English translation for reference purposes only
In case of any discrepancy, the Japanese version shall prevail

FY2025
Business Plans and
Matters Related to High Growth Potential



(TSE：4883)

Modalis therapeutics Corporation

March 27, 2025

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As requested by TSE, This document is updated once a year, and disclosure is scheduled to be made around March of each year. In the event of significant changes in the business plan, changes may be made irregularly,

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Major updates since the last report (August 2024 version)

P7	Updated corporate info
P25, 27, 35	Updated information on the industry environment
P40,41	Newly added to share note for our core-competence and tech strategy
P45, 56-60, 89-90	Updated development, patent, and partnering progress

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Outline of the strategy

- Adopt a business strategy centered on the development of MDL-101
- Prioritize research and development of neuromuscular diseases for which the know-how cultivated with MDL-101 can be applied
- Advance the development of subsequent programs on the premise of funding, such as partnering
- Resume development of neurological diseases on the condition of identifying delivery tools and allocating resources. Research will continue.

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Table of contents

1. Corporate Overview
2. Gene Therapy, Gene Editing
3. CRISPR-GNDM® and its advantages
4. Pipeline
5. Growth Strategy
6. Risk Information

1. Corporate Overview

Updated

Corporate Overview (As of December 31, 2024)

Modalis Therapeutics is a biotech company to develop CRISPR-based gene therapies

Name	Modalis Therapeutics Corporation (Ticker symbol: 4883)
Foundation	Jan 2016
President CEO	Haru Morita
HQs	3-11-5 Nihonbashi-Honcho, Nihonbashi-Lifescience-Bldg.2 7F Chuo-ku, Tokyo 103-0023 Japan
US subsidiary	Modalis Therapeutics Inc. (43 Foundry Avenue, Waltham, Massachusetts)
Business	Drug Development
Capital stock	1,441,083 thousand yen
Outstanding share	69,403,998 shares of common stock
Number of employee	16 (including 5 Ph.D.) (4 in Japan, 12 in US)

Date	History
Jan 2016	Founded in Tokyo as EdiGENE Corporation
Apr 2016	Established 100% owned US subsidiary EdiGENE Inc. (Now Modalis Therapeutics Inc.)
Aug 2019	Company name changed to Modalis Therapeutics
Apr 2020	Entered into a license agreement with **Editas Medicine**, Inc to obtain access to foundational CRISPR IP.
Aug 2020	Listing on Mothers, Tokyo Stock Exchange (Ticker symbol: 4883)
Oct 2021	Lab moved to To Waltham MA, which is adjacent to Cambridge
Apr 2022	Moved from the Mothers to the Growth market in accordance with the market reorganization classification of the Tokyo Stock Exchange.

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Modalis is a gene therapy company dedicated to translating evolutional science into life-changing treatments for rare disease patients.



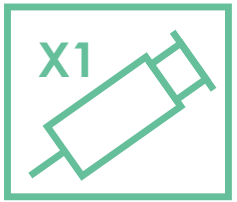
Every life deserves attention

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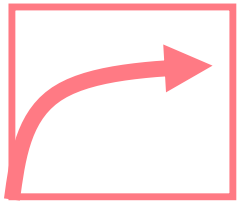
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CRISPR-GNDM® is a promising new therapeutic modality

Potential benefits of CRISPR-GNDM® Technology



Single dose
Doesn't require
Repeated dosing



Long-lasting
Sustained effect
for years or decades



Disease Modifying
Not just to reduces
symptoms but
gives cure

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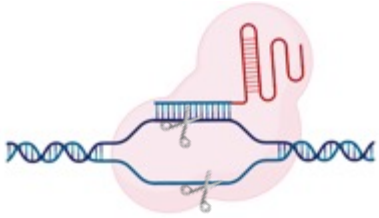
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Non-cleaving CRISPR = CRISPR-GNDM®

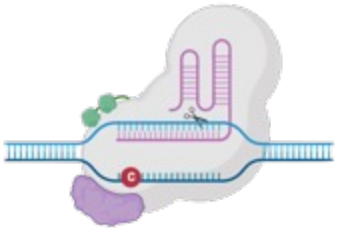
Enables treatment of genetic disorders by controlling epigenetic ON/OFF switch

GTx Technologies

Gene Editing | **Base/Prime Editing** | **siRNA / ASO**



Permanent Removal



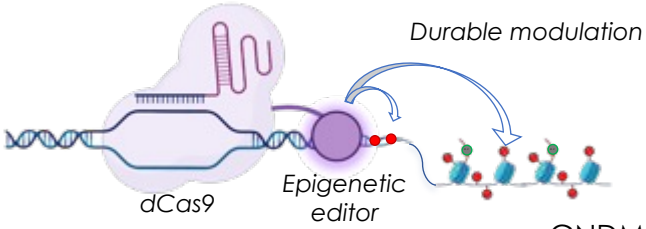
Permanent Replacement



Temporal silencing

Epigenome Editing(CRISPR-GNDM®)

Bind without cleaving
No DNA damage



GNDM=Guide Nucleotide Directed Modulation

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MODALIS Value Highlights

Established the first robust **epigenetic platform** for activation and inhibition of endogenous genes using CRISPR-GNDM® platform

Demonstrated sustained modulation of gene expression in multiple species (mouse, cyno) resulting in functional **efficacy without serious toxicities**

Pipeline of preclinical assets in **muscular dystrophies**, additional programs in CNS, cardiovascular and unlimited therapeutic potential in other areas

Manufacturing process established for challenging AAV capsids to enable tissue tropic delivery for lead programs

Experienced team with deep knowledge of platform

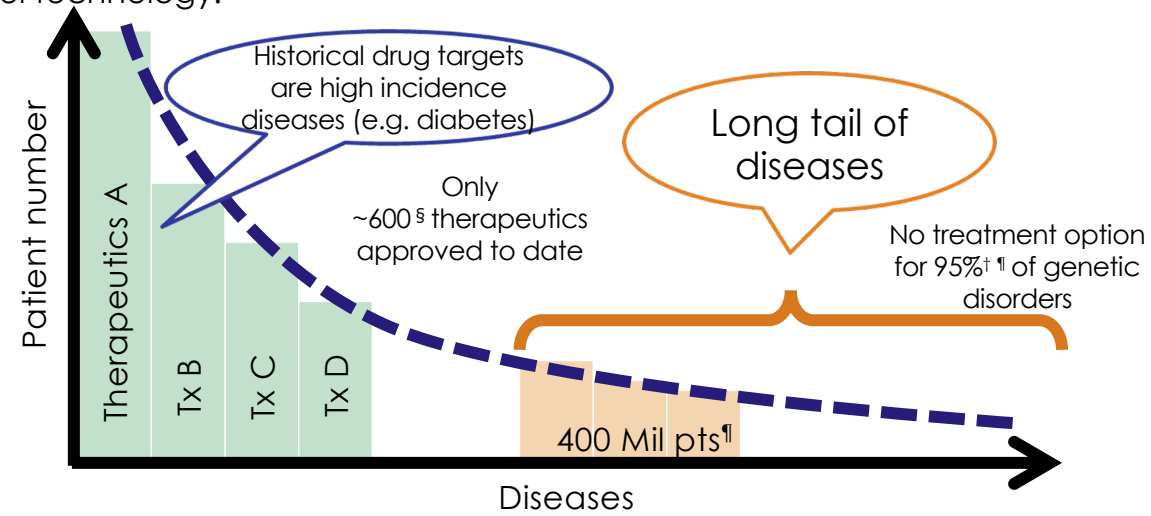
Strong **IP portfolio and strategy** that includes granted patents

Clear regulatory and clinical path in place based on recent FDA guidance

Providing a solution for the long tail of disease

Using technology to solve the problem of low productivity in the development of treatments for rare diseases

It is believed that of10,000* human diseases, about 7,000#are rare diseases which consist of "long tail" diseases. Of these, 80%† overlap with genetic disorders and 95% remain untreated. The company is committed to identifying cures with our powerful novel technology.



Scalable efficient approach is required to tackle the divided population

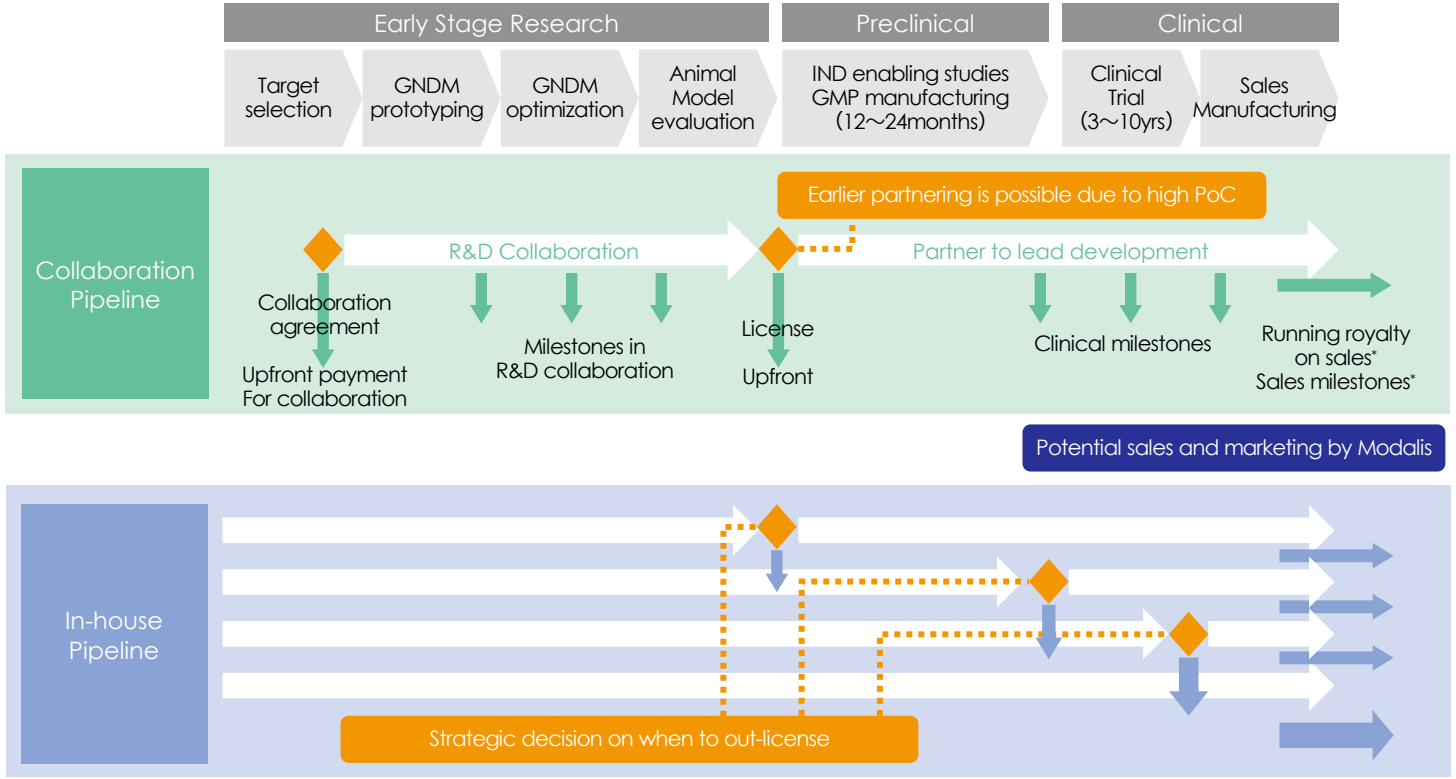
reference: *21st Century Cure Act, #NIH GARD †innovation.org ¶GlobalGenes.org
§Active therapeutics of 491 NME, 106 BLA, 17 cellular and gene therapy products @FDA as of 2019.7.22 Source from KEGG

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Business Model

Hybrid of own pipeline and collaboration pipeline

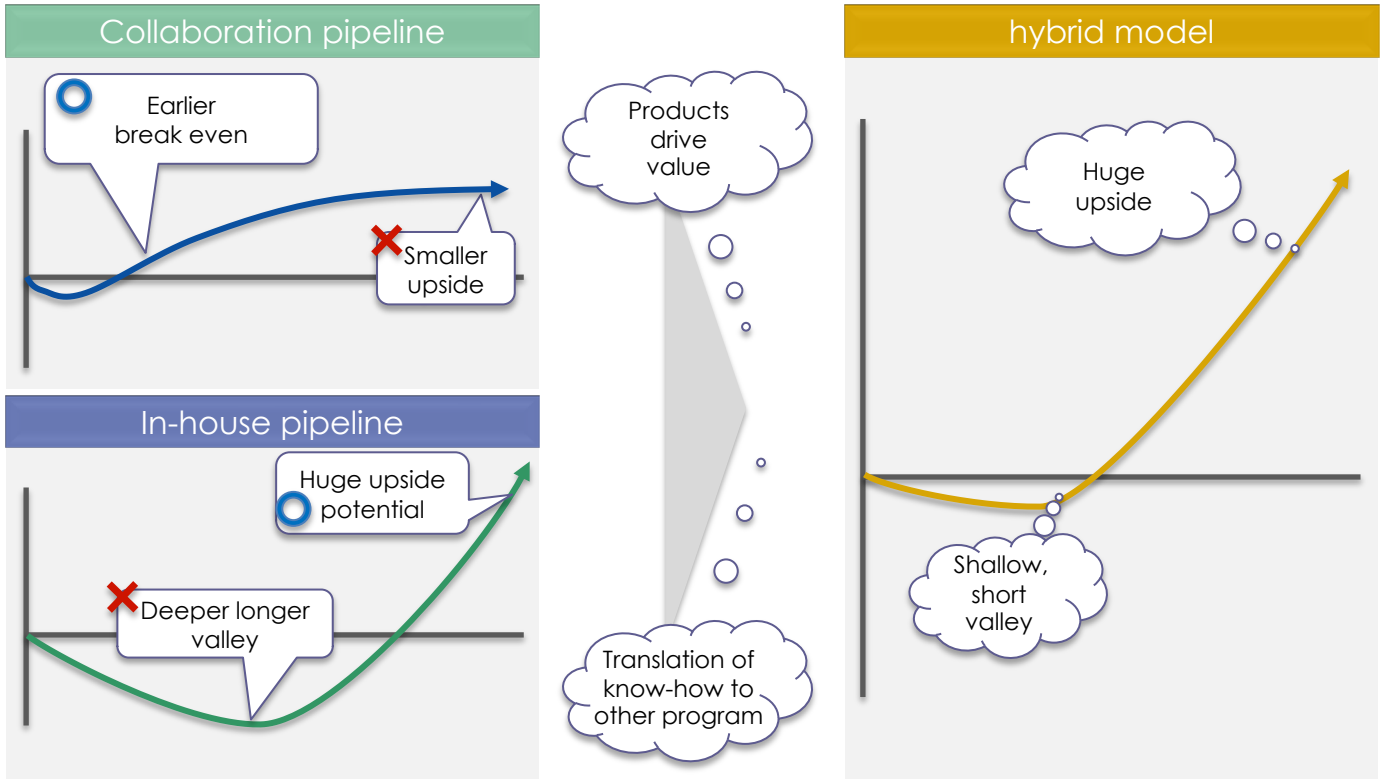


* future plan

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Modalis is pursuing a hybrid model

Combination of upside from in-house pipelines and earlier cash stream from collaboration pipelines

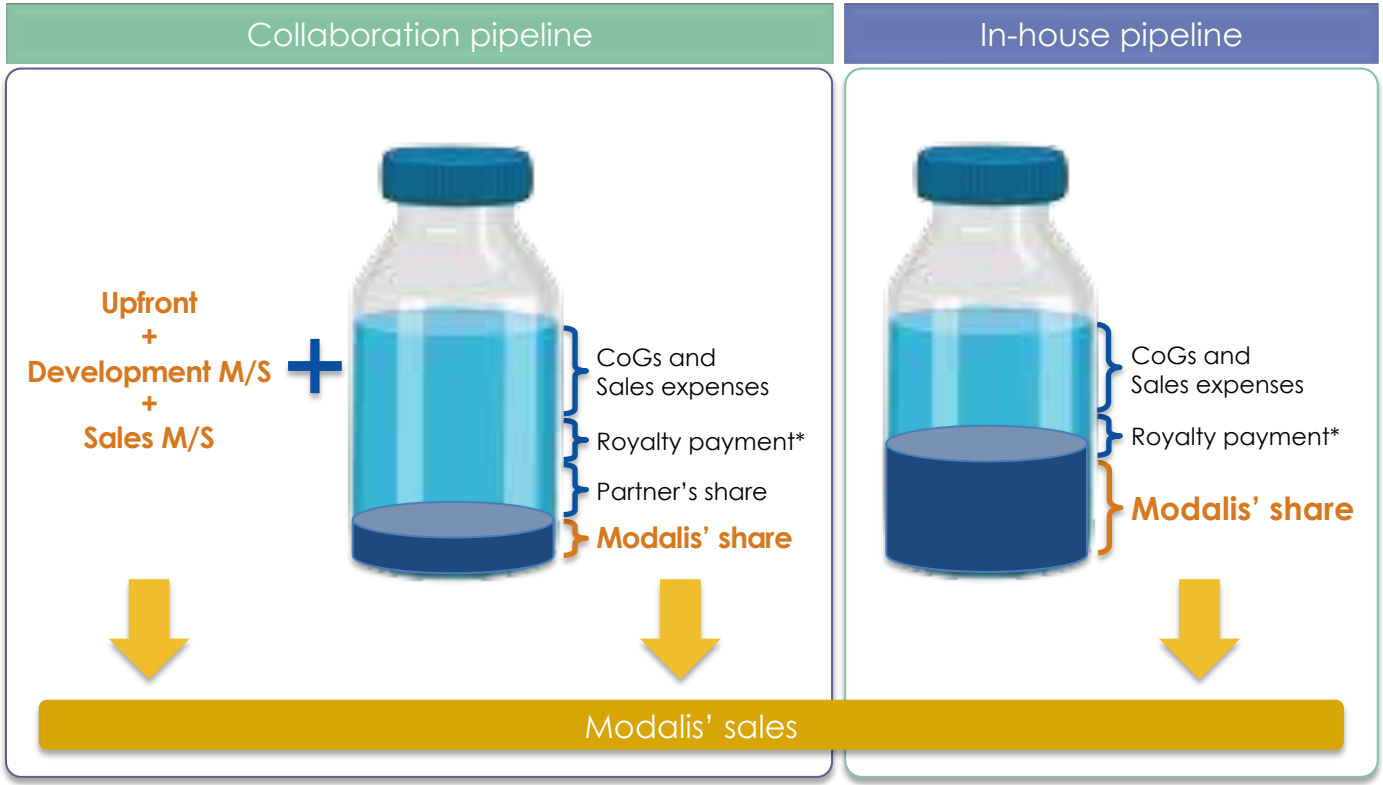


* The above is only an image and does not suggest or guarantee our future performance.

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Risk - profit share model

While collaboration model brings earlier cash, In-house pipeline has higher profit with higher risks

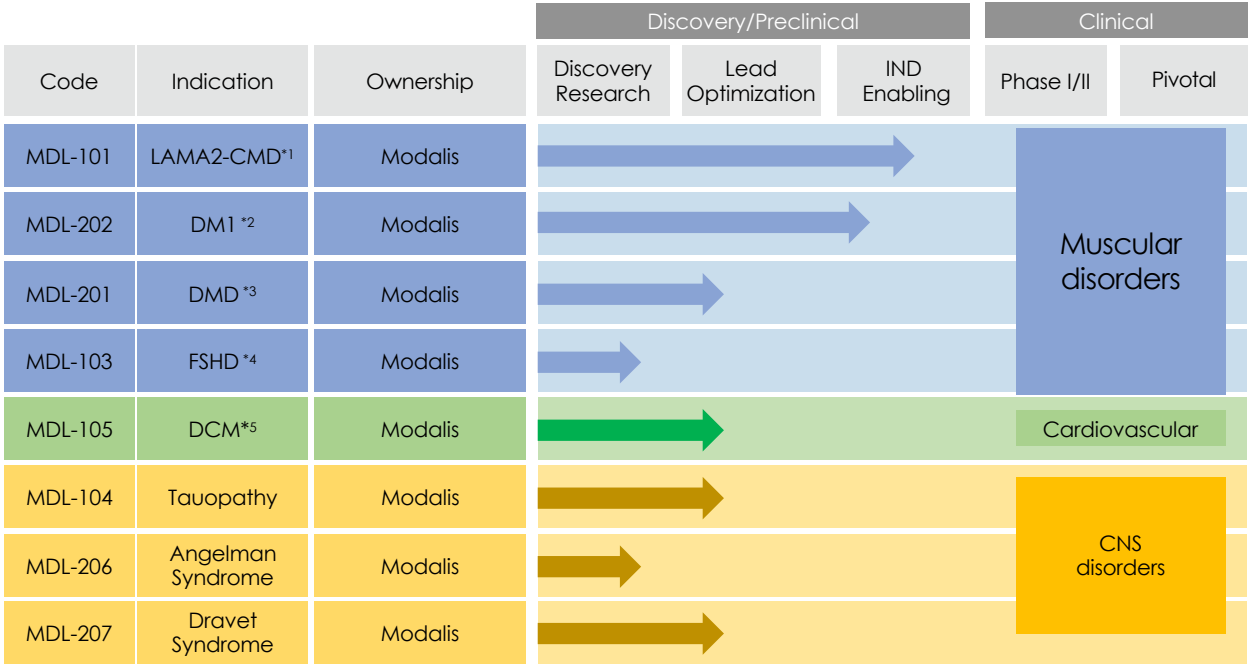


* : As a consideration for the licensed in intellectual property, a certain percentage of sales after market launch is paid to the intellectual property holding organization.

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Set the muscular disease-centered strategy

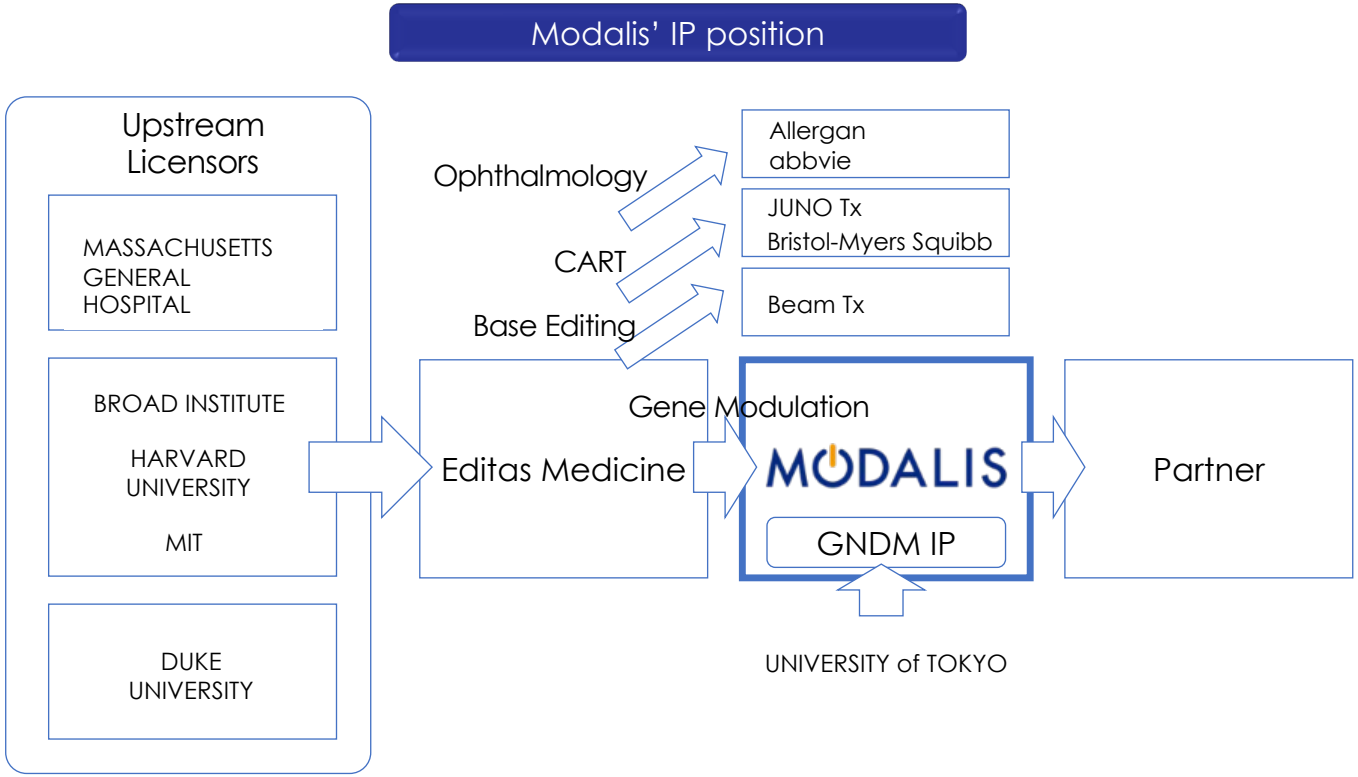


*1: LAMA2-related congenital muscular dystrophy
*2: Myotonic Dystrophy Type 1
*3: Duchene Muscular Dystrophy
*4: facioscapulohumeral muscular dystrophy
*5: Dilated Cardiomyopathy

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Intellectual Property position

Established IP with foundational CIRPSR IP from Broad and engineered Cas9 from Univ of Tokyo



