SAN RAFFAELE TELETHON INSTITUTE FOR GENE THERAPY

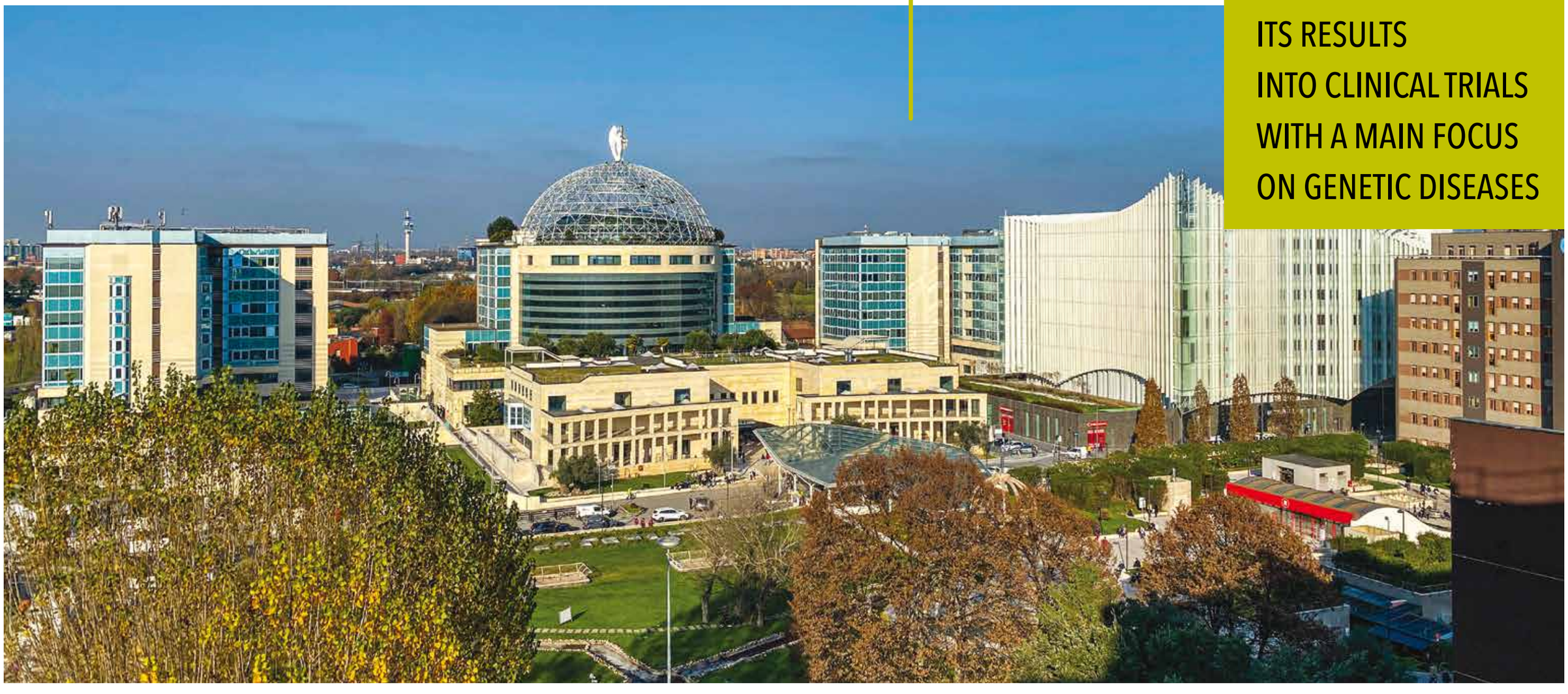
SR-Tiget

San Raffaele Telethon Institute for

GENE THERAPY

INDEX

WE PERFORM
CUTTING EDGE
RESEARCH ON GENE
AND CELL THERAPY
AND TRANSLATE
ITS RESULTS
INTO CLINICAL TRIALS
WITH A MAIN FOCUS
ON GENETIC DISEASES



SR-TIGET AT A GLANCE

Founded in **1996**, the San Raffaele Telethon Institute for Gene Therapy (**SR-Tiget**) is a joint venture between **Fondazione Telethon (FT)**, a major Italian charity funding research on rare genetic diseases, and **Ospedale San Raffaele (OSR)**, a research hospital of excellence certified by the Ministry of Health.

The Institute has been directed by **Luigi Naldini** since 2008 and is located in **Milan** (Italy) within the OSR campus, which includes a large multi-disciplinary research hospital, a biomedical research center, the Vita-Salute San Raffaele University and hosts several biotech companies.

