Translational Research Activities in Tokyo Medical Dental University

Takako Takai-Igarashi, PhD
Contents

- Brief introduction of Tokyo Medical and Dental University (TMDU)
  - TMDU organization
  - Biomedical PhD School of TMDU

- Three special education programs charged to Prof. Tanaka by Japanese government
  - International Educational Program for Interdisciplinary Disease Sciences
  - Reeducation program for students with jobs: Educational Program for Bio-Medical Omics Information Scientists
  - TITECH-TMDU Joint Education Program for Translational Biomedical Informatics

- My current research interests
  - Supervising PhD students
  - Research progress on Clinical-pedia for Inflammatory Bowel Disease
  - Development of a database and ontology for pathogenic pathways in periodontitis
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Tokyo Medical and Dental University (TMDU) **History**

- Founded in 1917 as the first national school of dentistry
- Medical school was founded in 1944
- Biomedical PhD school was founded in 2003.
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Goals of Education

1. Our PhD program can keep up meeting the rapidly changing needs of society in education, so that it specializes in education being dissociated from research faculty in the University.

2. Based upon the rapid advancement of life science, we will nurture scientist who can engage in the interdisciplinary research and development of leading-edge life science, while training them to be equipped with management skills built upon the analytical minds as life scientists, who can adopt the skills to pragmatic problem-solving.

3. We educate students to resolve practical problems in interdisciplinary and leading-edge life science.
Biomedical PhD School

Medical Research Institute (MRI)
Institute of Biomaterials and Bioengineering (IBB)

Affiliated Institutions
RIKEN Discovery Research Institute
RIKEN Brain Science Center
RIKEN Genomic Sciences Center
RIKEN Research Center for Allergy and Immunology
National Cancer Center
National Center of Neurology and Psychiatry
National Center for Child Health and Development
International Medical Center
Japanese Foundation for Cancer Research
The Tokyo Metropolitan Institute of Medical Science
National Institute of Advanced Industrial Science and Technology
Institute, Astellas Pharma, Inc.
NTT Data

Students can be supervised on their PhD theses by researchers of the affiliated institutes.
Biomedical Science Ph.D. Program

Degree Requirements

Master's Degree (2 years)
A student must attend the program for at least two years, acquire at least 30 units (20 classroom-units), and pass the master's thesis examination (open to the public) along with the final examination. Upon successful completion, a student will obtain the Master of Science Degree.

Doctoral Degree (3 years)
A student must attend the program for at least three years, acquire at least 20 units, and pass the doctoral dissertation examination (open to the public) along with the final examination. Upon successful completion of the program, a student will obtain the Doctorate Degree in Science.

Number of Faculty members exceeds the number of students each year.

Intensive care for the Students
### Curriculum of Biomedical PhD School (Japanese)

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>• Special Lectures of Overview of Bioscience</td>
<td>• Proteome Informatics</td>
<td>• Special Lectures on Molecular Structures</td>
</tr>
<tr>
<td>• Genome Informatics and Medicine</td>
<td>• Computational System Biology</td>
<td>• Modeling of Biological Systems</td>
</tr>
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<td>• Journal Club on Bio-Medical Research</td>
<td>• Bioinformatics Computation</td>
<td>• Genome Informatics</td>
</tr>
<tr>
<td>• Neuroscience</td>
<td>• Cellular Signal Transduction</td>
<td>• Biofunctional Molecules</td>
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<tr>
<td>• Immunology</td>
<td>• Regenerative Medicine and Cell Therapy</td>
<td>• Regulation of Cell and Tissue Development</td>
</tr>
<tr>
<td>• Overview of Bioscience</td>
<td>• Bio-inspired System</td>
<td>• Ethical Issues and History of Bioscience</td>
</tr>
<tr>
<td>• Genome and Gene Expression Analyses</td>
<td>• English Debate Practice</td>
<td>• Bioindustry-Academia Cooperation</td>
</tr>
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<td>• Proteome Analysis Practice</td>
<td>• Genetic Engineering</td>
<td>• A Seminar in Cell Biology</td>
</tr>
<tr>
<td>• Introduction to Scientific Writing in English</td>
<td>• Regulation of Cell Growth</td>
<td>• Development and Reproduction</td>
</tr>
<tr>
<td>• Chemical Biology</td>
<td>• OMICS-based Drug Discovery and Development</td>
<td>• Bio-Intelligence Science</td>
</tr>
</tbody>
</table>

**30 units are required for M.Sc. degree**

**20 units are required for PhD degree**
International PhD Program of Biomedical PhD School (since 2006)

- All the lectures and practices are given in English.
- Web based entrance examination.
- PhD Studentship with Japanese Governmental Fund.
- A school year starts October and ends in September.
- 13 foreign students are studying on their PhD theses (2009).

Academic Calendar for Master’s Course

<table>
<thead>
<tr>
<th>10</th>
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<td>Research supervised by multiple faculty of different expertise</td>
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<tr>
<td>Write a thesis openly reviewed for approval, to be a true PhD holder of global standard</td>
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<tr>
<td>Obtain the degree</td>
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</table>
Curriculum of International Biomedical Science PhD Program

Oct, 2009
- Omics Informatics
- Genome Informatics and Medicine
- Computational Systems Biology
- Regulation of Cell Growth
- Integrated Translational Research

Nov, 2009
- Omics Informatics
- Chemical Biology
- Development and Reproduction

Dec. 2009
- Cellular Signal Transduction
- Systems Biology
- Special Lectures on Molecular Structures

30 units are required for M.Sc. degree
20 units are required for PhD degree
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International Educational Program for Interdisciplinary Disease Sciences

Principle Investigator: Prof. Dr. Hiroshi Tanaka
Project Manager: Dr. Takako Takai-Igarashi
Special program for promotion of international alliances in education, funded by Japanese government, 2008-2010

- For development alliances and cooperation with universities overseas
  - Tokyo Medical Dental University
  - Kusyu University
  - Hokkaido University
  - Tohoku University
  - Tokyo University of Science
  - Nagaoka University of Technology

- 2,000,000$ in three years for each organization

6 universities are awarded out of 33 applicants.
International Educational Program for Interdisciplinary Disease Sciences, in TMDU

- Graduate students of TMDU can take lectures and research supervisions from professors in universities overseas, without going abroad.

