Research Collaboration with Chinese Third Military Medical University

Weisan Chen
School of Molecular Science
La Trobe University
Weisan.chen@latrobe.edu.au

Australia Chinese Association for Biomedical Science
About ACABS

The Australia Chinese Association for Biomedical Sciences Inc. (ACABS) is a large independent non-profit professional organisation established by Australian Chinese Scholars in the fields of biological and medical sciences. The organization has formal members of more than 70 professionals in the sectors of biological medical research and practice with the headquarter being currently in Melbourne.

Recent News

December 18 澳华生物医学协会2012圣诞新年联谊酒会于12月7日晚间在维多利亚州政府宴会厅举行

August 1 澳洲华人生物医学协会2012年会会议总结

August 1 澳洲华人生物医学协会2012年会及活动照片

July 10 ACABS Annual General Meeting and Career Seminar, 29 July 2012

June 26 ACABS与南京市投资促进委员会和高技术代表团在墨尔本举行洽谈会

February 15 读书报告3 - 俞澜
<table>
<thead>
<tr>
<th>Conference</th>
<th>Date</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Inaugural Australia-China Biomedical Research Conference</td>
<td>1-3 February 2007</td>
<td>Melbourne, Australia</td>
</tr>
<tr>
<td>The Second Australia-China Biomedical Research Conference</td>
<td>24-27 April 2009</td>
<td>Tianjin, China</td>
</tr>
<tr>
<td>The third Australia-China Biomedical Research Conference</td>
<td>28-30 April 2007</td>
<td>Melbourne, Australia</td>
</tr>
<tr>
<td>The fourth Australia-China Biomedical Research Conference</td>
<td>11-13 October 2013</td>
<td>Hangzhou, China</td>
</tr>
</tbody>
</table>
All started with A/Prof. Chao Wu

Deleted a photo on this slide.
Chao Wu was well looked after

Deleted a photo on this slide.
Third Military Medical University (中国人民解放军第三军医大学) is a Chinese military institution of higher learning, affiliated to the People's Liberation Army (PLA), located in Chongqing, founded in 1954, by the merger of former Sixth and Seventh Medical Universities.

was named "Seventh Military Medical University".

relocated to Shanghai in 1969, but moved back to Chongqing in 1975, and renamed as "Third Military Medical University".
Collaboration partner

Department of biological & pharmaceutical engineering, clinical microbiology and immunology

National Centre for immunological pharmaceutical engineering

Chongqing Centre for biological & pharmaceutical engineering & technology
Match can be opportunistic

• All started with a call from a close friend

• Sincerity

• Both sides are keen on science

• Relook at gaining/loosing time

• How much put in vs how much get out
Deleted a photo on this slide.
Sincerity...
Match can be opportunistic

• All started with a call from a close friend
• Sincerity
• Both sides are keen on science
• Relook at gaining/loosing time
• How much put in vs how much get out
<table>
<thead>
<tr>
<th>My Research interests</th>
<th>Their Research interests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellular immunity to Flu and melanoma antigens</td>
<td>Cellular immunity to <em>H. Pylori</em> and gastric cancer</td>
</tr>
<tr>
<td>T cell antigen discovery</td>
<td>T cell antigen discovery</td>
</tr>
<tr>
<td>Cancer and influenza vaccine</td>
<td><em>H. Pylori</em> vaccine</td>
</tr>
<tr>
<td>Cancer clinical trials</td>
<td><em>H. Pylori</em> clinical trials</td>
</tr>
</tbody>
</table>
Identifying the major antigen peptides recognized by CD8+ killer T lymphocytes

Influenza A Virus (IAV)

- 8 segmented ssRNA genome
- Allow reassortment easily

- 11 proteins:
  - **Nucleoprotein (NP)**
  - Hemagglutinin (HA)
  - Neuraminidase (NA)
  - Acidic polymerase (PA)
  - Matrix proteins (M1, M2)
  - Non-structural proteins (NS1, NS2)
  - Basic polymerase 1 (PB1, **PB1F2 (30,000 hits)**)
  - Basic polymerase 2 (PB2)
Systematically Identify major IAV CD8+ T cell peptides

