English translation for reference purposes only

FY2020 Financial Results



(TSE4883) Modalis therapeutics Corporation

February 12 , 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 (A)	FY2020 Outlook (B)	(A)－(B)	FY2019
Operating revenue	342	342	-	644
Operating expenses	740	762	(22)	487
R&D	531	557	(26)	303
SGA	208	205	3	183
Operating income	(398)	(420)	22	157
Ordinary income	(439)	(463)	24	146
Profit	(448)	(471)	23	140

Operating revenue

- Earning development milestone income for license(MDL-202), a new upfront payment(MDL-206), and collaborative R&D milestone income for three pipelines .

Operating expenses

- R&D and SGA were as planned
- R&D increased year on year as business progressed(primarily in personnel expenses, research material expenses)

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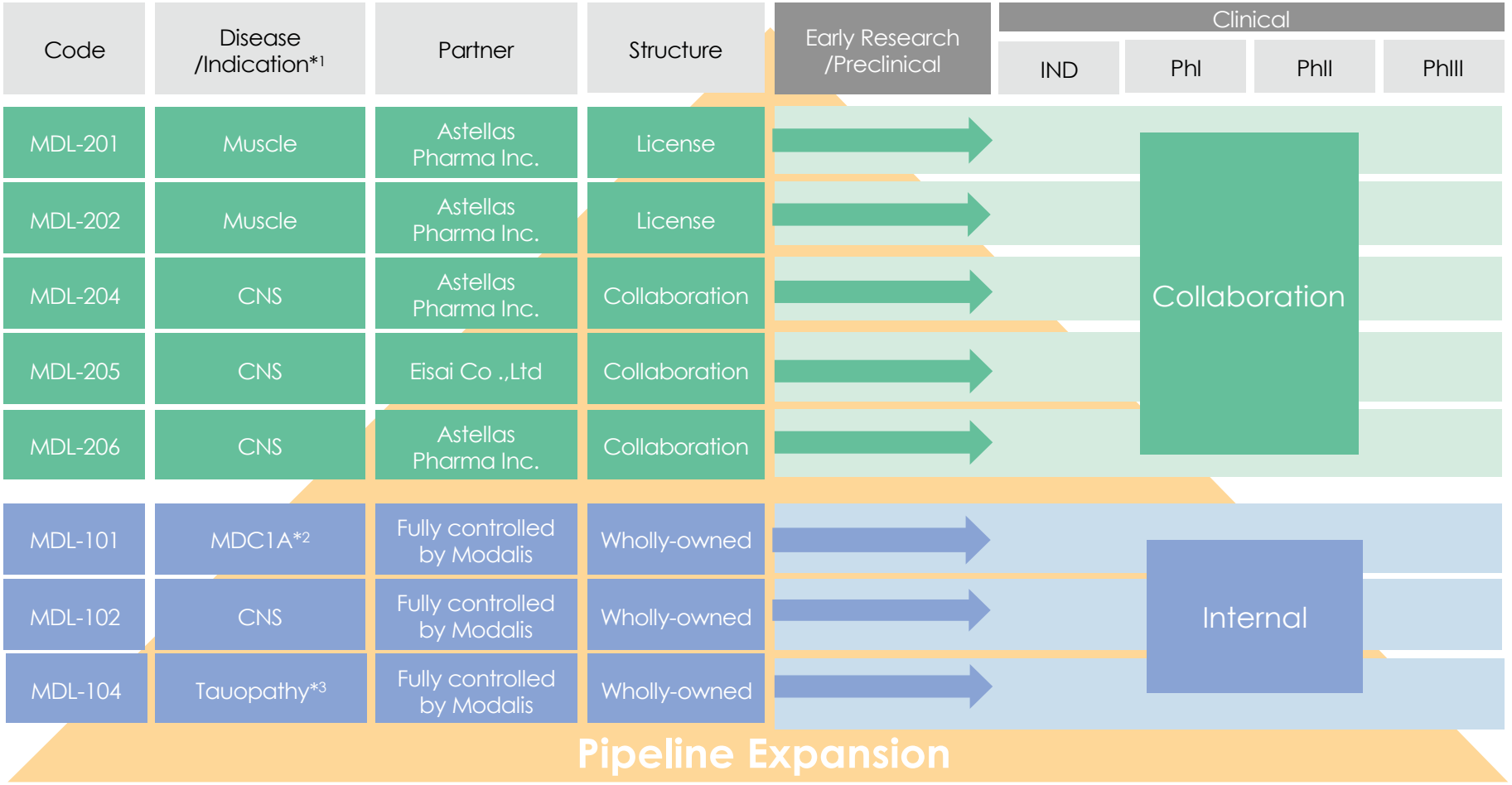
Pipeline



*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.

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BS & Financial Position

(Million Yen)

	FY2019 (A)	FY2020 (B)	(B) – (A)
Current assets	3,874	5,448	1,573
Cash & deposits	3,857	5,421	1,564
Non-current assets	63	828	765
Right to use patent	—	767	767
Total assets	3,938	6,277	2,338
Current liabilities	91	58	(32)
Non-current liabilities	4	11	7
Total liabilities	95	70	(25)
Total net assets	3,842	6,206	2,364
Total liabilities and net assets	3,938	6,277	2,338
Capital adequacy ratio	97.6%	98.9%	

- Stable financial base, High Equity ratio
- Obtained access to CRISPR/Cas9 foundational IPs from Editas Medicine, Inc

