



History of Cell-Based approaches in Duchenne muscular dystrophy

Pat Furlong

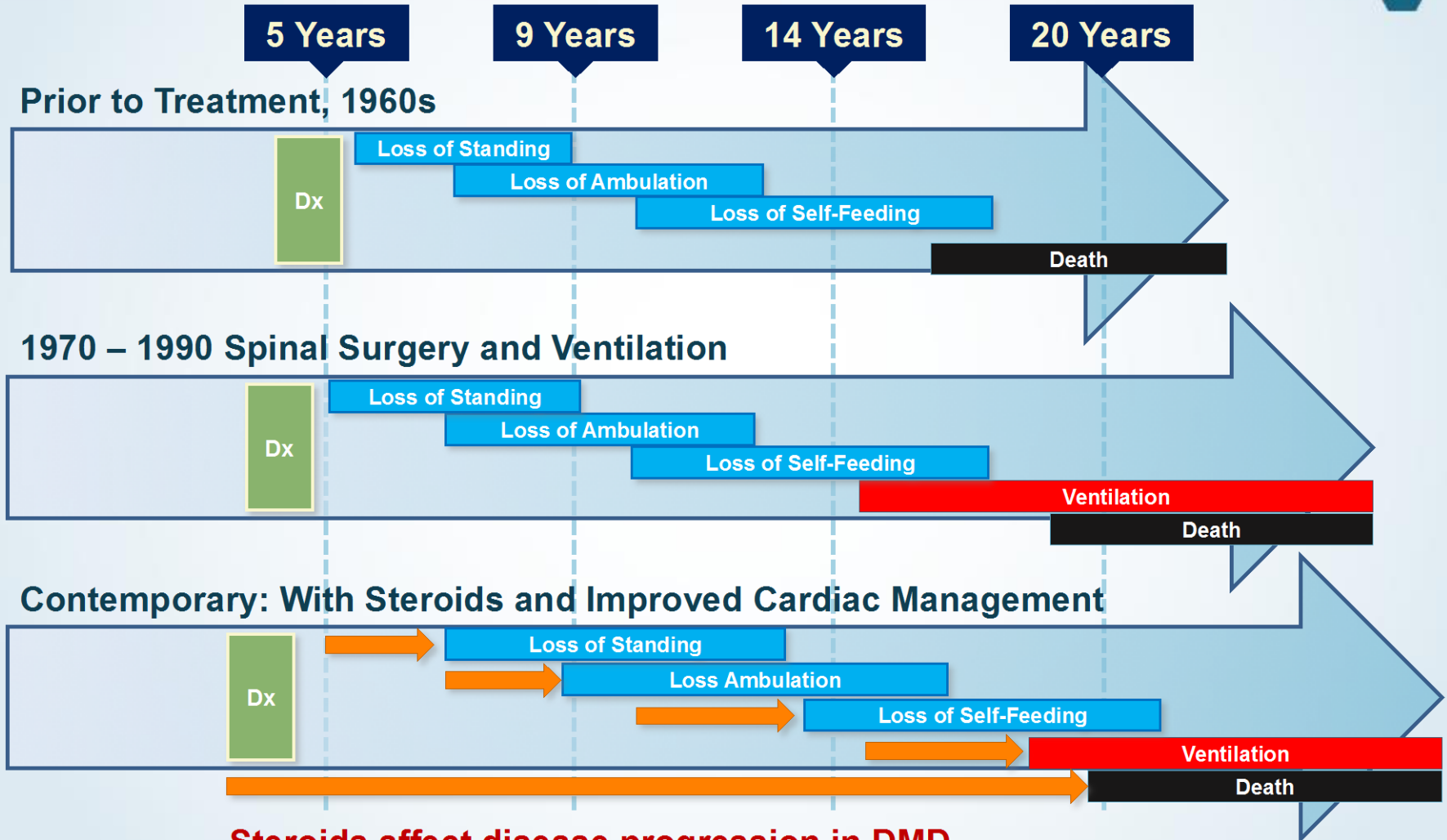
Duchenne Muscular Dystrophy

- Incidence 1:4600
- Diagnosis 3-5 years
- Early signs: speech delay, waddling gait, gower's maneuver
- 1990 –mean age of death = late teens
- 2016 mean age of death = mid 20's



