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Gene therapy in type 1 diabetes mellitus:

from the laboratory to clinical trials in humans

Gene therapy has been one of the great promises of modern medicine for decades. The idea is conceptually powerful: rather than treating the symptoms of a disease, it modifies the genetic instructions of cells to correct the problem at its source. However, the path from the laboratory to people with diabetes has been long and, in many cases, far more complex than expected.

WHAT IS GENE THERAPY AND WHY IS IT OF INTEREST IN TYPE 1 DIABETES MELLITUS?

The human body functions according to instructions written in DNA: genes. In type 1 diabetes (T1DM), the problem is not a defective gene—as occurs in other genetic diseases—but rather that the immune system, the body's defenses, mistakenly destroys the beta cells of the pancreas, which are the only cells capable of naturally producing insulin. Without them, glucose accumulates in the blood and the person with diabetes requires insulin injections throughout life. Although the cause is not genetic, gene therapy can use the language of DNA to provide healthy cells with new instructions and thereby compensate for the loss of beta cells. Three major strategies have been explored: converting other tissues in the body, such as muscle, into insulin producers; halting the autoimmune attack by genetically modifying immune system cells so that they stop attacking the pancreas; or protecting and regenerating the beta cells themselves. These strategies are not mutually exclusive, and they may need to be combined in the future.

Vectors are used to introduce these instructions into cells: small vehicles—usually viruses modified to make them harmless—capable of delivering genetic material into the targeted cells. Once inside, the cell reads these instructions and begins producing the desired protein. The most widely used type of vector at present is the adeno-associated virus, or AAV. This vector is chosen because it has very favorable safety characteristics for use in humans. AAV-based gene therapies »



» are already approved for several diseases, including an inherited form of blindness, spinal muscular atrophy in infants, and Duchenne muscular dystrophy, among others. Overall, more than 200 clinical trials based on AAV vectors are currently underway (1).

FROM THE LABORATORY TO THE CLINIC: AN ACCELERATING FIELD

Before any gene therapy reaches a patient with diabetes, its benefits and risks must be demonstrated in animal models. In the field of diabetes, this phase has been extraordinarily productive over the past 20 years. Different strategies have been successfully tested in diabetic mice: converting liver or intestinal cells into insulin-producing cells, protecting pancreatic beta cells from immune system attack, or transforming other cells so that they act like beta cells. In mice, several of these strategies have achieved sustained normalization of blood glucose, reversal of established diabetes, and even prevention of its development (2).

However, translating these laboratory results to people with diabetes has been much slower than expected. There are multiple reasons: the human body is far more complex than that of a mouse, the immune system reacts differently, safety require-

ments for treating people are much stricter, and producing the vector in the quantities and at the quality required for clinical use is itself a technological challenge. For years, the field progressed in laboratories without making the leap to the clinic, but this changed in 2026.

FROM ANIMALS TO PEOPLE WITH DIABETES: STRATEGIES IN THE CLINIC

In 2026, for the first time, 3 gene therapy strategies for T1DM reached the **clinical phase** in humans.

The first, and most advanced, is **KRIYA-839**, developed by the biotechnology company Kriya Therapeutics from technology developed by Dr. Fàtima Bosch's group at Centro de Biotecnología Animal y Terapia Génica (CBATEG) of Universitat Autònoma de Barcelona (Barcelona, Catalunya, Spain). It is administered by intramuscular injection and introduces 2 genes into the muscle cells of the patient with diabetes: the insulin gene and the glucokinase (GK) gene, a protein that acts as a glucose sensor.³ The combination of both genes creates a system in which, when blood glucose rises, the muscle detects it, produces insulin, and lowers glucose levels. When glucose levels are normal, the system remains inactive. This reduces the risk of low glucose levels (**Figure 1**). Data from Dr. Bosch's »

