AutoCRAT

Cellular Robot-Assisted Technologies for translation of discovery-led research in Osteoarthritis

Newsletter Spring 2021

What is AutoCRAT?

AutoCRAT is an EU Horizon 2020-funded project that will develop novel sustainable cell and cell-derived therapies for osteoarthritis (OA). The project will use human induced pluripotent stem cells to generate articular chondrocytes for cartilage repair and human induced mesenchymal stem/stromal cells (MSC) for the prevention and treatment of established OA. As extended goals, the project will investigate the potential of the MSC cell secretome as a next-generation therapy and will produce the therapeutics identified in the project using cost-effective robot-enabled processes in a novel manufacturing platform to expedite translation to patients.

The AutoCRAT consortium is composed of nine expert scientific teams in five European countries specialising in regenerative medicine, OA, preclinical efficacy and safety demonstration, GMP- and GAMP-compliant manufacturing of MSC, clinical trials for OA, regulatory affairs and health economics analysis.

Message from AutoCRAT Coordinator, Prof. Mary Murphy, NUI Galway

"Osteoarthritis (OA) is a degenerative disease of the joints caused by the breakdown of cartilage. It is the most common chronic joint condition, affecting more than 40 million people in Europe alone. Osteoarthritis is associated with severe pain and loss of function. As there are limited treatment options available, osteoarthritis imposes a huge burden on healthcare systems. OA can have a profound impact on quality of life for those with the condition. It also can affect families, employers, economies and society as a whole.

Prof Mary Murphy
AutoCRAT Coordinator

Treating OA with mesenchymal stem/stromal cells (MSCs) has yielded promising results in studies undertaken to date. However, we need to know more about how this treatment works. In AutoCRAT, we aim to deliver new therapies to repair cartilage, to help prevent the development of OA and to treat the condition once established. AutoCRAT will build on existing knowledge to identify the cells, secreted factors and cell products that can be used most effectively. Part of our work involves generating economically sustainable and reproducible therapeutic cell sources. We will also build the AutoCRAT Regenerative Medicine Factory, which will enable automated production of the chosen therapeutic agents economically, at scale and within the regulatory framework."

AutoCRAT has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement no 874671. The material presented and views expressed here are the responsibility of the author(s) only. The EU Commission takes no responsibility for any use made of the information set out.

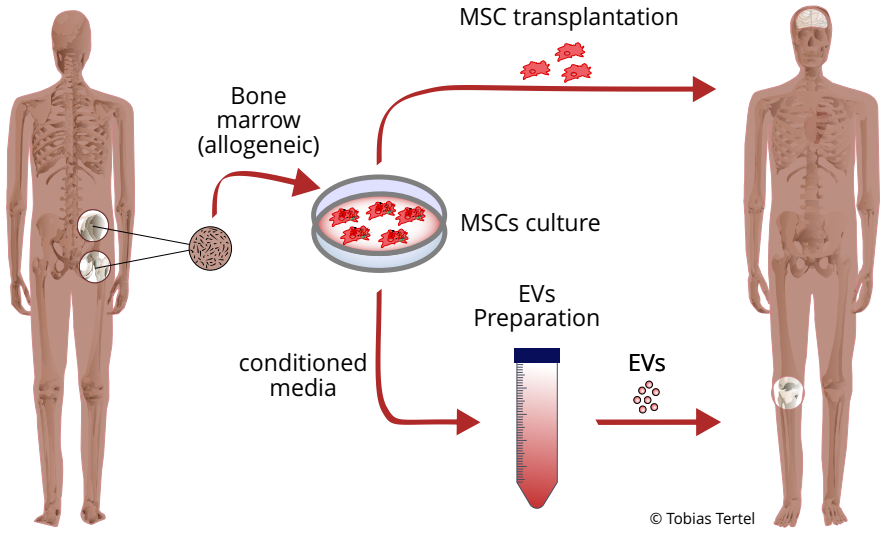
What are EVs? Where are they found? Why are they medically interesting?

Prof. Dr Bernd Giebel

Prof. Chiara Gentili

Within AutoCRAT, two research groups are working on the development of extracellular vesicle (EV)-based therapeutics, for the modulation of osteoarthritis. **Prof. Dr Bernd Giebel** heads a research group within the University Medicine Essen's Institute for Transfusion Medicine. As an expert in early human haematopoiesis and extracellular vesicles research, his group focusses on human hematopoietic stem cell biology and the therapeutic potential of MSC-derived EVs. **Prof. Chiara Gentili's** research team in the Department of Experimental Medicine (DIMES) at the Università degli Studi di Genova brings decades of experience with pre-clinical models for regenerative medicine and expertise in MSC and EV production for the treatment of osteoarthritis.

At the turn of the millennium, mesenchymal stem/stromal cells (MSCs) became popular research entities in regenerative medicine. Aiming to apply allogeneic off-the-shelf MSC products for acute conditions, like myocardial infarction and ischemic stroke, researchers began studying the interaction of allogenic MSCs with components of the immune system and showed that they exert immunomodulatory functions. Regarding their pro-regenerative and immunomodulatory potential, up to now MSCs have been applied in more than a thousand clinical trials to various patient cohorts, some confirming their therapeutic potential, others failing to show efficacy.



