History of Cell-Based approaches in Duchenne muscular dystrophy

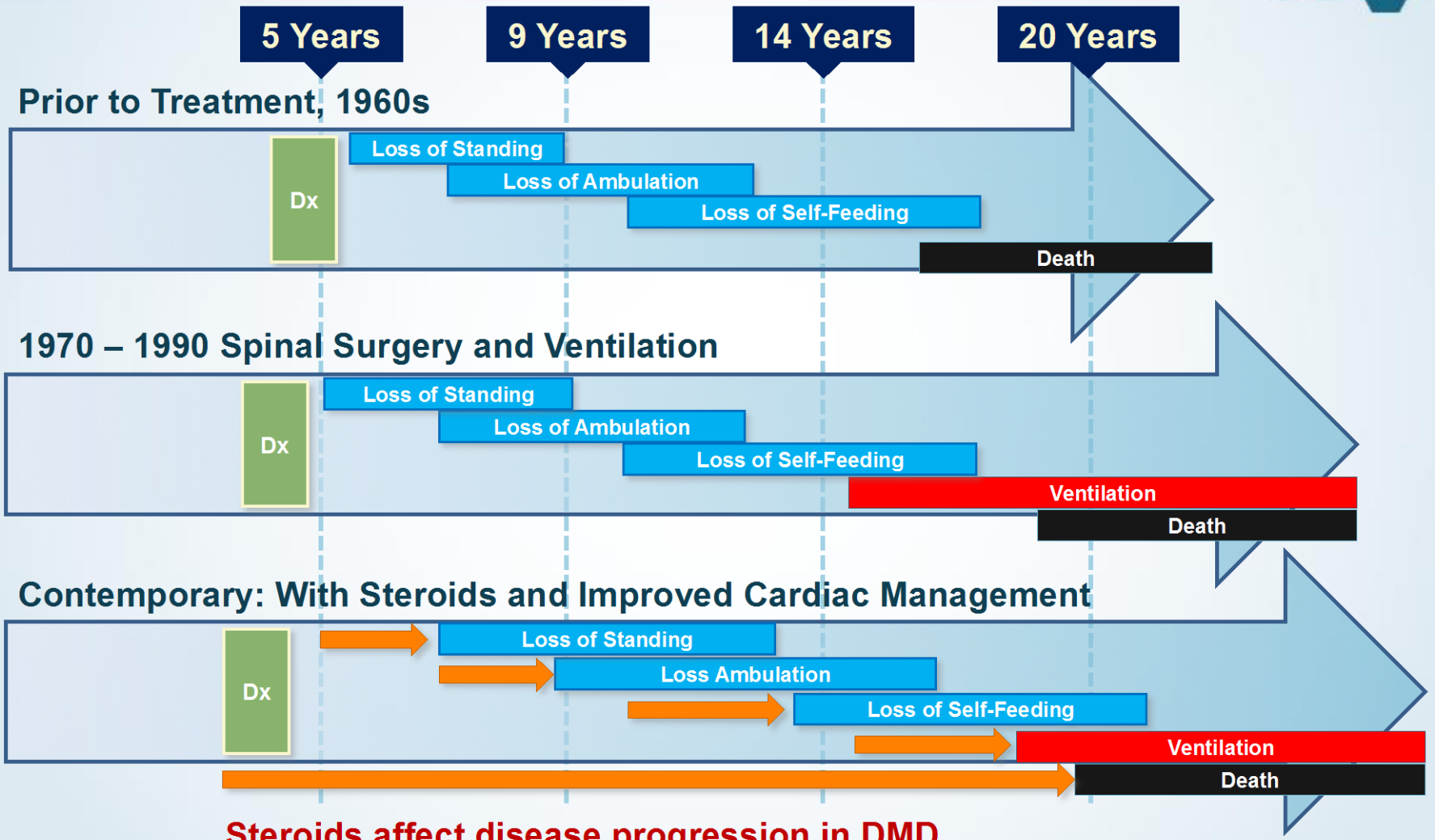
Pat Furlong

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)