Schematic Natural History of DMD

(Adapted from Bushby, Connor. *Clin Investig* (Lond). 2011; McDonald, et al. *Muscle Nerve*. 2013)



Steroids affect disease progression in DMD over the entire course of the disease, prolonging clinically meaningful functions (time to loss of milestones)

1990's

Myoblast Transfer as a potential therapy

- Issues:
- *Delivery*
- Migration, Engraftment
- Rejection

Myoblast Transfer in Duchenne Muscular Dystrophy

George Karpati, MD,* Djordje Ajdukovic, PhD,† Douglas Arnold, MD,* Robert B. Gledhill, MD,‡
Ronald Guttman, MD,§ Paul Holland, PhD,* Penelope A. Koch, MD,‡ Eric Shoubridge, PhD,*
Desmond Spence, MD,‡ Michel Vanasse, MD,¶ Gordon V. Watters, MD,‡ Michael Abrahamowicz, PhD,**
Catherine Duff, BSc,†† and Ronald G. Worton, PhD††

One biceps muscle of 8 patients with Duchenne muscular dystrophy was injected at 55 sites with a total of 55 million viable, purified, and contamination-free normal myoblasts (myoblast transfer). The other biceps of each patient was injected with a placebo to serve as a control. The procedure was blinded to the patients, parents, and investigators. Myoblasts derived from a biopsy specimen of the fathers were cultured and purified under strict conditions and carefully screened for microbial contamination. All patients received cyclophosphamide for immunosuppression for 6 or 12 months. No serious complications were observed after myoblast transfer, indicating that the procedure is safe. The overall therapeutic efficiency of myoblast transfer was poor as judged by the results in maximal voluntary force generation, dystrophin content of the muscle, magnetic resonance imaging of the muscle, and the lack of donor-derived DNA and dystrophin messenger RNA in the injected muscle. An improved efficiency of the take of myoblasts might be achieved by using younger cells and injecting the myoblasts with a myonecrotic agent (to increase the prevalence of regeneration) and a basal laminal fenestrating agent.

Karpati G, Ajdukovic D, Arnold D, Gledhill RB, Guttman R, Holland P, Koch PA, Shoubridge E, Spence D, Vanasse M, Watters GV, Abrahamowicz M, Duff C, Worton RG. Myoblast transfer in Duchenne muscular dystrophy. *Ann Neurol* 1993;34:8-17

NCBI Resources How To Sign in to NCBI

PubMed.gov US National Library of Medicine National Institutes of Health

PubMed Advanced Search

Format: Abstract

J Cell Physiol. 2009 Dec;221(3):526-34. doi: 10.1002/jcp.21895.

Cell based therapy for Duchenne muscular dystrophy.

Farini A¹, Razzini P, Erratico S, Torrente Y, Mereghetti M.

Author information

Abstract

Mutations in the dystrophin gene cause an X-linked genetic disorder: Duchenne muscular dystrophy (DMD). Stem cell therapy is an attractive method to treat DMD because a small number of cells are required to obtain a therapeutic effect. Here, we discussed about multiple types of myogenic stem cells and their possible use to treat DMD. The identification of a stem cell population providing efficient muscle regeneration is critical for the progression of cell therapy for DMD. We speculated that the most promising possibility for the treatment of DMD is a combination of different approaches, such as gene and stem cell therapy.

PMID: 19688776 DOI: 10.1002/jcp.21895

[PubMed - indexed for MEDLINE]

Facebook Twitter LinkedIn

Send to

Full text links

Wiley Online Library

Save items

Add to Favorites

Similar articles

[Therapy of Duchenne muscular dystrophy with umbilical co [Zhonghua Yi Xue Yi Chuan Xue Z...

Human mesenchymal stem cells ectopically expressing full-length dys [Hum Mol Genet. 2006

Review Development of therapy for Duchenne

2000-2010

PubMed.gov US National Library of Medicine National Institutes of Health

PubMed Advanced Search

Format: Abstract

Hum Mol Genet. 2006 Jan 15;15(2):213-21. Epub 2005 Dec 1.

Human mesenchymal stem cells ectopically expressing full-length of muscular dystrophy myotubes by cell fusion.

