Elucidation of enzyme reaction mechanism using a chemically synthesized substrate analog

Structure of enzyme analyzed by cryo-electron microscopy
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The University of Tokyo’s Faculty of Pharmaceutical Sciences has its origins in 1873 with the five-year pharmaceutical program in the First University District Medical School, the precursor of the University of Tokyo Faculty of Medicine; it will celebrate its 150th anniversary in 2023. In 1958, the Faculty of Pharmaceutical Sciences of the University of Tokyo became independent from the Faculty of Medicine and began a new chapter in its history.

The Faculty and Graduate School of Pharmaceutical Sciences is one of the smallest departments in the University of Tokyo with about 800 members. However, it is one of the largest departments specializing in basic research in the life sciences, and it is a department with a strong sense of unity that encourages interaction among laboratories. Graduates of the Faculty of Pharmaceutical Sciences, which emphasizes basic research, are leading experts in their fields in academia and key players in research and development in pharmaceutical and other companies. The Faculty of Pharmaceutical Sciences has two departments: the Department of Pharmaceutical Sciences and the Department of Pharmacy. The Department of Pharmaceutical Sciences focuses on the training of teachers and researchers at universities, national and public research institutes, and researchers at pharmaceutical companies. About 10% of the students in the Faculty of Pharmaceutical Sciences are in the Department of Pharmacy and study to become certified pharmacists while doing basic research. Our educational policy is to nurture advanced pharmacists who can respond to the social demands for advanced medical care, the separation of prescribing and dispensing, and proper use of medicines.

Pharmaceutical Sciences is a field of study that is concerned with overcoming diseases using small- and medium-size organic compounds, but in recent years, drug discovery using new methods or modalities that incorporate proteins and nucleic acids has also developed. What makes new methods of drug discovery possible is basic research to understand the biological phenomena related to diseases in molecular terms and to create techniques to manipulate these phenomena with compounds. Living organisms are composed of organic materials, and the more we learn about the behavior and structure of biomolecules that have been refined through evolution, the more surprising they become.

Pharmaceutical science is an academic field that aims to overcome diseases and create a healthy society by learning from living organisms and biomolecules, designing compounds, and creating drugs. Since the founding of the department, the spirit of placing the highest priority on basic research has been handed down from generation to generation. Today, research and education are conducted in the fields of organic chemistry, biophysics, molecular life sciences, and social pharmacy.

We are faced with infectious diseases and a super-aging society that we have never experienced before. At a time when society is facing difficult health issues, we believe that it is necessary to promote basic research that asks a variety of questions about life and disease. There are both necessity and randomness in the mechanisms of biological activities that organisms have acquired over their long history. For example, there is no single cause of cell abnormalities and no single mechanism for correcting cell abnormalities in diseases, so it is necessary to explore from multiple perspectives. Therefore, basic research aimed at expanding knowledge will lead to the discovery of unexpected molecules and reaction mechanisms involved in the pathogenesis of diseases, as well as breakthroughs in the development of compounds based on new theories for the manipulation of cellular functions. We will continue to contribute to the creation of a healthy society in harmony with nature through research and education in the Pharmaceutical Sciences.

MIURA Masayuki
Dean
Graduate School of Pharmaceutical Sciences
Faculty of Pharmaceutical Sciences
### History

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1873</td>
<td>Department of Pharmaceutical Manufacturing was established in Daiichi-Daigaku-Ku Igakko (The First University District Medical School) in Kanda Izumicho, Tokyo.</td>
</tr>
<tr>
<td>1874</td>
<td>Daiichi-Daigaku-Ku Igakko was renamed as Tokyo-Igakko (Tokyo Medical School).</td>
</tr>
<tr>
<td>1876</td>
<td>Tokyo-Igakko was moved to Hongo, Tokyo.</td>
</tr>
<tr>
<td>1877</td>
<td>Tokyo Daigaku, The University of Tokyo was established. Tokyo-Igakko was renamed as the University of Tokyo Faculty of Medicine. The organization of pharmaceutical education began with the establishment of Pharmaceutical Institute (later Department of Pharmaceutical Manufacturing in the Faculty of Medicine). For the first 10 years, instruction was given by foreigners and in particular a Dutch chemist Dr. J. E. Eijkman. He left a large amount of fine work in the study of components of various domestic medicinal plants.</td>
</tr>
<tr>
<td>1886</td>
<td>The University of Tokyo was renamed as Imperial University and the name of the Department of Pharmaceutical Manufacturing in the Faculty of Medicine was changed to the Department of Pharmacy in the Imperial University Medical College. Japanese who had returned from studies in Germany took over the education of students, carried out valuable investigations of their own, and also established the ground for pharmaceutical organic chemistry in Japan.</td>
</tr>
<tr>
<td>1897</td>
<td>The Imperial University was renamed as Tokyo Imperial University.</td>
</tr>
<tr>
<td>1919</td>
<td>A faculty system was introduced and renaming the Department of Pharmacy in the Medical College as the Department of Pharmacy in the Faculty of Medicine, Tokyo Imperial University.</td>
</tr>
<tr>
<td>1947</td>
<td>Tokyo Imperial University was renamed as The University of Tokyo.</td>
</tr>
<tr>
<td>1949</td>
<td>The University of Tokyo was established under the new system (Junior division for the first two years and Senior Division for the 3rd and the 4th years).</td>
</tr>
<tr>
<td>1953</td>
<td>The Graduate School of Chemistry-related was established (Master’s Program in the field of Pharmaceutical Sciences).</td>
</tr>
<tr>
<td>1955</td>
<td>Doctoral Program in the field of Pharmaceutical Sciences was added.</td>
</tr>
<tr>
<td>1958</td>
<td>The Department of Pharmacy separated from the Faculty of Medicine and became an independent faculty as the Department of Pharmaceutical Sciences, the Faculty of Pharmaceutical Sciences.</td>
</tr>
<tr>
<td>1960</td>
<td>The Department of Pharmaceutical Technochemistry was established.</td>
</tr>
<tr>
<td>1965</td>
<td>The Graduate School of Pharmaceutical Sciences, The University of Tokyo was established. (Department of Pharmaceutical Sciences and Department of Pharmaceutical Technochemistry)</td>
</tr>
<tr>
<td>1966</td>
<td>The Research Institute for Chemical Hazards was established.</td>
</tr>
<tr>
<td>1973</td>
<td>Two departments were unified into the Department of Pharmaceutical Sciences.</td>
</tr>
<tr>
<td>1986</td>
<td>The graduate school was reorganized along with the new system, &quot;Graduate School Priority System&quot; and reformed into three Departments, that is Pharmaceutical Chemistry, Pharmaceutical Biology, and Pharmaceutical Technology. Although the Faculty’s emphasis of education is shifted from the Undergraduate Program to the Graduate Program, most of the faculty members also continue undergraduate education.</td>
</tr>
<tr>
<td>2000</td>
<td>Clinical Pharmacy Course was established in the Master’s Program.</td>
</tr>
<tr>
<td>2004</td>
<td>Pharmaceutical Sciences Research Building was constructed.</td>
</tr>
<tr>
<td>2006</td>
<td>Following the revision of the School Education Act, the Faculty of Pharmaceutical Sciences started a new program with Department of Pharmaceutical Sciences (4-year program) and Department of Pharmacy (6-year program).</td>
</tr>
<tr>
<td>2008</td>
<td>Department of Integrated Pharmaceutical Sciences was added to the Graduate School, which consists of total 4 departments.</td>
</tr>
<tr>
<td>2010</td>
<td>The former 4 departments in the Master’s Program were abolished and the Department of Pharmaceutical Sciences was established. Clinical Pharmacy Course was abolished.</td>
</tr>
<tr>
<td>2012</td>
<td>The former 4 departments in the Doctoral Program were abolished. Department of Pharmaceutical Sciences and Department of Pharmacy were established in the Doctoral Program. Dual Speciality Course on Pharmacist Education was established.</td>
</tr>
</tbody>
</table>
### Number of Academic and Administrative Staff

**As of July 1, 2021**

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
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<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Academic Staff</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Professors</td>
<td>18</td>
<td>13</td>
<td>9</td>
<td>26</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>12</td>
<td>86</td>
<td>28</td>
<td>21</td>
<td>1</td>
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<tr>
<td><strong>Researcher</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td><strong>Administrative Staff</strong></td>
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<td></td>
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</tbody>
</table>

### Number of Students

**As of May 1, 2021**

<table>
<thead>
<tr>
<th>Undergraduates</th>
<th>Graduates</th>
<th>Master’s Program</th>
<th>Doctoral Program (Pharmaceutical Sciences)</th>
<th>Doctoral Program (Pharmacy)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>3rd year</td>
<td>85 (17)</td>
<td>90 (48)</td>
<td>8 (9)</td>
<td>11 (9)</td>
<td>194 (70)</td>
</tr>
<tr>
<td>4th year</td>
<td>90 (40)</td>
<td>99 (30)</td>
<td>82 (24)</td>
<td>181 (54)</td>
<td>40 (10)</td>
</tr>
<tr>
<td>5th year</td>
<td>8 (4)</td>
<td>46 (15)</td>
<td>46 (15)</td>
<td>78 (28)</td>
<td>164 (53)</td>
</tr>
<tr>
<td>6th year</td>
<td>26 (4)</td>
<td>78 (23)</td>
<td>78 (23)</td>
<td>164 (53)</td>
<td>5 (2)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>12 (8)</td>
<td>6 (2)</td>
<td>6 (2)</td>
<td>8 (2)</td>
<td>25 (8)</td>
</tr>
</tbody>
</table>

### Number of International Students

**As of May 1, 2021**

<table>
<thead>
<tr>
<th>Countries and Regions</th>
<th>Undergraduate</th>
<th>Graduate School</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Master’s</td>
<td>Doctoral</td>
<td>Research Student</td>
</tr>
<tr>
<td>Syria</td>
<td>1 (1)</td>
<td></td>
<td>1 (1)</td>
</tr>
<tr>
<td>India</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Korea</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>China</td>
<td>2 (15)</td>
<td>2 (15)</td>
<td>4 (15)</td>
</tr>
<tr>
<td>Taiwan</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Canada</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>United States</td>
<td>1 (1)</td>
<td></td>
<td>1 (1)</td>
</tr>
<tr>
<td>Poland</td>
<td>1 (1)</td>
<td></td>
<td>1 (1)</td>
</tr>
<tr>
<td>Nepal</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Germany</td>
<td>1 (1)</td>
<td></td>
<td>1 (1)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>2 (26)</td>
<td>23 (26)</td>
<td>28 (13)</td>
</tr>
</tbody>
</table>

( ) Female students

### Number of Research Students, etc.

**As of May 1**

<table>
<thead>
<tr>
<th>Year</th>
<th>2017</th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
<th>2021</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undergraduate-level</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graduate-level</td>
<td>15</td>
<td>12</td>
<td>9</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Undergraduate auditor</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>19</td>
<td>14</td>
<td>12</td>
<td>16</td>
<td>7</td>
</tr>
<tr>
<td>Commissioned researcher</td>
<td>8</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>27</td>
<td>18</td>
<td>14</td>
<td>20</td>
<td>7</td>
</tr>
</tbody>
</table>

### Number of Doctoral Degree Holders

**As of May 1**

<table>
<thead>
<tr>
<th>Year</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
<th>Cumulative Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Program Doctorate</strong></td>
<td>61</td>
<td>36</td>
<td>45</td>
<td>52</td>
<td>45</td>
<td>1,969</td>
</tr>
<tr>
<td><strong>Thesis Doctorate</strong></td>
<td>9</td>
<td>8</td>
<td>11</td>
<td>16</td>
<td>13</td>
<td>1,584</td>
</tr>
</tbody>
</table>