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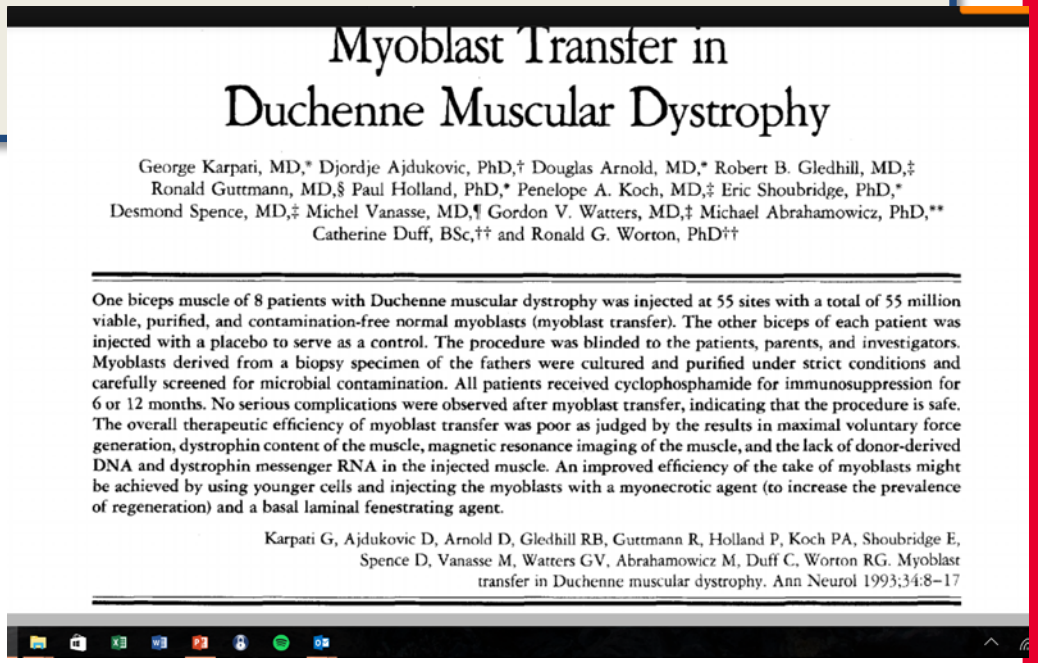
1990's
Myoblast Transfer as a potential therapy

- **Issues:**

- ***Delivery***

--Migration, Engraftment

-Rejection



Myoblast Transfer in Duchenne Muscular Dystrophy

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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, Guttmann 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

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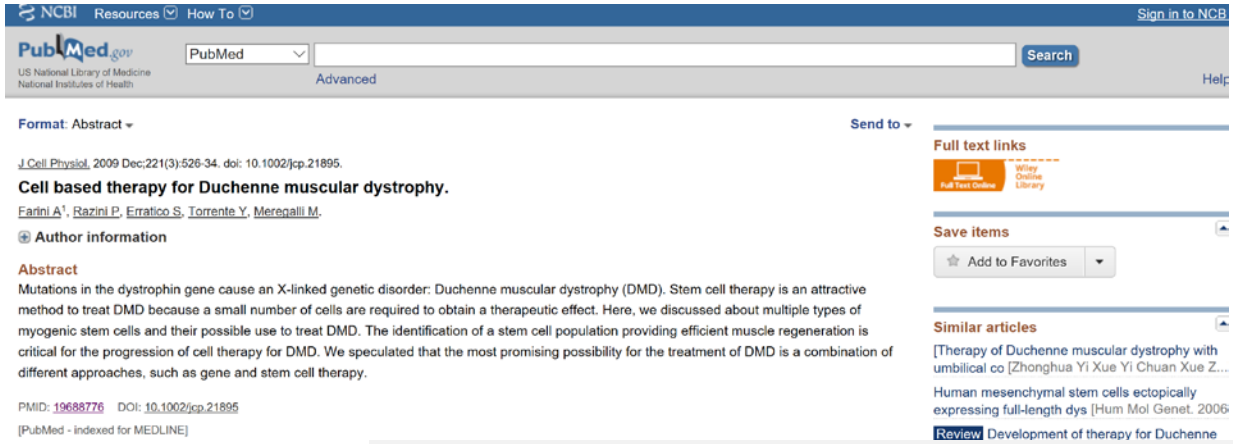
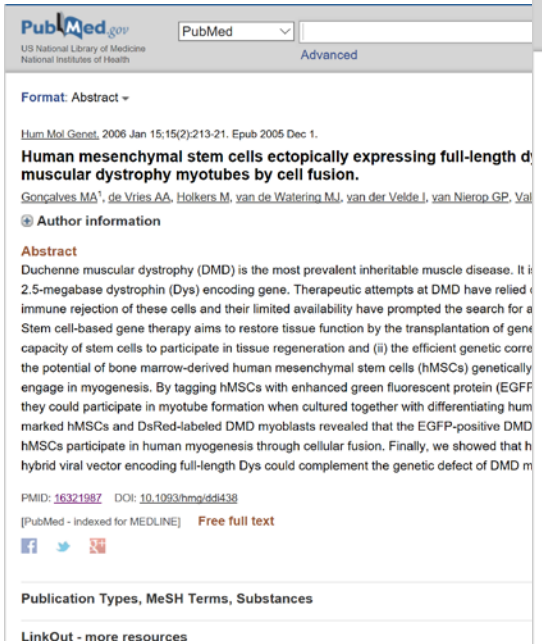
2000-2010





