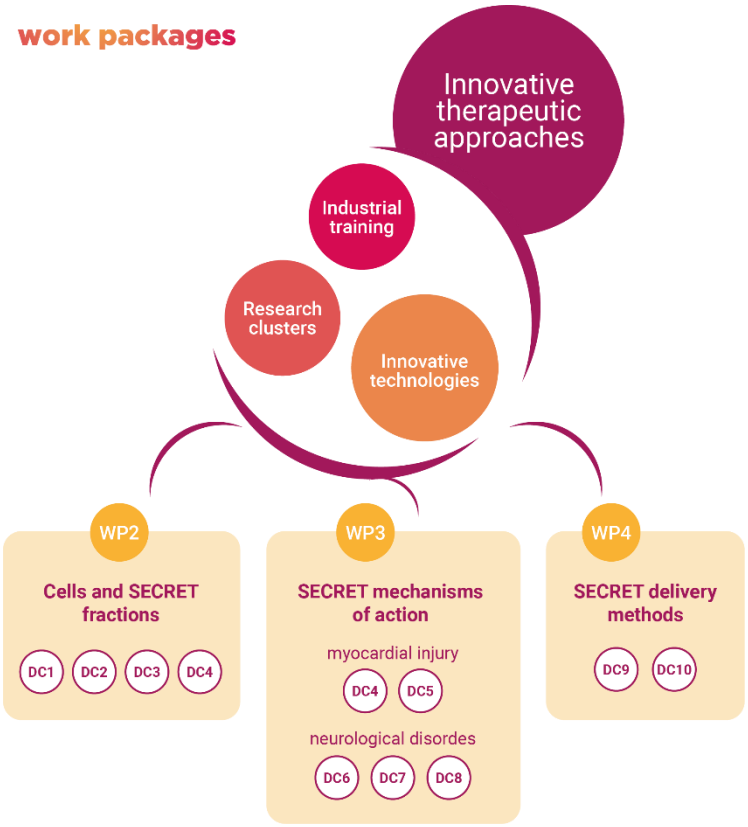
Marie Sklodowska-Curie Action Doctoral Network (MSCA-DN)

SECRET: "Exploring the therapeutic potential of perinatal cell SECRETomes"

SECRET Call for applications for 2 Doctoral (PhD) Training Positions in stem cell biology, paracrine signalling mechanisms, advanced delivery methods and pre-clinical models for regenerative medicine applications.

Offer Description

SECRET is a Doctoral Network funded by the European Union Horizon Europe Programme. The SECRET Consortium is a research network of leading European scientists from academia and industry, experts in human perinatal cells, extracellular vesicle biology, tissue engineering and biocompatible materials, to address key questions on SECRET through a coordinated, interdisciplinary effort in regenerative medicine. Through its research and training activities, the SECRET project will contribute to scientific advancement and innovation in Europe, ultimately leading to societal and economic benefits.



Participating in SECRET offers doctoral candidates many unique opportunities, including:

- A project as Marie Skłodowska Curie trainee in one of the participating institutions with the objective of receiving a doctoral degree (PhD).
- State-of-the art, exciting research in an international consortium with highly integrated research projects.
- Expert training in basic and applied research, along with a thorough understanding of the various phases involved in transitioning from pre-clinical to clinical research.
- A research training period in another consortium member's lab lasting from a few weeks up to six months, performed for the most part in a different EU country than the country where most of the project will take place.
- Training in both academic and commercial research environments.

- Salary according to EU guidelines for Marie Skłodowska Curie trainees, including mobility payments and family allowances where applicable.

Application Process

SECRET will select Doctoral Candidates through a 2-step recruitment process.
The selection procedure will be open, transparent, and merit-based, fully aligned with the Code of Conduct for the Recruitment of Researchers. Although the selection will be based on the quality of applications, gender balance will also be considered.
Applications (in English) must include:

- A **Motivation letter** which will include the motivation for the position, emphasizing the candidate's strength regarding the project and the requirements (max 3 pages);
- a **Complete CV** (max 2 pages);
- a **Summary of your Master thesis** (max 1 page);
- a **Transcript of your study results with scanned copy of your Master's Degree**. In case the Master's Degree has not been obtained yet at the closing date for application, the candidate has to submit a declaration signed by their supervisor or University official stating that the degree will be obtained by the time of PhD enrolment;
- **Two Reference letters** from relevant and appropriate referees or the names and contact details of two Referees (as former Supervisors/PIs).

