

3rd Chinese Plastic Surgery Stem Cell Research Conference

(Oct 28th, 2017, Boao)

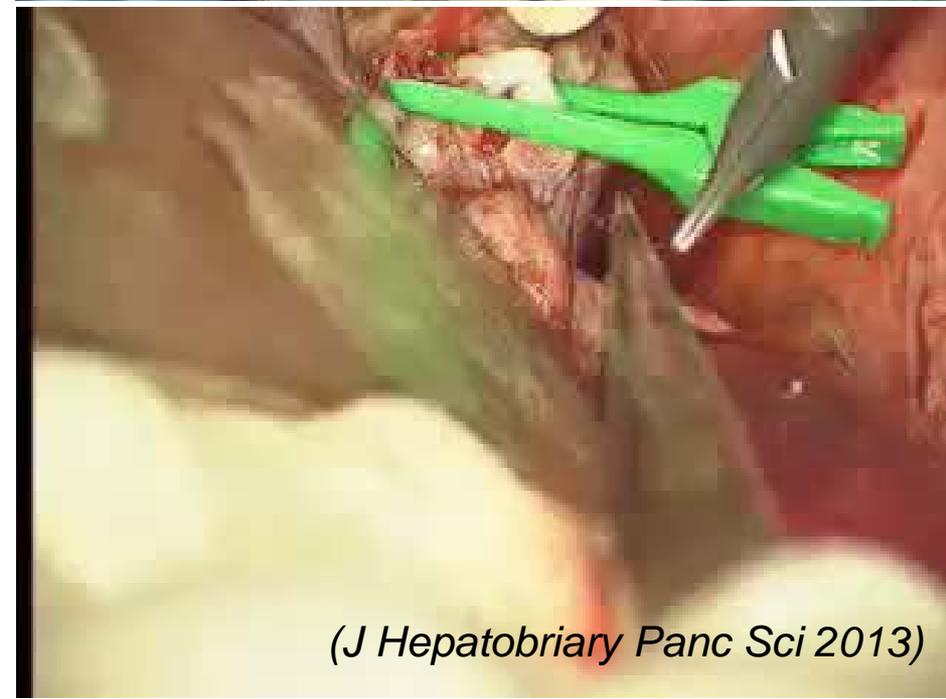
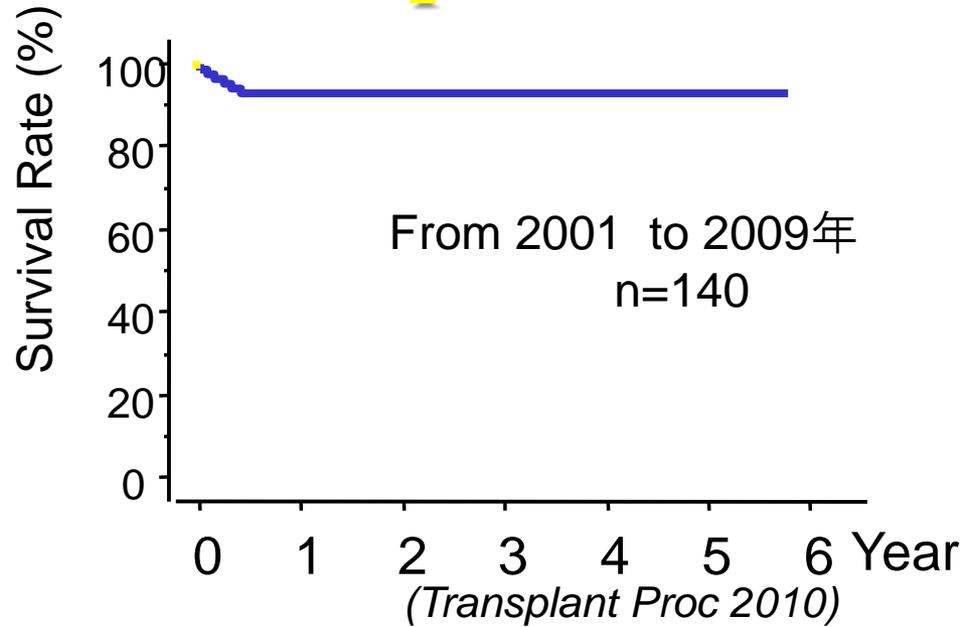
Organ Fabrication - Future for Medicine -



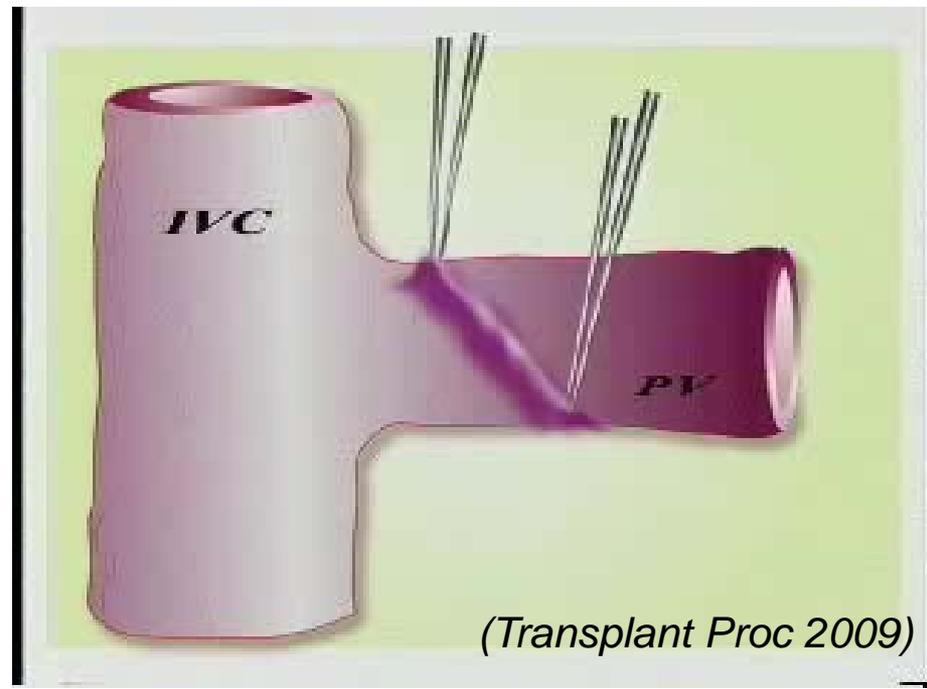
Eiji Kobayashi, MD, PhD

Keio University, School of Medicine

Microsurgery in Liver transplantation

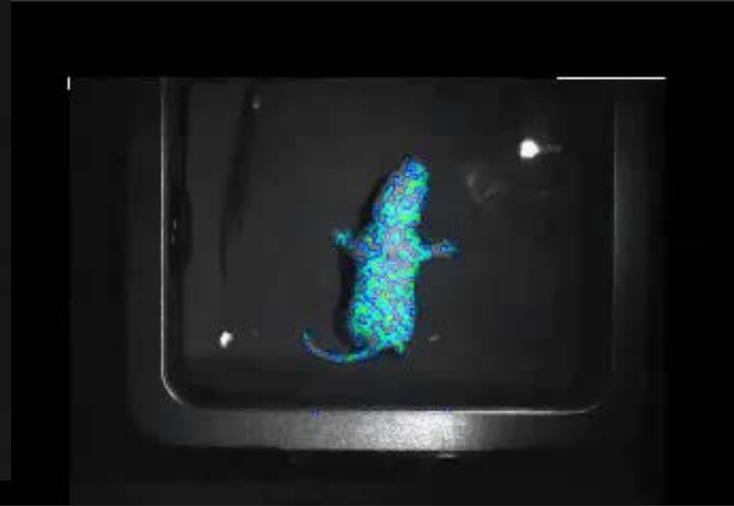


(J Hepatobiliary Panc Sci 2013)



(Transplant Proc 2009)

