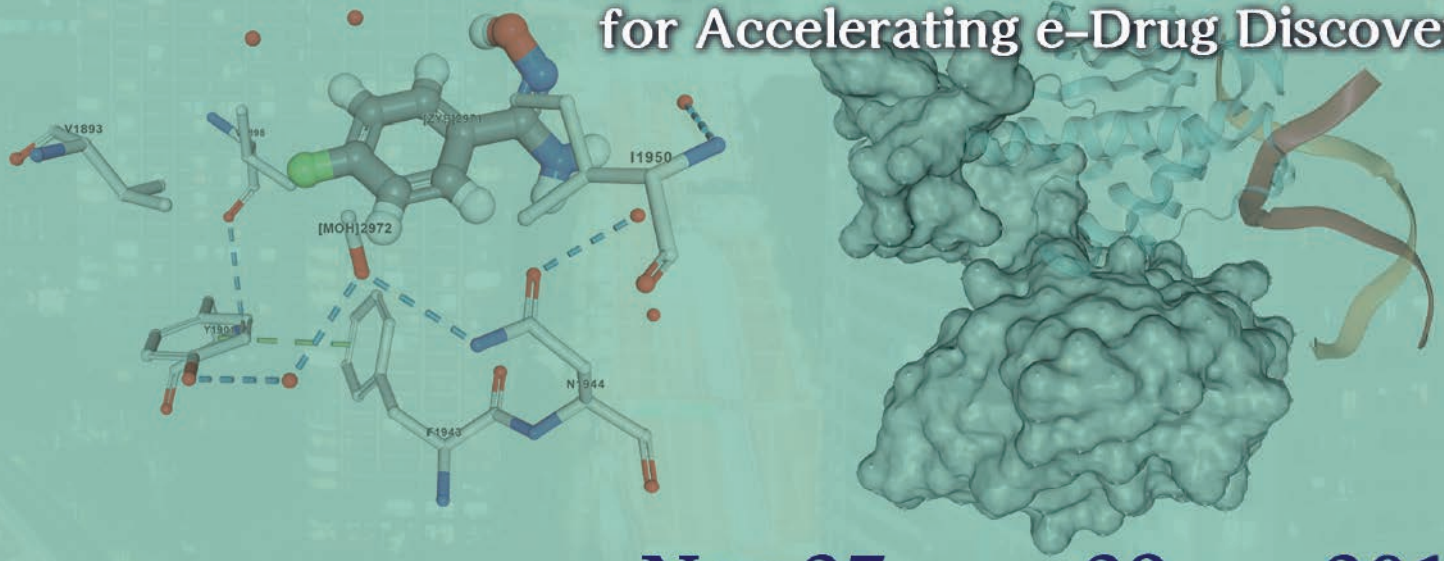
AHeDD2019/IPAB2019 Joint Symposium

Trends in Artificial Intelligence and Molecular Simulation for Accelerating e-Drug Discovery



Nov 27 (Wed.) – 29 (Fri.), 2019

Tonomachi King Skyfront Area, Kawasaki, Japan

The Kawasaki Life Science and Environmental Research Center (LiSE)
PeptiDream Inc.

AHeDD
Asia Hub for e-Drug Discovery

https://ahedd2019.ahead-biocomputing.co.jp

Main organizer

Certified NPO Initiative for Parallel Bioinformatics (IPAB)

Co-organizers

Middle-Molecule IT-based Drug Discovery Laboratory (MIDL), Tokyo Institute of Technology
Kawasaki City
Kawasaki Institute of Industrial Promotion
Innovation Initiative for Middle-Molecule Drug Discovery (IMD²)

Cooperation

Tokyo Institute of Technology

Endorsement

Research Organization for Information Science and Technology (RIST)
Information Processing Society of Japan
Biophysical Society of Japan
Chem-Bio Informatics Society (CBI)
Japanese Society for Bioinformatics (JSBi)
The Kanagawa Shimbun
The Nikkan Kogyo Shimbun, Ltd.
The Science News Ltd.

Organization Secretariat : Certified NPO Initiative for Parallel Bioinformatics (IPAB)
2-2-15 Hamamatsucho, Minato-ku, Tokyo 105-0013, Japan
Email: office@ipab.org URL: http://www.ipab.org/

Management Secretariat : Ahead Biocomputing, Co. Ltd
11-2 Ekimaehoncho, Kawasaki-ku, Kawasaki City, Kanagawa 210-0007, Japan
Email: ahedd2019@ahead-biocomputing.co.jp URL: https://ahead-biocomputing.co.jp/

AHeDD2019/IPAB2019 Joint Symposium

Trends in Artificial Intelligence and Molecular Simulation for Accelerating e-Drug Discovery

November 27 (Wed.) - 29 (Fri.), 2019 ／ Tonomachi King Skyfront Area, Kawasaki, Japan

Contents

General Information

AHeDD2019/IPAB2019 Joint Symposium

Trends in Artificial Intelligence and Molecular Simulation for Accelerating e-Drug Discovery

Period

November 27 (Wed.) - 29 (Fri.), 2019

Venue

Tonomachi King Skyfront Area, Kawasaki, Japan

- The Kawasaki Life Science & Enviromental Research Center (LiSE)
  3-25-13 Tonomachi, Kawasaki-ku, Kawasaki City, Kanagawa Japan 210-0821
- PeptiDream Inc.
  3-25-23 Tonomachi, Kawasaki-ku, Kawasaki City, Kanagawa Japan 210-0821

Symposium Chair

Yutaka Akiyama (Tokyo Institute of Technology)

Organization

Main organizer

Certified NPO Initiative for Parallel Bioinformatics (IPAB)

Co-organizers

Middle-Molecule IT-based Drug Discovery Laboratory (MIDL), Tokyo Institute of Technology
Kawasaki City
Kawasaki Institute of Industrial Promotion
Innovation Initiative for Middle-Molecule Drug Discovery (IMD²)

Cooperation

Tokyo Institute of Technology

Endorsement

Research Organization for Information Science and Technology (RIST)
Information Processing Society of Japan
Biophysical Society of Japan
Chem-Bio Informatics Society (CBI)
Japanese Society for Bioinformatics (JSBi)
The Kanagawa Shimbun
The Nikkan Kogyo Shimbun, Ltd.
The Science News Ltd.

Opening Address

AHeDD2019/IPAB 2019 Joint Symposium Chair

Yutaka Akiyama (Tokyo Institute of Technology)

It is our great pleasure to announce that AHeDD2019/IPAB2019 Joint Symposium will be held at Tonomachi King Skyfront area (LiSE and PeptiDream Inc.), Kawasaki City, Japan, during November 27-29, 2019.

The Kawasaki INnovation Gateway (KING) Skyfront is the flagship science and technology innovation hub of Kawasaki City. It is a 40 hectare area located in front of Tokyo International Airport, and was launched in 2013 as a base for research, industrial, and governmental sectors to work together to devise solutions to global issues in the life sciences and environment. We are really happy to welcome all of you to this new innovation area dedicated to novel scientific research.

The AHeDD2019/IPAB2019 international symposium will be held jointly as 10th AHeDD symposium and 18th IPAB symposium. In 2004, the scientists of Korea, China, and Japan working in the fields of Computer-Aided Drug Design formally agreed with to establish a meeting called Asia Hub for e-Drug Discovery (AHeDD). The 1st AHeDD meeting was held in 2005 at Jeju Island of Korea. Then we continued to have meetings on 2006 (Seoul), 2007 (Shanghai), 2008 (Tokyo jointly with IPAB2008), 2009 (Busan with KBSI-CBI), 2010 (Seoul), 2014 (Chengdu), 2017 (Melbourne with RACI), 2018 (KIST, Gangneung), and 2019 (King Skyfront, Kawasaki City). On page 16 of this symposium booklet, you can see the brief history of AHeDD meeting series.

On the other hand, IPAB, Initiative for Parallel Bioinformatics was founded on 1999, as a non-profit organization to accelerate high-performance computing for bioinformatics and drug discovery in Japan. On page 17, you can see the brief history of IPAB symposium series. IPAB has also organized open competitions for computational drug discovery on 2014, 2015, 2016, and 2017.

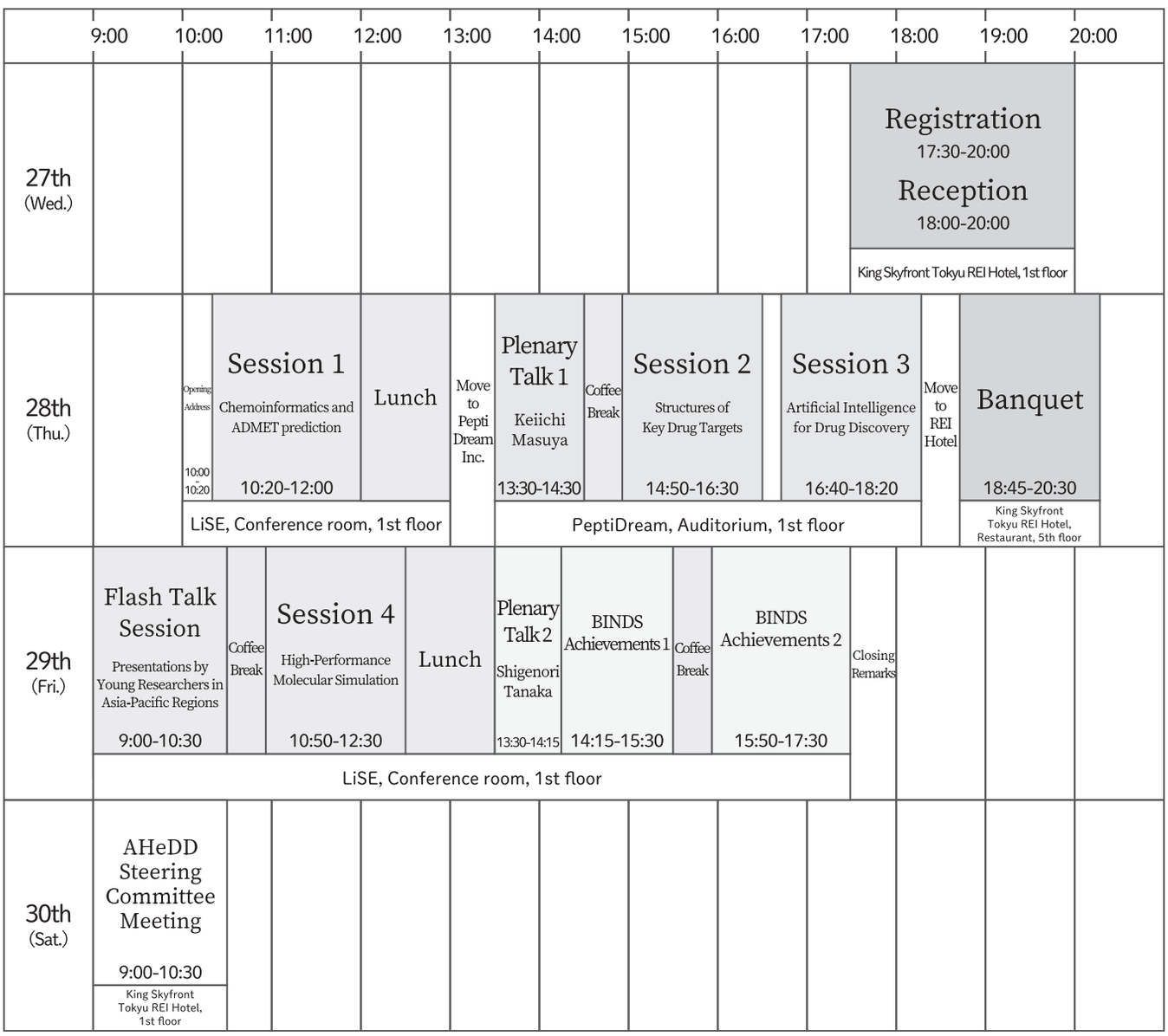
We are looking forward to seeing you in AHeDD2019/IPAB2019 Joint Symposium, at Tonomachi King Skyfront area, Kawasaki City, Japan, and having fruitful discussions on trends in artificial intelligence and molecular simulation for accelerating e-drug discovery.

AHeDD2019/IPAB2019 Joint Symposium Chair,
Yutaka Akiyama

Program at a Glance

27 (Wed.) - 30 (Sat.) November 2019

Tonomachi King Skyfront Area, Kasawaki, Japan



Time Table

Wednesday, 27th November 2019

17:30-20:00 Location : King Skyfront Tokyu REI Hotel, 1st floor

17:30-20:00 **Registration**
18:00-20:00 **Reception** Presentations from AHeDD representatives

Thursday, 28th November 2019

10:00-13:00 Location : LiSE, Conference room, 1st floor

10:00-10:20 **Opening address**
Yutaka Akiyama Professor, Department of Computer Science, Tokyo Institute of Technology, Japan
Shengyong Yang Professor, Department of Medicinal Chemistry, Sichuan University, China
Kyoung Tai No Professor, Department of Biotechnology, Yonsei University, Korea

10:20-12:00 **Session 1: Chemoinformatics and ADMET prediction** (Chairs: Liu Hong, and Kyong Tai No)

10:20-10:45 *In silico ADMET prediction and optimization*
Yun Tang Professor, School of Pharmacy, East China University of Science and Technology, China

10:45-11:10 *Syetems chemo-informatics and fragment based lead discovery*
Gyoonhee Han Professor, Department of Biotechnology, Yonsei University, Korea

11:10-11:35 *Prediction of membrane permeability and plasma protein binding of cyclic peptides*
Yutaka Akiyama Professor, Department of Computer Science, Tokyo Institute of Technology, Japan

11:35-12:00 *A proteochemometric approach for beta-lactam antibiotic response prediction in Staphylococcus aureus*
Jae Hong Shin Senior Scientist, Standigm Inc., Korea

12:00-13:00 **Lunch**

13:00-13:20 Move to PeptiDream (5 min. on foot)

13:30-18:20 Location : PeptiDream, Auditorium, 1st floor

13:30-14:30 **Plenary Talk 1** (Chair: Yutaka Akiyama)
Constrained peptides in drug discovery and development - various therapeutic applications offered by PeptiDream
Keiichi Masuya Executive Vice President, PeptiDream Inc., Japan

14:30-14:50 Coffee Break

14:50-16:30 **Session 2: Structures of Key Drug Targets** (Chairs: Takatsugu Hirokawa, and Yun Tang)

14:50-15:15 *CryoEM analysis of the GPCR neurotensin receptor 1-G protein complex for the future engineering of biased allosteric modulator*
Hideaki E. Kato Associate Professor, Komaba Institute for Science, The University of Tokyo, Japan

15:15-15:40 *Discovery and development of novel CCR5 antagonists*
Hong Liu Professor, Shanghai Institute of Materia Medica, CAS, China

15:40-16:05 *Molecular modeling study for identification of binding site of AIMP2-DX2 inhibitor*
Yuno Lee Senior Scientist, Korea Research Institute of Chemical Technology (KRICT), Korea

Time Table

16:05-16:30 *Computer aided drug discovery with natural compounds*
Kyoung Tai No Professor, Department of Biotechnology, Yonsei University / Director, BMDRC, Korea

16:30-16:40 Break

16:40-18:20 **Session 3: Artificial Intelligence for Drug Discovery** (Chairs: Weiliang Zhu, and Gyoonhee Han)

16:40-17:05 *Drug discovery with artificial intelligence: advances and challenges*
Shengyong Yang Professor, Department of Medicinal Chemistry, Sichuan University, China

17:05-17:30 *Multiple approaches to discover human DDX3 inhibitors for cancer therapeutics*
Keun Woo Lee Professor, Department of Biochemistry, Gyeongsang National University, Korea

17:30-17:55 *Visualizations within chemogenomic active learning reveal how protein descriptors are used and underlying truths about chemogenomic and single target QSAR model utility*
J. B. Brown Junior Associate Professor, Graduate School of Medicine, Kyoto University, Japan

17:55-18:20 *Bioinformatics-Facilitated Therapeutic Target discovery*
Feng Zhu Professor, College of Pharmaceutical Sciences, Zhejiang University, China

18:20-18:35 Move to King Skyfront Tokyu REI Hotel (5 min. on foot)

