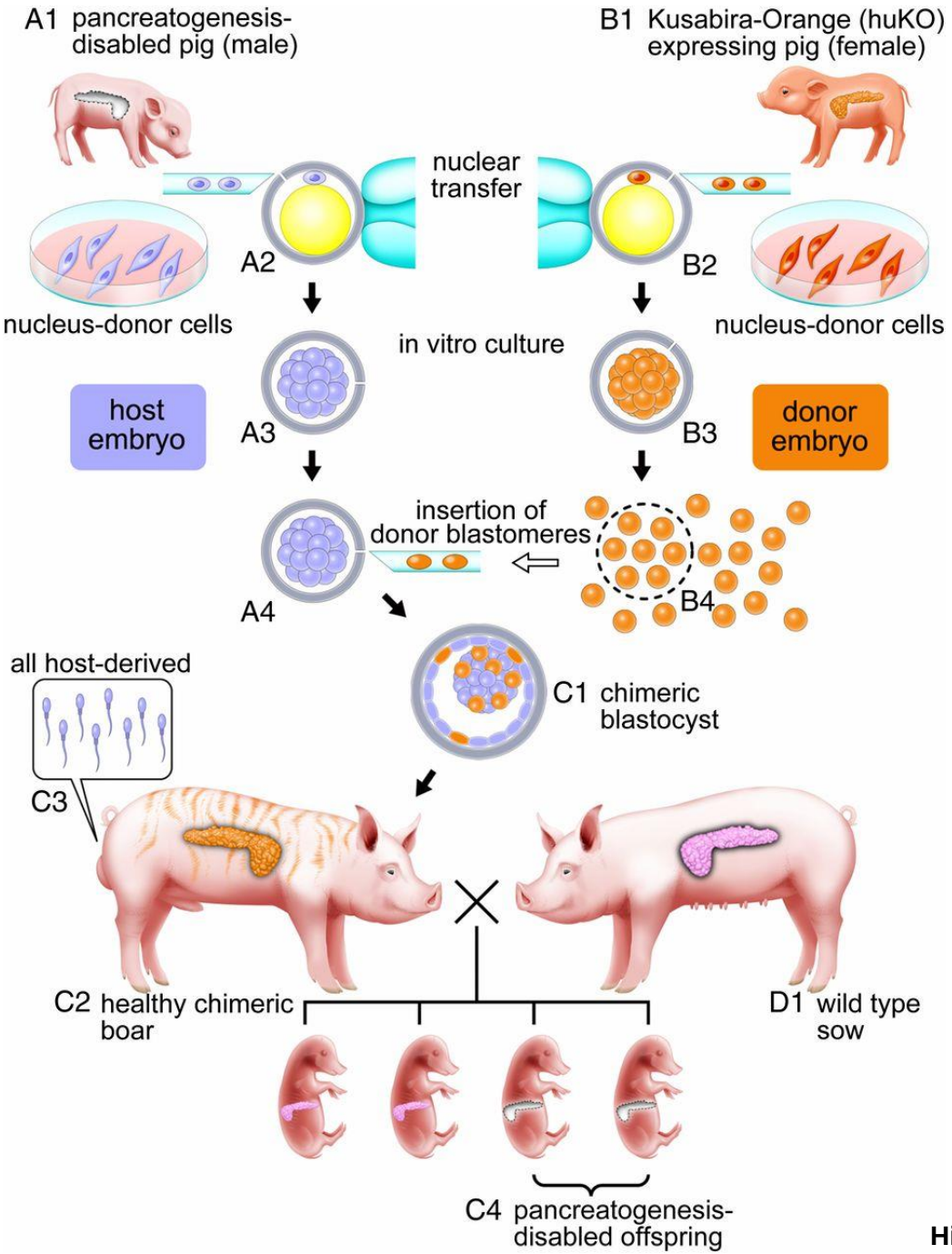
Nature Medicine 8, 1063 - 1065 (2002)

Chimeric pigs could grow human organs

Injecting human stem cells into pig embryos that have been genetically modified to lack specific organs could produce an unlimited supply of human organs for transplant



Graphic News, 2016



Hitomi Matsunari et al. PNAS 2013