English translation for reference purposes only

FY2023
Business Plans and
Matters Related to High Growth Potential



(TSE：4883)

Modalis therapeutics Corporation

August 7 , 2023

In case of any discrepancy, the Japanese version shall prevail

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New

Key Takeaway of the revised strategy

- 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 including new partnership
- 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 101 and 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.

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1. Corporate Overview

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Corporate Overview (As of July 31, 2022)

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	1,113,887,338 yen
Outstanding share	31,577,500 common stock
Number of employee	35 (including 10 Ph.D.) (4 in Japan, 31 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.)
Apr 2017	Entered into research collaboration with **Astellas** Pharma Inc.
Dec 2017	Expanded research collaboration with **Astellas**
Mar 2019	Established license agreement on a genetic disorder with **Astellas** Pharma Inc.
Aug 2019	Company name changed to Modalis Therapeutics
Sep 2019	Established 2nd license agreement on a genetic disorder with **Astellas** Pharma Inc.
Nov 2019	Entered into research collaboration with **Eisai** Inc.
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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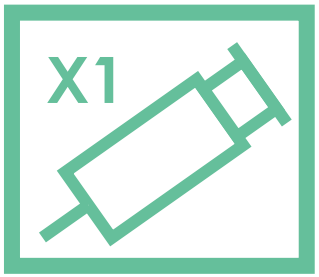
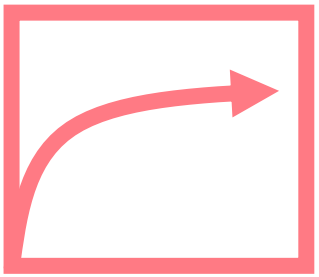
CRISPR-GNDM® is a promising new therapeutic modality

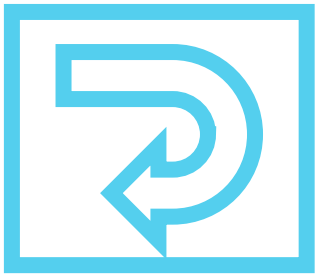
Potential benefits of CRISPR-GNDM® Technology



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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Modalis Value Highlights

- **Pioneering CRISPR-based epigenetic editing technology with development pipelines**
  - First and the leading CRISPR-based gene modulation/epigenetic editing technology that enables therapeutic applications
  - In the advanced program, animal PoC in mice and target engagement in NHPs are established. Completed Pre-IND, the development is underway for clinical.
- **Combination of the leading product that pioneers the proof-of-concept of technology and pipelines with high market potential**
  - MDL-101 as the ignitor and 202 as the value driver followed by programs as boosters
- **Muti-layered IP protection on the developed product**
  - Unique IP portfolio including access to CRISPR foundational IP
- **Efficient drug discovery platform with highly versatile applications**
  - For both GoF and LoF genetic disorders
  - Differentiated approach even within the gene therapy space
- **Senior leadership with proven track records and talented scientists**
  - Highly committed team that drives problem-solving

GoF: gain-of-function and LoF: loss-of-function

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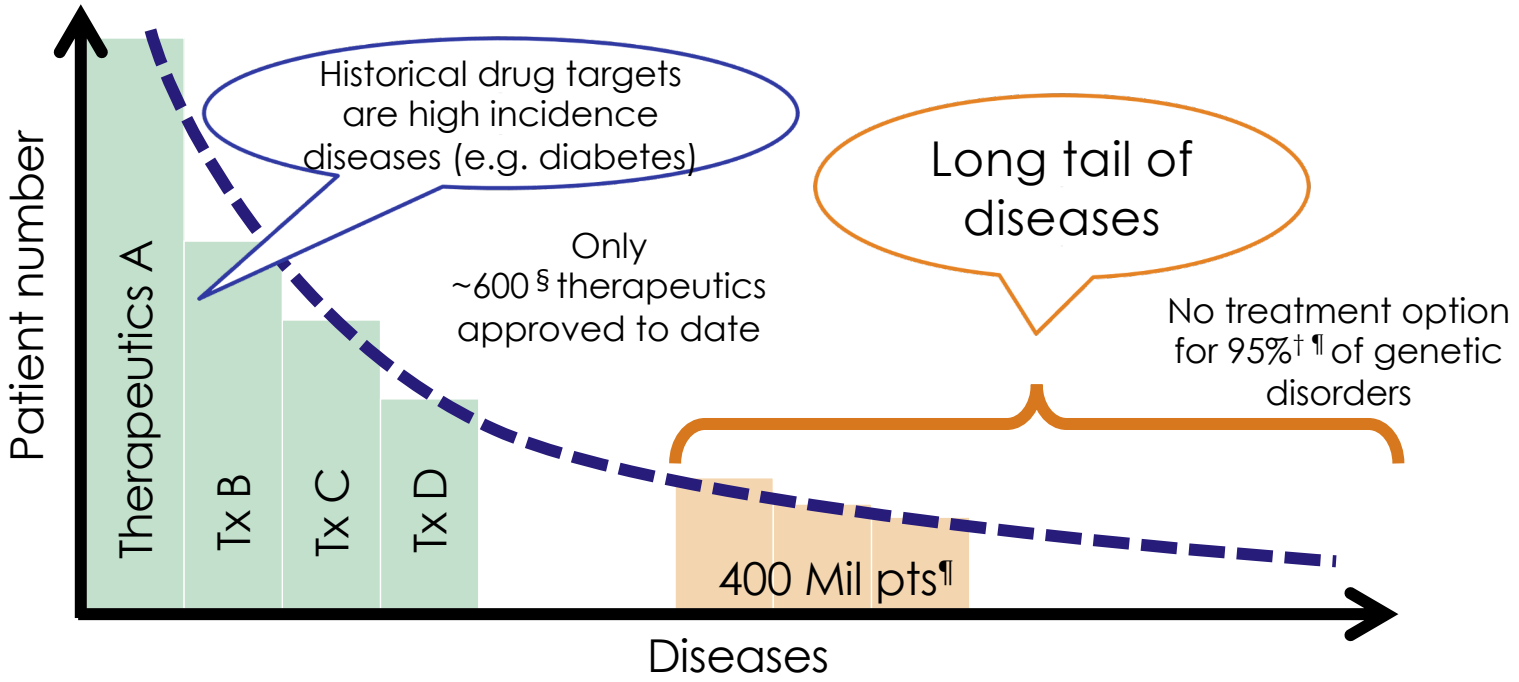
Provides solution for the long tail of disease

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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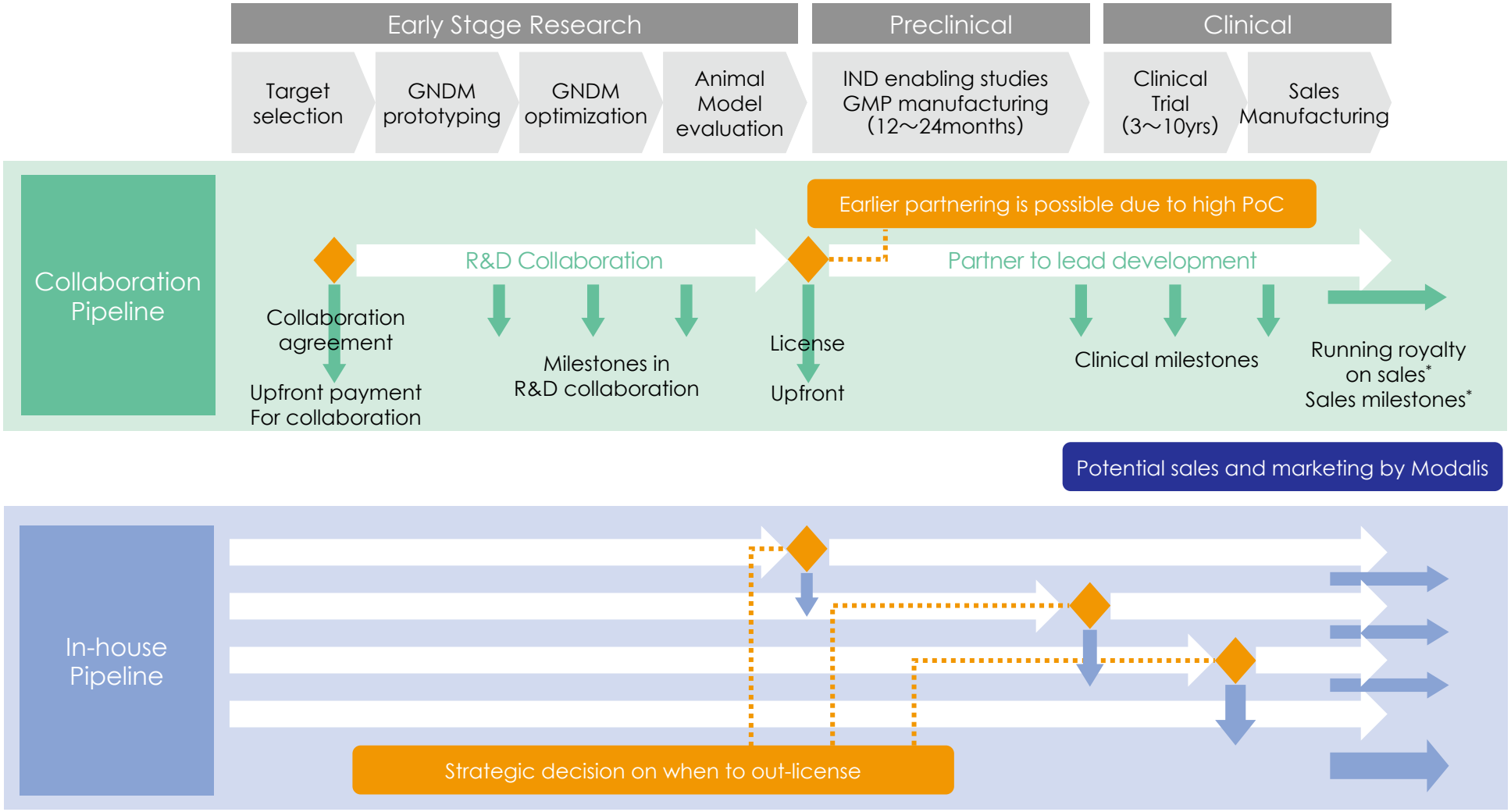
Business Model

Hybrid of own pipeline and collaboration pipeline



* future plan

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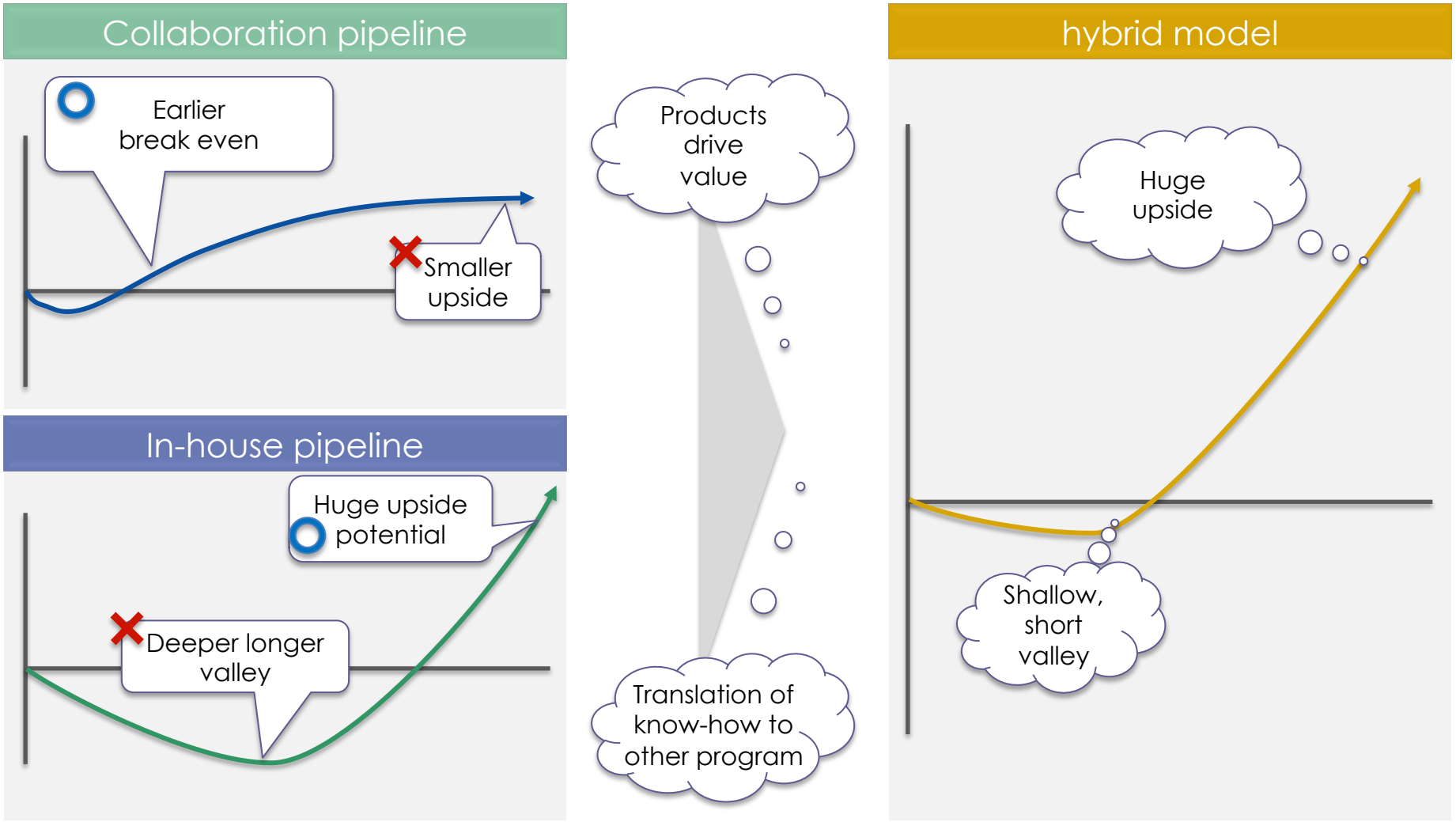
Modalis is pursuing a hybrid model

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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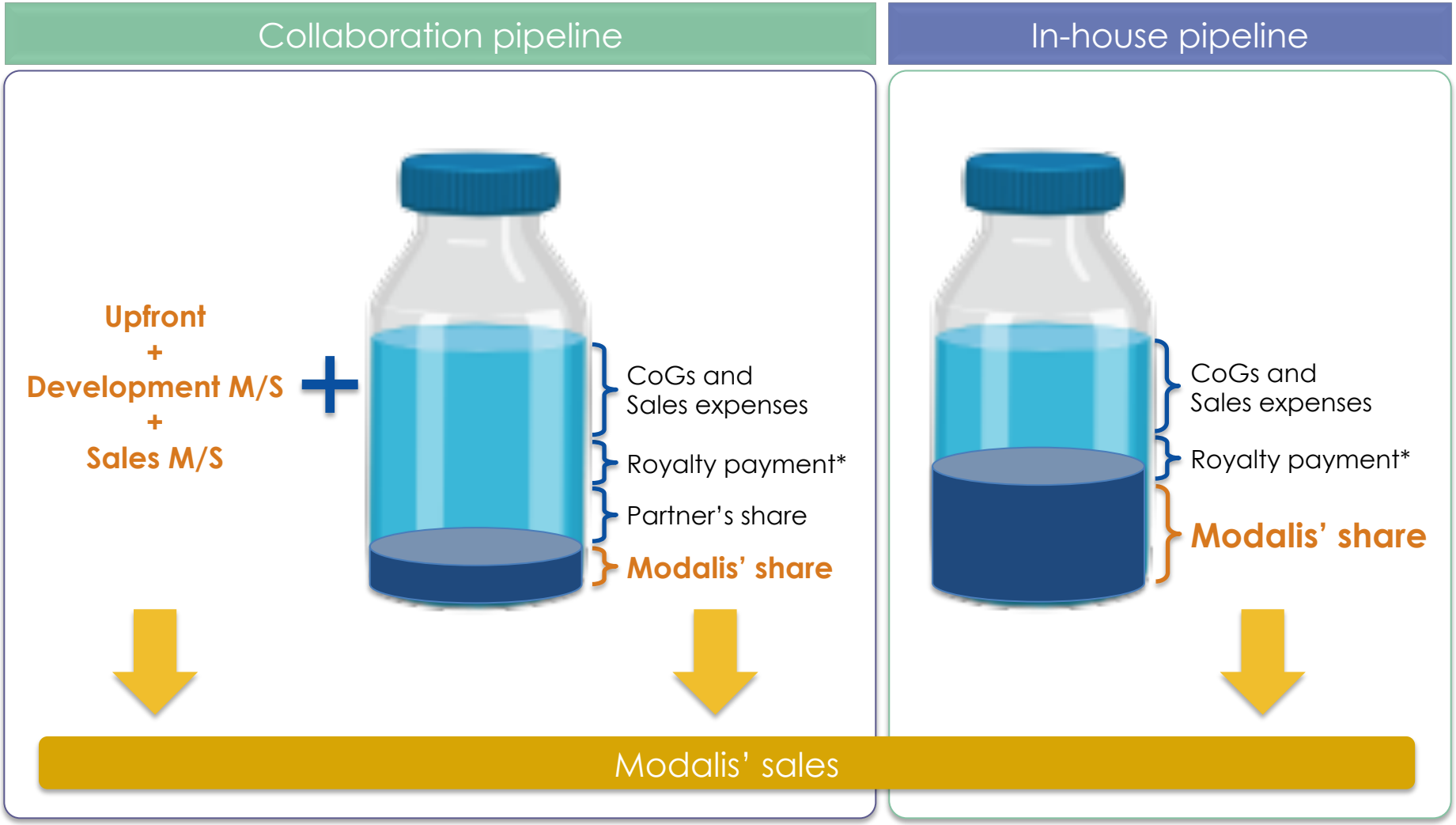
Risk - profit share model

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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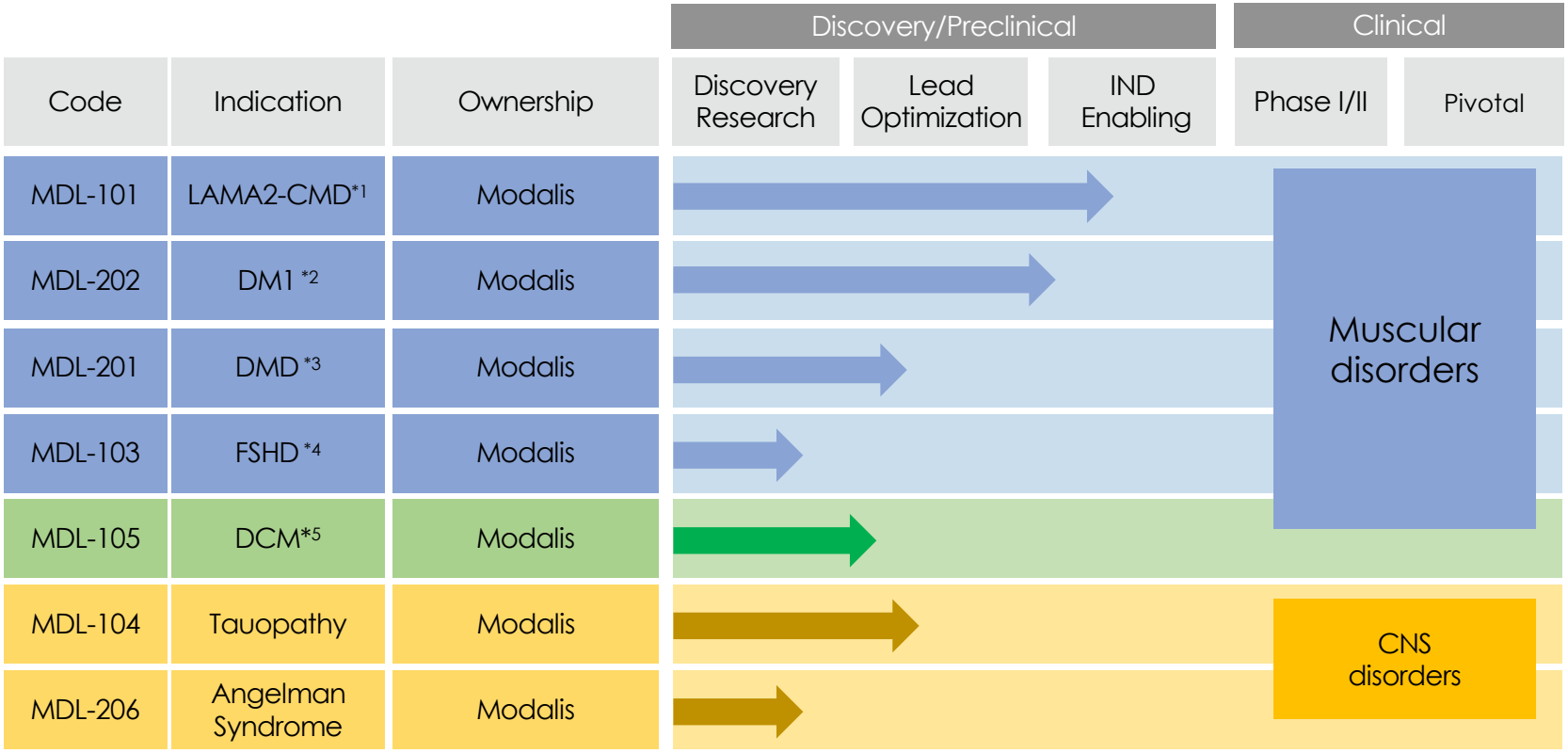
Revised

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

Note: The pipeline is being reorganized. For details, please refer to "4. Pipeline Status: Key Points of Pipeline Reorganization" on page 38.