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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

- Open Special Issues
- Published Special Issues
- Special Issue Guidelines

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Review Article

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

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Views	2,465
Citations	10
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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.

1. Introduction

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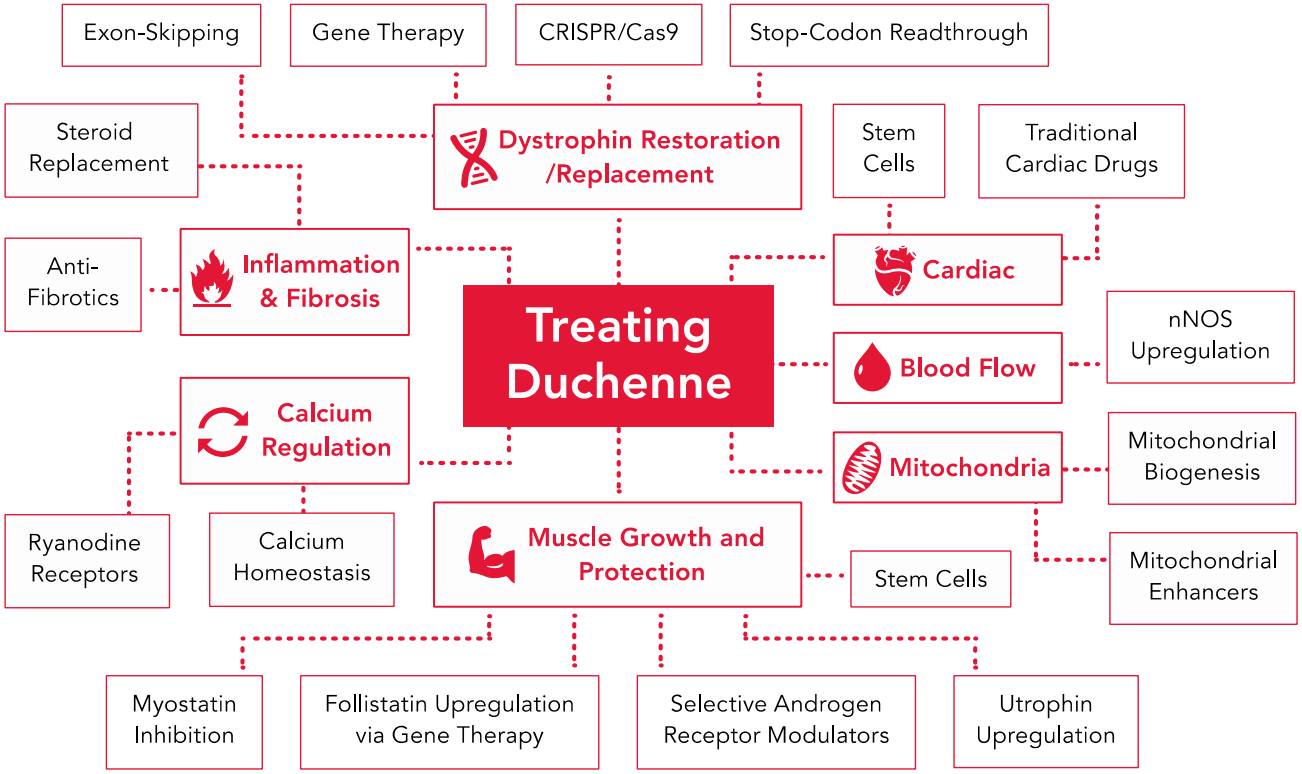
Duchenne Therapeutic Approaches



