

Arthritis gene therapy at an inflection point



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'Arthritis was the subject of the first human gene-therapy protocol for a nonlethal disease...'

Gene therapy is not for the faint of heart. Since its launch in 1989 [1], human gene therapy has been variously cast as visionary, feckless, a panacea and a dangerous folly. One of its pioneers is in jail, and another was sued successfully in civil court following the death of a clinical trial subject. Skeptics like to point out that it has killed approximately as many people as it has cured and, apart from two cancer gene therapies approved recently in China, there is little to show for nearly two decades of promises and expensive research.

Against these headwinds, arthritis gene therapy has made laudable progress. Proof of principle is well established in animal models, and a small number of clinical trials have been implemented (Table 1). However, we have reached the stage of diminishing returns with preclinical research. Pivotal clinical trials are needed to maintain momentum and confirm promise in human disease [2]. These will require a considerable injection of funding, without which research will stagnate and become largely condemned to re-inventing the wheel in animal models.

Arthritis gene therapy emerged in the early 1990s (Figure 1) and made quite rapid progress, leading, within a few years, to proof of concept in animal models of rheumatoid arthritis and osteoarthritis, and a Phase I clinical trial – remarkable achievements for a new area of research. As reflected in the publication history shown in Figure 1, the number of investigators remains limited, with approximately 30 papers appearing in the refereed literature each year at a remarkably constant rate since 1999. The fact that almost half of these publications are review articles is telling.

Arthritis was the subject of the first human gene-therapy protocol for a nonlethal disease [3], and consequently attracted much scrutiny from the regulatory agencies. The data from this trial confirmed that genes could be safely transferred to human joints and expressed within them [4]. Moreover, in a similar small, German study, each

of two subjects treated with this gene therapy appeared to mount a clinical response, one of them dramatically so [5] [Wehling *et al.*, Unpublished Data]. Nevertheless, the *ex vivo*, retrovirus-based approach used in these two studies is unlikely to find wide clinical application; *ex vivo* gene transfer using autologous cell culture is too cumbersome and costly, and concerns regarding insertional mutagenesis with retrovirus vectors have resurfaced. Subsequent clinical trials (Table 1) based on this approach have used allogeneic cells lines to reduce costs and, in one case, irradiation of cells to prevent cell division and thus tumorigenicity. In the search for an efficient vector that can be introduced safely into joints by intra-articular injection, most investigators have converged on adeno-associated virus (AAV).

Recombinant AAV has risen in popularity as a gene therapy vector because it is perceived to be safe and new technologies permit easier production of clinical-grade material [6]. Wild-type AAV causes no known disease and recombinant AAV vectors have been used safely in gene therapy trials of a number of single-gene disorders, as well as Parkinson's disease, Alzheimer's disease and cancer. Two large Phase III trials for prostate cancer using AAV are underway, and orphan drug status has been granted by the EU for AAV-mediated gene therapy for familial lipoprotein lipase deficiency.

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Everyone was thus flabbergasted when a young woman with rheumatoid arthritis died shortly after receiving a second injection of an experimental AAV-based gene therapeutic in her right knee [7]. The clinical trial and the circumstances surrounding this fatality have been discussed in detail elsewhere [8]. Although uncertainty still surrounds the precise role, if any, of the gene treatment in the subject's death, we know that she had disseminated histoplasmosis, which is a recognized risk factor when using TNF-blockers. After a detailed

investigation, the US FDA permitted the trial to resume with certain additional safeguards. Although this particular trial has been exonerated by the regulatory agencies, the episode has not helped the cause of arthritis gene therapy. In particular, it has provided ammunition for those who oppose, on principle, the use of gene therapy to treat nonlethal, nongenetic diseases such as arthritis. It has become more complicated for additional protocols to enter the clinic, and more difficult to obtain funding for arthritis gene therapy in general. It remains to be seen whether patient recruitment will be affected.

As the development of a gene therapeutic progresses from *in vitro* studies, via preclinical testing *in vivo*, into human clinical trials, the rate of progress slows and the cost increases dramatically (Figure 2). Elsewhere, we have made the case that, because proof of principle has been overwhelmingly demonstrated for local arthritis gene therapy in joints, priority should be given to implementing clinical studies [2]. However, for the reasons indicated above, this is easier said than done, and there are signs of an accumulation of research in front of the second inflection point in Figure 2.

Table 1. Human clinical trials of arthritis gene therapy.						
Transgene	Vector <i>ex/in vivo</i>	Phase	PI, institution or sponsor	OBA protocol number	Status	Subjects (n)
IL-Ra	Retrovirus <i>ex vivo</i>	I	Evans, Robbins, University of Pittsburgh, PA, USA	9406–074	Closed*	9
IL-1Ra	Retrovirus <i>ex vivo</i>	I	Wehling, University of Düsseldorf, Germany	N/A	Closed	2
HSV-tk [±]	Plasmid <i>in vivo</i>	I	Roessler, University of Michigan, MI, USA	9802–237	Closed	1
TNFR:Fc fusion protein (etanercept)	AAV <i>in vivo</i>	I	Mease, Targeted Genetics Corp., WA, USA	0307–588	Closed	15
TGF-β	Retrovirus <i>ex vivo</i>	I	Ha, Kolon Life Sciences, Kwacheon-City, Korea	N/A	Open	12
TGF-β	Retrovirus <i>ex vivo</i>	I	Mont, TissueGene Inc., MD, USA	0307–594	Open	4
TNFR:Fc fusion protein (etanercept)	AAV <i>in vivo</i>	I/II	Mease, Targeted Genetics Corp., WA, USA	0504–705	Enrolled Clinical hold lifted by US FDA December 2007	127

All of these target rheumatoid arthritis, except for the TissueGene Inc. and Kolon Life Sciences trials, which target osteoarthritis. The Targeted Genetics Corp. trial can also recruit subjects with psoriatic arthritis and ankylosing spondylitis.