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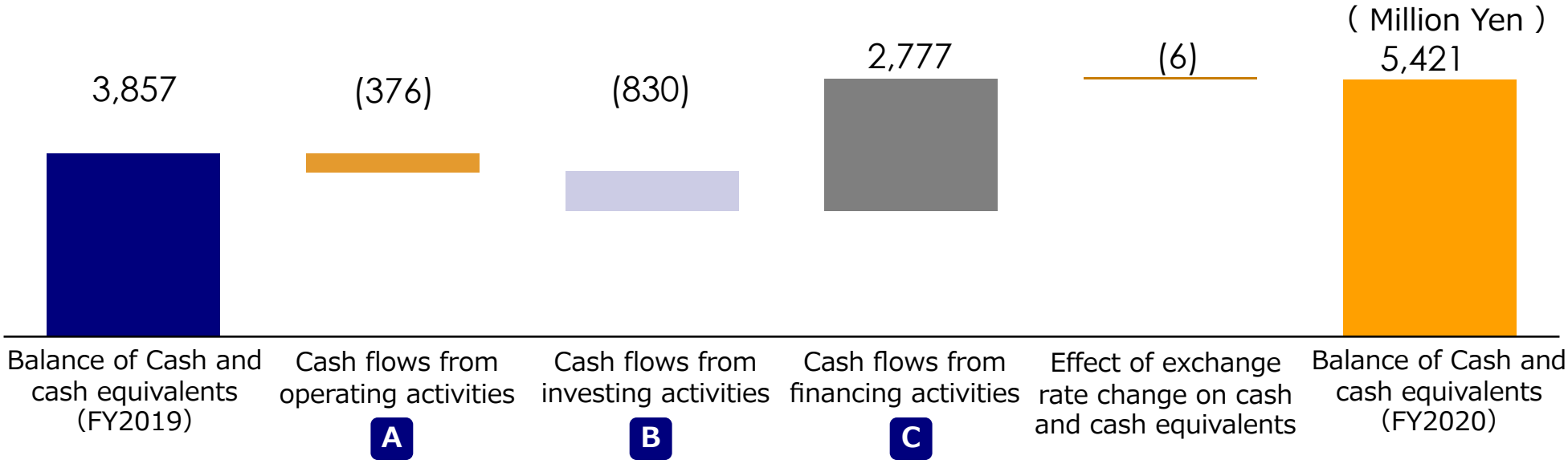
Cash Flow Status



A Cash flows from operating activities	• Loss before income taxes （△439）
B Cash flows from investing activities	• Purchase of intangible assets （△814）
C Cash flows from financing activities	• Proceeds from issuance of common shares （2,749） • Proceeds from issuance of stock acquisition rights （49）

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2. Key Topics

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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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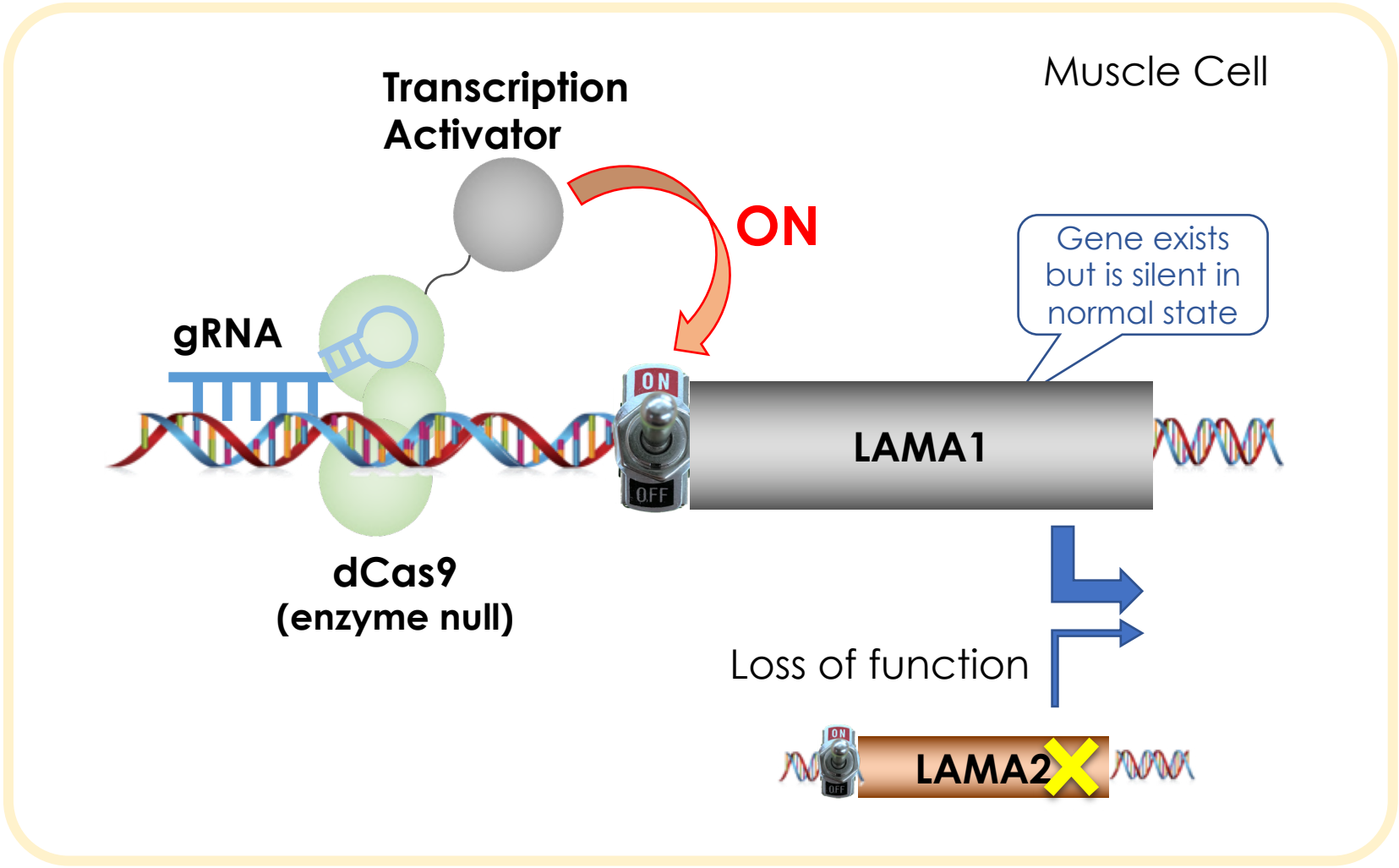
How GNDM cure MDC1A

