English translation for reference purposes only

For Investor Meeting of 2Q/FY2023

(TSE：4883)

Modalis therapeutics Corporation

August 8 , 2023

In case of any discrepancy, the Japanese version shall prevail

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1. CRISPR-GNDM® and its advantages

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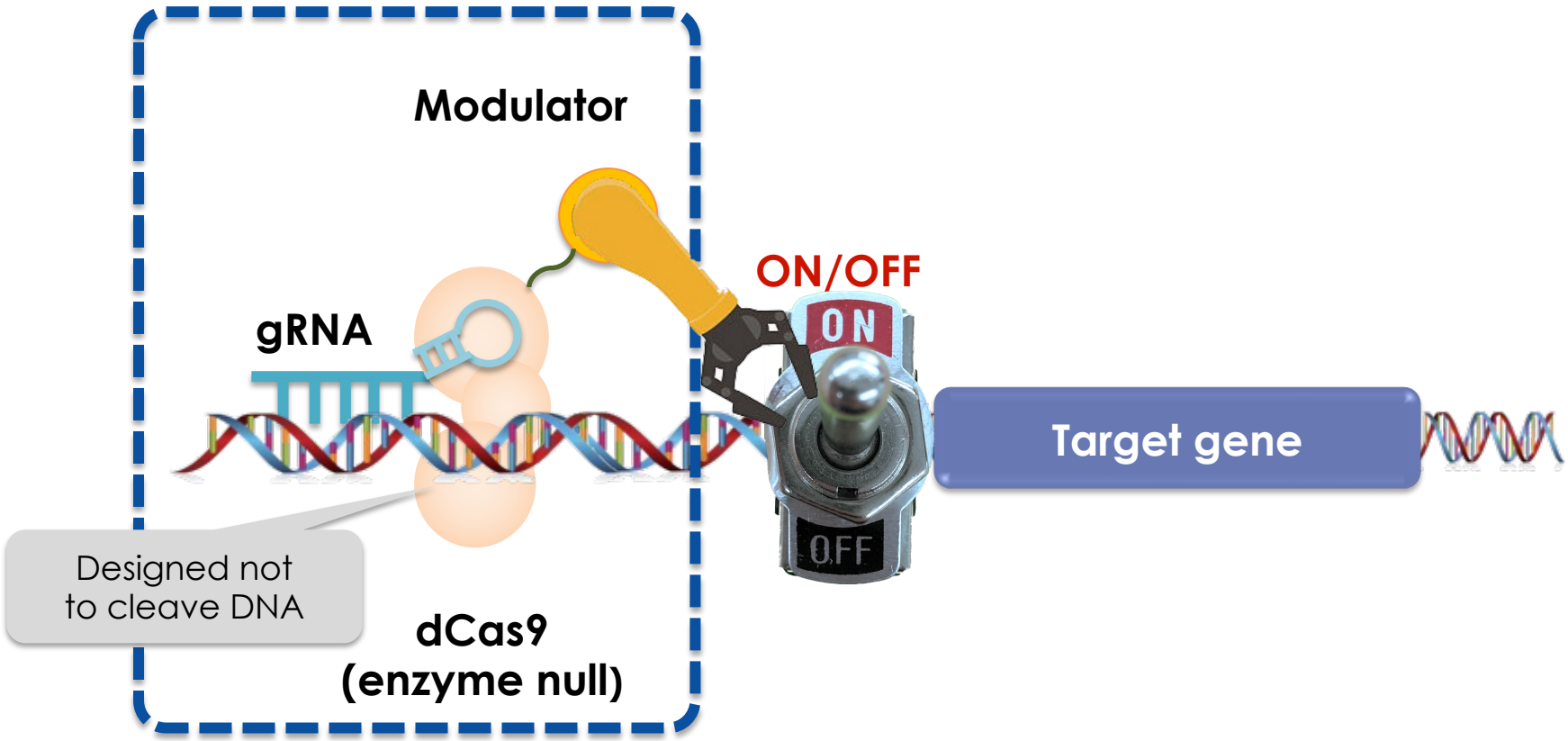
Non-cleaving CRISPR = CRISPR-GNDM®

Enables treatment of genetic disorders by controlling ON/OFF switch

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



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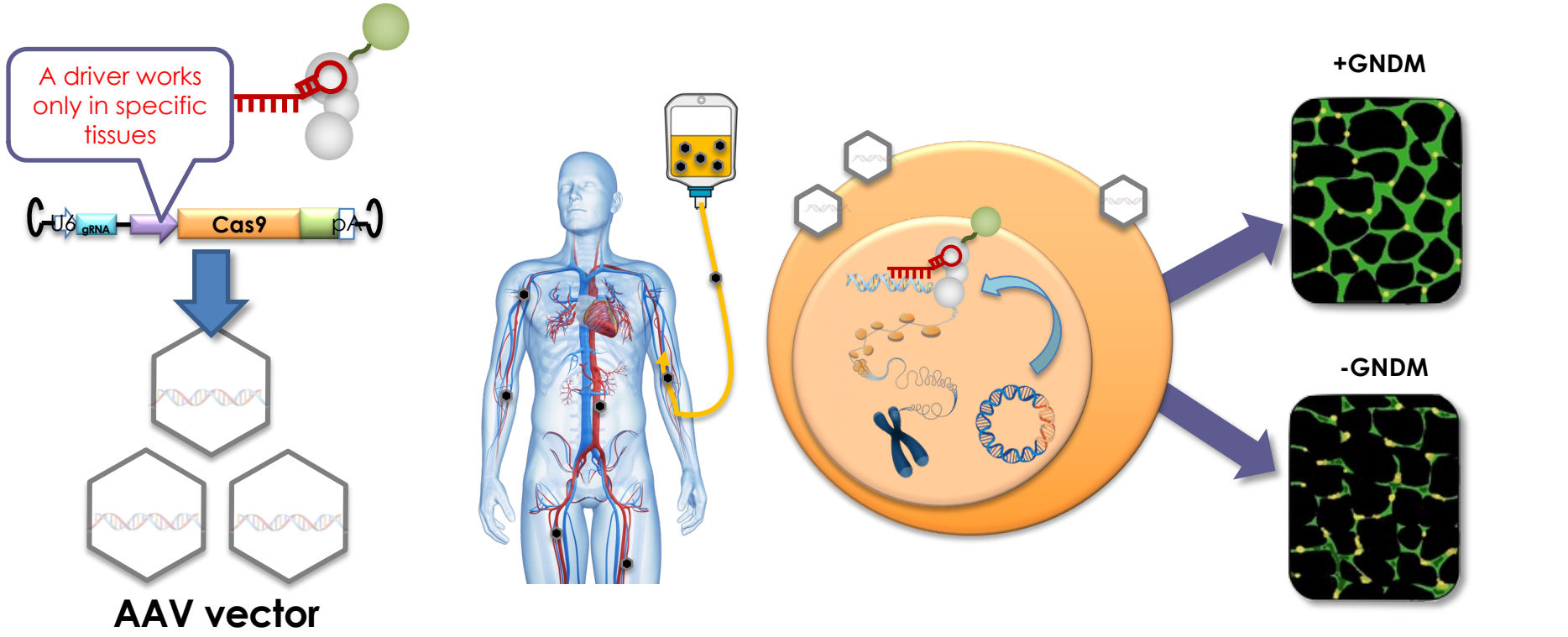
Delivery of CRISPR-GNDM® to target

Use AAV vector to deliver GNDM to target cell



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

	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

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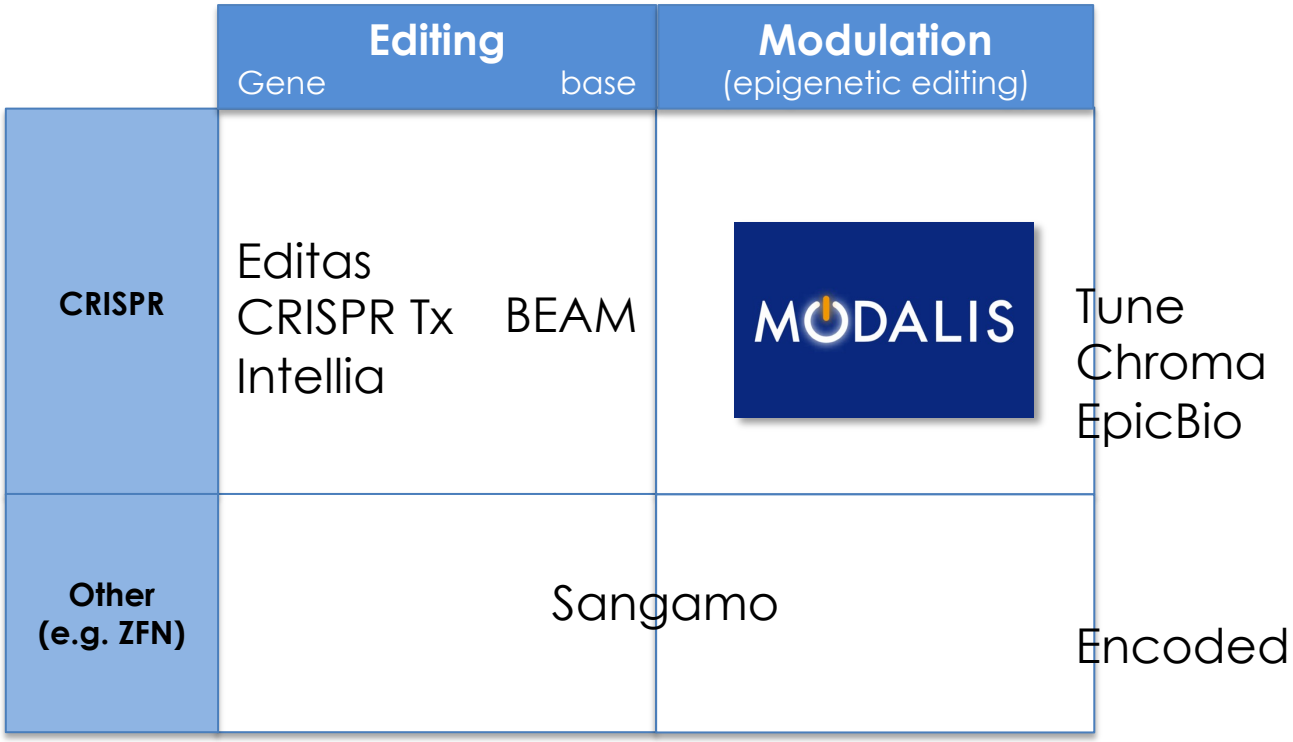
Modalis is uniquely positioned within the CRISPR field



