THE FUTURE OF KIDNEY TRANSPLANTATION

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AGENDA

- Where we are today on kidney transplantation
- How can we improve long-term results?
- Future of kidney transplantation
ESRD – SUBSTITUTIVE TREATMENT

KIDNEY TRANSPLANTATION

ESRD

HEMODIALYSIS ↔ PERITONEAL DIALYSIS

Survival
QoL
Economical
Survival benefit with kidney transplant

Days since transplantation (equal time from wait-listing)

Relative Risk (RR) of Death

0.00 0.50 1.00 1.50 2.00 2.50 3.00 3.50 4.00

0 100 200 300 400 500 600 700

Marginal donor kidney (MDK) recipient
Ideal donor kidney (IDK) recipient
Wait-listed dialysis (WLD) patient

Compared to WLD

<table>
<thead>
<tr>
<th></th>
<th>IDK</th>
<th>MDK</th>
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<tbody>
<tr>
<td>Time to Equal Risk (ER)</td>
<td>122d</td>
<td>185d</td>
</tr>
<tr>
<td>Time to Equal Survival (ES)</td>
<td>256d</td>
<td>531d</td>
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Improvement in acute rejection and short-term graft survival

Acute rejection / graft survival (%)

Acute rejection

1-year graft survival

Radiation    Prednisone    6-mercaptopurine

CsA, cyclosporin; ATG, antithymocyte globulin; MMF, mycophenolate mofetil
... the improvement in long-term renal allograft survival was modest

Kaplan–Meier estimates of cumulative graft half-lives by transplant year (forecasted)

Cumulative graft failure yearly attrition rates of first kidney transplant from deceased SCD donor in USA (n=120,675)

SCD, standard criteria donor.

CAN, CVD and malignancy are the leading causes of graft failure and death with a functioning graft.

ANZDATA registry data 2007–2011

**Causes of kidney graft failure**
- CAN, 69%
- Malignancy, 31%
- CVD, 34%
- Acute rejection, 5%
- Vascular, 5%
- Glomerulonephritis, 6%
- Other, 9%
- Technical problems, 1%
- Noncompliance, 4%

**Causes of death with functioning graft**
- Malignancy, 65%
- CVD, 34%
- Infection, 19%
- Miscellaneous, 10%
- Social, 7%

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How we can improve long-term results?

LIMITING FACTORS

- Limited transplant activity (increase waiting list)
  - Progressive increase rate of ECD

- Chronic allograft damage
  - Chronic allograft nephropathy – IFTA
  - CNI toxicity
  - Recurrent glomerulonephritis
  - Senescence

- Accelerated Death
  - Cardiovascular
  - Cancer
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How we can improve long-term results?

PROPOSALS

1) Renal transplant activity
2) Organ allocation
3) Immunosuppression
4) Medical management of transplant patients
How can we improve long-term results?

PROPOSALS

RENAL TRANSPLANT ACTIVITY

- Increase transplant activity (ECD)
- Increase living transplants
- Pre-emptive renal transplantation
The most important risk factor for ESRD patients is 

Unable to get a Renal Transplant !!!
Unadjusted graft survival in 21,836 recipients of living transplants by length of dialysis treatment before transplant.

Meier-Kriesche HU, Caplan B, Transplantation 2002
Relationship
Kidney Transplants 1997-2005

% Graft Survival

Living n=32,135
Cadaver n=84,306

Years

0 1 2 3 4

CTS Collaborative Transplant Study
How can we improve long-term results?

**PROPOSALS**

**ORGAN ALLOCATION**

- Reduce cold ischemia time
- HLA & Age & Gender & BMI Matching
  - HLA matching
  - Old for Old
- Improve graft viability
  - Perfusion machines
- Improve graft evaluation
  - Baseline renal biopsy
SUSTAINED IMPROVEMENT OF GRAFT SURVIVAL: IT IS FEASIBLE?

PROPOSALS

IMMUNOSUPPRESSION

- Individualize Immunosuppression
- Immunological monitoring
- Immunosuppressive therapies
SUSTAINED IMPROVEMENT OF GRAFT SURVIVAL: IT IS FEASIBLE?

PROPOSALS

MEDICAL MANAGEMENT OF TRANSPLANT PATIENTS

- Graft monitoring
- Cardiovascular risk factors
- Cancer
- Opportunistic viral infections
A sustained improvement in long-term graft and patient survival is feasible, but a strict follow-up of recipients and a multidisciplinary approach of renal transplant, including medical, nephrological, surgical and immunological aspects are absolutely necessary.
How we can improve long-term results?

