English translation for reference purposes only

FY2021 2Q Financial Results



(TSE4883) Modalis therapeutics Corporation

August 5, 2021

In case of any discrepancy, the Japanese version shall prevail

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1. Financial Highlights

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PL & Business Result

(Million Yen)

	FY2020 2Q	FY2021 2Q	(A)－(B)
Operating revenue	337	1	(336)
Operating expenses	298	478	180
R&D	204	349	145
SGA	94	129	35
Operating income	38	(477)	(515)
Ordinary income	29	(464)	(493)
Profit	26	17	(9)

Operating expenses

・R&D increased year on year as business progressed(primarily in personnel expenses, research material expenses)

Extraordinary income

・ Income of compensation　485 Million Yen (the Infringement of the Lock-Up System)

SGA: Selling and Generally Administrative Expenses
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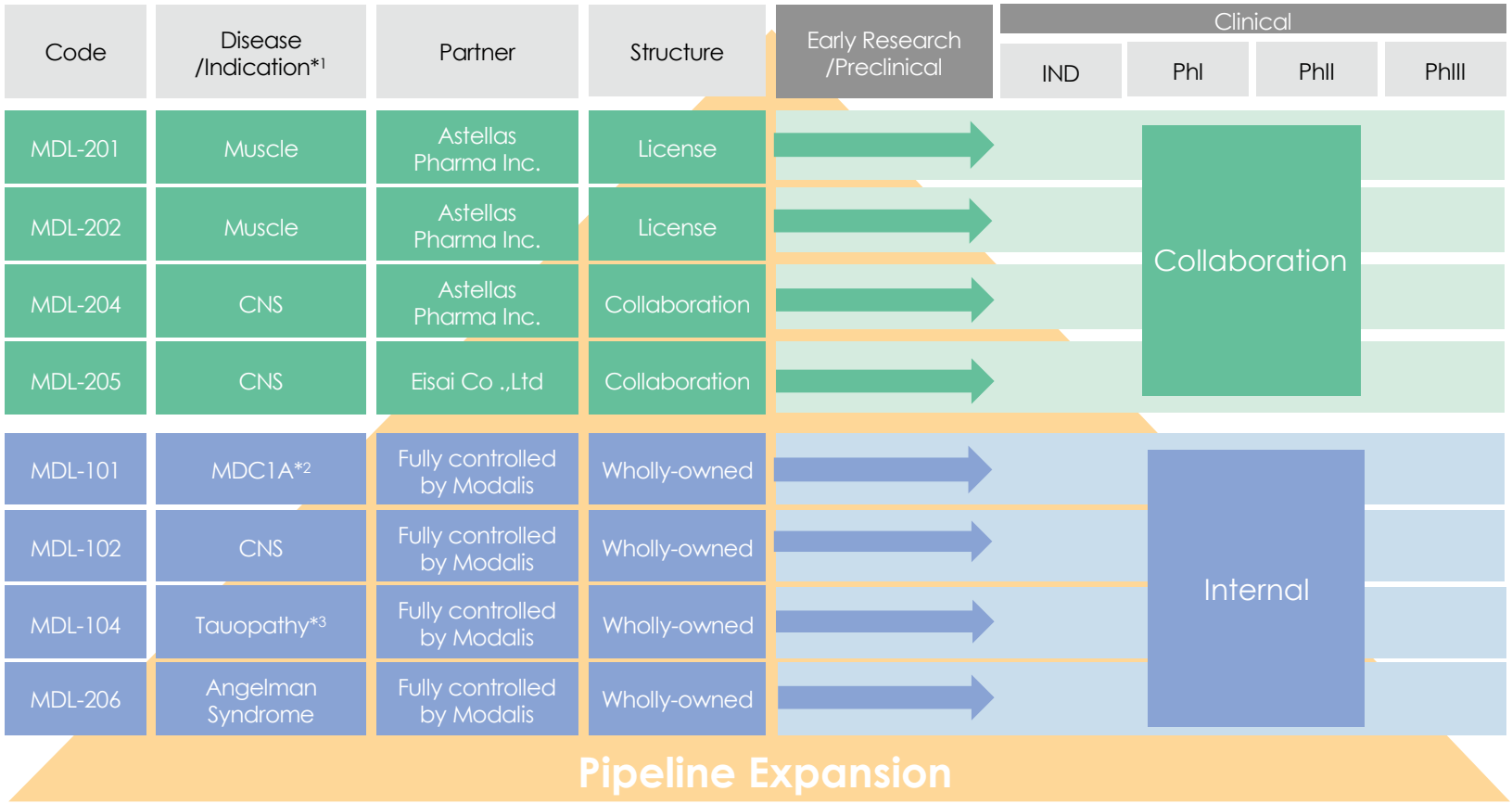
Pipeline



*1: We have adopted a strategy of withholding specific indications until the patent application is published for competitive reasons.
*2: MDC1A=Merosin-deficient congenital muscular dystrophy type 1A
*3: Tauopathy belongs to a class of neurodegenerative diseases involving the aggregation of tau protein. Correlation with Alzheimer's disease has been suggested.

MDL-101 : mMDL-101(mouse version) targeting mMDC1A is investigated in 2 mice disease models (mild and severe) and confirmed to reverse pathological condition in mice

MDL-206: While animal proof-of-concept is established, Astellas did not extend research collaboration due to strategic reason and Modalis regain all rights.

Steady progress has seen in other internal pipelines and collaboration pipelines.

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BS & Financial Position

（ Million Yen ）

	FY2020 (A)	FY2021 2 Q (B)	(B) – (A)
Current assets	5,448	5,847	399
Cash & deposits	5,421	5,784	363
Non-current assets	828	850	22
Right to use patent	767	736	(31)
Total assets	6,277	6,697	420
Current liabilities	58	91	33
Non-current liabilities	11	319	307
Total liabilities	70	410	340
Total net assets	6,206	6,287	81
Total liabilities and net assets	6,277	6,697	420
Capital adequacy ratio	98.9%	93.9%	

- Stable financial base, High Equity ratio
- Recorded access to CRISPR/Cas9 foundational IPs from Editas Medicine, Inc
- A portion of the licensing fees were received from the out-licensing party as a Non-current liability (refer to 4. Q & A ②)

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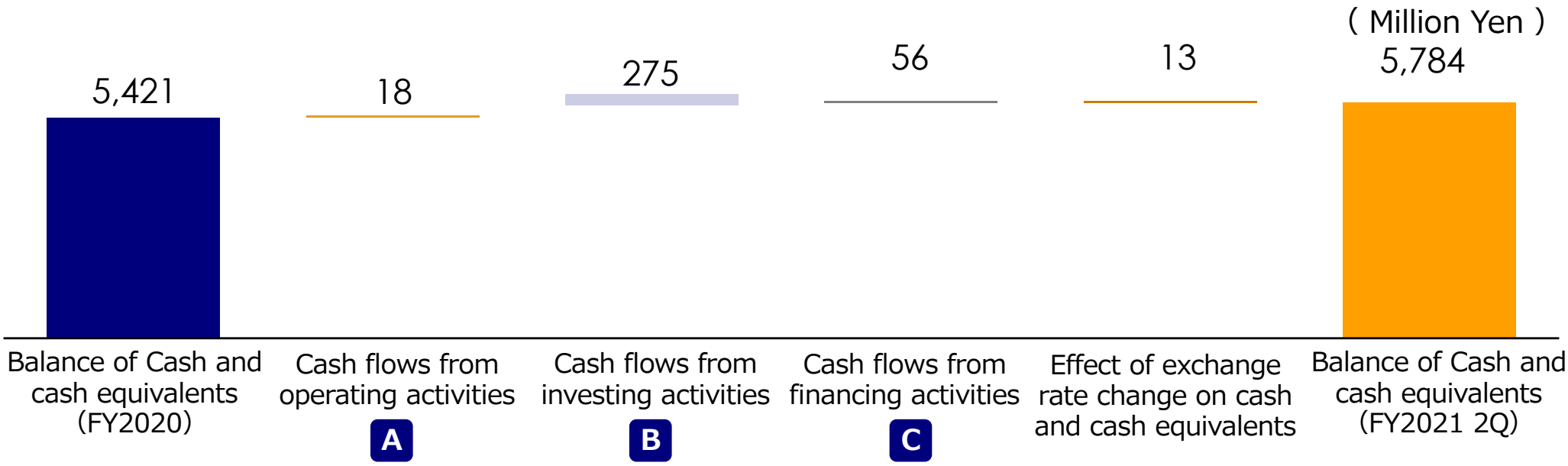
Cash Flow Status



