Disease Classification
- Psychiatry
- Neurology
- Ophthalmology
- Otorhinolaryngology
- Oral Surgery
- Respiratory
- Cardiology
- Gastroenterology
- Nephrology
- Urology
- Gynecology
- Hematology
- Musculoskeletal System
- Dermatology
- Endocrinology
- Oncology
- Infectious Diseases
- Pediatrics

Portfolio
2019
Development of Advanced Medicine at Nagoya University
FY2018 Japan Agency for Medical Research and Development
Project of Translational and Clinical Research Core Centers
Core Clinical Research Hospitals Associated Project

Modality
- Medicines
- Devices
- In Vitro Diagnostics
- Regenerative Medicines
- Combination Products
- Non-classifiable

NAGOYA UNIVERSITY
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<td>Development of Virus Specific Cytotoxic T cells Therapy for Refractory Viral Infection after Allogeneic Hematopoietic Stem Cell Transplantation</td>
<td>Nagoya University</td>
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<td>Optimization study of bone regeneration to improve prognostic QOL for defect of jaw bone cases such as tumor resection</td>
<td>Nagoya University</td>
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<td>Phase I study of piggyBac transposon mediated chimeric antigen receptor gene modified T cells for CD19 positive acute lymphoblastic leukemia</td>
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<td>Yoshiyuki Takahashi</td>
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<td>Phase 1 clinical trial to evaluate the safety of intra-bone marrow injection of adipose-derived mesenchymal stem cell and hematopoietic stem cell to enhance the engraftment in the setting of cord blood transplantations</td>
<td>Aichi Medical University</td>
<td>Takayuki Nakayama</td>
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<td>C30</td>
<td>The Evaluation of Efficacy and Safety of Rituximab (Genetical Recombination) in Refractory Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) Patients with Immunoglobulin G4 (IgG4) Autoantibodies in the Exploratory Clinical Trial (RECIPE Trial)</td>
<td>Nagoya University</td>
<td>Masahiro Iijima</td>
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- Psychiatry
- Neurology
- Geriatrics
- Dermatology
- Oral Surgery
- Respiratory
- Cardiology
- Gastroenterology
- Nephrology
- Urology
- Gynecology
- Hematology
- Oncology
- Pediatrics
- Infectious Diseases
2. Details of supported seeds
Disease Classification

Psychiatry
Neurology
Ophthalmology
Otorhinolaryngology
Oral Surgery
Respiratory
Cardiology
Gastroenterology
Nephrology
Urology
Gynecology
Hematology
Musculoskeletal System
Dermatology
Endocrinology
Oncology
Infectious Diseases
Pediatrics

Modality

Medicines
Devices
In Vitro Diagnostics
Regenerative Medicines
Combination Products
Non-classifiable
### Treatment for short stature by the FGFR3 inhibitory drug, meclizine

**Abstract**

FGFR3 is a negative regulator of longitudinal bone growth and over-activation of FGFR3 causes several short-limbed skeletal dysplasias. By FDA-approved drug screening, we identified that meclizine, an anti-histamine OTC drug, ameliorated abnormally activated FGFR3 signaling in vitro. Meclizine significantly increased the body length in mutant mice as well as in the wild type mice in vivo. The plasma concentration of meclizine during treatment was within the range that has been used in clinical settings. We examine potential clinical feasibility of meclizine for the improvement of short stature in FGFR3-related disorders.

### Advantages

- Growth hormone treatment is less effective.
- Bone lengthening surgery is too invasive.
- Oral administration can be acceptable for pediatric Intractable rare diseases.

### Patent Information

Utility patent

### Market Overview

1,000 in Japan, 60,000 in worldwide

### Stage of Development

- We have finished a physician-initiated phase I clinical trial.
- We will plan a repeated administration trial (phase I/II).
- We are negotiating license agreement with some pharmaceutical companies.