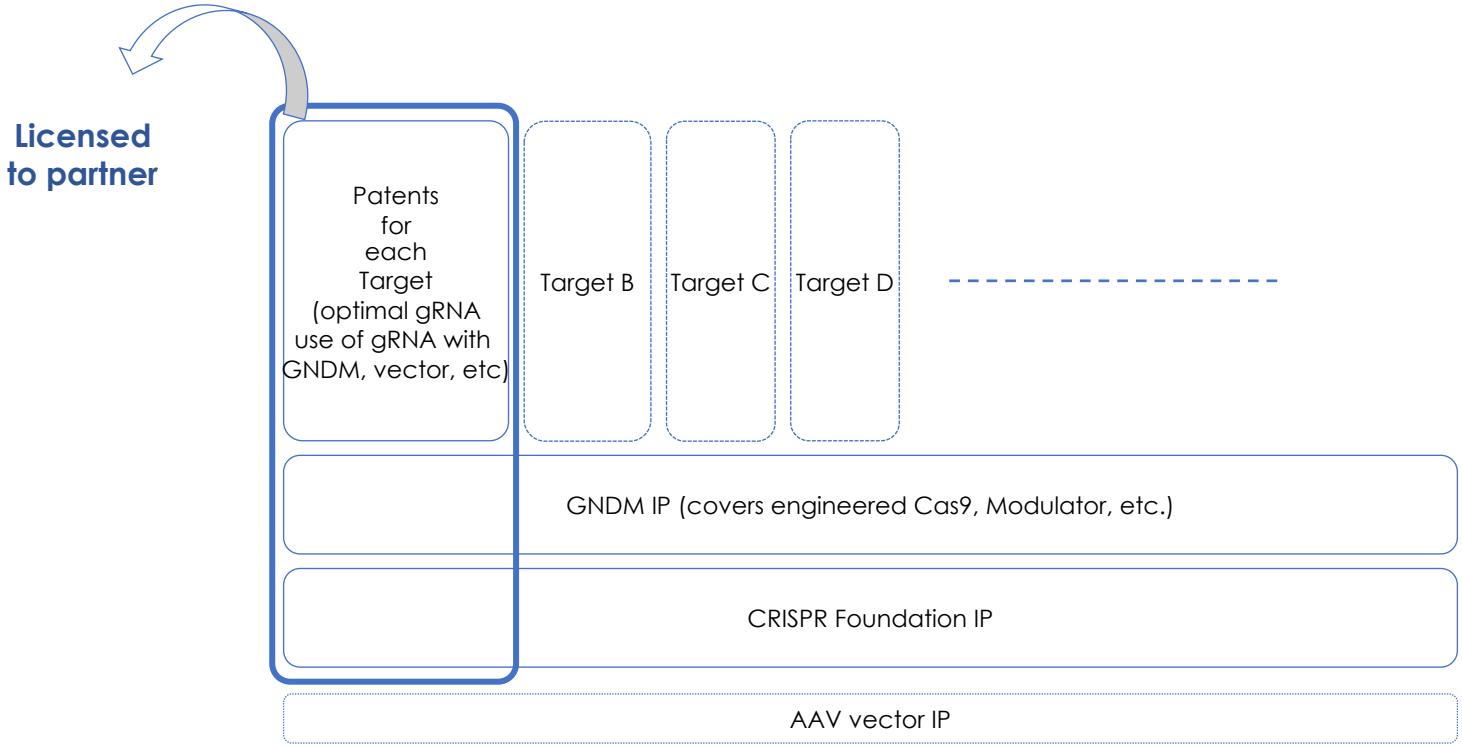
Source： disclosed information by each company

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Intellectual Property Structure

Each product will be protected by multiple layers of IP



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Management Team and Board of Directors

Seasoned team

Executive Officers

Haru Morita Co-founder, President, CEO, and Chair of the board
- REGiMMUNE, Founder, President and CEO
- Y's Therapeutics, Booz Allen and Company, Kyowa-KIRIN

Tetsuya Yamagata MD PhD: Chief Technology Officer
- Glaxo Smith Kline, Tempero Pharmaceuticals, Joslin Diabetes Center, Harvard Medical School

Yosuke Nakashima MBA: VP Operations and Business Development
- Sumitomo Chemical

Board of Directors

Haru Morita Co-founder, President, CEO, and Chair of the board

Hideki Takeda Board member
- President, Medical Patent Research
- Healios KK former president, Fujisawa (merged into Astellas)

Joseph S. McCracken DVM Board member
- Roche Head of Global license, Genentech, Sanofi

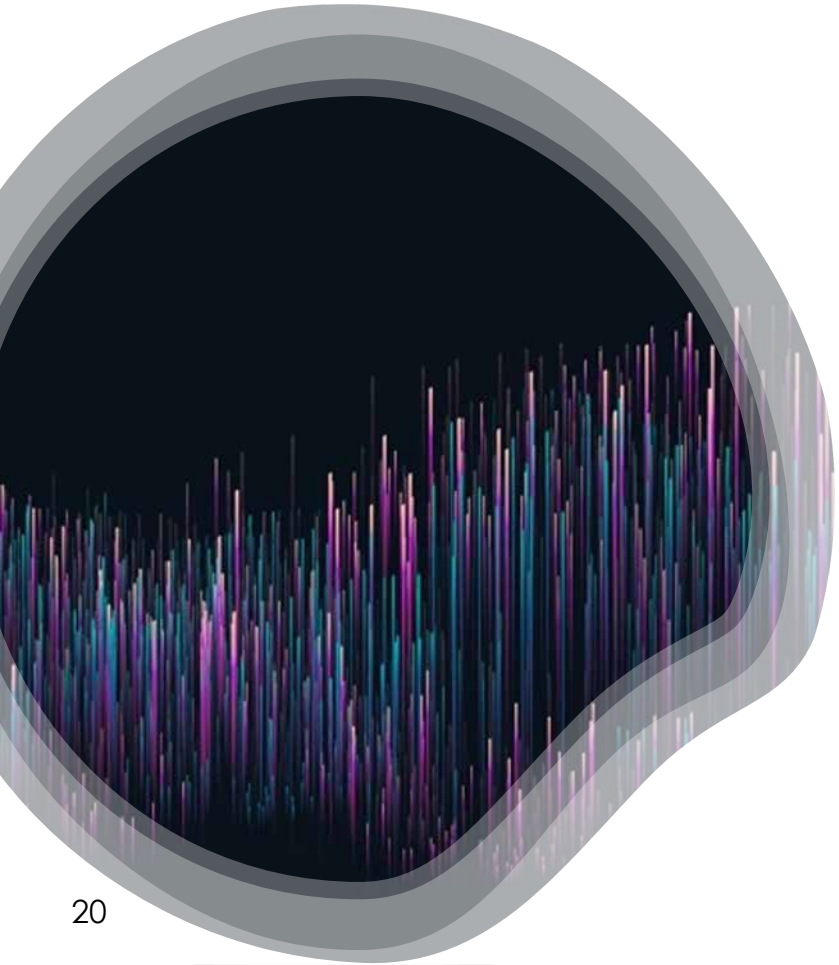
Miyuki Shimane Board member, Audit committee
- Chugai Pharma

Teruhisa Tajima Board member, Audit committee, CPA
- President Tajima CPA office
- Corporate Auditor (Quantum Biosystems, OncoTherapy, Prism Bioscience)

Toshio Furuta Board member, Audit committee, Attorney at Law
- Representing attorney, Clair Law Firm
- Corporate Auditor (NetYear Group, Canbas, Zenrin DataCom)



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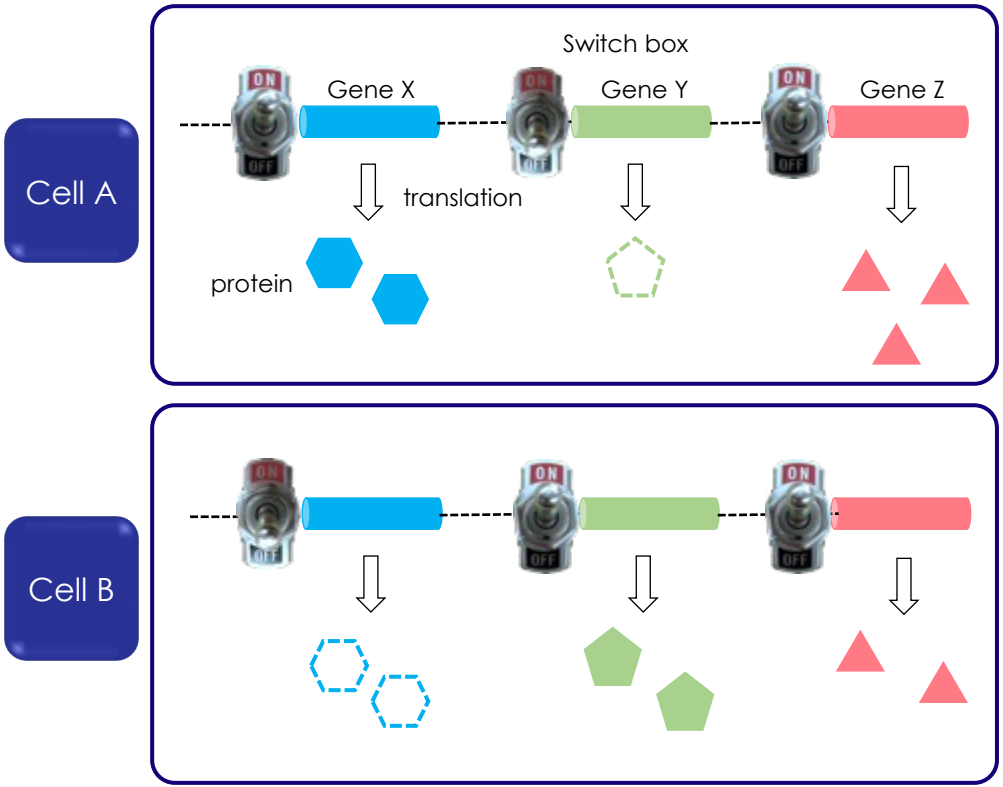


2． Gene Therapy and Gene Editing

20

How multiple cell types are created from the same DNA code

Each of 20,000 genes have ON/OFF switches that control cell type specific expression



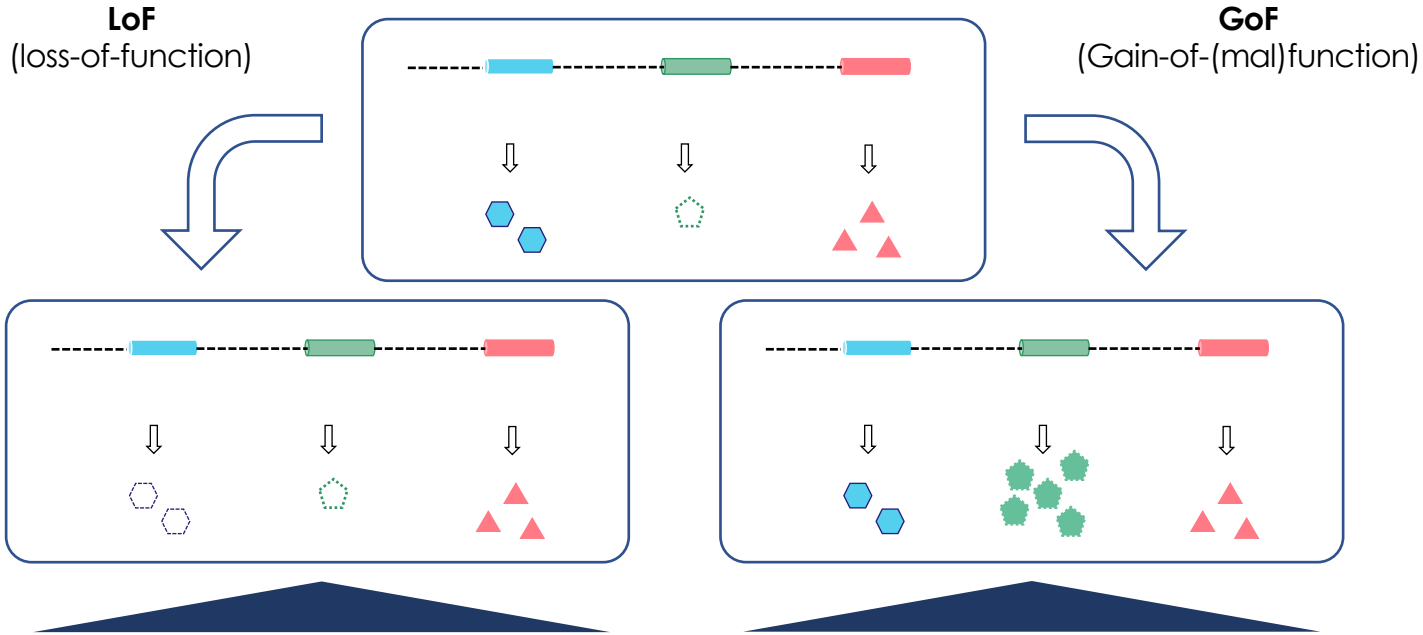
- There are **37.2 Trillion cells** in our body
- **200 cell types** in our body have the same DNA code despite differences in appearance and function
- Differences in cell types and their states are controlled by ON / OFF switches of the expression of **20,000 genes** coded by **3 billion bases of DNA**

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Genetic Disorders are caused by loss-of-function or gain-of-function

To address the issues, GTx supplement missing functions or silence the malfunction

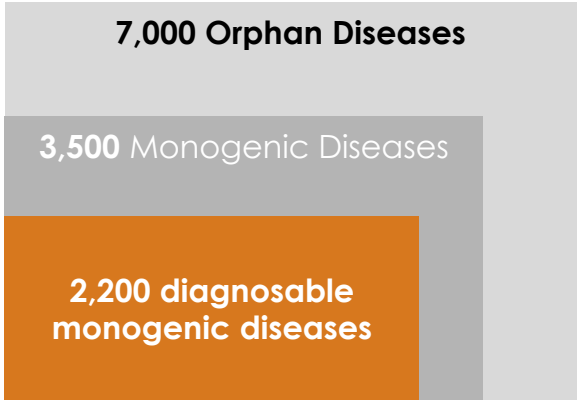


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Untapped opportunities in monogenic disorders

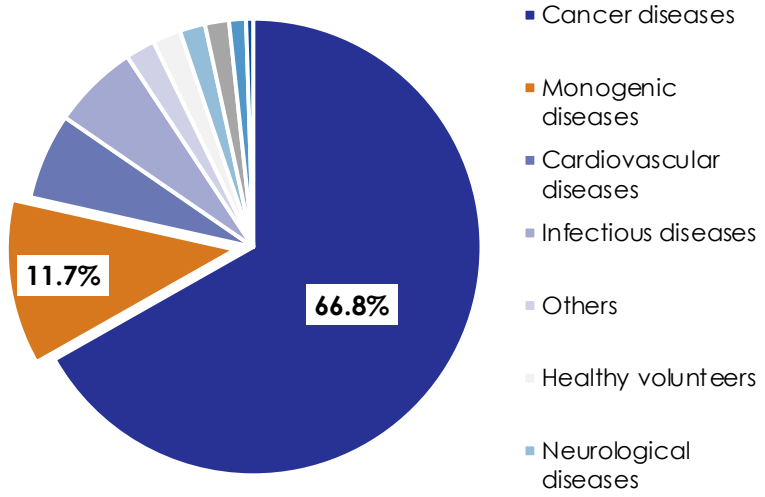
Only limited number of drugs are approved or in clinical development for monogenic disorders

Monogenic Disease



Source: Discovery Medicine

Breakdown of GTx clinical trials (1989~ Worldwide)

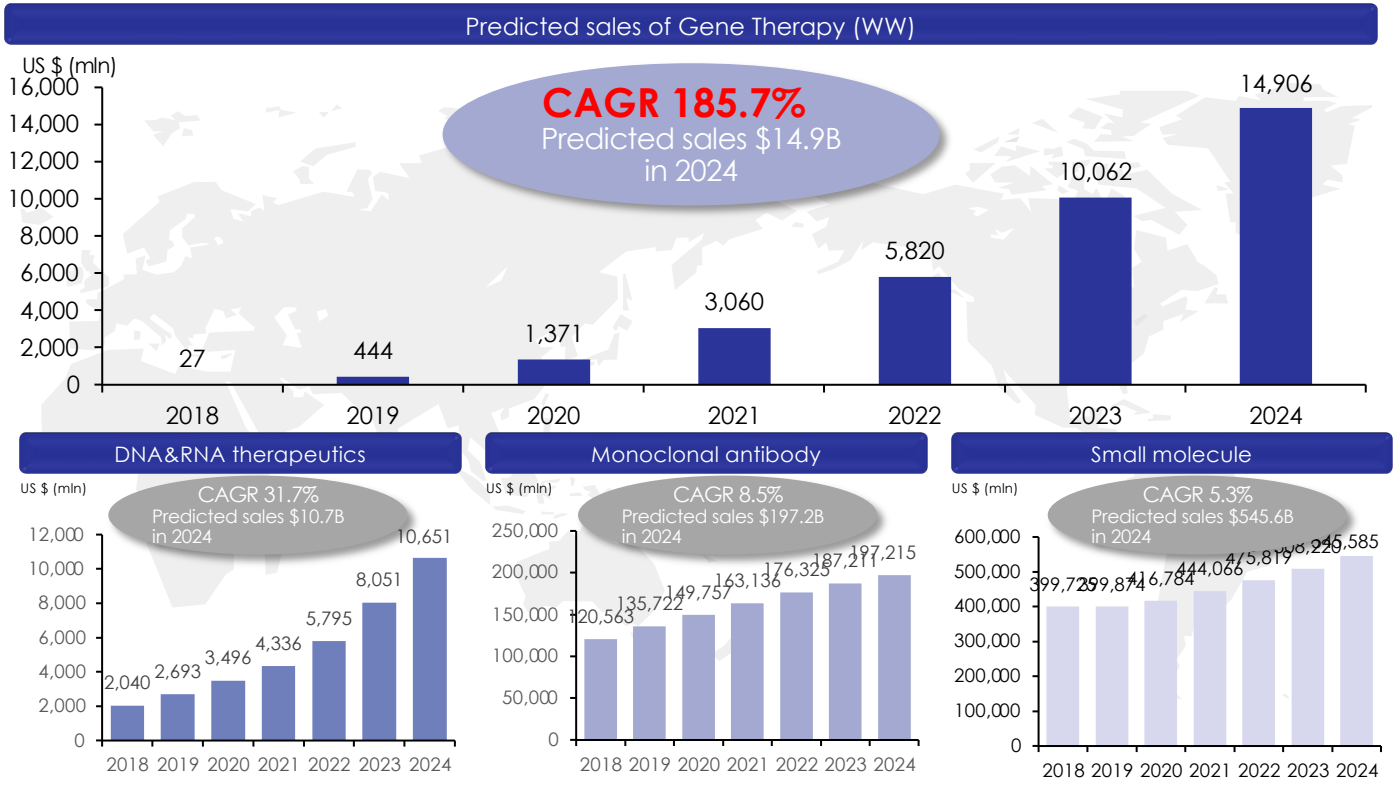


Source: The Journal of Gene Medicine (2019)

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Sales growth of pharmaceutical modalities

GTx is growing faster than other modalities



Source : Evaluate Ltd (in Aug 2019 data) *CAGR=2018 to 2024. 2019 to 2024 are predicted sales

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Updated

With the full approval of ELEVIDYS, 3 GTx have been approved in 2024

Based on recent successes, gene therapy is expanding its target from local to systemic administration

Gene therapies approved by US FDA

Trade Name	Year of Approval	cost	Indication	Manufacturer	Patient Population	WW market size* (mil USD)
Lxturna	2017	$850k	RPE65	Spark/Roche	2 per 100,000	$65M[#3]
Zolgensma	2018	$2.1M	SMA	Novartis (Avexis)	1 in 10,000 live births (Approx. 10,000 to 25,000 in US)	$1.3B[#3]
HEMGENIX	2022	$3.5M	Hemophilia B	uniQure CSL Behring	1 in 30,000 male	$88M[#3]
Vyjuvek	2023	$631k per patient year	DEB[*2]	Krystal	3.5–20.4 in 1 million	~$200M[#2]
ELEVIDYS		$3.2M	DMD	Sarepta	1 in 3,500 male birth	$4.1B[#4]
Roctavian		$2.9M	Hemophilia A	BioMarin	1 in 5,000 male	$262M[#4]
Casgevy		$2.2M	SCD	CRISPR Tx/Vertex	100,000 in America	>$2B[#5]
LYFGENIA		$3.1M		Bluebird		
Lenmeldy	2024	$4.25M	Metachromatic Leukodystrophy	Orchard/KyowaKirin	1 in 100,000 live birth	?
beqvez		$3.5M	Hemophilia B	pfizer	1 in 30,000 male	$88M[#3]
ELEVIDYS		$3.2M	DMD	Sarepta	1 in 3,500 male birth	$4.1B[#4]

Source: National Organization for Rare Disorder、#2 Fierce Biotech #3 Corporate website #4Grand view research #5 Fortune Business Insight

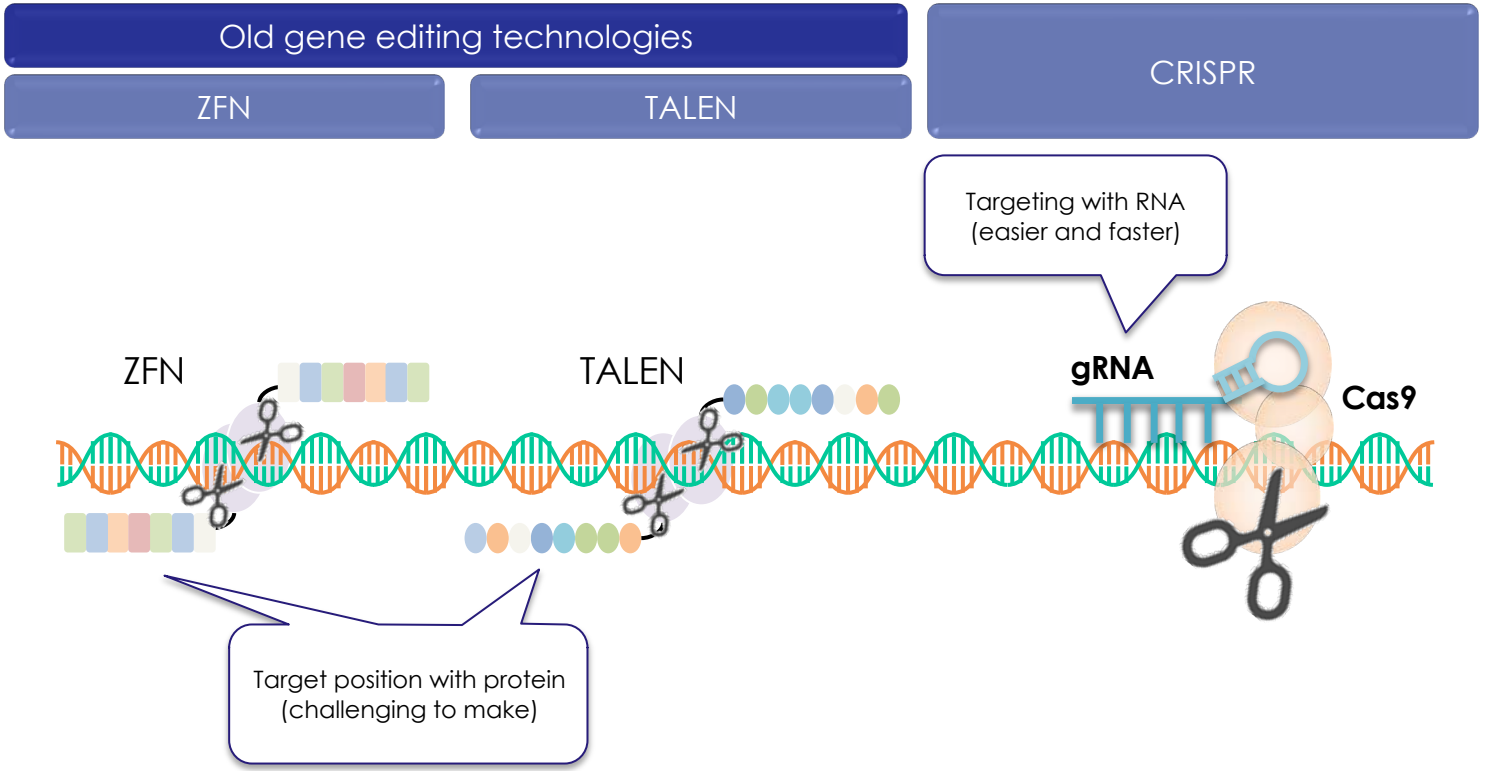
*1: Spinal muscular atrophy *2: dystrophic epidermolysis bullosa *3: Duchenne muscular dystrophy

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CRISPR is a novel gene editing technology

Faster and higher throughput due to limited variable region which is easily synthesizable as gRNA



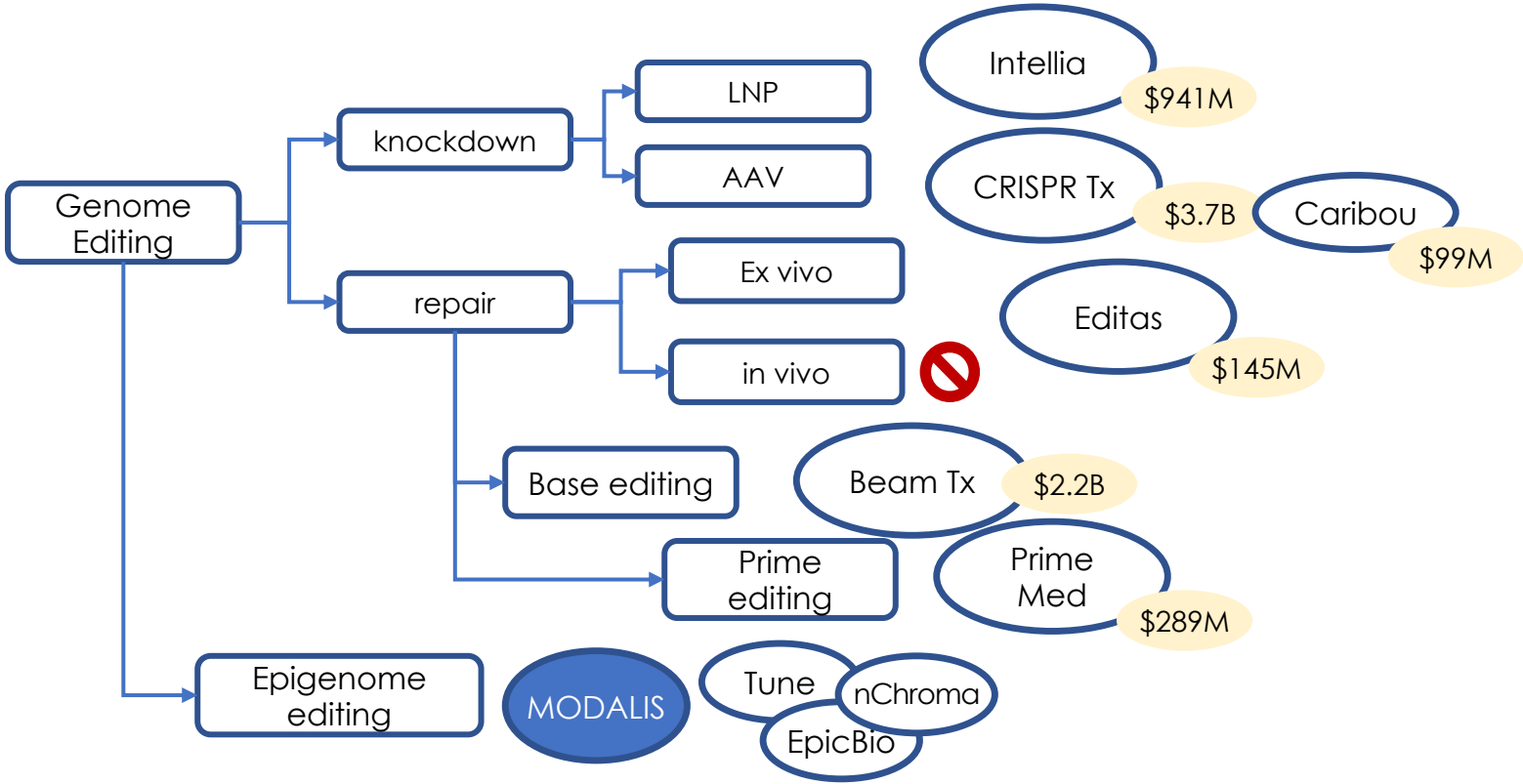
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New

Genealogy of CRISPR based Technology and major players

The whole CRISPR area has been expanding, but there are also areas that have become dead ends.