A Cash flows from operating activities	• Profit before income taxes (20)
B Cash flows from investing activities	• Proceeds from contribution received for right to use patent (329)
C Cash flows from financing activities	Proceeds from issuance of stock acquisition rights (56)

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2. Key Topics

MDL-101 updates with Mouse disease model data
MDL-206 targeting Angelman Syndrome

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MDL-101

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MDC1A

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

- Frequency: **1 in 30,000***
- Inheritance Pattern: **Autosomal Recessive**
- Early onset: apparent at birth or within the **first few months of life**
- Symptoms:
  Severe muscle weakness;
  Lack of muscle tone (hypotonia);
  Little spontaneous movement;
  Joint deformities (contractures);
  Heart problems and seizures.
- Life expectancy:
  Because of the serious health problems that occur in this form of the disorder, many affected individuals **do not survive past adolescence**.
- Genetic cause: **LAMA2** mutation

MDC1A: merosin- deficient congenital muscular dystrophy type 1A
*Orphanet

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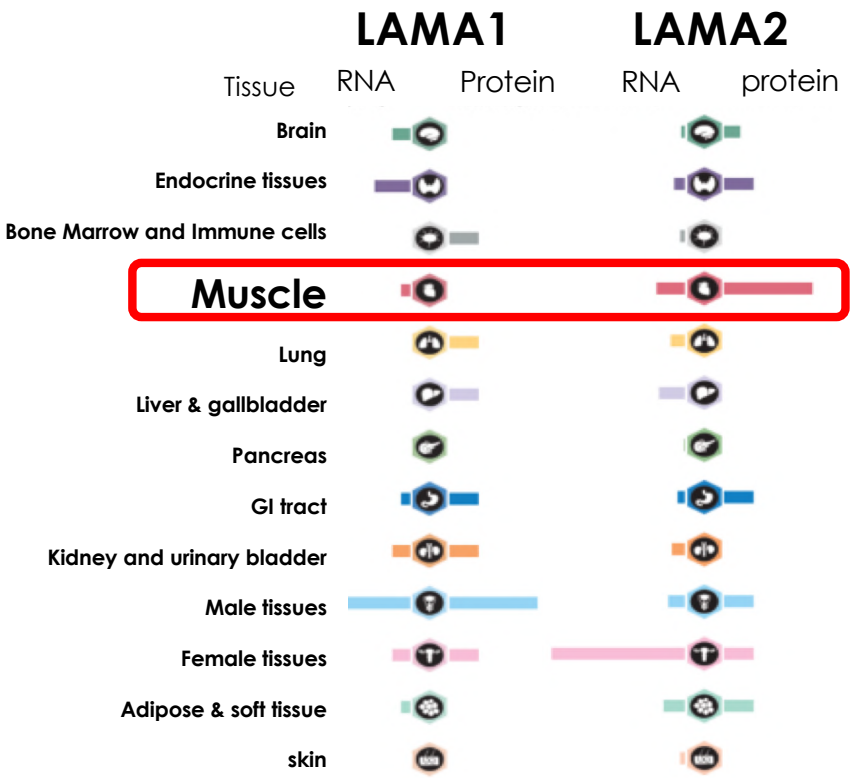
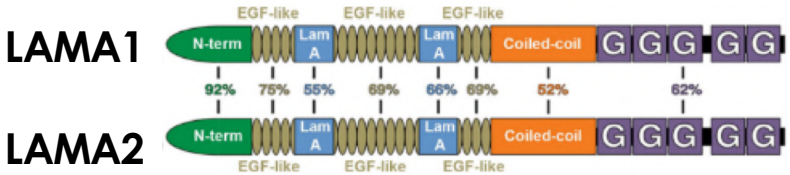
By activating the sister gene, LAMA1, GNDM compensates missing function of LAMA2

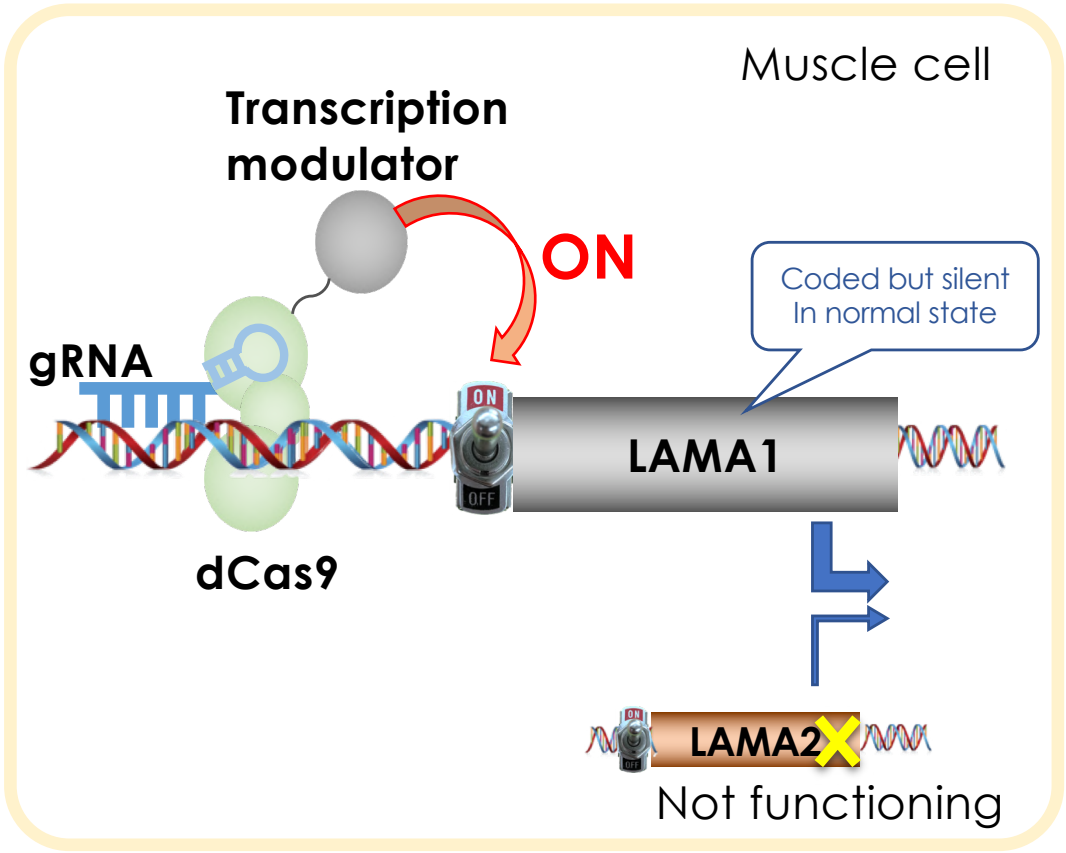
Exspression pattern of LAMA1and LAMA2 by tissues



