English translation for reference purposes only

FY2021 Financial Results



In case of any discrepancy,
the Japanese version shall prevail

MODALIS

Modalis therapeutics Corporation

(TSE : 4883)

February 14, 2022

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MODALIS

- is pioneering the first CRISPR-based gene modulation technology
- is the leading company in epigenetic modulation
- develops novel precision medicines for a genetic disorders for which there have been no cure





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Corporate Philosophy

Every life deserves attention

The company group, through drug discovery using the core platform technology "non-cutting CRISPR technology" (CRISPR-GNDM ® technology) to invent therapeutics targeting rare genetic disorders. True to our corporate philosophy of "every life deserves attention," we hope to contribute to society by giving patients hope to overcome their illness.

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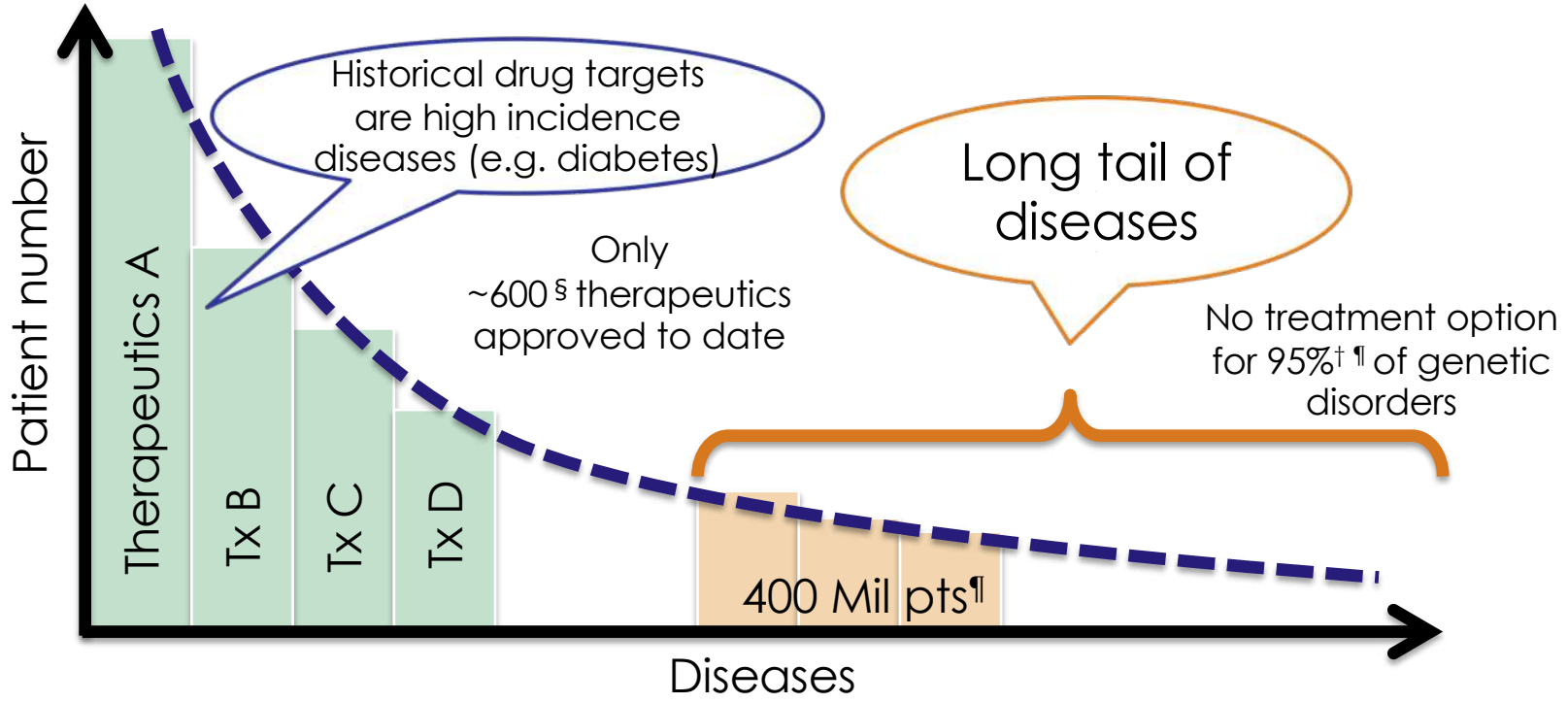
Provides solution for the long tail of disease

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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1. Financial Highlights

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PL & Business Result

(Million Yen)

	FY2020 (A)	FY2021 (B)	(B)－(A)
Operating revenue	342	1	(341)
Operating expenses	740	1,240	500
R&D	531	1,009	478
SGA	208	231	22
Operating income	(398)	(1,239)	(841)
Ordinary income	(439)	(1,231)	(792)
Profit	(448)	(738)	(290)