---

**Target Diseases (Applications)**

FGFR3-related skeletal dysplasias (achondroplasia, hypochondroplasia, thanatophoric dysplasia)

---

**Diagram**

- Oral administration of meclizine for 10 days to mutant mice (Fgr3<sup>ach</sup>) aged 7 days

---

**Completion of physician-initiated phase 1 clinical trial (December 2018)**
Project Title
The Evaluation of Efficacy and Safety of Rituximab (Genetical Recombination) in Refractory Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) Patients with Immunoglobulin G4 (IgG4) Autoantibodies in the Exploratory Clinical Trial (RECIPE Trial)

Organization
Nagoya University
Principal Investigator
Masahiro Iijima

**Rituximab can exert its therapeutic effect by selective intervention to the pathogenesis of refractory CIDP including IgG4 autoantibodies**

<table>
<thead>
<tr>
<th>Target Diseases (Applications)</th>
<th>CIDP (The expected efficacy is improvement of motor dysfunction in refractory CIDP, especially with IgG4 subclass autoantibodies.)</th>
</tr>
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<tr>
<td>Abstract</td>
<td>A certain rate of CIDP patients is involved in IgG4 autoantibodies and shows resistance to conventional therapies. Since rituximab performs strong suppression in antibody production by inhibiting B cells, it is expected as a fundamental therapeutics for refractory CIDP in which known and unknown autoantibodies could be involved. Therefore, we plan the investigator-initiated clinical trial (RECIPE Trial).</td>
</tr>
</tbody>
</table>
| Advantages                    | • Among conventional therapies (steroid, intravenous immunoglobulins (IVlg), plasmapheresis), IVlg is used as the first-line. On the other hand, for patients with IgG4 autoantibodies, IVlg is ineffective and the others are less effective. Rituximab is a molecular targeting therapy and selectively inhibits antibodies.  
  • This is the first trial to verify the efficacy of rituximab for refractory CIDP.  
  • Note that IgG4 is a specific subclass lacking complement binding ability, and rituximab is an ideal drug to eliminate the etiology of refractory CIDP involved in autoantibodies. |
| Patent Information            | None |
| Market Overview               | • CIDP is one of the intractable diseases in Japan, and the number of patients is estimated 4,926 in 2016. IgG4 autoantibody cases accounts for 10 to 20% of them. Since the involvement of unknown autoantibodies is also assumed, the specific number is unknown.  
  • IVlg is used as initial or relapse, and maintenance therapy for CIDP. While IVlg is expensive in the long term, rituximab can be expected to suppress long-term recurrence, resulting in low cost compared to other therapeutics. |
| Stage of Development          | • Exploratory clinical trial (Scheduled to start recruitment of trial participants from 1st quarter of 2019)  
  • Early approval or transition to confirmatory clinical trial is assumed. |
**Project Title**

Development of Virus Specific Cytotoxic T cells Therapy for Refractory Viral Infection after Allogeneic Hematopoietic Stem Cell Transplantation

**Organization**

Nagoya University

**Principal Investigator**

Yoshiyuki Takahashi

---

**Target Diseases (Applications)**

Refractory EBV associated Post-transplant Lymphoproliferative Disease (PTLD) after allogeneic hematopoietic stem cell transplantation

**Abstract**

Production of 3rd party derived virus specific cytotoxic T cells and infusion to the patient

**Advantages**

- eligible to rituximab resistant PTLD
- “off the shelf” product
- eligible for unrelated stem cell transplantation

**Patent Information**

Process patent

**Market Overview**

30 patients/year in Japan

**Stage of Development**

Clinical trial
Project Title
Development of a medical equipment to separate autologous adipose-derived regenerative cells (ADRCs) to perform a less invasive treatment of male stress urinary incontinence

Organization
Nagoya University
Principal Investigator
Momokazu Gotoh

Peri-urethral Injection of Autologous Adipose-derived Regenerative Cells (ADRCs)

Liposuction from the abdomen (0.5 to 1 hour)

Isolation of ADRCs

Cellution™ System

Harvest tissue and return to patient in a series of procedure

Transurethral injection (15 mins)

Target Diseases (Applications)
Stress urinary incontinence (SUI) in male (Improvement of stress urinary incontinence)

Abstract
The autologous tissue source is harvested from the abdomen by liposuction. ADRCs including stem cells are then isolated from the tissue without culture using the Cellution system. Finally, ADRCs are transurethrally injected into the urethral sphincter. An investigator-initiated clinical multi-center trial (ADRESU study) is ongoing for male SUI.

