Press release

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Allo-CAR-T cells: one step closer to standardized and accessible cell therapies

As part of the development projects of allogeneic cell therapies (from a healthy donor), researchers from Institut Curie, Gustave Roussy, CNRS and Inserm, have identified a combination of genes to target to reduce the destruction of injected cells by the immune system of patients, a major obstacle to these new treatments. Published in *Nature Biomedical Engineering*, these first results pave the way for the academic development of standardized CAR-T cells with enhanced efficiency.

CAR-T cell therapies (*Chimeric Antigen Receptor T-cells*) represent an innovative and personalized approach in oncology, particularly effective against certain blood cancers, such as leukemias and lymphomas. This technique is based on the genetic modification (CAR) of T-cells, cells of the immune system, to restore their ability to eliminate cancer cells. The modified T-cells can come from the patient, or from a healthy donor - these are called allogeneic CAR-T cells. The latter have several advantages, in particular in terms of accessibility, cost, standardization, as well as their consistent quality.

However, as with any injection of a foreign body, in the case of transplants, for example, there is a risk of rejection. Overcoming this major medical and scientific obstacle is the whole purpose of this study**. Thanks to the genome-wide CRISPR editing technique developed by Dr. Laurie Menger (Inserm researcher, head of an Inserm/Gustave Roussy research team focused on CAR-T cells), the researchers tested 18,400 genes at the same time, and thus identified the major targets allowing resistance to rejection in a non-compatible (allogeneic) host. Among these targets is the FAS gene, coding for a membrane receptor involved in cell death.** *"Our systematic use of CRISPR-Cas9 "molecular scissors" and the in vivo interrogation of candidate genes have allowed us to better understand the biology involved in allogeneic cell rejection and to accelerate the discovery of targets improving the persistence and effectiveness of cell therapies*", explains **Dr. Laurie Menger**.

Dr. Silvia Menegatti, postdoctoral researcher at Institut Curie on the team of Dr. Sebastian Amigorena, CNRS research director and team leader in the Immunity and Cancer Unit (Institut Curie, Inserm, University-PSL U932) then provided proof of concept and feasibility of the approach by establishing complex validation models involving human CAR-T cells. *"Our objective in this study was to identify genes from the injected cells that could act by reducing this response of the host immune system, while limiting tumor growth. It would thus be possible to produce modified T-cells to treat patients with different immune systems. These lymphocytes are called allo-CAR-T cells,*[1] " explains **Dr. Silvia Menegatti.** *"We have observed the benefit of the deactivation of two genes: B2M, demonstrated in previous studies, and a new gene, FAS,"* she continues. *"Indeed, when the expression of the FAS gene is blocked in the CAR-T cells, their survival in the host is longer, indicating that the immune system of the latter takes longer to destroy them. It is in a group of allo-CAR-T cells, where we blocked the*

[1] Allo-CAR-T cells: T-cells with allogeneic chimeric antigen receptors, meaning that they are genetically modified and that they come from a donor.

expression of FAS and another gene called CD3, that we observed the best efficiency of controlling the growth of leukemia tumor cells in our model, " elaborates **Silvia Menegatti.**

"I then established a collaboration with the University of Minnesota and Dr. Moriarty's team, to validate our targets by developing a precise, highly efficient and reliable genome editing technology for injection in patients, base-editing ", continues **Dr. Laurie Menger**.

These results suggest that the genetic modification of FAS in allo-CAR-T cells would improve their efficiency and reduce their destruction in the host, thus opening the way to potentially very promising clinical applications. *"The approaches and technologies that we have developed in this study could lead to a real transfer of research results to the clinic, so as to propose innovative, rapid and accessible therapies to patients in the coming years,"* concludes **Dr. Sebastian Amigorena.**

Reference: Silvia Menegatti, Sheila Lopez-Cobo, Aurelien Sutra Del Galy, Jaime Fuentealba, Lisseth Silva, Laetitia Perrin, Sandrine Heurtebise-Chrétien, Valentine Pottez-Jouatte, Aurelie Darbois, Nina Burgdoff, Anne-Laure Privat, Albane Simon, Marguerite Laprie-Sentenac, Michael Saitakis, Bryce Wick, Beau R. Webber, Branden S. Moriarity, Olivier Lantz, Sebastian Amigorena & Laurie Menger. **Ablation of FAS confers allogeneic CD3-CAR T-cells with resistance to rejection by T-cells and natural killer cells.** *Nature Biomedical Engineering*. November 18, 2024 DOI: 10.1038/s41551-024-01282-8

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About Institut Curie

Institut Curie, France's leading cancer center, combines an internationally renowned research center with a state-of-the-art Hospital Group that treats all cancers, including the rarest. Founded in 1909 by Marie Curie, Institut Curie has 3 sites (Paris, Saint-Cloud and Orsay) and employs more than 3,800 researchers, doctors and caregivers in its 3 missions: care, research and teaching. Institut Curie is a charitable foundation authorized to receive donations and bequests. Thanks to the support of its donors, Institut Curie is able to speed up discoveries, thereby improving treatments and the quality of life of patients.
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About Gustave Roussy
Ranked first French center, first European and fourth worldwide, Gustave Roussy is a global Centre of Excellence entirely dedicated to patients living with cancer. The Institute is a founding cornerstone of the Paris-Saclay Cancer Cluster oncology biocluster. A source of therapeutic innovations and diagnostic advances, the Institute welcomes nearly 50,000 patients each year, including 3,500 children and adolescents, and develops an integrated approach between research, care, and teaching. An expert in rare cancers and complex tumors, Gustave Roussy treats all cancers and at all ages. He offers his patients personalized care that combines innovation and humanity, where not only treatment, but also the physical, psychological, and social quality of life are taken into account. With 4,100 employees working at the two sites, Villejuif and Chevilly-Larue, Gustave Roussy brings together the expertise essential for high-level cancer research; 40% of the treated patients are included in clinical studies.
To learn more about Gustave Roussy and follow the news of the Institute: ***www.gustaveroussy.fr****, X, Facebook, LinkedIn, Instagram*

About Inserm:
Founded in 1964, Inserm is a public scientific and technological institute which operates under the joint authority of the French Ministries of Health and Research. The institute is dedicated to biomedical research and human health, and is involved in the entire range of activities from the laboratory to the patient's bedside. It also partners with the most prestigious research institutions in the world that are committed to scientific challenges and progress in these fields

About the CNRS

A major player in basic research on a global scale, the French National Scientific Research Centre (CNRS) is the only French organization active in all scientific fields. Its unique position as a multi-specialist allows it to combine different scientific disciplines to shed light on and understand the challenges of the contemporary world, in conjunction with public and socio-economic stakeholders. Together, the sciences put themselves at the service of sustainable progress that benefits the entire society.