Operating expenses

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

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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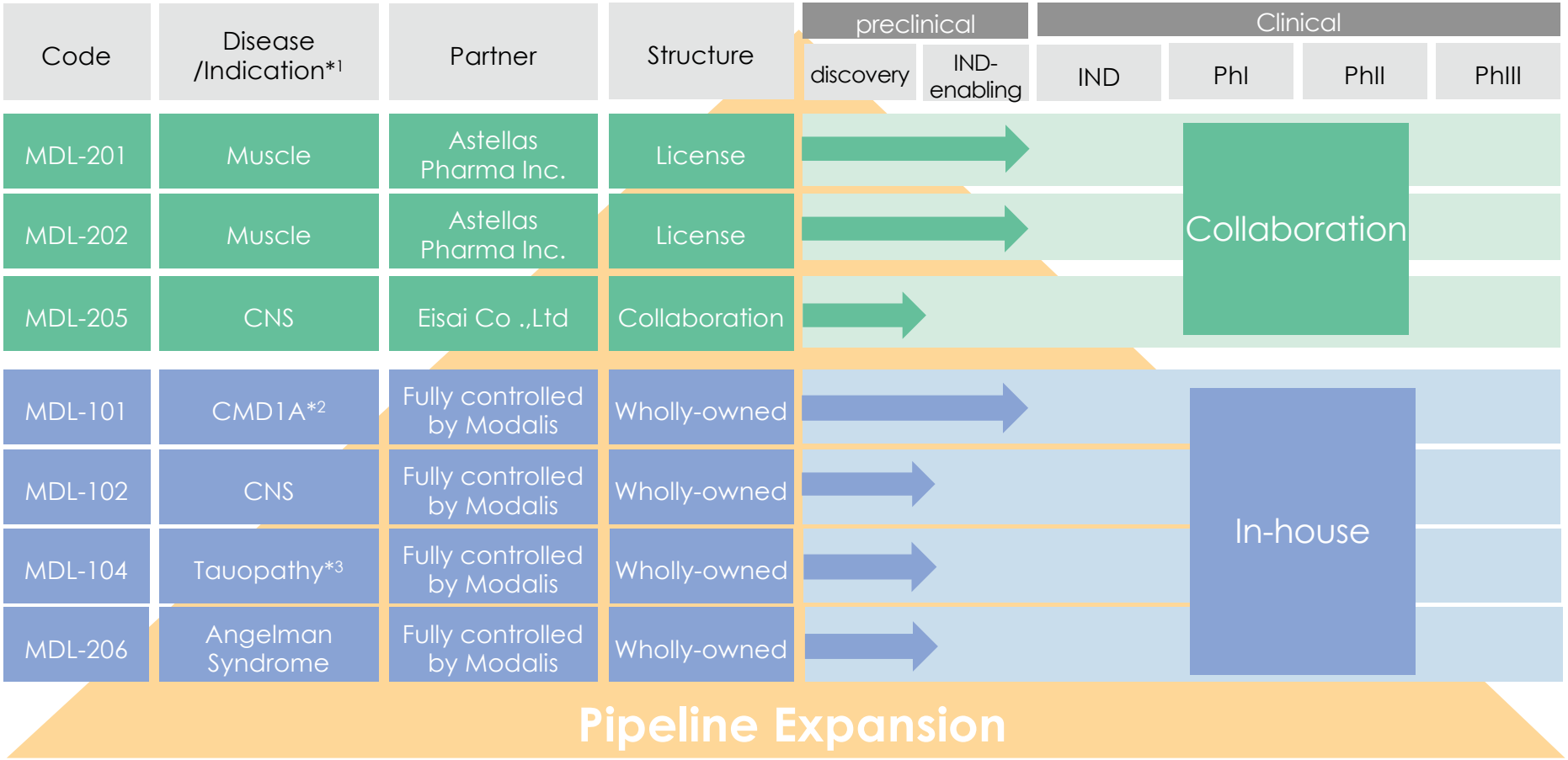
Pipeline



*1: We have adopted a strategy of withholding specific indications until the patent application is published for competitive reasons.
*2: CMD1A=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)

	FY2020 (A)	FY2021 (B)	(B) – (A)
Current assets	5,448	5,067	(381)
Cash & deposits	5,421	4,936	(485)
Non-current assets	828	1,002	174
Property, plant and equipment	49	223	174
Right to use patent	767	223	(63)
Total assets	6,277	704	(208)
Current liabilities	58	6,069	123
Non-current liabilities	11	181	328
Total liabilities	70	339	450
Total net assets	6,206	520	(657)
Total liabilities and net assets	6,277	5,549	(208)
Capital adequacy ratio	98.9%	6,069	

- 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

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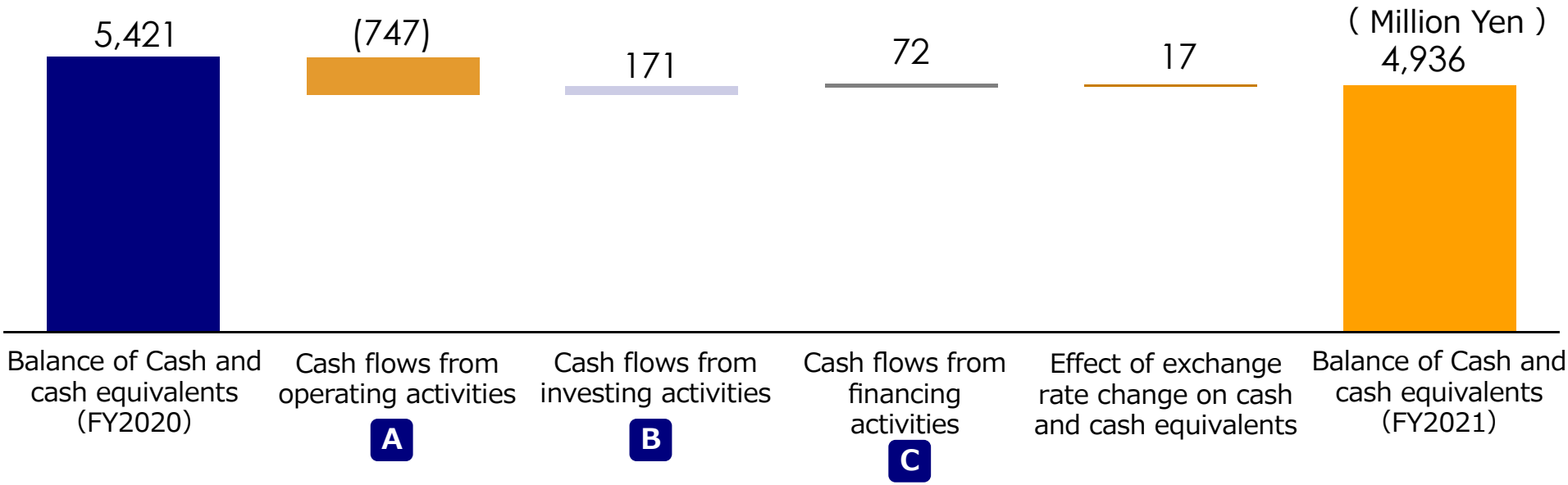
Cash Flow Status



A Cash flows from operating activities	• Loss before income taxes （△745）
B Cash flows from investing activities	• Proceeds from contribution received for right to use patent （329） • Purchase of property, plant and equipment （△107）
C Cash flows from financing activities	Proceeds from issuance of stock acquisition rights （72）

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2. Key Topics

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R&D summary

- MDL-101
  - IND enabling study on going
    - Pilot Tox and PK/PD for designing GLP studies
  - Preparing for interaction with FDA
    - Filing request of INTERACT meeting (1Q)
    - File Pre-IND meeting (4Q)
  - Process development team established and is up and running
- Other pipelines
  - Sets new target area and incubate a few pipelines
  - Pursuing research collaboration of MDL-205 with Eisai
  - Termination of MDL-204 research collaboration (Reported on Jan 7. see Q&A)
- Other
  - Multiple articles will be presented at ASGCT*(May 16 - 19th @DC)

