POLITECNICO DI MILANO

PhD in BIOINGEGNERIA / BIOENGINEERING - 38th cycle

PNRR_352 Research Field: UNRAVELLING THE MOLECULAR CORRELATION BETWEEN MECHANICAL INJURIES AND OSTEOARTHRITIS IN A CARTILAGE-ON-CHIP MODEL

Monthly net income of PhDscholarship (max 36 months)
€ 1250.0 In case of a change of the welfare rates during the three-year period, the amount could be modified.

Context of the research activity	
Motivation and objectives of the research in this field	Osteoarthritis (OA) is the most common form of arthritis and a major cause of disability in elderly, representing a huge economic burden for healthcare systems exceeding 200 million ¿/year in Europe. Despite OA¿s high prevalence, therapeutic options are predominately palliative and still far from restoring a physiological joint condition. As a consequence, OA ultimate treatment is represented by invasive surgery (arthroplasty/osteotomy), which still does not allow articular cartilage regeneration, but only delays OA progression. OA etiopathogenesis is multifactorial involving genetic, molecular and environmental influences. Among the different risk factors, prior joint injury and mechanical factors (i.e. misalignment, abnormal joint shape, overweight) are the most relevant. Articular cartilage (AC) is one of the most affected tissue during OA progression. In physiological conditions, articular chondrocytes are quiescent, fully differentiated cells responsible for homeostasis of adult AC. During OA, several catabolic components (e.g. tumor necrosis factor alpha TNF-alpha, interleukin IL-1beta and IL-6) in combination with excessive loading are involved in the trigger of cartilage matrix breakdown coupled with enhanced production of different extracellular matrix (ECM)-degrading enzymes (e.g. aggrecanases, ADAMTS, and collagenases, MMPs), pro-angiogenic factors, and recapitulation of developmental programs leading to inappropriate hypertrophic-like maturation and cartilage calcification.

	Acute and chronic injuries, often in the context of other risk factors (i.e. obesity, aging, metabolic disorders, genetic factors), have been proposed as potential triggers of local tissue damage and inflammation in OA, resulting in progressive joint degeneration. Molecular components, generally classified as damage-associated molecular patterns (DAMPs), have been postulated as transducer of these joint traumas. The number and diversity of DAMPSs inflammatory mediators found in OA joints and their complex roles in mediating host defence makes the clear understanding of pathways activated downstream a mechanical damage still far from been accomplished. This project intends to advance the current knowledge on major initial OA effectors by unravelling the role of mechanical injuries in triggering the OA cascade in a novel mechanically active microscale in vitro model. Specifically, the molecular effectors activated by cartilage mechanical damage will be identified. Overall, these advancements will help to identify new therapeutic options for targeting OA at the very early stage.
Methods and techniques that will be developed and used to carry out the research	The design and the development of new advanced microscale in vitro platforms will consider state-of-the-art technologies, micro- and nano-fabrication. Computational modeling will be used to optimize geometrical parameters. The main hypothesis behind the project is that mechanical damages of cartilage are the first triggers of OA cascade, causing the activation of specific molecular players in turn responsible for initiating a pathological switch of articular chondrocytes. Such hypothesis will be verified by taking advantage of the design and the development of new advanced microscale in vitro platforms. To this aim, state-of-the-art technologies, micro - and nano-fabrication approaches will be exploited, starting from a cartilage-on-chip (CoC) model previously developed by Prof. Rasponi group at Politecnico di Milano. Computational modeling will be used to optimize geometrical parameters. The proposed research plan is divided into 3 Actions. A1: Setup of mechanically induced pathological models. Association between abnormal joint loading and triggering of OA changes in cartilage will be assessed. The