Advantages
• Transurethral injection of ADRCs is a world-first treatment, which is less invasive using autologous cells without ex vivo culture.
• The series of this operation in which is isolation and injection of the ADRCs concludes few hours.
• There is no available treatment for mid to moderate male SUI in Japan.

Patent Information
3 related patents filed in Japan, one approved in U.S., 5 under application

Market Overview
Prevalence of male SUI: about one million patients in Japan

Stage of Development
Enrollment of targeted 45 patients was completed in March 2018. After data fixation in March 2019, the comprehensive report will be prepared aiming at PMDA approval and insurance coverage.
## Development of truss type external fixator

**Organization**  
Nagoya University

**Principal Investigator**  
Hitoshi Hirata

### PinFix

Easy to apply and highly versatile external fixator with truss structure

### Target Diseases (Applications)

- Fractures  
  Fresh fracture treatment and surgical collection of bone deformity in the upper extremity

### Abstract

PinFix is the first external fixator with truss structure which is highly versatile and easy to apply. It consists only of inexpensive parts. Which make it an ideal skeletal fixation device for countries and areas with limited medical finance and human resources.

### Advantages

Conventional external fixators have cantilever structure. Therefore, they need to be composed of thick and heavy metal parts to cope with high stress concentration around the joints. By contrast, in external fixators with truss structure, mechanical stress evenly dissipate along the pins and rods, thereby, effectively avoid stress concentration at the joints.

### Patent Information

- Japan 4304321 2009/5/15 External fixator  
- Korea 1377734 2014/3/14 External fixator

### Market Overview

3,000 patients in Japan and 180,000 in the world in a year

### Stage of Development

- Licence out to Meira Ltd. In 2016  
- Extension of indication to lower extremity
# The Development & Preclinical Evaluation of the Patient-Specific Cardiac Support Device (CSD) with less constraint on RV for Dilated Cardiomyopathy

**Project Title**
Multicenter clinical trial of the Patient-Specific Cardiac Support Device (CSD) with less constraint on RV for Dilated Cardiomyopathy

**Organization**
Nagoya University

**Principal Investigator**
Toshiaki Akita

**Abstract**
Multicenter clinical trial will be conducted to evaluate the safety and the usefulness of the Patient-Specific Cardiac Support Device (CSD) with less constraint on RV for Dilated Cardiomyopathy.

**Target Diseases (Applications)**
1. Idiopathic dilated cardiomyopathy (DCM)
2. Secondary cardiomyopathy
3. Ischemic cardiomyopathy

**Advantages**
1. Patient-specific design—Less invasive and more effective
2. Less constraint on RV—Preserve RV diastolic function and cardiac output
3. Multi-scale & multi-physics cardiac simulation by UT-Heart Inc.—Select the suitable candidate and predict the postoperative cardiac function

**Patent Information**
1. Basic patent registered:
2. Method of creating design paper for patient-specific heart correction net:
   - PCT⇒US, EP, CN, JP registered,
3. Heart correction net:
   - JP, US, CN registered, PCT⇒EP filing,
4. Registered design:
   - JP(2), CN(1), US(2), EP(1)

**Market Overview**
1. Huge market for heart failure treatment (650 millions people in US) (Japan: 1000 cases/year, 3.5 billion yen/year)
2. Superior technology to competitor (Mardil: Acorn CorCap successor)