- Action plans:
  - Form alliances with foreign universities.
  - Joint lectures with universities of alliances.
  - Host foreign graduate students and supervise their research projects.
  - Encourage many foreign students to apply to TMDU international PhD school.
Formation of Alliances with Foreign Universities

EU
- Heidelberg University, Germany
- Freiburg University, Germany
- The University of Glasgow, UK
- The University of Dundee, UK
- Ecole Nomale Supérieure de Lyon, France

USA
- Harvard Medical School, USA*
- Duke University, USA*

Asia
- Peking University, China
- China Medical University, China
- Fudan University, China
- Peking Union Medical College, China
- Shanghai Center for Bioinformatics Technology, China
- Hanoi Medical University, Vietnam

* Under negotiation
Joint lectures with universities overseas

Integrated Translational Research (2 units)
- Harvard Medical School, USA and Tokyo Medical Dental University, Japan
- Participate in CBMI Translational Science Seminar organized by Dr. Tonellato, Harvard Medical School
- TMDU students watch videos of the lectures, make weekly discussions with TMDU faculty (Dr. Fukuoka and Dr. Takai-Igarashi), and have weekly web meeting with Dr. Tonellato and his colleagues in Harvard Medical School.

Student: 5 graduate students registered (4 Japanese and 1 foreigner).
Grading: Examination 50%, Attendance 50%.

http://lpm.hms.harvard.edu/palaver/

Exam

Examination questions in BF224 Integrated Translational Research

【Q1】Give an example of application of informatics to the translational research and discuss it.

【Q2】Discuss what are required when you translate your research outcomes into practical applications.

【Q3】Discuss clinical services available in hospitals in the future on the basis of information on genome and proteome of patients as an application of the translational research.
Joint lectures with universities overseas

**Integrated Bioinformatics (2 units)**
- Take lectures of invited professors from universities overseas

Student: 6 graduate students registered (5 Japanese and 1 foreigner).
Grading: Examination 50%, Attendance 50%.

<table>
<thead>
<tr>
<th>Date</th>
<th>Lecturer</th>
<th>University</th>
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<tbody>
<tr>
<td>9/28/09</td>
<td>Shoko Yokoyama</td>
<td>Emory University, USA</td>
</tr>
<tr>
<td>9/29/09</td>
<td>Shoko Yokoyama</td>
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<td>9/30/09</td>
<td>Shoko Yokoyama</td>
<td>Emory University, USA</td>
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<td>Shoko Yokoyama</td>
<td>Emory University, USA</td>
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<tr>
<td>10/2/09</td>
<td>Shoko Yokoyama</td>
<td>Emory University, USA</td>
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<td>11/18/09</td>
<td>Jun Ogura</td>
<td>Ochanomizu, U.</td>
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<td>11/25/09</td>
<td>Jesper Jansson</td>
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<td>12/2/09</td>
<td>Gos Micklem</td>
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<td>University of Cambridge, UK</td>
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<td>12/3/09</td>
<td>Gos Micklem</td>
<td>University of Cambridge, UK</td>
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<td>12/9/09</td>
<td>Norihide Mori</td>
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<tr>
<td>1/13/10</td>
<td>Hiroko Sano</td>
<td>Ochanomizu, U</td>
</tr>
</tbody>
</table>

Prof. Dr. Yokoyama
“Bioinformatics of the Gene”
**Joint lectures with universities overseas**

**Applied Chemical Biology (2 units)**
- Take lectures of invited professors from universities overseas

**Student:** 4 graduate students registered (3 Japanese and 1 foreigner).

**Grading:** Examination 50%, Attendance 50%.

**Curriculum**

<table>
<thead>
<tr>
<th>Date</th>
<th>Lecturer</th>
<th>University</th>
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<tbody>
<tr>
<td>7/23/09</td>
<td>Fabian Mohr</td>
<td>Wuppertal University, Germany</td>
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<tr>
<td>7/23/09</td>
<td>Fabian Mohr</td>
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<td>7/24/09</td>
<td>Fabian Mohr</td>
<td>Wuppertal University, Germany</td>
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<td>10/14/09</td>
<td>Zhenning Wang</td>
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<td>10/14/09</td>
<td>Yan XIN</td>
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<td>Feng Li</td>
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<td>Yongjun Jiang</td>
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<td>10/14/09</td>
<td>Hiroyuki Kagechika</td>
<td>Tokyo Medical and Dental University</td>
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<tr>
<td>10/14/09</td>
<td>Shoji Yamaoka</td>
<td>Tokyo Medical and Dental University</td>
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<td>U. Minnesota Medical School, USA</td>
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<td>Li-Na Wei</td>
<td>U. Minnesota Medical School, USA</td>
</tr>
<tr>
<td>11/25/09</td>
<td>Kei Yura</td>
<td>Ochanomizu, University</td>
</tr>
</tbody>
</table>
A graduate student of Heidelberg University, Germany, will stay in TMDU for two months. She will take three lectures; B109 "Systems Biology", B108 "Omics Informatics", and BF211 "Chemical Biology" in TMDU International PhD School. She will take a special lecture for Japanese history and culture. She will make a tour to visit Japanese bio-venture companies in Tsukuba and Osaka. A Japanese PhD student works in helping her daily life as a Teaching Assistant. We have one more plan of student invitation from University of Glasgow, UK., in this educational year.
TMDU faculty members, having Prof. Tanaka as a leader, visit China Medical University and give lectures at the university.

TMDU faculty members also visit China Medical School and recruit undergraduate students, encouraging them to study PhD theses in Tokyo, also having Prof. Tanaka as a leader.

2 students entered to our international PhD school in 2008, and 4 students entered in 2009.

