Press Release

New study published in *Journal of Experimental Medicine* reveals a CARMIL2 mutation with therapeutic antitumor potential

Carmil Therapeutics to develop next-generation immunotherapies based on this innovation

Paris & Le Genest St Isle, June 23, 2025 Carmil Therapeutics today announces the publication of a landmark preclinical study in the *Journal of Experimental Medicine* (JEM)[1]. The study reveals that a gain-of-function (GOF) mutation in the CARMIL2 gene unlocks powerful T cell activity, offering a promising new avenue for the development of advanced immunotherapies.

The research was conducted by scientists at the Centre d'Immunologie de Marseille-Luminy (Aix-Marseille Université, CNRS, INSERM, CIML U1104), and Centre d'Immunophénomique (Aix-Marseille Université, CNRS, INSERM, CIPHE US012 and UMS/UAR 3367) under the leadership of Dr. Bernard and Marie Malissen, world-renowned experts in T cell biology and funded by the European Research Council (ERC). The study demonstrates that this CARMIL2-GOF mutation not only enhances T cell activation but also confers resistance to key immune checkpoint pathways, including PD-1 and CTLA-4.

> "*Our work shows that CARMIL2 is a critical modulator of the T-cell function,*" said Dr. Bernard Malissen, Emeritus CNRS Research Director, co-founder and Chief Scientific Officer of Carmil Therapeutics. "*This gain-of-function strategy offers new ways to boost the efficacy of adoptive cell therapies, notably for hard-to-treat solid tumors and refractory cancers.*"

Following this breakthrough, Inserm Transfert filed a patent in the name of INSERM, CNRS and Université Aix Marseille. Inserm Transfert and JC Discovery - another spin-off of INSERM co -founded by Dr B. Malissen, - put in place a Convention industrielle de formation par la recherche (CIFRE) around the project. Dr. B. Malissen co-founded Carmil Therapeutics in 2024. Carmil's mission is to translate this discovery into a new generation of immunotherapies. The company holds exclusive global rights from Inserm Transfert to develop therapeutic applications of CARMIL2-GOF variants.

> "*Carmil was created to turn this breakthrough into real-world treatments,*" added Dr. Arnaud Foussat, Chief Executive Officer of Carmil Therapeutics. "*We are now developing a novel therapeutic platform based on CARMIL2-GOF, both through internal programs and future alliances."*

A new mechanism to enhance T cell therapies

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1. Zhang F, Celis-Gutierrez J, Zhang L, Mellado V, Gelard L, Panigot S, Mori D, Lu L, Voisinne G, Vilarnau Wolek C, Mello M, Burlet-Schiltz O, Gonzalez de Peredo A, Fiore F, Roncagalli R, Liang Y, Malissen M, Malissen B. A CARMIL2 gain-of-function mutation suffices to trigger most CD28 costimulatory functions in vivo. J Exp Med. 2025 Aug 4;222(8):e20250339. doi: 10.1084/jem.20250339.

CD28 is a costimulatory receptor essential for optimal activation of naive T cells. The newly published study demonstrates that a CARMIL2 gain-of-function mutation can bypass the need for CD28 ligand engagement, while still delivering most of its immunological benefits. This creates a novel CD28-independent activation pathway, with significant implications for tumors that evade immune surveillance by downregulating CD80/CD86.

Importantly, the mutation also renders T cells resistant to PD-1 and CTLA-4 checkpoint inhibition, two major immunosuppressive mechanisms used by tumors. These findings position CARMIL2-GOF as a powerful new lever in adoptive cell therapy, particularly for enhancing the efficacy of CAR-T, TCR-T or TILs therapies.

A foundation for Carmil Therapeutics' platform

The data published in JEM are foundational to Carmil Therapeutics' scientific and therapeutic platform, establishing a new paradigm for intracellular immunomodulation. In particular, the study provides mechanistic insight into how CARMIL2-GOF reshapes intracellular signaling to drive superior T cell activity, with clear translational value for next-generation cell therapies.

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About Carmil Therapeutics
Carmil Therapeutics is a French biotechnology company developing a novel generation of T-cell therapies based on gain-of-function variants of the intracellular scaffold protein CARMIL2. Founded in 2024 and built on decades of research from Inserm, Carmil is advancing a proprietary platform to enhance the therapeutic efficacy of adoptive T cell therapies in cancer and autoimmune diseases. Carmil was financed by the French state within the framework of France 2030.

About Inserm Transfert
Inserm Transfert, the private subsidiary of the French National Institute of Health and Medical Research (Inserm), is responsible for value creation of Inserm and its academic partners' innovations in human health and promotes long-term technology transfers in line with international best practices. Inserm Transfert SA was founded in 2000, and manages, under a Public Service Management Contract (Concession de Service Public) the entire innovation value chain and the transfer of knowledge from Inserm's research laboratories to industry, from invention disclosure to industrial partnerships and startups incorporation. Inserm Transfert also offers services relating to setting up and managing national, European and international projects, as well as supporting the technology transfer of clinical research and health data/databases and cohorts. For more information: www.inserm-transfert.com