GNDM upregulation of LAMA1 gene in skeletal muscle

CRISPR-GNDM® targeting LAMA1



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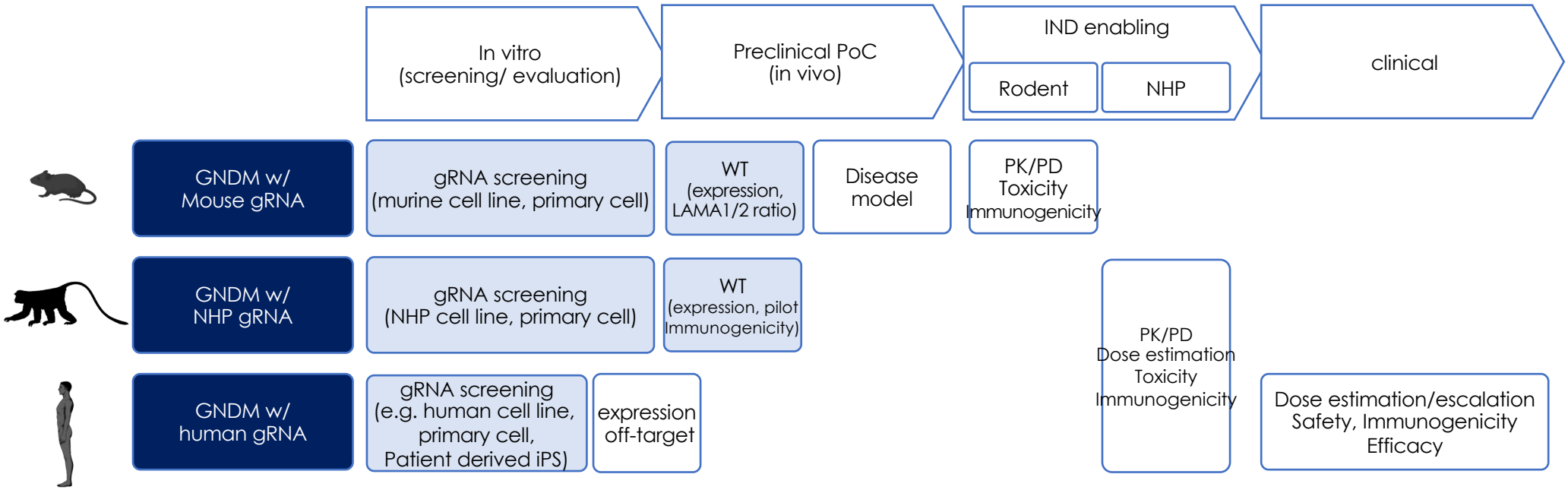
Completed in vivo studies of MDL-101with encouraging outcome, moving towards to IND enabling studies

Path to clinic for CRISPR-GNDM®



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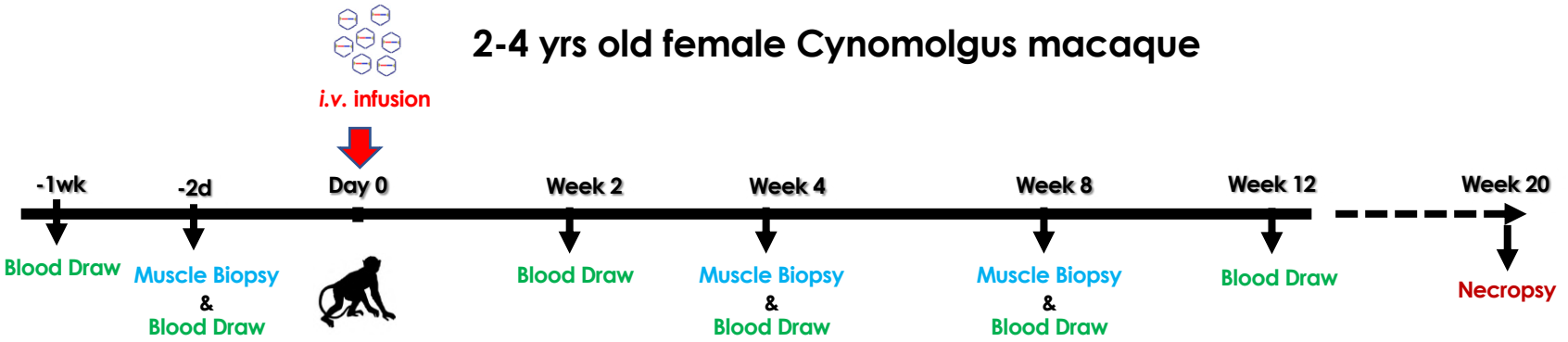
Cynos studies with cGNDM-LAMA1 address immunogenicity concerns