Our final goal is that undergraduate students of highly talented will gather to our international PhD school from many Asian universities.
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Educational Program for Bio-Medical Omics Information Scientists

**Principle Investigator:**
Professor Dr. Hiroshi Tanaka

**Project Manager:**
Dr. Takako Takai-Igarashi
Program for education in cutting-edge sciences, funded by Japanese government, 2002-2009

- Foster researchers who can promote cutting-edge sciences and its industrialization.
  - Interdisciplinary life sciences
  - Novel software development
  - Intelligent property
  - Biological statistics and biomedical informatics
  - Nanotechnology
  - Challenge to environmental crisis
  - Integration of social and life sciences
  - Innovation in informational technology

- 5,000,000$ in five year for each organization
Educational Program for Bio-Medical Omics Information Scientists in TMDU

- Funded to TMDU in 2006 – 2009
- Reeducation for people with jobs.
- Produce translational scientists who can apply omics to clinical medicine.
  - Provide education on informational technology for medical doctors and personnel.
  - Provide basic clinical medicine for bioinformatics researchers.
<table>
<thead>
<tr>
<th>First Year</th>
<th>Month</th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
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<tbody>
<tr>
<td>Nov</td>
<td>Basics</td>
<td>Biological Omics 1 18:30 ~ 21:00</td>
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<td>Dec</td>
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<td>Clinical Omics 1 18:30 ~ 21:00</td>
<td>2 units</td>
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<th>Month</th>
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<tr>
<td>May</td>
<td>Apllication</td>
<td>Statistical Genetics 18:30 ~ 21:00</td>
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<td>Jun</td>
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<td>Clinical Omics 2 18:30 ~ 21:00</td>
<td>2 units</td>
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<td>Oct</td>
<td>Practice</td>
<td>Research Project</td>
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**Requirement**
- Required 20 units
- Elective 10 units
- Total 30 units

**Exercise in Translational Research**
- 13:00 ~ 18:00
1. TMDU faculty in University Center for Biomedical Informatics
   - Bioinformatics
   - Exercise in Translational Research

2. TMDU faculty in Graduate School of Medical and Dental Sciences
   - Clinical Medicine
   - Clinical Omics 1,2

3. TMDU faculty in Graduate School of Biomedical Science
   - Biological Omics 1,2

4. Guest lectures from universities and research institutes
   - Statistical Genetics
   - Systems Pathology 1,2

5. Guest lectures from pharmaceutical companies
   - Omics-based Drug discovery 1,2
   - Exercise in Translational Research
University of Tokyo
Tokyo Women’s Medical University
Keio University
Kyushu University
Waseda University
Kinki University
Osaka University
Kitasato university
Riken
Pharmaceuticals and Medical Devices Agency

Japan Pharmaceutical Manufacturers Association
GlaxoSmithKline
Novartis
Mitsubishi Tanabe pharma
daiichi-Sankyo
Astellas
D Three Research
Daiwa Securities
CliniPro Co., Ltd
## Exercise in Translational Science in 2007

<table>
<thead>
<tr>
<th>Date</th>
<th>Time</th>
<th>Contents</th>
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<tbody>
<tr>
<td>Oct 13</td>
<td>13:00-18:00</td>
<td>Case studies in Bioethics</td>
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<tr>
<td>Oct 20</td>
<td>13:00-18:00</td>
<td>Protocols for clinical trials</td>
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<tr>
<td>Oct 27</td>
<td>13:00-19:00</td>
<td>Analysis of clinical information with SAS</td>
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<tr>
<td>Nov 10</td>
<td>13:00-19:00</td>
<td>Visit at a hospital of clinical trials</td>
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<td>Visit at a bio-venture company</td>
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<td>Visit at Site Management Organization (SMO)</td>
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<td>Dec 8</td>
<td>13:00-19:00</td>
<td>Business proposals</td>
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<td>Dec 15</td>
<td>13:00-19:00</td>
<td>Experiments with microarray</td>
</tr>
<tr>
<td>Dec 22</td>
<td>13:00-19:00</td>
<td>Experiments with microarray</td>
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</tbody>
</table>

## Additional Notes
- Write a short paper on the research results and make a poster-presentation at a workshop for 'omics-based medicine'.
- Analysis of microarray data with R
- Presentation of individual research project
Research projects in 2008

- Role of hepatic stem cells in liver cancer based on microarray data from patients.
- Invasive carcinoma into portal of liver based on microarray data from patients.
- Effect of alcohol and smoking on carcinoma in oral cavity based on microarray data from patients.
- Investigation of Intestinal cancer based on microarray data from patients.
- A new method to estimate accurate gene expression values from microarray data.
- Determination of protein sequences from MASS spectra data, preliminary study.
- Evaluation of a new clustering method ‘affinity propagation’ with biomedical data.
- Ontology-based modeling of ‘clinical path’, preliminary study.
- Development of a pathway database for side-effects of steroids, preliminary study.
- Development of a pathway database for glyco signaling and diseases, preliminary study.
- Prioritization of candidate genes from GWAS data on Bipolar patients, preliminary study.
- Principal Component Analysis on microarray data from Bipolar patients.
- Promoter region analysis on microarray data from FOXO transgenic mice, preliminary study.
- Hormone therapy on breast cancer, a study in recent progress.
- Architecture and Evolution of Protein-Protein Interaction Networks, a study in recent progress.
### The number of students graduated this program

<table>
<thead>
<tr>
<th>Year</th>
<th>First Class</th>
<th>Second Class</th>
<th>Third Class</th>
<th>Forth Class</th>
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<tbody>
<tr>
<td>2005</td>
<td>18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>18</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td></td>
<td></td>
<td></td>
<td>20 (estimation)</td>
</tr>
<tr>
<td>2009</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Proceed to PhD course of Graduate School of Medical and Dental Sciences: 11
Backgrounds of the students

The First Class: 18
- Medical Doctor
- Pharmaceutist
- Other Medical Personnel

The Second Class: 14
- Life Science
- Informatics
- Social Science
- Graduate Student

The Third Class: 18
- Medical Doctor
- Pharmaceutist
- Other Medical Personnel
All the lectures are available in e-learning
References of lectures are available on Web

- Leroy Hood and David Galas, The digital code of DNA, Nature, 421, 444-448, 2003*
- Science, 309: 1508-, 2005 RNA特集号*
- モデル生物について*
- 比較ゲノム学について*
  (http://www.nature.com/ng/journal/v35/n10/index.html#ed)
- NIHのRoadmap*
- Human Cancer Genome Project
  - Nature 437: 1233-1234, 2005
  - S. J. Elledge and G. J. Harmon, Science, 439-441, 2005
- 考察課題
  - International Human Genome Sequencing Consortium, Finishing the euchromatic sequence of the human genome, Nature 431, 931-945, 2004
  - Bird05*
  - F. Collins et al., A vision for the future of genomic research, Nature, 422, April 24, 835-847, 2003*
  - C. Cantor and M. Nelson, Haplotyping in biomedicine-practical challenge, Nature Biotechnology 23, 21-22, 2005
Out of 50 graduates, 21 have changed their careers; 11 proceeded to PhD course of Graduate School of Medical and Dental Sciences and 1 obtained a faculty position in TMDU.