Cross-border academia collaboration in the world

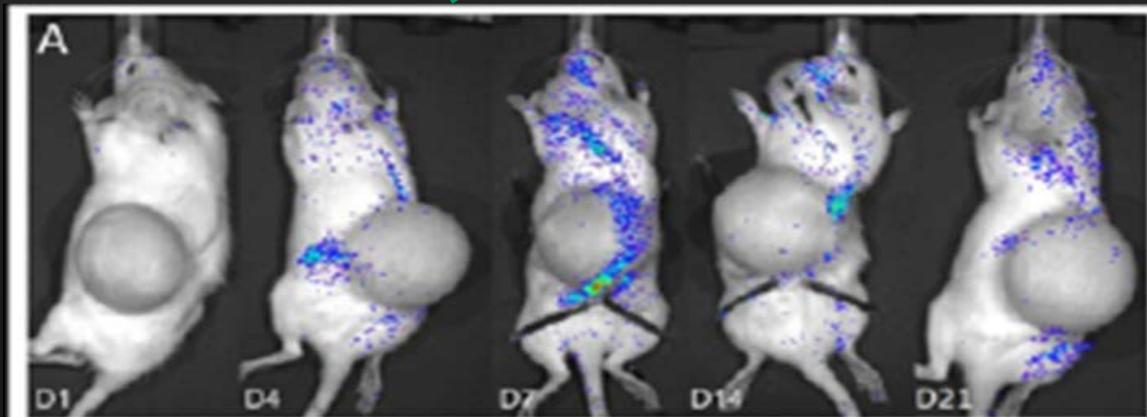


“Bio-Imaging Rat” developed world-first by Prof. Kobayashi in the early years of 2000s



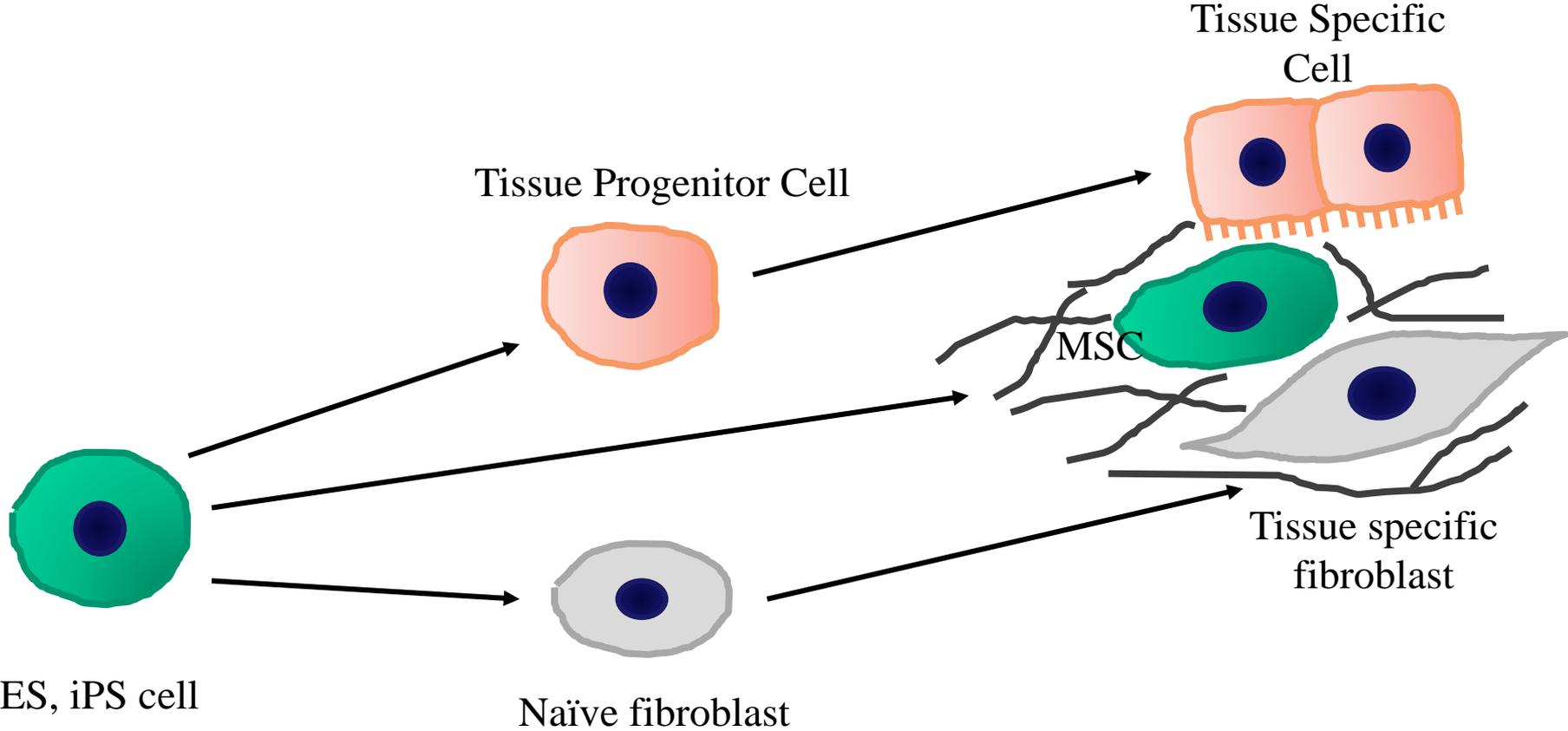
(Shanghai 2015)

Translational Research in Shanghai 9th People's Hospital



(Zhou S, Li QF, et al 2015)

Concept of Tissue/Organ Formation with Extracellular Matrix (ECM)



(Kobayashi E 2017)

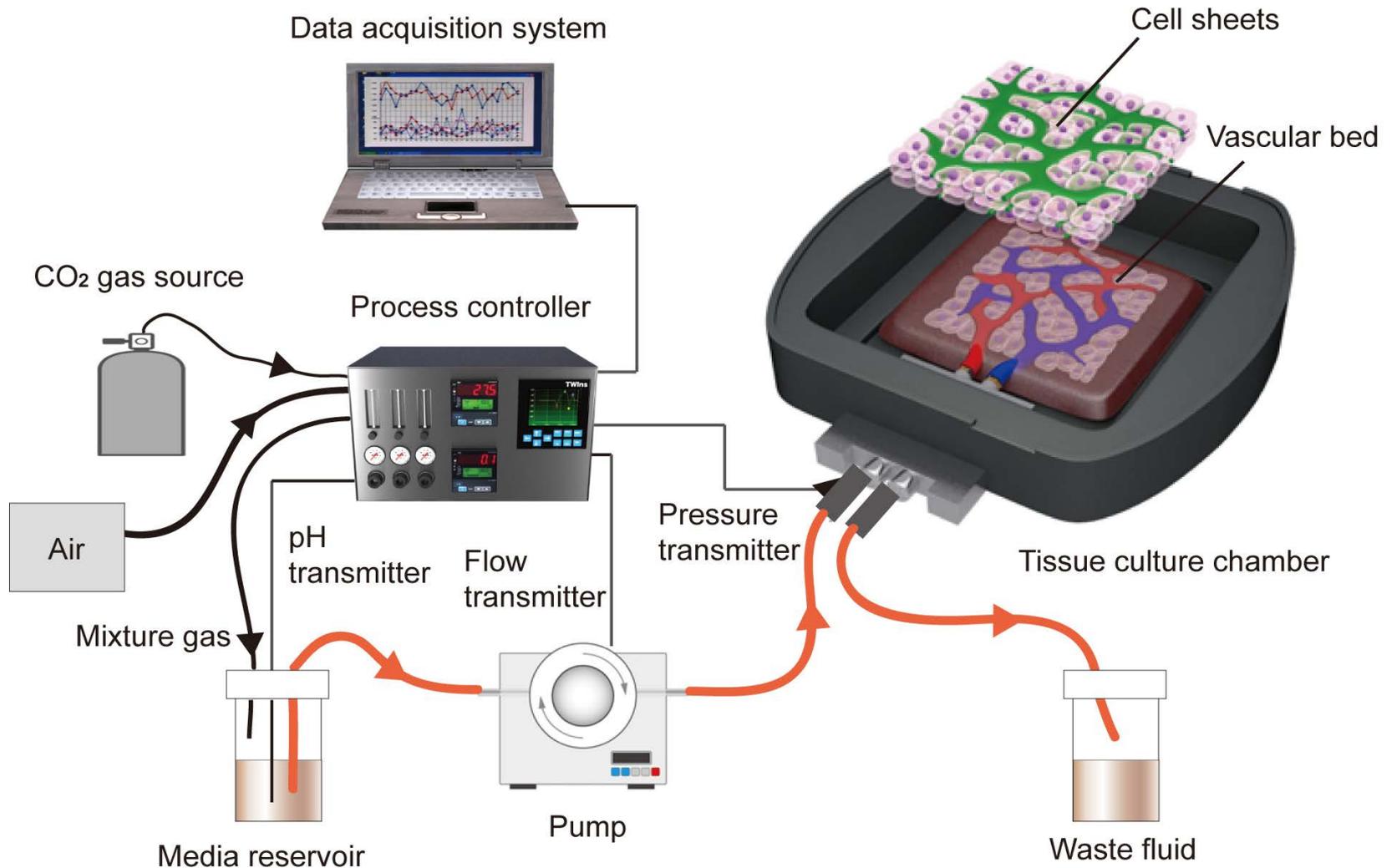
Strategy for Creating `Transplantable Organs`

