ASHBi SEMINAR

Controlling gene activation by enhancers through a drug-inducible topological insulator

Lecturer: **Dr. Taro Tsujimura**

Research Assistant Professor
Department of Physiology, Keio University School of Medicine

Date: Wednesday, 3rd July 2019
Time: 15:30–16:30
Venue: seminar room 102, Faculty of Medicine Bldg. A

While regulation of gene-enhancer interaction is better understood, its application remains limited. We reconstituted arrays of CTCF binding sites and devised a synthetic topological insulator with tetO for chromatin-engineering (STITCH). By coupling STITCH with tetR linked to the KRAB domain to induce heterochromatin and disable the insulation, we developed a drug-inducible system to control gene activation by enhancers. We applied this to dissect MYC regulation in human iPS cells, and obtained several important insights in gene regulation. In this seminar, I will demonstrate these results and discuss how the system would be useful in the field of chromatin conformation, particularly when combined with approaches of single cell genomics.

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ASHBi SEMINAR

Mitogen competition regulates spermatogenic stem cell homeostasis in an open niche

Lecturer: **Dr. Yu Kitadate**

The National Institute for Basic Biology (NIBB) ,
National Institutes of Natural Sciences

Date: Friday, 5th July, 2019
Time: 16:30-18:30
Venue: seminar room 107, building D

In many tissues, homeostasis is maintained by physical contact between stem cells and an anatomically defined niche. However, we questioned how the stem cell pool is maintained in tissues where motile stem cells intermingle among differentiating progeny. We found that competition for a limited supply of FGFs secreted by lymphatic endothelial cells leads to self-organized density homeostasis of spermatogenic stem cells in mouse testis. We propose that this model provides a generic and robust mechanism to support stem cell homeostasis in open niche environments.

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Hosted by: Institute for the Advanced Study of Human Biology (ASHBi)

ASHBi SEMINAR

Seeing is believing: new insights into causes of aneuploidy in mouse and human eggs

Lecturer: **Dr. Agata Zielinska**

Max Planck Institute, Dept. Meiosis, Goettingen, Germany (Melina Schuh's lab) and University of Cambridge, UK

Date: Friday, 26th July 2019
Time: 17:00–18:00
Venue: seminar room 102, Faculty of Medicine Bldg. A

Chromosome segregation errors during female meiosis are a leading cause of pregnancy loss, Down's syndrome and human infertility. While even eggs from young women frequently contain a wrong number of chromosomes, egg quality declines further with advancing female age. Yet, why human oocytes are exceptionally error-prone is still largely unclear. In our research, we use advanced microscopy techniques to uncover the aspects of chromosome segregation machinery that prime the ageing mammalian egg for aneuploidy.

ASHBi SEMINAR

Single cell transplantation assay unveiled a novel model of hematopoiesis

Lecturer: Dr. Ryo Yamamoto

Research associate, Institute for Stem Cell Biology and Regenerative Medicine
Stanford University School of Medicine

Date: Wednesday, 7th August 2019
Time: 16:00–17:00
Venue: seminar room 107, Faculty of Medicine Bldg. D

In the classical model, hematopoietic stem cells (HSCs) give rise to multipotent progenitors (MPPs) of reduced self-renewal potential and that MPPs eventually produce lineage-committed progenitor cells in a stepwise manner. Using single-cell transplantation combined with 5-lineage tracing system, we unexpectedly found myeloid-committed stem cells (MySCs) together with HSCs. Paired-daughter cell assays revealed that HSCs can directly differentiate into MySCs (yielding HSC-MySCs pairs). These results provide the first experimental evidence that the loss of self-renewal and the stepwise progression through specific differentiation stages are not essential for lineage commitment of HSCs. Furthermore, we found a special subset of aged MySCs (termed latent-HSCs), which re-acquire multipotency following transplantation into secondary recipients.

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ASHBi-CiRA SEMINAR

Rapid protein depletion by the auxin-inducible degron technology and an application to study genome maintenance in human cells

Lecturer: **Dr. Masato Kanemaki**

National Institute of Genetics

Date: Monday, 26th August 2019
Time: 16:30-18:00
Venue: Lecture Hall 104, 1st floor,
Center for iPS Cell Research and Application Bldg.