MDL-101 NHP pilot toxicity study design

Cohorts	Test articles	Dose (vg/Kg)	Number of animals
Control	Mock	0	3
Low Dose	AAV – cGNDM-LAMA1	1.1×10^{13}	2
High Dose	AAV – cGNDM-LAMA1	1.1×10^{14}	3



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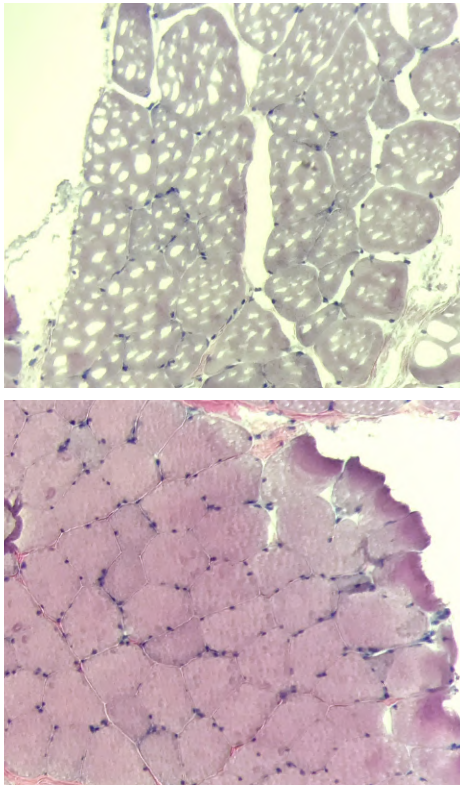
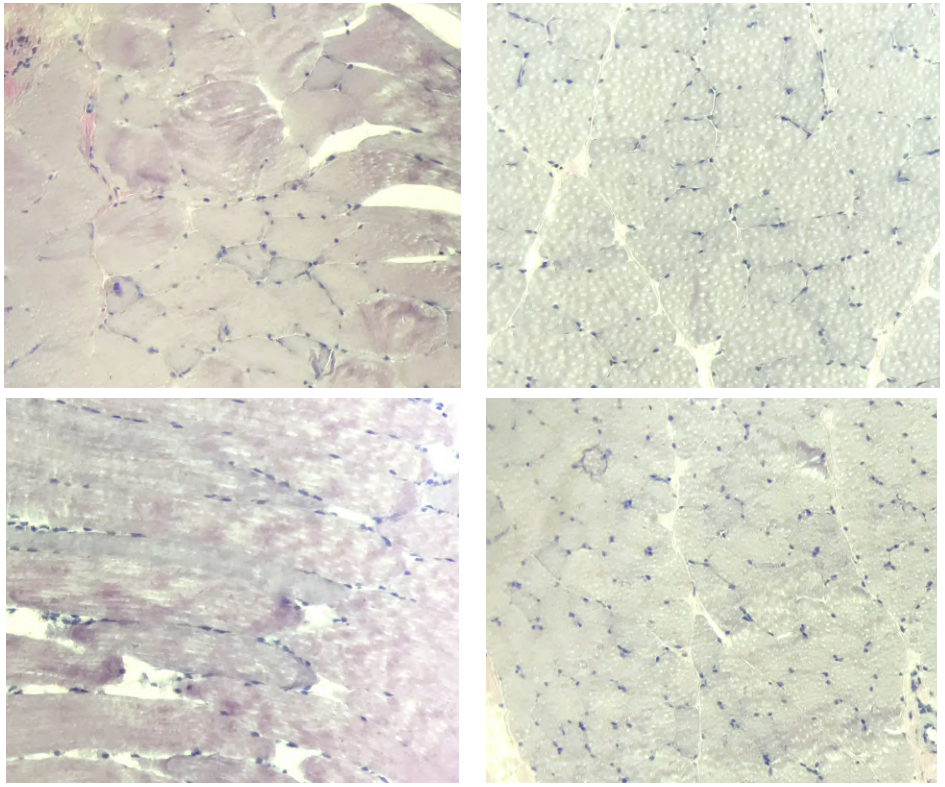
No lymphocyte infiltration detected in AAV transduced muscle

Uninjected



High Dose



4W-

8W-post AAV injection

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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 are ongoing
    - LAMA-1 expression by GNDM is significantly higher than published data which demonstrated restoration of function
- Cyno
  - NHP studies with AAV-cyMDL-101
    - Mild anti-Cas9 immune reaction elicited in AAV injected animals
    - **No obvious lymphocytes infiltration in target tissues**
    - Persistent GNDM expression detected in high dose group up to 8wks (or longer)
    - LAMA-1 mRNA expression induced in high dose group



The major safety concern is dispelled

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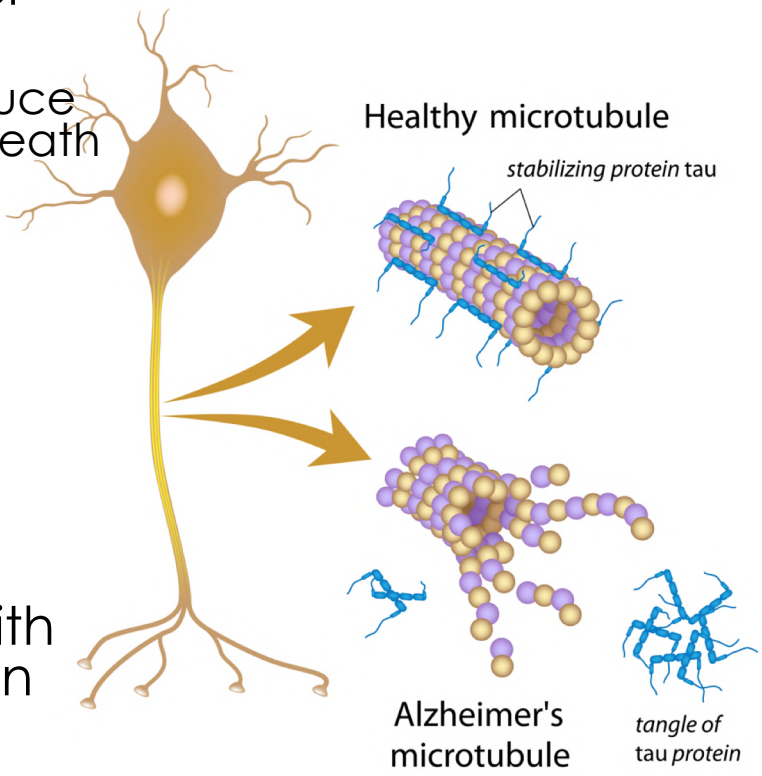
Tau is a center of attention in treating Alzheimer diseases