Strategy	POC in Small Animals	POC in Pigs
(1) In Vivo Bioreactor	Pancreas (<i>Kobayashi T, et al. Cell 2010</i>)	Pancreas (<i>Matsunari H, et al. PNAS 2013</i>)
	Pancreas (<i>Yamaguchi T, et al. Nature 2017</i>)	Liver (<i>Fisher JE, et al. Liver Transplant 2013</i>)
	Kidney (<i>Usui J, et al. Am J Path 2012</i>)	Liver (<i>Hsu H, et al Transplant Proc 2017</i>)*
	Liver (<i>Hata T, et al. Ann Surg 2013</i>)*	Pig/Human Chinera (<i>Wu J, et al Cell 2017</i>)
(2) Organ Buds	Kidney (<i>Stem Cells 2012</i>)*	Pancreas (<i>Hammerman M, et al. Organogenesis 2012</i>)
	Kidney (<i>Cell Stem Cell 2014</i>)	Kidney (<i>Yokote S, et al. PNAS 2015</i>)*
	Liver (<i>Nature 2013</i>)	
	Liver (<i>Scientific Reports 2017</i>)*	
(3) Ex vivo fabrication	Heart (<i>Ott HC, et al. Nature Med 2008</i>)	Kidney (<i>Ann Surg 2012</i>)
	(Decellular) Kidney (<i>Ross EA, et al. JASN 2009</i>)	Liver (<i>Cell Transplant 2012</i>)
	Liver (<i>Uygun BE, et al. Nature Med 2010</i>)	Heart (<i>Cardio Thrac Surg 2016</i>)
	(Tissue Expand) Lung (<i>Ott HC, et al. Nature Med 2010</i>)	Liver, Kidney, Spleen, Bone, etc (<i>Kobayashi E, et al. unpublished</i>)*
	(Organ culture) Heart (<i>Sekine H, et al. Nature Com 2013</i>)*	

* Author's

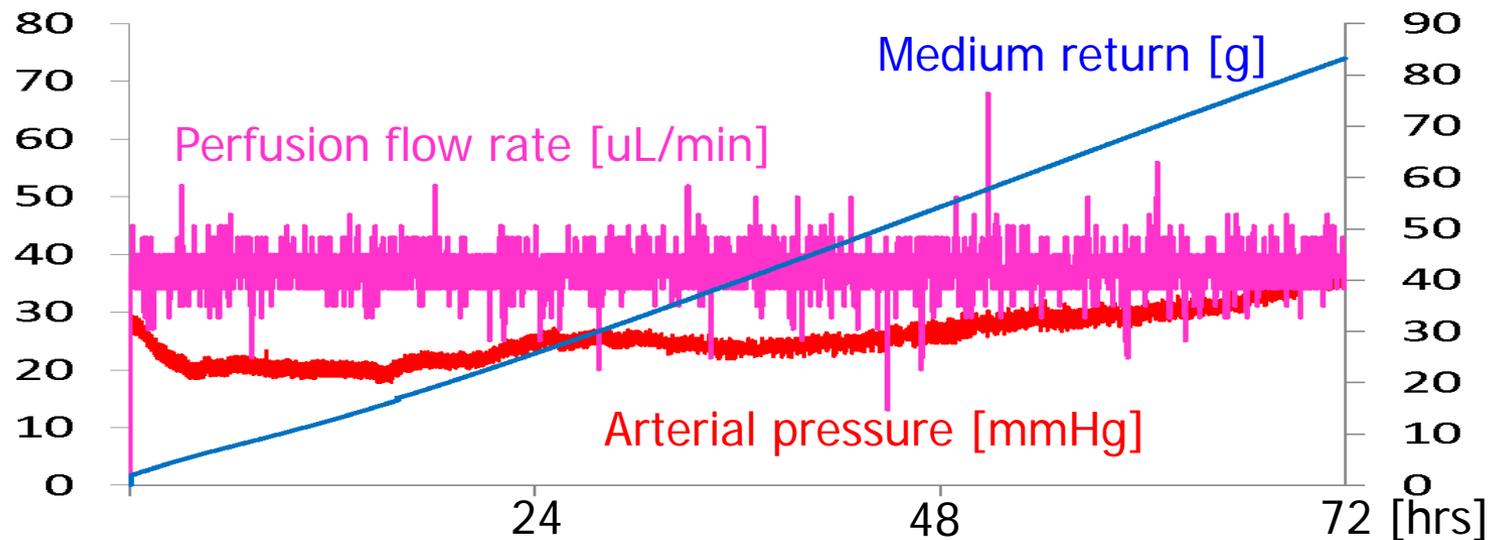
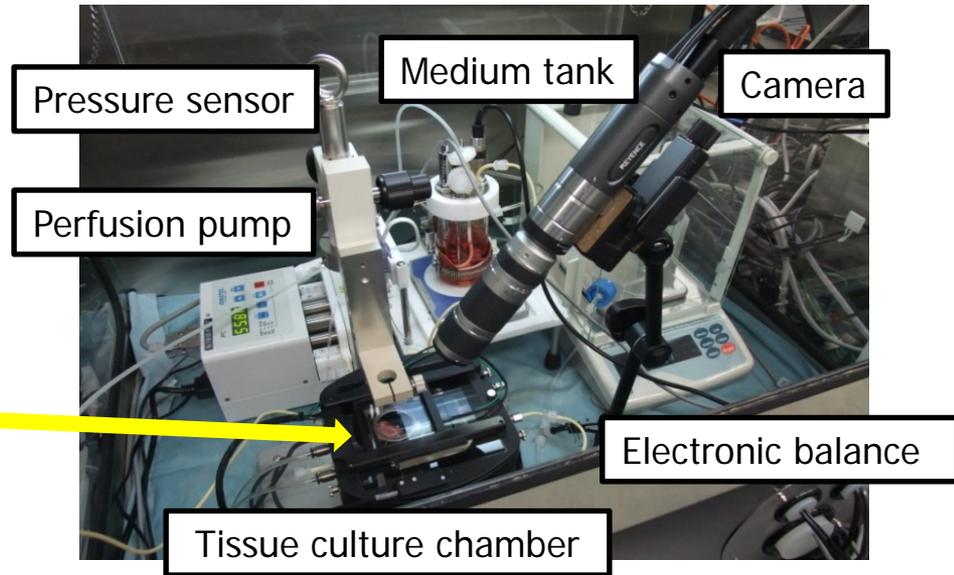
(*Kobayashi E 2017*)

Schematic illustration of the concept used for in vitro engineering of 3-D tissue with perfusable blood vessels

