Immunogenomics/immunopharmacogenomics: exploring our immune system

Poh Yin Yew, Ph.D

OncoTherapy Science, Inc.
Immunogenomics:
A field which uses genomics tools such as next generation sequencing to unravel the complexity of the human immune system including TCR, BCR and HLA

Pharmacogenomics:
A field which applies genetic/genomic information (germline variation, somatic mutation, gene expression etc.) for better understanding of drug response

Immunopharmacogenomics
Immune system

First line of defense
Protect the body from harmful substances

Innate Immunity
• Epithelial Barrier
• Phagocytes
• Natural Killer cells

Adaptive Immunity
• T cells
• B cells
T cell receptor (TCR)

- **T cells**
  - involved in immune system

- **T cell receptor (TCR)**
  - Expressed on the surface of T cells
  - Recognition of antigen
  - Heterodimer (α+β or δ+γ linked together by a disulfide bridge)

Figure from Immunopharmacogenomics, Springer
Rearrangement of TCR

Genomic DNA
TCR alpha

Vαn  Vα2  Vα1  J  C

Rearranged DNA

Rearrangement of TCR alpha and beta

α

β

T cell

Genomic DNA
TCR beta

Vβn  Vβ2  Vβ1  Dβ1  J  Cβ1  Dβ2  J  Cβ2
Rearrangement of TCR

- During rearrangement, nucleotides are deleted from V(D)J exons and/or inserted between VJ (alpha), or VD and DJ (beta) junctions.

**CDR3** recognizes specific antigen
Each CTL has a unique TCR.

### Characterization of enormous individual differences in our immune responses

- **TCR**
- **CTL**

Millions of different T cells with unique TCRs

Number of unique T cells in our body = ???

The differences in T cell repertoire influence the response of various cancer treatments and are associated with various human autoimmune diseases.

### Next Generation Sequencing (NGS)
- Characterize millions of TCRs
gDNA-based vs cDNA-based TCR sequencing

(a) Genomic DNA

Multiplex PCR: V and J specific primers

(b) mRNA / cDNA

Multiplex PCR: V and J specific primers OR V and C specific primers

5’ RACE PCR: Adaptor and C specific primer
<table>
<thead>
<tr>
<th>TCR-specific PCR Amplification</th>
<th>Genomic DNA</th>
<th>mRNA·cDNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiplex PCR (V and J specific primers)</td>
<td>Multiplex PCR (V and J specific primers or V and C specific primers)</td>
<td>5’ RACE PCR (C and adaptor specific primers)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PCR bias</th>
<th>High</th>
<th>High</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novel exons</td>
<td>Not detectable</td>
<td>Not detectable</td>
<td>Detectable</td>
</tr>
<tr>
<td>T cells in Tissue</td>
<td>High background</td>
<td>Low background</td>
<td>Low background</td>
</tr>
<tr>
<td>Functionality</td>
<td>No</td>
<td>Reflected</td>
<td>Reflected</td>
</tr>
<tr>
<td>Quantification of T cells</td>
<td>Yes</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Analysis of paraffin-fixed tissue</td>
<td>Yes</td>
<td>Hard</td>
<td>Hard</td>
</tr>
</tbody>
</table>
TCR sequencing - workflow

Samples collection
PBMC
Tissue
Fluid

RNA extraction

Tissue Fluid Samples
RNA extraction
RNA Extraction

TCRA
TCRB

cDNA synthesis
“SMART” Adaptor

TCRA
Tissue Fluid Samples
cDNA synthesis

Sequencing

Machine: Illumina MiSeq
Read length: 2 X 300bp
Run time: ~ 56 hours

PCR

TCRA
TCRB
TCR analysis - CDR3 determination

Reads (fastq file)

V(D)J decomposition

• Reference = IMGT database
• Mapping to V, D, J, C exons
• Analysis of junction sequences between V, D and J

Mapped reads

CDR3 determination and clonotyping

Nucleotide sequences
Amino acid sequences
Nucleotide sequences
Amino acid sequences