Application documents in a **single pdf file** should be sent by email to relevant project supervisors (see email address in individual project descriptions). **The subject line of the email must be in the following format: "*SECRET: application for Project#_Title of PhD project*".**

The closing date for applications is **15th of May, 2025.**

Applicants are advised to familiarise themselves thoroughly with the projects, for which they apply and be ready to answer questions on their chosen topics. The SECRET Consortium selection committee reviews all applications as soon as possible after the application deadline. As soon as a decision is made, we will notify candidates. If candidates are still eligible after the pre-selection, they will be informed about the possible next step(s) in the selection procedure, including an initial screening interview by telephone or videoconferencing. The most promising candidates may then be invited to a **in-person interview, within July 2025**, at the host institution or a further videoconference, potentially with several other project supervisors

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Research projects offered by SECRET

DoC	Project Title	Primary Supervisor	Institution	EU State
1	In vitro characterization of perinatal cell secretomes and their effect on innate immunity	PAROLINI, Ornella **CLOSED**	Università Cattolica del Sacro Cuore (UCSC)	IT
2	In vitro characterization of perinatal cell secretomes and their effect on adaptive immunity	PAROLINI, Ornella **CLOSED**	Università Cattolica del Sacro Cuore (UCSC)	IT
3	Establishment and optimization of the scaled production of therapeutic EVs	GIEBEL, Bernd **CLOSED**	Universitatsklinikum Essen (UKEssen)	GE
4	Identify the most cardio-active secretome from perinatal cells for cardiac repair	BOLLINI, Sveva sveva.bollini@unige.it	Università degli Studi di Genova (UniGe)	IT
5	Development of an optimized human 3D organoid-on-plate microfluidic platform for disease modelling and screening	LANZ, Henriëtte **CLOSED**	MIMETAS B.V (MIM)	NL
6	Evaluate and unravel the neuroprotective features of perinatal cell-derived secretomes using hiPSC-derived brain organoids.	PONSAERTS, Peter **CLOSED**	Universiteit Antwerpen (UA)	BE
7	Evaluate and unravel the neuroprotective features of perinatal cell-derived secretomes in a mouse model of neuro-inflammation, -degeneration and -regeneration.	PONSAERTS, Peter **CLOSED**	Universiteit Antwerpen (UA)	BE
8	In vivo validation of three selected secretomes in a stroke mouse model	HERMANN, Dirk **CLOSED**	Universitatsklinikum Essen (UKEssen)	GE
9	Injectable supramolecular hydrogels and microfabricated patches for the controlled release of secretome/EV fractions for cardiac regeneration	PIRES, Ricardo A. **CLOSED**	Universidade do Minho (UMINHO)	PT
10	Development of biomaterial-based vehicles for the delivery of secretome fractions to the CNS regions affected by multiple sclerosis and ischemic stroke	REIS, Rui L. info@i3bs.uminho.pt	Universidade do Minho (UMINHO)	PT

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DoC4	**Identify the most cardio-active secretome from perinatal cells for cardiac repair**
Host Institution	Università degli Studi di Genova (UniGe)
Primary Supervisor	BOLLINI, Sveva
Email address	sveva.bollini@unige.it;
Planned duration	36 months
Subject Area	Cardiac repair and regeneration, Stem cell research, Paracrine biology and regenerative medicine

Introduction: You will be working as PhD Student in The Cellular and Experimental Biology Unit, under the direct supervision of prof. Sveva Bollini, MSc., PhD, Associate Professor in Experimental Biology and Coordinator of the PhD Programme of Biotechnology in Translational Medicine at UniGe (https://dimes.unige.it/sveva.bollini%40unige.it . Prof. Bollini has major know-how in human amniotic fluid-derived stem cell paracrine biology for cardiac repair and regeneration. She has published more than 60 articles in international peer-reviewed journals (H-index: 29, total citations: 3885); Prof. Bollini has broad expertise in the daily supervision of undergraduates, PhD Students and Post Docs. She is a member of the Cardiovascular Sub-Committee of the International Society for Cell and Gene Therapy, of the European Society of Cardiology Working Group on Cardiovascular Regenerative and Reparative Medicine Nucleus and of the Council of the International Society for Heart Research. The work will be performed within the laboratory space in UniGe-DIMES. This includes in-house advanced tissue and cell culture facilities, biochemical and molecular biology equipment, advanced flow-cytometry and FACS-sorting instruments, genome sequencing platforms, electron transmission, confocal, two-photon and deconvolution microscopes. UniGe has independent research premises and facilities and has access to scientific and technological resources in the IRCCS Policlinico San Martino Hospital in Genova on the basis of a collaborative agreement. This includes a recently renovated Animal Facility fully operational for preclinical models of cardiac injury and equipped with state-of-the-art non-invasive ultrasound and MRI imaging equipment.