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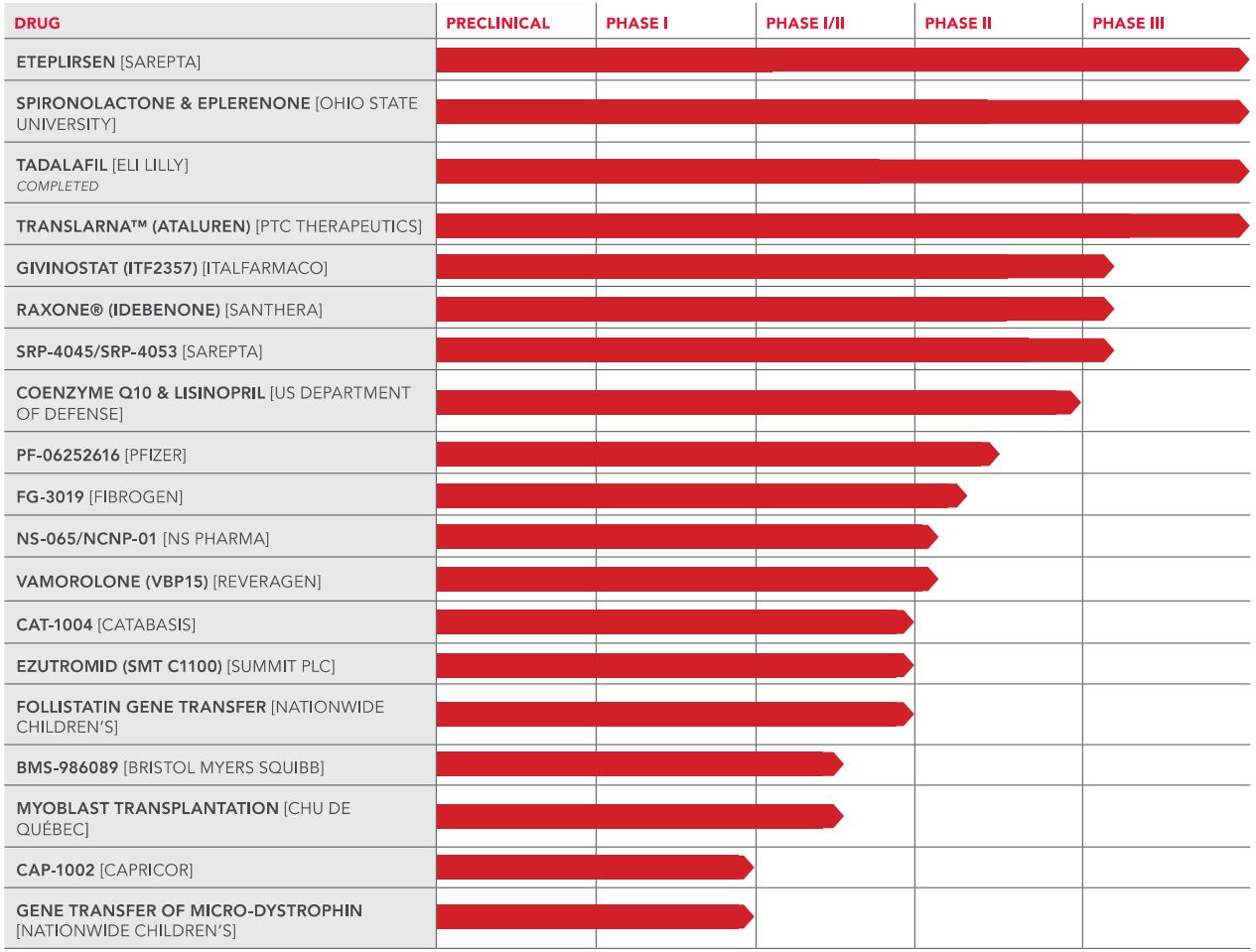
Clinical trials pipeline



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

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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

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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

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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

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