( ) Numbers indicate MEXT Scholarship Students

### Current Status of Graduates

<table>
<thead>
<tr>
<th>Academic Year</th>
<th>Undergraduate-level Graduates</th>
<th>Graduate School Graduates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Master’s program</td>
<td>Doctoral program</td>
</tr>
<tr>
<td>Pharmaceutical Sciences</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemical industry companies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Financial, insurance, &amp; trading companies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education, government, research institutes, etc.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (Number employed)</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Seeking for further education (Graduate school)</td>
<td>72</td>
<td>66</td>
</tr>
<tr>
<td>Research student, other undergraduate course, etc.</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Study abroad</td>
<td></td>
<td></td>
</tr>
<tr>
<td>JSRS special researcher, etc.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>76</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong> (Number graduating/completing program)</td>
<td>76</td>
<td>6</td>
</tr>
</tbody>
</table>

( ) Numbers indicate MEXT Scholarship Students

-current-
Pharmaceutical sciences is an academic field that covers development of pharmaceuticals and their applications. The field encompasses fundamental, life-related substances and their interactions with life; using organic chemistry, physical chemistry, and biochemistry as a base, upon which is built a wide range of research fields, including interdisciplinary areas. With these parallel 6-year and 4-year programs, the Faculty of Pharmaceutical Sciences not only provides traditional training in basic research for drug discovery but also offers some courses in advanced training for pharmacists. (Graduates of the Department of Pharmacy are qualified for the national examination for pharmacists.) No differentiation is made between the Departments of Pharmacy and Pharmaceutical Sciences from the College of Arts and Sciences until entering higher education, allowing students to gain an ample understanding of research content before deciding between the two departments in their fourth year.

Our doctoral program in the Department of Pharmaceutical Sciences, established in 2012, also provides a Dual Specialty Course on Pharmacist Education allowing students to be qualified for the national examination for pharmacists. (This is provided for students who enter the University of Tokyo by the 2017 school year and graduate from the Department of Pharmaceutical Sciences, Faculty of Pharmaceutical Sciences.)
Pharmaceutical Sciences Education Program

Pharmaceutical sciences is an academic field that covers development of pharmaceuticals and their applications. The field encompasses fundamental, life-related substances and their interactions with life; using organic chemistry, physical chemistry, and biochemistry as a base, upon which is built a wide range of research fields, including interdisciplinary areas. With these parallel 6-year and 4-year programs, the Faculty of Pharmaceutical Sciences not only provides traditional training in basic research for drug discovery but also offers some courses in advanced training for pharmacists. (Graduates of the Department of Pharmacy are qualified for the national examination for pharmacists.) No differentiation is made between the Departments of Pharmacy and Pharmaceutical Sciences from the College of Arts and Sciences until entering higher education, allowing students to gain an ample understanding of research content before deciding between the two departments in their fourth year.

Our doctoral program in the Department of Pharmaceutical Sciences, established in 2012, also provides a Dual Specialty Course on Pharmacist Education allowing students to be qualified for the national examination for pharmacists. (This is provided for students who enter the University of Tokyo by the 2017 school year and graduate from the Department of Pharmaceutical Sciences, Faculty of Pharmaceutical Sciences.)
Department of Pharmaceutical Sciences

Taking on the goal of the previous Department of Pharmacy curriculum, the Department aims to educate high-quality researchers, focusing on developing personnel in the fields of drug discovery and basic life-science research. With a capacity of 90 percent of all students, the Department offers graduates a two-year master’s program, then to a three-year doctoral program. The curriculum is nearly identical to the Department of Pharmacy until the third year, allowing students to experience on-the-ground medical treatment even if they intend to pursue research.

Department of Pharmacy

In response to the advancement of medical care, the purpose of this establishment is to train and develop high-quality pharmacists. One large difference from the Department of Pharmaceutical Sciences is that the program includes six-month practical hospital/pharmacy training. The Department’s capacity is 10 percent of all students, providing high-quality pharmacy education to a small number of students, aiming to create personnel who will be able to lead this field. Six-year pharmacy departments are well over capacity across all of Japan; to avoid disruption, the University of Tokyo’s Faculty of Pharmacy will collaborate with the University of Tokyo Hospital and local pharmacies in order to provide smooth, uninterrupted practical training.

Faculty Curriculum

Lectures and practicums lie in the center of the education at the Faculty of Pharmaceutical Sciences. They are provided to students in order for them to acquire the broad knowledge and the perspectives of pharmacists, as well as to have a clear view when they decide which field of pharmacy they should enter as specialists. One can say that lectures provided to faculty students are the essence of pharmaceutical sciences. Furthermore, reflecting the diversity in research areas in the Faculty of Pharmaceutical Sciences, the pharmacy practicums encompass a wide range of training areas. It is efficiently designed in a way that students will be able to put organic chemistry, physical chemistry, biochemistry and clinical pharmacy into practice. When students enter into their fourth year, each student will be allocated to a class of his/her own choice and will have opportunities to get hands-on experience in the cutting-edge pharmacy through the participation in research projects.

Department of Pharmaceutical Sciences 80 credits
(Compulsory: 62 credits, Elective: 18 credits or more)

Department of Pharmacy 120 credits
(Compulsory: 109 credits, Elective: 11 credits or more)

2nd year: Autumn 1

<table>
<thead>
<tr>
<th>Course Title</th>
<th>Credits</th>
<th>Course Outline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analytical Chemistry I</td>
<td>1</td>
<td>This course covers chemical equilibrium, qualitative and quantitative chemical analysis, and instrumental analysis.</td>
</tr>
<tr>
<td>Organic Chemistry II</td>
<td>1</td>
<td>Fundamental organic chemistry which contains Acid and Base, Nucleophilic Substitution and Elimination Reactions.</td>
</tr>
<tr>
<td>Molecular Biology</td>
<td>1</td>
<td>Students will lean the fundamentals of molecular biology to understand the life sciences.</td>
</tr>
<tr>
<td>Cell Biology</td>
<td>1</td>
<td>Students will learn the fundamentals of cell biology to understand the life sciences.</td>
</tr>
<tr>
<td>Radiation Chemistry</td>
<td>1</td>
<td>Lectures pertaining to the fundamentals, applications and biological effects of isotopes and radiation (which are indispensable for the fields of medicine and pharmaceutical sciences) will be given.</td>
</tr>
</tbody>
</table>
Organic Chemistry I  
1 Students will learn the fundamentals such as stereochemistry, structural chemistry, reduction and oxidation.

Physical Chemistry II  
1 Lectures are aimed to allow students to understand important concept of thermodynamics, acquire the physicochemical perspectives and learn methods that are important in pharmaceutical sciences.

Physiological Anatomy of Human Body  
1 Students will learn the structures and functions of each organ (i.e., anatomy and physiology) as the basic knowledge for them to understand pharmacotherapy and pathophysiology.

Physical Chemistry I  
1 Students will aim to acquire the physiochemical concept by understanding quantum chemistry and spectroscopy.

Introduction to Pharmaceutical Sciences  
1 The outline, history and the future vision of pharmaceutical sciences will be explained in an easy to understand manner, allowing students to think about the relationship between pharmaceutical sciences and society in terms of industry and medical care. Moreover, students will learn some of the latest studies in the field of pharmaceutical sciences.

Biostatistics  
1 Students will receive lectures and practicums regarding statistical methods and experimental methods used for drug evaluations.

2nd year: Autumn 2

<table>
<thead>
<tr>
<th>Course Title</th>
<th>Credits</th>
<th>Course Outline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organic Chemistry IV</td>
<td>1</td>
<td>Students will learn the typical reaction of carbonyl compounds.</td>
</tr>
<tr>
<td>Analytical Chemistry II</td>
<td>1</td>
<td>This course covers qualitative chemical analysis, instrumental analysis, separation sciences, and analytical methods in clinical chemistry.</td>
</tr>
<tr>
<td>Physical Chemistry III</td>
<td>1</td>
<td>Students will learn the hierarchy of protein structure, various intermolecular interactions, enzyme structures and the theory of enzyme reaction.</td>
</tr>
<tr>
<td>Microbiology and Chemotherapy</td>
<td>1</td>
<td>The basic biochemical and genetic methods will be outlined using microorganisms such as E-coli as materials. Students will also learn the mechanisms of action of antibiotics.</td>
</tr>
<tr>
<td>Molecular Embryology</td>
<td>1</td>
<td>Developmental genetics will be outlined, and their application to drug discovery science will be explained.</td>
</tr>
<tr>
<td>Pharmacology I</td>
<td>1</td>
<td>Students will learn the fundamentals of pharmacology in order to understand actions of drugs that affect the autonomic nervous system and the circulatory system.</td>
</tr>
<tr>
<td>Functional Biology</td>
<td>1</td>
<td>Students will learn the fundamental of higher-order function cell to understand life sciences.</td>
</tr>
<tr>
<td>Pathology</td>
<td>1</td>
<td>Pathological changes of cells and tissues, classification and treatment of diseases will be explained.</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>1</td>
<td>To achieve proper use of the pharmaceutical products, and contribute to the drug development, the lecture explains the pharmacokinetics, a theoretical scheme for quantitatively understanding the disposition of drugs in the body, and describes the factors that cause inter-individual variation in drug disposition and response.</td>
</tr>
<tr>
<td>Organic Chemistry III</td>
<td>1</td>
<td>Students will learn chemical reaction theories such as substitution reaction, radical reaction, reduction/oxidation reaction and addition reaction, as well as the organic electron theory which is important for understanding chemical reaction.</td>
</tr>
<tr>
<td>Drug Discovery and Development</td>
<td>1</td>
<td>Researchers who have succeeded in pharmaceutical companies will be invited to the class to talk about the current situation and future perspectives of drug discovery.</td>
</tr>
</tbody>
</table>
### 3rd year: Spring 1

<table>
<thead>
<tr>
<th>Course Title</th>
<th>Credits</th>
<th>Course Outline</th>
<th>Credits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interactive Organic Chemistry</td>
<td>1</td>
<td>The fundamentals of organic chemistry by practicum and group discussion will be outlined and reviewed.</td>
<td>4 6</td>
</tr>
<tr>
<td>Pharmacology II</td>
<td>1</td>
<td>Students will understand drug actions that affect the central nervous system, endocrine system and immune system by learning the physical function and mental function.</td>
<td>4 6</td>
</tr>
<tr>
<td>Health Chemistry</td>
<td>1</td>
<td>The impact of environmental materials toward organisms will be explained.</td>
<td>4 6</td>
</tr>
<tr>
<td>Clinical Pharmacology</td>
<td>1</td>
<td>Students will learn the fundamentals of pharmacotherapy and clinical development with the clinical perspectives from pathophysiology through pharmacokinetics, clinical pharmacology to clinical testing. Students will also learn diagnoses, treatment and clinical trials in real-life situations from experts in the departments of clinicopathology, internal medicine, surgery and radiology to understand the disease “cancer.”</td>
<td>4 6</td>
</tr>
<tr>
<td>Immunology</td>
<td>1</td>
<td>Students will understand the immune system and the immune response to infections and allergies in the level of dynamic behaviors of tissues, cells and molecules.</td>
<td>4 6</td>
</tr>
<tr>
<td>Laboratory Works of Pharmaceutical Sciences I</td>
<td>5</td>
<td>To acquire fundamental experimental operations, and experience basic organic reactions and some practical synthesis of organic compounds.</td>
<td>4 6</td>
</tr>
<tr>
<td>Laboratory Works of Pharmaceutical Sciences II</td>
<td>3</td>
<td>Basic experiments in bio-organic chemistry (extraction, isolation, identification and biosynthesis of natural organic compounds; the fundamentals and applications of the extinction method and the fluorescence method; learning high-speed liquid chromatography; drug metabolism reaction experiments; enzyme kinetics; visits to the Experimental Station for Medicinal Plant Studies)</td>
<td>4 6</td>
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</table>