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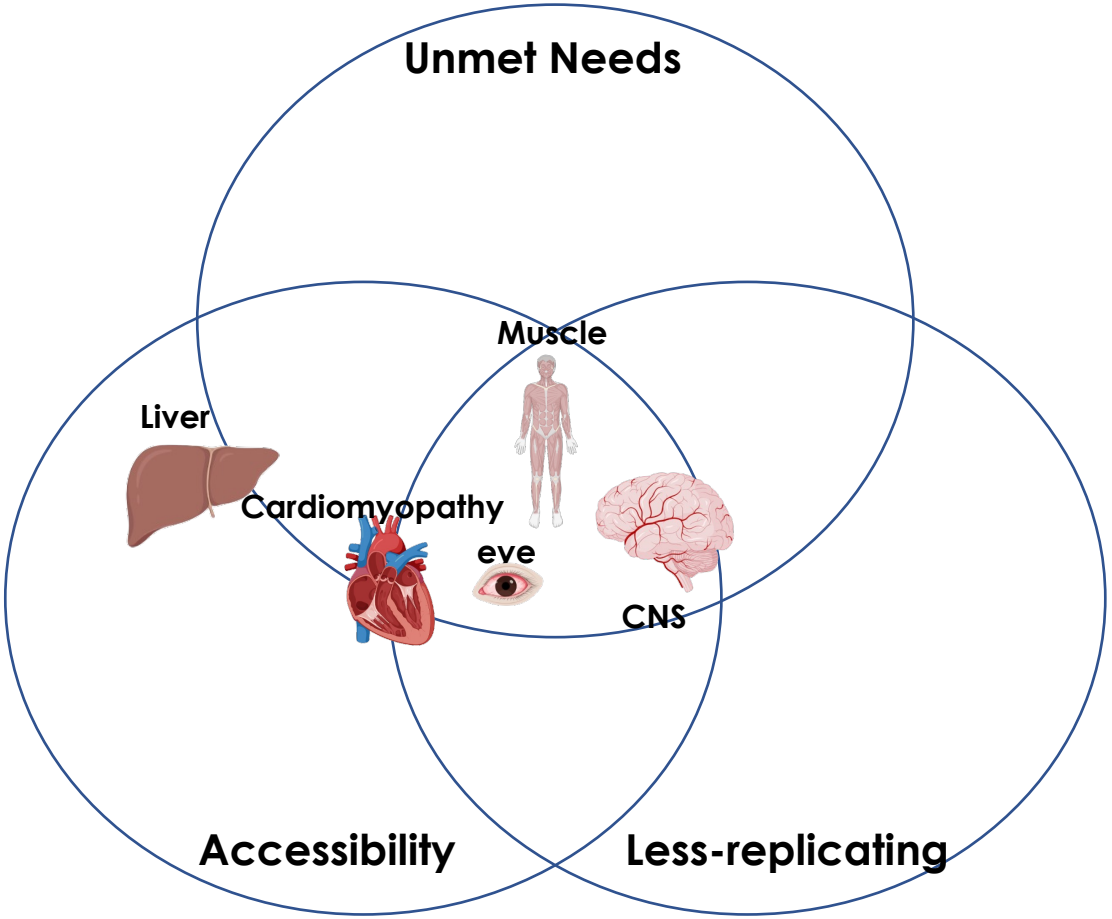
Modalis focuses on muscle, CNS, and cardiomyopathy

Target selection for Modalis' gene therapies



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2. Topics in 2Q and pipeline status

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Gene therapies approved by US FDA

Drug price and market size of gene therapies

Trade Name	cost	Indication	Manufacturer	Patient Population	WW market size* (mil USD)
Lxturna	$850k	RPE65	Spark/Roche	2 per 100,000	$65M ♭
Zolgensma	$2.1M	SMA	Novartis (Avexis)	1 in 10,000 live births (Approx. 10,000 to 25,000 in US)	$1.3B ♭
HEMGENIX	$3.5M	Hemophilia B	uniQure CSL Behring	1 in 30,000 male	$88M ♭
ELEVIDYS	$3.2M	DMD	Sarepta	1 in 3,500 male birth	$4.1B #
Roctavian	$2.9M	Hemophilia A	BioMarin	1 in 5,000 male	$262M #

♭ each company's website
#Grand view research, WW market size

Source: National Organization for Rare Disorder, Companies websites

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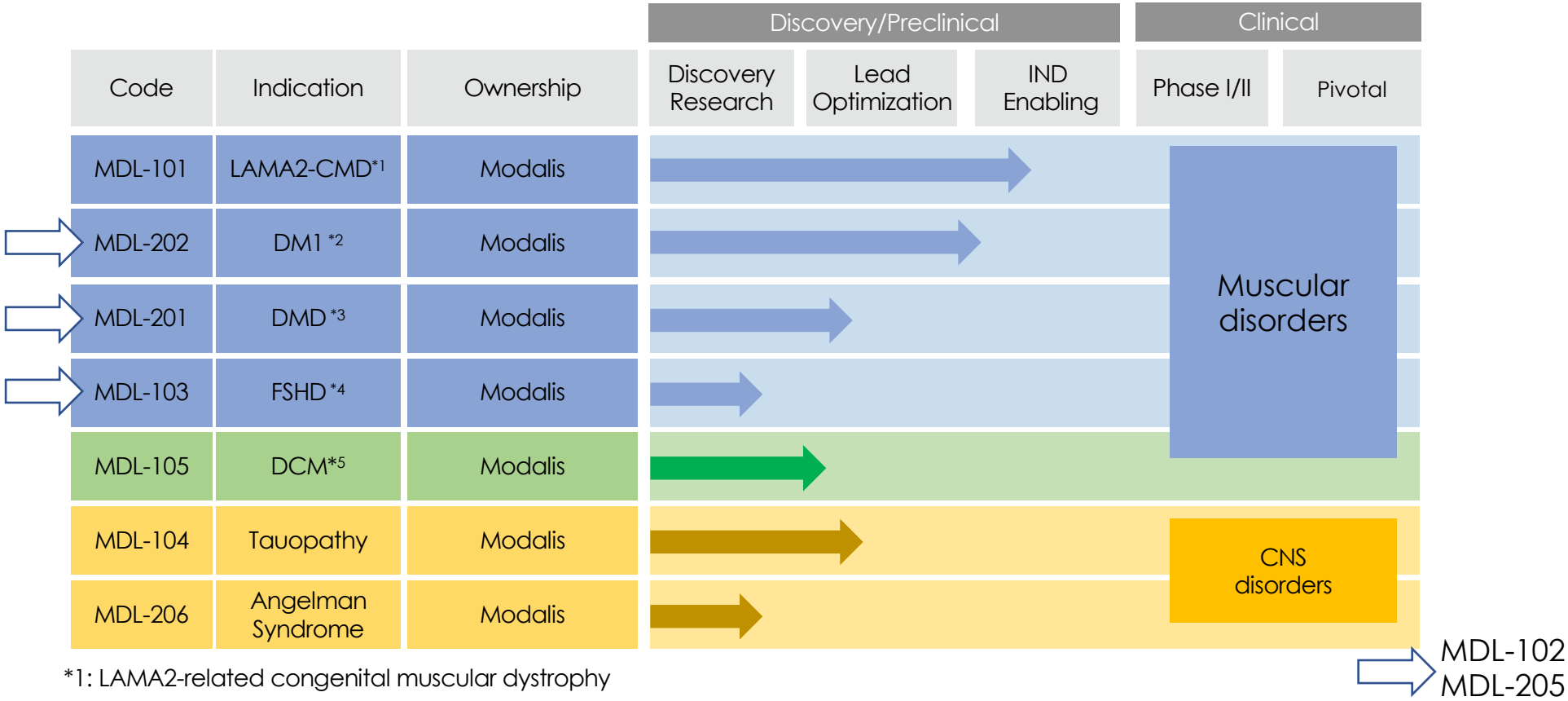
Modalis regained rights of MDL-201 and 202 from Astellas

- Modalis regained the rights of MDL-201 and 202 from Astellas
- The target indications of the programs are DMD and DM1, respectively
- The market size of the indications is relatively large and Modalis will gain new revenue opportunities throughout new partnership or commercialization.
- Applying the know-how accumulated in the development of MDL-101 including the muscle tropic capsid, Modalis will strengthen the products
- As target engagement is confirmed in the NHP study of MDL-101, the company has confidence that the new version of the molecules that share the same vector system shall have extrapolated efficacy and safety.
- As new assets have been added, the company sharpened its strategy to put focus on MDL-101 and MDL-202.
- With this reacquisition, the company reorganize the pipeline to shift to muscular diseases where delivery and our know-how are well established
- The development of CNS programs will be resumed, subject to resource allowances while research continues.

Reorganized pipeline and set the muscular disease-centered strategy

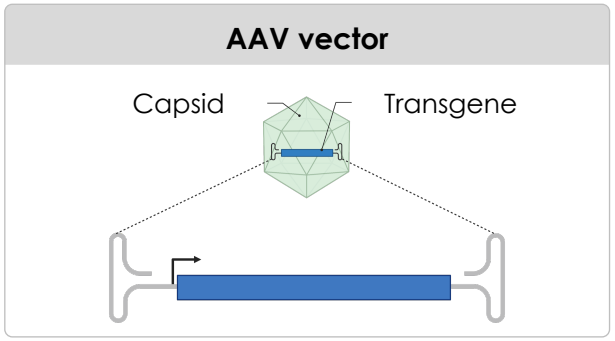


*1: LAMA2-related congenital muscular dystrophy
*2: Myotonic Dystrophy Type 1
*3: Duchene Muscular Dystrophy
*4: facioscapulohumeral muscular dystrophy
*5: Dilated Cardiomyopathy

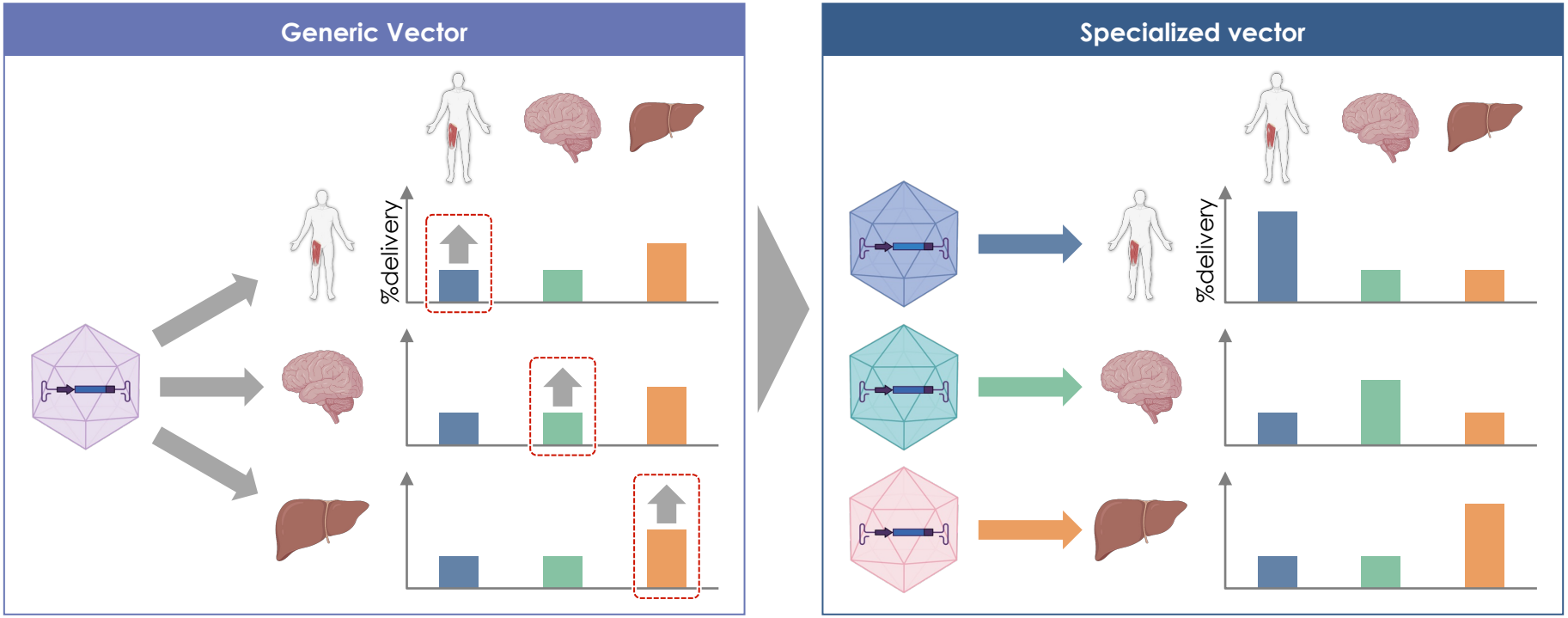
The other topics in pipeline reorganization

- Modalis adds MDL-103 which targets FSHD by silencing Dux4 gene and the company has incubated for years.
- Continue CNS programs including MDL-104 but muscle programs are put higher priority
- MDL-102 and MDL-205 were deprioritized from the pipeline.