- 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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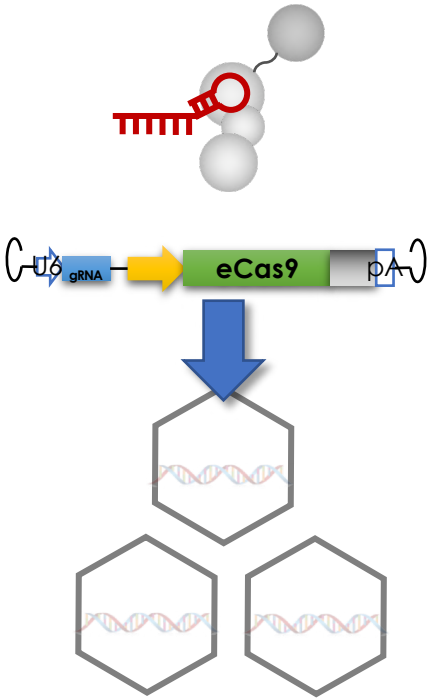
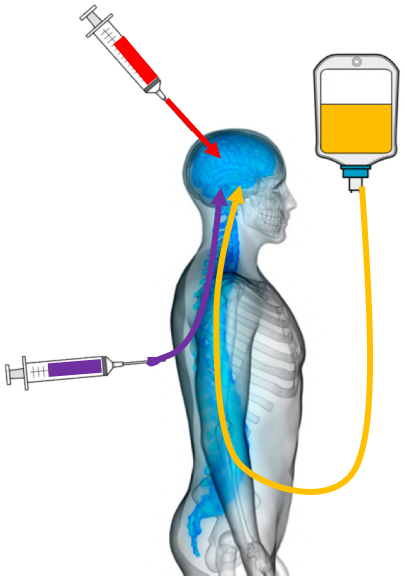
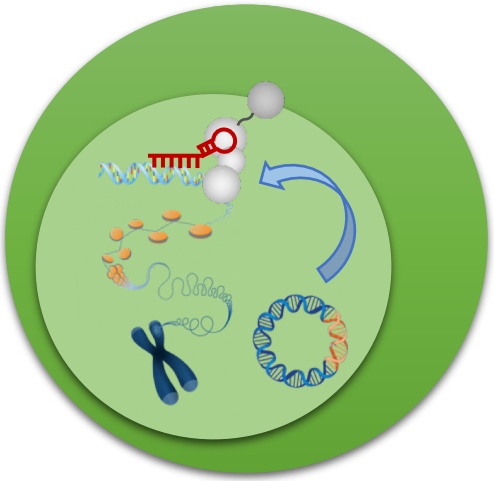
Single-administration of AAV - CRISPR-GNDM® to lower all tau forms at DNA level



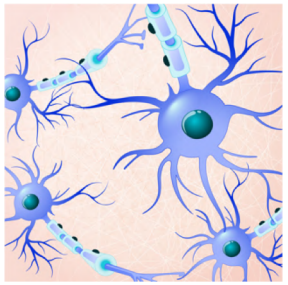
AAV vector



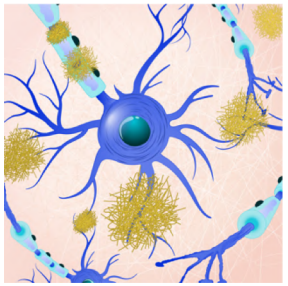
Non-integrating Virus vector



+GNDM



-GNDM (AD)



1. Packing into one AAV
2. Administration route Intracranial, Intrathecal or Intravenous
3. CRISRP-GNDM® reduce Tau at the DNA level
4. Reduce Tau Prevents Neuro-degeneration