	previously developed CoC will be optimized and exploited to model ¿dose-response¿ of healthy articular chondrocytes (AC) to dynamic cyclic overload. Induction of a cartilage phenotypic switch towards OA (i.e. degradation, inflammation, calcification, senescence) will be verified and down-regulation of clinically-relevant OA biomarkers (e.g. FRZB, GREM1) used as verification of correlation. A2: Unravel mechanical damage-related molecular pathways. Molecular players mediating pathological responses from A1 will be elucidated by analyzing both the secretome released by mechanically damaged and control CoC models and the digested tissues. An unbiased approach (i.e. proteomic analysis) will be primarily followed. In parallel, involvement of hypertrophy-related pathways (i.e. BMP, Wnts, FGF, IHH/PtHrP, MMP13, VEGF) will be directly assessed based on our preliminary data. Once identified, the role of selected candidates in mediating mechanical injuries will be verified in the CoC. A3: Translational actions. Results of A2 will be clinically validated and their potential translation tested. AC derived from OA patients will be exploited to generate OA CoC models. Specific inhibitors of identified pathways will be used: restoration of healthy tissues phenotype in presence of inhibitors, even under harsh OA-like mechanical conditions uniquely mimicked in the CoC model, will suggest possible targets for new pharmacological formulations.
Educational objectives	The project aims to train the PhD student in organs-on-chip technology, microfluidics, microfabrication, soft-lithography, cell culture applications, micro-bioreactors.
Job opportunities	The research will be carried out in strong cooperation with BiomimX Srl and University of Basel, which has career opportunities in the emerging field of organs-on-chip. The research will be carried out by an interdisciplinary consortium, bringing both basic and translational research expertise and long-lasting experience in human joint

	diseases. Politecnico di Milano (IT) - POLIMI unit has access to microfabrication facilities. It has renowned experience in developing and studying biological models within custom-designed microfluidic devices for cell cultures and tissue engineering, with a focus in the field of cartilage tissue engineering.
Composition of the research group	0 Full Professors 2 Associated Professors 0 Assistant Professors 5 PhD Students
Name of the research directors	Prof. Marco Rasponi

Contacts
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Additional support - Financial aid per PhD student per year (gross amount)	
Housing - Foreign Students	--
Housing - Out-of-town residents (more than 80Km out of Milano)	--

Scholarship Increase for a period abroad	
Amount monthly	625.0 €
By number of months	6

National Operational Program for Research and Innovation	
Company where the candidate will attend the stage (name and brief description)	BiomimX Srl; www.biomimx.com
By number of months at the company	10
Institution or company where the candidate will spend the period abroad (name and brief description)	University of Basel; biomedizin.unibas.ch/en
By number of months abroad	6

Additional information: educational activity, teaching assistantship, computer availability, desk availability, any other information
Attinenza alla tematiche, alle missioni/componenti prescelte del bando PNRR ex D.M. 352, art.6

Il progetto riguarda l'avanzamento della conoscenza di base in un'area a forte impatto tecnologico (quella degli organi su chip), con dirette ripercussioni nell'ambito delle scienze della vita. Il progetto mira a favorire il trasferimento tecnologico dall'università all'impresa, avendo come obiettivo lo sviluppo di tecnologie di immediato interesse per il partner aziendale e per le quali il partner internazionale è key opinion leader. Pertanto si prevede di arrivare a un livello di sviluppo tecnologico tale da poter pianificare il loro ingresso sul mercato nazionale e internazionale alla fine del progetto stesso. Per tale motivo, il progetto si inquadra nella missione 4 (M4C2 - Dalla ricerca all'impresa).

Impresa, presso cui si svolgerà l'attività esterna

nome: BiomimX Srl
settore: R&D nel settore delle scienze della vita
link: www.biomimx.com
mesi previsti: 10
Descrizione sintetica attività:
BiomimX sviluppa soluzioni organi-su-chip, principalmente per la determinazione precoce dell¿effetto di farmaci e chemicals in termini di efficacia e tossicità. Nell'ambito del presente progetto verranno implementati modelli organotipici della patologia osteoartrosica umana, sui quali saranno svolte attività di identificazione e validazione di nuovi biomarkers.

A shared desk and a PC will be given to the student for the time needed to carry out research. A limited budget will be available for travelling and purchases, too.