<table>
<thead>
<tr>
<th>Instances of career changes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before</strong></td>
</tr>
<tr>
<td>Employee of IT company</td>
</tr>
<tr>
<td>Clinical doctor</td>
</tr>
<tr>
<td><strong>After</strong></td>
</tr>
<tr>
<td>CEO of a venture company of clinical information</td>
</tr>
<tr>
<td>Director of a venture company of biomedicine</td>
</tr>
<tr>
<td>Researcher of a Research Institute</td>
</tr>
</tbody>
</table>
After 5-years project

**Future Development in TMDU**

- Establish as a new major of Graduate School of Biomedical Science

**Future Development in Society**

- We have established the Japan Association for Omics-based Medicine in 2007.
- The graduates have membership of this association. They can continue lifelong education in the association.
Contents

○ Brief introduction of Tokyo Medical and Dental University (TMDU)
  ● TMDU organization
  ● Biomedical PhD School of TMDU

○ Three special education programs charged to Prof. Tanaka by Japanese government
  ● International Educational Program for Interdisciplinary Disease Sciences
  ● Reeducation program for students with jobs: Educational Program for Bio-Medical Omics Information Scientists
  ● TITECH-TMDU Joint Education Program for Translational Biomedical Informatics

○ My current research interests
  ● Supervising PhD students
  ● Research progress on Clinical-pedia for Inflammatory Bowel Disease
  ● Development of a database and ontology for pathogenic pathways in periodontitis
TITECH-TMDU Joint Education Program for Translational Biomedical Informatics

**Principle Investigator:**
Prof. Dr. Naoki Yonezaki,  
**Tokyo Institute of Technology (TITECH)**

**Project Manager in TITECH:**
Prof. Dr. Akihiko Konagaya  
Prof. Dr. Masayuki Yamamura

**Project Manager in TMDU:**
Prof. Dr. Hiroshi Tanaka  
Dr. Takako Takai-Igarashi
Program for Enhancing Systematic Education in Graduate Schools, funded by Japanese government, since 2005

- Funded for advanced graduate education that meets the international standard and the needs of international society.
- $1,000,000 - $1,500,000 in 3 years for each organization.
- Funded to 97 universities in 2005
  - 46 universities in 2006
  - 126 universities in 2007
  - 66 universities in 2008
  - 29 universities in 2009.

TMDU was funded for ‘International PhD School for Biomedical Science’.

TMDU was funded for ‘Global Linkage program’.

TITICH and TMDU are jointly funded for this program.
TITECH-TMDU Joint Education Program in Translational Biomedical Informatics.

- We aim for the production of double-major students capable of solving the translational biomedical issues, such as disease modeling, drug discovery, and preventive health care, with cutting-edge computational technologies.

- Objectives to be studied:
  - Disease modeling with genome-wide OMICS information
  - Academia drug discovery for orphan diseases
  - Preventive health care with personal genome information
Development of joint education program in Translational Biomedical Informatics

- Joint education program
  - IT
  - Supercomputer
  - Computational Mathematics
  - TITECH
  - Modeling of Living System
  - Omics data and Clinical records from Patients
  - Data and Knowledge warehouse Cloud / Grid
  - Personalized Medicine
  - TMDU
  - University Hospital
  - Drug Discovery
  - Clinical Science
  - Life Science

- IT
- Computational Mathematics
- Supercomputer
- TITECH
- Modeling of Living System
- Omics data and Clinical records from Patients
- Data and Knowledge warehouse Cloud / Grid
- Personalized Medicine
- TMDU
- University Hospital
- Drug Discovery
- Clinical Science
- Life Science
Curriculum
A matrix of lectures on informatics and biological medicine

Advanced Topics
- Computational Mathematics course
- Informational Technology course
- Biological Modeling course
- Drug Design course
- Clinical Medicine course
- Preventive Medicine course

Background Subjects
- Computational Statistics
- Database
- Systems Modeling
- Molecular Biology
- Clinical OMICS
- Multifactor Diseases

Exercise
- High-performance Computing
- Programming
- Synthetic Biology
- Computational Chemistry
- Genome Sciences
- Multivariate Analysis

Basics
- Inverse Problem
- Bioinformatics
- Physiology
- Pharmacology
- Pathology
- Geriatrics

2 units / subject
six courses

Tokyo Institute of Technology
Tokyo Medical and Dental University
How to obtain major and minor degrees

Take 3 Courses (15 subjects / 30 units)
Credit transfer

Joint education program
Multi-supervisor

PhD (Engineering) Minor: Medicine
PhD thesis
Thesis
M.Sc.
Undergraduate: Informatics
Other universities

PhD (Medicine) Minor: Engineering
PhD thesis
Undergraduate: Medical School
Other universities
Contents

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My current research interests

Dr. Takako Takai-Igarashi
Project Associate Professor
School of Biomedical Science,
Tokyo Medical and Dental University
Supervise PhD students with jobs

- 11 graduates from Biomedical Omics Informatics education program entered Graduate School of Medical and Dental Sciences of TMDU in order to PhD degrees.
- 3 graduates from the program are in preparation for the entrance examination to the graduate school.
- I am supervising them, 14 in total. All have their own jobs besides PhD studies, except Naoko.
D2 students (4-years PhD course)

- **Satoru Suzuki**
  - Working with a pharmaceutical company
  - Theme: “Development of Clinical-pedia on Inflammatory Bowel Disease”
  - Under the supervision of Dr. Tonellato, HMS, and in the collaboration with Dr. Fukuoka, TMDU.

- **Tadashi Urashima**
  - Working with a pharmaceutical company
  - Theme: “Model based drug development on sodium channel blockers for arrhythmia”
  - In the collaboration with Prof. Kume, Tottori University.
D2 students (4-years PhD course)

- **Naoko Kasahara**
  - She had worked with an IT company but resigned when entering graduate school. She is now working as a TA in the graduate school.
  - Theme: “Simulation analysis of complement activation mechanism by integral equation”
  - In the collaboration with Prof. Konagaya, TITIECH.