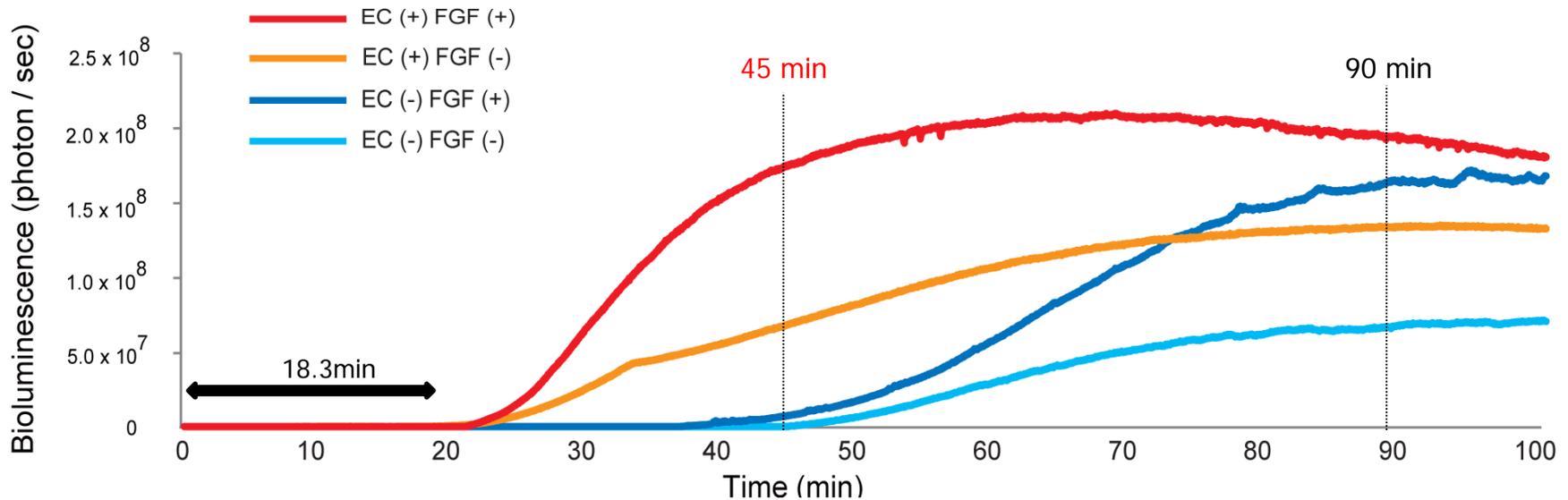
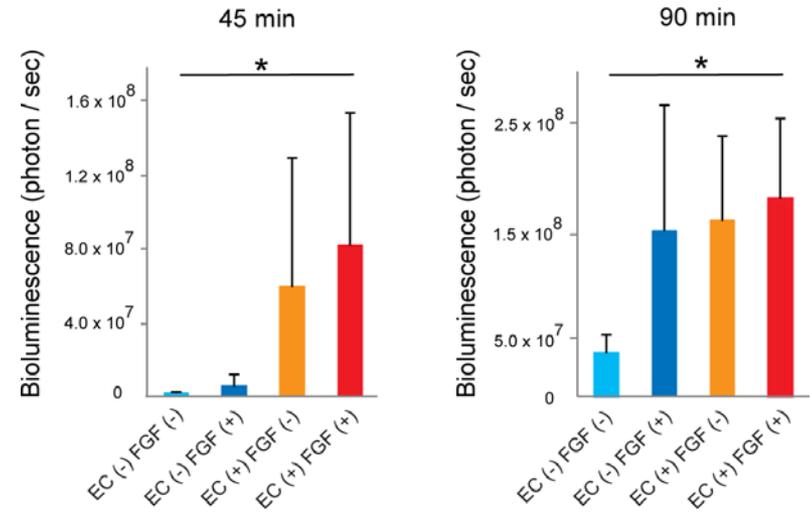
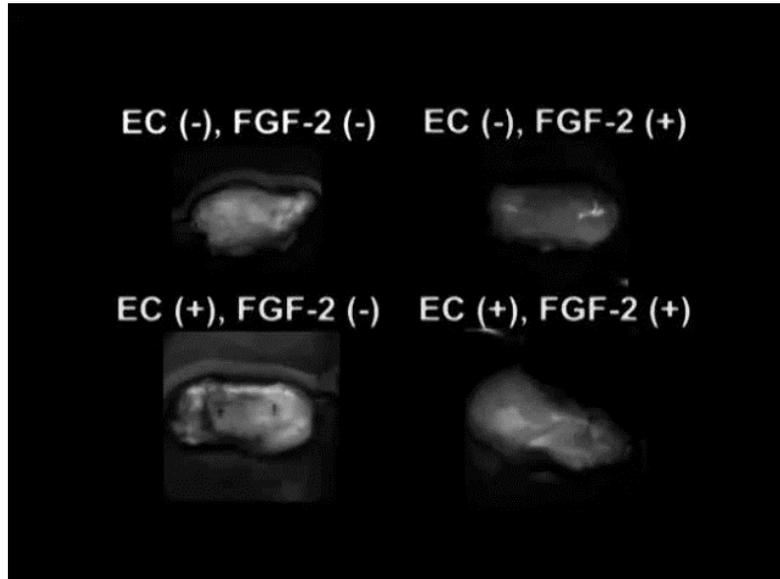


(Sekine H, et al. Nature Com 2013)

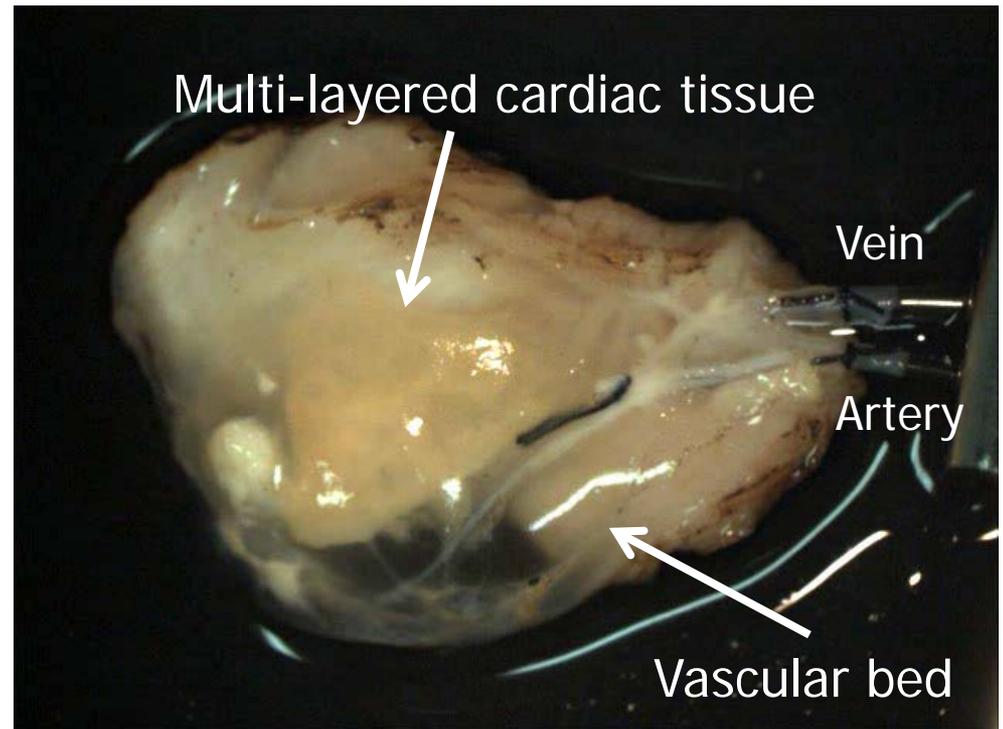
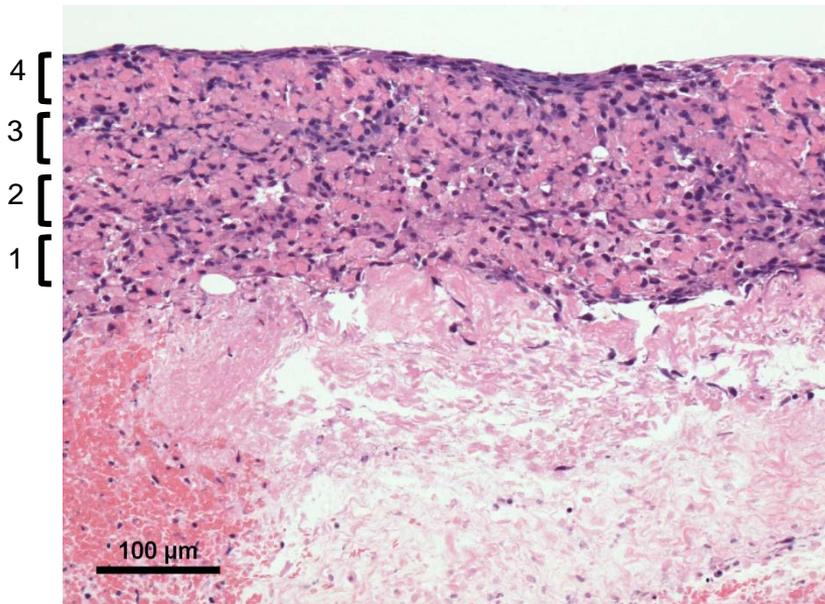
Bioreactor set up and tissue perfusion culture