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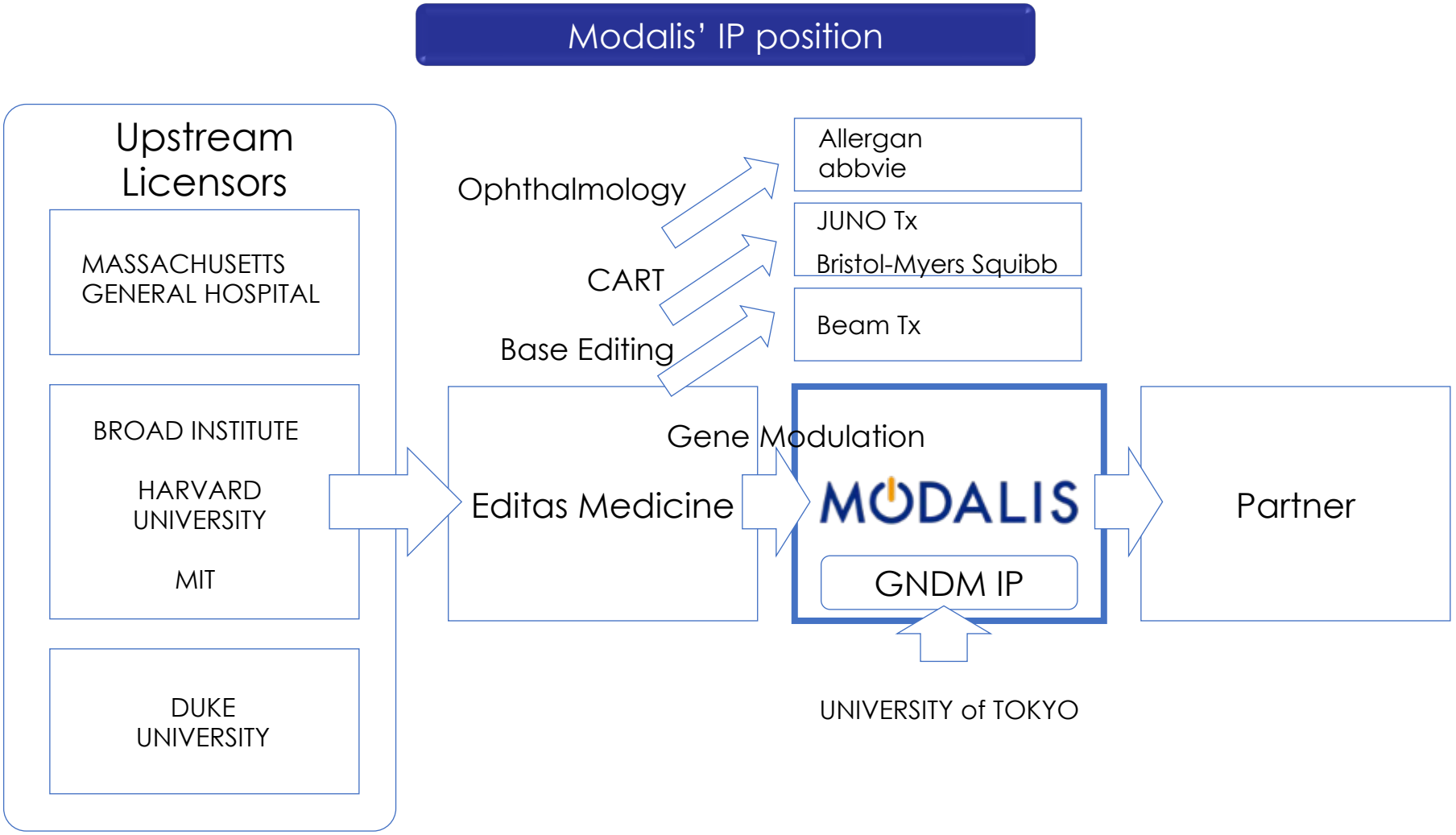
IP position

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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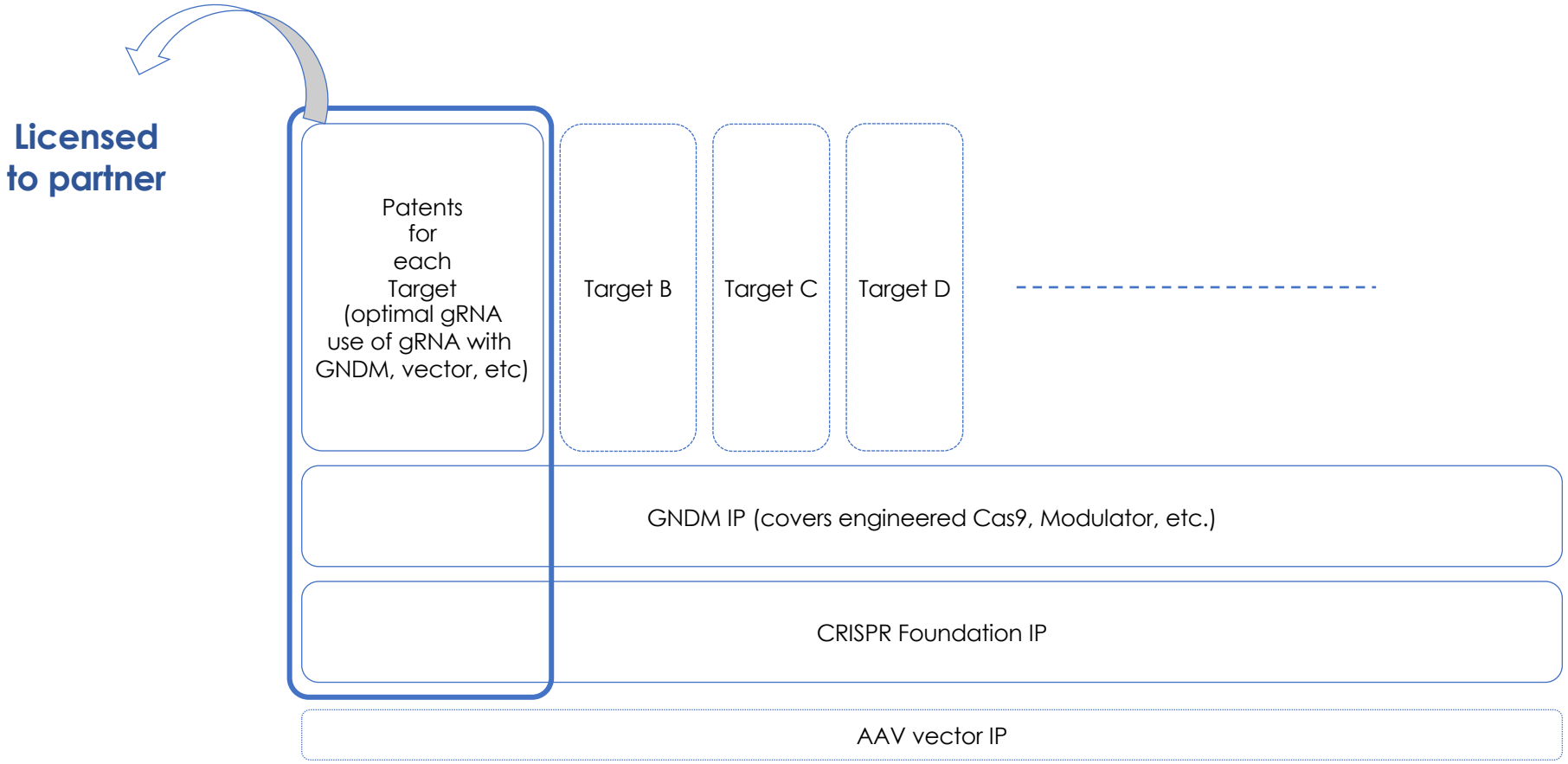
Each product will be protected by multiple layers of IP



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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: SVP, Chief Technology Officer
- Glaxo Smith Kline, Tempero Pharmaceuticals, Joslin Diabetes Center, Harvard Medical School

Naoki Kobayashi MBA: SV, Chief Financial Officer
- Former CFO at Oncolysbiopharma, Hatena, and Argens, Argenes, Deloitte Tohmatsu, Daikyo Real estate

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

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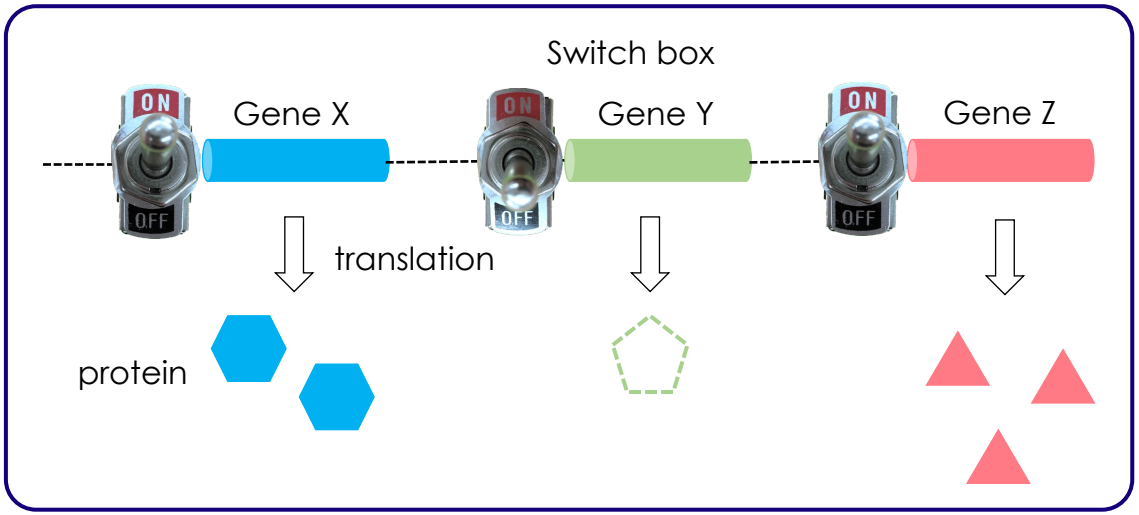
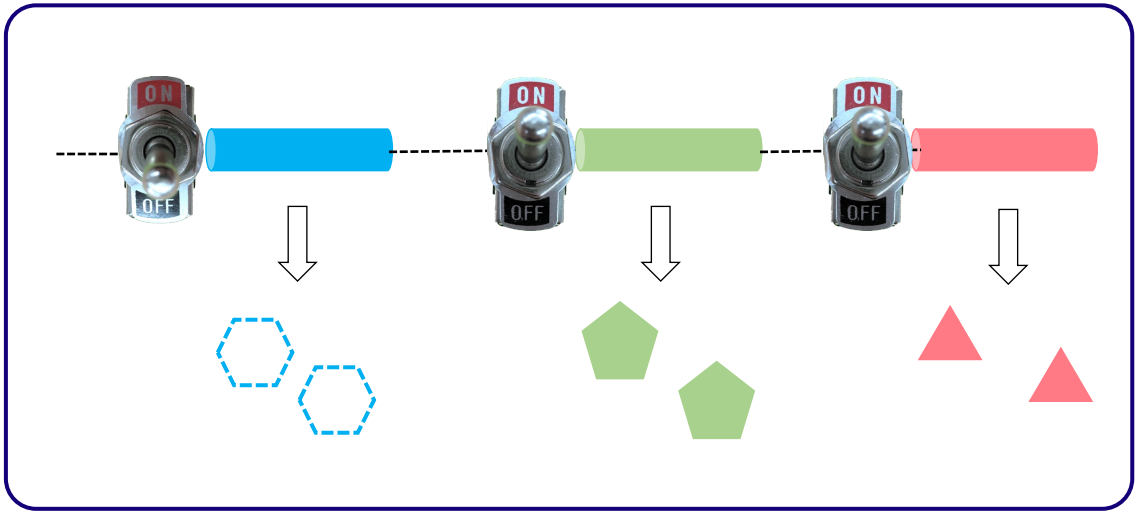
How multiple cell types are created from the same DNA code

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

Cell A



Cell B



- 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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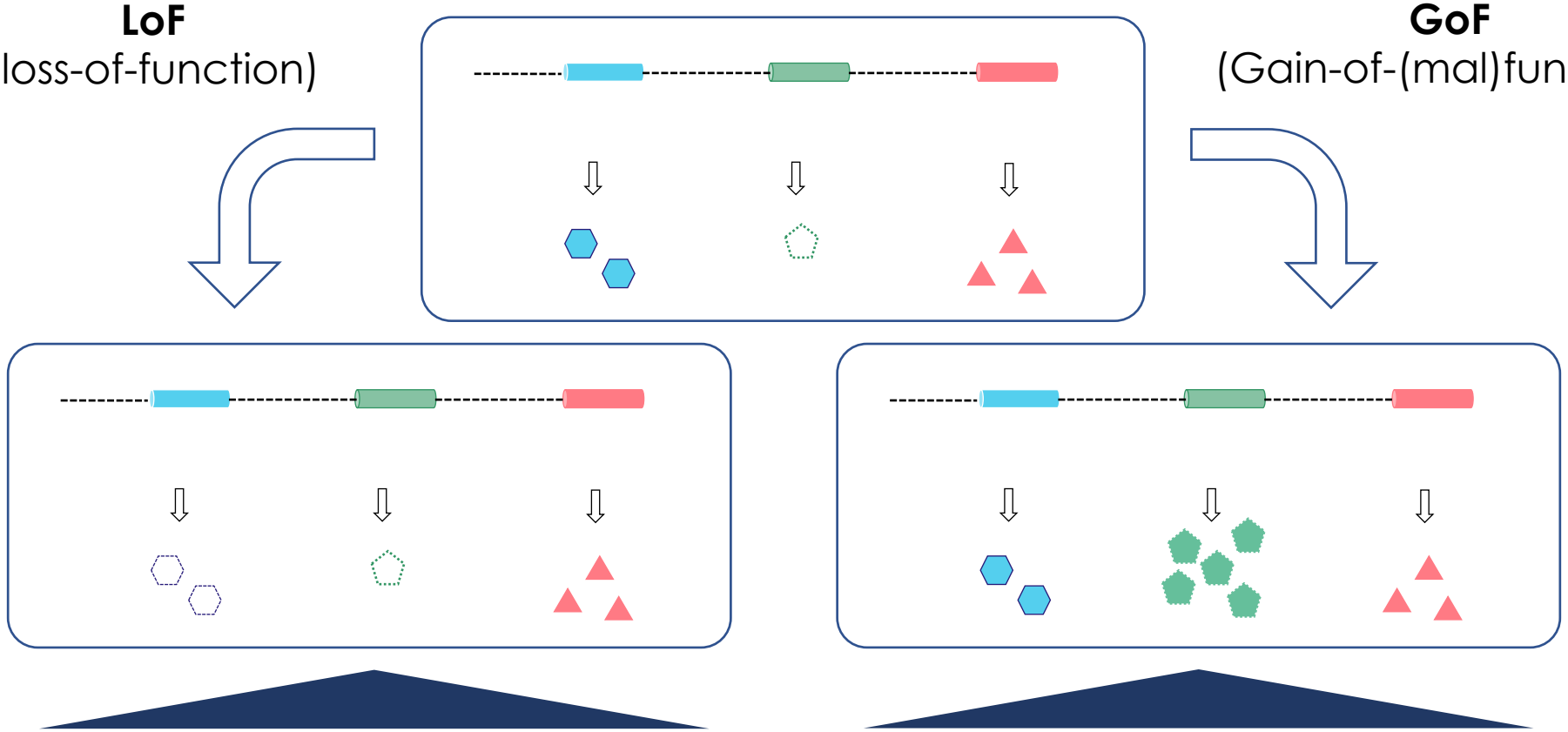
Genetic Disorders

They are caused by LoF or GoF

LoF
(loss-of-function)

GoF
(Gain-of-(mal)function)



Supplement missing function
GTx

Silence malfunction

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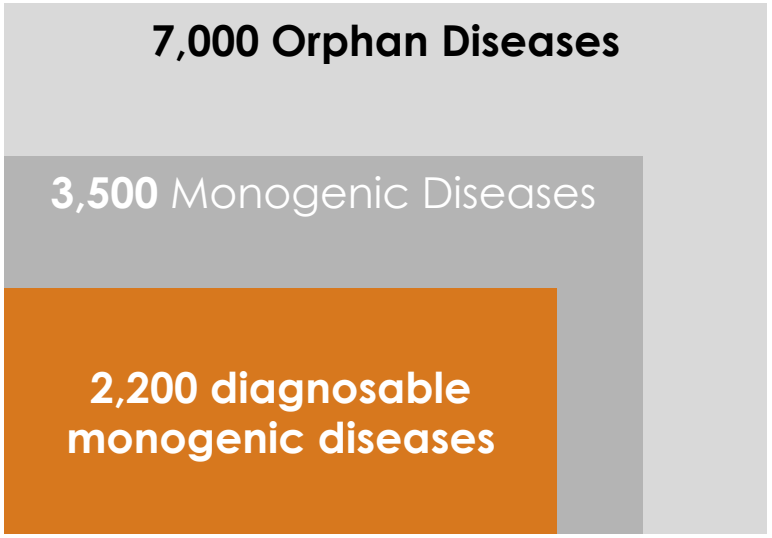
Untapped opportunities in monogenic disorders

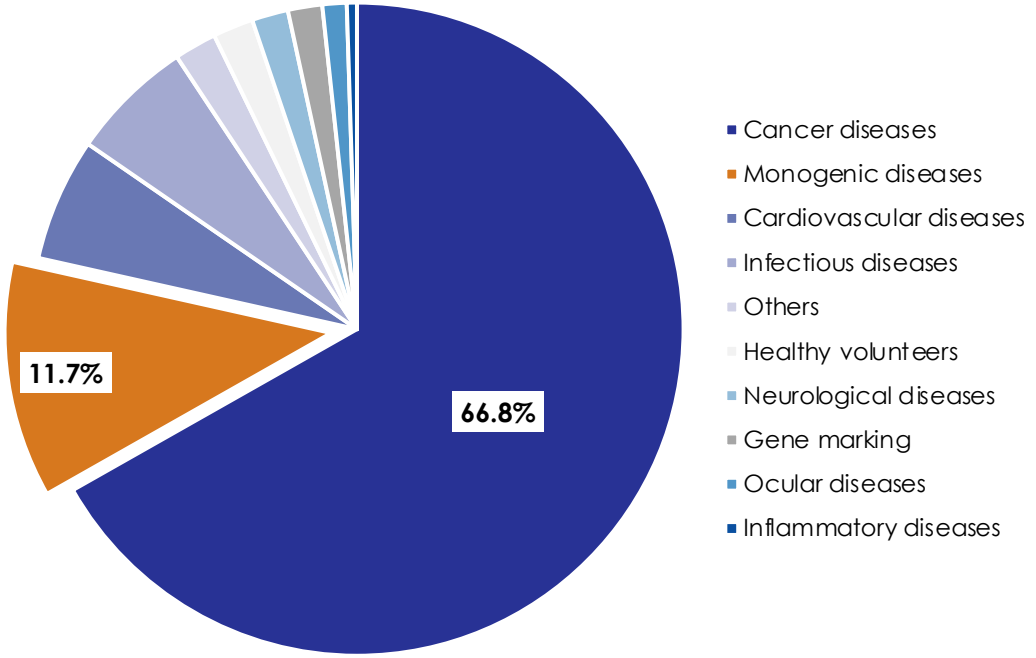
Limited number of drugs are approved or in clinical development for monogenic disorders

Monogenic Disease



Source: Discovery Medicine

Breakdown of GTx clinical trials (1989~ Worldwide)



Source: The Journal of Gene Medicine (2019)