18:45-20:30 Location : King Skyfront Tokyu REI Hotel, Restaurant, 5th floor

18:45-20:30 **Banquet**

Friday, 29th November 2019

8:30-17:45 Location : LiSE, Conference room, 1st floor

8:30- 9:00 Coffee and Donuts

9:00-10:30 **Flash Talk Session:** Presentations by Young Researchers in Asia-Pacific Regions
(Chair: Masahito Ohue) (4 min + 1 min Q&A)

9:00-9:05 *Systematic construction of the cosolvents sets for cosolvent MD (CMD) with the large-scale simulation*
Keisuke Yanagisawa JSPS Research Fellow, Department of Biotechnology, The University of Tokyo, Japan

9:06-9:11 *Investigation of protein-protein interactions and hot spot region between PD-1 and PD-L1 by fragment molecular orbital method*
Hocheol Lim Researcher, Bioinformatics & Molecular Design Research Center, Korea

9:12-9:17 *Metagenome analysis implies bacterial community and gene category composition disorder in periodontal disease sites*
Kazuki Izawa Researcher, Department of Computer Science, Tokyo Institute of Technology, Japan

9:18-9:23 *In silico drug discovery targeting Hippo pathway and YAP-TEAD protein protein interactions for small molecules anti cancer agent*
Jongwan Kim Researcher, Bioinformatics & Molecular Design Research Center, Korea

Time Table

9:24-9:29 *Discovery of leucyl-tRNA synthetase (LRS) PPi inhibitor for modulating mTORC1 pathway via the chemical biology approach*
Chulho Lee Research Associate, Department of Biotechnology, Yonsei University, Korea

9:30-9:35 *Novel computational approach for natural product (NP) research: development of natural compound molecular fingerprint (NC-MFP) for exploring new NP-based drugs*
Myungwon Seo Graduate Student, Department of Biotechnology, Yonsei University, Korea

9:36-9:41 *Predicting membrane permeability for cyclic peptides*
Yasushi Yoshikawa Specially Appointed Assistant Professor, Department of Computer Science, Tokyo Institute of Technology, Japan

9:42-9:47 *Development of prediction model for onset of disease and risk factor analysis*
Atsuyoshi Matsuda CEO, Logbii, Inc., Japan

9:48-9:53 *GCMQA: a novel single-protein structure model quality assessment method using graph convolution*
Rin Sato Graduate Student, Department of Computer Science, Tokyo Institute of Technology, Japan

9:54-9:59 *Contest-based compound screening enables identification of chemically diverse inhibitors of target proteins*
Shuntaro Chiba Researcher, MIH, RIKEN, Japan

10:00-10:05 *Underestimated non-covalent interactions in protein data bank*
Zhijian Xu Associate Professor, Shanghai Institute of Materia Medica, CAS, China

10:06-10:11 *Evaluation of a self-balanced force field for biomolecule simulations*
Sungbo Hwang Graduate Student, Department of Biotechnology, Yonsei University, Korea

10:12-10:17 *Application of informatics approaches to compound library design for intractable target chemical spaces*
Kazuyoshi Ikeda Specially Appointed Associate Professor, Division of Physics for Life Functions, Keio University, Japan

10:18-10:23 *Learning-to-rank for ligand-based virtual screening*
Masahito Ohue Assistant Professor, Department of Computer Science, Tokyo Institute of Technology, Japan

10:30-10:50 Coffee Break

10:50-12:30 **Session 4: High-Performance Molecular Simulation** (Chairs: Keun Woo Lee, and Shengyong Yang)

10:50-11:15 *Development of the rapid QM/MM molecular dynamics techniques aimed at medium molecular drug discovery*
Hiroaki Nishizawa Assistant Professor, Center for Computational Sciences, University of Tsukuba, Japan

11:15-11:40 *New methods for highly efficient MD simulation*
Weiliang Zhu Professor, Shanghai Institute of Materia Medica, CAS, China

11:40-12:05 *Next generation accelerated supercomputing: Cygnus system at University of Tsukuba*
Taisuke Boku Director, Center for Computational Sciences, University of Tsukuba, Japan

12:05-12:30 *In silico Drug Discovery using Molecular Modeling and Simulation*
Takatsugu Hirokawa Professor, University of Tsukuba / Team Leader, molprof, AIST, Japan

12:30-13:30 **Lunch**

Time Table

Friday, 29th November 2019

9:00-17:45 Location : LiSE, Conference room, 1st floor

13:30-17:30 **AMED BINDS project special sessions**

13:30-14:15 **Plenary Talk 2** (Chair: Takatsugu Hirokawa)
Perspectives of computational drug discovery: AMED-BINDS activities in Japan
Shigenori Tanaka
Professor, Department of Computational Science, Kobe University / AMED BINDS Project Officer, Japan

14:15-15:30 **BINDS Achievements 1** (Chair: Takatsugu Hirokawa)

14:15-14:40 *In silico drug discovery based on structural informatics and FMO method*
Teruki Honma Group Leader, BDR, RIKEN, Japan

14:40-15:05 *Molecular simulation studies on protein functions and improvement of the efficiency of cryo-EM data collection by machine learning*
Tohru Terada Associate Professor, Interfaculty Initiative in Information Studies, The University of Tokyo, Japan

15:05-15:30 *Structural modeling of the entire EhV-ATPase in multiple states using cryo-EM data and homology modeling*
Yu Yamamori Research Scientist, AIRC, AIST, Japan

15:30-15:50 Coffee Break

15:50-17:30 **BINDS Achievements 2** (Chair: Teruki Honma)

15:50-16:15 *Finding a drug candidate regulating protein function at an allosteric site*
Yuko Ito Research Scientist, molprof, AIST, Japan

16:15-16:40 *MD simulations and QM/MM analysis to gain insight into protein functions*
Yoshitaka Moriwaki Assistant Professor, Department of Biotechnology, The University of Tokyo, Japan

16:40-17:05 *Improving the virtual screening ability using machine learning*
Masakazu Sekijima Unit Leader, ACDD / Associate Professor, IIR, Tokyo Institute of Technology, Japan

17:05-17:30 *Combination of molecular dynamics simulations and small-angle X-ray scattering experiments*
Mitsunori Ikeguchi Professor, Graduate School of Medical Life Science, Yokohama City University, Japan

17:30-17:45 Closing Remarks

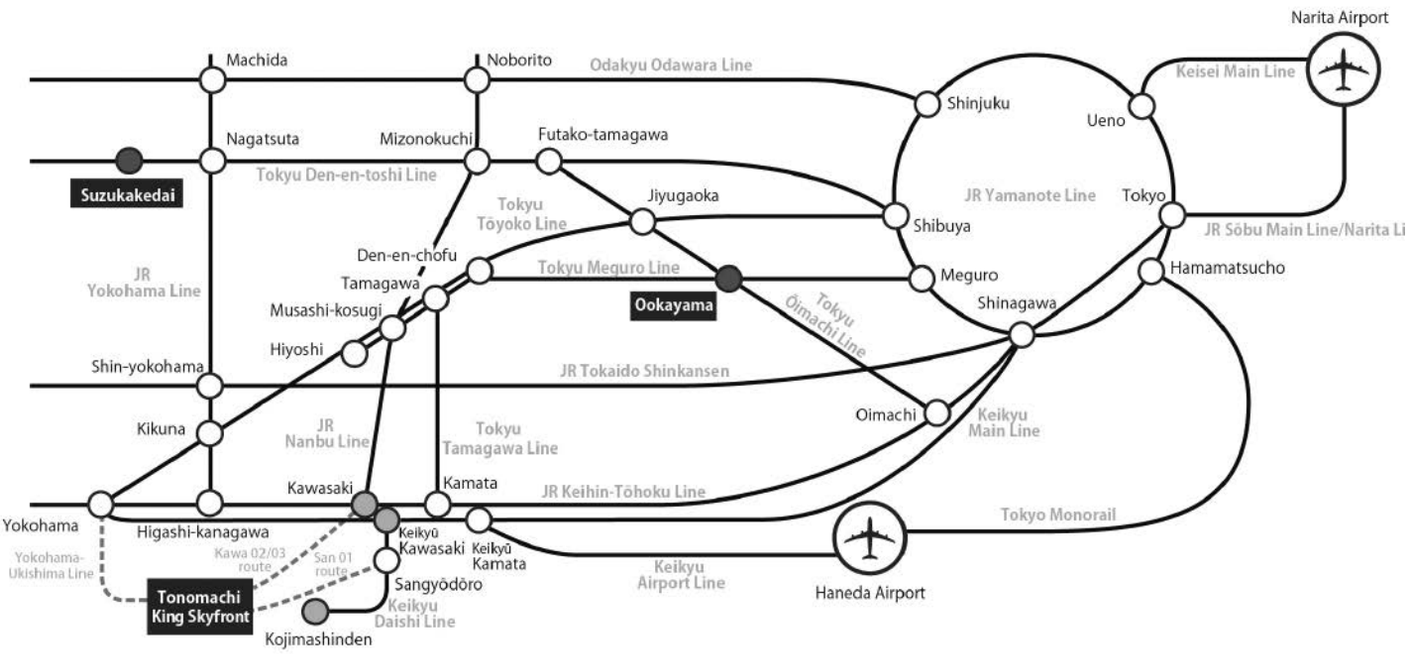
Saturday, 30th November 2019

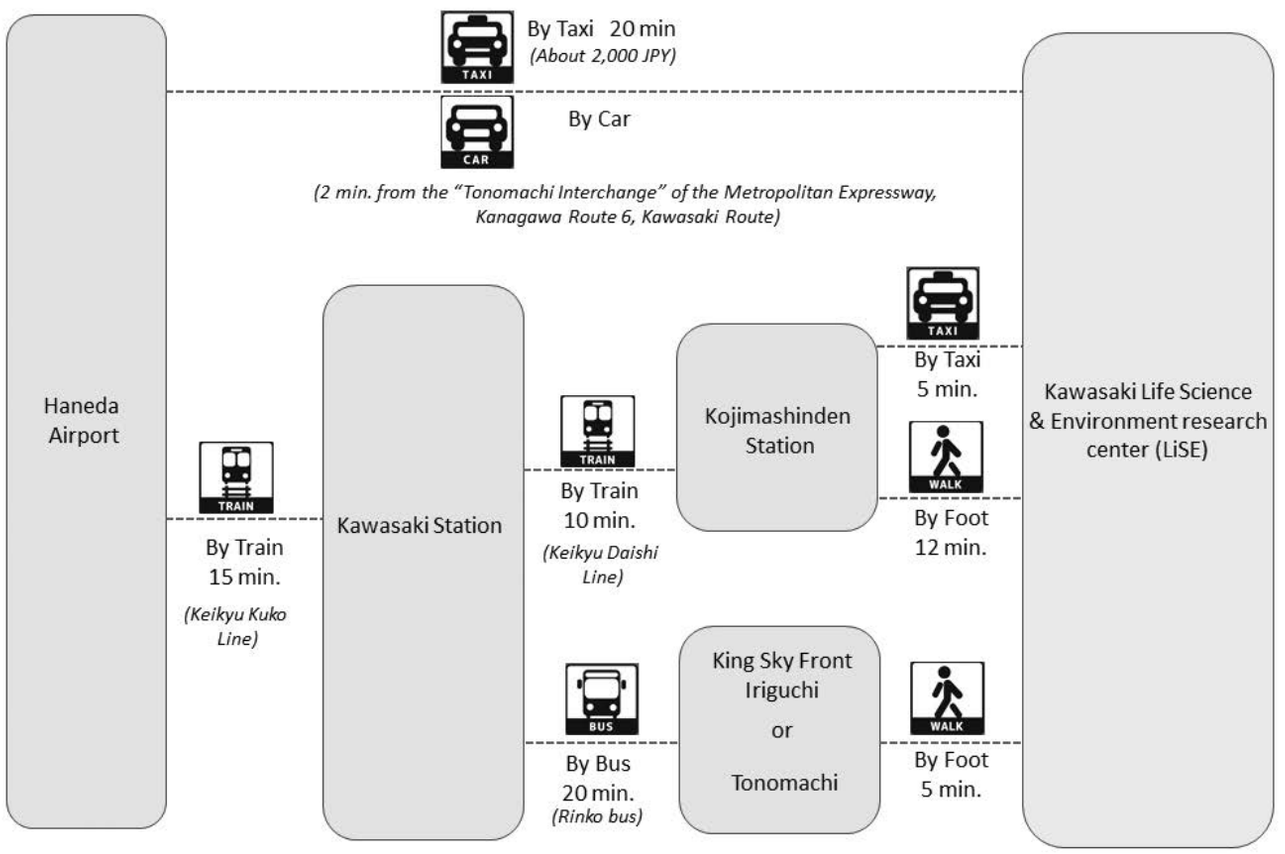
9:00-10:30 Location : King Skyfront Tokyu REI Hotel, 1st floor

9:00-10:30 AHeDD Steering Committee Meeting

Access

From Haneda Airport

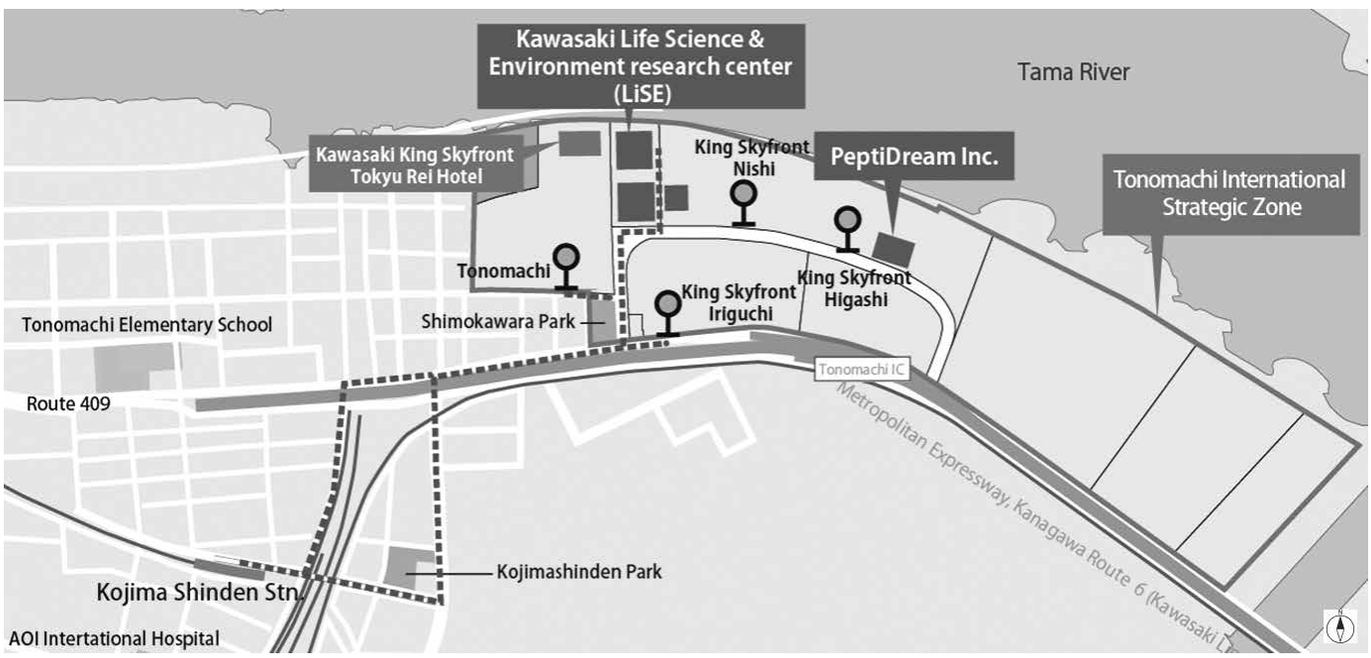




Access

Venue

Tonomachi King Skyfront Area, Kawasaki, Japan

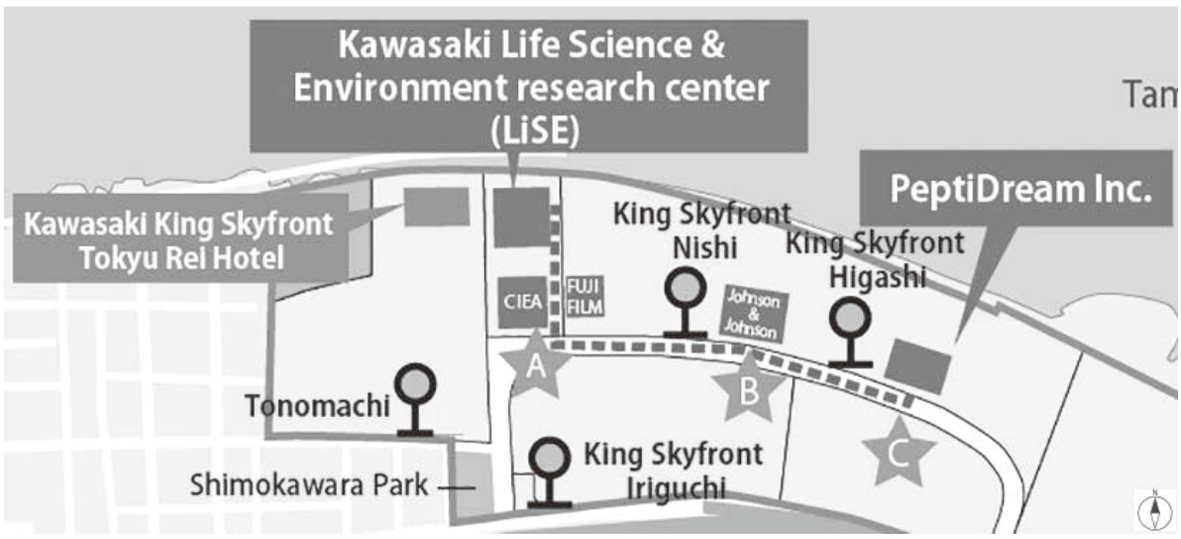


・Kawasaki Life Science & Enviromental Research Center (LiSE)
3-25-13 Tonomachi, Kawasaki-ku, Kawasaki City, Kanagawa Japan 210-0821

・PeptiDream Inc.
3-25-23 Tonomachi, Kawasaki-ku, Kawasaki City, Kanagawa Japan 210-0821

Access

Direction From LiSE to PeptiDream Inc.（11/28）



A

Exit from the main entrance of LiSE and go straight.
Turn left at the end of the road.

