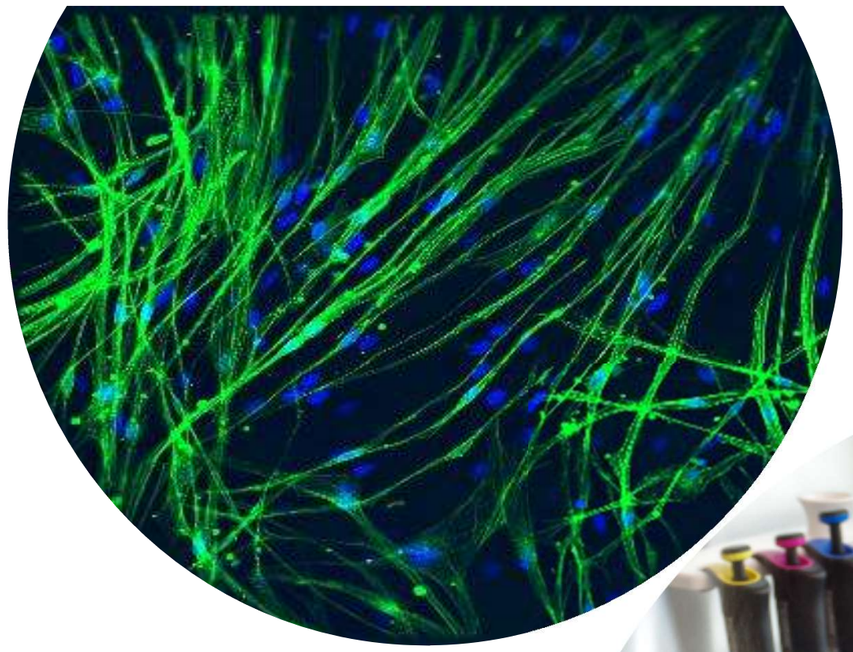
anagenesis

BIOTECHNOLOGIES



Small molecules to enhance skeletal muscle regeneration from stem cells

www.anagenesis-biotech.com

NCE for Duchenne Muscular Dystrophy & other muscular diseases

DMD: an unmet medical need

X Chromosome defect

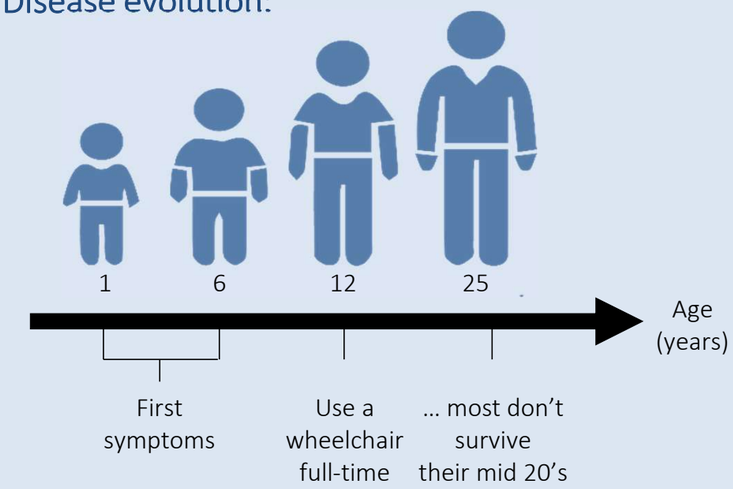
1 in 3500 Male births

100% Fatal condition

Mutation in the Dystrophin gene

Cost to society: 100 k€/year/patient

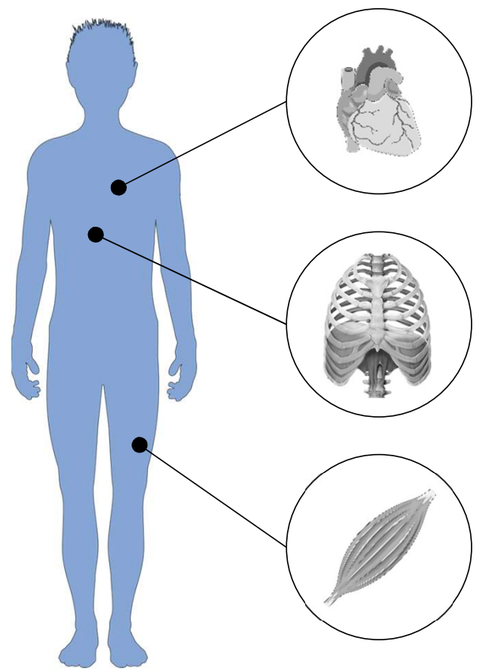
Disease evolution:



Number of cases

DMD affects all striated muscles

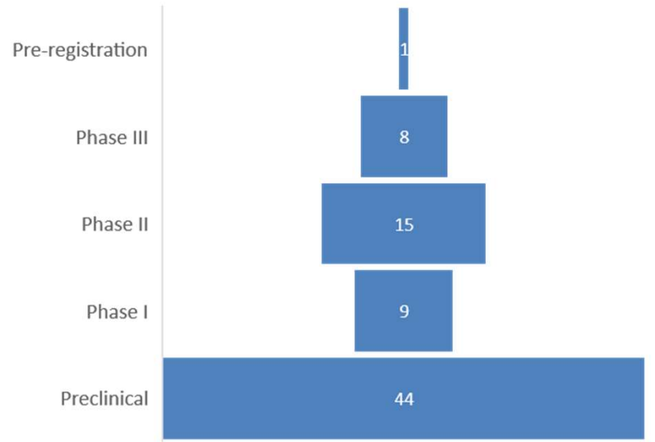
(skeletal muscles, diaphragm & heart)



5 drugs on the market:

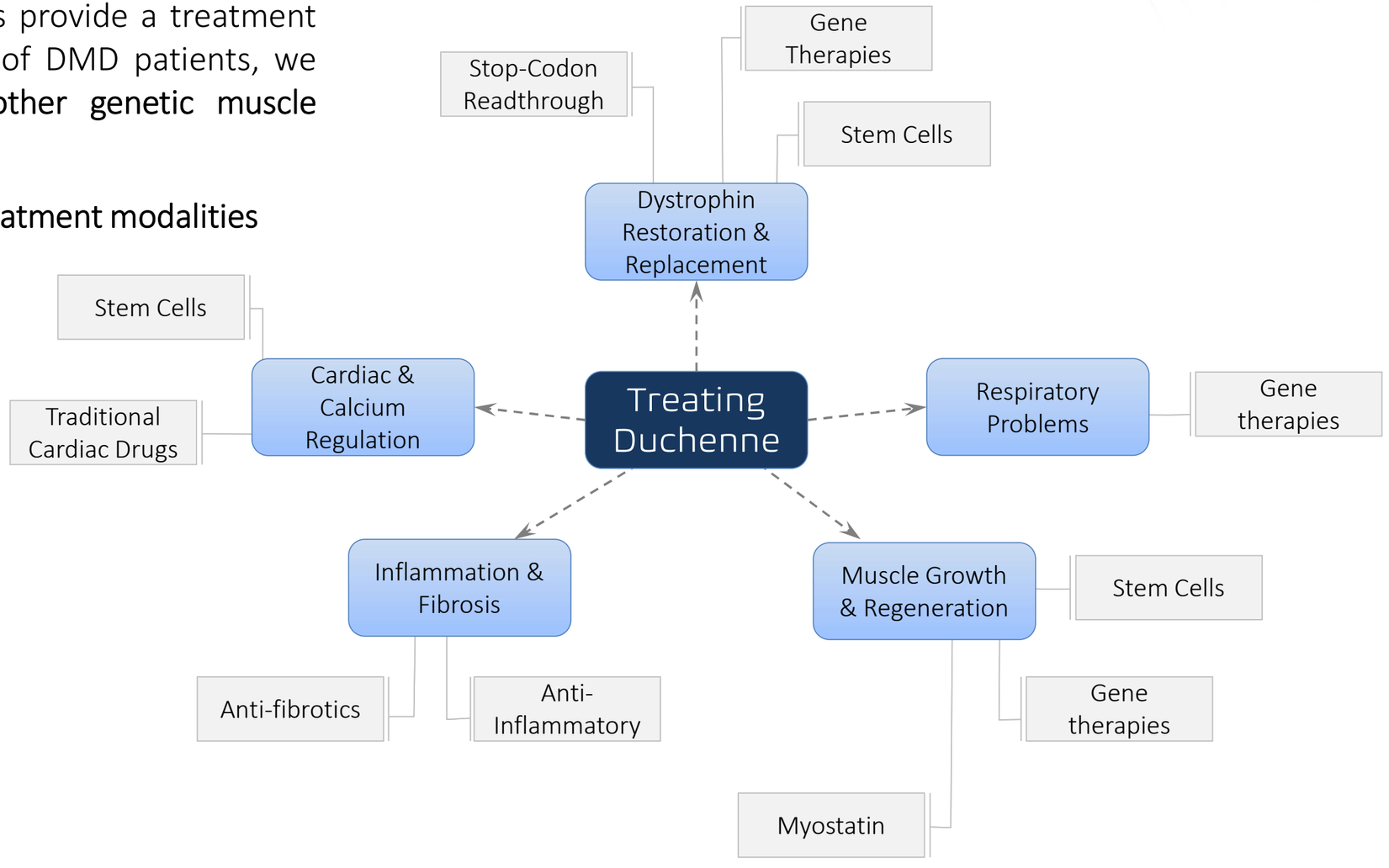
- 2 corticosteroids (SOC)
- 3 exon skipping drugs
- 1 codon read-through drug

Pipeline development stage



Value creation potential of Anagenesis compounds for DMD

- While current treatment strategies provide a treatment option for a small subpopulation of DMD patients, we **target all DMD patients & all other genetic muscle diseases**
- **Possible combination with other treatment modalities**

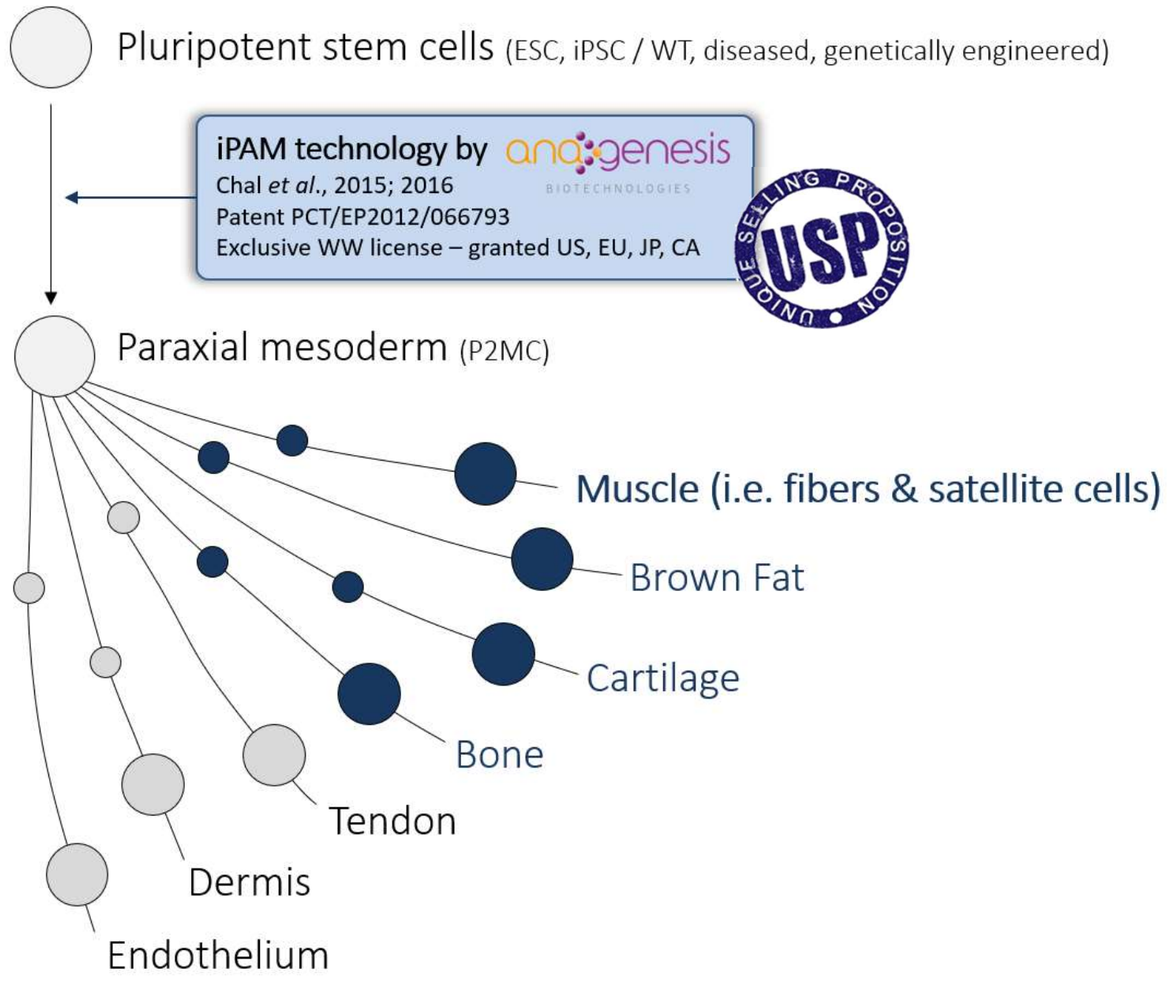


Our technology: Anagenesis IP & KH to generate paraxial mesoderm and its derived lineages from pluripotent stem cells