- **Eiichi Ueno**
  - Working with a medical devise company.
  - Theme: “Molecular mechanisms in heard of hearing having mutations in Connexin gene by Virtual Cell simulation tool”
  - Giving advice by Prof. Kitamura, TMDU
D1 students (4-years PhD course)

- **Asami Suzuki**
  - Dentist
  - Theme: “Development a database for pathological pathways in periodontitis”
  - In the collaboration with Prof. Numabe, Nippon Dental University.

- **Tadashi Ebara**
  - Working with an IT company.
  - Theme: “Semi-automatic construction of ontology from literatures in molecular pathology”.
  - In collaboration with Dr. Terashima (pathologist), TMDU
○ Tarou Kishimoto
  ● Working with research institute of a pharmaceutical company.
  ● Theme: “Determination of protein sequences and their chemical modifications from MASS spectra data”
  ● In the collaboration with his colleagues.

○ Yasunori Ohto
  ● Working with an IT company.
  ● Theme: “Evolutional analysis of gene silencing by epigenetic regulation”.
  ● Under supervision of Dr. Niimura, TMDU
D1 students (4-years PhD course)

- **Hajime Sawai**
  - Pharmaceutist
  - Theme: “Prioritization of candidate genes from GWAS data on Bipolar patients”
  - Giving advice by Dr. Kamitsuji, Stagen Co. (genetical statistician).

- **Yasuha Tanaka**
  - Pharmaceutist
  - Theme: “Prediction of side-effects of steroid drugs with statistical potential in chemical-protein bindings”
  - Under supervision of Prof. Yura, Ochanomizu University.
Kazuo Iida

- Working with an IT company.
- Under a year's leave of absence because of personal reason.
- Theme: not yet determined.
- **Akihiko Hoshi**
  - Working with a food and chemical company.
  - Theme: “Development of a pathway databases for Glyco signaling and diseases”
  - In collaboration with Prof. Ogawa, Ochanomizu U. (glyco-chemistry).

- **Hisahi Hasegawa**
  - Working with an law office.
  - Theme: “Promoter region analysis on microarray data from FOXO transgenic mice”
  - In collaboration with Dr. Kamai, TMDU (the transgenic mice are of his production).
○ Yasufumi Fukui

- Working with an electrical products company.
- Theme: “Evaluation of a new clustering method ‘affinity propagation’ with biomedical data”
- In collaboration with his colleague.
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Clinical-pedia and network analysis on Inflammatory Bowel Disease

Satoru Suzuki¹, Takako Takai-Igarashi¹, Yutaka Fukuoka¹, Hiroshi Tanaka¹, and Peter Tonellato²

¹ Tokyo Medical and Dental University
² Harvard Medical School
Background

- Inflammatory Bowels Disease (IBD) is rapidly increased in Europe, North America and even in Japan, maybe due to westernization of Japanese lifestyle. Genetic studies suggest IBD as a multiple gene disease. Genome-wide Association (GWA) studies identified NOD2(16q12) and IBD5(5q31) as strongly associated genes to IBD pathology and at least 10 additional candidate loci so far. However neither molecular pathology nor effective treatments have been reported on IBD.
Research object

- Network analysis on comprehensive collection of related genes to Intestinal Bowel Disease (IBD) and its associated diseases.
  - IBD associated diseases
    - Diseases to which the same drugs are indicated as IBD.
    - Complications of IBD.
  - We firstly selected 6 target diseases which the same drugs are indicated as IBD.
Diseases to which the same drugs are indicated as IBD

6 diseases and drugs having indications to the diseases (in Japan)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Crohn's disease</th>
<th>Ulcerative colitis</th>
<th>Ileitis</th>
<th>Rheumatoid Arthritis</th>
<th>Behçet's syndrome</th>
<th>Graft versus Host Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>mesalazine</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>salazopyrine</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>infliximab</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>azathioprine</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
</tr>
</tbody>
</table>

Information on the drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Category</th>
<th>Target protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>mesalazine</td>
<td>NSAID</td>
<td>PPARγ, NFKB</td>
</tr>
<tr>
<td>salazopyrine</td>
<td>NSAID</td>
<td>-</td>
</tr>
<tr>
<td>infliximab</td>
<td>anti-TNF antibody</td>
<td>TNF</td>
</tr>
<tr>
<td>azathioprine</td>
<td>immunosuppressant</td>
<td>IMPDH</td>
</tr>
</tbody>
</table>
Data collection on disease related-genes

- According to the protocol developed by Dr. Tonellato in Clinical-pedia, we collected genes related to the 6 target diseases from 9 databases: Gene Cards, Huge Navigator, GAD, PharmGKB, HGMD, EXPASY, GenATLAS, WikiGenes, and OMIM.
## Genes collected

<table>
<thead>
<tr>
<th></th>
<th>Crohn's disease</th>
<th>Ulcerative colitis</th>
<th>Ileitis</th>
<th>Rheumatoid Arthritis</th>
<th>Behçet's syndrome</th>
<th>Graft versus Host Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene Cards</td>
<td>51</td>
<td>500</td>
<td>23</td>
<td>0</td>
<td>5</td>
<td>63</td>
</tr>
<tr>
<td>Huge Navigator</td>
<td>274</td>
<td>176</td>
<td>21</td>
<td>352</td>
<td>91</td>
<td>86</td>
</tr>
<tr>
<td>GAD</td>
<td>128</td>
<td>111</td>
<td>0</td>
<td>175</td>
<td>40</td>
<td>3</td>
</tr>
<tr>
<td>PharmGKB</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>93</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>HGMD</td>
<td>1</td>
<td>6</td>
<td>0</td>
<td>19</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>EXPASY</td>
<td>19</td>
<td>16</td>
<td>0</td>
<td>83</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>GenATLAS</td>
<td>13</td>
<td>13</td>
<td>0</td>
<td>58</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>WikiGenes</td>
<td>111</td>
<td>93</td>
<td>0</td>
<td>255</td>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>OMIM</td>
<td>37</td>
<td>39</td>
<td>2</td>
<td>142</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>399</strong></td>
<td><strong>630</strong></td>
<td><strong>43</strong></td>
<td><strong>732</strong></td>
<td><strong>102</strong></td>
<td><strong>162</strong></td>
</tr>
</tbody>
</table>
Network analysis -1

- We produced networks on the collected genes by STRING @EMBL.
  - Eliminate edges deduced by text-mining.
  - Take edges with the highest confidence.
  - Add nodes (genes) deduced by STRING when the nodes are within one steps from at least two of the collected genes.

