厦门大学器官移植研究所
Organ Transplantation institute
of Xiamen University

Working Summary and Prospect of Organ Transplantation

——器官移植展望及我们如何应对挑战

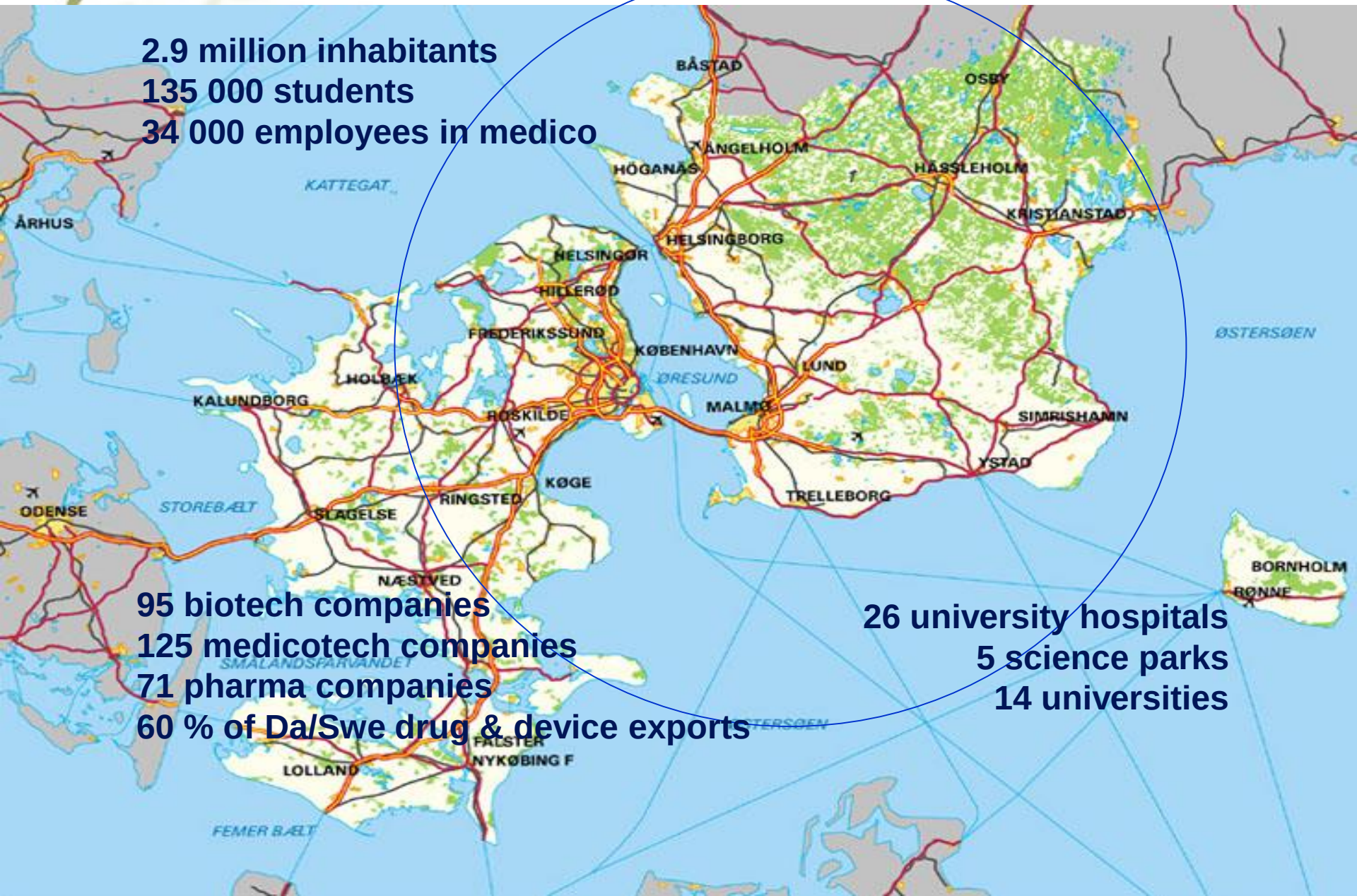
齐忠权 Zhongquan Qi, MD, Ph. D

－厦门大学医学院器官移植研究所
－哈尔滨医科大学附属第一医院肾脏病中心

Sweden


Sweden
International boundary
National capital
Railroad
Road
0 50 100 Kilometers
0 50 100 Miles
Lambert Conformal Conic Projection, SP 47N/62N
Norwegian Sea
NORWAY
FINLAND
RUSSIA
ESTONIA
LATVIA
LITHUANIA
DENMARK
Gulf of Bothnia
Gulf of Finland
Baltic Sea
ALAND ISLANDS
Oslo
Stockholm
Helsinki
Tallinn
Riga
Copenhagen
Base 802434 (A04937) 2-96

Medicon Valley



Lund University

38,000 undergraduate students
3,000 postgraduate students
80 educational programmes
1,000 courses

6,500 employees (45% women)
540 professors (12% women)
Turnover SEK 5,000 million

Malmo

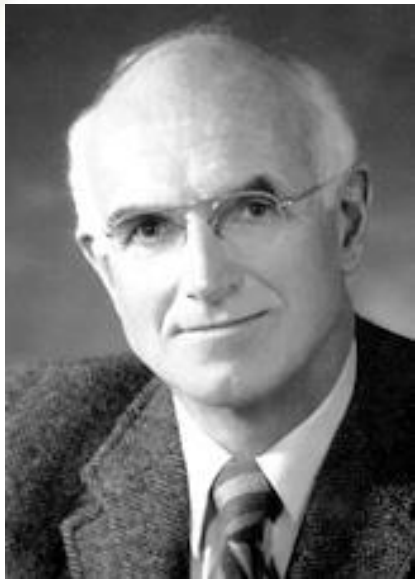
CRC of University Hospital

Malmö

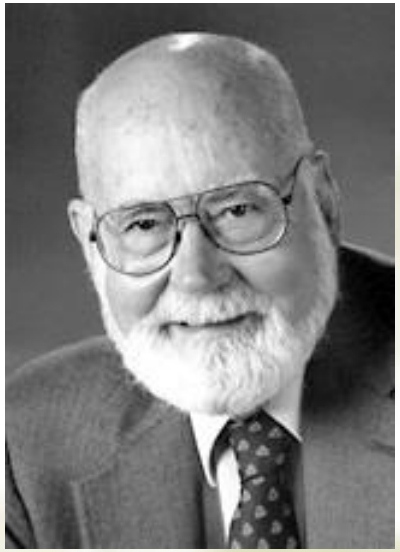
1990 The Nobel Prize

in Physiology & Medicine

"**Organ** and cell transplantation
in the treatment of human disease"



Joseph E. Murray
Brigham and Women's Hospital
Boston
b. 1919

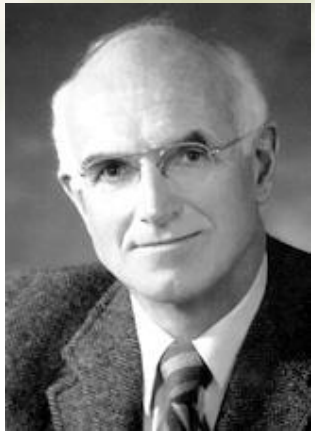


E. Donnall Thomas
Fred Hutchinson Cancer
Research Center
Seattle
b. 1920

Oct, 1954 Mr. Richard Herrick
(24 years old, with chronic renal failure

admitted to the Peter Brent Brigham Hospital

To make sure that he and his brother were **identical** twins



Dr. Joseph Murray asked
the police in Boston
to document their fingerprint patterns.
and its confidentiality was breached.

Skin grafts were exchanged between the twins and were not rejected.

A.D.A.M.

TRANSPLANT IMMUNOLOGY

- Clinical transplantation

Classifications

Limitations

- Mechanism of graft rejection

Antigen presentation, and Immune response

MHC antigen

- Tolerance induction

Choose the right donor

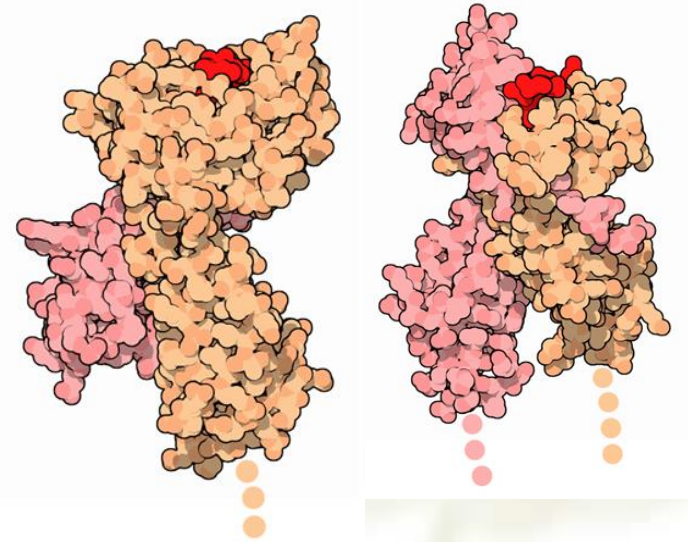
Immunosuppressive drugs

Pretreatment of Donor or recipient

Mechanism of graft rejection

HLA

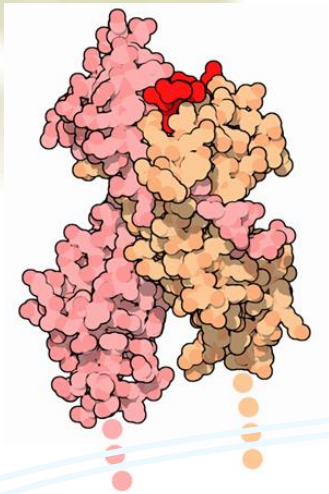
Any cell displaying some other HLA type is "non-self" and is an invader, resulting in the rejection of the tissue bearing those cells.

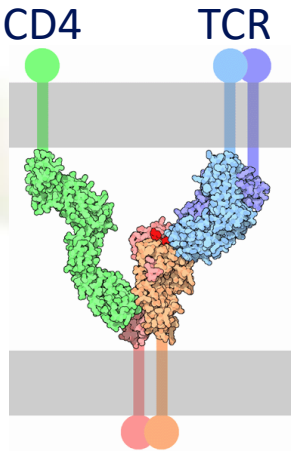


MHC Class I MHC Class II

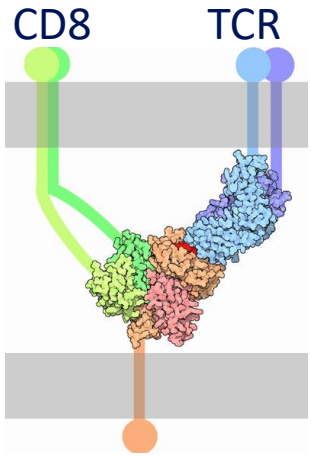
•Key part in antigen presentation

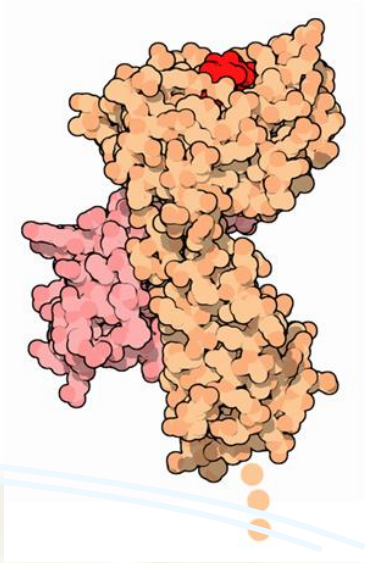
•As a most important antigen





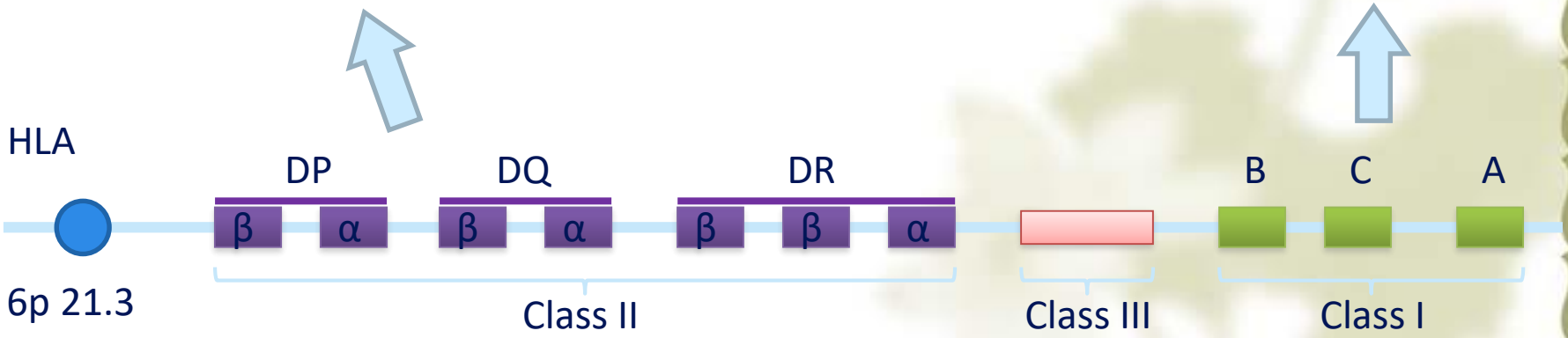
MHC Class II



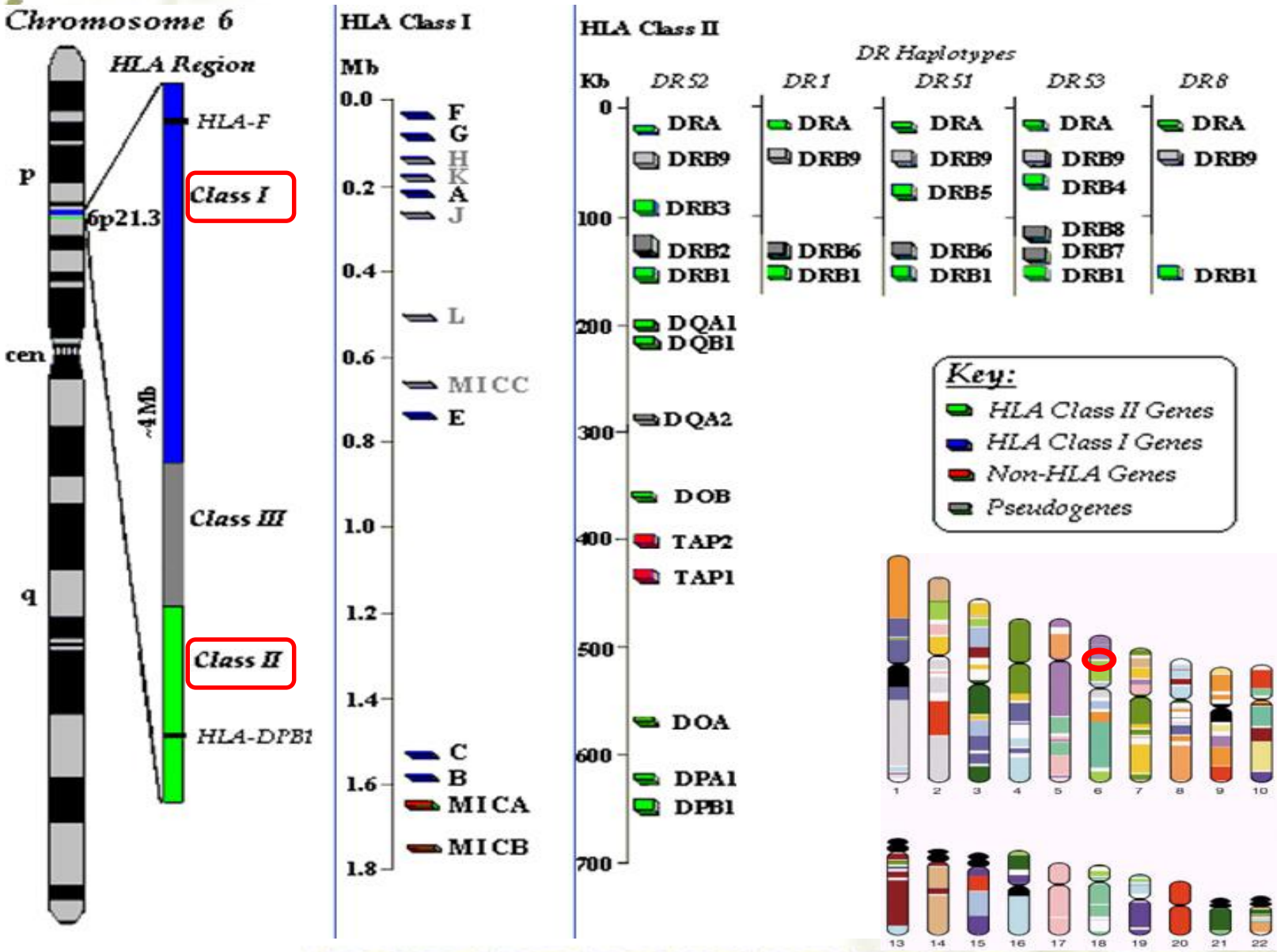


MHC Class I

Inner of APC Cell



HLA Gene


Chromosome 6
HLA Region
HLA-F
p
Class I
6p21.3
cen
~4Mb
Class III
q
Class II
HLA-DPB1
HLA Class I
Mb
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
F
G
H
K
A
J
L
MICC
E
C
B
MICA
MICB
HLA Class II
DR Haplotypes
Kb
DR52
DR1
DR51
DR53
DR8
0
100
200
300
400
500
600
700
DRA
DRB9
DRB3
DRB2
DRB1
DQA1
DQB1
DQA2
DOB
TAP2
TAP1
DOA
DPA1
DPB1
DRB5
DRB6
DRB4
DRB8
DRB7
Key:
HLA Class II Genes
HLA Class I Genes
Non-HLA Genes
Pseudogenes
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
X
Y