In vitro perfusable blood vessel formation and viable cardiac tissue fabrication



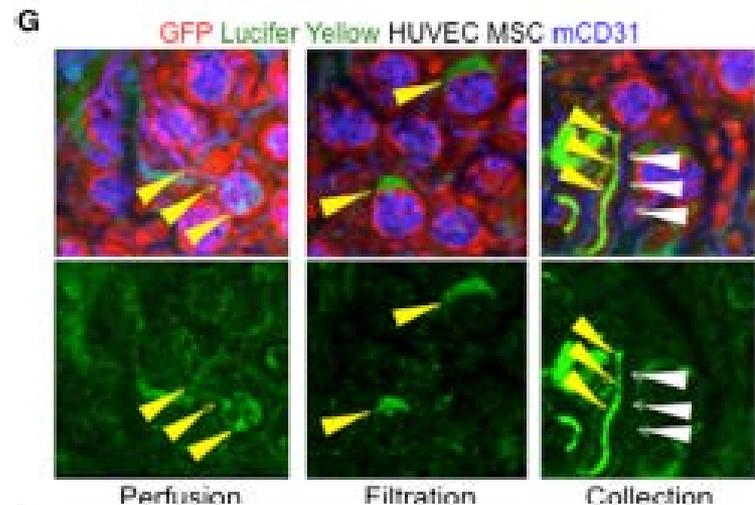
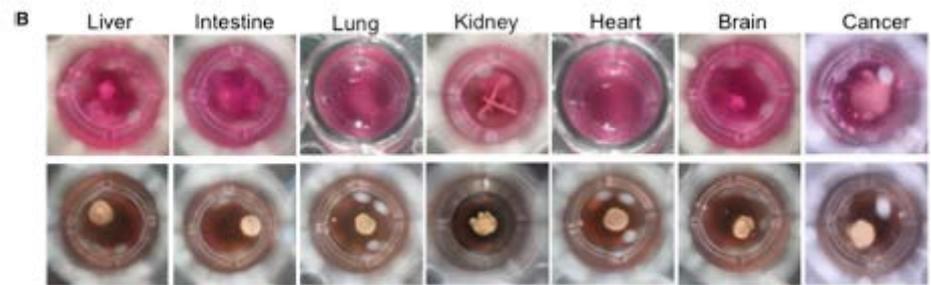
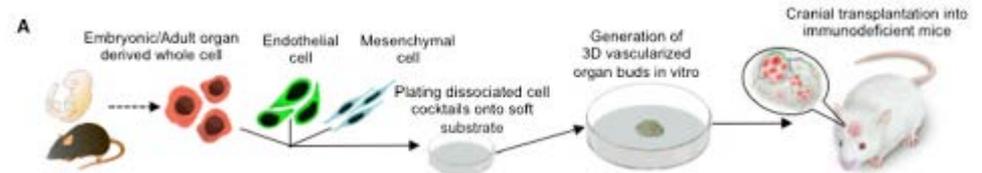
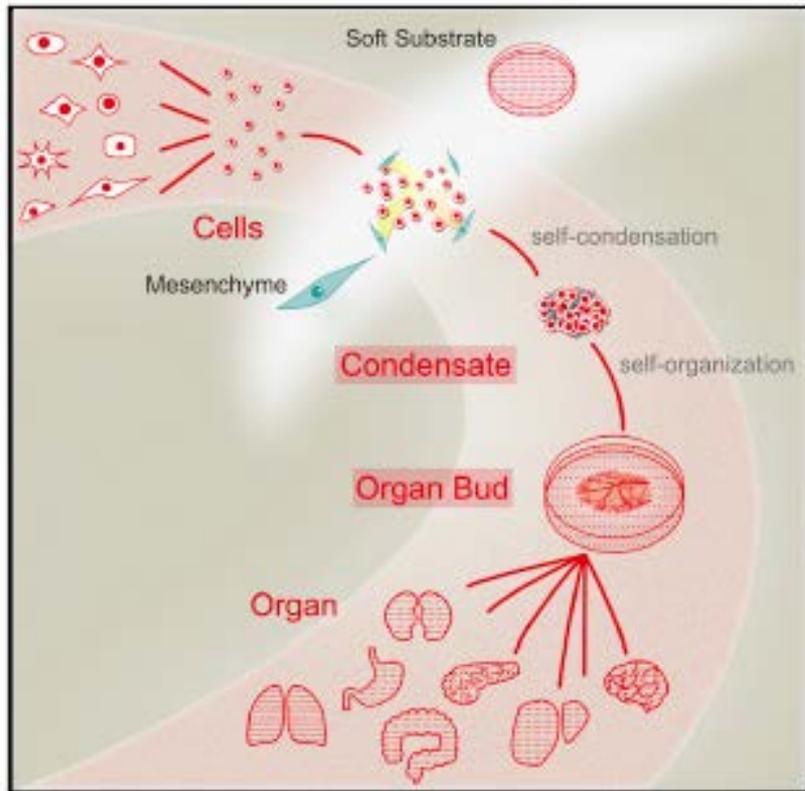
Multi-step overlaying of triple-layer cardiac cell sheets for scale up



12 days after perfusion culture

(Sekine H, et al. Nature Com 2013)

Vascularized and Complex Organ Buds from Diverse Tissues via Mesenchymal Cell-Driven Condensation



Takebe T, Enomura M, Yoshizawa E, Kimura M, Koike H, Ueno Y, Matsuzaki T, Yamazaki T, Toyohara T, Osafune K, Nakauchi H, Yoshikawa HY, Taniguchi H.
Cell Stem Cell. 2015