![Network diagram](image)

- Genes added by STRING deduction
- Original genes we collected
Network analysis -2

- We extracted intersections of individual gene-networks on the 6 target diseases.

<table>
<thead>
<tr>
<th>Gene Set Description</th>
<th>Crohn's Disease</th>
<th>Ulcerative Colitis</th>
<th>Ileitis</th>
<th>Rheumatoid Arthritis</th>
<th>Behçet's Syndrome</th>
<th>Graft versus Host Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genes collected from databases</td>
<td>399</td>
<td>630</td>
<td>43</td>
<td>732</td>
<td>102</td>
<td>162</td>
</tr>
<tr>
<td>Genes in expanded networks by STRING</td>
<td>413</td>
<td>677</td>
<td>165</td>
<td>762</td>
<td>241</td>
<td>207</td>
</tr>
</tbody>
</table>

Intersections of the 6 networks

<table>
<thead>
<tr>
<th>Gene Set Description</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genes intersecting 6 out of 6 disease-networks</td>
<td>11</td>
</tr>
<tr>
<td>Genes intersecting 5 out of 6 disease-networks</td>
<td>37</td>
</tr>
<tr>
<td>Genes intersecting 4 out of 6 disease-networks</td>
<td>92</td>
</tr>
</tbody>
</table>
Network analysis -3

- We investigated related disease to the 37 genes (intersecting 5 out of 6 networks) by Huge Navigator.
- Diseases other than initial targets were found.
## Top 31 diseases related to the 37 genes (5 out of 6 networks)

<table>
<thead>
<tr>
<th>Rank</th>
<th>Disease Description</th>
<th>Genes Annotated</th>
</tr>
</thead>
<tbody>
<tr>
<td>31</td>
<td>Infant, Premature, Diseases</td>
<td>31</td>
</tr>
<tr>
<td>31</td>
<td>Asthma</td>
<td>24</td>
</tr>
<tr>
<td>29</td>
<td>Disease Progression</td>
<td>24</td>
</tr>
<tr>
<td>28</td>
<td>Crohn Disease</td>
<td>24</td>
</tr>
<tr>
<td>28</td>
<td>Inflammation</td>
<td>23</td>
</tr>
<tr>
<td>28</td>
<td>Bronchiolitis, Viral</td>
<td>23</td>
</tr>
<tr>
<td>28</td>
<td>Respiratory Syncytial Virus Infections</td>
<td>23</td>
</tr>
<tr>
<td>27</td>
<td>Arthritis, Rheumatoid</td>
<td>22</td>
</tr>
<tr>
<td>27</td>
<td>Diabetes Mellitus, Type 1</td>
<td>22</td>
</tr>
<tr>
<td>26</td>
<td>Lupus Erythematosus, Systemic</td>
<td>22</td>
</tr>
<tr>
<td>26</td>
<td>Multiple Sclerosis</td>
<td>22</td>
</tr>
<tr>
<td>26</td>
<td>Chronic Disease</td>
<td>22</td>
</tr>
<tr>
<td>25</td>
<td>Graft vs Host Disease</td>
<td>21</td>
</tr>
<tr>
<td>24</td>
<td>Lung Neoplasms</td>
<td>21</td>
</tr>
<tr>
<td>24</td>
<td>Colitis, Ulcerative</td>
<td>21</td>
</tr>
<tr>
<td>24</td>
<td>Acute Disease</td>
<td>24</td>
</tr>
<tr>
<td>24</td>
<td>Cardiovascular Diseases</td>
<td>24</td>
</tr>
<tr>
<td>24</td>
<td>Premature Birth</td>
<td>24</td>
</tr>
<tr>
<td>24</td>
<td>Recurrence</td>
<td>24</td>
</tr>
<tr>
<td>23</td>
<td>Myocardial Infarction</td>
<td>23</td>
</tr>
<tr>
<td>23</td>
<td>Behcet Syndrome</td>
<td>23</td>
</tr>
<tr>
<td>21</td>
<td>Arthritis, Juvenile Rheumatoid</td>
<td>22</td>
</tr>
<tr>
<td>21</td>
<td>Breast Neoplasms</td>
<td>22</td>
</tr>
<tr>
<td>21</td>
<td>Disease Susceptibility</td>
<td>22</td>
</tr>
<tr>
<td>21</td>
<td>Stomach Neoplasms</td>
<td>22</td>
</tr>
<tr>
<td>21</td>
<td>Infection</td>
<td>22</td>
</tr>
<tr>
<td>21</td>
<td>Osteoporosis</td>
<td>21</td>
</tr>
<tr>
<td>21</td>
<td>Hypersensitivity, Immediate</td>
<td>21</td>
</tr>
<tr>
<td>21</td>
<td>Periodontitis</td>
<td>21</td>
</tr>
<tr>
<td>21</td>
<td>Lymphoma, Non-Hodgkin</td>
<td>21</td>
</tr>
<tr>
<td>3</td>
<td>Ileitis</td>
<td>3</td>
</tr>
</tbody>
</table>

The number of genes annotated to the disease in Huge Navigator.
### Top 31 diseases related to the 37 genes (5 out of 6 networks)

<table>
<thead>
<tr>
<th>Rank</th>
<th>Disease</th>
<th>Rank</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>31</td>
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<td>24</td>
<td>Acute Disease</td>
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<tr>
<td>31</td>
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<td>24</td>
<td>Cardiovascular Diseases</td>
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<tr>
<td>29</td>
<td>Disease Progression</td>
<td>24</td>
<td>Premature Birth</td>
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<tr>
<td>28</td>
<td>Crohn Disease</td>
<td>24</td>
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<td>Inflammation</td>
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<tr>
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<td>Graft vs Host Disease</td>
<td>21</td>
<td>Osteoporosis</td>
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<tr>
<td>24</td>
<td>Lung Neoplasms</td>
<td>21</td>
<td>Hypersensitivity, Immediate</td>
</tr>
<tr>
<td>24</td>
<td>Colitis, Ulcerative</td>
<td>21</td>
<td>Periodontitis</td>
</tr>
<tr>
<td>24</td>
<td></td>
<td>21</td>
<td>Lymphoma, Non-Hodgkin</td>
</tr>
<tr>
<td>23</td>
<td></td>
<td>3</td>
<td>Ileitis</td>
</tr>
</tbody>
</table>