Mechanism of graft rejection

Antigen presentation, and Immune response

Antigen presentation

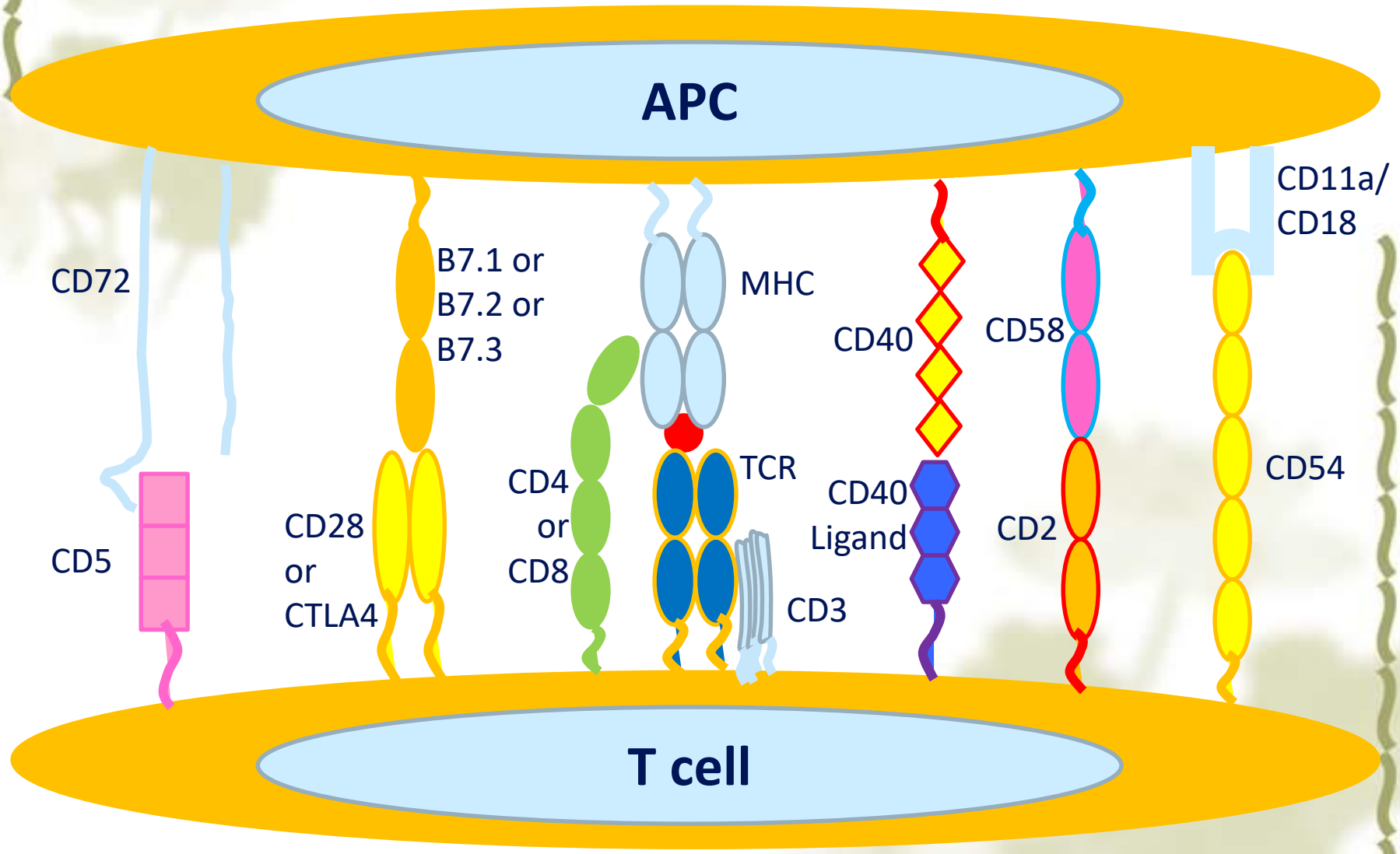
⇩

T Cell activation

⇩

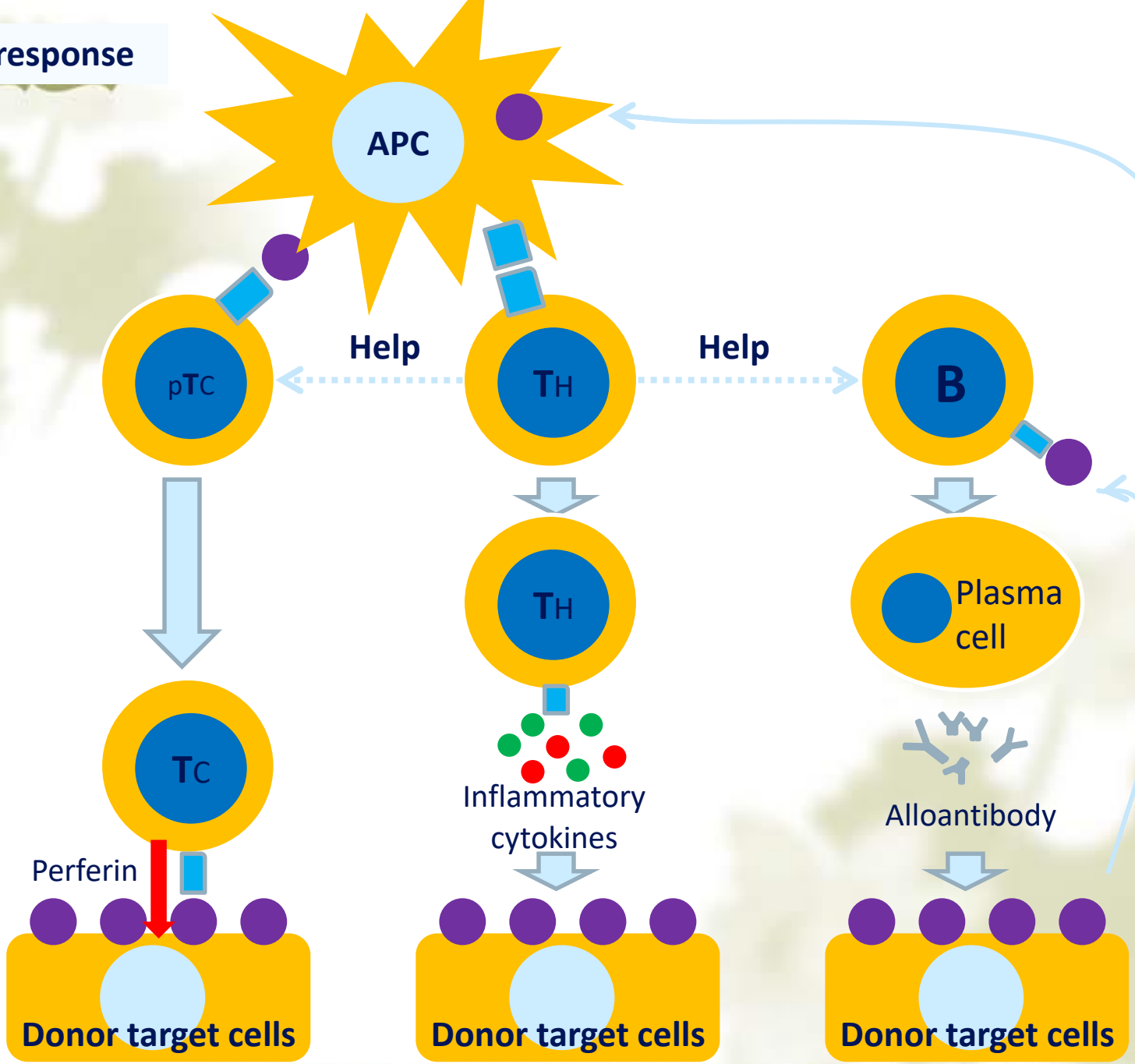
Immune response

T Cell activation



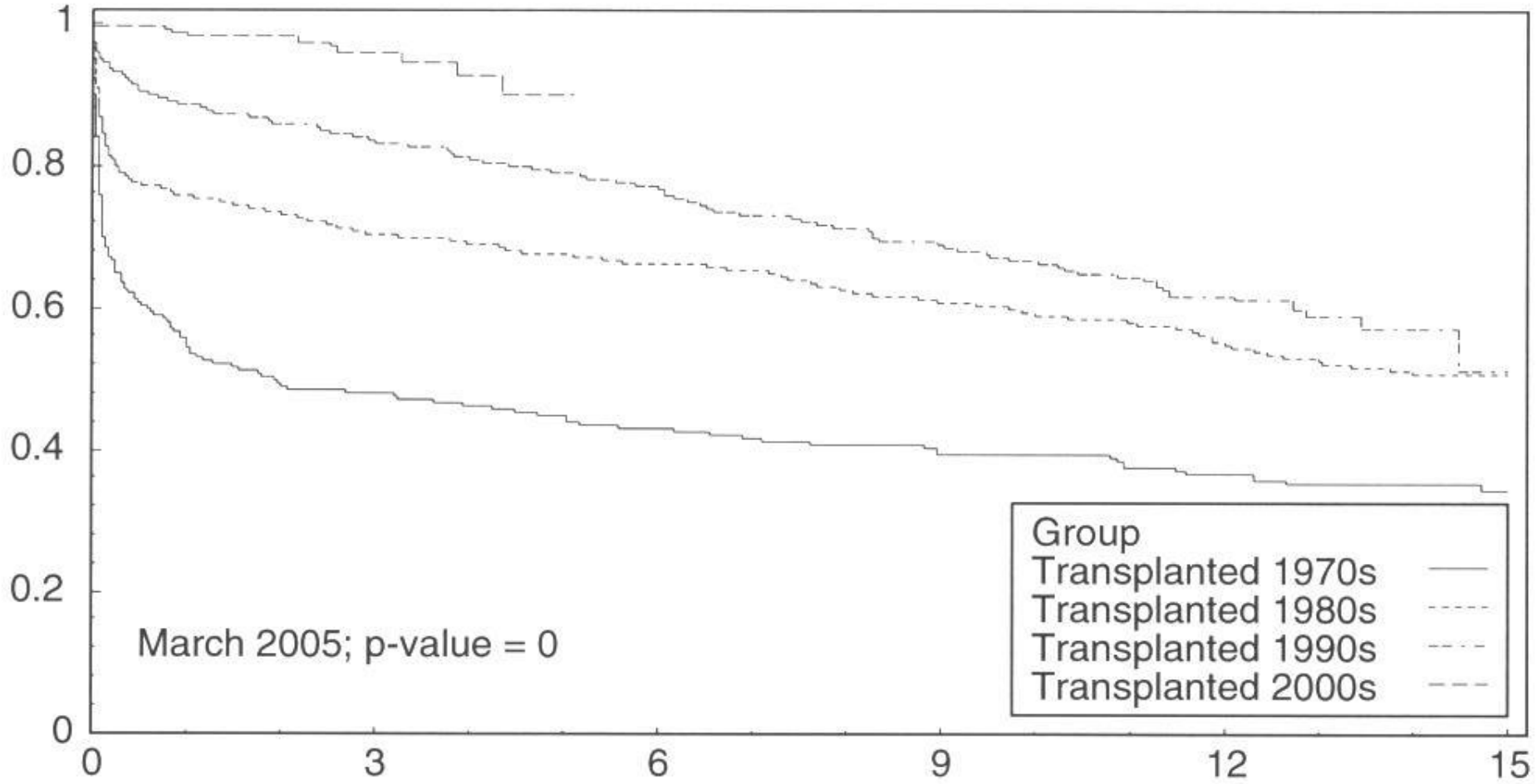
Cell surface interactions involved in activation of T cells