Protein structure of LAMA1 and 2



CRISPR-GNDM® targeting LAMA1



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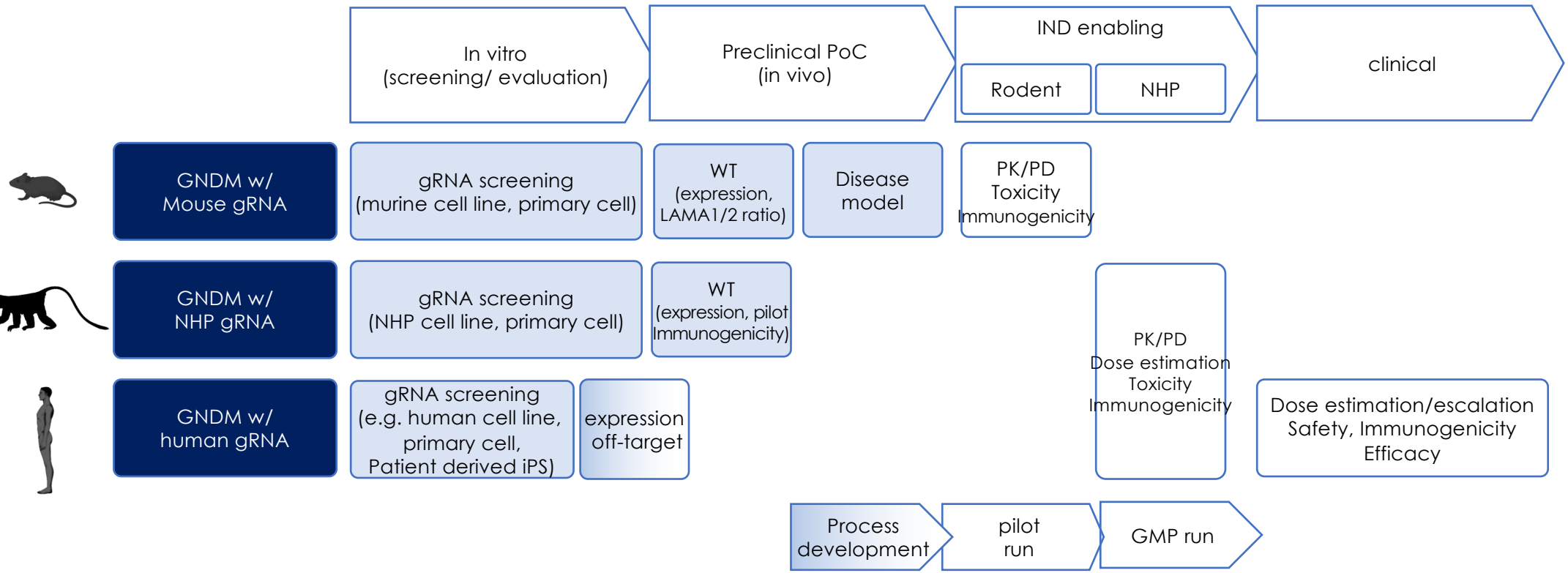
Having convincing animal data both in 2 species, moving forward to IND enabling studies with establishing manufacturing process

Path to clinic for CRISPR-GNDM®



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Available MDC1A mouse models

Model	**Strain**	**Mutation/protein product**	**Phenotype**
dy/dy	129	Unknown spontaneous mutation/reduced expression of seemingly normal a2 chain	Lethal within 6 months of age. Moderate muscular dystrophy; peripheral neuropathy; defective central nervous system myelination; hearing loss; aberrant thymocyte development
dy^{2j}/dy^{2j}	C57BL/6J	Spontaneous mutation in LN domain/**slightly reduced expression** of truncated a2 chain devoid of LN domain	Normal lifespan. **Mild** muscular dystrophy; peripheral neuropathy
dy^{w}/dy^{w}	C57BL/6J	Knock-out of *Lama2 and* Knock-in *LacZ*/**complete deficiency**	Lethal at 4 to 6 weeks of age. **Severe** muscular dystrophy; peripheral neuropathy
dy^{3k}/dy^{3k}	129	Knock-out/complete deficiency	Lethal at 4 weeks of age. Severe muscular dystrophy; peripheral neuropathy; impaired spermatogenesis; defective odontoblast differentiation
dy^{nmj417}/dy^{nmj417}	C57BL/6J	Introduced point mutation in LN domain/normal levels	Normal lifespan. Mild muscular dystrophy; peripheral neuropathy

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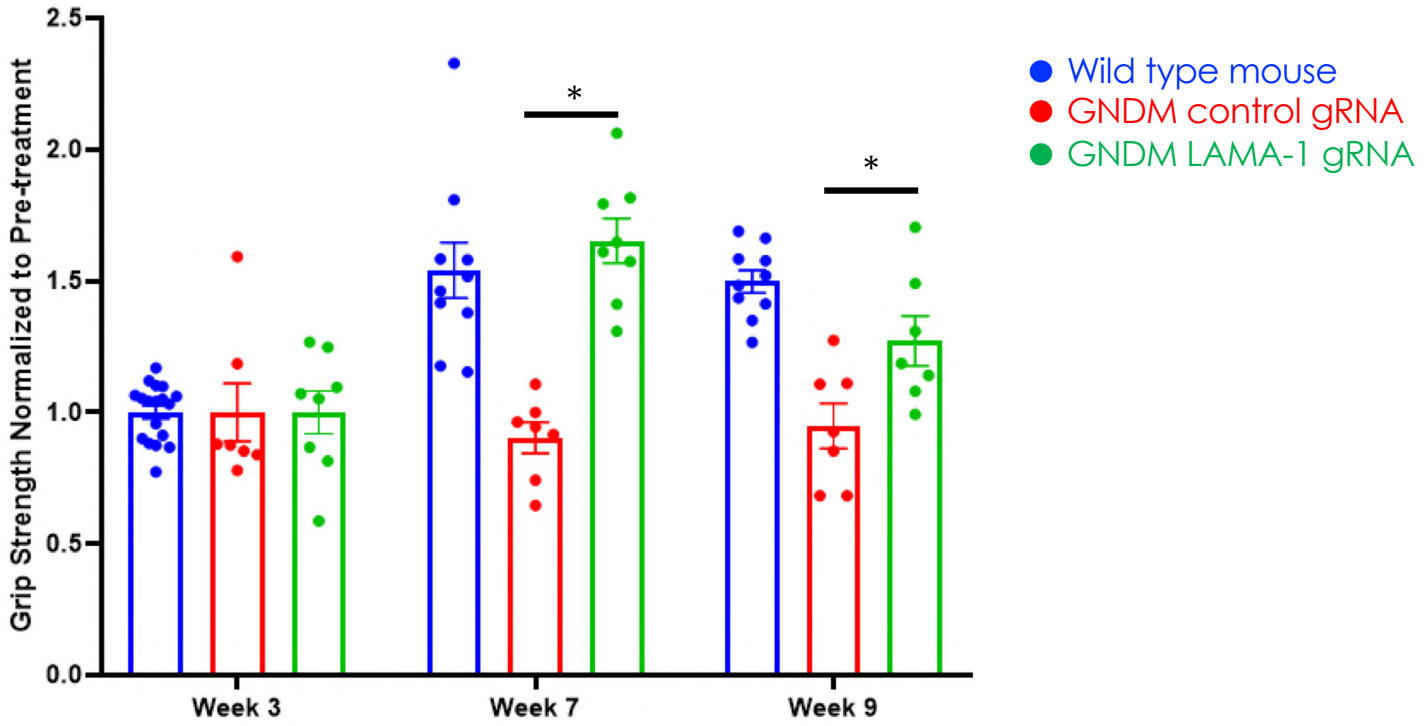
GNDM reverses Grip Strength in dy2j mice

dy2j/dy2j Grip Strength Data (Forepaws)