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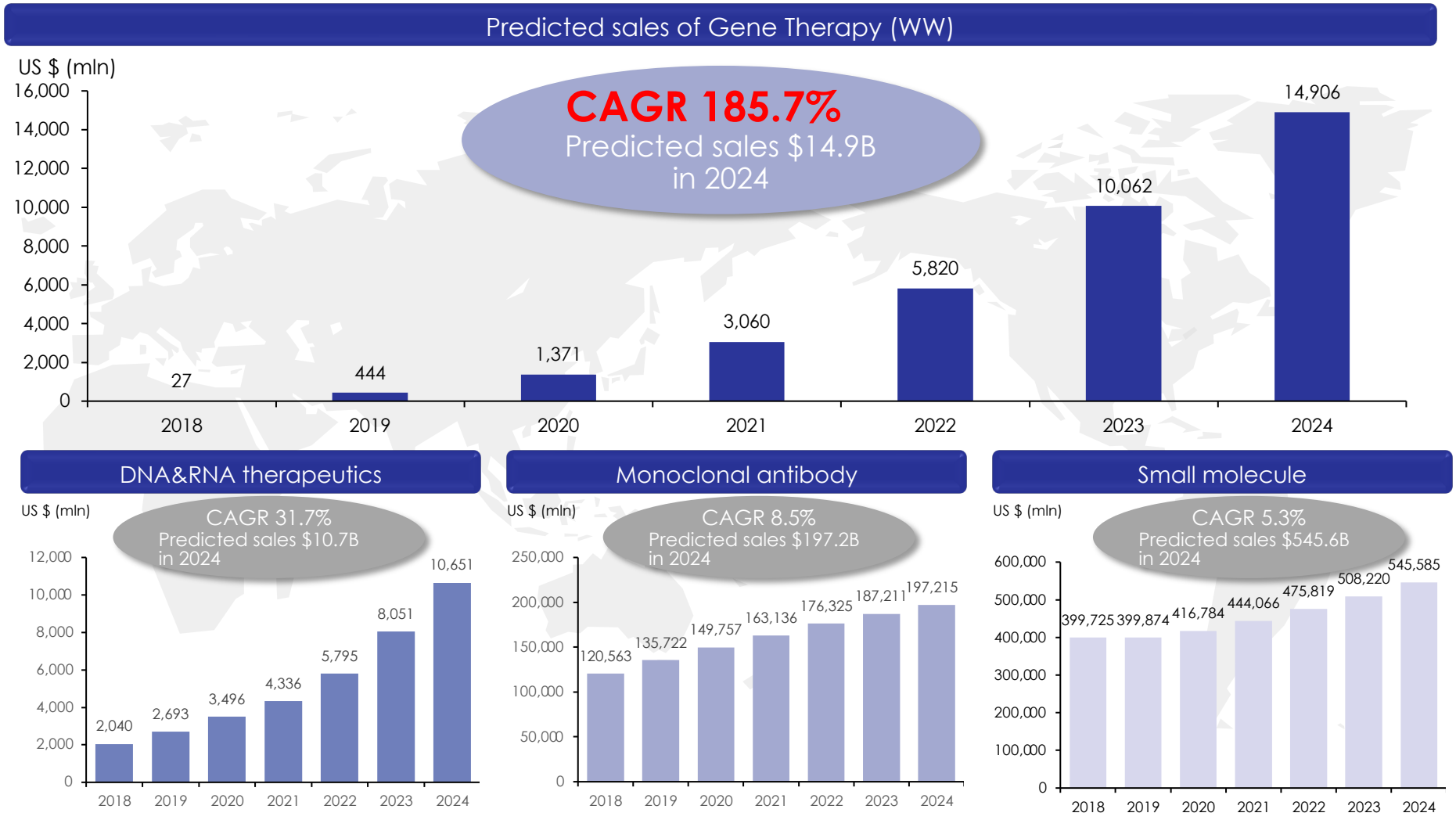
Sales growth of pharmaceutical modalities

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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CRISPR is a novel gene editing technology

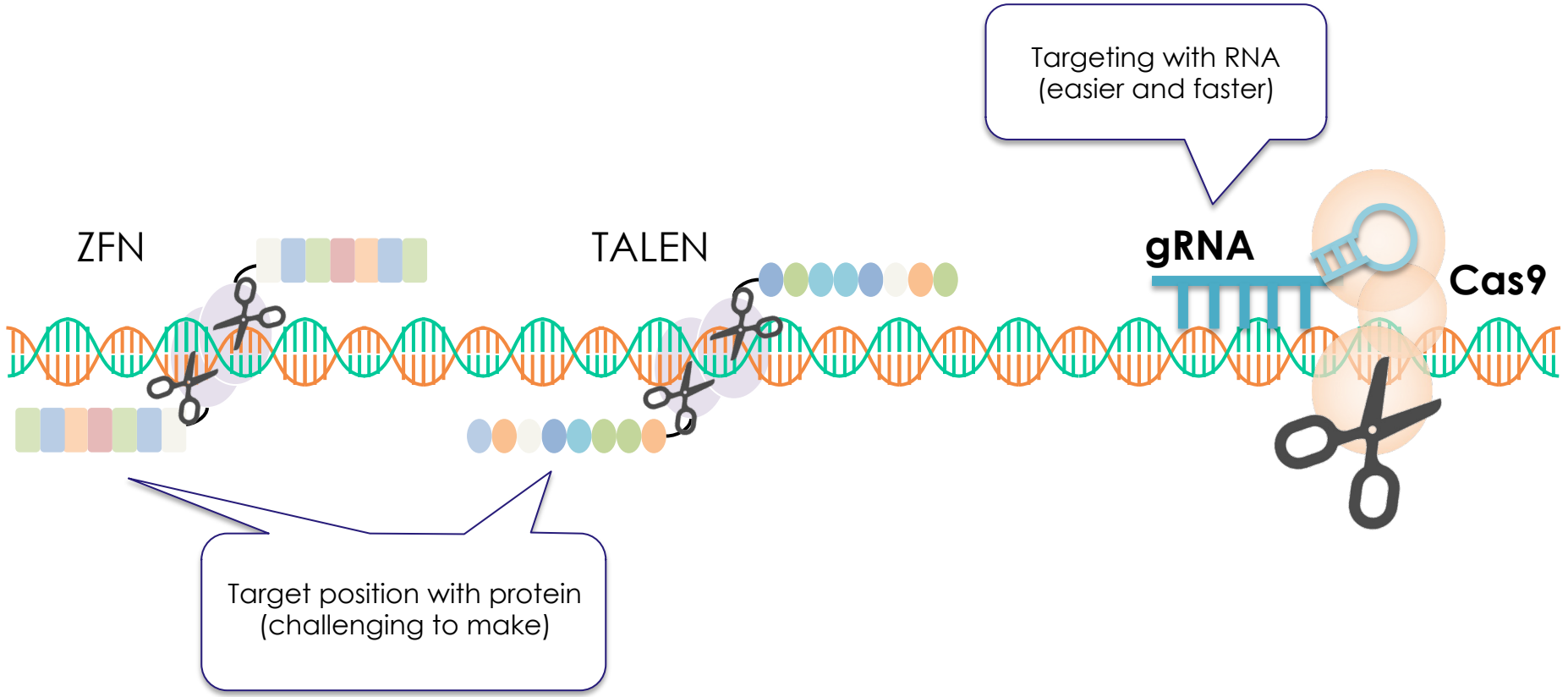
Faster and higher throughput due to limited variable region which is easily synthesizable as gRNA

Old gene editing technologies

ZFN

TALEN

CRISPR



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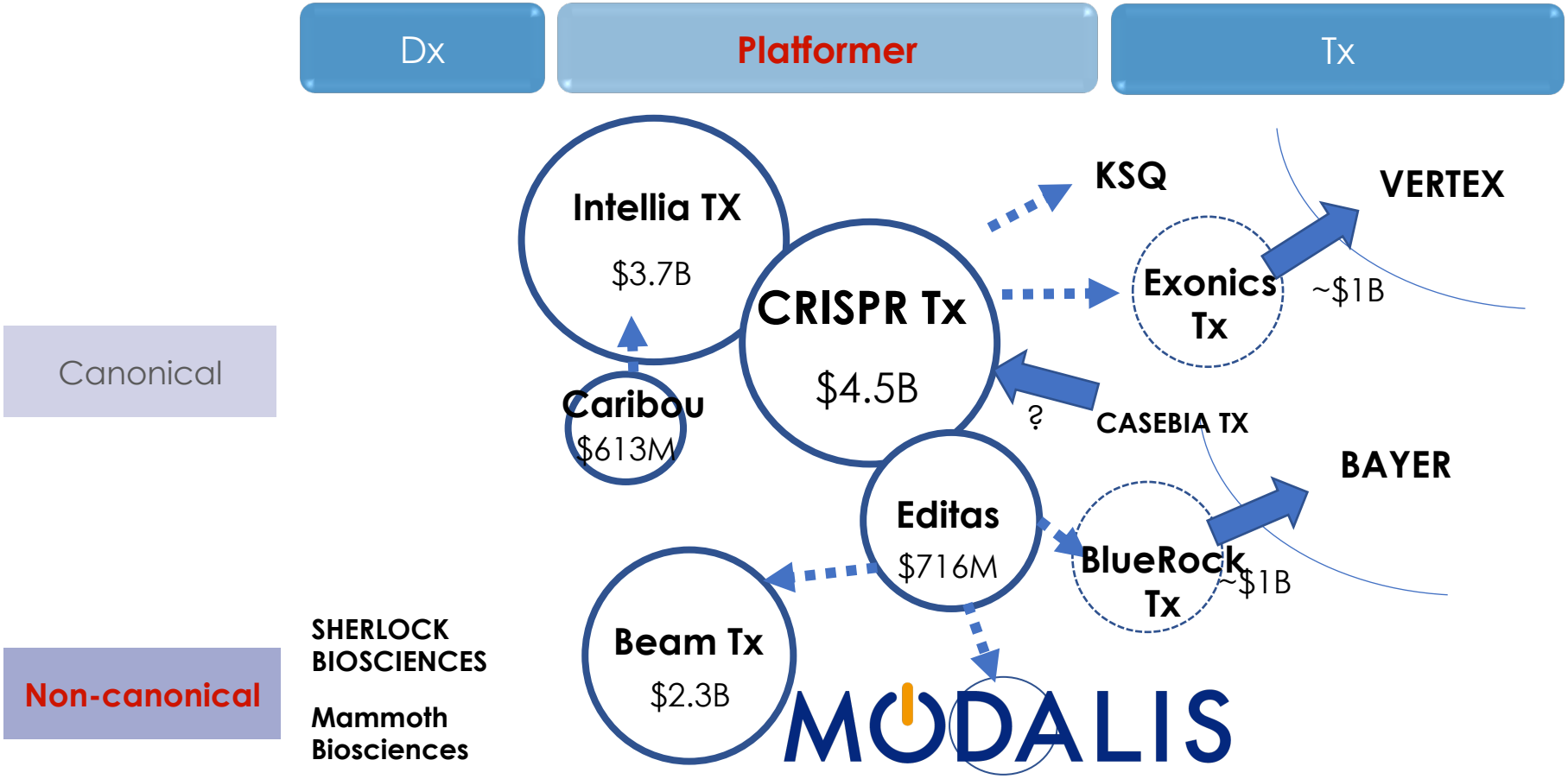
Major players in CRISPR field

Modalis established unique position in CRISPR companies, most of which reached >$1B



Source: stock info. The figures represent market cap as of End of Jul,2023 or value at the time of acquisition.
Dotted circle represent acquired companies

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Market size

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 [b]
Zolgensma	$2.1M	SMA	Novartis (Avexis)	1 in 10,000 live births (Approx. 10,000 to 25,000 in US)	$1.3B [b]
HEMGENIX	$3.5M	Hemophilia B	uniQure CSL Behring	1 in 30,000 male	$88M [b]
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 [#]

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

Source: National Organization for Rare Disorder, Companies websites

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3. CRISPR-GNDM® and its advantages

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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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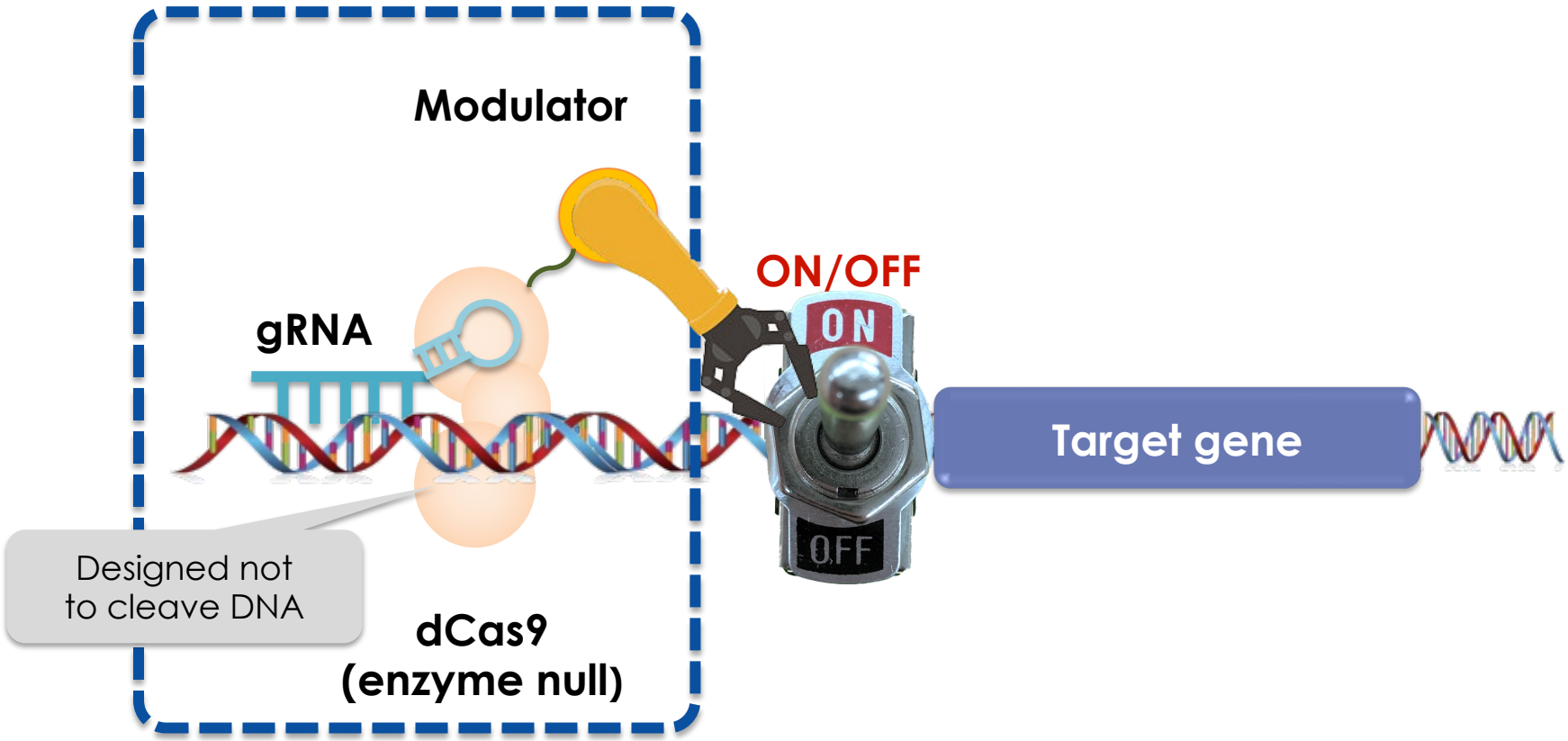
Non-cleaving CRISPR = CRISPR-GNDM®

Enables treatment of genetic disorders by controlling ON/OFF switch

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



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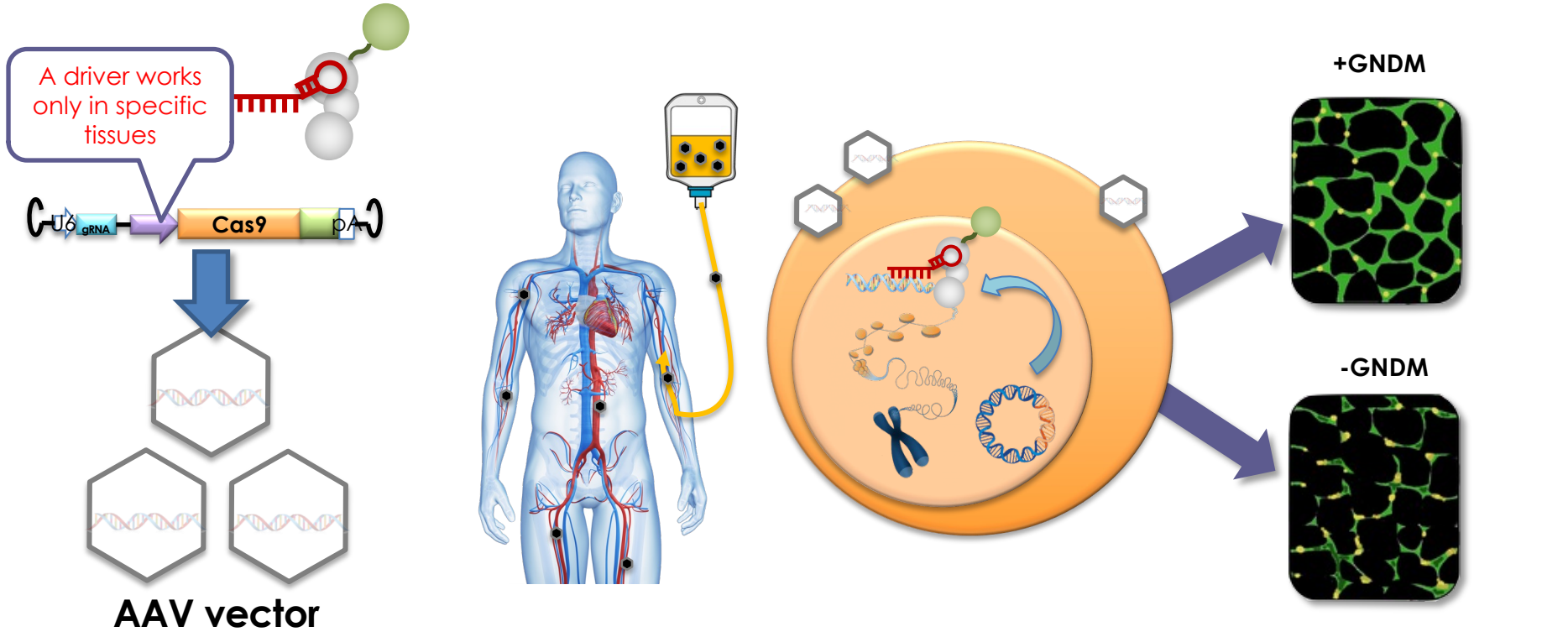
Delivery of CRISPR-GNDM® to target

Use AAV vector to deliver GNDM to target cell



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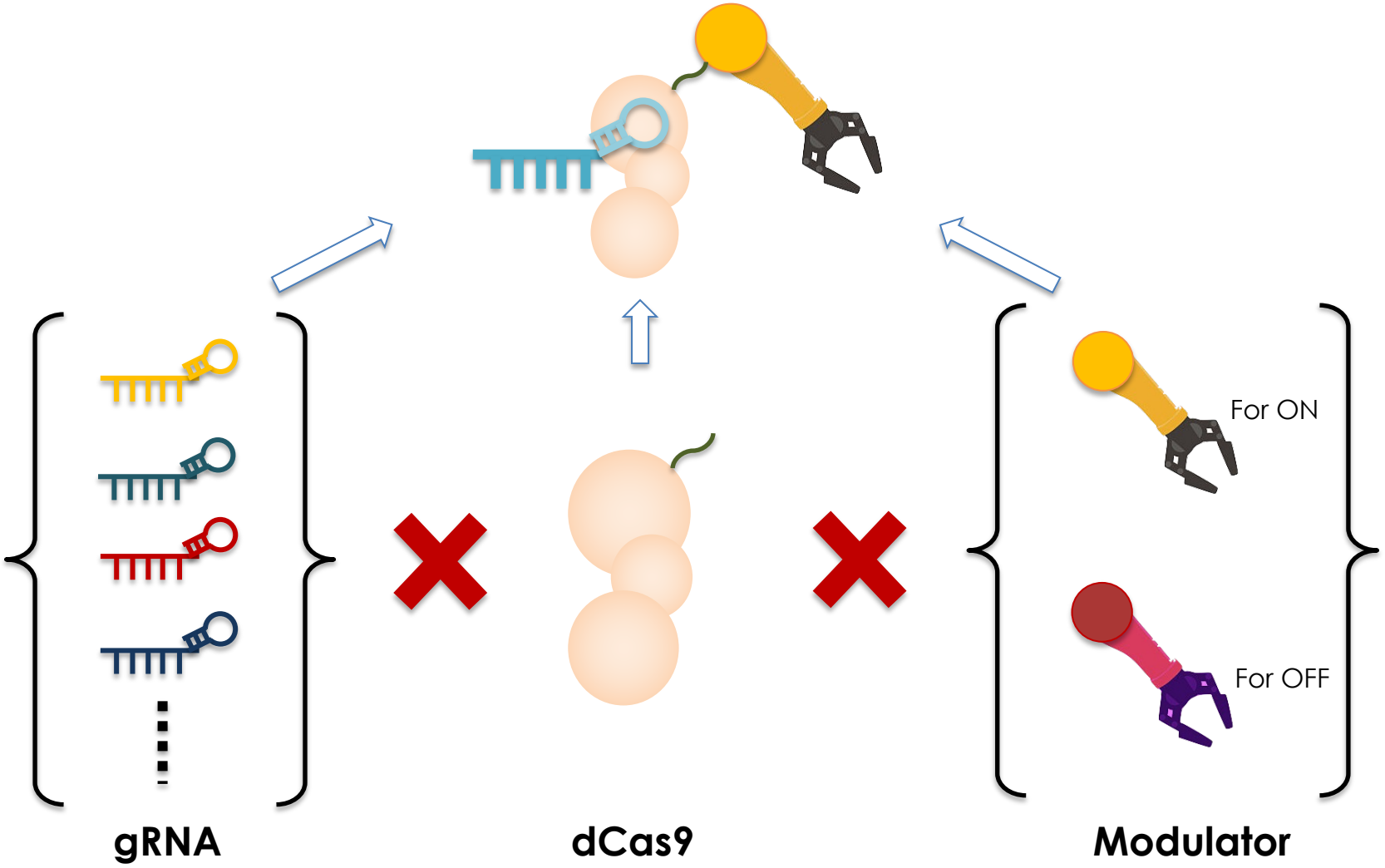
Scalability of GNDM