Genetic perturbation is a powerful way to analyze the function of proteins in vivo. For this purpose, we pioneered to develop the auxin-inducible degron (AID) technology (Nishimura et al, Nat. Meth., 2009). By combining with CRISPR-based genome editing, it is now possible to generate AID conditional mutants of human cells (Natsume et al., Cell Reports, 2016; Yesbolatova et al. Methods, 2019). I would like to share the history as well as our recent improvements. Finally, I would like to share our findings regarding a new DNA synthesis pathway caused by an artificial degradation of the replisome and to discuss its relation to meiotic recombination.

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ASHBi SEMINAR

Exploring the Downstream Effects of Epigenetic Driver Mutations in Cancer: Disease informs Basic Science

Lecturer: **Dr. Jacek Majewski**

Department of Human Genetics
McGill University and Genome Quebec Innovation Centre

Date: Tuesday, 10th September 2019
Time: 17:00–18:30
Venue: seminar room 102, Faculty of Medicine Bldg. A

Epigenetic dysregulation is a key driver event in many cancers. Our group aims to understand chromatin alterations caused by oncogenic mutations in histone genes, specifically mutations affecting the H3K27 and H3K36 residues. We use CRSIPR genome editing coupled with genome-wide approaches such as RNA-seq, ChIP-seq, and WGBS. In addition to cancer relevance, our work provides insights into basic chromatin biology, particularly interdependencies between various chromatin modifications.

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ASHBi SEMINAR

Circuit dynamics of the entorhinal cortex in associative learning and in Alzheimer's disease

Lecturer: **Dr. Kei M Igarashi**

Department of Anatomy and Neurobiology
Center for the Neurobiology of Learning and Memory
Institute for Memory Impairments and Neurological Disorders
University of California, Irvine

Date: Wednesday, 11th September 2019
Time: 17:00–18:00
Venue: seminar room 107, Faculty of Medicine Bldg. D

The entorhinal cortex is a gateway of information into the hippocampus, playing a critical role in learning and memory. The entorhinal cortex is anatomically divided into two cortical regions, the medial entorhinal cortex (MEC) and the lateral entorhinal cortex (LEC). Electrophysiological investigations into the functions of MEC in the past two decades have discovered grid cells and other spatially-representing cells critical for animals' spatial navigation and spatial memory.

Although these findings accelerated investigations into spatial memory, spatial memory holds only a portion of brain's memory function. What about associative memory? Associative memory is indeed the most common form of memory; suppose you sniff a smell of curry and it suddenly reminds you of dinners with your parents in good old days. Despite its importance, circuit mechanisms for associative memory is still very unclear, and our lab have been striving to identify such mechanisms. We previously showed that the LEC, rather than MEC, has a critical role in the formation of associative memory (Igarashi et al., Nature 2014). In our lab at UC Irvine, we recently found that, of two molecularly-defined principal cell types of superficial LEC, one neuron type plays a major role in enabling animals' acquisition of associative memory. We also found that the release of dopamine from the VTA into the LEC is critical for the acquisition of associative memory. Although dopamine has been thought to play a critical role in memory, it's function in the hippocampus remained enigmatic. Our data point to critical role of entorhinal dopamine release in associative memory.

In the second half of my talk, I would like to discuss our recent findings in the analyses of the entorhinal cortex of Alzheimer's disease (AD) mouse model. The entorhinal cortex has been known to be a first brain region that shows atrophy in the early stage of AD. Nonetheless, it is still unclear what type of activity in the entorhinal-hippocampal circuit is affected in AD. We previously found that gamma oscillations are impaired in the MEC (Nakazono et al., Front Syst Neurosci 2017). I will talk about our recent finding on the impairment of place cells and grid cells in AD mouse model.