TRBV15

2nd cysteine

phenylalanine

TRBJ2-5

CFLDIRSPGLGDATAMYLCA

agcagagagagagagcttccgaaaaagacccagtacctggtgcaccacc

SREARAVRKKTTIQFGPGTRL
### VNJ decomposition of TCRA

<table>
<thead>
<tr>
<th>TRAV</th>
<th>TRAJ</th>
<th>VdelNum</th>
<th>JdelNum</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRAV26-1</td>
<td>TRAJ17</td>
<td>1</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>TRAV10</td>
<td>TRAJ42</td>
<td>4</td>
<td>7</td>
<td>GG</td>
</tr>
</tbody>
</table>

### CDR3 determination of TCRA

<table>
<thead>
<tr>
<th>TRAV</th>
<th>TRAJ</th>
<th>CDR3 sequences</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRAV26-1</td>
<td>TRAJ17</td>
<td>CIVRVKAGNKLTF</td>
<td>12320</td>
</tr>
<tr>
<td>TRAV10</td>
<td>TRAJ42</td>
<td>CVVGGGSQGNLIF</td>
<td>2031</td>
</tr>
</tbody>
</table>

- VdelNum = number of nucleotide deleted at 3’ of V segment
- JdelNum = number of nucleotide deleted at 5’ of J segment
- N = the nucleotides added during VJ rearrangement
- Count = The observed reads for a specific combination of V, J and CDR3 sequences
### TCRB analysis

#### VNJ decomposition of TCRB

<table>
<thead>
<tr>
<th>TRBV</th>
<th>TRBD</th>
<th>TRBJ</th>
<th>Vdel Num</th>
<th>Jdel Num</th>
<th>N1</th>
<th>D</th>
<th>N2</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRBV6-1</td>
<td>TRBD2</td>
<td>TRBJ2-2</td>
<td>6</td>
<td>1</td>
<td>A</td>
<td><em>GGACTAG</em>*******</td>
<td>T</td>
</tr>
<tr>
<td>TRBV4-1</td>
<td>TRBD1</td>
<td>TRBJ2-7</td>
<td>4</td>
<td>1</td>
<td>TTCTCCCG G</td>
<td>GGGACAG GG***</td>
<td>-</td>
</tr>
</tbody>
</table>

#### CDR3 determination of TCRB

<table>
<thead>
<tr>
<th>TRBV</th>
<th>TRBJ</th>
<th>CDR3 sequences</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRBV6-1</td>
<td>TRBJ2-1</td>
<td>CASRGLVNTGELFF</td>
<td>10500</td>
</tr>
<tr>
<td>TRBV4-1</td>
<td>TRBJ2-7</td>
<td>CASSLRGTGYEQYF</td>
<td>2230</td>
</tr>
</tbody>
</table>

- VdelNum = number of nucleotide deleted at 3’ of V segment
- JdelNum = number of nucleotide deleted at 5’ of J segment
- N1 = the nucleotides added during VD rearrangement.
- * in the D segment indicated the deleted nucleotides during rearrangement.
- N2 = the nucleotides added during DJ rearrangement.
- Count = The observed reads for a specific combination of V, J and CDR3 sequences
Evaluation of TCR diversity and clonality

**Diversity Index:**
- A quantitative measure that reflects how many different types (unique clones) there are in a dataset.

\[
D_S = \left[ \sum_{i=1}^{K} \frac{n_i(n_i - 1)}{N(N - 1)} \right]^{-1}
\]

<table>
<thead>
<tr>
<th>Clonal expansion</th>
<th>High</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diversity ((1/D_S))</td>
<td>Low</td>
<td>High</td>
</tr>
</tbody>
</table>
TCR analysis – Unmapped reads

Unmapped reads

Unmapped part

• Remapped to reference genome including intronic region
• May identify novel exon which are not deposited in the reference database
• May discover abnormalities in V(D)J recombination
Examples: Unmapped part analysis

a)

TRA V1-1 genomic DNA

TRA V1-1 exon 1

exon 1

exon 2

novel TRA V1-1del

5' end portion of exon 2

3' end portion of exon 2

b)

TRB V7-6 genomic DNA

TRB V7-6 exon 1

exon 1

exon 2

novel TRB V7-6variant

TRB V7-6 exon 1

5' end portion of exon 2

3' end portion of exon 2

novel TRB V7-6del

Publications from the University of Chicago

**TCR analysis of cancer patients treated with cancer peptide vaccines**

Quantitative T Cell Repertoire Analysis by Deep cDNA Sequencing of T Cell Receptor α and β Chains using Next-Generation Sequencing (NGS)

*Summary:

Characterization of T cell repertoire in cancer patients treated with cancer peptide vaccines.*

Characterization of T cell repertoire in tumor tissues and blood in advanced colorectal cancers through deep T cell receptor sequencing.