Big innovations have been brought to AAV vectors recently

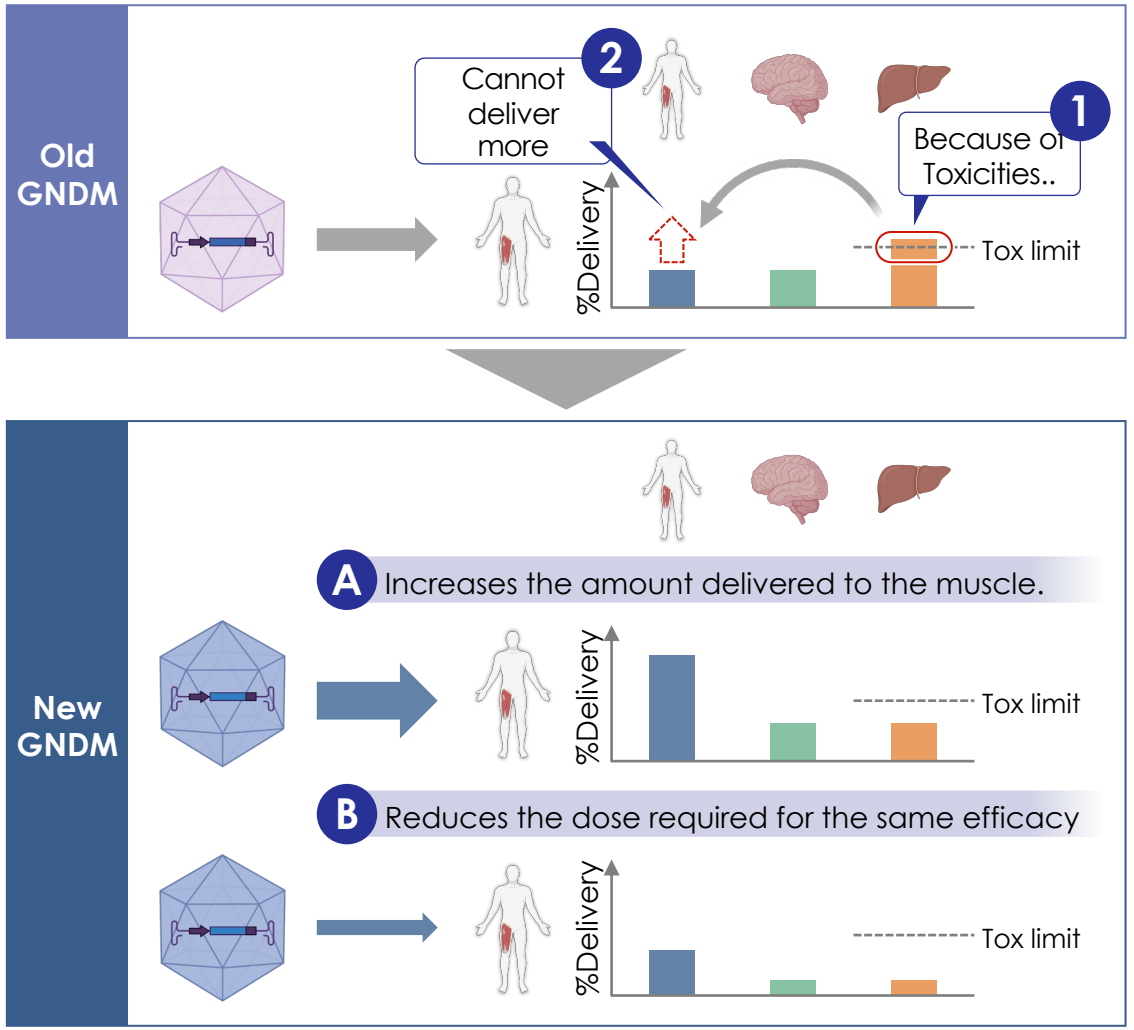


- Previously, generic vectors such as AAV2, 6, 8, and 9 were universally used for all target diseases
- Those capsids are predominantly sequestered in the liver after systemic injection, and cause hepatotoxicity which limits dose of AAVs.
- Recently developed engineered vectors have a much higher tropism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



Transition to specialized capsid is the need of the field and will be beneficial in the long run

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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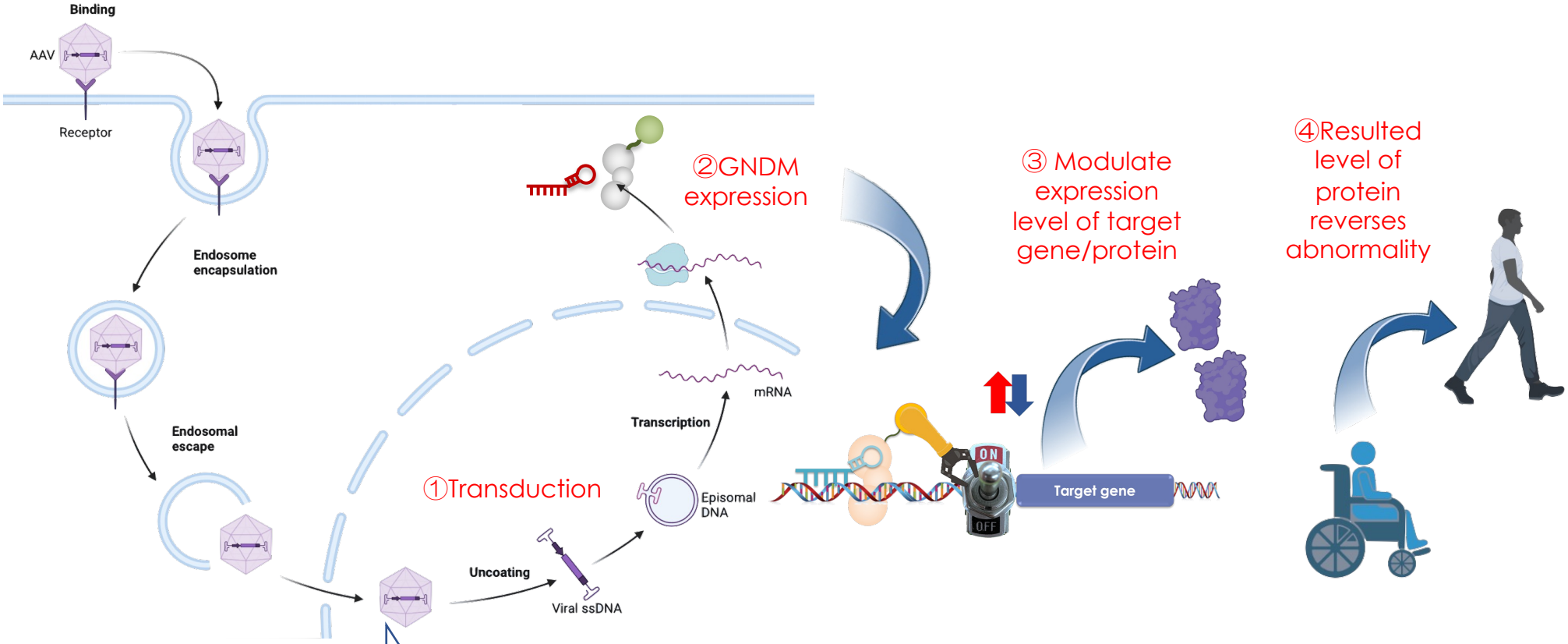
Among the 4 steps to demonstrate efficacy, 2 steps are common to the muscle programs and confirmed to function in NHP



①AAV Transduction → ②GNDM expression → ③Modulation of target → ④Efficacy

Vector system (platform)

gRNA

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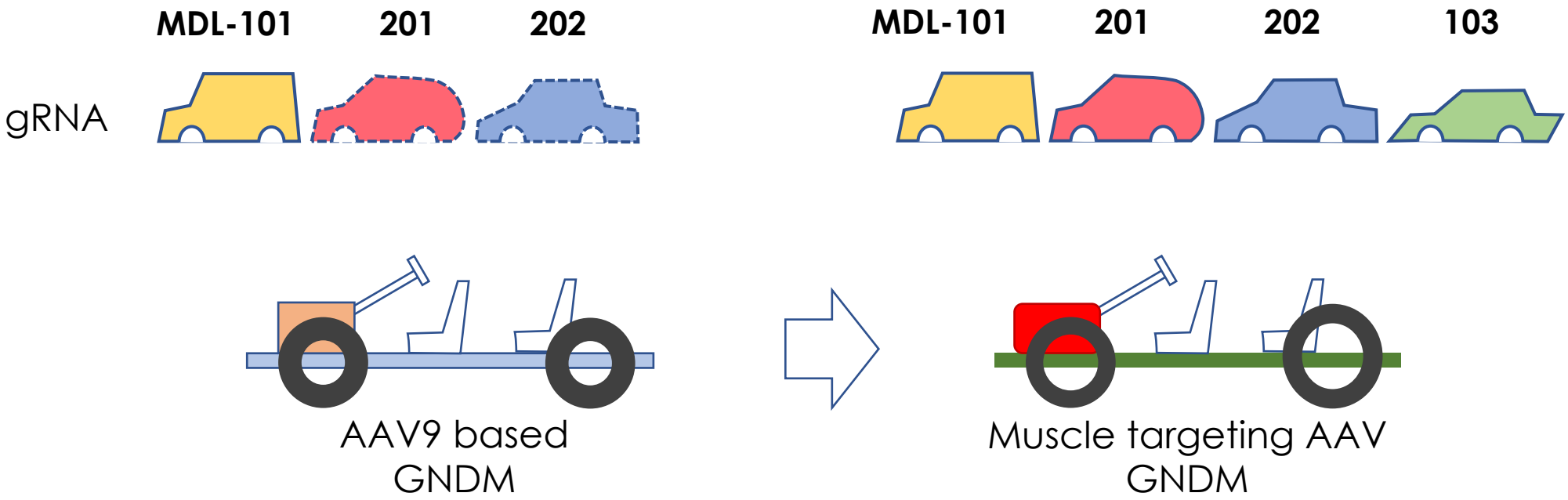
Like MDL-101 which has already been transplanted to the new system, 201and 202 will be transferred together with 103 to increase their potency



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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-in-class and the first LAMA2-CMD treatment

Prevalence	**1 in 30,000*** 10,000 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: *Ophanet #*Modalis assumption based on prevalence and potential*

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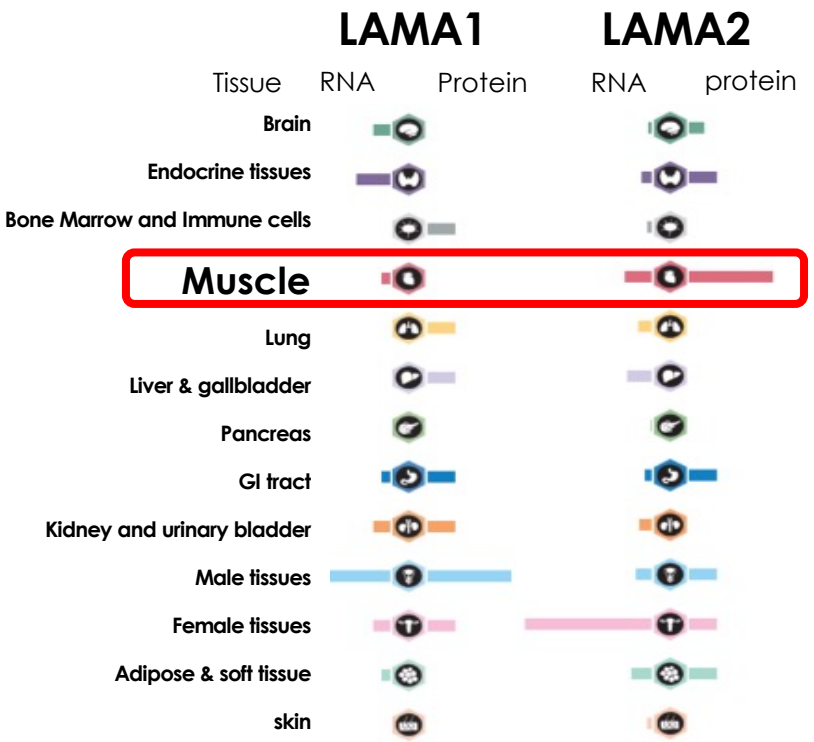
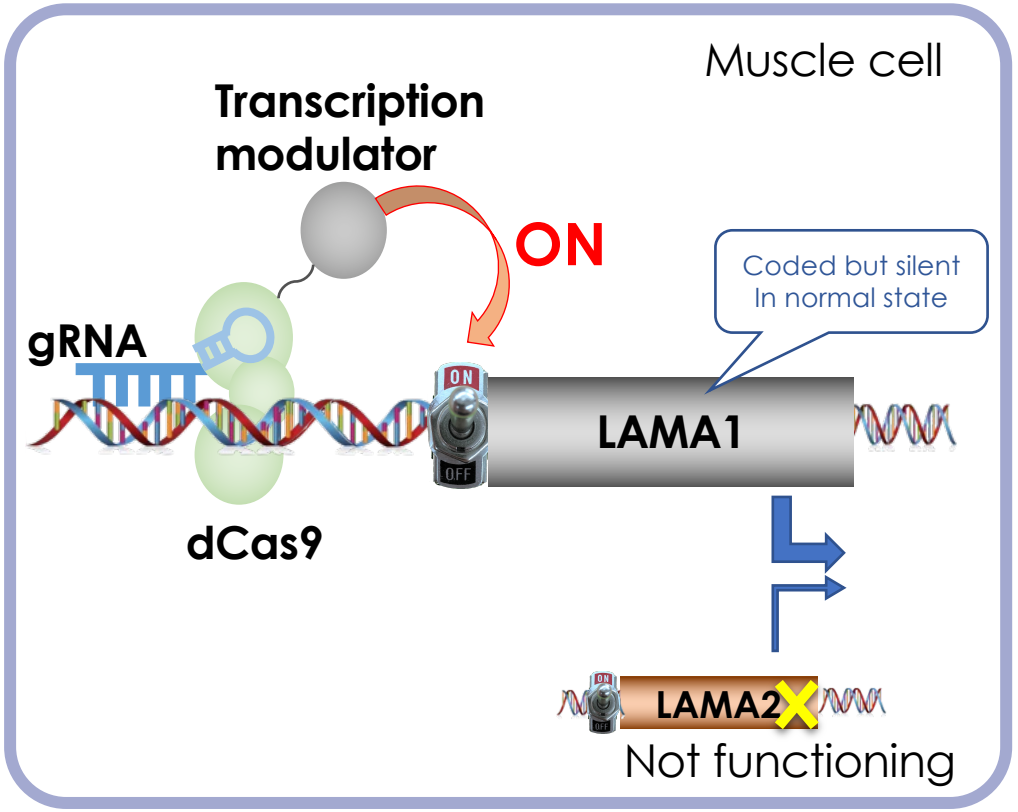
By activating the sister gene, LAMA1, GNDM compensates missing function of LAMA2, which is too big to be addressed by regular GTx