### 3rd year: Autumn 1

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<tr>
<th>Course Title</th>
<th>Credits</th>
<th>Course Outline</th>
<th>Credits</th>
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</thead>
<tbody>
<tr>
<td>Molecular Physiological Chemistry</td>
<td>1</td>
<td>The latest knowledge regarding acceptance and transduction of extracellular signaling molecules such as hormones will be explained.</td>
<td>4 6</td>
</tr>
<tr>
<td>Clinical Pharmacy</td>
<td>1</td>
<td>Aiming for understanding pharmaceutical sciences in medical care, the following subjects will be outlined: the medical system; drug development, and its efficacy and safety; diseases and their therapeutic agents; medical care and pharmacists; fundamentals of drug compounding/formulation; drug administration guidance and drug history management; and clinical pharmacokinetics.</td>
<td>4 6</td>
</tr>
<tr>
<td>Medicinal Chemistry II</td>
<td>1</td>
<td>Students will learn organic chemistry of biologically active substances and pharmaceutical molecules, as well as that of molecular design.</td>
<td>4 6</td>
</tr>
<tr>
<td>Metabolism and Disease</td>
<td>1</td>
<td>Metabolism and various diseases caused by metabolic failure will be explained.</td>
<td>4 6</td>
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</table>
### 4th year: Spring 1

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<tr>
<th>Course Title</th>
<th>Credits</th>
<th>Course Outline</th>
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<tbody>
<tr>
<td>Public Health</td>
<td>1</td>
<td>Students will learn the fundamentals of the general idea of health, epidemiology, pharmaecoepidemiology and pharmacoconomics.</td>
</tr>
<tr>
<td>Pharmaceutical and Medical Businesses</td>
<td>1</td>
<td>Students will learn the basics of strategic management to understand what exactly company/research institute management means. The structure and characteristics of medical care/pharmaceutical industry will also be explained.</td>
</tr>
<tr>
<td>Pharmaceutical Affairs Law and Patent Law</td>
<td>1</td>
<td>Students will learn the basics of the Patent Act and pharmacy-related laws and regulations.</td>
</tr>
<tr>
<td>Pharmaceutical Regulatory Science</td>
<td>1</td>
<td>Drug development and efficacy evaluation methods, domestic and overseas drug development environment and guidelines will be explained using specific examples.</td>
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### 4th year (Department of Pharmaceutical Sciences)

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<tr>
<th>Course Title</th>
<th>Credits</th>
<th>Course Outline</th>
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<tbody>
<tr>
<td>Special Laboratory Works of Pharmaceutical Sciences</td>
<td>20</td>
<td>Students will be allocated to a laboratory in the Faculty of Pharmaceutical Sciences (including the Dept. of Pharmacy, the Univ. of Tokyo Hospital), and participate in frontline pharmaceutical research.</td>
</tr>
</tbody>
</table>
Pharmaceutical education experienced major changes beginning with students entering in the 2006 school year. As a result, the University of Tokyo’s Faculty of Pharmaceutical Sciences established two new departments: The Department of Pharmaceutical Sciences, a four-year program designed to train researchers in basic drug discovery, and the Department of Pharmacy, a six-year program that qualifies graduates for the national examination for pharmacists. New graduate schools were also established based on student progression through their programs.

In April of 2010, we established a master’s program in pharmaceutical sciences for graduates of the four-year Department of Pharmaceutical Sciences program. This research program unites the four departments that previously existed, creating a single department instead.

In April of 2012, we established a doctoral program in pharmaceutical sciences for graduates of the master’s program (duration of program: three years), along with a doctoral program in pharmacy for graduates of the six-year Department of Pharmacy program (duration of program: four years). The doctoral program in pharmaceutical sciences also offers a Dual Specialty Course on Pharmacist Education to qualify four-year doctoral graduates for the national examination for pharmacists (Only applied to those students enrolled at the University of Tokyo in April, 2017 and graduated from the Department of Pharmaceutical Sciences, Faculty of Pharmaceutical Sciences).

The main part of graduate school curriculum is “special research” through participations in research conducted in each laboratory. At the Graduate School lectures are targeted at students in master’s program/doctoral program(Department of Pharmacy). Those lectures are highly specialized, covering the latest information in the field, thus allowing them to be the world’s top class.

### Master’s Program (two-year program)
- Department of Pharmaceutical Sciences
- 30 credits or more including 20 credits of special research in pharmaceutical sciences must be completed.

### Doctoral program
- Department of Pharmaceutical Sciences (three-year program)
- 20 credits or more including 20 credits of special research in pharmaceutical sciences must be completed.

- Department of Pharmacy (four-year program)
- 30 credits or more including 20 credits of special research in pharmaceutical sciences must be completed.

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<tr>
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<tbody>
<tr>
<td>Laboratory Works of Pharmaceutical Sciences VI</td>
<td>20</td>
<td>Students will be assigned to a laboratory in the Faculty of Pharmaceutical Sciences and participate in frontline pharmaceutical research. They will also independently conduct research and study for practical hospital/pharmacy training.</td>
</tr>
<tr>
<td>Practice for Clinical Pharmacy II</td>
<td>4</td>
<td>To work as a pharmacist in the clinical practice of hospital and pharmacy, students will acquire basic requirements for drug treatment and team approach medical care/regional medical care from perspective of patients and living people. For Practice for Clinical Pharmacy III・IV, students will acquire basic knowledge, skills and attitude required for fulfilling pharmacists' duties within the University, such as preparation and formulation of drugs and drug administration guidance.</td>
</tr>
<tr>
<td>Practice for Clinical Pharmacy III</td>
<td>10</td>
<td>In order to understand duties and responsibilities of hospital pharmacists and be able to participate in team approach to medical care; students will acquire basic knowledge, skills and attitude required for fulfilling pharmacists' duties, such as preparation and formulation of drugs and drug administration guidance.</td>
</tr>
<tr>
<td>Practice for Clinical Pharmacy IV</td>
<td>10</td>
<td>In order to understand social roles and responsibilities of pharmacies and be able to participate in medical care in their local communities; students will acquire basic knowledge and skills regarding, and attitude toward, pharmacy services under health insurance, drug supply and management, information provision, health examinations and relationship with medical institutes and local communities.</td>
</tr>
<tr>
<td>Special Laboratory Works of Pharmaceutical Sciences</td>
<td>20</td>
<td>Students will be allocated to a laboratory in the Faculty of Pharmaceutical Sciences (incl. Dept. of Pharmacy, the Univ. of Tokyo Hospital) and participate in frontline pharmaceutical research.</td>
</tr>
<tr>
<td>Course Title</td>
<td>Credits</td>
<td>Course Outline</td>
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<tr>
<td>Special Studies for Pharmaceutical Science I</td>
<td>20</td>
<td>To gain a foothold toward specialization; learn pharmaceutical modes of thought and logical, cutting-edge methodology; and develop advanced analytical skills through practice, seminars, and individualized laboratory research activities</td>
</tr>
<tr>
<td>Special Studies for Pharmaceutical Science II</td>
<td>20</td>
<td>To establish deep roots in a specialization; learn pharmaceutical modes of thought and logical, cutting-edge methodology; and develop advanced analytical skills through individualized laboratory research activities</td>
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### Department of Pharmacy

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<tr>
<th>Course Title</th>
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<th>Course Outline</th>
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<tbody>
<tr>
<td>Practical Studies for Clinical Pharmacy</td>
<td>4</td>
<td>To acquire the practical methodology, awareness of the issues, and independence to respond to the needs of society in sophisticated medical environments</td>
</tr>
<tr>
<td>Practical Studies for Social Pharmacy</td>
<td>4</td>
<td>To acquire the practical methodology, awareness of the issues, and independence to respond to the needs of society in medical administration environments</td>
</tr>
<tr>
<td>Practical Studies for Drug Discovery</td>
<td>4</td>
<td>To acquire the practical methodology, awareness of the issues, and independence to respond to the needs of society in drug discovery environments</td>
</tr>
<tr>
<td>Special Studies for Pharmacy</td>
<td>20</td>
<td>To learn—through practice, seminars, and individualized laboratory research activities—comprehensive methodology pertaining to the interaction of molecules and organisms for the purpose of discovering and appropriately using pharmaceuticals</td>
</tr>
</tbody>
</table>
Laboratory of 
Organic and Medicinal Chemistry

Synthesis of novel intelligent molecules which link chemical structures to biological functions in organic and medicinal chemistry

Research Topics

1. Synthesis of new compounds exhibiting characteristic structural features and properties, finally relevant to biological functions
2. New reactions to functionalize aromatic compounds based on designed superelectrophiles
3. Design and synthesis of intelligent molecules, which will have impacts on functions of membrane proteins
4. Computational modeling and simulations of organic and macromolecular systems

Our aims of researches emphasize on design and synthesis of structurally novel organic molecules, which are characteristic in terms of structural (bonding) features and intrinsic functions such as chemical reactivities and biological functions. Designs of such novel molecules are based on our finding new chemistry including ground-state stable non-planar amide peptides and nitrosamines, and structures of multiply positively charged molecules. We study nitrogen-pyramidal amides and related nitrosamines, i.e., molecules that take nonplanar structures, different from the common planar amides. We apply this chemistry to construction of molecules of highly ordered structures such as helix peptide mimetics stable in water. We also develop new chemistry involving dication or trication molecules and apply them as superelectrophiles to synthesize a variety of novel multifunctionalized aromatic compounds, which are pharmaceutically relevant. We are also creating chemical molecules, which will be useful to controlling biological events of membrane proteins such as ion channels, neurotransmitters and G-protein-coupled receptors. These molecules also contribute to understanding the physiological functions of these membrane proteins. We combine all the experimental projects with computational chemistry, which will lead to deep understanding of the underling chemistry.


Laboratory of Synthetic Natural Products Chemistry

Total synthesis and functional analysis of biologically active natural products

Research Topics

1. Development of new synthetic methodologies for total synthesis
2. Total synthesis of highly oxygenated polycyclic natural products
3. Total synthesis and functional analysis of ion channel-forming molecules
4. Total synthesis and functional analysis of antimicrobial molecules
5. Synthesis of new artificial molecules by modification of natural products templates

Natural products have been tremendously important in biology and human medicine because of their power to modulate signal transductions of biological systems. Since the removal of sub-structures of the natural products often leads to significant losses of their activity, total chemical syntheses of their entire structures with a precision at an atomic level are necessary to provide sufficient amounts of material required for biological and medical applications. Architecturally complex natural products with molecular weight over 1000 are capable of highly specific interactions with their target proteins. Therefore, they are powerful agents for selectively controlling intricate biological systems. The goal of our research program is efficient, practical and flexible syntheses of gigantic natural molecules, which include highly oxygenated polycyclic natural products as well as ion channel-forming peptides. At the core of this research program is the development of new strategies for assembling architecturally complex natural products in a concise fashion. These synthetic developments would enable unified synthesis of new artificial analogs by modification of natural products templates. The new synthetic methods for the natural products and the synthetic analogs will allow us to tailor and enhance their drug like properties, to gain control over diverse signal transductions thereby offering new research methods for the study of life science.
The main theme of our research is the development of revolutionary catalyses facilitating new drug design and synthesis. In this direction, we would like to promote human health based on the catalysis development. Chemical synthesis in 21st century should be clean, robust, and concise, no matter how complex the target molecules are. The “ideal synthesis” will be only possible by new catalytic methodologies. Moreover, new catalyses will expand the diversity of readily available building blocks, leading to structurally novel artificial drug design. Sustainability based on new catalysis is another direction of our research. Specifically, we are interested in catalytic activations of small molecules such as H2 and O2.

