Eliciting a potent antitumor immune response using tumor antigens derived from human endogenous retroviruses (HERVs): A new class of targets to expand the benefits of cancer immunotherapy.

Lyon, January 27, 2022 - ErVaccine Technologies, a preclinical-stage biotechnology company, today announces the publication of a new paper in *Science Advances* journal, demonstrating the value of using antigens derived from human endogenous retroviruses (HERVs) specifically overexpressed by tumor cells as targets for new immunotherapy approaches.

Using an innovative method based on bioinformatics analysis followed by proteomic validation, ErVaccine Technologies is developing next-generation therapeutic vaccines and cellular immunotherapies targeting so-called "unconventional" tumor antigens, such as those derived from HERVs. These antigens are shared by different tumor types. Their use would provide a therapeutic solution for a larger number of patients.

This scientific publication, entitled '*Identification of shared tumor epitopes from endogenous retroviruses inducing high avidity cytotoxic T cells for cancer immunotherapy*', outlines results which make it possible to consider triple-negative breast cancer as a first indication, and then to target other pathologies such as ovarian cancer, sarcoma, glioblastoma and acute myeloblastic leukemia as subsequent indications. The proteomics work was conducted in collaboration with Complete Omics.

"We have shown that tumor cells not only aberrantly express certain endogenous retroviruses, but also present on their surface antigenic fragments or "epitopes" of a viral nature derived from these sequences. These epitopes can induce specific T lymphocytes that will recognize and kill tumor cells expressing these endogenous retroviruses. We will therefore therapeutically exploit the fact that tumor cells express viral fragments, fossils of ancestral infections, because they have lost genome regulation mechanisms. The epitopes we have identified will be used in a therapeutic vaccination to induce a strong antitumor immune response in the patient. We will also directly engineer T cells with receptors specific for these epitopes to redirect them against the tumor. ***This opens up new therapeutic perspectives in the treatment of cancers that respond insufficiently to current immunotherapies, such as breast and ovarian cancers, sarcomas and certain leukemias****,"* explains Professor Stéphane Depil, Founder of ErVaccine Technologies.

About 8% of the human genome consists of sequences of retroviral origin, namely HERVs. HERVs are relics of ancient retroviral infections that affected the germ line of primates and their ancestors along the last 100 million of years. HERVs are kept silent in normal cells but can be aberrantly expressed by tumor cells. Because of their similarity to viral protein fragments recognized as foreign by the immune system, **HERV-derived antigens are prime targets, shared by different tumors, for the development of novel cancer vaccines or T-cell based therapies**, especially in tumors that respond poorly to current checkpoint inhibitor (anti-PD1/-PD-L1) immunotherapy approaches.

ErVaccine Technologies has developed a novel bioinformatics approach to identify epitopes (antigen fragments presented to T cells by HLA* molecules) derived from HERVs associated with cancer in solid tumors and expressed in a large number of patients.

Six candidates among the HLA-A2* epitopes present in many patients were selected for in-depth immunological evaluation.

In vitro tests confirmed the immunogenicity of these epitopes, which induced high avidity CD8+ T cell clones. These T cells specifically recognize and kill HLA-A2+ tumor cells presenting HERV epitopes on HLA molecules on their cell surface. In addition, CD8+ T cells specific for these epitopes were identified among tumor-infiltrating lymphocytes from HLA-A2+ breast cancer patients. Finally, it was shown that HERV-specific T cells lyse primary tumor cells in 3D cultures (tumor organoids), generated from tumors of patients with triple-negative breast cancer.

- These virus-like epitopes are of major interest **for the development of cancer vaccines or T-cell based therapies**, especially in the case of many tumors with low mutational burden, which poorly respond to anti-PD-1/-L1.
- These results show that **HERV-derived targets** constitute a class of "virus-like" tumor antigens **shared by specific tumor subtypes**.
- In addition, the characterization of T receptors (TCRs) specific to these HERV-derived epitopes could also lead to the development of a **cellular immunotherapy based on T cells "engineered" to express the TCR of interest**. These modified T cells would then be redirected specifically to the tumor.

*les antigènes des leucocytes humains (en abrégé, HLA, de l'anglais *human leukocyte antigen*) sont le complexe majeur d'histocompatibilité (CMH) chez l'humain. Ce sont des molécules à la surface des cellules qui permettent l'identification par le système immunitaire

About ErVaccine Technologies

ErVaccine Technologies is a preclinical stage biotechnology company, founded in October 2019 by Professor Stéphane Depil, an onco-hematologist and researcher at CLB, with more than 15 years of experience in pharmaceutical development in oncology. ErVaccine is a spin-off of the Centre Léon Bérard (CLB)/*Centre de Recherche en Cancérologie de Lyon* (CRCL), specializing in the development of next-generation therapeutic vaccines, and modified T-cell immunotherapies, targeting new families of so-called "unconventional" tumor antigens such as those derived from endogenous retroviruses. ErVaccine Technologies determines tumor epitopes commonly shared among patients based on novel bioinformatics algorithms to identify candidate epitopes that are then validated by proteomic approaches and immunological tests. The first indication targeted is triple-negative breast cancer, with results generated in ovarian cancer, sarcoma and acute myeloblastic leukemia. The company is integrated within a leading comprehensive cancer center @Cancer Research Center of Lyon (CRCL)/Centre Léon Bérard, with a team of high-level experts.
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