Goncalves MA¹, de Vries AA, Holkers M, van de Watering MJ, van der Velde J, van Nierop GP, Van

Author information

Abstract

Duchenne muscular dystrophy (DMD) is the most prevalent inheritable muscle disease. It is caused by mutations in the 2.5-megabase dystrophin (Dys) encoding gene. Therapeutic attempts at DMD have relied on the use of myoblast transplantation. However, immune rejection of these cells and their limited availability have prompted the search for a Stem cell-based gene therapy aims to restore tissue function by the transplantation of gene capable of stem cells to participate in tissue regeneration and (ii) the efficient genetic correction of the potential of bone marrow-derived human mesenchymal stem cells (hMSCs) genetically engage in myogenesis. By tagging hMSCs with enhanced green fluorescent protein (EGFP) they could participate in myotube formation when cultured together with differentiating human marked hMSCs and DsRed-labeled DMD myoblasts revealed that the EGFP-positive DMD hMSCs participate in human myogenesis through cellular fusion. Finally, we showed that a hybrid viral vector encoding full-length Dys could complement the genetic defect of DMD mice.

PMID: 16321987 DOI: 10.1093/hmg/ddl438

[PubMed - indexed for MEDLINE] Free full text

Facebook Twitter LinkedIn

Publication Types, MeSH Terms, Substances

LinkOut - more resources

NCBI Resources How To Sign in to NCBI

PubMed.gov US National Library of Medicine National Institutes of Health

PubMed Advanced Search

Format: Abstract

Mol Ther. 2007 May;15(5):867-77. Epub 2007 Mar 27.

Stem and progenitor cells in skeletal muscle development, maintenance, and therapy.

Péault B¹, Rudnicki M, Torrente Y, Cossu G, Tremblay JP, Partridge T, Gussoni E, Kunkel LM, Huard J.

Author information

Abstract

Satellite cells are dormant progenitors located at the periphery of skeletal myofibers that can be triggered to proliferate for both self-renewal and differentiation into myogenic cells. In addition to anatomic location, satellite cells are typified by markers such as M-cadherin, Pax7, Myf5, and neural cell adhesion molecule-1. The Pax3 and Pax7 transcription factors play essential roles in the early specification, migration, and myogenic differentiation of satellite cells. In addition to muscle-committed satellite cells, multi-lineage stem cells encountered in embryonic, as well as adult, tissues exhibit myogenic potential in experimental conditions. These multi-lineage stem cells include side-population cells, muscle-derived stem cells (MDSCs), and mesoangioblasts. Although the ontogenic derivation, identity, and localization of these non-conventional myogenic cells remain elusive, recent results suggest their ultimate origin in blood vessel walls. Indeed, purified pericytes and endothelium-related cells demonstrate high myogenic potential in culture and in vivo. Allogeneic myoblasts transplanted into Duchenne muscular dystrophy (DMD) patients have been, in early trials, largely inefficient owing to immune rejection, rapid death, and limited intramuscular migration—all obstacles that are now being alleviated, at least in part, by more efficient immunosuppression and escalated cell doses. As an alternative to myoblast transplantation, stem cells such as mesoangioblasts and CD133+ progenitors administered through blood circulation have recently shown great potential to regenerate dystrophic muscle.

PMID: 17387336 DOI: 10.1038/mt.sj.6300145

[PubMed - indexed for MEDLINE]

Facebook Twitter LinkedIn

Publication Types, MeSH Terms, Substances

LinkOut - more resources

Send to

Full text links

nature publishing group

Save items

Add to Favorites

Similar articles

Identification and characterization of a non-satellite cell muscle resident [Nat Cell Biol. 2010]

A Pax3/Pax7-dependent population of skeletal muscle progenitor cells. [Nature. 2005]

Myogenic specification of side population cells in skeletal muscle. [J Cell Biol. 2002]

Review The potential of muscle stem cells. [Dev Cell. 2001]

Review The emerging biology of satellite cells and their therapeutic potential [Trends Mol Med. 2008]

See reviews...

See all...

Cited by over 100 PubMed Central articles

Pericytes: A newly recognized player in wound healing. [Wound Repair Regen. 2016]

2010- Progress?