- **Unique technology from the laboratory of Olivier Pourquié**, a world expert in the field of musculo-skeletal development and stem cells
- The Pourquié lab has discovered a process to generate **unlimited quantities of paraxial mesodermal cells *in vitro***, an embryonic structure giving rise to muscle, brown fat, cartilage, bone, tendon, dermis and endothelium tissues

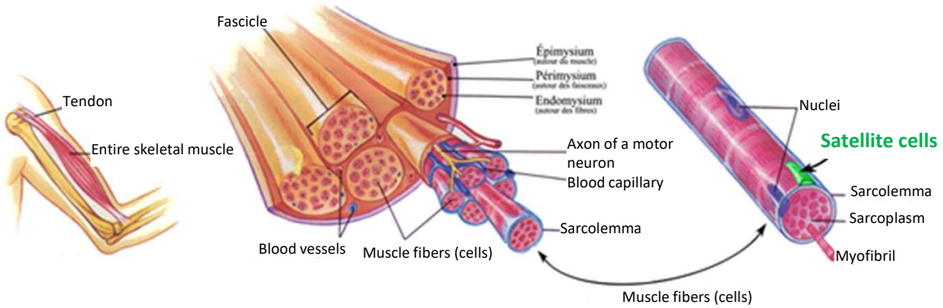
HARVARD MEDICAL SCHOOL

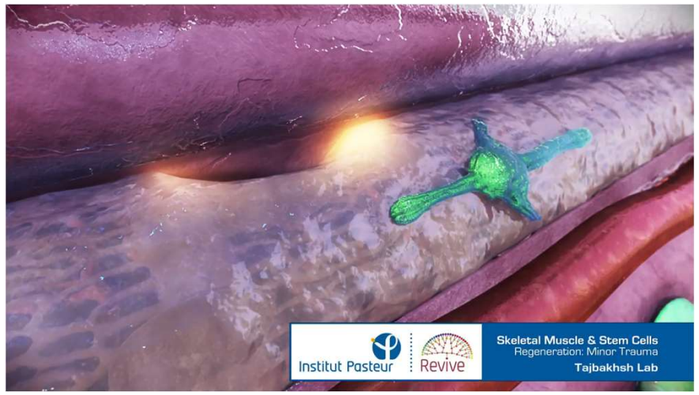
BWH BRIGHAM AND WOMEN'S HOSPITAL



Satellite cells become non-functional in DMD

- Satellite cells are muscle stem cells, aiming at repairing muscle injuries:

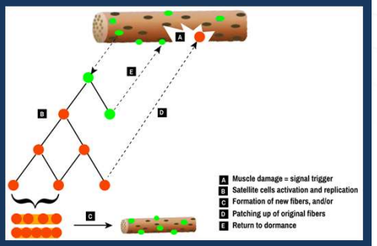




From https://www.youtube.com/watch?v=lICMwXNpnLY

- In certain conditions, such as DMD, satellite cell dysfunction (due to intrinsic defects and/or environmental factors) impairs muscle regeneration process, ultimately leading to muscle wasting

Muscle regeneration process



Muscle injury

↓

Nearby satellite cell activation

↓

Satellite cell asymmetric division

↓

Progenies (myoblasts) proliferation & fusion

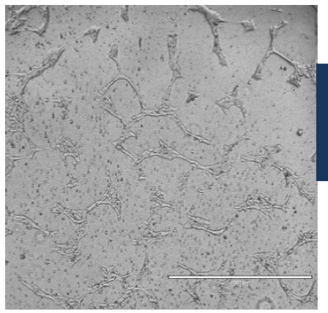
↓

Regenerated muscle fibers & satellite cell pool maintenance

Applying our technology: hPSC-derived muscle satellite cells

" A unique technology that allows the generation & differentiation of satellite cells together with muscle fibers"

Day 0



Induced Pluripotent Stem cells (iPSC)

Differentiation process

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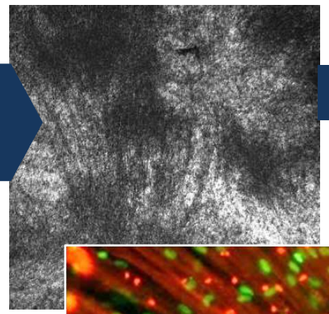
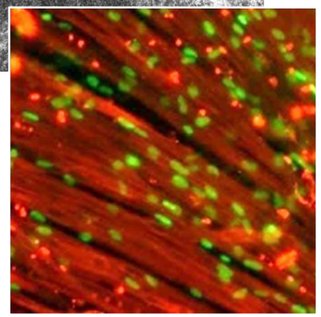
(patented **PCT/EP2012/066793**)

Day 34





Muscle fibers & satellite cells (Pax7⁺) cells

Enrichment

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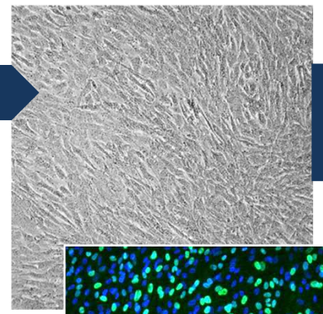
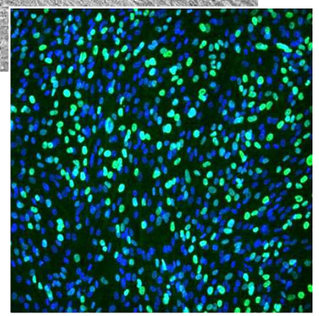
Know-how
(not published)

Day 40



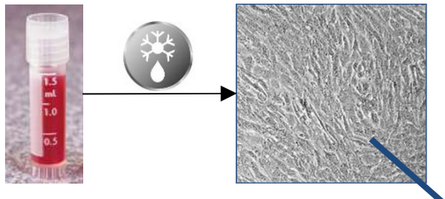


100% muscle progenitors containing 30-50% of Pax7⁺ cells
(can be banked frozen)

Downstream applications

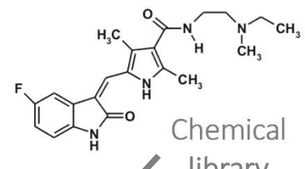
HCS for discovery of NCE

Identifying compounds acting on DMD muscle satellite cells in our HCS assay



Human iPSC-derived DMD Muscle progenitors

≈30-50% of **Satellite cells** (i.e. Pax7⁺ cells)