Exspression pattern of LAMA1and LAMA2 by tissues



CRISPR-GNDM® targeting LAMA1



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Status of Development of MDL-101

- What have been done
  - Mouse model data in two disease strains (dy2j and dyW) and wildtype
    - Upregulation of LAMA–1 gene and protein along with GNDM expression
    - Improvement in biochemical and physiological readouts as well as prolonged survival
    - Sustained expression of GNDM in WT mice for 2 years
  - pilot NHP study to explore dose and to assess immune reaction against GNDM
  - Process development initiated for the GMP campaign in collaboration with a CDMO.
  - INTERACT meeting with FDA (Jul)
  - Changed to a muscle-specific capsid and new constructs have been evaluated in rodents and NHPs.
    - Positive results including meaningful LAMA-1 expression have been obtained.
  - Redesigning the manufacturing process for the new version molecule
  - KOL meetings and drafting clinical synopsis and protocol
  - **Received pre-IND response from FDA(June 2023)**
- Next steps:
  - Continue IND enabling GLP tox and PK/PD
  - Continue process development and pilot productions for GMP campaign

KOL: Key Opinion Leader

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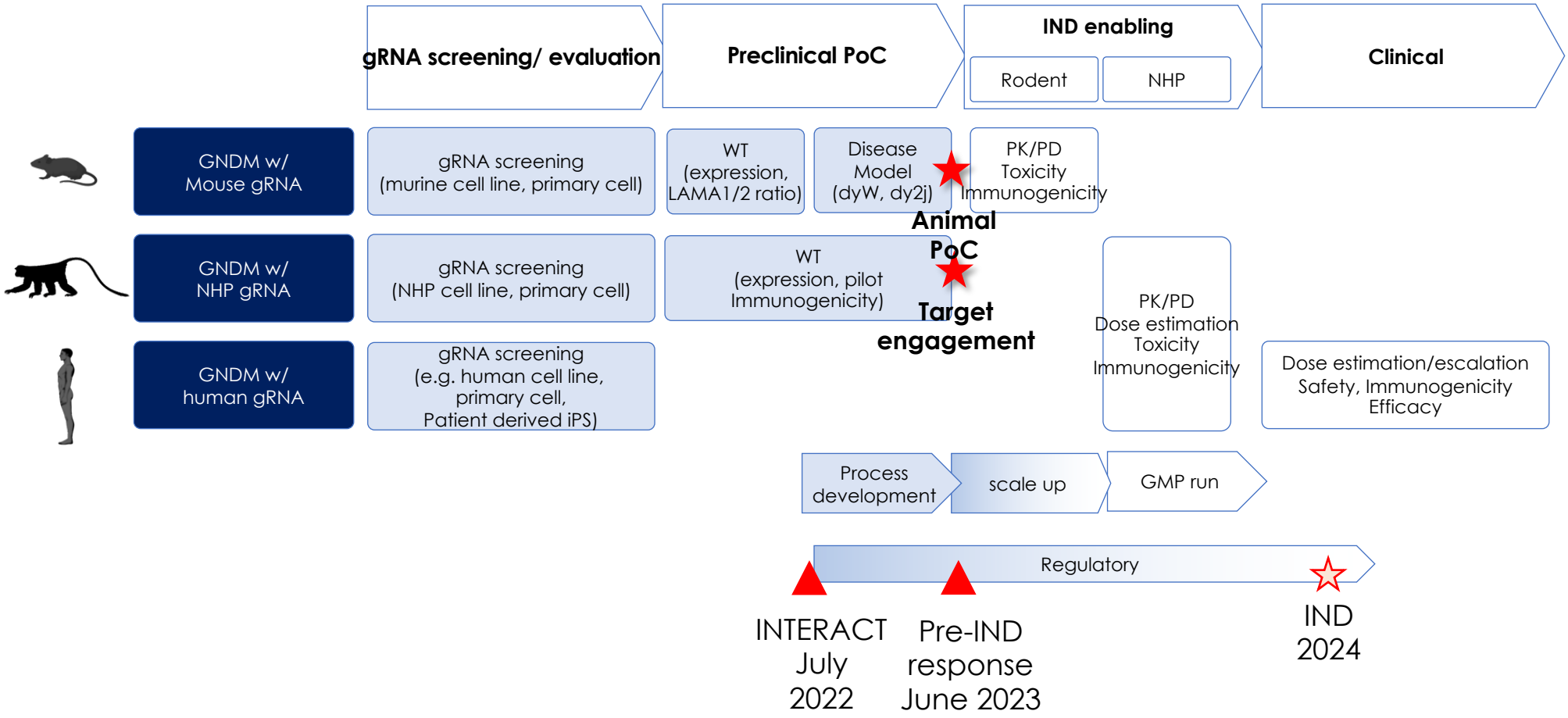
Conducting IND enabling studies as well as process development

Current status of MDL-101 and road map to clinic



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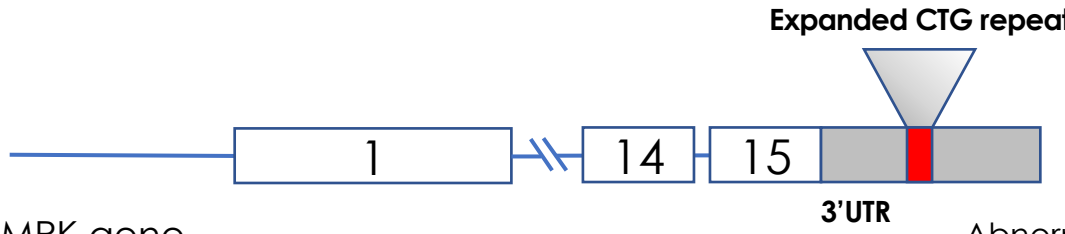
DM1 is caused by abnormal splicing rooted from CTG extension in 3'UTR of DMPK gene

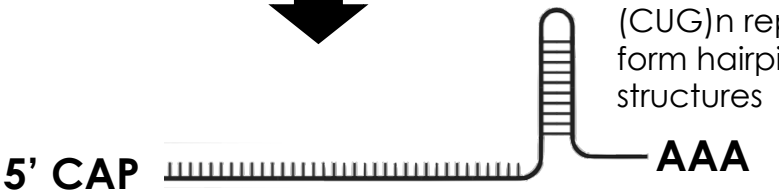
DM1disease causing mechanism



DMPK gene

Abnormally expanded (CUG)n repeats form hairpin-like structures

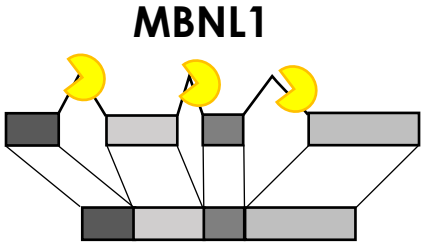
DMPK mRNA With CUG repeat



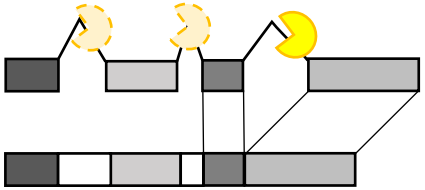
MNBL binds to hairpin-like structures

RNA to accumulate in nucleus by sequestering isoforms of the MBNL

Splicing in healthy people



MBNL1 contributes normal splicing



MNBL goes back to functioning in normal splicing

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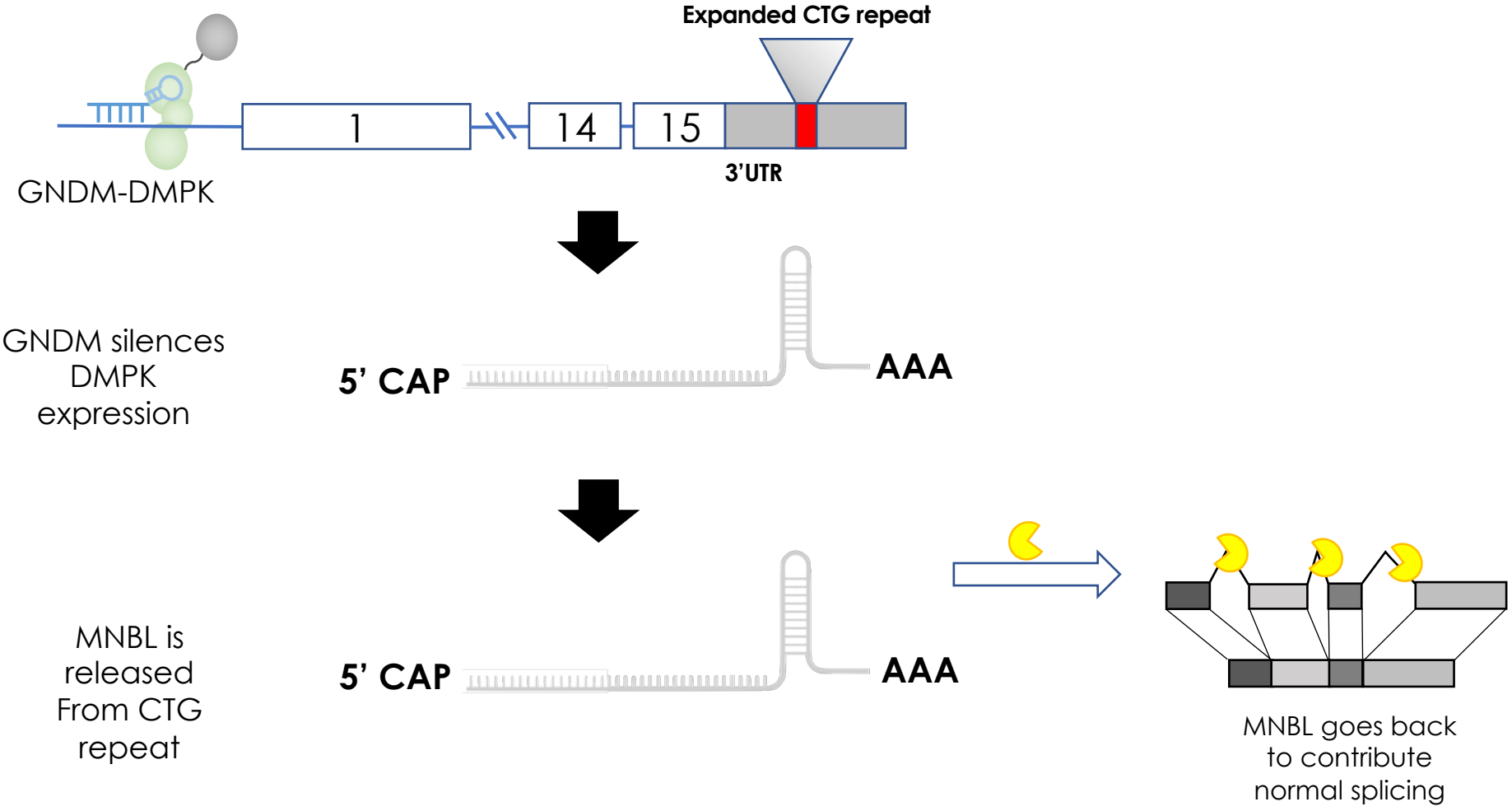
MDL-202 silences DMPK expression and release splicing protein MNBL to function properly in muscle cells