Immune response



Graft survival

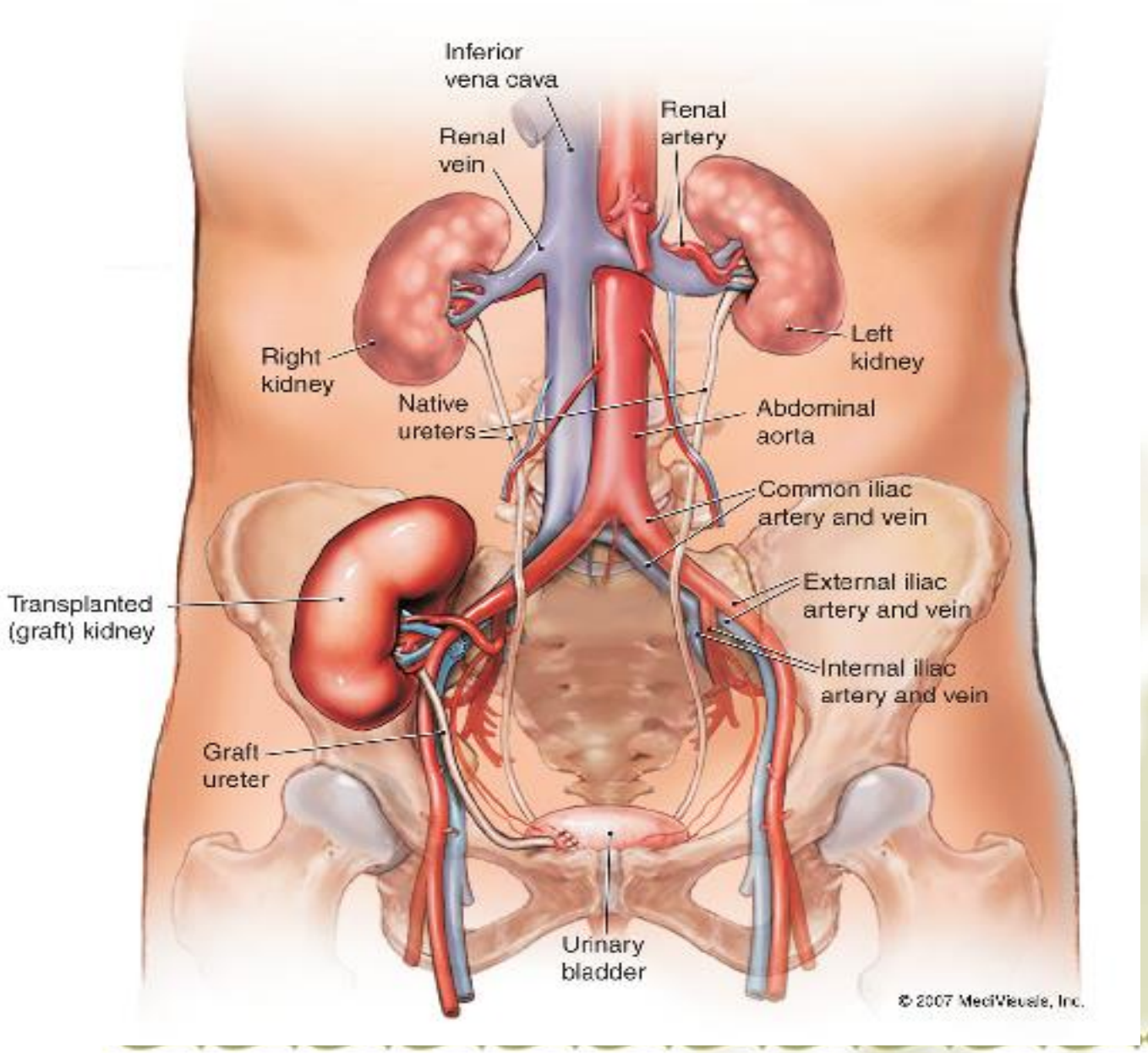
Renal transplantation 1969-

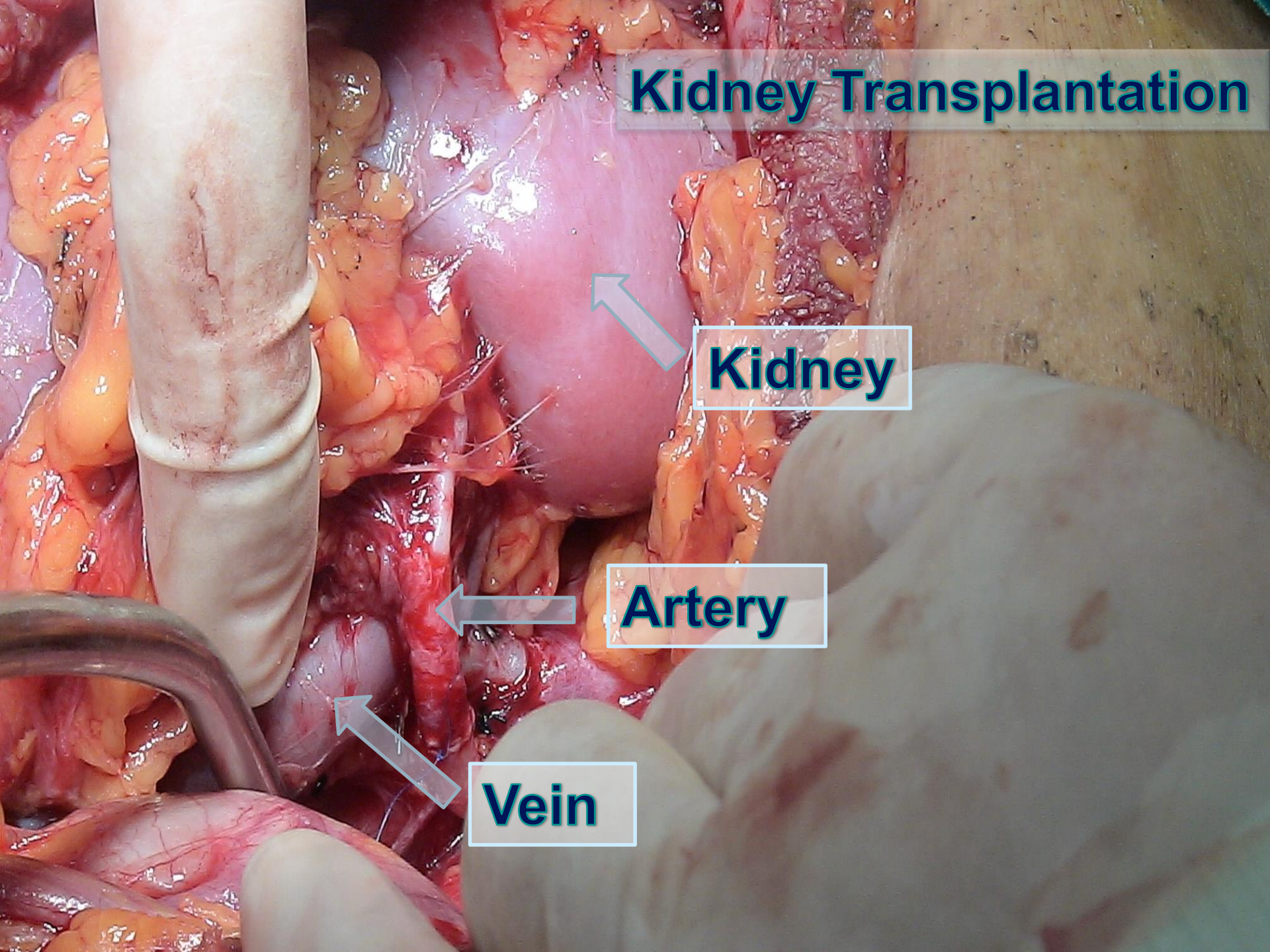


Number at Risk

313	111	88	75	60	49
542	344	293	241	190	158
570	456	354	197	79	1
278	102	0	0	0	0

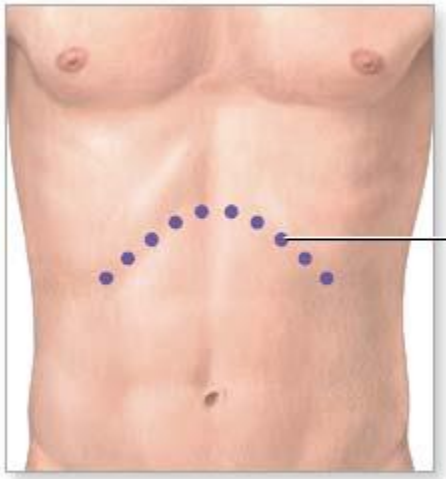
A Grafted (Transplanted) Kidney

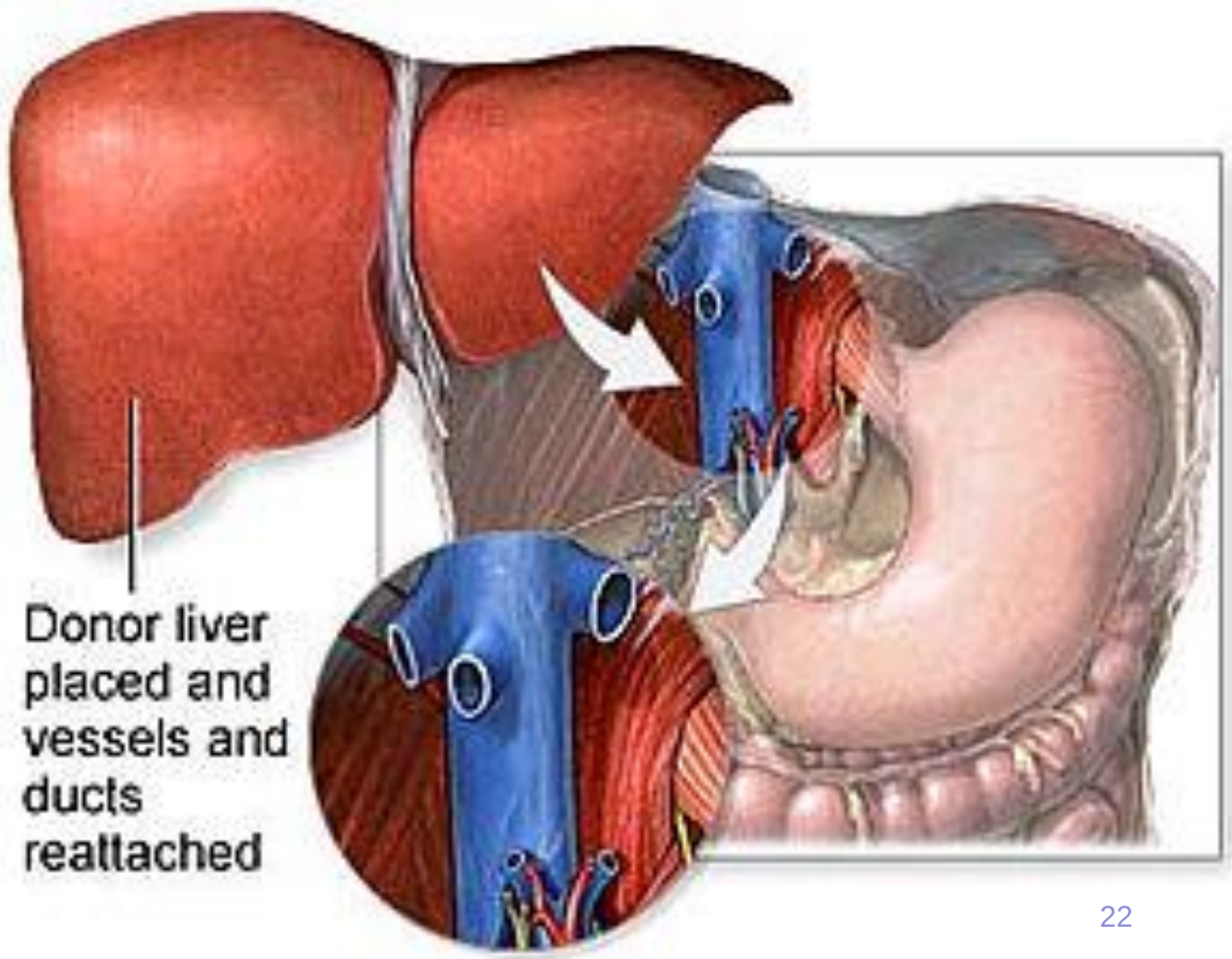



Kidney Transplantation
Kidney
Artery
Vein

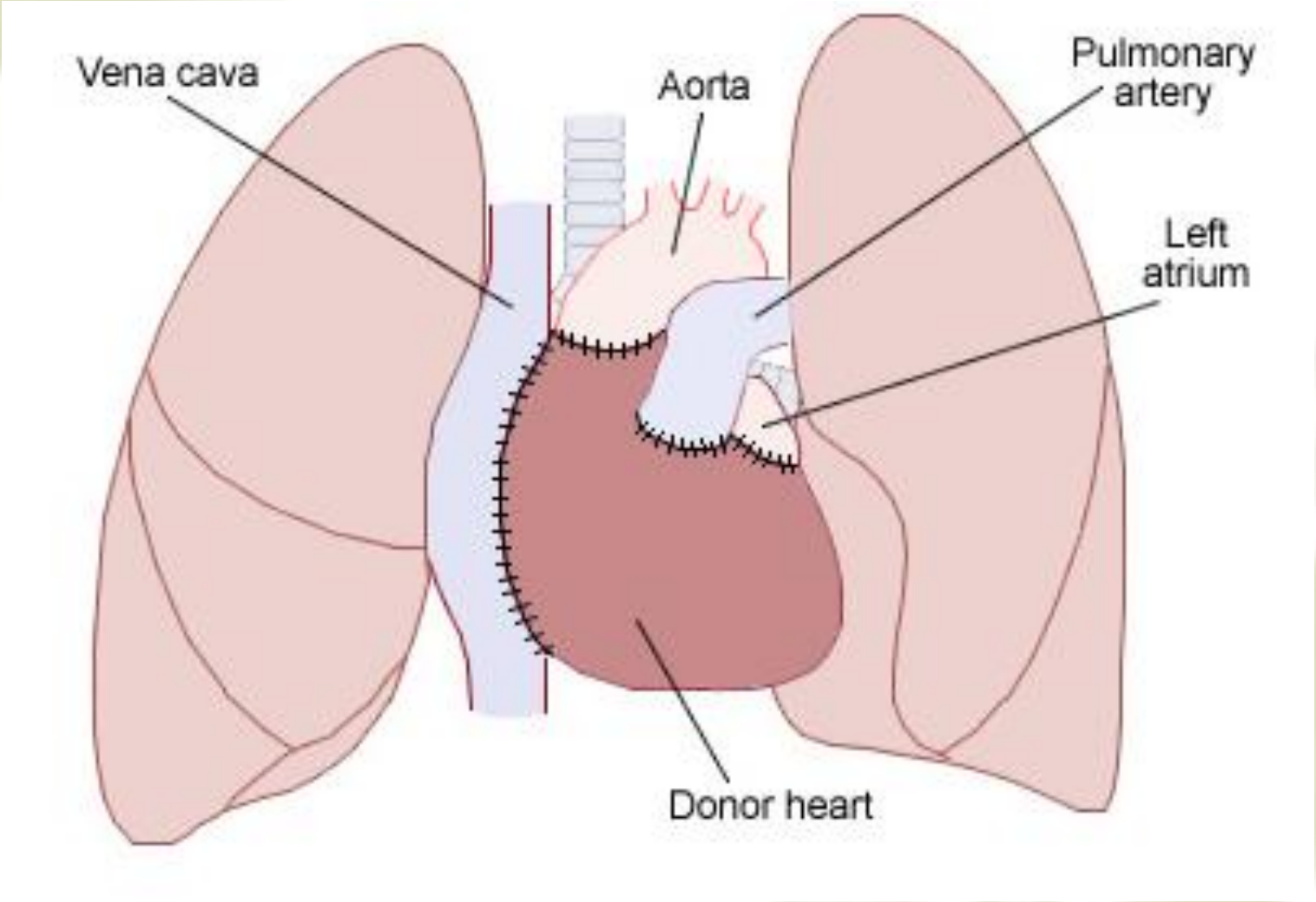

2006 6 8

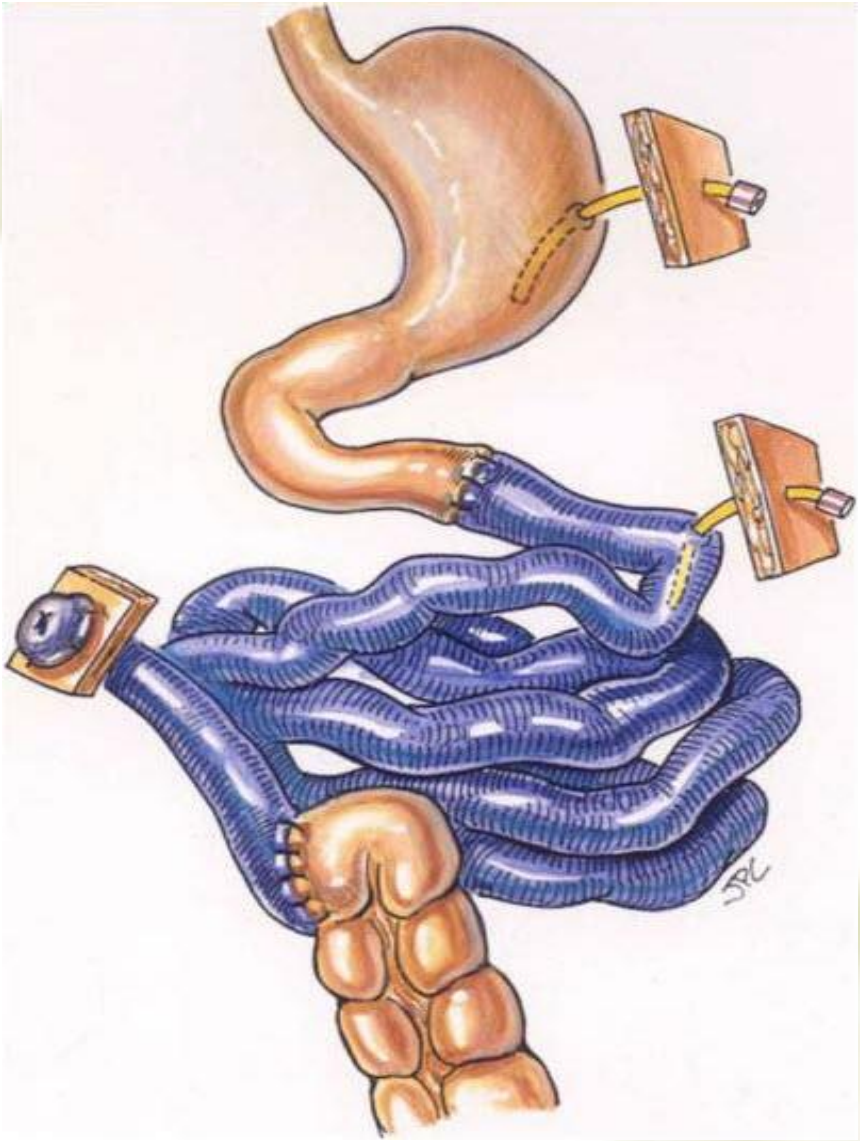
Liver Transplantation



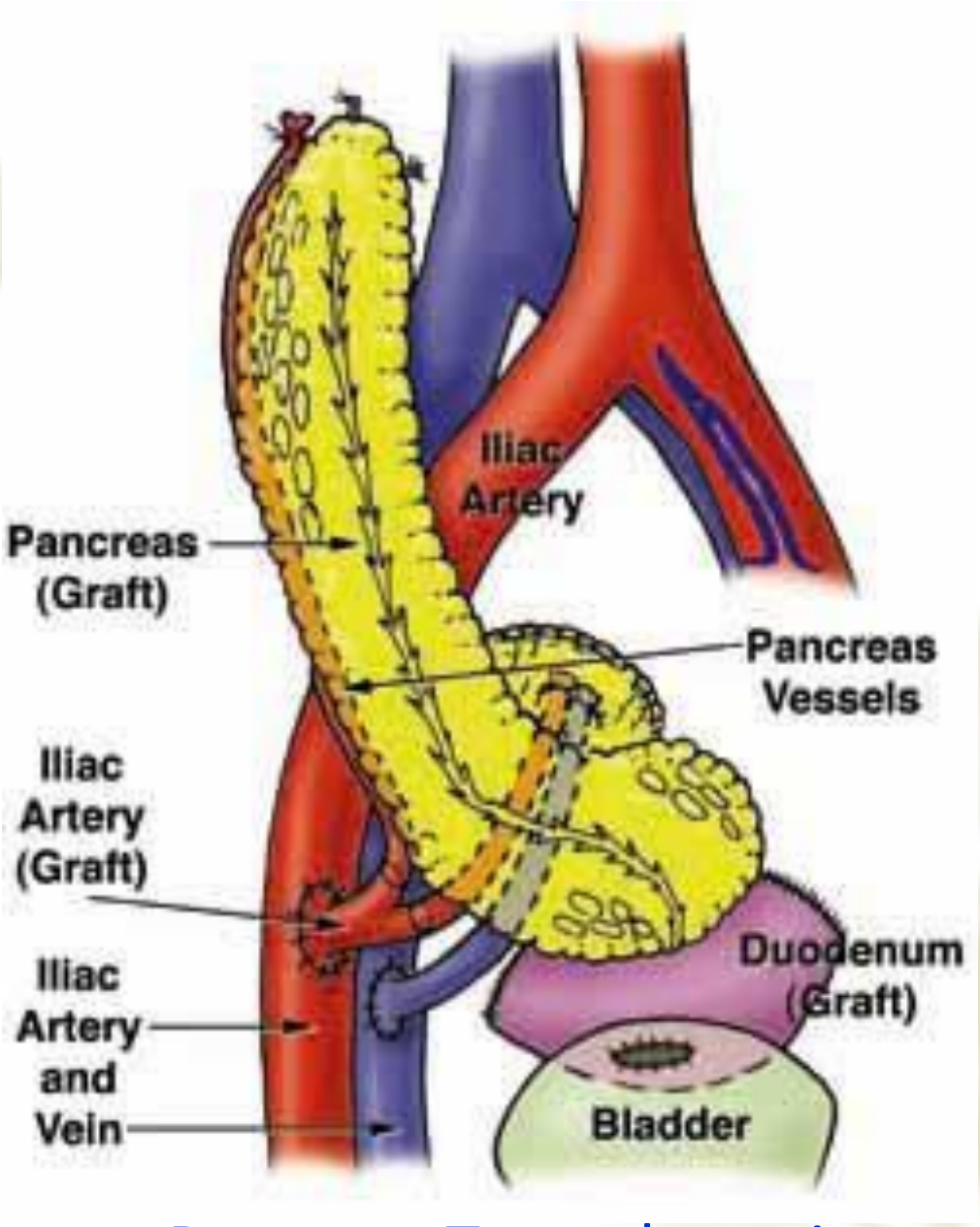


Heart Transplantation



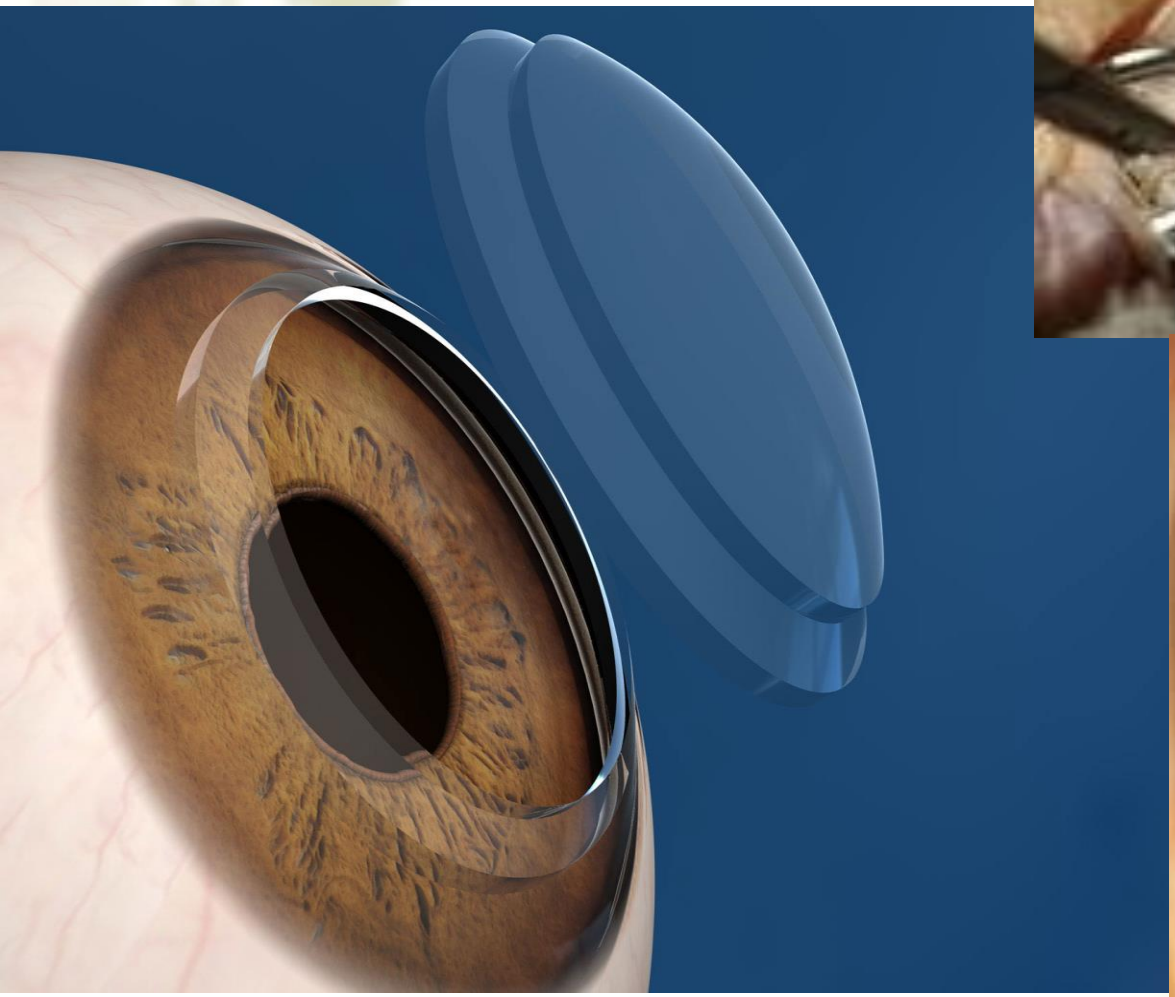


Intestine Transplantation

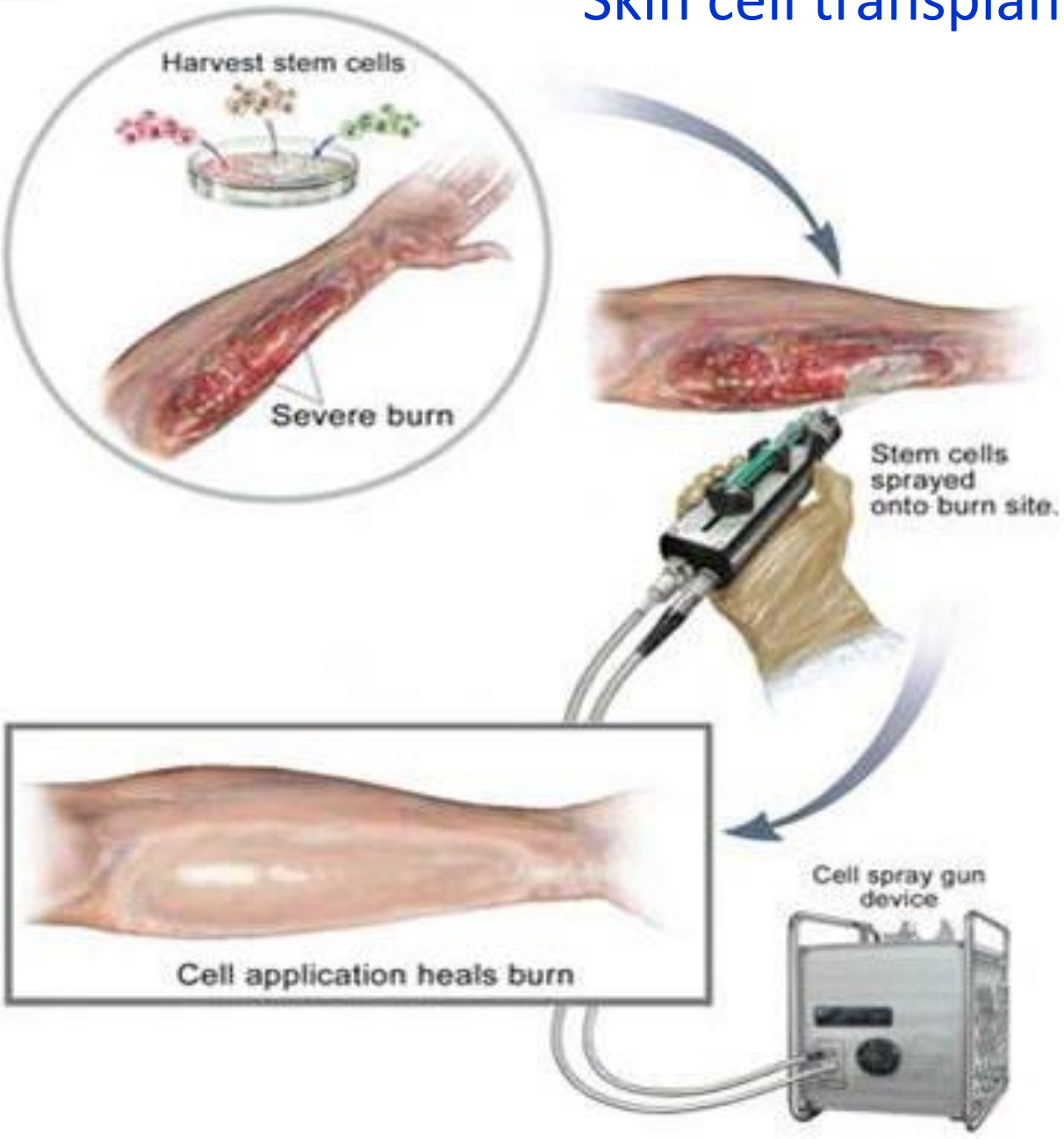


Pancreas Transplantation