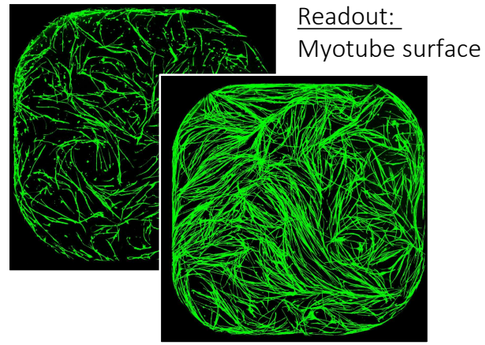
Chemical library

QC parameters:
- ☑ Pax7⁺ cells > 30%
- ☑ Dose Response to positive control

3-day incubation

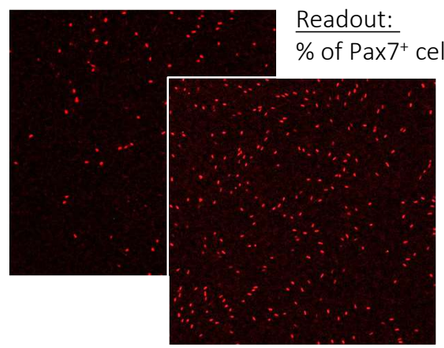
QC parameters:
- ☑ Z' factor > 0.5
- ☑ Reproducible positive control's EC50

Compounds increasing myotube content ?



Readout:
Myotube surface

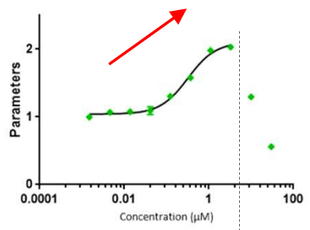
Effect on Pax7⁺ cells ?



Readout:
% of Pax7⁺ cells

Our selected compounds: myogenic while positively preserving muscle satellite cells

Compounds increasing myotube content



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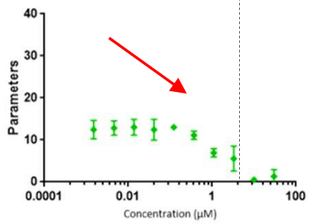
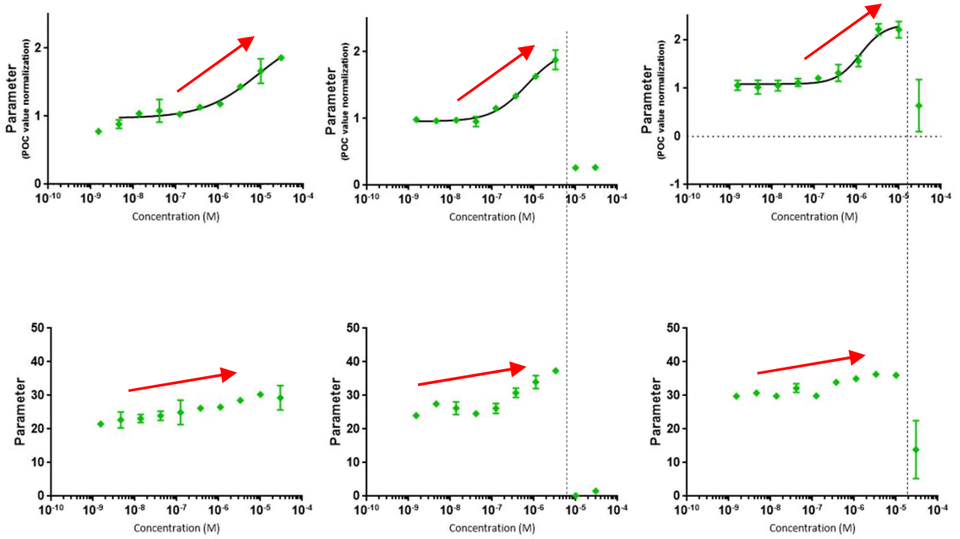
Effect on Pax7⁺ cells

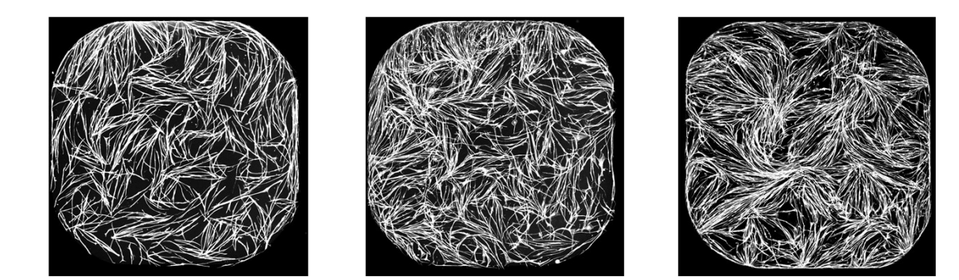


All other drugs for DMD promoting muscle regeneration do decrease satellite cells
(e.g. Corticoids, HDACi)

Profiles of our 3 tool compounds (Kinase inhibitors)

ANA-11297 | ANA-21505 | ANA-21506





Best product profile:

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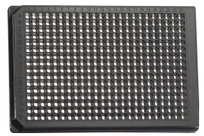
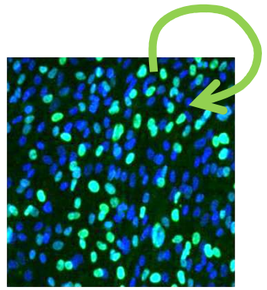
Promoting muscle regeneration while ensuring long term regeneration capabilities

In vivo translation of *in vitro* activity of ANA-21506 tool compound

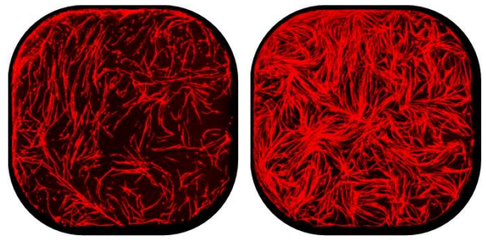
In vitro



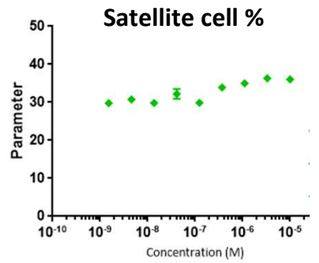
Myotube assay on Human DMD Muscle Progenitors



Muscle progenitors containing 30-50% of satellite cells



Pictures of DMSO- (left) and ANA-21506- (right) treated wells, showing increased myotube content (alpha-actinin⁺), obtained by satellite cell differentiation

