The University of Tokyo

Translational Research Support at The University of Tokyo

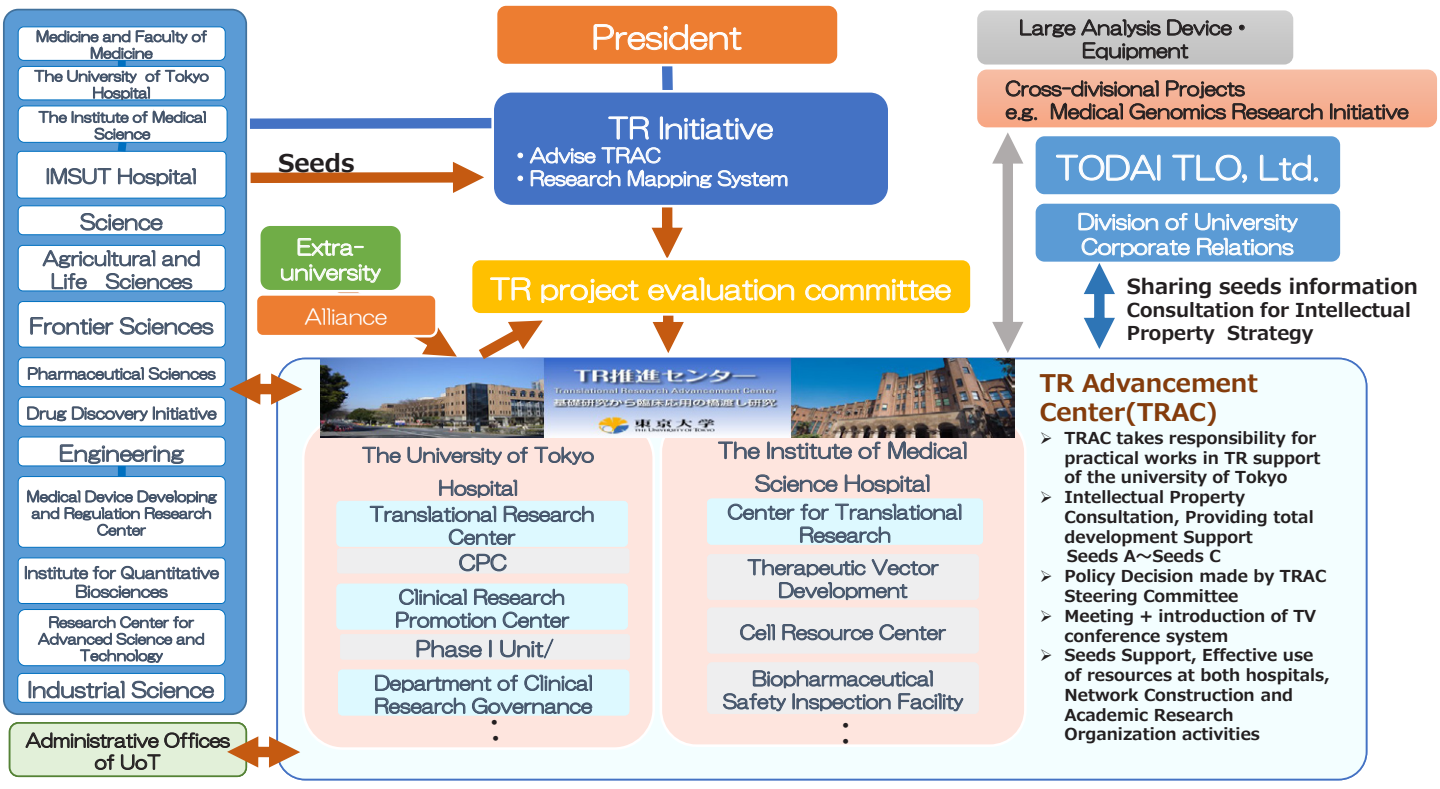
東京大学
THE UNIVERSITY OF TOKYO

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 AMED Translational Research program; Strategic PRomotion for practical application of INnovative medical Technology (Manager:Yutaka Osuga, Vice Director, the University of Tokyo Hospital/Professor of Gynecologic Surgery).