For more information visit www.sr-tiget.it

SR-TIGET HAS GAINED WORLDWIDE RECOGNITION AS A CENTER OF EXCELLENCE IN THE FIELD OF CELL AND GENE THERAPY

>250
People from 15 different countries

329
Publications 2018-2022 with an average IF of 11.934

221
Active patents and/or patent applications

139
Patients treated with gene therapy since 2000

2
Gene therapy drugs approved

In its **25-year history**, SR-Tiget has provided pioneering and continued contributions to the gene and cell therapy field with relevant discoveries in **vector design, gene transfer and gene editing** strategies, **stem cell biology**, identity and mechanism of action of **regulatory cells** in immune responses and **innate immune cells in cancer.**

SR-Tiget has also established the resources and framework for translating these advances into novel experimental therapies and has implemented **several successful gene therapy clinical trials** for inherited immunodeficiencies, blood and lysosomal storage disorders, which have already treated 139 patients and led to the filing and marketing approval of 2 novel advanced therapy medicines.

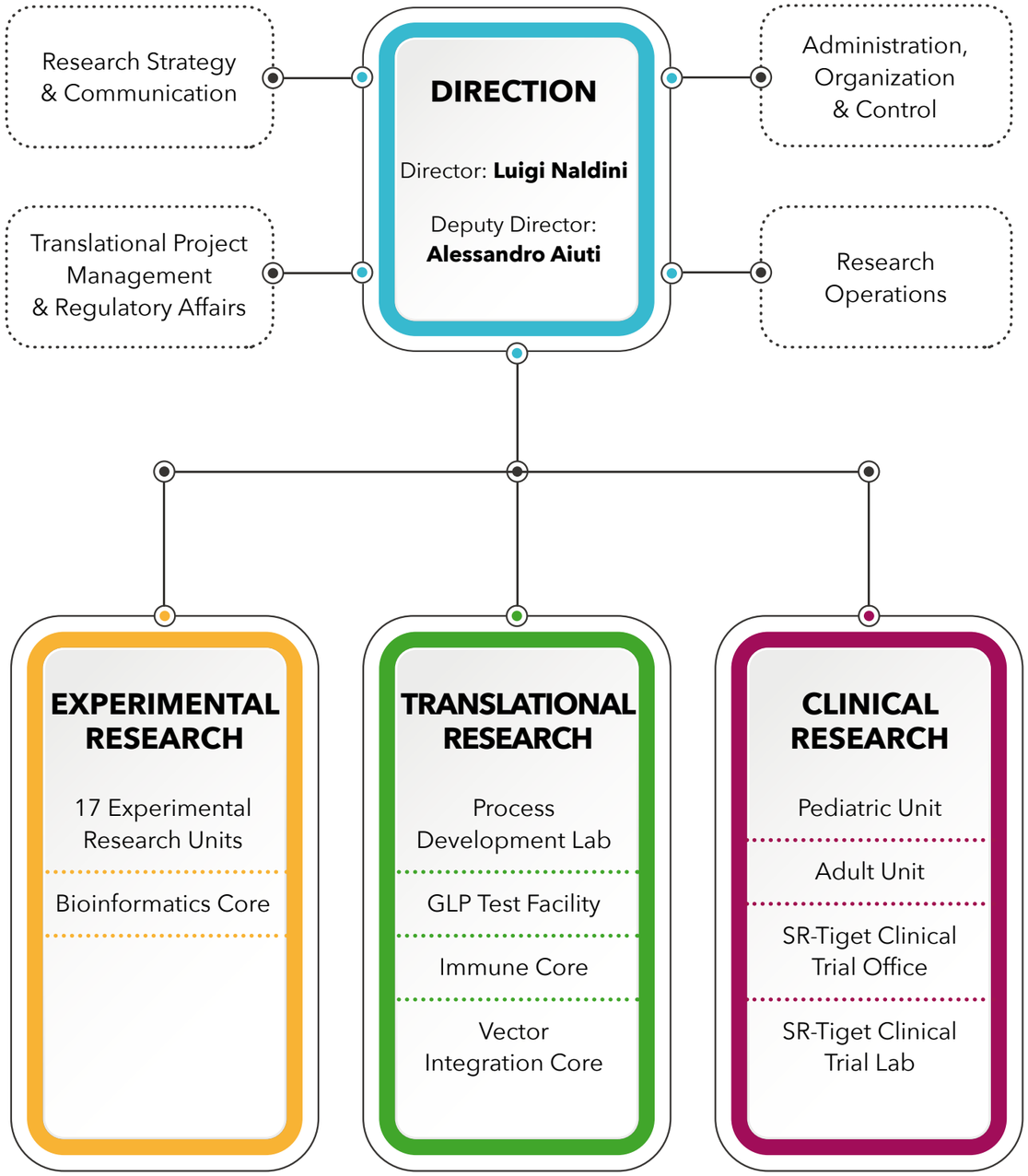
More recently SR-Tiget has also embarked on developing **applications of its cell and gene therapy platforms to the treatment of certain types of cancer**.