### Diseases associated with inflammation

- Crohn Disease
- Inflammation
- Bronchiolitis, Viral
- Respiratory Syncytial Virus Infections
- Lupus Erythematosus, Systemic
- Multiple Sclerosis
- Chronic Disease
- Graft vs Host Disease
- Lung Neoplasms
- Colitis, Ulcerative
- Ileitis
Genes in the intersection and inflammation

- Genes in the intersection can represent a biological system common to the 6 target diseases.
- The represented biological system looks inflammation.
- We can produce a ‘gene profiling on a drug’ on the basis of diseases having indications to the drug.
Coming studies -1

- Apply this network analysis to all the available drugs to produce ‘comprehensive gene profiling on drugs’.
  - List all the available drugs.
  - Collect diseases having indications to the each drug.
  - Collect genes related to the each disease by clinical-pedia protocol.
  - Produce gene networks by STRING.
  - Extract common networks for every drug.
  - Cluster all the drugs on the basis of similarities between the associated gene networks.
Coming studies -2

- Apply this network analysis to complications of IBD.
  - Investigate molecular mechanisms common to complications of IBD.
  - Reported complications of IBD
    - Arthritis
    - Skin rashes
    - Ulcers
    - Toxic megacolon
    - Strictures
    - Fistulas
    - Eye problems
    - Liver disease
    - Pulmonary parenchymal disease
    - Serositis
    - Chrohn’s disease associated carcinoma
Contents

- Brief introduction of Tokyo Medical and Dental University (TMDU)
  - TMDU organization
  - Biomedical PhD School of TMDU

- Three special education programs charged to Prof. Tanaka by Japanese government
  - International Educational Program for Interdisciplinary Disease Sciences
  - Reeducation program for students with jobs: Educational Program for Bio-Medical Omics Information Scientists
  - TITECH-TMDU Joint Education Program for Translational Biomedical Informatics

- My current research interests
  - Supervising PhD students
  - Research progress on Clinical-pedia for Inflammatory Bowel Disease
  - Development of a database and ontology for pathogenic pathways in periodontitis
Development of a database and ontology for pathogenic pathways in periodontitis*

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Periodontitis and its health risk

- Periodontitis is an inflammation disease that affects the periodontal tissue and associated with an increased health risk of angina, myocardial infarction, and fetal cardiovascular events. Despite accumulation of biomedical research on periodontitis pathology at the molecular level, there has been no systematization for biological pathways in periodontitis.
Prof. Tanaka proposes the idea that a pathogenic cell has the ability to stabilize its pathogenic state by transforming a 'healthy' pathway into a different one that is specific for the pathogenic state.

Different pathways support different status of cells.
Background -2
Healthy and pathogenic cells

- The public databases, such as KEGG, Reactome, and TRANSPATH, cover wide range of biological pathways; however the currently available pathways mostly account for cells not in a pathogenic but in the normal ('healthy') status. In contrast, most of the gene expression data are obtained from cells in a pathogenic status.

- With a database for disease specific pathways you may obtain better results from gene expression analysis.
Research object

- Develop a pathway database for molecular pathology in periodontitis.
- Develop a technique to systematize information not only on molecular reactions but also on cellular and anatomical environments where molecular reactions occur.
Systematization of multiple layered information in representation of diseases

Represent the knowledge in ontology and XML-tagged text.

initiate <property>inflammatory</property> <phenomena>bone loss</phenomena>
Result -1
Data collection

- We investigated 185 abstracts collected by keyword search for ‘periodontitis and osteoclast’ in PubMed on July 31, 2008.
- We collected manually 698 causal relationships from 185 abstracts.
Result -2
XML tags in causal relationships data

- We represented causal relationships information in plain text and marked up conceptual terms in the text by XML tags.
- We collected binary relationships between entities which cellular and anatomical environments are annotated in XML-tagged natural language.
**XML tags and optional attributes used in semi-structured representations of causal relationships data in our database.**

<table>
<thead>
<tr>
<th>XML tag</th>
<th>specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>relation</td>
<td>a causal relationship</td>
</tr>
<tr>
<td>pathID</td>
<td>an internal ID of a causal relationship</td>
</tr>
<tr>
<td>refID</td>
<td>an internal ID of a reference paper</td>
</tr>
<tr>
<td>pubmed</td>
<td>a PubMed ID of a reference paper</td>
</tr>
<tr>
<td>disease</td>
<td>a disease</td>
</tr>
<tr>
<td>from</td>
<td>a causal part of a binary relationship</td>
</tr>
<tr>
<td>to</td>
<td>a consequent part of a binary relationship</td>
</tr>
<tr>
<td>bio</td>
<td>a molecule (e.g. gene, protein, metabolite) originating in a human cell</td>
</tr>
<tr>
<td>bacteria</td>
<td>a molecule (e.g. gene, protein, metabolite) originating in bacteria</td>
</tr>
<tr>
<td>chemical</td>
<td>a chemical and drug</td>
</tr>
<tr>
<td>cell</td>
<td>a cell</td>
</tr>
<tr>
<td>organ</td>
<td>an organ</td>
</tr>
<tr>
<td>organism</td>
<td>a species</td>
</tr>
<tr>
<td>complex</td>
<td>a complex of biological objects (e.g. intracellular signaling cascade)</td>
</tr>
<tr>
<td>phenomena</td>
<td>a phenomenon including both a 'biological phenomenon' and a 'pathological condition, sign and symptom'</td>
</tr>
<tr>
<td>property</td>
<td>a qualifier to the other marked up conceptual terms</td>
</tr>
</tbody>
</table>
<?xml version="1.0"?>
<all_relations>
<relation>
  <pathID>1</pathID>
  <refID>164</refID>
  <pubmed>18538847</pubmed>
  <disease>periodontitis</disease>
  <from>
    <organism>bacterial</organism> <phenomena>infection</phenomena> and <property>inflammatory</property> conditions
  </from>
  <to>promote the <phenomena>differentiation</phenomena> of <cell>monocytes</cell> to <phenomena>bone-resorbing</phenomena> <cell>osteoclasts</cell></to>
</relation>
<relation>
  <pathID>2</pathID>
  <refID>164</refID>
  <pubmed>18538847</pubmed>
  <disease>periodontitis</disease>
  <from>
    <bacteria>LPS</bacteria> and <bio>TNF-alpha</bio>
  </from>
  <to>mediate <phenomena>differentiation</phenomena> of the <cell>monocytes</cell> to <cell>osteoclast-like cells</cell></to>
</relation>
</all_relations>
Result – 3
Ontology for molecular pathology of periodontitis