Background: Cardiovascular disease (CVD) represents the foremost cause of mortality and morbidity worldwide, with steadily increasing incidence due to ageing population growth. Cardiac dysfunction leading to heart failure (HF) may arise from myocardial infarction (MI), inflammatory- and cancer-related cardiomyopathy. Despite pharmacological progress, effective cardiac repair represents an unmet clinical need, with heart transplantation the only option for end-stage HF. Translational research recently focused on analysing cell cross-talks within the myocardial microenvironment to enhance clinically relevant mechanisms of endogenous repair. Paracrine modulation of the injured heart has gained increasing attention as a candidate approach for quenching inflammation exacerbation, while preserving functional cardiomyocytes and limiting fibrosis. Human mesenchymal stromal cells (hMSC) actively release bioactive components in their secretome, as the whole of soluble factors secreted in the cell-conditioned medium (hMSC-CM) in vitro. Within the hMSC secretome, extracellular vesicles (EVs) have been identified as appealing candidate therapeutics, recapitulating most of the parental cell paracrine effects. While adult hMSC have shown an excellent safety profile in clinical assessments, human perinatal MSC stem cells and from extra- embryonic tissues (i.e. amniotic fluid) may offer significant advantage, being highly proliferative and developmentally more immature, thus suggesting a promising cardio-active secretome.

Objectives: The selected Candidate will optimize the isolation of secretome fractions from in vitro cultured human amniotic fluid-derived stem cells (hAFSC), obtained from left over samples of II trimester amniotic

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fluid (fetal hAF) from routine prenatal screening, following written informed consent of the donors. In vitro functional assays on target cardiovascular cells will be carried out to define the cardioprotective potential of hAFSC secretome formulations (hAFSC-CM versus hAFSC-EVs). The most promising secretome formulation will be further validated on 3D cardiac organ-on-plate system with investigation of the mechanism of action. In vivo confirmation of the most cardioactive hAFSC secretome will be finalized in a preclinical rodent model of myocardial infarction, by optimized in situ delivery.

Expected Results: **R1:** Identification of in vitro fetal hAFSC secretome formulations endowed with relevant cardio-protective and immunomodulatory potential in vitro. **R2:** Identification of the most cardioactive secretome formulation (hAFSC-CM vs -EVs) by 3D modelling; **R3:** Definition of paracrine factor formulation within the selected secretome with therapeutic relevance for enhancing cardiac repair in vivo.

Secondments: **(1)** Training on state-of-the-art advanced EV separation techniques will be performed during a secondment at UKEssen (Germany) under supervision of prof. Bernd Giebel; **(2)** Optimization of hiPSC differentiation into cardiomyocytes and design of functional test will be performed during a secondment at Istituto CardioCentro Ticino (Switzerland) under supervision of prof. Lucio Barile; **(3)** Complex co-culture design and 3D design modelling will be learnt during a secondment in MIMETAS with Dr. Henriette Lanz; **(4)** Single cell nuclei RNAsequencing analyses from cardiac samples from the preclinical rodent MI model will be carried out during secondment at Amsterdam University Medical Centre with Prof. Monika Gladka (The Netherlands).

Enrolment in Doctoral degree(s): Universita' di Genova – Department of Experimental Medicine (DIMES)

Project-specific selection criteria: Candidates should hold a Master's degree (Master of Science or equivalent) in Chemistry, Biochemistry, Biotechnology, Biomedical Sciences, Biomedical Engineering or related areas or will have obtained it by October 2025 at the latest. Knowledge in chemical synthesis is valorized, as well as experience in analytical techniques, such as, HPLC, NMR, and mass spectrometry. Additionally, it is also valorized practical experience in cell culture, including cytotoxicity assessment, protein/gene expression analysis, etc. Candidates must not have resided in Italy for more than 12 months in the 3 years immediately before the recruitment date, nor have carried out their main activity (work, studies, etc.) in Italy during that period. Highly valued and appreciated are the following expertise: Synthesis and processing of biomaterials; Characterization of biomaterials, including the use of HPLC, NMR, mass spectrometry, DLS, rheology, absorption/fluorescence spectroscopy; Cell culture (cytotoxicity assessment, protein/gene expression analysis, etc.). Candidates should be highly motivated, flexible, with great team-work and problem-solving attitude and present good communication skills.