INSTITUTE ASSETS

- Leadership in **lentiviral gene transfer** technology
- Pioneering contribution to the **genome and epigenome editing** field
- Robust **translational capacity** in developing applications of gene transfer and gene editing
- State-of-the-art **stem cell transplantation center** for adult and pediatric patients
- **In house facilities** and resources supporting
  - **Translational research** (GLP Test Facility, Process Development Lab, Vector Integration Core, Immune Core)
  - **First-in-human phase I/II gene therapy trials** (Clinical Research Unit, Clinical Trial Office, Regulatory Affairs Office, Clinical Lab)
- Strategic **alliances with pharma and biotech** and successful **launch of biotech startups**
- Roster of young PIs venturing into **new technologies and emerging biological concepts**
- Access to **state-of-the art research facilities**

THE INSTITUTE

ORGANIZATION



EXPERIMENTAL RESEARCH

Pathogenesis and therapy of primary immunodeficiencies	Alessandro Aiuti
Pathogenesis and therapy of lysosomal storage diseases with skeletal involvement	Maria Ester Bernardo
Liver gene therapy	Alessio Cantore
Senescence in stem cell aging, differentiation and cancer	Raffaella Di Micco
Human hematopoietic development and disease modeling	Andrea Ditadi
Gene transfer into stem cells	Giuliana Ferrari
Translational stem cell and leukemia research	Bernhard Gentner
Mechanisms of peripheral tolerance	Silvia Gregori
Gene/neural stem cell therapy for lysosomal storage diseases	Angela Gritti
Retrovirus-host interactions and innate immunity	Anna Kajaste-Rudnitski
Epigenetic regulation and targeted genome editing	Angelo Lombardo
Safety of gene therapy and insertional mutagenesis research	Eugenio Montini
Mechanisms of inflammation in health and disease	Alessandra Mortellaro
Gene transfer technologies and new gene therapy strategies	Luigi Naldini
Targeted cancer gene therapy	Luigi Naldini
Genomics of the innate immune system	Renato Ostuni
Pathogenesis and treatment of immune and bone diseases	Anna Villa
Bioinformatics core	Ivan Merelli

TRANSLATIONAL RESEARCH

Process Development Lab — Marina Radrizzani

Responsible to validate, optimize and scale up cell manufacturing protocols and assays stemming from research laboratories with the aim of establishing proprietary know-how and making procedures suitable for direct transfer to GMP manufacturing facilities.

GLP Test Facility — Paola Albertini and Giuliana Ferrari

First certified academic Good Laboratory Practice (GLP) center in Italy for performing biodistribution, toxicology/tumorigenicity and validation studies on gene and cell therapy products.

Vector Integration Core — Eugenio Montini

Performs tracking of vector integration sites as readout of cell growth at clonal level, in basic research studies and technology development, in preclinical safety studies and in gene therapy patients.

Immune Core — Silvia Gregori

Supports preclinical investigations of gene and cell therapies focusing on immune related aspects and sets up immunological analyses to be used for immune monitoring in clinical trials.

CLINICAL RESEARCH

Clinical Research Unit — Alessandro Aiuti

Dedicated infrastructures and personnel with expertise for conducting early and late clinical trials of Advanced Therapy Medicinal Products according to Good Clinical Practice. It operates in close collaboration with the other clinical units of Ospedale San Raffaele, and in particular with the **Pediatric Immuno-Hematology Unit** led by **Alessandro Aiuti** and the **Hematology and Bone Marrow Transplant Unit** led by **Fabio Ciceri**. The approach to the patients is holistic, taking charge of all the medical, nursing, psychological and logistical aspects thanks to a multidisciplinary team.

SR-Tiget Clinical Trial Office — Stefano Zancan

Manages SR-Tiget clinical trials during each phase of development, from planning to closure, acting as reference point for internal committees (Ethical Committees, Pharmacovigilance Office) and external Authorities (EMA, AIFA, Istituto Superiore di Sanità, Ministry of Health).

SR-Tiget Clinical Lab — Matias Soncini

In charge of performing non-routine experimental assays for measuring clinical trial endpoints and storing patient samples. To ensure data integrity and reliability, analyses are performed according to Good Clinical Laboratory Practices.

SUPPORTING FUNCTIONS

Research Strategy & Communication Office — Aida Paniccia

Supports the Direction in the scientific management of the Institute, monitoring the implementation of research strategies, coordinating SR-Tiget communication and fostering the growth of the SR-Tiget researcher community.

Translational Project Management & Regulatory Affairs Unit — Michela Gabaldo

Responsible for developing optimized drug development plans and identifying the most suitable opportunities of Regulatory Authority engagement with the goal to accelerate clinical development of SR-Tiget Advanced Therapy Medicinal Products also managing collaborative projects with commercial partners, when involved.

Administration, Organization & Control Unit — Renata Ponzè

Responsible for budget planning and control, purchasing, invoicing and personnel administration, and to ensure that appropriate administrative procedures are in place for an effective co-management with Fondazione Telethon and Ospedale San Raffaele.

Research Operations Office — Tiziano Di Tomaso

In charge of logistical coordination of the Institute's operations, including supervision of safety, infrastructures, maintenance of equipment and acquisition of new instruments, management of common laboratory stocks and software licenses.

WORKING IN AN EFFICIENT AND CONCERTED MANNER

SCIENTIFIC LIFE

A NURTURING ENVIRONMENT WHICH PROMOTES THE GROWTH OF THE RESEARCH COMMUNITY

The dynamic scientific life of SR-Tiget is nourished by a **wide offer of activities**, which expose researchers at all career stages to a variety of enriching interactions, both internal and external.