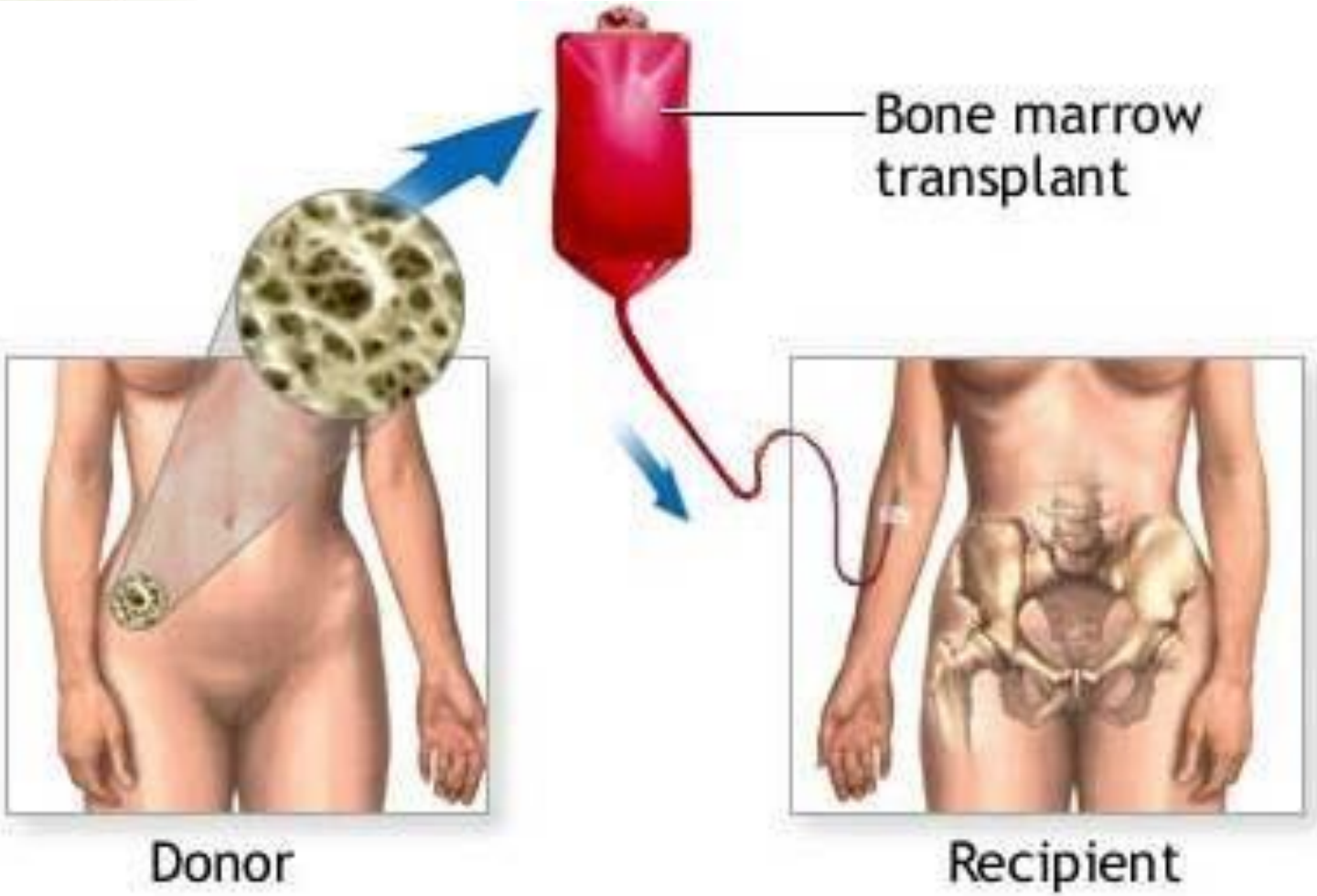
Cornea Transplantation



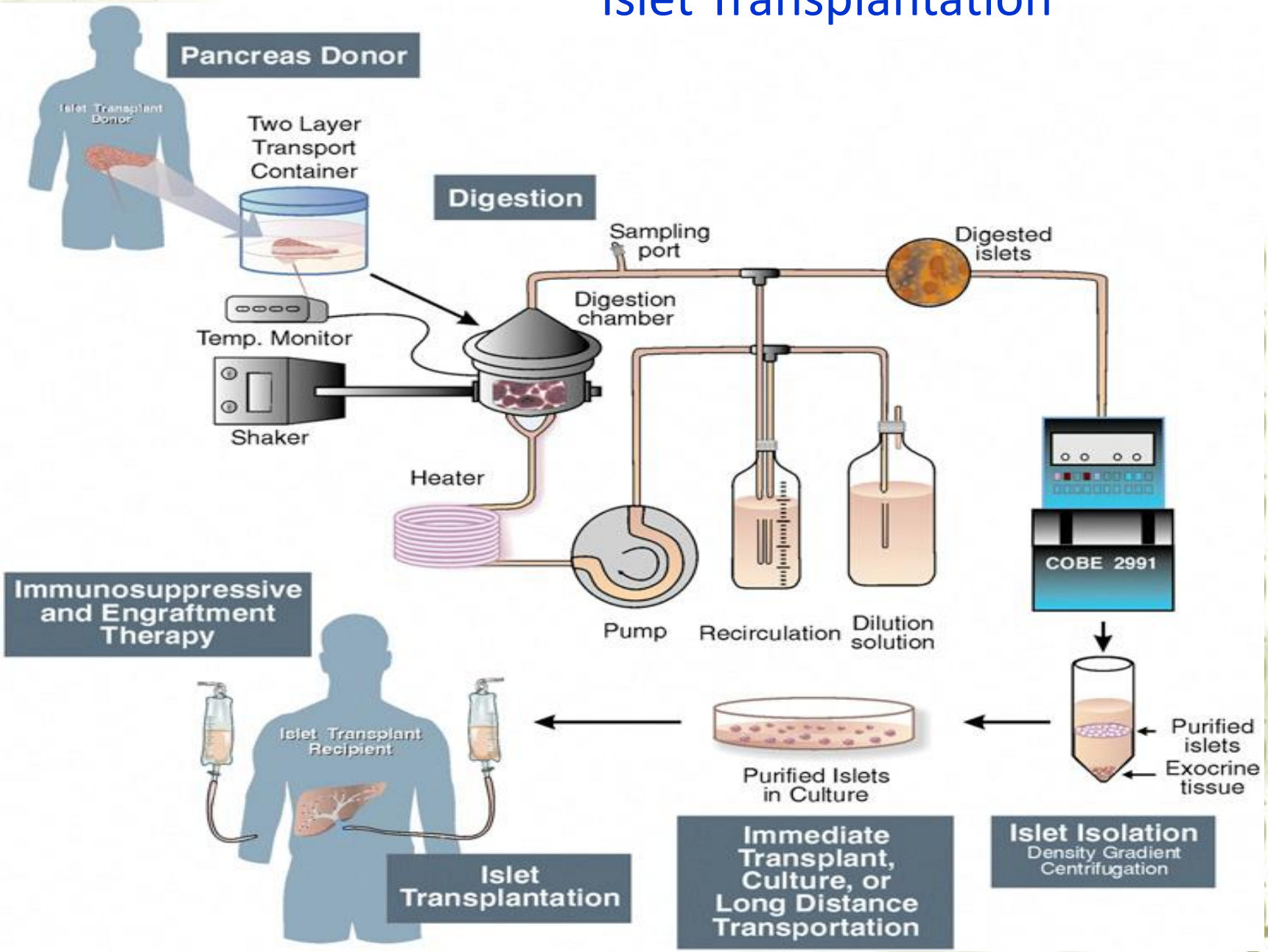
Skin cell transplantation

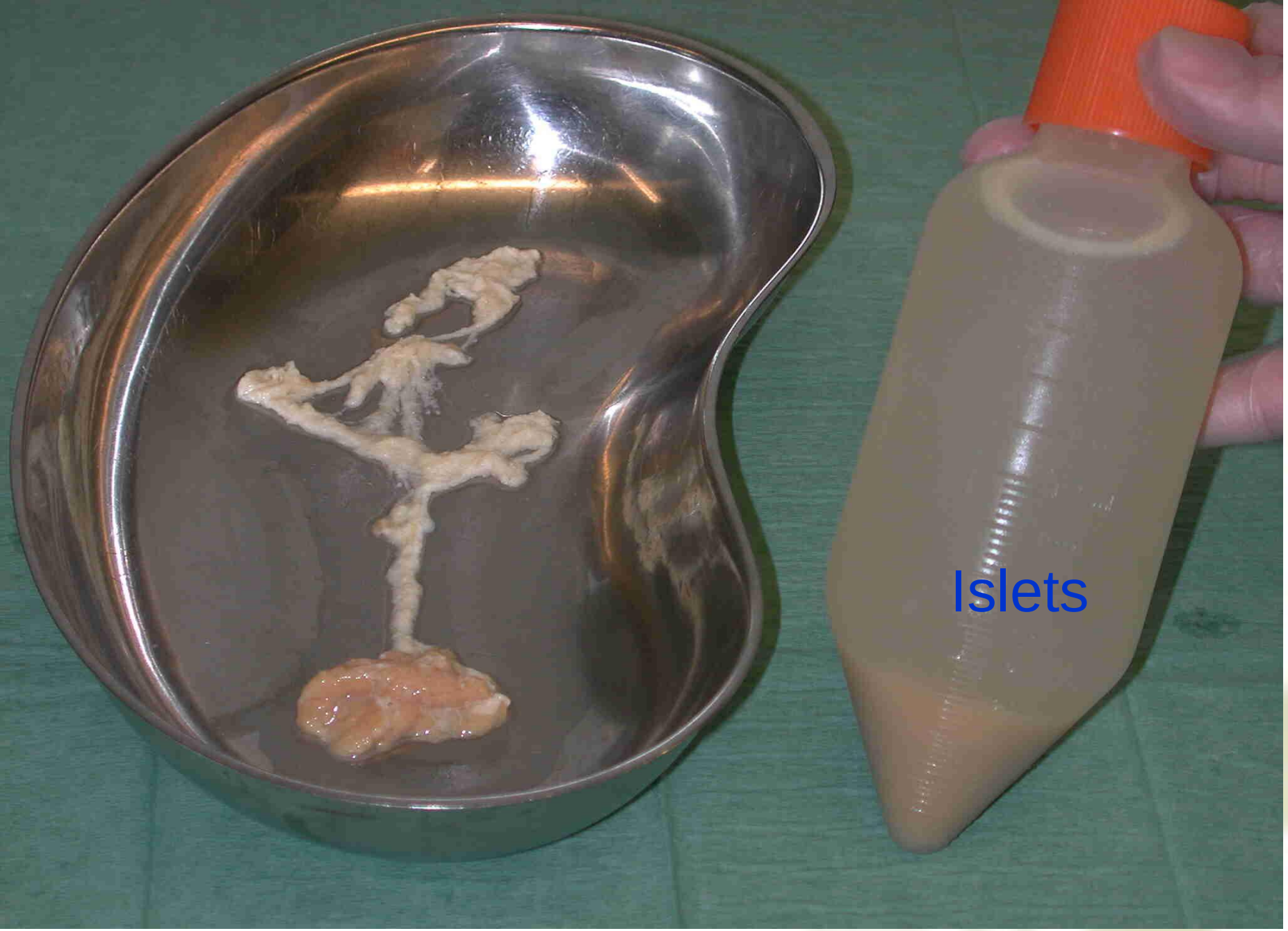


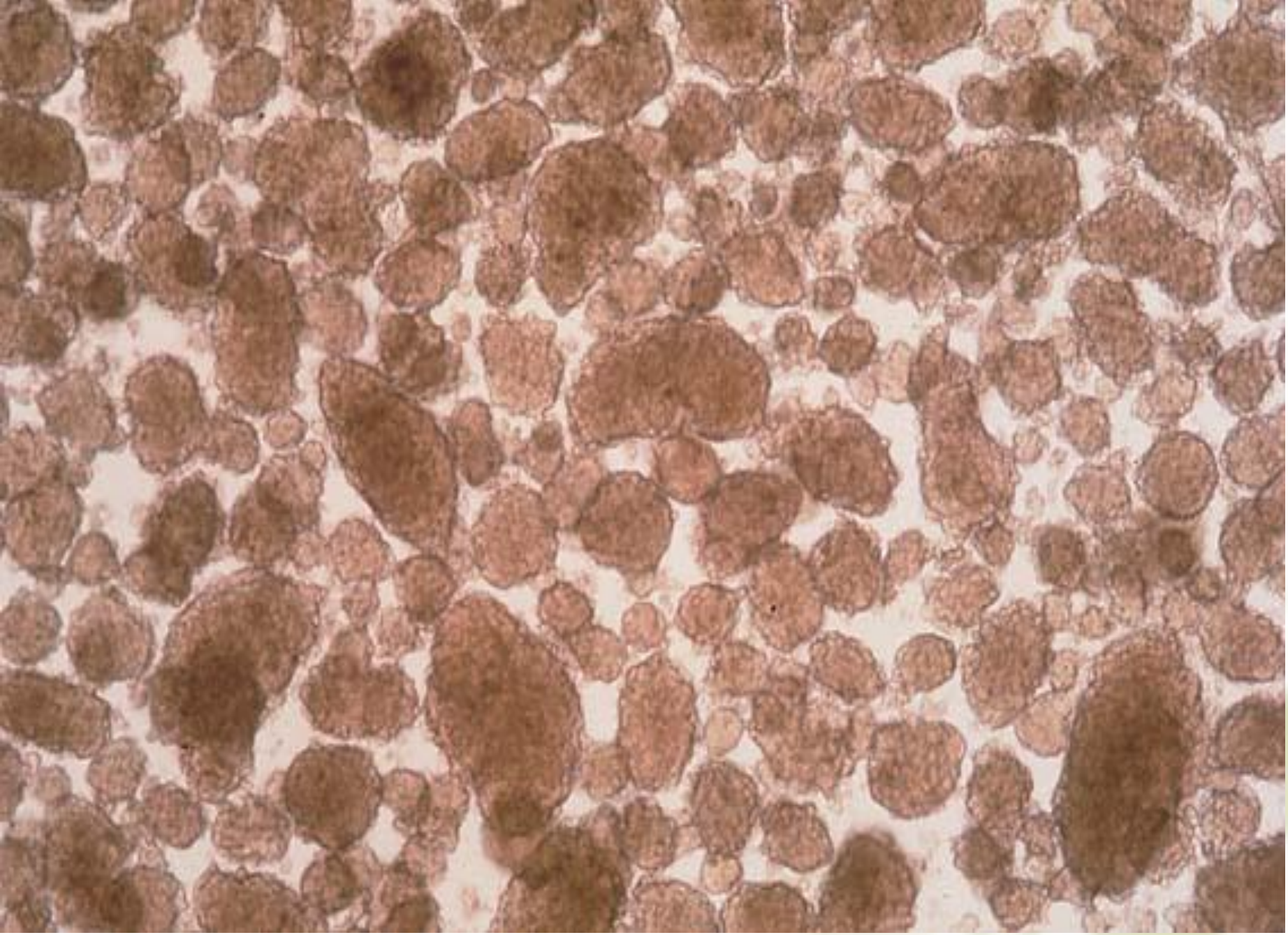
Cell transplantation



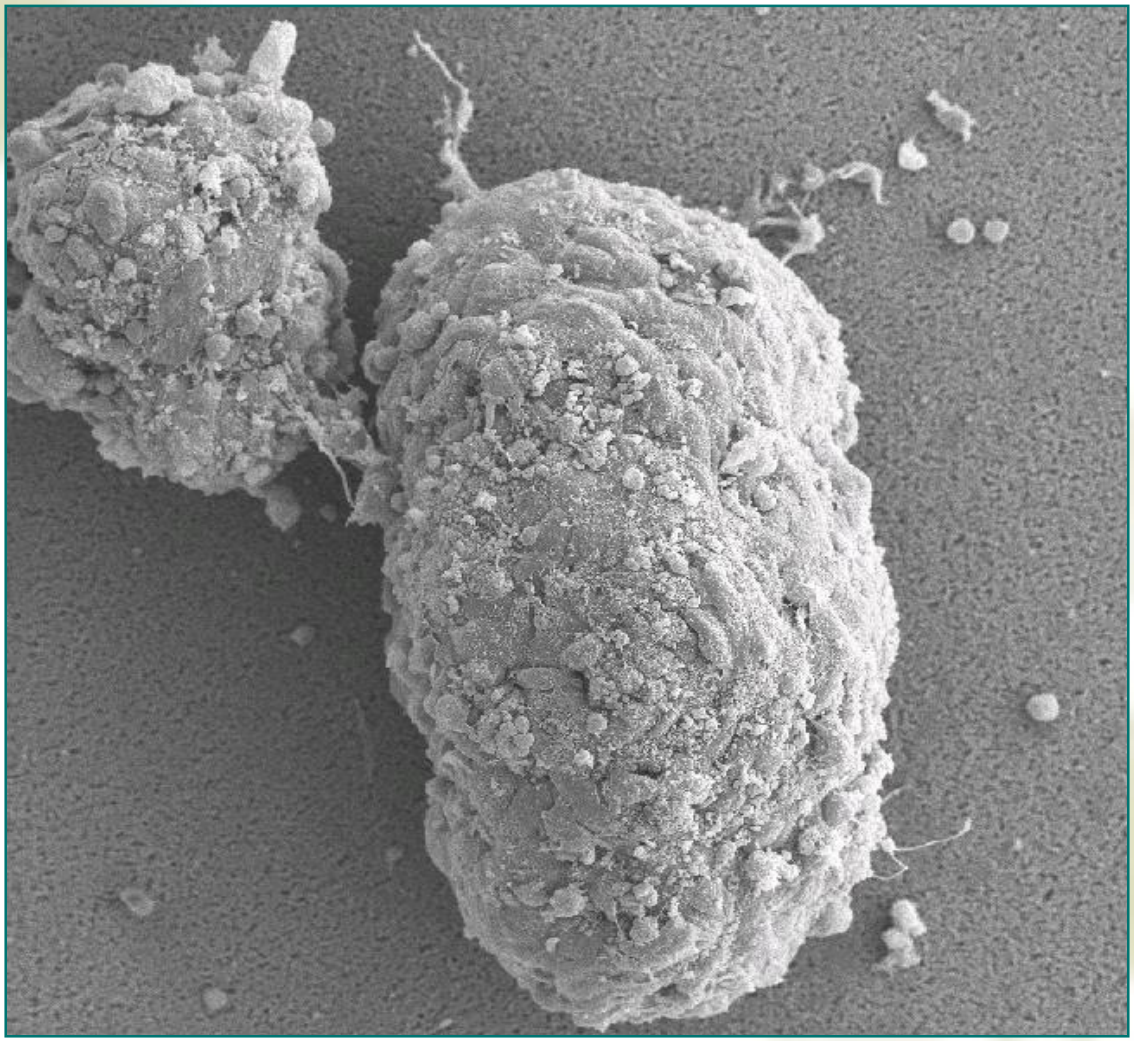
Islet Transplantation




Islets



Islets



Islet Transplantation

Dialysis

6 hours per day, 3 times every week

In Sweden

- **1995—1999:** **Lund University, Ph.D**
- **1999—2001:** **Lund University,**

  Post doctoral research
- **2001—2006:** **Malmo Hospital**

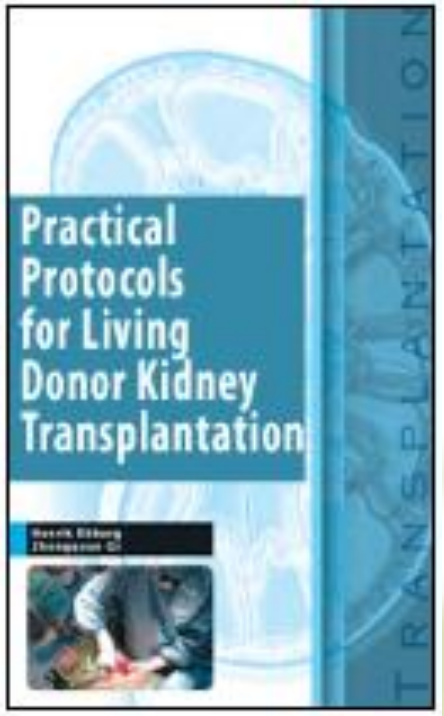
  Transplant Surgery,

  Researcher

In Sweden

Basic research

- Mechanism of Transplant rejection
- Immunosuppressive development
- Published more than 30 SCI papers