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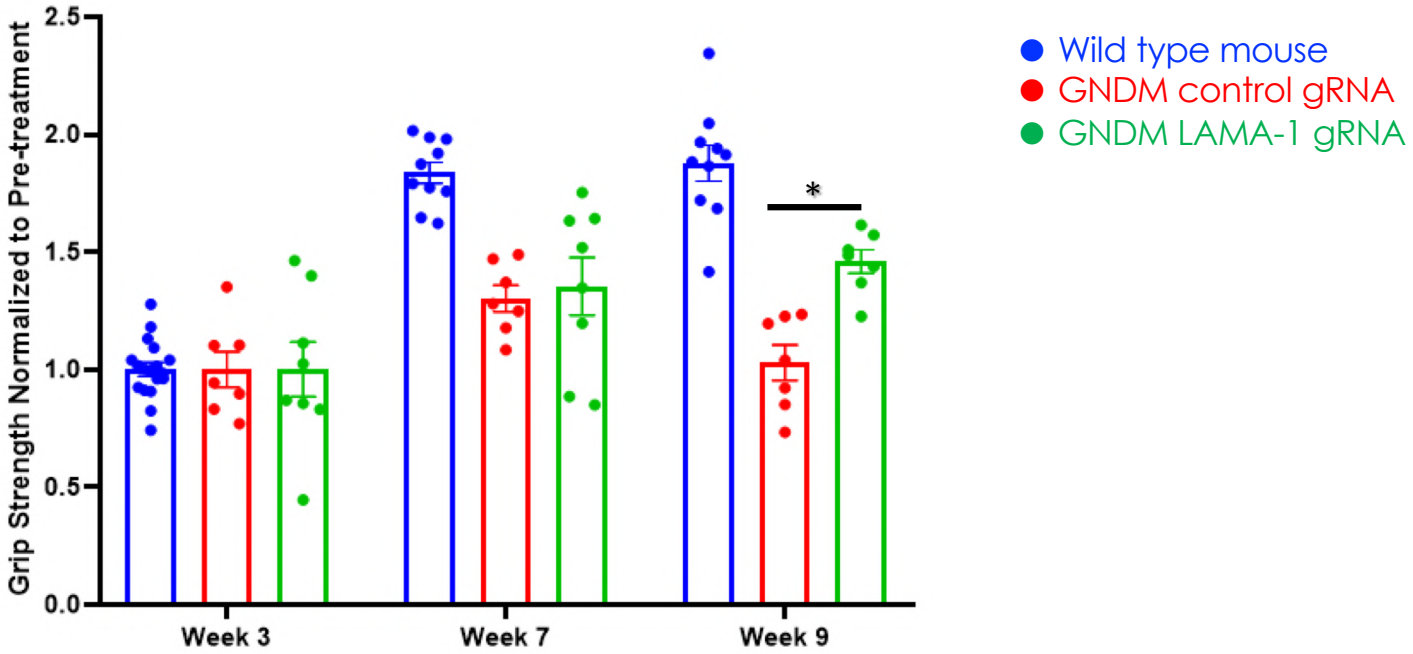
GNDM reverses Grip Strength in dy2j mice

dy2j/dy2j Grip Strength Data (allpaws)



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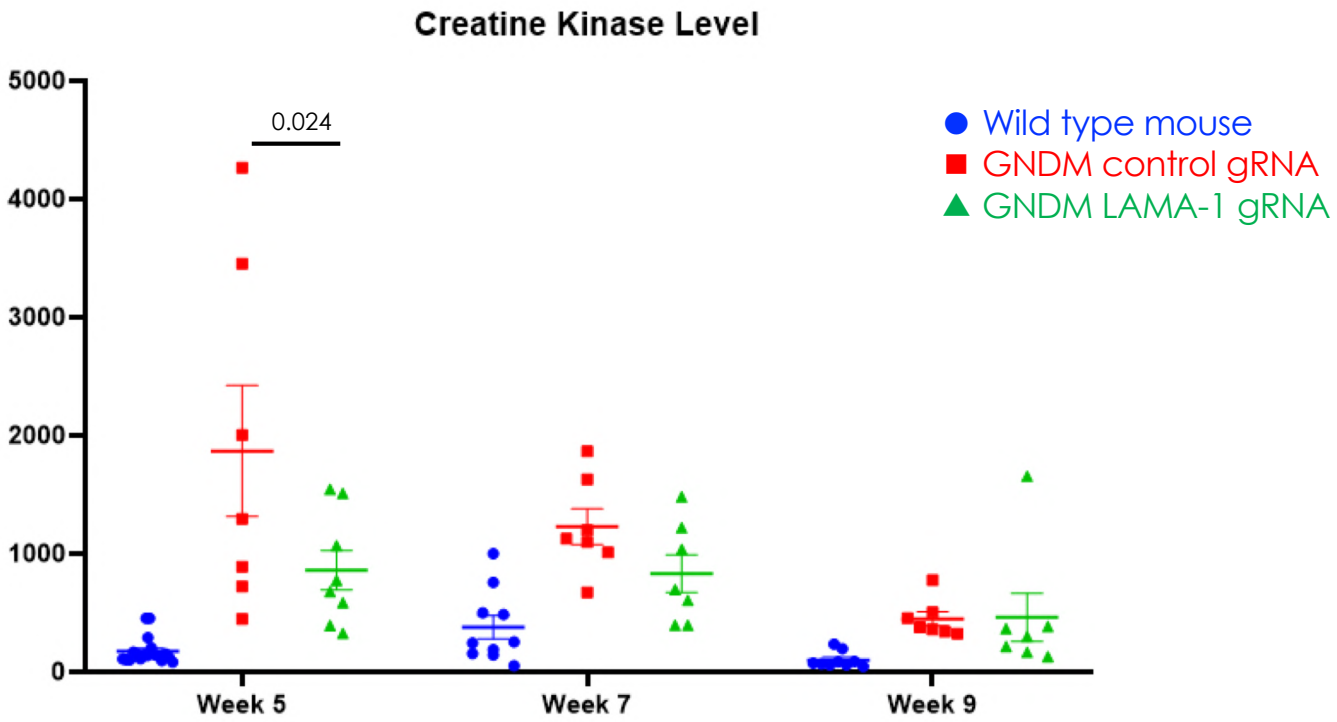
CK level significantly improved at wk5



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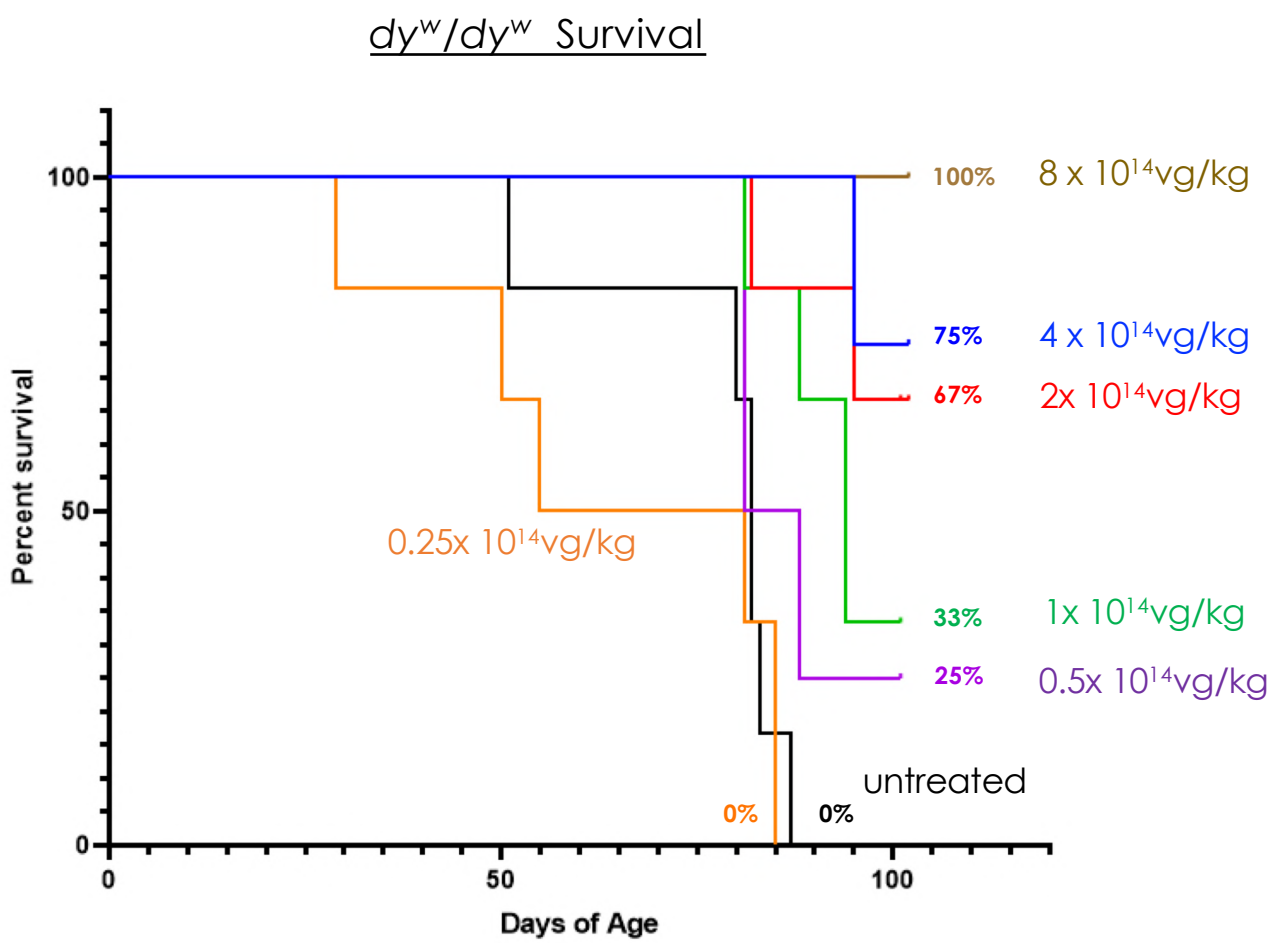
mMDL-101 prolongs mice survival at tolerable dose in dyW