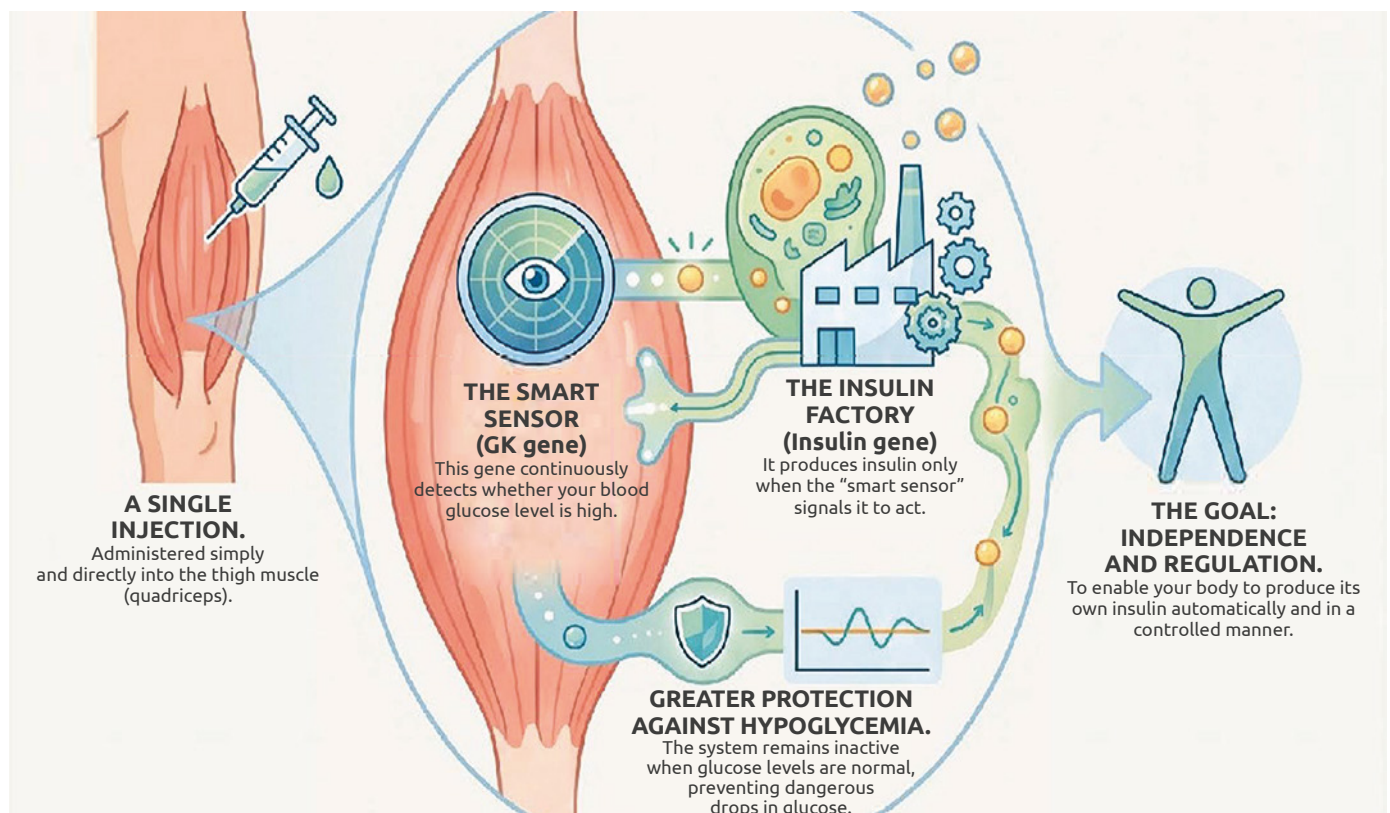


Figure 1. Mechanism of action of KRIYA-839 gene therapy: following a single intramuscular injection, the glucokinase (GK) gene acts as a glucose sensor, regulating insulin production according to the body's needs (Source: own elaboration).