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



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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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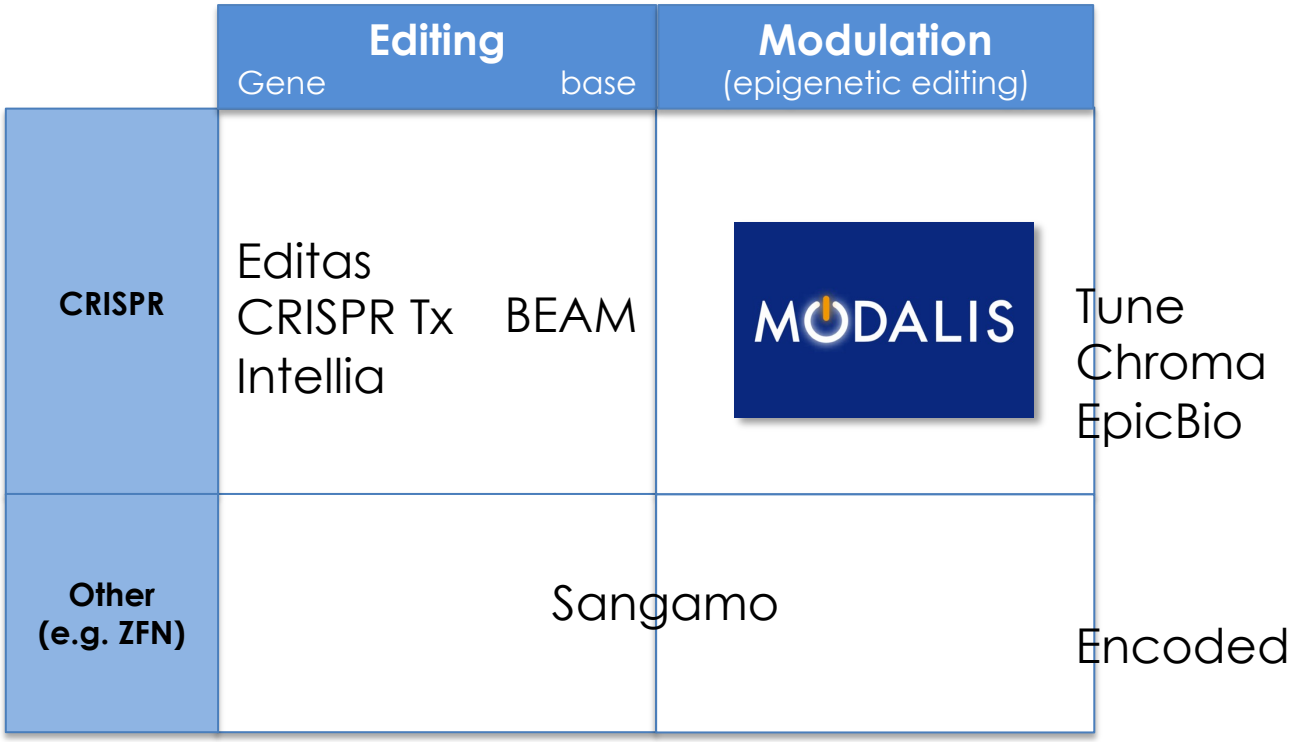
Modalis is uniquely positioned within the CRISPR field



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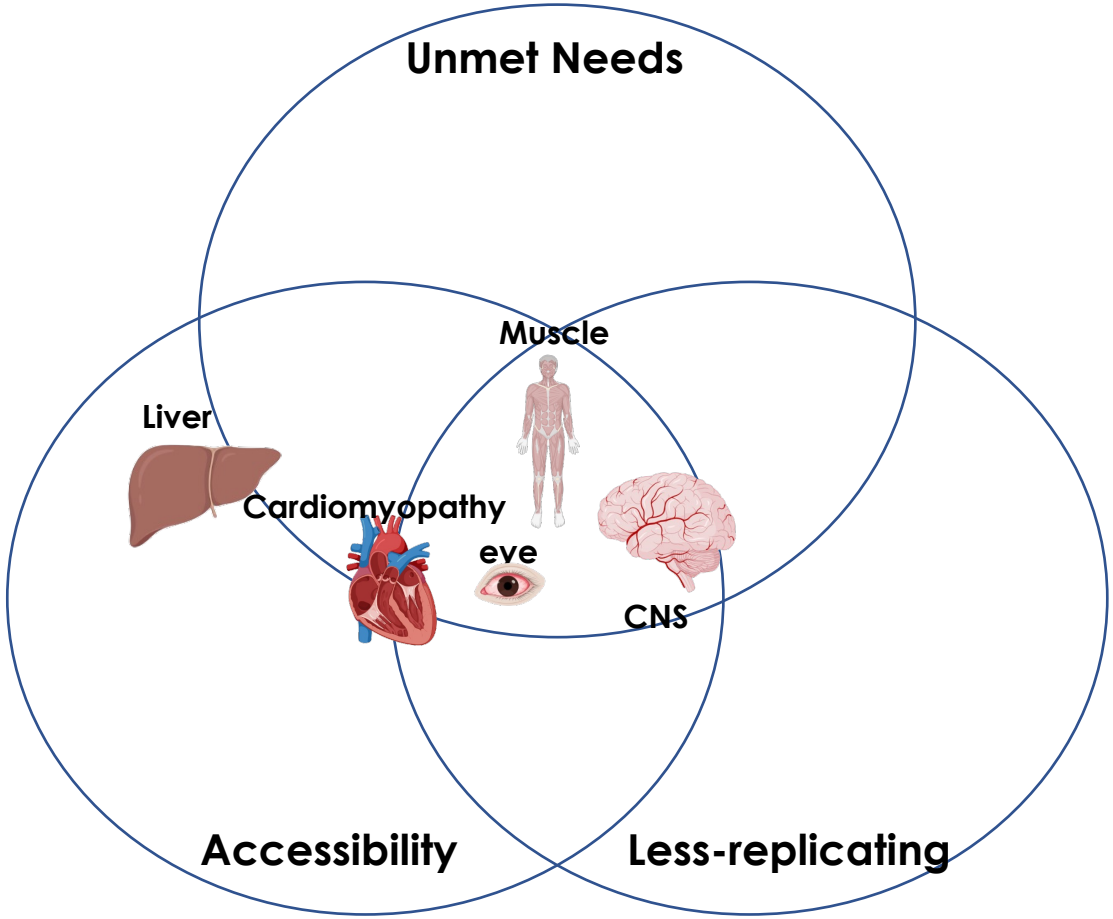
Revised

Modalis focuses on muscle, CNS, and cardiomyopathy

Target selection for Modalis' gene therapies



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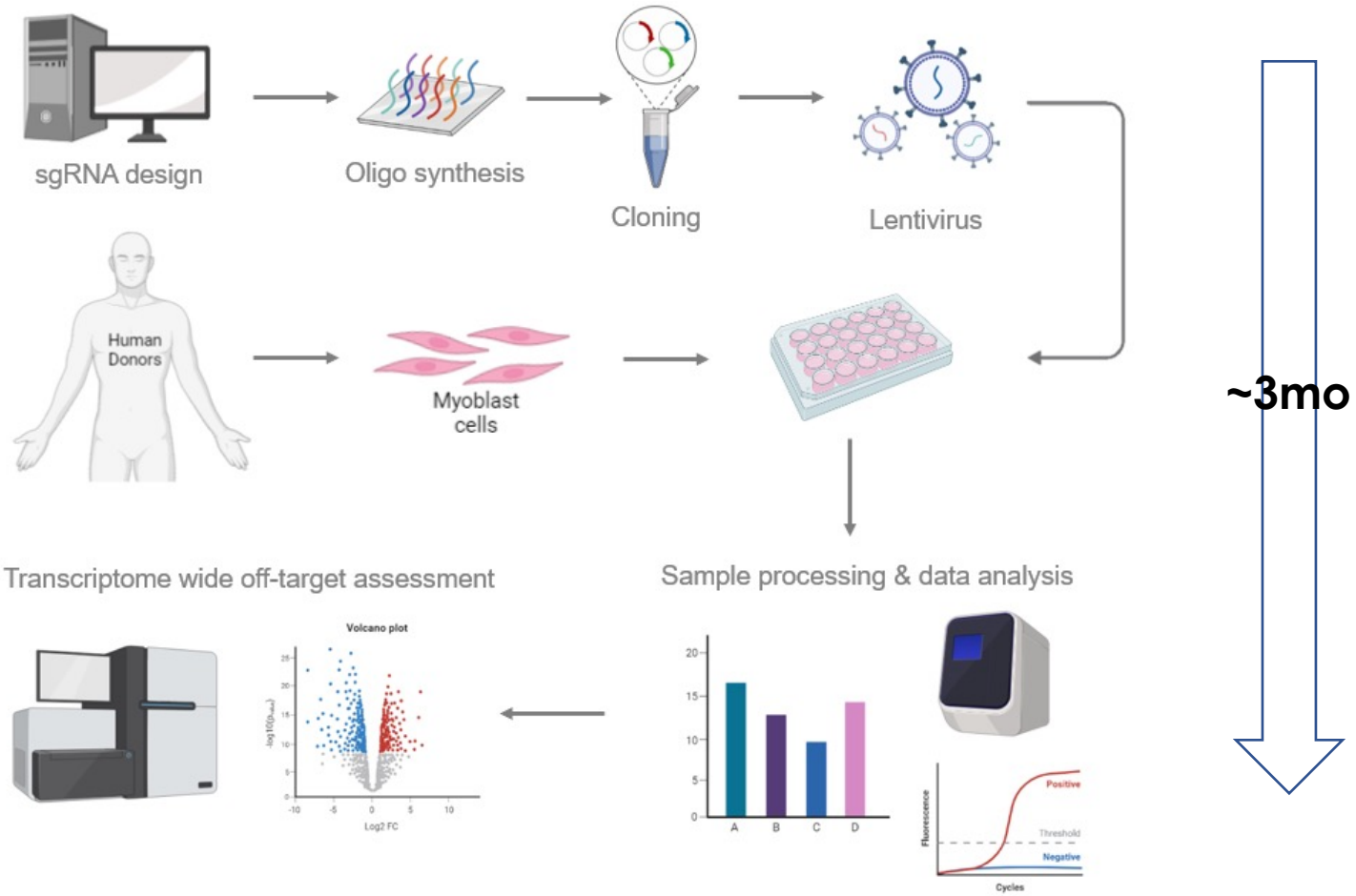
CRISPR-GNDM® platform efficiently identifies optimal gRNA

Lead candidate screening in human primary myoblast cells



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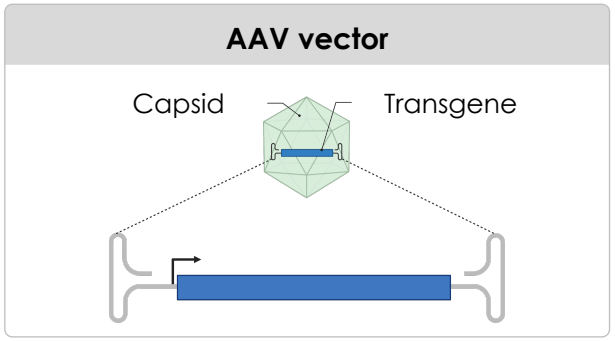
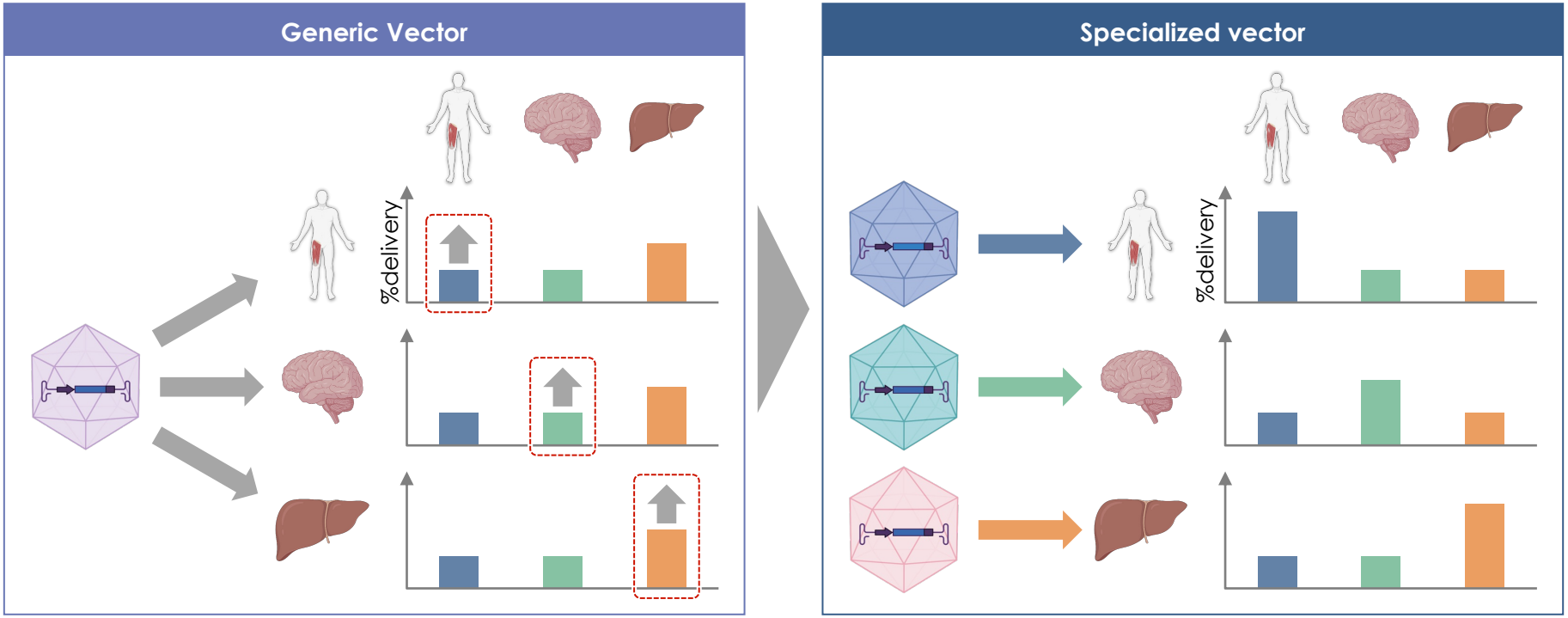
Big innovations have been brought to AAV vectors recently



- 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



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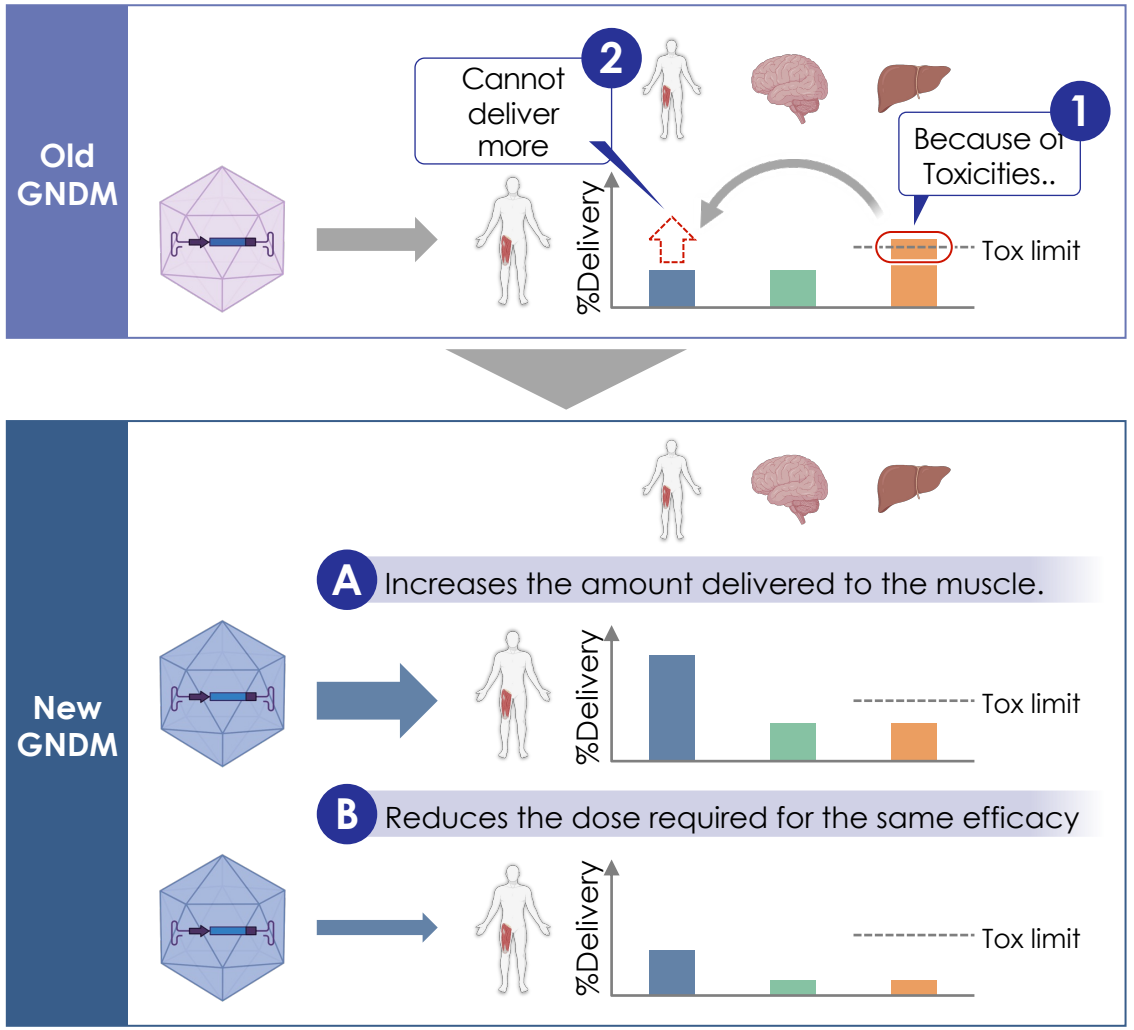
Transition to specialized capsid is the need of the field and will be beneficial in the long run

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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4. Pipeline

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New

Summary of pipeline reorganization

- As we regained rights of MDL-201 and 202 from Astellas, Modalis reorganize the pipeline.
- Put higher priority on muscle programs in which the company has stronger confidence and data throughout the development of MDL-101
- Modalis adds MDL-103 which targets FSHD by silencing Dux4 gene and the company has incubated for years.
- CNS programs including MDL-104 have been deprioritized but continue to put in research effort.
- MDL-102 was removed from the pipeline.