B

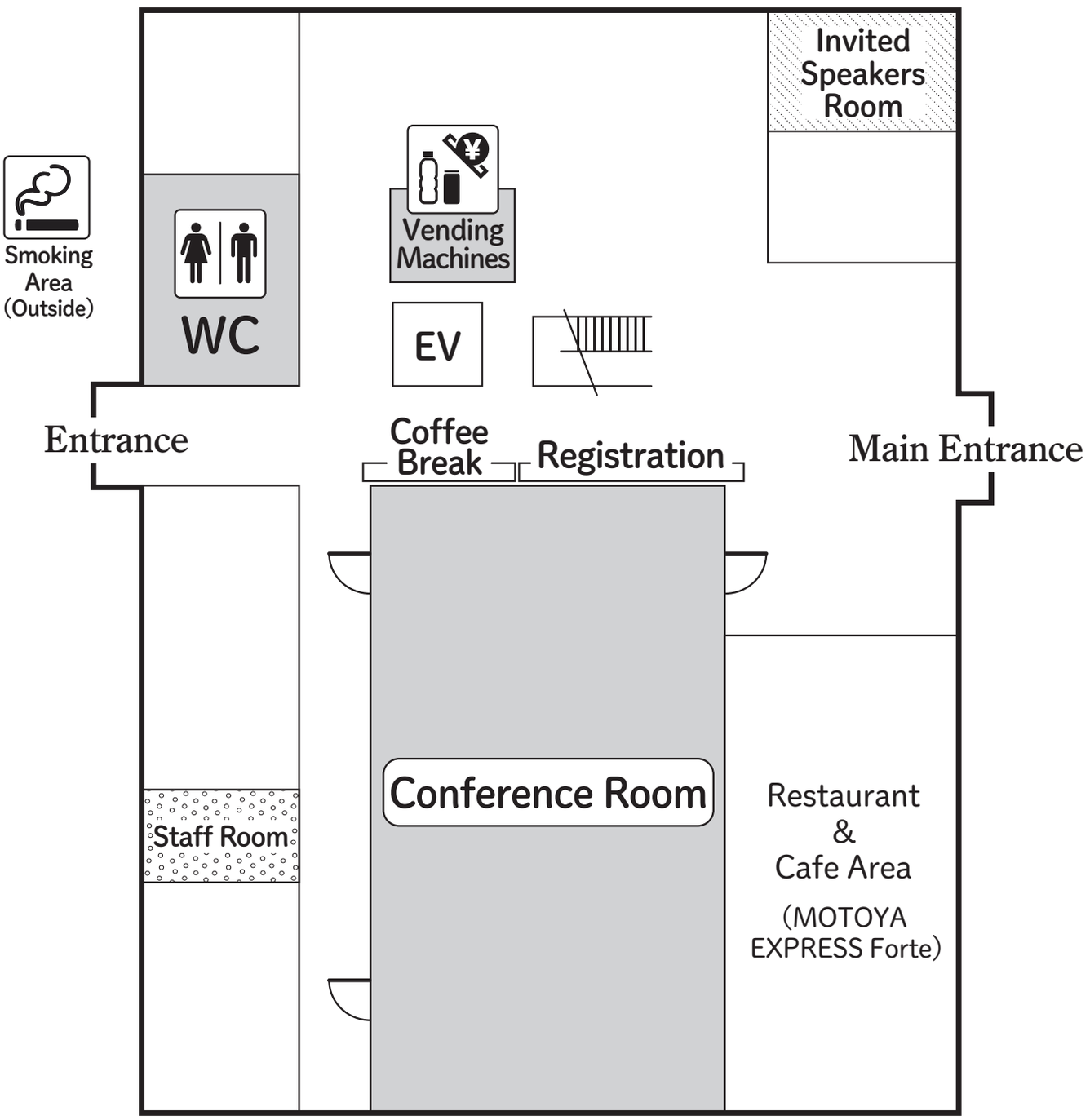
Go straight and pass Johnson & Johnson on your left.
Keep going straight.

C

You will see Peptidream Inc. on your left.

Floor Map

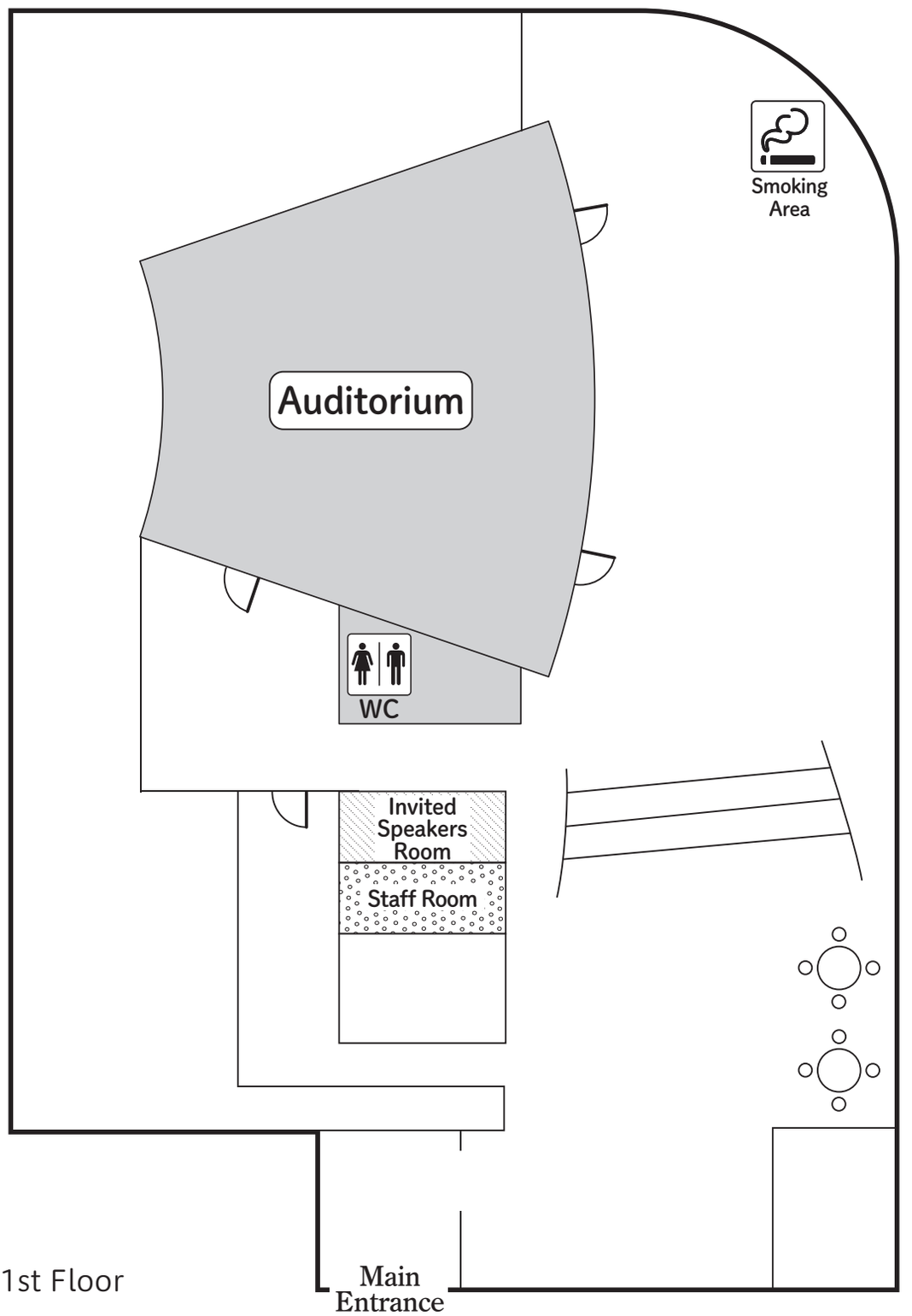
Kawasaki Life Science & Environment research center (**LiSE**) Floor Map



1st Floor

Floor Map

PeptiDream Inc. Floor Map



Information for Participants

1. Registration

● Registaration date
11/27 (Wed.)　17:30- 20:00　(Kawasaki King Skyfront Tokyu REI Hotel, 1st Floor)

● Information desk open hours
11/27 (Wed.)　17:30- 20:00　(Kawasaki King Skyfront Tokyu REI Hotel, 1st Floor)
11/28 (Thu.)　10:00- 12:00　(LiSE, Conference Room, 1st Floor)
　　13:30- 18:20　(Peptidream Inc., 1st Floor)
11/29 (Fri.)　09:00- 17:30　(LiSE, Conference Room, 1st Floor)

● Advance registration
Open : 9/10 (Fri.), 2019
Close : 11/20 (Wed.) , 2019
Receive a name badge and a program booklet at the registration desk.

● On-site registration
Those who have not completed advance registration are required to register on-site at the registration and information desk.

● Registration fee
Regular：35,000 JPY,　Student：15,000 JPY
(including Welcome Reception, Banquet, Lunch, and not including accommodation)

● Name badge
Please be sure to wear your name badge throughout the meeting.
Entry without the badge is NOT acceptable.

● Receipt
A receipt is attached to the name badge. If you need another receipt form, it will be issued in exchange for the one attached to your name badge.

2. Services & Facilities

● Baggage
The organizers can not keep any baggages and we are not responsible for lost or stolen valuables.

● Lunch
A Lunch box will be provided after Session1 (11/28), and Session 4 (11/29).
Please follow the instructions of the staff.

Information for Participants

3. Prohibited Items

● Photography & recording
Photography and recording with camera, video, mobile phone and any device is NOT allowed for the presentation materials.
Please note that official photo and video recording will be performed by the organizers.

● Smoking
Please smoke in a designated area.

● Mobile phone use
Please set your mobile phone on the silent mode or off, and make sure it will not make noises during lectures/presentations.

4. Contact

● During the meeting
Information Desk

11/27 (Wed.)	17:30- 20:00	(at Kawasaki King Skyfront Tokyu REI Hotel, 1st Floor)
11/28 (Thu.)	10:00- 12:00	(at LiSE, Conference Room, 1st Floor)
	13:30- 18:20	(at PeptiDream Inc., 1st Floor)
11/29 (Fri.)	09:00- 17:30	(at LiSE, Conference Room, 1st Floor)

● Before or after the meeting
≪ Organization Secretariat ≫
Certified NPO Initiative for Parallel Bioinformatics (IPAB)
IPAB Office, 2-2-15 Hamamatsucho, Minato-ku, Tokyo Japan 105-0013
Email: office@ipab.org

≪ Management Secretariat ≫
Ahead Biocomputing, Co. Ltd.
Kawasaki Frontier Bldg. 4F, 11-2 Ekimaehoncho, Kawasaki-ku, Kawasaki City, Kanagawa Japan 210-0007
Email: ahedd2019@ahead-biocomputing.co.jp

Committee

AHeDD2019/IPAB2019 Symposium Chair

Yutaka Akiyama, Department of Computer Science, Tokyo Institute of Technology, Japan

AHeDD Board Members

Kyoung Tai No, Department of Biotechnology, Yonsei University, Republic of Korea
Keun Woo Lee, Department of Biochemistry, Gyeongsang National University, Republic of Korea
Shengyong Yang, Department of Medicinal Chemistry, Sichuan University, China
Yun Tang, School of Pharmacy, East China University of Science and Technology, China
Weiliang Zhu, Shanghai Institute of Materia Medica, China
Hualiang Jiang, Shanghai Institute of Materia Medica, China
Yutaka Akiyama, Department of Computer Science, Tokyo Institute of Technology, Japan
Takatsugu Hirokawa, University of Tsukuba/molprof AIST, Japan
Yasuteru Shigeta, University of Tsukuba, Japan
David Winkler, Monash University, Australia
Jonathan Baell, Monash University, Australia
Vladimir Poroikov, Head of Department for Bioinformatics and Laboratory for Structure-Function Based Drug Design, Russia
Dmitry I. Osolodkin, Head of Laboratory of Antivirals, Russia
Yu Zong Chen, National University of Singapore, Singapore

IPAB Board Members

Nobuyuki Tanaka (Early Reflections Co., Ltd., Vice President of IPAB)
Masahito Ohue (Ahead Biocomputing, Co. Ltd.)
Masakazu Sekijima (Tokyo Institute of Technology)
Takatsugu Hirokawa (National Institute of Advanced Industrial Science and Technology)

Local Organizing Committee Chair

Masahito Ohue, Tokyo Institute of Technology, Japan

Local Organizing Committee Members

Kazuki Izawa, Tokyo Institute of Technology, Japan
Fumio Kurayama, Tokyo Institute of Technology, Japan
Kanako Ozeki, Initiative for Parallel Bioinformatics, Japan
Naoki Sato, Tokyo Institute of Technology, Japan
Tomomi Tanaka, Tokyo Institute of Technology, Japan
Yasushi Yoshikawa, Tokyo Institute of Technology, Japan

AHeDD History

Asia Hub for e-Drug Discovery (AHeDD)

Date	Contents	Location
2002.7.12	Dr. Akiyama-Dr. No; Exchange e-DD Information	Seoul, Republic of Korea
2002.9.14	Dr. Akiyama, Attend BMDRC Symposium on “Protein Structure for Drug target” , discussion on research collaboration	Seoul, Republic of Korea
2003.9.17	Dr. Akiyama- Dr. No, Discussion on collaboration of e-DD Education	Seoul, Republic of Korea
2004.6.3	Dr. Jiang – Dr. No: Discussion on the foundation of e-DD collaboration hub.	Seoul, Republic of Korea
2004.6.19-24	Dr. No, Visit DDDC, first draft on AHeDD, visit DD related Institutes	Shanghai, China
2004.8.24	Dr. Jiang Visit BMDRC, Attend Symposium, meeting with e-DD Researchers	Seoul, Republic of Korea
2004.9.29-30	Dr. No; Visit CBRC, discuss on AHeDD	Tokyo, Japan
2004.11.24	Dr. Akiyama: Visit BMDRC, Seminar, meeting with Korean e-DD Researchers	Seoul, Republic of Korea
2005.8.26	Sub session in 11th Asian Chemical Congress, “Cheminformatics for Drug Discovery and Development” – AHeDD	Seoul, Republic of Korea
2005.8.27-29	AHeDD Jeju Workshop (1st)	Jeju, Republic of Korea
2005.10.26-29	Korean Delegates attended CBRC2005 / ISCBB2005, Visit MEXT	Tokyo, Japan
2006.5.22-24	AHeDD meeting (2nd)	Seoul, Republic of Korea
2007.4.16-19	AHeDD 2007 Symposium (3rd)	Shanghai, China
2008.2.2, 3.24	Virtual Lab. Preparing meeting	China /Republic of Korea
2008.10.16-17	AHeDD 2008 / IPAB 2008, Tokyo (4th)	Tokyo, Japan
2009.11.5-6	AHeDD 2009, Two sessions in CBI-KSBSB Joint Conference (5th)	Busan, Republic of Korea
2010.12.18	AHeDD 2010, Yonsei University (6th)	Seoul, Republic of Korea
2013.10.8-12	CMTPI-2013	Seoul, Republic of Korea
2014.11.11-12	AHeDD 2014 (7th)	Chengdu, China
2017.7.26-27	AHeDD 2017 (8th)	Melbourne, Australia
2018.9.26-29	AHeDD 2018 Symposium (9th)	Gangneung, Republic of Korea
2019.11.27-30	AHeDD 2019 / IPAB 2019 Joint Symposium (10th)	Kawasaki, Japan

IPAB History

Initiative for Parallel Bioinformatics（IPAB）

Initiative for Parallel Bioinformatics（IPAB）was founded in December 1999 and is a non-profit organization. IPAB was certified as a "certified NPO organization Initiative for Parallel Bioinformatics（IPAB）" on 7 November, 2003. IPAB is a group of individual researchers and private companies aiming at contributing to the research and industrialization of bioinformatics and biomedical computing, by means of state-of-the-art information technologies, like as parallel processing, Grid technology, machine learning, artificial intelligence, etc.