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

Yutaka Osuga
Manager at the University of Tokyo for The Translational Research program; Strategic PRomotion for practical application of INnovative medical Technology, TR-SPRINT
Vice Director/Head of 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 institute for quantitative biosciences 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 Promotion 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 Pl Unit for conducting phase one tests. To accelerate development of engineering seeds, we utilize Molecular and Life Innovation platform of the University of Tokyo and Medical-Engineering World leading Innovative Graduate Study (WINGS). Genomic medicine is also our focus, and we established an efficient supporting system from clinical and research standpoints of view. In order to engage in translational research constantly, we are in the process of expanding and enhancing the related departments and supporting outside facilities.

IMSUT Hospital as a project hospital that furthers translational research

Hiroshi Yotsuyanagi
Director, IMSUT Hospital

The IMSUT (The Institute of Medical Science, The University of Tokyo) Hospital is the only hospital in Japan affiliated with a research institute attached to a national university. It has an important role as a project hospital, conducting work such as early-stage clinical studies and translational research (TR) to connect cutting-edge research to clinical practice. As our aim is to be a center for the clinical development of innovative medical technology, we have put systems in place to enable TR to proceed smoothly, in keeping with the needs of the modern age, and assembled a full and varied range of specialist staff at IMSUT Hospital's Center for Translational Research (CTR). Our supporting departments for TR include Cell Resource Center, Therapeutic Vector Development Center and the Department of Biopharmaceutical Safety Inspection. At the University of Tokyo, the Translational Research Initiative is the university-wide organization with overall control of TR. The IMSUT Hospital has responsibility for one branch of the TR Advancement Center (TRAC), in conjunction with the University of Tokyo Hospital. Another feature of the IMSUT Hospital is that it acts a National Joint Usage hospital, taking in "out-of-school" seeds as well as seeds developed at the university. We expect the IMSUT Hospital to be widely used as a place for furthering clinical research in high-level projects. In 2014, we established the Center for Gene & Cell Therapy (CGCT), with a focus on cancer and intractable diseases, taking our hospital in a new direction. In the US and Europe, gene therapy is enjoying a resurgence, with increasing clinical research activity to put the technology to practical use. The IMSUT-CGCT will further TR in its role as a center for gene and cell therapies in Japan.

TR Organizations and Facilities at the University of Tokyo Hospital

Translational Research 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 Promotion 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

Center for Translational Research

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.

Therapeutic Vector Development Center

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 IMSUT Hospital and Shinshu University 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.

Cell Resource Center (IMSUT-CRC)

Since 1997, we have been manufacturing, testing and storing cell products for gene and cell therapy. IMSUT-CRC has been registered as a cell processing facility (FC3150141) since 2015. Recently, we have engaged in manufacturing and providing cell products from preclinical use to those of clinical trials sponsored by pharmaceutical companies, such as mesenchymal stromal cell products for clinical trials (IMSUT-CORD), research purpose cord blood cells for National BioResorce Project, and research of dendritic cell therapy by neoantigen stimulation.