WHAT CAN BE STATED IS THAT 2026 IS A TURNING POINT: FOR THE FIRST TIME, SEVERAL GENE THERAPY STRATEGIES FOR T1DM HAVE SIMULTANEOUSLY CROSSED THE THRESHOLD INTO HUMAN CLINICAL RESEARCH

» group demonstrated that a single injection into the muscle normalized blood glucose in diabetic mice, improved long-term glycaemic control, and did not cause low glucose levels (4). These results were subsequently confirmed in dogs with diabetes: a single intramuscular injection was sufficient to maintain normal blood glucose levels for > 8 years, without the need for insulin, without low glucose levels, and without immunosuppressive medication (5, 6). Its human clinical phase, the PROGRESS trial, will include adults with T1DM who will receive this single injection and be followed for 1 year, with the aim of assessing its safety and whether it improves blood glucose control. The stated long-term objective is for people with diabetes to no longer require insulin (3).

The second trial is **IMMUNOSTEM**, promoted by Altheia Science, and follows a completely different approach: rather than creating an alternative source of insulin, its objective is to stop the autoimmune attack before it completely destroys the pancreatic beta cells (7). To achieve this, stem cells—cells capable of developing into different types of immune cells—are collected from the patient with diabetes, genetically modified so that they suppress the autoimmune attack, and then reintroduced into the body. The trial is currently recruiting people with diabetes, with follow-up planned through August 2029.

Finally, **UP421**, developed by Sana Biotechnology, deserves special mention. Results in a single person with diabetes with 14 months of follow-up have shown that insulin-producing donor cells, genetically modified so that the immune system does not recognize them as foreign, can survive and function without the need for immunosuppressive medication (8). Unlike **IMMUNOSTEM**, the modified cells are obtained from a donor rather than from the patient with diabetes, which entails a different immunological profile.

WHAT WE STILL DO NOT KNOW: UNANSWERED QUESTIONS

It would be irresponsible to present these advances without discussing the challenges that remain. They are real and substantial.

The **immune system's** reaction to the vector. Although AAVs have very favorable safety characteristics, the immune system may react against them. For this reason, all 3 trials include some form of medication to control this reaction, following experience with other gene therapies already used in humans (9).

Durability. AAVs do not permanently modify cellular DNA, so insulin production could decrease over time. Adult muscle is relatively stable, but there are no long-term human data. If efficacy were to decrease, could the injection be repeated? Previous immune reactions against the vector could make this difficult. In **IMMUNOSTEM**, the vector does permanently modify the DNA of the cells, which in principle ensures a more durable effect, but requires longer follow-up.

Glucose control in real-life situations. This challenge is specific to KRIYA-839. The pancreas regulates insulin in response to multiple signals from the body: blood glucose, but also amino acids from food, intestinal hormones, and the nervous system. Genetically modified muscle containing the insulin and GK genes, in contrast, detects only blood glucose levels. Will this be sufficient during intense exercise, an infection, or stress? The PROGRESS trial will need to answer this question. **IMMUNOSTEM** and **UP421**, by preserving or restoring beta cells themselves, maintain the pancreas's natural regulatory system, which in theory is an advantage.

Cost. Gene therapies approved to date have very high costs for the public health care system.¹⁰ All 3 strategies are single-administration treatments, which in principle makes them more economical in the long term than chronic treatment, but whether they will ultimately become available through public healthcare systems and at what price remains to be determined.

WHEN COULD THIS REACH CLINICAL PRACTICE?

The answer is that the road is long: after the current trials, studies involving more people with diabetes will be required and, if the results are positive, regulatory bodies—such as the European Medicines Agency—will

» have to review and approve them before the treatments can become available in hospitals. Each step takes years.

What can be stated is that 2026 marks a turning point: for the first time, several gene therapy strategies for T1DM have simultaneously crossed the threshold into human clinical research. Until re-

cently, all of this was molecular biology in a laboratory or results obtained in animal models. Now these are trials involving people with diabetes. That is not the same thing.

"In the T1DM community, we are used to hearing that this will arrive in 10 or 15 years. It is very exciting to be able to

say that this is actually happening right now".

Jeremy Pettus, endocrinologist at the University of California San Diego and principal investigator of the PROGRESS trial.