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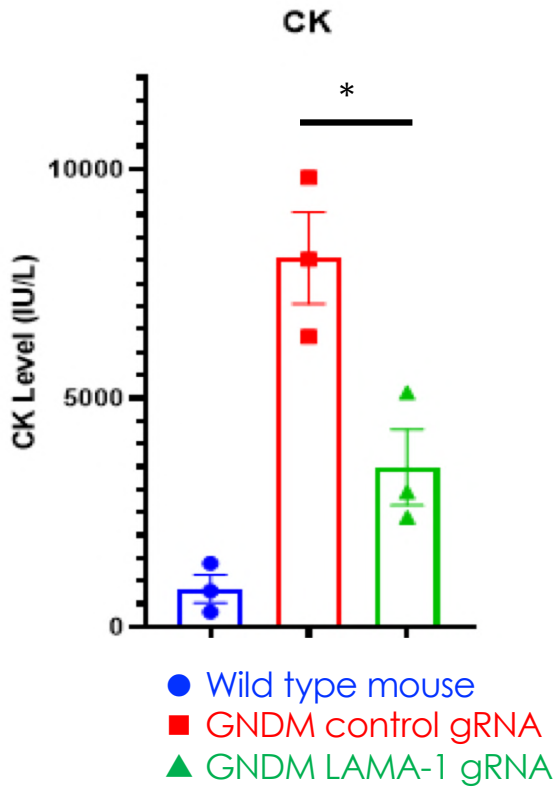
CK levels are recovered by GNDM treatment

dyW　P2 Injection Efficacy Blood Chemistry Data @Week 4



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In vivo study Summary

- Mouse
  - in vivo upregulation of LAMA-1 in skeletal and cardiac muscles using a Lama-1 specific gRNA
    - Strong GNDM mRNA expression
    - LAMA-1 mRNA expression induced up to 50% of endogenous LAMA-2 mRNA
    - GNDM/Cas9 protein expression detected by IHC
    - LAMA-1 protein broadly expressed in muscle tissues by IHC
  - Efficacy study in MDC1a disease models completed
    - **Confirmed significant improvement in dyW and dy2J disease models**
      - **GNDM expressed in muscle tissues**
      - **LAMA-1 expressed in various muscle tissues**
      - **No significant toxicity observed**
      - **Muscle related score significantly improved**
      - **Body weight (dyW)**
      - **Grip (dy2j and dyW)**
      - **Blood Chemistry (dy2J and dyW)**
- Cyno
  - NHP studies with AAV-cyMDL-101
    - Mild anti-Cas9 immune reaction elicited in AAV injected animals
    - No obvious lymphocytes infiltration nor tissue destruction observed in muscle tissues
    - Persistent GNDM expression detected in muscle tissues in high dose group up to the end the study(20wks)

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MDL-206

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Completion of a Research Collaboration on Angelman Syndrome

- Modalis and Astellas have been prosecuting their Angelman Syndrome program through discovery activities with Modalis' proprietary technology, CRISPR-GNDM.
- This is a highly differentiated approach to treat Angelman syndrome, which is a serious disorder and constitutes an area of high unmet medical need.
- The collaboration with Astellas has allowed us to advance our understanding of the CRISPR-GNDM® platform for the treatment of Angelman Syndrome and to establish animal Proof-of Concept
- Astellas has notified us today of its decision not to extend the joint research program for MDL-206, which has been underway since 2020.
- Additional research programs with Astellas will continue as currently planned.

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Modalis regains all rights

- Upon the separation, Modalis regains all rights to develop gene therapies targeting Angelman Syndrome with CRISPR-GNDM® technology.

- This allows Modalis to fully leverage its expertise in engineering, biology, regulatory, and manufacturing of gene therapies to expand its wholly owned CRISPR-based portfolio to include Angelman Syndrome.

- Modalis further regains the right to partner its Angelman Syndrome programs in the future.

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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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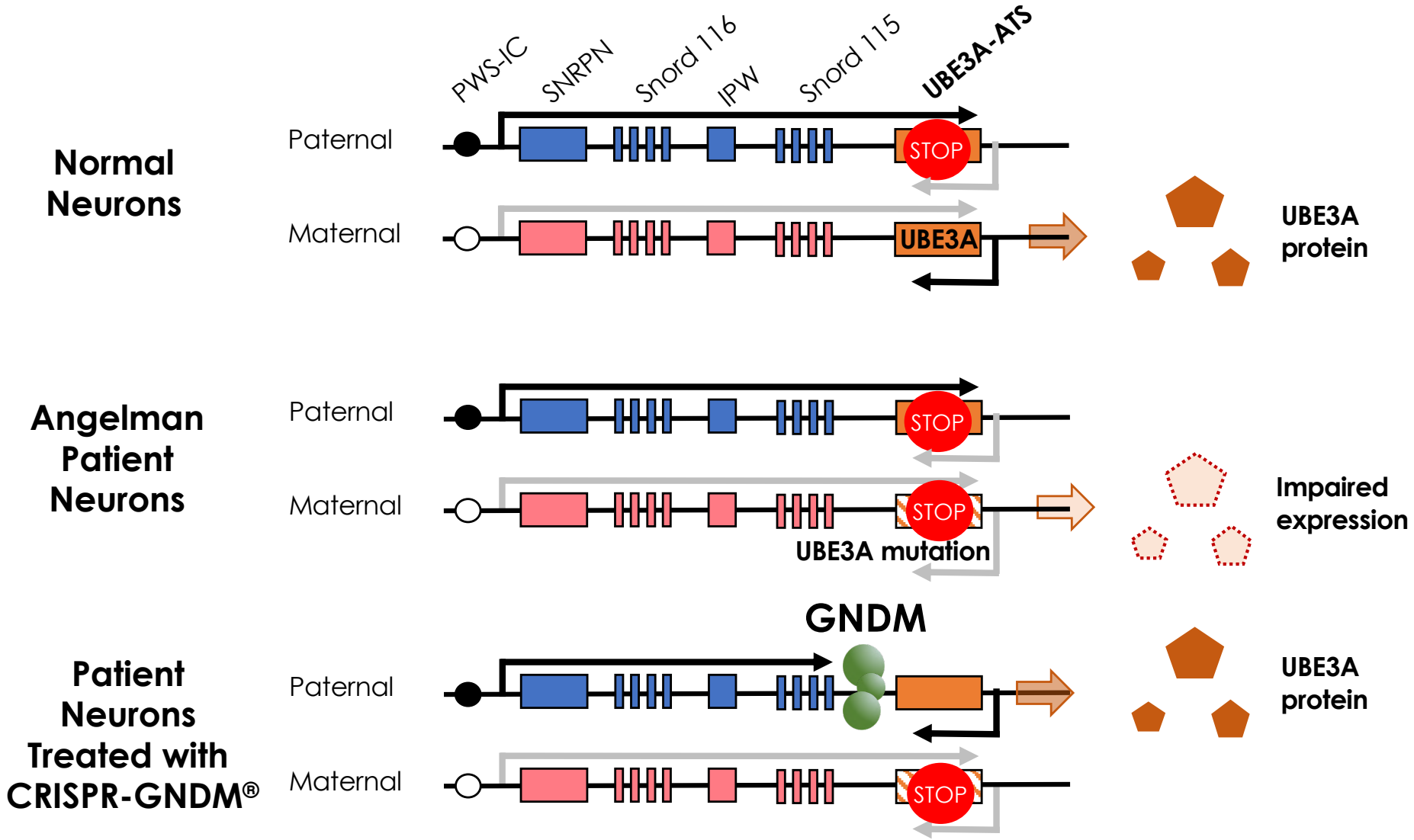
By blocking ATS transcript, GNDM un-silences UBE3A expression



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Summary of status and development plan

- Modalis has confirmed target engagement of CRISPR-GNDM® based molecule in disease model mice studies.
- While there are several molecules being studied in the field including ASO, Gene Therapy, and small molecule, no marketed drug nor late-stage product in development.
- Modalis continue to work on human version molecule to bring it into clinic.
- As Modalis regain its world-wide right to develop and commercialize the product, it will try to find partner for this product.