**Jang M, Yew PY, Hasegawa K, et al. OncoImmunology, 2015**
Characterization of T cell repertoire in tumor tissues and blood in advanced colorectal cancers through deep T cell receptor sequencing.

Highly clonal T cell receptor repertoire among regulatory T cells in follicular lymphoma tissues – correlation with the CD8+ T cell receptor repertoire

**Choudhury NJ, Kiyotani K, Yap KL et al. European Urology Focus, 2015**
Low T-cell Receptor Diversity, High Somatic Mutation Burden, and High Neoantigen Load as Predictors of Clinical Outcome in Muscle-invasive Bladder Cancer

**TCR analysis of hematopoietic stem cell transplant recipients**

Yew PY, Alachkar H, Yamaguchi R, et al. *Bone Marrow Transplantation, 2015*
Quantitative characterization of T cell repertoire in allogeneic hematopoietic stem cell transplant recipients.

**TCR analysis of autoimmune diseases**

Chapman CG, Yamaguchi R, Tamura K, et al. *Inflammatory Bowel Diseases, in press, 2016*
Characterization of T-cell Receptor Repertoire in Inflamed Tissues of Patients with Crohn's Disease through Deep Sequencing

**Review paper**

Choudhury NJ and Nakamura Y. *Cancer Science, in press, 2016*
Importance of immunopharmacogenomics in cancer treatment: Patient selection and monitoring for immune checkpoint antibodies
TCR sequencing projects:
Characterizing T cell repertoire in:

1. Allogeneic hematopoietic stem cell transplant (HSCT) recipients
2. Patients with Crohn’s Disease
3. Patients with Follicular lymphoma
4. Patients with Muscle-invasive Bladder Cancer
Quantitative characterization of T cell repertoire in allogeneic hematopoietic stem cell transplant (HSCT) recipients


Bone Marrow Transplantation, 2015, 50(9):1227-1234
Hematopoietic Stem Cell Transplantation (HSCT)

- HSCT = the most effective therapy for patients with AML
GVL vs GVHD vs Relapse

- Unrelated Donor
- HLA-identical Sibling Donor
- T-cell Depleted Marrow
- Syngeneic

With Immunosuppressant:
- GvHD → GvL → Relapse

Without Immunosuppressant:
- GvHD → GvL → Relapse

Figure from http://www.regimmune.com/product-pipeline/gvhd/
## Patients Characteristic

<table>
<thead>
<tr>
<th></th>
<th>Matched Donor</th>
<th>Haplo-cord</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>HLA identical relative</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>HLA identical unrelated</td>
<td>7</td>
<td>-</td>
</tr>
<tr>
<td>Age</td>
<td>42-73</td>
<td>26-67</td>
</tr>
<tr>
<td>Conditioning regimen</td>
<td>Flu/Mel/Campath or Clo/Mel/Campath</td>
<td>Flu/Mel/anti-thymocyte globulin</td>
</tr>
<tr>
<td>Acute GVHD</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Relapsed</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

GVHD, Graft-versus-host disease; Flu, fludarabine; Mel, melphalan
Patients with higher % of cord-derived cells at Day 30 had significantly higher TCR diversity at Day 100.
TCR repertoire diversity and source of donor stem cells

No significant difference between patients underwent MD and haplo-cord transplant
Proportions of 10 most abundant CDR3: GVHD vs non-GVHD

Significant Expansion of TCRB Clones in GVHD Patients
Proportions of 10 most abundant CDR3: Non-relapsed - GVHD vs non-GVHD

GVHD significantly correlates with expansion of TCRA and TCRB clones.
TCR repertoire and correlation with relapse