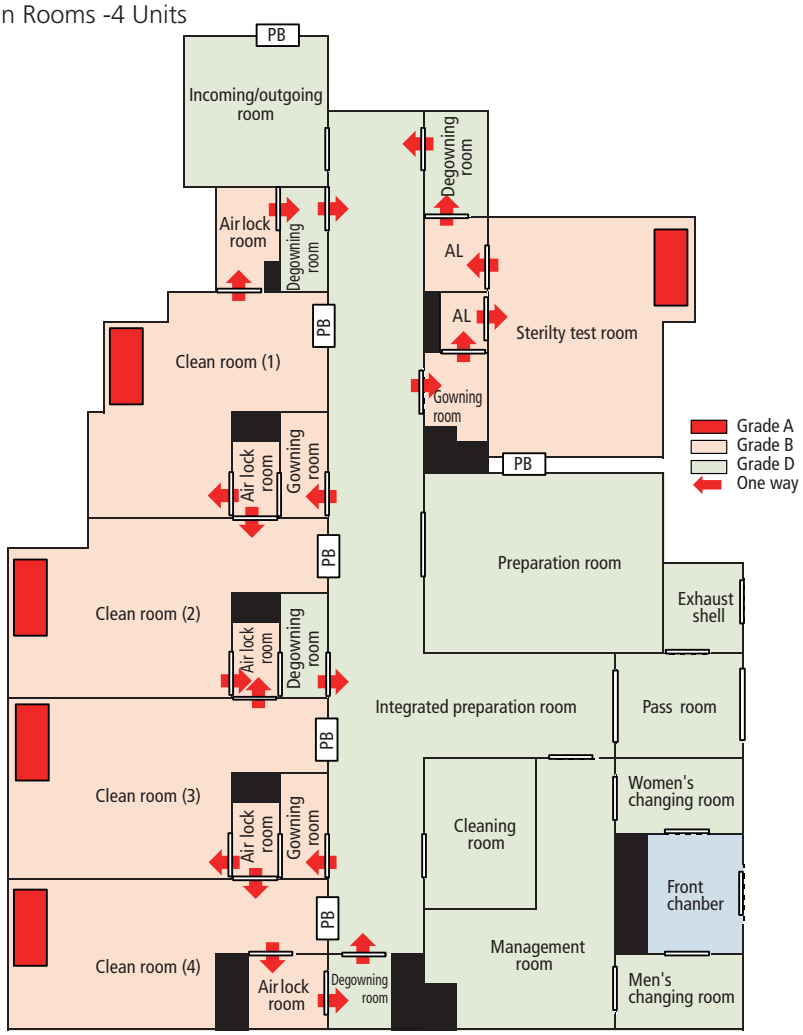
Cell Processing Center (CPC)

■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 the Act to Ensure the Safety or Regenerative Medicine, and cell therapy and regenerative medicine fully comply with the required laws and ordinances.

■Outline

Location: Central Clinical Service Buildg.2, Floor 9 The University of Tokyo Hospital
Area: 210㎡
Facilities: Clean Rooms -4 Units



■Equipment

Various types of machines necessary for cultivation, such as safety cabinets, CO2 incubators, etc., are installed.


Clean room


Preparation room


Management room

Therapeutic Vector Development Center

■Role It 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.

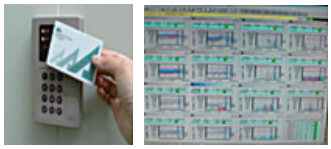
Vector Unit

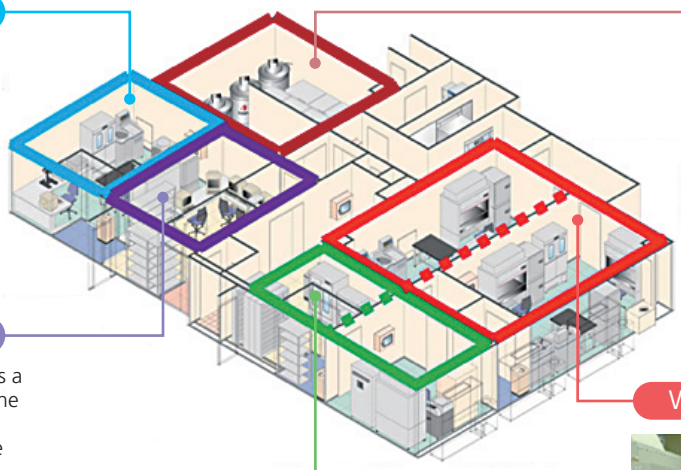
Quality Control

Quality tests of the products are conducted.

Operation Monitoring Section

The facility is monitored 24 hours a day, including entry and exit of the personnel, temperature and humidity, room pressure, and the level of cleanness.





Product Preservation Section

Products (vector producing cells, vectors, and cells from individual patients before and after gene transfer) are stored at ultra-low temperature.

Vector Production Section 1,2

There are two vector preparation rooms, that allow simultaneous production of two different vectors.

Material Storage/ Pre-Section for Vector Production

Materials are handed using the pass box, preventing exposure to foreign compounds.

