Cell therapy for DMD:

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Diseases affecting the haematopoietic system and the epithelia have been successfully treated with cell or ex vivo gene therapy. Why?

In these tissues it is possible to ablate diseased cells (myeloablation, surgical ablation) and thus create space for transplanted cells.

This is impossible for tissues such as brain, cardiac or skeletal muscle

The first cell therapy for DMD was carried out in the late 80’

Terry Partridge

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Conversion of mdx myofibres from dystrophin-negative to -positive by injection of normal myoblasts

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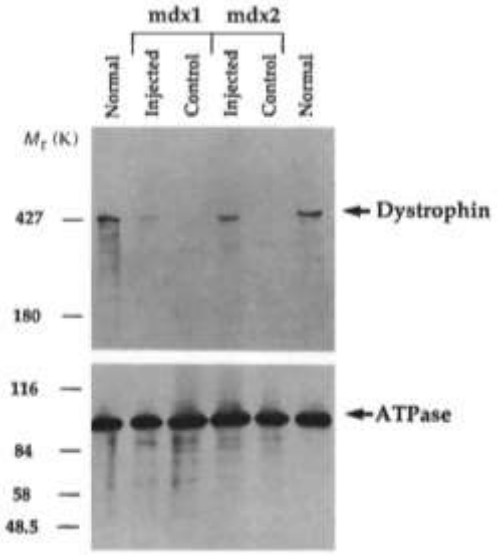
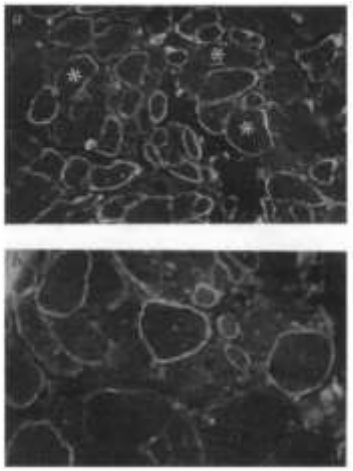
An important corollary to the recent advances in our understanding of the primary cause of Duchenne muscular dystrophy[1–6], is the validation of genuine genetic homologues as animal models of the disease[7,8] in which potential therapies can be tested. The persistent skeletal muscle necrosis that characterizes human Duchenne muscular dystrophy[9] is also seen in the mdx mouse[10–13] and is, in both, a consequence of a deficiency of dystrophin[6,7], probably within the muscle fibres themselves[14–16]. As injected muscle precursor cells of one genotype can fuse with host muscle fibres of a different genotype and express the donor genes[17,18], we decided to test grafts of normal muscle precursor cells to see if they could induce synthesis of dystrophin in innately dystrophin-deficient mdx muscle fibres. We show that injected normal muscle precursor cells can fuse with pre-existing or regenerating mdx muscle fibres to render many of these fibres dystrophin-positive and so to partially or wholly rescue them from their biochemical defect.





Results showed colonization of dystrophic mouse muscle and high-level dystrophin production.
This led to immediate clinical trials in DMD patients in US and Canada

These trials showed that:

1. Myoblast transplantation is safe
2. Little if any donor derived dystrophin may be detected.
3. Not enough to modify the force of transplanted muscles
4. And thus, this approach did not show clinical efficacy

After more than twenty years of work dedicated to increase efficacy…..

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Myoblast transfer therapy:
Is there any light at the end of the tunnel?

V. Mouly[1], A. Aamiri[2], S. Périé[1,3], K. Mamchaoui[1], A. Barani[1], A. Bigot[1], B. Bouazza[1], V. François[1], D. Furling[1], V. Jacquemin[1], E. Negroni[1], I. Riederer[1], A. Vignaud[1], J.L. St Guily[1,3] & G.S. Butler-Browne[1].