Clinical research

- Hundreds of cases of transplants
- Clinical renal transplant guidelines

活体供肾肾脏移植
临床规范

Henrik Ekberg（瑞典）
齐 忠 权（中国）

TRANSPLANTATION

www.tts.org

TTS Council


RUSSIA
KAZAKHSTAN
MONGOLIA
KYRGYZSTAN
TAJIKISTAN
CHINA
INDIA
NEPAL
BHUTAN
BANGLADESH
BURMA
LAOS
THAILAND
VIETNAM
CAMBODIA
MOROCCO
ALGERIA
TUNISIA
LIBYA
MAURITANIA
MALI
NIGER
CHAD
SENEGAL
THE GAMBIA
GUINEA-BISSAU
GUINEA
BURKINA FASO
GHANA
NIGERIA
TOGO
BENIN
SIERRA LEONE
LIBERIA
CÔTE D'IVOIRE
EQ. GUINEA
C.A.R.
CAMEROON
GABON
REP. OF THE CONGO
DEM. REP. OF THE CONGO
ANGOLA
ZAMBIA
MOZAMBIQUE
NAMIBIA
ZIMBABWE
BOTSWANA
MADAGASCAR
LESOTHO
SWAZILAND
SOUTH AFRICA
TRINIDAD AND TOBAGO
GUYANA
SURINAME
French Guiana (FRANCE)
BRAZIL
BOLIVIA
PERU
SOUTH ATLANTIC OCEAN
PACIFIC OCEAN
Equator
PAPUA NEW GUINEA
SOLOMON ISLANDS
Antarctica


Happy New Year! Zhongquan Qi From Xiamen University 2007-12-31

China – Great Development

In 2005, there were in China

- 3,500 liver transplants performed

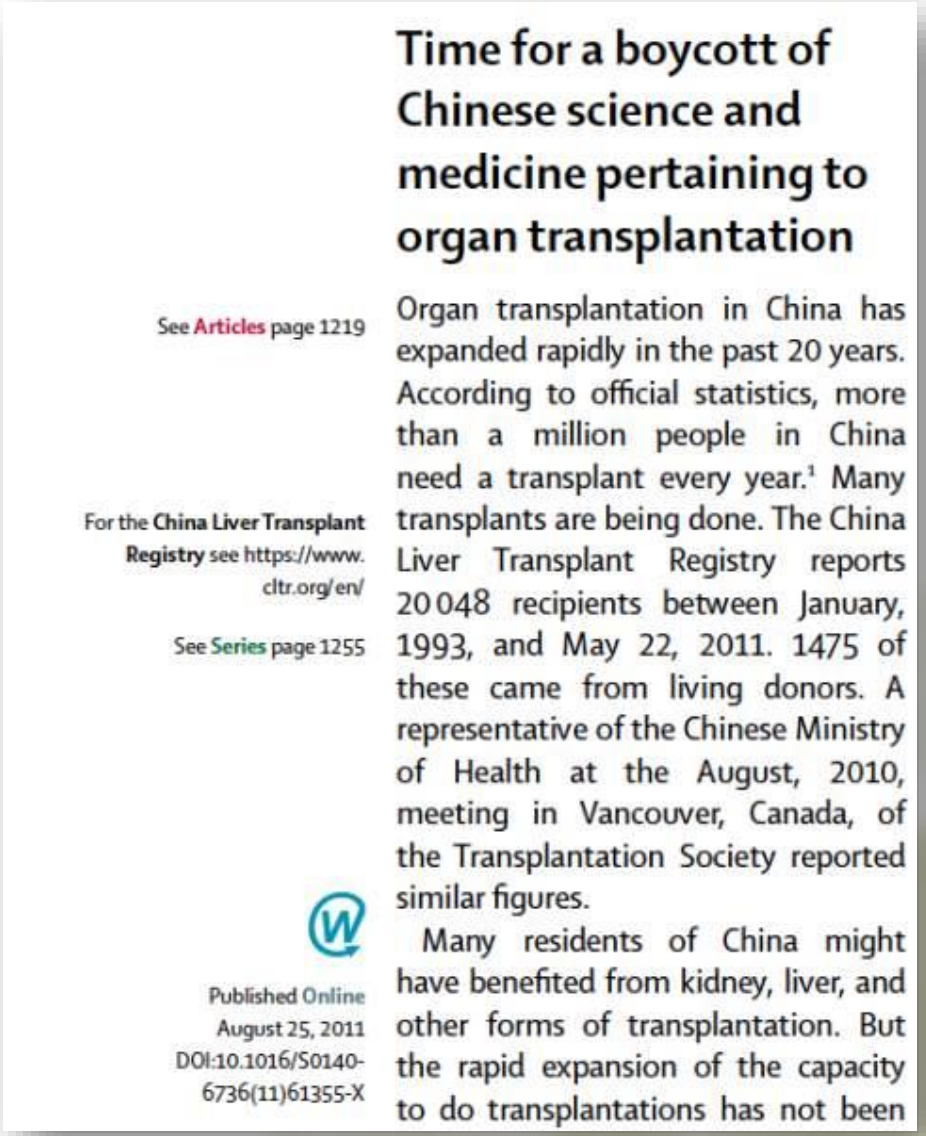
  (in 13 hospitals performing more than 100)

- 8000 kidney transplants
- 200 heart transplants
- 70 lung transplants

Dr. Zhu Jiye of Beijing University People's Hospital

2011年10月，《Lancet》刊登文章：

- 抗议中国不合法使用器官；
- 呼吁拒绝接收中国一切临床移植的研究文章。



Time for a boycott of Chinese science and medicine pertaining to organ transplantation

See Articles page 1219

Organ transplantation in China has expanded rapidly in the past 20 years. According to official statistics, more than a million people in China need a transplant every year.[1] Many transplants are being done. The China Liver Transplant Registry reports 20 048 recipients between January, 1993, and May 22, 2011. 1475 of these came from living donors. A representative of the Chinese Ministry of Health at the August, 2010, meeting in Vancouver, Canada, of the Transplantation Society reported similar figures.

For the **China Liver Transplant Registry** see https://www.cltr.org/en/

See Series page 1255

Many residents of China might have benefited from kidney, liver, and other forms of transplantation. But the rapid expansion of the capacity to do transplantations has not been

Published Online August 25, 2011 DOI:10.1016/S0140-6736(11)61355-X

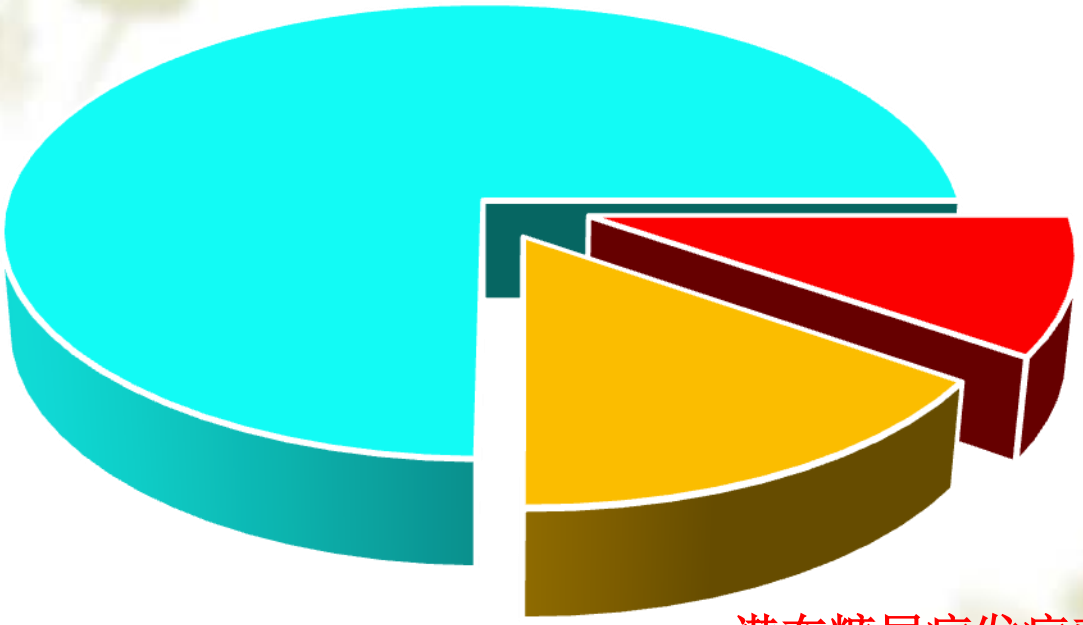
The Lancet, October 2011:378(9798):1218.

重大疾病导致的器官衰竭

已经成为我国的重大社会问题。

- 全球每年有**1700万**人死于心脏病。
- 全球每年有**700万**人死于癌症。
- 全球每年有**380万**人死于糖尿病。
- 我国每年有**30万**人死于肝功能衰竭。
- 我国每年有**100万**人死于冠心病，**150万**死于高血压并发症。
- 我国尿毒症发病率以每年**10%**增加，有**150万**人依赖肾脏病代替治疗生存。

中国糖尿病流行病学调查



已发糖尿病发病率达9.7%

≈1.33亿

潜在糖尿病发病率达15.5%

≈2.13亿

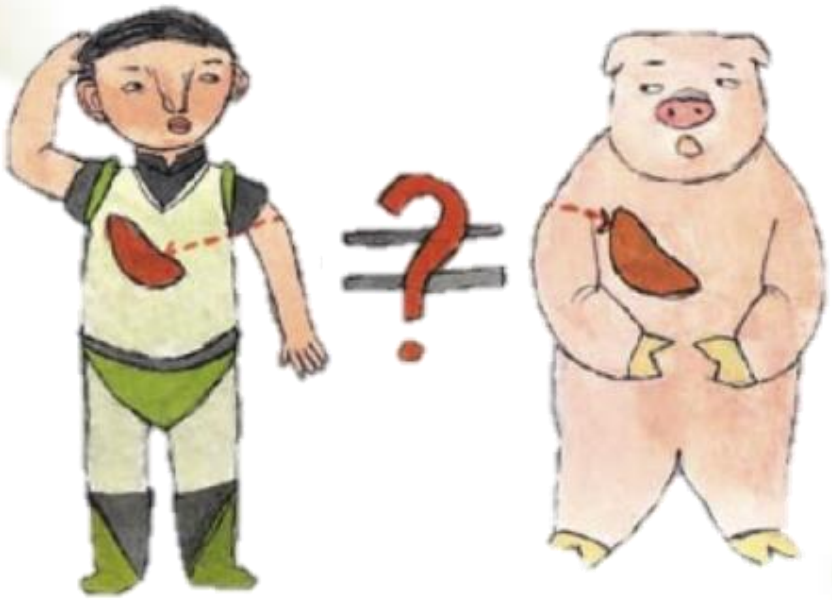
N Engl J Med 2010:362(12): 1090-1101

供体短缺严重制约了中国器官移植医学的发展

<1%

开展器官移植 1万

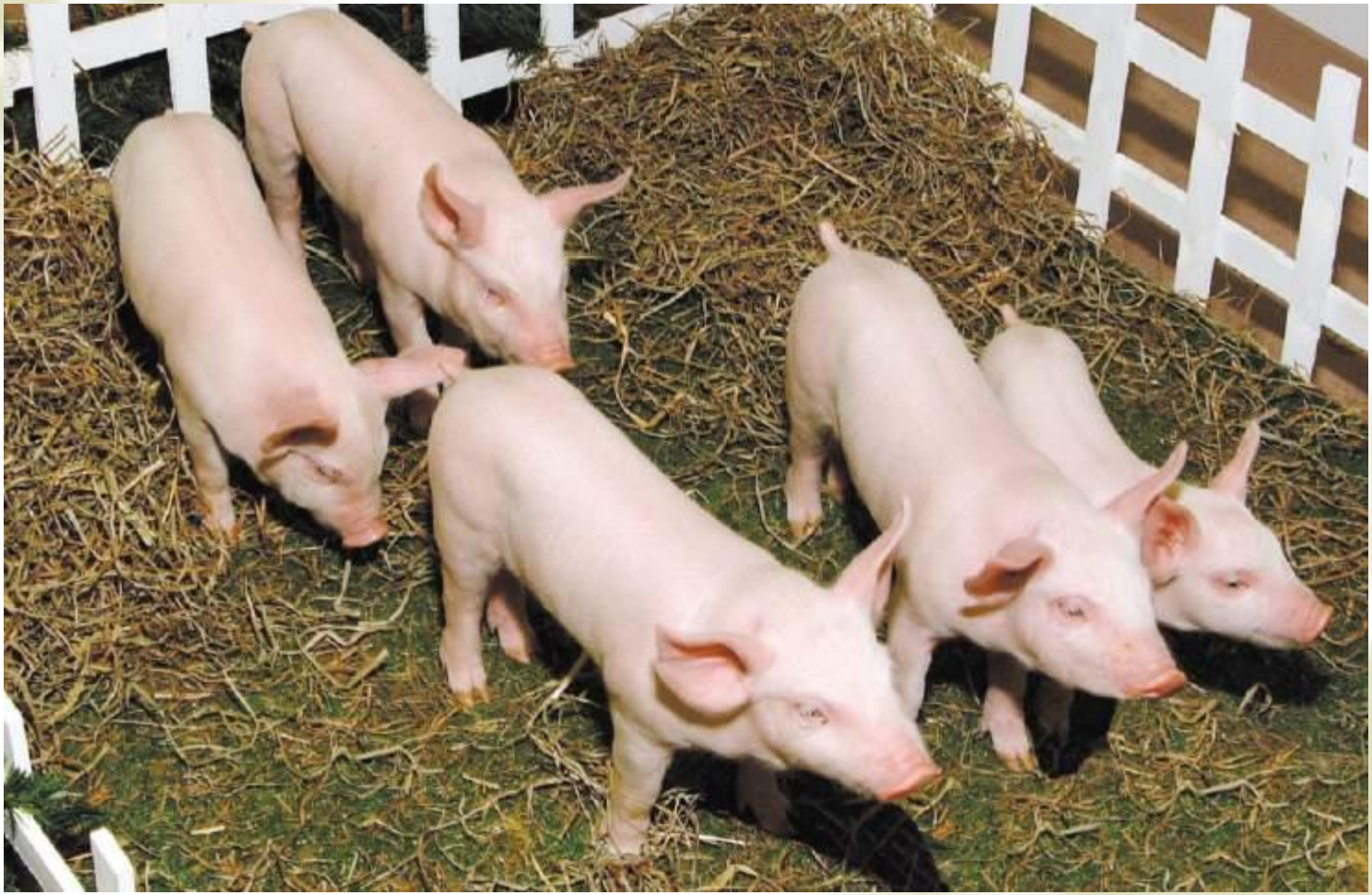
等待器官移植 150万



同种器官移植 ⇒ 异种器官移植


YES !

GalT-KO猪的诞生为猪-NHPs异种移植的开展奠定了坚实的基础。



Nature biotechnology 2002(20): 251-255

异种移植面临的主要障碍

转基因修饰
+
免疫抑制策略

超急性排斥

迟发型抗体介导的排斥

异种体液排斥

记性细胞排斥

异种移植面临的主要障碍

转基因修饰+免疫抑制策略

超急性排斥

迟发型抗体介导的排斥

异种体液排斥

记性细胞排斥

凝血功能障碍
Coagulation dysfunction
炎症反应
Inflammation

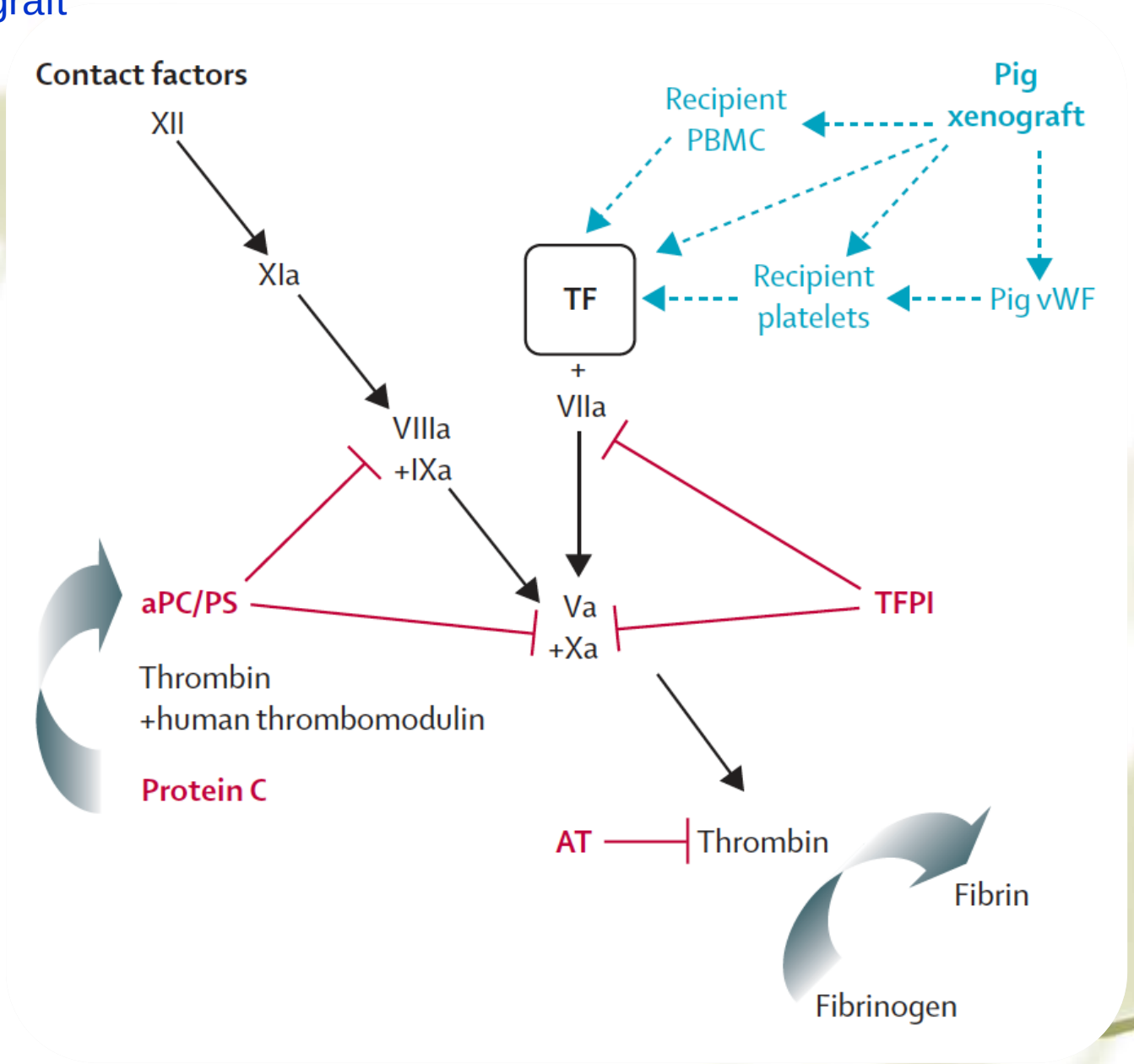
移植物失功

心、肾、肝、肺等异种实体器官移植几年内不会在临床开展

Strategies to resolve the Coagulation dysfunction

- Additional transgene pig: GTKO/hCRP/CD39
- Intensive immunosuppressive therapy
- MSC cotransplantation

Figure 4: Major features of the human coagulation cascade in response to a pig xenograft



THE LANCET

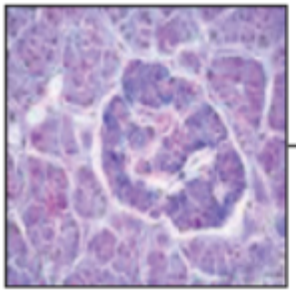
Clinical xenotransplantation: the next medical revolution?

Burcin Ekser, Mohamed Ezzelarab, Hidetaka Hara, Dirk J van der Windt, Martin Wijkstrom, Rita Bottino, Massimo Trucco, David K C Cooper

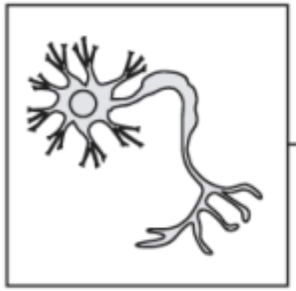
Search strategy and selection criteria

We searched Medline and PubMed for articles published in English between 2001 and 2011. Search terms included "xenotransplantation", "xenograft", in combination with "large animals", "pig", "porcine", "baboon", "monkey", and "nonhuman primate". Selection was based on our accumulated experience in the specialty. We also reviewed seminal articles published more than 10 years ago.

