

## Advanced Clinical Research Center

# Division of Advanced Medicine Promotion 先端医療開発推進分野

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*Our mission is to assist the development of translational research. For this purpose, it is critical to discover new “seeds” and to eradicate blockades until the clinical utilization. We also assist the conduct of clinical trials at IMSUT Hospital. At IMSUT Hospital, we work together with the staffs of Center for Translational Research. Concurrently, to concur blockades on translational research, we have been engaging in research on regulatory science and biostatistics.*

### 1. Assistance of Clinical Trials/TRs at Research Hospital

Masanori Nojima, Fumitaka Nagamura

At IMSUT Hospital, we work together with the staffs of Center for Translational Research. The assistance of Translational (Clinical) Research Coordinators is indispensable for the conduct of clinical trials, especially for TR. The activities of Coordinators are the results of the collaboration between Division of Advanced Medicine Promotion and Center for Translational Research. In 2023, we supported 4 sponsor-investigator clinical trials.

### 2. Approach for epigenome and multi-omics research by methodology of bioinformatics and biostatistics

Masanori Nojima

Epigenome and multi-omics research using clinical samples in collaborative study or public database of comprehensive omics-analysis. We are now focusing on the multi-omics approach integrating DNA methylation, mRNA expression, and miRNA, and building statistical models to assess functional link-

age.

### 3. Statistical consulting for basic research

Masanori Nojima

For basic researchers, we suggest exploratory statistical approach and molecular epidemiological approach.

### 4. Statistics and Quality control in Clinical Trials

Masanori Nojima, Mitsumi Tokunaga, Fumitaka Nagamura

We have planned and performed data management, monitoring, and statistical works in clinical trials.

[Data management]: Planning, EDC and CRF preparation, registration, allocation, database management, data cleaning, coding

[Monitoring]: Monitoring for drug management

[Statistics]: Planning and perform for statistical analyses, Sample size calculation.

## 5. A review of criteria strictness in “Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials”

Masanori Nojima, Fumitaka Nagamura

To assess safety in vaccine development, stricter grading scales, such as the “Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials” issued by the U.S. Food and Drug Administration (FDA grading scale), are required. However, concern exists that their strictness may lead to an overestimation of some adverse events (AEs). We analyzed the details of AEs in a phase I clinical trial of a preventive vaccine for infectious diseases. In this trial, we observed the high occurrence of Grade 1 or greater AEs in hemoglobin changes from baseline value, and hypernatremia, and hypokalemia by FDA grading scale. The range considered as non-AE according to the FDA grading scale shifted or became narrower when compared to reference intervals, especially for a Japanese cohort.

Regarding a decrease in hemoglobin from baseline, the criterion of “any decrease” used for a Grade 1 AE was too strict and we suggest this be omitted. Upper and lower limits of AE criteria for sodium and potassium should be equal to, or 10–20% above, the reference interval consistent with other toxicities determined by laboratory tests. Consideration should be given to the issues surrounding the criteria that determine AEs before conducting clinical trials.

## 6. Approach for epigenome and multi-omics research by methodology of bioinformatics and biostatistics

Masanori Nojima

Epigenome and multi-omics research using clinical samples in collaborative study or public database of comprehensive omics-analysis. We are now focusing on the multi-omics approach integrating DNA methylation, mRNA expression, and miRNA, and building statistical models to assess functional linkage.

## Publications

1. Motoki Amai, Masanori Nojima, Yoshikazu Yuki, Hiroshi Kiyono, Fumitaka Nagamura. A review of criteria strictness in “Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials”. *Vaccine*. 2023 Aug 31;41(38):5622-5629. doi: 10.1016/j.vaccine.2023.07.072. Epub 2023 Aug 1.
2. Tokiko Nagamura-Inoue, Fumitaka Nagamura. Umbilical cord blood and cord tissue banking as somatic stem cell resources to support medical cell modalities. *Inflamm Regen* 2023 Dec 5;43(1):59. doi: 10.1186/s41232-023-00311-4.
3. Tokiko Nagamura-Inoue, Seiko Kato, Yuho Najima, Masamichi Isobe, Noriko Doki, Hisashi Yamamoto, Naoyuki Uchida, Atsuko Takahashi, Akiko Hori, Masanori Nojima, Kazuteru Ohashi, Fumitaka Nagamura, Arinobu Tojo. Immunological influence of serum-free manufactured umbilical cord-derived mesenchymal stromal cells for steroid-resistant acute graft-versus-host disease. *Int J Hematol*. 116(5):754-769, 2023.
4. Miyagami T, Nishizaki Y, Imada R, Yamaguchi K, Nojima M, Kataoka K, Sakairi M, Aoki N, Furusaka T, Kushi S, Yang KS, Morikawa T, Tohara H, Naito T. Dental Care to Reduce Aspiration Pneumonia Recurrence: A Prospective Cohort Study. *Int Dent J*. 2024 Jan 13:S0020-6539(23)00974-7. doi: 10.1016/j.identj.2023.11.010. Epub ahead of print.
5. Miura S, Kurimoto Y, Maruyama R, Nojima M, Sasaki K, Masuda T, Nishioka N, Iba Y, Kawaharada N, Naraoka S. Initial two-day blood pressure management after endovascular aneurysm repair improves midterm outcomes by reducing the incidence of early type II endoleak. *J Vasc Surg*. 2023 Oct 10:S0741-5214(23)02081-5. doi: 10.1016/j.jvs.2023.10.003. Epub ahead of print. PMID: 37827245.
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7. Kazama T, Ando K, Ueno N, Fujiya M, Ito T, Maemoto A, Ishigami K, Nojima M, Nakase H. Long-term effectiveness and safety of infliximab-biosimilar: A multicenter Phoenix retrospective cohort study. *PLoS One*. 2023 Sep 12;18(9):e0288393. doi: 10.1371/journal.pone.0288393. PMID: 37699041; PMCID: 37699041.
8. Nasuno M, Shimazaki H, Nojima M, Hamada T, Sugiyama K, Miyakawa M, Tanaka H. Serum leucine-rich alpha-2 glycoprotein levels for predicting active ultrasonographic findings in intestinal lesions of patients with Crohn’s disease in clinical remission. *Medicine (Baltimore)*. 2023 Aug 11;102(32):e34628. doi: 10.1097/MD.00000000000034628. PMID: 37565885; PMCID: PMC10419375.
9. Nishizaki Y, Kuroki H, Ishii S, Ohtsu S, Watanabe C, Nishizawa H, Nagao M, Nojima M, Watanabe R, Sato D, Sato K, Kawata Y, Wada H, Toyoda G, Ohbayashi K. Determining Optimal Intervals for

In-Person Visits During Video-Based Telemedicine Among Patients With Hypertension: Cluster Randomized Controlled Trial. JMIR Cardio. 2023

Jun 8;7:e45230. doi: 10.2196/45230. PMID: 37161483; PMCID: PMC10288346.