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ASHBi SEMINAR

The cortical network processing three-dimensional object structure in the human and nonhuman primate brain

Lecturer: Dr. Peter Janssen

Professor, Laboratorium voor Neuro-en Psychofysiologie
The Leuven Brain Institute, KU Leuven, Belgium

Date: Tuesday, 17th September 2019
Time: 17:00–18:00
Venue: seminar room 107, Faculty of Medicine Bldg. D

Our world consists of three-dimensional (3D) objects. The primate visual system devotes considerable resources to analyze the 3D structure of objects defined by binocular disparity, both in the dorsal and in the ventral visual stream. I will review a series of studies in extrastriate cortex of the macaque monkey, i.e. in inferotemporal cortex (ITC) and the anterior intraparietal area (AIP). These studies have investigated the functional Magnetic Resonance Imaging (fMRI) activations related to 3D structure defined by binocular disparity, the properties of single neurons selective for 3D structure, the correlation between neural activity and the perceptual report of the animal, and how electrical microstimulation and reversible inactivation of clusters of neurons influence perceptual decisions on 3D structure. Microstimulation and reversible inactivation studies during fMRI also shed light on the flow of visual information in the network processing 3D object structure. To understand how the visual system achieves these 3D object representations, we have investigated the neural representation of 3D structure in mid-level visual areas (PIP in the dorsal stream and TEO in the ventral stream), guided by fMRI studies in monkeys. Finally, I will present new data obtained using intracortical recordings in human visual cortex, which may shed light on the homology between monkey and human areas . Together, single-cell, imaging and perturbation studies in monkeys, combined with imaging and single-cell recordings in humans, provide insight into the unique role of the dorsal and ventral visual stream, and the widespread cortical networks that support 3D object vision.

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ASHBi SEMINAR

Optogenetic interrogation of the attention network in primates

Lecturer: **Dr. Wim Vanduffel**

Professor, Laboratorium voor Neuro-en Psychofysiologie
The Leuven Brain Institute, KU Leuven, Belgium

Date: Friday, 27th September 2019
Time: 17:00–18:00
Venue: Seminar Room 107, Faculty of Medicine Bldg. D

I will discuss results of a combined opto-fMRI-electrophysiology study aimed to determine differences in top-down and bottom-up control of attention. Optogenetic inactivation of LIP in monkeys resulted in spatially selective and attention-dependent changes in single unit activity and behavioral performance. We also found surprisingly robust optogenetic-induced changes in fMRI activity throughout nodes of the attention network, as well as changes in task-driven functional connectivity. Our results show that ultra-short reversible inactivation of LIP only during the cue period can affect top-down and bottom-up driven covert spatial attention behavior, as well as local activity and network dynamics.

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ASHBi SEMINAR

Cracking the Code of Rare Diseases: Understanding Mechanisms and Developing New Therapies

Dr. Aris N. Economides

Vice President – Research
Skeletal Diseases TFA & Genome Engineering Technologies
Co-founder & Head of Functional Modeling
Regeneron Genetics Center, Regeneron Pharmaceuticals, Inc.

Date: Tuesday, 15th October 2019
Time: 18:00-19:00
Venue: Meeting room C, 5th floor, Outpatient Treatment Ward

The advent of modern sequencing methods has greatly amplified the number of human genetics findings and continuously generates many novel genotype-phenotype correlations across the spectrum of both the frequency of the genetic variant as well as the phenotype – i.e. covering common diseases, as well as rare, and ultra-rare ones. However, even in the space of monogenic (Mendelian) disorders where the link between a genetic variant and disease is most often causal, the biological mechanisms through which the genetic variant of interest results in disease is most often not obvious. Understanding those biological and molecular mechanisms are a prerequisite to the development of therapies (particularly disease-modifying, rather than palliative therapies) for any given rare genetic disorder. Such understanding not only sets the stage for rational exploration of therapies but also provides novel insights into basic biological mechanisms and the function of genes in vivo. During my seminar I demonstrate this premise using fibrodysplasia ossificans progressiva (FOP) as a first example. I will describe how our findings on the mechanism of action of the FOP-causing variant of the receptor-encoding gene ACVR1 has provided paradigm-breaking insights on signaling via this receptor and also provided a potential part to therapy, culminating into a clinical trial in FOP with a putative disease- modifying drug. Then I will discuss some of the work that we have been pursuing at the Regeneron Genetics Center, focusing on several novel discoveries from our genotype- phenotype ascertainment in Founder Populations (i.e. genetically isolated populations), particularly the Amish. Lastly, I will describe a new method for enzyme replacement therapy to demonstrate the importance of continued technological advancement in biologic drugs. These three vignettes, although distinct in content, provide the three pillars that are required for expanding our understanding of Rare Genetic Diseases: genetic discovery (and proper diagnosis), ascertainment of the biological mechanism resulting in the disease, and technological breakthroughs in drug design in order to provide better therapeutic options.