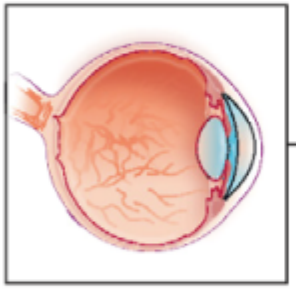
David K. C. Cooper



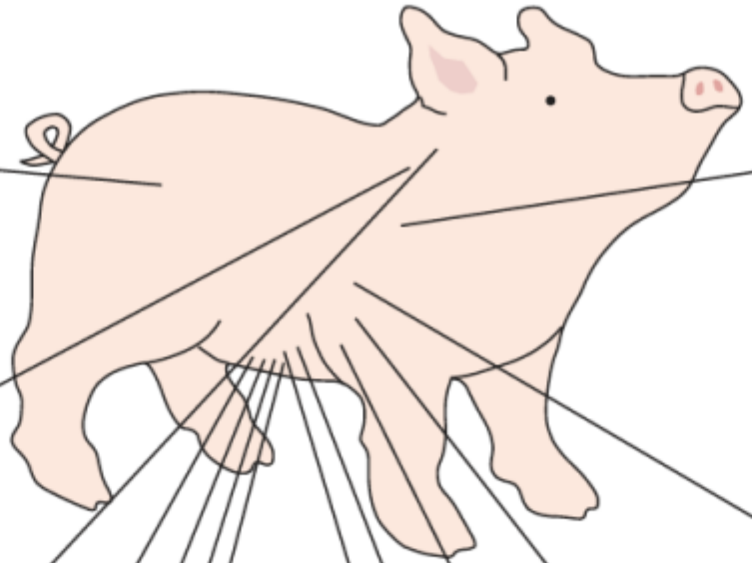
Pancreatic islets
(diabetes mellitus)

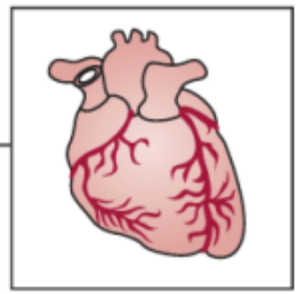


Neuronal cells
(Parkinson's and Huntington's diseases)

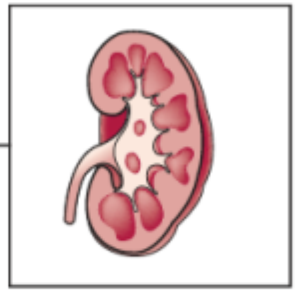


Eye tissues
(corneal and neuro-retinal blindness)

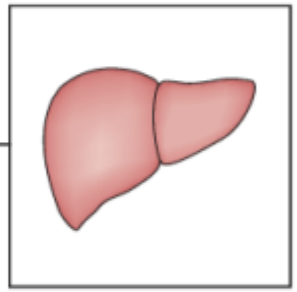




Heart
(bridge to allotransplantation, end-stage cardiac disease)

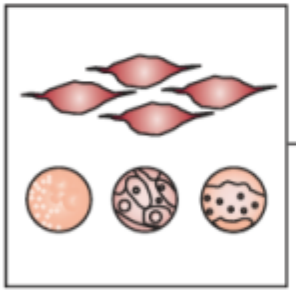


Kidney
(end-stage renal disease)



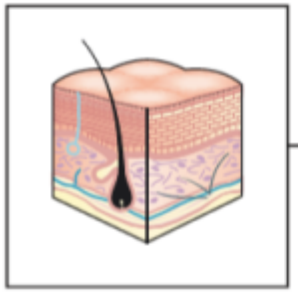
Liver
(bridge to allotransplantation, end-stage hepatic disease)

Red blood cells
(bleeding, anaemia)

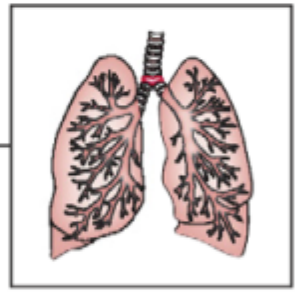


Mesenchymal stem cells
(cytotherapy)

Decellularised heart valve
(cardiac valve replacement)

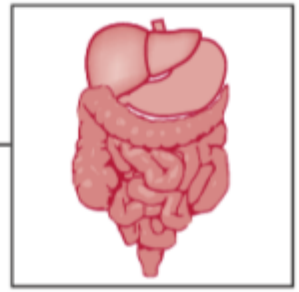


Decellularised pig tissues
(ligament, small intestinal stroma, skin, bone, cartilage)
(general surgery and orthopaedic surgery)



Lung
(end-stage pulmonary disease)

Small bowel
(bridge to allotransplantation, intestinal insufficiency, eg, short-bowel syndrome)



Multivisceral
(multiorgan failure)

Pig organs

- Pancreatic islets
- Neuronal cells
- Hepatocytes
- Corneas
- Red blood cells

Strategies to resolve the remaining barriers

- Coagulation dysfunction
- T-cell response
- Physiology
- Safety
- Regulatory, legal, and ethical issues

Table: Genetic modifi cations of pigs produced for xenotransplantation research

	Purpose and indications of modification
Human CD59[6]	Complement regulation
Human CD55[7]	Complement regulation
Human H-transferase[8]	Reduction of Gal antigen expression
Human CD46[9]	Complement regulation
GTKO[10]	Deletion of Gal antigen expression
Endo-β-galactosidase C[11]	Reduction (but not deletion) of Gal antigen expression
Human TFPI[12]	Antagonise the function of tissue factor
Human TRAIL[13]	Control mechanisms of rejection mediated by cellular components of immune system
vWF-deficient[14]	Inhibit platelet activation
PERV siRNA[15]	Prevention of PERV activation
Porcine CTLA4-Ig[16]	Local co-stimulation blockade; T-cell suppression
Human thrombomodulin[17]	Anticoagulation (activates protein C)
HLA-E/human beta-2-microglobulin[18]	Protection against cytotoxicity of human natural killer cells
Human A20[19]	Anti-inflammatory; antiapoptosis
CIITA-DN[20]	Suppression of T-cell activation
Human Fas ligand[21]	Protection against cytotoxicity of human CD8+ and natural killer cells
Human GnT-III[22]	Downregulation of antigenicity to human natural antibodies
Human heme oxygenase 1[23]	Antiapoptosis; cytoprotection; anti-inflammatory
Human ENTPD1 (CD39)*	Anticoagulation and anti-inflammatory; conversion of ATP to ADP and AMP

Figure 2: Longest survival times of organ and cell xenotransplantation from pigs to non-human primates

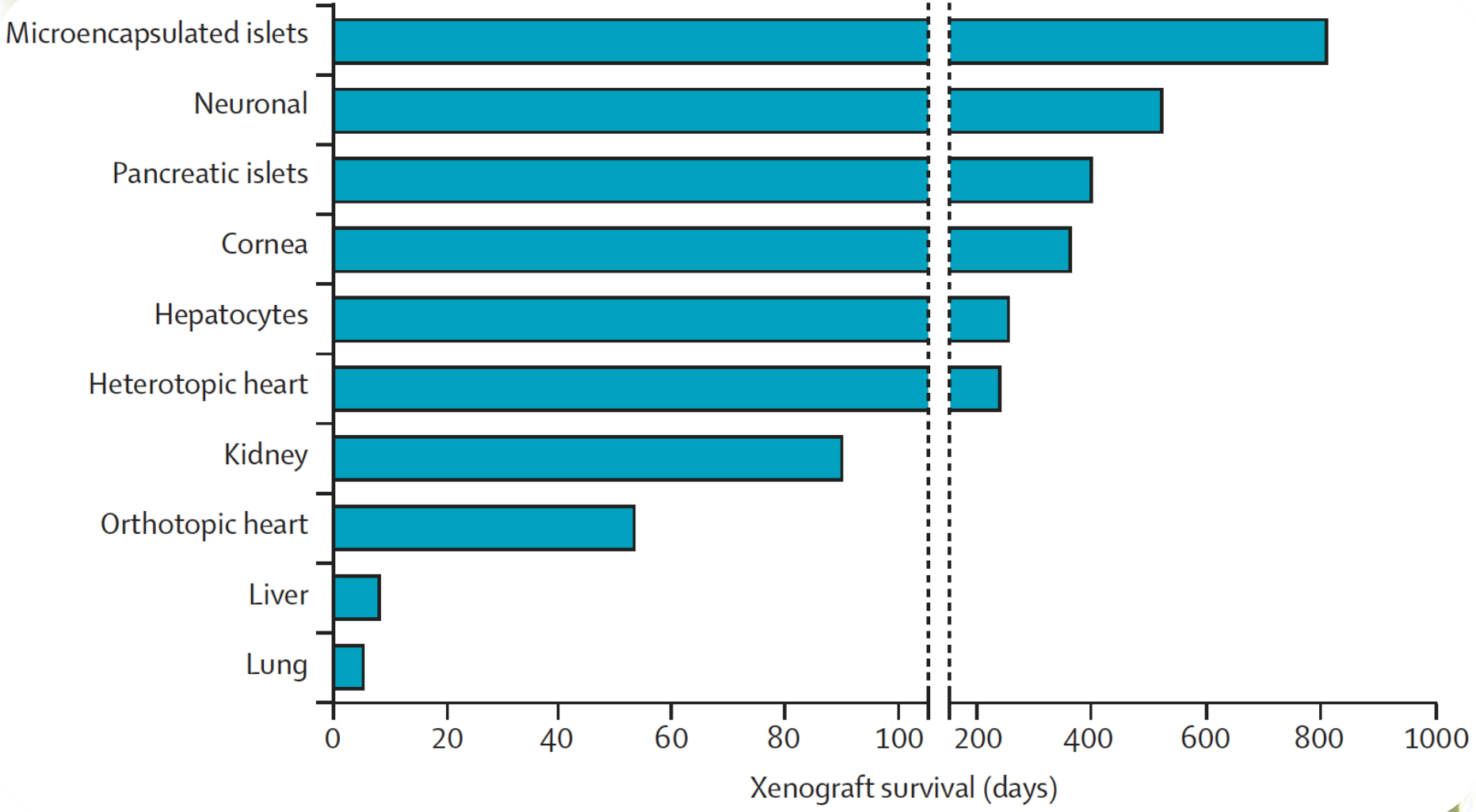


Figure 5: Transplantation of islets from a pig transgenic for hCD46 into the portal vein of a diabetic monkey

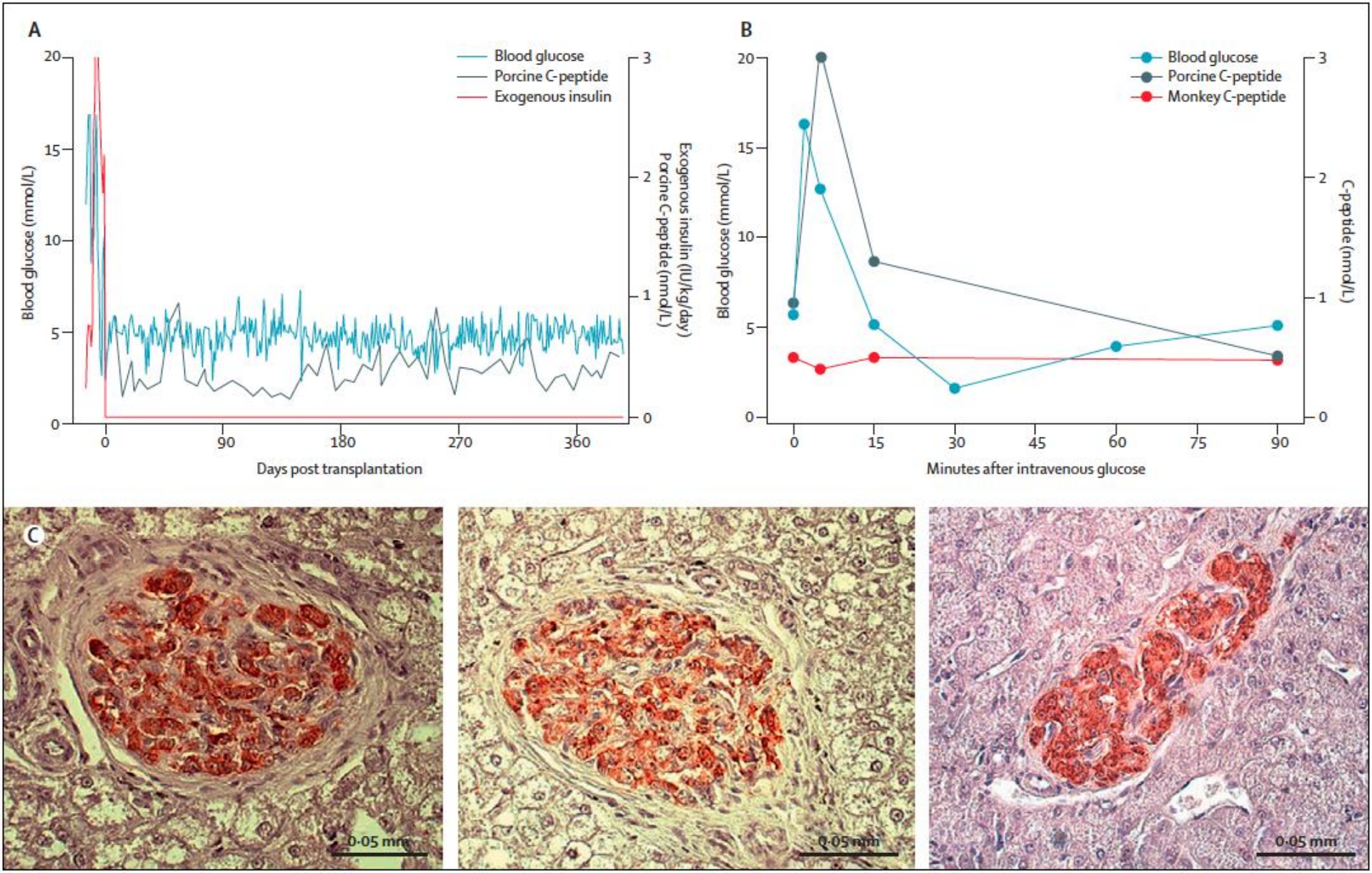
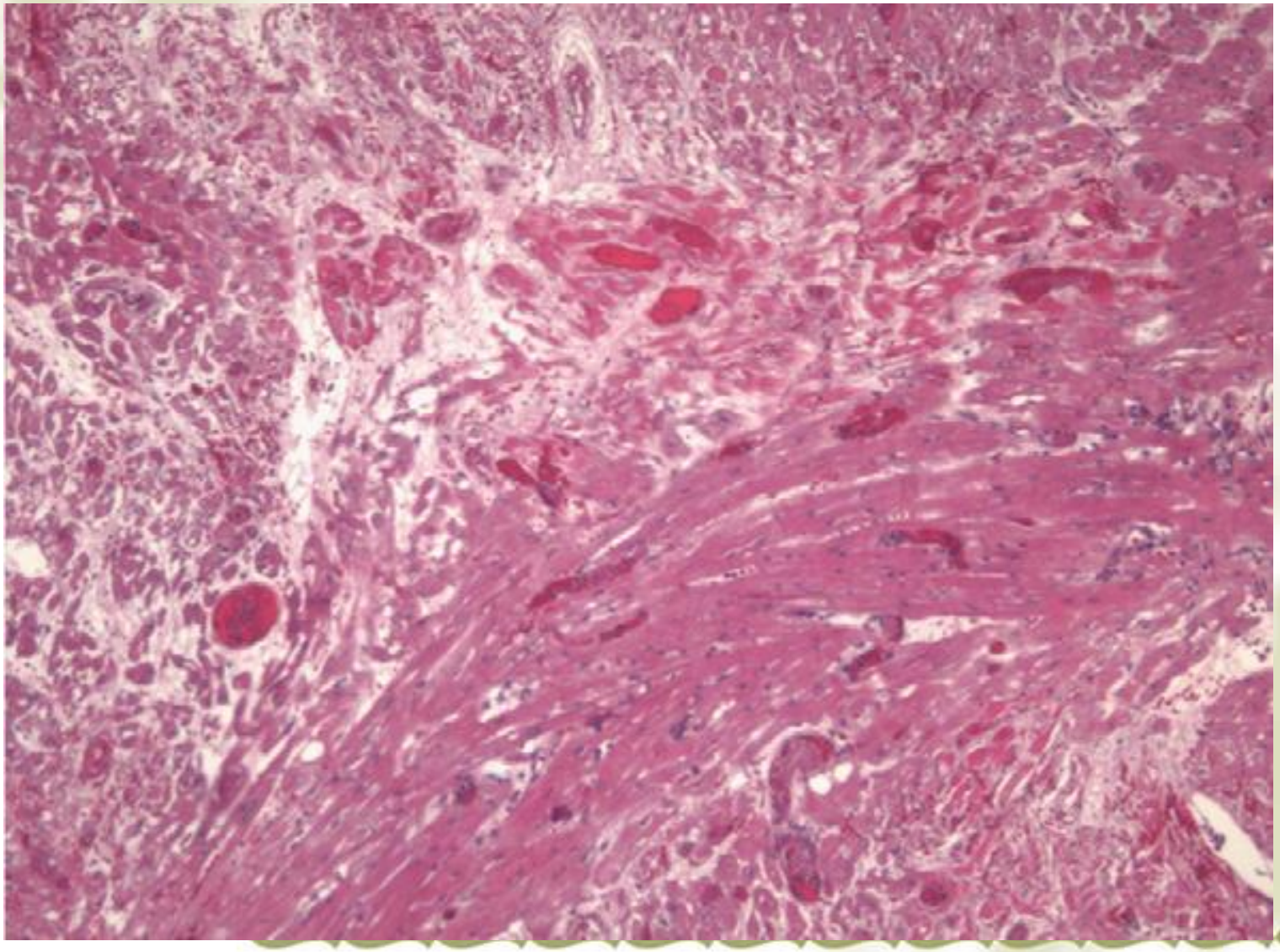


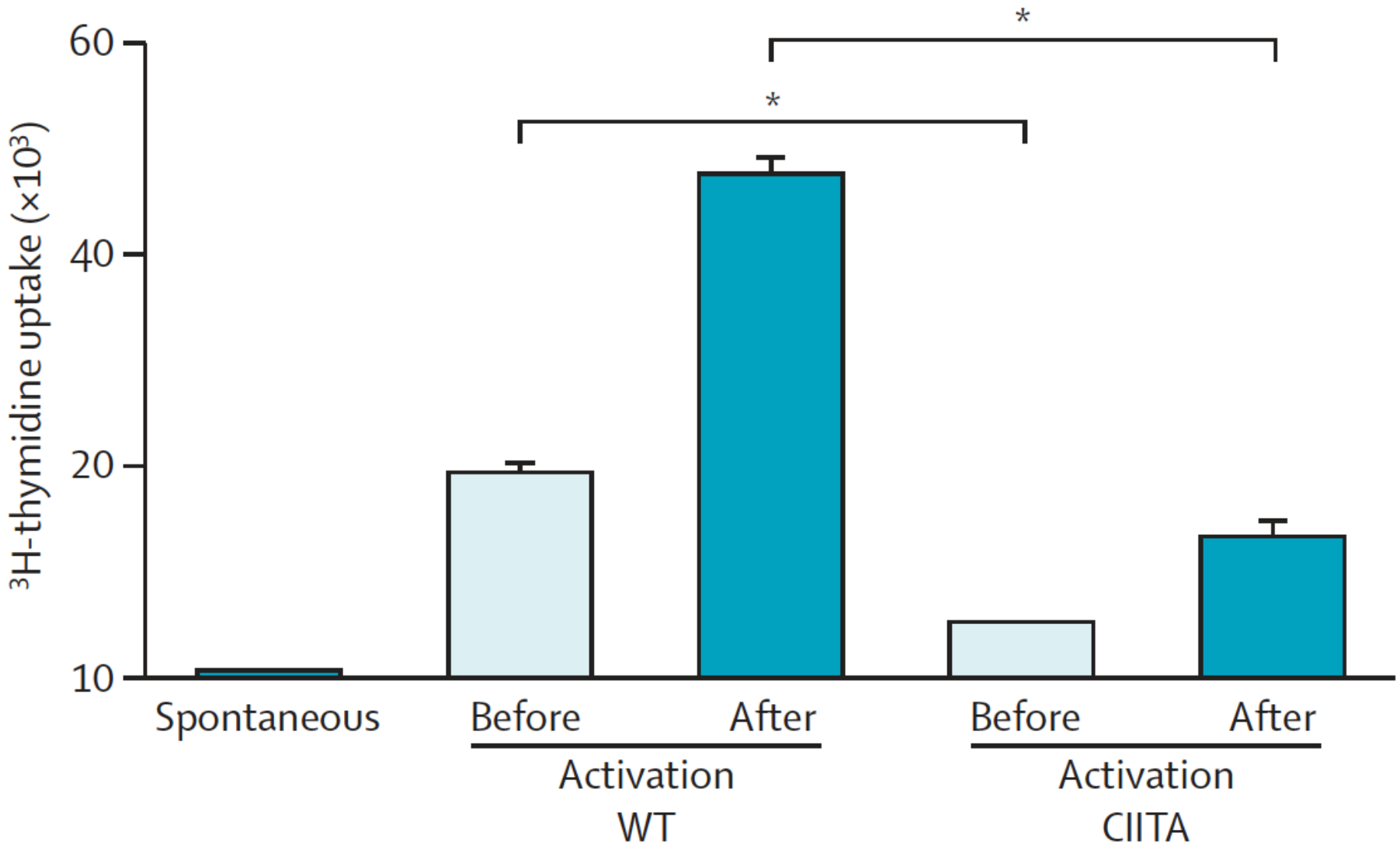
Figure 3: Typical features of thrombotic microangiopathy in a pig heart 6 months after heterotopic transplantation into an immunosuppressed baboon.



