*Health Intelligence Center*

# Division of Health Medical Computational Science
# 健康医療計算科学分野


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*The mission of this division is to develop computational science for transforming biomedical data to knowledge. By making full use of supercomputers, we are now focusing on annotation, translation and interpretation of genomic data including RNA sequences for supporting cancer research and clinical sequence.*

## 1. Computational Science for Cancer Research

### a. A temporal shift of the evolutionary principle shaping intratumor heterogeneity in colorectal cancer


**Saito T[1,3], Niida A, Uchi R[1], Hirata H[1], Komatsu H[1], Sakimura S[1], Hayashi S[2], Nambara S[1], Kuroda Y[1], Ito S[1], Eguchi H[1], Masuda T[1], Sugimachi K[1], Tobo T[1], Nishida H[3], Daa T[3], Chiba K[2], Shiraishi Y[2], Yoshizato T[4], Kodama M[3], Okimoto T[3], Mizukami K[3], Ogawa R[3], Okamoto K[3], Shuto M[3], Fukuda K[3], Matsui Y[5], Shimamura T[5], Hasegawa T[6], Doki Y[7], Nagayama S[8], Yamada K[9], Kato M[10], Shibata T[10,11], Mori M[7], Aburatani H[12], Murakami K[3], Suzuki Y[13], Ogawa S[4], Miyano S, Mimori K[1]: [1]Kyushu University Beppu Hospital, [2]Laboratory of DNA Information Analysis, Human Genome Center, Institute of Medical Science, The University of Tokyo, [3]Oita University Hospital, [4]Kyoto University, [5]Nagoya University Graduate School of Medicine, [6]Division of Health Medical Data Science, Health Intelligence Center, Institute of Medical Science, The University of Tokyo, [7]Osaka University, [8]Cancer Institute Hospital, [9]Takano Hospital, [10]National Cancer Center Research Institute, [11]Laboratory of Molecular Medicine, Human Genome Center, Institute of Medical Science, The University of Tokyo, [12]Research Center for Advanced Science and Technology, The University of Tokyo, [13]Department of Computational Biology and Medical Sciences, Graduate School of Frontier Sciences, The University of Tokyo**


Advanced colorectal cancer harbors extensive intratumor heterogeneity shaped by neutral evolution; however, intratumor heterogeneity in colorectal precancerous lesions has been poorly studied. We perform multiregion whole-exome sequencing on ten early colorectal tumors, which contained adenoma and carcinoma in situ. By comparing with sequencing data from advanced colorectal tumors, we show that the early tumors accumulate a higher proportion of subclonal driver mutations than the advanced tumors, which is highlighted by subclonal mutations in KRAS and APC. We also demonstrate that variant allele frequencies of subclonal mutations tend to be higher in early tumors, suggesting that the subclonal mutations are subject to selective sweep in early tumorigenesis while neutral evolution is dominant in advanced ones. This study establishes that the evolutionary principle underlying intratumor heterogeneity shifts from Darwinian to neutral evolution during colorectal tumor progression.

Simulation methodology is employed in this

study by using supercomputers.

### b. Cancer evolution and heterogeneity

**Mimori K[1], Saito T[1], Niida A, Miyano S**

Undoubtedly, intratumor heterogeneity (ITH) is one of the causes of the intractability of cancers. Recently, technological innovation in genomics has promoted studies on ITH in solid tumors and on the pattern and level of diversity, which varies among malignancies. We profiled the genome in multiple regions of nine colorectal cancer (CRC) cases. The most impressive finding was that in the late phase, a parental clone branched into numerous subclones. We found that minor mutations were dominant in advanced CRC named neutral evolution; that is, driver gene aberrations were observed with high proportion in the early - acquired phase, but low in the late-acquired phase. Then, we validated that neutral evolution could cause ITH in advanced CRC by super - computational analysis. According to the clinical findings, we explored a branching evolutionary process model in cancer evolution, which assumes that each tumor cell has cellular automaton. According to the model, we verified factors to foster ITH with neutral evolution in advanced CRC. In this review, we introduce recent advances in the field of ITH including the general component of ITH, clonal selective factors that consolidate the evolutionary process, and a representative clinical application of ITH.

### c. Neutral theory in cancer cell population genetics

**Niida A, Iwasaki WM[14], Innan H[14]: [14]The Graduate University for Advanced Studies**

Kimura's neutral theory provides the whole theoretical basis of the behavior of mutations in a Wright-Fisher population. We here discuss how it can be applied to a cancer cell population, in which there is an increasing interest in genetic variation within a tumor. We explain a couple of fundamental differences between cancer cell populations and asexual organismal populations. Once these differences are taken into account, a number of powerful theoretical tools developed for a Wright-Fisher population could be readily contribute to our deeper understanding of the evolutionary dynamics of cancer cell population.

## 2. Implementation of Cancer Clinical Sequence

In collaboration with Professor Yoichi Furukawa (Division of Clinical Genome Research, Advanced Clinical Research Center), Professor Arinobu Tojo (Division of Molecular Therapy, Advanced Clinical Research Center), Research Associate Professor Koichiro Yuji (Project Division of International Advanced Medical Research), IMSUT Research Hospital, and Human Genome Center, we have been implementing cancer genomic medicine since 2011. Some reports are published [1,4,8, 11-12]. Use of IBM Watson for Genomics assisted experts who are responsible for diagnosis and therapy.

### a. Artificial Intelligence for Cancer Genomic Medicine: Understanding Cancer is Beyond Human Ability

**Miyano S**

We have been running cancer clinical sequence based on whole genome, whole exome, panels, RNA sequencing and epigenetic analysis at our institute. When focused on hematology/oncology, it takes four days for a patient from signing informed consent (IC) to receiving diagnosis. This five-day process consists of IC, specimen collection, whole exome sequencing, whole exome sequence data analysis, interpretation/translation of mutations by oncologists, determining the diagnosis combined with all pathological data and returning the result (therapy if any) to the patient. Therapies are not only drugs but also hematopoietic stem cell transplantation. A pipeline Genomon for analyzing cancer genomes and RNA sequences by next-generation sequencers plays one of the key roles. It is running on the supercomputer system SHIROKANE at our Human Genome Center. The bottleneck of interpretation/translation was drastically resolved by employing IBM Watson for Genomics in harmony with our in-house human curation pipeline. We report how our system works as a conglomerate of oncologists, cancer biologists, bioinformaticians augmented with Watson and Genomon.

## Publications

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