Note: The yellow circle shows the market capitalization as of the closing price on March 4, 2025.

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3. CRISPR-GNDM® and its advantages

Gene Modulation is CRISPR 2.0



"I think one interesting possibility is that we'll see CRISPR being used not to edit genomes, or at least not to make permanent changes to genomes, but **instead to regulate them, to control levels of human proteins that are produced from different genes.** This is a newer way of using the CRISPR technology. I think it has a lot of potential to allow control of cells that doesn't require actual permanent chemical changes being made to the DNA."

-Jennifer Doudna, Nobel Prize Winner on CRISPR
Source: "Fresh Off Her Nobel Prize Win, Jennifer Doudna Predicts What's Next for CRISPR"

CRISPR-GNDM®

*Source: Interview on Future Human "Fresh Off Her Nobel Prize Win, Jennifer Doudna Predicts What's Next for CRISPR"

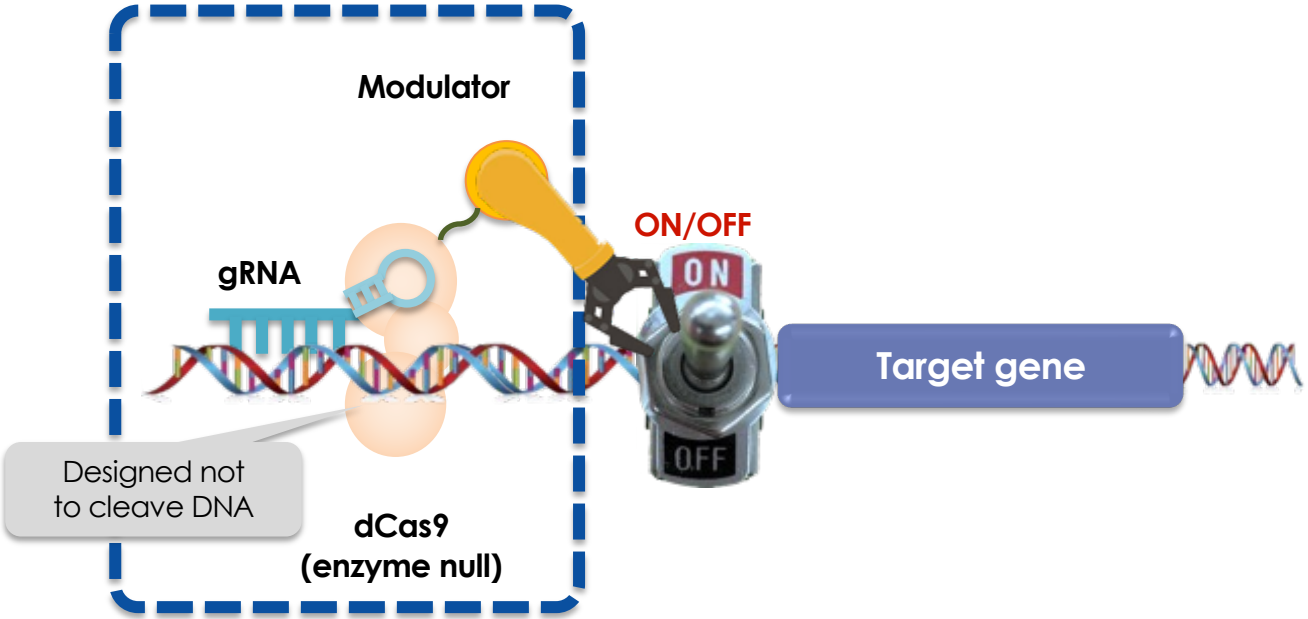
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Non-cleaving CRISPR = CRISPR-GNDM®

Enables treatment of genetic disorders by controlling ON/OFF switch

CRISPR-GNDM® (Guide Nucleotide-Directed Modulation) platform

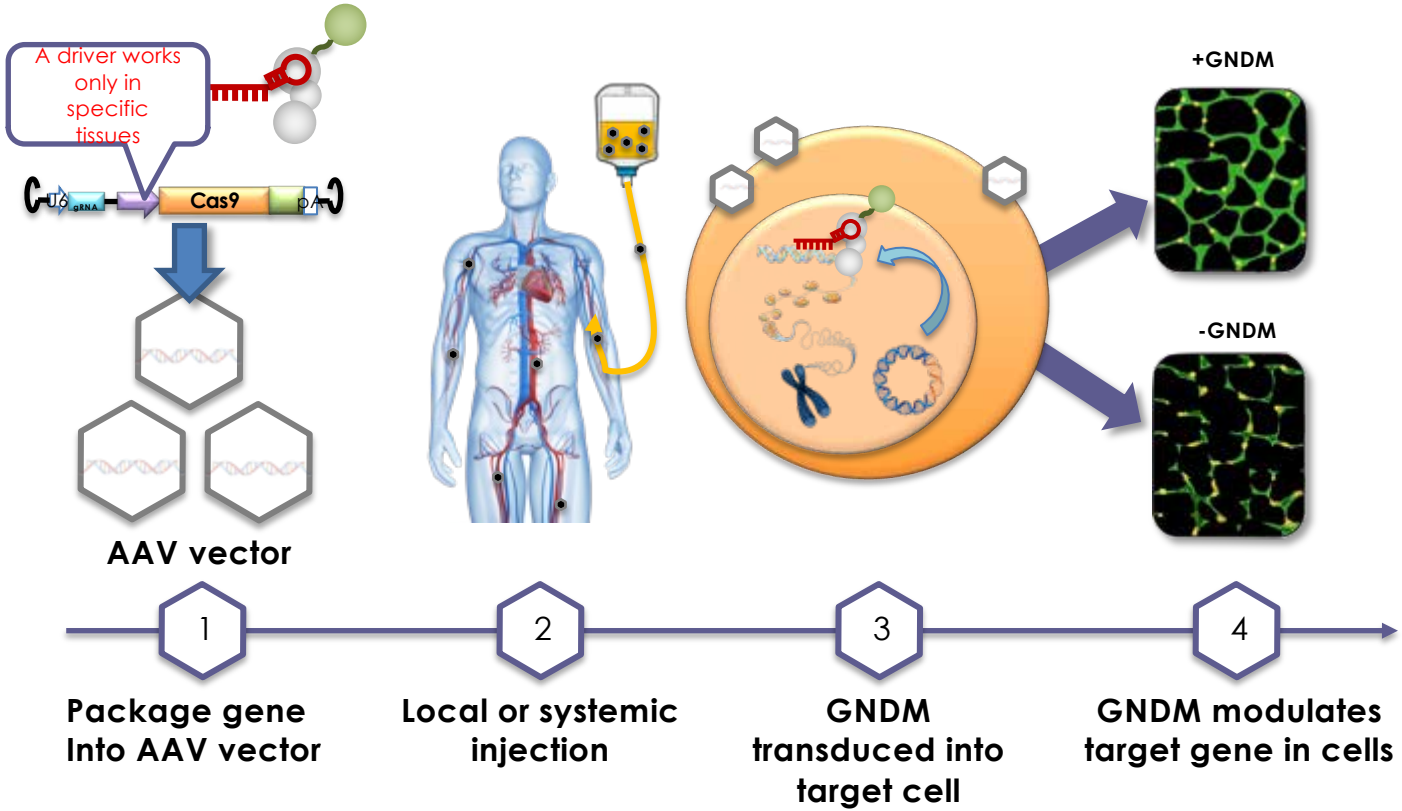


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Delivery of CRISPR-GNDM® to target

Use AAV vector to deliver GNDM to target cell

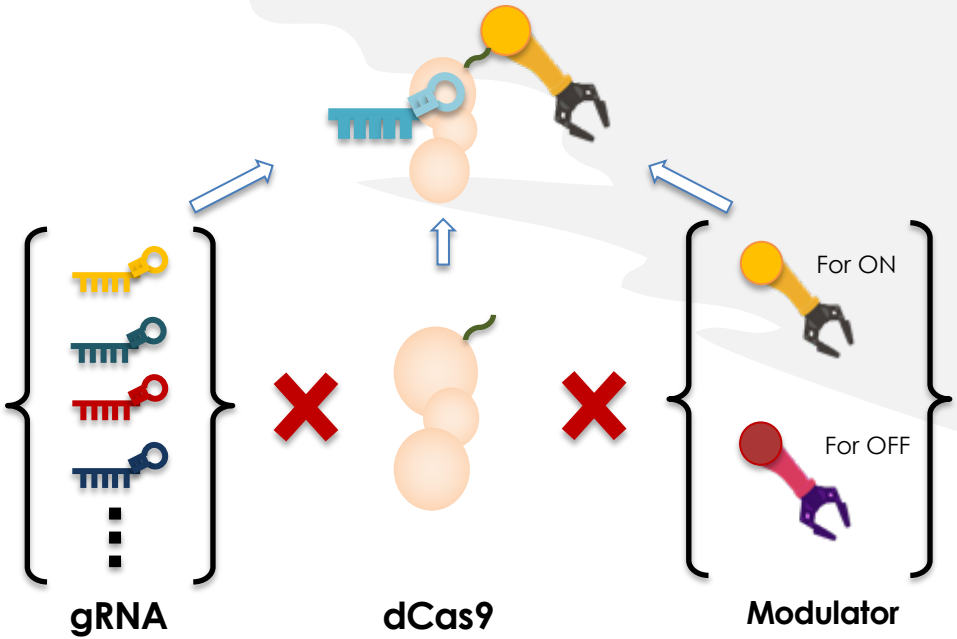


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GNDM is scalable

gRNA is the only variable which is unique for each target. Other components are off-the-shelf to assemble.



Precision technologies are not *one-thing-fits-all*

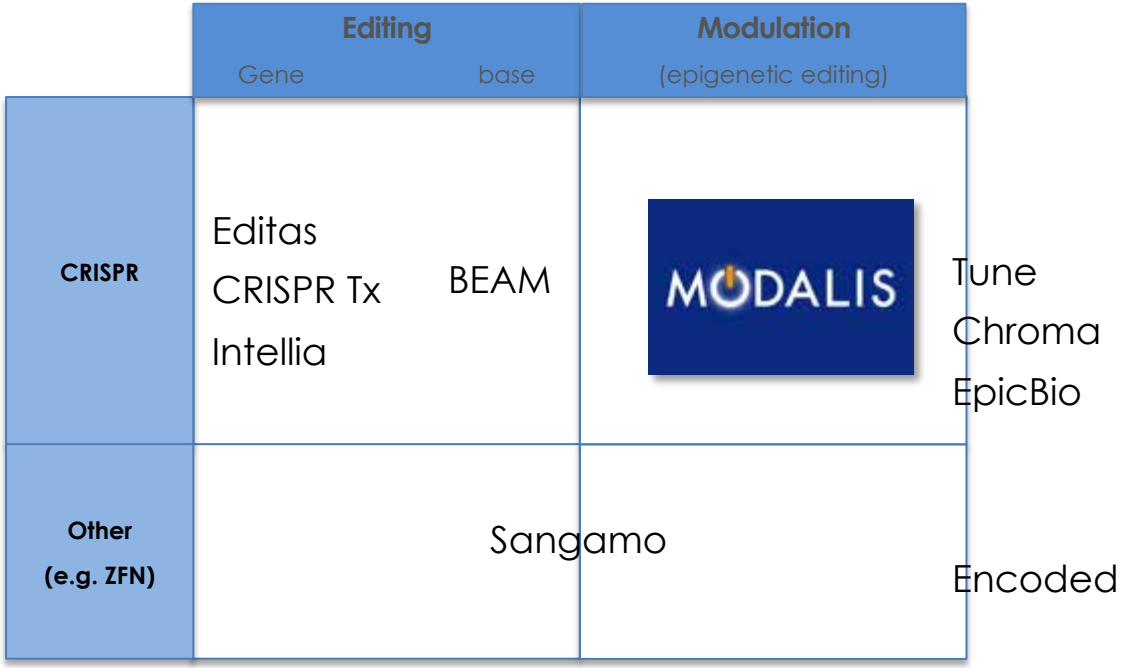
there are many disorders that GNDM has the advantage over the other technologies



	Conventional Gene therapy	Gene Editing	ASO siRNA	CRISPR-GNDM
Precise targeting	Yes	Yes	Delivered to off-target tissues	Yes
Durability	Years	Permanent	Require repeated injection	Years
Applications	LoF ONLY	Mostly GoF	GoF only	**LoF and GoF**
Target gene limitation	Limited to small size genes	Limited to a specific point of mutation	Causative tissue is limited (e.g. liver)	**Size agnostic**
effect on DNA	none	Causing double-strand break	none	none

LOF=Loss of function, GOF=gain of function

Modalis is uniquely positioned within the CRISPR field



Updated

Epigenome editing competitive landscape

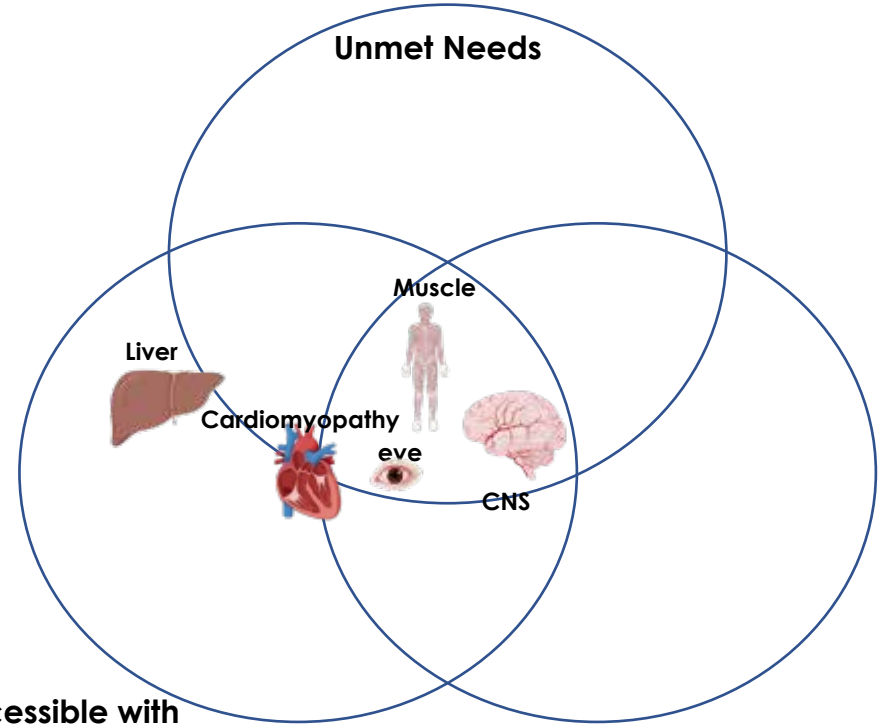
There was movement in the year-end to new year, and the survival of the fittest became clear

Company	Year Founded	Funding	Platform	Pipeline/Target indication	Stage of Development
MODALIS	2016	Public	CRISPR-GNDM x AAV	• MDL-101/LAMA2-CMD • MDL-201/DMD **Gene activation**	PreIND completed IND enabling
Tune Therapeutics	2020	**Series B ($175M, 2025)**	DNMT-KRAB fusion dCas9 x LNP	Une-401 for HBV **Gene suppression**	**CTA approval from NZ on HBV**
Chroma Medicine	2021	**Merged into nChroma (Dec 2024)**	DNMT-KRAB fusion dCas9 x LNP	CRMA-1001 for PCSK9 **Gene suppression**	**Unclear**
Epic Bio	2022	Series A ($55M Jul 2022)	Cas12f-fused with demethylation enzyme x AAVrh74	EPI-321/FSHD **Gene suppression**	IND enabling

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Muscle and CNS are the areas with huge unmet medical needs

Target selection for Modalis' gene therapies

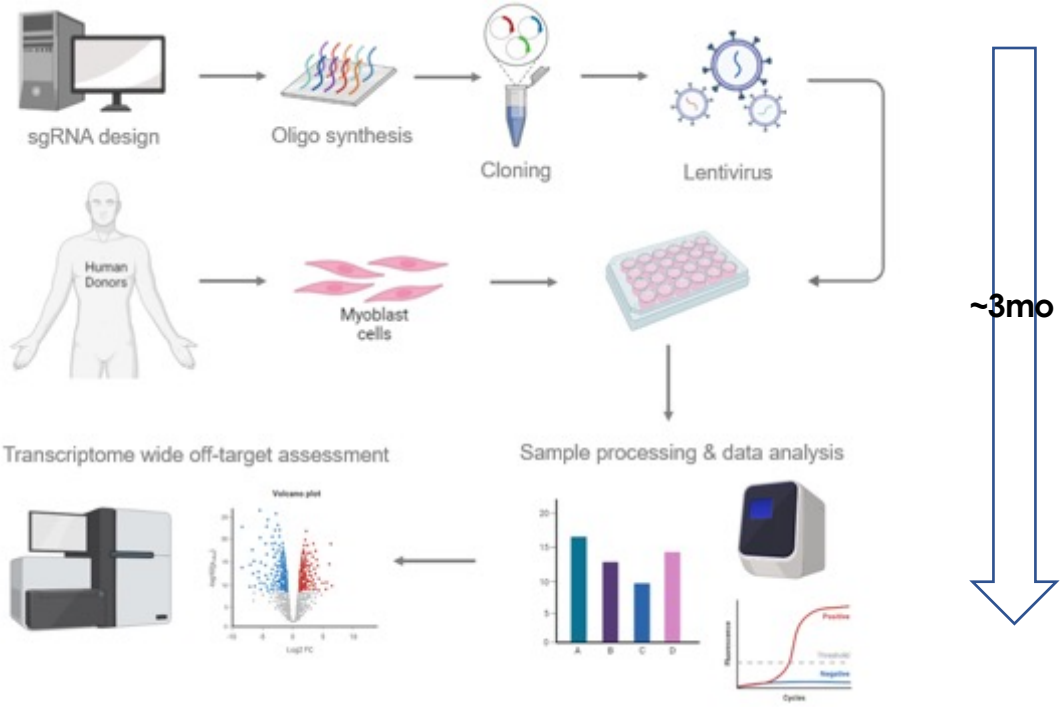




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CRISPR-GNDM® platform efficiently identifies optimal gRNA

Lead candidate screening in human primary myoblast cells

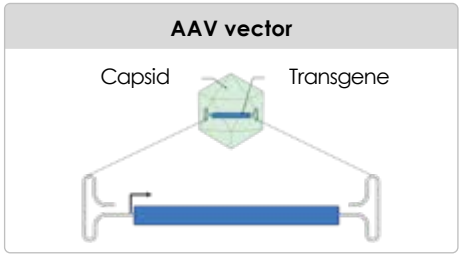


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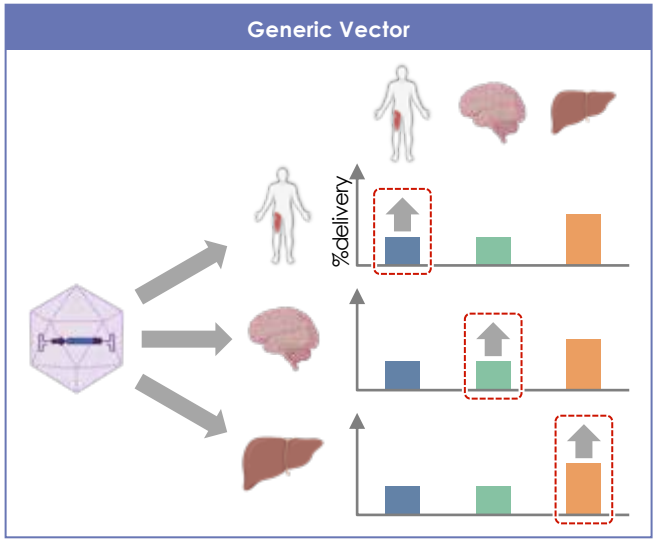
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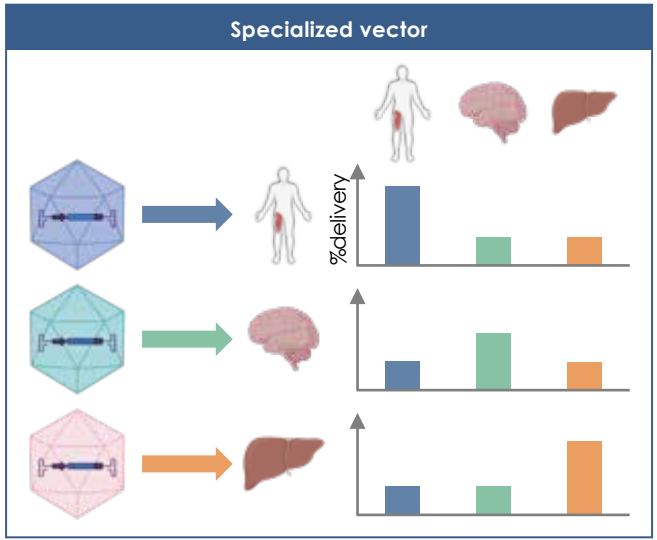
A big innovation has been brought to GTx field

By moving from generic capsids to selective capsids, payloads can be selectively delivered to target tissues



- Previously, generic vectors such as AAV2, 6, 8, and 9 were universally used for all target diseases
- Those capsids are predominantly sequestered in the liver after systemic injection, and cause hepatotoxicity which limits dose of AAVs.
- Recently developed engineered vectors have a much higher tropism to each target organ



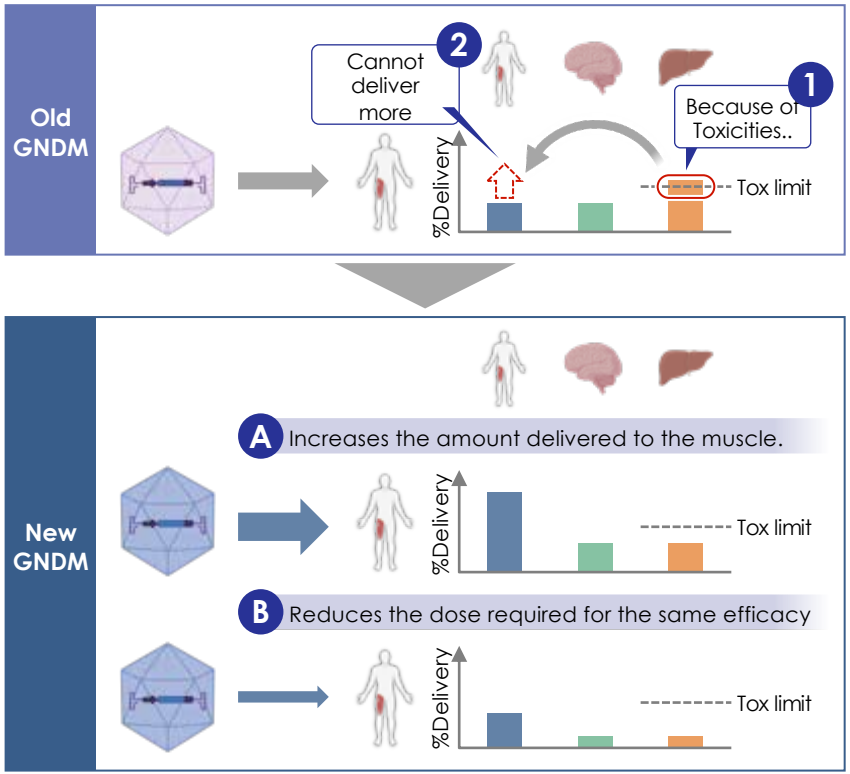


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Transition to specialized capsids is the need of the field

Selective capsids deliver more to target organs while delivering less to off-targets, lowering toxicity issues

In musclular disorders like MDL-101



- Does of generic capsids were limited by the off-target toxicity of capsid itself, such as hepatotoxicity and thrombosis

- By shifting to specialized capsids, the transduction efficiency to the target organ can be increased, which can

- **A** increase the amount delivered to the target organ without reaching toxic levels in other organs, or
- **B** reduce the dose required to achieve the same efficacy.

- As a result, there will be benefits in terms of costs, etc.