MDK-202's mechanism of action



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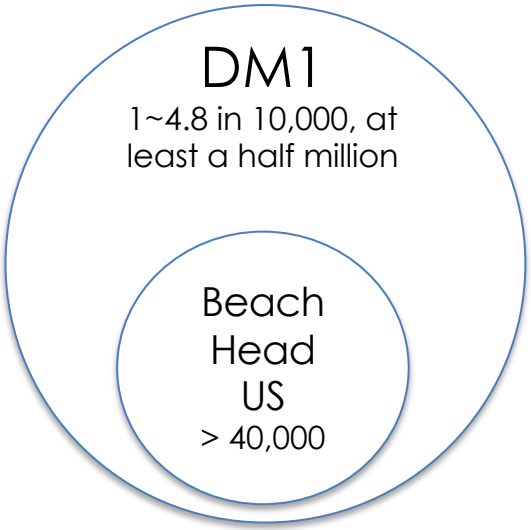
DM1 has relatively large prevalence in muscular disorders

Prevalence of DM1

- 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)



DM1: Myotonic Dystrophy Type 1

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

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Duchenne Muscular Dystrophy (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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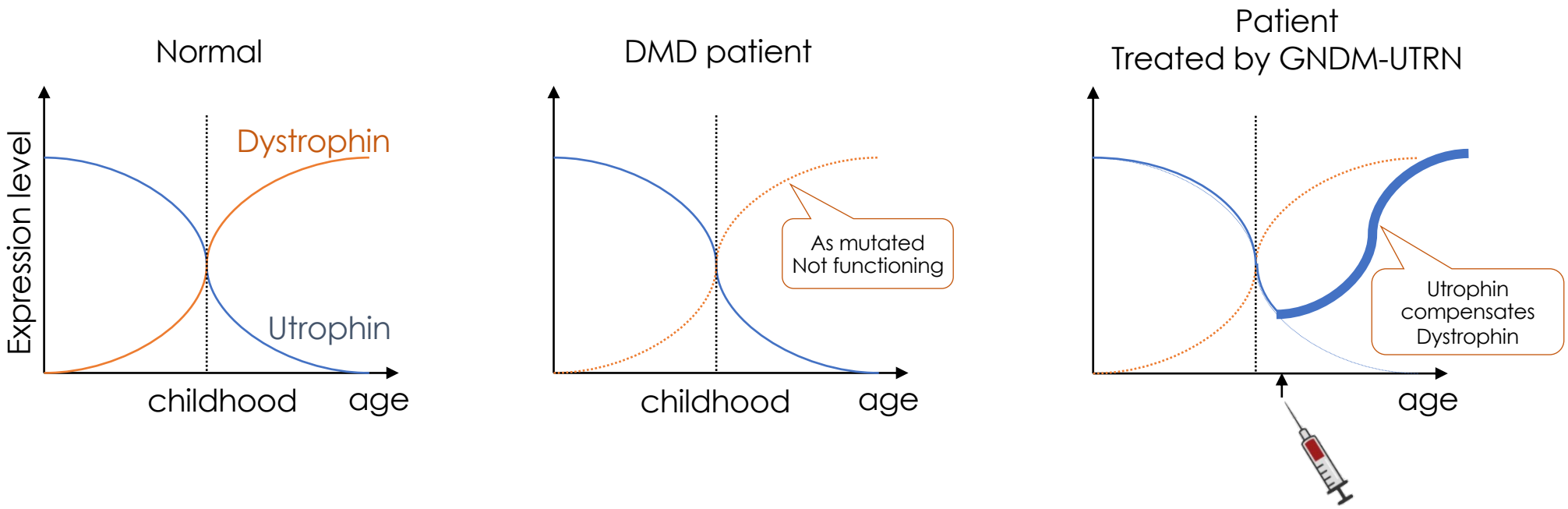
UTRN-GNDM reactivate Utrophin gene to compensate non-functioning Dystrophin gene in DMD patient

Concept of GNDM-UTRN to re-activate UTRN gene



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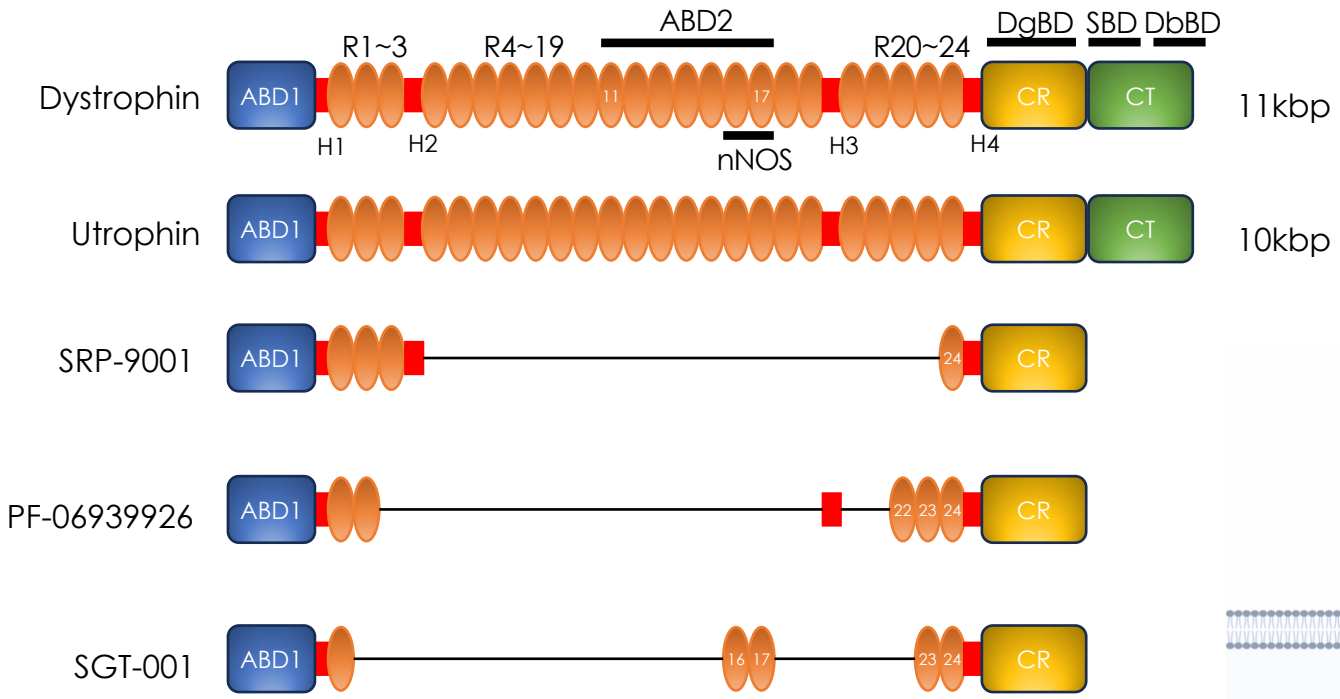
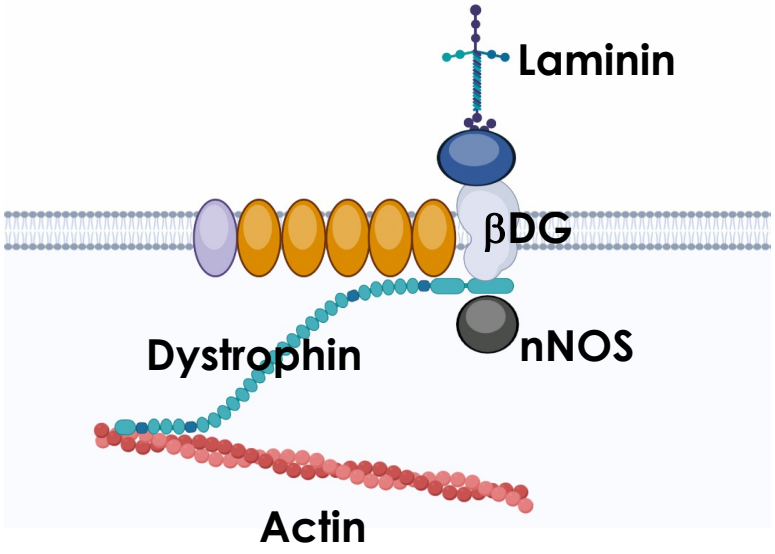
As WT is too large to fit into the AAV, several groups are developing mini-dystrophins knowing they are less functional

Dystrophin/Utrophin Structure and mini-Dystrophins





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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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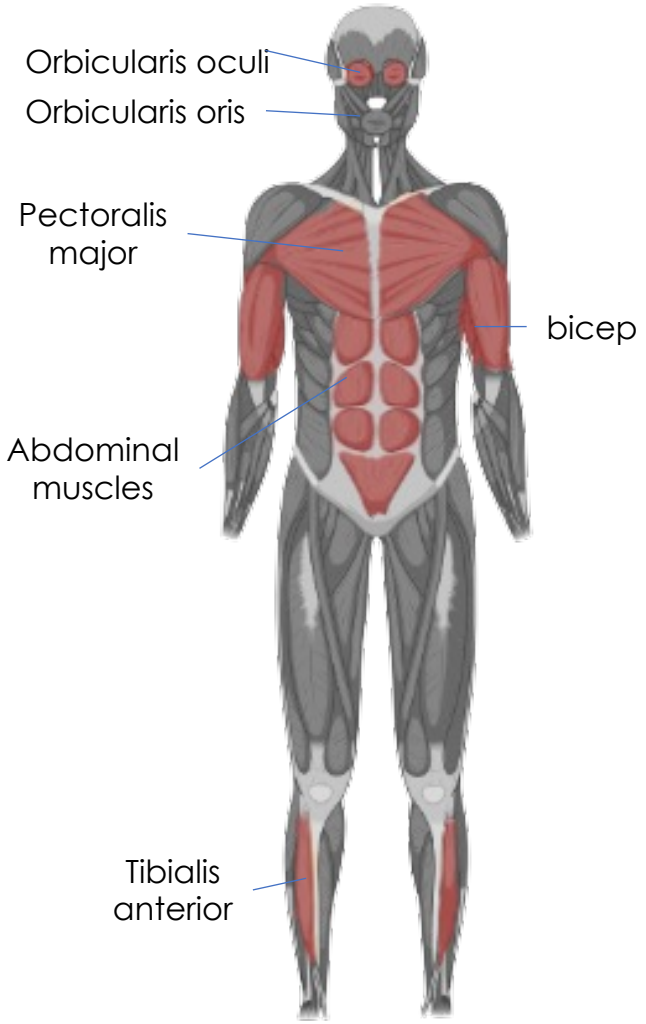
FSHD is a genetic muscle disorder in which the muscles of the face, shoulder blades and upper arms are most affected

Facioscapulohumeral muscular dystrophy (FSHD) is the **most common** autosomal dominant form of muscular dystrophy, affecting approximately **1 in 8000** individuals worldwide.

FSHD usually begins before age 20, with weakness and atrophy of the muscles around the eyes and mouth, shoulders, upper arms and lower legs. Later, weakness can spread to abdominal muscles and sometimes hip muscles.