**Non-GVHD**

TCRA

TCRB

**GVHD**

TCRA

TCRB
Summary

- TCR repertoire of patients with higher % cord cells on day 30 after haplo-cord transplant were significantly more diverse on day 100 compared to TCRs in patients with lower % of cord cells

- GVHD patients:
  - Lower TCR diversity, expansion of certain clones

- Non-GVHD and non-relapsed patients
  - Higher TCR diversity

- TCR analysis of hematopoietic stem cell transplant recipients:
  - Understanding of the immunological response of patients after transplantation
  - Understanding the immune reconstitution after transplantation
TCR sequencing projects: Characterizing T cell repertoire in:

1. Allogeneic hematopoietic stem cell transplant (HSCT) recipients

2. Patients with Crohn’s Disease

3. Patients with Follicular lymphoma

4. Patients with Muscle-invasive Bladder Cancer
Characterization of T-cell Receptor Repertoire in Inflamed Tissues of Patients with Crohn’s Disease through Deep Sequencing


Inflammatory Bowel Diseases, 2016, in press
Crohn’s disease (CD)

- A chronic, relapsing inflammatory bowel disease (IBD), characterized by an abnormal inflammatory response to intestinal microbes in a genetically susceptible patient.

Genetic susceptibility → CD

Environmental factors → CD

Intestinal microbes → CD

Host immune response → CD
Patients characteristic

17 CD patients

Tissue
- 12 biopsy from the neo-terminal ileum of post-operative recurrent CD patients
- 5 surgical resections of terminal ileum of CD patients

Blood
- 17 PBMC samples
Comparison of TCR Diversity between Tissue and Blood in CD

**TCRA**

- **Blood:**
  - Diversity (1/Ds)
  - P = 0.0045

- **Tissue:**
  - Diversity (1/Ds)

**TCRB**

- **Blood:**
  - Diversity (1/Ds)
  - P = 0.000080

- **Tissue:**
  - Diversity (1/Ds)
The Neo-Terminal Ileum: Rutgeert’s score: Colonoscopy 6 months after surgery to re-stratify

**Rutgeert’s 0**
- Normal ileal mucosa

**Rutgeert’s 1**
- <5 aphthous ulcers

**Rutgeert’s 2**
- >5 aphthous ulcers, normal intervening mucosa

**Rutgeert’s 3**
- Ulceration without normal intervening mucosa

**Rutgeert’s 4**
- Severe ulceration with nodules, cobblestoning, or stricture
Correlation of one clonotype with Disease Severity

CASSWTNGEQYF (TRBV10-1, TRBJ2-7)

Frequency (% of reads)

P = 0.015

Rutgeerts score
Summary

- TCR diversity in mucosal tissue was significantly lower compared the matched PBMCs.
  - Expansion of certain T cell clones in the inflamed intestinal tissue.

- The abundance of one clonotype is correlated with severity of disease recurrence, based on Rutgeerts score.

- TCR analysis of Crohn’s disease patients:
  - Understanding about the immunological reaction in CD
TCR sequencing projects:
Characterizing T cell repertoire in:

1. Allogeneic hematopoietic stem cell transplant (HSCT) recipients

2. Patients with Crohn’s Disease

3. Patients with Follicular lymphoma

4. Patients with Muscle-invasive Bladder Cancer
Highly clonal regulatory T-cell population in follicular lymphoma - inverse correlation with the diversity of CD8+ T cells.


OncolImmunology, 2015, 4(5):e1002728.
### Patients characteristic

<table>
<thead>
<tr>
<th>ID</th>
<th>Age</th>
<th>Age at Diagnosis</th>
<th>Grade</th>
<th>Stage at Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT 1</td>
<td>84</td>
<td>81</td>
<td>II-IIIA</td>
<td>III</td>
</tr>
<tr>
<td>PT 2</td>
<td>84</td>
<td>83</td>
<td>IIIA</td>
<td>IV</td>
</tr>
<tr>
<td>PT 3</td>
<td>76</td>
<td>70</td>
<td>II</td>
<td>I</td>
</tr>
<tr>
<td>PT 4</td>
<td>72</td>
<td>61</td>
<td>I-II</td>
<td>II</td>
</tr>
<tr>
<td>PT 5</td>
<td>77</td>
<td>77</td>
<td>I-II (80%), IIIA (20%)</td>
<td>IV</td>
</tr>
<tr>
<td>PT 6</td>
<td>71</td>
<td>55</td>
<td>I-II</td>
<td>I</td>
</tr>
</tbody>
</table>