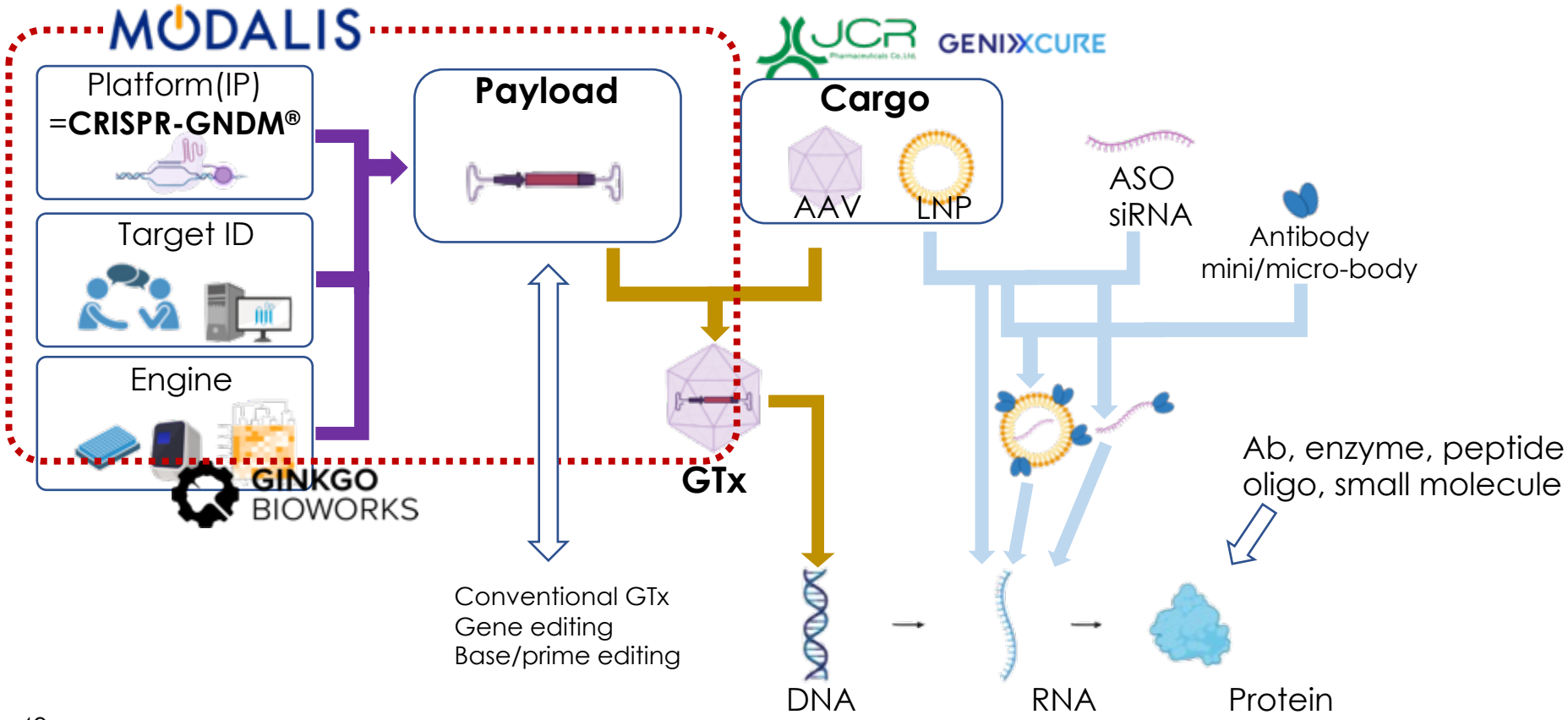
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New

MODALIS' core competence and collaboration

In the increasingly complex games, the necessary capabilities are accessed through partnership.



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New

Essentials of Technology Strategy

- Focus on mechanisms that can only be achieved through epigenome editing
  - Prioritize gene activation over silencing, which competes with other modalities
- Focus on disease groups that can make use of the characteristics of gene therapy
  - Aim to solve severe diseases that are life-threatening
- Target diseases that originate in organs for which delivery has been established or is expected to be established in the future
  - Focus on development of muscle and central nervous system diseases

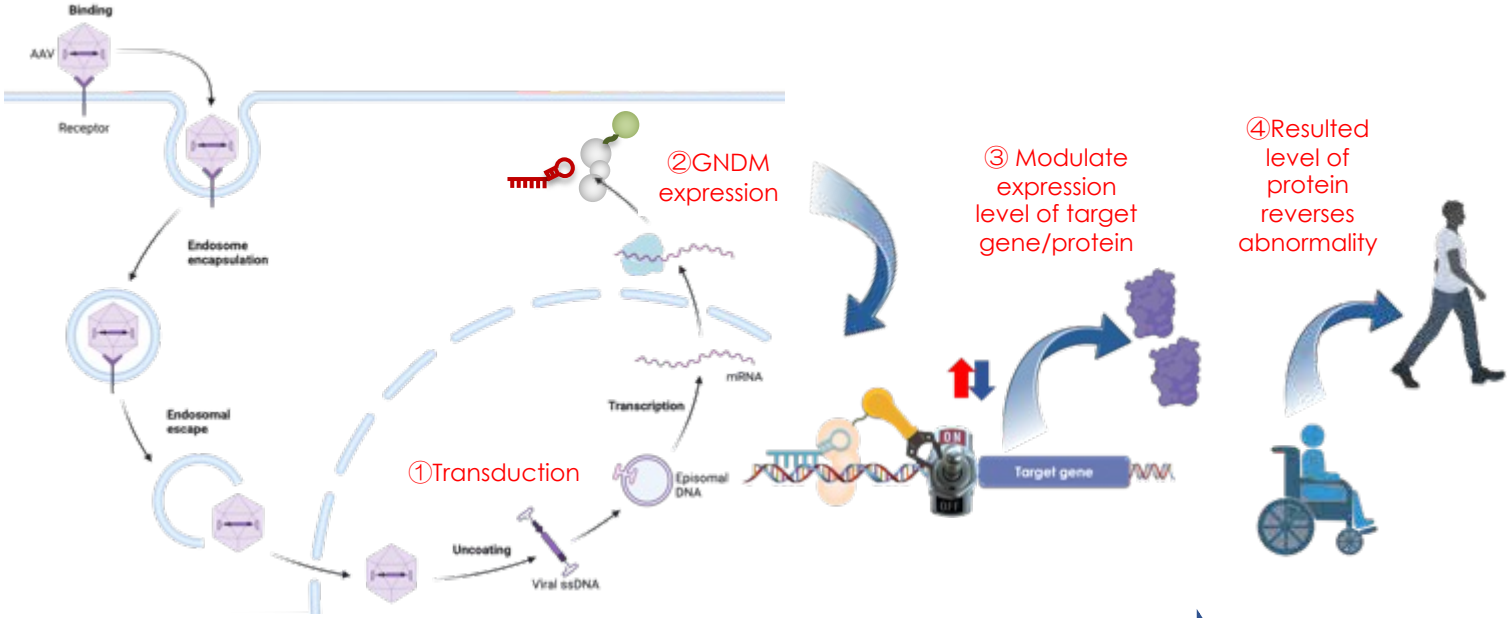
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4. Pipeline

There are 3 steps for GNDM before providing efficacy

The GNDM is transduced, expressed and engages to the target to show efficacy



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All muscle programs share the same platform as MDL-101

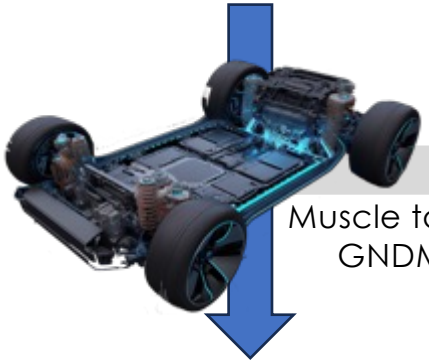
Other muscle programs can be achieved with relatively lower risk and effort











Muscle targeting AAV
GNDM platform



MD-101



MDL-202



MDL-201



MDL-103

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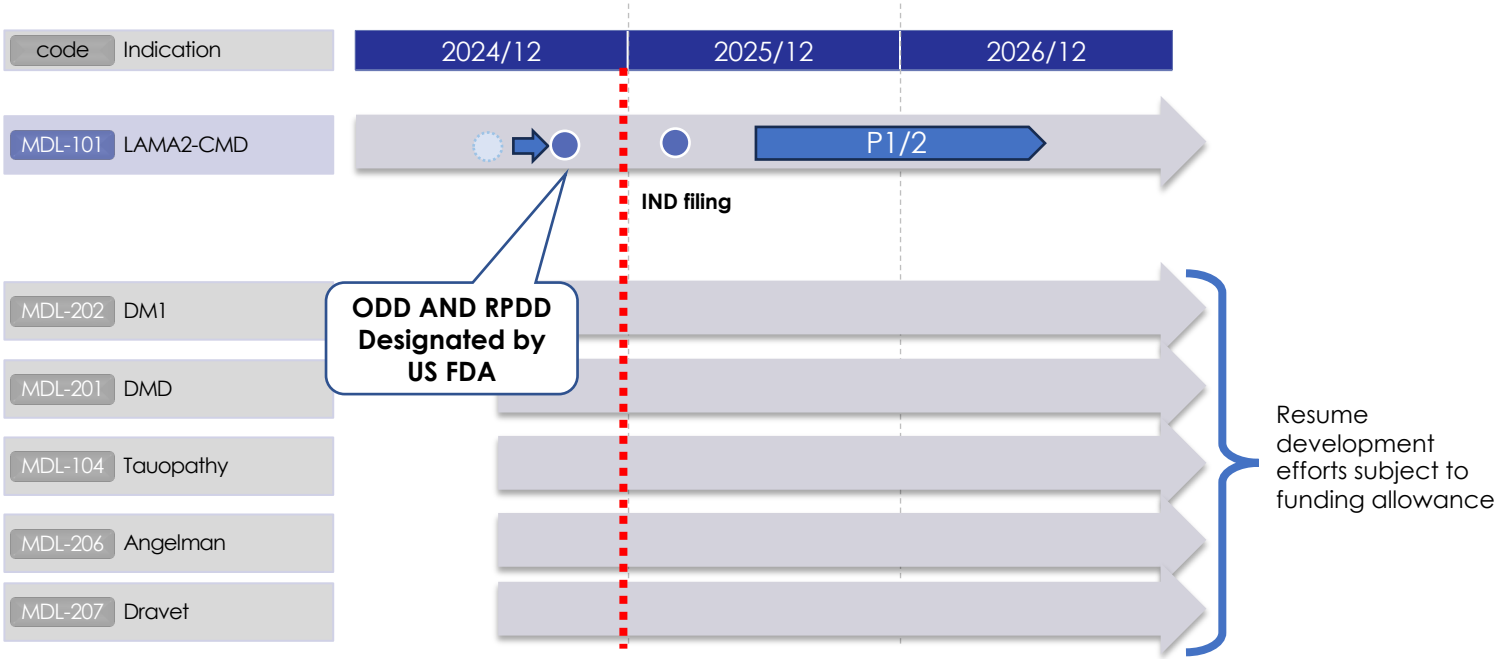
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Updated

ODD and RPDD received

Development continues with the aim of entering clinical trials for MDL-101 in 2025.

Pipeline status



- Scheduled milestone events are informational in the future and subject to change

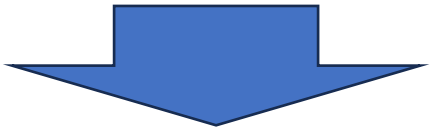
#: ODD: Orphan Disease designation, RPDD: Rare Pediatric disease designation

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Advantages of ODD and RPDD are…

- **Orphan Drug Designation**
  - Tax deduction for clinical trial expenses
  - Exemption from application fees, etc.
  - Exclusive status for 7 years after market launch

- **Rare Pediatric Disease Designation and Priority Review Voucher Programs**
  - Granting priority review voucher after application for approval (The voucher program will end soon)



Reviewed by the rarity and medical relevance of the target disease, etc.

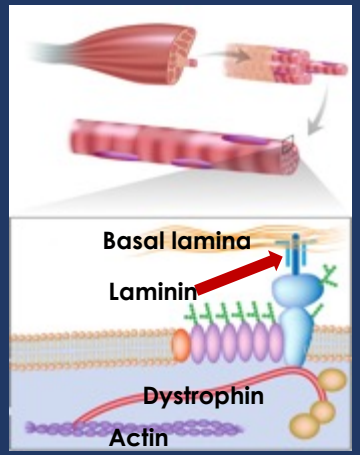
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LAMA2-CMD (aka CMD1a)

Severe muscular dystrophy caused by loss of function mutation in LAMA2 gene

MDL-101

Potential to be the first LAMA2-CMD gene activation therapy



Prevalence	**8.3 in 1 million*** 2500 in US	
Disease Onset	Apparent at birth or within a few months after birth	
Disease Burden	Patients do not survive past adolescence	• Severe muscle weakness • Lack of muscle tone (hypotonia) • Little spontaneous movement • Joint deformities (contractures) • Heart problems and seizures
Disease Causing Gene	**LAMA2 mutation**	
Commercial opportunity	**$500M+**	

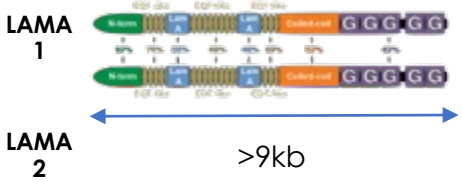


Source: *Estimating the Prevalence of LAMA2 Congenital Muscular Dystrophy using Population Genetic Databases (2023)

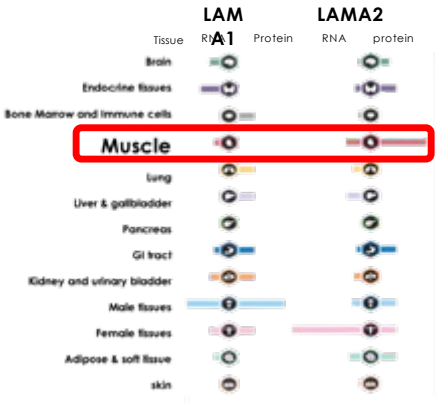
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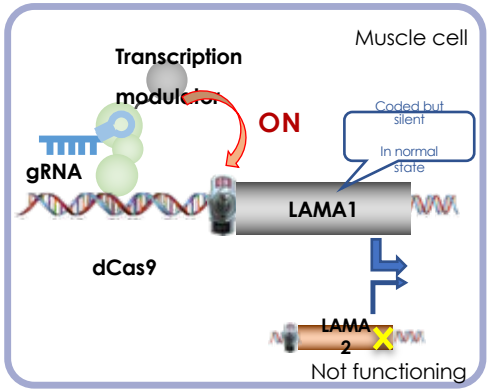
Protein structure of LAMA1 and 2



Exspression pattern of LAMA1and 2 by tissues



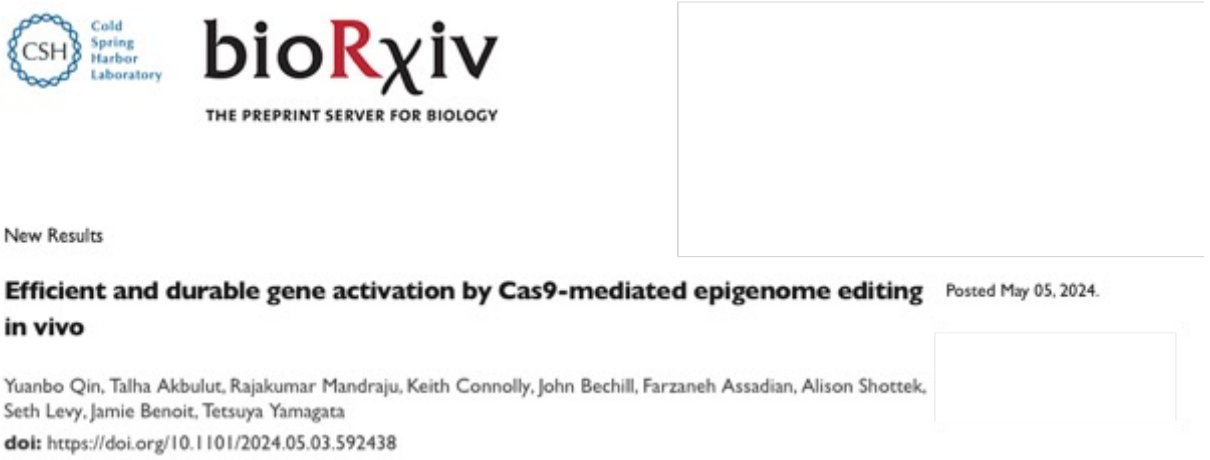
CRISPR-GNDM® targeting LAMA1



MDL-101 activates LAMA-1, compensates for the missing function of LAMA2, which is too large for classical gene therapy approach

Published paper on preclinical data on MDL-101 using CRISPR-GNDM®

MODALIS' first publication of CRISPR based epigenome editing



Cold Spring Harbor Laboratory

bioRxiv

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New Results

Efficient and durable gene activation by Cas9-mediated epigenome editing in vivo

Posted May 05, 2024.

Yuanbo Qin, Talha Akbulut, Rajakumar Mandraju, Keith Connolly, John Bechill, Farzaneh Assadian, Alison Shottek, Seth Levy, Jamie Benoit, Tetsuya Yamagata

doi: https://doi.org/10.1101/2024.05.03.592438

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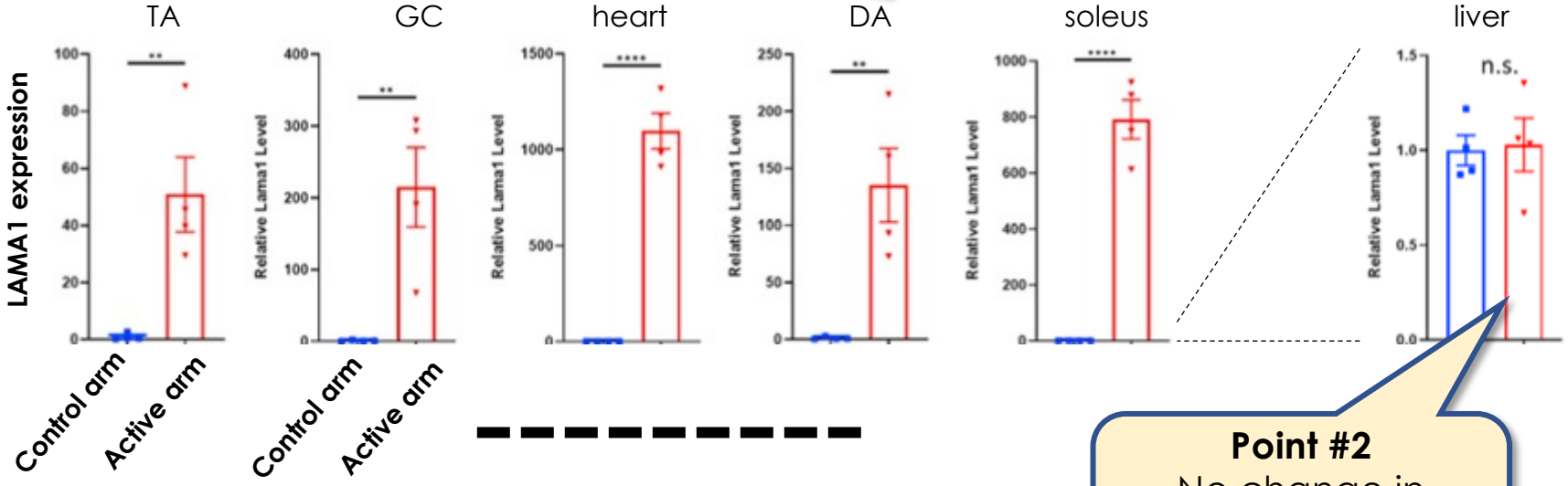
49

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From the paper

GNDM administration increased LAMA1 in a wide range of muscle tissues, with no change in non-muscle tissues

Point #1
LAMA1 is widely expresses in muscle tissues



Point #2
No change in expression level in liver

TA: tibialis anterior GC: Gastrocnemius DA: Diaphragm

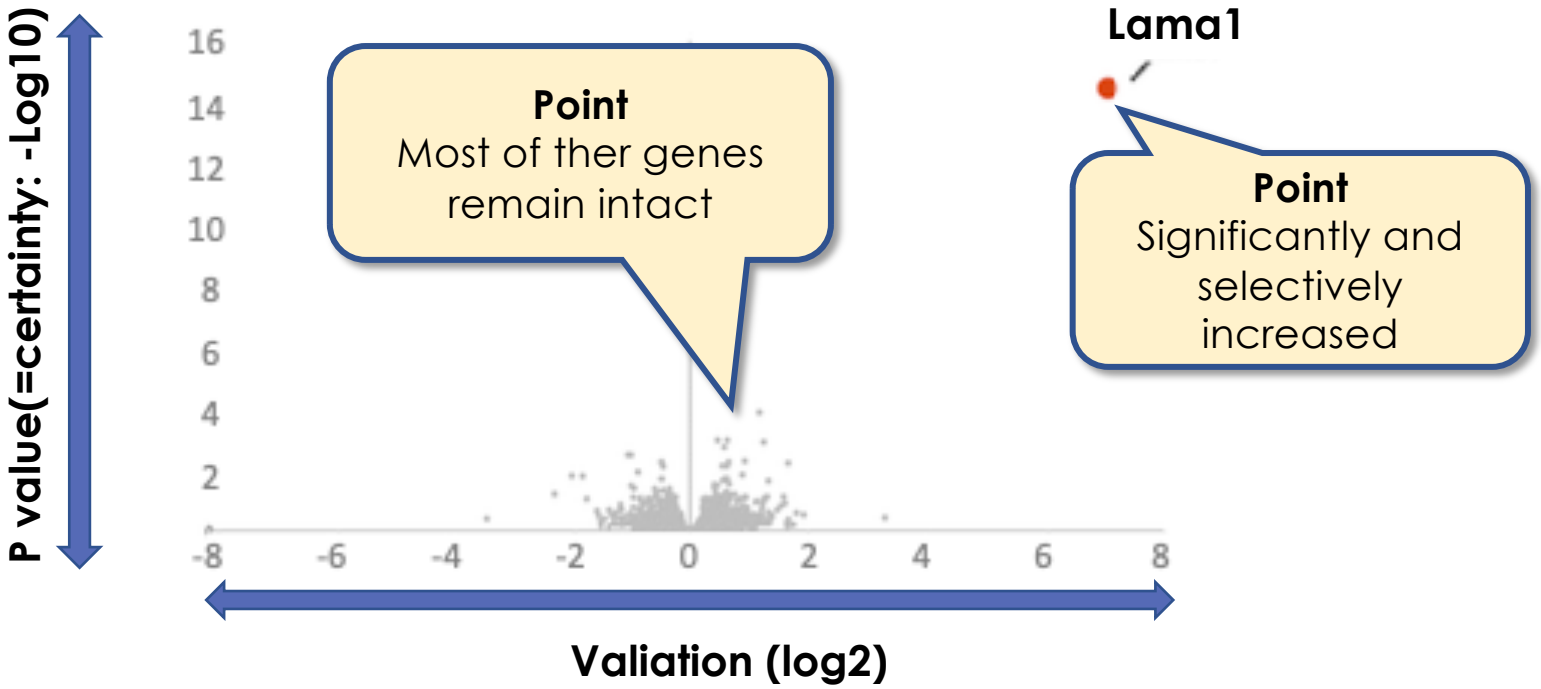
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From the paper

