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Genetically Modified Adipocytes (GMACs): a new frontier for ex vivo gene therapy

With its unique and proprietary genetically modified adipocyte (GMAC) platform, CellGenTech is developing novel ex vivo gene therapies and has achieved the first-in-human study of an adipocyte-based gene therapy.

Over the past decade, numerous gene-therapy products have been approved and launched in major markets around the world, from the US and Europe to China and Japan, principally for immune and hematological indications. Most of these are ex vivo gene-therapy products in which a patient's own cells are removed, genetically altered, and then reimplanted. The majority of these ex vivo therapeutics employ either T cells engineered to express chimeric antigen receptors (CARs) to create CAR-T cells, or genetically modified hematopoietic stem cells (HSCs).

CellGenTech, headquartered in Chiba, Japan, is pioneering the use of a new cell type—adipocytes suitable for gene therapy—for ex vivo applications in a range of diseases caused by single-gene defects, including disorders of lipoprotein metabolism, hemophilia, lysosomal diseases, and the currently untreatable condition retinitis pigmentosa. In October 2022, CellGenTech reported the first-in-human administration of an adipocyte-based ex vivo gene therapy that is being developed through its GMAC platform for the treatment of patients deficient in the enzyme lecithin cholesterol acyltransferase (LCAT)[1].

Adipocytes suitable for gene therapy have been historically neglected compared with HSCs, in part because the latter were among the earliest kinds of stem cell to be discovered and studied in detail, which provided the scientific basis for applications to treat hematological conditions.

However, the increasing recognition that adipose tissue contains therapeutically useful cells, adipocytes suitable for gene therapy, with numerous advantages over other stem-cell sources, has made adipocytes an attractive option for novel gene-therapy applications. CellGenTech is at the forefront of developing this new gene-therapy approach to create clinically and commercially successful products.

The GMAC platform

Fat tissue has been an underappreciated and underutilized source of cells for therapeutic applications. But that is changing, with CellGenTech leading the way, building on research over the past two decades that has revealed adipose tissue to be a valuable source of cells for use in regenerative medicine and gene-therapy applications. Adipocytes suitable for gene therapy have several advantages over mesenchymal stem cells (MSCs) and HSCs.

The first relates to the initial step of ex vivo gene therapy: harvesting cells from patients. MSCs and HSCs are often sourced from bone marrow, which requires invasive procedures; HSCs can sometimes also be harvested from peripheral blood, although this is frequently not possible. Obtaining adipocytes suitable for gene therapy is much easier. Adipose tissue in the form of subcutaneous abdominal fat is typically abundant in patients and removing it via lipectomy is both safe and minimally invasive.

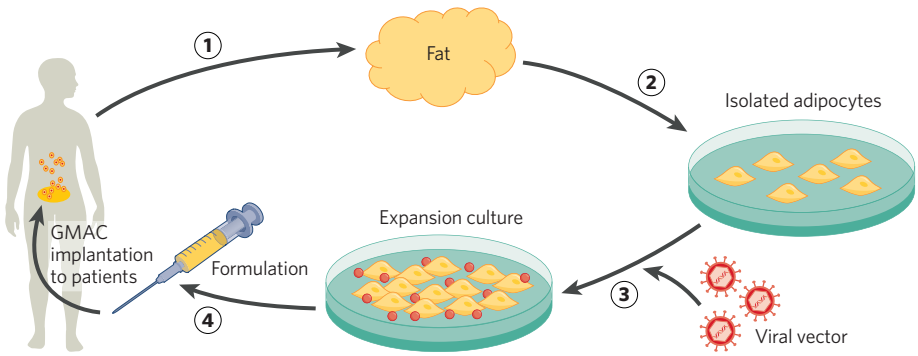

Fig. 1 | The unique GMAC platform. Subcutaneous abdominal fat is removed from the patient (**1**), and adipocytes are stably isolated from the tissue (**2**). Purified adipocytes are then transduced with viral vectors to introduce the therapeutic gene into the adipocytes (**3**), which are subsequently reimplanted into the patient (**4**). GMAC, genetically modified adipocyte.

A second crucial advantage of adipocytes suitable for gene therapy is that they are long lived. In humans, the average lifespan of adipocytes is roughly 10 years, with some reaching 15 or 20 years[2]. This means that genetically modified adipocytes can continue to express introduced genes for many years, even decades, providing the basis for CellGenTech's single-dose 'one-and-done' approach.

> **CellGenTech's lead GMAC pipeline asset is being developed in partnership with DyDo Pharma and with support from the Japan Agency for Medical Research and Development**

A third important feature of adipocytes is their stability over time coupled with their low tumorigenic potential, based on the terminal differentiation-mediated resistance to tumor development[3].

