

The University of Tokyo

Translational Research Support at The University of Tokyo



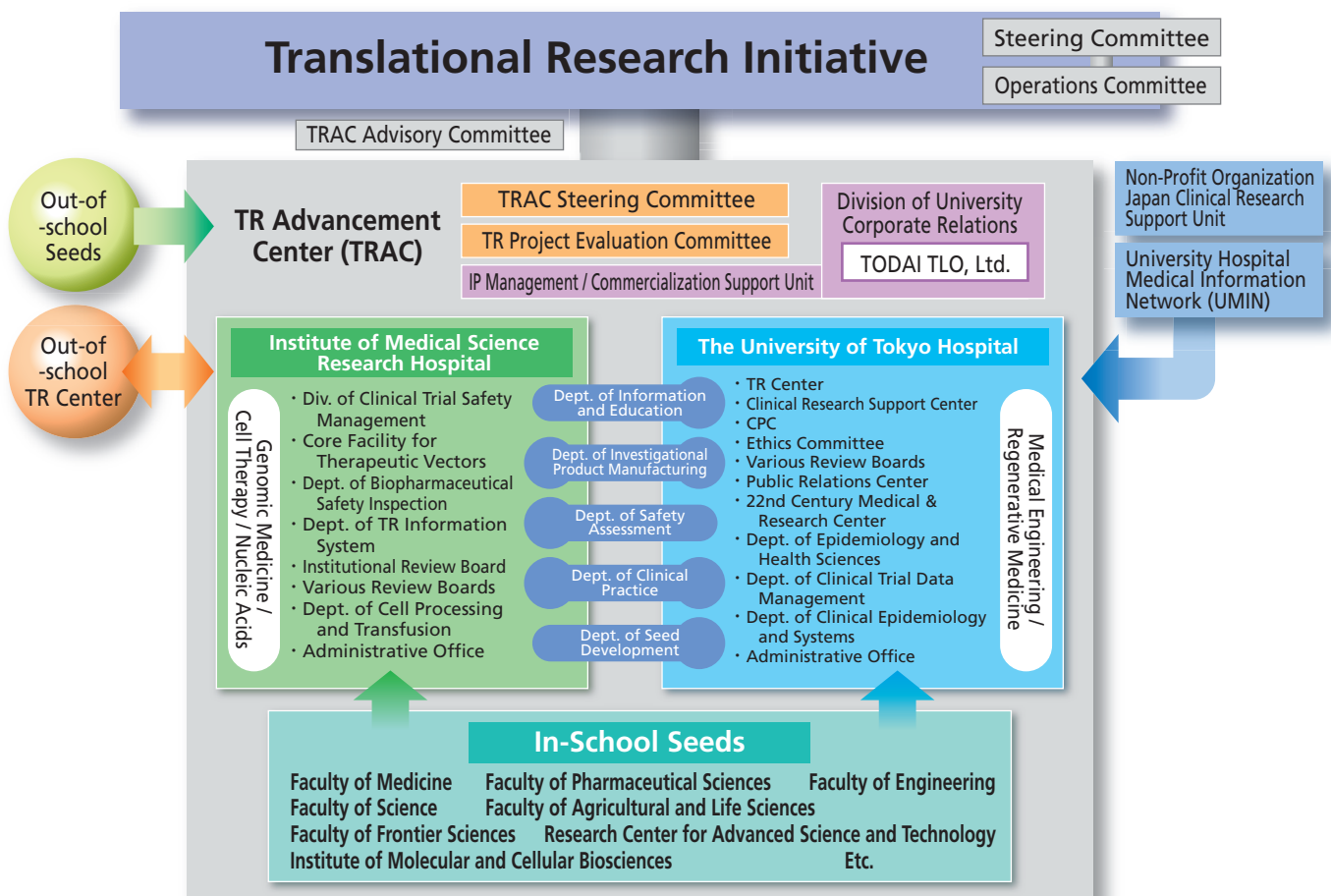
東京大学
THE UNIVERSITY OF TOKYO

Translational Research Support System at the University of Tokyo

Translational research is a discipline in which fundamental research results are bridged to clinical applications. In order to link fruitful fundamental researches with clinical researches in an integrated and timely fashion, the formation of a center that can strongly promote and support translational research is needed.

At the University of Tokyo, the Translational Research Initiative set up in the main campus oversees all translational research activities. In addition, the Translational Research Advancement Center (TRAC) was established under the Translational Research Initiative for managing the assessment of scientific seeds and intellectual property rights, and for forming translational research networks in and outside of the school, all under the scheme of the MEXT Translational Research Acceleration Network Program (Manager for the University of Tokyo: Nobuhito Saito, Head of Education and Research Support, the University Hospital/Professor of Neurosurgery).