As most systemically administered MSCs are recovered in the lungs of recipients and hardly in affected tissues, the long-lasting dogma that MSCs act in a cell replacement role became challenged. Quickly, researchers postulated that they mainly act in a paracrine cell-to-cell communication capacity. After confirming that MSC conditioned media exerted comparable therapeutic effects to administered cells, several groups began to search for active components in MSC conditioned media. The groups of Giovanni Camussi and Sai Kiang Lim showed in 2009 and 2010 that MSCs' therapeutic activity was recovered in vesicle enriched culture media fractions. After defining microvesicles as budding from the plasma membrane and exosomes as derivatives of the endosomal compartment, and because different vesicular entities cannot yet be experimentally separated from each other, the scientific community agreed in experimental settings to the use of the term 'extracellular vesicles' instead of more specified terms. Using EVs for therapeutic purposes has many advantages over cells. For example, EV-based therapeutics are easier to handle and can be separated by filtration. In recent years, the therapeutic EV field has grown exponentially. MSC-EV products, like their parental cells, modulate immune responses in animal models and have been efficaciously used to treat an otherwise treatment-resistant human with Graft-versus-Host Disease.

Meanwhile, many groups approach the clinic intending to apply MSC-EV products to different patient cohorts, including those with COVID-19. Although pre-clinical data are very encouraging and MSC-EVs, in principle, provide promising therapeutic agents for the future, several translation

challenges remain. For now, production protocols are not standardized, and apparently, not all MSCs are competent in releasing therapeutically active EVs. Despite reports that MSC-EVs possess immunomodulatory, pro-regenerative, pro-angiogenic and/or anti-apoptotic properties, their precise mechanisms of action remain unclear. Collaborative research as in AutoCRAT is required to improve MSC-EV production platforms and to explore the MSC-EVs' therapeutic potential to warrant effective translation into the clinic.

Please follow this link for the references related to the article above.

The AutoCRAT Team

Partner in the Spotlight: Valitacell

Headquartered in Dublin, **Valitacell** (https://www.valitacell.com/) is a biotechnology SME developing innovative technologies to aid and improve drug discovery and development. Founded in 2014, their main focus is on developing analytical technologies to assess key process parameters and product critical quality attributes in both biologics and cell therapy biomanufacturing. With 13 employees, Valitacell's combined knowledge of bioprocessing with deep learning and predictive analytics delivers an unprecedented and unique level of bioprocess performance.

Within AutoCRAT, Valitacell are developing their Quantum and ChemStress technology platforms for human mesenchymal stromal cell (hMSC) characterisation, focusing on hMSC secretome assessment and functional profiling during bioreactor-based expansion. These analytical tools will be fully automated within the AutoCRAT QC arm at the IPT Fraunhofer facility in Germany.

Valitacell Technologies: The **Quantum platform** underpins a range of simple, high-throughput target quantification and detection assays. It is based on fluorescence polarisation technology which we use to measure probe:target interactions. Fluorescence Polarisation-based detection can be performed on all multimode plate readers, and is fully automatable, thereby allowing fully scalable workflows. In AutoCRAT, Valitacell are investigating the use of their Quantum platform in hMSC secretome assessment, focusing on specific secreted factors of interest such as extracellular vesicles.

ChemStress Fingerprinting is an information-rich, analytical assay supplying data on the functional quality of cells in specific culture media environments. This novel platform characterises cells using a panel of specific, small molecule chemical stressors to generate a unique biological signature or 'Fingerprint'. Initially deployed in CHO based biomanufacturing cell line development and media QC, Valitacell are adapting this platform for hMSC functional profiling, with potential applications in donor release and acceptance as well as media and process development, and optimisation.

AutoCRAT

Recent Dissemination Highlights

At a virtual **International Society of Liquid Biopsy (ISLB)** conference October 30th, 2020, **Prof. Dr Bernd Giebel** of University Medicine Essen gave a presentation *"Mesenchymal Stem Cell-derived Extracellular Vesicles, a novel Tool in Regenerative Medicine."*

Prof Frank Barry

Profs. Mary Murphy and Frank Barry from NUI Galway presented at the **RenalToolBox Marie Curie ITN workshop** on October 13- 14, 2020. AutoCRAT Coordinator Prof. Murphy's talk was titled *"Mesenchymal Stromal Cells for Modulation of Disease Progression in Osteoarthritis: Mechanistic to Translational Insights"* and Prof. Barry's was *"Stromal Cell Therapy for Arthritic Disease: Evidence, Mechanism and Production."*

On September 17th, 2020, **Prof. Dr Bernd Giebel** of the University Hospital Essen introduced AutoCRAT at the **DGTI 2020 meeting** during the DGTI/DGHO Joint Session. Prof Giebel's talk was titled *"Therapeutic Potential of extracellular vesicles."*

As a consortium, we send our sincere thanks to Jelena Ochs of Fraunhofer IPT, who is taking up a new position. Jelena has been an excellent colleague and partner through AUTOSTEM (grant no. 667932) and AutoCRAT. We wish her the best of success at CellGenix where she will begin as a project manager in Business Development in May.

Read our interview with Jelena from June 2020 here.

AutoCRAT Facts

Duration: The AutoCRAT project will run for 4 years from 1 January 2020 to 31 December 2023.
Coordinator: Prof in Regenerative Medicine Mary Murphy, Regenerative Medicine Institute, National University of Ireland Galway, Galway, H91 W2TY, Ireland.
Budget: € 7,452,770

Website: https://www.autocrat.eu/
Social Media: https://twitter.com/AutoCRAT2020 and https://www.facebook.com/AutoCRAT2020/

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