**Stage of Development**
1. To establish the safety of this device through small feasibility clinical trial in 2019
2. To establish the efficacy for improvement in cardiac function, cardiac remodeling indices, and QOL through investigator-initiated clinical trials in 2020-2021
3. To verify the UT-Heart simulation model by comparing the predicted and measured values of UCG & pressure study (accuracy: within less than 5%)
### Practical use of new diagnostic and therapeutic equipment for early stage lymphedema

**Organization**
Nagoya University

**Principal Investigator**
Hitoshi Hirata

---

**Early diagnosis and novel treatment for lymphedema**

#### Lymphatic vessels
Part of circulatory system

Immune reaction, maintenance of body fluid and macromolecule balance, lipid absorption

#### Problems of lymphedema
Pathology?
Diagnostic criteria?
Etiology?
Once progressive, Hard to treat

---

Recent reports: Lymphatic dysfunction → lymphedema

Treatment of lymphedema ※ PROPER evaluation & intervention

---

#### Target Diseases (Applications)
Lymphedema

#### Patent Information

#### Expected Effect
Lymphedema is a potential side effect of cancer surgery, especially in breast cancer and uterine cancer. Once lymphedema is developed, it can be difficult to treat. Based on the evaluation of the lymphatic system in early stage of each patient, we will establish a novel treatment algorithm for the lymphedema.

#### Market Overview
Breast cancer (about 80 thousands/year) patients are increased recently in Japan. Lymphedema patients are living in Japan. The number of lymphedema patients are increasing at the rate of 6,000 per year. Worldwide, about 1.38 million women are diagnosed with breast cancer per year.

#### Other
The physician-led clinical trial are currently underway.
Regenerative treatment by autologous cells

Transplantation to the jaw of bone defect which is caused a tumor, trauma etc…

<table>
<thead>
<tr>
<th>Target Diseases (Applications)</th>
<th>Defect of jaw bone due to maxillofacial injury, tumor, and cystectomy</th>
</tr>
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<tbody>
<tr>
<td>Abstract</td>
<td>Examine the effectiveness and safety of bone-regeneration medicine using bone marrow derived mesenchymal cells (MSCs) differentiated from autologous MSCs. Using a mixture of β-TCP, platelet rich plasma, thrombin, and calcium chloride as a bone filling agent, the effects of the presence or absence of addition of MSCs are compared.</td>
</tr>
<tr>
<td>Advantages</td>
<td>It is less invasive and can create large bones compared to existing therapies.</td>
</tr>
<tr>
<td>Market Overview</td>
<td>Oral Cancer: about 7,800 (in Japan)</td>
</tr>
</tbody>
</table>
| Stage of Development           | • Approval of Advanced Medical Category B, Exploratory  
                               • Confirm the effectiveness of cell transplantation  
                               • Search for an efficient cell source |
Phase I study of piggyBac transposon mediated chimeric antigen receptor gene modified T cells for CD19 positive acute lymphoblastic leukemia

**Abstract**
Production of autologous CD19 CAR-T cells and infusion back to the patient

**Advantages**
PiggyBac transposon mediated gene transfer (non-viral gene transfer)
Reduced cost

**Patent Information**
Process patent

**Market Overview**
600 patients/year in Japan

**Stage of Development**
Clinical trial
A novel treatment for perinatal brain damage with Muse cells

Nagoya University
Yoshiaki Sato

Perinatal hypoxic ischemic encephalopathy (HIE)

Muse cells (Multilineage-differentiating stress enduring Cells)

Abstract
Multilineage-differentiating stress enduring (Muse) cells exist in bone marrow, skin, adipose, and other mesenchymal tissues, as well as in the connective tissues of many organs. So far, our non-clinical study with HIE model rats showed that Muse cells administered intravenously were detected in the injured brain, and ameliorated behavioral and learning impairments and movement abnormalities. The administration of Muse cells should be a promising therapy for HIE.