MEETINGS

SR-Tiget researchers benefit from a rich calendar of regular meetings including:

- **SR-Tiget Lab Meeting**: a weekly opportunity for junior research staff to practice giving talks in front of a broad audience by presenting the results of their projects;
- **SR-Tiget Progress Report:** senior research staff report monthly on the progress of their research groups;
- **SR-Tiget Clinical Meeting**: Principal Investigators report on projects in advanced stage of preclinical development and the results of ongoing clinical trials. These meetings are crucial to bridge the gap between experimental scientists and clinicians, and to timely address the rationale and clinical feasibility of prospective translational projects;
- **External Guest Seminars**: organized by the SR-Tiget Postdoc Seminar Committee, giving the community an additional opportunity to interact with external experts;
- **SR-Tiget Retreat**: a yearly occasion to review research programs, enhance scientific discussions and interactions, promote social gathering and commitment to the Institute mission;
- Weekly Seminars and a yearly Retreat organised by Ospedale San Raffaele.

PUBLIC ENGAGEMENT

SR-Tiget research aims at having a **concrete impact** on people life. In line with this, the Institute staff is actively involved in public engagement by taking part in **initiatives organized by Fondazione Telethon** (such as the series of events held within the yearly foundraising Television Marathon), and partecipating to **science festivals** and **outreach activities** with schools and patient associations.

TRAINING

SR-Tiget actively promotes the **professional growth of trainees at all stages**, offering courses covering the most exciting and active research areas in the field and providing training in the transferable skills required for a successful career in academia and beyond.

Internships

SR-Tiget laboratories offer internship opportunities to motivated master students from all universities. Trainees benefit from a dynamic scientific environment and have access to activities organised by the host labs and the Institute (e.g. journal clubs, seminars, retreats, etc.).

Doctoral Training

The Institute hosts students enrolled in the Gene and Cell Therapy curriculum of the International PhD Course in Molecular Medicine at the Vita-Salute San Raffaele University. This dedicated PhD track aims to train young scientists in the study of genetic diseases and in the development of new gene and cell therapy strategies, and sees several SR-Tiget PIs involved.

Postdoctoral Training

SR-Tiget is committed to support postdoctoral researchers in their professional development, providing training aimed at broadening both their research and soft skills and preparing them for the next step of their career.

CAREERS

SR-Tiget is committed to support the professional development of scientists and to actively pursue the recruitment of brilliant young investigators, investing in training and mentoring.

PROJECT LEADERS: A TRACK TO INDEPENDENCE

SR-Tiget has put in place a career track for the progression of non-independent Senior Researchers in order to tackle the issue of lack of intermediate roles in the research hierarchy. Project Leaders are senior postdoctoral fellows, who work under the scientific supervision, funding, technical and administrative support of a Group Leader and are supported in their path to independence.

MANAGEMENT TRAINING

Success in science requires more than individual talent and this is particularly true for an Institute like SR-Tiget, which reached its milestones thanks to successful synergies. The Institute has built on this by investing on formal management training for Group Leaders and Project Leaders, in order to provide them with additional skills to succeed in their leadership role.

RECRUITING NEW GROUP LEADERS

SR-Tiget is always committed to enhance its inward mobility by recruiting promising young Group Leaders through a transparent and rigorous process.

ALUMNI

We have outstanding records of outwards mobility, attesting to SR-Tiget mentorship capabilities. Examples of staff that proceeded to faculty positions are: Maria Grazia Roncarolo (to Stanford University); Rosa Bacchetta (to Stanford University); Alessandra Biffi (to Harvard University); Luca Biasco (to Harvard University); Marita Bosticardo (to NIH); Michele De Palma (to EPFL); Pietro Genovese (to Harvard University), Brian Brown (to Mount Sinai School of Medicine), Alice Giustacchini (to University College London).

SUPPORTING YOUNG RESEARCHERS AND INVESTING IN CAREER DEVELOPMENT

SR-TIGET IN THE INTERNATIONAL CONTEXT

Active role in scientific societies and organizations including American Society of Gene and Cell Therapy (ASGCT), European Society of Gene and Cell Therapy (ESGCT), International Society for Stem Cell Research (ISSCR), American Society of Hematology (ASH), European Group for Blood and Marrow Transplantation (EBMT), European Hematology Association (EHA) and Accademia Nazionale dei Lincei, the oldest scientific academy in the world serving also as scientific and cultural advisor to the President of the Italian Republic.

Called to take part in advisory and policy making committees including Committee for Advanced Therapies of the European Medicines Agencies, World Health Organization, US National Academy of Sciences.