Cell Unit

Entrance Airlock room

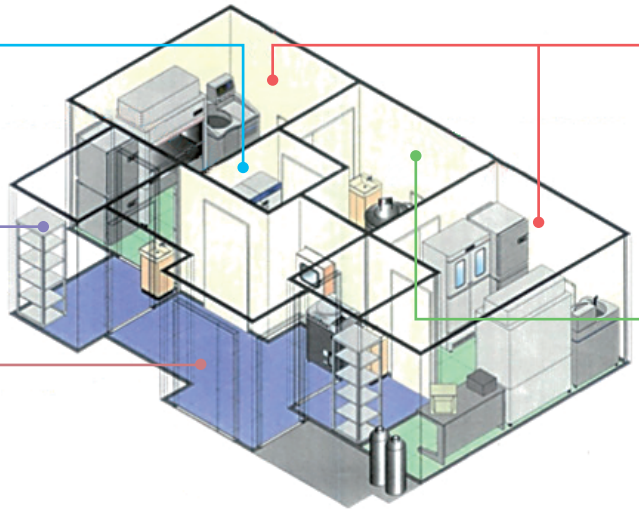
Sterile coverall will be worn in this section.

Exit Airlock room

Sterile coverall will be removed in this section.

Front Clean room

Used for monitoring of cleanliness level, preparation of incoming goods, and autoclaving of medical wastes.



Cell Manipulation Section 1,2

There are two cell preparation rooms, that allow simultaneous manipulation of cells from two individuals.

Pre-Section for Cell Manipulation

Material preparation and cell storage room. The prepared cells are frozen and stored in liquid nitrogen tanks.

TR Verification Laboratory
(Department of Biopharmaceutical Safety Inspection)

■Role

This department has been supporting translational researches (TR) by validating the safety of experimental therapeutic approaches and biopharmaceutical products for clinical trials.

■Duties

1. GMP-compliant laboratory analysis to examine the presence of bacteria, fungi, mycoplasma, and endotoxin in biopharmaceutical products [Reservation required].

Test / Target	Method	Detail	Required Days
Sterility Test	Membrane filter method	Sterility is examined by culture after filtration <applicable to samples containing antibiotics>	14-16 days
	Direct culture	Sterility is examined directly by culture <appropriate for standard samples>	
Mycoplasma Testing	Nucleic Acid Amplification	The existence of mycoplasma is examined by PCR	1-3 days
	Specific enzyme detection	Mycoplasma-specific enzyme is quantified by luminometer	
	Culture method	The existence of mycoplasma is examined by culture in liquid and agar medium	28-30 days
Bacterial Endotoxin Test	Turbidimetric method	Endotoxin is quantified by examining gel time with toxinometer.	1-3 days

2. Environment monitoring to test the contamination of microorganism in the facilities
We evaluate the contamination of microorganisms in the facilities by culturing the submitted samples from airborne or surface sampling. Identification and drug susceptibility checks of microorganisms are also available when the first screening is positive.

■Equipment

A specialized clean room is installed.


Window for handing 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 Translational Research Center
Tel: 03-5800-9070, E-mail: trc@h.u-tokyo.ac.jp

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

Center for Translational Research
Institute of Medical Science Research Hospital
Tel: 03-5449-5462, E-mail: dctsm@ims.u-tokyo.ac.jp

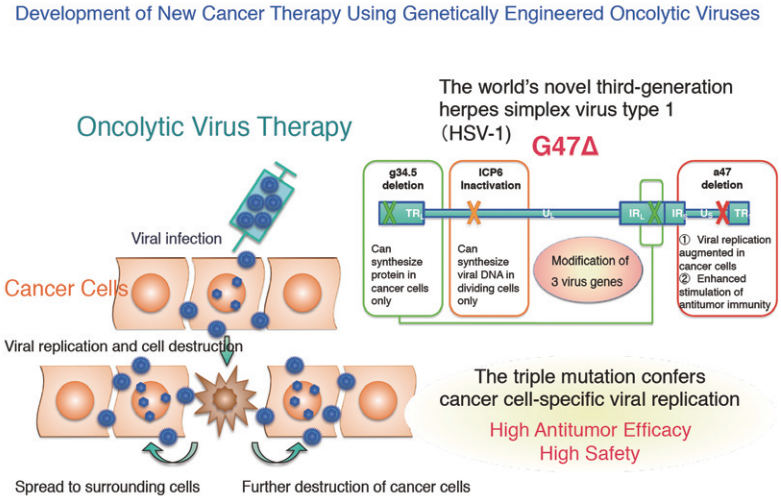
Case Samples of TR Support

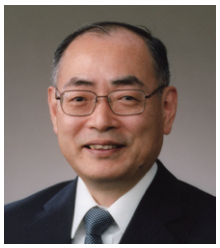
Development of New Cancer Therapy Using Genetically Engineered Oncolytic Viruses