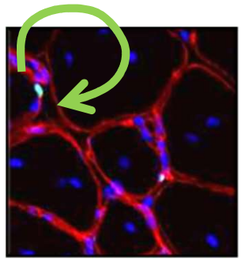


Preservation of satellite cell pool upon ANA-21506 dose increase

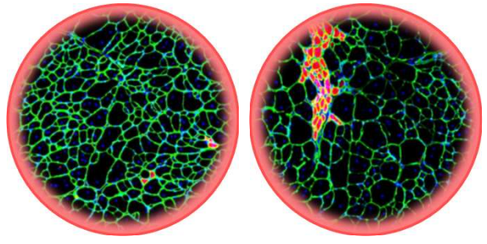
Treatment with **ANA-21506** → Mobilization of muscle satellite cells → Myogenic/pro-regenerative effect **AND** Satellite cell pool maintenance

In vivo

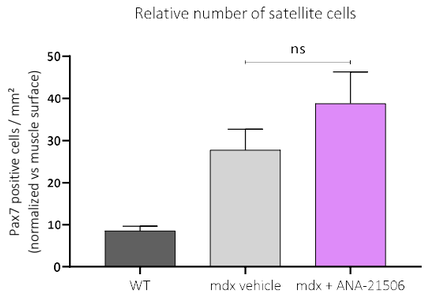
Treatment of B10.mdx mice



Satellite cells, basal lamina and nuclei



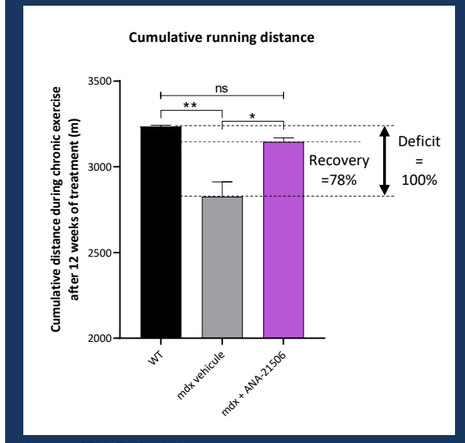
Muscle cross sections of mdx vehicle mouse (left) and ANA-21506-treated mdx mouse (right), showing newly regenerated fibers (MYH3⁺), basal lamina & nuclei



Maintenance of satellite cell pool upon ANA-21506 treatment in mdx mice, ensuring long term regeneration capabilities

In vivo

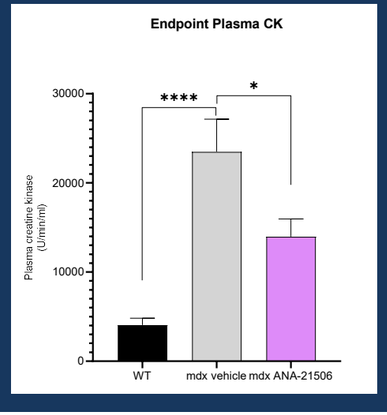
Improved muscle function



Improved performances in chronic exercise upon treatment with ANA-21506

Mean ± SEM (7-10 mice)
Statistics: 2 way-ANOVA, Tuckey's post hoc test;
*:p<0,05 ; **:p<0,01

Decreased muscle damage



Decreased plasma CK levels upon treatment with ANA-21506

Quantitation were performed by CK enzymatic assay on total plasma (10 mice in WT group, 7 mice in 21506 group and 9 mice in vehicle group). Mean ± SEM. Statistical analysis using ANOVA with Dunnett's multiple comparison post-test.
*****:p-value<0.0005;*
**:p-value<0.05.*

Derivatives of ANA-21506

-> LEAD op' stage for Anagenesis NCE (ANA-124621)

600 Kinase inhibitors tested in our myotube assay

3 tool compounds selected

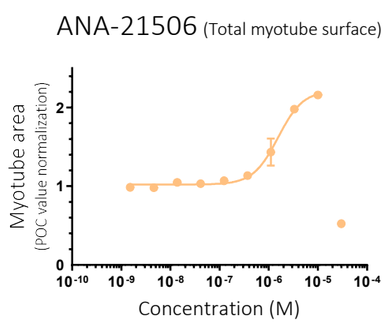
180 molecules designed and tested for SAR and optimization purposes

1 first patent filed

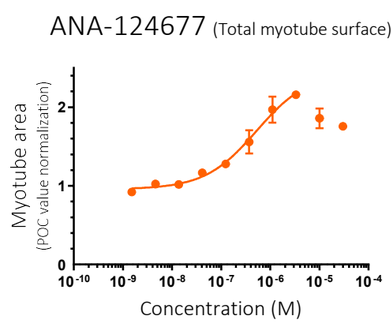
13 selected hits

2 NCE compounds tested *in vivo*

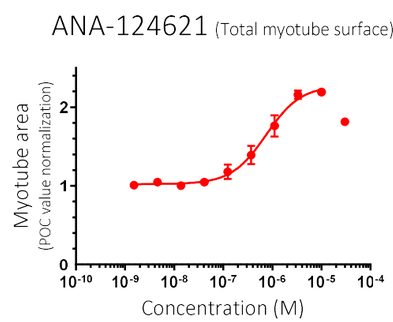
1 LEAD compound selected for LeadOp (ANA-124621)



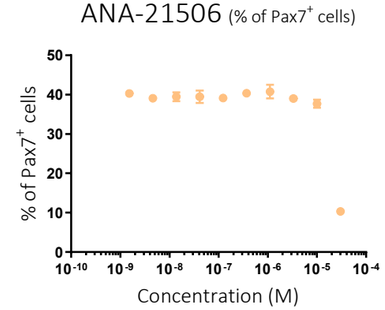
ANA-21506 (Total myotube surface)



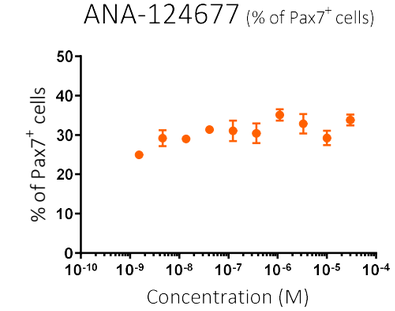
ANA-124677 (Total myotube surface)



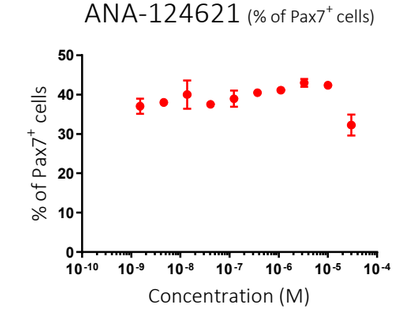
ANA-124621 (Total myotube surface)