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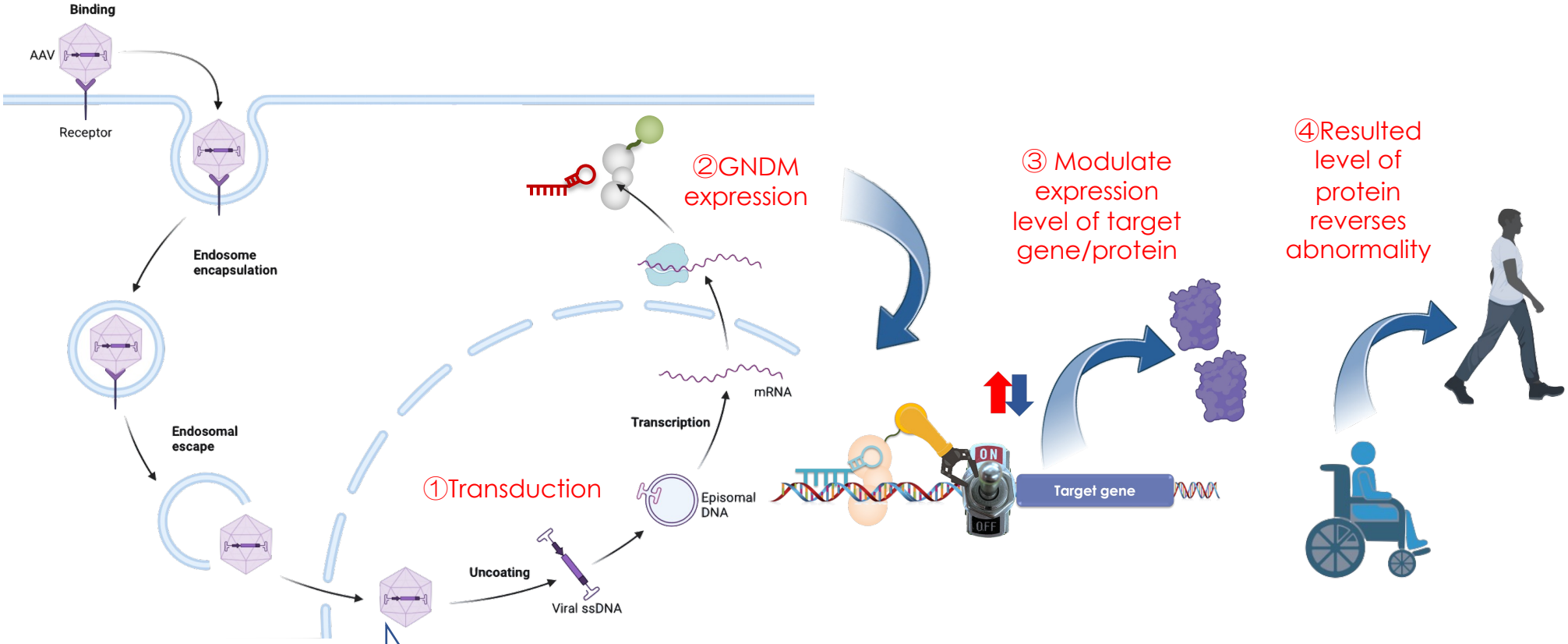
Among the 4 steps to demonstrate efficacy, 2 steps are common to the muscle programs and confirmed to function in NHP



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

Vector system (platform)

gRNA

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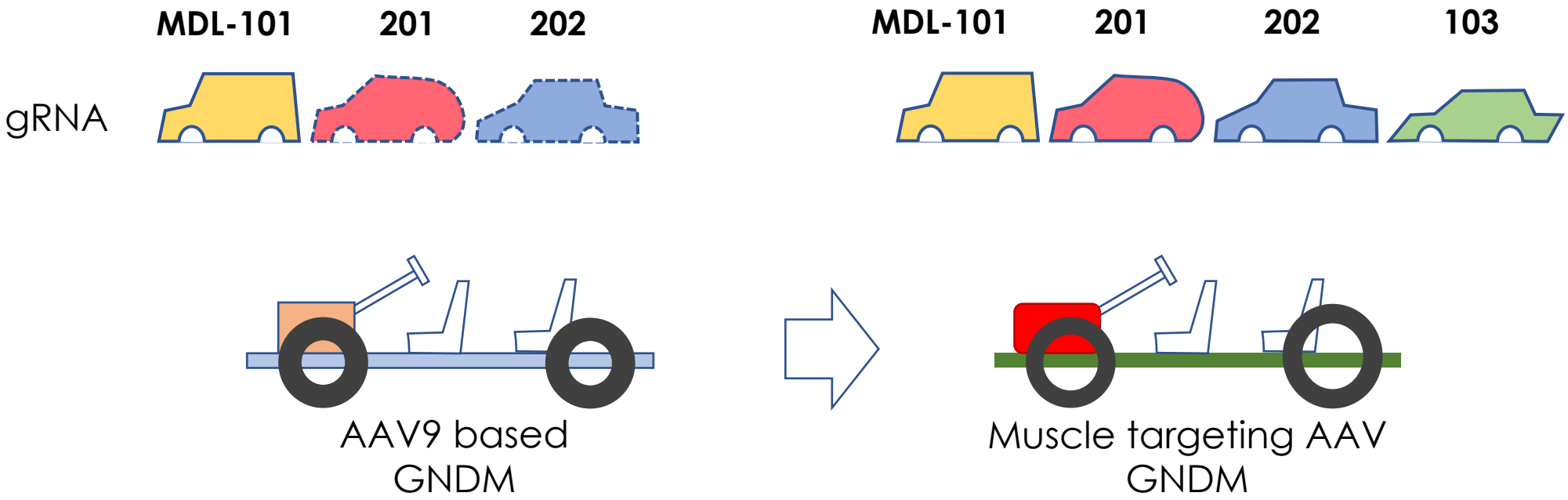
New

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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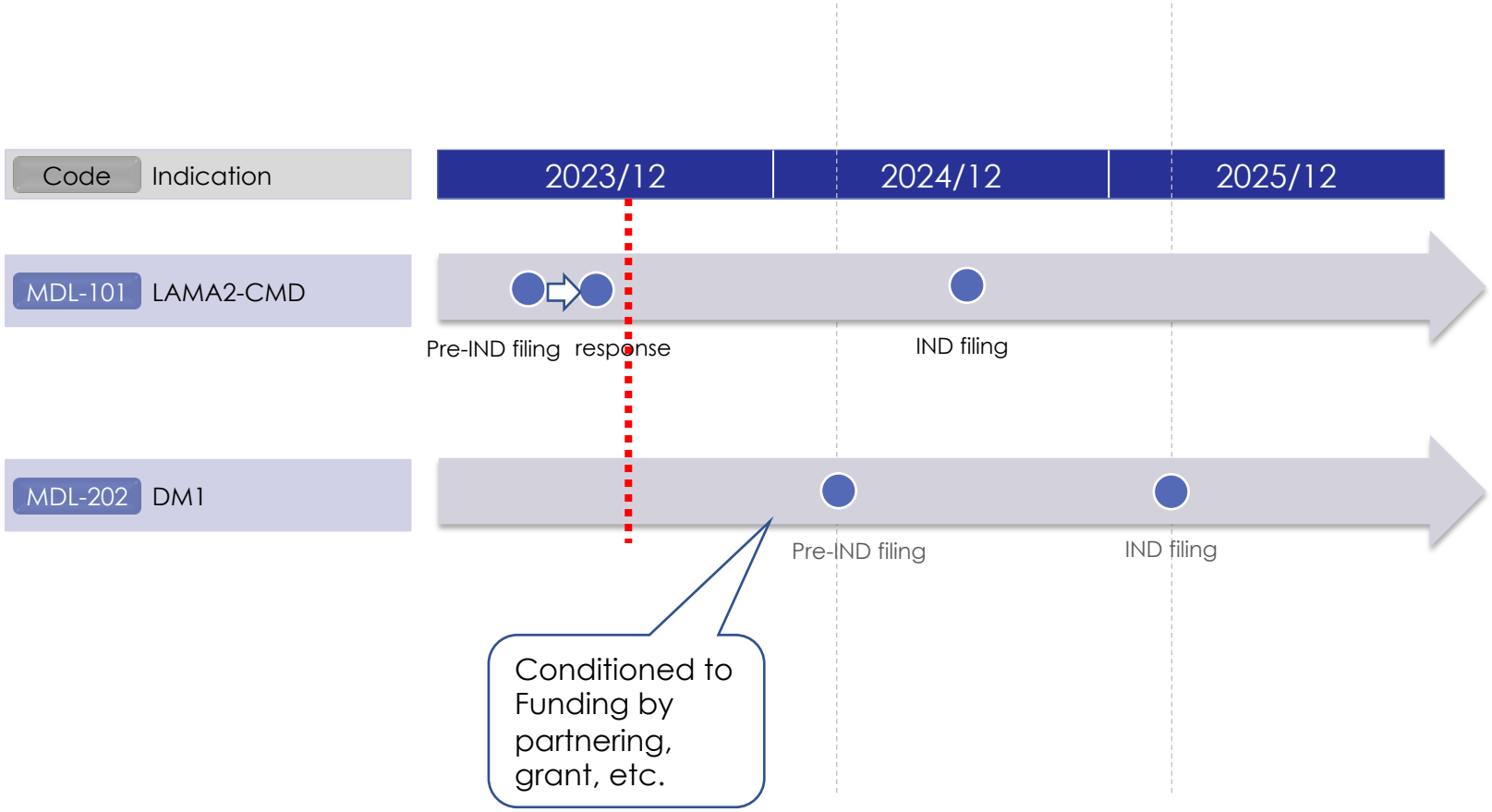
Revised

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

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Revised

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 • Pre-IND 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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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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Revised

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 meeting 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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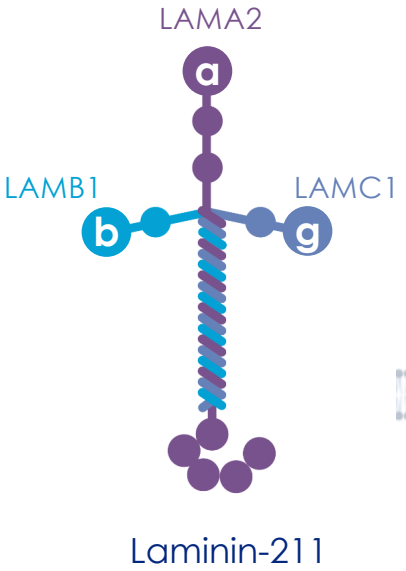
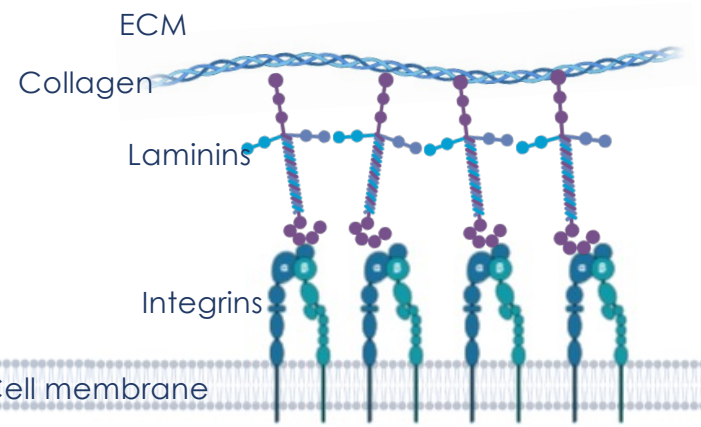
Loss of LAMA2 causes congenital muscular dystrophy type 1A (LAMA2-CMD)



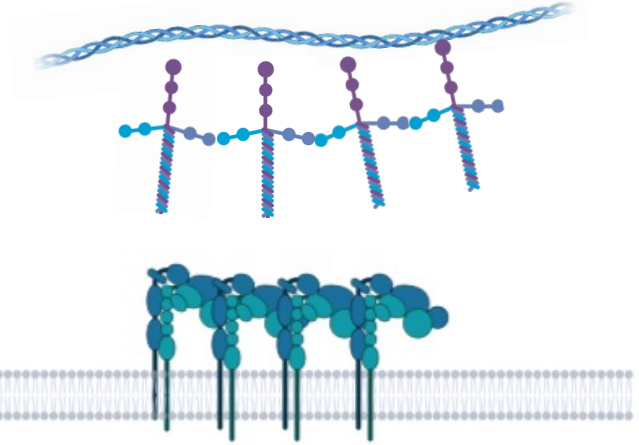
Laminin-211

Normal LAMA2 Function



- Strongly expressed in skeletal muscle.
- Protects muscle from contraction stress.
- Influences signal transmission through dystroglycan and integrins

LAMA2 Loss-of-function



- Most **common** form of congenital muscular dystrophy.
- Currently **no cure** available.

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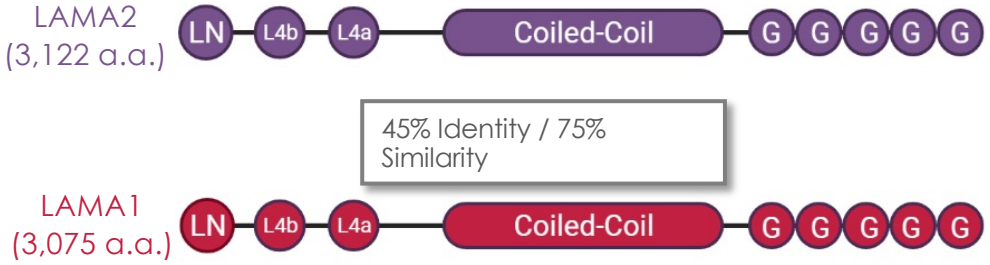
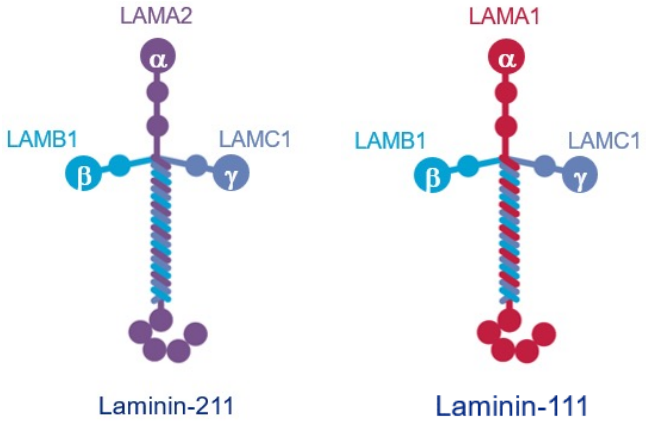
LAMA1 can compensate the loss of LAMA2 function in vivo





Laminin-211 | Laminin-111

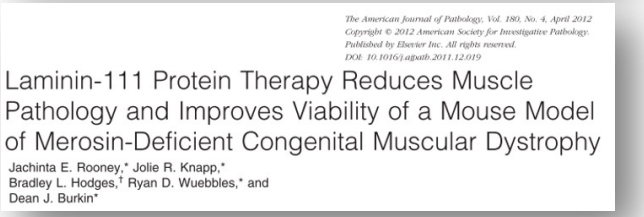
Expression in muscle tissue: High | None



Human Molecular Genetics, 2004, Vol. 13, No. 16 1775–1784
doi:10.1093/hmg/ddh190
Advance Access published on June 22, 2004

Laminin α1 chain reduces muscular dystrophy in laminin α2 chain deficient mice

Kinga Gawlik[1], Yuko Miyagoe-Suzuki[2], Peter Ekblom[1], Shin'ichi Takeda[2] and Madeleine Durbeej[1,*]



The American Journal of Pathology, Vol. 180, No. 4, April 2012
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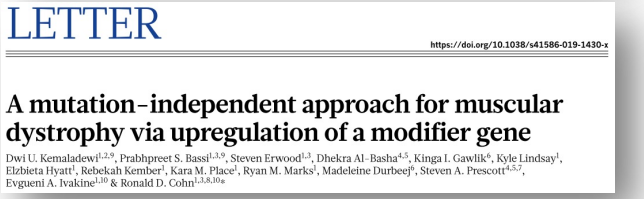
DOI: 10.1016/j.ajpath.2011.12.019

Laminin-111 Protein Therapy Reduces Muscle Pathology and Improves Viability of a Mouse Model of Merosin-Deficient Congenital Muscular Dystrophy

Jachinta E. Rooney,* Jolie R. Knapp,* Bradley L. Hodges,† Ryan D. Wuebbles,* and Dean J. Burkin*



LETTER

https://doi.org/10.1038/s41586-019-1430-x

A mutation-independent approach for muscular dystrophy via upregulation of a modifier gene

Dwi U. Kemaladewi[1,2,9], Prabhpreet S. Bassi[1,3,9], Steven Erwood[1,3], Dhekra Al-Basha[4,5], Kinga I. Gawlik[6], Kyle Lindsay[1], Elzbieta Hyatt[1], Rebekah Kember[1], Kara M. Place[1], Ryan M. Marks[1], Madeleine Durbeej[6], Steven A. Prescott[4,5,7], Evgueni A. Ivakine[1,10] & Ronald D. Cohn[1,3,8,10]✉

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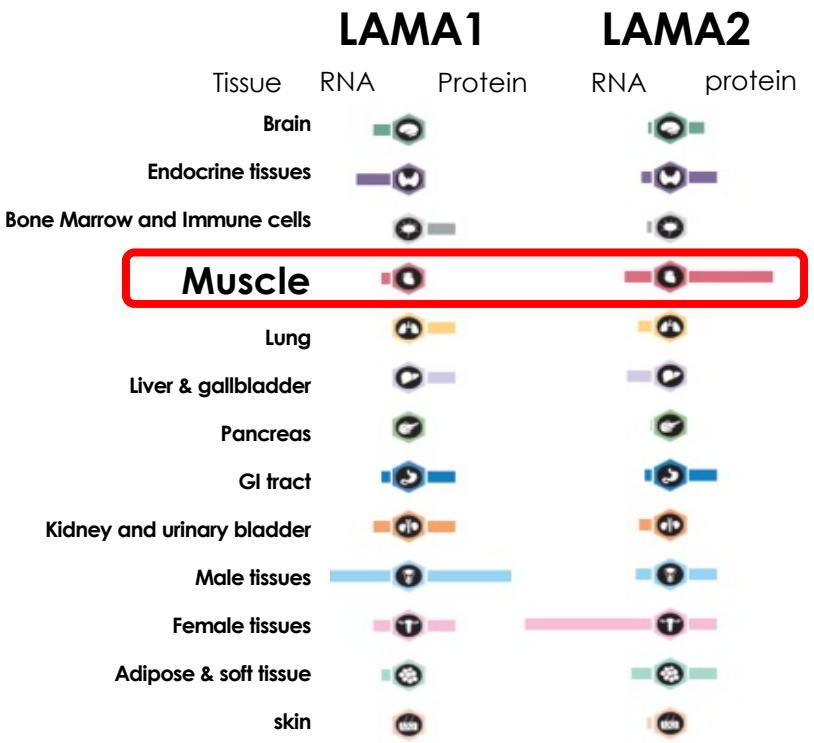
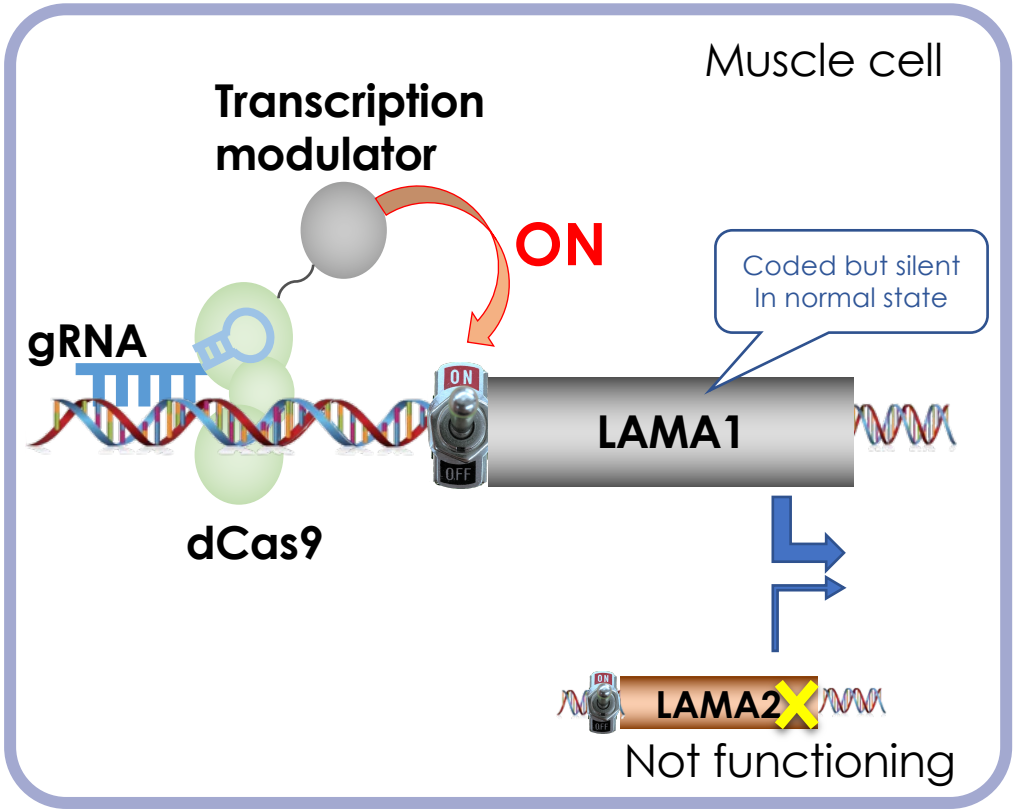
By activating the sister gene, LAMA1, GNDM compensates missing function of LAMA2, which is too big to be addressed by regular GTx