GNDM selectively upregulates LAMA1

gene perturbation by GNDM-LAMA1 in RNAseq

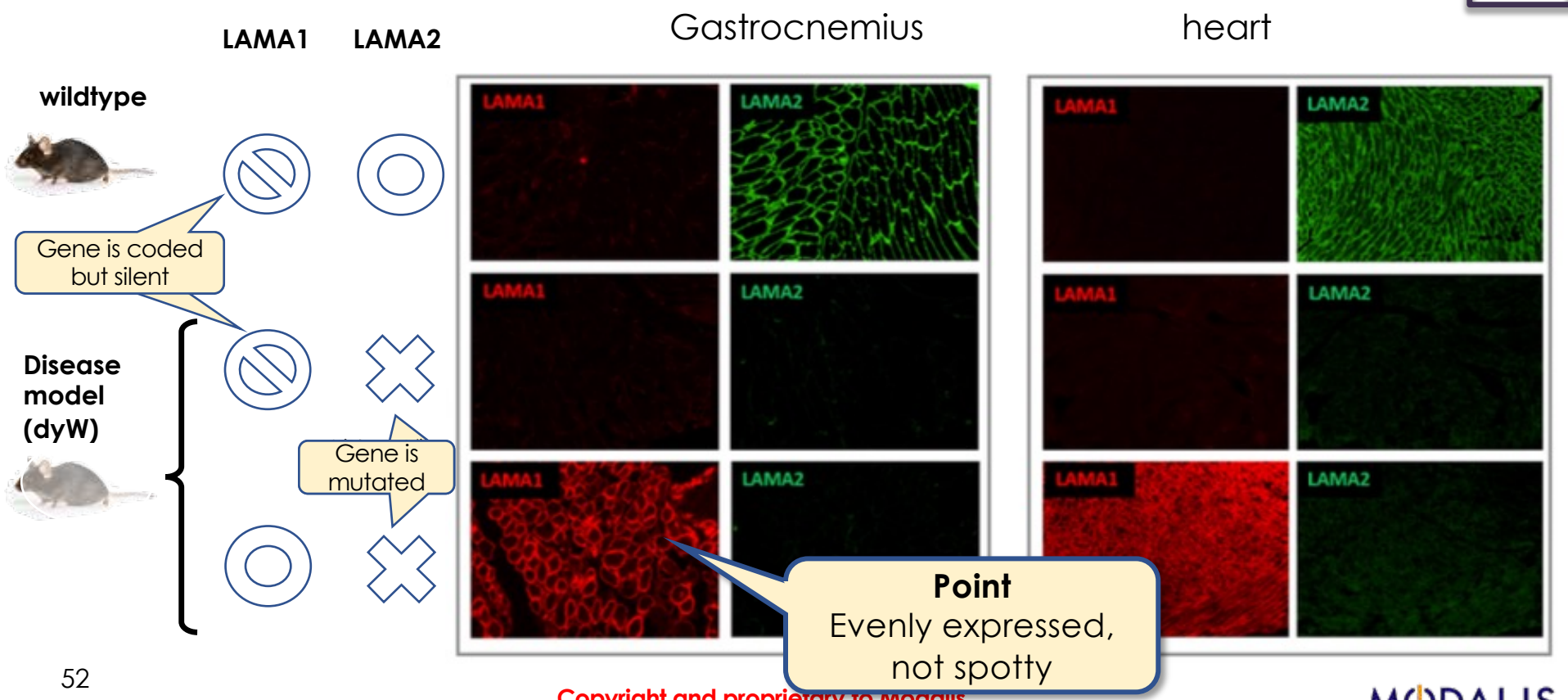


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From the paper

LAMA1 is distributed in many skeletal and heart muscles



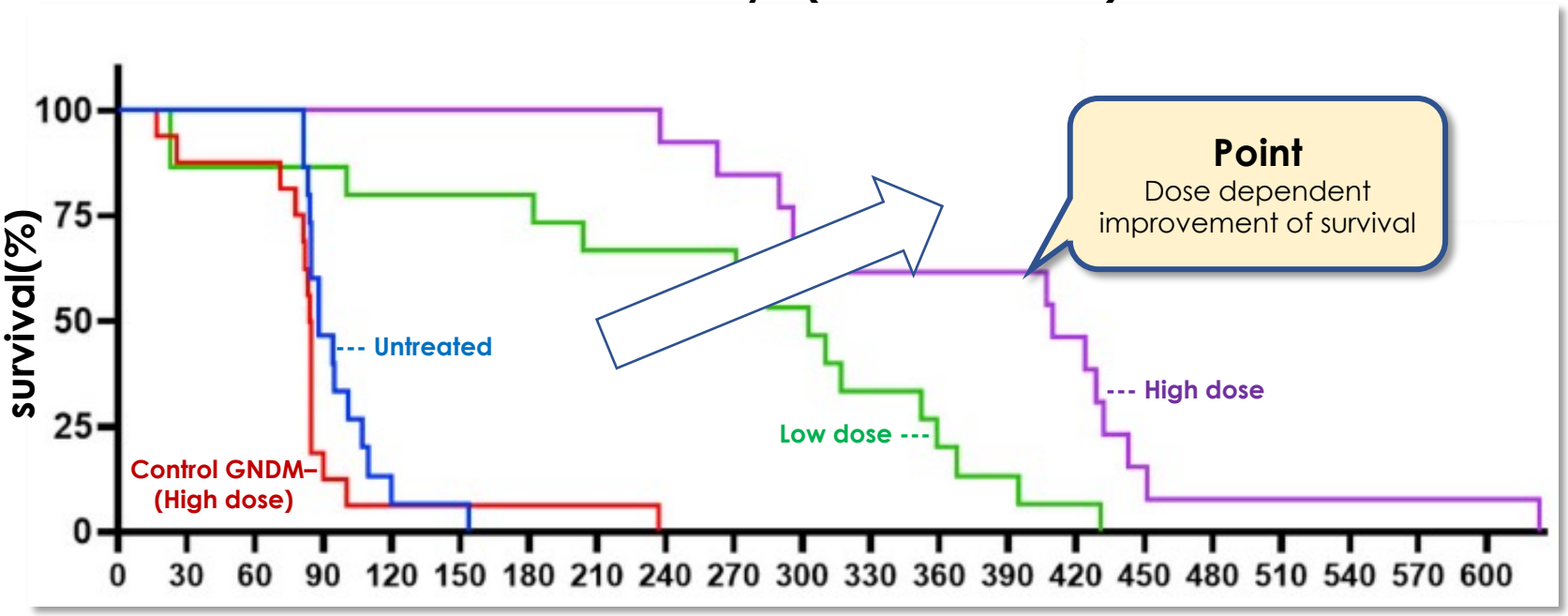
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From the paper

MDL-101 administration significantly improves survival

Survival curve of dyW(disease model)mice



Days post injection (d)

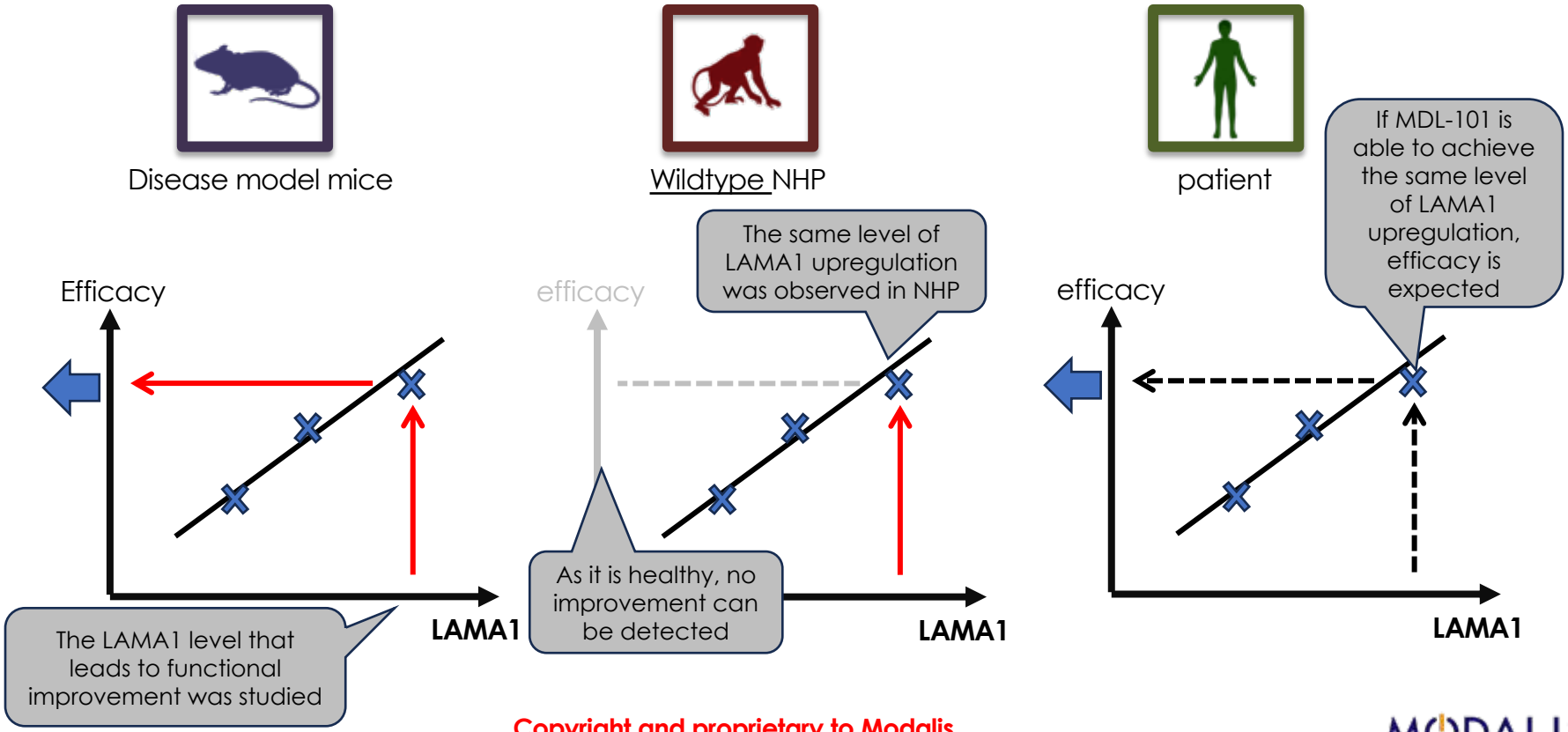
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From the paper

LAMA1 was upregulated to the potentially effective level

LAMA1 elevated in monkeys to the level of functional improvement at the mouse pathological condition observed

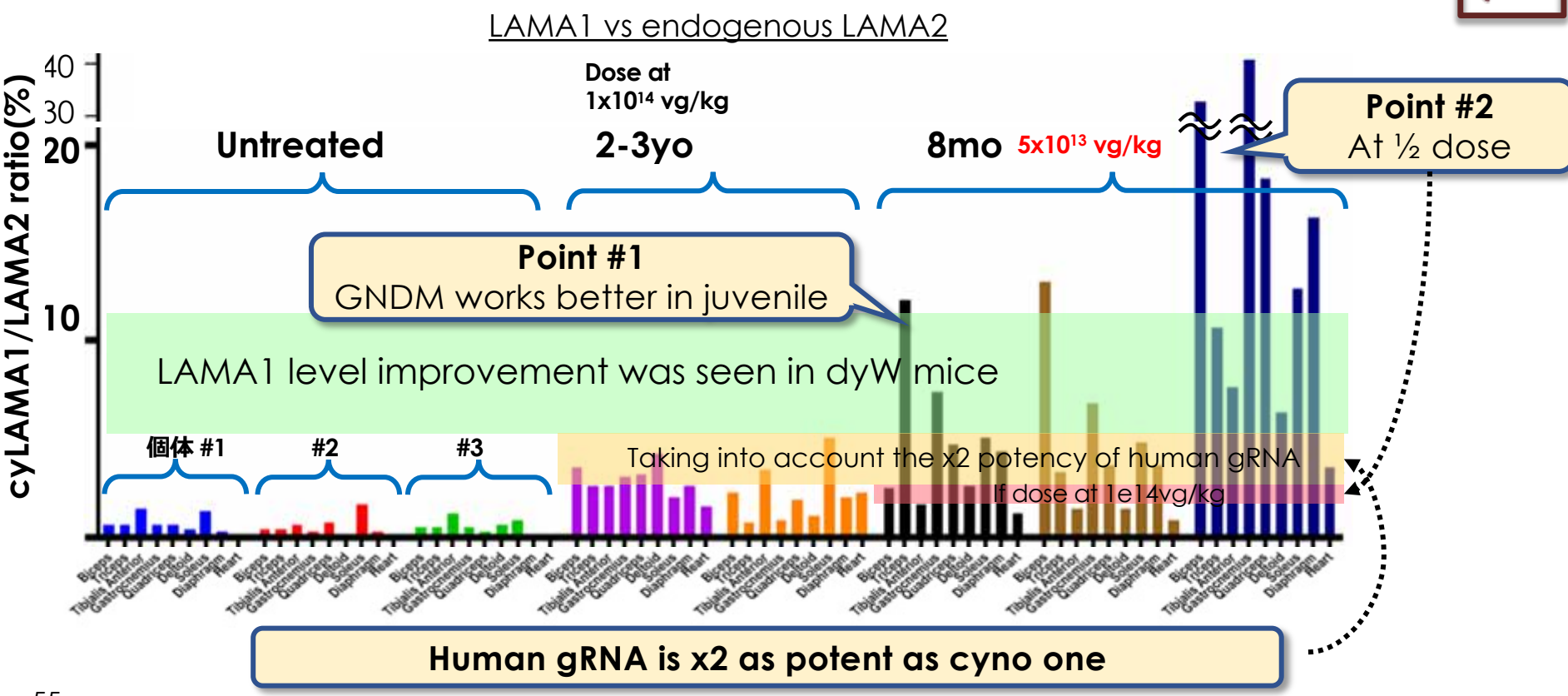


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From the paper

10-20% of endogenous LAMA2, which shall show efficacy, is expected in clinic



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Updated

Publication and conference presentations

Starting with the publication of MDL-101 papers, we will continue to disseminate information as a leader in the field of epigenome editing at conferences.

bioRxiv
THE PREPRINT SERVER FOR BIOLOGY

Efficient and durable gene activation by Cas9-mediated epigenome editing in vivo

Yuanbo Qin, Talha Akbulut, Rajakumar Mandraju, Keith Connolly, John Bechill, Farzaneh Assadian, Alison Shottek, Seth Levy, Jamie Benoit, Tetsuya Yamagata

doi: https://doi.org/10.1101/2024.05.03.592438

By 2024/3Q

CELL & GENE THERAPY SUMMIT-2024

18TH ANNUAL BIOPROCESSING SUMMIT
SOLVING TODAY'S CHALLENGES, LEADING TO TOMORROW'S ADVANCES

Gene Therapy Immunogenicity Summit

Nanopore Community Meeting Boston

2024/4Q

Genome Editing Therapeutics Summit
Shaping the Future of Therapeutic Gene Editing
FORMERLY KNOWN AS CRISPR 2.0



Oral presentation:
Title: **Epigenome editing with CRIPSR-GNDM® as a treatment platform for unmet medical conditions**
Date: Dec 5, 2024
Session title: Progressing Epigenome Editors into the Clinic

Reported
The progress of our MDL-101 development and future strategy

The industry's attention was drawn to our achievements in leading the world in epigenome editing

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Updated

Impact of the presentations

- Multiple inquiries from pharmaceutical and biotech companies about partnerships
- The girl in the top right is a 2-year-old girl from Brazil. She visited our MA office
- The girl in the bottom right is a 1-year-old girl born in India. She was found to have muscle weakness shortly after birth, and a genetic diagnosis revealed that she had LAMA2-CMD

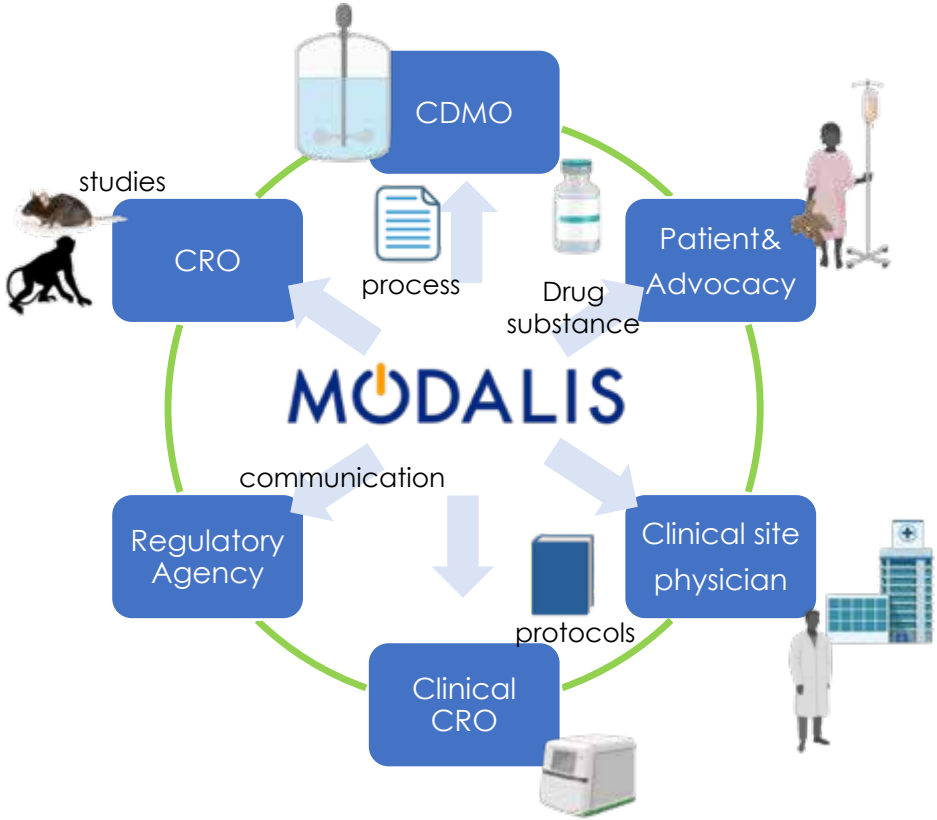
(both photos are published with the consent of the parents)



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Modalis has set up the network for the clinical trial and is working with them





Copyright and proprietary

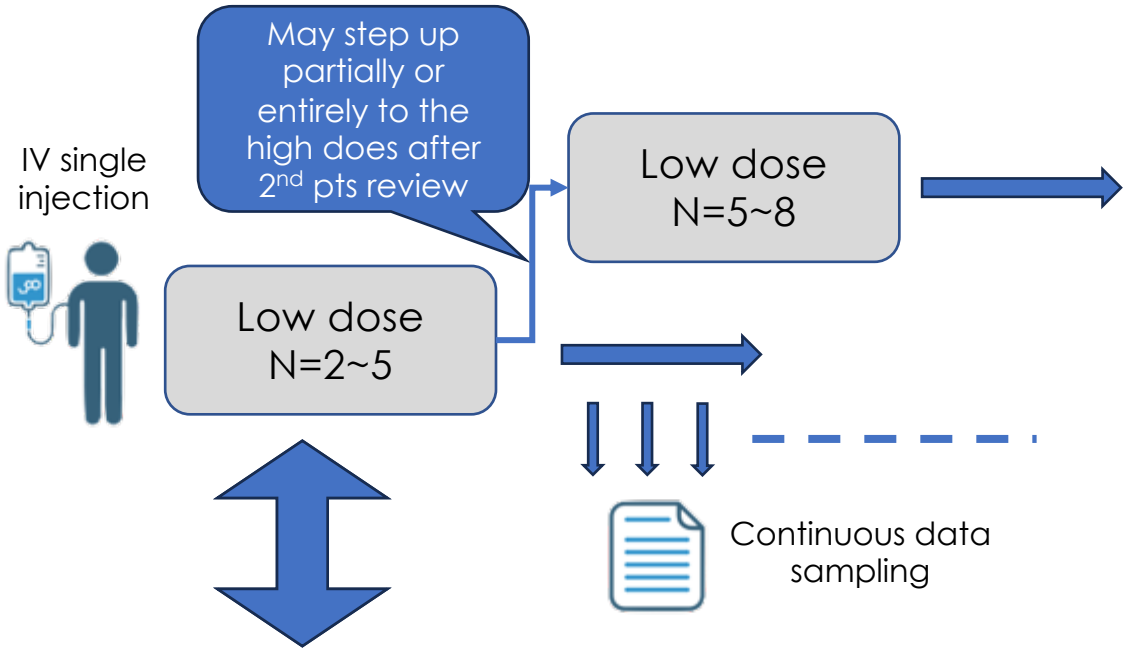
Updated

Design of the FIH trial

Phase 1/2, open-label, dose-escalation study

Summary of MDL-101-001 phase 1/2 Open-Label Dose-Escalation Study

- Male or female patients **36 months** of age and younger
- Clinical phenotype and Lama2 gene mutations and/or decreased LAMA2 staining in muscle consistent with LAMA2-CMD
- Stable background medications
- No independent ambulation or sitting



Comparison with Natural History Study in the US, France, and Netherland (NCT06354790, NCT04299321, NCT06132750)

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New

Summary of MDL-101 for LAMA2-CMD

Resolve technical obstacles for IND. The remainder is GLP toxicity testing and GMP

- Achieved so far
  - ✓ Confirmed efficacy in mice disease model and target engagement in NHP with the muscle tropic capsid version MDL-101
  - ✓ Completed a juvenile NHP study that confirmed comparable or better LAMA1 expression than adult NHP study
  - ✓ Confirmed long term expression of GNDM and LAMA1 in disease model mice
  - ✓ KOL meetings and drafting clinical synopsis and protocol
  - ✓ Presented development updates of MDL-101 as a late-breaking abstract at ASGCT
  - ✓ Received Pre-IND response from FDA (June)
  - ✓ Established a feasible manufacturing process with reasonable yield and quality
  - ✓ Initiating GLP tox study
  - ✓ Received follow up question to the preIND response
  - ✓ ODD and RPDD designations approval (Sep, Oct)
- Next steps:
  - ☐ Continue IND enabling GLP tox and PK/PD
  - ☐ Pilot productions and GMP campaign
  - ☐ IND filing

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MDL-101 is potentially the first epigenome-editing therapeutic program to enter the clinic

01

CRISPR-GNDM efficiently targets and upregulates LAMA1 gene

02

STRONG ANIMAL POC CONFIRMED IN MICE *IN VIVO* INCLUDING FUNCTIONAL IMPROVEMENT

03

THE PROCESS TO MANUFACTURE THE MOLECULE WITH MUSCLE-SPECIFIC VECTOR HAS BEEN ESTABLISHED WITH FEASIBLE PRODUCTIVITY, YIELD AND QUALITY

04

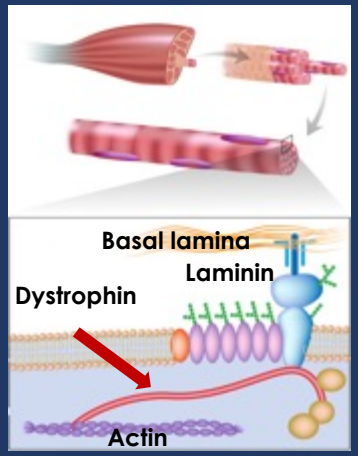
THE INJECTION OF THE PRODUCT DID NOT CAUSE DETRIMENTAL SAFETY ISSUES IN MICE AND NHPS

Duchenne Muscular Distrophy (DMD)

A type of muscular dystrophy caused by mutation in Dystrophin gene

MDL-201

Potentially best-in-class molecule by rebooting UTRN gene expression by GNDM



Prevalence	**1 in 3,500 to 5,000 male newborns**	Relatively high in genetic disorders
Disease onset	most commonly appears **between 3 and 6 years old**	
Disease Burden	Most severe clinical symptoms of all the muscular dystrophies including muscles weakness and atrophy	Motor development begins to slow in early childhood and muscle weakness progresses, followed by cardiomyopathy, scoliosis, and respiratory complications
Cause of disease	Disruption or mutation in Dystrophin gene	Loss of dystrophin and abnormal histological development of muscle necrosis and regeneration
Market size	**$1.1BM** 2022	Expected to grow at CAGR=42.5% with approval of new therapeutics

*Source: https://doi.org/10.1212/WNL.0000000000011425

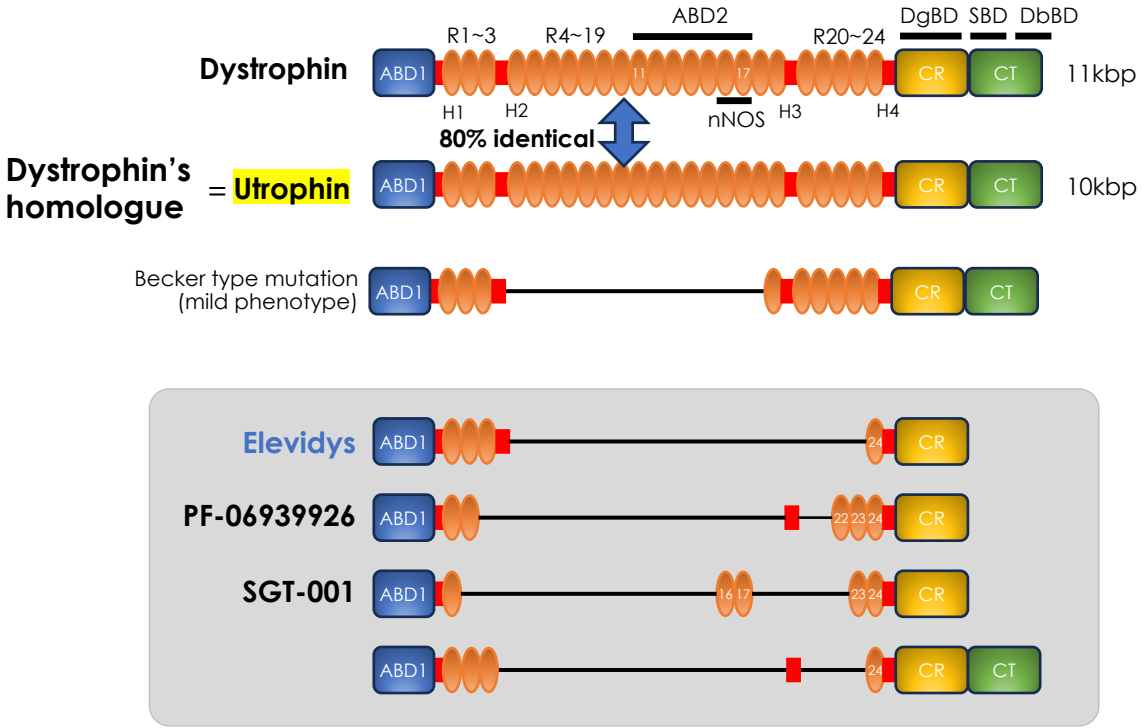
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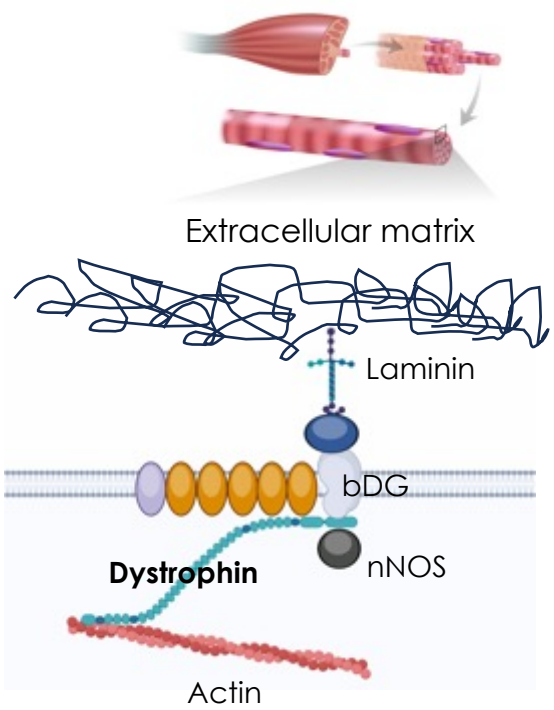
Dystrophin's function and structure

Current competing drugs use smaller proteins at the expense of functionality due to the size limitation