Organizer: Prof. Motoko Yanagita
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ASHBi DISTINGUISHED SEMINAR

DSGRN: an efficient tool for understanding regulatory networks

Lecturer: Dr. Konstantin Mischaikow

Professor, Department of Mathematics
Rutgers University, The State University of New Jersey

Date: Monday, 28th October 2019
Time: 17:00–18:00
Venue: Seminar room 103
        Faculty of Medicine Bldg. A

Based on a novel mathematical approach to dynamics, DSGRN is software that takes as input a regulatory network and outputs a database that provides for any parameter value a coarse description of the global dynamics.

The purpose of this talk is to explain why DSGRN is a potentially powerful tool for dealing with problems in systems biology. To do this we will present several examples including a network involving the tumor suppressor p53, and the Rb-E2F system that is responsible for the restriction point dynamics in mammalian cells.

In the first example, we will indicate that DSGRN can quickly analyze the network of interest and that simple queries can identify conditions on the system that permit oscillations.

In the second example, we will show that DSGRN can be used to quantify how well a network can carry out a particular function, in this case acting as a robust switch. This is a nontrivial task since it involves understanding the behavior of the system under a variety of conditions, where almost by definition the system cannot have a unique behavior at each condition. We will also show how this quantification can be used to preferably identify potential simplified models for the RB-E2F system.

Organizer: Prof. Yasuaki Hiraoka

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ASHBi SEMINAR

Perceptual saccadic suppression starts in the retina

Dr. Ziad Hafed

Professor, Center for Integrative Neuroscience
University of Tübingen, Germany

Date: Monday, 18th November 2019
Time: 16:00–17:00
Venue: Seminar Room 103&107, Faculty of Medicine Bldg. A

Visual sensitivity is strongly impaired around the time of rapid eye movements. This robust perceptual phenomenon, called saccadic suppression, is frequently attributed to active suppressive signals that are directly derived from eye movement commands. Here we show instead that visual-only mechanisms, activated by saccade-induced image shifts, can account for all perceptual properties of saccadic suppression that we have investigated. Such mechanisms start at the very first stage of visual processing in the brain, the retina. Critically, suppression originating in the retina outlasts perceptual suppression around the time of saccades, suggesting that extra-retinal movement-related signals, rather than causing suppression, may instead act to shorten it. Our results demonstrate a far-reaching contribution of visual processing mechanisms to perceptual saccadic suppression, starting in the retina, without the need to invoke explicit motor-based suppression commands.

ASHBi SEMINAR

The role of the superior temporal sulcus (STS) in controlling social gaze following

Dr. Hans-Peter Thier

Professor, Department of Cognitive Neurology
University of Tübingen, Germany

Date: Monday, 18th November 2019
Time: 17:00–18:00
Venue: Seminar Room 103&107, Faculty of Medicine Bldg. A

Primates follow the other´s gaze to an object of interest to the other, allowing the two agents to establish joint attention. Whereas humans exploit both eye and head gaze cues, monkeys rely mostly on head gaze. This difference notwithstanding, human gaze and monkey gaze following have similar functional features, qualifying them as domain specific capacities that share similar, possibly homologous neural architectures. A central hub in a putative network subserving gaze following is a distinct patch of cortex in the STS. As shown by our comparative fMRI work this gaze following patch (GFP) is selectively activated if observers shift attention to a target determined by the other´s gaze. The monkey GFP contains a distinct set of gaze following neurons that seem to establish a linkage between the other´s gaze direction and the object, singled out by the other´s gaze, if this linkage is pertinent within the prevailing context. Microstimulation of the monkey GFP establishes a causal role of these neurons. If microstimulation is applied in a period in which the information needed for the linkage between gaze and object becomes available, gaze following is compromised. In short, the GFP plays a causal role in orchestrating gaze following and its executive control.