The Translational Research Advancement Center has the following supporting departments; Information and Educational Department, Test Object Manufacturing Department, Safety Assessment Department, Clinical Implementation Department, and Solutions/Services Development Department. In addition, the university hospital, Institute of Medical Science, and Institute of Medical Science Research Hospital all cooperate in running translational research operations. The above supporting departments are equipped so that they may respond to requests inside and outside of the university. In addition, at the Translational Research Advancement Center, a patent attorney dedicated to translational research can respond to consultation requests regarding intellectual property acquisition, patent infringement, etc., in order to strengthen intellectual property strategies.



Introduction to TR Center at the University of Tokyo

Nobuhito Saito

Manager at the University of Tokyo for Translational Research Acceleration Network Program
Vice Director/Head of Education and Research Support, The University of Tokyo Hospital



The University of Tokyo is a university with a multitude of research courses and facilities. A great deal of fundamentals, development, and practical research unfold in the fields of medical treatment and life sciences in not only its faculty of medicine and Institute of Medical Science, but also in the faculties of engineering, pharmaceutical sciences, physical sciences, agricultural and life sciences, and frontier science, as well as the molecular and cellular biology research facility and research center for advanced science and technology, leading to the university's distinction for possessing a multitude of scientific seeds for solutions, products, and services. A "Translational Research Initiative" is a cross-school function which will oversee the development of the translational research at this university. Under the guidance of the Translational Research Initiative, the "TR Promotion Center," made up of staff from the university hospital and Institute of Medical Science Research Hospital, etc., will undertake the actual operations. The results of these works are ultimately returned to society through the Tokyo University Division of University Corporate Relations and TODAI TLO, Ltd. (Tokyo University Technology Licensing Organization).

At the university hospital, the "TR Center" plays a crucial role as a center for TR in the Hongo Campus, also acting as a point of contact for external facilities. The TR Center mainly digs up new solution ideas and takes charge of support activities leading up to clinical studies. At the clinical study stage, the "Clinical Research Support Center" (CresCent) will be part of the translational research, taking charge of clinical trials in cooperation with the TR Center. In-hospital facilities have been equipped with the CPC (Cell Processing Center) and P1 Unit for conducting phase one tests. In order to engage in translational research constantly, we are in the process of expanding and enhancing the related departments.

We invite you to make use of the Institute of Medical Science for your Translational Research

Kohzoh Imai

Director of the IMSUT Hospital, Institute of Medical Science, the University of Tokyo(IMSUT)



The University of Tokyo, one of the Ministry of Education, Culture, Sports, Science and Technology (MEXT)'s centers for translational research, has been strengthening its bases at the Institute of Medical Science and its Research Hospital on the Shirokanedai Campus, along with the university hospital.

At the Institute of Medical Science and it's the IMSUT Hospital, besides appointing a fixed number of professors (physicians) in a field of regulatory science, we have also newly hired a number of specially appointed the IMSUT assistant professors, instructors and posted a clinical research coordinator. In addition, we have proactively employed nurses and pharmacists who show motivation in translational research and early stage clinical trials in order to develop new medical treatments in the fields of cancer, infectious disease, and rare disease, such as virus treatments, regenerative medicine (for alveolar bones and joints), rice-based vaccines, cancer vaccines, new forms of targeted therapy, and amino acid treatment for muscle atrophy.

The Core Facility for Therapeutic Vectors (CFTV) and the Biopharmaceutical Safety Inspection Facility are facilities unique to the Institute of Medical Science, which we would be happy to open access to researchers from other universities. This year in particular, we feel there is a solid foundation for new partnerships with other universities. Please feel free to contact us on this matter. By combining our strength and developing translational research and early stage clinical trials of Japanese origin, we would like to assist with medical treatment the world over.

TR Organizations and Facilities at the University of Tokyo Hospital



TR Center

The center provides support for turning the researches into practical applications in such areas as illness condition, diagnoses, and treatments, by researchers in and outside of the university. Also, through cooperation with other departments, organizations outside of the school, and the industry, the center promotes developing ideas solutions and services, matching needs with solutions, human resource development, infrastructure improvement, intellectual property management, and more. It also supports TR protocol planning, manufacturing of investigational product and its quality management, safety assessment, TR education, the provision of information to clinical researchers, communicating information inside and outside of the school, etc.