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

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. The first-in-the-world clinical development of G47Δ results in a new drug approval in Japan in 2021 as the first oncolytic virus drug in the World for malignant brain tumors. Clinical trials are ongoing in patients with olfactory neuroblastoma, prostate cancer or malignant mesothelioma. 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

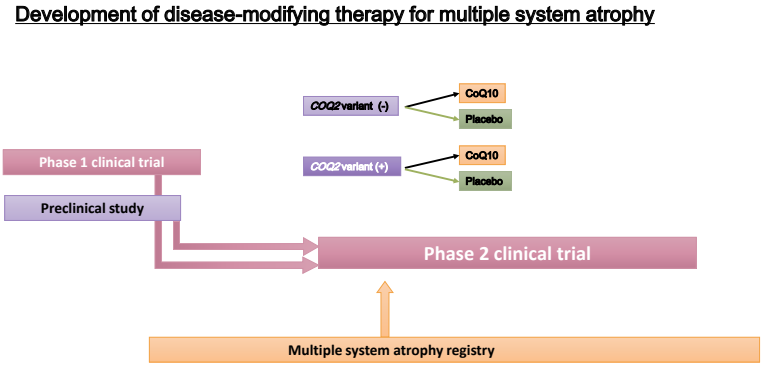




Development of disease-modifying therapy for multiple system atrophy

Project Leader: **Shoji Tsuji** (Project Professor of Molecular Neurology, Graduate School of Medicine, The University of Tokyo)

Multiple system atrophy (MSA) is an adult-onset neurodegenerative disease with autonomic failure combined with various combinations of Parkinsonism and cerebellar ataxia. The number of patients with MSA in Japan is estimated to be 12,000. The etiology of MSA remains to be elucidated and efficacious treatment for MSA has not been established.
Although the frequency is rare, we identified multiplex families with MSA and discovered pathogenic variants in COQ2 gene encoding an enzyme involved in the biosynthesis of coenzyme Q10 (CoQ10). We furthermore revealed that a COQ2 variant is a risk factor for developing MSA. Recent studies have revealed that CoQ10 levels are decreased in the blood, cerebrospinal fluid and cerebellum even in MSA patients who do not carry the COQ2 variant. Taken together, supplementation of CoQ10 is expected to be an efficacious disease-modifying therapy for MSA.
Since we plan to use a high dose of CoQ10, we conducted a phase 1 clinical trial to confirm safety and pharmacokinetics of administration of a high dose CoQ10. We then started a phase 2 clinical trial to investigate the clinical efficacy of supplementation of a high dose CoQ10 in suppressing progression of MSA.

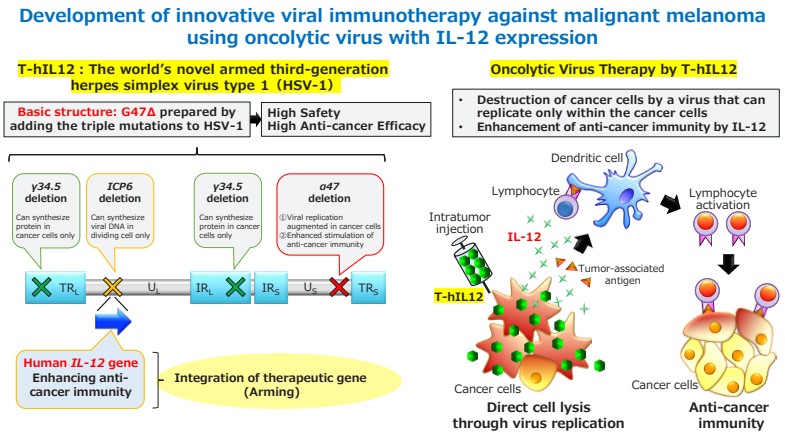


Development of Innovative Viral Immunotherapy against Malignant Melanoma Using Oncolytic Virus with IL-12 Expression