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3. Growth Strategy

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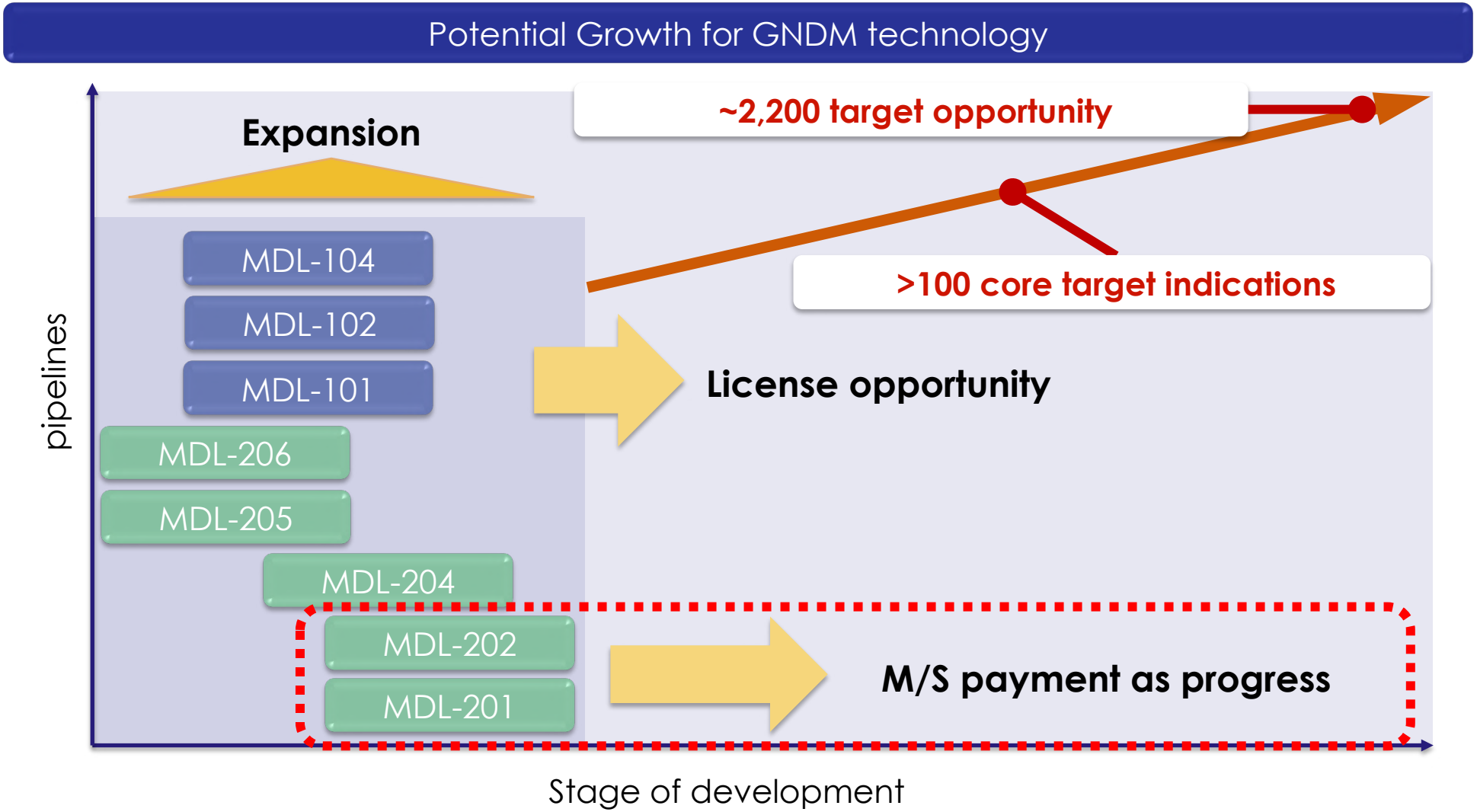
Growth Strategy
opportunity expands two dimensionally



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GNDM is efficient approach both for LoF and GoF mutation

In LoF disorders

single

Point of Mutation(s)

diversified

Limited only to ex vivo application

Base editing

Gene editing

Gene Therapy

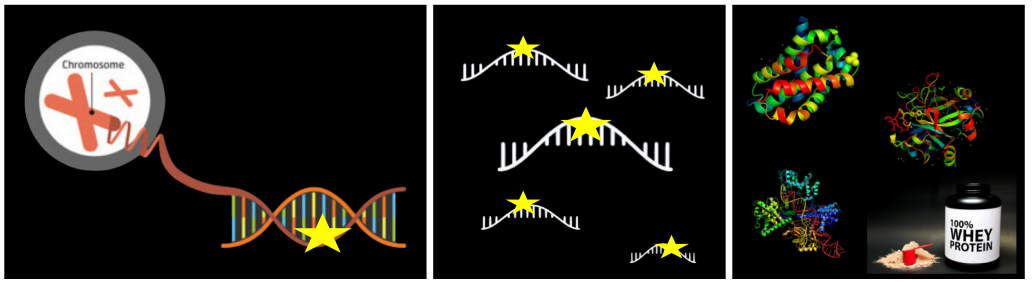
- **GNDM** (CRISPR)
- ZFP-TF (ZFN)

small — **Gene Size** — Large

In GoF disorders

Targets for suppression

DNA ⇨ RNA ⇨ Protein



1 mutant allele	Multiple copies	varied
GNDM Editing(K/D)	Si RNA ASO	Protein(Ab) peptide Small molecule