About twenty years later, myoblast transplantation showed some efficacy for a localized form of MD and with autologous myoblasts transplanted only in the pharyngeal muscles

Time to swallow decreases with high cell dose

Autologous … for Oculophary… a Phase I/II…

Sophie Périé[1–4], Capucin… el Mamchaoui[2–4], Belaïd Bouazza[2–4], Jean … Bruno Eymard[7], Gillian Butler-Browne[2–4]…

[1]Service d'Oto-Rhino-Laryngologie… [2]Université Paris VI Pierre et Marie… hospitalier Pitié-Salpétrière, Paris, … publique-Hôpitaux de Paris (APHP… René Laennec, 80054 Amiens Ced… Pitié Salpêtrière, Faculté de Médec… de Caen, Centre de Compétences … 30001, 14033 CAEN CEDEX 9, Fr…), Hôpital Tenon, Paris, France; …ogie, UM76, INSERM U974, Groupe …BT501, Hôpital Saint Louis, Assistance …l, Hematology Department, Avenue …ulaires, Institut de myologie, Hôpital …le Paris (APHP), Paris, France; [8]CHU …ation, Avenue de la Côte de Nacre, CS

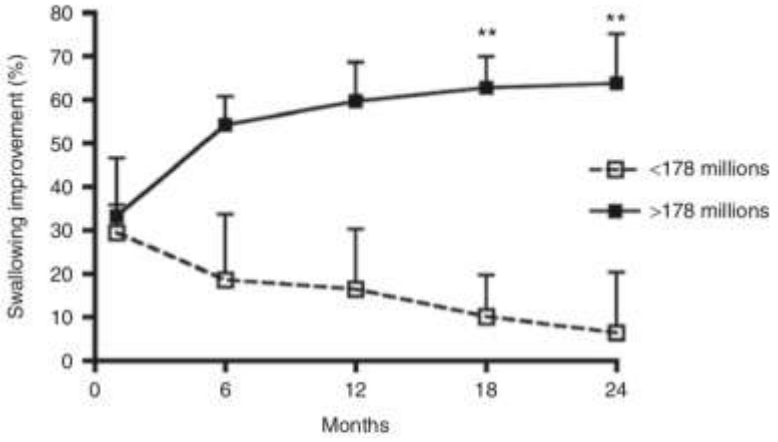


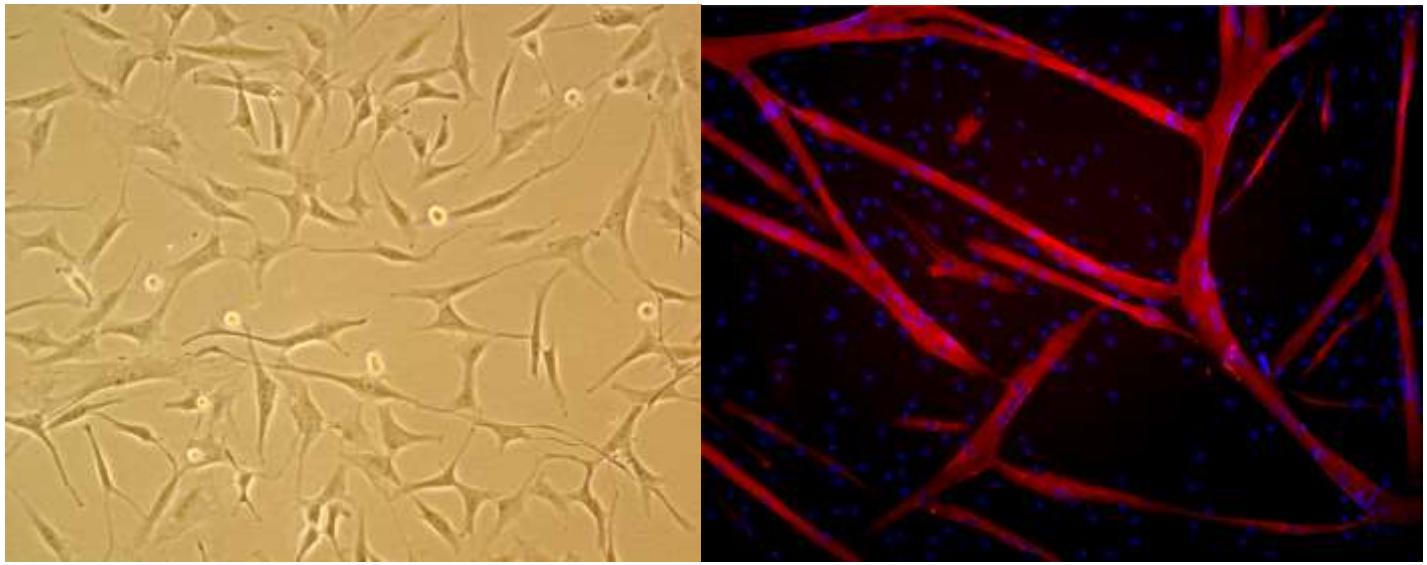
Figure 5 Correlation between the number of cells injected and the improvement of the time of swallowing. The percentage of swallowing improvement is determined between the time of swallowing preoperatively and each time point. 178 millions cells represent the median of the number of cells injected in this trial. Each group contains six patients, with no statistical difference in swallowing preoperatively. Mann-Whitney test (**$P < 0.01$).