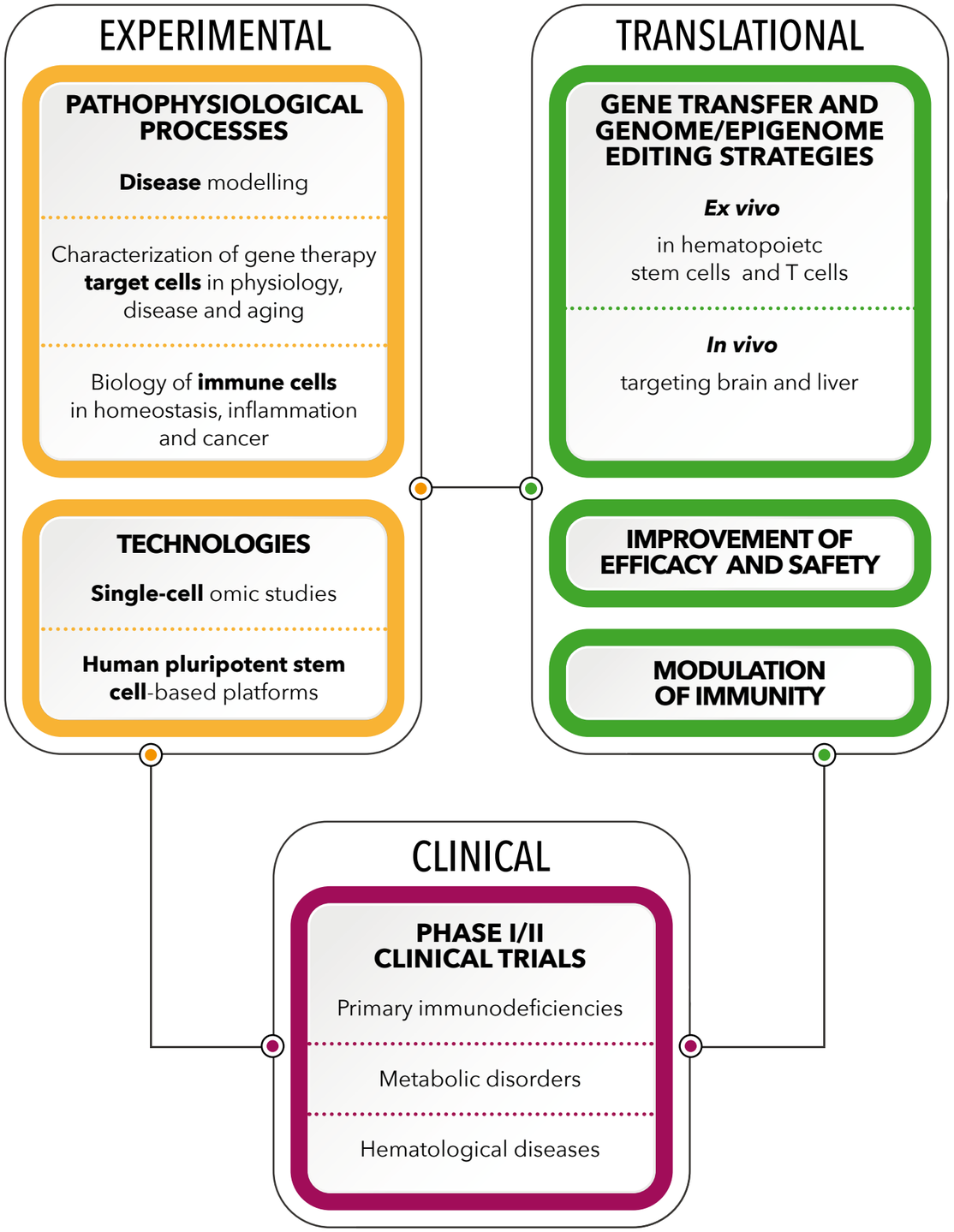
International prizes in recognition of major contribution to the field including the Ernest Beutler Prize from the American Society of Hematology and the Louis-Jeantet Prize to Luigi Naldini, the Else Kröner Fresenius Prize for Medical Research to Alessandro Aiuti; several SR-Tiget members have received ASGCT and ESGCT Outstanding Achievement Awards, ASGCT Excellence in Research Awards and ESGCT Young Investigator Awards.

SR-Tiget members invited to give keynote lectures and plenary talks and involved in the organization of international conferences.

Proven track record of attracting funding through highly competitive international calls: SR-Tiget Principal Investigators have been recipients of multiple prestigious ERC grants and coordinators of EU-funded research consortia; several SR-Tiget early career researchers have been awarded with Marie Skłodowska Curie Fellowships.

FROM RESEARCH TO CLINICAL CARE

RESEARCH INTERESTS



SR-Tiget mission is primarily focused on performing **Translational Research**, devoted to the development of new gene and cell therapy strategies up to clinical testing. This involves a continuous effort to match the best suitable strategy to each selected disease, to ameliorate their efficacy and safety and to develop approaches to monitor immune responses to gene and cell products. These goals provide the rationale for selecting topics and allocating resources to the more basic studies.

Experimental Research efforts are aimed to gain a better understanding of the diseases and target cell types under investigation and to develop technological advances for their improved isolation, manipulation and transplantation.