Exspression pattern of LAMA1and LAMA2 by tissues



CRISPR-GNDM® targeting LAMA1



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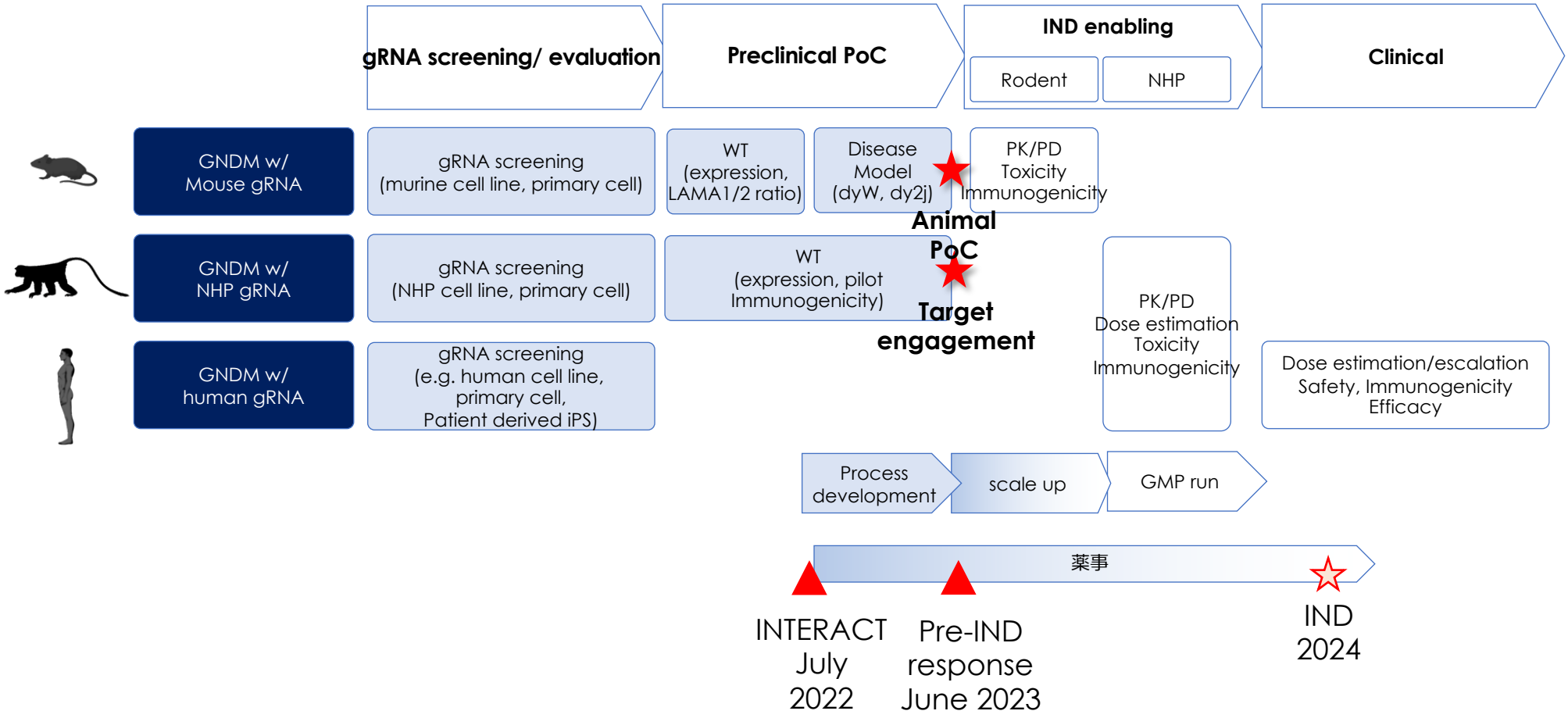
Conducting IND enabling studies as well as process development

Current status of MDL-101 and road map to clinic



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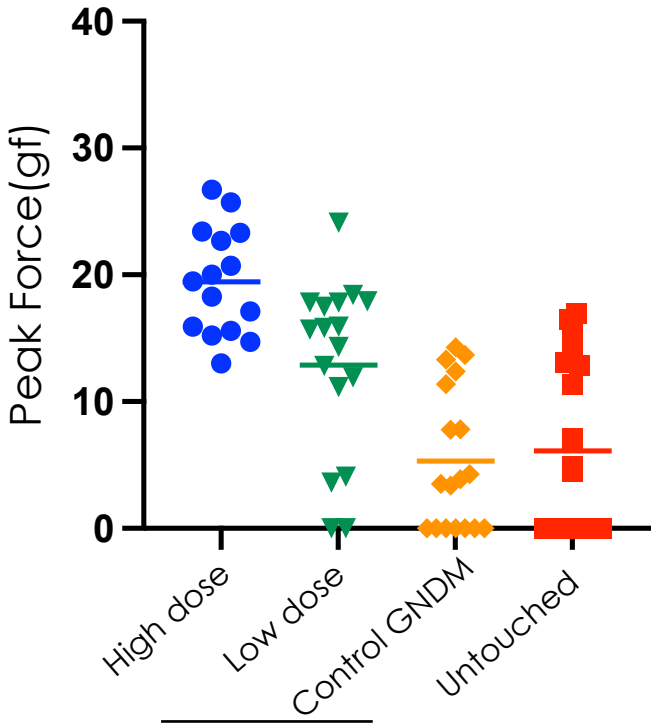
Mice study demonstrated significant improvement in muscle function

Grip Strength Forepaws



- dyW (severe MDC1a model) mice injected with GNDM (control gRNA, or active gRNA at low and high dose) compared with untouched.
- Grip strength assay on 34-day post injection.

In addition to the survival benefit, the functional improvement is confirmed

average of 3 trials

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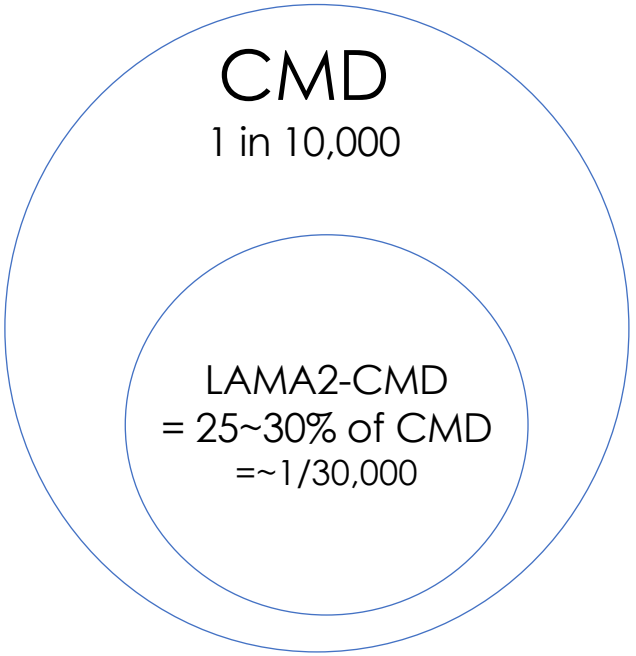
MODALIS

Prevalence of LAMA2-CMD

- Exact prevalence of LAMA2-CMD is still unknown but...
  - The prevalence of congenital muscular dystrophies (CMD) has been estimated between
    - 1-9/100,000
  - LAMA2-CMD is about ~30% of CMD:
    - **~1/30,000** with regional variation



CMD: congenital muscular dystrophy

Source: orpha.net

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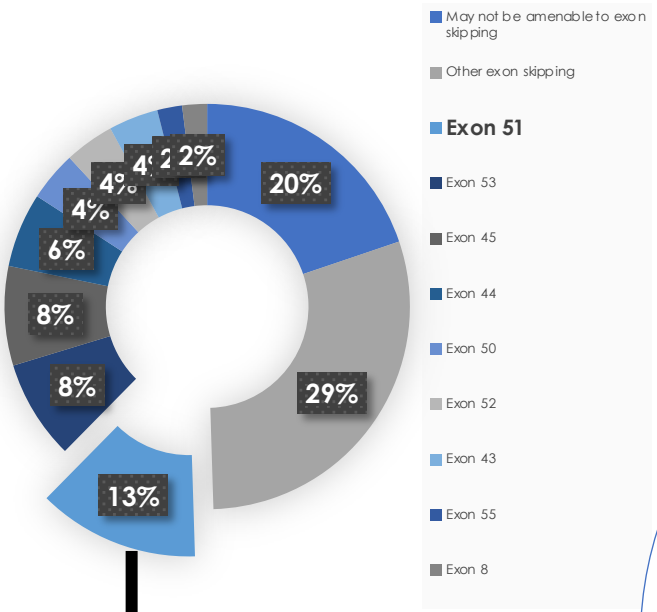
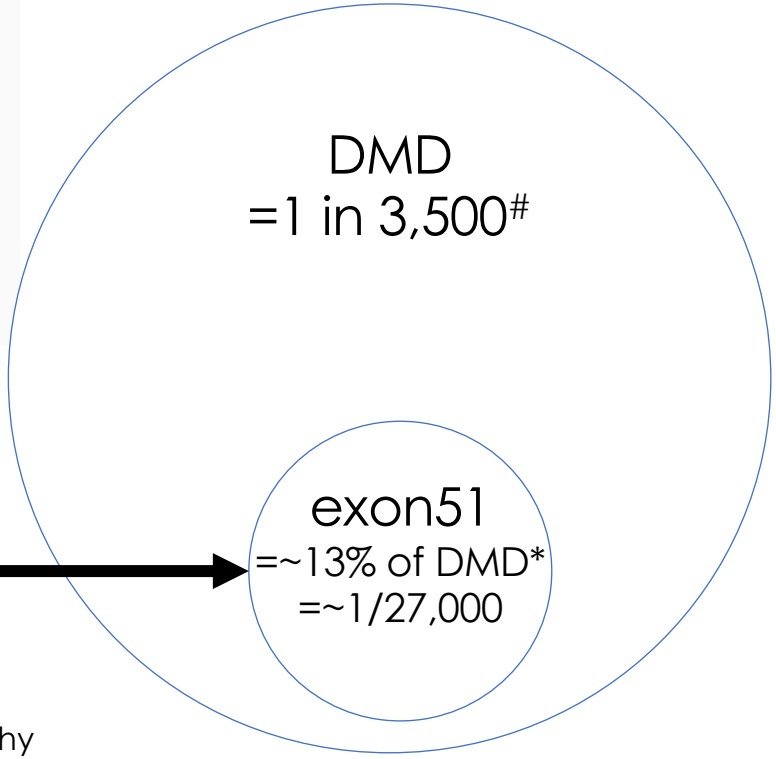
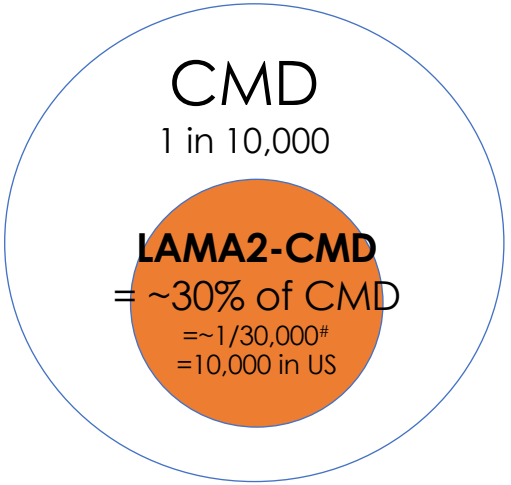
LAMA2-CMD is about the same size to DMD caused by Exon 51 mutation







DMD: Duchenne muscular dystrophy

*https://www.cureduchenne.org/cure/exon-skipping/

#Source: www.orpha.net

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NEW

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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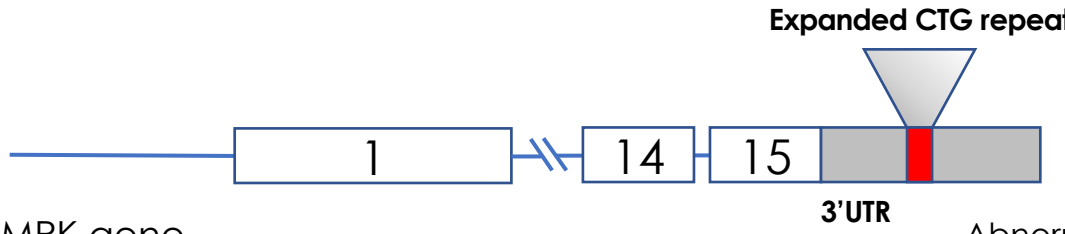
MODALIS

NEW

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

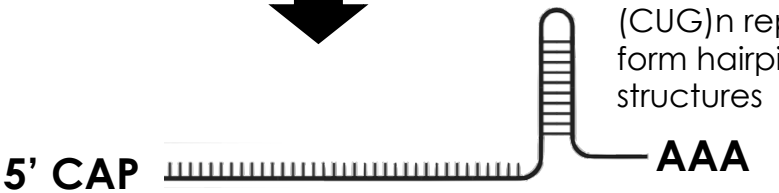
DM1disease causing mechanism



DMPK gene

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

DMPK mRNA With CUG repeat

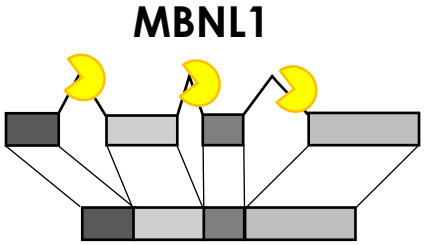


MNBL binds to hairpin-like structures

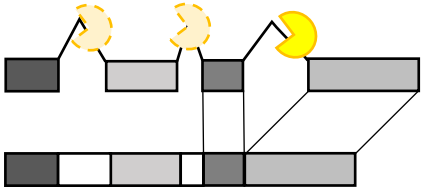
RNA to accumulate in nucleus by sequestering isoforms of the MBNL



Splicing in healthy people



MBNL1 contributes normal splicing



MNBL goes back to functioning in normal splicing

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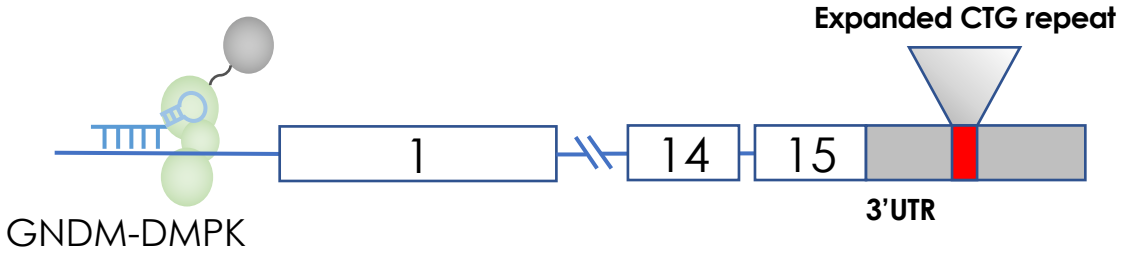
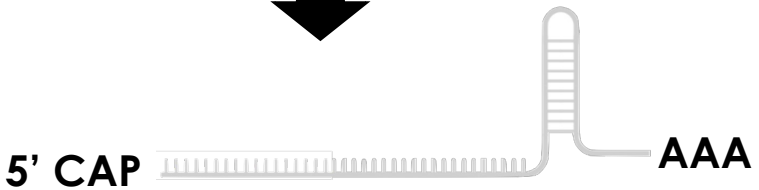
NEW

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

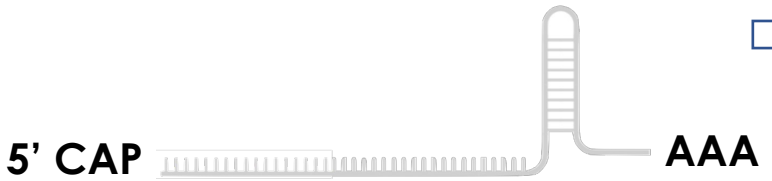
MDK-202's mechanism of action

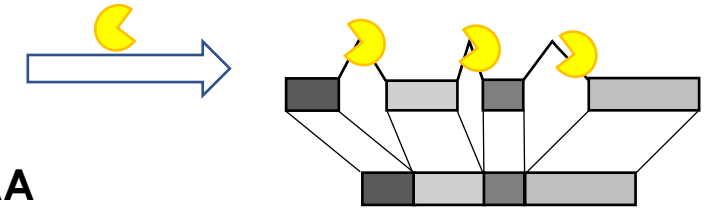


GNDM silences DMPK expression



MNBL is released From CTG repeat





MNBL goes back to contribute normal splicing

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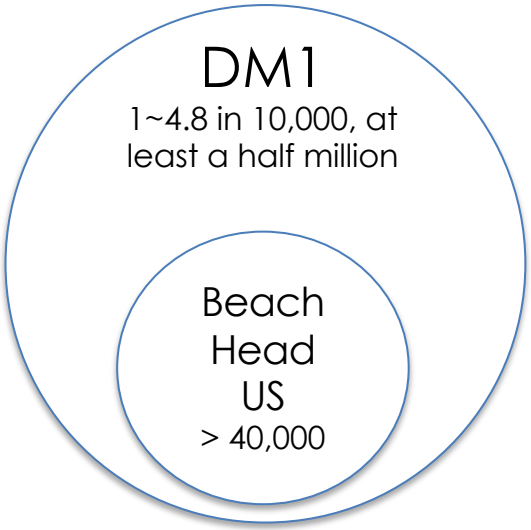
NEW

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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NEW

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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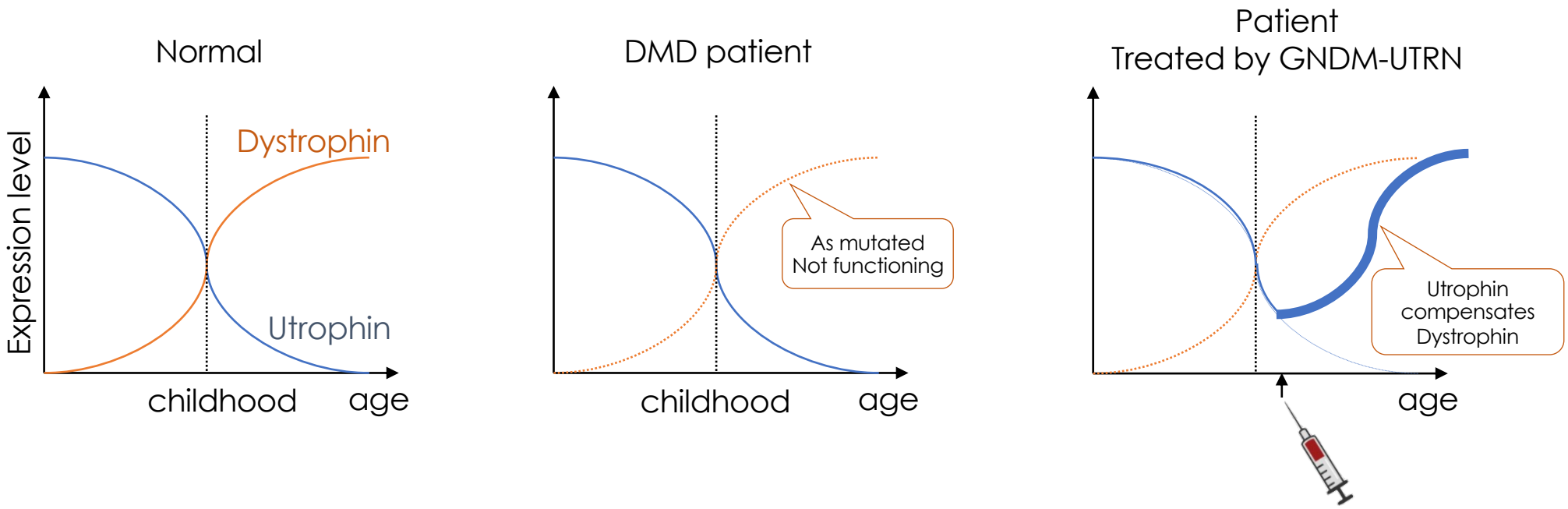
NEW

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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NEW

Facioscapulohumeral Muscular Dystrophy (FSH, 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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NEW

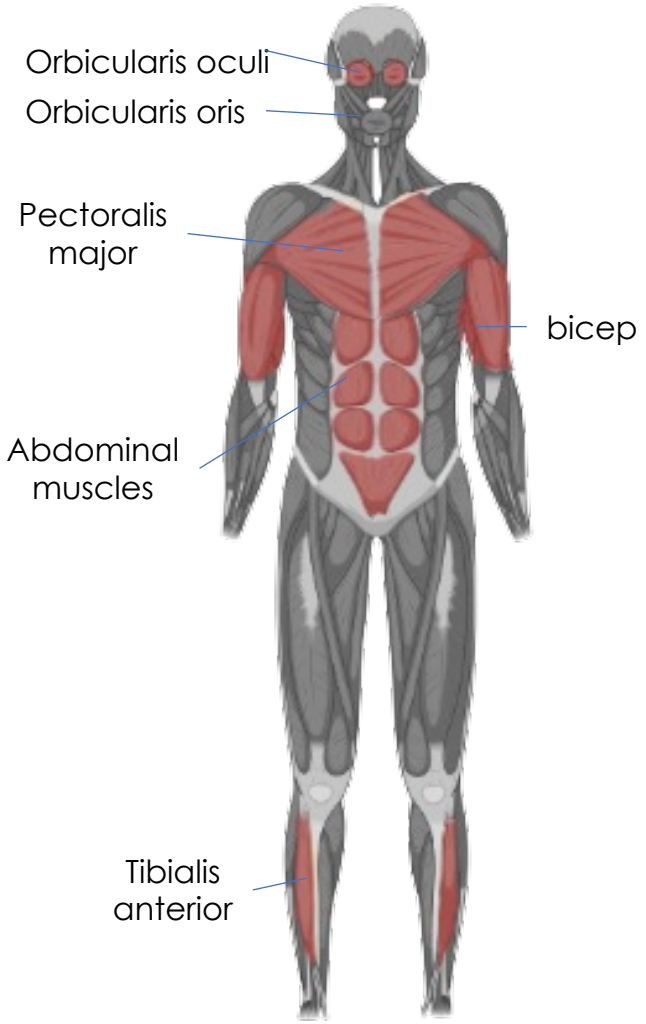
FSHD is a genetic muscle disorder in which the muscles of the face, shoulder blades and upper arms are most affected