**Research Topics**

1. Development of new catalysis to facilitate complex molecule synthesis
2. Clean, robust, and concise synthesis of pharmaceuticals and their leads
3. Catalytic H2 and O2 activation
4. Conceptually new approach to promote human health

The main theme of our research is the development of revolutionary catalyses facilitating new drug design and synthesis. In this direction, we would like to promote human health based on the catalysis development. Chemical synthesis in 21st century should be clean, robust, and concise, no matter how complex the target molecules are. The “ideal synthesis” will be only possible by new catalytic methodologies. Moreover, new catalyses will expand the diversity of readily available building blocks, leading to structurally novel artificial drug design. Sustainability based on new catalysis is another direction of our research. Specifically, we are interested in catalytic activations of small molecules such as H2 and O2.
Laboratory of Natural Products Chemistry

We establish the mechanisms of natural product biosynthesis as a science in their own right, to construct a rational system for the production of new and useful substances

**Research Topics**

1. The biosynthesis and bioengineering of medicinal natural products (genome mining, engineered biosynthesis)

2. The enzyme biocatalysts (structure-function analysis, enzyme engineering, mechanistic studies)

3. The search for bioactive substances and isolation/structure determination

Natural organic compounds, prominent among which are antibiotics such as penicillin, are gifts from nature, and the benefits they have bestowed upon humankind as sources for the pharmaceuticals, etc., that maintain health is inestimable. In our laboratory, we study the process of biosynthesis of natural organic compounds produced by plants and microorganisms, using not only the foundation discipline of organic chemistry, but also incorporating the methods of biochemistry and molecular biology in an effort to understand the enzymes that catalyze each biosynthesis reaction and the functions and control mechanisms of the genes that govern their expression at the molecular level. In addition, we are expanding our research into “biosynthesis engineering,” by which rational systems for the biological production of new and useful substances can be designed and constructed, based on the mechanisms of biosynthesis that have been brought to light. We also are carrying out research on the mechanisms by which the bioactivity of natural products is expressed, while at the same time searching for natural products that are active in intracellular signaling.

Concept of “biosynthesis engineering,” by which non-natural compounds are generated
Laboratory of Advanced Elements Chemistry

Understanding of chemical phenomena at the atomic and electron levels and creation of a new science of materials through flexible construction of molecules

Research Topics

1. Research on structure, bonding, aromaticity, and movement of molecules
2. Development of new reactions to freely manipulate chemical bonds
3. Theoretical and synthetic chemistry for manipulating light
4. Research on the origin of life and the evolution of matter

Our laboratory focuses on understanding the properties and phenomena of substances by “language of chemistry” such as molecules, atoms, and electrons (Seeing/Knowing); on developing reactions that manipulate the bonds between atoms completely in control (Designing); and on producing functional materials (Producing).

In our laboratory, we strive to develop technologies for the precise chemical conversion of tiny, tiny molecules less than 1 billionth of a meter in size (nanometer scale; nm). Thanks to recent advances in spectroscopy and theoretical calculation, it is getting possible to accurately predict and reproduce snapshots of the state of the electrons that form materials, as well as of reactions between molecules. With the 3 methods, namely, synthetic chemistry, spectroscopy, and theoretical calculation as the pillars of our science, we expand upon elements chemistry in an interdisciplinary manner as we meet the challenges of elucidating life phenomena and creating a new materials science.

Chemistry A European Journal

Developing new reactions and designing/producing new materials based on computational chemistry and theoretical chemistry (Adopted for the cover of Chemistry: A European Journal)

Life sciences and materials science that open new frontiers in basic organic chemistry and elemental chemistry

Prof. M. Uchiyama
Assoc. Prof.
K. Miyamoto
Project Assoc. Prof.
K. Hirano
Assist. Prof.
C. Wang
Project Assist. Prof.
N. Toriumi

http://www.f.u-tokyo.ac.jp/~kisoyuki/

Miyamoto, K., Narita, S., Masumoto, Y., Hashishin, T., Kimura, M., Ochiai, M., Uchiyama, M.

Sato, H., Hashishin, T., Kanazawa, J., Miyamoto, K., Uchiyama, M.

Hirano, K., Morimoto, K., Fujisaka, S., Miyamoto, K., Muranaka, A., Uchiyama, M.

Xu, N.-X., Li, B.-X., Wang, C., Uchiyama, M.

Kondo, M., Kanazawa, J., Ichikawa, T., Shimokawa, T., Nagashima, Y., Miyamoto, K., Uchiyama, M.
Laboratory of Chemistry and Biology

"Chemical Biology" and "Chemical Medicine" in order to promote life science research and to develop novel medical tools

Research Topics

1. Fundamental photophysical and photochemical research to establish rational design principle for novel chemical tools
2. Theoretical design, synthesis and biological application of novel chemical tools, including sensor molecules and signal perturbation techniques for cellular signaling molecules, such as Ca\textsuperscript{2+} ion, reactive oxygen species, or various enzymes
3. Development of chemical tools, e.g., MRI probe and fluorescent probe, for diagnostic imaging and their in vivo application
4. Clinical use of our newly developed fluorescence probes for rapid imaging of tumor with human clinical fresh specimens
5. Research on drug discovery: Searching for novel lead compounds that control disease-related proteins, and development of high-quality screening systems

Our laboratory conducts research on the analysis and perturbation of dynamic living systems, using chemistry as a powerful tool. One of the important goals in modern life sciences is to elucidate the dynamic behaviors of biomolecules in situ in the living cells/organisms. So far, our laboratory has succeeded in developing bioimaging probes/other chemical tools including signal perturbation methodology and high quality screening systems by applying the probe design strategies that we established. Likewise, we utilize our probe design principle to establish chemical tools for clinical use, including a tumor-specific intraoperative fluorescence imaging methodology. On top of that, we are now conducting dozens of pilot clinical trial projects by utilizing above mentioned chemical tools with external collaborators in domestic hospital and abroad.

The above-described areas of research have attracted enormous attention in recent years under the name of "Chemical Biology", and we believe that they will open up new horizons in life sciences.


Laboratory of Bioanalytical Chemistry

We measure the functions of biomolecules at the level of a single molecule to elucidate vital functions

Research Topics

1. Research on the principles of action by which biomolecular machines such as molecular chaperonin and ribosomes operate
2. Single-molecule fluorescence imaging of intracellular mRNA processing and transport
3. Development of micro nanodevices for analyzing the functions and interactions of biomolecules

In order to understand living organisms, it is necessary to conduct research at a variety of different levels. The lowest level is that at which biomolecules such as proteins and DNA work. When these come together, biological supramolecules, cells, organs, and the like are created, while at the higher end, individual organisms, societies, and ecosystems are constituted. We focus on the level of the smallest unit, the “biomolecule,” together with the level of the “cell,” at which life functions are first expressed, to find answers to questions like “By what mechanisms do biomolecules function?” and “When they aggregate, what kinds of systems do they construct?” Concretely speaking, we bind a fluorescent dye to a single biomolecule and observe it with a sensitive fluorescence microscope. Some biomolecules can exhibit their functions even at the level of the single molecule. For example, the motor protein known as kinesin moves on rail proteins called microtubules. Humankind does not at this point in time possess the technology for creating this kind of molecular machine, but we believe that humankind will be able to make this kind of molecular machine in the near future through research on the motor protein. On the other hand, self-assembly of a variety of different biomolecules creates complex systems which differ greatly from manmade ones. By researching such biological systems, we close in on the mysteries of life.

Fluorescence microscope system for imaging single molecules within living cells

The principle of single-molecule imaging of enzyme reaction (ATPase) using evanescent illumination
Laboratory of Physical Chemistry

Approaching life from dynamic structural information obtained by original NMR strategies.

Research Topics

1. Functional mechanism of biologically and pharmacologically important proteins based on dynamic structural information.

2. Functional mechanism of biomolecules that regulate signal transduction and energy metabolism based on interaction analysis.

3. Development of nuclear magnetic resonance (NMR) techniques to analyze the structure and dynamics of high-molecular-weight proteins.

4. Sample preparation strategies to reproduce the functional environment of biomolecules and sophisticated stable isotope labeling methods.

5. In-cell NMR and its application to intracellular drug discovery.

The structural information of proteins plays a vital role in elucidating biological functions and their applications to drug discovery. In addition, it has become clear that proteins do not adopt only a single conformation but also an equilibrium among multiple functional conformations. These dynamic properties are directly related to the expression and regulation of protein functions. In our lab, we analyze the structure and dynamics of proteins mainly by using NMR to understand biological phenomena through elucidating the functional mechanisms of biomolecules.

We focus on membrane proteins, such as G-proteincoupled receptors (GPCRs) and transporters, as well as macromolecules that regulate intracellular signal transduction and energy metabolism, which are important in biological and pharmaceutical sciences. By developing original NMR methods, we have obtained structure and dynamics information of the macromolecules of interest that were previously difficult to analyze. In addition, we are developing an in-cell NMR strategy to analyze the structure and dynamics of proteins in the actual cellular environment and extending these strategies to establish intracellular drug discovery.

Fig.1: Biological phenomena elucidated by dynamic structural analysis using NMR in our laboratory. (A) Structural equilibrium determines transcriptional activity of multidrug-resistant transcription factors (Proc Natl Acad Sci (2019) 116, 19963). (B) Drug efficacy of each ligand of GPCR (β2 adrenergic receptor) (Nat Commun (2012) 3, 1045; Angew Chem Intl Ed (2014), 53, 13378)

Fig2: Novel NMR experiments developed in our laboratory and their application to mAb (J Med Chem (2020) 63, 5360; Nat Methods (2019) 16, 333)
Laboratory of Protein Structural Biology

Determining three-dimensional structures of proteins and nucleic acids, and elucidating their functions in living cells

**Research Topics**

1. Structural analyses of proteins and nucleic acids using X-ray crystallography and small angle X-ray scattering
2. Structures of immune-system proteins and their complexes
3. Structures of proteins in signal transduction and their complexes
4. Single particle analysis by cryo-electron microscopy

Structural biology seeks to provide a complete and coherent picture of biological phenomena at the molecular and atomic level. The three-dimensional structure of macromolecules at an atomic level can create an actual picture of how they work. These days, structural biology is also called structural cell biology and/or structural life science, and is changing into the research field toward life science. Our laboratory aims at achieving a comprehensive understanding of structure/function relationships of key cellular components and processes, and roles in living cells. In the elucidation of three-dimensional structures, X-ray crystallography is extensively used since this method provides us with detailed structural information on the biological functions and roles. We also take an interdisciplinary approach, combined with methods of biophysics, biochemistry, molecular biology, genetic and protein engineering. Moreover, we take small angle X-ray scattering (SAXS) and cryo-electron microscopy (cryo-EM). SAXS can provide a wealth of structural information on biomolecules in solution and is compatible with a wide range of experimental conditions. Cryo-EM has triggered a revolution in structural biology and has become a newly dominant discipline. Especially, single particle cryo-EM has become a powerful method for atomic structure determination. With these structural biological approaches, we can obtain the information on three dimensional structures that are required for drug design and discovery.