*ASGCT: American Society of Gene & Cell Therapy
https://annualmeeting.asgct.org

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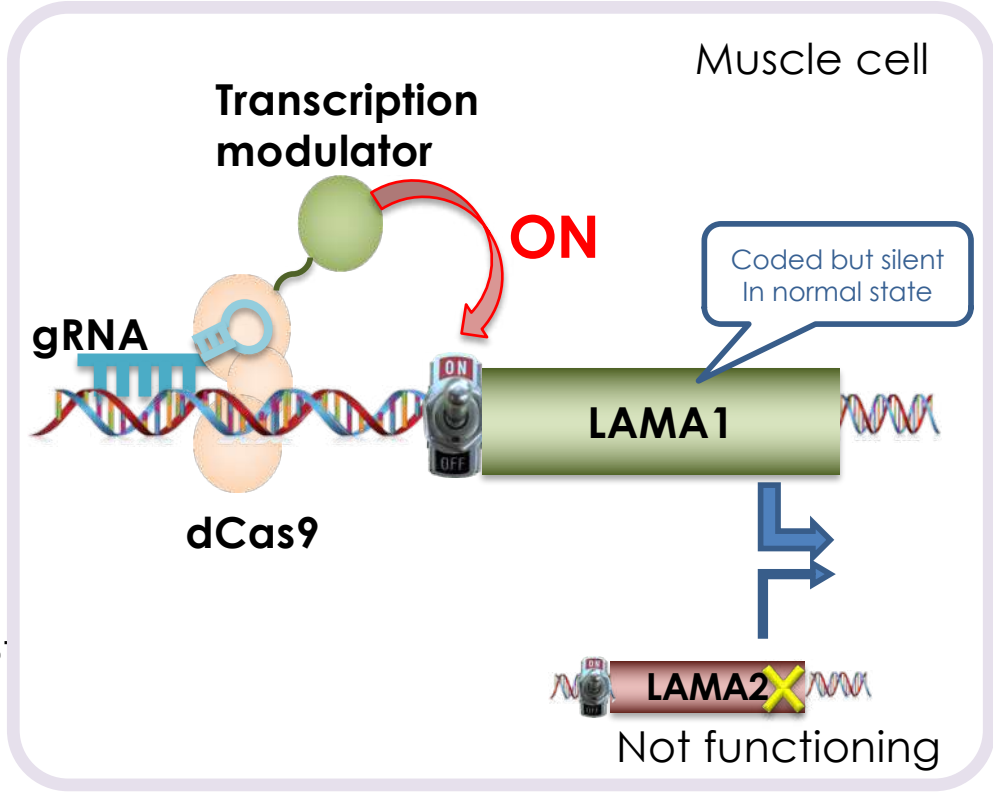
CMD1A

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 o the disorder, many affected individuals **do not survive past adolescence**.
- Genetic cause: **LAMA2** mutation

CRISPR-GNDM® targeting LAMA1



*Orphanet

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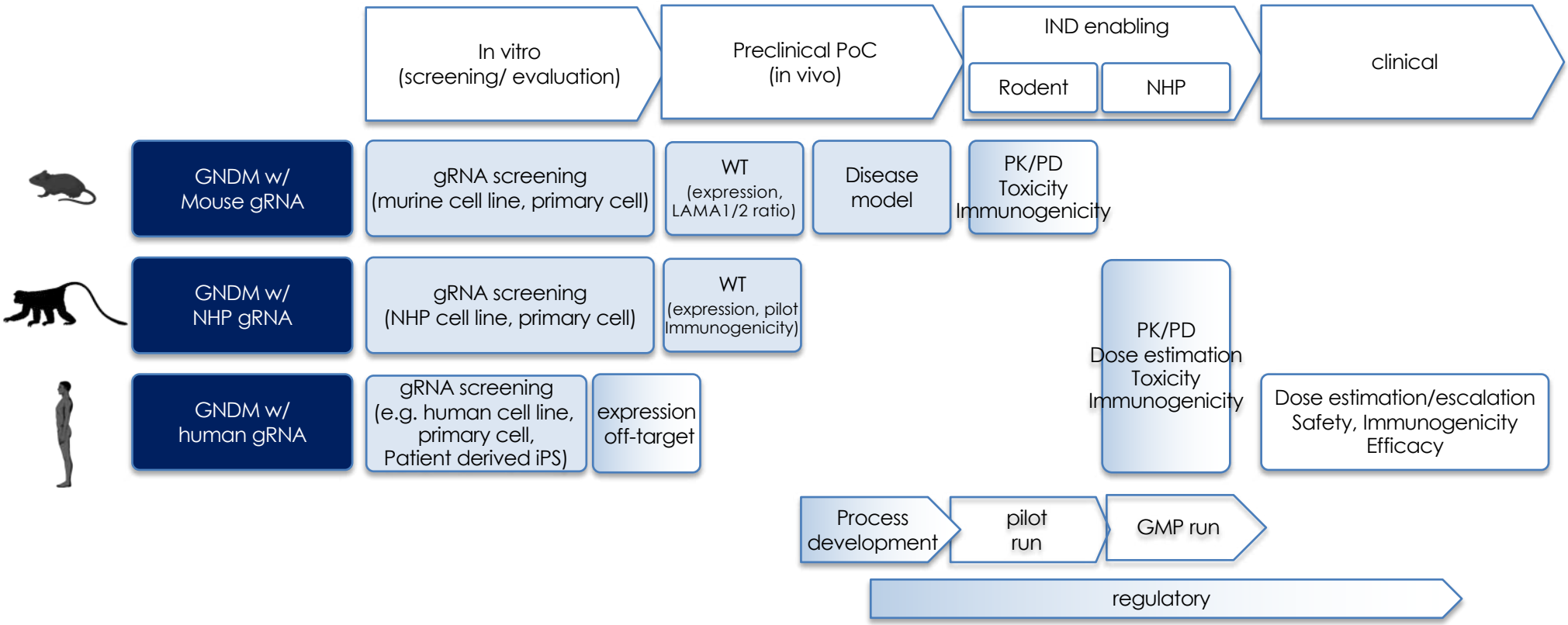
Conducting IND enabling studies as well as process development

Path to clinic for CRISPR-GNDM®



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Summary of MDL-101

- Reported by 3Q/2021
  - Mouse disease model data in two strains (dy2j and dyW)
    - 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
  - Formed a strategic alliance with 1st tier CDMO for GMP manufacturing

- Achieved thereafter
  - Establish process development team to initiate manufacturing activities
  - Initiated 2nd NHP study with AAV9 with further optimized gRNA
  - Further optimization of GNDM cassette and locking in final construct (codon usage, cassette orientation, etc.)

