The establishment and application of Clinical Bio-bank of Kidney Diseases

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1950s: The first Renal Division established by late Prof. Shu-Xian Wang, the founder of modern nephrology in China

- The first key lab of Ministry of Health
  - Metabolism and kidney diseases

- 1950s: the first group of postgraduates in Nephrology
History of Renal Division

 منذ أوائل 1980s، أ. د. Hai-yan Wang

- 1992: Key Lab of Renal Disease، Ministry of Health
- 1992: Institute of Nephrology، Peking University
- 2003: Beijing Municipal Key Discipline
- 2007: State Key Discipline
- 2010: Innovative Research Group of the National Natural Science Foundation of China (NSFC)
- 2011: Key Lab of CKD Prevention and Treatment، Ministry of Education
Clinical sectors

- Two wards: 77 beds
  - One critical care unit: 6 beds
- Outpatient clinics: 50,000 pts/year
  - Several specialized clinics including CKD
- HD center: 250 pts
- PD center: 400 pts (CAPD)
- Renal pathology: 2000 renal biopsy/year
- Ultrasonic center of nephrology
- Clinical lab:
Establishment of bio-bank

- 1980s: sera & urine at the day of renal biopsy
  - Renal tissues & clinical data at presentation
- 1990s: DNA of pts with renal biopsy
- 2000s: follow up clinics
  - Clinical data
  - Sera
  - Urine?

- Now: computer & Web-based modern management system
Database & Bio-bank

- **Database with follow-up data**
  - Glomerular diseases
  - Tubulointerstitial disease
  - CKD cohort

- **Bio-bank**
  - Renal tissue, DNA, sera, urine

http://www.renal-online.org
# Data and Sample Collection

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>No. of Patient</th>
<th>No. of Patient with long term FU (&gt;1y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD</td>
<td>250</td>
<td>200</td>
</tr>
<tr>
<td>PD</td>
<td>400</td>
<td>310</td>
</tr>
<tr>
<td>IgAN</td>
<td>2000</td>
<td>600</td>
</tr>
<tr>
<td>CKD</td>
<td>400</td>
<td>200</td>
</tr>
<tr>
<td>Drug-induced</td>
<td>500</td>
<td>200</td>
</tr>
<tr>
<td>Lupus Nephritis</td>
<td>450</td>
<td>200</td>
</tr>
<tr>
<td>ANCA associated GN</td>
<td>1000</td>
<td>300</td>
</tr>
<tr>
<td>Anti-GBM Disease</td>
<td>400</td>
<td>200</td>
</tr>
<tr>
<td>Primary GN</td>
<td>300</td>
<td>200</td>
</tr>
</tbody>
</table>
Research groups

- Clinical Epidemiology & CKD
- Molecular Genetics
- Cellular Biology
- Pathophysiology & Animal Experiments
- Renal Pathology
- Renal Immunology
- Renal Clinical Examination
Application of renal bio-bank

- IgA nephropathy
- Anti-GBM disease
- Anti-neutrophil cytoplasm autoantibody (ANCA) disease
- ......
Application of renal bio-bank

- IgA nephropathy
  - The most common glomerular disease in Chinese
  - Renal biopsy 2000 cases
  - Long-term follow up: 600 cases
- Anti-GBM disease
- Anti-neutrophil cytoplasm autoantibody (ANCA) disease
- ......
Nature History of IgA Nephropathy in China

204 IgA Nephropathy Patients

with long-term follow up (5-15 ys)

One Year Renal survival 94.4%
Five Year Renal survival 85.1%
Ten Year Renal survival 77.1%

Around 1/5 to 1/4 patients will enter ESRD in 10 years

Association of Factors Related to Progression Rate in a large population with IgA Nephropathy: A Prospective Study

- **Sample size:** 600
  - Follow-up: 1-4 years
- **Time-average proteinuria**
- **Time average blood pressure**

<table>
<thead>
<tr>
<th>TA-MAP</th>
<th>Slope (ml/min.1.73m²/yr; Mean±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;90</td>
</tr>
<tr>
<td>2</td>
<td>90-100</td>
</tr>
<tr>
<td>3</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>p</th>
<th>TA-proteinuria (g/d)</th>
<th>Slope (ml/min.1.73m²/yr; Mean±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0 to 0.5</td>
<td>1.3 ± 7.2</td>
</tr>
<tr>
<td>2</td>
<td>0.5 to 1.0</td>
<td>-1.4± 9.8</td>
</tr>
<tr>
<td>3</td>
<td>1.0 to 2.0</td>
<td>-2.3± 8.4</td>
</tr>
<tr>
<td>4</td>
<td>2.0 to 3.0</td>
<td>-8.3± 10.3</td>
</tr>
<tr>
<td>5</td>
<td>&gt;3.0</td>
<td>-13.7± 12.7</td>
</tr>
</tbody>
</table>

Unpublished data
Deglycosylated IgA1 is associated with pathological phenotype and outcome

- **107 case IgAN**: cross sectional
- **Serum deglycosylated IgA1** is associated with pathological phenotypes:


- **128 IgAN**: 8 year follow up
- **Stratified using serum α-2,6 sialic acid**
  - Normal (n=107)
  - Decreased (n=21)