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

K/D: Knock-down

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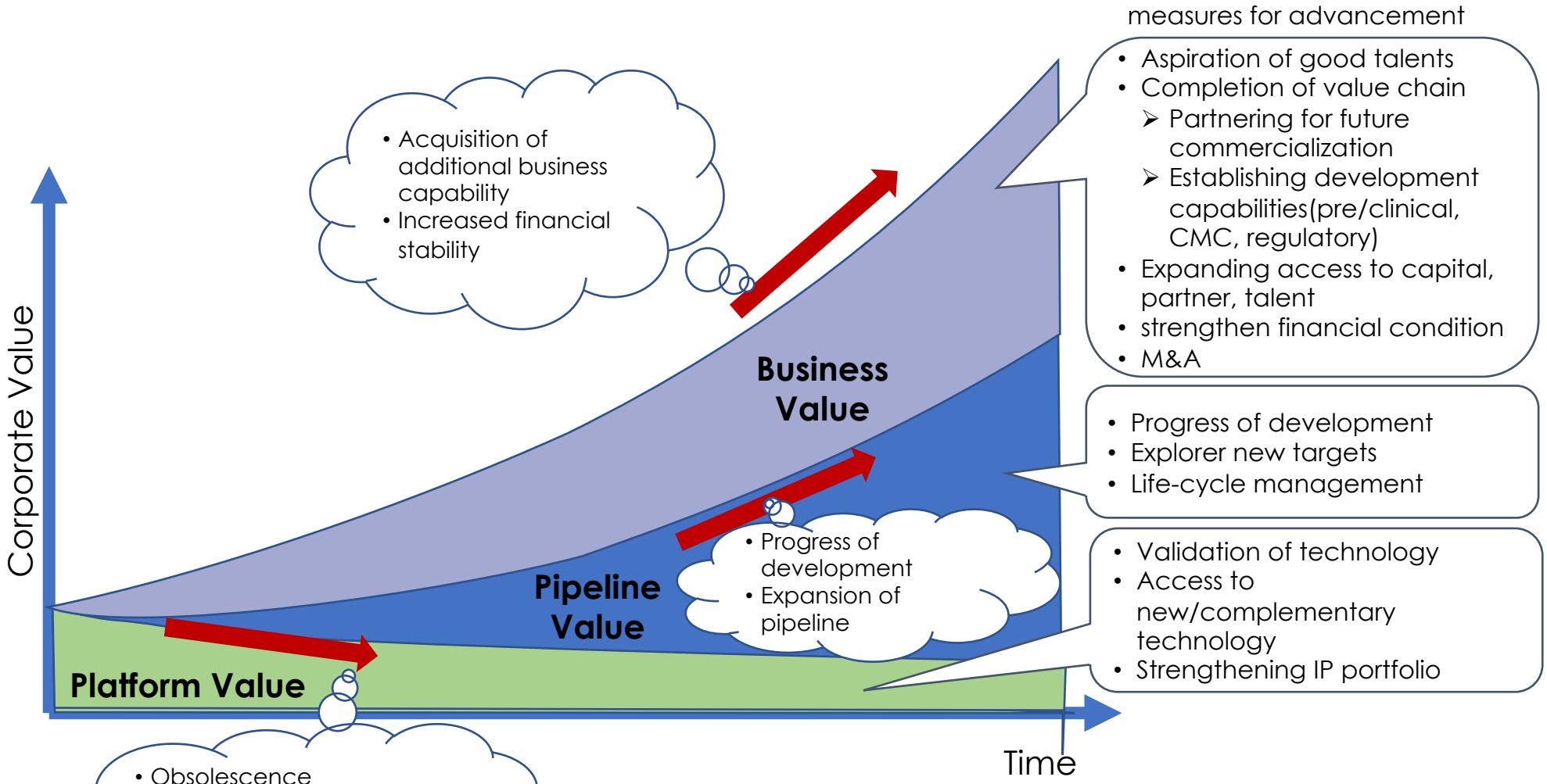
Composition of Modalis' value and measures for advance



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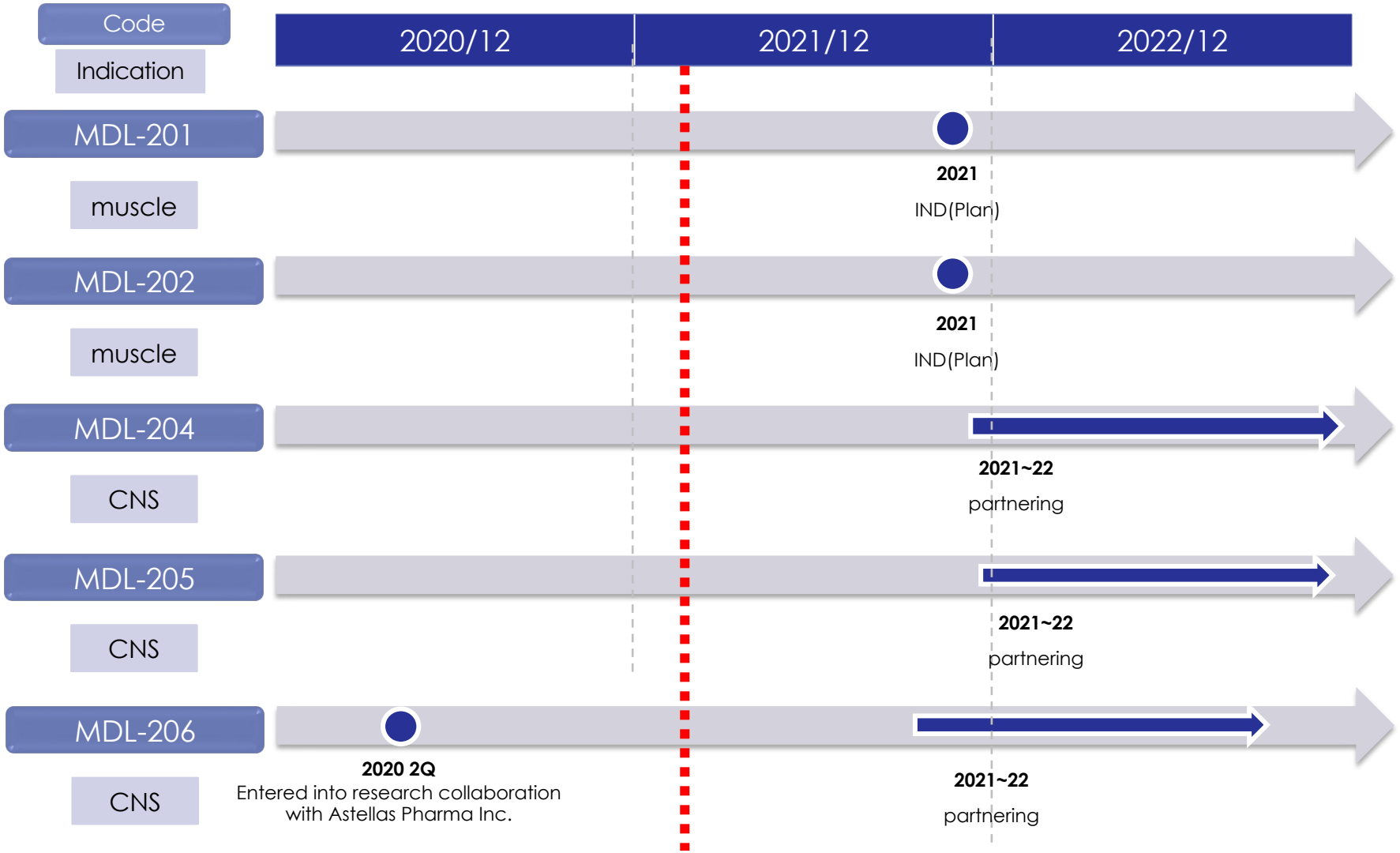
Collaboration pipeline

