GENETIC DIAGNOSTICS AND THERAPY 21 LTD.

CELL AND GENE THERAPY LTD.

The Evolution of Drug Development in Liver Fibrosis Therapy

2 + 2 = 5

Why?

Innovative Synergy for a Supra-additive Effect!

GENETIC DIAGNOSTICS AND THERAPY 21 LTD.

A breakthrough approach to gene therapy

CELL AND GENE THERAPY LTD.

Founded in 2015 in London (UK), Cell and Gene Therapy Ltd. has emerged as a leading biotech company and a principal member of an international group specializing in the development of gene therapy drugs. The core concept of the products lies in the masterful combination of traditional and innovative elements, creating a supra-additive effect and forging a unique solution. Within this concept, the following components are envisioned:

Unique DNA Vectors

Our DNA vectors, developed and patented as a platform solution, elegantly combine efficacy, safety, and flexibility by integrating universal or tissue-specific and inflammation-activated promoters with coding sequences of target genes.

Multiplicity of Targets

Therapeutic diversity in achieved through the use of a composition of next-generation DNA vectors containing genes, each of which is directed at corresponding target.

Advanced Delivery Systems

The use of modern delivery systems enables the attainment of therapeutically significant concentrations of target proteins, thereby maximizing the drug's therapeutic effect.

Technological Excellence

The use of proven technologies allows the drug to be manufactured at various standard biotechnological facilities, achieving both competitive pricing and high profitability.

Focus on Pathology

Priority is given to the careful selection of targets within pathological biological processes, focusing on underlying mechanisms rather than merely addressing disease symptoms, to achieve effective and sustainable therapeutic outcomes.

Use of Native Genes

The use of native genes ensures harmonious integration with natural biological processes, reducing the risk of adverse reactions and enhancing the drug's biocompatibility.

Precision Delivery

The use of optimal promoters ensures accurate and efficient delivery of DNA vectors to target cells, enhancing overall therapy efficacy and minimizing off-target effects.

Regulatory Compliance

The vectors' structural elements, developed as part of our platform solution, fully comply with FDA and EMA requirements, ensuring strict safety and efficacy standards.

Our development priorities focus on diseases that currently have no effective treatments available, such as **multiple sclerosis, Alzheimer's disease, Parkinson's disease, liver fibrosis,** along with numerous other diseases. Furthermore, we are dedicated to addressing **type 2 diabetes mellitus and obesity,** as well as rare and orphan diseases.

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Unique and innovative non-viral DNA vectors

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Since 2015, an international team of scientists, spearheaded by our company, has dedicated extensive intellectual resources and cutting-edge research efforts to this project, ultimately leading to the development of a groundbreaking universal platform solution — non-viral DNA vectors series VTvaf17 and GDDT1.8NAS — for creating advanced genetic tools in the rapidly evolving fields of biomedical and genetic technologies. These DNA vectors incorporate the unique RNA-out regulatory element from the Tn10 transposon, thus enabling antibiotic-free positive selection, and offering the following key advantages:

Maximum Safety

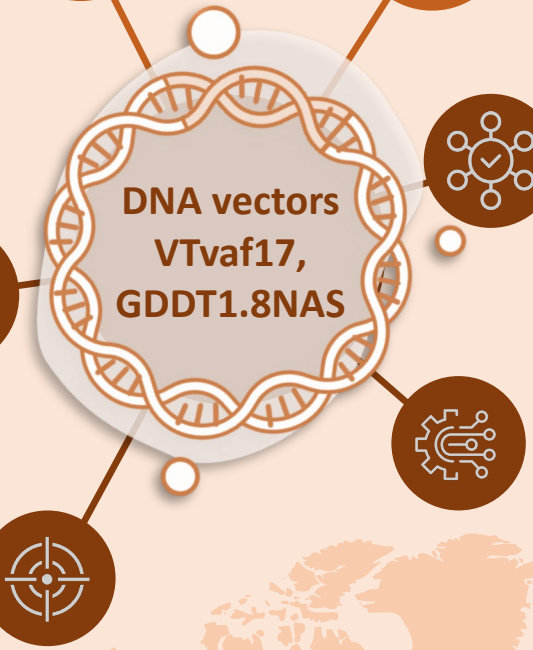
The **absence of antibiotic resistance genes** and **viral genome sequences** in our DNA vectors, in accordance with EMA and FDA recommendations, ensures the highest safety. This distinct combination in a non-viral DNA vectors makes our solution **one-of-a-kind globally**.

Nature-like Mechanism

The use of **non-modified native genes** ensures seamless integration with natural biological processes, minimizing the risk of adverse reactions.

Precision Expression

By integrating **cell-specific and inflammation-activated promoters**, our drugs achieve precise and effective expression of genes in target cells while minimizing undesirable side effects.



Superior Performance

By incorporating **advanced delivery systems** into our drug, we achieve therapeutically significant concentrations of target proteins.

Multiply Therapeutic Targets

Creation of a **unique composition of genes** empowers our drugs to simultaneously target multiple therapeutic pathways, achieving a synergistic effect.

Technological Excellence

Implementation of high-tech manufacturing techniques optimizes production processes, achieving **exceptional efficiency** and **significant cost reductions**.

The intellectual property associated with this project is protected by **more than 30 patents** across various countries worldwide, highlighting the **unique** and **innovative** nature of the product.