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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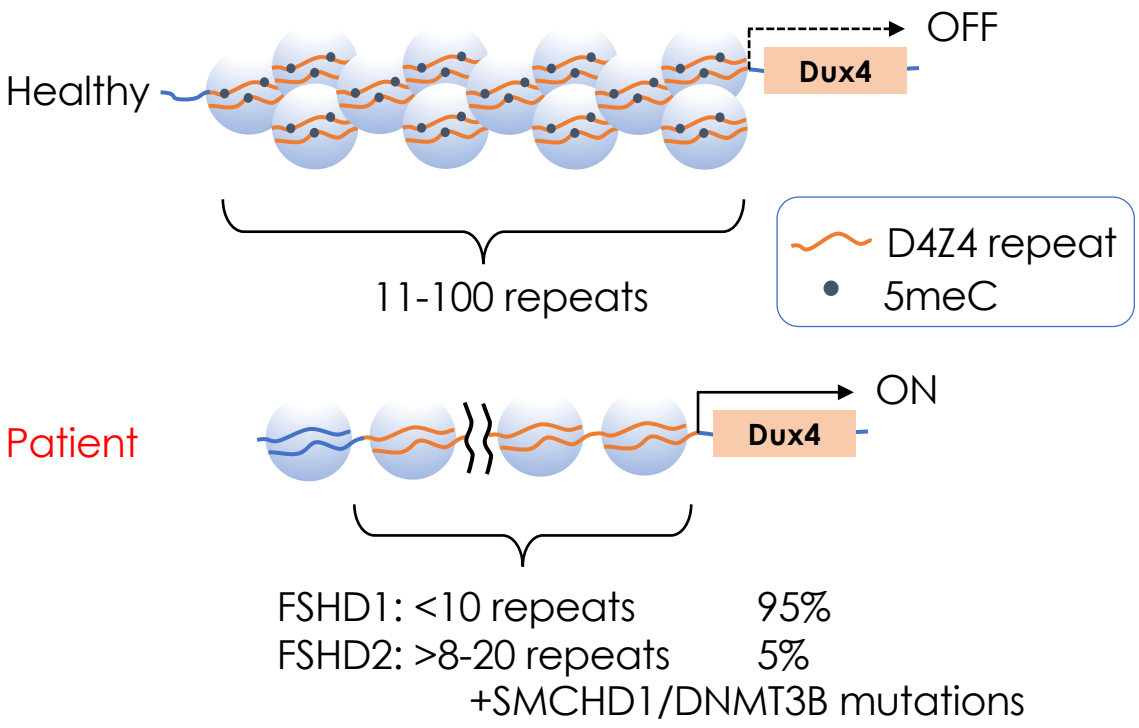
NEW

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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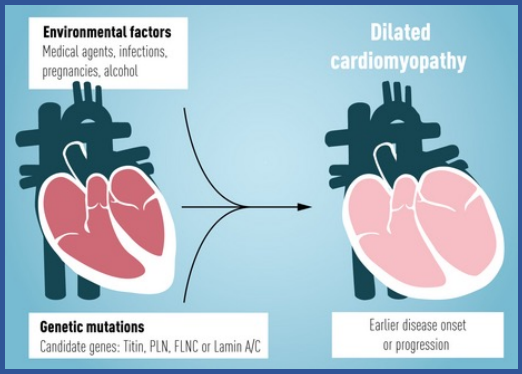
Dilated Cardiomyopathy (DCM)

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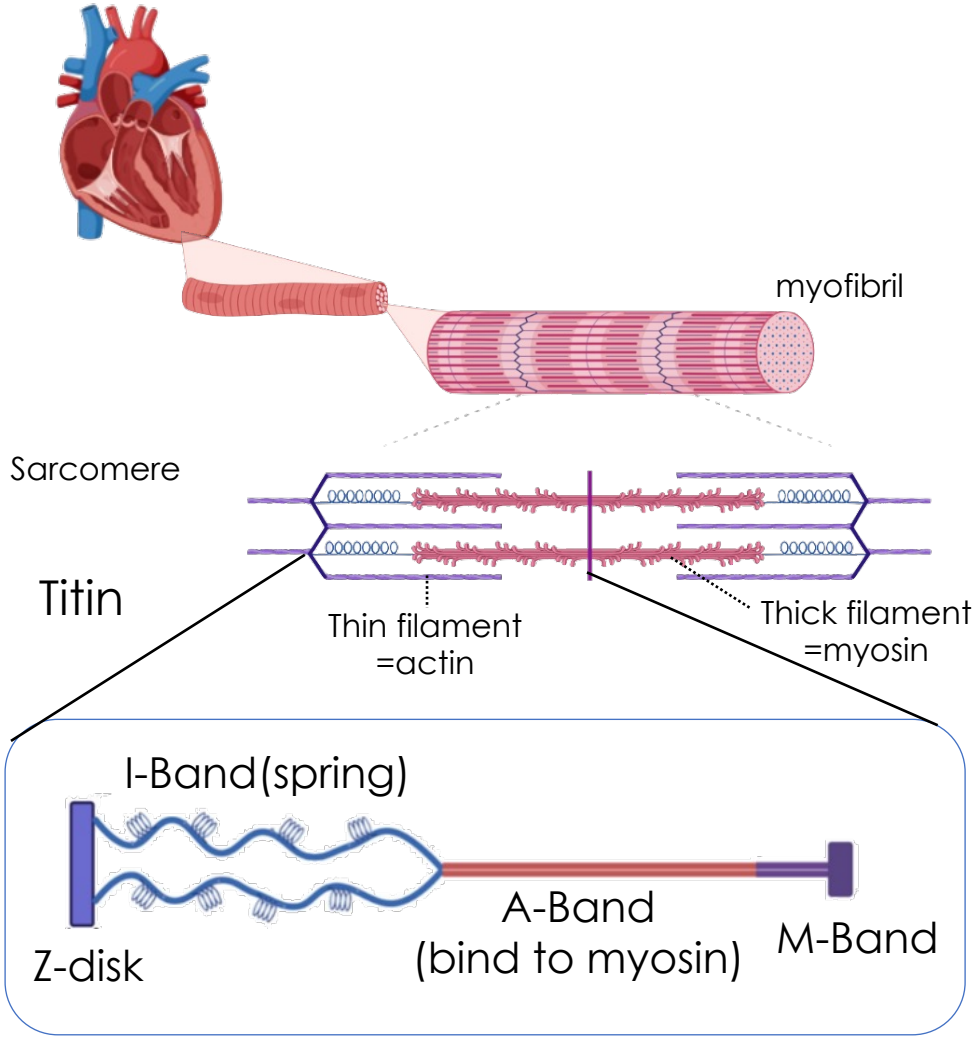
TTN is the largest human protein - which is too large for AAV packaging

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)



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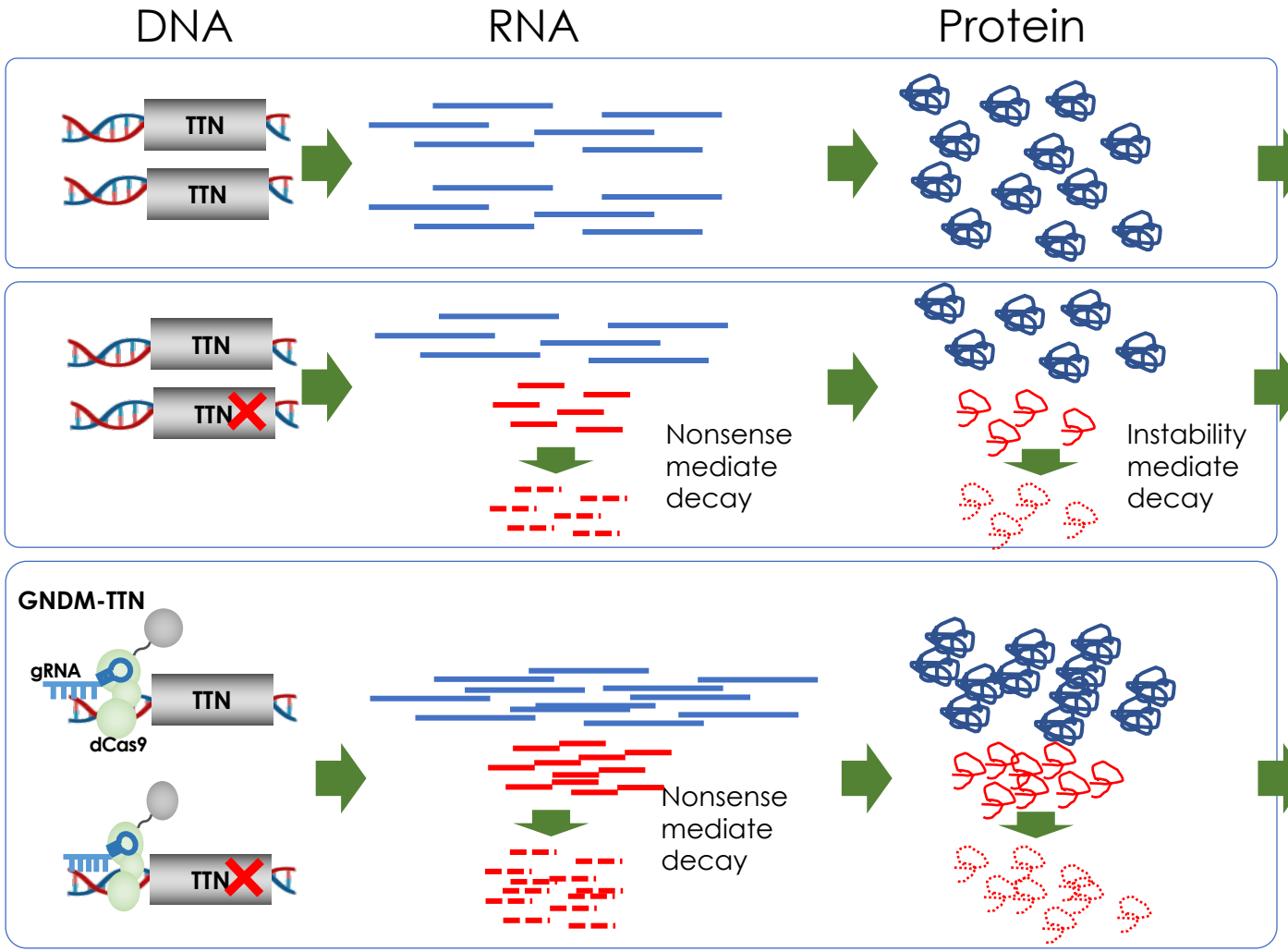
Product concept:
Activate TTN gene to boost TTN protein in DCM patients

Working hypothesis of GNDM based DCM therapy



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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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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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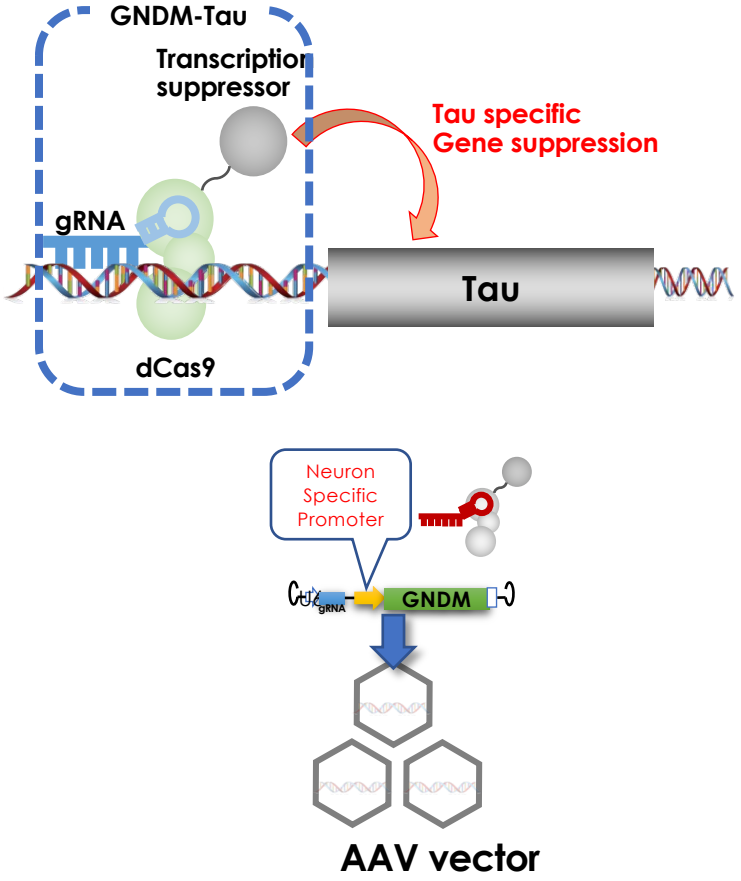
Product concept of Tau suppressor by CRISPR-GNDM®

- 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



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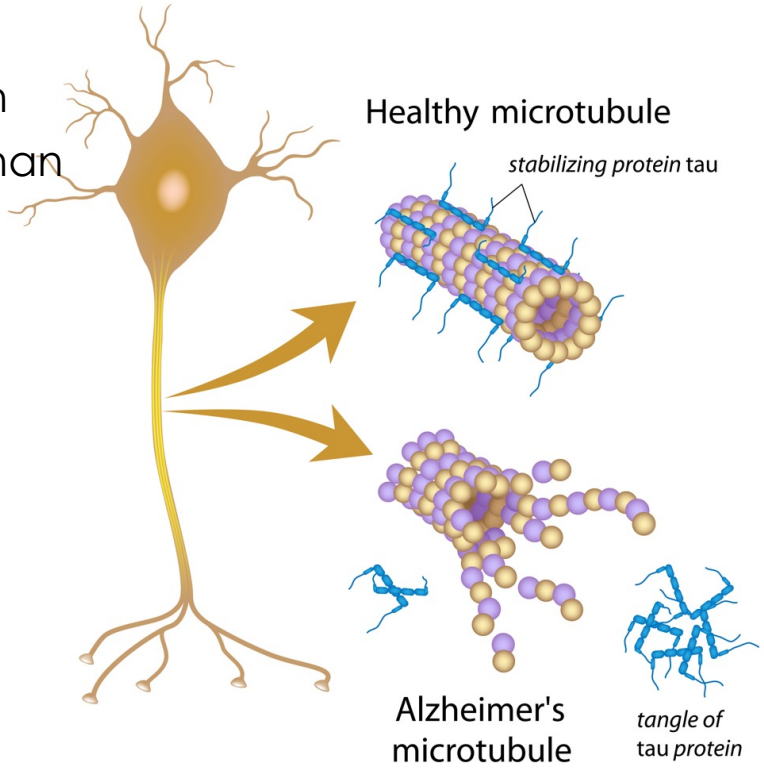
Tau is a center of attention in treating Alzheimer diseases

- 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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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 (Perkinson 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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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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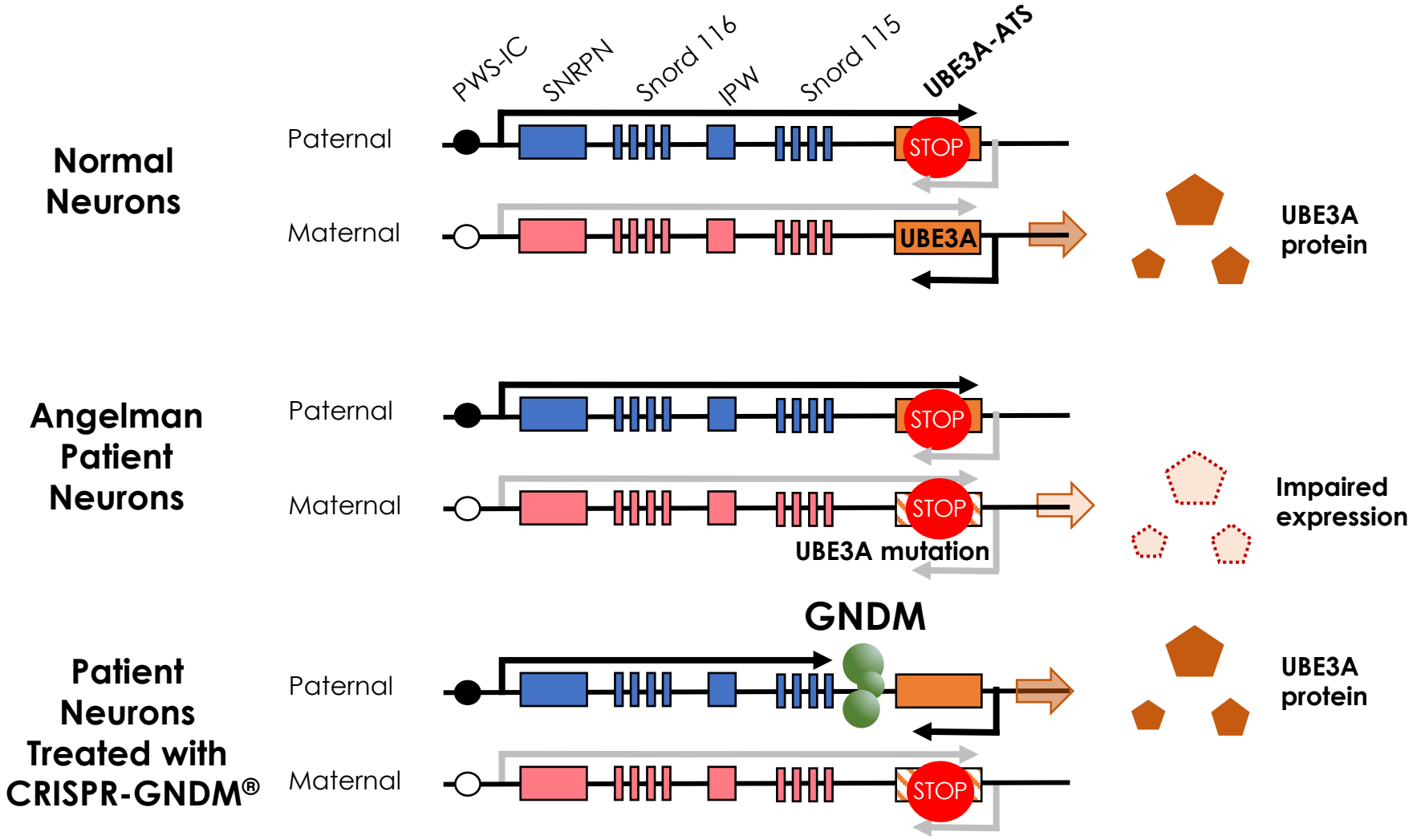
By blocking ATS transcript, GNDM un-silences UBE3A expression



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5. Growth Strategy

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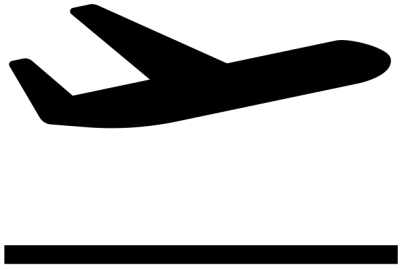
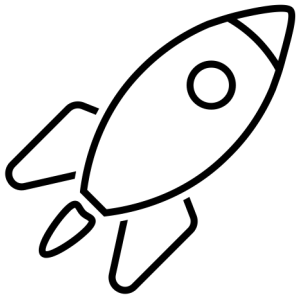
Diversified pipeline with their own missions

Pioneer the gene modulation With highly suitable indications	Expand technology opportunity with products for larger opportunity	Further approach to challenging applications
MDL-101	**MDL-202**	**Other programs**