Clinical Research Support Center

This center supports clinical trials and independent clinical studies seamlessly, from the development of cutting-edge medical treatment to the provision of optimal medical treatment while coordinating with related departments. Such endeavors are carried out by trained expert staff made up of physicians, pharmacists, nurses, clinical technologists, biostatisticians, and back-office workers. The TR Center mainly supports the process leading up to the commencement of clinical trials - upon the implementation of clinical studies, the Clinical Research Support Center takes over the duties.

CPC (Cell Processing Center)

This is a specialized facility in which a variety of requirements necessary for the manufacture and cultivation of human cells and systems used in cell therapy and regenerative medicine can be fulfilled.

Institutional Review Board and Various Other Review Board

These are organizations that inspect whether clinical research and trials are being planned and implemented properly.

Organizations of Institute of Medical Science and Research Hospital



Division of Clinical Trial Safety Management

The facility supports development of protocol and standard operating procedure, manages clinical trials (project management), supports the implementation of tests by clinical research coordinators, and provides information relating to TR to researchers, among other things. The department also formulates plans for educational activities and human resources development.

Core Facility for Therapeutic Vectors (CFTV)

CFTV is a facility for preparation of viral vectors for gene therapy, as well as foreign gene transduced cells for cell therapy. The clinical grade virus used in the oncolytic virus therapy at the University of Tokyo Hospital has been prepared here.

Department of Biopharmaceutical Safety Inspection

The safety of biopharmaceuticals such as cells that have been administered in clinical studies are verified here.

Department of Translational Research Information System

Information regarding translational research from the Institute of Medical Science, as well as domestic and international sources, are gathered and distributed here.

Institutional Review Board and Various Other Review Board

These are organizations that inspect whether clinical research and trials are being planned and implemented properly.

Department of Cell Processing and Transfusion (Clinical Cellular Engineering)

The department operates the Clinical Cellular Engineering Facility and manufactures cells necessary for regenerative treatment and cell therapy, as well as separates and preserves cells from umbilical cord blood, etc. used for research purposes. Cells that are manufactured here are used for alveolar bone regenerative treatment and various types of dendritic cell treatments implemented in the past.

The University of Tokyo Hospital

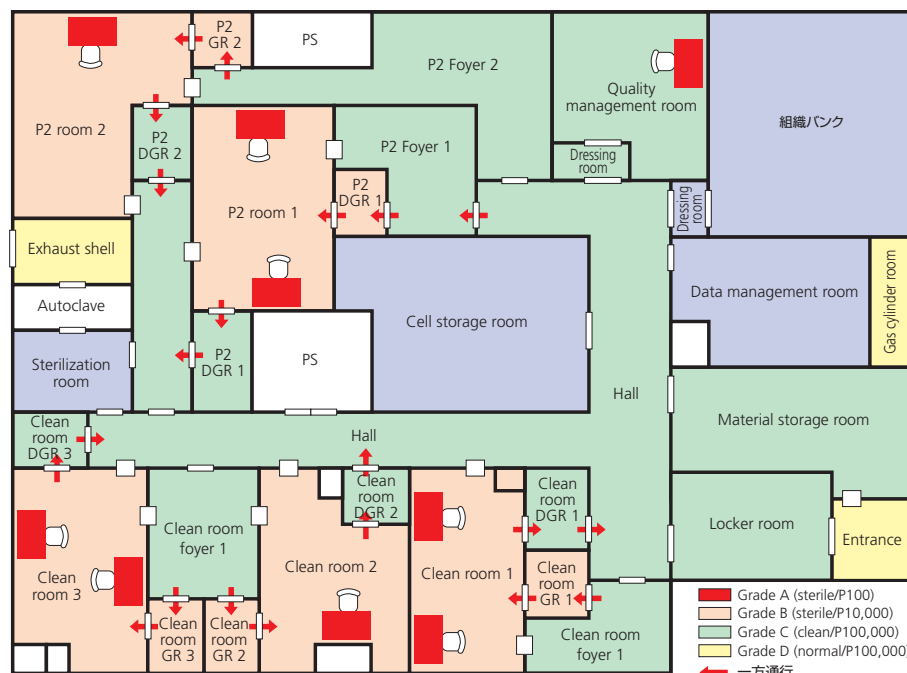
Cell Processing Center (CPC)

What is CPC?

It is a specialized facility in which a variety of requirements necessary for the manufacture and cultivation of human cells and systems used in cell therapy and regenerative medicine can be fulfilled. Designs, construction, and operation are performed in accordance with GMP standards, and cell therapy and regenerative medicine fully comply with the required laws and ordinances. In addition, the CPC includes a specialized facility able to support the formulation of viral drugs used in virotherapy and gene therapy.