	Date	Title	Japanese Title
1st	2000.12.1	Toward Bioinformatics in 21st Century	21 世紀のバイオインフォマティクスに向けて
2nd	2001.11.30	Bioinformatics and Business Models of Post-Sequence Era in 21st Century	21 世紀のバイオインフォマティクスと ポストシーケンス時代のビジネスモデル
3rd	2002.11.29	Biogrid	バイオグリッドについて
4th	2003.11.28	Integration of Cellular Network Information	細胞ネットワーク情報の統合化
5th	2004.12.3	IPAB 5th Anniversary	IPAB 創立5周年記念
6th	2006.2.10	Exploring Potential of Bionanotechnology	バイオナノの可能性を探る
7th	2006.12.11	It is time for Bioinformatics!	今こそバイオインフォマティクス!
8th	2007.11.29	Next Generation Supercomputers and Bioinformatics	次世代スパコンとバイオインフォマティクス
9th	2008.10.16-17	AHeDD 2008 / IPAB 2008 Joint Symposium Novel Acceleration Technologies for Drug Discovery, Genome Analysis, and Clinical Informatics	IPAB2008 / AHeDD2008 合同シンポジウム 創薬・ゲノム・医療情報処理のアクセラレーション
10th	2009.11.27	IPAB 10th anniversary next 10 years - Big data in medicine and biology -	IPAB 創立10周年記念 これからの10年 ～医学・生物学の大量データ～
11th	2010.12.3	Advanced Biology Research opened by Supercomputing	スーパーコンピューティングが拓く先端的バイオ研究
12th	2011.12.9	Massively parallel supercomputer and biocomputing	超並列スパコンとバイオ計算
13th	2012.12.7	Drug discovery, Clinical Application and Big Data	創薬・医療とビッグデータ
14th	2013.12.6	Exascale Computing and Drug Discovery Open Innovation	エクサスケール・コンピューティングと 創薬オープンイノベーション
15th	2014.12.5	Infectious Diseases and Computer-Aided Drug Discovery	感染症とコンピュータ創薬
16th	2016.3.11	Biodata Analysis in IoT / Cloud era	IoT/ クラウド時代のバイオデータ解析
17th	2017.3.3	Machine Learning and Artificial Intelligence	機械学習と人工知能
18th	2019.11.27-29	AHeDD 2019 / IPAB 2019 Joint Symposium Trends in Artificial Intelligence and Molecular Simulation for Accelerating e-Drug Discovery	IT 創薬を加速する AI・シミュレーション技術の新潮流

Plenary Talk 1

(Chair: Yutaka Akiyama)

Constrained Peptides in Drug Discovery and Development
Various therapeutic applications offered by PeptiDream

Keiichi Masuya Ph.D.
Executive Vice President
PeptiDream Inc.

We have PDPS (Peptide Discovery Platform System) which is a revolutionary next-generation hit finding platform for peptide drug discovery, for the discovery and development of constrained peptides, small molecules, and peptide-drug conjugate (PDC) therapeutics.

Constrained peptides represent highly valuable chemical matter for using in biologically target validation, identifying hit itself, and also finding key pharmacophore for design of small molecules.
During recent 3 to 4 years, we have steadily expanded the area of utilizing “peptide binders and hits” for various therapeutic applications and also different purposes.

We actually have more than 100 project portfolio which includes peptide therapeutics, small molecule therapeutics, peptide-drug conjugate (PDC) therapeutics, such as BBB-penetrating carrier peptides, carrier-peptides for RI therapeutics, and so on.
This presentation will summarize our approaches with several recent key topics.

Keiichi Masuya, Ph.D.

PeptiDream Inc.

Executive Vice President

Keiichi Masuya obtained Ph.D. in 1998 (Tokyo Institute of Technology), and Research Fellowship of the Japan Society for the Promotion of Science for Young Scientists (1995-1998). From 1998-2001, he worked at Mitsubishi Pharma.

He joined Novartis Pharma Japan in 2001, received an oncology President Award in 2004, then moved to Basel Headquarters of Novartis Pharma in 2005.

He received a VIVA award as a Novartis leading scientist in 2012. He managed several development compounds in the field of oncology.

He joined PeptiDream Inc. in 2014, currently as Executive Vice President and Board Member, and also Executive Officer/Chief Science Advisor in PeptiStar Inc.

Plenary Talk 2

(Chair: Takatsugu Hirokawa)

Perspectives of computational drug discovery: AMED-BINDS activities in Japan

Shigenori Tanaka*
Kobe University, Japan
*tanaka2@kobe-u.ac.jp

The BINDS (Basis for Supporting Innovative Drug Discovery and Life Science Research) program of AMED (Japan Agency for Medical Research and Development) has been running since April 2017. The objective of this program is to establish an innovative platform to expedite the therapeutic applications of early-stage drug discovery and medical technology advances by providing and sharing key technological infrastructure, including: synchrotron facilities at SPring-8 and the Photon Factory, cyro-electron microscopes (EMs), chemical compound libraries, and next-generation DNA sequencers. Specialists in state-of-the art technologies in the fields of structural biology, protein production, high-throughput screening of chemical compounds, lead compound structural modifications and extensions, genome analysis, and *in-silico* screening, will support and assist the life science and drug development projects of researchers who submit their proposals to members of the BINDS program.

The *in-silico* analysis unit of BINDS contains nine research groups and its mission includes: (1) Supports on (a) predictions of 3D structure of protein, PPI (protein-protein interaction) and ligand binding mode, (b) structural informatics for virtual screening, and (c) various chemoinformatics techniques; (2) Supports for protein dynamics studies based on integrated structural analyses by X-ray crystallography, NMR, SAX, XFEL and cryo-EM; (3) Promotion and facilitation of developed tools and databases for the availability for researchers (in collaboration with the platform optimization unit of BINDS); (4) Improvement and expansion of tools and facilities for more efficient supports.

In this talk, in addition to recent activities of the *in-silico* analysis unit of BINDS, I will illustrate my own research activities on computational drug discovery mainly on the basis of quantum chemistry, molecular dynamics and machine learning. Through all these presentations, I would like to show some perspectives on the future of *in-silico* drug discovery technology as an essential part in multi-disciplinary innovative collaborations.

Shigenori Tanaka, Ph.D.

Department of Computational Science
Graduate School of System Informatics
Kobe University

Professor

Shigenori Tanaka received his PhD in theoretical physics in 1986 from the University of Tokyo. He worked as a research associate at the University of Tokyo, and later as a researcher at the Toshiba Research and Development Center. Meanwhile, he worked at the California Institute of Technology in 1995~~-~~1996 as a visiting researcher. Since 2004, he has been a professor at Kobe University.

He was also a project leader for JST-CREST "Development of biomolecular calculation software on the basis of the fragment molecular orbital method" in 2004-2010 and is currently a program officer of *in-silico* analysis unit of AMED-BINDS. His primary research interests are the development of first-principles computational methods for biomolecular systems and their applications for bottom-up modeling of biological phenomena.

Session 1

Chemoinformatics and ADMET prediction

(Chairs: Liu Hong, and Kyong Tai No)

In Silico ADMET Prediction and Optimization

Yun Tang*

Shanghai Key Laboratory of New Drug Design, School of Pharmacy, East China University of Science and Technology, 130 Meilong Road, Shanghai 200237, China

*E-Mail: ytang234@ecust.edu.cn

Chemical ADMET properties play key roles in drug discovery and development, which accounts for about 40% of drug failures. Therefore, it is urgent to evaluate chemical ADMET properties as early as possible. However, experimental evaluation of ADMET properties is costly and time-consuming, so it is reasonable and practicable to develop *in silico* methods to predict chemical ADMET properties by fully taking advantage of big data and artificial intelligence technology.

In the past ten years, we have carried out a series of studies on ADMET prediction and optimization. (1) By mining and collecting data from literature and open source databases such as PubChem, we constructed ADMET related databases[1]; (2) built a large number of ADMET prediction models based on machine learning methods; (3) developed an ADMET optimization method, named ADMEToptopt, based on scaffold hopping methods[2]; (4) built a web server named admetSAR (http://lmmd.ecust.edu.cn/admetsar1/)[1], recently upgraded to version 2.0 (http://lmmd.ecust.edu.cn/admetsar2/)[3], which is widely used worldwide. Our goal is not only to predict ADMET properties at the lead discovery stage, but also to optimize ADMET properties during the lead optimization stage.

References

[1] Cheng F, Li W, Zhou Y, *et al*. admetSAR: a comprehensive source and free tool for assessment of chemical ADMET properties. *J. Chem. Inf. Model.*, 2012, 52(11): 3099-3105.

[2] Yang H, Sun L, Wang Z, *et al*. ADMEToptopt: a web server for ADMET optimization in drug design via scaffold hopping. *J. Chem. Inf. Model.*, 2018, 58(10): 2051-2056.

[3] Yang H, Lou C, Sun L, *et al*. admetSAR 2.0: web-service for prediction and optimization of chemical ADMET properties. *Bioinformatics*, 2019, 35(6): 1067-1069.

Systems Chemo-informatics and Fragment based Lead Discovery

Chulho Lee,[1,*] Doona Song,[1] Gyoonhee Han[1,2,*]

[1]*Department of Biotechnology, Yonsei University, Republic of Korea*

[2]*Department of Pharmacy, Yonsei University, Republic of Korea*

*gyoonheet@yonsei.ac.kr.

The drug discovery research in the post-genomic has been based on the discovery of novel and validated drug targets. This research trend allowed "target rich" environment but the actual drug discovery process has been suffered by "bottle neck" of the good drug candidates. Now a day, the chemistry side of drug discovery has been more concerned on the innovated drug discovery platform such as artificial intelligence (AI) The combined efforts of chemical biology and chemo-informatics have been more productive way for improving overall efficiency of the overall process. Systems chemo-informatics and fragment-based lead discovery of the biological targets for their chemical ligands may afford an efficient method for small molecule entity in many disease areas.

References

[1] Novel pendrin inhibitor attenuates airway hyperresponsiveness and mucin expression in experimental murine asthma. Journal of Allergy and Clinical Immunology, https://doi.org/10.1016/j.jaci.2019.07.016

[2] Control of leucine-dependent mTORC1 pathway through chemical intervention of leucyl-tRNA synthetase and RagD interaction. Nature Communications 2017, 732.

[3] Small-molecule binding of the axin RGS domain promotes β-catenin and Ras degradation. Nature Chemical Biology 2016, 12, 593-600.

Prediction of Membrane Permeability and Plasma Protein Binding of Cyclic Peptides

Satoshi Sugiyama, Jianan Li, Yuta Yamada, Shotaro Murata,
Yasushi Yoshikawa, Masahito Ohue, and Yutaka Akiyama*
Department of Computer Science, Tokyo Institute of Technology, Japan
*akiyama@c.titech.ac.jp

Cyclic peptide drugs are attracting broad attentions because of their higher target specificity and promising feasibility as PPI inhibitors. However, even though they can provide excellent target affinity, their tendency of lower membrane permeability and lower plasma protein binding (PPB) bring severe difficulties in terms of ADMET of the compound. Thus we have been developing computational methods to quickly predict membrane permeability and PPB of candidate cyclic peptides, in order to efficiently guide the whole peptide design process which are currently lead only by the experimental capacity of rapid peptide display system.

Our approach toward membrane permeability prediction is composed of several different elements: machine learning-based regression model with 2D chemical descriptors, 3D descriptors combined with intensive peptide conformation search, as well as full molecular dynamics (MD) simulation of membrane permeation phenomenon. Because membrane permeation occurs in milli-seconds and it is prohibitively long time for a straightforward MD simulation. We combine enhanced-sampling techniques and power of large-scale GPU clusters (Tokyo Tech's TSUBAME3.0 equipped with 2160 x P100 in total, and AIST's ABCI system equipped with 4352 x V100 GPUs in total). Membrane permeability can be directly calculated when its potential mean force profile is correctly obtained, or roughly estimated using sampled 3D conformations involved in the permeation steps based on our machine-learning model.

On the other hand, for the prediction of plasma protein binding (PPB), we mainly utilize machine learning techniques (random forest, SVR, deep learning, etc.). Our model works reasonably good for smaller cyclic peptides and now we are trying to expand its boundary to larger peptides. We have collected experimental PPB data for cyclic peptides, and also developed a technique to utilize the PPB data publicly available for small molecules [1].

References

[1] Tajimi T, Wakui N, Yanagisawa K, Yoshikawa Y, Ohue M, Akiyama Y. Computational prediction of plasma protein binding of cyclic peptides from small molecule experimental data using sparse modeling techniques, BMC Bioinformatics, 19(Suppl 19): 527, 2018.

A proteochemometric approach for beta-lactam antibiotic response prediction in *Staphylococcus aureus*

Jae Hong Shin,[1,*] DongJun Kim,[2] Mina Rho [2,*]

[1]*Standigm Inc., Korea*

[2]*Department of Computer Science, Hanyang University, Korea*

*jaehong.shin@standigm.com, *minarho@hanyang.ac.kr

Antibiotics resistance is becoming a great threat to human health in worldwide. To develop new antibiotics, every synthesized chemical compound is evaluated by antibiotic activity assay across resistance strains which is time consuming and laborious. Here, we attempt to build a proteochemometric model to predict beta-lactam antibiotics responses across *Staphylococcus aureus*. We first collected structures of beta-lactam and their antibiotic responses, and protein sequences of four different penicillin binding proteins (PBP1-4), which may be involved in beta-lactam resistance, from 18 strains of *S. aureus*. We then integrated structural information of beta-lactam with protein sequences. The compiled dataset consists of 210 samples including 118 beta-lactam structures and their antibiotic responses across 18 strains. The Random Forest models is employed to build a classification model with recursive feature selection since we generated very large features (p = 5165) including molecular descriptors representing beta-lactam structures and position specific mutations for PBP proteins of *S. aureus*. In results, we successfully built a model resulting in f1-score of 0.847 with the classification error of 16.2%. Our random forest model consists of 47 features including molecular descriptors and position specific mutations of penicillin binding proteins (PBP1-4). We also conducted a leave-one-out cross validation and it resulted in f1-score of 0.816 with the classification error of 19.0%. In addition to antibiotic response prediction, our model is able not only to capture important chemical features correlating to antibiotic responses but also important mutation positions in proteins which may help to understand protein structural mechanism of resistance.

References

[1] Darst BF, Malecki KC, Engelman CD. Using recursive feature elimination in random forest to account for correlated variables in high dimensional data. *BMC Genet*. 2018;19(Suppl 1):65. Published 2018 Sep 17. doi:10.1186/s12863-018-0633-8

[2] Ventola CL. The antibiotic resistance crisis: part 1: causes and threats. *P T*. 2015;40(4):277–283.