CellGenTech's unique GMAC platform begins with adipose tissue harvested from patients. This fat tissue is then treated with collagenase to create a mixture of cells, which is subsequently subjected to floating centrifugation to isolate lipid-loaded (and therefore floating) cells. These cells then undergo one week of ceiling culture to obtain highly purified and proliferative preadipocytes, after which they are transduced with a retroviral or lentiviral vector carrying a therapeutic DNA insert, before being subjected to expansion culture to yield billions of mature, genetically modified adipocytes that are implanted back into the patient. The whole process, from lipectomy to reimplantation, takes three weeks (Fig. 1).

A first-in-human study

CellGenTech's lead GMAC pipeline asset is being developed, in partnership with DyDo Pharma and with support from the Japan Agency for Medical Research and Development (AMED), for the treatment of familial lecithin:cholesterol acyltransferase (LCAT) deficiency (FLD), a rare but severe inherited disease that currently has no effective treatment. Cholesterol esterification catalyzed by LCAT is the most critical step in cholesterol homeostasis, and mutations that disrupt its activity lead to the accumulation of unesterified cholesterol and phospholipids in the blood, with decreasing levels of cholesteryl esters.

This metabolic defect leads to numerous symptoms, including eye problems due to accumulation of cholesterol on the cornea, increased risks of atherosclerosis and cardiovascular disease, and kidney disease—with renal failure being the major cause of morbidity and mortality in FLD. Treatment generally focuses on managing symptoms and preventing complications like kidney failure or heart disease. But LCAT replacement therapy has not been developed or commercialized, and while dietary therapy is used it does not provide a fundamental solution.

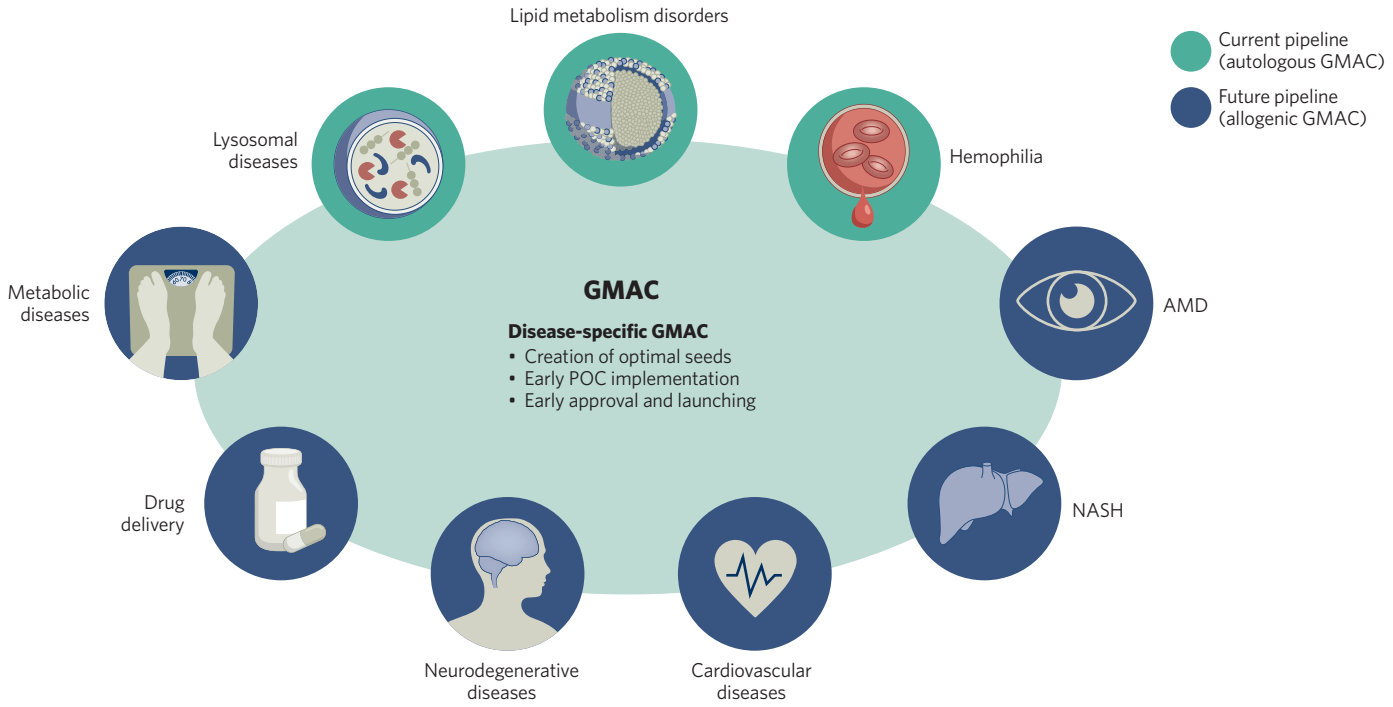

Fig. 2 | GMACs: a future of expanding indications. CellGenTech's current GMAC-driven pipeline is focused on autologous therapies created using patients' own cells (shown in green). Moving forward, CellGenTech plans to expand the pipeline with allogenic therapies using cells derived from donors (shown in blue) that target a range of indications with large markets, as well as developing GMACs for drug delivery. AMD, age-related macular degeneration; GMAC, genetically modified adipocyte; NASH, non-alcoholic steatohepatitis; POC, proof of concept.