Some experts divide FSHD into **adult-onset** and **infantile-onset** forms. The adult-onset is far more common.

Currently no curative treatment option exists



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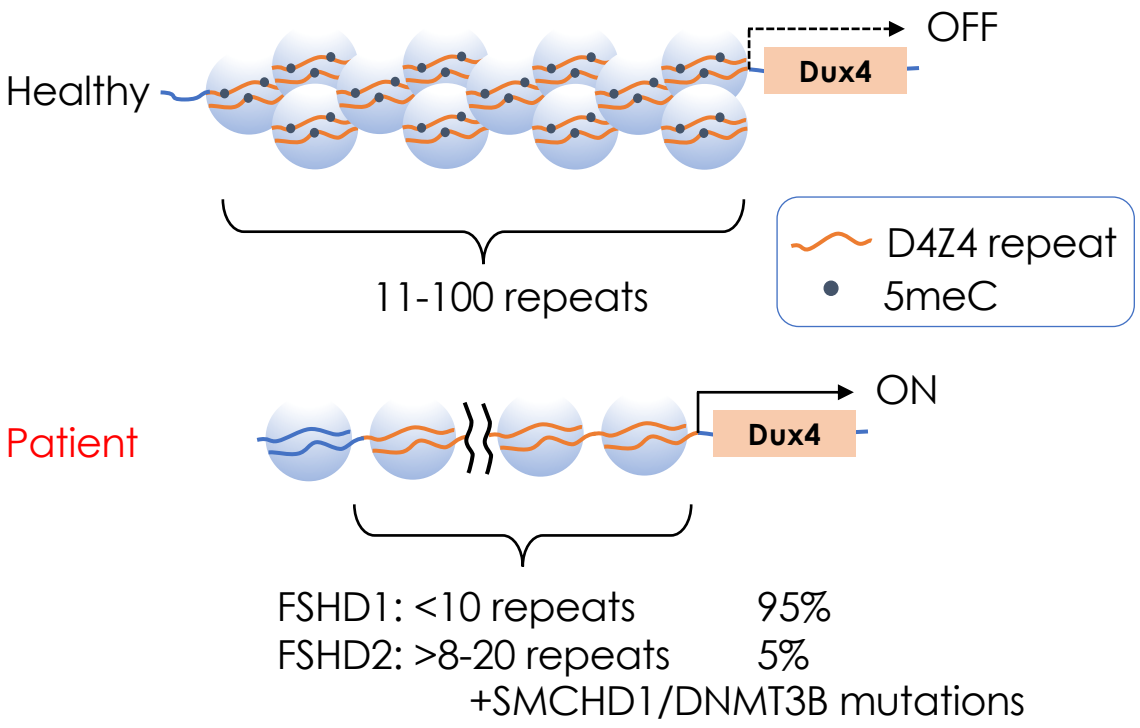
FSHD disease mechanism

Inappropriate expression of 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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What has been achieved and coming next

	What has been achieved	What's coming next
MDL-101 LAMA2-CMD	• Animal PoC in disease model mice • Target engagement in NHP • PreIND with FDA (June 2023) • Presentation at ASGCT 2023	• GLP-Tox • GMP manufacturing • IND (2H 2024)
MDL-202 DM1	• Animal PoC in disease model mice • Regain rights from Astellas	• Transplantation to muscle tropic capsid • Target engagement in NHP with new version molecule • Partnering
Other	• MDL-201 (DMD) • MDL-103 (FSHD) • MDL-105 (DCM) • CNS programs	• Transplantation to muscle tropic capsid • Animal PoC (FSHD, DCM)0 • Target engagement in NHP with new version molecule • Partnering • Continuing research • Explorer neurology capsids and LNPs • Partnering

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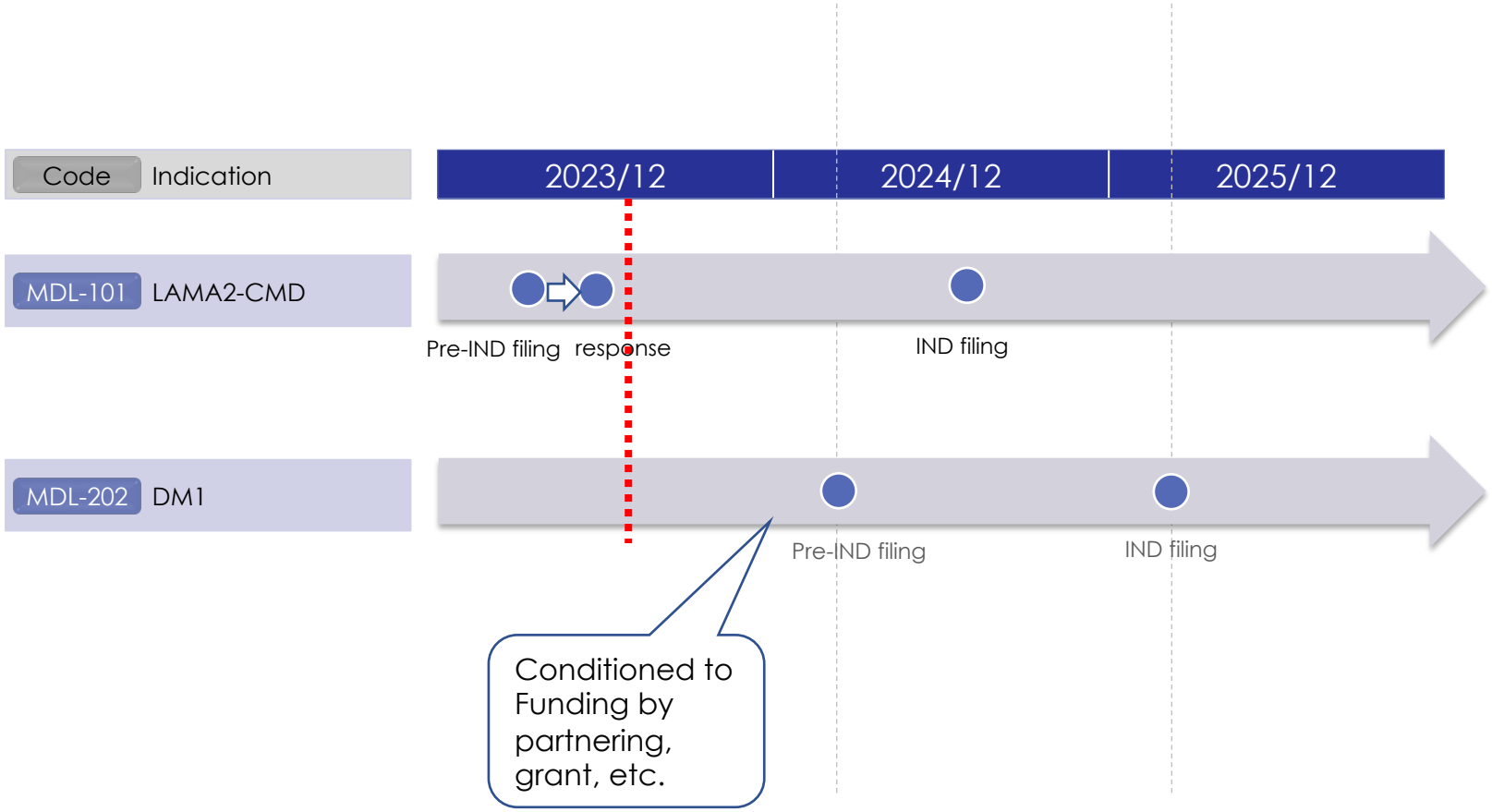
Status of the focused pipeline

As regained rights of MDL-201 and 202, reorganized pipelines and put higher priority on muscle disorder programs



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

3. Financial status

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PL & Business Result

(Million Yen)

	FY2022 2Q (A)	FY2023 2Q (B)	(B) – (A)
Operating revenue	40	-	(40)
Operating expenses	908	1,044	136
R&D	778	906	128
SGA	130	138	8
Operating income	(868)	(1,044)	(176)
Ordinary income	(780)	(995)	(215)
Current Profit	(775)	(1,033)	(258)

Operating expenses

- R&D increased year on year as business progressed(primarily in personnel expenses, research material expenses, rent fee, expenses for conducting clinical trials of MDL-101 and yen depreciation against US dollar)

Extraordinary loss

- Impairment loss on fixed assets

SGA: Selling and Generally Administrative Expenses

BS & Financial Position

(Million Yen)

	FY2022 (A)	FY2023 2Q (B)	(B) – (A)
Current assets	3,061	2,782	(279)
Cash & deposits	2,933	2,591	(342)
Non-current assets	68	72	4
Total assets	3,129	2,855	(274)
Current liabilities	141	278	137
Non-current liabilities	47	45	(2)
Total liabilities	188	323	135
Total net assets	2,941	2,532	(409)
Total liabilities and net assets	3,129	2,855	(274)
Capital adequacy ratio	93.4%	88.0%	

- High Equity ratio
  Under financing to secure a more stable financial base
- Decrease in property, plant and equipment and intangible assets due to impairment loss

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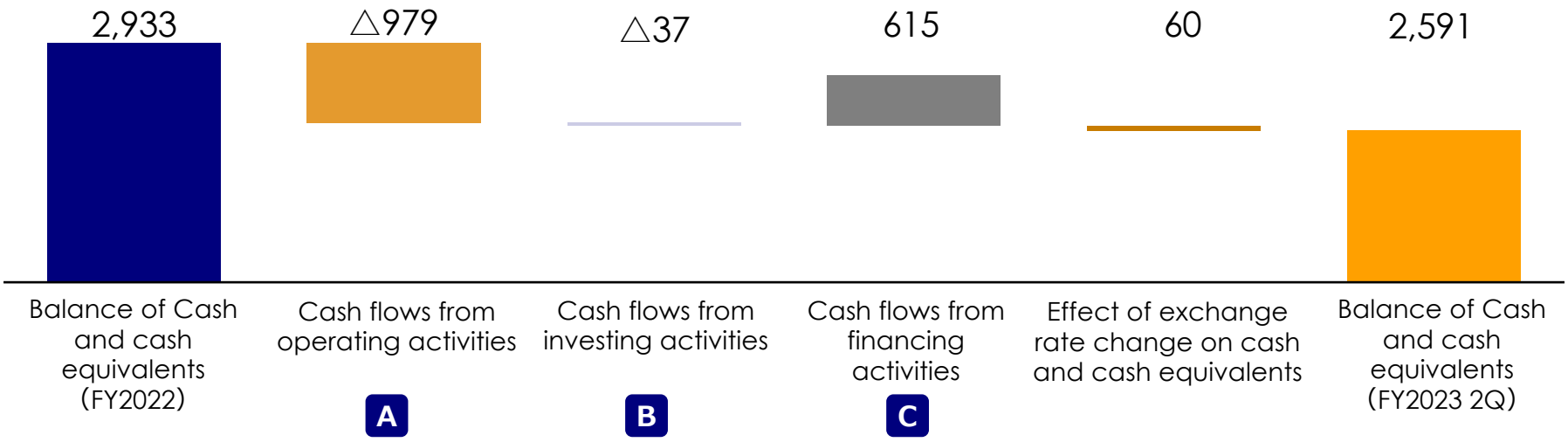
Cash Flow Status

(Million Yen)



A Cash flows from operating activities	• Loss before income taxes （△1,032） • Impairment loss （37）
B Cash flows from investing activities	• Purchase of property, plant and equipment （△37）
C Cash flows from financing activities	• Proceeds from issuance of stock acquisition rights （618）

MODALIS

4. Growth Strategy

Diversified pipeline with their own missions

Pioneer the gene modulation With highly suitable indications

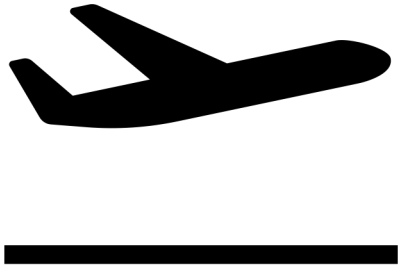
MDL-101

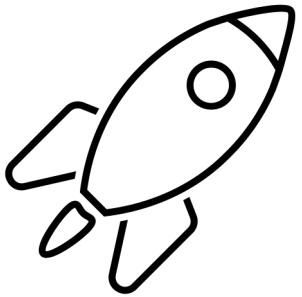
Expand technology opportunity with products for larger opportunity