Session 2

Structures of Key Drug Targets
(Chairs: Takatsugu Hirokawa, and Yun Tang)

CryoEM analysis of the GPCR neurotensin receptor 1-G protein complex for the future engineering of biased allosteric modulator

Hideaki Kato*

The University of Tokyo, Japan

**hekato@bio.c.u-tokyo.ac.jp*

G protein-coupled receptor (GPCR) family is one of the largest membrane receptor protein families in human, and they are involved in almost every physiological process. About one-third of FDA-approved drugs target GPCRs and they represent very attractive drug targets[1]. The neurotensin receptor 1 (NTSR1) is one of such GPCRs involved in regulation of blood pressure, body temperature, weight, and response to pain. NTSR1 couples to multiple G-protein subtypes, but the molecular details of G-protein activation remain unknown. In this seminar, I will present 3Å structures of the human NTSR1 in complex with the heterotrimeric G_{i1} protein in two distinct conformations (C and NC state)[2]. While the C-state complex is similar to recently reported GPCR-$G_{i/o}$ complexes, the G protein in the NC state is rotated by ~45 degrees relative to the receptor. NTSR1 in the NC state exhibits features of both active and inactive conformations, suggesting that the structure represents an intermediate along the G-protein activation pathway. This structural information provides insights into the complex process of G-protein activation and paves the way for the future engineering of biased allosteric modulator to control the specific G protein and/or arrestin signaling pathway.

References

[1] Santos R *et al.* A comprehensive map of molecular drug targets, *Nat. Rev. Drug Discov.,* 16, 19-34, 2017.

[2] Kato HE *et al*. Conformational transitions of a neurotensin receptor 1-G_{i1} complex, *Nature*, 572, 80-85, 2019.

Discovery and Development of Novel CCR5 Antagonists

Jiang Wang, Huan Chen, Jian Li, Beili Wu, Yong-Tang Zheng*, Hualiang Jiang, Hong Liu*

[a]*State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zu Chong Zhi Road, Shanghai 201203, China*

[b]*Key Laboratory of Bioactive Peptides of Yunnan Province, Key Laboratory of Animal Models and Human Disease Mechanisms of Chinese Academy of Sciences, KIZ-CUHK Joint Laboratory of Bioresources and Molecular Research in Common Diseases, Kunming Institute of Zoology, Chinese Academy of Sciences, Kunming, Yunnan 650223, China*

*hliu@simm.ac.cn; zhengyt@mail.kiz.ac.cn

CC-chemokine receptor 5 (CCR5) is an attractive target for preventing the entry of human immunodeficiency virus 1 (HIV-1) into human host cells. Maraviroc is the only CCR5 antagonist, and it was marketed in 2007. To overcome the shortcomings of maraviroc, structure-based drug design was performed to minimize CYP450 inhibition and to enhance anti- HIV potency and bioavailability. A series of novel 1-heteroaryl-1,3-propanediamine derivatives were synthesized, displaying CCR5-antagonist activities in the 2.3−296.4 nM range. Among these, compounds 21 and 34 were the most potent CCR5 antagonists, with excellent in vitro anti-HIV-1 activity, low cytotoxicity, and an acceptable pharmacokinetic profile. Furthermore, the X-ray crystal structures of compounds 21 and 34 bound to CCR5 were determined at 2.8 Å resolution. Compound 34 exhibited no CYP450-inhibition activity, which overcomes the potential drug−drug interaction of maraviroc. Compound 34 represents a promising drug candidate for HIV-infection treatment.

Keywords: CCR5, antagonist, HIV-1, CYP450, drug candidate

References

[1] Tan, Q. X.; Zhu, Y.; Li, J.; Chen, Z. X.; Han, G. W.; Kufareva, I.; Li, T. T.; Ma, L. M.; Fenalti, G.; Li, J.; Zhang, W. R.; Xie, X.; Yang, H. Y.; Jiang, H. L.; Cherezov, V.; Liu, H.; Stevens, R. C.; Zhao, Q.; Wu, B. L. Structure of the CCR5 chemokine receptor-HIV entry inhibitor maraviroc complex. Science 2013, 341, 1387−1390.

[2] Walker, D. K.; Abel, S.; Comby, P.; Muirhead, G. J.; Nedderman, A. N.; Smith, D. A. Species differences in the disposition of the CCR5 antagonist, UK-427,857, a new potential treatment for HIV. Drug Metab. Dispos. 2005, 33, 587−595.

[3] Peng, P.; Chen, H.; Zhu, Y.; Wang, Z.; Li, J.; Luo, R.; Wang, J.; Chen, L.; Yang, L.; Jiang, H.; Xie, X.; Wu, B.;* Zheng, Y.;* Liu. H.* Structure-Based Design of 1-Heteroaryl-1,3-Propanediamine Derivatives as a Novel Series of CC-chemokine Receptor 5 (CCR5) Antagonists. J Med. Chem. 2018, 61, 9621−9636.

Molecular modeling study for identification of binding site of AIMP2-DX2 inhibitor

Yuno Lee,* Srigouri Huddar and Sunkyung Lee

Korea Research Institute of Chemical Technology, Daejeon 34114, Korea

*yunolee1@krict.re.kr

Alternative splicing variant of Aminoacyl-tRNA synthetase-interacting multifunctional protein2 (AIMP2) lacking exon2, AIMP2-DX2 (hereafter DX2), was identified as an oncogene differently from AIMP2 [1]. Recently, our collaborators have been found that inhibition of the protein-protein interaction between DX2 and HSP70 suppressed the DX2-mediated tumor progression [2]. Since structural understanding of target protein could be important to overcome huge obstacles in drug discovery, 3D structures of the proteins have been analyzed by experimental X-ray crystallography and NMR. But it is difficult to identify the disordered flexible region on many target proteins using traditional analysis tools. Due to the significance of this flexible region for protein function, many efforts are being devoted. DX2 also has a disordered flexible region in the N-terminal site, N-loop consisting of 50 amino acids. To study the binding mechanism of BC-DXI-inhibitor with DX2-N-loop, we performed molecular dynamics (MD) simulations. From the result of MD simulations, we found that BC-DXI-inhibitor binds to the pocket surrounded DX2-N-loop and GST-N domain, and the binding key residues were successfully proved by mutagenesis experiments. This MD study also suggested the inhibition mechanisms of BC-DXI-inhibitor, competitive interference to access of HSP70 and masking of HSP70 binding residues located in surface of DX2 by conformational change of DX2 induced by hydrophobic intramolecular interaction between DX2-N-loop and GST-N in bound state of BC-DXI-inhibitor.

References

[1] Choi JW, Kim DG, Lee AE, Kim HR, Lee JY, *et al*. Cancer-Associated Splicing Variant of Tumor Suppressor AIMP2/p38: Pathological Implication in Tumorigenesis. *PLOS Genetics*, 7(3), e1001351, 2011.

[2] Lim S, Cho HY, Kim DG, Roh Y, Son S, *et al*. Tumor-promoting interaction between heat shock protein 70 and AIMP2-DX2, *Nature Chemical Biology*, in revision.

Computer Aided Drug Discovery with Natural Compounds

Ji Young LEE[1], Sangwon LEE[1,2], Ayoung BAEK[1], Myungwon SEO[2], Kyoung Tai NO[1,2,*]

[1]*Bioinformatics and Molecular Design Research Center, Seoul Korea*

[2]*Department of Biotechnology, Yonsei University, Seoul Korea*

**ktno*@bmdrc.org

Natural products on Earth contain huge number of structurally diverse compounds and most of the compounds are involved in the physiological activity of living organisms. For this reason, many drugs have been developed from natural compounds or chemically modified natural compounds. It has been studied by many researchers for a long time to find natural compounds with physiological activity, but the traditional natural product research strategy is low in R&D efficiency due to the need for much time and labor intensity.

To overcome the shortcoming of the natural product research, BMDRC working on two projects, 1) on developing a (MS / MS big data)-(High precision MS / MS spectrometer)-(ANN based Artificial Intelligent) fusion system that determines the structure of the molecules involved in an extract without separating each compound from the extract, 2) among the 300,000 known natural compounds, 3000 representative compounds with structural representativeness and high drug-like structure (both rule of five & rule of four) compounds were selected and construct NP3000 library. By combining 1) & 2), we will construct natural product research platform, Flora Genesis system.

This presentation, we will introduce the progress of the Flora Genesis system construction and will show some of research results performed with currently built system though there are still a lot to be developed and added to the system.

Session 3

Artificial Intelligence for Drug Discovery
(Chairs: Weiliang Zhu, and Gyoonhee Han)

Drug discovery with artificial intelligence: advances and challenges

Xin Yang, Yifei Wang, Shengyong Yang*

State Key Laboratory of Biotherapy and Cancer Center, West China Hospital,
Sichuan University, Chengdu, Sichuan 610041, China

*yangsy@scu.edu.cn

The research and development (R&D) cycle for innovative small-molecule drugs faces many challenges, such as high cost-to-market, limited success in clinical trials, and long cycle times. The productivity of drug R&D in the pharmaceutical industry remains on the decline, despite record expenditures. Courses leading to this situation might be complicated. However, the complexity of drug R&D could be one of the key reasons. Artificial intelligence (AI) provides opportunities for dealing with this kind of complex task. AI, specifically, deep learning, has made great progress in the past years, and has been successfully applied in areas such as image and voice recognition, natural language processing, auto-driving, and intelligence game. AI has also been applied to the drug R&D. Nevertheless, the progress of AI's application in drug R&D is still slower than that in aforementioned areas. We will in this presentation make a summary to the history of AI, AI's application in drug R&D, and challenges of AI algorithms faced in drug–related studies. Several research works that have been done recently by us to improve the performance of AI algorithms in drug-related studies will be presented as well.

References

[1] Yang X, Wang Y, Byrne R, Schneider G, Yang S, Concepts of Artificial Intelligence for Computer-Assisted Drug Discovery. *Chem. Rev*. 119, 18, 10520-10594, 2019.

Multiple Approaches to Discover Human DDX3 Inhibitors for Cancer Therapeutics

Keun Woo Lee

Division of Applied Life Science (BK21 Program), Gyeongsang National University (GNU), 501 Jinju-daero, Gazha-dong, Jinju, 52828 Republic of Korea

E-mail: kwlee@gnu.ac.kr

DDX3 belongs to RNA helicase family that demonstrates oncogenic properties and has gained wider attention due to its role in cancer progression, proliferation and transformation. Mounting reports have evidenced the role of DDX3 in several cancers making it a promising target. In order to find out proper inhibitor against DDX3 we employed three different strategies: 1) traditional pharmacophore modeling and virtual screening, 2) butein modification, 3) *De novo* fragment designing. First, common feature pharmacophore and the receptor-based pharmacophore models were generated and subsequently validated and utilized as 3D queries to screen the InterBioScreen database. This resulted in one best compound, curcumin, that was escalated to molecular dynamics simulation studies and in vitro analysis was conducted on three cell lines such as MCF-7, MDA-MB-231 and HeLa, which were evaluated along with exemestane. Furthermore, via the 2nd and 3rd approaches, additional seven compounds were computationally designed and synthesized.

The computationally retrieved compound was docked into the active site of the protein target (PBD code 2I4I) to estimate the binding affinity. The compound has interacted with two key residues and has displayed stable molecular dynamics simulation results. The obtained results illuminate the use of curcumin and the synthesized compounds can be adapted as alternative DDX3 inhibitors and can serve as a chemical scaffold to design new small molecules. Additionally, our results elucidate that the combinatorial treatments may show better results, paving way for new research avenues.

Recently we also challenge to develop smarter CADD system or server which is able to use AI or ML algorithms for better efficiency. With Korea Chemical Bank (KCB) data we are trying to build AI-based CADD server which can help basic drug design work for open users. The draft version will be introduced in the talk.

Visualizations within chemogenomic active learning reveal how protein descriptors are used and underlying truths about chemogenomic and single target QSAR model utility

J.B. Brown*

Kyoto University Graduate School of Medicine, Life Science Informatics Research Unit, Japan

*jbbrown@kuhp.kyoto-u.ac.jp

Despite the concept of active learning for drug discovery being published in 2003 [1], it was not until only a few years ago that large-scale databases of chemogenomic databases became available, and at AHeDD 2017 and 2018, I presented our work in the applications of active learning for chemogenomic-based drug discovery, where it has become clear that a careful selection of a reduced number of ligand-target pairs approaches the same predictive performance as if one had used all available data for estimator (model) building [2]. Asymptotic performance holds regardless of whether the active learning is retrospective (selection and prediction on the full dataset) or semi-prospective (withheld data that will not be available for selection and model building) [3].

Recently, our group further pushed to further clarify the domain of applicability of active learning by executing a semi-prospective study in which compounds classified as non-probes were used to extract patterns and predict bioactivity on probes classified as chemical probes (specificity, potency). We particularly focused on the role of protein target descriptors, starting with a biologically meaningless baseline identity descriptor and comparison to improvements obtained with amino acid subsequence frequency descriptors. The key question, ***how*** the improvement was achieved, was investigated and has refined expectations for machine learning in drug discovery [4]. In this talk, I will discuss these findings and how they impact the philosophy by which we approach e-drug discovery.

References

[1] Warmuth, M.K. et al., 2003. J. Chem. Inf. Comput. Sci. 43, 667–673.

[2] Reker, D. et al., 2017. Future Med. Chem. 9, 381–402.

[3] Rakers, C. et al., 2018. ChemMedChem. 13, 511-521.

[4] Polash, A.H. et al., 2019. Molecules 24, 2716.

Bioinformatics-Facilitated Therapeutic Target Discovery

Prof. Feng ZHU*

College of Pharmaceutical Sciences, Zhejiang University, China

*zhufeng@zju.edu.cn

With the advent of the era of bioinformatics and artificial intelligence (AI), the bioinformatics-facilitated drug discovery (especially the discovery of novel therapeutic target) has attracted great interest from the researchers. In this report, I would like to introduce the most recent advances in my lab (Lab of Innovative Drug Research and Bioinformatics), which included: (1) the target big data and the construction of deep learning algorithm, and (2) the development of the target identification methods based on multiple OMICs data. Welcome to visit our website at: https://idrblab.org/

References

[1] Yin J, Sun W, Li F, …, Zeng S*, Yu L*, **Zhu F***. VARIDT 1.0: variability of drug transporter database. *Nucleic Acids Res*, doi: 10.1093/nar/gkz779, 2019.

[2] Wang Y, Zhang S, Li F, …, Chen Y*, **Zhu F***. Therapeutic target database 2020: enriched resource for facilitating research and early development of targeted therapeutics. *Nucleic Acids Res*, doi: 10.1093/nar/gkz981, 2019.

[3] Yang Q, …, Qiu Y*, **Zhu F***. Consistent gene signature of schizophrenia identified by a novel feature selection strategy from comprehensive sets of transcriptomic data. *Brief Bioinform*, doi: 10.1093/bib/bbz049, 2019.

[4] Tang J, Fu J, Wang Y, …, **Zhu F***. Simultaneous improvement in the precision, accuracy and robustness of label-free proteome quantification by optimizing data manipulation chains. *Mol Cell Proteomics*, 18, 1683-1699, 2019.

[5] **Zhu F***, …, Chen Y*. Clinical success of drug targets prospectively predicted by in-silico study. *Trends Pharmacol Sci*, 39, 229-231, 2018.

[6] Li B, Tang J, Yang Q, …, **Zhu F***. NOREVA: normalization and evaluation of MS-based metabolomics data. *Nucleic Acids Res*, 45, 162-170, 2017.

Session 4

High-Performance Molecular Simulation
(Chairs: Keun Woo Lee, and Shengyong Yang)

Development of the rapid QM/MM molecular dynamics techniques aimed at medium molecular drug discovery

Hiroaki Nishizawa

Center for Computational Sciences, University of Tsukuba

nisizawa@ccs.tsukuba.ac.jp

Molecular dynamics (MD) has been employed for investigating the properties of biomolecular systems. In several cases, MD simulations are performed by the molecular mechanical (MM) approach because a long time step is required for obtaining sufficient sampling. However, the MM approach cannot accurately describe a biomolecular system including a metal ion because the interaction parameters do not change during MM simulations. On the other hand, metal ions play a crucial role in the living body. For example, amyloid fibrils of amyloid-β (Aβ) peptides cause Alzheimer's disease. During the initial formation of the amyloid fibrils, metal ions form coordinate bonds with the Aβ peptides and precipitate the aggregation of Aβ peptides. A quantum mechanical/molecular mechanical (QM/MM) approach based on the density-functional tight-binding (DFTB) theory[1] is a useful tool for analyzing such a chemical reaction system in detail. However, since the computational cost of the DFTB calculation is proportional to the cube of the system size, the number of atoms for QM region is limited to small. In this study, an efficient DFTB method by the combination of the DFTB method with the divide-and-conquer (DC) method is developed[2] aimed at MD simulation for medium-size molecules. For assessing the performance of this method, the computational cost and energy deviations are investigated for simple molecules. Furthermore, DFTB/MM-MD simulations are conducted for a system consisting of two Aβ peptides and a zinc ion in explicit water.