Outline

Established: April, 2007
 Location: Central Clinical Service Buldg.2, Floor B1 The University of Tokyo Hospital
 Area: 380m²
 Facilities: Clean Rooms -3 Units, Clean Rooms with P2 Support -2 Units



Management and Operation System

The center is managed and run by the CPC Steering Committee, as well as its sub-committee the Operations Committee. In addition, the CPC Project Committee oversees the acceptance and progress management of projects.

Equipment

Equipment inside of the Workrooms (Clean Rooms)

Various types of machines necessary for cultivation, such as safety cabinets, CO2 incubators, etc., are installed. In addition, cell preservation rooms and sterilized rooms are also installed.



A cold box for medicinal use with a freezer (left) and a safety cabinet that can accommodate biohazard materials (right)



CO2 Incubator (On the left is a stationary bottle roller)



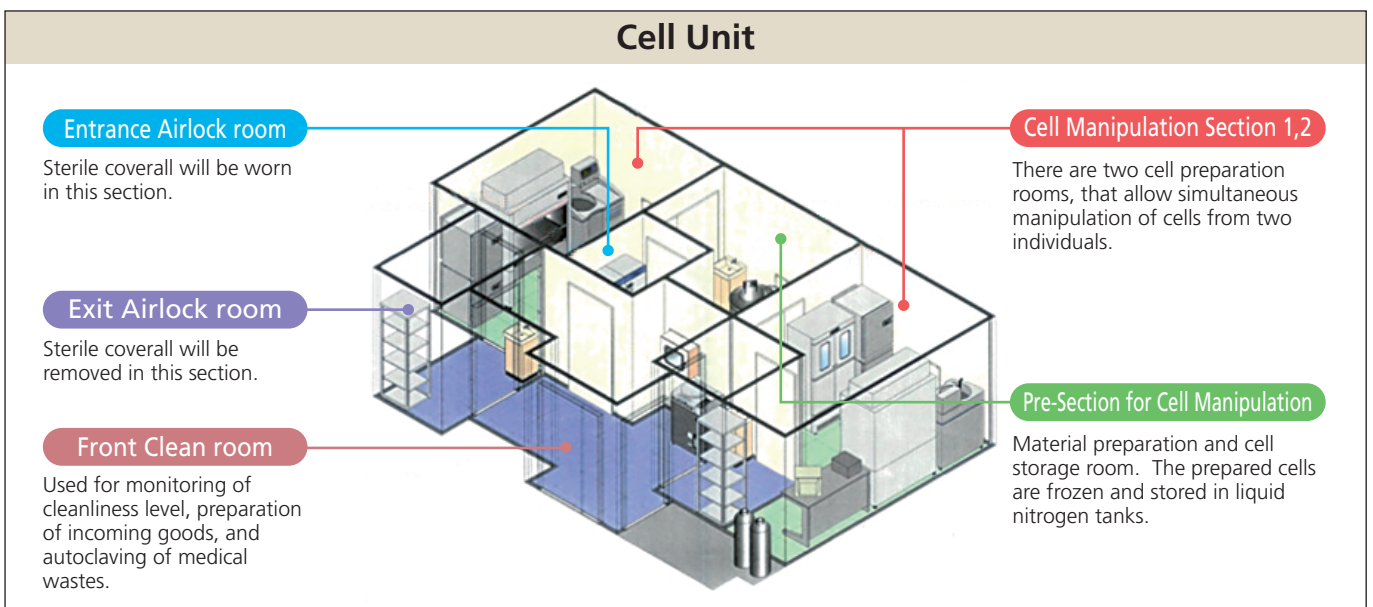
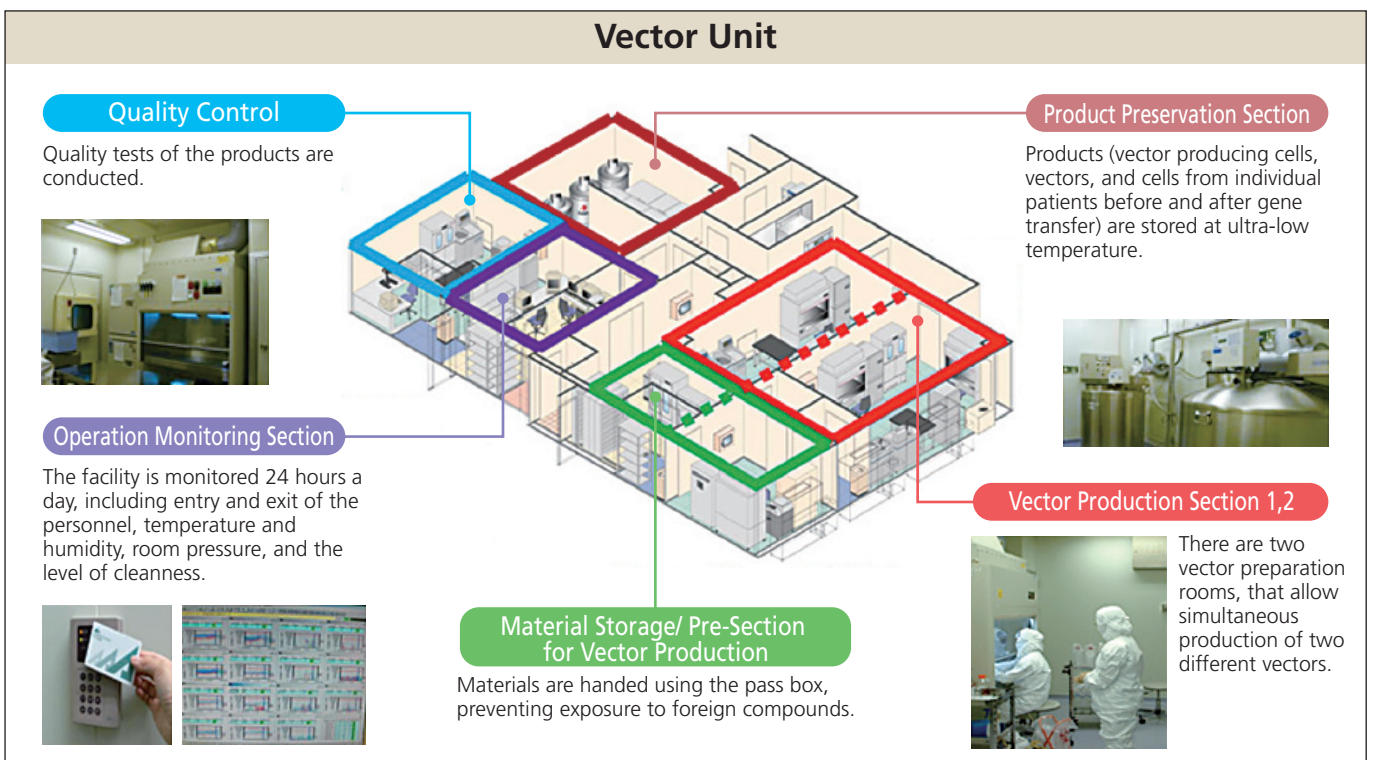
Automatically supplied liquid nitrogen cell storage tank