ANA-21506 (% of Pax7+ cells)



ANA-124677 (% of Pax7+ cells)



ANA-124621 (% of Pax7+ cells)

ANA-21506
= Tool compound, used as reference

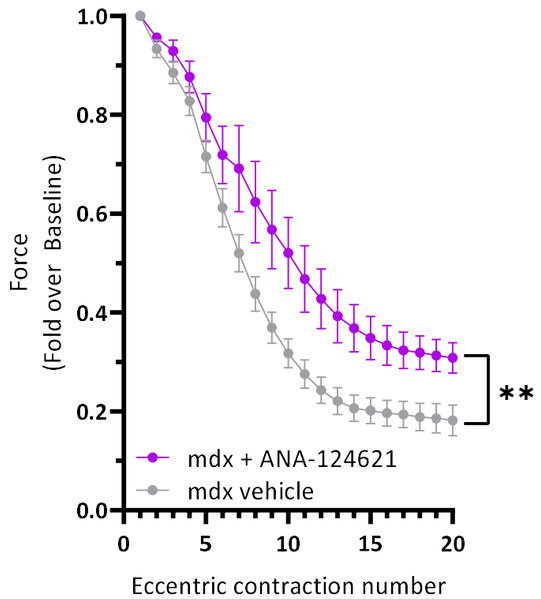
ANA-124677 ANA-124621
= 2 NCE compounds selected to go *in vivo*

Improved activity & efficacy, less toxicity of our new compounds, while keeping satellite cells pool

LEAD compound ANA-124621 increases muscle mass & improves resistance to injury in a mdx mouse model

☑ Better resistance to eccentric injuries

Susceptibility to injury

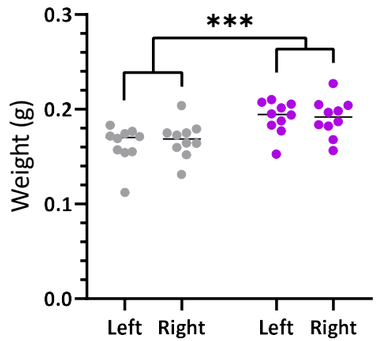


The treatment of *B10.mdx* mice with ANA-124621 for 7 days results in significantly reduced susceptibility of the plantar flexor muscle group to eccentric contraction-induced injury. At the 20th contraction, mice treated with ANA-124621 had 70% more force than their vehicle counterpart.

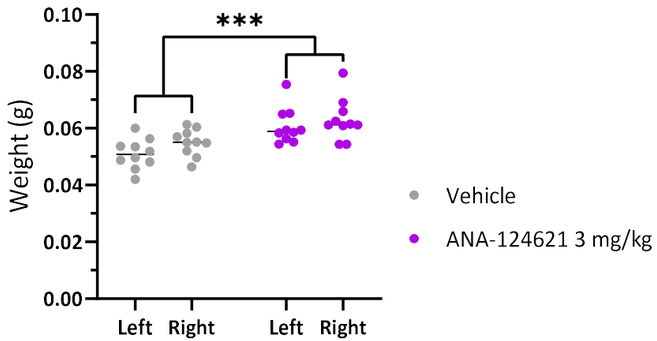
*Relative loss in torque throughout 20 eccentric contractions (n = 10). Data presented as means ± SEM. Statistical analysis: mixed model ANOVA; ** P < 0.01 vs. vehicle throughout the experiment.*

☑ Increased muscle mass

Gastrocnemii weight



Tibialis anterior weight

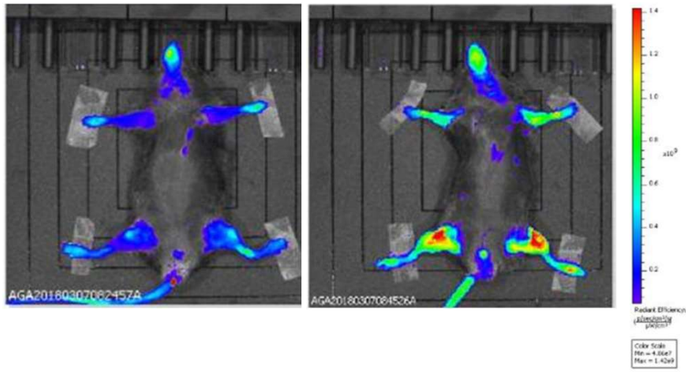


The treatment of *B10.mdx* mice with ANA-124621 for 21 days results in significantly higher muscle weight (+ 16%).

*Left and right Gastrocnemius and Tibialis anterior muscle weight (n = 10). Data presented as means ± SEM with individual data as dots. Statistical analysis: mixed model ANOVA; *** P < 0.001 vs. vehicle overall for all muscles.*

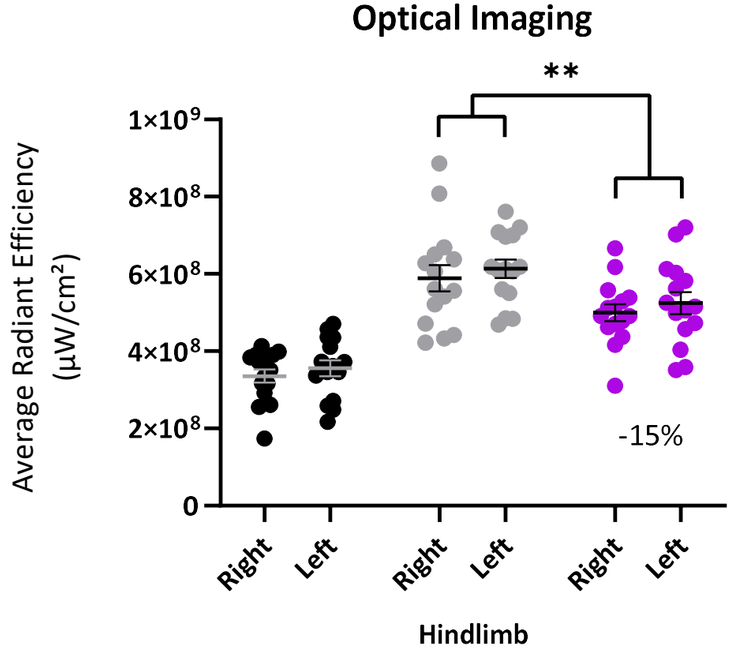
By acting on satellite cells, our ANA-124621 compound promoted muscle regeneration, as indicated by muscle mass increase, leading to protection from eccentric injury