- Both XML tags and all the marked-up conceptual terms were taken up into our ontology.
- In defining its higher concepts, we refer to Mizoguchi's top ontology.
- The ontology consists of 404 conceptual terms.
A hierarchy of top categories in our ontology.

Based on Mizoguchi’s top ontology.
A hierarchy of top categories in our ontology.

- entity
  - physical thing
  - continuant
    - molecule
      - complex of molecules
      - cell
        - antigen-representing cell
        - blood cell
        - bone marrow cell
        - connective tissue cell
        - epithelial cell
        - myeloid cell
      - organ
        - hemic and immune system
        - musculoskeletal system
        - stomatognathic system
        - tissue
      - living organism
        - human
        - bacteria
        - complex of living organisms
    - occurring
      - phenomenon
        - biological phenomenon
        - pathogenic condition, sign, and symptom
        - disease
      - state
  - abstract thing
  - quality
  - property

Based on MeSH of NCBI.
A hierarchy of top categories in our ontology.

Molecules originating in bacteria and acting as pathogens

Periodontitis distinguishes itself by involving various microorganisms in its molecular etiology.
Pathogenic states of cells and organs.
A hierarchy of top categories in our ontology.

Qualifier to other conceptual terms belong to ‘physical thing’ category.

‘Inflammatory’ qualifies ‘bone destruction’
Result – 4, Pathway graphs

We constructed 20 pathways by grouping binary relationships data.

- **microbiological factor**
  - 1) *Aggregatibacter actinomycetemcomitans* (A. a.) infection
  - 2) *Prophylomonas gingivalis* (P. g.) infection
  - 3) *Treponema denticola* (T. d.) infection

- **immune factor**
  - 4) adiponectine influence

- **drug and chemical factor**
  - 5) baicalin treatment
  - 6) bisphosphonate treatment
  - 7) cemetidine treatment
  - 8) conjugated linoleic acid (CLA) treatment
  - 9) capsular-like polysaccharide antigen (CPZ) treatment
  - 10) DHA treatment
  - 11) indomethacin treatment
  - 12) kariotoxin influence
  - 13) parthenolide (PAR) treatment
  - 14) parathyroid hormone (PTH) treatment
  - 15) polymyxin B treatment
  - 16) taurine treatment
  - 17) tetracyclines treatment
  - 18) thalidomide treatment

- **environmental factor**
  - 19) smoking (nicotine) influence,

- **systemic disease**
  - 20) type II diabetes influence.
An example of pathway graphs. It shows flowcharts of pathogenic pathways starting at *Prophylomonas gingivalis* (*P. g.*) infection and ending up with osteoclastogenesis and bone resorption.
<table>
<thead>
<tr>
<th>Secreted molecules originating in human cells</th>
<th>Intracellular molecules originating in human cells</th>
<th>Molecules originating in bacteria</th>
<th>Cells</th>
</tr>
</thead>
</table>

**Bacteria**

**Biological phenomena**

**Chemicals and drugs (not included in this figure)**

Numbers attached to edges indicate internal IDs of reference papers.

**Intercellular relations with active effect**

**Intracellular relations with active effect**

**Suppressive effects**

**Components of a cell**
Cellular interactions mediated by secreted protein are mostly interested in periodontitis researches.

- *e.g.* neutrophil secretes PGE2, which activates osteoclast, which then secretes cathepsin K, which eventually leads osteoclastogenesis.
We implemented application programs in Perl to manipulate users’ requests against causal relationships data and the ontology.
In a tree-like view of ontology, 'infection' is selected, which retrieves causal relationships data associated with 'infection'. In the data, 'bisphosphonate pathway' is selected, which opens the pathway graph, in which nodes and edges are hyper-liked.
Result – 6
Integration of Pathway Graph and Ontology

- We implemented an ontology viewer associated with the pathway graphs. The viewer gives you a part of the ontology that is associated with a pathway. While the entire ontology represents all the biological entities contributing to periodontitis, a part of the ontology accounts for cellular and tissue specific contexts illustrating contextual information in time and space where molecular interactions in a pathway occur.
Integration of Pathway Graph and Ontology

Whole of Ontology

Automatically extracted

A part of ontology illustrates a certain pathway
The pathway graph (a) describes a flowchart of pathogenic influence of *T.d.* bacteria ending up with osteoclastogenesis. The partial ontology (b) accounts for (a) indicates that this pathway occurs in osteoclast cells of gingival tissue upon infection by *Treponema denticola* or *Treponema socranskii* bacteria with the consequence of osteoclastogenesis and periodontitis.

The partial ontology created by Perl API on demand by a user.
There are pathway databases including ontologies for pathways, like KEGG and BioCyc. While these specify a 'process' itself, our ontology specifies individual components in a 'process', in order to specify the molecular mechanisms underlying pathogenesis in periodontitis.

There is one database include the entry of ‘periodontitis’: Comparative Toxicogenomics Database (CTD); however CTD include no information on pathways.
Discussion - 2

- MeSH ontology of NCBI includes most of all the conceptual terms in our ontology. We then regard our ontology as a sort of subset of MeSH ontology that specifies the molecular pathology in periodontitis. Taking into account the large size and complexity of MeSH ontology, it is worth to define a subset of the ontology that specifies molecular pathology of individual diseases, as our ontology shows.
I appreciate for your kind attention. Questions and comments shall be sent to takai@cim.tmd.ac.jp. Thank you!