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CG-LF481: Gene therapy for liver fibrosis

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We have developed the unique gene therapy candidate **CG-LF481** for the treatment of liver fibrosis that activates the processes of fibrosis remodeling and hepatocyte regeneration—all tasks that require orchestrating many genes, yet have traditionally carried risks for healthy cells. This is a challenge for conventional pharmacology but we overcome it by using a) composite promoter, which activates only in the target cells and only under inflammation, b) two-stage administration regimen, c) a meticulously selected gene set, thereby delivering therapy exactly where it is needed while eliminating risks to healthy cells.

Focus on Pathology

Priority attention is given to the processes of fibrosis remodeling and to the processes of hepatocyte regeneration, which involve cellular repair, proliferation, and tissue remodeling

Multiplicity of Targets

Therapeutic versatility is achieved through the use of innovative DNA vectors containing a carefully designed and precisely optimized composition of genes responsible for a range of biological processes that are intricately associated with the disease.

Advanced Delivery Systems

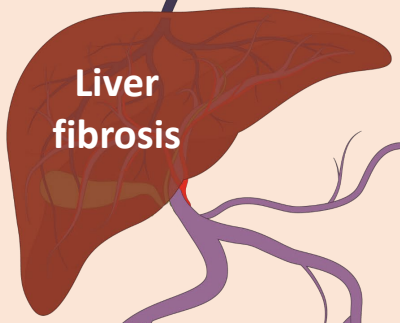
A complex of cationic liposomes + PEG with *** functionalization's been selected as the delivery system, which ensures the achievement of therapeutically significant concentrations of target proteins, thereby maximizing the therapeutic effect.

Technological Excellence

The use of proven technologies allows the drug to be manufactured at various standard biotechnological facilities, achieving both competitive pricing and profitability.

Treatment Protocols

Two-Stage Administration: The drug is administered sequentially, with each stage targeting a specific goal: 1. Fibrosis remodeling; 2. Hepatocyte regeneration to restore liver function — ensuring maximum drug efficacy and minimizing potential adverse effects.



Unique DNA Vectors

Our therapeutic DNA vectors of GDDT1.8NAS series developed and patented as a platform solution, elegantly combine efficiency, safety, and the flexibility to vary with universal and tissue-specific promoters and coding sequences of genes.

Use of Native Genes

The use of native genes C**, C***, C***, A***, M***, C**, H**, A**, C***, H**, E**, V***, A***, I*** ensures harmonious integration with natural biological processes, thereby reducing the risk of adverse reactions and enhancing the drug's biocompatibility.

Precision Delivery

The use of combinations of tissue-specific and inflammation-activated promoters ensures precise and effective delivery of DNA vectors into target cells, further enhancing overall therapeutic efficiency and consequently minimizing ectopic effects.

Regulatory Compliance

The composition of structural elements of the vectors, developed and patented as part of a platform solution, fully complies with FDA and EMA requirements, guaranteeing adherence to strict safety and efficacy standards.

Method of administration

Intra-arterial administration with vibrational stimulation of the liver , FUS , intravenous hydration, maintaining hyperthermia in the liver are aimed at ensuring maximum penetration and effective drug's distribution into the target tissues of the patient's liver.

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CG-LF481: Gene therapy for liver fibrosis

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The project's strategy involves the creation of a pharmaceutical agent for the therapeutic implementation of the following biological processes directly related to the disease, for which there are currently no registered medications. A treatment regimen - two-stage pulse administration - was selected to maximize drug efficacy while minimizing uncontrolled therapeutic-gene interactions:

Exposure Period

Therapeutic Stage 1

Utilization of fibrotic areas of the liver

At this stage, the main focus is on the inactivation of reactive hepatic stellate cells, polarization of macrophages into a reparative phenotype, and opsonization of scar tissue components for subsequent phagocytosis.

Task	Description
Targeted collagenolysis	Selective degradation of excessive collagen fibers within the fibrotic tissue to facilitate scar resorption and matrix remodeling
Inactivation of HSC	Suppression of fibrogenic hepatic stellate cell activity and TGF-β signaling to halt collagen synthesis and fibrosis progression
Recruitment of Monocytes	Attraction of monocytes into the fibrotic area followed by their differentiation into reparative macrophages
Macrophage Polarization to M2c	Macrophage transition into the M2c phenotype, promoting scar resorption and phagocytosis of cellular debris
Opsonization/ Efferocytosis	Enhancement of recognition and removal of ECM fragments through opsonization and efferocytosis mechanisms

Therapeutic Stage 2

Regeneration of parenchyma and stroma

The main aspects of regeneration include activation and expansion of hepatic progenitor cells (HPC/LPC), proliferation and survival of mature hepatocytes, induction of angiogenesis and vessel maturation. Consequently, the normal architecture and functional activity of the liver will be reestablished.

Task	Description
Activation of HPC/LPC	Stimulation of proliferation and migration of hepatic progenitor cells into the injury zone
Hepatocytes Proliferation	Enhancement of viability and proliferation of remaining functional hepatocytes to restore liver parenchyma
Angiogenesis and Vessel Maturation	Induction of new blood vessel formation and stabilization to restore microcirculation in regenerating tissue
HPC → Hepatocytes	Activation of the Wnt signaling pathway to promote differentiation of progenitors into hepatocytes
HPC → Cholangiocytes	Activation of the Notch signaling pathway to drive progenitor differentiation into bile duct epithelial cells