- Next steps:
  - INTERACT meeting and pre-IND meeting
  - IND enabling GLP tox and PK/PD

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R&D summary

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- Other
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*ASGCT: American Society of Gene & Cell Therapy
https://annualmeeting.asgct.org

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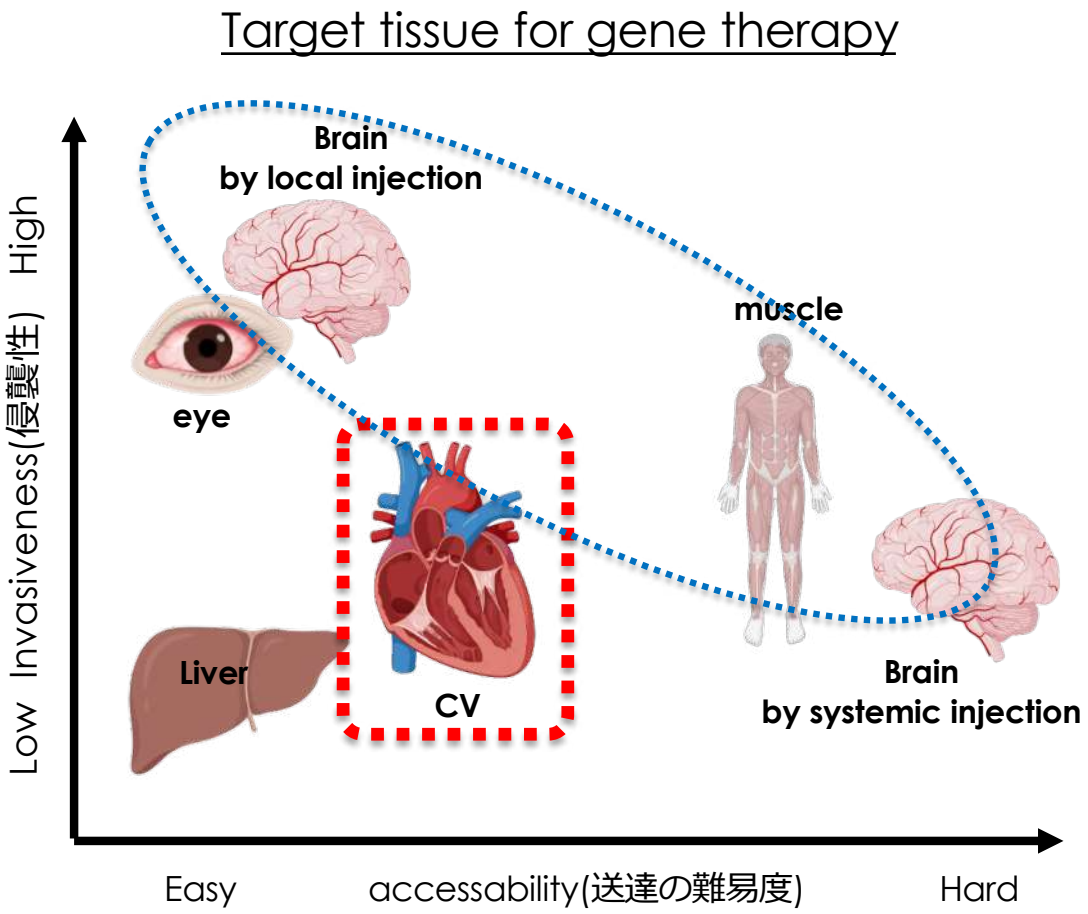
CV is our next horizon



- Modalis has focused mainly on CNS and muscle disease area
- Our accumulated know how allow us to explorer new disease area
- CV is one of the reachable tissue by AAV systemic injection

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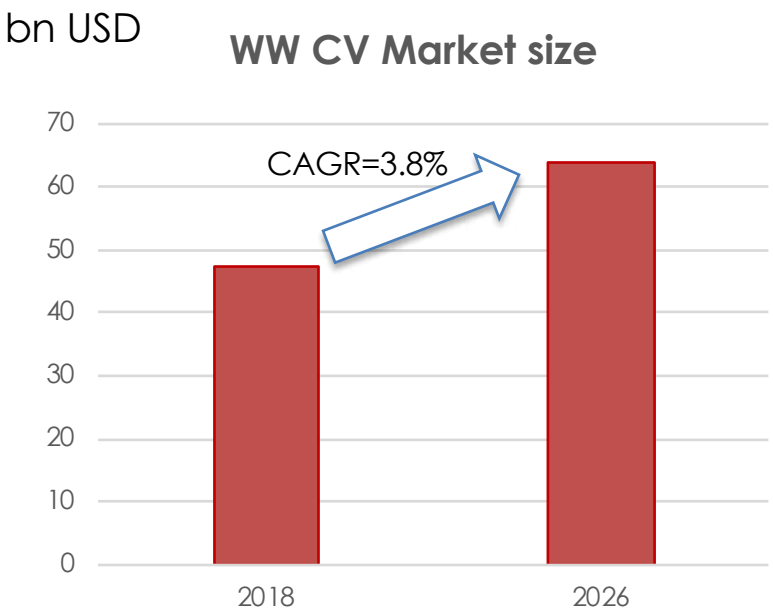
There are huge opportunities in CV area



Source: Fortune Business Insight

Cardiac genetic disorders	Proposed Causative genes
Severe hypercholesterolemia	LDLR, APOB, ABCG5, ABCG8, ARH, PCSK9
Hypertrophic Cardiomyopathy (HCM)	MYBPC3, MYH7, TNNI3, TNNT2, TPM1, MYL2, FHL1, MYL3, GLA, PRKAG2, NEXN, ACTC1, LAMP2, PLN
Dilated Cardiomyopathy (DCM)	TTN, DSP, MYH7 , LMNA, TNNT2, TPM1, VCL TCAP, LDB3, MYBPC3, ABCC9, DES, TNNI3 ACTC1, SGCD, PLN, TAZ
Arrhythmogenic right ventricular Cardiomyopathy (ARVC)	PKP2, DSP, DSG2, DSC2

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Other business progresses

- Partnering
  - MDL-101: Partnering discussion ongoing with pharma/biotech companies
  - MDL-205: Research collaboration ongoing with Eisai. Opt-in discussion will be made upon completion
  - Research collaboration: In discussion with pharma/biotech companies on new targets