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3. Growth Strategy

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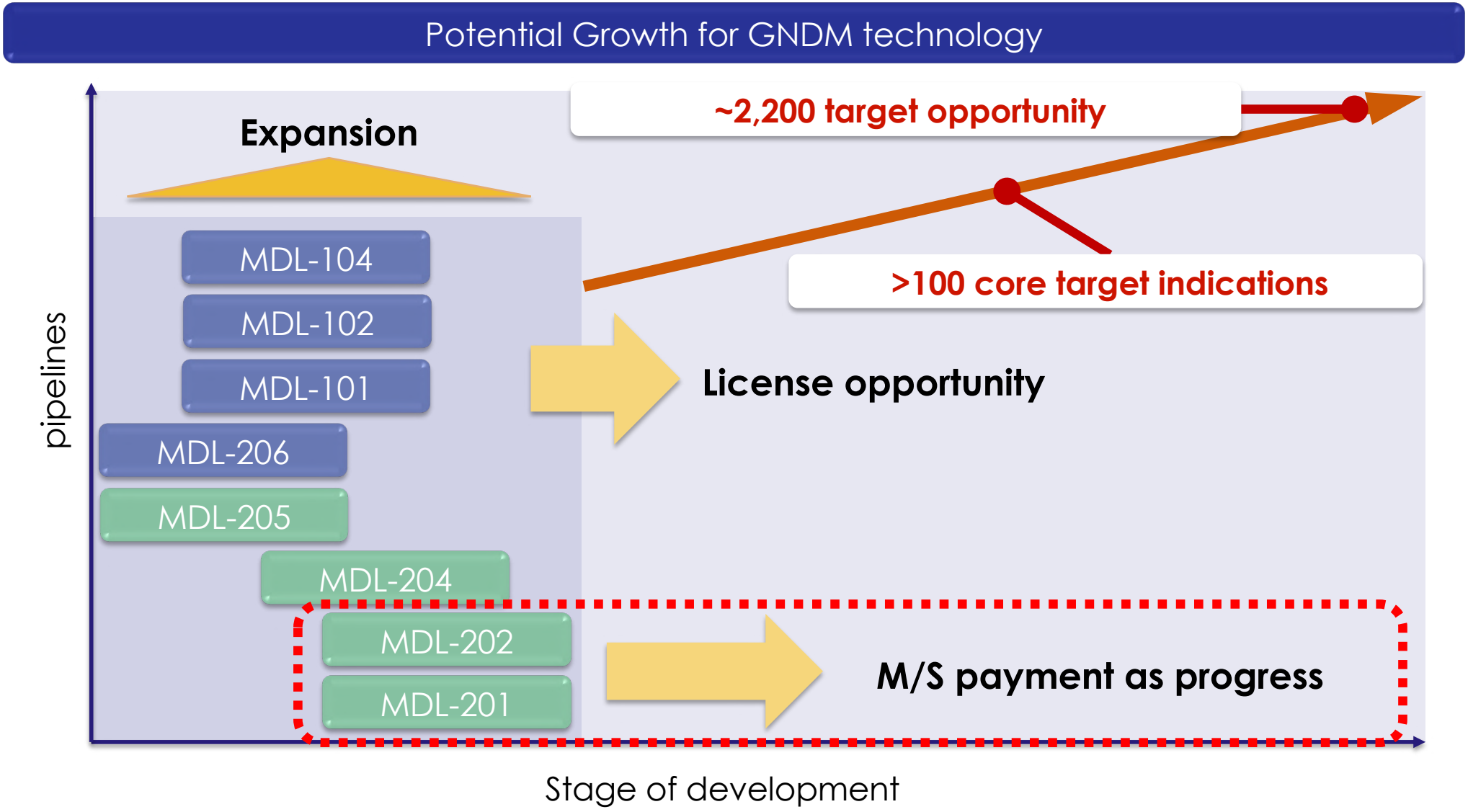
Growth Strategy
opportunity expands two dimensionally



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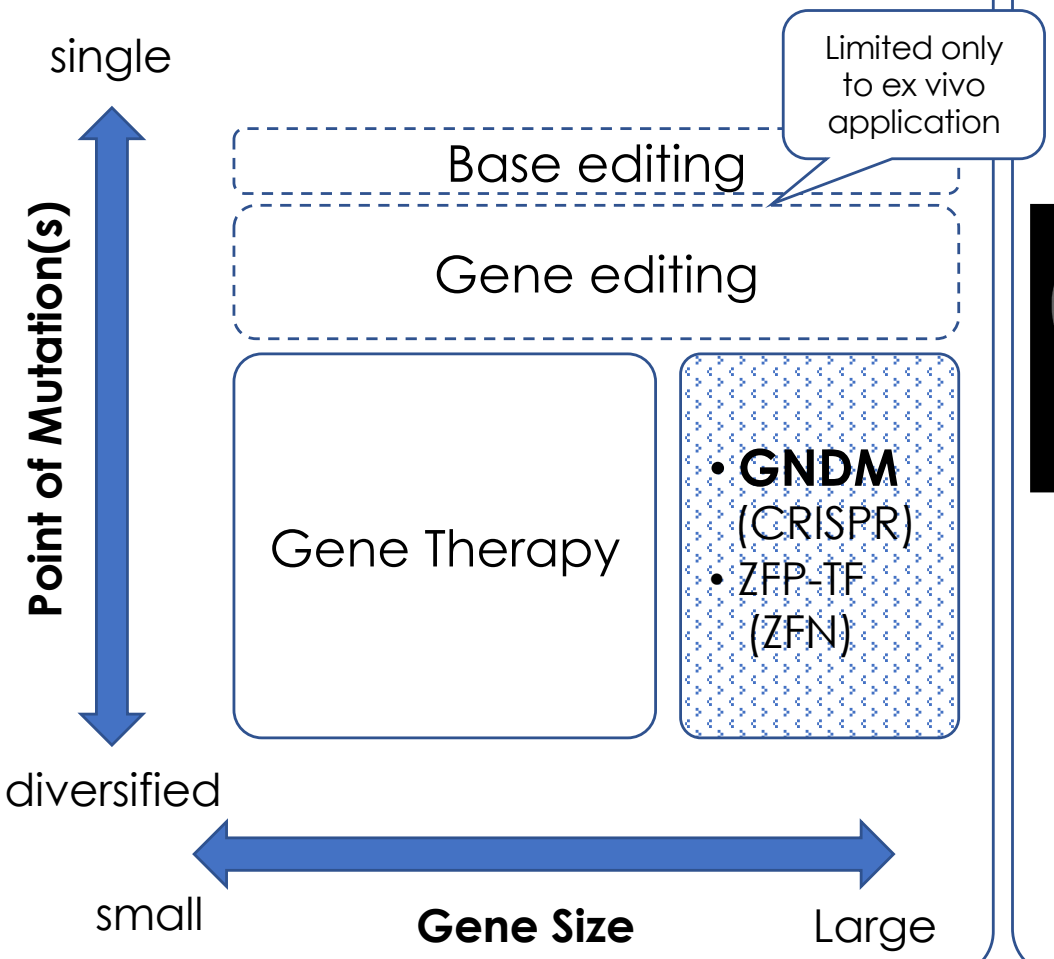
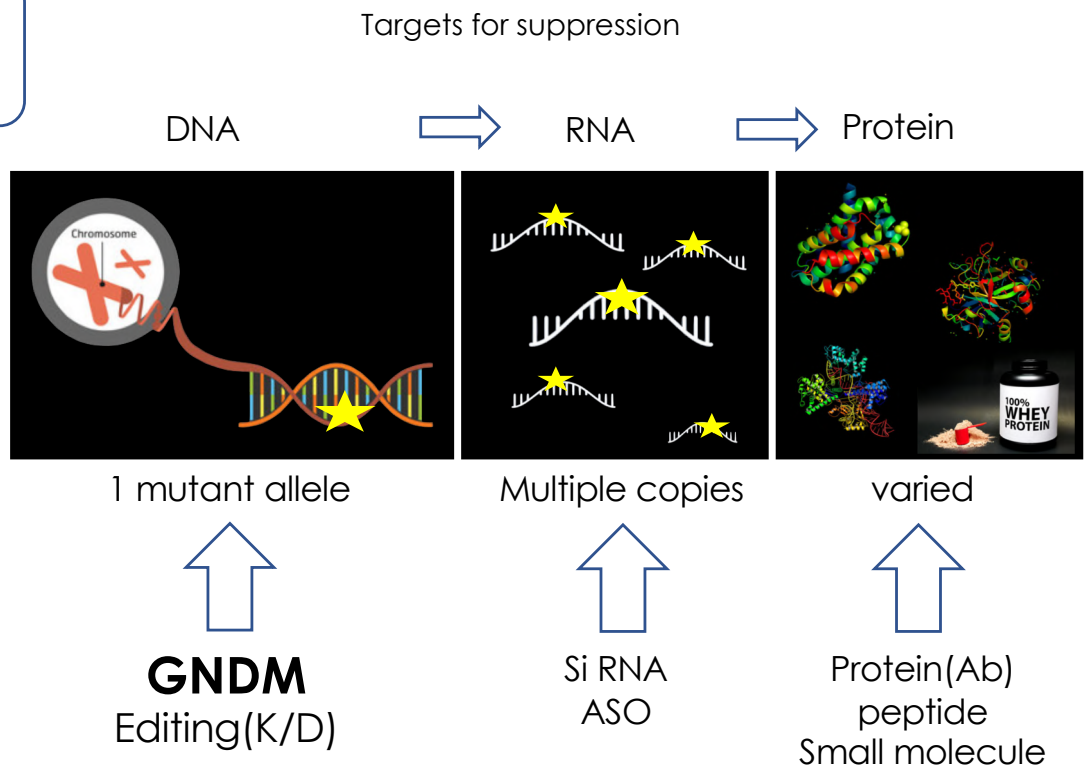
GNDM is efficient approach both for LoF and GoF mutation

