

Press Release (strict embargo until 8 pm CET, Friday 17 October 2025.)

How immune cells deliver their deadly cargo

When immune cells strike, precision is everything. New research reveals how natural killer and T cells orchestrate the release of toxic granules – microscopic packages that destroy virus-infected or cancerous cells. The study led by researchers from CeMM, St. Anna CCRI, MedUni Vienna, Med Uni Graz, the University Hospital Bonn (UKB) and the University of Bonn, published in *Science Immunology* (DOI: 10.1126/sciimmunol.ado3825), uncovers an unexpected link between lipid metabolism and the immune system's ability to deliver its lethal cargo, offering new insights into diseases caused by genetic defects.

Our immune system relies on specialized cells, such as natural killer (NK) cells and T cells, to find and destroy dangerous invaders like viruses or cancer cells. To do this, they release "packages" filled with powerful molecules – so-called cytotoxic granules – that kill infected or cancerous cells. Although some key molecules have been identified through immune disorders and their effects, others that might be important for this release mechanism are still unknown.

In their new study published in the renowned journal *Science Immunology* (DOI: 10.1126/sciimmunol.ado3825) a team of scientists led by Kaan Boztug, Professor at the Medical University of Vienna, Principal Investigator at the St. Anna Children's Cancer Research Institute, Adjunct Principal Investigator at the CeMM Research Center for Molecular Medicine as well as Director of the Clinic for Pediatric Immunology and Rheumatology at UKB and member of the ImmunoSensation² Cluster of Excellence at the University of Bonn, together with Artem Kalinichenko, Assistant Professor at Medical University of Graz and former senior Postdoc at St. Anna CCRI and CeMM as well as Jakob Huemer, former PhD student at CeMM, (both former members of the research group of Kaan Boztug), has made a discovery that changes the way we understand how our immune system fights disease.

By using a CRISPR-based genetic screening approach, the researchers identified a set of unexpected genes that play a key role for the precise release of cytotoxic granules in human NK and T cells. Surprisingly, many of these genes are connected to cellular lipid metabolism. The team discovered that specific lipids help guiding important proteins to the right place inside immune cells, including targeted release of cytotoxic granules and the delivery of their deadly packages to keep the body safe.

This breakthrough not only helps explain how immune cells work but also sheds light on diseases caused by genetic defects, such as certain rare nerve disorders and inherited immune problems. "By systematically exploring genetic pathways and combining functional genomics with mechanistic follow-up, we have uncovered a new group of genes that control how T and NK cells function and kill both virus-infected cells or tumor cells," says co-first author Artem Kalinichenko.

"It's fascinating to see how molecules originally known from neuronal biology and associated with lipid metabolism and modification are also key for a distinct immune defense mechanism," adds Jakob Huemer, co-first author of the study. "Our findings open up new questions about how shared cellular pathways shape very different biological systems."

"This work showcases the power of collaborative, curiosity-driven research," concludes senior author Kaan Boztug. "We were able to uncover a completely unexpected connection between

lipid biology and immune cell function and thereby link seemingly unrelated biological processes. These findings will further help us improve diagnosis of patients with rare immune defects, and are also relevant for future development of cancer immunotherapy approaches."

The research was carried out in international collaboration with teams from Austria, France, Sweden, and Finland, and represents an important step forward in understanding how our bodies fight infections and cancer.

Pictures attached

Photo: Boztug, Kalinichenko, Huemer ©St. Anna CCRI

Photo: Artem Kalinichenko, Med Uni Graz ©Fischer

Scientific Images: Images of immune synapses formed by NK-92 cells. Red: cytotoxic/lytic granules; Green: sphingolipids, GM1 or GB3; Cyan: Actin staining. © Kalinichenko

The Study "Protein palmitoylation and sphingolipid metabolism 1 control regulated 2 exocytosis in cytotoxic lymphocytes" was published in Science Immunology on October 17th 2025. DOI: DOI: 10.1126/sciimmunol.ado3825

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Funding: This work was supported by European Research Council (ERC), the Vienna Science and technology Fund (WWTF), the Austrian Academy of Science (ÖAW), the Medical University of Vienna (MedUni Wien), the Federal Ministry for Digital and Economic Affairs of Austria and the National Foundation for Research, Technology and Development of Austria to the Christian Doppler Research Association.

The **CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences** is an international, independent and interdisciplinary research institution for molecular medicine under the scientific direction of Giulio Superti-Furga. CeMM is oriented towards medical needs and integrates basic research and clinical expertise to develop innovative diagnostic and therapeutic approaches for precision medicine. Research focuses on cancer, inflammation, metabolic and immune disorders, rare diseases and aging. The Institute's research building is located on the campus of the Medical University and the Vienna General Hospital.

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St. Anna Children's Cancer Research Institute (St. Anna Kinderkrebsforschung, St. Anna CCRI) is an international and interdisciplinary research institution dedicated to developing innovative diagnostic, prognostic, and therapeutic strategies for the treatment of children and adolescents with cancer. Taking into account the specific features of childhood tumors, dedicated research groups in tumor genomics and epigenomics, immunology, molecular and cell biology, bioinformatics, and clinical research work together to align the latest scientific findings

with clinical needs and sustainably improve the well-being of young patients.

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The **Medical University of Vienna (MedUni Vienna)** is one of the longest-established medical education and research facilities in Europe. With almost 8,600 students, it is currently the largest medical training center in the German-speaking countries. With more than 6,500 employees, 30 departments and two clinical institutes, twelve medical theory centers and numerous highly specialized laboratories, it is one of Europe's leading research establishments in the biomedical sector. MedUni Vienna also has a medical history museum, the Josephinum.

As one of Germany's leading university hospitals, the **University Hospital Bonn (UKB)** combines top performance in medicine and research with excellence in teaching. Each year, more than half a million patients receive inpatient and outpatient care at the UKB. Around 3,500 students are enrolled in medicine and dentistry, and more than 600 people are trained annually in healthcare professions. With approximately 9,900 employees, the UKB is the third-largest employer in the Bonn/Rhine-Sieg region. In the *Focus* hospital ranking, the UKB ranks first among university hospitals in North Rhine-Westphalia and has the second-highest case-mix index nationwide. In 2024, the UKB secured nearly €100 million in third-party funding for research, development, and teaching. The F.A.Z. Institute has named the UKB "Germany's Training Champion" and "Germany's Most Sought-After Employer" for the fourth consecutive year. Current figures can be found in the annual report at: geschaeftsbericht.ukbonn.de

The **Medical University of Graz (Med Uni Graz)** is one of Austria's leading institutions for medical education and biomedical research. With around 2,500 employees and more than 2,600 students, MedUni Graz combines cutting-edge research, innovative teaching, and patient-oriented clinical practice. The university has a particular focus on metabolism in health and disease, alongside strong research programs in cancer, cardiovascular and metabolic disorders, neuroscience, and immunology, supported by state-of-the-art core facilities and interdisciplinary research centers.