

 <p>UniSR Università Vita-Salute San Raffaele</p>	<p>APPLICATION TO ACT AS SUPERVISOR AND RESEARCH PROJECT PROPOSAL</p>	<p>MO 20-5 ed. 02 of 16/01/2026 PO 20 Page 1 of 12</p>
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The undersigned

SURNAME CRIPPA

FIRST NAME STEFANIA born in *CARATE B.za* Prov. MB on 21/02 /1982

Unit: SAN RAFFAELE TELETHON INSTITUTE FOR GENE THERAPY, Pathogenesis and therapy of LSDs with skeletal involvement Unit

Residency/Postgraduate

School:

Email address: cripa.stefania@hsr.it

Role:

- Vita-Salute San Raffaele University Professor/Lecturer
- Vita-Salute San Raffaele University Researcher/Lecturer
- Group Leader of the hospital site -----
- Project Leader of the hospital site -----
- Other: Research Associate

I hereby declare that, within the framework of the PhD Course for which I wish to submit the project described below:

- I am already a Supervisor;
- I am applying for the first time as a Supervisor (CV attached);
- I am applying as a Supervisor as three years have elapsed since my last Application as Supervisor and the submission of a research project (CV attached).

I further declare that (select the applicable option(s)):

- although I am less than four years away from retirement as a university professor/researcher, I will hold a documented institutional role at the hospital _____, for at least one year beyond the official duration of the course.
- I serve as Supervisor for no. __ PhD candidates enrolled at other universities and I comply with the University requirement regarding the maximum number of five PhD candidates that may be supervised.

¹ To be indicated only for research projects associated with the Physician Scientist programme



I would like to present a project:

- With a duration of three years**
 With a duration of two years within the Physician Scientist (PhS) programme

as part of the PhD course in:

- Molecular Medicine

PhD Curriculum: Basic and Applied Immunology and Oncology

Cell and Molecular Biology

Clinical and Experimental Medicine

Neurosciences and Experimental Neurology

Gene and Cell Therapy

Cognitive and Behavioural Sciences

The project consists in:

1. Basic Research
2. Translational Research
3. Basic/ Translational research using animal models
4. Clinical research
5. Clinical research involving interaction with patients

If items 2 and/or 3 is/are selected, I declare that

I HAVE OBTAINED the approval of the responsible Institutional Animal Care and Use Committee-IACUC number 1442 -1473

I HAVE NOT YET OBTAINED the approval of the responsible Institutional Animal Care and Use Committee-IACUC

If items 4 and/or 5 is/are selected, I declare that the project:

HAS NOT YET OBTAINED approval from the Ethics Committee (EC).

HAS OBTAINED, or is part of a broader study that has obtained, approval from the Ethics Committee (EC); study code and date Tiget 09, 07 Jun 2017

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If items 4 and/or 5 is/are selected, I declare that the project:

- HAS NOT OBTAINED** the resolution of the Institution
- HAS OBTAINED** the resolution of the Institution on _____

I further declare (select the applicable option(s)):

- that I have the availability of the funds necessary to finance a scholarship for the proposed project and I confirm that I have contacted the Doctoral Office regarding the management of the administrative procedures related to the funding;
- that I have the availability of funds to support the research (i.e. funds for materials, reagents, and instruments required for research activities);
- that, in the case of a clinical research project, it will include a basic or translational research component to be carried out in a laboratory to be specified in the research plan, whose head will act as co-supervisor.
- that I have adequate workspace and a permanent workstation available for the PhD candidate who will be selected to carry out the project;
- that the proposed project can be reasonably completed within the three-year legal duration of the programme;
- that the PhD student, within the activities of the relevant PhD program, will carry out only their specific doctoral project;
- that the PhD student will be the first author/author of the main publication resulting from his/her project and of all publications (also after graduation) that are mainly based on his/her experimental work;
- that, in the event that the PhD student is not the recipient of a UniSR grant (i.e. has won a position without a grant), I am willing to cover the cost of their scholarship with funds at my disposal. I am aware that the grant must not amount to less than the minimum required by the Ministerial Decree of 23 February 2022, amounting to € 16,243 gross per year, for three years;
- that the study is co-funded by an industrial partner or that a commercial exploitation of the findings resulting from the project's research activity is conceivable, with a potential delay in the publication of the results. I therefore commit to promptly inform potential candidates of such circumstances.