Clinical Research translates basic science and platform innovations into novel experimental protocols for the treatment of diseases with severe unmet need. SR-Tiget has established the resources and framework for conducting first-in-human phase I/II gene therapy trials with successful results so far in the implementation of gene therapy of inherited immunodeficiencies, hematological diseases and lysosomal storage disorders.

WHAT IS GENE THERAPY

Gene therapy is an approach that aims at treating a disease by targeting its genetic roots through the replacement, repair or counteraction of a malfunctioning gene. Gene therapy bears the promise of a long-term clinical benefit with a single administration of the treatment.

At SR-Tiget, our gene therapy approaches include:

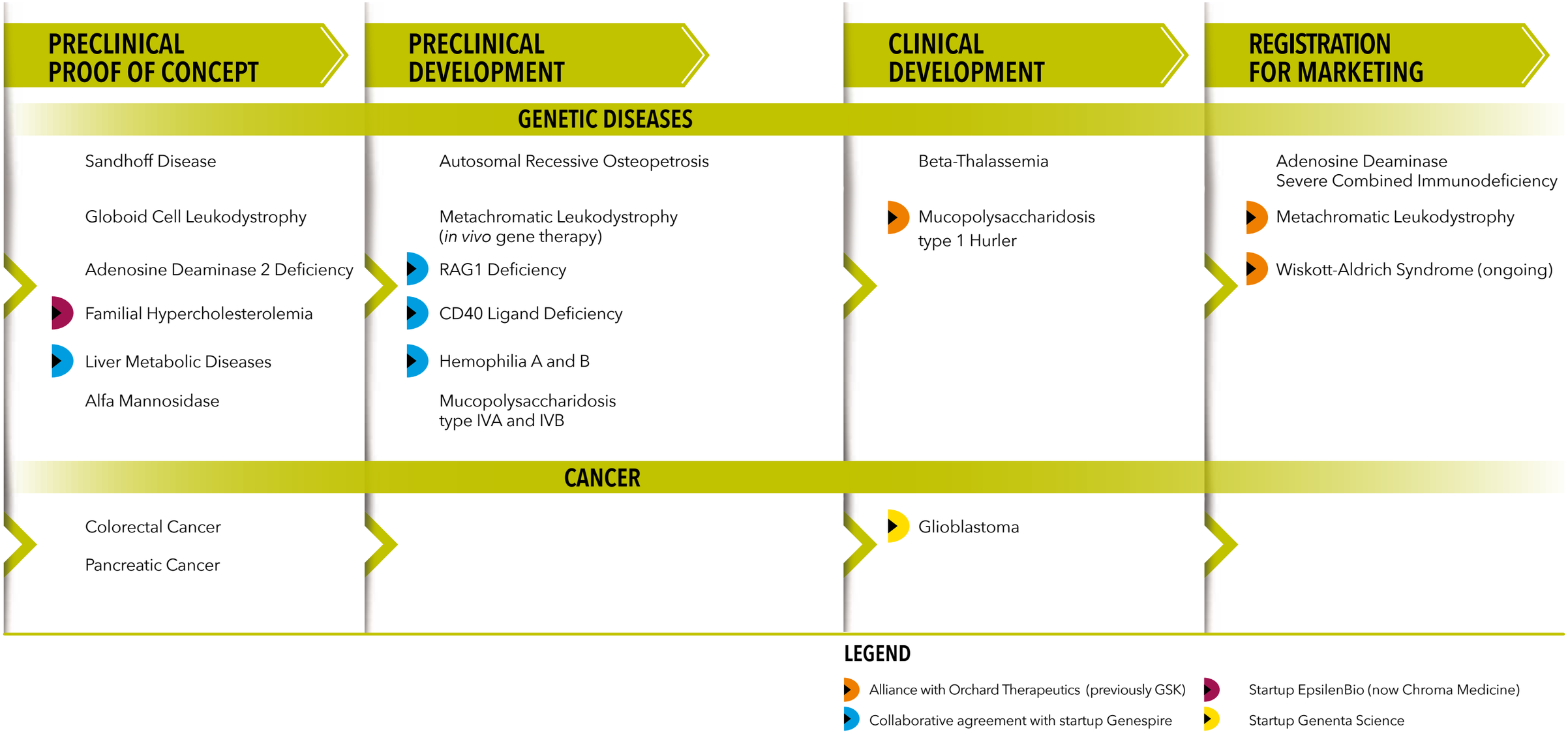
- **Gene transfer**: addition of a functional copy of a faulty or missing gene delivered through a viral vector.
- **Genome editing**: disruption, insertion or correction of a specific DNA sequence of a disease-causing locus to abrogate or restore its function.
- **Epigenome editing**: modulation of the expression of a gene through the stable modification of chromatin conformation without altering the underlying DNA sequence.

FROM BENCH TO BEDSIDE AND BACK: A VIRTUOUS CIRCLE TO ACCELERATE RESEARCH AND IMPROVE CLINICAL CARE

TARGET DISEASES

SR-Tiget target diseases are represented along the translational pipeline, showing how the Institute's portfolio of gene and cell therapies embraces the **full spectrum of drug development**.