In LoF disorders



In GoF disorders



LoF: Loss of function
GoF: Gain of (mal)function

K/D: Knock-down

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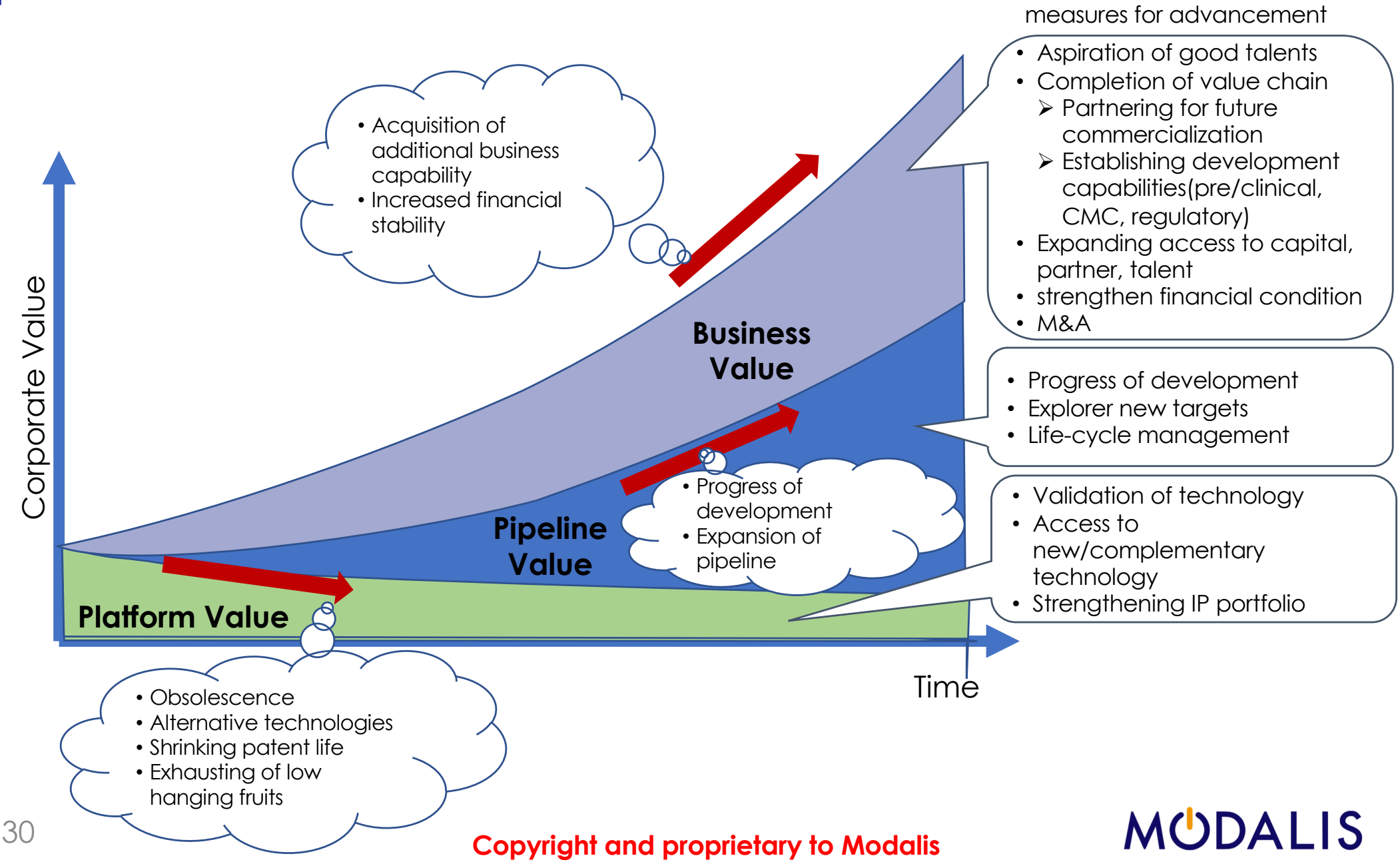
Composition of Modalis' value and measures for advance



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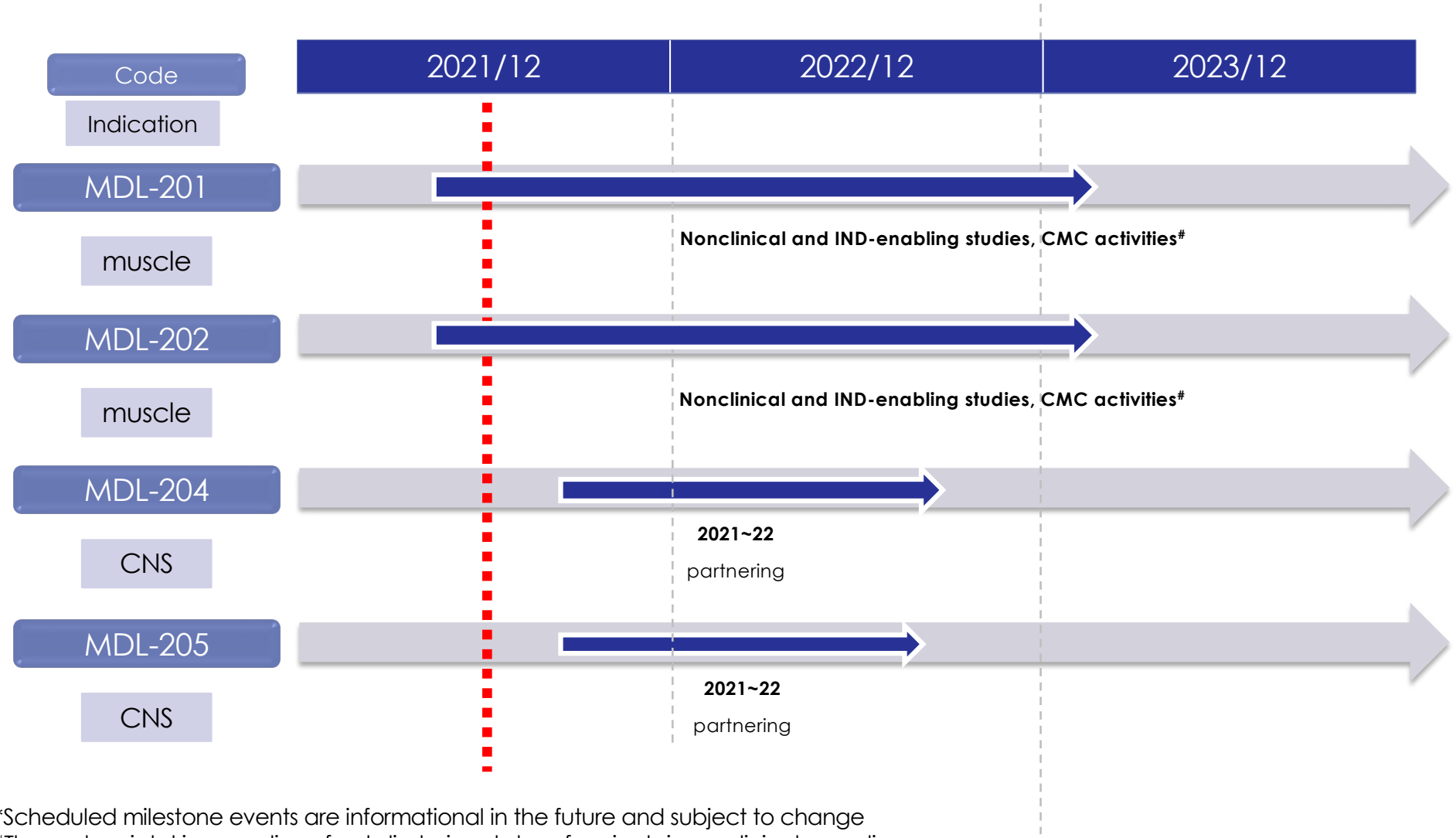
Collaboration pipeline