Multi-cellular spheroid

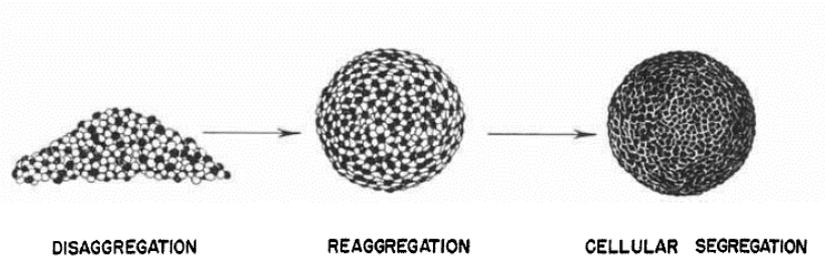
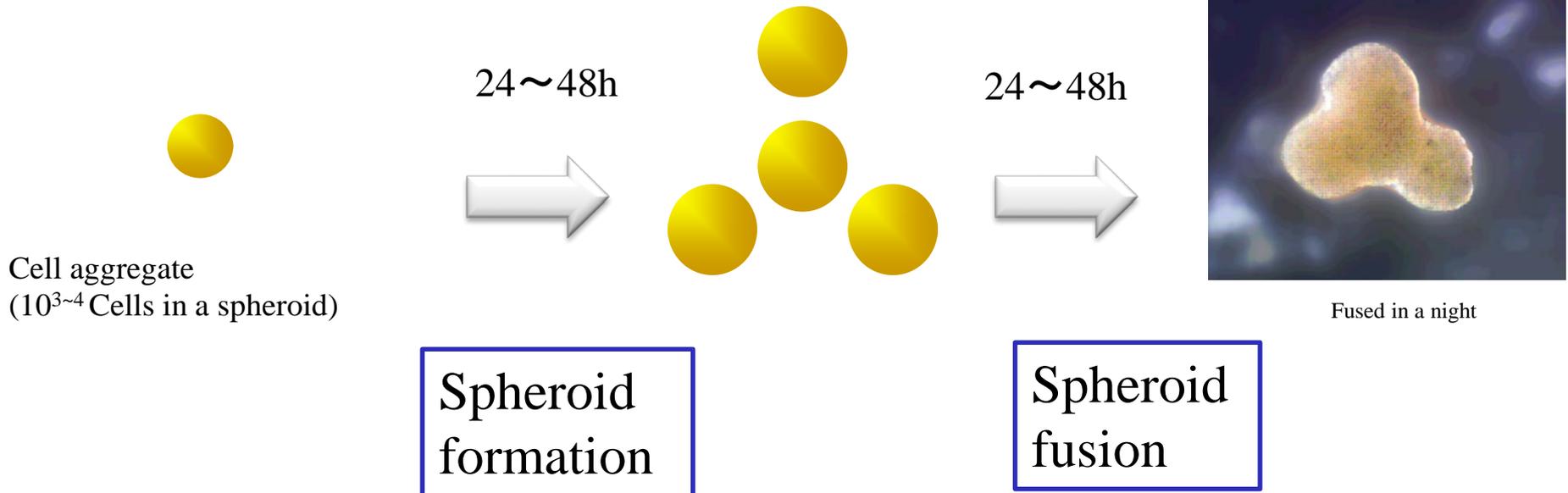


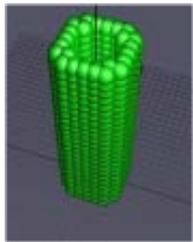
Fig. 10 A piece of the medullary plate and a piece of prospective epidermis are excised and disaggregated by means of alkali. The free cells are intermingled (epidermal cells indicated in black). Under re-adjusted conditions the cells re-aggregate and subsequently segregate so that the surface of the explant becomes entirely epidermal.

The Journal of Experimental Zoology 5:245-258, 1907

The Journal of Experimental Zoology 128: 1, 53-120, 1955



Development of “Bio 3D Printer”



3D Design



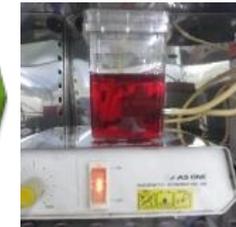
Spheroids



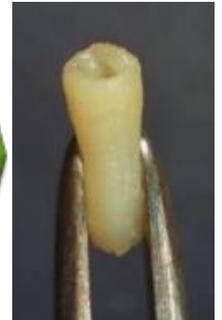
Bio 3D Printer
RegenoVA



3D printed



Maturation

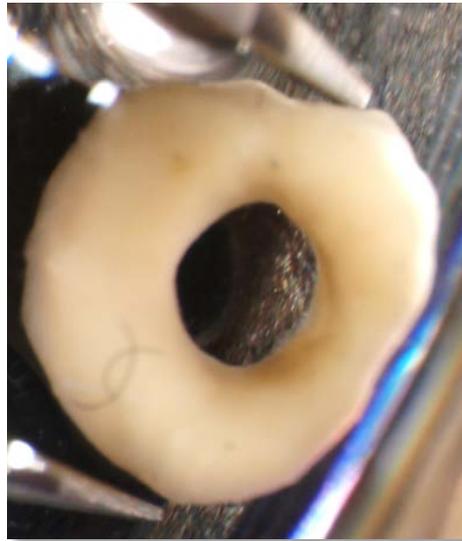


(By Nakayama K, et al)

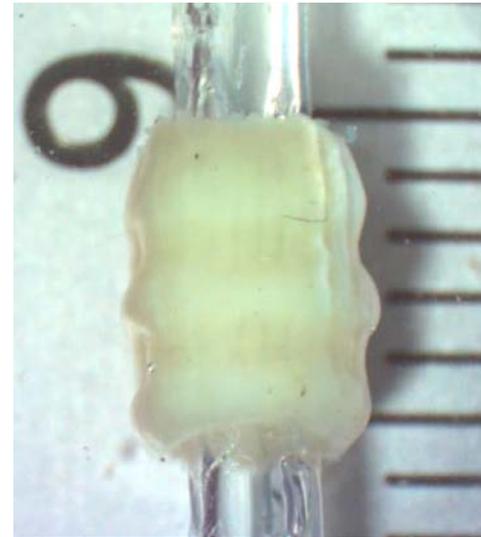
We have many pipelines



Meniscus



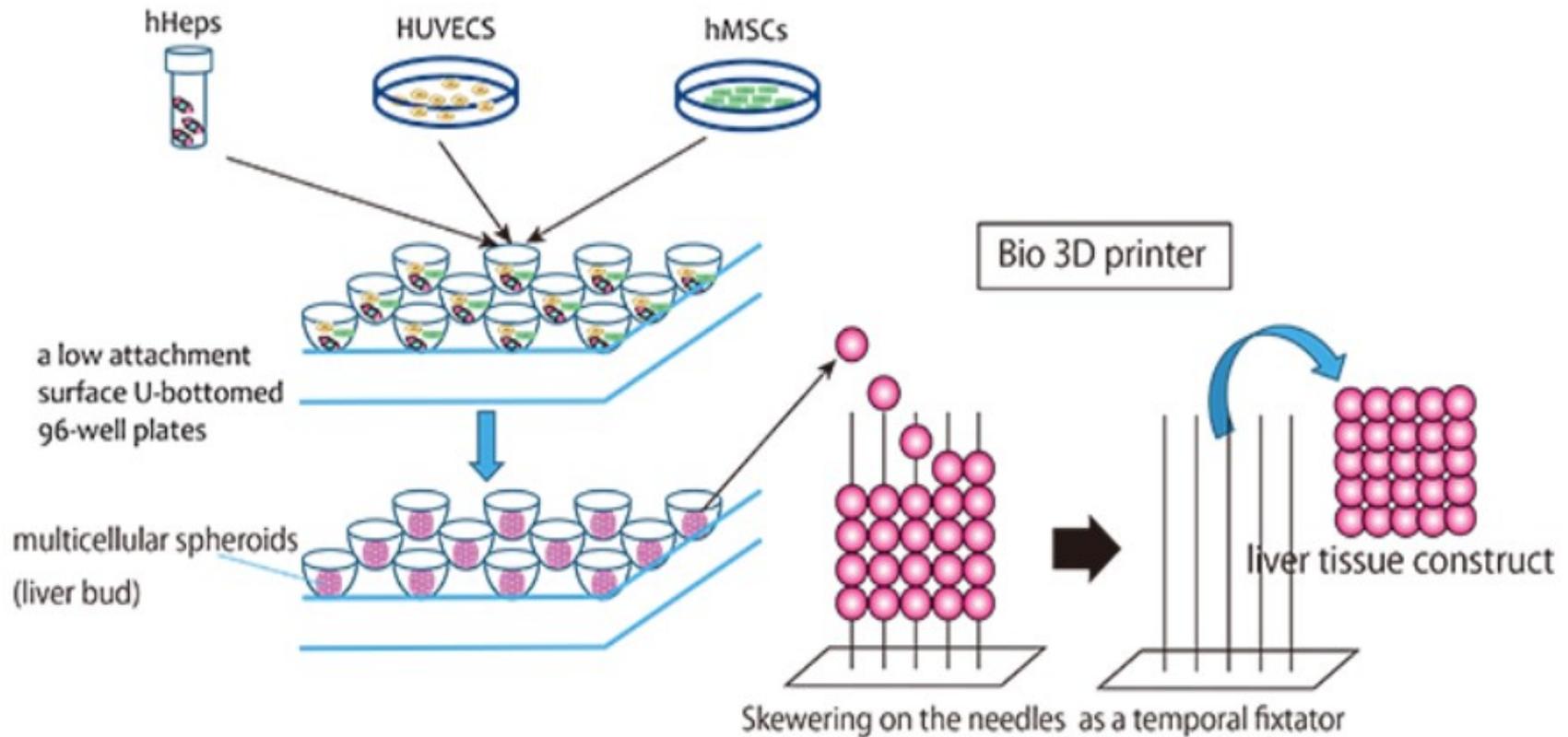
Liver



Trachea

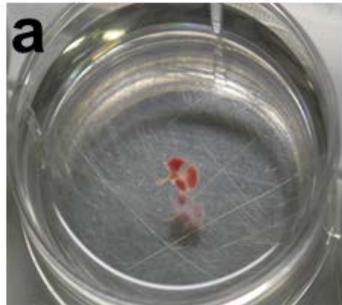
(By Nakayama K, et al)