Dystrophin/Utrophin and mini-Dystrophin structure



Dystrophin's function

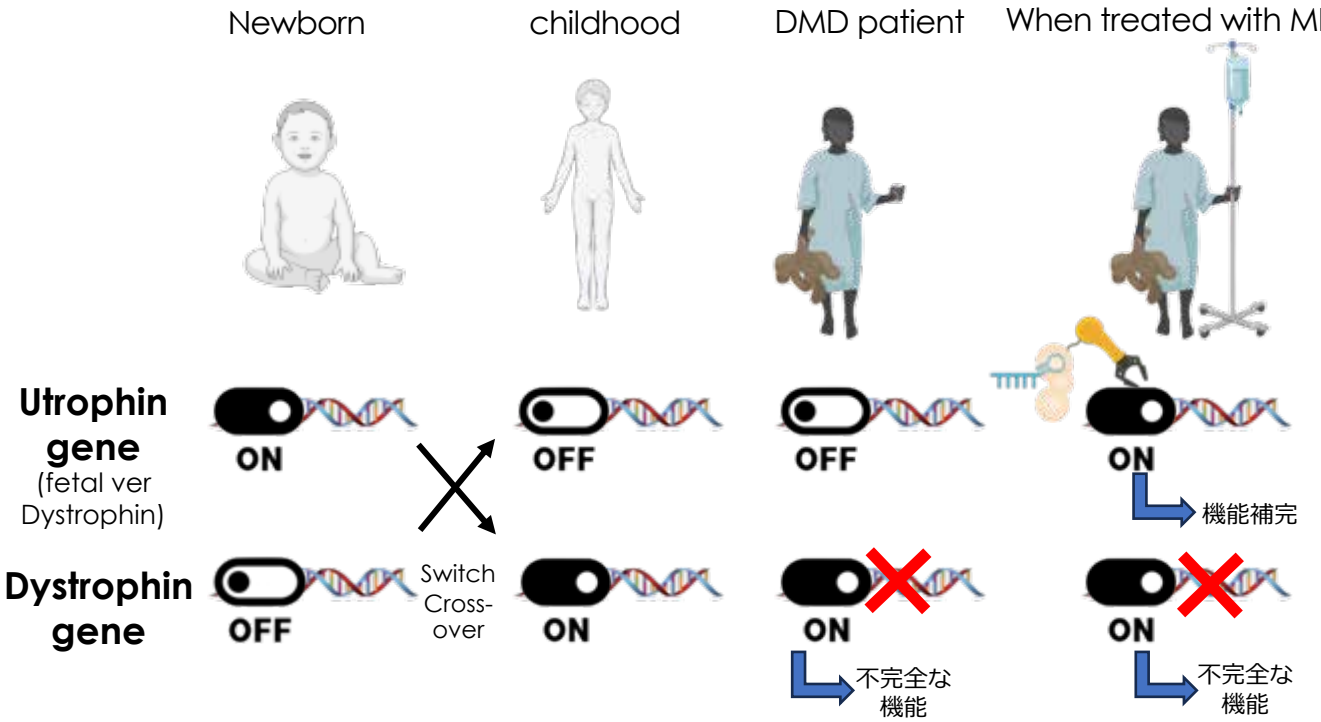


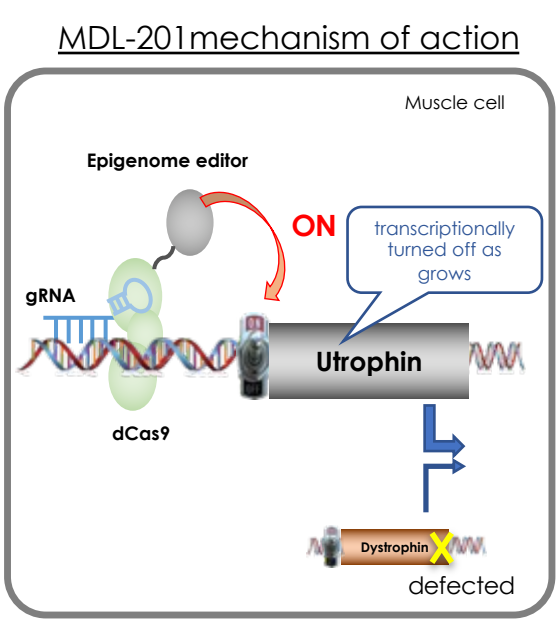
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MDL-201 therapeutic concept

Reboot Utrophin genes , which is intact in patient, to compensate Dystrophin function





activating Utrophin using GNDM is expected to have a greater medicinal effect than mini-Dystrophin

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MDL-201 potentially is a best-in-class DMD gene therapy that surpasses micro/mini-dystrophin approaches

01

Utrophin retains functional domains that are absent in µ-dystrophin

02

MDL-201 shows higher functional improvement than µ-Dystrophin in mouse pathological models

03

MDL-201 shares the same platform as MDL-101, on which much experience has been accumulated

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Myotonic dystrophy type 1(DM1)

extension of CTG repeat in 3' UTR of DMPK gene

MDL-202

Potential to be the first-in-class and the first DM1 treatment

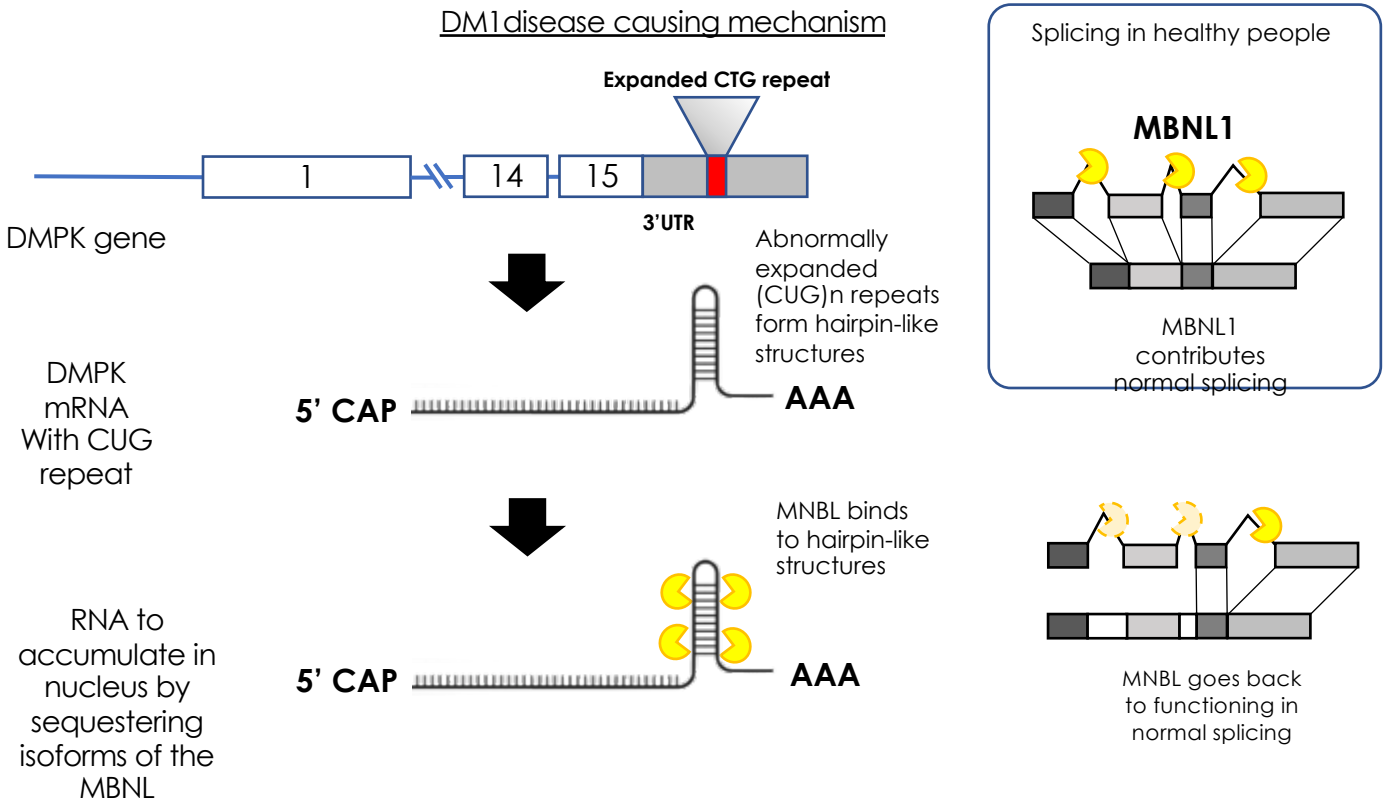
Prevalence	**1-4.8 in 10,000** (1 in 2,300*)	DM is the most common muscular dystrophy among adults of European ancestry
Disease onset	DM1 can occur from birth to old age	Age at onset is between 20 and 70 years (typically onset occurs after age 40)
Disease Burden	muscle weakness and wasting (atrophy), myotonia	DM causes weakness of the voluntary muscles, although the degree of weakness and the muscles most affected vary greatly according to the type of DM and the age of the person with the disorder
Cause of disease	Microsatellite expansion in 3' UTR of DMPK gene	Extended CTG repeat capture MBNL1 protein which is essential for normal splicing
Market size	**$2.2B #** By 2032	$80M market as of 2022 without any treatment but is expected grow

*Source: Myotonic Disease Foundation # DelveInsight (including both DM1 and DM2)

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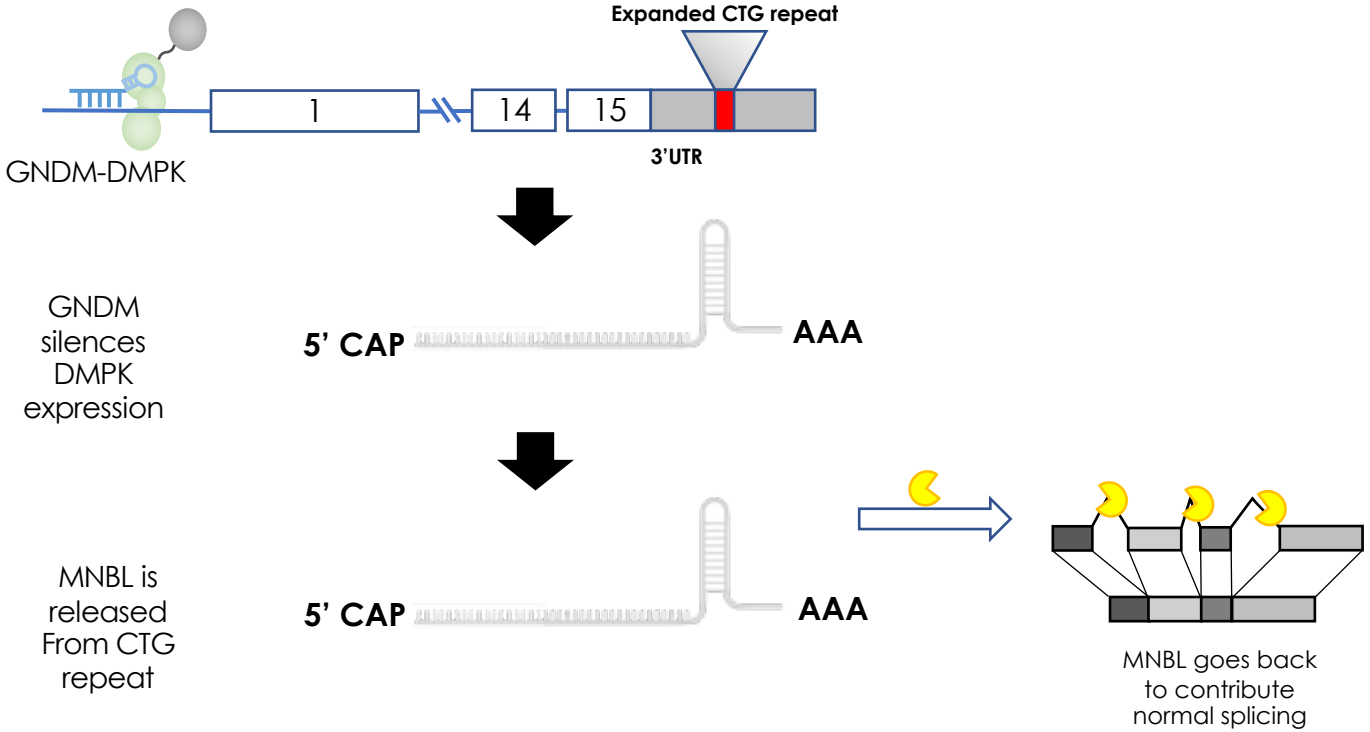
DM1 is caused by abnormal splicing rooted from CTG extension in 3'UTR of DMPK gene



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MDL-202 silences DMPK expression and release splicing protein MNBL to function properly in muscle cells

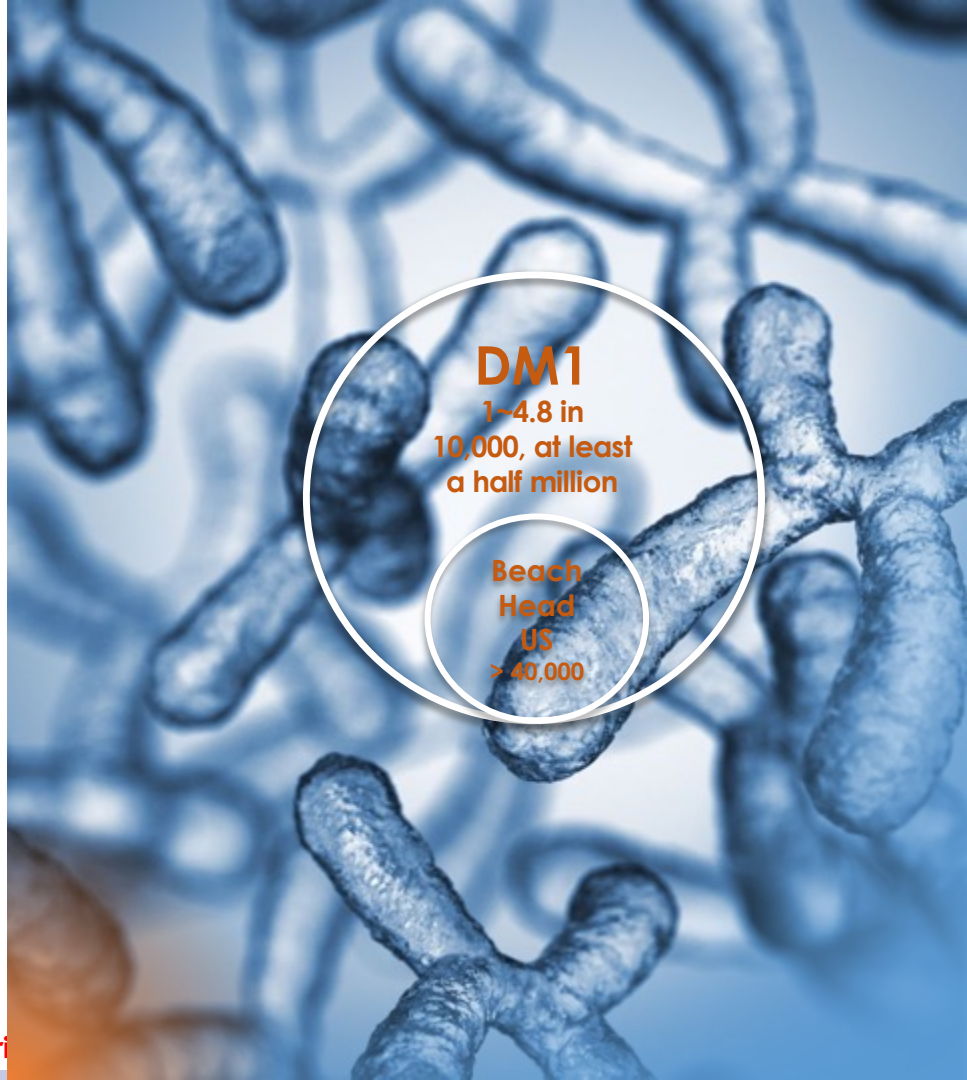
MDK-202's mechanism of action



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DM1 has relatively large prevalence in muscular disorders

- Prevalence was estimated at 1 in 8,000-10,000, but recent population-wide screening estimated: mutation prevalence of 4.8 in 10,000 individuals
- DM1 can affect newborns to older adults
- US>40,000 individuals (Japan>10,000)



Source: Marta Pascual-Gilabert, The myotonic dystrophy type 1 drug development pipeline: 2022 edition

Copyright and propri

MDL-202 offers a feasible and fastest path to the clinic

01

Modalis has candidate Myo tropic AAV-based molecules confirmed in NHP

02

Modalis has established a manufacturing process available for large-scale production

03

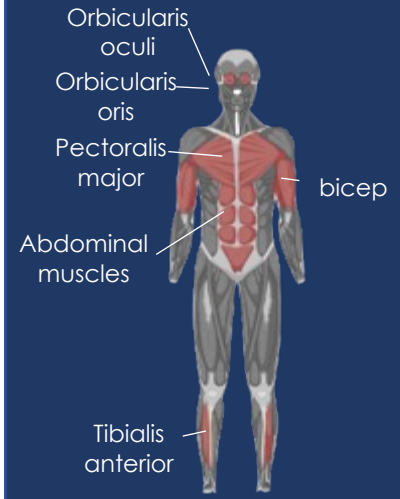
Modalis had INTERACT and PreIND meetings and knows what is required for IND

Facioscapulohumeral Muscular Dystrophy (FSHD)

A type of muscular dystrophy caused by impaired Dux4 gene expression

MDL-103

Potentially first-in-class treatment by silencing expression of toxic Dux4 gene product



Prevalence	**1 in 10,000-20,000**	Muscular dystrophy most frequent in adults
Disease Onset	Often not recognized until the 20s and tends to worsen during adolescence	Progression of disease to face, shoulders, and arms is generally slow
Disease Burden	weakness of the facial muscles, the stabilizers of the scapula, or the dorsiflexors of the foot	Symptoms of asymmetrical (unbalanced) muscle weakness Visual impairment, vascular abnormalities, hearing impairment, etc.
Disease Causing Gene	Over expression of Dux4 gene	DUX4 is originally expressed in germline cells but need to be suppressed in somatic cells
Commercial opportunity	**$500M+**	

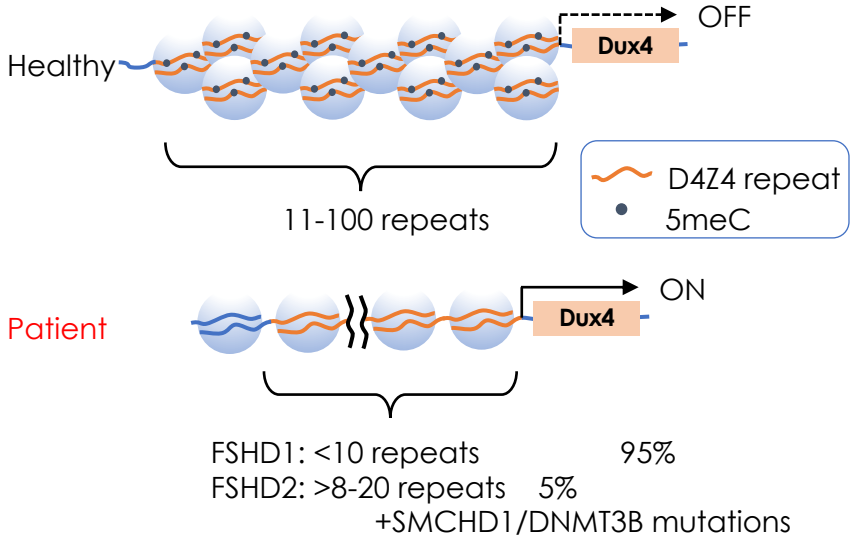
Source: https://doi.org/10.1212/WNL.0000000000011425
Orphanet, Raymond A. Huml MD A concise guide

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FSHD disease mechanism

Inappropriate expression of toxic Dux4 in skeletal muscles



- The D4Z4 repeat region at location 4q35 on chr4
- Healthy has numerous highly **methylated** D4Z4 repeats
- FSHD-1 and -2 affected has **hypomethylated** D4Z4 repeats.
- FSHD-1 non-manifesting, or unaffected has few repeats, but these have **higher methylation**

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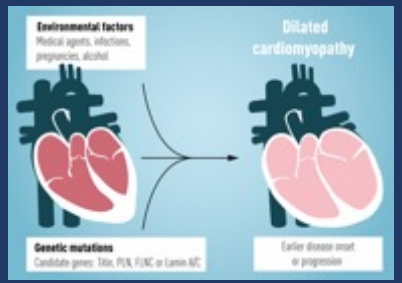
MODALIS

Dilated Cardiomyopathy (DCM)

A condition in which the heart becomes enlarged

MDL-105

Potential first-in-class precision medicine targeting DCM caused by TTN truncated variant mutations



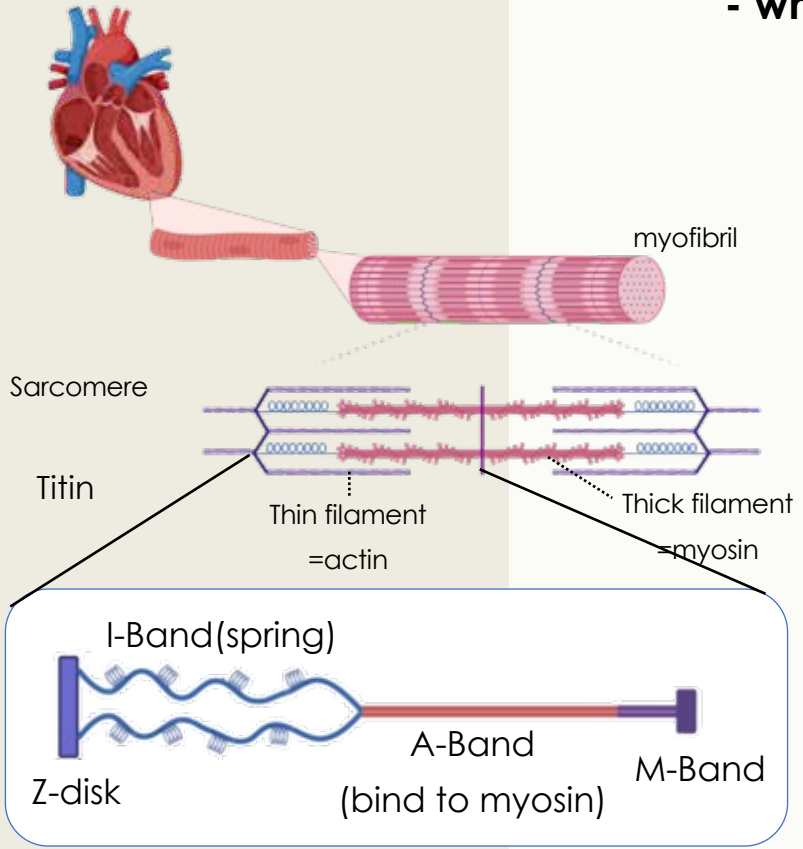
Prevalence	**1 in 250-2,500#**	• ~20% of DCM is estimated to be caused by TTN variant • Half is by truncated variant
Disease Onset	Middle age around **20-60 yo**	
Disease Burden	Five-year survival rate is about **50%***	• Without treatment, the 1-year survival is 70%–75%, with a 5-year survival of as low as 50% • Patients goes to a heart transplantation
Disease Causing Gene	Mutation in **TTN, MYH7, MYBPC3**	
Commercial opportunity	**>$300M**	• Estimated to grow at CAGR=4.1% and reach $421M by 2027#

Source: picture MayoClinic *https://doi.org/10.1111/joim.12944 #Global Industry Analysts, Inc

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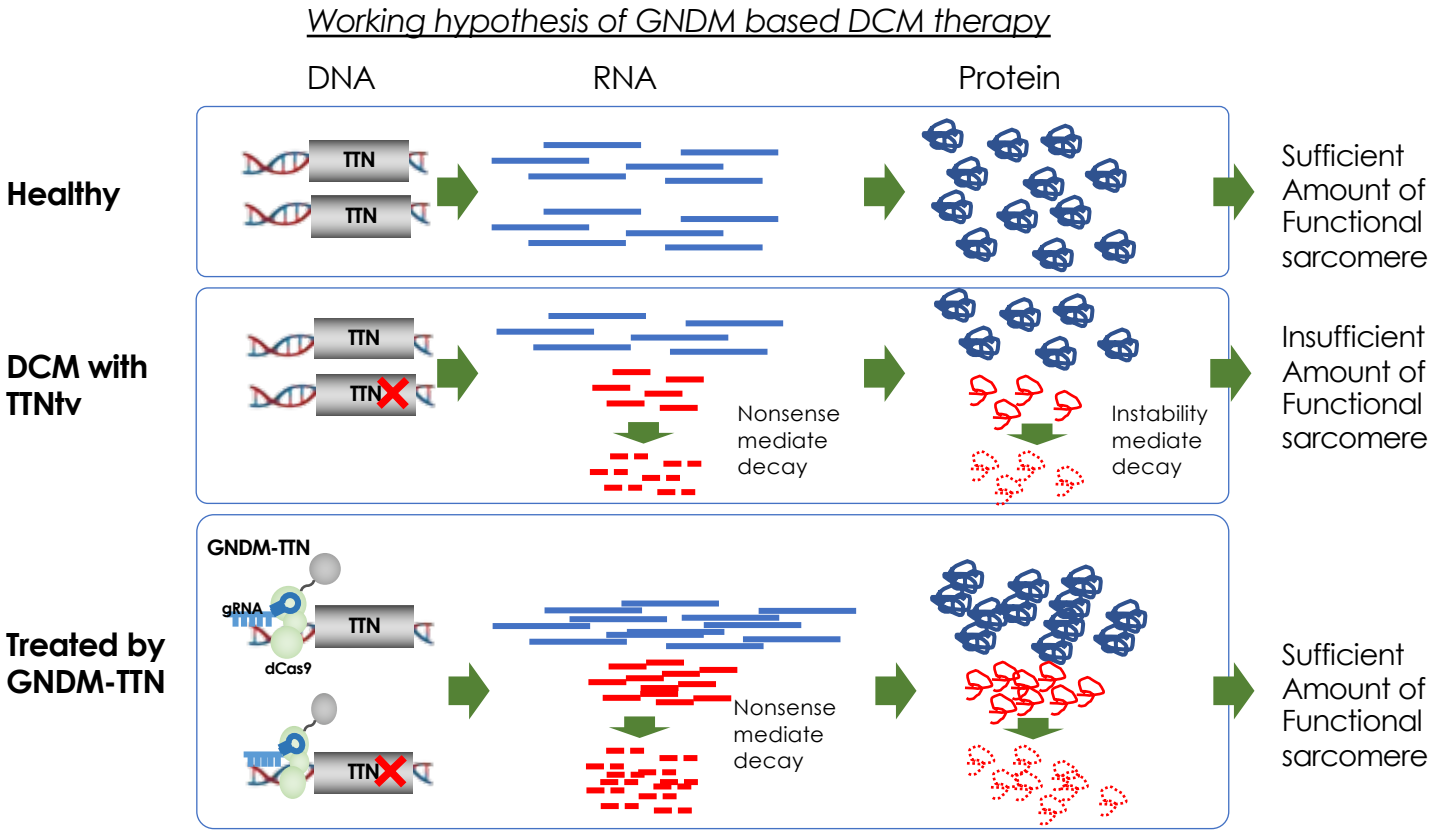
TTN is the largest human protein - which is too large for AAV packaging



- **Largest** human protein
  - 35,000 amino acids /17kb
  - 363 exons
  - Acts as spring in sarcomere
  - Tension during relaxation
- **Abundant** in human body
  - Third most abundant protein in muscle next to myosin and actin
  - Adult human contains approximately 0.5 kg of titin
- **~90% mutations** are truncated variant (TTNtv)

MDL-105 returns TTN protein levels to normal through transcriptional activation of TTN

Restore normal sarcomera levels by boosting TTN



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Why GNDM for TTN?