Diseases under investigation include **primary immunodeficiencies** (e.g. Adenosine Deaminase Severe Combined Immunodeficiency, Wiskott-Aldrich Syndrome and Adenosine Deaminase 2 Deficiency), **hematological diseases** (e.g. beta-thalassemia and hemophilia), **bone diseases** (e.g. ostepetrosis) **lysosomal storage disorders** (e.g. leukodystrophies and different types of mucopolysaccharidosis), other **metabolic diseases** (e.g. familial hypercholesterolemia) and some types of **cancers**.



INDUSTRIAL ALLIANCES AND STARTUPS

The most advanced steps of the Institute development pipeline are undertaken in the context of strategic **alliances with industrial partners** or through the **spin-off of startup biotech companies**, which are crucial to secure the resources and the multidisciplinary expertise required to attain the ultimate goal of delivering the therapies to patients.

STARTING FROM 2004, THE INSTITUTE HAS BEEN INVOLVED IN A NUMBER OF STRATEGIC ALLIANCES SET UP BETWEEN OSR, FONDAZIONE TELETHON AND KEY INDUSTRY PLAYERS IN THE CELL AND GENE THERAPY FIELD

ORCHARD THERAPEUTICS (2018-ongoing)

SANOFI (2017-2021)

EDITAS MEDICINE (2016-2018)

BIOGEN (2014-2017)

GLAXOSMITHKLINE (2010-2018)

SANGAMO THERAPEUTICS (2004-2015)

A UNIQUE R&D HUB BRINGING TOGETHER ACADEMIA AND INDUSTRY TO MAKE TRANSLATIONAL MEDICINE A REALITY

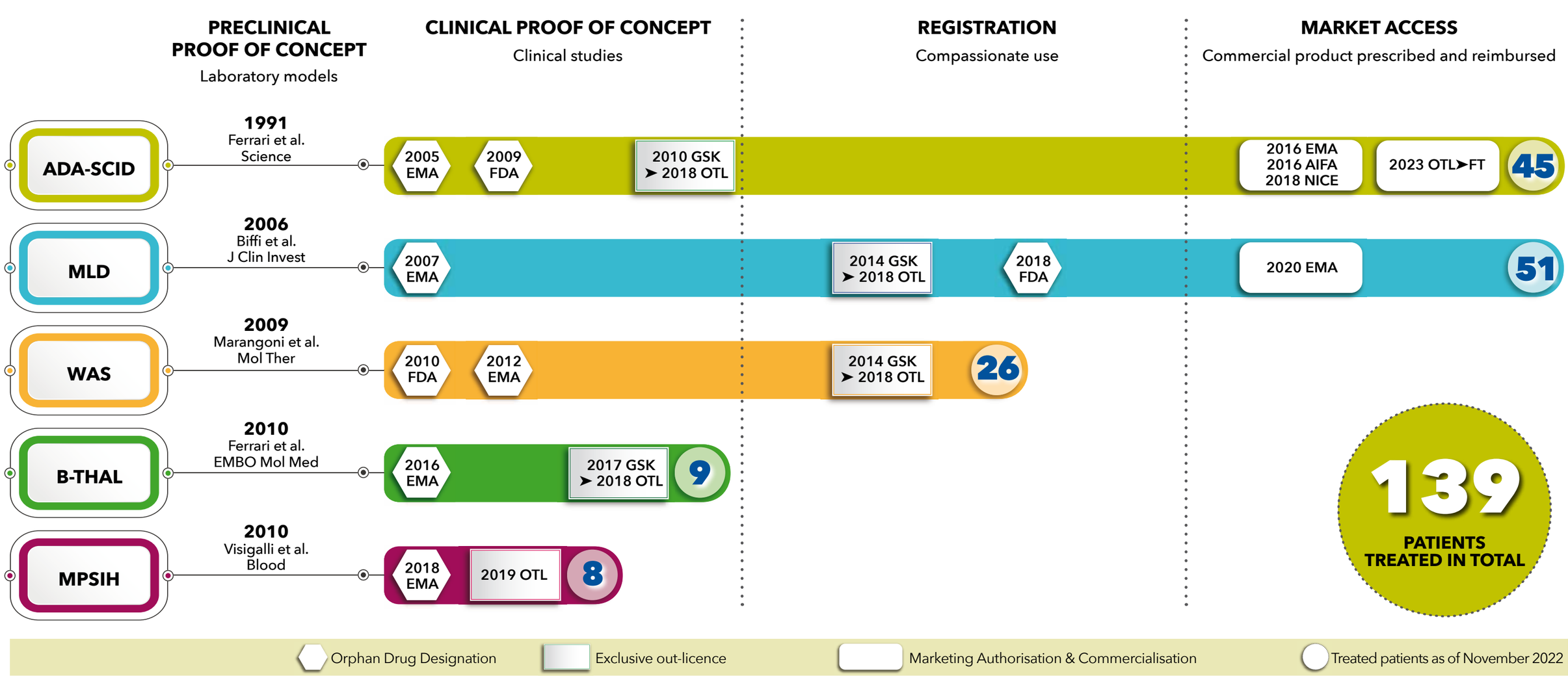
More recently, three startup companies stemmed from SR-Tiget research.