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ASHBi SEMINAR

Marmoset as a Model System for Studying Neural Basis of Vocal Communication

Dr. Xiaoqin Wang

Professor, Department of Biomedical Engineering
Johns Hopkins University

Date: Friday, 22nd November 2019
Time: 17:00–18:00
Venue: Seminar Room 106, Faculty of Medicine Bldg. C

Vocal communication is one of the most important natural behaviors of both humans and many animal species. In the past, studies of echolocating bats and songbirds have provided important insights into neural mechanisms of vocal communication. In comparison, much less has been learned from non-human primates. The common marmoset (Callithrix jacchus), a highly vocal New World monkey species, has emerged in recent years as a promising model system for studying neural basis of hearing and vocal communication. Marmoset offers several critical advantages over other non-human primate species, including a rich vocal repertoire in captivity, a relatively short postnatal development period and the feasibility in generating genetically modified models. In the past 20 years, my laboratory has pioneered a number of behavioral and electrophysiological techniques to study neural activity in the marmoset brain during natural vocal behaviors. Our studies have shed important light on the brain mechanisms for processing communication sounds. They also demonstrated the tremendous potentials of the marmoset as a primate model for studying neural mechanisms underlying vocal communication and social interactions.

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ASHBi SEMINAR

Genetic Engineering and Neural-behavioral Phenotyping of a Macaque Model of Autism Spectrum Disorder

Dr. Yang Zhou

Principal Investigator, Montreal Neurological Institute-Hospital

Assistant Professor, Department of Neurology and Neurosurgery
Faculty of Medicine, McGill University

Date: Wednesday, 4[h] December 2019
Time: 11:00–12:00
Venue: Seminar Room 106, Faculty of Medicine Bldg. C

Mutation or disruption of the SHANK3 (SH3 domain and ankyrin repeat) gene at the 22q13.3 locus represents a highly penetrant, monogenic risk-factor for Autism Spectrum Disorder (ASD) and is a leading cause of Phelan–McDermid Syndrome (PMS). Recent advances in gene editing enabled the creation of genetically engineered non-human primate (NHP) models of brain disorders. Such NHP models might better approximate some neural and behavioral features of ASD than rodents and allow for gaining a better neurobiological understanding of ASD as well as developing treatment strategies. I will be presenting a collaborative effort during my postdoctoral training on a study of macaque monkeys carrying germline-transmissible SHANK3 mutation generated with CRISPR/Cas9-mediated gene editing. The founder mutants exhibited sleep disturbances, motor deficits, and increased repetitive behaviors, as well as social and learning impairments. Examining resting-state brain activity in founder monkeys with functional magnetic resonance imaging revealed altered local and global connectivity patterns indicative of circuit abnormalities. Our findings of altered brain connectivity and compromised behavioral performance in SHANK3 mutant macaques parallel some aspects of the gene-circuit-behavior dysfunction in human ASD and PMS.

ASHBi SEMINAR

Molecular organization of the genome

Dr. Yuichi Taniguchi

Unit Leader, Laboratory for Cell Systems Control
RIKEN Center for Biosystems Dynamics Research

Date: Monday, 9th December 2019
Time: 16:00–17:00
Venue: Seminar Room 103&107, Faculty of Medicine Bldg. A

Since the discovery of the DNA double helix by Dr. Watson and Crick in 1953, a long-standing question is how the DNA molecule is higher-order structured in the cell as the genome. Recently we developed a method to analyze 3D structure of genomic DNA in cells at the resolution of its basic structural unit, the nucleosome, composed of DNA wrapping around histone octamers [1]. This method, named Hi-CO, can analyze 3D positions and orientations of every nucleosomes across the genome, based on next generation sequencing and super-computer analyses. The data revealed that nucleosomes in yeast genome are irregularly folded with reflecting epigenetic status at each genomic locus, and its arrangement comprises two basic folding motifs: α-tetrahedron and β-rhombus analogous to α-helix and β-sheet motifs in protein folding. In this seminar, I will present molecular-level organizational principles of the genome revealed by Hi-CO, as well as our recent challenges on super-sensitive disease diagnoses based on a 3D single molecule imaging technology [2] [3].