Signature of the Supervisor



Date 26-03-26



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When applicable:

Group Leader Prof. /Dr. MARIA ESTER BERNARDO

Signature

Date __31.03.2026__-----

Please note that the information provided on the following pages (unless otherwise indicated) will be made public on the University website. Therefore, it is important not to include confidential information, in compliance with any confidentiality obligations towards third parties and to protect the potential patenting of such information. For any questions, please consult the PhD Office.

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PROJECT

Supervisor:

STEFANIA CRIPPA

Title:

Modelling skeletal defects in MPSIVA to enhance HSPC-GT
therapeutic efficacy

Curriculum:

Molecular Medicine Gene and Cell Therapy

Link to the personal page of the University or relevant hospital site website:

<https://research.hsr.it/en/institutes/san-raffaele-telethon-institute-for-gene-therapy.html>

Description of the Project (max 3,000 characters including spaces)

Background/gap of knowledge

Mucopolysaccharidosis type IVA (MPSIVA) is a genetic disorder caused by defects in GALNS activity, a lysosomal enzyme responsible for keratan sulphate and chondroitin sulphate degradation. This leads to accumulation of undegraded substrates, triggering cell damage in several tissues, including skeletal systems (1,2). Patients manifest severe skeletal dysplasia. Recent studies by our institute demonstrated the superior safety and efficacy of Hematopoietic Stem/Progenitor Cells (HSPC)-gene therapy (GT) to treat skeletal manifestations in LSDs (3-5). Based on these results, our laboratory is developing an innovative HSPC-GT approach to treat MPSIVA in the context of a novel platform approach. However, the pathophysiological mechanisms and cellular components responsible for MPSIVA are largely unknown, due to the absence of animal models fully recapitulating the human skeletal pathology (6,7). This limits our understanding of MPSIVA skeletal pathology and the potential to enhance and monitor the therapeutic efficacy of new therapies.

Rationale and hypothesis

To overcome these limitations, we hypothesize that the development of humanized skeletal tissue models using patient-derived cells will be essential for comprehensively investigating disease mechanisms and cellular contributors, thereby enhancing the therapeutic efficacy of HSPC-GT as a potential curative option for MPSIVA patients. Furthermore, these models will be employed to study the cross-correction mechanisms mediated by HSPC-GT approaches, or eventually to test novel therapeutic approaches to treat skeletal defects.



Objectives and specific aims

Aim1. Establishment of a biobank of patient-derived cells

Mesenchymal stromal cell (MSCs) lines, reproducing the enzyme deficit, will be generated through advanced gene editing tools. Primary MSCs will be also isolated from patients when available. iPSCs will be also generated by reprogramming of patients' cells or eventually iPSCs from healthy-donor will be gene-edited to reproduce patients' mutations.

Aim2. Establishment of MSCs- and iPSCs-based humanized skeletal models

The PhD student will be involved in the differentiation of MSCs to generate hypertrophic cartilage and model endochondral ossification in vivo (8). iPSCs will be employed to generate three-dimensional bone-like structures (9,10).

Aim3. Dissect molecular and cellular abnormalities underlying skeletal disease in MPSIVA patients

To reach this aim, gene profiling approaches, including single cells analysis and spatial transcriptomics, will be employed together with advanced microscopy to analyse the skeletal models at steady state and in HSPC-GT therapeutic settings, enabling the study of underlying mechanisms responsible for metabolic and functional disease and correction.

Expected outcomes

Overall, this project is expected to characterize the complex pathogenic cascade underlying tissue and cellular skeletal alterations in MPSIVA and elucidate the mechanisms of metabolic and functional correction, with the ultimate goal of improving HSPC-GT to treat MPSIVA.

Skills that the student should acquire (max. 600 characters including spaces):

The PhD student will acquire cellular skills, including cell culture isolation and characterization, cell reprogramming, tissue modelling, gene manipulation, lentiviral vector production, and molecular and biochemical techniques. He/she will also develop skills to perform in vivo study. The student will acquire the required scientific background and expertise to independently conduct his/her experiments, critically discuss the results and their biological significance, and



propose project advancements. The student will discuss the project during internal, institutional, and international meetings.