GENENTA SCIENCE
focused on the development of cancer immunotherapy. In 2021 the company was listed on Nasdaq, becoming the first italian biotech on the American stock exchange market.

EPSILEN BIO
whose mission is to develop therapies based on the epigenetic silencing platform. In 2021, it has been acquired by Chroma Medicine, giving rise to the largest epigenetic editing company in the world.

GENESPIRE
whose portfolio includes the development of *ex vivo* gene editing therapies and liver-directed *in vivo* gene therapies based on advanced lentiviral vectors.

CLINICAL TRIALS



SR-Tiget pioneered the field of *ex vivo* gene therapy with the first registration of a product - an hematopoietic stem cell (HSC)-based gene therapy employing γ-retroviral vectors - to treat Adenosine Deaminase Severe Combined Immunodeficiency (**ADA-SCID**), a severe form of immunodeficiency. With more than 20 years of follow-up of the first treated patients, this seminal work provided evidence of substantial clinical benefit and resulted in the EU marketing authorization for this therapy, thanks to a strategic collaboration between Fondazione Telethon, OSR and Glaxosmithkline (GSK).

The successful results obtained with ADA-SCID provided a rationale for extending the approach to other diseases, employing the more advanced lentiviral vector (LV) platform. In particular, two clinical trials for Wiskott-Aldrich Syndrome (**WAS**) and Metachromatic Leukodystrophy (**MLD**), started in 2010, have completed the treatment phase and are showing evidence of persistent and clear therapeutic benefits in all treated patients. In 2020 the European Medicines Agency has given marketing authorization of the gene therapy for of MLD, which will be commercialized by Orchard Therapeutics (OTL). A third HSC-gene therapy clinical trial with LV for beta-thalassemia (**B-THAL**), started in 2015, has provided evidence of safety and efficacy in the first patients. In addition, in 2018 we initiated a first-in-human clinical trial of LV-based HSC-gene therapy for Mucopolysaccharidosis type 1 Hurler (**MPSIH**), which is already showing promising preliminary results.

APPROVED GENE THERAPY DRUGS

2 OUT OF 11
GENE THERAPY DRUGS APPROVED IN EU HAVE BEEN DEVELOPED AT SR-TIGET

26th May 2016
EU marketing authorization

GENE THERAPY FOR ADA-SCID

The first *ex vivo* gene therapy worldwide for the treatment of **ADA-SCID**.
It consists of autologous CD34+ cells transduced to express the gene encoding for the Adenosine Deaminase enzyme.
Developed at **SR-Tiget** and brought to the market under the alliance among **Fondazione Telethon**, **Ospedale San Raffaele** and **GlaxoSmithKline.**

17th Dec 2020
EU marketing authorization

GENE THERAPY FOR MLD

The first *ex vivo* gene therapy worldwide for the treatment of **MLD**.
It consists of autologous CD34+ cells transduced to express the gene encoding for the ARSA enzyme.
Developed at **SR-Tiget** and brought to the market under the alliance among **Fondazione Telethon**, **Ospedale San Raffaele** and **Orchard Therapeutics.**

Every year several patients from all around the world come to Milan to be treated with gene therapy at SR-Tiget: Fondazione Telethon created the **Just like home** Program in order to support the access to the therapy. The treatment often implies a long journey, from distant countries and a prolonged stay in Milan for patients and their families, as well as further periodical checks during the following years. The staff of the Program works to **create the best conditions to access the therapy**, contributing to the success of the treatment and reducing the negative emotional and logistical impacts on the family life.
The Just like home Program offers the families an **accommodation** for the whole period of stay providing also **practical, psychological, language and cultural support**. A dedicated Care Coordinator is the point of reference during the whole treatment and works closely with a multidisciplinary team that includes psychologists, cultural mediators and, if necessary, professionals able to provide ad hoc services (e.g. teachers, caregivers, professional educators, etc.).

78
FAMILIES WELCOMED UNTIL 2020

29
COUNTRIES OF ORIGIN

FOUNDING PARTNERS

Fondazione Telethon is a a major Italian charity whose mission is to advance biomedical research towards the cure of rare genetic diseases. Throughout its more than 30 years of activity, the Fondazione Telethon has invested over €475 million in funding over 2,600 projects to study 540 diseases, involving more than 1,600 researchers.
www.telethon.it/en.

Ospedale San Raffaele is a clinical-research-university hospital certified by the Ministry of Health established in 1971 to provide international-level specialized care for the most complex and difficult health conditions. Since 2012 OSR is part of Gruppo Ospedaliero San Donato, the leading hospital group in Italy. The hospital is a multi-specialty center with over 50 clinical specialties and has over 1,300 beds. Research at OSR focuses on integrating basic, translational and clinical activities to provide the most advanced care to our patients.
www.hsr.it

CAMPUS MAP

SR-Tiget spaces

Hospital sectors
Research sectors
University
Parking
Taxi
Chapel
Information
Subway
Hotel
Emergency

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