- TTN mutations are “definitive” for DCM (ClinGen)
- TTN mutations are associated with 15-23% of DCM cases
- TTNtv is a haploinsufficiency rather than dominant negative
  - produce non-functional protein
- No direct approach to target TTN has been reported as too big to treat



Targeting TTN by GNDM is a unique and differentiated approach

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Status of Development of MDL-105

- Achievements so far
  - Human gRNA screening completed
    - Filed patent
  - Introduced mice disease model
    - The model is not reproduced in our hands
  - Initiated animal PoC study
    - With muscle tropic capsids
  - Discussion on the strategy with CV experts

- Next steps
  - Explorer disease models that can evaluate molecule s with
  - Explorer funding including partnership opportunities
  - Reconsider timing of PreIND contingent on identifying and pursuing disease model study and funding.

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Tauopathy (incl. Alzheimer's Disease)

Neurodegenerative disorders caused by misfolding of the tau protein

MDL-104

Potentially best-in-class molecule by silencing Tau expression

Prevalence	**1 in 9 above 65*** 55 million in ww	60-80% of cognitive disorders
Disease Onset	Progressed in **6-8 yrs**	Slow and chronic progression, depending on the individual
Disease Burden	progressive disease beginning with mild memory loss	possibly leading to loss of the ability to carry on a conversation and respond to the environment.
Disease Causing Gene	Multiple causes have been proposed but not yet known	APO-E, PSEN1, PSEN2 and many other gene mutations reported All mutations are associated with Aβ hyperactivity
Commercial opportunity	**$4.2B** in 2022#	Estimated to grow to $15.6B by 2030#

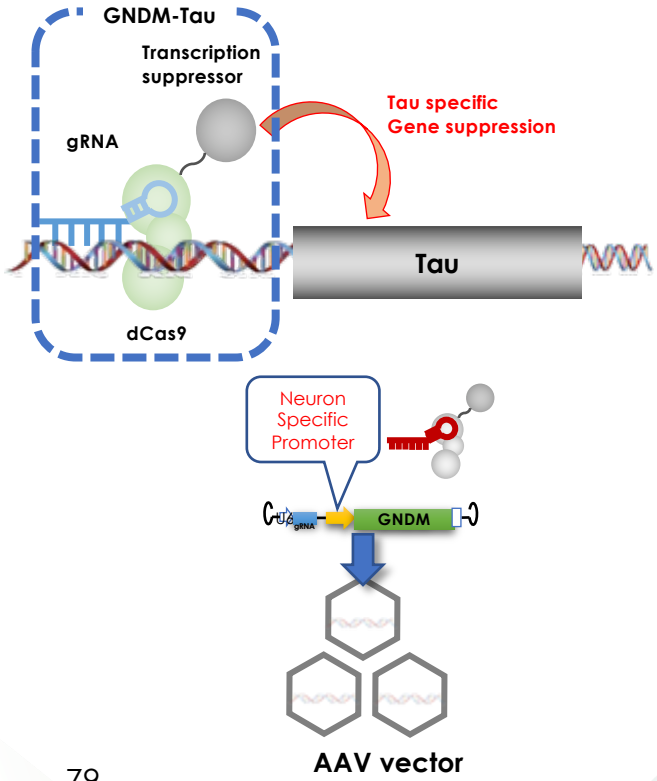
Source: * Alz.org (for Alzheimer Disorder) #Grand View Research

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MDL-104 suppress Tau at transcription level

MDL-104's mechanism of action





- Reversing the pathogenic conditions of Tauopathy by partial or full suppression of Tau gene that leads to reduction of Tau protein in the brain
- GNDM-Tau, driven by neuron specific promoter delivered by AAV9 or alternative capsid
- ICM (intra-cisterna magna) injection to achieve efficient brain delivery and to avoid high-dose AAV related toxicities

AD and FTD are our primary choice for the initial indication but multiple potential diseases

	Prevalence	Target in Brain	Major symptom	Progression
AD	1 in 9 above 65 1 in 3 above 85	cortex and hippocampus	memory, movement, language, judgment, behavior, and abstract thinking	6-8yrs
CBD	~5 in 100k low in Asian	multiple areas of the brain	Balance, Memory, muscle control, speech	6-8yrs
PSP	5-17 in 100k	Basal ganglia and brain stem	movement, control of walking (gait) and balance, speech, swallowing, eye movements and vision, mood and behavior, and thinking (Parkinson-like symptom)	~7yrs
FTD	2-10% of dementia	frontal and temporal lobes	apathy, change in personality, lack of inhibition, obsessive behavior	~8yrs
AGD	18.8% to 80% of PSP 41.2% to 100% of CBD	Limbic system	cognitive decline, personality changes, urine incontinence and cachexia	3 months
Chronic traumatic encephalopathy	0.79% of population	Various	depression, explosivity, short-term memory loss, executive dysfunction and cognitive impairment	Decades
Post-encephalitic parkinsonism	Unknown	Substantia nigra	Parkinsonism	Unknown
Subacute sclerosing panencephalitis	2:10,000 people infected with measles	cortical atrophy, white matter lesions	personality changes, mood swings, depression, muscle spasms, seizures, loss of vision, and dementia	4 yrs

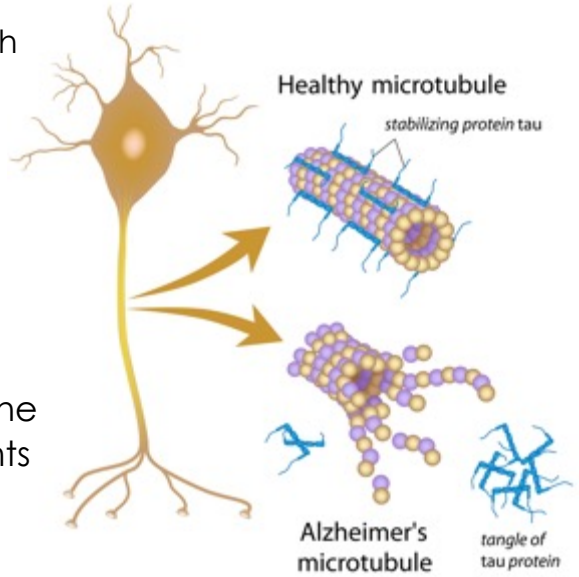
AD: Alzheimer's Disease
CBD:Corticobasal degeneration
PSP: progressive supranuclear palsy
FTD: Frontotemporal dementia
AGD: Argyrophilic grain disease

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Tau is a center of attention in treating Alzheimer diseases

- Tau correlates with clinical symptoms and neuronal loss in Alzheimer's disease and other primary tauopathies.
  - Tau aggregates and tangles are thought to induce neuronal degeneration, synaptic loss and cell death
  - Tauopathies include a range of high value and orphan clinical diseases
    - AD (Alzheimer's Disease)
    - FTLD (Frontal Lobar Degeneration)
    - PSP (Progressive Supranuclear Palsy)
    - CBD (Corticobasal Degeneration)
    - Pick's disease
- Tau is likely to be a better target than Aβ because the tau burden correlates better with clinical impairments than does the Aβ burden
- Tau knockout has few adverse effects
- Therefore, reducing total Tau expression is a logical therapeutic strategy



Source: Congdon EE, Nature Review Neurology 2018 "Tau-targeting therapies for Alzheimer disease"

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Status of Development of MDL-104

- Achievements so far
  - Evaluation of the human version molecule with hTau and humanized Tau mice
    - Robust Tau suppression is confirmed both in Cortex and Hippocampus.
  - Initiation of biodistribution study in NHP
  - Discussion on target indications with KOLs
    - Alzheimer's disorder (AD) and/or Frontotemporal dementia (FTD)

- Next steps
  - Explorer delivery methods including CNS tropic capsids
  - Reconsider timing of PreIND and IND contingent on identification of delivery tools and funding.

hTau mouse（mMAPT knockout, hMAPT transgenic)
humanized MAPT mouse （aka MAPT（H2.1）-GR = mouse MAPT replaced with human MAPT gene)

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Angelman Syndrome

CNS disorder caused by impaired UBE3A gene expression

MDL-206

Potentially first-in-class treatment by unsilencing UBE3A gene expression

Prevalence	**1 in 10,000 to 20,000**	• 60,000 patients WW (2017) • 20,000 in US
Disease Onset	typically diagnosed at **6 to 12 months**	Seizures may begin at 2 to 3 years.
Disease Burden	Developmental delay	small head, specific facial appearance, intellectual and developmental disability, speech impairment, balance and movement problems, seizures, and sleep problems
Disease Causing Gene	Mutation in maternal allele of **UBE3A**	5-26% has unknown mechanism
Commercial opportunity	**$330M** 2017	US, EU, and Japan

Source: Orpha.net

Angelman syndrome Market and Epidemiology forecast (delveinsight.com)

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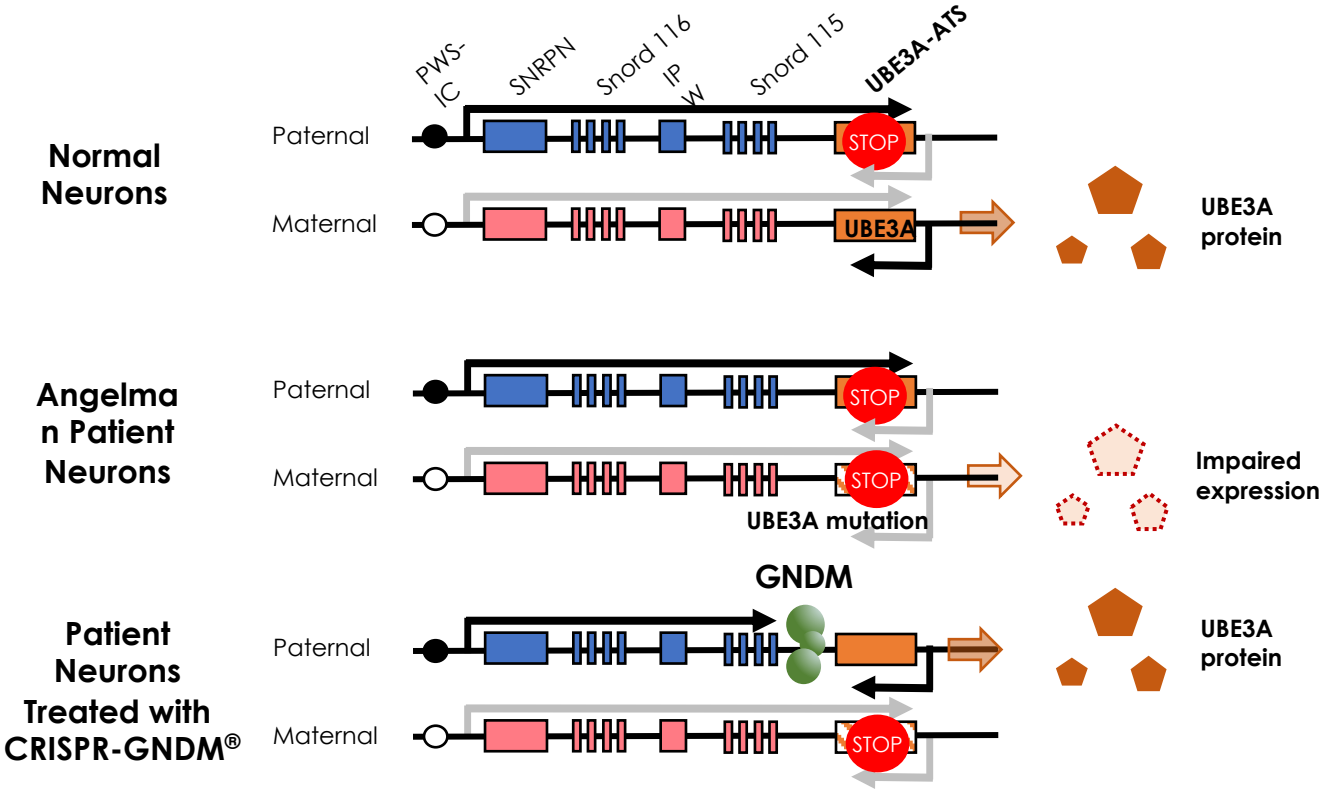
What is Angelman syndrome?

- Angelman syndrome (AS) is a rare neuro-genetic disorder that occurs in **one in 15,000 live births** or **500,000 people** worldwide.
- It is caused by a loss of function of the **UBE3A gene** in the 15th chromosome derived from the mother.
- Angelman syndrome shares symptoms and characteristics with other disorders including **autism**, **cerebral palsy** and **Prader-Willi syndrome**.
- People with AS have developmental problems that become noticeable by the **age of 6 – 12 months**. Other common signs and symptoms usually appear in early childhood like **walking and balance disorders**, **gastrointestinal issues**, **seizures** and **little to no speech**.

Source: Angelman Syndrome Foundation

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By blocking ATS transcript, GNDM un-silences UBE3A expression



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Status of Development of MDL-206

- Achievements so far
  - Animal PoC established with disease mice model
  - Up-regulates the UBE3A gene by GNDM based molecule is confirmed with UBE3A heterozygous mice

- Next steps
  - Verification of superiority over approaches using other modalities
  - Planning and validation of clinical development strategies, including route of administration, capsid modifications, etc.
  - In parallel, partnering efforts to fund the program

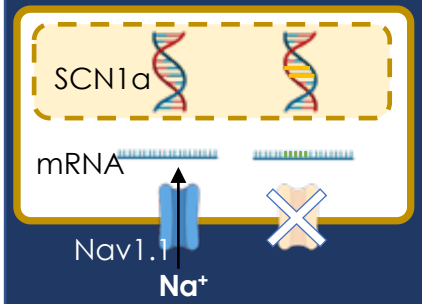
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Dravet Syndrome

A type of epilepsy caused by haploinsufficiency mutation in SCN1A gene

MDL-207

Potential to be the best-in-class and first precision medicine for Dravet Syndrome



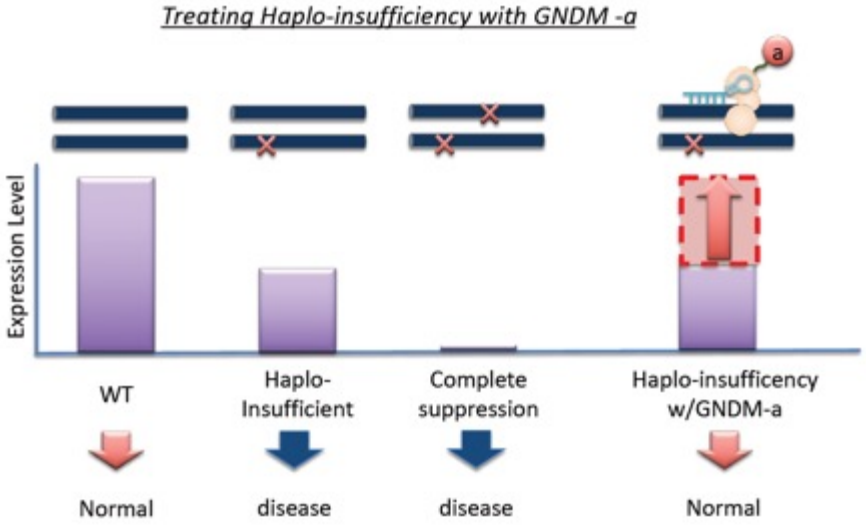
Prevalence	**1 in 20,000-40,000*** ~10,000 in US	
Disease Onset	Seizure starts between **1 and 5 yo**	
Disease Burden	**10-20%** of DS patients pass away before reaching adulthood	• SUDEP (sudden unexpected death in epilepsy patients) • status epilepticus (SE). • Autism-like spectrum (ASD) • Attention deficit hyperactivity disorder (ADHD)
Disease Causing Gene	**SCN1A**	• Haploinsufficiency of SCN1A
Commercial opportunity	**$500M+**	• Currently with no curable drugs • The market is estimated to grow at CAGR of 9.6% # driven by new therapeutics

Source: *Epilepsy foundation #Technavio

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A simple solution is to double up SCN1a protein expression



Company	Modality	MOA	Route	Stage	IND
Enoded Therapeutics	AAV-ETN (regulatory element)	• Overexpress regulatory element for Scn1a • Upregulate endogenous Scn1a expression specifically in GABAergic inhibitory neurons	ICV	IND cleared	2021
E-Rare	Adenovirus-Scn1a	• Restore Scn1a mRNA and Nav1.1 protein levels	ICV	Preclinical	TBD
UCL	Lentivirus-Scn1a	• Restore Scn1a mRNA and Nav1.1 protein levels	ICV(?)	Preclinical	TBD
OPKO	AntagoNAT	• Binds to the DNA and removes an endogenous repressor of SCN1A • Restore Scn1a mRNA and Nav1.1 protein levels	IT	Preclinical	TBD
PTC therapeutics	Small molecule (nonsense reading through)	• Read through premature nonsense stop signals on mRNA and allow the cell to produce a full-length, functional protein (not specific to Scn1a)	Oral	Phase 2 (pending?)	N/A
Stoke Therapeutics	ASO (TANGO)	• Reduce non-productive mRNA and increase productive Scn1a mRNA via modulation of splicing • Increase in the levels of mature mRNA and Nav1.1 protein	i.c.v.	Preclinical	2020

Patents related to MDL-101, 201 and 202 were granted and registered in China and Japan

- LAMA1 patent granted in JPN (Jan 2025)
  - Treatment method for muscular dystrophy targeting LAMA1
  - JP2022-509664
- UTRN patent Granted in CHN(June)
  - METHOD FOR TREATING MUSCULAR DYSTROPHY BY TARGETING UTROPHIN GENE
    CHN 201980075173.0
- DMPK patent issued in CHN(June) and JPN (Sep)
  - METHOD FOR TREATING MUSCULAR DYSTROPHY BY TARGETING DMPK GENE
    CN 113785066B, JP2022-518586



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Achievements of the programs and coming milestones

	Achievement so far	Coming milestones
MDL-101 LAMA2-CMD	• Animal PoC • Target engagement in monkeys • Pre-IND response • Establishment of manufacturing process • ODD (Sep) and RPDD (Oct) received • Data presentation (July, Aug, Sep and **Dec**)	• GLP-Tox • GMP manufacturing • IND (2025)

その他	• Established animal PoC
	  • MDL-201 (DMD)
	  • MDL-104 (Tauopathy)
	  • MDL-205 (Angelman syndrome)
	  • MDL-207 (Dravet syndrome)
	• MDL-103 (FSHD)
	• MDL-105 (DCM)
	• **Research collaboration with JCR moved to the 2nd phase.**
	• Collaboration with Ginkgo Bioworks
	• Entered MOU with GenixCure
		• Transition to a New Capsid Version (MDL-201) and validation in animals
		• Explore optimal capsid and route of administration for CNS program
		• Allocation of development funds through partnering
		• Animal PoC
		• Continuing Research and Moving to Next Steps

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5. Growth Strategy

Diversified pipeline with their own missions

Pioneer the gene modulation With highly suitable indications

MDL-101

Expand technology opportunity with products for larger opportunity

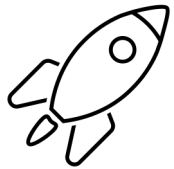
MDL-201, 202

Further approach to challenging applications

Other programs

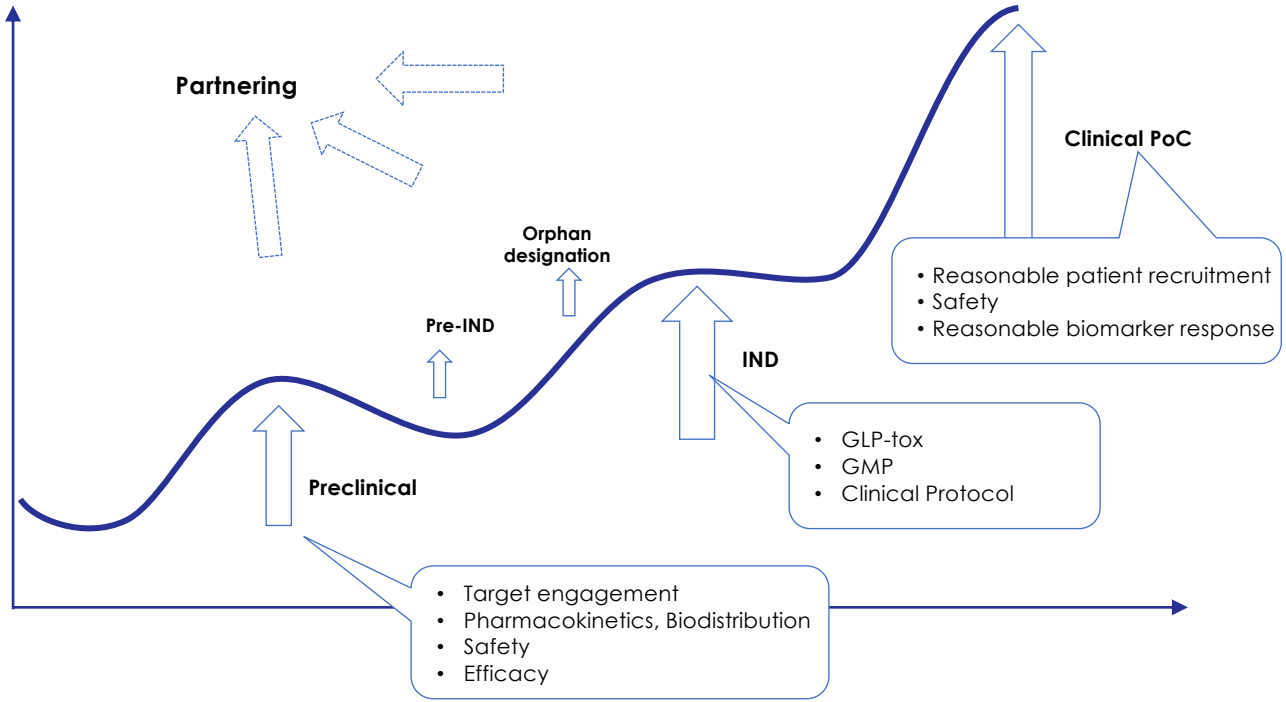






Future pre-clinical and clinical trials are expected to increase the value of the company.

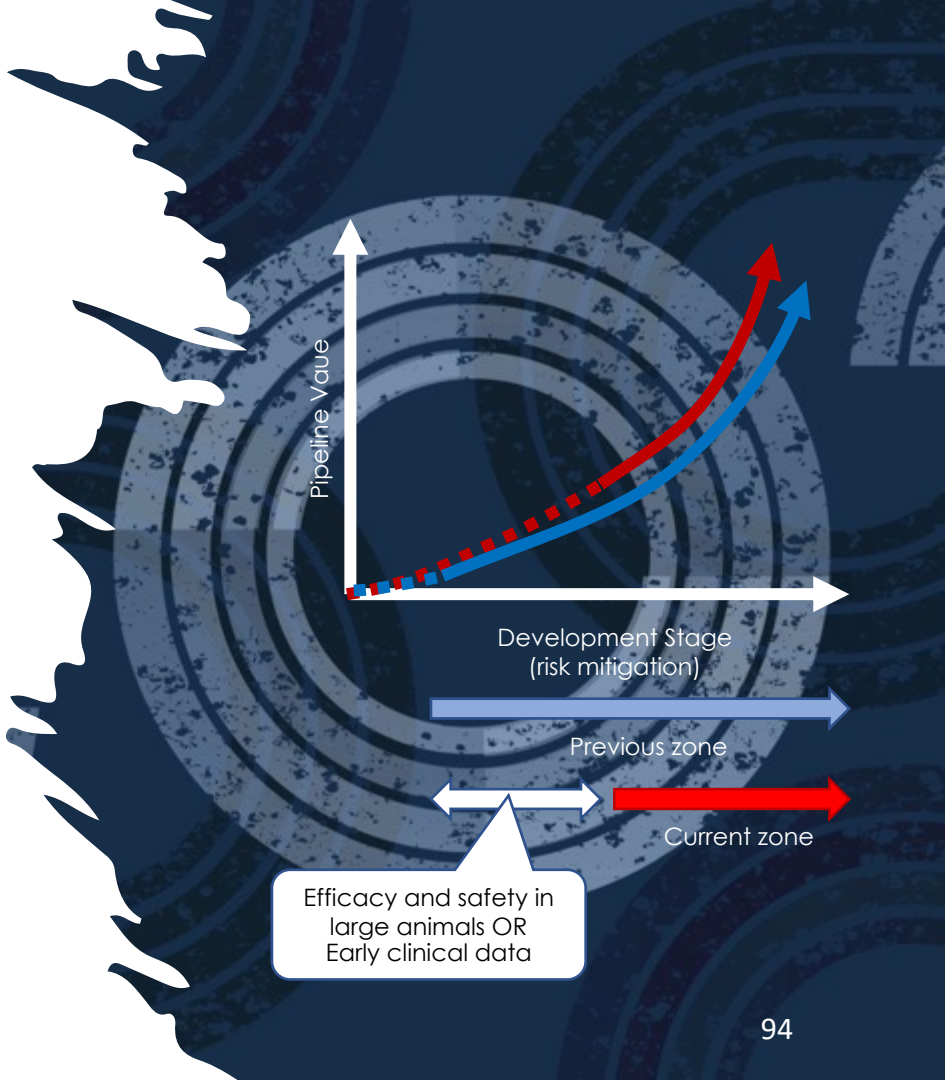
Expected milestone events and impact on corporate value



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Partnering strategy

- We try to maximize the number of diseases that can be developed by CRISPR-GNDM®. On the other hand, given our limited resources, it is important for us to find partners with whom we can share risk/profit.
- Partnering will be undertaken when conditions and timing are deemed appropriate based on the value and business characteristics of each pipeline.
- Take an open stance on forms of partnering, including licensing, option deals, and co-development
- At the same time, we will negotiate the timing and scheme of the alliance in a manner that allows us to accumulate our own development know-how, with a view to improving the efficiency of future development and maximizing profits.