In 2022, CellGenTech reported a first-in-human study of LCAT-GMAC, retrovirally transduced to carry a functional version of the *LCAT* gene[1]. As FLD is a very rare condition, just one patient was recruited to receive the therapy: a 34-year-old Japanese man homozygous for a missense mutation in the *LACT* gene. After implantation of LCAT-GMAC, follow-up observations were performed fortnightly for the first 24 weeks, with further assessments once every four weeks for the next three months, and thereafter every 12 weeks up to a total of 240 weeks.

This long-term study of an individual with FLD who was treated with LCAT-GMAC did not reveal any safety concerns. No severe adverse events associated with implantation were observed, including implantation-site reaction, toxicity, or signs of deterioration in hepatic or renal function. Retrovirus-mediated gene transduction carries a potential risk of generating replication-competent retroviruses (RCRs), but analysis of the patient's peripheral blood revealed no evidence of this complication.

This study demonstrated signs of therapeutic effect in the patient. In particular, LCAT-GMAC implantation was followed by long-term induction of LCAT activity, and amelioration of hemolysis and proteinuria. Hemolytic reactions disappeared as early as two weeks after implantation and the daily excretion of urinary protein decreased from about 1,000 mg before implantation to 100–200 mg after 96 weeks post-implantation, with the effect being sustained.

Pipeline

In addition to the lead pipeline asset, LCAT-GMAC, CellGenTech has a further four GMAC-based products in early-stage development.

Two are focused on hemophilia: HA-GMAC, carrying the clot-promoting factor VIII gene, which is being developed, with support from AMED, for hemophilia A; and HB-GMAC, carrying the factor IX gene, for hemophilia B. Both diseases are currently managed by regular infusions of the missing defective clotting factors, but there is no long-term cure for either.

> **CellGenTech plans to expand the range of indications targeted with the GMAC platform to go beyond rare genetic-deficiency diseases to include major disease classes**

A third candidate therapy is being developed by CellGenTech in partnership with KYORIN Pharmaceutical Co., Ltd. for the treatment of Fabry disease, a rare genetic lysosomal-storage disorder caused by mutations in the gene encoding α-galactosidase (α-GLA). Dysfunction of the α-GLA enzyme leads to a buildup of the fat molecule globotriaosylceramide in various organs and tissues, particularly the kidneys, heart, and nervous system, often leading to premature death. GLA-GMAC is a long-term alternative to the current standard of care—enzyme-replacement therapy—providing α-GLA for a long period of time by implanting GMAC to achieve a 'one and done' treatment.

CellGenTech's fourth pipeline product, nerve growth-related factor (NGRF)-GMAC, is designed for the treatment of retinitis pigmentosa, another rare genetic disorder that leads to gradual degradation of the retina and, consequently, loss of vision and blindness.

Moving forward, CellGenTech plans to expand the range of indications targeted with the GMAC platform to go beyond rare genetic-deficiency diseases to include major disease classes with large markets, with the goal of supplying therapeutic and risk-reducing proteins expressed by GMAC implants. The indications the company has in its sights include age-related macular degeneration, non-alcoholic steatohepatitis, and cardiovascular, metabolic, and neurodegenerative diseases (Fig. 2). CellGenTech also plans to develop the GMAC platform for allograft formulation and drug delivery applications to facilitate the administration of microRNA (miRNA) and exosomes to patients.

The versatility of the GMAC platform creates many therapeutic opportunities across diverse disease areas, which CellGenTech has begun to explore, often in partnership with other pharma companies. CellGenTech welcomes discussions with potential future collaborators to apply GMACs to bring new treatment options to patients in need.

1. Aso, M. et al. *Heliyon* **8**, e11271 (2022). https://doi.org/10.1016/j.heliyon.2022.e11271
2. Arner, P. et al. *Nature* **478**, 110–113 (2011). https://doi.org/10.1038/nature10426
3. Takahashi, N. et al. *Cancer Res.* **79**, 3088–3099 (2019). https://doi.org/10.1158/0008-5472.CAN-18-2693

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