CELL TYPE
ENGRAFTMENT
MIGRATION
DIFFERENTIATION
DELIVERY
REJECTION

Journal Menu

- About this Journal
- Abstracting and Indexing
- Aims and Scope
- Annual Issues
- Article Processing Charges
- Articles in Press
- Author Guidelines
- Bibliographic Information
- Citations to this Journal
- Contact Information
- Editorial Board
- Editorial Workflow
- Free eTOC Alerts
- Publication Ethics
- Reviewers Acknowledgment
- Submit a Manuscript
- Subscription Information
- Table of Contents

BioMed Research International
Volume 2014 (2014), Article ID 964010, 12 pages
<http://dx.doi.org/10.1155/2014/964010>

Review Article
Stem Cell Transplantation for Muscular Dystrophy: The Challenge of Immune Response

Sara Martina Maffioletti,¹ Maddalena Novello,² Karen English,³ and Francesco Saverio Tedesco¹

¹Department of Cell and Developmental Biology, University College London, London WC1E 6DE, UK
²Experimental Hematology Unit, Division of Immunology, Transplantation and Infectious Diseases, San Raffaele Scientific Institute, 20132 Milan, Italy
³Institute of Immunology, Department of Biology, National University of Ireland Maynooth, County Kildare, Ireland

Received 14 February 2014; Accepted 5 June 2014; Published 26 June 2014

Academic Editor: Fabio Rossi

Copyright © 2014 Sara Martina Maffioletti et al. This is an open access article distributed under the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract

Treating muscle disorders poses several challenges to the rapidly evolving field of regenerative medicine. Considerable progress has been made in isolating, characterizing, and expanding myogenic stem cells and, although we are now envisaging strategies to generate very large numbers of transplantable cells (e.g., by differentiating induced pluripotent stem cells), limitations directly linked to the interaction between transplanted cells and the host will continue to hamper a successful outcome. Among these limitations, host inflammatory and immune responses challenge the critical phases after cell delivery, including engraftment, migration, and differentiation. Therefore, it is key to study the mechanisms and dynamics that impair the efficacy of cell transplants in order to develop strategies that can ultimately improve the outcome of allogeneic and autologous stem cell therapies, in particular for severe disease such as muscular dystrophies. In this review we provide an overview of the main players and issues involved in this process and discuss potential approaches that might be beneficial for future regenerative therapies of skeletal muscle.