References

[1] Elstner M, Porezag D, Jungnickel G, Elsner J, *et al*. Self-consistent-charge density-functional tight-binding method for simulations of complex materials properties, *Phys. Rev. B*, 58, 7260–7268, 1998.

[2] Nishizawa H, Nishimura Y, Kobayashi M, Irle S, Nakai H, Three pillars for achieving quantum mechanical molecular dynamics simulations of huge systems: Divide-and-conquer, density-functional tight-binding, and massively parallel computation, *J. Comput. Chem.*, 37, 1983–1992, 2016.

New Method for Highly Efficient MD Simulation

Cheng Peng, Jinan Wang, Zhijian Xu, Weiliang Zhu*

Shanghai Institute of Materia Medica, Chinese Academy of Science, Shanghai 201203, China

* wlzhu@simm.ac.cn

Not only appropriate structural conformation, but also dynamic properties are important for understanding proteins' function. Although the number of experimentally determined protein structures is rapidly increased in PDB, it is still a great challenge to obtain dynamic properties of proteins by experimental protocol. Replica exchange molecular dynamics (REMD) simulation is a popular enhanced sampling method, which is widely used for exploring atomic mechanism of protein conformational change. However, REMD requires huge computational resources, largely limiting its application. In this talk, I will show you the methods we developed for improving the availability and efficiency of a variant of REMD, namely vsREMD and its application on adenylate kinase (AdK) as an example. While vsREMD required less than 40% of the replicas for conventional REMD, it achieved consistent results with that from conventional REMD and experimental studies. Thus, vsREMD is able to characterize protein conformational change and associated free energy profile for better understanding proteins' function.

Next Generation Accelerated Supercomputing: Cygnus System at University of Tsukuba

Taisuke Boku

Director, Center for Computational Sciences, University of Tsukuba

taisuke@ccs.tsukuba.ac.jp

HPC (High Performance Computing) is now one of the most important technologies to proceed any scientific field including drug discovery. The traditional supercomputing facilities have been contributing to the scientific calculations which require very high performance of floating point computation. With such a background, today's world leading supercomputers are equipped with GPU (Graphics Processing Unit) beside of ordinary CPU (Central Processing Unit). Actually, about half of the systems in TOP-10 machines in the world are the large cluster systems with tens of thousands of GPUs.

However, the request for new fields of scientific computation such as deep learning is much more complicated where the traditional simple computing power cannot cover it. One of the big change in the processor architecture is the change of floating point precision, FP16 (16-bit half precision floating point) for example. Although new generation of GPUs and CPUs are supporting such a request nowdays, we need more aggressive challenge for new system architecture not only for high performance but also for high performance per energy consumption.

In our Center for Computational Sciences, University of Tsukuba, we have been researching the original technologies toward next generation accelerating supercomputing. GPU is still the main player for it, but we need to consider wider variety and possibility of other kind of accelerators. One of the key technologies for processor architecture recently focused is FPGA (Field Programmable Gate Array) where the logic circuit itself can be programmed by some specific hardware description language according to the algorithm of target application. We are building a new method to combine GPU and FPGA together in a single system to compensate the weak point of GPU to be covered by the flexibility of FPGA toward complicated algorithms and problems. As the practical testbed for this challenge, our center introduced the world first cluster combing GPU and FPGA technologies for advanced scientific research. In this talk, I will introduce such a new concept of supercomputing with system development and applications toward next generation accelerated supercomputing.

In silico Drug Discovery using Molecular Modeling and Simulation

Takatsugu Hirokawa[1,2,*]

[1]*Molecular Profiling Research Center for Drug Discovery, National Institutes of Advanced Industrial Science and Technology, Tokyo, Japan*

[2]*Department of Chemical Biology, Faculty of Medicine, University of Tsukuba, Ibaraki, Japan*

*t-hirokawa@aist.go.jp

With the development of increasing number of genome sequence data and protein structure determination, pharmacological and drug discovery research based on the structural biology data have been accelerated. However, some of experimental structural data may be inconvenient to use for drug discovery due to the constraints on crystallization conditions or undesirable biological state. Molecular modeling and simulation can help to bridge the gap between original state of experimental structural data and drug discovery oriented structural models. Structural models from the collaboration between the experimental data and in silico technology will be useful to guide sophisticated drug discovery process. In some collaboration projects, we proposed the supporting and developing of in silico drug discovery using molecular modeling and simulation based on fundamental technologies such as homology modeling, docking simulation and molecular dynamics (MD) simulation [1-3]. Our goal is to achieve in silico drug discovery technology having high practicability for translational research in relationships between pharmaceutical industry and academia.

References

[1] Shiba-Ishii A, *et al.* Stratifin Inhibits SCF(FBW7) Formation and Blocks Ubiquitination of Oncoproteins during the Course of Lung Adenocarcinogenesis. *Clin Cancer Res.* 2019 May 1;25(9):2809-2820.

[2] Toyoda Y, *et al.* Ligand binding to human prostaglandin E receptor EP(4) at the lipid-bilayer interface. *Nat Chem Biol.* 2019 Jan;15(1):18-26.

[3] Asamitsu K, *et al*. MD simulation of the Tat/Cyclin T1/CDK9 complex revealing the hidden catalytic cavity within the CDK9 molecule upon Tat binding. *PLoS One.* 2017 Feb 8;12(2):e0171727.

Flash Talk Session

Presentations by Young Researchers in Asia-Pacific Regions

(Chair: Masahito Ohue)

Systematic construction of the cosolvents sets for cosolvent MD (CMD) with the large-scale simulation

Keisuke Yanagisawa,[1] Yoshitaka Moriwaki,[1] Tohru Terada,[2,3] Kentaro Shimizu[1,2,*]

[1] *Department of Biotechnology, Graduate School of Agricultural and Life Sciences, The University of Tokyo, Japan*

[2] *Interfaculty Initiative in Information Studies, The University of Tokyo, Japan*

[3] *Agricultural Bioinformatics Research Unit, Graduate School of Agricultural and Life Sciences, The University of Tokyo, Japan*

*shimizu@bi.a.u-tokyo.ac.jp

Cosolvent MD (CMD) is an MD simulation of a protein in explicit water molecules mixed with cosolvent molecules. The simulation has been used for hotspot detection [1,2], binding site identification [3] and binding energy estimation [3]. Existing methods (i.e. MixMD [1,2], SILCS [3], and MDmix [4]) utilize small molecules which represent functional groups of compounds, such as isopropanol and benzene; however, different sets of cosolvents were used in these studies and no guidelines have been proposed for the selection of the cosolvents except for use of the functional groups. Thus we aimed to propose a method to construct a set of cosolvents in a rational way.

In the present study, we extracted typical substructures from FDA approved drugs and generated > 130 cosolvent structures. For each cosolvent molecule, we conducted 10-ns CMD simulations 20 times to generate a spatial probability distribution map of cosolvent atoms (Pmap). After that, the relationships between the cosolvents were visualized based on the similarity between the Pmaps. We found a cosolvent pair with the Pmap similarity greater than 0.75 tended to share similar structural features. Using the Pmap similarity, we performed a K-means clustering on the cosolvents. Instead of using the centroids, we selected a representative from each cluster so as to maximize the worst similarity between the representative and any member in the cluster. When we set $K = 15$, every cosolvent had > 0.75 similarity to one of the representatives.

References

[1] P Ghanakota *et al*., *J Chem Inf Model*, 58, 784−793, 2018.

[2] PMU Ung *et al*., *Biopolymers*, 105, 21−34, 2016.

[3] VD Ustach *et al*., *J Chem Inf Model*, 59, 3018−3035, 2019.

[4] D Alvarez-Garcia & X Barril, *J Med Chem*, 57, 8530−8539, 2014.

Investigation of protein-protein interactions and hot spot region between PD-1 and PD-L1 by fragment molecular orbital method

Hocheol Lim,[1,2,*] Jongwan Kim,[1,2] Jiaxin Liu,[1] Kyoung Tai No[2,*]

[1]*Department of Biotechnology, Yonsei University, Seoul, Republic of Korea*

[2]*Bioinformatics and Molecular Design Research Center (BMDRC), Yonsei University, Seoul, Republic of Korea*

*ihc0213@yonsei.ac.kr

Inhibitors to interfere protein-protein interactions (PPI) between programmed cell death 1 (PD-1) and programmed death ligand-1 (PD-L1) block evasion of cancers from immune surveillance. Analyzing hot spot residues in PPI is important for small-molecule drug development. In order to find out hot spots on PPI interface in PD-1/PD-L1 complex, we analyzed PPI in PD-1/PD-L1 with a new analysis method, 3-dimensional scattered pair interactions energies (3D-SPIEs), which assorts significant interactions with fragment molecular orbital (FMO) method. By additionally analyzing PPI in PD-1/antibody and PD-L1/antibody complexes, and small-ligand interactions in PD-L1/peptide and PD-L1/small-molecule complexes, we narrowed down the hot spot region with 3D-SPIEs-based interaction map, which integrates PPI and small-ligand interactions. Based on the map, there are two hot spot regions in PPI of PD-1/PD-L1 and the first hot spot region is important for inhibitors. In particular, Y56, E58, and N66 in the first hot spot of PD-L1 are important for PD-L1-antibodies and small-inhibitors in common, while M115 is important for small-inhibitors. Therefore, the 3D-SPIEs-based map would provide valuable information for designing new small-molecule inhibitors to inhibit PPI of PD-1/PD-L1 and the FMO/3D-SPIEs method provides an effectual tool to understand PPI and integrate PPI and small-ligand interactions at a quantum mechanical level.

Metagenome analysis implies bacterial community and gene category composition disorder in periodontal disease sites

Kazuki Izawa [1, *], Kazuko Shibayama [2], Masahito Ohue [1],
Kazuyuki Ishihara [2], Yutaka Akiyama [1]

[1] *Department of Computer Science, School of Computing, Tokyo Institute of Technology, Japan*

[2] *Microbiology, Department of Basic Science, Tokyo Dental College, Japan*

* *izawa@bi.c.titech.ac.jp*

Periodontal disease is a complex infection caused by various bacteria accumulated in gingival sulcus as plaque. In previous study, some bacterial species are considered as the causative because they are isolated from periodontal disease sites [1]. However, recent metagenomic approach reveals that the causatives are resident bacteria. Therefore, periodontal disease now considered that it caused by dysbiosis in plaque [2].

In this study, to reveal the differences in bacterial community and gene category composition between periodontal disease site and healthy site in Japanese, we sampled 28 plaques including healthy and disease sites from 5 healthy and 14 affected persons. The sequences from plaque samples were aligned to 16S rRNA database distributed by NCBI with BLAST and KEGG genes database with GHOSTZ-GPU [3] for bacterial community and gene category composition analysis, respectively. These alignment results were post-processed by MEGAN and HUMAnN, and the composition data were subjected to the multivariate analysis.

The multivariate analysis suggests several taxonomic and gene category features and PERMANOVA implies these features represent the states of sites ($p < 0.05$). This result suggests that suggested features are useful to early detection and risk evaluation of periodontal disease.

References

[1] Socransky SS, Haffajee AD. Dental biofilms: difficult therapeutic targets, *Periodontol 2000*, 28, 12-55, 2002.

[2] Honda K, Littman DR. The microbiome in infectious disease and inflammation, *Annu Rev Immunol.* 30, 759-795, 2012.

[3] Shuji Suzuki, Masanori Kakuta, Takashi Ishida, Yutaka Akiyama. GPU-Acceleration of Sequence Homology Searches with Database Subsequence Clustering, *PLoS ONE*, 11(8): e0157338, 2016.

In silico drug discovery targeting Hippo pathway and YAP-TEAD Protein Protein Interactions for small molecules anti cancer agent

Kim, Jongwan ,[1,2*] No, KT[1,2]

[1]*Computational Systems Biology Lab.,Department of Biotechnology, Yonsei University, Seoul, Republic of Korea*

[2]*Bioinformatics and Molecular Design Research Center, Yonsei Engineering Research Park,Seoul, Republic of Korea*

Hippo pathway is one of important pathways regulating tissue growth and proliferation. Dysregulation on this pathway can result in overgrowth of phenotypes because of a malfunction of stem cell proliferation, differentiation and apoptosis, which are directly involved with components to cancer cell developments. Protein-Protein interaction (PPI) in YAP (yes-associated protein) and TEAD (transcriptional enhancer associate domain) is a key interaction which regulate cancer cell growth in hippo pathway. Regulating YAP-TEAD Protein-Protein interaction by small molecules could play an important role in cancer therapy. In this study, we identified small molecules inhibiting YAP-TEAD interactions by in silico approach. Molecular hits were identified by pharmacophore based virtual screening. The hit compounds from virtual screening were tested by surface plasmon resonance(SPR), Luciferase activity test. As a result, several hit compounds were identified to inhibit YAP-TEAD protein-protein interactions. These selected hit compounds also evaluated by molecular docking study, and FMO(Fragment Molecular Orbital) binding energy calculations. Overall results, we identified hit compounds to inhibit YAP-TEAD PPIs, and also analyzed hit compound's binding interaction energy to TEAD Protein.

Discovery of Leucyl-tRNA Synthetase (LRS) PPi inhibitor for modulating mTORC1 pathway via the chemical biology approach

Chulho Lee,[1,2,*] Doona Song,[1,2] Gyoonhee Han[1,2,*]

[1]*Department of Integrated OMICS for Biomedical Science, Yonsei University, South Korea.*

[2]*Translational Research Center for Protein Function Control, Department of Biotechnology, Yonsei University, South Korea.*

*chulho.l41@yonsei.ac.kr, gyoonhee@yonsei.ac.kr

In the early stage of drug discovery, various computational methods such as in silico hit prioritization and virtual screening, as well as chemical and biological information helped to shorten the discovering process from hit to lead. Leucyl-tRNA synthetase (LRS) is known as a leucine sensor for modulation of mTORC1 pathway. We exhibited the leucine sensing function of LRS for mTOR activation could be decoupled from its catalytic activity. Based on these research background, we discovered Leucyl-tRNA synthetase (LRS) PPI inhibitors that modulate the mTORC1 signaling pathway. The lead compound was successfully discovered via optimization using pharmacophore generated from the active screened compounds, and the mechanisms of action (MoA) was proved with active chemical by chemical biology approach.

References

[1] Kim JH, et al. Control of leucine-dependent mTORC1 pathway through chemical intervention of leucyl-tRNA synthetase and RagD interaction. *Nat Commun,* 8, 732, 2017.

Novel computational approach for natural product (NP) research: development of natural compound molecular fingerprint (NC-MFP) for exploring new NP-based drugs

Myungwon Seo,[1, *] Hyun Kil Shin,[3] Yoochan Myung,[4] Sungbo Hwang,[1, 2] Kyong Tai No[1, 2, **]

[1]*Department of Biotechnology, College of Life Science and Biotechnology, Yonsei University, Seoul, Republic of Korea*

[2]*Bioinformatics and Molecular Design Research Center, Yonsei Engineering Research Park, Seoul, Republic of Korea*

[3]*Department of Predictive Toxicology, Korea Institute of Toxicology, Daejeon, Republic of Korea*

[4]*Department of Biochemistry and Molecular Biology, Bio21 Institute, University of Melbourne, Melbourne, Victoria 3010, Australia*

*seomyungwon@gmail.com

**ktno@bmdrc.org

A natural compound (NC) produced by a living organism.[1] Since many of new drugs candidates are analogous to or derived from the NCs[2], computer-aided research on the relationship between the NPs and their biological activities have been widely studied by describing the molecular structure. Since structure of NC has distinctive structural characteristics compared to synthetic compound[3], previously developed topological descriptors have limitation in expressing molecular structure of specific NC.