MDL-202

Further approach to challenging applications

Other programs

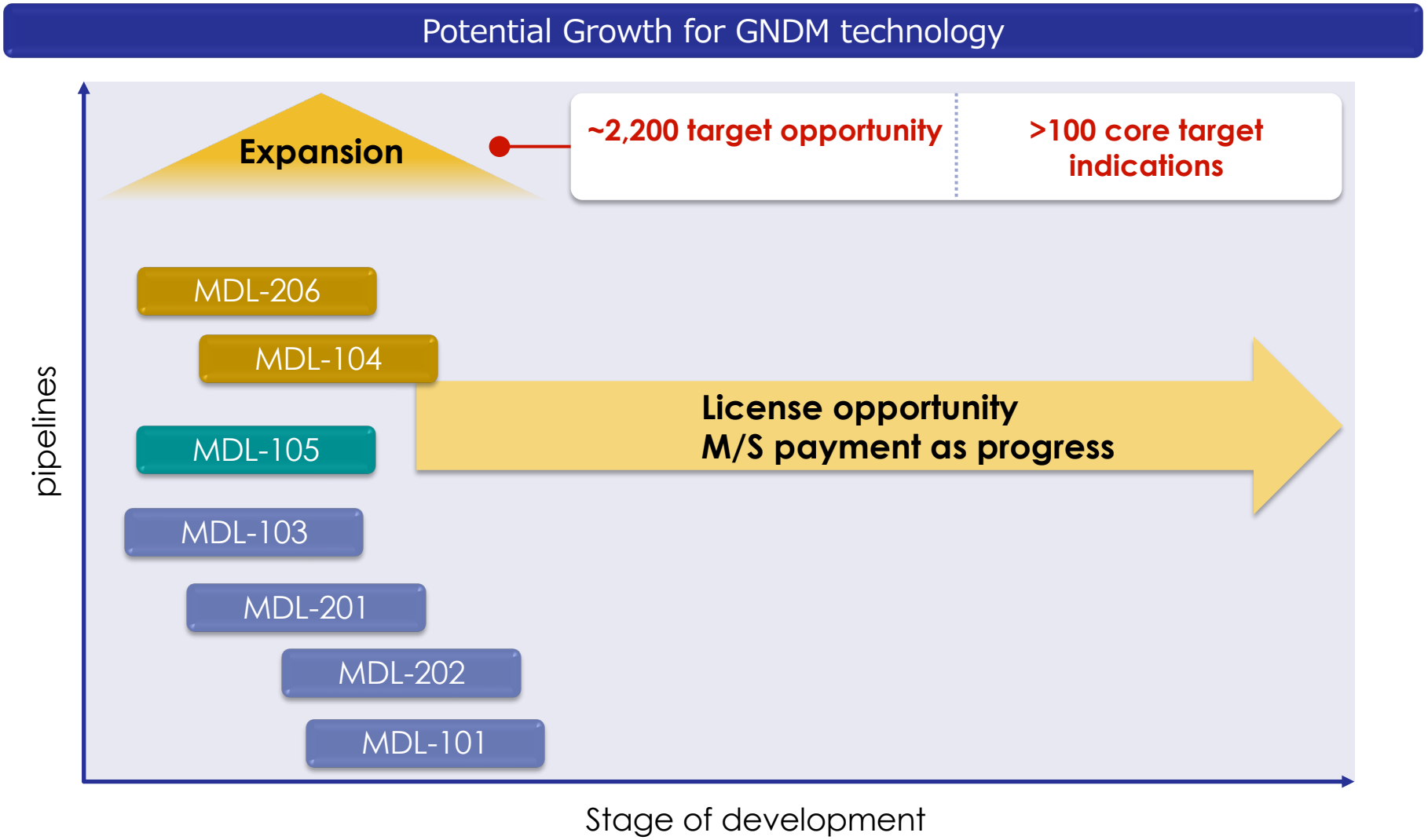




MODALIS

Growth Strategy

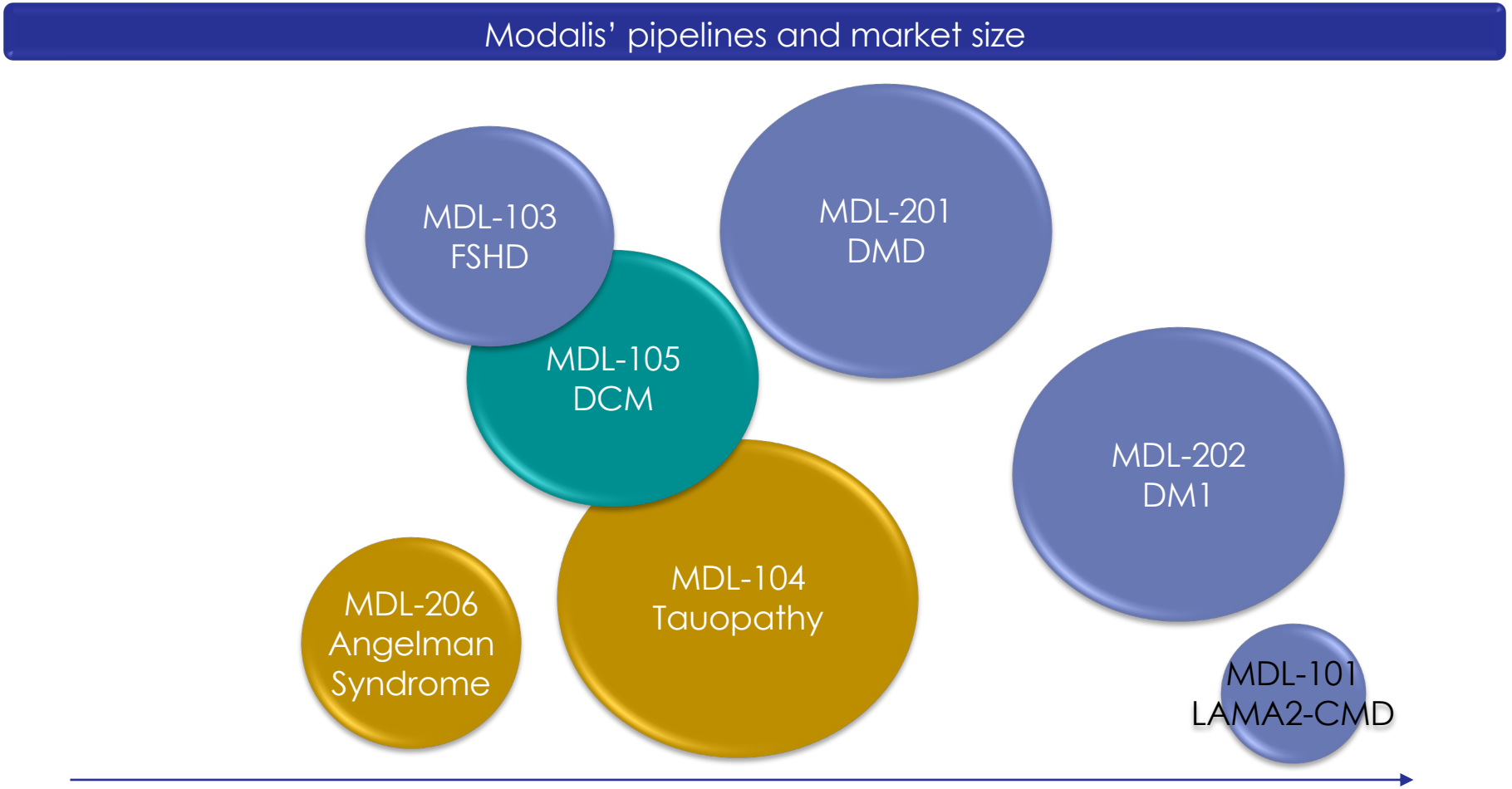
opportunity expands two dimensionally



MODALIS

Modalis' pipelines and market size

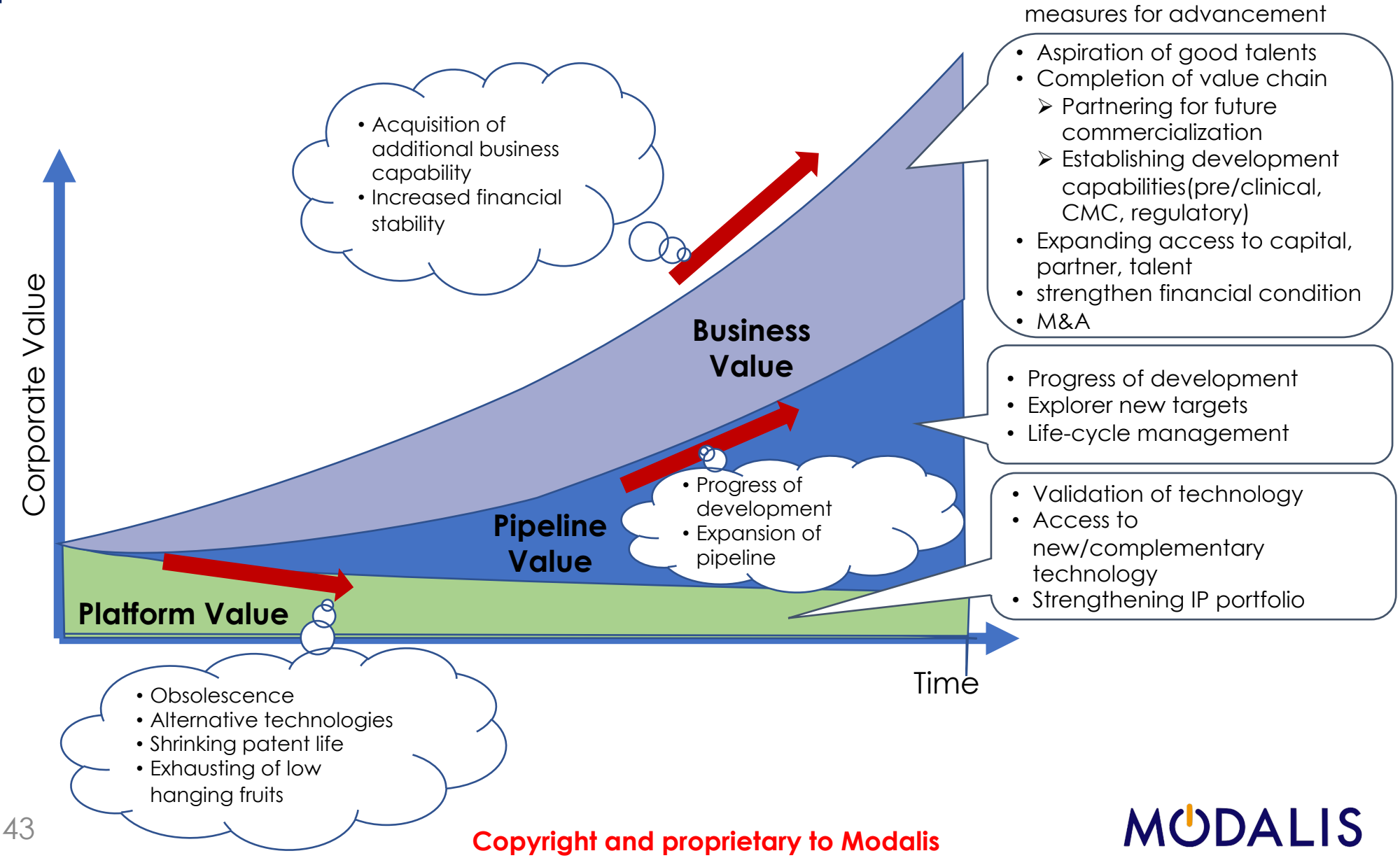
Large indication programs follow MDL-101 which paves the clinical path