PBMC

1/10 flu-infected PBMC

expansion of flu-specific T cells

rVV-BCL individual flu proteins

IFN-γ ICS

Identification of best antigens

expansion of flu-specific T cells

overlapping synthetic peptides

IFN-γ ICS

Identification of antigenic regions

PBMC

18mer-pulsed APC

expansion of peptide-specific T cells

defined synthetic peptides

Selected HLA-matching BLC

IFN-γ ICS

Determination of minimum epitope, MHC restriction
Systematically Identify major IAV CD8+ T cell peptides

**A2+20090923**

A*0101,0201; B*0801,5101; C*0701,1601

---

**Donor 20090923(A2+)**

**Flu protein-coding rVV**

0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5

**CD8+IFN-g+**

rVM1 rVM2 rVMA rVVNS1 rVVNS2 rVPA rVVPA1 rVVPA2 rVNP rVVPA3 rVVHA Flu virus BCL only

---

**Flu protein-coding rVV**

- A2+20090923
- A*0101,0201; B*0801,5101; Cw*0701,1601

---

**A2+20090923**

A*0101,0201; B*0801,5101; Cw*0701,1601
<table>
<thead>
<tr>
<th>Year</th>
<th>Epitope Linear Sequence</th>
<th>Starting Position</th>
<th>Epitope Source Molecule</th>
<th>MHC Allele Narr</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>GILGFVFTL</td>
<td>58</td>
<td>Matrix protein 1</td>
<td>HLA-A2</td>
</tr>
<tr>
<td>2002</td>
<td>AIMDKNIIL</td>
<td>122</td>
<td>Non-structural protein 1</td>
<td>HLA-A*0201</td>
</tr>
<tr>
<td>2000</td>
<td>FMYSDFHFI</td>
<td>46</td>
<td>Polymerase acidic protein</td>
<td>HLA-A*0201</td>
</tr>
<tr>
<td>2000</td>
<td>NMLSTVLGV</td>
<td>413</td>
<td>RNA-directed RNA polymerase subunit</td>
<td>HLA-A*0201</td>
</tr>
<tr>
<td>2000</td>
<td>SLENFRAYV</td>
<td>225</td>
<td>Polymerase acidic protein</td>
<td>HLA-A*0201</td>
</tr>
<tr>
<td>2000</td>
<td>SLCPIRGWAI</td>
<td>75</td>
<td>Neuraminidase</td>
<td>HLA-A*0201</td>
</tr>
<tr>
<td>1987</td>
<td>GKNĐTLEVLMMEWLKTRPIL</td>
<td>34</td>
<td>Matrix protein 1</td>
<td>HLA-A2</td>
</tr>
<tr>
<td>1987</td>
<td>RGLQRRRFVQNALNGNG</td>
<td>72</td>
<td>Matrix protein 1</td>
<td>HLA-A2</td>
</tr>
<tr>
<td>2001</td>
<td>CVNGSCFTV</td>
<td>213</td>
<td>neuraminidase</td>
<td>HLA-A*0201</td>
</tr>
<tr>
<td>2007</td>
<td>FLKDVEMESM</td>
<td>166</td>
<td>polymerase PB1</td>
<td>HLA-A2</td>
</tr>
<tr>
<td>2008</td>
<td>GLFGAIAGFI</td>
<td>344</td>
<td>haemagglutinin</td>
<td>HLA-A*0201</td>
</tr>
<tr>
<td>2008</td>
<td>VLLVSLGAI</td>
<td>541</td>
<td>haemagglutinin</td>
<td>HLA-A*0201</td>
</tr>
<tr>
<td>2008</td>
<td>SGPLKAECIAQRLEDV</td>
<td>17</td>
<td>Matrix protein 1</td>
<td>HLA-A*0201</td>
</tr>
<tr>
<td>2008</td>
<td>GLIYNRMGA</td>
<td>129</td>
<td>matrix protein 1</td>
<td>HLA-A2</td>
</tr>
<tr>
<td>2008</td>
<td>ILSPLTKGIL</td>
<td>51</td>
<td>matrix protein 1</td>
<td>HLA-A2</td>
</tr>
<tr>
<td>2008</td>
<td>QIAILVTTTV</td>
<td>25</td>
<td>neuraminidase</td>
<td>HLA-A2</td>
</tr>
<tr>
<td>2008</td>
<td>QLVWMACHSAA</td>
<td>327</td>
<td>nucleocapsid protein</td>
<td>HLA-A2</td>
</tr>
<tr>
<td>2008</td>
<td>TTYQRTRAL</td>
<td>146</td>
<td>nucleocapsid protein</td>
<td>HLA-A2</td>
</tr>
<tr>
<td>2008</td>
<td>ALQLLLEV</td>
<td>102</td>
<td>nonstructural protein 2</td>
<td>HLA-A2</td>
</tr>
<tr>
<td>2008</td>
<td>ITFMQALQLL</td>
<td>97</td>
<td>nonstructural protein 2</td>
<td>HLA-A2</td>
</tr>
<tr>
<td>2008</td>
<td>QLMWALGENMA</td>
<td>365</td>
<td>Polymerase acidic protein</td>
<td>HLA-A2</td>
</tr>
<tr>
<td>2008</td>
<td>RTMAWTVVNSI</td>
<td>84</td>
<td>polymerase PA</td>
<td>HLA-A2</td>
</tr>
<tr>
<td>2008</td>
<td>FSMELPSFGV</td>
<td>505</td>
<td>Polymerase basic protein 1(PB1)</td>
<td>HLA-A2</td>
</tr>
<tr>
<td>2008</td>
<td>FVANFSMEL</td>
<td>501</td>
<td>Polymerase basic protein 1(PB1)</td>
<td>HLA-A2</td>
</tr>
<tr>
<td>2008</td>
<td>FVELLARSI</td>
<td>45</td>
<td>PB1 polymerase protein</td>
<td>HLA-A2</td>
</tr>
<tr>
<td>2008</td>
<td>LLFLKVPA</td>
<td>7</td>
<td>Polymerase basic protein 1(PB1)</td>
<td>HLA-A2</td>
</tr>
<tr>
<td>2008</td>
<td>MMMGMFNML</td>
<td>407</td>
<td>Polymerase basic protein 1(PB1)</td>
<td>HLA-A2</td>
</tr>
<tr>
<td>1999</td>
<td>AIMDKNIML</td>
<td>122</td>
<td>Non-structural protein 1</td>
<td>HLA-A*0201</td>
</tr>
</tbody>
</table>