References (max. 15)

1. Tomatsu, S., et al. (2011). Mucopolysaccharidosis type IVA (Morquio A disease): clinical review and current treatment. *Curr. Pharm. Biotechnol.* 12, 931-945. 10.2174/138920111795542615
2. Peracha, H., et al. (2018). Molecular genetics and metabolism special edition: diagnosis diagnosis and prognosis of mucopolysaccharidosis IVA. *Mol. Genet. Metab.* 125, 18-37. 10.1016/j.ymgme.2018.05.004
3. Visigalli, I., et al. (2010). Gene therapy augments the efficacy of hematopoietic cell transplantation and fully corrects mucopolysaccharidosis type I phenotype in the mouse model. *Blood* 116, 5130-5139. 10.1182/blood-2010-04-278234
4. Gentner, B., et al. (2021). Hematopoietic stem- and progenitor-cell gene therapy for Hurler syndrome. *N. Engl. J. Med.* 385, 1929-1940. 10.1056/NEJMoa2106596
5. Consiglieri, G., et al. (2024). Early skeletal outcomes after hematopoietic stem and progenitor cell gene therapy for Hurler syndrome. *Sci. Transl. Med.* 16, eadi8214. 10.1126/scitranslmed.adi8214
6. Tomatsu, S., et al. (2003). Mouse model of N-acetylgalactosamine-6-sulfate sulfatase deficiency (Galns^{-/-}) produced by targeted disruption of the gene defective in Morquio A disease. *Hum. Mol. Genet.* 12, 3349-3358. 10.1093/hmg/ddg366
7. Berti M., et al. (2026). Development and characterization of a model of mucopolysaccharidosis type IVA for evaluating therapies targeting bone disease. *Dis Model Mech.* 2026 Feb 1;19(2):dmm052540. doi: 10.1242/dmm.052540.
8. Scotti C., et al. (2013) Engineering of a functional bone organ through endochondral ossification. *Proc Natl Acad Sci U S A.* 2013 Mar 5;110(10):3997-4002. doi: 10.1073/pnas.1220108110.



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9. Craft AM., et al. (2015) Generation of articular chondrocytes from human pluripotent stem cells. *Nat Biotechnol.* 2015 Jun;33(6):638-45. doi: 10.1038/nbt.3210.
10. Jacobsen C, Craft AM. (2019) Retinoic-acid-induced osteogenesis of hiPSCs. *Nat Biomed Eng.* 2019 Jul;3(7):504-506. doi: 10.1038/s41551-019-0422-3.

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The information below will not be displayed on the University website in the description of the projects offered for the academic year, and will be used for internal project assessment only.

Experimental plan (Between 2,000 and 3,000 characters including spaces):

To be completed for all types of projects; however, for CLINICAL PROJECTS, please specify:

1. *If Observational prospective, cross-sectional, or retrospective) or retro/prospective, quality of life, pharmacological, pathophysiology, genetics, epidemiological, registry/data collection, biobank, diagnostic accuracy, in vitro diagnostic device (IVD), nutraceutical/supplement, appropriateness; OR interventional (pharmacological, surgical, procedure, or medical device, and if a drug will be used, indicate the phase – I, II, III, or IV);*
2. *If a drug will be used, specify whether it has a marketing authorisation (MA), whether it will be used according to the MA or whether it does not have a MA;*
3. *If the study does not regard a drug, specify what will be studied (e.g. medical device, surgical procedure, diagnostic procedure, food supplement, etc.). If the study will use a medical device, please specify: whether it is CE marked. If CE marked, please indicate whether it will be used according to the approved use or for a new use.*
4. *Indicate the laboratory on which you intend to rely for the basic or translational part.*

Mucopolysaccharidosis type IVA (MPSIVA) is a genetic disorder caused by defects in GALNS activity, a lysosomal enzyme responsible for keratan sulphate and chondroitin sulphate degradation. This leads to accumulation of undegraded substrates, triggering cell damage in several tissues, including skeletal systems. Patients manifest severe skeletal dysplasia. Recent studies by our institute demonstrated the superior safety and efficacy of Hematopoietic Stem/Progenitor Cells (HSPC)-gene therapy (GT) to treat skeletal manifestations in LSDs. Based on these results, our laboratory is developing an innovative HSPC-GT approach to treat MPSIVA. However, the pathophysiological mechanisms and cellular components responsible for MPSIVA are largely unknown, due to the absence of animal models fully recapitulating the human skeletal pathology. This limits our understanding of MPSIVA skeletal pathology and the potential to enhance and monitor the therapeutic efficacy of new therapies.

To overcome these limitations, we hypothesize that the development of humanized skeletal tissue models using patient-derived cells will be essential for comprehensively investigating disease mechanisms and cellular contributors, thereby enhancing the therapeutic efficacy of HSPC-GT as a potential curative option for MPSIVA patients.

