



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

Newsletter 2023

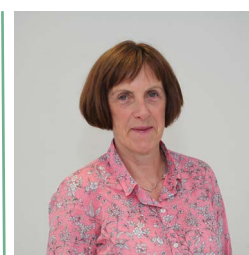
What is AutoCRAT?

AutoCRAT is an EU Horizon 2020-funded project that aims to develop novel sustainable cell and cell-derived therapies for osteoarthritis (OA). The project is exploring the use of human induced pluripotent stem cells (hiPSCs) to generate articular chondrocytes for cartilage repair and human induced mesenchymal stem cells (hiMSCs) for the prevention and treatment of established OA. As extended goals, the project is investigating the potential of the hiMSC 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, with at-line product testing, to expedite translation to patients.

The AutoCRAT consortium is composed of nine 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 Prof. Mary Murphy, University of Galway, as she reflects on our work so far...

In AutoCRAT we have generated sustainable, reproducible cell sources for hiMSCs. These cells have been characterized to confirm their similarity to primary human MSCs. Our hiMSCs have been studied and demonstrate beneficial effects. To date, studies with hiCHOs (human induced chondrocytes) show promising therapeutic potential. Extracellular vesicles (EVs) harvested from hiMSC from early to late passages appear biologically effective in vitro also. In our in vivo work, we have tested a thermosensitive injectable hydrogel to use as a carrier for cells and EVs for intra-articular injection as a potential treatment of OA.



*Prof Mary Murphy
AutoCRAT Coordinator*

Scalable, automatable and adaptive AutoCRAT production processes have been devised for the cultivation of hiPSCs, the differentiation of hiPSCs to hiMSCs, the culture of hiMSCs at an appropriate scale and the differentiation of hiPSCs to hiCHOs. We continue to optimise protocols to isolate hiMSC-derived hiEVs. In addition, the build of the AutoCRAT automated production platform and development of tools for at-line assessment of manufactured therapeutics continue to progress.

As we enter the final phase of AutoCRAT, we look forward to the achievement of our key goals and objectives.



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Partner in the Spotlight: Fraunhofer Institute for Production (IPT)

The Fraunhofer Institute for Production Technology (IPT), headquartered in Aachen, Germany, develops system solutions for the networked, adaptive production of sustainable and resource-efficient products and associated services. Their focus is on process technology, production machines, production quality and metrology, and technology management, and range from the fundamentals to the digital transformation of production. The Fraunhofer IPT is part of the Fraunhofer-Gesellschaft, Europe's largest application-oriented research organisation.



Fraunhofer IPT develops and optimizes new and existing methods, technologies and processes for the production of the future. Understanding production not only in its steps but in the totality of all processes and interconnections between the elements of the process chain, they develop highly specialized individual technologies and complete system solutions for sustainable production on behalf of customers.

New demands from the capital markets require companies to rethink productivity: moving away from a purely financial approach to a broader view of the sustainability of processes and products. More efficient manufacturing processes and energy-saving machinery and equipment can help to reduce overall production costs, create flexibility and resilience for businesses and protect the climate and nature.

Within AutoCRAT, Fraunhofer IPT leads the workstream on automation for the production of AutoCRAT cells and EVs. They are building the AutoCRAT Regenerative Medicine Factory (ARM-F) and contributing to work on regulatory compliance and economic evaluation of the ARM-F.

With approximately 480 employees, Fraunhofer IPT is working to make production processes, systems and products more climate-friendly and ecological on behalf of customers and project partners who set out on the path to more sustainable and resource-conserving production.

AutoCRAT partners in Ireland and Germany celebrate Unistem Day



On March 10th, 2023, AutoCRAT partners at the University of Galway and Pintail Limited in Ireland, and Fraunhofer Institute of Production Technology IPT and University Hospital Essen in Germany took part in Unistem Day by offering lessons, debates, and visits to the laboratories, secondary school students and teachers engaged with the concepts and methodologies involved in stem cell research. Unistem Day is an annual pan-European event organised by the University of Milan. The day is solely dedicated to the dissemination and outreach of stem cell science and research, providing an opportunity to foster learning, discovery and debate on the themes of knowledge and innovation in stem cell research. The event showcases cutting-edge research, paints a picture of the daily work of a scientist, and explores the mechanisms behind scientific breakthroughs, including cultural expectations.

The AutoCRAT Team



OLLSCOIL NA GAILLIMHE
UNIVERSITY OF GALWAY



UNIVERSITÀ DEGLI STUDI
DI GENOVA



Leiden University
Medical Center



University Medicine Essen
University Hospital



UNIVERSITY OF GOTHENBURG

How is AutoCRAT engaging with people with osteoarthritis?

Much of our research relies on cell and tissue samples donated by people with osteoarthritis during joint replacement surgeries as a result of OA. Researchers can obtain cartilage and bone from the surgical waste material, as well as cells from the people who have consented and agreed to allow this material to be used. We sincerely thank these people with OA for donating their tissue and helping advance osteoarthritis research.