A large-scale high-pressure steam sterilizer

Core Facility for Therapeutic Vectors (CFTV)

- Role** CFTV is a facility to support the translation of cutting-edge investigational therapeutic methods from the bench to the bedside.
- Duties** Systematic production and storage of cells and viral vectors in current Good Manufacturing Practice (cGMP) grade which can be used in clinical trials.
- Outline of Facility** This facility is composed of a "Vector Unit", for cGMP production and storage of viral vectors and transduced cells, and a "Cell Unit", for preparation of vector transduced or peptide pulsed cells. The facility has obtained ISO9001 certification.



Department of Biopharmaceutical Safety Inspection

■ Role

The facility monitors the environment of the Cell Processing Center while performing safety verification on biopharmaceuticals such as cells, which have been manufactured compliant with GMP.

■ Duties

1. GMP-compliant analysis to test for the presence of bacteria, fungi, endotoxins, and mycoplasma within biopharmaceuticals.
 - Bacteria, Fungi: A sterility test using facilities and procedures that are GMP-compliant
 - Sterility Test A: An inspection of a sample that does not include antibodies
 - Sterility Test B: An inspection through a sterility test with a sample that includes antibodies (membrane filter method)
 - Endotoxins: Uses a specialized toxin meter
 - Mycoplasma: Extraction using the PCR method
2. Analysis to test for the presence of bacteria in the environment

■ Equipment

A specialized clean room is installed.



Window for handling preparations



Clean bench

It is possible for researchers from outside of the university to use the University of Tokyo Hospital CPC, the Institute of Medical Science Core Facility for Therapeutic Vectors as well as its Biopharmaceutical Safety Inspection Facility. For more information including the usage fees, please contact below.