We are now carrying out structural biological researches into immune-system proteins, nuclear proteins and proteins in signal transduction.
Laboratory of Health Chemistry

Exploration of new functions for biomembranes and their constituent lipids

**Research Topics**

1. Reveal the physiological and pathological functions of lysophospholipids that work via GPCR
2. Discover new bioactive lipids and their receptors
3. Identify novel molecules involved in phospholipid biosynthesis and homeostasis, and elucidating their functions.

Biological membranes are composed of more than 1,000 lipid molecular species, and each of them is thought to have a specific function. Recently, some functions of lipids have been elucidated, and it is becoming clear that lipid molecules play essential roles in physiological situations such as reproduction, development, angiogenesis, and cell proliferation, and in pathological processes such as cancer and fibrosis development. On the other hand, the recent progress of mass spectrometry has revealed that there are more lipid molecules with unknown functions in the body. Unlike proteins, lipid molecules are not encoded by genes and lipid synthesis usually involves multiple proteins. Therefore, investigating the function of lipids is much more complicated than that of proteins. We are tackling to clarify the functions of various phospholipids by using the latest technologies including mass spectrometry and mass spectrometry imaging.

Our research results are promising to be applied to drug discovery and biomarker discovery.
Mechanisms of cell division and their application to drug development

**Research Topics**

1. Mechanisms of centrosome duplication and its theoretical model
2. Mechanisms of cell division regulated by divergent molecular machineries
3. Identification and characterization of non-coding RNAs that regulate cell division
4. Comparative cancer cell biology and its application to anticancer drug development
5. Forward genetic analysis of cell-cell communication with human cells

Our laboratory mainly focuses on understanding the mechanisms of cell division, with a particular emphasis on the molecular basis and theoretical model of centrosome duplication. We are also interested in elucidating how divergent molecular machineries, including a protein complex and protein-lncRNA complex, regulate somatic and meiotic cell division. Based on these studies, we then explore a new approach to develop a novel anti-cancer therapy. To this end, we currently use the combination of innovative and multi-disciplinary methods including molecular biology, biochemistry, biophysics, structural biology, genetics, computer simulation and cell biology.

Furthermore, to understand molecular mechanisms and basic principles underlying a wider range of biological phenomena in vivo, we are also trying to establish a forward genetic approach with in vitro reconstitution of human cell-cell communication.
Molecular Investigation of Brain Development, Homeostasis and Diseases

Research Topics

1. Investigation of the mechanisms responsible for the regulation of neural stem-progenitor cell fate during neocortical development
2. Investigation of genetic and epigenetic regulation of neuronal differentiation-maturation and activation-plasticity
3. Identification and characterization of the embryonic origin of adult neural stem cells
4. Dysregulation of neural stem-progenitor cell fate in neurodevelopmental disorders
5. Investigation of innate immune responses and their relation to brain development and disorders

The human body is composed of hundreds of different cell types that each perform distinct functions but which (except for the germline) all contain the same genetic information. A fundamental question with regard to tissue development is how tissue stem cells or multipotent progenitor cells give rise to various cell types in appropriate numbers and at the right locations to achieve tissue organization. Our laboratory has focused on identifying the mechanisms and logic that underlie the regulation of neural stem-progenitor cell fate both during embryonic brain development and in adulthood. We are currently investigating genetic and epigenetic regulation of neural stem-progenitor cell fate and neuronal maturation as well as the genesis and maintenance of adult neural stem cells. We are also studying the relevance of these processes to neurodevelopmental disorders.
Laboratory of Genetics

Molecular logic underlying the formation and maintenance of cell society in the body

Research Topics

1. Regulatory mechanisms of non-apoptotic caspase
2. Metabolic regulation of development, regeneration, growth and aging
3. Molecular mechanisms of phenotype expressivity
4. Mechanisms of tissue size control during development
5. Cellular plasticity in tissue homeostasis and environmental responses

Programmed cell death functions in dynamic tissue formation and remodeling. We have revealed that in the embryonic development, or aging process, caspases are activated by physiological stresses and exert not only apoptosis but also regulatory functions. We aim to reveal how caspase and metabolisms are involved in the determination of phenotype expressivity during development, growth, regeneration and aging. We also study the mechanisms of tissue size control during development and cellular plasticity in tissue homeostasis and environmental responses. We believe that our research would stimulate and encourage students and researchers to have the breadth of vision for life science research and provide new insights into the molecular logic underlying the formation and maintenance of cell society in the body.


Figure
Confocal stack image of the Drosophila pupal notum. In this picture, caspase-3 activated cells (magenta) are observed in the midline (left picture). Visualization of tissue stem cells in Drosophila adult midgut and Cladonema medusa tentacle. Multipotent stem cells contribute to tissue homeostasis and environmental responses (right picture).
From signal transduction to drug discovery

Research Topics

1. Signal transduction and functions of ASK family proteins
2. Exploration of novel signaling molecules involved in cell death and stress responses
3. Molecular mechanisms of pathogenesis induced by dysfunction of stress signaling

The Laboratory of Cell Signaling has been focusing on analyses of the intracellular signal transduction, through which we seek to elucidate molecular basis of human diseases and identify novel drug targets. Our current research mainly focuses on the pathophysiological roles of stress responsive signals in various diseases such as cancers, immune disorders, cardiovascular diseases and neurodegenerative diseases. In addition to molecular genetic tools such as mice, flies and worms as well as basic experimental techniques from molecular cloning to protein biochemistry, we always incorporate novel analytic technologies such as mass spectrometry-based proteomic analysis and genome-wide RNAi screening systems into our research exploring “target molecules and molecular mechanisms”. By taking advantage of such experimental approaches, we aim to open up new fields in pharmaceutical sciences with paying attention to whole body physiology, diseases and drug discovery.
Elucidating various biological phenomena controlled by proteolysis

**Research Topics**

1. The action mechanisms of the proteasome, a multisubunit macromolecular complex responsible for regulated protein degradation in eukaryotic cells

2. Proteasome dysfunction in human diseases (senescence, malignant tumors, inflammation, neurodegeneration)

3. The mechanism of maintenance of protein homeostasis by the ubiquitin-proteasome system

4. The mechanism of T-cell positive selection by the thymus-specific proteasome

The proteasome is a supramolecular proteolytic apparatus that exists in all eukaryotic cells. The proteasome plays pivotal roles in various cellular functions by selectively degrading ubiquitinated proteins. It is also central to the maintenance of protein homeostasis (proteostasis). In recent years, it has become evident that the impairment of proteostasis is a hallmark of senescence, and the decline of proteasome function is drawing attention as one of the primary factors. Indeed, it has been shown that age-associated diseases develop as proteasome function declines with age, and that artificial increase in proteasome activity prolongs the healthy lifespan in nematodes and Drosophila. However, in mammals, means to enhance proteasome function has not been found at present. This is because in mammals the proteasome is controlled more complicatedly and because the mechanisms by which the proteasome function decreases with aging and by which a decrease in proteasome function causes senescence are not understood. On the other hand, it has become clear that inhibition of proteasome function is an important therapeutic strategy in malignant tumors where proteasome hyperactivity is observed.

The ultimate goal of Laboratory of Protein Metabolism is to create a method of intervention in pathologies involving proteasome dysfunction. To this end, we are researching detailed mechanisms of action and regulation of the proteasome by using techniques such as molecular and cell biology, comprehensive gene screening, proteomics, and mouse genetics.
Laboratory of Immunology and Microbiology

Understanding the principles of immunological tolerance and homeostasis

Research Topics

1. Mechanisms of immunological tolerance and homeostasis
2. Mechanisms of regulatory T cell development and function
3. Mechanisms of memory CD8 T cell maintenance

The immune system has evolved the ability to distinguish “self” from “non-self” to maintain homeostasis of the body. The immunological “self” is established in an adaptive and acquired manner through continuous interactions with changing internal as well as external environments. The ultimate goal of this laboratory is to elucidate, throughout multiple layers, from molecules, cells, cell populations, tissues, to individuals, the principles that govern the development of such immunological “self” and its transformation during diseases. Towards this end, we focus on a cell-extrinsic, dominant control mechanism of the immune system that depends on a subpopulation of T lymphocytes called regulatory T (Treg) cells. As one approach, we elucidate how mutations in the Foxp3 gene, encoding a transcription factor critical for Treg cell development and function, lead to a breakdown of immunological tolerance and homeostasis.

Fig. 1: Disintegration of immunological “self” underlies a variety of diseases

Fig. 2: Foxp3-expressing regulatory T (Treg) cells are indispensable for immunological tolerance and homeostasis
Elucidation of the mechanisms determining pharmacokinetic properties of drugs that contributes to drug design, and safe and effective utilization of drugs

**Research Topics**

1. Establishment of the methodologies for in vitro-in vivo extrapolation of drug pharmacokinetics and pharmacological effect
2. Elucidation of molecular mechanisms determining the intestinal absorption of drugs, clearance of drugs from liver/kidney and drug transport at the barrier organs such as blood-brain barrier
3. Prediction of the effect of genetic polymorphisms of metabolic enzymes/transporters on the inter-individual variations of drug pharmacokinetics
4. Establishment of the methodologies for the quantitative prediction of drug-drug interaction risks
5. Elucidation of mechanisms for the membrane trafficking of transporters
6. Development of qualitative and quantitative prediction methods by in silico analysis for pharmacokinetic properties of drugs
7. Understanding of drug effects by data-driven analysis

Pharmacological and adverse effects of drugs depend on their pharmacokinetic properties, which determine their exposure to the targets. Our laboratory aims to establish methods for quantitative and theoretical prediction of pharmacokinetic properties of new chemical entities in humans based on the molecular mechanisms. In particular, we investigate the impact of transporters on the elimination of drugs from the liver and kidney, the distribution of drugs into their target organs e.g., the brain, and drug absorption in the small intestine, in order to develop drug screening systems and to elucidate the mechanisms of drug-drug interaction, and interindividual variation in pharmacokinetics of drugs. We have also started research on the regulation of membrane trafficking of the transporters using low molecular weight compounds to cure transporter related-diseases. Research achievements in this laboratory contribute to predicting and evaluating rational pharmacokinetic properties in drug development, drug review and regulation, and in clinical use, and to developing medical therapy for transporter related-diseases.

**An example of a drug successfully designed to minimize interindividual variation in pharmacokinetics by considering transporter characteristics.**

As a high-throughput screening system for hepatobiliary transport, uptake and efflux transporters are simultaneously expressed in a single polarized cell (double transfectant).
Laboratory of

Chemical Pharmacology

Pharmacological approach toward the brain: from molecule to animal

Research Topics

1. Exploring a new dimension of brain function via Brain-AI hybrid
2. Studying brain network operation using multicellular activity recording
3. Studying neuronal network formation during development

Pharmacology includes two aspects: 1) to analyze the biological action of drugs and 2) to search the strategies for developing treatments for diseases. We conduct our pharmacological research by taking advantage of state-of-the-art technologies and a wide range of knowledge from molecule to animal.

We focus on the roles of the cerebral limbic system and cerebral cortex, in particular, the hippocampus and amygdala, which are involved in learning, memory, and emotion.

Our experimental techniques cover from genetics, biochemistry, and cell biology to electrophysiology, histochemistry, and behavioral pharmacology. Recent technical advances have allowed us to investigate the neuronal network dynamics on far larger scales than hitherto. Functional multineuron calcium imaging reveals the dynamics of network activity with single cell/synapse resolution (Upper Figure), through which we elucidate the structural and functional relationship that generates spatiotemporally organized spike patterns. We also address the mechanisms of learning and memory using in situ mapping learning-relevant neuronal circuits with immediate early genes with cellular and temporal resolution (Lower Figure).