Abstract

Full-Text PDF

Full-Text HTML

Full-Text ePUB

Full-Text XML

Linked References

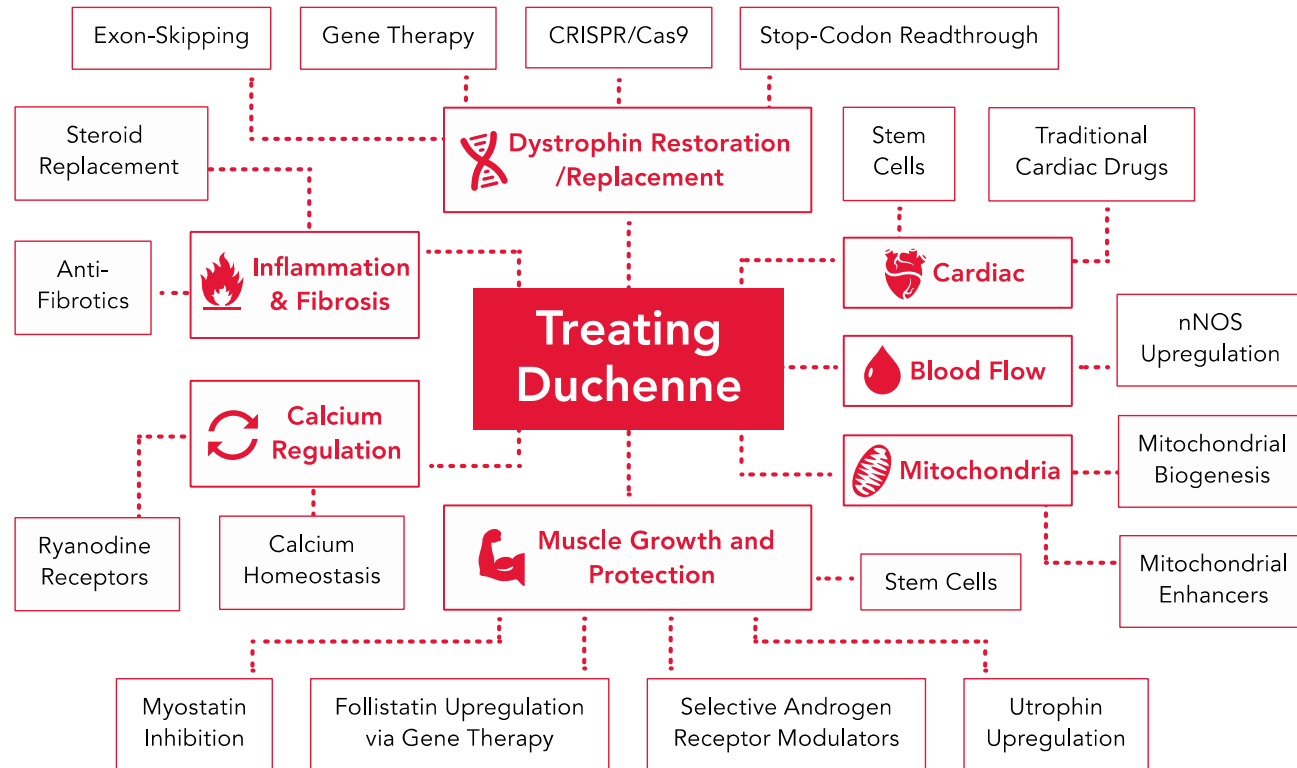
Citations to this Article

How to Cite this Article

Complete Special Issue

Views	2,465
Citations	10
ePub	25
PDF	540

Duchenne Therapeutic Approaches



Clinical trials pipeline

DRUG	PRECLINICAL	PHASE I	PHASE I/II	PHASE II	PHASE III
ETEPLIRSEN [SAREPTA]					
SPIRONOLACTONE & EPLERENONE [OHIO STATE UNIVERSITY]					
TADALAFIL [ELI LILLY] COMPLETED					
TRANSLARNA™ (ATALUREN) [PTC THERAPEUTICS]					
GIVINOSTAT (ITF2357) [ITALFARMACO]					
RAXONE® (IDEBENONE) [SANTHERA]					
SRP-4045/SRP-4053 [SAREPTA]					
COENZYME Q10 & LISINOPRIL [US DEPARTMENT OF DEFENSE]					
PF-06252616 [PFIZER]					
FG-3019 [FIBROGEN]					
NS-065/NCNP-01 [NS PHARMA]					
VAMOROLONE (VBP15) [REVERAGEN]					
CAT-1004 [CATABASIS]					
EZUTROMID (SMT C1100) [SUMMIT PLC]					
FOLLISTATIN GENE TRANSFER [NATIONWIDE CHILDREN'S]					
BMS-986089 [BRISTOL MYERS SQUIBB]					
MYOBLAST TRANSPLANTATION [CHU DE QUÉBEC]					
CAP-1002 [CAPRICOR]					
GENE TRANSFER OF MICRO-DYSTROPHIN [NATIONWIDE CHILDREN'S]					

*Pipeline graphic represents the clinical trial FAQ sheets included in this booklet and it not intended to be a comprehensive list.

2016 – targeted delivery

- Capricor: CAP-1002- Cardiosphere-derived cells (CDCs) which are clusters of cells obtained from heart cells. demonstrated that they possess regenerative properties, meaning the cells are able to promote growth of new heart cells.
- ? Exosomes - technology which may have the potential as a next generation therapeutic platform in regenerative medicine

Hope-Duchenne

- Sponsor: Capricor Inc.
- Randomized, open label study of the safety and effectiveness of multi-vessel Intracoronary Delivery of Allogeneic Cardiosphere-derived Cells in patients with cardiomyopathy secondary to DMD
 - *Allogeneic: not of self, tissues or cells genetically dissimilar*
- Coax cardiac stem cells to regenerate normal cardiac cells

Study Design/completed

- Age: ≥ 12 years
- N = 24
 - 12 treatment
 - 12 placebo
- DSMB look early on
 - Group 1: 1st 3 to 8 boys enrolled
 - Look at 72 hours post-infusion data

2016-Modeling pathology?

- Human iPSC-based 3D Microphysiological System for Modeling DMD Cardiomyopathy
- Human iPSC-based 3D microphysiological system for modeling DMD skeletal muscle pathology
- ?? Will this model adequately model disease burden

PP
MD



Pat@parentprojectmd.org

ParentProjectMD.org

Parent Project
Muscular Dystrophy
LEADING THE FIGHT TO END DUCHENNE