〈CONTACT〉

For the University of Tokyo Hospital CPC

The University of Tokyo Hospital TR Center
Tel: 03-3815-5411 (Ext. 33585), E-mail: trc@h.u-tokyo.ac.jp

For Institute of Medical Science Core Facility for Therapeutic Vectors/ Biopharmaceutical Safety Inspection Facility

Division of Clinical Trial Safety Management
Institute of Medical Science Research Hospital
Tel: 03-5449-5462, E-mail: imshtr-adm@umin.ac.jp

Case Samples of TR Support



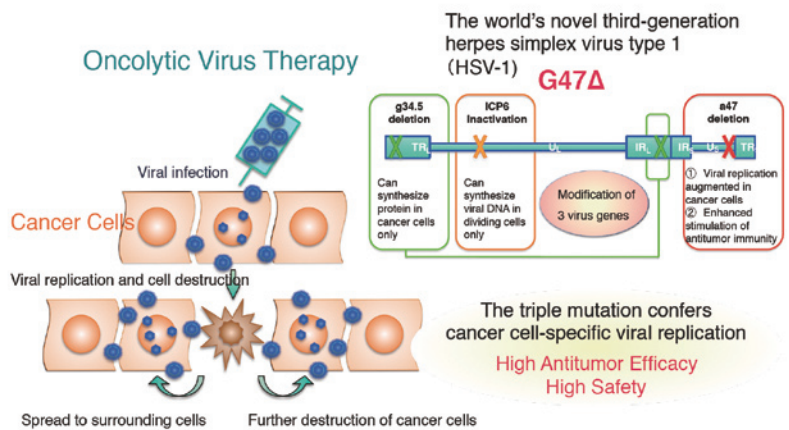
Development of New Cancer Therapy Using Genetically Engineered Oncolytic Viruses

Project Leader: **Tomoki Todo** (Division of Innovative Cancer Therapy, Institute of Medical Science, the University of Tokyo)

Oncolytic virus therapy is a rapidly developing means for treating cancer, in which viruses are genetically engineered in order to restrict virus replication to tumor cells. We have developed a triple-mutated, third-generation oncolytic HSV-1, G47Δ, by introducing an additional genetic mutation in the viral genome of G207, a second-generation HSV-1 used in clinical trials in the US. G47Δ exhibits improved replication properties in cancer cells and augmented antitumor immunity while preserving safety. In this project, G47Δ is clinically developed via trials in malignant brain tumor patients. The ultimate aim is to establish a new treatment modality that can be applied to a vast variety of solid cancer.

Support from TR Center: Regulatory issues, manufacturing of clinical grade virus products, responding to inquiries for clinical trials

Development of New Cancer Therapy Using Genetically Engineered Oncolytic Viruses

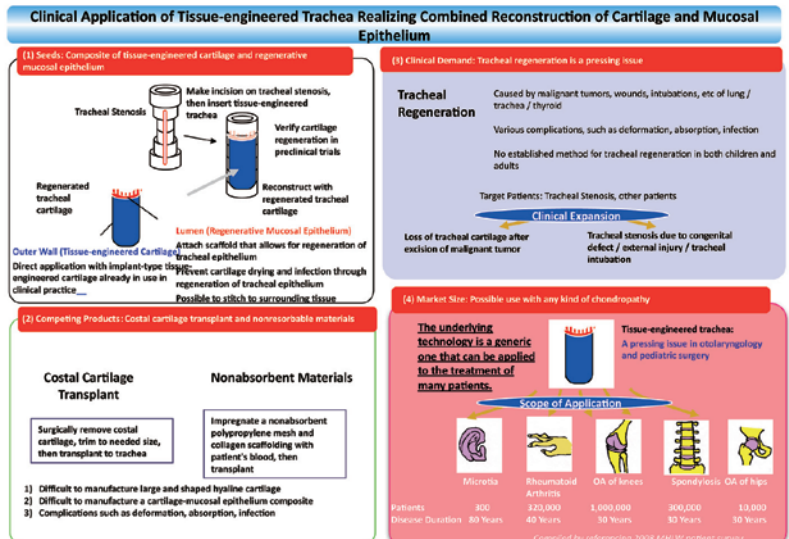


Clinical Application of Tissue-engineered Trachea Realizing Combined Reconstruction of Cartilage and the Mucosal Epithelium

Project Leader: **Tsuyoshi Takato** (22nd Century Medical and Research Center, Tissue Engineering, Oral-Maxillofacial Surgery, Dentistry and Orthodontics, the University of Tokyo Hospital)