FUTURE PROPOSALS

- Personalized therapy
  - Genetic identification donor & recipient

- Biomarkers
  - Immunological status
  - Graft dysfunction

- Co-Stimulation blockers

- Immunotolerance
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Reprogramming-based strategies: raising hopes for the development of alternative therapeutics

Reprogramming

In vitro

Regeneration

Lineage conversion

In vivo

Pluripotent stem cells

In vitro

Cell transplantation

Cell transplantation
Pluripotent stem cells and lineage conversion: generating kidney cells in a dish for further transplantation.
Differentiation of human pluripotent cells towards renal progenitor-like cells. 

This is the first time that a complex chimeric organ culture has been established for the differentiation of human pluripotent cells.

Establishment of a suitable model for kidney developmental studies, disease modeling and drug discovery.

Demonstration that both, wild-type and patient-specific pluripotent cells (PKD) can be further specified into specific sub-types of somatic cells.

Demonstration that wild-type and patient-specific pluripotent cells (PKD) can assemble and integrate into 3D chimeric structures.
1) Demonstration that the mammalian kidney is able to elicit a neo-nephrogenic regenerative response upon injury.

2) Demonstration that neo-nephrogenesis occurs as a consequence of the re-activation as well as extended activity of fundamental developmental programs normally restricted to embryogenesis.

3) Establishment of the first regenerative model for the mammalian kidney.

4) Demonstration that neo-nephrogenesis occurs as a consequence of newly formed multilineage structures rather than by proliferation of resident differentiated somatic cell populations as seen during cellular regeneration and tubular repair.
Genes play key role in organogenesis
Similarity in ontogeny among different animal species
Harnessing the power of stem cells for regenerative medicine
**Genome editing technologies**

One-cell embryo genome editing (CRISPR/CAS9)

**Targeted Gene Correction of Laminopathy-Associated LMNA Mutations in Patient-Specific iPSCs**

Guang-Hui Liu, Keiichiro Suzuki, Jing Qu, Ignacio Sanscho-Martinez, Fei Yi, Mo Li, Sachin Kumar, Emmanuel Nivet, Jessica Kim, Rupa Devi Soligalla, Ilir Dubova, April Goebel, Nongluk Prongthongkum, Ho-Lin Fang, Kun Zhang, Jeanne P. Loring, Louise C. Laverty, and Juan Carlos Izpisua Belmonte

**LETTER**

Recapitulation of premature ageing with iPSCs from Hutchinson–Gilford progeria syndrome

Guang-Hui Liu, Basam Z. Barkbo, Sergio Ruiz, Dinh Diep, Jing Qu, Sheng-Lian Yang, Athanasiadis D. Panopoulos, Keiichiro Suzuki, Leo Kurian, Christopher Wahl, James Thompson, Stephanie Bourn, Ho-Lin Fang, Ignacio Sanscho-Martinez, Kun Zhang, John Yates III, & Juan Carlos Izpisua Belmonte

**LETTER**

Progressive degeneration of human neural stem cells caused by pathogenic LRRK2

Guang-Hui Liu, Jing Qu, Keiichiro Suzuki, Emmanuel Nivet, Mo Li, Nuria Montserrat, Fei Yi, Xingling Xu, Sergio Ruiz, Weid Zhang, Ulrich Wagner, Audrey Kim, Bing Ren, Ying Li, April Goebel, Jessica Kim, Rupa Devi Soligalla, Ilir Dubova, James Thompson, John Yates III, Concepcion Rodriguez-Esteban, Ignacio Sanscho-Martinez, & Juan Carlos Izpisua Belmonte
Chimeric-competent ESCs/iPSCs

ESC

Rodent ESCs

EpiSCs

Lineage-specific stem cells

Mouse

Human

BF

Kusabira-Orange
Our strategy

Chimeric-competent ESCs/iPSCs

One-cell embryo genome editing (CRISPR/CAS9)
Proof of concept

Rat ESCs → PDX1 sgRNA → Host → Chimeras

Rats → Mice

Rat ESCs

Chimeras

Host
Application: Gene editing in one-cell pig embryo

Human naïve ESCs/iPSCs
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THANK YOU !!!