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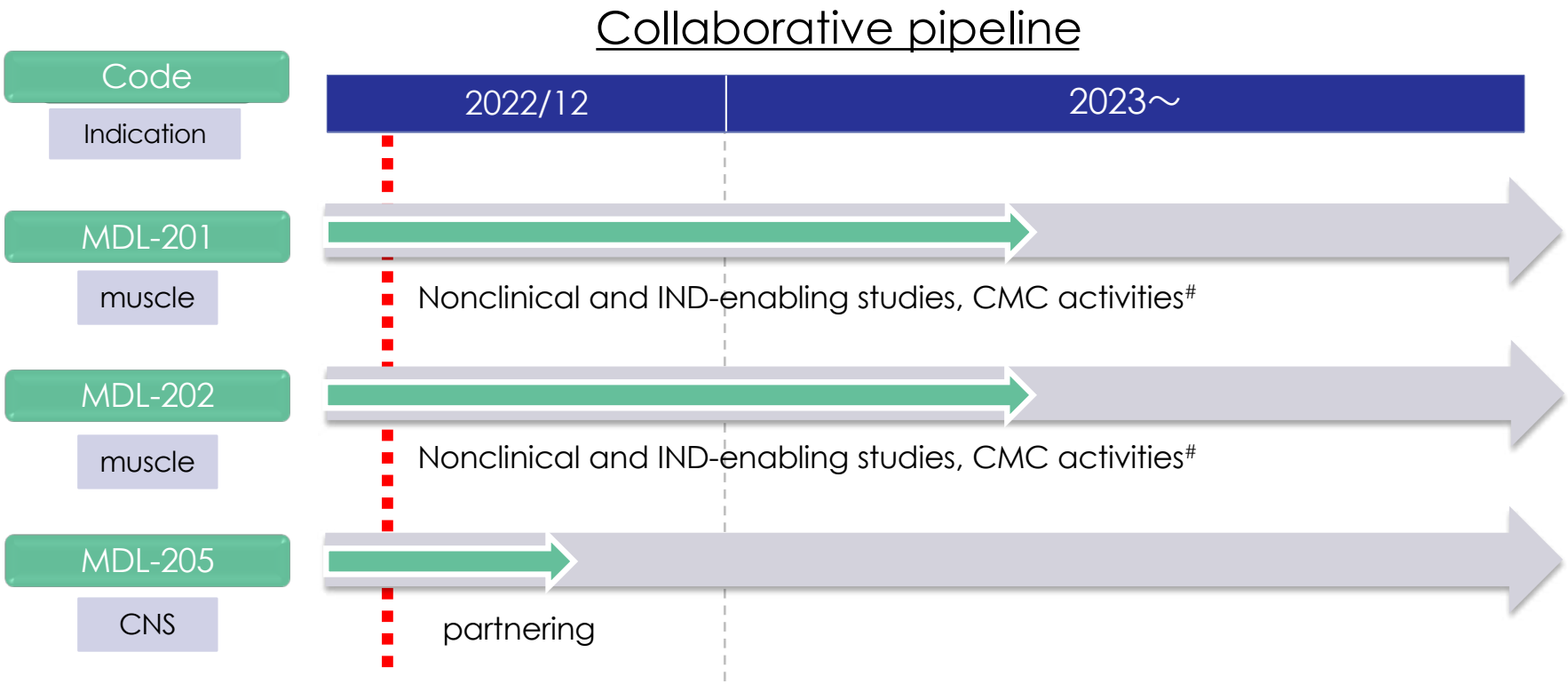
Steady progress in IND enabling of 201 and 202
Decision will be made on 205 in 1H 2022



*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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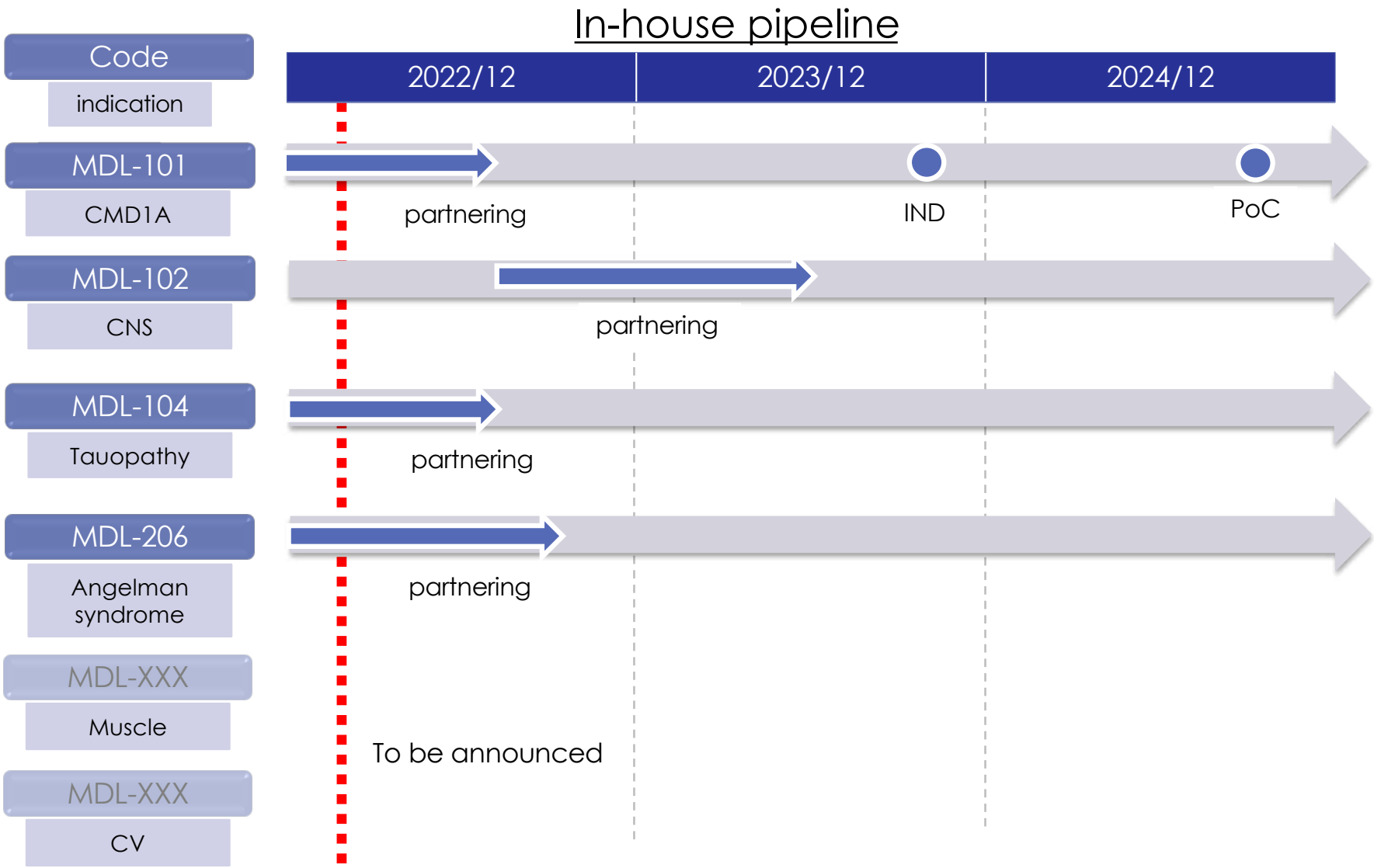
Several pipelines are coming out in this year