PI Prof. Ingrid Meulenbelt and Dr Yolande Ramos of Leiden University Medical Center (LUMC) conduct an OA 'public and patients in research' group. The group of ten typically meet in person every two to three months in Leiden to discuss research on OA within and outside the group. They work as a team to offer mutual help with research proposals and to prioritize gaining broad societal support for research. Prof. Meulenbelt, Head of the OA Research Group at the LUMC, remarks: "Initially, it was the funding agencies in the Netherlands who believed that it was important to involve patients in research project design. But once we started the PPA group, we realized it was a highly valuable exercise for us and for the PhD students to engage with the patients because we are not medical doctors. The group provides an additional dimension to the work we are doing. This is an enrichment forward and back. The group helps us to communicate our fundamental research, especially our abstract -omics work, (for example genomics, transcriptomics, proteomics, metabolomics) in an understandable way."



Prof. Frank Barry of the University of Galway took part in an interview that aired on January 25th, 2023. In the Arthritis Ireland *Inflammation Nation* podcast episode titled "New Horizons for Osteoarthritis Patients," Prof. Barry discusses his current research and the human trial resulting from the ADIPOA2 (grant no. 643809) project, foundational research for AutoCRAT.

AutoCRAT partners work with other EU-funded projects

During the week of March 27-31st, 2023, Pintail Limited's Danielle Nicholson and University Hospital Essen's Dr Tobias Tertel participated in the knowledge exchange activities of an Erasmus+ project called *GenEthics – Discussing the Controversial Bioethical Issue of Stem Cell Research as an important Issue of our time in the European Context* (grant no. 2020-1-DE03-KA229-077566_1). Secondary school students and teachers from Sweden, Germany and Romania engaged in science and ethics discussions, and hands-on activities in the labs in Essen.

October 12th was Stem Cell Awareness Day and with EU-funded projects working with MSCs, PREMSTEM (grant no. 874721) and HEALIKICK (grant no. 874889), we took to social media to celebrate our partners' involvement in the field. We created and shared a [short video](#) to showcase what our researchers find exciting about AutoCRAT and their work with stem cells.

Our website includes a section of 'Related Projects' that briefly describes and links to the EU-funded projects funded under the same Societal Challenge, and others that our partners have been or are involved in currently. The list includes AIDPATH, AutoSTEM, and others.



Dissemination Matters

Recent Presentations in 2023

At the Tissue Engineering and Regenerative Medicine International Society (TERMIS) meeting in Manchester, UK, March 28- 31st, 2023, AutoCRAT researchers presented their work: Prof. Chiara Gentili (UNIGE) spoke about the *Paracrine functionalities of hiMSCs cultured in clinical grade system: in vitro biological validation of hiMSC-derived EVs for the treatment of osteoarthritis*. U of Galway PhD candidate Dale Creaven spoke on *Upscaling the Production of hiMSC in a bioreactor format*. Jason Hunt (U of Galway) presented a poster entitled *Assessment of the Therapeutic Potential of Induced Pluripotent Stem cell-derived mesenchymal stromal cells*.

In London, Laura Herbst of Fraunhofer IPT facilitated a talk titled *Automating autologous and allogeneic cell therapies* at the Advanced Therapy Congress on March 15th, 2023.

University of Galway PhD candidates Jason Hunt and Dale Creaven presented posters at the 2023 Osteoarthritis Research Society International (OARSI) World Congress in Denver, Colorado, March 17-20, 2023. Jason presented: *Upscaling Manufacturing of Human Induced Pluripotent-derived Mesenchymal Stromal Cells in a 1-L Bioreactor System*. Dale's poster was titled: *In vitro Assessment of the Therapeutic Potential of Induced Pluripotent Stem Cell-derived Mesenchymal Stromal Cells (iMSCs)*.

Recent Publications 2022–2023

Palamà, M.E.F., Coco, S., Shaw, G.M., Reverberi, D., Ghelardoni, M., Ostano, P., Chiorino, G., Sercia, L., Persano, L., Gagliani, M.C., Cortese, K., Pisignano, D., Murphy, J.M., Gentili, C. (2023). Xeno-free cultured mesenchymal stromal cells release extracellular vesicles with a “therapeutic” miRNA cargo ameliorating cartilage inflammation in vitro. *Theranostics*, 13(5), 1470-1489. DOI: <https://doi.org/10.7150/thno.77597>.

F. Biermann; S. Gräfe, S; T. Bergs; R.H. Schmitt, Additively Manufactured Robot Gripper Blades for Automated Cell Production Processes. *Processes* 2022, 10, 2080. DOI: <https://doi.org/10.3390/pr10102080>.

Yolande F. M. Ramos, Tobias Tertel, Georgina Shaw, Simon Staubach, Rodrigo Coutinho de Almeida, Eka Suchiman, Thomas B. Kuipers, Hailiang Mei, Frank Barry, Mary Murphy, Bernd Giebel, Ingrid Meulenbelt, Characterizing the secretome of licensed hiPSC-derived MSCs, *Stem Cell Res Ther* 13, 434 (2022). DOI: <https://doi.org/10.1186/s13287-022-03117-2>.

H. Evenbratt, L. Andreasson, V. Bicknell, M. Brittberg, R. Mobini and S. Simonsson, Insights into the present and future of cartilage regeneration and joint repair, *Cell Regen* 11, 3 (2022). DOI: <https://doi.org/10.1186/s13619-021-00104-5>.

Learn more at www.autocrat.eu

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