28 HLA-A2 epitopes (Sept 2010). Blue sequences are contained in PR8 (Mountain Sinai)
Systematic identification of immunodominant CD8\(^+\) T-cell responses to influenza A virus in HLA-A2 individuals

Chao Wu\(^{a,b}\), Damien Zanker\(^b\), Sophie Valkenburg\(^c\), Bee Tan\(^b\), Katherine Kedzierska\(^c\), Quan Ming Zou\(^a\), Peter C. Doherty\(^c,1\), and Weisan Chen\(^b,1\)

\(^a\)Department of Clinical Microbiology and Immunology, Third Military Medical University, Chongqing 400038, China; \(^b\)Ludwig Institute for Cancer Research, Austin Health, Heidelberg, Victoria 3084, Australia; and \(^c\)Department of Microbiology and Immunology, Melbourne University, Parkville, Victoria 3052, Australia
Identifying Major CD4+ T cell antigen in *H. pylori*

**Helicobacter *Pylori***

- Gram-negative
- Identified in 1982 by Marshall & Warren
- 1.7 million base-pair genome
- encodes for ~ 1,550 genes

Barry Marshall  
Robin Warren
Some research, especially some translational research, might be easier to be conducted in China than in Australia

with written informed consent. Gastric diseases were diagnosed in 1115 subjects by both endoscopic and histopathologic diagnosis and these subjects were screened for *H pylori* infection status; blood samples from these subjects were collected at the

59 helico+ and HLA-DR15+ (~10%) patient samples were collected and analyzed in detail.
HpaA88-100-specific CD4+ T cell response is associated with less severe *H. pylori*-associated gastric diseases

- **A** IFN-γ+ % total CD4+
  - Gastritis: \( P<0.0001 \)
  - Peptic ulcer: \( P=0.0002 \)
  - Gastric cancer: \( P=0.0021 \)

- **B** IFN-γ+ % total CD4+
  - Antral gastritis: \( P<0.0001 \)
  - Pangastritis: \( P=0.0211 \)
  - Atrophy gastritis: \( P>0.5 \)

- **C** IFN-γ+ % total CD4+
  - Duodenal ulcer: \( P=0.0016 \)
  - Gastric ulcer: \( P=0.0001 \)