For patients who are suffering from the function loss or tissue damage have in trachea or respiratory tract, its reconstruction is currently performed using transplantation of cartilage from the rib cartilage or nonabsorbent materials. However, both of these treatment methods often result in complications such as deformation, absorption, and infection; accordingly, there is no established method of treatment. Those responsible for the project have developed large-scale tissue-engineered cartilage with shape and firmness, have already carried out clinical research on human stem cells for nasal cartilage, and have already established the basic technology for the manufacture of tissue-engineered cartilage. Using this method, the manufacture of large-scale tracheal cartilage is possible. It is also anticipated that regeneration of the outer skin of the lumen and prevention of necrosis through inventive use of scaffolding materials will become possible in the future. In this project, in addition to reproducing the shape of the trachea, regenerated trachea cartilage (which will regenerate both cartilage and tracheal mucous membranes) will be manufactured, and the respiratory tract will be reconstructed. Through physician-led clinical trials, we aim for verification of the safety and validity of regenerated tracheal cartilage.

Support from TR Center: Use of CPC, regulatory compliance support, etc.



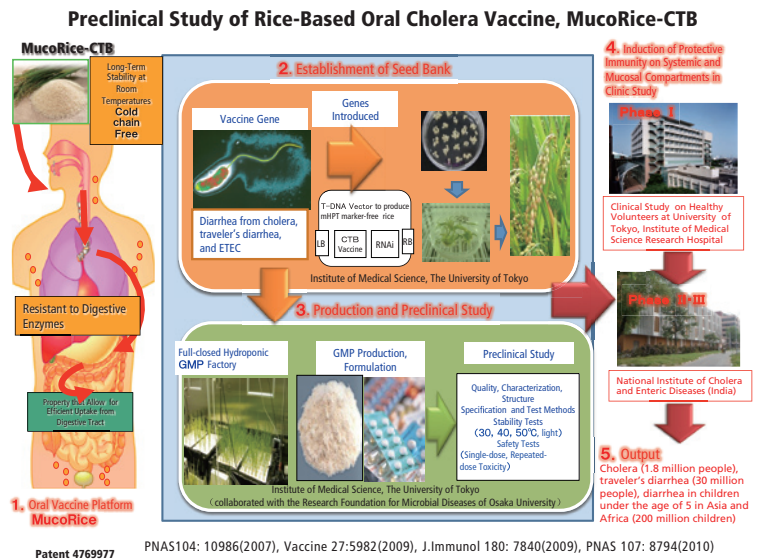


Preclinical Study of Rice-based Oral Cholera Vaccine, MucoRice-CTB

Project Leader: **Hiroshi Kiyono** (Mucosal Immunology, Institute of Medical Sciences, the University of Tokyo)

A rice-based vaccine (or MucoRice™) has recently attracted interest as a vaccine production, storage and delivery system for oral immunization. Our findings showed that MucoRice-CTB expressing B subunit of cholera toxin (CTB) antigen was stable at room temperature for three years without loss of immunogenicity. Thus, we adapted the technology to develop a cold-chain free oral vaccine (MucoRice-CTB) against diarrhea from *V. cholera* and/or toxigenic *E. coli*. The aim of the study is to conduct preclinical study for clinical trials of MucoRice-CTB. To that end, first a seed bank must be established, and then, for the purpose of ensuring quality, the rice plant will be cultivated within the full-closed hydroponic GMP factory at the University of Tokyo's Institute for Medical Sciences. The cultivated rice seeds are polished and then made into a powder preparation. The method of formulation, physical chemical property, methods for specification, stability and safety studies are established. After stability and safety tests have been conducted, we will aim for physician-led clinical trials at the IMSUT Hospital.

Support from TR Center:
Test planning and design,
regulatory compliance



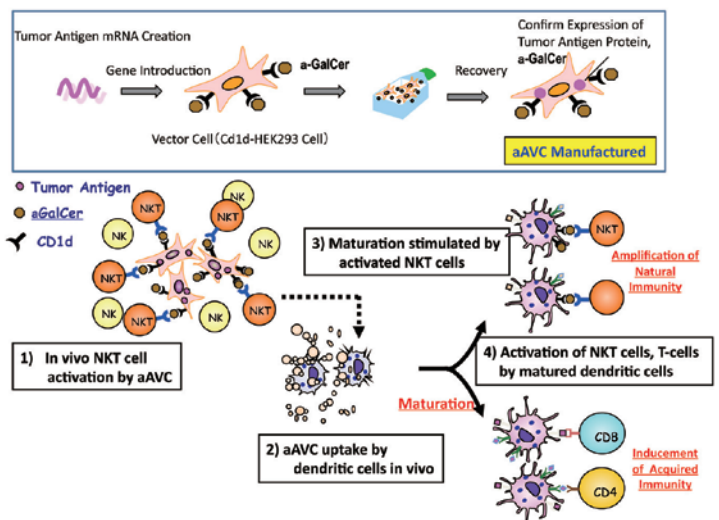
(Example of TR Support Outside of the University)