LEAD compound ANA-124621 decreases inflammation in a mdx mouse model



This optical-imaging method allows to capture presence of Cathepsin B, an enzymatic biomarker that has previously been shown to be upregulated in muscles of both DMD patients and mdx mouse models. It primarily localize to macrophage infiltrating areas. This method allows ***a measure of efficacy for drugs designed to reduce inflammation*** *and damage in dystrophic muscle in pre-clinical trials.*

☑ Anti-inflammatory effect



The treatment of *D2.mdx* mice with ANA-124621 for 4 weeks results in significantly reduced inflammation, as assessed by average photon counts

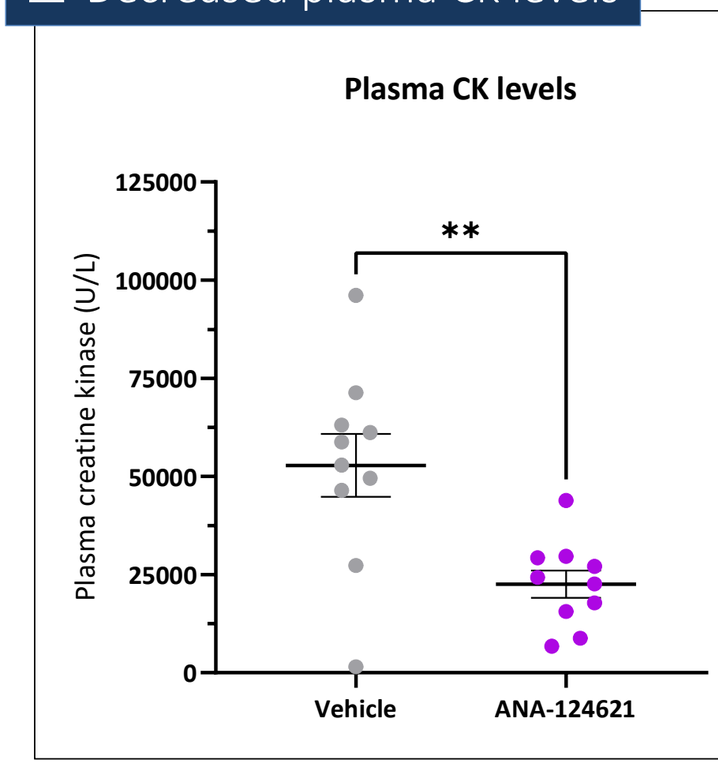
*Average Radiant Efficiency (n = 13-15). Data presented as means ± SEM. Statistical analysis: mixed model ANOVA; ** p < 0.01 vs. D2.mdx vehicle.*

LEAD compound ANA-124621 decreases endpoint plasma Creatine Kinase in a mdx mouse model

"Creatine kinase (CK) is a protein found in cardiac and skeletal muscle. Serum CK levels are routinely used as an indicator of muscle damage in dystrophic mice and are even used as a diagnostic tool in human DMD. Levels of this muscle protein are measured in the serum under the assumption that increased serum CK levels in the blood are representative of increased muscle damage, sarcolemma membrane fragility, and a poor disease phenotype."

TREAT-NMD Neuromuscular Network

☑ Decreased plasma CK levels



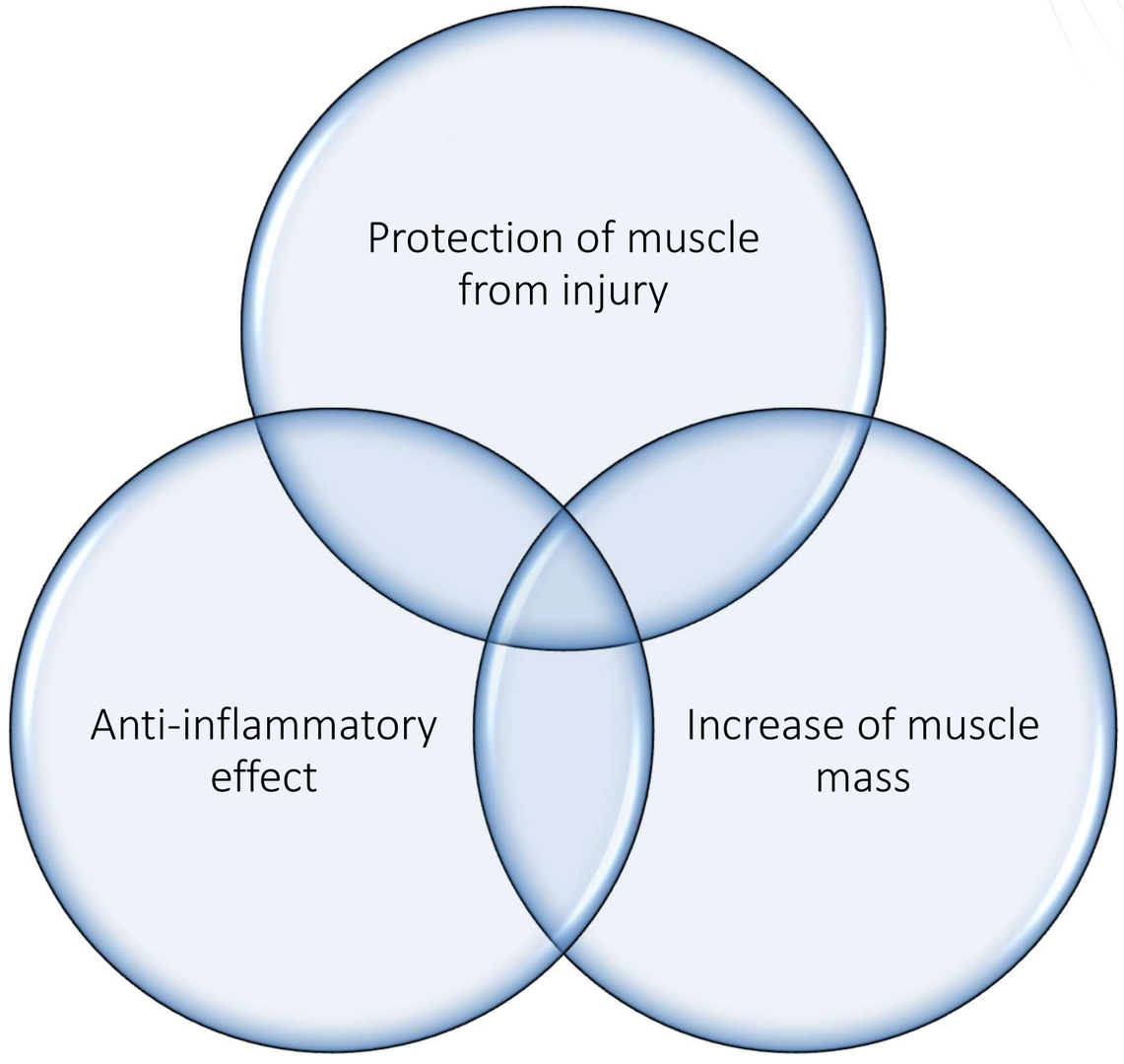
The treatment of *B10.mdx* mice with ANA-124621 for 21 days results in significantly lower plasma CK levels.