The project is structured according to the following experimental plan:

Aim1. Establishment of a biobank of patient-derived cells

Mesenchymal stromal cell (MSCs) lines, reproducing the enzyme deficit, will be generated through advanced gene editing tools. Primary MSCs will be also isolated from patients when available. iPSCs will be also generated by reprogramming of patients' cells or eventually iPSCs from healthy-donor will be gene-edited to reproduce patients' mutations.



Aim2. Establishment of MSCs- and iPSCs-based humanized skeletal models

The PhD student will be involved in the differentiation of MSCs to generate hypertrophic cartilage and model endochondral ossification in vivo. iPSCs will be employed to generate three-dimensional bone-like structures.

Aim3. Dissect molecular and cellular abnormalities underlying skeletal disease in MPSIVA patients

To reach this aim, gene profiling approaches, including single cells analysis and spatial transcriptomics, will be employed together with advanced microscopy to analyse the skeletal models at steady state and in HSPC-GT therapeutic settings, enabling the study of underlying mechanisms responsible for metabolic and functional disease and correction.

Furthermore, these models and the data generated though their extensive analysis will be employed to study the cross-correction mechanisms mediated by HSPC-GT approaches, or eventually to test novel therapeutic approaches to treat skeletal defects. They will be further exploited to identify novel disease biomarkers to follow disease progression and implement diagnostic treatment and assessment of therapeutic efficacy.

Available methods and experimental models (max. 600 characters including spaces):

To be completed for all types of projects; however, for CLINICAL PROJECTS, please specify:

1. *whether participants (patients and/or healthy volunteers) will be recruited;*
2. *whether biological samples will be taken from participants (patients and/or healthy volunteers);*
3. *whether the biological samples will be stored in a Biobank (specify which Biobank);*
4. *whether biological samples are already stored and available in a Biobank (specify which Biobank);*
5. *whether biological samples or data will be collected in addition to those already included in the routine standard of care from routine practice (specify type of samples/data, quantity and timing);*
6. *whether procedures will be required in addition to those already included in the routine standard of care from routine practice (e.g. Consultations, laboratory tests, clinical/instrumental examinations). Specify the additional procedures, quantity and timing).*

Available cells:

- MSOD and MSOD-BMP2 cell line (MSCs)
- HD iPSCs



Methods for modelling:

- Validated gRNAs to induce GALNS deficiency
- Validated methods for patients' cell reprogramming (in collaboration with R. Chimienti, DRI, OSR)
- MSC Chondrogenic differentiation and in vivo endochondral ossification
- iPSC chondrogenic differentiation and bone modelling (in collaboration with A. Craft, Boston Children's Hospital)

Method for analysis:

- Gene profiling of bone models (in collaboration with A. Craft, Boston Children's Hospital)

Role of the PhD student (max. 600 characters including spaces):

The PhD student will acquire cellular skills, including cell culture isolation and characterization, cell reprogramming, tissue modelling, gene manipulation, lentiviral vector production, and molecular and biochemical techniques. He/she will also develop skills to perform in vivo study. The student will acquire the required scientific background and expertise to independently conduct his/her experiments, critically discuss the results and their biological significance, and propose project advancements. The student will discuss the project during internal, institutional, and international meetings.

Impact of the expected results in the field of research (max. 600 characters including spaces):

Overall, this project is expected to characterize the complex pathogenic cascade underlying tissue and cellular skeletal alterations in MPSIVA and elucidate the mechanisms of metabolic and functional correction, with the ultimate goal of improving HSPC-GT to treat MPSIVA. Furthermore, this study will generate a robust and comprehensive data set to complement in vivo studies for clinical translation and support the use of in vitro human models for regulatory clinical translation.

In the case of clinical research, include the timeline for the project approval process up to the authorizing resolution of the Institution.



Period of attendance at a foreign institution

Mandatory for the PhD course in Cognitive and Behavioral Sciences

The PhD course in Cognitive and Behavioral Sciences encourages attendance at foreign universities and research institutes, promoting the acquisition of advanced skills and methodologies in international contexts.

Please indicate whether a period of activity at a foreign institution is planned. If so, specify:

- *Host institution (name of the University/Institute and country)*
- *Duration of stay (not less than 3 months)*
- *Integration with the research project (describe how this experience will contribute to the objectives of the proposed project)*

The information provided is not binding and may be subject to modifications based on the project's development and available opportunities.

For the use by the PhD Office

FOR OPINION - (ONLY for Programs divided into Curricula)

Signature of the Curriculum Supervisor _____ Date

FOR APPROVAL

Signature of the PhD Course Coordinator