[1] Ohno, M., Ando, T., Priest, D. G., Kumar, V., Yoshida, Y., Taniguchi, Y. "Sub-nucleosomal genome structure reveals distinct nucleosome folding motifs", Cell 176, 520-534 (2019)
[2] Taniguchi, Y., Choi, P. J., Li, G., Chen, H., Hearn, J., Babu, M., Emili, A. & Xie, X. S. Quantifying E. coli proteome and transcriptome with single-molecule sensitivity in single cells. Science 329, 533-538 (2010)
[3] Taniguchi, Y., Nishimura, K. Microscope, focusing unit, fluid holding unit, and optical unit. Patent #6086366 (JP), #9880378 (US), #2983029 (EP)

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ASHBi SEMINAR

Uncovering the operating principles of genome through RNA biology

Dr. Hiroshi Suzuki

Fellow
Koch Institute for Integrative Cancer Research
Massachusetts Institute of Technology

Date: Tuesday, 10th December 2019
Time: 17:00–18:00
Venue: Seminar Room 102, Faculty of Medicine Bldg. A

In this seminar, we introduce our quantitative and integrative approaches in RNA and genome biology. Recent advances in microRNA research facilitate a system-level understanding of how microRNAs are regulated and regulate their targets, with applications to synthetic biology. From the quantitative and evolutional standpoints, microRNAs are tightly linked to super-enhancers, which shape cell-type specific transcriptomes. By focusing on super-enhancer and RNA polymerase II, we further discuss roles of phase separation in the operating principles of super-enhancer and transcription.

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ASHBi SEMINAR

An emerging picture of functional DNA sequences in the human genome

Dr. Yasuhiro Murakawa

Team Leader, RIKEN-IFOM Joint Laboratory for Cancer Genomics
RIKEN Center for Integrative Medical Sciences

Date: Tuesday, 17th December 2019
Time: 16:00–17:00
Venue: Seminar Room 103&107, Faculty of Medicine Bldg. A

Little is known about the basic principles of the human genome, the blueprint of our life. We are developing new methodologies that combine biochemistry, deep sequencing and informatics, to characterize both conserved and non-conserved genes and regulatory elements in the human genome. In particular, using our original NET-CAGE technology, we have accurately mapped transcribed enhancers, which are the key cis-regulatory elements that generate cell-type specific transcriptomes. In this presentation, I will talk about our ongoing efforts to decode functional DNA sequences in human health and disease.

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ASHBi SEMINAR

Physiological and genetic approaches to identify primate cortico-basal ganglia structures generating anxiety

Dr. Ken-ichi Amemori

Program-Specific Associate Professor, Hakubi Center for
Advanced Research and Primate Research Institute, Kyoto University

Date: Friday, 24th January 2020
Time: 16:00–17:00
Venue: Seminar Room, Ground Floor, Faculty of Medicine Bldg. B

A fundamental goal of psychiatry is to control mood and anxiety in humans. Despite its importance, we have not yet elucidated the brain mechanism of mood and anxiety disorders. It is thus critical to systematically study the causal role of the emotional circuit in the non-human primates (NHPs), whose brain structures are homologous to humans. We introduced an approach-avoidance conflict task to elicit anxiety-like behavior and identified a cortico-striatal circuitry that causally generates anxiety states by combining multiple physiological methods. We will further employ cutting-edge genetic techniques and functional imaging to approach the structural basis of "anxiety circuitry" in NHPs and humans.

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ASHBi SEMINAR

Systematic profiling of the T cell receptor repertoire in intestinal inflammation

Dr. Shigeki Nakagome

Assistant Professor
School of Medicine, Trinity College Dublin

Date: Wednesday, 12ᵗʰ February 2020
Time: 11:00–12:00
Venue: Seminar Room, 1st Floor, Faculty of Medicine Bldg. B

The intestine has its own unique environments in which host immune cells are inevitably exposed to a persistent threat of microbial attack. Host tolerance to gut bacteria is essential for symbiosis. T cell receptors (TCRs) expressed on the T cell surface play a critical role in discriminating pathogenic from symbiotic bacterial. However, a failure of this step may trigger dysregulated immune responses to those friendly bacteria and result in inflammatory bowel disease (IBD). Quantifying the TCR repertoire in IBD patients, we developed a genomic profiling approach that tracks the generation, expansion, and elimination of self-reactive T cells in the intestine. We further applied a probabilistic modelling to decipher the stochastic nature of somatic recombination that generates the immense diversity of TCRs. This talk will provide proof-of-concept for the quantitative statistical approaches that advance our understanding of TCR function and its role in the breakdown of host tolerance to gut bacteria.

Organizer: Dr. Taro Tsujimura