In this study, novel molecular fingerprint, called Natural Compound Molecular Fingerprints (NC-MFP) was developed for explaining NC structures related to biological activities. The NC-MFP consists of scaffolds, scaffold-fragment connection points (SFCP), and fragments. The scaffolds of NC-MFP constructed based on both the BM method and the classification system of Dictionary of Natural Product database (DNP). Two kinds of binary classification tasks were introduced for evaluation purpose. Task I is classifying NCs in commercial DB into NC or synthetic compound. Task II is classifying whether NCs with inhibitory activity in seven biological target proteins is active or inactive. In the result of tasks, NC-MFP outperformed compared with other molecular fingerprints. Therefore, NC-MFP is potent molecular descriptor for virtual screening of NC for NP-based new drugs development

References

[1] All natural. *Nat Chem Biol*, 2007. **3**(7): p. 351.

[2] Newman, D.J. and G.M. Cragg, Natural Products as Sources of New Drugs from 1981 to 2014. *J Nat Prod*, 2016. **79**(3): p. 629-61.

[3] Rodrigues, T., et al., Counting on natural products for drug design. *Nat Chem*, 2016. **8**(6): p. 531-41.

Predicting membrane permeability for cyclic peptides

Yasushi Yoshikawa,* Satoshi Sugiyama, Yuta Yamada, Shotaro Murata, Masahito Ohue, Yutaka Akiyama

Department of Computer Science, School of Computing, Tokyo Institute of Technology, Meguro-ku, Tokyo 152-8550, Japan.

*yoshikawa@c.titech.ac.jp

Following small molecule and antibody drugs, cyclic peptides are getting attention as one of the new drug modalities. It is considered that cyclic peptides can have high potency to the drug targets like antibody drugs and good pharmacokinetics properties like small molecule drugs. For that reason, cyclic peptides could be drugs which inhibit intracellular protein-protein interactions. However, there is a problem that most cyclic peptides are not membrane permeable with the exceptions such as cyclosporine A. “Chameleonic” properties have been proposed as membrane permeation mechanisms of cyclic peptides[1]. But research about the pharmacokinetics properties, including membrane permeability, has not progressed compared to that of small molecules. This is a major challenge for developing cyclic peptide drugs.

In order to address that problem, we are developing a method to predict passive membrane permeability of cyclic peptides by combining machine learning and molecular mechanics simulations. In this presentation, an overview of our effort will be introduced.

Reference

[1] Whitty, A. *et al.* Quantifying the chameleonic properties of macrocycles and other high-molecular-weight drugs. *Drug Discovery Today* **21**, 712–717 (2016).

Development of prediction model for onset of disease and risk factor analysis

Atsuyoshi Matsuda,[1,*] Hinako Toyama,[1] Kenji Araki,[2] Taisuke Ogawa,[2] Ryosuke Matsuo[2]
Kenichiro Shimai,[3] Atsushi Shibata,[4]
Yasuyuki Ohara,[1] Megumi Koshiba,[1] Yuji Naraki,[1] Yuki Sumiya,[1]

[1] *Logbii, Inc., Japan*

[2] *University of Miyazaki Hospital, Japan*

[3] *Chiba University Hospital, Japan*

[4] *Advanced Institute of Industrial Technology, Japan*

*atsuyoshi.matsuda@logbii.com

In recent years, doctors' hard work has become a problem in Japan, which can lead to missing signs of serious complications. If it is possible to predict complications, it will help doctors and improve patient outcomes. In former studies, prediction of complications in type 2 diabetes[1], and prediction of complications of pneumonia after cerebral hemorrhage[2] were researched. But there are few studies that analyze risk factors with machine learning analysis. We developed a prediction model based on machine learning for the onset of disease for the purpose of helping doctors and improving the prognosis of patients. We also analyzed how each risk factor affected the prediction. We used the data of patients admitted to University of Miyazaki Hospital.

References

[1] Tanaka S, Tanaka S, Iimuro S et al. Predicting Macro-and Microvascular Complications in Type 2 Diabetes: The Japan Diabetes Complications Study/the Japanese Elderly Diabetes Intervention Trial Risk Engine., Diabetes Care, 36, 1193-1199, 2013.

[2] Matsumoto K et al. Predicting the complication of pneumonia after cerebral hemorrhage by the level of consciousness at admission., Japan Association for Medical Informatics, 2018.

GCMQA: a novel single-protein structure model quality assessment method using graph convolution

Rin Sato,[1,2] Takashi Ishida[1,*]

[1]*Department of Computer Science, School of Computing, Tokyo Institute of Technology, 2-12-1 W8-76 Ookayama, Meguro-ku, Tokyo 152-8550, Japan*

[2]*AIST-Tokyo Tech Real World Big-Data Computation Open Innovation Laboratory (RWBC-OIL), National Institute of Advanced Industrial Science and Technology (AIST)*

*ishida@c.titech.ac.jp

Tertiary structure information of a drug-target protein is useful in drug discovery. However, experimental determination of a protein structure is a hard task and thus computational structure prediction methods from its amino acid sequence have been researched. Model quality assessment, which estimates the quality of predicted structure models for selecting the final prediction, is one of the most crucial processes in protein tertiary structure predictions. Most state-of-the-art single-model assessment methods use machine learning and residue-wise features [1]. In such features, interactions among residues are implicitly included as calculated interaction energy and local structure properties, such as the secondary structures. Thus, the interaction between residues is not directly used in the learning process.

To solve this problem, we proposed a novel single-mode quality assessment method that assesses local structure quality based on interaction among residues by using graph convolution neural networks [2]. We defined a graph of a protein structure whose node represents a residue and edge represents the interaction between residues. We trained a graph convolutional neural network for the graph to output the quality of local structure of a residue. We evaluated the performance of the proposed method and the proposed method showed a significant improvement compared with previous methods.

References

[1] Uziela K, Hurtado DM, Shu N, Wallner B, Elofsson A. ProQ3D: Improved model quality assessments using deep learning. Bioinformatics. 2017;33:1578–80.

[2] Fout A, Byrd J, Shariat B, Ben-Hur A. Protein Interface Prediction using Graph Convolutional Networks. In: Guyon I, Luxburg U V, Bengio S, Wallach H, Fergus R, Vishwanathan S, et al., editors. Advances in Neural Information Processing Systems 30.

Contest-based compound screening enables identification of chemically diverse inhibitors of target proteins

Shuntaro Chiba[1], Masakazu Sekijima[2]

[1]*RIKEN Medical Sciences Innovation Hub Program, Japan*

[2]*Department of Computer Science, School of Computing, Tokyo Institute of Technology, Japan*

shuntaro.chiba@riken.jp

At the early stages of drug discovery, there is a need to identify compounds with functional potency, such as inhibitory activity against a target protein. This could be achieved by utilizing computational approaches that can select potentially active compounds from a compound library containing a vast number of chemically diverse compounds; rather than resorting to high-throughput screening, which is challenging due to cost-effectiveness. The important aspect is deciding which method should be employed before conducting experimental assessment. Computational selecting methods are typically assessed retrospectively and are not compared under similar experimental conditions; thus, impeding the aforementioned decision. Hence, with an objective to assess various methods prospectively under identical experimental conditions; and to be able to identify active compounds against a target protein simultaneously, we conducted a series of compound proposal contests in 2014[1], 2015[2], and 2016[3], where participants were asked to propose potential actives from approximately two million compounds. In the first and second contests, approximately 60 and 180 compounds for each group, and in total 600 and 1991 compounds, respectively, were experimentally assessed. In both contests, cumulatively proposed compounds were found to be chemically diverse than was possible with the use of a single method. Further, especially in the second contest, we identified a statistically warranted prediction method from among 11 participating groups. More importantly, identified actives were chemically diverse as well.

References

[1] Chiba S, Ikeda K, Ishida T, Gromiha MM, Taguchi Yh, Iwadate M, et al. Identification of potential inhibitors based on compound proposal contest: Tyrosine-protein kinase Yes as a target. *Sci Rep*, 5, 17209, 2015.

[2] Chiba S, Ishida T, Ikeda K, Mochizuki M, Teramoto R, Taguchi YH, et al. An iterative compound screening contest method for identifying target protein inhibitors using the tyrosine-protein kinase Yes. Sci Rep, 7, 12038, 2017.

[3] Chiba S et al., manuscript submitted.

Underestimated Noncovalent Interactions in Protein Data Bank

Zhijian Xu,* Weiliang Zhu*

CAS Key Laboratory of Receptor Research, Drug Discovery and Design Center, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, 201203, China

*zjxu@simm.ac.cn, wlzhu@simm.ac.cn

Noncovalent interactions (NCIs) play essential roles in the structure and function of biomacromolecules. There are various NCIs, e.g., hydrogen bonds (HBs), halogen bonds (XBs), cation-π, π-π interactions, and ionic bonds. The distribution of experimental determined NCIs could be observed in protein data bank (PDB). The proportion of side-chain XBs to overall XBs decreases as structural resolution becomes lower and lower, indicating the underestimation of the XBs in PDB. With a systematic search in the PDB, we found that the HB number per residue in proteins decreases as structural resolution becomes lower, implying that HBs are overlooked even today, regardless of the type of refinement approach used. By utilizing the ratio of the observed HBs over pseudo HBs, we demonstrated that HBs in both protein-ligand and protein-protein interfaces are overlooked in structures deposited in PDB. After the QM/MM optimization of 12 protein-ligand complexes, we showed that the overlooked HBs could be recovered. Similarly, cation-π, π-π and ionic interactions were found to be significantly lost, manifesting the universal underestimation of various NCIs. Considering the vital role of NCIs, it is important to recover the NCIs to facilitate drug design, to explore protein-protein interaction and to study protein structure and function.

References

[1] Xu, Z, Zhang, Q, Shi, J, Zhu, W. Underestimated noncovalent interactions in protein data bank. *J. Chem. Inf. Model*, 59, 3389-3399, 2019

[2] Zhang, Q, Xu, Z, Zhu, W. The underestimated halogen bonds forming with protein side chains in drug discovery and design. *J. Chem. Inf. Model*, 57, 22-26, 2017

[3] Zhang, Q, Xu, Z, Shi, J, Zhu, W. Underestimated halogen bonds forming with protein backbone in protein data bank. *J. Chem. Inf. Model*, 57, 1529-1534, 2017

Evaluation of a Self-Balanced Force Field for Biomolecule Simulations

Sung Bo Hwang,[1] Kyoung Tai No[1,2,*]

[1]*Yonsei University, Department of Biotechnology, Republic of Korea*

[2]*Bioinformatics & Molecular Design Research Center, Republic of Korea*

*ktno@yonsei.ac.kr

The self-balanced force field (SBFF) proposed herein is the result of over 25 years of work and was developed by integrating a set of potential energy function in which each term in an intermolecular potential energy function is derived based on experimental values, such as the dipole moments, lattice energy, proton transfer energy, and X-ray crystal structures. The term, "self-balanced", is used to emphasize the idea that the experimental observables that are considered to be the most relevant to each term are used for the parameterization, rather than parameterizing all observables together against the target value. We evaluated the SBFF in three ways. First, the conformational energy differences of 18 organic compounds were examined because we adapted MM3[1] to describe the intramolecular interactions. Second, a molecular docking simulation was conducted to determine the suitability in a biomolecule simulation to examine the capability of expressing an energy-stable structure of the biomolecules. Last, logP calculation was applied for 193 neutral peptides to show how well the SBFF combines with a generalized solvation free energy density model[2], which was specifically designed for the SBFF. Therefore, we concluded that the SBFF provides reliable information based on the structure in a biological system and interprets the biological phenomena accurately by providing more accurate evidence of the biological phenomena.

References

[1] Allinger NL, Yuh YH, Lii JH. Molecular mechanics. The MM3 force field for hydrocarbons. 1. *Journal of the American Chemical Society*, 111, 8551-8566, 1989.

[2] Lee SH, Cho K-H, No KT, *et al*. A generalized G-SFED continuum solvation free energy calculation model. *Proceedings of the National Academy of Sciences*, 110, E662, 2013.

[3] No KT. Grant JA. Scheraga, HA. Determination of net atomic charges using a modified partial equalization of orbital electronegativity method. 1. Application to neutral molecules as models for polypeptides. *The Journal of Physical Chemistry*, 94, 4732-4739, 1990.

Application of informatics approaches to compound library design for intractable target chemical spaces

Kazuyoshi Ikeda,* Yugo Shimizu, Bao Yu, Masanori Osawa

Keio University, Faculty of Pharmacy, Division of Physics for Life Functions, Japan

*ikeda-kz@pha.keio.ac.jp

In recent years, artificial intelligence (AI) represented by deep learning has been applied to biochemistry and drug discovery. To improve the accuracy of prediction models using the AI technologies, quality and quantity of data are required.

Protein-protein interactions (PPIs) are recognized as essential targets in recent drug discovery. Recently, screening data targeting PPIs have been registered [1] in drug discovery databases such as ChEMBL[2]. It also includes PPI inactive data (i.e., compounds that have been confirmed not to bind PPI). According to our analysis, the results of NIH screening campaigns, those with a hit rate exceeding 1% account for 17% of the total screening. However, there are few screenings with a hit rate exceeding 1% when targeting PPI (less than 1% in the total). That is, the hit rate of screenings for the PPI targets using the conventional compound library is considerably low.

Our group (Keio University) is now developing an in-silico platform to design various chemical libraries such as HTS diversity library, focused-library as well as core-library. So far, we developed a relational database of chemical libraries for designing PPI inhibitors. This research would uncover the role of data-resources to supply new compound information to drug-targets with limited data volumes such as PPI. Finally, we would discuss how important is data science for AI drug discovery.

References

[1] Morelli X, Bourgeas R, Roche P., Curr Opin Chem Biol. 2011 Aug;15(4):475-81.

[2] ChEMBL: https://www.ebi.ac.uk/chembl/

[3] PubChem: https://pubchem.ncbi.nlm.nih.gov/

Learning-to-rank for ligand-based virtual screening

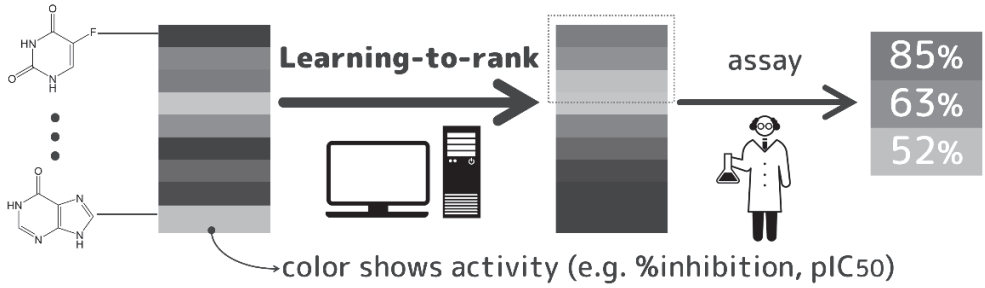
Masahito Ohue*, Shogo D. Suzuki, Yutaka Akiyama

Department of Computer Science, School of Computing, Tokyo Institute of Technology, Japan

* ohue@c.titech.ac.jp

Learning-to-rank (LTR) is a machine-learning method that is widely used for information retrieval and for learning the order relation between data. Activity values cannot be obtained directly; instead, the prediction result of a compound is obtained in the form of a list arranged according to the activity. The characteristics of LTR can be considered to fall between those of regression and binary classification. LTR is more robust against errors compared to regression, and higher accuracy can be expected when the ranking order is generated. After virtual screening, experiments with biochemical assays are generally performed for verification. However, the number of compounds that are selected for experimental verification is frequently limited in advance because of limited budgets, time, and experimental facilities. These problems can be overcome by employing LTR methods, which can rank compounds with high accuracy in descending order of possible activity, and which are suitable for virtual screening.

We developed two LTR methods for virtual screening [1][2]. PKRank [1] can use activity data of different targets for learning and is useful for finding hits of a target that have a lack of known ligands. SPDRank [2] uses a technique that ignores the ranking of similar activity ligands and is an effective method for learning from experimental values with large errors such as high-throughput screening.



References

[1] Suzuki SD, Ohue M, Akiyama Y. PKRank: A novel learning-to-rank method for ligand-based virtual screening using pairwise kernel and RankSVM, *Artif Life Robt ics*, 23(2): 205-212, 2018.

[2] Ohue M, Suzuki SD, Akiyama Y. Learning-to-rank technique based on ignoring meaningless ranking orders between compounds, *J Mol Graph Model*, 92:192-200, 2019.