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

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3. Growth Strategy

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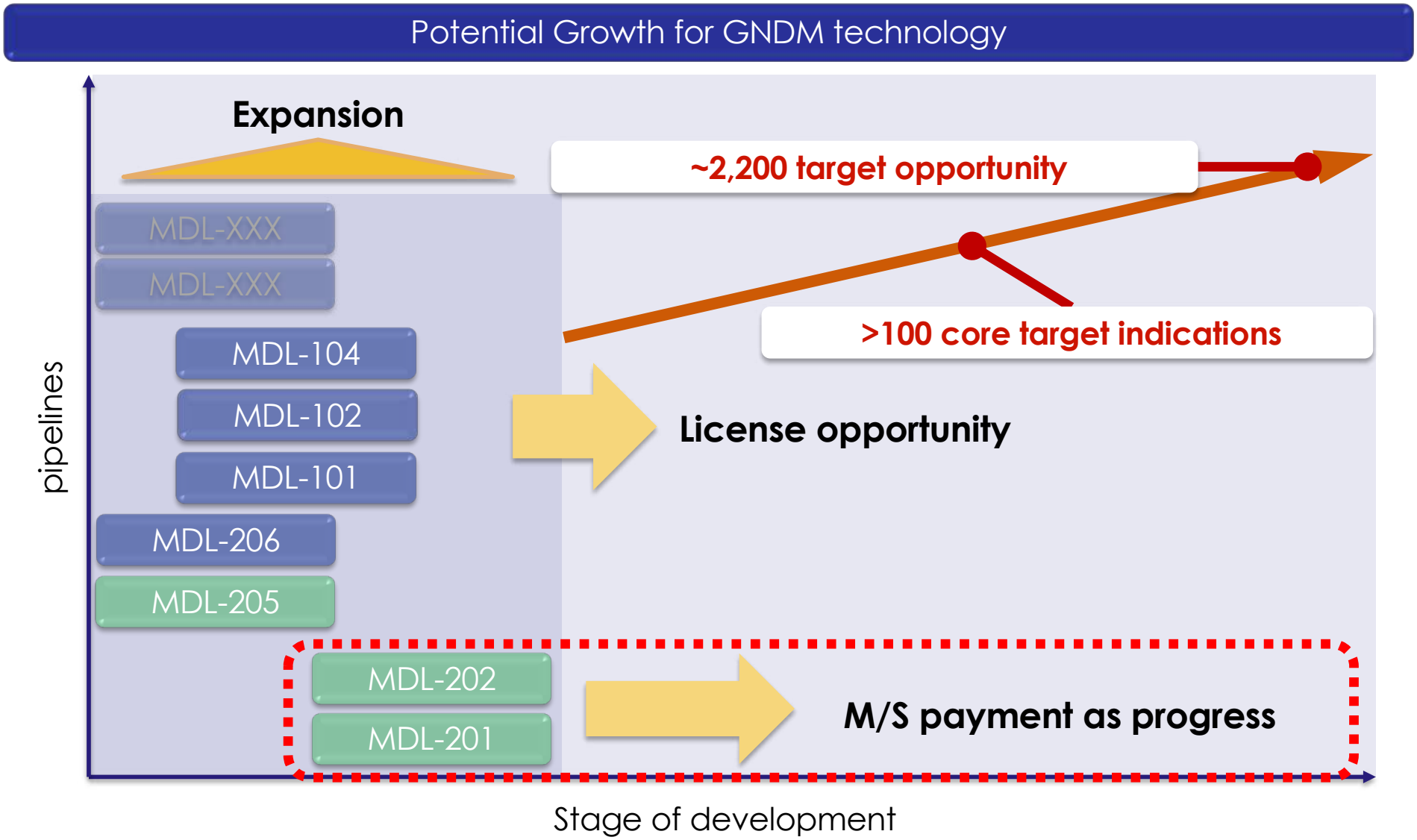
Growth Strategy

opportunity expands two dimensionally



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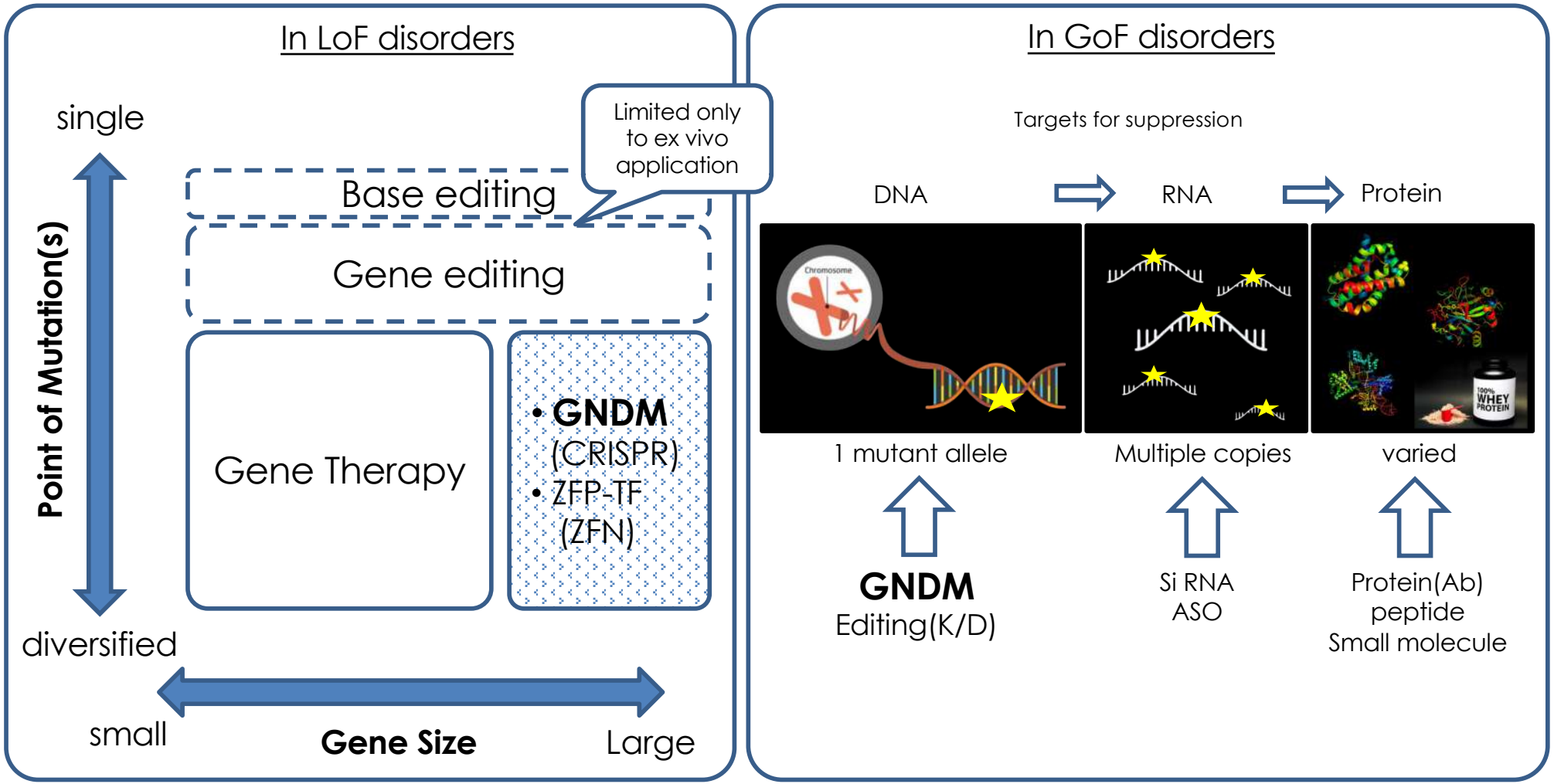
GNDM is efficient approach both for LoF and GoF mutation