Development of Human Artificial Adjuvant Vector Cells

Project Leader: **Shinichiro Fujii** (RIKEN Research Center for Allergy and Immunology)

Those in charge of the project previously took note of the fact that dendritic cells mature after NKT cells, which are associated with natural immunity. They have developed a new immunotherapy system that can deliver the cancer antigens specifically to dendritic cells. We finally established such system as "Human artificial adjuvant vector cells (aAVC)". The aAVC was manufactured by adding the synthetic glycolipid α -GalCer, which potentially activates NKT cells, to allogeneic cells which had been introduced with mRNA encoding tumor associated protein antigens. Upon administering aAVCs to mice, dogs, it was apparent that both natural and acquired immunity were activated, and that the division and multiplication of T-cells, which target special antigens, is highly efficient. This was because the administered aAVC was killed by natural immunity and then captured by dendritic cells in the body, and subsequently the T cell response was apparent in an antigen specific manner. As future plans, we will establish aAVC-expressing tumor antigen (WT1 or NY-ESO-1) that has already been applied in other clinical settings. In the pre-clinical studies aimed for a clinical application, we will pay attention and determine the cell doses and dosage intervals in addition to verifying the safety of aAVC.

Support from TR Center:
Test planning and design,
regulatory compliance



Projects Currently Being Supported at the University of Tokyo TR Center

Project shown in the table below are currently supported at the University of Tokyo TR Center. Should a member of a corporation be interested, please contact us. We will create an opportunity to match you with a researcher.

	Project Name	Notes	Contact*
1	Development of Human Artificial Adjuvant Vector Cells (Adjuvant vector cells with WT1/NY-ESO1 manifestation)	Currently seeking a partner business	A
2	Biomarker for stomach/pancreatic cancer		A
3	Research and development for minute stitches that do not require ligatures		A
4	Creation of a retinal pigment epithelium sheet that uses new, temperature-responsive culture plates		A
5	Development of a new medicine--an anti-FGF2 aptamer for the treatment of chronic rheumatoid arthritis		B
6	Preclinical Study of Rice-based Oral Cholera Vaccine, MuocRice-CTB		B
7	Clinical application of a material that inhibits new plasmin chemosynthesis in patients with inflammatory diseases		B
8	Development of recombined measles that features tumor cell-solubility for the treatment of breast cancer		B
9	Development of prognostication equipment through biomarker panels for heart and kidney diseases		A
10	Treatment of renal cell carcinoma by autologous tumor lysate-pulsed dendritic cells incorporating an immunoregulatory program		A
11	Intraperitoneal autologous $\gamma\delta$ T cell therapy for refractory gastric cancer with ascites		A
12	Clinical application of implant-type tissue-engineered cartilage for cleft lip-nose		A
13	Regenerative medicine for corneal epithelial stem cell deficiency with serum and feeder-free corneal limbal epithelial cell culture sheets using new, temperature-responsive culture plates	Currently seeking a partner business	A
14	A lymphedema prevention method		A
15	Development of New Cancer Therapy Using Genetically Engineered Oncolytic Viruses		B
16	Promotion, through networking, of an alveolar bone regeneration process using cultivated osteoblast cells derived from one's own bone marrow		B
17	The development of regenerative therapy for gonarthrosis with hemophilia using mesenchyme stem cells from one's own bone marrow		B
18	Clinical application of tissue-engineered trachea realizing combined reconstruction of cartilage and the mucosal epithelium		A

* A : The University of Tokyo Hospital,
B : Institute of Medical Science

For Researchers Seeking TR Support

The University of Tokyo TR Center provides assistance in connecting the quality basic research to clinical applications, regardless of whether the researchers are in or outside of the university. We are able to offer support not just with the usage of facilities such as the CPC, but in various other ways as well.

Our support can be offered in;

- Investigational product manufacturing at the CPC
- Consultation regarding regulatory affairs related to PMDA, the Ministry of Health, Labor, and Welfare (assistance in pharmaceutical affairs consultation on R&D strategy and IND application, etc.)
- Planning of clinical trial protocol
- Data center tasks

(We are able to undertake other tasks not listed above. Please ask for more information.)

If you wish to receive support, please feel free to contact us using the details below.

Contact

The University of Tokyo Hospital TR Center

<http://trac.umin.jp/hospital/>
Tel: 03-3815-5411 (Ext. 33585) E-mail: trc@h.u-tokyo.ac.jp

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