Advantages
Muse cells have the potential to self-renew and can differentiate into various types of somatic cells. Moreover, Muse cells readily integrate into injured sites and mediate tissue repair via tissue-specific differentiation.

Patent Information
Filed patent application

Market Overview
As the frequency of occurrence of HIE is 2 to 4 people per 1,000 live births, the marketability is considered to be great.

Stage of Development
We have been evaluating the treatment effect and safety with clinical grade Muse cells product in non-clinical studies and performing several experiments to reveal the underlying mechanism of the treatment effect of the Muse cells on HIE. We are going to proceed to an investigator-initiated clinical trial after this project.
3. Services
Clinical Trials

Center for Advanced Medicine and Clinical Research

- Creating Documents
  - Protocol
  - Investigator’s Brochure
  - Informed Consent Form
  - Manufacturing Related Documents of GMP for Investigational Drugs

- Creating Standard Operating Procedures
  - Operating Procedure for Outsourcing to Study Coordinating Committee
  - Operating Procedure for Clinical Study Coordinating Committee
  - Operating Procedure for Issuing Protocol and a Sample of Case Report Forms
  - Operating Procedure for Investigator’s brochure
  - Operating Procedure for Creating an Informed Consent Form
  - Operating Procedure for Handling Safety Information
  - Operating Procedure for Keeping Records
  - Operating Procedure for Efficacy and Safety Evaluating Committee
  - Operating Procedure for Auditing
  - Operating Procedure for Issuing the Clinical Study Report
  - Operating Procedure for Sample Storage/Management/Transport
  - Operating Procedure for Study Drug Management

Preparation phase

Data Coordinating Center

- Statistical Analysis
  - Plan for Statistical Matters of Clinical Study (Trial Design, Sample Size, Proposal and Description of Statistical Analysis Part)
  - Creating the Statistical Analysis Plan (SAP)

- Data Management
  - Creating a Structure of Case Registration and Assignment System
  - Creating a Structure of Data Management System

- Creating Standard Operating Procedures
  - Operating Procedure for Monitoring
  - Operating Procedure for Data Management
  - Operating Procedure for Case Registration and Assignment
  - Operating Procedure about Biostatistics
Clinical Trials

Center for Advanced Medicine and Clinical Research

- Project Management
- Issuing the Report
  - Clinical Study Report
  - Statistical Analysis Report
- Support for Clinical Research
  - Support for Minister in Verifying Conformance to Guidelines (Regenerative Medicine, Gene Treatment, Advanced Medicine)
  - Consultation with PMDA
  - Coordination
  - Monitoring (Investigator Initiated Study)
  - Study Drug Management at Study Coordinating Office
  - Study Drug Management
  - Support for Administration Office
  - Auditing
- Implementation phase
- Reporting phase

Data Coordinating Center

- Support for Clinical Research
  - Support for Data Monitoring Committee
- Statistically Analysis
  - Programming and Data Analysis in accordance with SAP, Mock
  - Gene Expression / DNA methylation Data
  - SNP/CNV Data
- Data Management
  - Maintenance of Case Registration and Assignment System
  - Enrollment and Assignment
  - Maintenance of Data Management System
  - Data Management
Patent

- Support for Patent Application
- Support for Patent Investigation

Pharmaceutical Affairs

- Communication with Regulatory Agencies
4. Facility
The center supports the innovation of gene, cell, and tissue products for advanced medicine. (ISO9001:2015)
Major Equipment

Bio-bank Sample Storage Room

HiSeq 2500 (Illumina)
Luminex 200 (MERCK MILLIPORE)
FLUOVIEW FV10i (OLYMPUS)

FACSaria™ Fusion (BD)

21 ultra-deep freezers
Freezer Room
Sample Preparation Room
Sample Preparation Room

Temperature Monitoring System
high-speed centrifuge
microscope

Freezer refrigerator

CO₂ incubator

biological safety cabinet