We believe that these novel approaches open up a new avenue for our mesoscopic understandings of network function and malfunction associated with depression, stress-relevant disease, and epilepsy.
Laboratory of Neuropathology and Neuroscience

From understanding the molecular pathogenesis of neurodegenerative and psychiatric diseases to development of therapeutics and novel basic science

Research Topics

1. Research on Aβ metabolism (production, secretion and clearance) and its regulatory mechanisms
2. Understanding the cellular pathology after Aβ deposition towards the development of diagnostics
3. Elucidation of mechanism of amyloid formation deposited in the brains of patients
4. Investigation of the pathological function of microglia in Alzheimer disease
5. Understanding the molecular pathomechanisms of Parkinson disease
6. Elucidation of molecular mechanism of propagation of α-synuclein pathology
7. Biological and pathological roles of synaptic adhesion molecules in psychiatric disorders
8. Development of exercise program for dementia prevention

Aim of our laboratory is that understanding the molecular pathogenesis of neurodegenerative and psychiatric diseases to develop novel approaches to therapeutic, prevention and diagnosis. Also, we are pursuing novel basic science by understanding the molecular basis of diseases. Especially, we are studying Alzheimer disease, autism spectrum disorder and schizophrenia to identify the pathological mechanisms and therapeutic targets of these diseases at molecular levels. To understand the disease condition, we have to realize the basic mechanisms of cells and living organisms, and vice versa. We believe that this disorder-to-normal cycle in research is a basis of modern disease and basic biology, and bolsters both scientific areas by novel knowledge and technology. From this standpoint, we proceed disease-oriented molecular and cellular research in a multidisciplinary manner by mutual collaborations with organic chemists, structural biologists, physicians and pharmaceutical companies.

Molecular and cellular pathologies in Alzheimer disease
Laboratory of
Pharmaceutical Regulatory Science

Establishing scientific drug evaluation

Research Topics

1. Advancing methods for rational drug evaluation
2. Analyzing drug development behaviors and policies
3. Evaluating drug regulation and guidelines
4. Developing systems to implement the above policies and guidelines

The goal of our research is to establish scientific principles and methods in drug evaluation with societal perspectives in mind. Pharmaceutical research and development (R&D), clinical development in particular, regulatory review and approval of new drugs, and post marketing activities are our research interests. We provide evidence on R&D efficiency, performance and outcomes of regulations, and public health impact through rigorous analysis based on economic models. Conflicts in global pharmaceutical R&D, including recent launch delay of new drugs in Japan and so-called ethnic differences, are always high on our agenda. Aside from the research activities, we also make efforts to develop human resources in both private and public sectors with up-to-date knowledge, ethics, and philosophy, and rationale in drug evaluation. We offer lectures for graduate and undergraduate students, and a half-year training course for industry and regulatory professionals. We aim to secure transparency and social responsibility on drug regulation through our research and educational programs.
Laboratory of
Medicinal Plant Chemistry
(Experimental Station for Medicinal Plant Studies)

An overall analysis is made of the old-yet-new drugs known as “medicinal plants” (crude drugs) to develop new ways of using them (utilizing the resources in the Experimental Station for Medicinal Plant Studies)

Research Topics

1. The cultivation of medicinal plants and tissue cultures
2. The production of useful secondary metabolites, using plant tissue culture technology
3. Chemistry and biosynthesis of plant-derived biologically active substances

Since prehistoric times, plants have been the principal material used as drugs by humankind. Many have fallen by the wayside through a long process of trial and error (human experiments), and the ones that remain can be considered the crude drugs of the present day. In recent years, the percentage of all drugs accounted for by antibiotics and biologics has increased, but the importance of plant-derived pharmaceuticals is by no means diminished and has led to the discovery of new drugs such as Taxol and vinblastine. Thus, the study of medicinal plants is by no means completed, and is continuing to evolve. The Experimental Station for Medicinal Plant Studies, formally established in 1973, is located adjacent to the Kemigawa Athletic Ground. The saplings transplanted there back then have grown large and now form a dense enclosure of trees around the garden.

At the research lab in Hongo, we conduct research on the production of useful secondary metabolites using plant tissue culture technologies (from the induction of culture cells to the production of substances). Some of the research topics we are currently pursuing are the biosynthesis of diterpene constituents from Gymnosperm plant cultured cells, the production and biosynthesis of diterpene alkaloids using cultured tissue of monkshood, the production and biosynthesis of phenylethanoids using cultured cells of olive, and the production of biologically active constituents of Egyptian medicinal plants by means of plant tissue culture technologies.

Research on immunoglobulin diversification and gut microbial regulation by intestinal IgA

**Research Topics**

1. Mechanism of gut microbial regulation by intestinal IgA

2. Molecular mechanism of somatic hypermutation of immunoglobulin genes

3. Search for IgA class switch inducer

The immune response has evolved to protect us from pathogenic infectious agents and toxic foreign substances. In acquired immune response, antigen stimulation of B cells induces two distinct genetic alterations in the immunoglobulin (Ig) loci: somatic hypermutation (SHM) and class switch recombination (CSR), both of which require an enzyme, activation-induced cytidine deaminase (AID). After these processes, among diversified Ig repertoire, selected high-affinity Igs efficiently defend host. AID plays a crucial role in host defense but it introduces DNA cleavage into Ig loci and aberrantly into non-Ig loci causing lymphoma. Our aim is to answer ‘how AID’s activity targets Ig loci specifically’ using AID mutant protein and mutant knock-in mice and to understand the precise molecular mechanism of SHM and CSR.

Recently dysbiosis (gut commensal microbial imbalance) is frequently reported to be associated with illnesses such as inflammatory bowel disease (IBD), obesity, cancer, etc. We found that the high-affinity intestinal IgA produced by SHM is important to control non-pathogenic gut bacteria as well as pathogens. Our main question is how intestinal IgA recognizes and targets a huge variety of gut bacteria. We have isolated a useful monoclonal IgA to modulate gut microbiota leading to symbiosis (balanced host-microbial relationship in gut). We aim at applying the findings of our basic research to practical medicine.

Major Research Topics

1. Mechanism of gut microbial regulation by intestinal IgA

We generated hybridomas from IgA producing cells in small intestine of wild type mice. We selected W27 monoclonal IgA as a best gut microbial modulator because of its strong binding ability specifically against colitogenic bacteria. We are analyzing the bacterial target molecule for W27 to control microbial community, and will elucidate the reason why IgA selects that target in the point of physiological view. We aim at the development of therapeutic W27 IgA antibody.

2. Molecular mechanism of SHM

We have found that a N-terminal mutant AID (G23S; glycine to serine mutation at the 23rd AA) showed defective SHM but relatively intact CSR both in vitro and in vivo, suggesting the N-terminus of AID may be the domain responsible for SHM-specific co-factor binding. Through the search of SHM-specific co-factor, we will understand how AID distinguishes SHM from CSR.

3. Search for IgA CSR inducer

Upon antigen stimulation B cells can undergo CSR to IgG, IgE or IgA isotype. However, what induces B cells to each isotype specifically is not completely understood. We focus on searching a novel IgA CSR inducer, which may drive IgA CSR instead of IgE CSR at mucosal surface, helping prevent allergy, as well as enhance the mucosal immunity.
Investigation of chromatin dynamics in germ cells

Research Topics

1. Profiling sperm-retained histones
2. Elucidating the sperm chromatin structure
3. Investigation of the mechanism of histone retention in sperm during histone-protamine exchange

"Neuronal cells are who you are, while germ cells are where you came from."— This is the word by a leading scientist in the field of germ cell research. Somatic cells including neuronal cells compose ourselves, while germ cells play transgenerational roles. Recently, scientists demonstrated that not only DNAs but also certain non-DNA factors can be transgenerationally transferred from ancestors to progenies. The substance of this is non-DNA material is supposed to "epigenome" such as chromatin and small RNAs, although the real entity hasn’t been determined. For now, the most possible idea is that the parental epigenetic information in their germ cells is altered upon stress responses and transferred to the progeny by fertilization.

In our laboratory, we are investigating how epigenetic information is established in germ cells (especially in male germ cells) and altered upon various stress responses using biochemical, molecular biological, and genomic approaches. In addition, we are trying to utilize our research outcome for sperm quality control in Assisted Reproductive Technologies (ART).

An example of our research achievement. Mammalian sperm nuclei are tightly condensed due to the highly basic proteins called protamines. This unique chromatin structure prevents us from performing various kinds of biochemical approaches to investigate the characteristics of sperm chromatin. In order to overcome this problem, we developed a new method to artificially remove protamines from sperm chromatin by treating them with nucleoplasm (left figure). This treatment enabled us to extract histone-DNA complex from sperm chromatin, then we performed Chromatin Immunoprecipitation-Sequencing (ChiP-seq) to determine where histones are retained in sperm genome. The result tells us that histones are scattered across the genome and exhibit modest enrichment in repeat regions. Interestingly, post-translationally modified histones are retained in specific genome elements depending on the patterns of their modifications (right figure). Recently, paternal lifestyle and habits are supposed to be transferred to their children through sperm. This phenomenon is called “epigenetic inheritance”, and our research outcome is expected to provide a useful knowledge for understanding its molecular mechanisms.
Elucidating various life phenomena through stem cell research

Research Topics

1. Molecular mechanism of stem cell self-renewal
2. Epigenetics of stem cell aging
3. Epigenetics of cancer

Stem cells have the remarkable capacity to both self-renew and give rise to many types of more specialized cells in the body, which explains their great therapeutic potential in regenerative medicine. But that’s not the only reason stem cells have become such a hotbed of scientific inquiry. These cellular transformers also offer an invaluable research tool for probing the disease mechanisms that underpin cancer, aging and a host of other health problems. Our major interest is to elucidate the mechanisms of self-renewal and multi-lineage differentiation of hematopoietic stem cells (HSCs). We are also interested in how the deregulated HSC functions are associated with aging of our body and the development of age-related hematological malignancies. We approach these issues mainly from the view point of epigenetics, such as DNA and histone modifications and higher order chromatin architecture.
Laboratory of
Nucleic acids research

Investigation of the molecular functions of nucleic acids (especially, RNA), and development of nucleic acid therapeutics

Research Topics

1. Investigation of molecular mechanisms of noncoding RNAs for the gene regulation.
2. Investigation of physiological and pathological roles of membrane-less organelle.
3. Development of basic technology to control nucleic acid medicine.

Nucleic acids such as DNA and RNA play a central role in gene expression flow. This laboratory has been focusing on investigation of roles of nucleic acids. We have revealed that long noncoding RNAs regulate the cellular responses against stresses such as pathogenic infection, heat shock, and DNA damage. We also investigate physiological and pathological roles of membrane-less organelle formed by nucleic acids and RNA binding proteins. In addition, we have revealed the biological significances of RNA turnover regulated by RNA binding proteins through omics-based approaches. Based on these achievement, we also develop technologies for nucleic acid therapeutics.