Strategies to resolve T-cell response

- Additional transgene pig: GTKO/hCRP/CTLA4-ig
- MHC II-Knockdown pigs: CIITA-Knockdown

Figure 6: Human CD4+ T cell proliferation in mixed lymphocyte reaction to quiescent and activated WT and CIITA-knockdown pAEC



The future of XenoTx

Safety

Fuctional

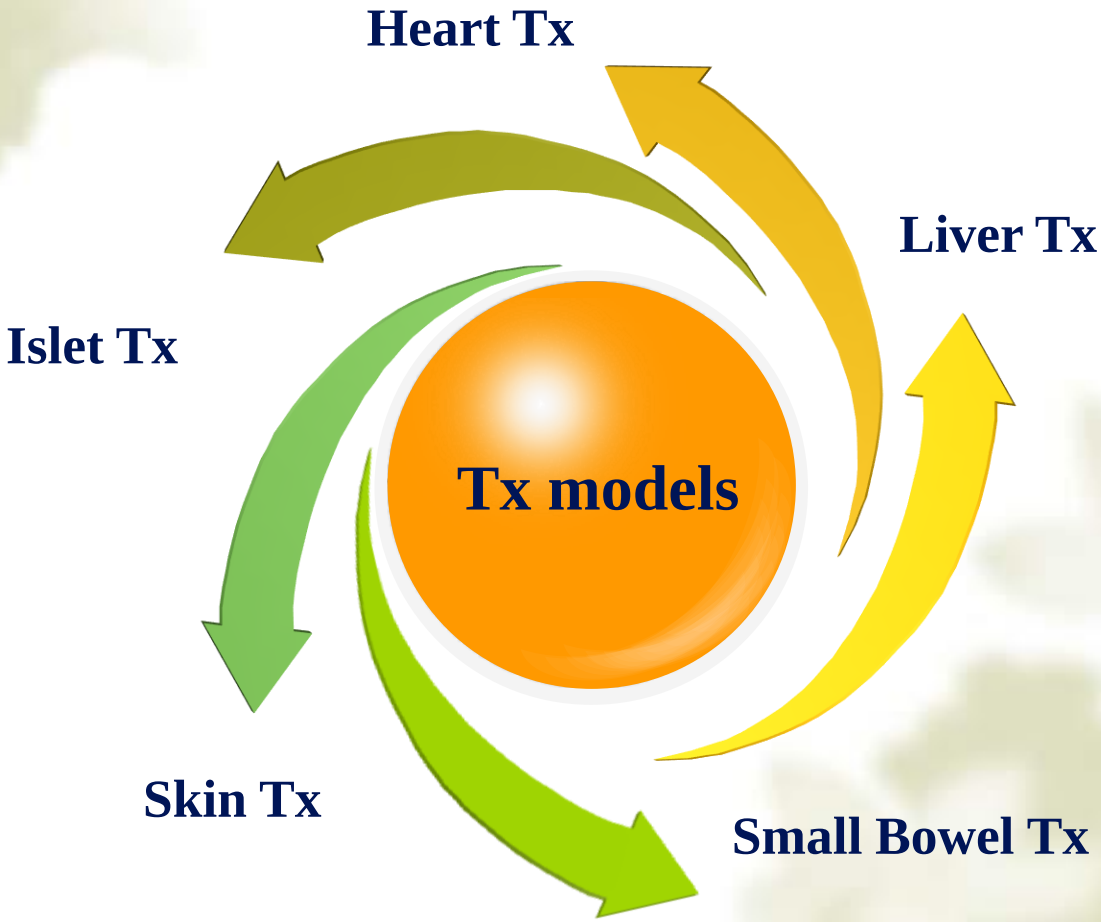
Reality

Soon

Encouraging

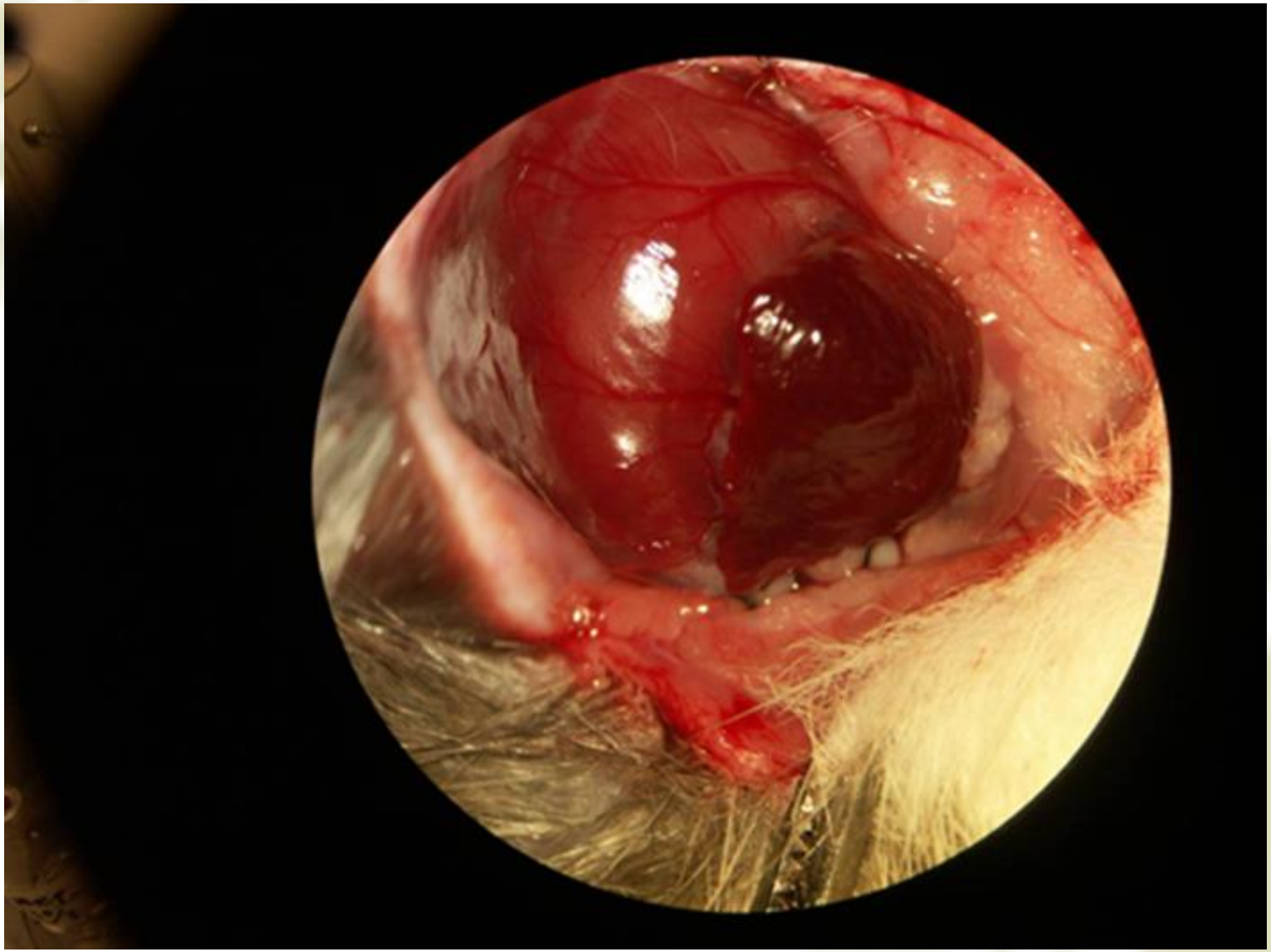
前期工作基础及相关介绍

Transplantation models

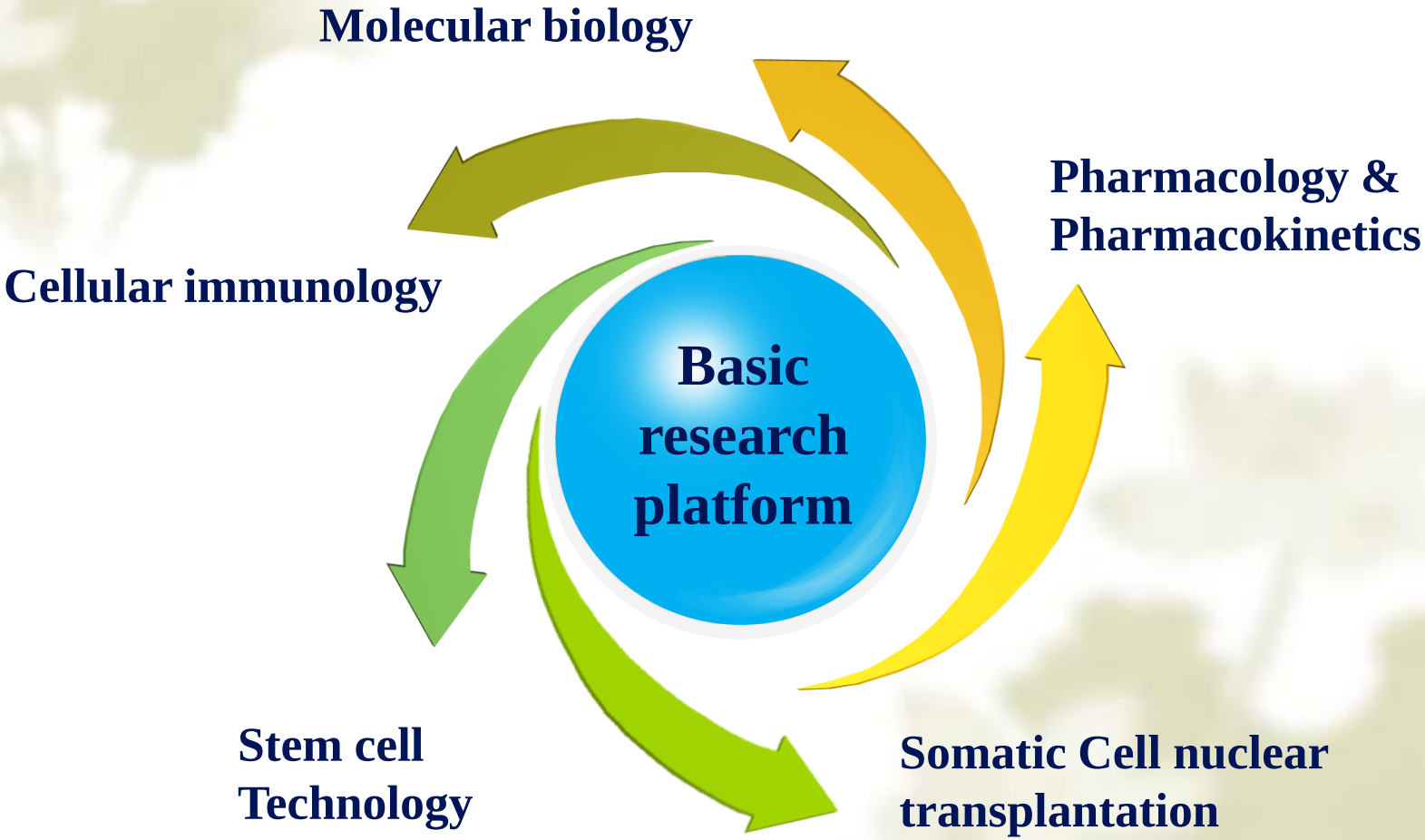


Transplant model

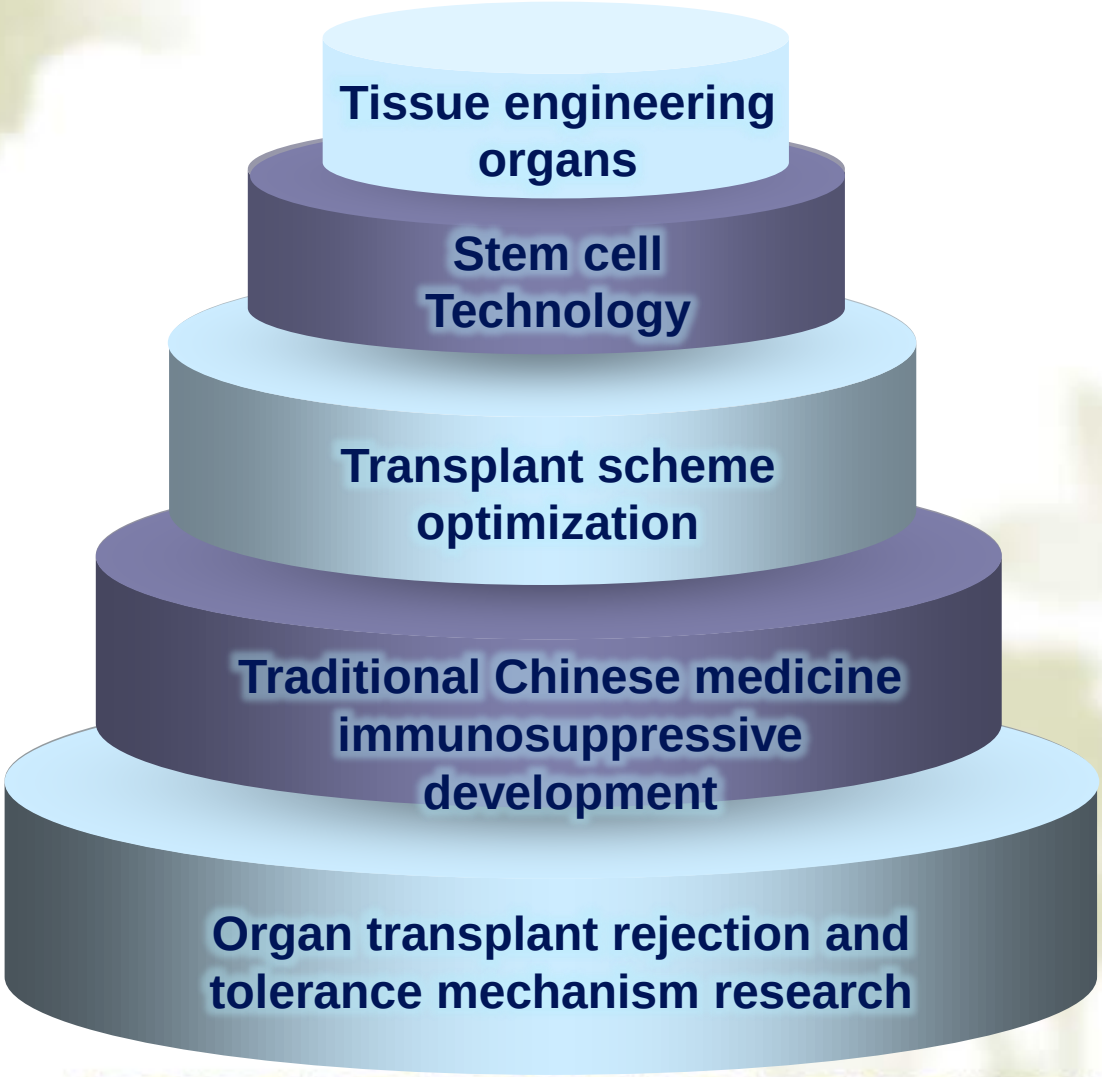
Heart transplantation model



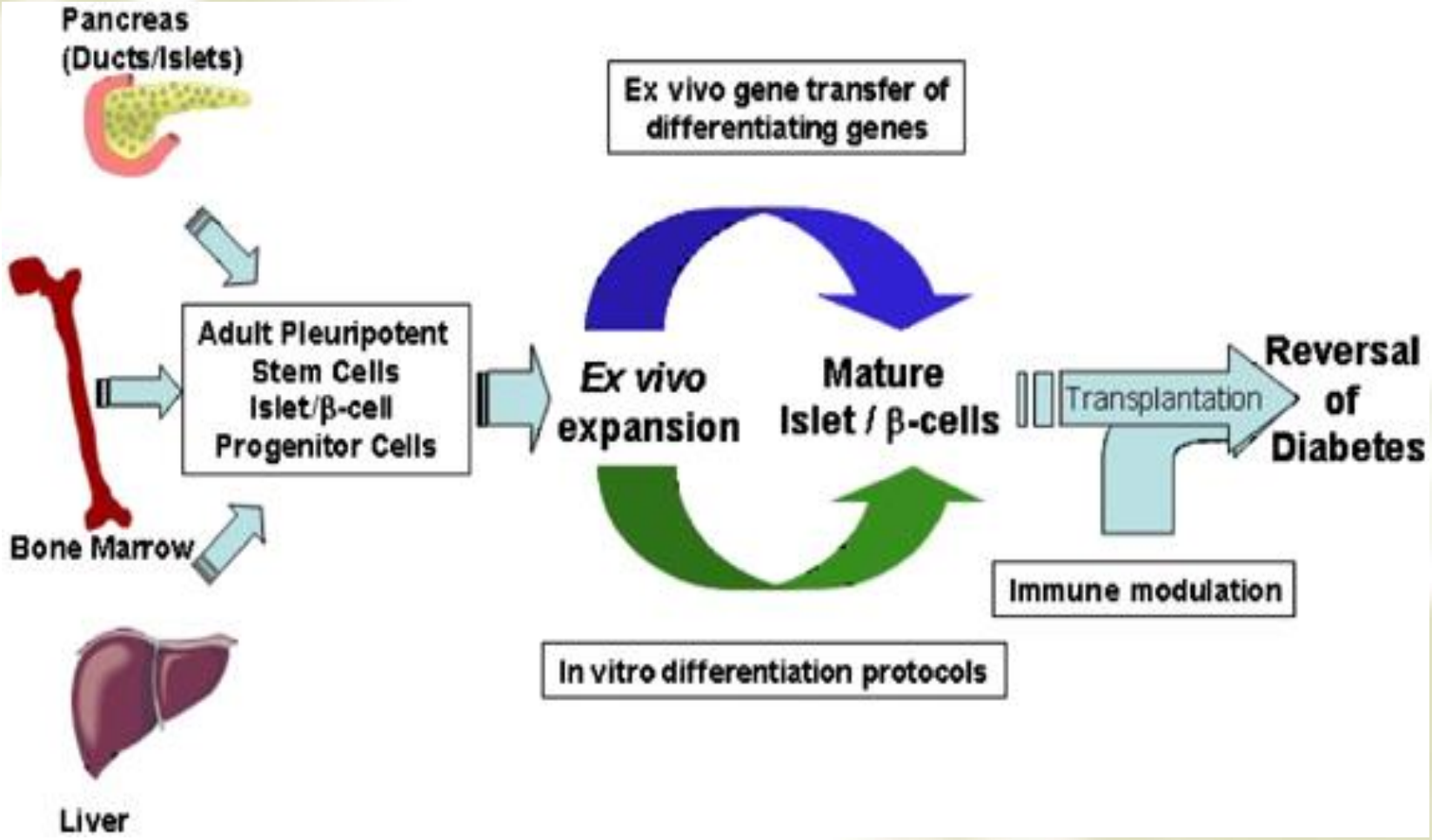
Basic research platform



Main Contents of Research

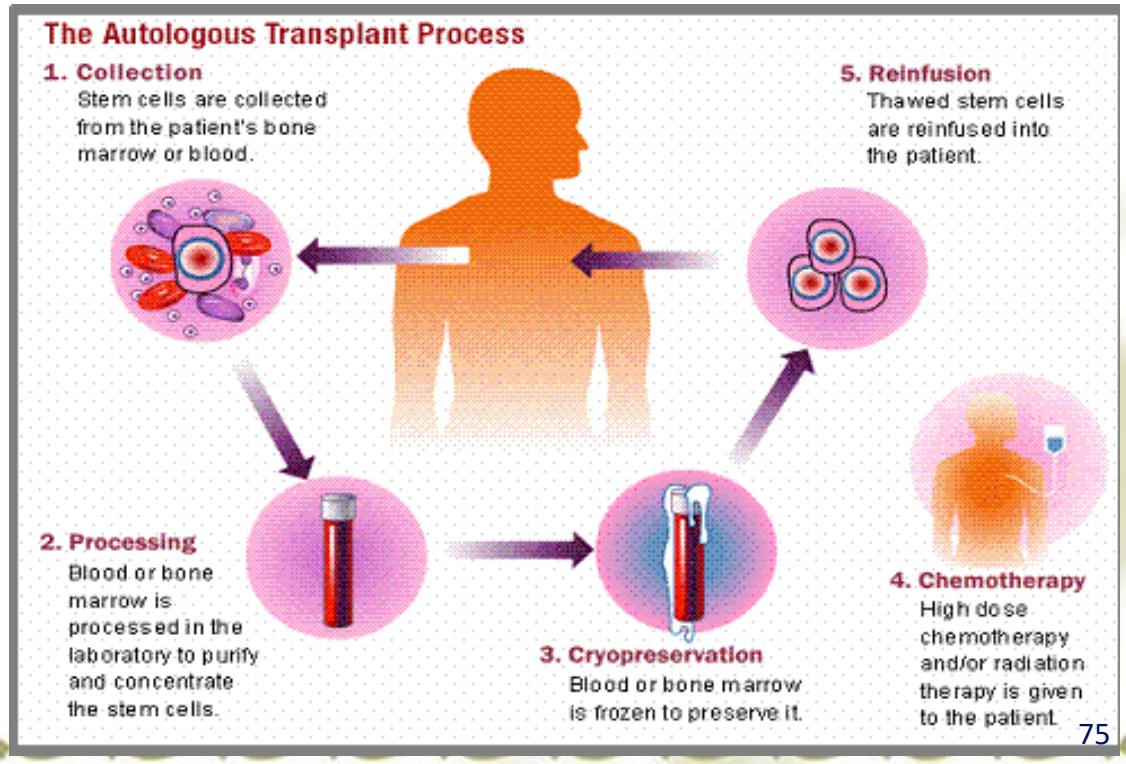


Stem cell technology & iPS



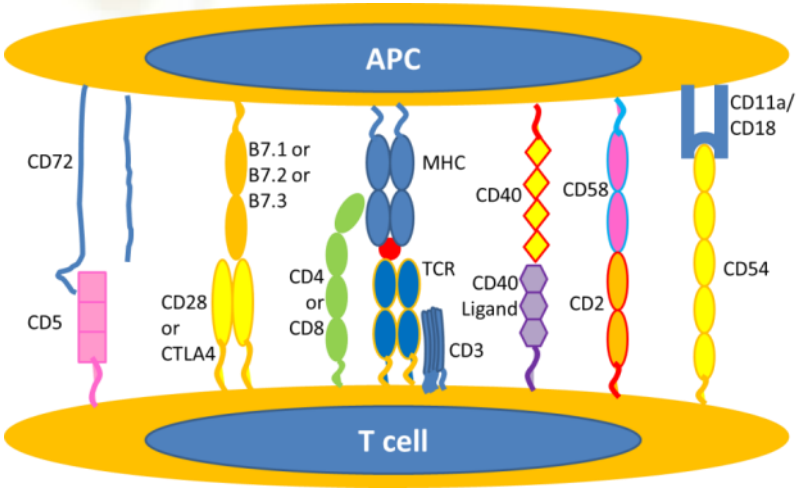
Autologous Stem Cell Transplantation

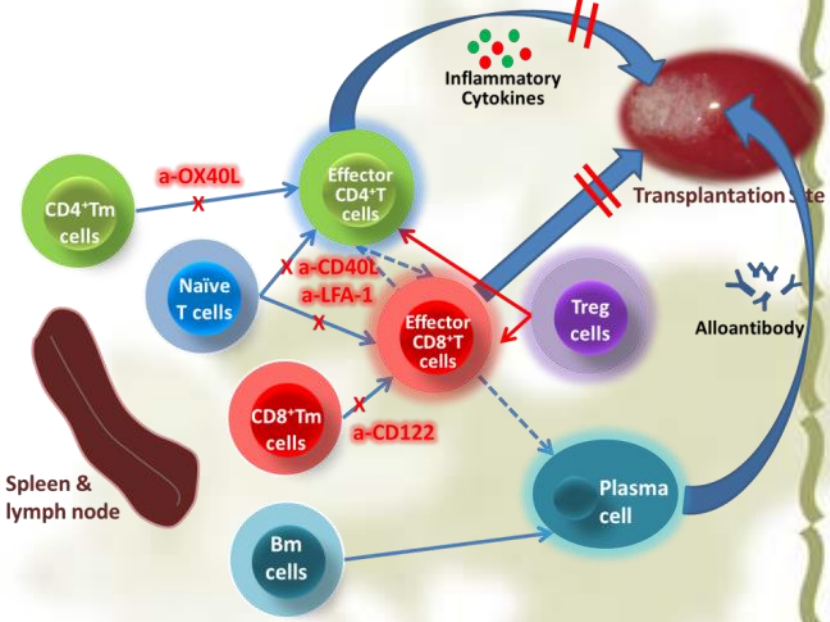
If you already have an organ transplant, a kidney or a heart, when you undergo ASCT, your regenerating immune system may learn to tolerate the transplant as it learns to tolerate your own organs.



Organ transplant rejection and tolerance mechanism research

T-cells and stimulate signaling pathways research





Mechanism study of Tm mediated rejection

Organ transplant rejection and tolerance mechanism research

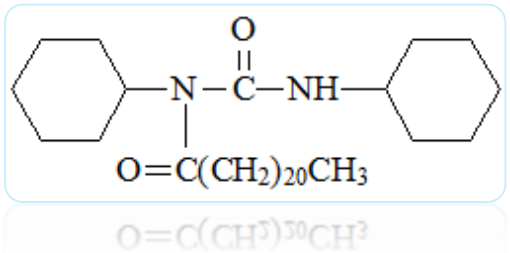
- Prevention of acute and chronic allograft rejection by combinations of tolerogenic dendritic cells. Scand J Immunol. 2010; 73(2): 91-101.
- Combined costimulation blockade inhibits accelerated rejection mediated by alloantigen-primed memory T cells in mice. Immunol Invest. 2009; 38(7): 639-51.
- Monoclonal antibody against CD44 prolongs heart allograft survival in alloantigen-primed mice. Scand J Immunol. 2010; 71(5): 345-52.
- Anti-CD44 Monoclonal Antibody Inhibits Heart Transplant Rejection Mediated by Alloantigen-primed CD4+Tm in Nude Mice. Immunol Invest. 2010; 39(8): 807-10.
- Suppressing memory T cell activation induces islet allograft tolerance in xenoantigen-primed mice. Transpl Int. 2010; 23(11): 1154-63.
- Combination of antibodies inhibits accelerated rejection mediated by memory T cells in xenoantigen-primed mice. Xenotransplantation. 2010; 17(6): 460-8.
- The recall alloresponse following retransplantation is more intense compared with the T cell memory-transfer model. Immunol Invest. 2010; 39(1): 39-53.
- Combined application of blocking antibodies and microRNA interference in inhibiting CD44 Expression. Transplant Proc. 2010; 42(7): 2777–81.
- The major histocompatibility complex (MHC) of the secondary transplant tissue donor influences the cross-reactivity of alloreactive memory cells. Scand J Immunol. 2011; 73(3):190-7.

2009~2010 Related

SCI Papers 9 Published

Traditional Chinese medicine immunosuppressive development

Isatis root



Derivatives
Compounds K

Patent

Immunosuppression
Research & Application