3 D printing of a Liver bud originated from human cell source



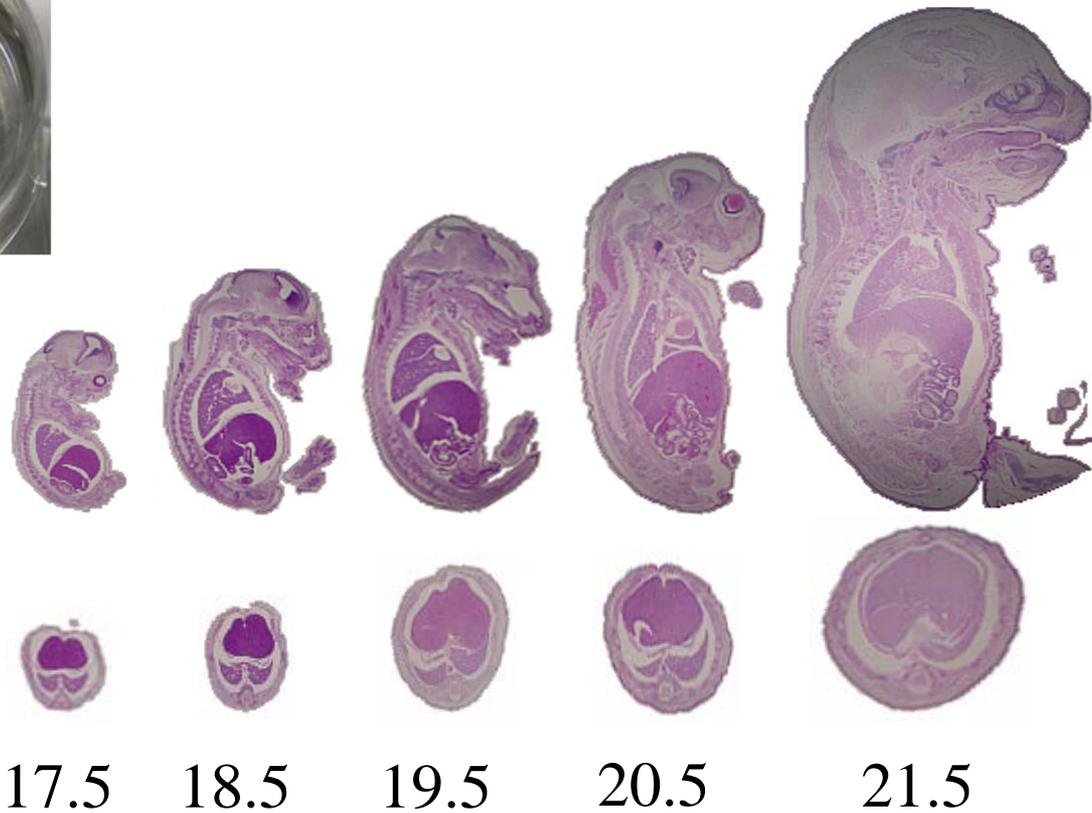
(Yanagi Y, et al. Scientific Reports 2017)