Network-based study of gene expression. Gene expression is precisely regulated by many steps, such as transcription, RNA processing, and RNA decay. We study the regulatory network of gene expression flow based on molecular biology, biochemistry, genomics, and multi-omics. In addition, we develop novel technologies contributing on development of nucleic acids therapies.
Laboratory of Clinical Pharmacokinetics
(The University of Tokyo Hospital)

Systems-pharmacological studies for drug development in the next-generation

Research Topics

1. Therapies for lifestyle-related diseases based on the comprehensive understanding of molecular mechanisms that control the transport of endogenous small molecules

2. Therapies for bone metabolism diseases based on the comprehensive understanding of the dynamic control mechanisms of signal molecules involved in bone resorption and formation

3. Quantitative understanding of the pharmacological and toxicological effects of molecular targeted anti-cancer drugs to establish clinical applications and new drug discovery techniques

4. Large-scale omics analysis to establish methods of preventing and treating adverse drug reactions based on the quantitative understanding of underlying molecular mechanisms

5. Clinical pharmacokinetics based on detailed quantification of related molecular functions

It has been recognized very well that we need to describe / predict the functions of cells, tissues and organisms from the function of each constituent molecule in a quantitative manner in order to understand the life activities. Although we have used such approach in analyzing and predicting the drug disposition in humans, it is quite important for us to expand the concept to the analysis of pharmacological / toxicological actions of drugs in humans. We are using such “systems-pharmacological” methods to solve many kinds of problems that remain great challenges in drug discovery, such as how to identify the most effective target molecules among numerous candidates, and how to comprehensively predict the adverse drug reactions in humans.
Drug lifetime management for development of excellent drugs, proper use of drugs, and evolution of drugs

Research Topics

1. Development and practice of methodologies for the collection, evaluation, analysis, and distribution of drug post-marketing information
2. Creation of programs for promoting proper use and evolution of drugs in community healthcare
3. Development of new features in the community pharmacy to practice the above-mentioned 2
4. Specification, standardization, and digitization of drug information, and their clinical applications
5. Quantitative prediction of the effects of biodisturbance factors on pharmacokinetics and drug effects

Our university’s Faculty of Pharmaceutical Sciences bears the social mission of promoting drug discovery and the proper use and evolution of drugs while improving the quality of drug therapies. To these ends, this course in Drug lifetime management pursues various research to ensure that the developed drugs can amply exhibit their effects and lead a substantial “drug life.”

The research topics of this course are that (1) the proper collection of drug information (DI), (2) evaluation/analysis of DI based on pharmacokinetics and pharmacodynamics and quantitative prediction of changes in pharmacokinetics and drug effect due to various risk factors, (3) Quantitative evaluation and analysis of the individual cases, (4) Creation of archive based on the optimal specification/standardization/digitization of DI, and (5) their proper provision to the clinical field. Concretely speaking, the content of our research is to seize drug post-marketing problems (including trouble and needs related with drugs), to make a proposal, to the pharmaceutical field, for evolving drugs and their information in order to solve the problems, and to feedback them to the clinical field.

The central dogma of pharmaceutical development consists of the cycle of drug discovery → proper use of drugs → post-marketing drug development → drug discovery and so on.
Maximizing and evaluating true "value" of various medical interventions, not only its impact for health care budgets but for health outcomes, to maintain and improve public health care system.

**Research Topics**

1. Health Technology Assessment (HTA)
2. Health economic analyses for drugs / medical devises
3. Surveys on public healthcare system / reimbursement system
4. Research on QOL (Quality of Life) instruments

There are growing concern about the cost issue of medical care interventions, as the sustainability of universal health coverage system is threatened with the increase of health care budget, in particular with introduction of expensive medications, such as drugs for cancer, hepatitis or life style diseases. Many stakeholders in Japan, not only health economists but also physicians, governmental decision makers, and industry officers have keen interest on health economics and outcomes research (HEOR), including QOL survey.

Efficiency data, or cost-effectiveness data, would play more role in decision making process, as well as efficacy and safety data would do.

We define the word "HEOR" with broader definition; any kind of researches which can maximize/quantify the value of particular medical interventions and/or disease area. Then, our research topics would range from narrower ones, like cost-effectiveness analyses of particular products to broader ones, like conceptual research for QOLs and the analytical methods.
Drug discovery research for development of innovative therapies against brain and neurological disorders

**Research Topics**

1. Understanding the role of intracellular trafficking in the pathogenesis of neurological disorders
2. Drug discovery research for accelerating the clearance of aggregated proteins in the brain
3. Development of innovative therapies for recovery of damaged neuronal circuits

We are facing super-aging society, and developments of diagnostics, prevention and therapeutics against brain and neurological disorders (e.g., dementia) have been required. However, to date, only a limited number of drugs for these diseases has been available. Our laboratory aims to understand the pathogenesis of brain and neurological disorders and identify key molecules that lead to development of prevention and therapeutics. At the same time, we seek biomarker molecules for early and specific diagnosis of the disorders. Our laboratory also conducts mutual collaborative researches between academia, industry and students. We believe that such collaborative approaches will lead to development of innovative therapies against these neurological diseases and help to establish the healthy super-aging society with multi-generational relationships. Also, advanced research experiences in our laboratory would cultivate next generation researchers for drug discovery.


Social Cooperation Program of Fluorescence Chemical Medicine

Creation of novel clinical technologies for fluorescence medicine on the basis of new technologies and concepts of organic chemistry

Research Topics

1. Establishing an efficient method to find out novel fluorescent probes which provide a solution for clinical needs
2. Development of fluorescence detection method and related technologies applicable to clinical diagnosis
3. Basic research required to solve the problems described above, including optimization of fluorescent probes

According to recent statistics, one in two Japanese people will have cancer in their lifetime. Hence, development of more accurate, easier to perform, and less expensive detection method of tumors during surgery is important. In addition, more precise diagnostic technologies for neurological diseases and infectious diseases are also significant. To address the social needs, we apply fluorescent activatable probe technologies based on organic chemistry, to provide a solution to the problems. In particular, we will develop effective strategies for screening clinically useful probes, and also perform actual screening to create “fluorescent navigation drugs”. Further, we will try to overcome difficulties which hinder the applications of the probes to actual clinical diagnosis, and optimize the properties of the probe, when needed. In the course of the research and the development, it might be required to solve various problems by collaborating with clinical researchers and cooperate researchers. Through such practices, we educate human resources who can explore the novel field of “Fluorescence Chemical Medicine”.

Fluorescent detection of breast cancer using gGlu-HMRG

Clinical research data using breast cancer surgery specimens. The probe reacted with an enzyme overexpressed in the breast cancer tissue and strongly fluoresced.
Inducing targeted protein degradation by chemical compounds

**Research Topics**

1. Development of new technologies to induce protein degradation
2. Development of SNIPER compounds that degrade disease causative proteins

When the mechanisms of various diseases are deeply understood at the molecular level, we can develop molecularly targeted drugs that specifically inhibit disease causative proteins. However, it is not possible to develop molecularly targeted drugs against all proteins. In particular, many intracellular proteins without enzymatic activity have been considered to be undruggable. Protein knockdown technology, which specifically degrades target proteins, is a promising technology to develop novel drugs against undruggable targets. Chimeric compounds such as PROTACs and SNIPERs are attracting attention because they enable the rational development of compounds that degrade proteins of your interest.

In our laboratory, we have developed a series of SNIPER compounds that degrade various target proteins. SNIPERs recruit IAP ubiquitin ligases to target proteins for ubiquitylation and proteasomal degradation. We are currently developing new technologies to induce protein degradation, which include cancer-specific or tissue-specific degradation of target proteins. We are also developing new compounds that degrade disease causative proteins.

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SNIPER compound induces ubiquitylation and proteasomal degradation of target protein.
Social Cooperation Program of Molecular Pharmacology of Malignant Diseases

Research on hematopoietic stem cells and hematopoietic malignancies toward the development of new therapeutic approaches

**Research Topics**

1. Elucidation of the mechanism of drug resistance
2. Development of drug combination therapies
3. Therapy with immune activation in the treatment of hematopoietic malignancies
4. Elucidation of T cell function in clonal hematopoiesis

We aim to elucidate the mechanisms of drug resistance and to develop combination therapies in order to overcome drug resistance of hematopoietic malignant cells. To determine which genes contribute to becoming drug resistance, we utilize genome-wide libraries for Crispr-A system and culture cells transduced with each sgRNA in the presence of drugs. In addition, pathway analysis of the gene groups identified by this method will reveal the mechanism of drug resistance and the mechanism of action. We will then devise drug combination therapies by revealing the mechanisms of drug resistance. We have obtained interesting research results on HDAC inhibitors and DNA methyltransferase inhibitors. In the future, we will also investigate other drugs and expand the scope of our research. Immune checkpoint inhibitors have attracted attention for their efficacy in the treatment of malignant tumors. By using G0 marker mice, our group has reported that 1) leukemic stem cells of chronic myeloid leukemia (CML) after the treatment are in G0 phase and express PD-L1, 2) IRAK inhibitors suppress PD-L1 expression and augment the therapeutic effect of tyrosine kinase inhibitors (TKIs), and 3) the combination therapy with TKIs and anti-PD-L1 antibody has a dramatic synergistic effect on murine CML models. Immune activation is a crucial strategy for the treatment of malignant tumors, and we aim to develop new effective therapies, including drug combination therapies.

On the other hand, it has received attention that approximately 10% of healthy elderly people have clonal hematopoiesis (CH) with one leukemia-related gene mutation. People with CH have a 10-fold higher incidence rate of hematopoietic malignancies than healthy people without CH. Therefore, CH can be assumed to be a preleukemic state. Interestingly, the incidence rate of atherosclerotic disease is about twice as high in people with CH, one in four cancer patients has CH, and cancer patients with CH have significantly worse prognosis. We assume that those high incidence rate and worse prognosis can be caused by abnormal function of T cells with CH.
In 1869, the Meiji government decided to adopt German medicine and asked the minister of the North German Federation to send 2 instructors. In 1871, Müller (chief Army physician/staff surgeon) and Hoffman (Navy physician/staff internist) arrived in Japan and assumed their duties at the University East Building (Tôkô) in Shitaya Izumibashi (precursor of the Faculty of Medicine, University of Tokyo).

Müller and Hoffman, who were under the direct supervision of the Meiji Minister of Education, had absolute authority over medical education in Japan. A new curriculum was established with 3 preparatory years (changed to 2 the following year) and a 5-year main program.

Müller and Hoffman regarded “pharmaceutical sciences” as an independent branch of the natural sciences that was closely related to medicine, and they proposed the establishment of a pharmaceutical institute. This took shape in 1873 as the Department of Pharmaceutical Manufacturing, established in The First University District Medical School. Müller returned to Germany in 1875. In October of 1895, upon the third anniversary of his death, a bust of Müller was erected to honor him as a benefactor of Japanese medicine and pharmaceutical sciences.

Dr. Shimoyama was born in Owari Inuyama in 1853. In 1873, after transferring to the Department of Pharmaceutical Manufacturing, The First University District Medical School (the precursor of the Faculty of Pharmaceutical Sciences, University of Tokyo), he graduated in 1878. He gave the “address in reply” at the first degree-conferring ceremony held by the Faculty of Medicine. Müller and Hoffman regarded “pharmaceutical sciences” as an independent branch of the natural sciences that was closely related to medicine, and they proposed the establishment of a pharmaceutical institute. This took shape in 1873 as the Department of Pharmaceutical Manufacturing, established in The First University District Medical School. Müller returned to Germany in 1875. In October of 1895, upon the third anniversary of his death, a bust of Müller was erected to honor him as a benefactor of Japanese medicine and pharmaceutical sciences.

Dr. Shimoyama became a professor of the Department of Pharmacy in the Faculty of Medicine in 1887, and a professor of a laboratory of Pharmacognosy, the Department of Pharmacy in 1893. While devoting great efforts to education and research, he also helped to cultivate successors through the establishment of the Pharmaceutical Society of Tokyo (the present Pharmaceutical Society of Japan) and the creation of a privately funded medicinal herb garden (Zekô Yakuen), etc.