Traditional Chinese medicine immunosuppressive development

Also：

Cordyceps sinensis

Arsenical

Common Threewingnut Root


正式运转
2008
2009
3篇SCI文章
迅速发展的
厦门大学器官移植研究所
2010
17篇SCI文章
2011
24篇SCI 文章

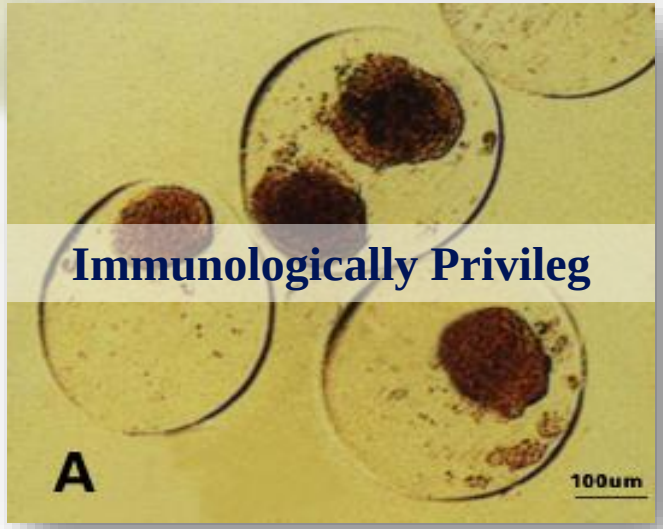
Traditional Chinese medicine immunosuppressive development

- Synergistic effects of Isatis tinctoria L. and tacrolimus in the prevention of acute heart rejection in mice. Transpl Immunol. 2009; 22(1-2): 5-11.
- An N-(alkylcarbonyl)anthranilic acid derivative prolongs cardiac allograft survival synergistically with cyclosporine A in a high-responder rat model. Transpl Immunol. 2010; 23(4): 180-4.
- Isatis tinctoria L. combined with co-stimulatory molecules blockade prolongs survival of cardiac allografts in alloantigen-primed mice. Transpl Immunol. 2010; 23(1-2): 34-9.
- Arsenic trioxide combined with co-stimulatory molecule blockade prolongs survival of cardiac allografts in alloantigen-primed mice. Transpl Immunol. 2010; 24(1): 57-63.

2009~2010 Related

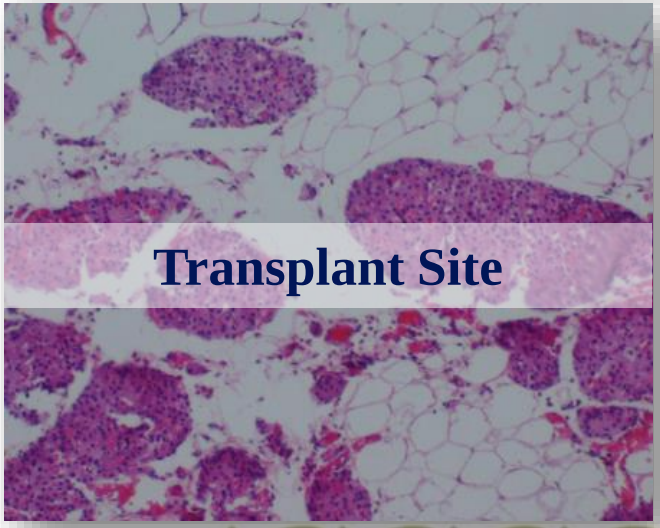
SCI Papers 4 Published

Transplant scheme optimization

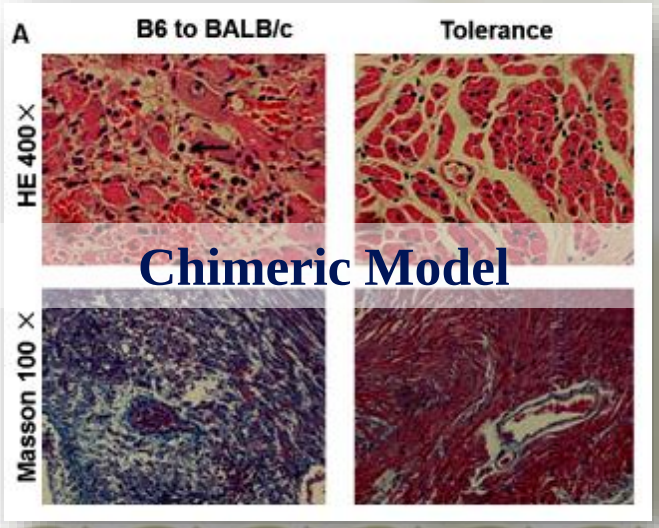


Immunologically Privileg

Islet Size



Transplant Site



Chimeric Model

Transplant scheme optimization

- Allotransplantation of sulphate glucomannan-alginate barium (SGA)-microencapsulated rat islets for the treatment of diabetes mellitus. Immunol Invest. 2009; 38(7): 561-71.
- Small islets are essential for successful intraportal transplantation in a diabetes mouse model. Scand J Immunol. 2010; 72(6): 524-40.
- Inhibition of alloantigen-primed memory CD4+ and CD8+ T cells by hematopoietic chimerism in mice. Scand J Immunol. 2010; 72(2): 86-93.

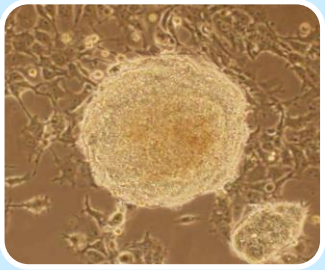
2009~2010 Related

SCI Papers 3 Published

Stem cell Technology

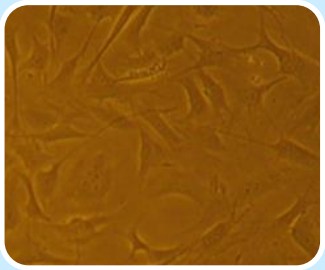
Somatic Cell nuclear transplantation

- Technical Prepared
- Embryonic Chimera Mouse



iPS Technology

- Acquire iPS Cell
- Differentiation Study Next



MSCs Used in Transplantation

- Stabilized Separation Methods
- Used in Transplantation

Stem cell Technology

- Allotransplantation of sulphate glucomannan-alginate barium (SGA)-microencapsulated rat islets for the treatment of diabetes mellitus. Immunol Invest. 2009; 38(7): 561-71.

2009~2010 Related

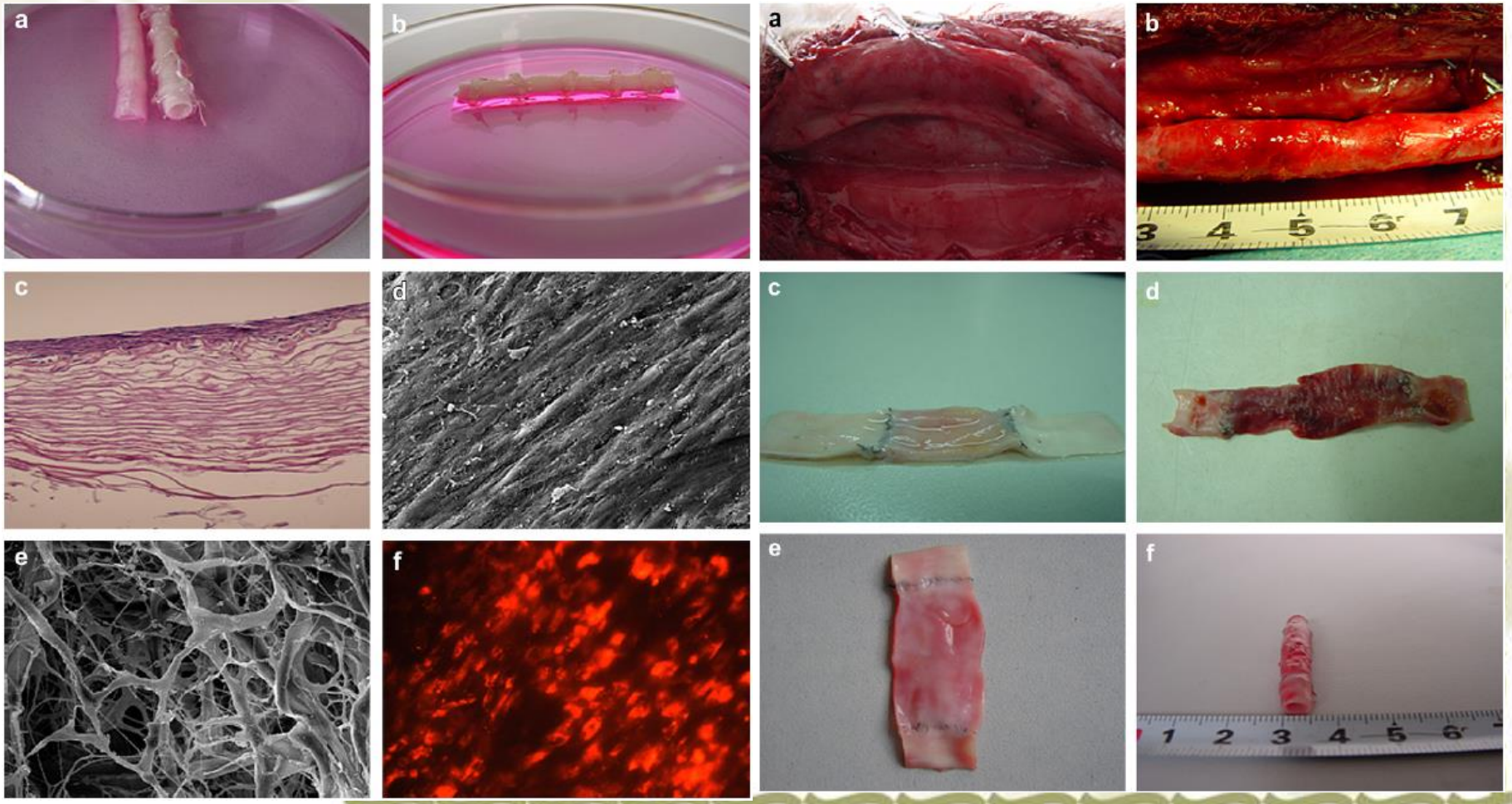
- Small islets are [illegible] for successful intraportal transplantation in a diabetes mouse model. Scand J Immunol. 2010; 72(6): 504-10.

SCI Papers 3 Published

- Inhibition of [illegible] cells by hematopoietic chimerism in mice. Scand J Immunol. 2010; 72(2): 86-93.

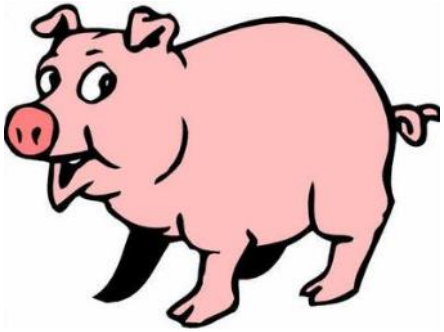
Tissue engineering organs

Constructing Tissue Engineering Vessels, *Biomaterials*



Focus on：

- Xeno-Transplantation
- Transgenic Animal
- Tissue Engineering Organs
- Stem Cell Used in Transplantation



厦门大学器官移植研究所

Thanks for your attention!

O.T.I Health
Xiamen University