Development of Rat Fetus and Liver bud



13.5

1 cm



17.5

18.5

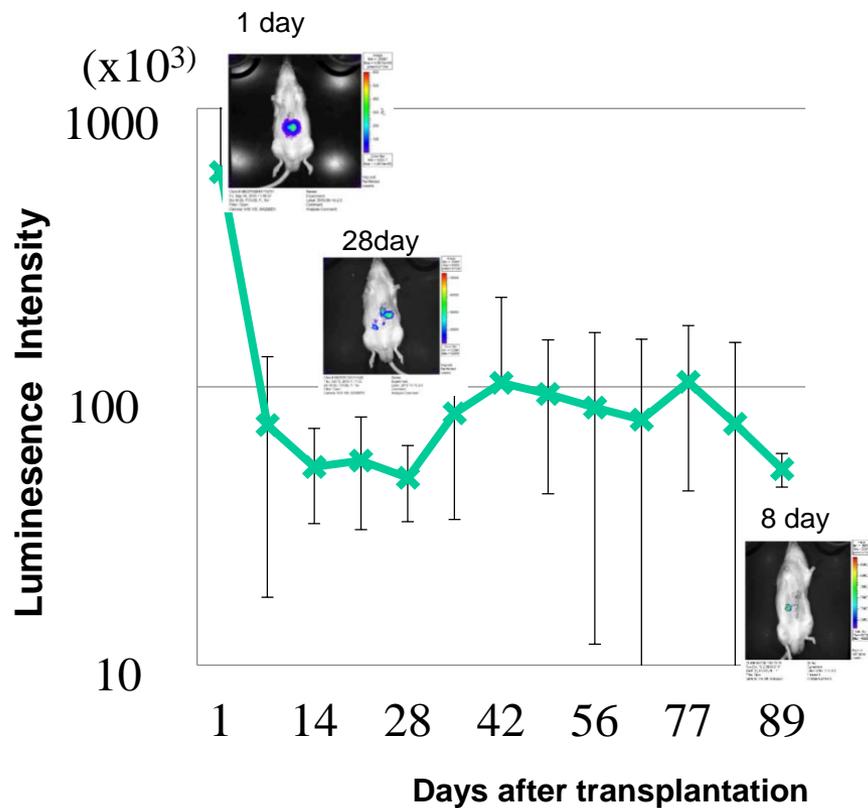
19.5

20.5

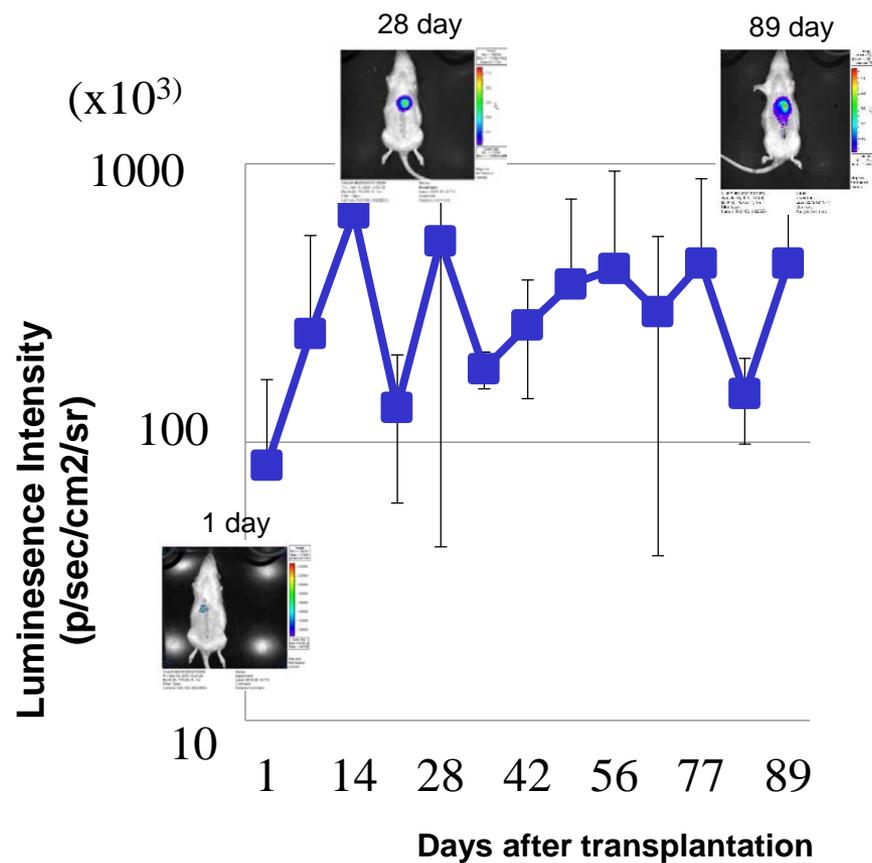
21.5

Getational Days

A. Heterotopic Transplantation



B. Orthotopic Transplantation

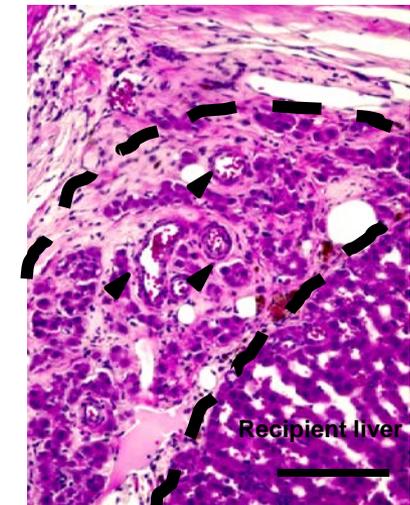
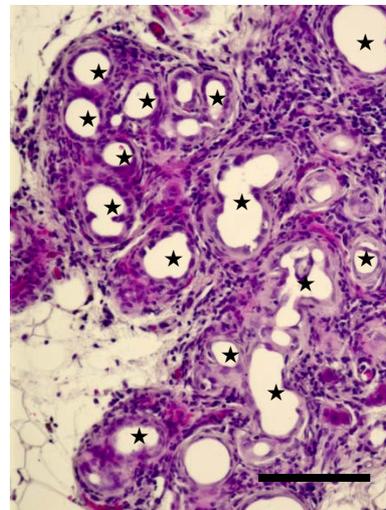
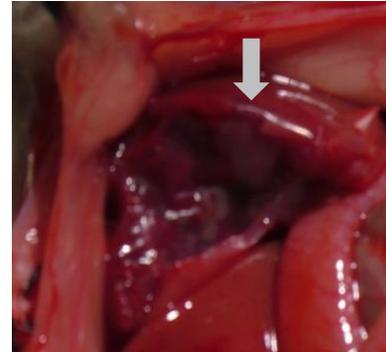
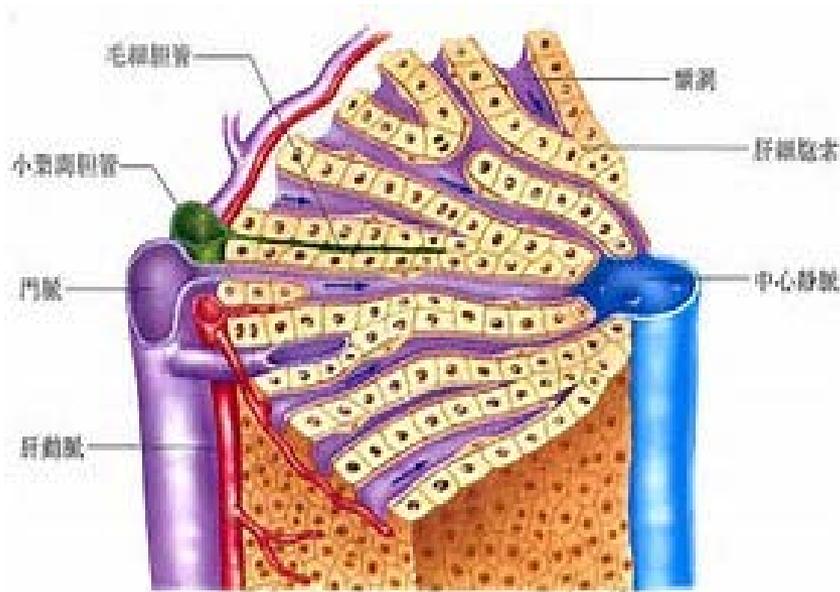


(Yanagi Y, et al. Scientific Reports 2017)

Passible mechanisms form histological examinations

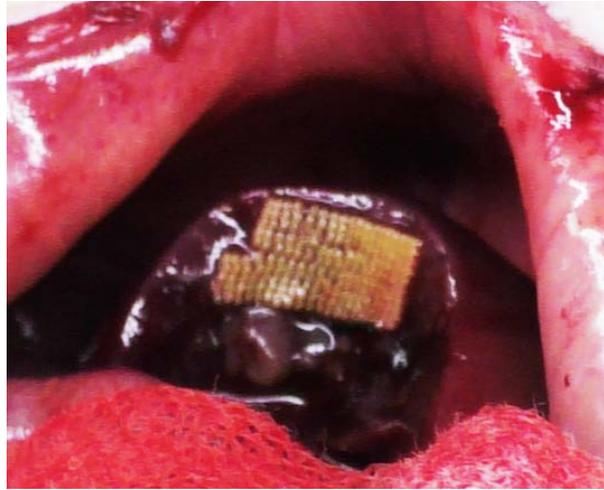
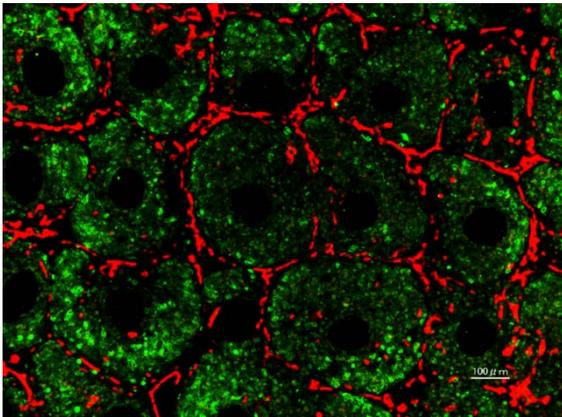
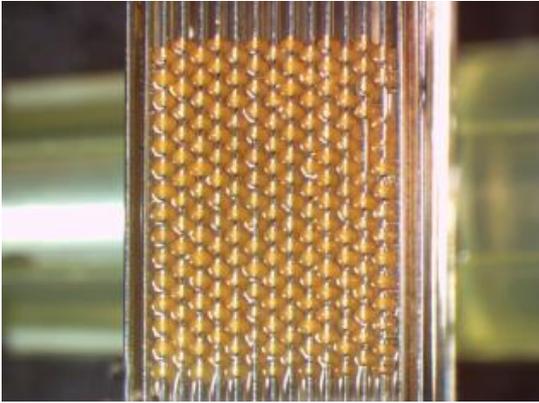
Orthotropic Tx

Heterotopic Tx



(Yanagi Y, et al. Scientific Reports 2017)

In vivo and *ex vivo* methods of growing a human cell derived liver bud through tissue connection



Green—hu-hepatocytes
Red—hu-endothelial cell



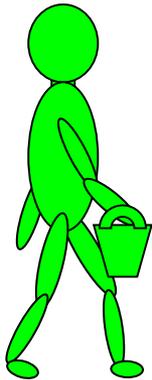
Broun- hu-Alb

(Yanagi Y, et al. Scientific Reports 2017)

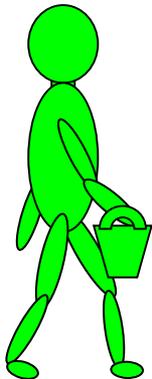
“*Translational Research*”



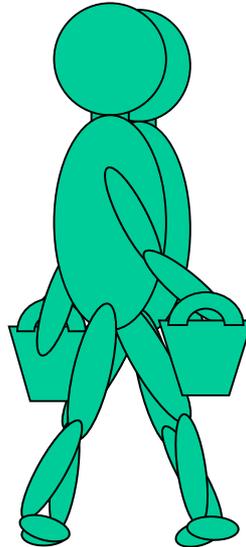
Medicine



Basic Science



Bioethics



Expert Clinician

(Kobayashi E & Montero EF. Act Cri Bras 20;194,2005)

Acknowledgement

Shall we do our best for the suffering patients