Dr. Shimoyama died suddenly in February of 1912 while still in service as an educator. In remembrance of him, a bronze statue was erected beside the Pharmaceutical Sciences Building in 1913.
After Graduating from Graduate School of Pharmaceutical Sciences

Graduates of Faculty of Pharmaceutical Sciences, who have acquired a comprehensive fundamental understanding and applied knowledge of the field, receive extremely high respect, resulting in relative easiness to find a job. Over 90 percent of graduates choose to move forward to Graduate School of Pharmaceutical Sciences, the University of Tokyo. An increasing number of applications from the University of Tokyo, other universities, and foreign universities take an annual entrance exam in August. We have seen more and more of a social trend that prefers an individual with a researcher background and research experience higher than a Master's level. Our graduates who completed either undergraduate or graduate courses find positions in a wide array of fields, such as pharmaceuticals, chemical, and food related companies, universities, as well as government agencies. Half of graduate students opt for the doctoral course. After acquiring a PhD., they find vast opportunities not only in the academic field, such as universities and public research agencies, but in researching departments of companies, as leaders of projects.

Graduate School of Pharmaceutical Sciences, The University of Tokyo (Master's Program)

Graduate School of Pharmaceutical Sciences, The University of Tokyo (Doctoral Program)

Other advanced degrees in different schools

Government agencies and private enterprises

Others

University, government agencies, public research labs, and overseas postdoctoral research fellow

Others
Undergraduate

There are roughly 80 students in each grade at the Faculty of Pharmaceutical Sciences, and this is one of the smallest faculties at the University of Tokyo. New students form close friendships in no time after starting their first year. They attend lectures and engage in pharmaceutical training, all the while maintaining close relationships with faculty members. Lectures encompass a broad range of academic fields closely related to real life medicine. Assistant professors and graduate students as teaching assistants also take part in the pharmaceutical training classes. Second-year students begin to attend lectures on specialized topics for three days at the Hongo campus in the fall after receiving liberal arts education at the Komaba campus. In the third year, students sit in on lectures in the morning and engage in pharmaceutical training in the afternoon. Lectures become more specialized, and during training sessions students work in groups of two to four. Fourth-year students work in the laboratory of their choice, and they begin to focus less on classes and more on their senior research project.

Students must choose either the four-year program of the Department of Pharmaceutical Sciences or the six-year program of the Department of Pharmacy in their fourth year. Students who choose the Department of Pharmaceutical Sciences must complete a year-long senior research project in order to complete their degree. Those who decide on the Department of Pharmacy begin to work in the laboratory while they receive laboratory training for clinical pharmacy. At the end of the fourth year, students are expected to go through the Pharmaceutical Common Achievement Tests for clinical pharmacy. In the fifth year, students receive training for clinical pharmacy, and work in their laboratories. In the sixth year, students dedicate their time to working on their senior research project until graduation.

Postgraduate

Each laboratory and related laboratories (Institutes) of the Graduate School of Pharmaceutical Sciences and the Department of Pharmacy of the University of Tokyo Hospital conducts leading research in their specialized areas of focus. Students at the start of their graduate studies begin their research career by attending seminars and conducting experiments in world-renowned laboratories which are equipped with state-of-the-art facilities.

Campus Social Events

All the members form close-knit friendships, and this is not just because it is a relatively small department. The department hosts a slew of social events that include but are not limited to sports events, and activities with international students and researchers. These events contribute to the growth of friendships and close bonds outside of academic life. The close bonds of the students and researchers in this department foster collaboration, and this leads to a wider spectrum of academic insights and new developments in research.
With the dream of doing cosmetic research in Japan, I decided to take a master’s degree in Japan after graduating from Beijing University of Chemical Technology. Fortunately, with the acceptance of Pro. Funatsu, I won the opportunity to join the Laboratory of Bioanalytical Chemistry.

In the first year, as a research student, I started my research while preparing for the entrance exam of the Graduate School of Pharmaceutical Sciences. At first, I was a little uneasy because of the different major and new language environments. However, with the kind help from members of my laboratory, I quickly adapt to life at the University of Tokyo.

In the second year, I passed the entrance exam successfully and became a master student. During my master’s degree, I did two research projects, but one of the projects did not go well at first. Even so, my mentors and seniors continued giving me useful guidance, which encouraged me a lot. Then we started to collaborate with the Laboratory of Advanced Elements Chemistry and Ajinomoto. Finally, we completed the research successfully. Though the research experience, I began to realize the importance of cooperation because it allows us to analyze problems from multiple perspectives and find solutions more effectively.

In addition to laboratory life, I had many unforgettable experiences at the University of Tokyo. ISAR organized a variety of activities, such as international student trips, dumpling parties, and various Japanese cultural experience activities, which enabled me to enhance communication and understand different cultures. Also, ISAR provided Japanese classes and helped me to apply for a dormitory and scholarship. I appreciate all members of ISAR, especially, my Japanese teacher Ezure-sensei. She not only taught me Japanese but also gave me much good advice on my life and career plan. Thanks to these supports, I was able to complete my studies and found my ideal job.

After graduation, I entered a cosmetics company as I wish. My main job is to develop new skincare products. I have been working for two years and a half. However, I still miss lovely people, beautiful campus, and delicious Akamon Ramen of the University of Tokyo. I hope you can come here to pursue your dreams, and I believe this university can help you to make your dream come true!
In March of 2011, Japan was hit by a major earthquake, followed by a devastating tsunami and nuclear power plant leakage. It was not over a month after this catastrophe that I first flew to Tokyo to pursue an MS degree. Tokyo was the first city I ever lived in away from the comfort of home, family, and friends. Besides the initial safety concerns, there were many other adversities that had to be faced: my whole new life in a foreign land as an independent adult, adapting to a different culture and learning the local language, and as a graduate student, struggling to pursue a career in research. Many of my doubts and worries were resolved through communication with and support of the staff at ISAR. Not only so, ISAR provides free one-on-one Japanese language classes that, for me, were not only helpful in understanding Nihongo, but were also an emotional outlet and source of enjoyment and support. ISAR also organized many activities for international students, most memorable of which were the yearly outing to sight-see places around Tokyo and visit pharmaceutical companies, watching sumo wrestling, the sumptuous dinner on yakatabune, and the dumpling-making events, among others. The teachers and advisers at ISAR also helped me prepare for my interview to obtain scholarship support for my PhD studies. There are just too many fond memories to recall during the short 5-and-a-half years that I was in Japan, most of which are thanks to ISAR and the friends I've made in the Graduate School of Pharmaceutical Sciences.

Right after finishing my PhD, I went to the University of Connecticut to do postdoctoral research work, still in the field of natural products chemistry. Then, recently, I have just started my second stint as a postdoc in the field of asymmetric catalysis at a new research university in China, called the Westlake University. Although it is an entirely different research realm and yet another foreign country for me, I am confident that my experiences in Japan and the earnest work attitude and learning spirit instilled in me during my graduate studies at the University of Tokyo will continue to guide me in becoming my ideal researcher – one that values, and is of significance to, the society and humanity.

On a lighter note, the University of Tokyo was also where I first met my husband, and now, we have a little boy. Whereas I came to Tokyo alone, it gifted me with my most precious family, and my heart has never felt more complete!

Seven years ago, thanks to the opportunity provided by Prof. Uchiyama, I came to the University of Tokyo after graduating from Fudan University (China). To this day, I still clearly remember the tension and excitement when I first entered Japan from the Narita Airport.

In the first year, I learned the basics of scientific research while strengthening my Japanese ability as a research student at the Advanced Elements Chemistry Lab (the Uchiyama Lab.). During that hard period, my supervisors, seniors, and ISAR teachers had helped me a lot. In particular, the basic literacy of scientific research taught by Assistant Prof. Wang and Japanese conversation skills taught by Hirayama-sensei had become the most solid foundation and support my future life in Japan.

After entering the master course in the second year, I started the research project about organometal chemistry. Thanks to the perfect research conditions of the University of Tokyo and the professional supports of my lab mates, the project was carried out smoothly and several interesting results were obtained, which greatly increased my enthusiasm for scientific research. Also, with the improvement of Japanese speaking, communicating with lab mates had become more frequently. Through the conversation, I had a deeper understanding of Japanese society. Also, ISAR teachers had always given me a lot of care, consulting, and helping with various issues, such as Japanese studying, scholarships, or various travel and social activities to enrich my life in Japan.

After obtaining the master’s degree, I chose to enter the Ph.D. course. With the help from my supervisors and seniors. I luckily became the JSPS Research Fellow DC1, which not only financially but also mentally supported me. The Ph.D. life was exhilarating and fulfilling. Prof. Uchiyama gave me a lot of freedom to explore topics that interested me, which was a very precious and rewarding experience. After graduation, I entered a pharmaceutical company in Japan to engage in medical research. There are bound to be more challenges in the future, and the seven years of experience at the University of Tokyo gives me strong confidence and sufficient courage to face them. Thanks to every person who appeared in my life and gave their kindly help to me.
The International Student Advising Room (ISAR), established in 1994, provides a variety of services to support international students and researchers. [http://www.f.u-tokyo.ac.jp/~israr/en/isar/index.html](http://www.f.u-tokyo.ac.jp/~israr/en/isar/index.html)

**ISAR offers:**
- Advisory assistance and a counseling service
- Information for prospective international students
- Event planning
- Inter-university academic exchange program
- Information services

**Japanese Language Class**

The Japanese Language Class provides an opportunity to learn Japanese language to international students, researchers and their spouses. It also deals with a broad range of topics on Japanese society, culture, history, etc. There are a variety of courses offered from elementary to advanced level.

**Academic Exchange Agreements between Universities**

**USA**
- The University of Texas M. D. Anderson Cancer Center

**Sweden**
- The Sahlgrenska Academy, University of Göthenburg

**Germany**
- Research Training Group 1873, The University of Bonn
- Shenyang Pharmaceutical University

**P.R.China**
- School of Pharmacy, Sungkyunkwan University

**Republic of Korea**
- Chulalongkorn University
- The Netherlands
- Leiden University
- UK
- University of Cambridge
The Experimental Station for Medicinal Plant Studies is located about 30 km east of the Hongo Campus. Its 6,123 m² plant specimen garden includes the medicinal plants that are considered important for the students’ education. This garden serves a variety of purposes, including maintenance of plant lineages; research on plant breeding and cultivation; collection and cultivation of medicinal plants native to Japan as well as introduced from overseas; research on medicinal plant ingredients from the standpoints of chemistry, pharmacology, biosynthesis, plant physiology, and pharmacognosy; and research on the medicinal plant cultivation and maintenance. The grounds of the Experimental Station also encompass a greenhouse, administration building, and laboratory building. At present, about 250 varieties of plants are under cultivation. Each year, 3rd-year students receive practical training in the plant specimen garden during the summer session. In 1982, the laboratory for medicinal plant studies was set up within the building in Hongo Campus and have continued research until now.

The University Museum, The University of Tokyo (Hongo Campus) houses a Pharmaceutical Sciences Division on its first floor, where a large number of specimens – mainly crude drugs and medicinal plants – are stored and managed.

In October 2004, the first rooftop herb garden, with an area of approximately 100 m², was created on the rooftop of the auditorium of Pharmaceutical Sciences Research Building for enabling the students to come into close contact with medicinal plants. Several dozen varieties of medicinal plants are cultivated in light soil with a depth of about 60 cm, equipped with an automatic irrigation system.

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<th>Books</th>
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Hongo Campus

Pharmaceutical Sciences Building

Graduate School of Pharmaceutical Sciences
Faculty of Pharmaceutical Sciences

Pharmaceutical Sciences Research Building
Left panel:
Elucidation of enzyme reaction mechanism using a chemically synthesized substrate analog

Right panel:
Structure of enzyme analyzed by cryo-electron microscopy

[ Natural Products Chemistry ]

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