ATTD 2026 Congress, Barcelona. Catalunya. Spain. **D**

CONCLUSIONS

- In 2026, 3 gene therapy strategies simultaneously crossed the threshold into clinical research in T1D: KRIYA-839 (muscle as an insulin producer), IMMUNOSTEM (suppression of the autoimmune attack), and UP421 (genetically modified donor insulin-producing cells). This is the first time this has occurred.
- Fundamental questions remain to be answered—duration of the effect, immune response, glyce-mic control in real-life situations, and cost—and the path to clinical practice is long: each phase of development takes years, in addition to review by regulatory bodies and assessment by healthcare systems before the treatment can reach people with T1DM.
- This is a genuine advance. It is not the cure. But for the first time, gene therapy in T1DM is being applied to people with diabetes.

REFERENCES

1. Geng G, Xu Y, Hu Z, Wang H, Chen X, Yuan W, et al. Viral and non-viral vectors in gene therapy: current state and clinical perspectives. *EBioMedicine*. agost de 2025;118:105834. doi:10.1016/j.ebiom.2025.105834 PubMed PMID: 40602323; PubMed Central PMCID: PMC12271757.
2. Khartabil N, Avoundjian A. Gene Therapy and Diabetes: A Narrative Review of Recent Advances and the Role of Multidisciplinary Healthcare Teams. *Genes*. 20 de juny de 2025;16(1):107. doi:10.3390/genes16010107
3. Pettus J. Gene therapy for type 1 diabetes: the PROGRESS study. *Dins*. Barcelona: Medscape; 2026. Disponible a: <https://www.medscape.com/viewarticle/gene-therapy-be-studied-treating-type-1-diabetes-2026a10009xh?form=fpf>
4. Mas A, Montané J, Anguela XM, Muñoz S, Douar AM, Riu E, et al. Reversal of Type 1 Diabetes by Engineering a Glucose Sensor in Skeletal Muscle. *Diabetes*. 1 de juny de 2006;55(6):1546-53. doi:10.2337/db05-1615
5. Callejas D, Mann CJ, Ayuso E, Lage R, Grifoll I, Roca C, et al. Treatment of Diabetes and Long-Term Survival After Insulin and Glucokinase Gene Therapy. *Diabetes*. 1 de maig de 2013;62(5):1718-29. doi:10.2337/db12-1113
6. Jaén ML, Vilà L, Elías I, Jimenez V, Rodó J, Maggioni L, et al. Long-Term Efficacy and Safety of Insulin and Glucokinase Gene Therapy for Diabetes: 8-Year Follow-Up in Dogs. *Mol Ther Methods Clin Dev*. 15 de setembre de 2017;6:1-7. doi:10.1016/j.omtm.2017.03.008 PubMed PMID: 28626777; PubMed Central PMCID: PMC5466581.
7. Altheia Science. A first-in-human clinical trial using a gene therapy with patient's own stem cells to treat early type 1 diabetes (IMMUNOSTEM). *ClinicalTrials.gov*; 2025. Identifier: NCT06938334 [Internet]. Clinical Trials Register; 2026. Disponible a: <https://clinicaltrials.gov/study/NCT06938334>
8. Carlsson PO, Hu X, Scholz H, Ingvast S, Lundgren T, Scholz T, et al. Survival of Transplanted Allogeneic Beta Cells with No Immunosuppression. *N Engl J Med*. 4 de setembre de 2025;393(9):887-94. doi:10.1056/NEJMoa2503822
9. Ertl HCJ. Immunogenicity and toxicity of AAV gene therapy. *Front Immunol*. 2022;13:975803. doi:10.3389/fimmu.2022.975803 PubMed PMID: 36032092; PubMed Central PMCID: PMC9411526.
10. Iglesias-Lopez C, Agustí A, Vallano A, Obach M. Current landscape of clinical development and approval of advanced therapies. *Mol Ther Methods Clin Dev*. 10 de desembre de 2021;23:606-18. doi:10.1016/j.omtm.2021.11.003 PubMed PMID: 34901306; PubMed Central PMCID: PMC8626628.