Project Leader: **Ryuhei Okuyama** (Department of Dermatology, Shinshu University School of Medicine)

Oncolytic viral therapy is a therapeutic method using viruses with replication in cancer, but not normal tissues, by unique modification to viral genome. The oncolytic virus destroys cancer by direct cell lysis through virus replication. It also induces anti-cancer immunity in the process of immunological elimination of the virus, and acts as an efficient cancer vaccine. This study aims at clinical development of T-hIL12, an armed oncolytic herpes simplex virus type 1 (HSV-1). T-hIL12 acquires not only high safety, but also replication ability specific for cancer which leads to powerful anti-tumor effect, because the basic structure is G47Δ, a triple-mutated, third generation oncolytic HSV-1. Furthermore, human *IL-12* gene is incorporated in T-hIL12 for further enhancing the induction of anti-cancer immunity. T-hIL12 is a domestically produced oncolytic virus, which follows G47Δ, and is the first next-generation oncolytic virus product armed with a variety of functional genes. We are developing the armed oncolytic virus originating in Japan and aim for the development of an innovative cancer therapy responding to various solid cancers including melanoma.

Support from TR Center:
Regulatory issues, preparation and conduct of clinical trial



(Example of TR Support Outside of the University)

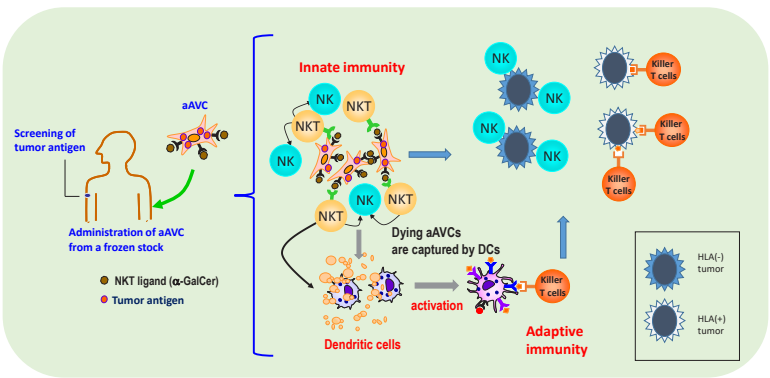
Development of a new therapeutic cellular drug against cancer "artificial adjuvant vector cells"

Project Leader: **Shin-ichiro Fujii** (Leader, Laboratory for Immunotherapy, RIKEN Center for Integrative Medical Sciences (IMS)/Vice Program Director, RIKEN program for Drug Discovery and Medical Technology Platforms)

Since tumors are often composed of a mixture of HLA class I^- and class I^+ cells, both innate and adaptive immunity are crucial for cancer immune surveillance. However, precise therapeutic strategies to restore such surveillance in cancer patients have yet to be developed. DCs, as "nature's adjuvants", play a pivotal role in determining the character and magnitude of an immune response. Therefore, we have studied the role of DCs *in situ* for anti-tumor immunity by focusing on the link between innate and adaptive immunity. As an *in vivo* DC targeting strategy, we have established artificial adjuvant vector cells (aAVCs) by using $CD1d^+$allogeneic cells loaded with α-GalCer, a ligand for NKT cells, and transfected with tumor antigen-encoding mRNA, thus combining the adjuvant effects of NKT cell activation with delivery of antigen to DCs. This approach can lead to the generation of long-term memory T cells and effective anti-tumor immunity. We have completed the regulatory science consultation for discussing the pharmaceutical quality and the design of a clinical study with the Pharmaceuticals and Medical Devices Agency. We completed the physician-initiated phase I clinical trial of aAVC-WT1 for refractory or relapsed acute myelogenous leukemia, which were conducted by Department of Hematology/Oncology, The Institute of Medical Science, The University of Tokyo since July, 2017 and have moved to Phase II in January, 2021.

Support from TR Center:
Preparation and conduct of clinical trial

Antitumor mechanism by tumor antigen-expressing artificial adjuvant vector cell (aAVC) therapy



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 Translational Research Center

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