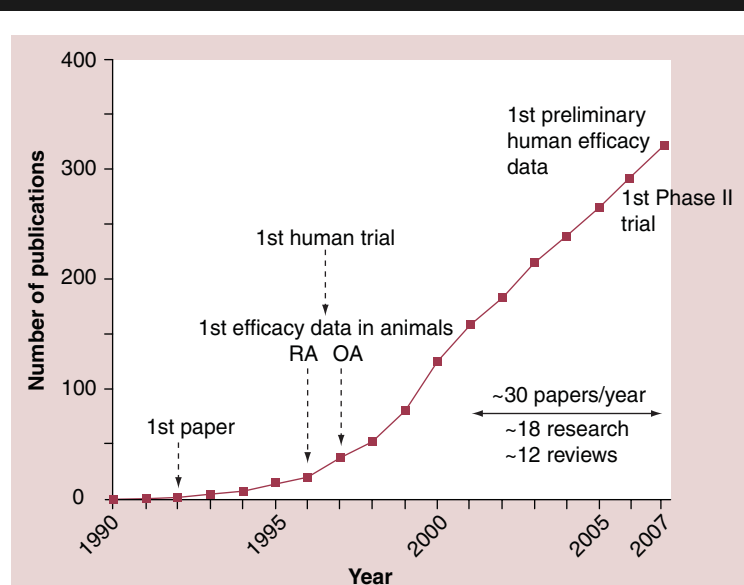
*Described in [3–5].

*When HSV-tk is expressed in conjunction with ganciclovir administration, it kills synovial cells and produces a synovectomy.

AAV: Adeno-associated virus; HSV-tk: Herpes simplex virus thymidine kinase; N/A: Not applicable; OBA: Office of Biotechnology Activities; PI: Principal investigator; TNFR: TNF receptor.

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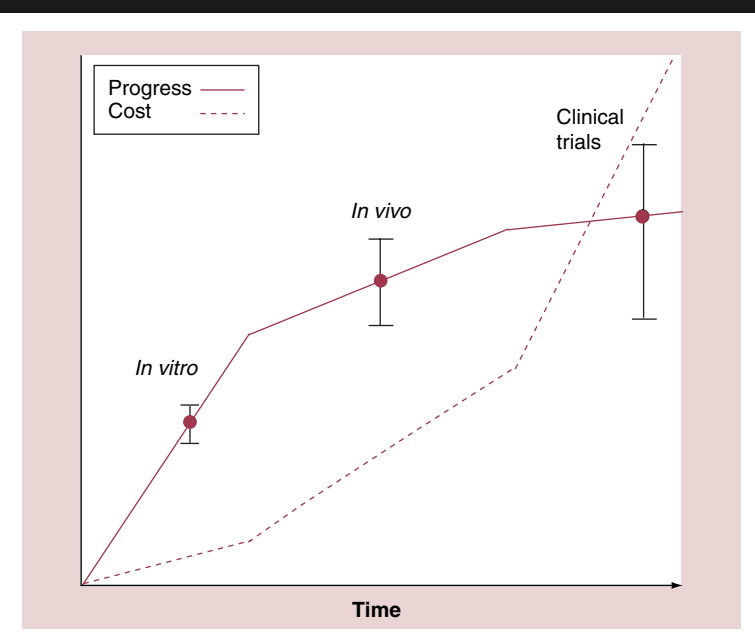
Figure 1. English language publications on arthritis gene therapy in the refereed literature.



Based on a PubMed search using 'arthritis gene therapy' as the search term. OA: Osteoarthritis; RA: Rheumatoid arthritis.

For those of us in academia, it is increasingly difficult to fund clinical gene therapy trials through traditional granting mechanisms.

Figure 2. Rate of progress, statistical variation of data, and cost as arthritis gene-therapy research moves from *in vitro* laboratory research via preclinical testing into clinical trials.



Industry is also tough. Large pharmaceutical companies tend to shy away from gene therapy owing to liability, the extended time-lines for bringing a gene therapeutic to market, and questionable profitability. The biotechnology industry is more receptive, but, in most cases, lacks the necessary resources. Venture capitalists fail to see an exit strategy within their short time horizons. Moreover, nongenetic treatments for rheumatoid arthritis have been very successful both medically and commercially. This is not the case for osteoarthritis, which provides enticing opportunities for gene therapy, especially as the disease is local, common and difficult to treat [9].

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Given these constraints, it will require persistence, ingenuity and probably some luck to get beyond the second inflection point. Best of all would be dramatic clinical improvement in subjects enrolled in a clinical trial. At the moment there is only one Phase II trial in progress (Table 1), and this was interrupted by the death of a trial subject. However, enrolment and treatment of all subjects is now complete and we eagerly await the release of the results. The logic behind a local gene therapy for arthritis is persuasive, and has stood the test of time. The preclinical data are extremely encouraging, and we have inched our way into early human trials. With sufficient resources, we can undertake the robust clinical trials necessary to develop effective products [10].

Financial & competing interests disclosure

CH Evans is on the Scientific Advisory Board of Tissue-Gene Inc., MD, USA, for which he receives an honorarium. Evans is working with Molecular Orthopaedics Inc., NC, USA, to develop adeno-associated virus-based gene therapies for osteoarthritis. He owns no stock in Molecular Orthopaedics Inc. and receives no financial compensation. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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