Achieved and expected Milestone events*



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

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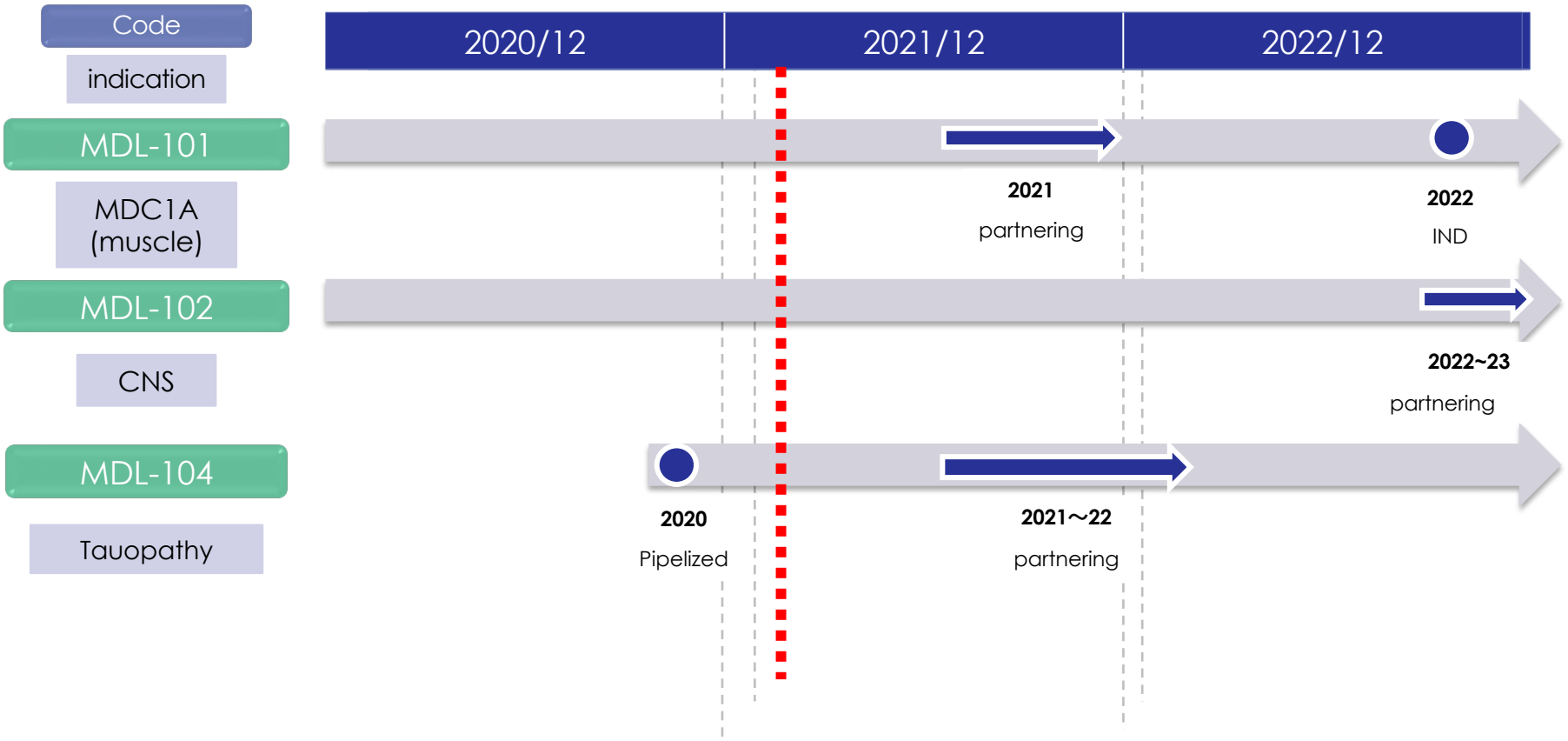
Internal pipeline

Expected milestones by end 2021*



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

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2021　PL & Business outlook

- The earnings forecasts for fiscal year 2021 are not presented due to the difficulty of formulating reasonably accurate estimates at this time.

- At present, there are many uncertain factors affecting our business performance, including the progress of negotiations with our partners, significant fluctuations in performance due to upfront payments for licensing, the possibility of concluding agreements with new partners, and the acquisition of new pipelines. In regard to the future outlook, the Company believes it is difficult to calculate an appropriate and rational figure, so the Company has decided not to disclose the full-year earnings forecast. When it becomes possible to make a forecast, the Company will promptly make an announcement.

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