- The patient samples were single-cell suspensions derived from diagnostic FL biopsy specimens (pre-treatment lymph node).
- CD8\(^+\), CD4\(^+\)CD25\(^-\) and CD4\(^+\)CD25\(^+\) were isolated.
- The Treg control samples were single-cell suspensions of nonmalignant lymph node biopsies from three nonfollicular lymphoma patients.
Oligoclonal enrichment of Treg TCRs in FL tumors

The % = The total percentage of 5 most abundant TCRB sequences

Follicular lymphoma biopsies

<table>
<thead>
<tr>
<th>PT1</th>
<th>PT2</th>
<th>PT3</th>
</tr>
</thead>
<tbody>
<tr>
<td>68.23%</td>
<td>80.73%</td>
<td>89.00%</td>
</tr>
<tr>
<td>n = 676</td>
<td>n = 1247</td>
<td>n = 341</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PT4</th>
<th>PT5</th>
<th>PT6</th>
</tr>
</thead>
<tbody>
<tr>
<td>68.34%</td>
<td>58.40%</td>
<td>80.75%</td>
</tr>
<tr>
<td>n = 528</td>
<td>n = 760</td>
<td>n = 499</td>
</tr>
</tbody>
</table>

Nonmalignant lymph node biopsies

<table>
<thead>
<tr>
<th>Control 1</th>
<th>Control 2</th>
<th>Control 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>40.28%</td>
<td>11.07%</td>
<td>48.10%</td>
</tr>
<tr>
<td>n = 8479</td>
<td>n = 20696</td>
<td>n = 8609</td>
</tr>
</tbody>
</table>

76.24 ± 11.17%

33.15 ± 19.52%
Diversity of Treg TCRs is lower in FL tumors

Simpson's Index of Diversity (SID)

Follicular lymphoma biopsies

Nonmalignant lymph node biopsies

$P = 0.0409$
CD8+ T cell repertoire & infiltration pattern in FL tissue

PF/IF ratio: PF = perifolllicular, IF = intrafollicular
A Special Case Study: Patient 4

The graph shows the sequencing count as a percentage of total in-frame reads for Treg, CD8, and CD4 cells. The sequences are compared between TCRA and TCRB.
A Special Case Study: Patient 4

<table>
<thead>
<tr>
<th>ID</th>
<th>Sex</th>
<th>Age</th>
<th>Age at Disease</th>
<th>Grade</th>
<th>Stage at Disease</th>
<th>Treatment</th>
<th>Response to treatment</th>
<th>Alive</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT 4</td>
<td>Male</td>
<td>72</td>
<td>61</td>
<td>I-II</td>
<td>II</td>
<td>No</td>
<td>NA</td>
<td>yes</td>
</tr>
</tbody>
</table>

CD4

CD8

Treg (FOXP3)
Nonsynonymous SNV mutations were found in both HLA class II and class I molecules of patient 4.
Summary

- Strong enrichment of regulatory T cells was observed commonly in FL specimens
- Tumors with perifollicular CD8+ T cell distribution tend to have stronger enrichment of CD8+ T cell
- One interesting case (Patient 4):
  - Missense mutations at the peptide binding domains in both HLA class I and II molecules
  - May alter the peptide antigens displayed
- TCR sequencing combined with exome sequencing of FL patients
  - Understanding the immune microenvironment of FL patients
  - Identify the targetable antigens for T cell based therapeutic strategies
TCR sequencing projects: Characterizing T cell repertoire in:

1. Allogeneic hematopoietic stem cell transplant (HSCT) recipients
2. Patients with Crohn’s Disease
3. Patients with Follicular lymphoma
4. Patients with Muscle-invasive Bladder Cancer
Low T-cell Receptor Diversity, High Somatic Mutation Burden, and High Neoantigen Load as Predictors of Clinical Outcome in Muscle-invasive Bladder Cancer