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

K/D: Knock-down

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Modalis is uniquely positioned within the CRISPR field

	Editing Gene base	Modulation (epigenetic editing)
CRISPR	Editas CRISPR Tx BEAM Intellia	MODALIS
Other (e.g. ZFN)	Sangamo	

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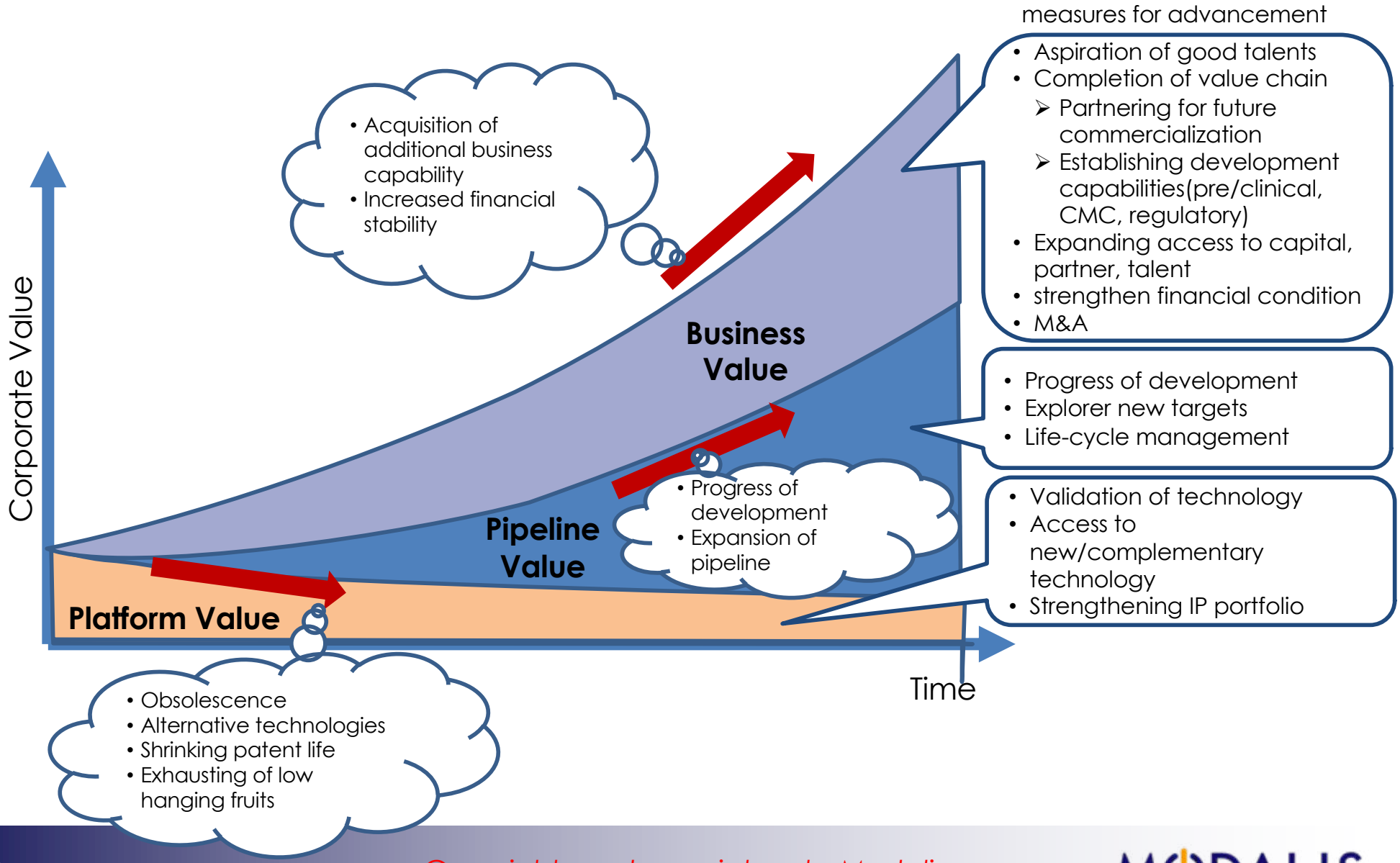
Composition of Modalis' value and measures for advance