Recommended reading:

- ***First Characterization of Human Amniotic Fluid Stem Cell Extracellular Vesicles as a Powerful Paracrine Tool Endowed with Regenerative Potential.*** Balbi C. et al. Stem Cells Transl Med 2017 May; 6(5):1340-1355. doi: 10.1002/sctm.16-0297;
- ***Reactivating endogenous mechanisms of cardiac regeneration via paracrine boosting using the human amniotic fluid stem cell secretome*** Balbi C. et al., Int J Cardiol. 2019 Jul 15:287:87-95. doi: 10.1016/j.ijcard.2019.04.011;
- ***The Human Fetal and Adult Stem Cell Secretome Can Exert Cardioprotective Paracrine Effects against Cardiotoxicity and Oxidative Stress from Cancer Treatment.*** Villa F. et al. Cancers (Basel). 2021 Jul 24;13(15):3729. doi: 10.3390/cancers13153729;
- ***Investigating the Paracrine Role of Perinatal Derivatives: Human Amniotic Fluid Stem Cell-Extracellular Vesicles Show Promising Transient Potential for Cardiomyocyte Renewal.*** Costa A. et al. Front Bioeng Biotechnol. 2022 Jun 8:10:902038. doi: 10.3389/fbioe.2022.902038. eCollection 2022.

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DoC10	**Development of biomaterial-based vehicles for the delivery of secretome fractions to the CNS regions affected by multiple sclerosis and ischemic stroke**
Host Institution	Universidade Do Minho (UMINHO)
Primary Supervisor	REIS, Rui L. and ARAÚJO, Ana R.
Email address	info@i3bs.uminho.pt;
Planned duration	36 months
Subject Area	biomedical engineering, biomaterials and drug delivery systems

Introduction: The University of Minho (UMinho: https://www.uminho.pt/EN/uminho/Pages/default.aspx) was founded in 1973 and it is organized in 12 schools/institutes. The 3B's Research Group is a subunit of the Research Institute on Biomaterials, Biodegradables and Biomimetics (I3Bs) dedicated to biomaterials, tissue engineering, regenerative medicine and stem cells. 3B's is one of the most cited groups in Europe in these fields and collaborates closely with the UMinho's Medical School (ICVS) creating the ICVS/3B's Associate Laboratory, recognized by the Portuguese Government for its Excellent scientific outputs in the (bio)medical area. You will be working as PhD Student in the 3B's Research Group, under the direct supervision of Prof. Rui L. Reis, PhD, DSc, Full Professor in Biomaterials, Tissue Engineering, Regenerative Medicine & Stem Cells at the University of Minho, Portugal (https://3bs.uminho.pt/people/18) and Dr. Ana Rita Araújo, PhD, Junior Researcher of the University of Minho. Prof. Reis is president of the I3Bs Institute and founding director of the 3B's Research Group and an elected member of the National Academy of Engineering (USA, since 2016). He is author of >20 patents, >1600 original papers (including in high impact journals, e.g., Nat Chem, Adv Mater, JACS, Prog Pol Sci, ACS Nano, Biomaterials, among many others), has an H-index of 114 (ISI WoK), and was already responsible for the supervision of >70 PhD theses and >80 Post Docs. He is an expert in the development of regenerative strategies based on the use of natural-based polymers and to explore biomimetic approaches in tissue engineering. Dr. Araújo has been working in the field of neurodegeneration for >10 years, she has experience in the nanoscale manipulation of materials and in the development of nanosystems able to reduce the toxicity of amyloids and to modulate cellular behaviour. The 3B's headquarters include various labs dedicated to chemical synthesis, microfabrication, cell culture, microbiology, as well as chemical, physical and biological characterization. These labs are equipped with a wide range of state-of-the-art techniques to develop and characterize biomaterials, as for example, goniometer, DMA, QCM-D, SPR, UV-VIS spectrophotometry, X-Ray microtomography system (MICRO-CT), analytical and preparative HPLC, GPC, FTIR, MALDI, ESI-MS, AFM, SEM, DSC, DLS, among many others. The 3Bs facilities also include standard equipment for cell culture, molecular biology (RT-PCR, flow cytometry, etc.), confocal and fluorescent scanning microscopes. An animal facility with small animals (mice, rats and rabbits) is also available.