Achieved and expected Milestone events*



*Scheduled milestone events are informational in the future and subject to change
#The partner is taking a policy of not disclosing status of projects in preclinical or earlier

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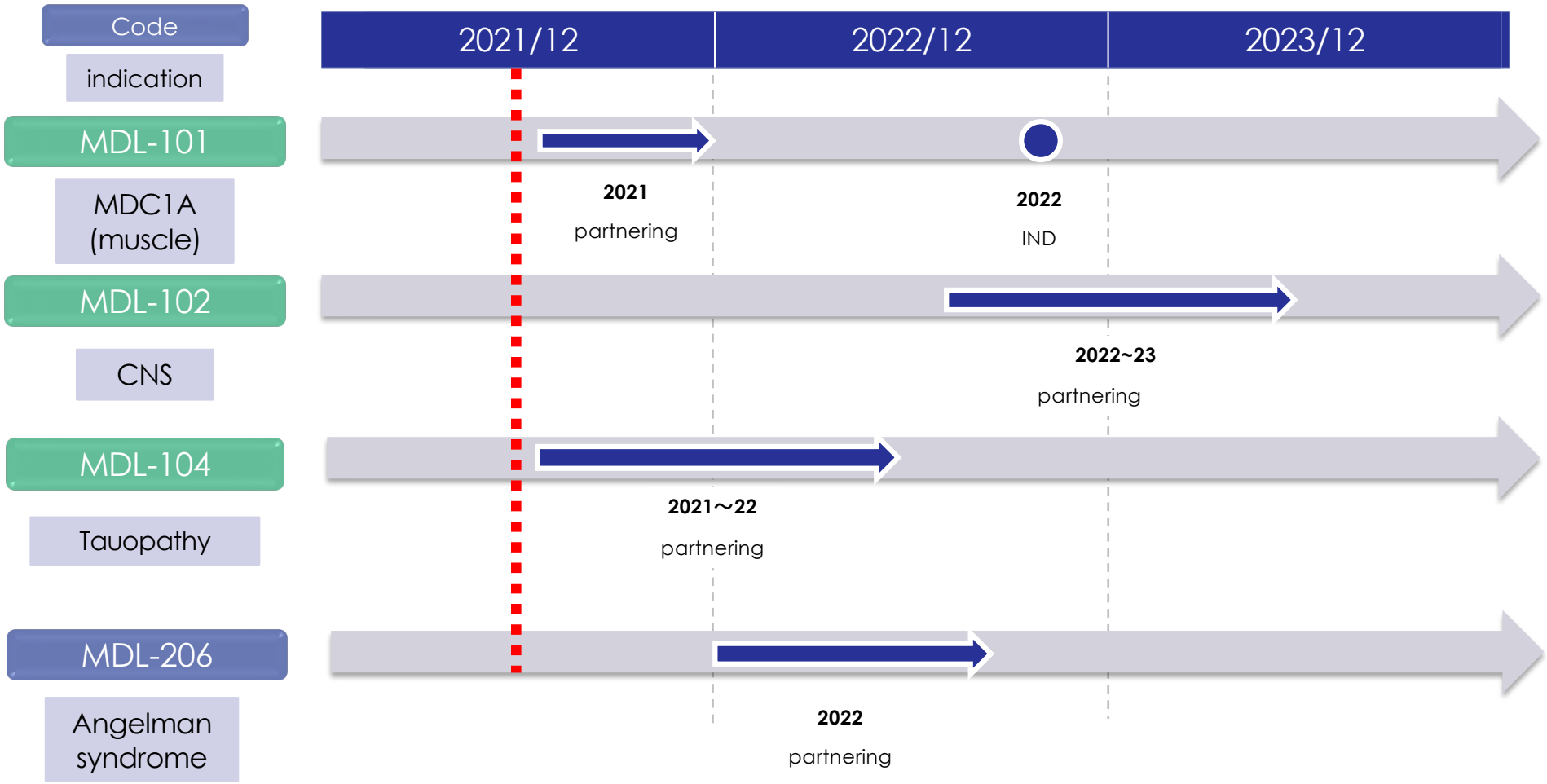
Internal pipeline

Expected milestones by end 2023*



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

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4. Q & A

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Q & A ①

Q)
What does the sublicense deal of which Modalis and Astellas entered into certain CRISPR/Cas9 foundational patents for use in this second quarter mean to Modalis' business?

A)
This outcome was already contemplated under the terms of our existing license agreements for the two programs entered into in 2019 as well as under our business plan. The detail of the deal is not disclosed due to strategic reason. This was in line with our existing arrangements and our business plan and therefore this will not have impact on our business while this allows our partner, Astellas, and licensed products to pursue further development.

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Q & A ②

Q)
From 2021 Q2 there are non-current liabilities reported. What are the details of this liability? Furthermore, what type of impact will this have on the business results?

A)
Modalis has secured the CRISPR/Cas9 basic patent license (patent right) from Editas Medicine Inc ("Editas"). In 2021 Q2, a portion of the licensing fees were received from the out-licensing party. As a result, the amount is being reported as a non-current liability.

The non-current liability in question will depreciate in accordance with the duration of the licensing agreement, so the corresponding depreciation expense for the license (patent right) will be effectively offset on the PL Statement.

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Q & A ③

Q)
Having got animal data, what is the current partnering status and plan for MDL-101

A)
With the very positive safety profile we confirmed in NHP and efficacy data in 2 mice disease models, we started to share the data with potential party to advance our partnering discussion.

While we hire experts in manufacturing, this does not necessarily mean we pursue the clinical trial by ourselves. We believe manufacturing is one of the key element in the gene therapy product development and process development will contributes to the value of the pipeline as well as advancing the program without any delay.

Modalis believes it can engage with a partner within 2021.

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Q & A ④

Q)
Regarding the violation of the lock-up system, do you believe the matter to be completely resolved after receiving a payment of 484 million yen from Mr. Akira Katayama?

A)
As reported in a press release on March 29, 2021, the proposed payment of 484 million yen from Mr. Akira Katayama for the the serious impacts incurred by the company was received, but we do not believe that this matter has been fully resolved with the receipt of 484 million yen.

After the incident, the company contacted our underwriter, the Tokyo Stock Exchange, and a lawyer to investigate any appropriate measures that could be taken and examined the matter in detail. We will continue to consider all possibilities and take appropriate measures in the future.

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