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Aim of Fundraising

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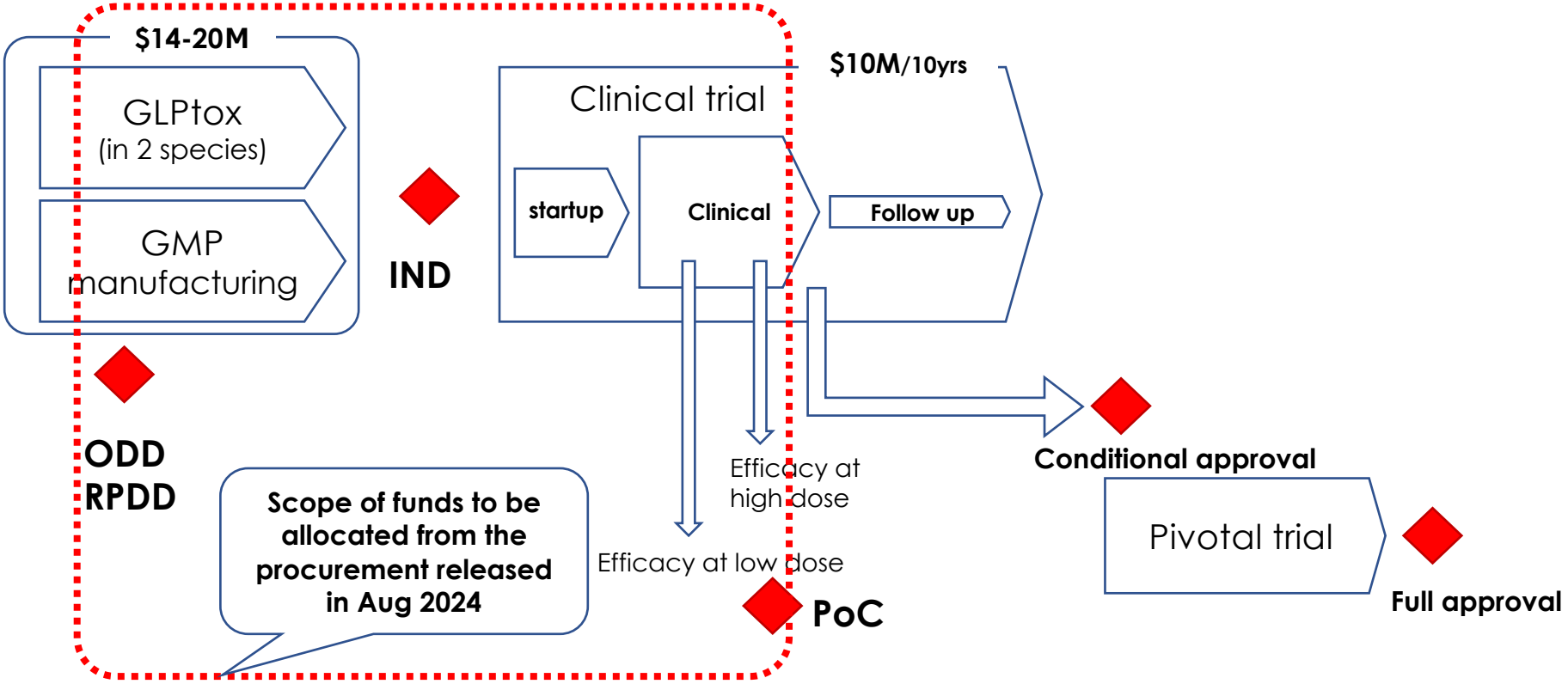
Secure funding until the next value inflection point

- As a result of the increased partnering hurdles in the biotech industry, P2 or PoC and beyond is a prerequisite.
  - Only 9.1% of assets in the P3 stage are partnered* according to 2023 data.
- Securing funds to reach PoC is key to winterizing through the biotech ice age
- Conversely, if a company is able to reach PoC without partner, in-house sales (= higher profit margin potential) becomes in range

Source "Biopharma Dealmaking: Time for a Rethink?" by Lumanity at Swiss HLG Conference 2024

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MDL-101 *Value Inflection Points and* Funds Needed to Reach Them



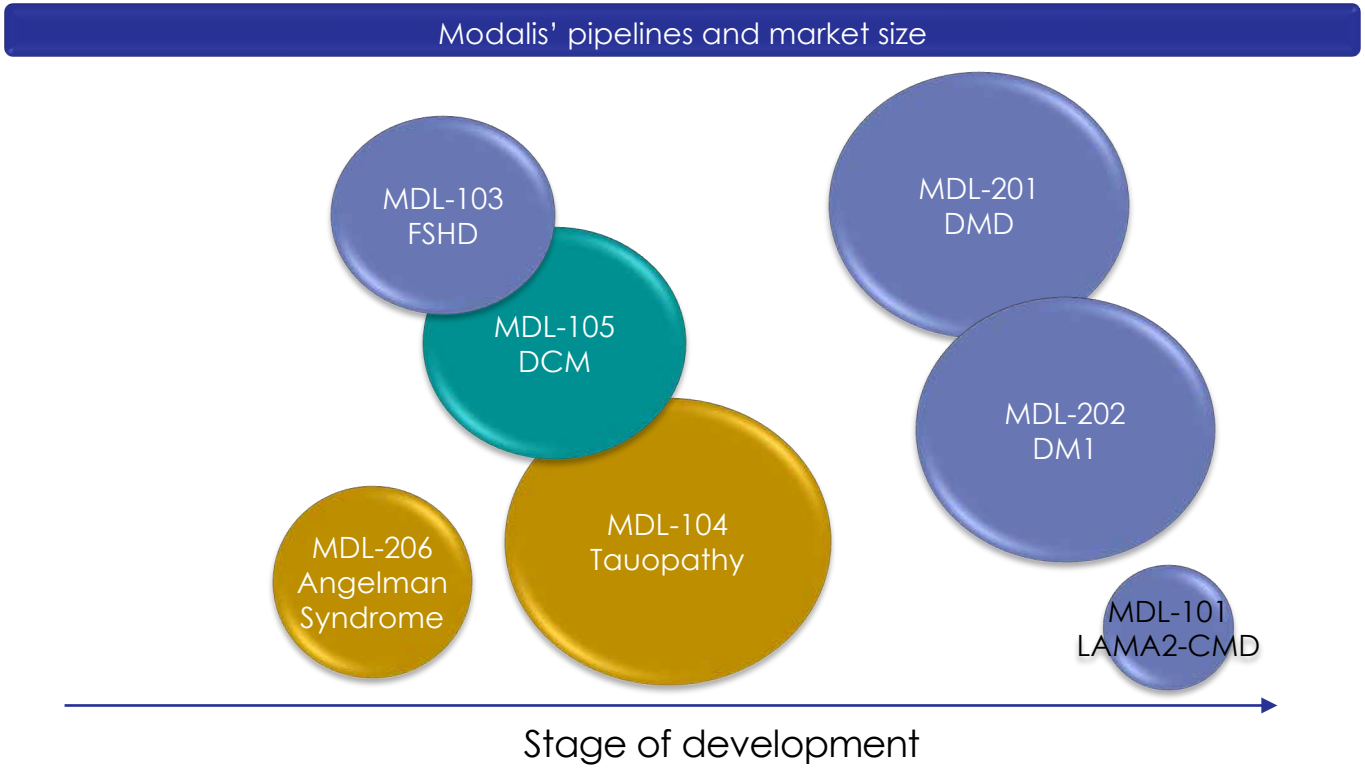
Note) The demand for funds is stated in U.S. dollars because it is primarily generated in U.S. dollars, and the Japanese yen equivalent may fluctuate depending on exchange rates.

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Updated

Modalis' pipelines and market size

Large indication programs follow MDL-101 which paves the clinical path



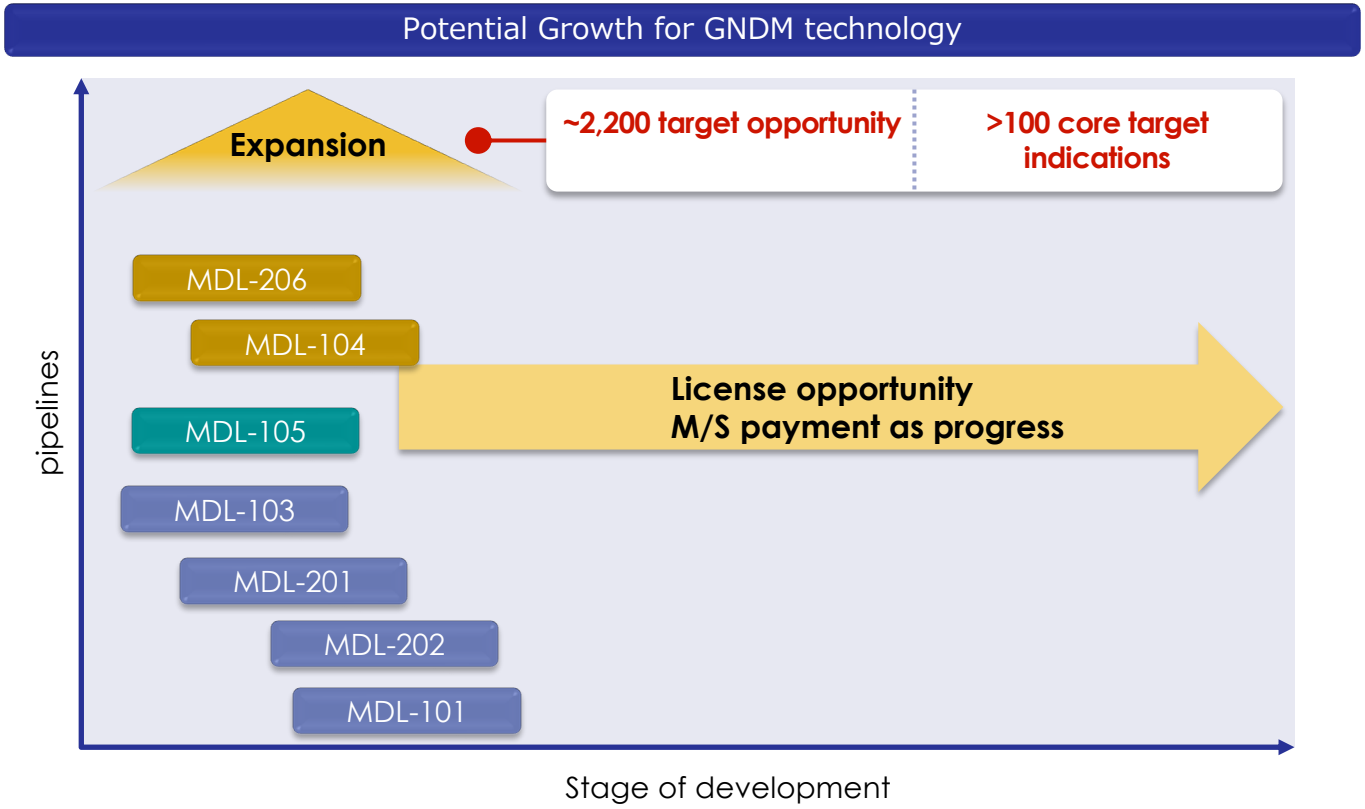
※ Size of circles represents an image of market size or patient number of each indication

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Growth Strategy

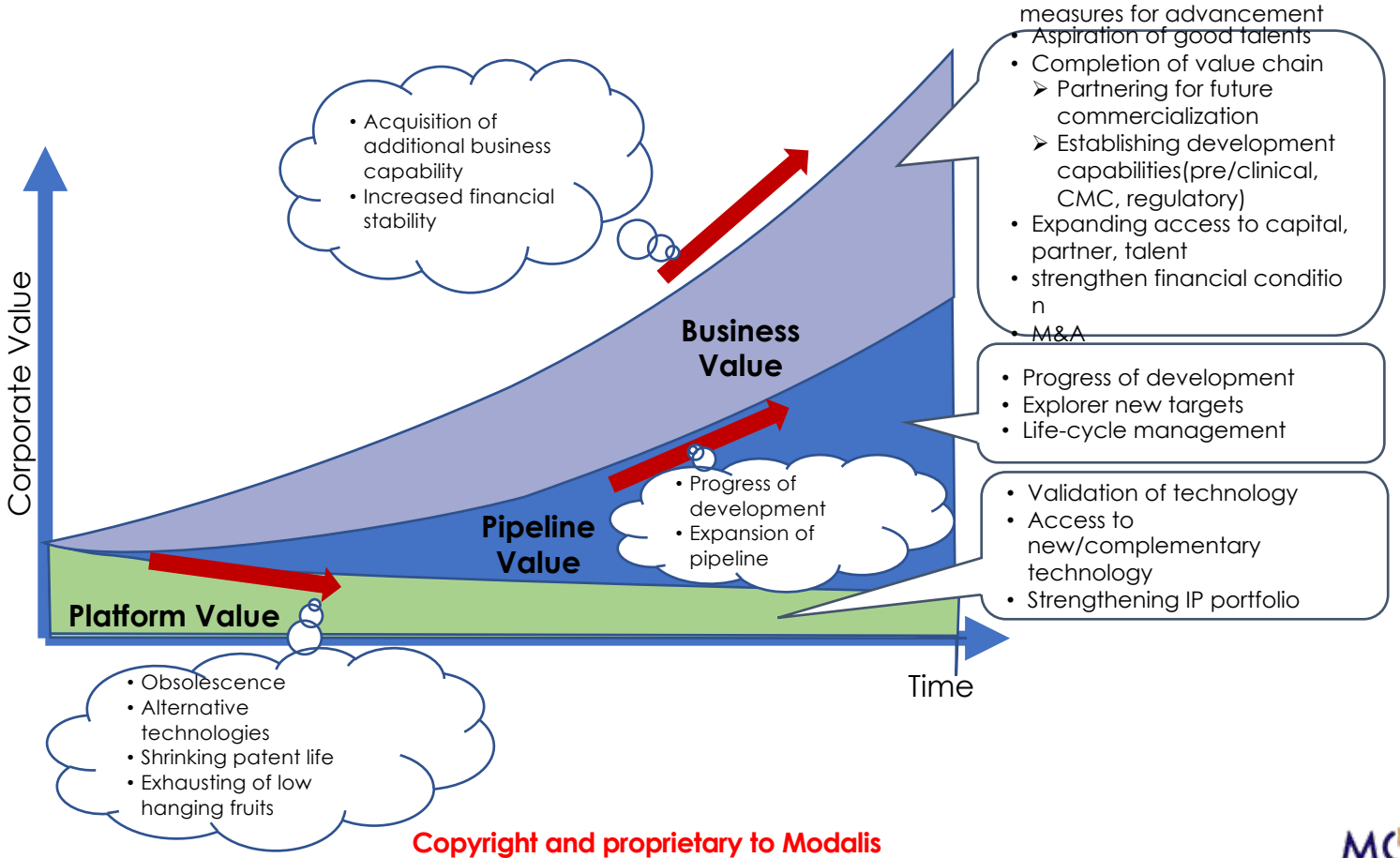
opportunity expands two dimensionally



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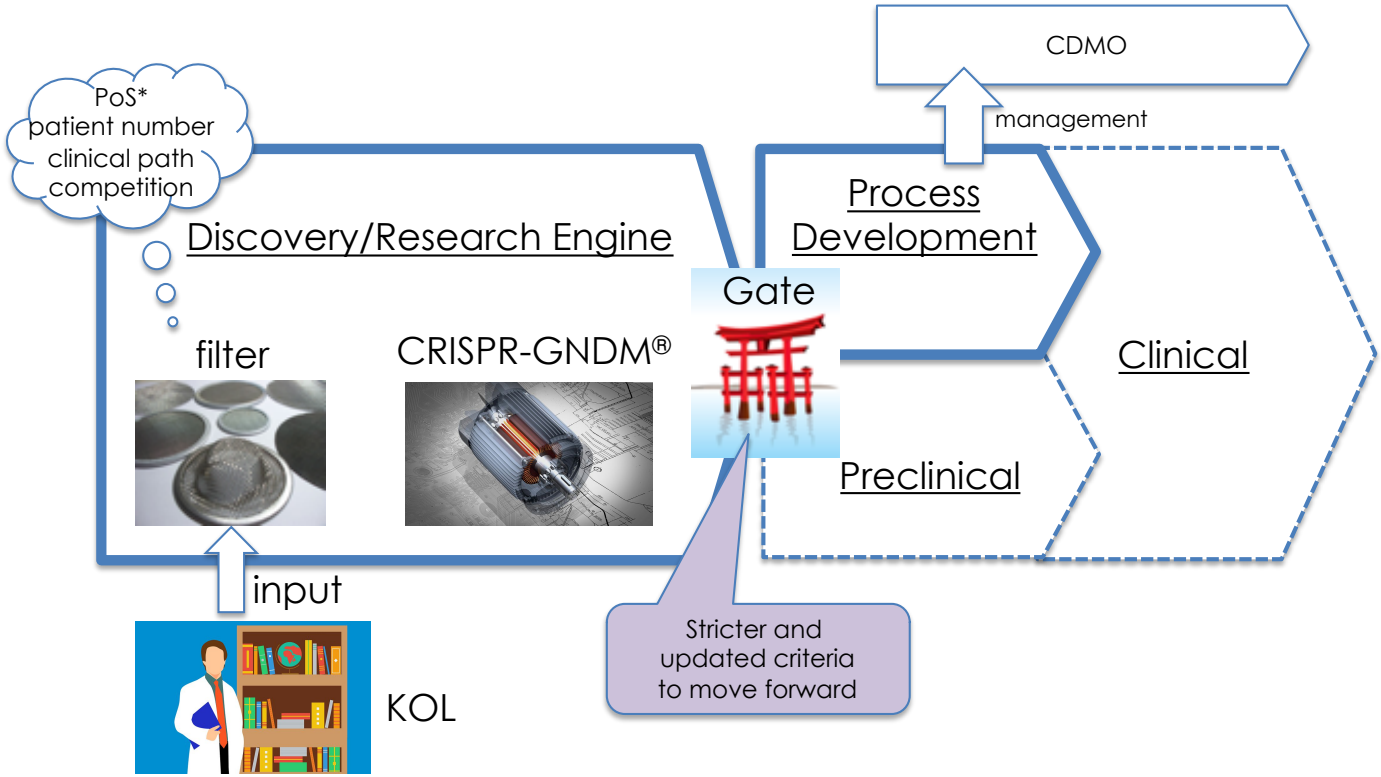
Composition of Modalis' value and measures for advance



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Upon transition from R to D, which cost time and money, stricter decision is made for higher ROI and better resource allocation.

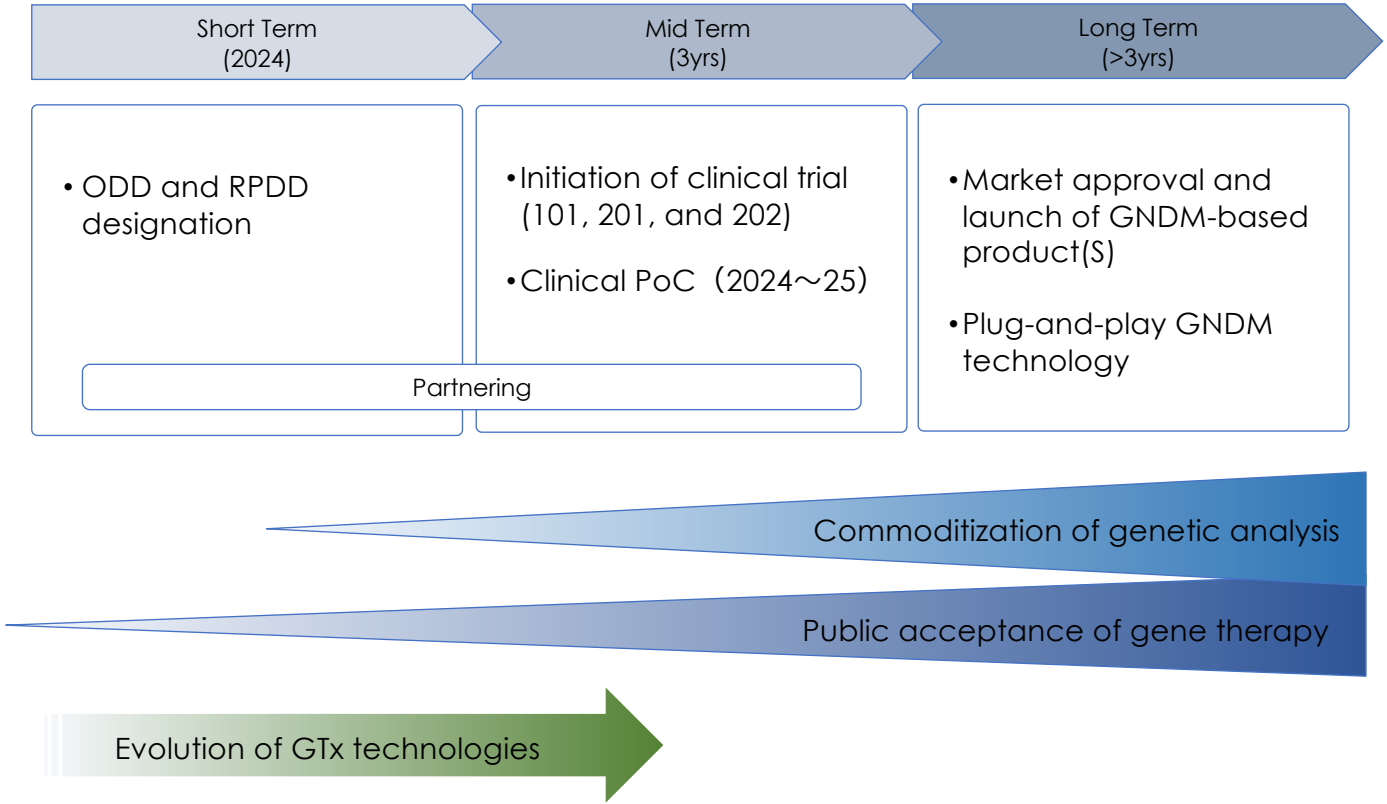


PoS: Probability of success

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The future Modalis envisioned



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6. Risk infomation

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Known Risks and Preventative Measures（1）

Topic	Main Risks	Probability	Level of Impact	Preventative Measure(s)
(1) Risks related to the research and development of gene therapies	The risk of unforeseeable problems developing due to working with cutting-edge experimental medical treatments	Low	High	Constantly monitoring cutting-edge scientific technologies and related businesses, making pertinent judgements, taking appropriate actions
	Due to gene editing technology being a field with steady progress and rapid advancement, there is a possibility of new technologies appearing and risk of competing with other modalities	Low	High	Ensuring we are using the most up-to-date version of the underlying technologies in our research and subsequently monitoring new trends in technologies, and adopting necessary technologies as needed R&D will be carried out with priority given to pipelines with competitive advantage, and portfolio reviews such as discontinuation decisions will be made as needed for diseases for which competitive advantage cannot be maintained
(2) Risks related to the pharmaceutical industry	The risk of failure or decision to suspend development caused by a certain product or technology used in pharmaceutical development	Moderate	High	Regularly reviewing risk mitigation measures and making appropriate modifications to our portfolio when collaborating with partner companies and adding pipelines to our portfolio
(3) Risks related to execution of business activities	Due to the fact that execution and related decisions are driven by our partners, there is a possibility development is suspended and the risk of contract cancellation even if there are no failures during development	Moderate	High	Aiming to stabilize for the future and maximize profits through the stratification of our pipelines and strategically adding to our portfolio
	The risk of delays in the timeline if appropriate business coordination measures are not made regarding production that is entrusted to external parties, preclinical experiments, etc.	Low	High	Performing appropriate project management, concurrently negotiating with various candidate service providers, and securing a slot to prevent delays in the timeline

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Known Risks and Preventative Measures（2）

Topic	Main Risks	Probability	Level of Impact	Preventative Measure(s)
(4) Risks related to intellectual property rights	The risk that patents other than the originally introduced license will be required while the basic patent is in a disputed state.	Low	High	Striving to secure patents for each project (including the Company's own patents) and concurrently investigating the introduction of necessary patents
(5) Risks related to business performance, financial condition, etc.	The risk that recorded profits will not be stable, since profit is strongly influenced by the license agreements, milestones, etc.	Moderate	High	Using a hybrid model to stabilize for the future and maximize profits through the stratification of our pipelines and strategically adding to our portfolio
	The risk of significant events related to the going concern assumption.	Moderate	High	Using a hybrid model to stabilize for the future and maximize profits through the stratification of our pipelines and strategically adding to our portfolio
(6) Risks related to the company structure	The risk that we are unable to secure talented individuals who possess technical knowledge or skills for scientific research and development	Low	High	To attract talent, we are engaged in R&D that appeals to potential candidates and creating a favorable working environment in addition to adopting of a restricted stock unit system to recruit competitively
	The risk that negative gossip or rumors influence the public credibility of the Company group	Low	Moderate	Misinformation and rumors are taken seriously, and the Company maintains their position by the equitable, fair, and timely disclosure of information

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