AMED BINDS Project Special Sessions

In silico drug discovery based on structural informatics and FMO method

Teruki Honma*

RIKEN Center for Biosystems Dynamics Research, Japan

*honma.teruki@riken.jp

To accelerate biological study and drug discovery, the aim of our laboratory is developing new technologies for in silico screening of biological tools and drug candidates. Our basic concept is the integration of both informatics (statistical analysis, artificial intelligence (AI), etc.) and molecular modeling theories (molecular dynamics (MD) simulation, quantum mechanics (QM), etc.) to design promising drug candidatess. PALLAS, MUSES, LAILAPS, and FMO-PBSA[1] as well as AI -based ADMET prediction models were developed for the efficient in silico screening based on the concept. Recently, the world first quantum mechanics calculation database for protein systems named FMO-DB[2] has been released. In this session, the outline of the technologies raised above and examples applied to drug discovery will be introduced.

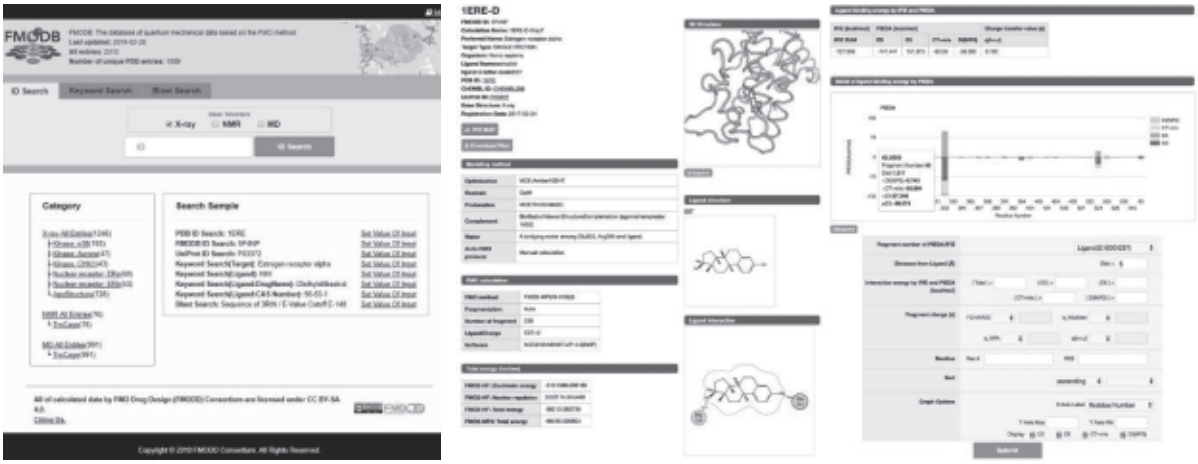


Figure. Web interface and detailed FMO calculation data pages

References

[1] Watanabe C, *et al*. Theoretical Analysis of Activity Cliffs among Benzofuranone Class Pim1 Inhibitors Using the Fragment Molecular Orbital Method with Molecular Mechanics Poisson-Boltzmann Surface Area (FMO+MM-PBSA) Approach. J Chem Inf Model, 57(12), 2996-3010, 2017.

[2] https://drugdesign.riken.jp/FMODB/

Molecular simulation studies on protein functions and improvement of the efficiency of cryo-EM data collection by machine learning

Tohru Terada,[1,2,*] Yuichi Yokoyama,[1] Yoshitaka Moriwaki,[2] Kentaro Shimizu[1,2]

[1]*Interfaculty Initiative in Information Studies, The University of Tokyo, Japan*

[2]*Graduate School of Agricultural and Life Sciences, The University of Tokyo, Japan*

[*]tterada@iu.a.u-tokyo.ac.jp

In the BINDS projects, we are conducting collaborative researches with experimental researchers to clarify protein function mechanisms. Among these researches, we will first talk about a molecular dynamics (MD) study of a multidrug transporter, MdfA [1]. MdfA is a H^+/drug antiporter working on the cell membrane of bacteria. When a proton binds to the protein, its conformation is changed from an outward-open conformation to an inward-open conformation. The proton is then released to the cytoplasm and a drug binds to the protein. As a result, the outward-open conformation is restored and the drugs is released to the periplasm. Since experiments have shown two acidic residues are important for the function, we performed MD simulations for the protein with one or both of the residues protonated. When a specific residue was protonated, the protein conformation was changed to an occluded conformation from both the inward-open and the outward-open conformations. Based on these results, we proposed a mechanism of the functional conformational change. We will next talk about a new method we have developed to facilitate the collaborative researches. Recent advances in cryo-electron microscopy (cryo-EM) have enabled protein structure determination at an atomic resolution. Cryo-EM specimens are prepared by rapidly freezing the protein solution on a metal grid coated with holey carbon film; this results in the formation of an ice film on each hole. The thickness of the ice film is a critical factor for high-resolution structure determination—ice that is too thick degrades the contrast of the protein image, while ice that is too thin excludes the protein from the hole. Thus, trained researchers have to manually select “good” regions with an appropriate ice thickness. To alleviate this time-consuming burden, we have developed a deep learning-based method to identify such “good” regions from low-magnification EM images.

Reference

[1] Nagarathinam K, *et al.* Outward open conformation of a Major Facilitator Superfamily multidrug/H^+ antiporter provides insights into switching mechanism” *Nat Commun,* 9, 4005, 2018.

Structural modeling of the entire *Eh*V-ATPase in multiple states using cryo-EM data and homology modeling

Yu Yamamori,[1*] Jun Tsunoda,[2,3] Ray Burton-Smith[3], Song Chihong[3], Ryota Iino[2,4], Kazuyoshi Murata[2,3], Kentaro Tomii[1]

[1]*National Institute of Advanced Industrial Science and Technology, AIST, Japan,* [2]*SOKENDAI, Japan*

[3]*National Institute of Physiological Science NIPS, Japan,* [4]*Institute of Molecular Science IMS, Japan*

*yu.yamamori@aist.go.jp

While many studies have focused on F-ATPase, the overall structure of V-ATPase in *Enterococcus hirae* (*Eh*V-ATPase) in addition to the mechanism of an ATP-driven ion-pump remain unclear. Most recently, single-molecule analysis proposed that the chemo-mechanical scheme of the catalytic domain of *Eh*V-ATPase is involved in the different sub-states from F_1-ATPase [1]. The first entire structure was also obtained at 17Å resolution using single-particle cryo-electron microscopy (cryo-EM) with Zernike phase plate [2]. In this study, we tried to obtain 3D models of the entire *Eh*V-ATPase, which include the multiple states, with all non-hydrogen atoms, based on the density maps from the low resolution cryo-EM map. Our modeling protocols of *Eh*V-ATPase, which is based on our own structure-prediction scheme [3], were as follows: 1) Homology models were built based on results of profile-profile alignment. 2) Model selection was initially performed with the correlations between individual models and the density maps, and finally the models were evaluated structurally using empirical scoring functions such as verify-3D. 3) Molecular dynamics simulations were performed with restraints between the selected models and the density map. The constructed models are expected to be valuable to understand the ion-pumping mechanism of *Eh*V-ATPase.

Acknowledgement

This study is partially supported by BINDS from AMED under grant number JP19am0101110 (support number 1445).

References

1. Iida T, Minagawa Y, Ueno H, Kawai F, Murata T, Iino R. Single-molecule analysis reveals rotational subsets and chemo-mechanical coupling scheme of *Enterococcus hirae* V_1-ATPase, *J. Biol. Chem*. (2019), in press.
2. Tsunoda J, Song C, Imai F. L, Takagi J, Ueno H, Murata T, Iino R, Murata K, Off-axis rotor in *Enterococcus hirae* V_1-ATPase visualized by Zernike phase plate single-particle cryo-electron microscopy, *Scientific Report*. (2018) 8:1563.
3. Nakamura T., Oda T., Fukasawa Y., Tomii K., "Template-based quaternary structure prediction of proteins using enhanced profile-profile alignments", *PROTEINS*, (2018) 86 1:274-282.

Finding a drug candidate regulating protein function at an allosteric site

Yuko Ito,* Yuji Tokunaga, Koh Takeuchi, Takatsugu Hirokawa

Molecular Profiling Research Center for Drug Discovery,

National Institute of Advanced Industrial Science and Technology, Japan

*yuko.ito@aist.go.jp

Protein kinases are major drug targets for oncology. There has been an increasing interest in non-ATP competitive kinase inhibitors, because they can offer higher selectivity and improved biochemical efficiency. However, a framework for rational design to identify non-ATP-competitive inhibitors has not been well established, because their inhibition mechanisms are diverse, and in most cases their targeting pockets are not obvious in crystal structures. Most of allosteric inhibitors thus far have been accidentally discovered. As such, rational design of allosteric inhibitor is critical need in drug development. Here, through computational and empirical approaches, we designed allosteric inhibitors for the MAP kinase ERK2 of which constitutive activation is found in many types of cancer cell. This work may expand the possibility of the ERK2 inhibitors and also represent a shift from the conventional paradigm of drug design.

MD simulations and QM/MM analysis to gain insight into protein functions

Yoshitaka Moriwaki,[1,*] Tohru Terada,[2,3] Kentaro Shimizu[1,2]

[1] *Department of Biotechnology, Graduate School of Agricultural and Life Sciences, The University of Tokyo, Japan*

[2] *Interfaculty Initiative in Information Studies, The University of Tokyo, Japan*

[3] *Agricultural Bioinformatics Research Unit, Graduate School of Agricultural and Life Sciences, The University of Tokyo, Japan*

*moriwaki@bi.a.u-tokyo.ac.jp

Molecular Dynamics (MD) simulations are highly useful to analyze time-resolved motions of biological macromolecules such as proteins and internal water molecules at atomic resolution. QM/MM is also a powerful computational method to study reactions in the macromolecules that are essential for their functions. Here, we introduce two case studies of proteins, PHBH and LFS, using these computational methods to gain insight into their functions that are intractable experimentally. PHBH is a flavoprotein monooxygenase that has been studied for more than 40 years [1]. We have found that the L199V/Y385F mutant can produce gallic acid besides the original product, 3,4-dihydroxybenzoate, and elucidated the mechanism, which involves a water-mediated hydrogen bond network and regiochemistry observed in 400-ns MD simulations. The second topic is LFS, an enzyme of onion that produces lacrimatory factor. Although the lacrimatory factor is very familiar with our daily life, the producing mechanism from its substrate, (*E*)-1-propenesulfenic acid, has not been characterized until recently. Our QM/MM calculations suggest that LFS catalyzes transfer of a proton from the sulfenic acid of the substrate to 2-carbon with the help of Glu88, Tyr102, and Tyr114. This mechanism is distinct from the other known LFSs, but consistent with the experimental data [2]. Taken together, we have suggested that these calculation methods are also applicable to understanding of functional mechanism of drugs, which is of increasing significance for today.

References

[1] Entsch B, Ballou DP, Massey V. Flavin-oxygen derivatives involved in hydroxylation by *p*-hydroxybenzoate hydroxylase, *J Biol Chem, 251,* 2550–2563, 1976.

[2] Arakawa T, Sato Y, Takabe J, Masamura N, Kato M, Aoyagi M, Kamoi T, Tsuge N, Imai S, Fushinobu S. Structure of *Allium* lachrymatory factor synthase elucidates catalysis on sulfenic acid substrate, *bioRxiv*, DOI: 10.1101/142687

Improving the virtual screening ability using machine learning

Masakazu Sekijima*
Advanced Computational Drug Discovery Unit, Tokyo Institute of Technology, *Japan*
*sekijima@c.titech.ac.jp

Virtual screening is a promising computational method for obtaining novel hit compounds in drug discovery. It aims to enrich potentially active compounds from a large chemical library for further biological experiments. However, the accuracy of current virtual screening methods is insufficient.

Drug discovery requires to find molecules that interact with targets with high affinity and specificity. Virtual screening application has been developed to this goal. However, current methods still show relatively weak predictive power.

In this work, we proposed a new virtual screening method named Visual Inspection Network (VisINet) inspired by image classification. We will show how recent advances in computer vision can be applied to structure-based virtual screening by adopting a CNN model based on the ResNet architecture.

References

[1] N. Yasuo and M. Sekijima, "Improved Method of Structure-Based Virtual Screening via Interaction-Energy-Based Learning", Journal of Chemical Information and Modeling, 59 (3), pp. 1050-1061, DOI: 10.1021/acs.jcim.8b00673 , 2019.

Combination of Molecular Dynamics Simulations and Small-angle X-ray Scattering Experiments

Mitsunori Ikeguchi*

Yokohama City University, Graduate School of Medical Life Science, Japan

*ike@yokohama-cu.ac.jp

Protein dynamics is crucial for protein functions. To investigate protein dynamics, molecular dynamics (MD) simulation now becomes a powerful tool with the advance of computational resources such as parallel computers and GPU. Among experiments of structural biology, the small-angle X-ray scattering (SAXS) is a unique experiment, because SAXS is capable of providing structural information *in solution* even for very flexible proteins. However, the SAXS data are limited to low resolution. Therefore, the combination of MD simulation and SAXS, called MD-SAXS, has been demonstrated to be useful for studies of protein dynamics in solution. In this talk, the recent applications of the MD-SAXS method as well as the recent development of the hybrid method of coarse-grained MD and SAXS (CG-MD-SAXS method) will be presented.

References

[1] Oroguchi T, Hashimoto H, Shimizu T, Sato M, Ikeguchi M, Intrinsic dynamics of restriction endonuclease EcoO109I studied by molecular dynamics simulations and x-ray scattering data analysis. *Biophys. J.*, 96, 2808-2822, 2009.

[2] Anami Y, Shimizu N, Ekimoto T, Egawa D, Itoh T, Ikeguchi M, Yamamoto K, Apo- and antagonist-binding structures of vitamin D receptor ligand-binding domain revealed by hybrid approach combining small-angle x-ray scattering and molecular dynamics, *J. Med. Chem.* 59, 7888-7900, 2016.

[3] Ekimoto T, Kokabu Y, Oroguchi T, Ikeguchi M, Combination of coarse-grained molecular dynamics simulations and small-angle X-ray scattering experiments, *Biophys. Physicobiol.* in press.

Sponsors

The AHeDD2019/IPAB2019 Joint Symposium is supported by the following organizations and companies.

Gold Sponsors

DeNA Co., Ltd.

Johnson & Johnson Services, Inc.

Lifematics Inc.

PeptiStar Inc.

Silver Sponsors

General Incorporated Association, Japan Biological Informatics Consortium（JBIC）

aceRNA Technologies Co., Ltd.

Ahead Biocomputing, Co. Ltd.

Baobab Pharm Co., Ltd.

Biomodeling Research Co., Ltd.

BIOTECH LAB INC.

Cosmo Bio Co., Ltd.

Early Reflections Co.

Fast Track Initiative, Inc.

HPCTECH Corporation

IMSBIO Co., Ltd.

Innovations and Future Creation Inc.（MIRAI SOUZOU）

Institute for Theoretical Medicine, Inc.

KISHIDA CHEMICAL Co., Ltd.

Korea Research Center for Theoretical Physics and Chemistry（KRCPC）

LISIT., Co., Ltd

Logbii, Inc.

MITSUI KNOWLEDGE INDUSTRY CO., LTD.

MOLCURE Inc.

MOLSIS Inc.

MVP Inc.

Research Institute of Systems Planning, Inc.

Schrodinger K.K.

Shalx Inc.

TEIJIN PHARMA LIMITED.

X-Ability Co., Ltd.

The Bank of Yokohama, Ltd. Kawasaki Branch

AHeDD2019/IPAB2019 Joint Symposium

Trends in Artificial Intelligence and Molecular Simulation
for Accelerating e-Drug Discovery

November 27 (Wed.) - 29 (Fri.), 2019
Tonomachi King Skyfront Area, Japan

Publisher Certified NPO Initiative for Parallel Bioinformatics (IPAB)

Organization Secretariat
Certified NPO Initiative for Parallel Bioinformatics (IPAB)
IPAB Office, 2-2-15 Hamamatsucho, Minato-ku, Tokyo Japan 105-0013
Email: office@ipab.org
URL: http://www.ipab.org/

Management Secretariat
Ahead Biocomputing, Co. Ltd.
Kawasaki Frontier Bldg. 4F, 11-2 Ekimaehoncho, Kawasaki-ku, Kawasaki City, Kanagawa Japan 210-0007
Email: ahedd2019@ahead-biocomputing.co.jp
URL: https://ahead-biocomputing.co.jp/