Quantitation were performed by CK enzymatic assay on total plasma (10 mice per group). Mean ± SEM. Statistical analysis using Welch t-test.
*** :p-value<0.01.*

In vivo activities of LEAD compound ANA-124621

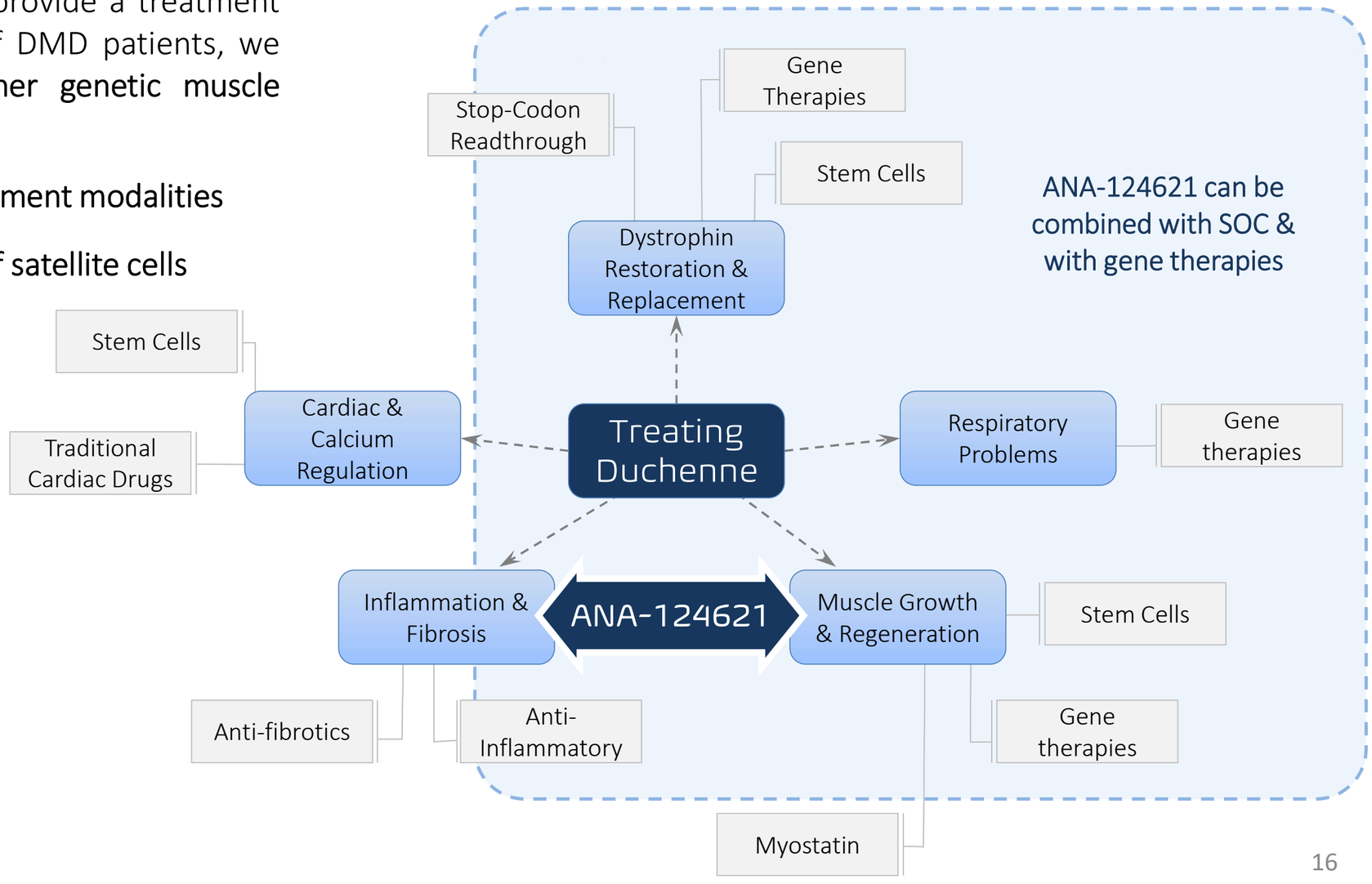
-> Summary

ANA-124621



Value creation potential of Anagenesis compounds for DMD

- While current treatment strategies provide a treatment option for a small subpopulation of DMD patients, we **target all DMD patients & all other genetic muscle diseases**
- Possible combination with other treatment modalities
- Reversion of SOC-induced decrease of satellite cells



Large market for our muscle drugs: DMD and more

Anagenesis products have the potential to transform the disability caused by dystrophin loss of function in all DMD patients, all genetic muscle diseases and chronic muscle diseases and with a potential for multiple related clinical indications.

DMD Therapies

The global DMD market is expected to reach over $10.7 billon by 2026 (CAGR of 48%).
(Persistence Market Research)

Incidence :
1/3500 boys

SARCOPENIA

The global sarcopenia market is expected to reach over $3 billon by 2025.
(The Market News 24)

Prevalence:
25% - 60 years
60% - 80 years

SPINAL MUSCULAR ATROPHY

The global SMA market is expected to reach over $6 billon by 2028 (CAGR of 16%).
(Global Data)

Incidence :
1/6000

AMYOTROPHIC LATERAL SCLEROSIS

The global ALS market is expected to reach $1.2 billion by 2029 (CAGR of 19%).
(Research And Markets)

Incidence :
1/50000

And could be used after MUSCLE INJURY ; in VOLUMETRIC MUSCLE LOSS combat- and trauma-induced in combination with our cell therapy, etc.

Incidence :
i.e. Soccer: 15 muscle injuries per season for a squad of 25 players

- All DMD patients experience muscle loss and so present a potential market for our treatments
- 42 600 DMD patients in US and EU ⇨ more than **$1,3 billion sales potential per year** only with NCEs*

* The annual cost of the majority of orphan medicines in Europe is below $50,000, while the median annual cost per orphan drug in the US is ~$32,000 (IQVIA)

Investment opportunity

- Round A EOY 2021
- 20 m€ sought
- IND end 2022
- Clinical POC end 2024
- Syndicate with existing investors
- Lead or co-lead investor sought

Anagenesis' people