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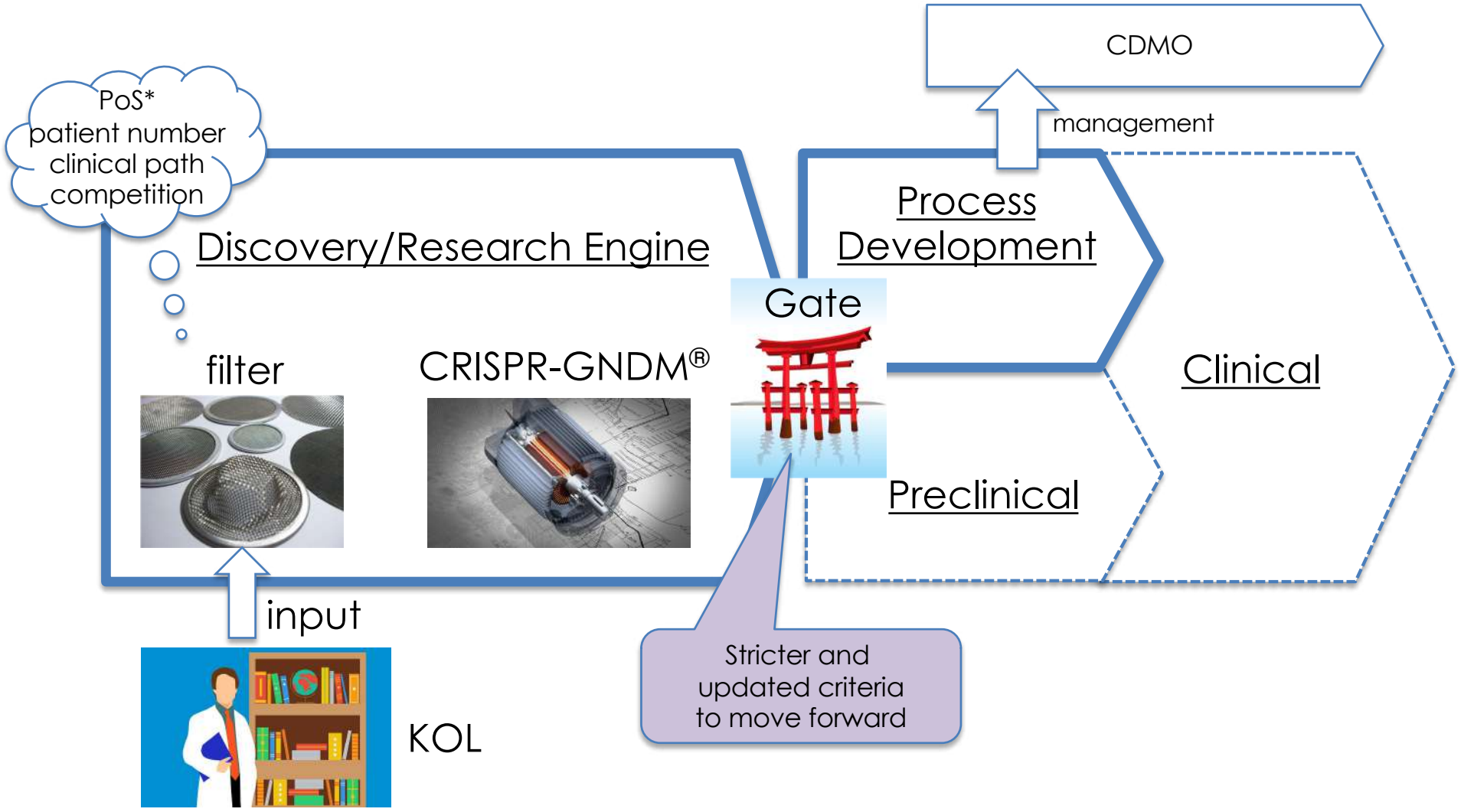
Upon transition from R to D, which cost time and money, stricter decision is made for higher ROI and better resource allocation.



PoS: Probability of success

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4. Q & A

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Q1: What is the future of your relationship with Astellas? [reprint]

A) To date, we have conducted a total of five joint research projects with Astellas, two of which have resulted in licensing agreements.
With the conclusion of the MDL-204 collaboration, there are no ongoing research collaborations with Astellas. However, we continue to maintain a good relationship through collaboration on two licensed pipelines, MDL-201 and MDL-202, as well as exploring other collaboration opportunities.
We've confirmed that Astellas continues to explore the existing pipelines licensed to it, MDL-201 and MDL-202, currently in the pre-clinical stage.

* Please note that this information is subject to change without notice. Please understand.
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Q2: What is the difference between MDL-206, which Modalis regained rights and put into in-house pipeline in August 2021, and the current MDL-204? [reprint]

A) While both pipelines use the same CRISPR-GNDM® technology approach to create gene therapies, each pipeline has its own technical challenges specific to the target gene, patient population size, and competition from other modalities.
In the case of MDL-206, the decision to continue the pipeline as our own was based on reasons such as the target Angelman Syndrome's affinity to the technology and the difficulty of approaching it with other modalities, as well as the assumed efficacy based on existing data. However, the decision to discontinue MDL-204 was based on a comprehensive judgment that it was not sufficiently superior or reasonable.

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Q3: Do you foresee any increase or decrease in the pipelines in the future? [reprint]

A) We have several new candidates, including those for which we are currently exploring the possibility of collaboration and those that are being incubated in-house. We plan to promote these to the pipeline at an appropriate stage.
Among existing pipelines, we will promptly discontinue those for which we believe there is no longer a possibility to continue research and development, such as MDL-204.
We believe that it is reasonable to optimize the size and quality of our portfolio by conducting an appropriate metabolism.
We also believe that making decisions at an early stage, especially at the research stage, is effective in increasing the chances of success in the costly development stage.

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Q4: Several epigenetic modulation companies were established at the end of last year, will this affect the competitive environment?

A) We are delighted to see that epigenetic modulation is now widely recognized as an effective drug discovery technique.

The Company believes that, in addition to the protection provided by our existing intellectual property, we can continue to maintain our leading position by based on the collective experience we have gained in the six years since our establishment.

	Editing		Modulation (epigenetic editing)
	Gene	base	
CRISPR	Editas CRISPR Tx Intellia	BEAM	MODALIS
Other (e.g. ZFN)	Sangamo		

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Q5: Does the outcome of CTGTAC meeting impact on Modalis' development?

A) FDA's Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) held a meeting on September 2nd and 3rd, 2021 (https://www.fda.gov/advisory-committees/advisory-committee-calendar/cellular-tissue-and-gene-therapies-advisory-committee-september-2-3-2021-meeting-announcement#event-information)

This was to discuss the toxicity risks of adeno-associated virus (AAV) vector-based gene therapy product.

The meeting was held in response to toxicities observed in animals and humans after administration of gene therapy products including (1) hepatoxicity, (2) Thrombotic Microangiopathies (TMA), (3) Dorsal Root Ganglia neuronal loss, (4) brain MRI abnormalities, and (5)AAV vector integration and oncogenicity. We understand that the objective of the meeting was to provide recommendations for strategies to minimize the risk to patients receiving gene therapy products.

This will not significantly affect our development guidelines or timeline as most of the toxicities are not new to us and we have set up certain countermeasures, but we will take appropriate action based on our understanding of the authorities' awareness of the issue.

The Company has been following up on necessary regulatory guidance, reports, meetings, and the latest papers related to gene therapy in a fairly extensive and timely manner, including this meeting, so the information can be reflected in the Company's strategy as needed.

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