Systemic delivery for widespread forms of muscular dystrophy

1. Most forms of muscular dystrophies affect entire groups of muscles needed for posture, ambulation and breathing. In these case multiple injections (many thousands would be needed) are extremely difficult if not impossible with current technology.
2. Myogenic cells able to cross the vessel wall and thus to be delivered systemically (or into the artery irrorating a specific anatomical district) would be desirable.

Mesoangioblasts

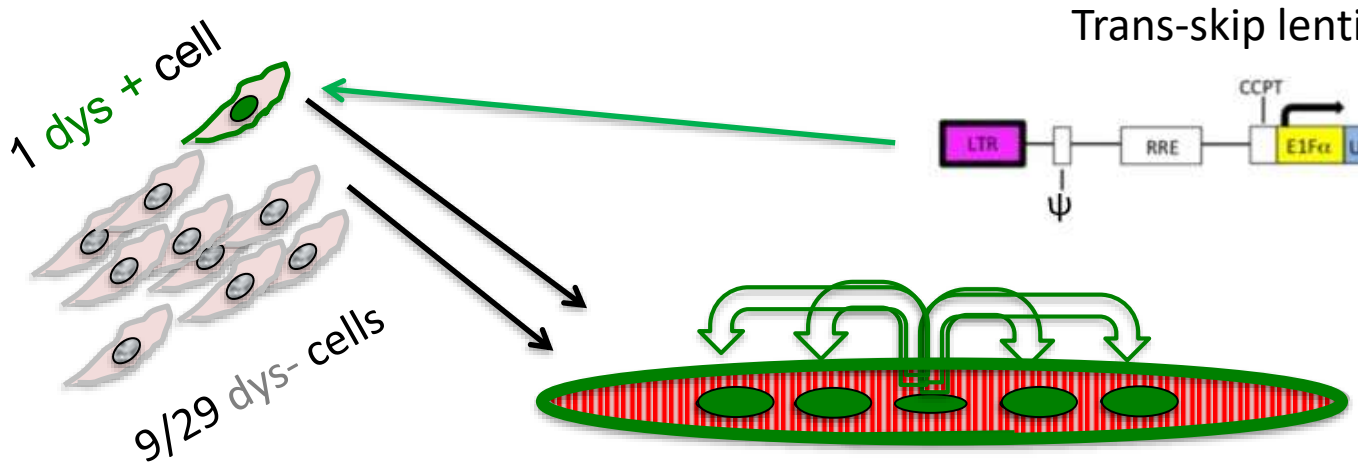
1. Are a subset of vessel associated pericytes,
2. They differentiate into smooth or skeletal muscle.
3. Most importantly, they adhere and cross the vessel wall.



We carried out pre-clinical work on small and large animal models

Results of a first in man trial of HLA-matched donor mesoangioblast transplantation showed that the trial was safe but not efficacious, essentially because engraftment was too low (<1%)

Through cell-delivered exon skipping snRNA we may correct neighbouring nuclei of DMD muscle fibres and amplify dystrophin production



Trans-skip lentivector (U7snRNA)

All corrected Non corrected 1/30 corrected