*H. pylori*-associated gastric diseases
A Dominant CD4+ T-Cell Response to *Helicobacter pylori* Reduces Risk for Gastric Disease in Humans

Li Chen, Bin Li, WU-CHEN YANG, JIA-LIN HE, NING-YI LI, JIAN HU, YA-FEI HE, SHU YU, ZHUO ZHAO, PING LUO, JIN-YONG ZHANG, HAI-BO LI, MING ZENG, DONG-SHUI LU, BO-SHENG LI, HONG GUO, SHI-MING YANG, GANG GUO, XU-HU MAO, WEISAN CHEN, CHAO WU, and QUAN-MING ZOU

1Department of Clinical Microbiology and Immunology, College of Medical Laboratory Science, and 2Department of Gastroenterology, Xinqiao Hospital, Third Military Medical University, Chongqing, China; 3Department of Outpatients, Institute of Logistic Engineering of People’s Liberation Army; Chongqing, China; 4National Institutes for Food and Drug Control, Beijing, China; and 5T Cell Laboratory, School of Molecular Science, La Trobe University, Bundoora, Victoria, Australia
• They have conducted a phase III *H. pylori* clinical trials in school kids (2005) before the discovery of the specific CD4+ T cell antigens – we could sample those kids and look for these specific immune responses

• Incorporating the new findings into the next clinical trials -- next generation, individually tailed vaccine

• We are also explore other opportunities to study immunity to other pathogens, such as potential vaccines against antibiotics-resistant bacteria
Issue Highlights

- Second Cancers in Patients Treated for Gastric MALT Lymphoma
- Risk of Esophageal and Stomach Cancers in Patients With AIDS
- Similar Therapy but Different Regional Outcomes for HCV Infection
- Can Activated Hepatic Stellate Cells Revert to Quiescence?

Also: Acknowledging Joint First Authorship
1. Li Chen, Bin Li, Wuchen Yang, Jialin He, Ningyi Li, Shu Yu, Zhuo Zhao, Ping Luo, Jinyong Zhang, Dongshui Lu, Ping Chen, Haibo Li, Hong Guo, Gang Guo, Xuhu Mao, Weisan Chen*, Chao Wu*, and Quanming Zou*. A dominant CD4+ T-cell response to Helicobacter pylori is associated with decreased risk of gastric diseases in Chinese, *GASTROENTEROLOGY* (2013); 144:591–600 (* co-senior authors)

2. Yuan Zhuang, Liu-Sheng Peng, Yong-Liang Zhao, Yun Shi, Xu-Hu Mao, Weisan Chen, Ken C. Pang, Xiao-Fei Liu, Tao Liu, Jin-Yu Zhang, Hao Zeng, Kai-Yun Liu, Gang Guo, Wen-De Tong, Yan Shi, Bin Tang, Na Li, Shu Yu, Ping Luo, Wei-Jun Zhang, Dong-Shui Lu, Pei-Wu Yu, Quan-Ming Zou. CD8+ T cells That Produce Interleukin-17 Regulate Myeloid-Derived Suppressor Cells and are Associated with Survival Time of Patients with Gastric Cancer, *GASTROENTEROLOGY* (2012); 143:951–962


5. Emma Grant*, Chao Wu* Kok-Fei Chan, Sionda Eckle, Mandvi Bharadwaj, Quan Ming Zou, Katherine Kedzierska and Weisan Chen. Nucleoprotein of influenza A virus is a major target of immunodominant CD8+ T cell responses. *Immunology and Cell Biology* (2013); 91:184-194.
Acknowledgements

T cell Lab
• Damien Zanker
• Sara Oveissi
• Kok-Fei Chan
• Bee Tan
• Heather Jackson
• Kun Xiao

Melbourne Uni, Microbiology
• Emma Grant
• Dr. Katherine Kedzierska

Critical reagents
• rVV—NIH
• Dr Jon Yewdell & Jack Bennink

The Third Military Medical University
• Chao Wu
• Chen Li
• Zhuang yuan
• Zou Quanming
• Etc etc

Flu Program colleagues
• Prof. Peter Doherty
• Prof. Ann Kelso
• Prof. David Jackson
• Prof. Steve Turner
• Prof. Lori Brown