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

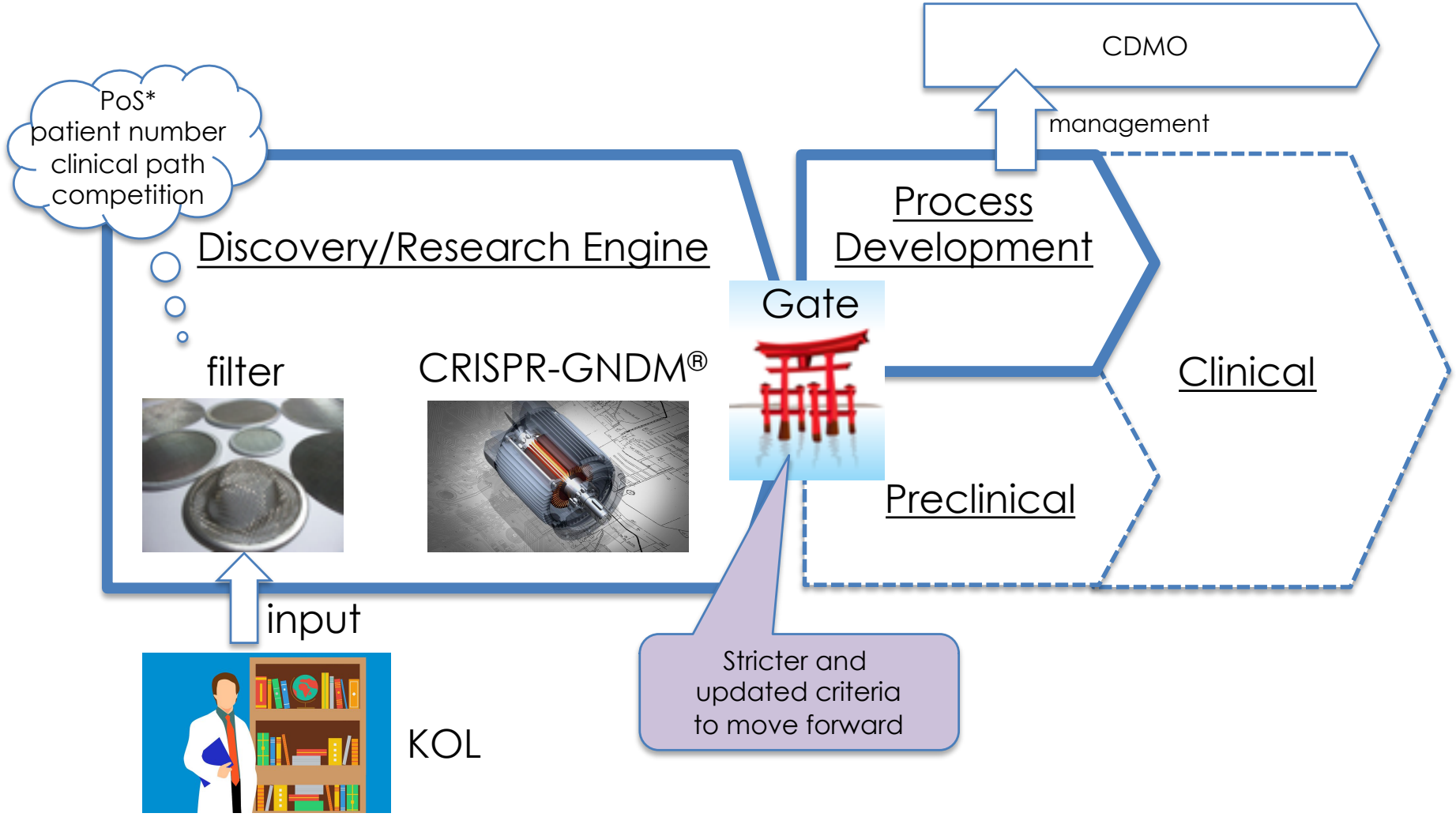
MODALIS

Composition of Modalis' value and measures for advance



MODALIS

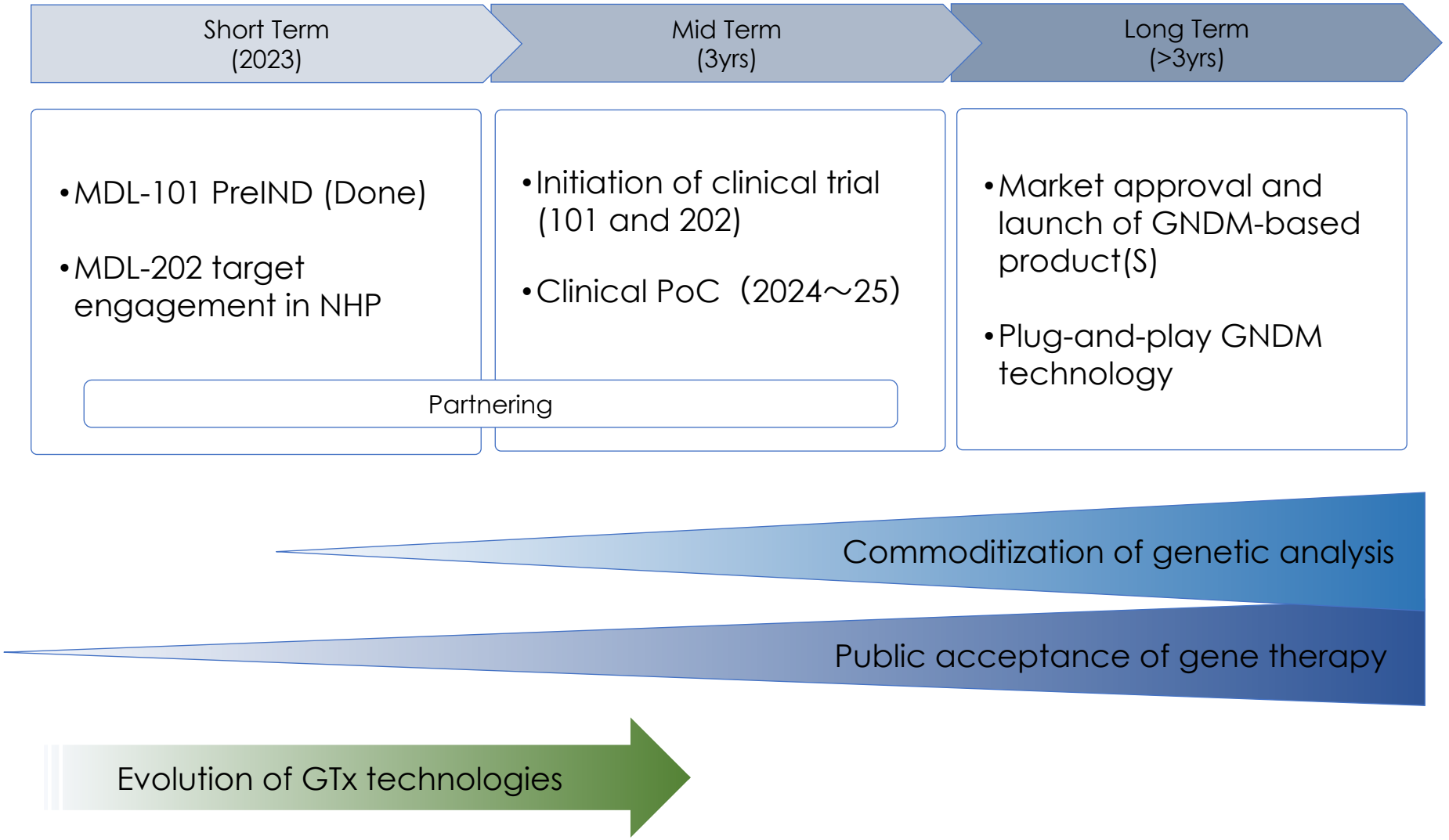
Upon transition from R to D, which cost time and money, stricter decision is made for higher ROI and better resource allocation.



PoS: Probability of success

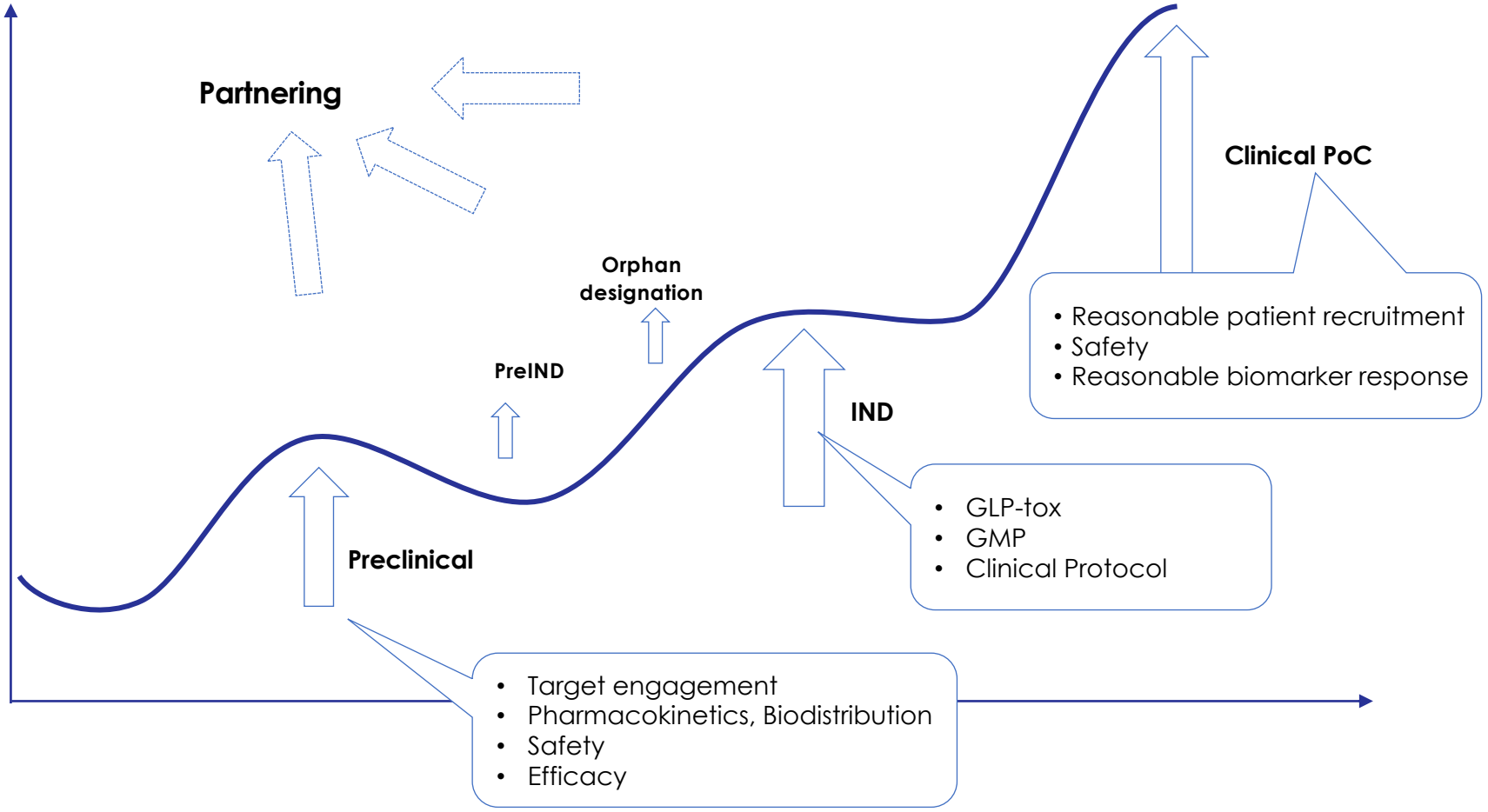
MODALIS

The future Modalis envisioned



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

Expected milestone events and impact on corporate value



MODALIS

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.

Status of partnering

Change in the partnering environment

- Value curve along with the progress of development is comparable to that of the past or is on an increasing trend.
- On the other hand, optimism about GTx receded, and a trend toward caution is obvious.

Status of wholly owned pipelines

- **MDL-101**:While conducting development to achieve clinical entry asap, also negotiating with potentials to realize partnering.
- **MDL-202**:Obtaining data with new version vector and will try to find a partner who funds development
- **MDL-104**:R&D is underway. Discussions for partnering in FY2023 are ongoing in parallel.
- **MDL-201, 103, 105**: R&D is ongoing. We plan to partner with the company when it reaches the appropriate stage of patent filing, acquisition of development data, and so on.