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J Am Acad Orthop Surg 2018;26:e36-e38

DOI: 10.5435/JAAOS-D-17-00695

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Arthritis Gene Therapy Approved in Korea

On July 12, 2017, South Korea approved the world's first gene therapy for arthritis.¹ This product, Invossa (TissueGene), is based on a line of allogeneic human chondrocytes that have been transduced with a retrovirus encoding transforming growth factor- β_1 .

To avoid possible insertional mutagenesis, the transduced cells are first irradiated at a dose that prevents cell division without limiting transgene expression. The cells are then mixed in a 1:3 ratio with nontransduced, non-irradiated chondrocytes from the same donor before being shipped to the physician for injection into knee joints with moderate osteoarthritis in which standard pharmacologic and physical therapy has been unsuccessful. Invossa was not given disease-modifying osteoarthritis drug (DMOAD) designation.

Invossa has completed phase II trials in the United States.² Phase III trials are expected to begin in early 2018 under a special protocol assessment agreement with the US FDA. Because genetically modified chondrocytes can be allografted into sites of cartilage damage where they continue to express transgenes,³ this product holds additional potential for cartilage repair. A phase II clinical trial of this application has been completed.⁴

Only four other gene therapies had previously been authorized by the regulatory authorities of any jurisdiction for any indication: two cancer treatments and two

treatments for rare genetic diseases (Table 1). Since then, the FDA has approved the use of chimeric antigen receptor-T lymphocytes (CAR-T cells) for the management of acute lymphoblastic leukemia and large B-cell lymphoma.

The concept of arthritis gene therapy was first published 25 years ago,⁵ and the first human clinical trial was published just over a decade ago.⁶ The latter, also an ex vivo protocol using a retroviral vector, delivered the interleukin-1 receptor antagonist (IL-1Ra) to the metacarpophalangeal joints of patients with rheumatoid arthritis. There has since been a small number of additional clinical trials in arthritis gene therapy^{2,6-12} (Table 2).

According to ClinicalTrials.gov, two additional phase I studies are in the pipeline, one for osteoarthritis¹³ and the other for rheumatoid arthritis.¹⁴ Both use adeno-associated virus as the vector to deliver IL-1Ra for osteoarthritis¹⁵ and interferon- β for rheumatoid arthritis¹⁶ by intra-articular injection.

Progress in arthritis gene therapy has been slow and fitful.^{17,18} However, after many reversals, the field of gene therapy as a whole is gaining considerable momentum and attracting the attention of both venture capital and big pharma.¹⁹ Thus, there is every expectation that approved genetic medicines will become available for arthritis, musculoskeletal regenerative medicine,²⁰ and various other orthopaedic indications²¹ in the not too distant future.

Table 1**Approved Gene Therapies by Country or Geographic Region**

Indication	Vector (Delivery Mode)	Gene Product	Name	Country or Geographic Region	Year Approved
Head and neck carcinoma	Adenovirus (in vivo)	p53	Gendicine (Sibiono GeneTech)	People's Republic of China	2003
Lipoprotein lipase deficiency	Adeno-associated virus (in vivo)	Lipoprotein lipase	Glybera (UniQure)	Europe	2012
Melanoma	Herpes simplex virus (in vivo)	Granulocyte-macrophage colony-stimulating factor	Imlygic (Amgen)	United States, Europe	2015
Adenosine deaminase deficiency	Retrovirus (ex vivo)	Adenosine deaminase	Strimvelis (GlaxoSmithKline)	Europe	2016
Osteoarthritis	Retrovirus (ex vivo)	Transforming growth factor- β_1	Invossa (TissueGene)	South Korea	2017 (July)
Acute lymphoblastic leukemia	Lentivirus (ex vivo)	Chimeric antigen receptor	Kymriah (Novartis Pharmaceuticals)	United States	2017 (August)
Large B-cell lymphoma	Lentivirus (ex vivo)	Chimeric antigen receptor	Yescarta (Kite Pharma)	United States	2017 (October)

Table 2**Completed Clinical Trials on the Use of Gene Therapy for Arthritis**

Transgene	Vector (Delivery Mode)	Phase(s)	Clinicaltrials.gov Identifier
IL-1Ra ^{6,7}	Retrovirus (ex vivo)	I	Predates clinicaltrials.gov
Etanercept ^{8,9,a}	Adeno-associated virus (in vivo)	I, II	NCT00617032 NCT00126724
TGF- β_1 ^{2,10-12,b}	Retrovirus (ex vivo)	I, II, III	NCT02341 NCT00599 NCT01671 NCT02341 NCT02071

IL-1Ra = interleukin-1 receptor antagonist, TGF- β_1 = transforming growth factor- β_1

^a Etanercept is a protein formed of two p75 tumor necrosis- α receptors fused to the Fc domain of IgG₁.

^b These trials form the basis for Invossa.

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