Interaction between variants of two glycosyltransferase genes ST6GALNAC2 and C1GALT1 in IgA nephropathy. – association with clinical phenotypes

Combination Therapy of Prednisone and ACE Inhibitor Versus ACE-Inhibitor Therapy Alone in Patients With IgA Nephropathy: A Randomized Controlled Trial

CLINICAL TRIAL PROTOCOL

TESTING Study

Therapeutic Evaluation of Steroids in IgA Nephropathy Global study
Protocol Number:
Version Number: 1.0
Date: 22 February 2011 (draft)

“A collaboration between the Peking University Institute of Nephrology, the George Institute for Global Health and renal researchers around the world”
Application of renal bio-bank

- IgA nephropathy
- Anti-GBM disease
  - A rare autoimmune disease
  - Patients: 400 cases
  - Long-term follow up: 200 cases
- Anti-neutrophil cytoplasm autoantibody (ANCA) disease
- ......
Anti-GBM disease

- Identification of natural anti-GBM antibodies
- Immune characteristics of anti-GBM antibodies are associated with clinical phenotypes and disease progression
- Epitope spreading of anti-GBM antibodies
- Susceptible gene for Chinese with anti-GBM disease: HLA-DRB1*1501 allele

Summary of the change of immune characteristics of anti-GBM antibodies during disease progression

- **Normal individuals**
  - Natural anti-GBM

- **Pts-A**
  - Anti-GBM (+)
  - Normal renal function

- **Pts-B**
  - Anti-GBM (+)
  - Mild/moderate Renal damage

- **Pts-C**
  - Anti-GBM (+)
  - Severe renal damage

**Epitope spreading**
- $\alpha_3$ Ea Eb
- $\alpha_3$, $\alpha_4$

**Switching of IgG subclass**
- IgG2, IgG4

**Increase of affinity**
- lower

**Epitopes within $\alpha_3$**
- $\alpha_1$, $\alpha_2$, $\alpha_3$, $\alpha_4$ and $\alpha_5$

**IgG1, IgG2, IgG3, and IgG4**

**Individualized therapy**
**T-cell regulation?**

Cui Z, Zhao MH. *Nat Rev Nephrol* 2011 Jul 19. Epub
Application of renal bio-bank

- IgA nephropathy
- Anti-GBM disease
- Anti-neutrophil cytoplasm autoantibody (ANCA) disease
  - Autoimmune disease---major cause of RPGN
  - Patients: 1000 cases
  - Long-term follow up: 400 cases

- ......
ANCA disease in Chinese

- Predominance of MPO-ANCA in Chinese
  - 426 cases: MPO vs PR3: 6.7:1
- Elderly: 99/234 (42.3%)
  - MPO vs PR3: 19:1

Caucasian: MPO:PR3=1:1

Natural autoantibodies to MPO and PR3 are present in normal individuals

- Healthy individuals possess NAAs against MPO, and PR3
- MPO-NAA has lower titer, lower affinity and restricted IgG subclass
- The MPO-NAA induced respiratory burst of neutrophils was significantly weaker (p=0.036)

Cui et al. Kidney Int 2010;78:590-7
ANCA disease and complement activation

- **MPA**: pauci-immune
  - C3c (-)
  - C3d & MAC co-localization
  - FB & MAC co-localization
  - No C4d deposition

- Complement activation via alternative pathway is involved in pathogenesis of ANCA disease

## Pauci-immune CrGN: with & without ANCA

<table>
<thead>
<tr>
<th>Clinical and pathological manifestation</th>
<th>ANCA positive</th>
<th>ANCA negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>elderly</td>
<td>younger</td>
<td></td>
</tr>
<tr>
<td>More proteinuria</td>
<td></td>
<td>Less extra-renal involvement</td>
</tr>
<tr>
<td>Worse renal prgnosis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Peripheral PMN degranulation           | ++           | ++++         |
| Kidney PMN infiltration                | ++           | ++++         |
| Complement activation pathway          | alternative  | C4d staining, MBL ? |
| AECA and target antigen                | ++++         | ++           |

**RPGN classification**

Etiology different ?

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2005-2010: English Publications

- Peer-reviewed English papers
  - Corresponding author: 152
  - 70% of them are based on our clinical bio-bank

  - Based on clinical bio-bank: 15
Competitive talented young generation
------recent 5 years

- The new century talent program, ministry of education:
  - 6 winners

- Research star project in Beijing:
  - 3 winners

- Project of National Natural Science Foundation for Young Scholars
  - 6 winners
Implementation of PU-UM collaboration

- Exchange and Implementation of standardized protocols
- Molecular Medicine approach to renal diseases
- Initiation of projects at both sides:
  - Implementation of Molecular Medicine approach to IgAN
  - Cross validation of candidate molecular biomarkers in GN cohorts at PU and UM
- Bilateral visiting and training of faculties
  - Academic visiting (UM: Matthias Kretzler and Wenjun Ju; PU: Hai-yan Wang, Hong Zhang and Yu-qing Chen)
  - Junior faculties training (Li-jun Liu)
  - CKD coordinator exchange (Chrysta)
  - Technician training on site (Court)
Thank you