Background: Ischemic stroke (IS) and multiple sclerosis (MS) are both neurological conditions that result in significant damage to neural tissue. IS occurs due to an interruption in the brain's blood supply, leading to tissue damage, loss of neurological function, neuroinflammation, and neurodegeneration. In contrast, MS is an autoimmune disorder characterized by the progressive destruction of myelin sheaths around neurons, which impairs neural signalling and causes neuroinflammation. Despite their different underlying mechanisms, both conditions share common outcomes, including tissue damage, loss of neurological function, and neurodegeneration. This highlights the need for effective neural regeneration strategies. Importantly, biomaterials, mimicking the brain's extracellular matrix (ECM), offer a promising solution for supporting neural recovery post-stroke. Moreover, there are also evidence that perinatal cells' secretome can be used as a regenerative strategy under this context. This project focuses on developing glycopeptide-

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based micelles and hydrogels that mimic neural ECM components like mimetics of hyaluronan and collagens. These biomaterials will be designed to cross the blood-brain barrier and release the secretome's therapeutic proteins. Using micelles of short peptide/saccharide amphiphiles as a starting point, we will enhance their properties for targeting damaged tissue and releasing the secretome formulations. These systems will be validated in vitro and in vivo using models of MS and IS. This project aims to develop glycopeptide-based micelles with tuneable properties to target the damaged tissue and release secretome-based proteins inducing a functional recovery following neurological impairments.

Objectives: In this PhD project, the selected candidate will prepare micelles and hydrogels for the loading of secretome/extracellular vesicles fractions and their local delivery to the central nervous system regions affected by multiple sclerosis and ischemic stroke. The loading conditions of the secretome/extracellular vesicles fractions obtained from perinatal cells and their local delivery will be optimized, followed by the validation of the efficacy of the engineered systems using in vitro and in vivo models of multiple sclerosis and ischemic stroke (in collaboration with the University of Antwerp, Belgium, Prof. Peter Ponsaerts).

Expected Results: R1: Micelle formulations with adequate size to load secretomes fractions. **R2:** Secretome loaded micelles that can cross the blood-brain barrier and reach the affected regions of the central nervous system. **R3:** Hydrogel formulations that can load secretome fractions and maintain their bioactivity for long periods of time, as well as to release them to the surrounding environment over time. **R4:** Micellar and/or hydrogel formulations that promote the regeneration of the central nervous system tissues affected by multiple sclerosis and ischemic stroke.

Secondments: (1) Training on the preparation of hAFSC secretomes at University of Genova (Italy), under supervision of Prof. Sveva Bollini; **(2)** Training on perinatal cell isolation (hAMSC and hUC/WJ-MSC) and preparation of secretome fractions at Eugenia Menni Research Centre (CREM, Brescia, Italy) under the supervision of Prof. Antonietta Silini;**(3)** In vivo evaluation of the developed secretome/extracellular vesicles-loaded systems at the University of Antwerp (Belgium), under the supervision of Prof. Peter Ponsaerts.

Enrolment in Doctoral degree(s): Universidade Do Minho, Institute on Biomaterials, Biodegradables and Biomimetics.

Project-specific selection criteria: Candidates should hold a Master's degree (Master of Science or equivalent) in Chemistry, Biochemistry, Biotechnology, Biomedical Sciences, Biomedical Engineering or related areas or will have obtained it by October 2025 at the latest. The candidates must not have resided in Portugal for more than 12 months in the 3 years immediately before the recruitment date, nor have carried out their main activity (work, studies, etc.) in Portugal during that period. Knowledge in chemical synthesis is valorized, as well as experience in analytical techniques, such as, HPLC, NMR, and mass spectrometry. Additionally, it is also valorized practical experience in cell culture, including cytotoxicity assessment, protein/gene expression analysis, etc. Candidates should have the ability to work in a multidisciplinary team and present good communication skills.

Recommended reading:

- ***Glycopeptide-Based Supramolecular Hydrogels Induce Differentiation of Adipose Stem Cells into Neural Lineages.*** Vânia I. B. Castro, Ana R. Araújo, Filipa Duarte, António Sousa-Franco, Rui L. Reis, Iva Pashkuleva and Ricardo A. Pires, ACS Appl. Mater. Interfaces 2023, 15, 25, 29998–30007. doi: 10.1021/acsami.3c05309
- ***Carbohydrate amphiphiles for supramolecular biomaterials: Design, self-assembly, and applications.*** Alexandra Brito, Salma Kassem, Rui L. Reis, Rein V. Ulijn, Ricardo A. Pires and Iva Pashkuleva, Chem 2021, 7, 11, 2943-2964. doi: 10.1016/j.chempr.2021.04.011
- ***Redox-Responsive Micellar Nanoparticles from Glycosaminoglycans for CD44 Targeted Drug Delivery.*** Ana M. Carvalho, Raquel Teixeira, Ramón Novoa-Carballal, Ricardo A. Pires, Rui L. Reis and Iva Pashkuleva, Biomacromolecules, 2018, 19, 7, 2991-2999. doi: 10.1021/acs.biomac.8b00561

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