European Urology Focus, 2015, http://dx.doi.org/10.1016/j.euf.2015.09.007
Whole exome sequencing (43 samples) &
Targeted gene sequencing (38 samples)

Somatic mutations in any of six DNA repair genes (ATM, ERCC2, FANCD2, PALB2, BRCA1, and BRCA2)

- **Carriers:**
  - Higher overall somatic mutation burden (307.4 mutations/case)
- **Non-carriers:**
  - 155.4 mutations/case

Previous study: Exome sequencing of MIBC

<table>
<thead>
<tr>
<th>Carriers (n=25)</th>
<th>Non-carriers (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median RFS = 32.4 months</td>
<td>Median RFS = 14.8 months</td>
</tr>
</tbody>
</table>

\[ P = 0.0435 \]
\[ HR = 0.46 \]
Hypothesis

Mutations in DNA repair genes → Higher overall somatic mutation burden → Neoantigens → Clonal expansion of TILs → Low TCR diversity (clonal expansion of CD8+ cells) is associated with better prognosis
Workflow

TCR sequencing of 38 samples (Recurrent vs Non-recurrent) → Whole exome sequencing → Neoantigens prediction
TCR diversity and recurrence risk

Non-recurrent patients had lower TCRB diversity index

$P = 0.080$
Patients with lower TCRB diversity index had significantly longer RFS
Recurrence and number of predicted neoantigens

Non-recurrent Patients had higher average number of predicted neoantigens
Patients with high antigen load and low TCRB diversity index had longer RFS.
Summary

- Low TCRB diversity index correlate with oligoclonal TIL expansion and longer RFS

- Patients with a high number of neoantigens and low TCRB diversity had longer RFS

- TCR analysis and exome sequencing of MIBC patients
  - Understanding the molecular patterns of antitumor immune response in MIBC
  - Provide us the valuable prognostic information on the clinical course of MIBC
TCR analysis will contribute to:

- understanding of complex interaction between cancer and the immune system,
- understanding of cancer therapy mechanism, either in the setting of human studies or mouse models,
- patient selection - characterizing the best responders for cancer therapy,
- monitoring and assessment of ongoing cancer therapy.
**Future directions**

**BCR sequencing**
- To obtain a better understanding in the fundamental of immunology and the pathophysiology of various disease such as autoimmune diseases, food allergy etc.

**Single cell analysis**
- Identify the pair in BCR or TCR
  - important for subsequent functional analysis
- Investigate the heterogeneity in gene expression among T cells.
Part I Technologies

1. Deep Sequencing of T-Cell and B-Cell Receptors with Next-Generation DNA Sequencers
   Miran Jang and Poh Yin Yew

2. A TCR Sequence Data Analysis Pipeline: Tcrip
   Rui Yamaguchi, Seiya Imoto, and Satoru Miyano

Part II Applications

3. Prediction of Drug-Induced Adverse Reactions: Skin Hypersensitivity and Liver Toxicity
   Kazuma Kiyotani

4. Selection and Monitoring of Patients for Immunotherapy (Peptide Vaccines)
   Xiao Liu and Justin Kline

5. Patient Selection and Monitoring for Immunotherapies: Challenges for Immune Checkpoint Antibody and Cell Therapies
   Noura Choudhury

6. Better Understanding of Rejection After Organ Transplantation
   Houda Alachkar

7. Better Understanding of Severe Immunological Reactions: Autoimmune Diseases
   Kenji Tamura and Kazuma Kiyotani

8. Better Understanding of Severe Immunological Reactions: Food Allergy
   Tu H. Mai
• Prof. Yusuke Nakamura
• Members from Nakamura lab, the University of Chicago

• Prof. Satoru Miyano
• Prof. Seiya Imoto
• Dr. Rui Yamaguchi
Thank you very much for your attention!!

tcr-info(at mark)oncotherapy.co.jp

Japanese : http://www.oncotherapy.co.jp/service/
English : http://www.oncotherapy.co.jp/en/service/