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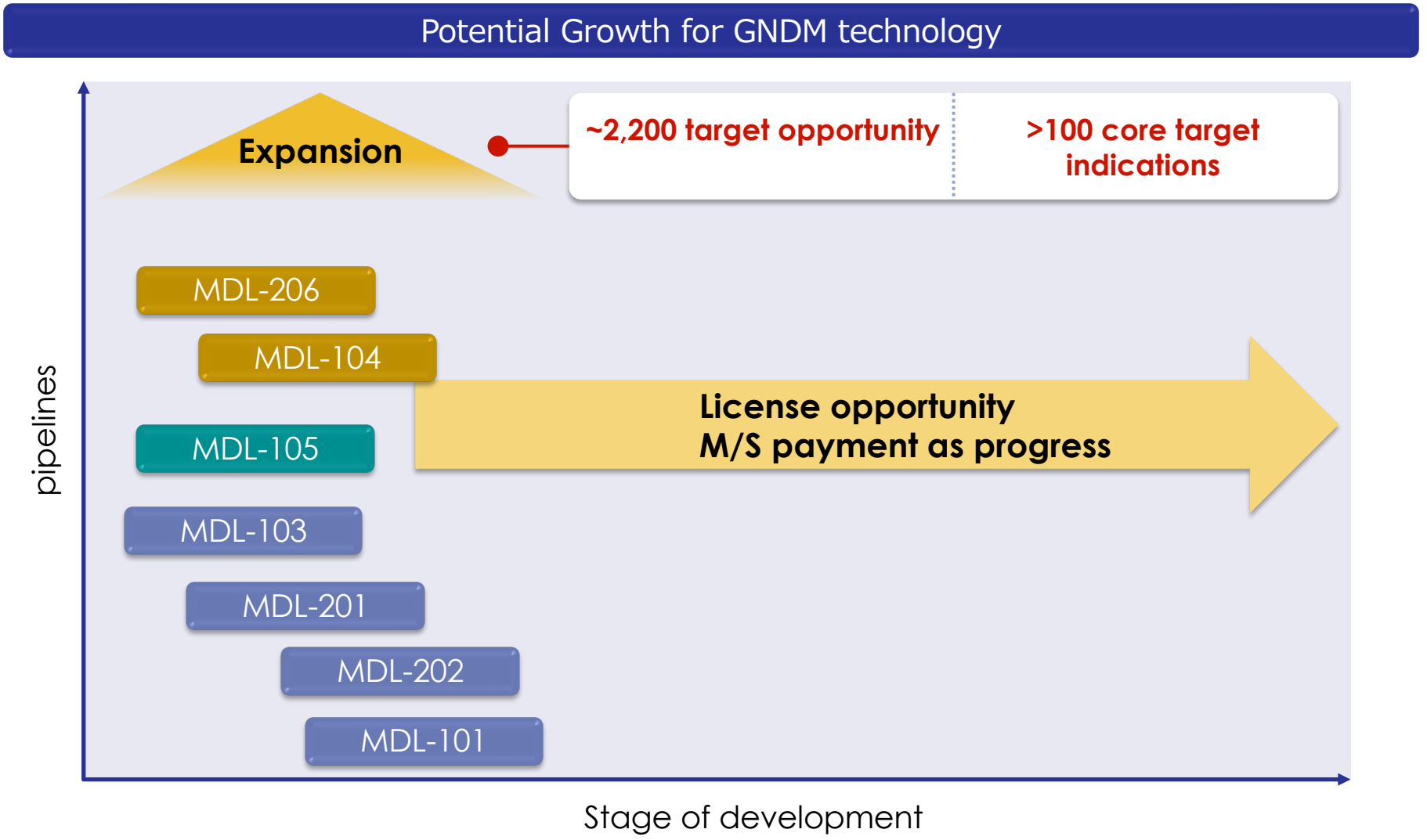
Growth Strategy

opportunity expands two dimensionally



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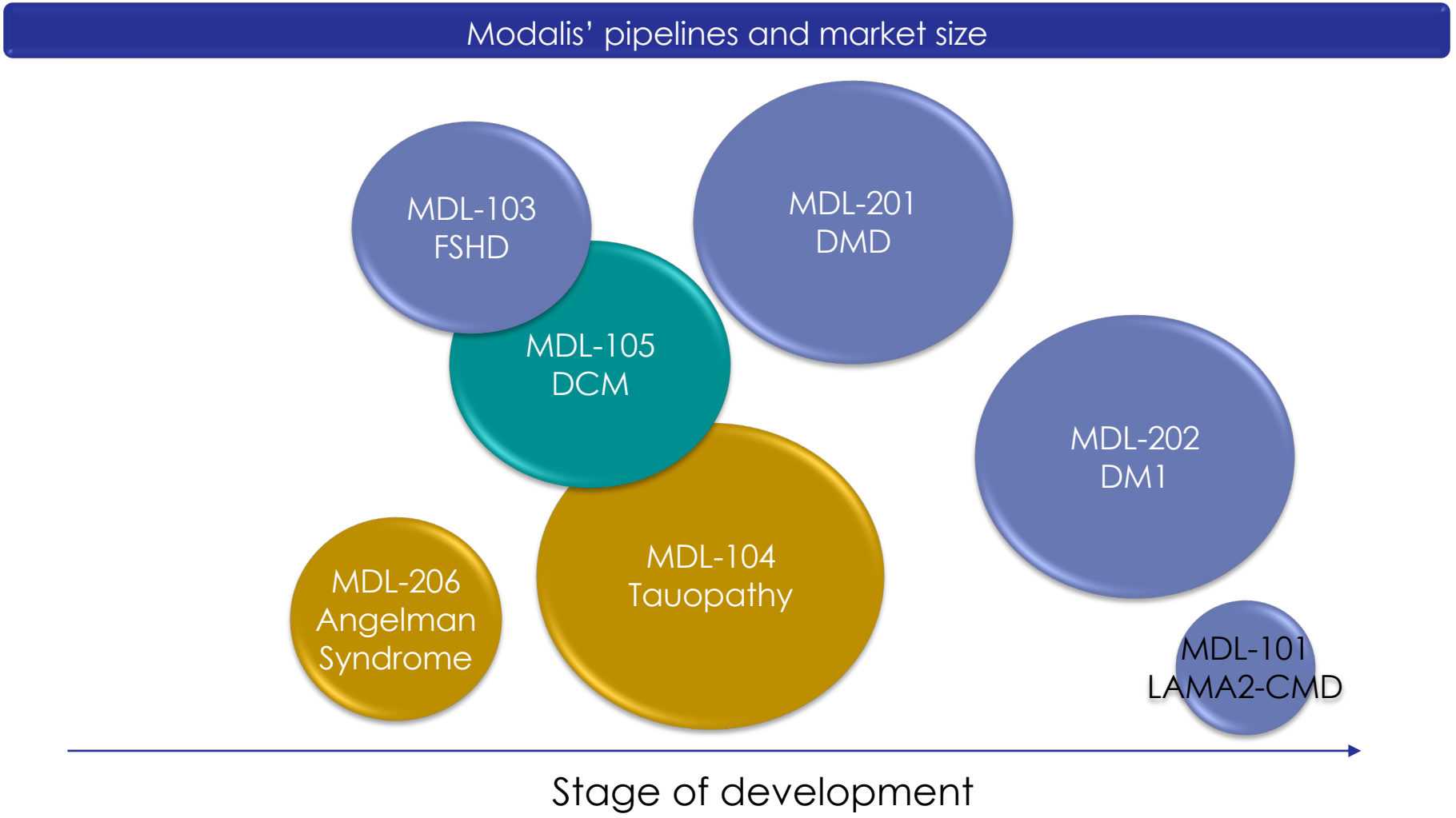
Modalis' pipelines and market size

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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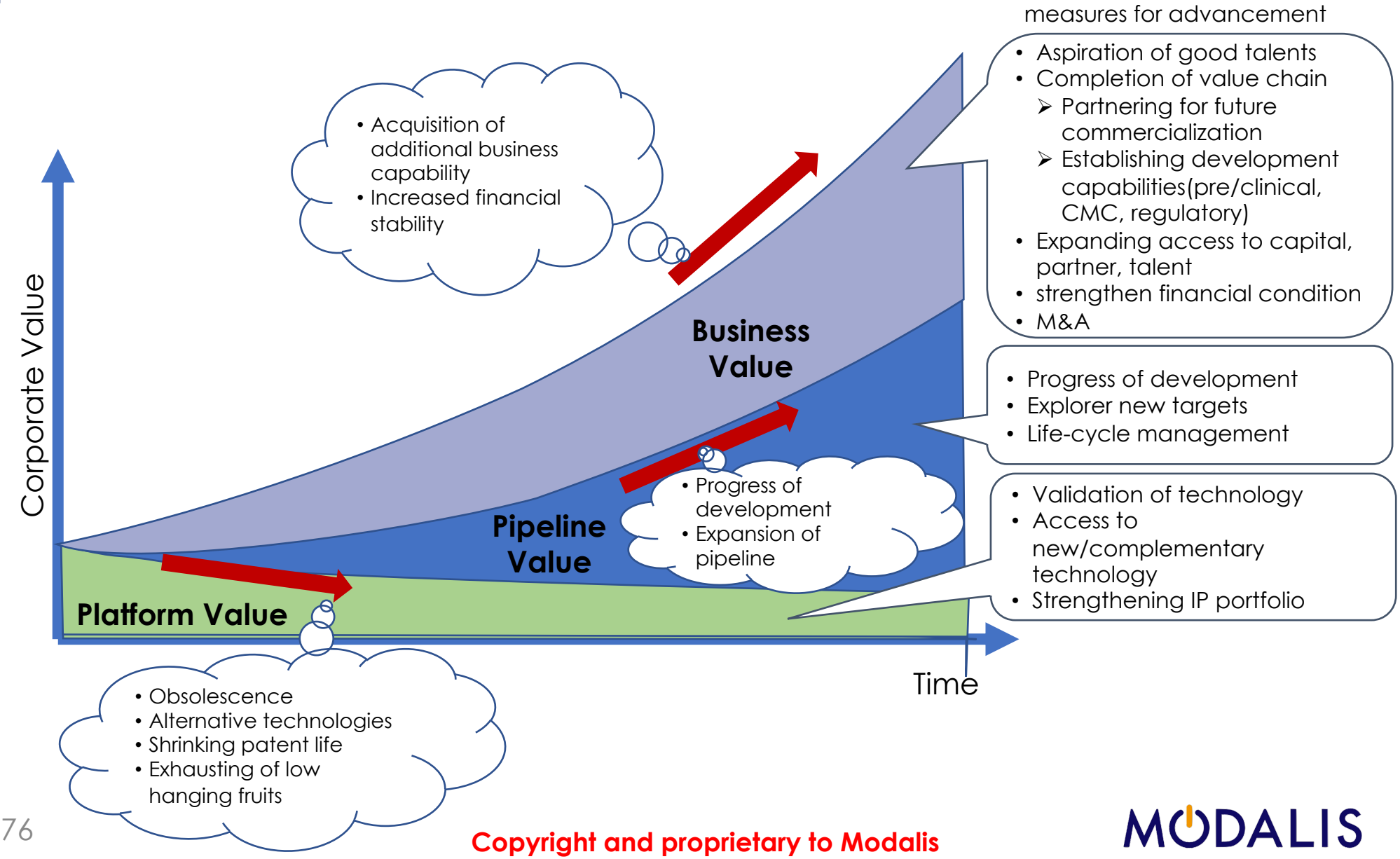
Composition of Modalis' value and measures for advance



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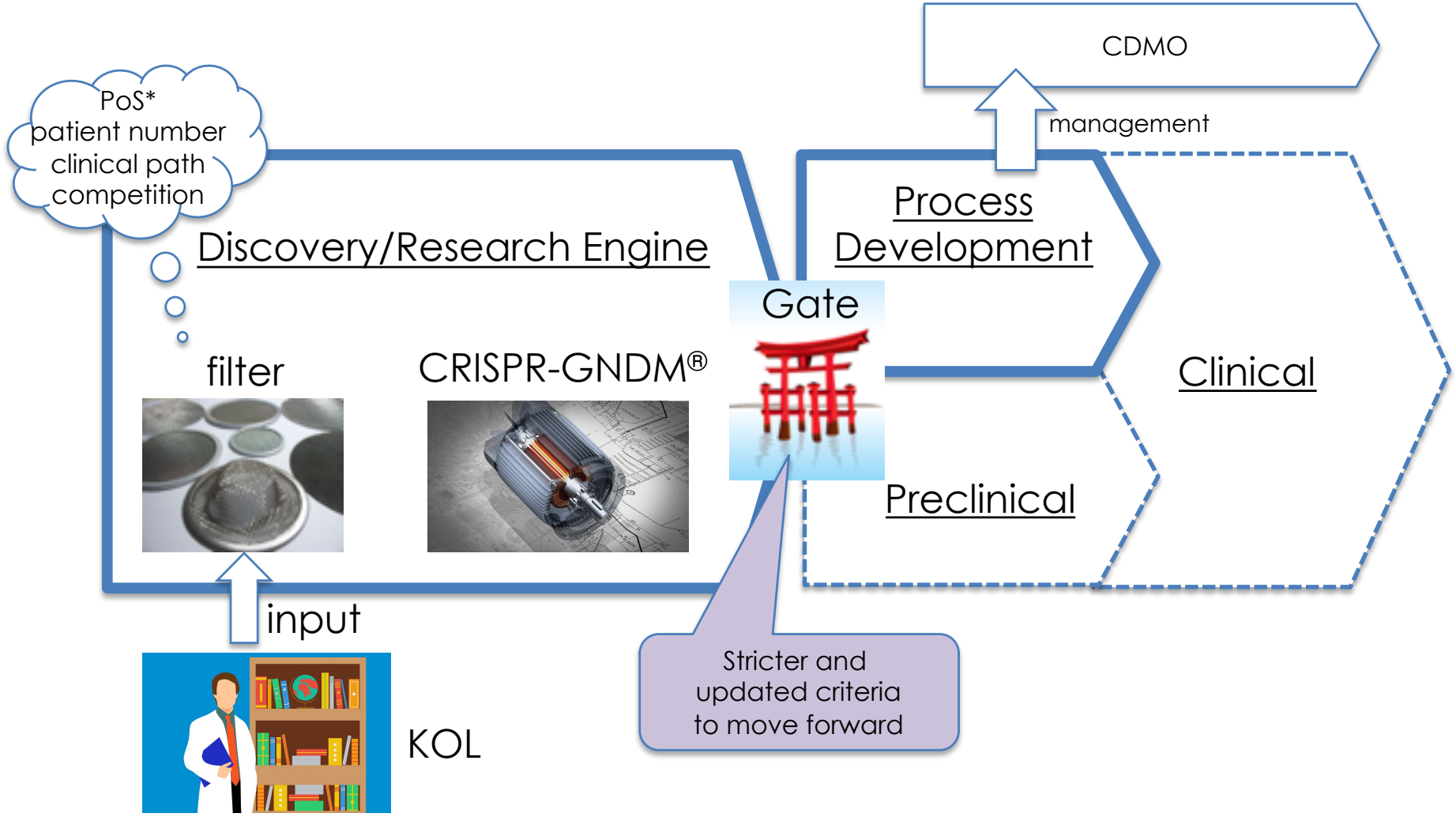
Upon transition from R to D, which cost time and money, stricter decision is made for higher ROI and better resource allocation.



PoS: Probability of success

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The future Modalis envisioned

Short Term (2023)	Mid Term (3yrs)	Long Term (>3yrs)
• MDL-101 Pre-IND (Done) • MDL-202 target engagement in NHP	• Initiation of clinical trial (101 and 202) • Clinical PoC (2024～25)	• Market approval and launch of GNDM-based product(S) • Plug-and-play GNDM technology

Partnering

Commoditization of genetic analysis

Public acceptance of gene therapy

Evolution of GTx technologies

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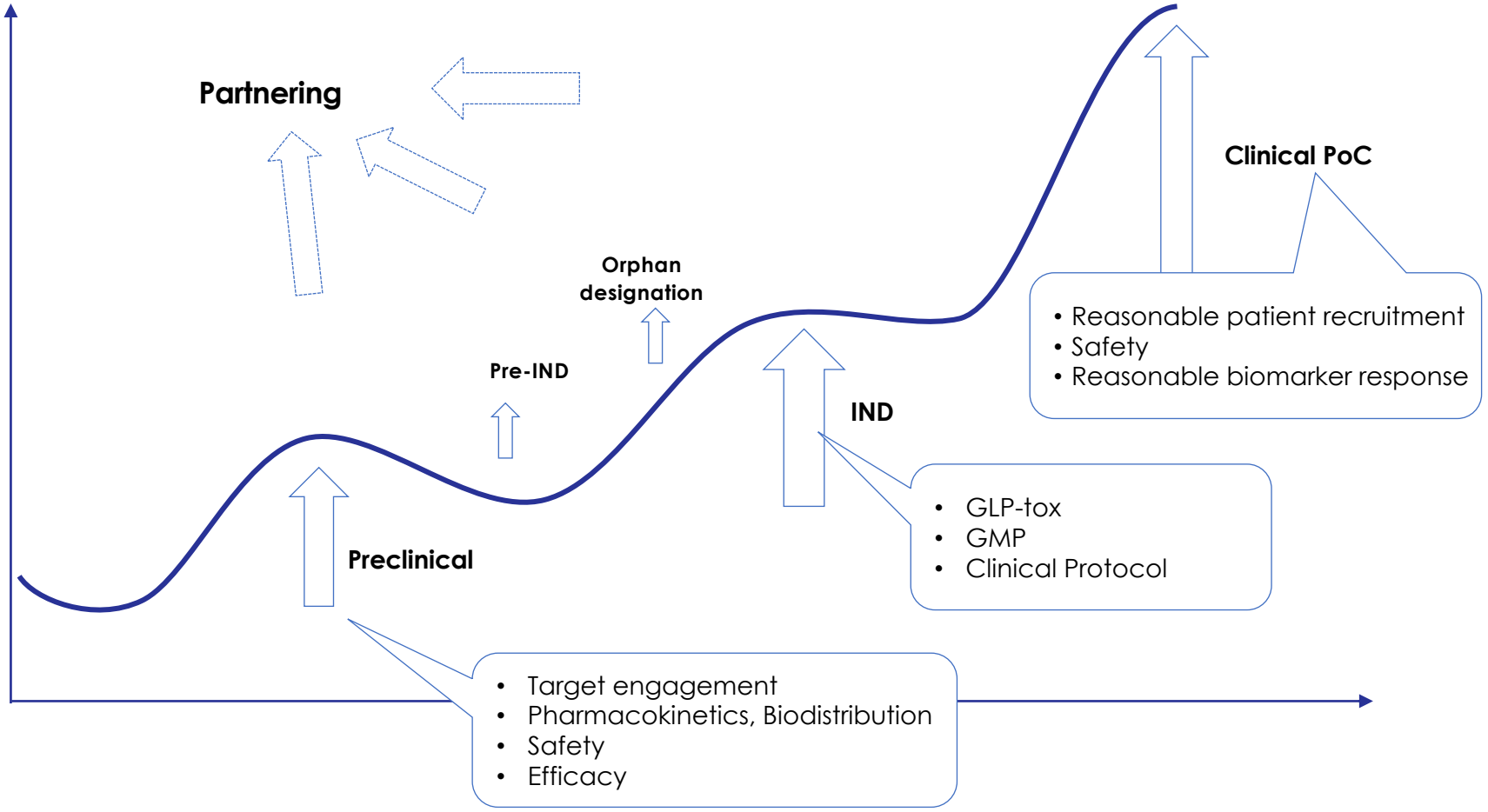
Future pre-clinical and clinical trials are expected to increase the value of the company.

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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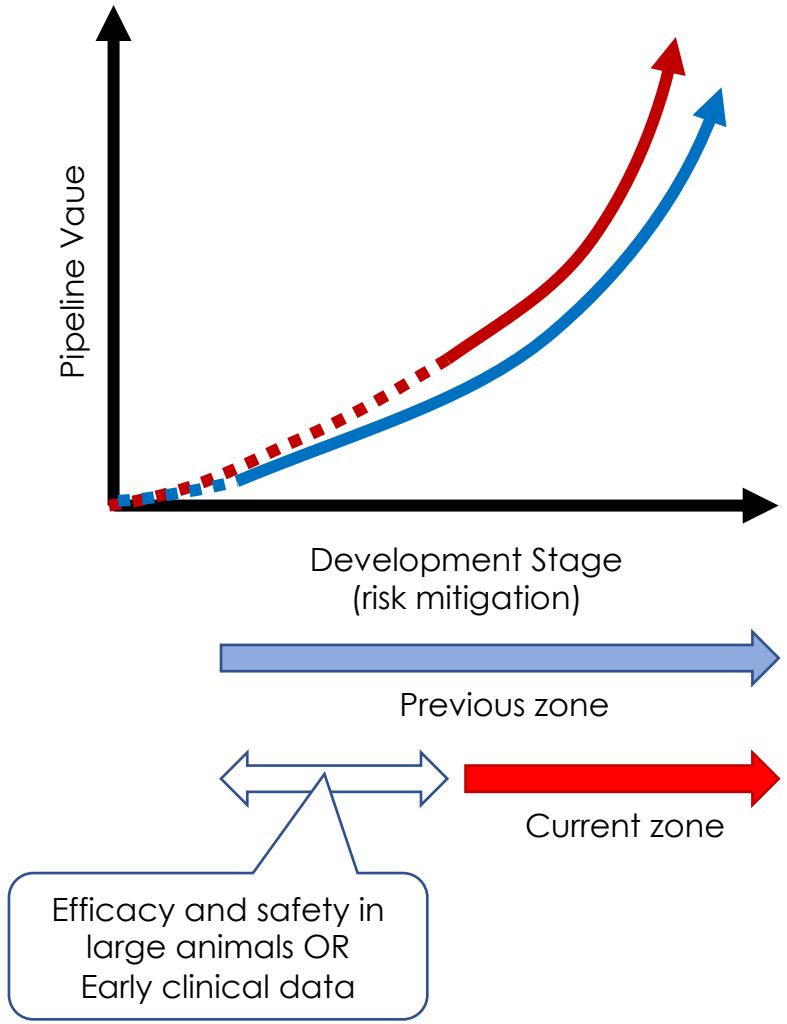
Status of partnering

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.



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6. Risk Information

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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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