English translation for reference purposes only

FY2022 3Q
Financial Results



In case of any discrepancy,
the Japanese version shall prevail

MODALIS

Modalis therapeutics Corporation
(TSE：4883)
November 7, 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 genetic disorders for which there have been no cure













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Corporate Philosophy

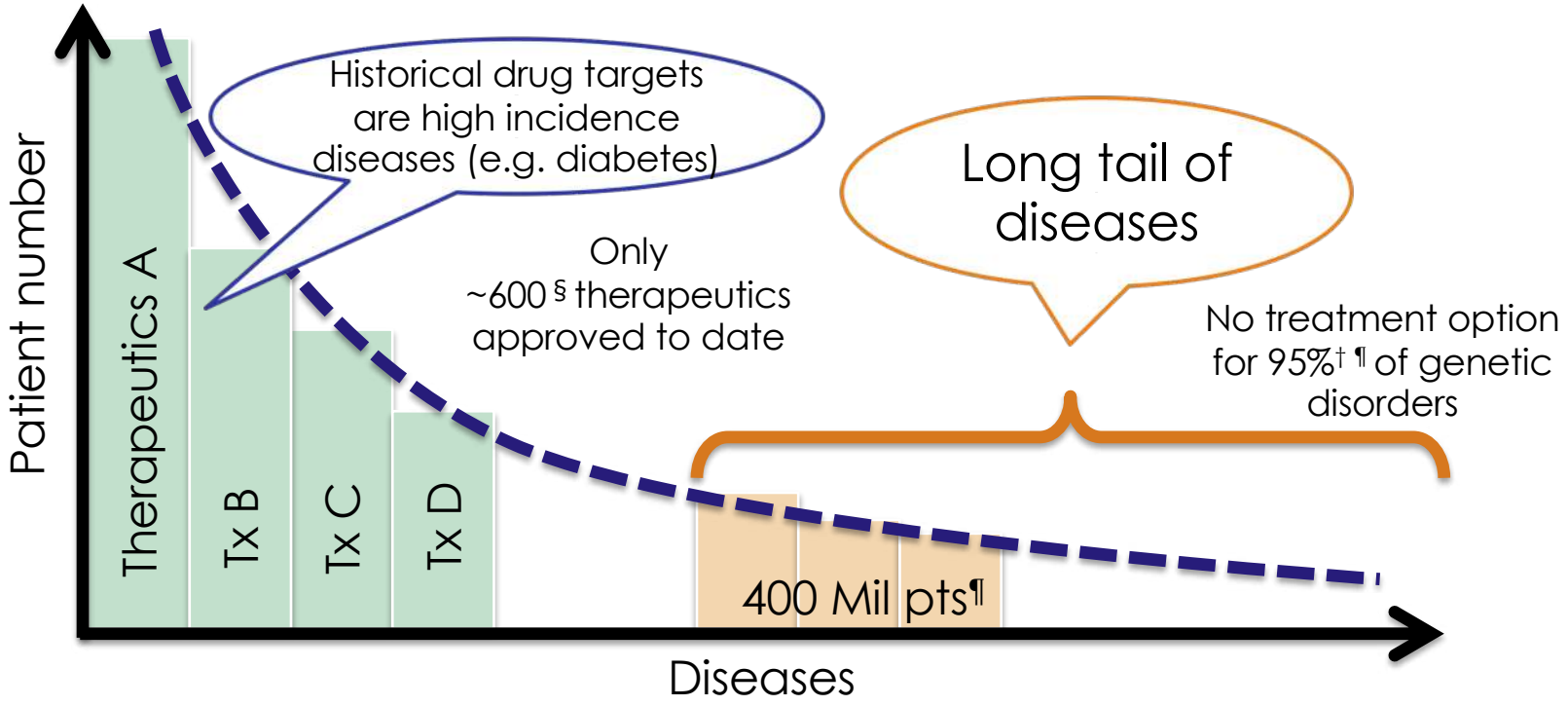
Every life deserves attention

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)

	FY2021 3Q (Nine Months) (A)	FY2022 3Q (Nine Months) (B)	(B) – (A)
Operating revenue	1	40	39
Operating expenses	678	1,478	800
R&D	493	1,290	797
SGA	185	188	3
Operating income	(677)	(1,438)	(761)
Ordinary income	(661)	(1,314)	(653)
Profit	(181)	(1,309)	(1,128)

Operating revenue

・Earning collaborative R&D milestone income

Operating expenses

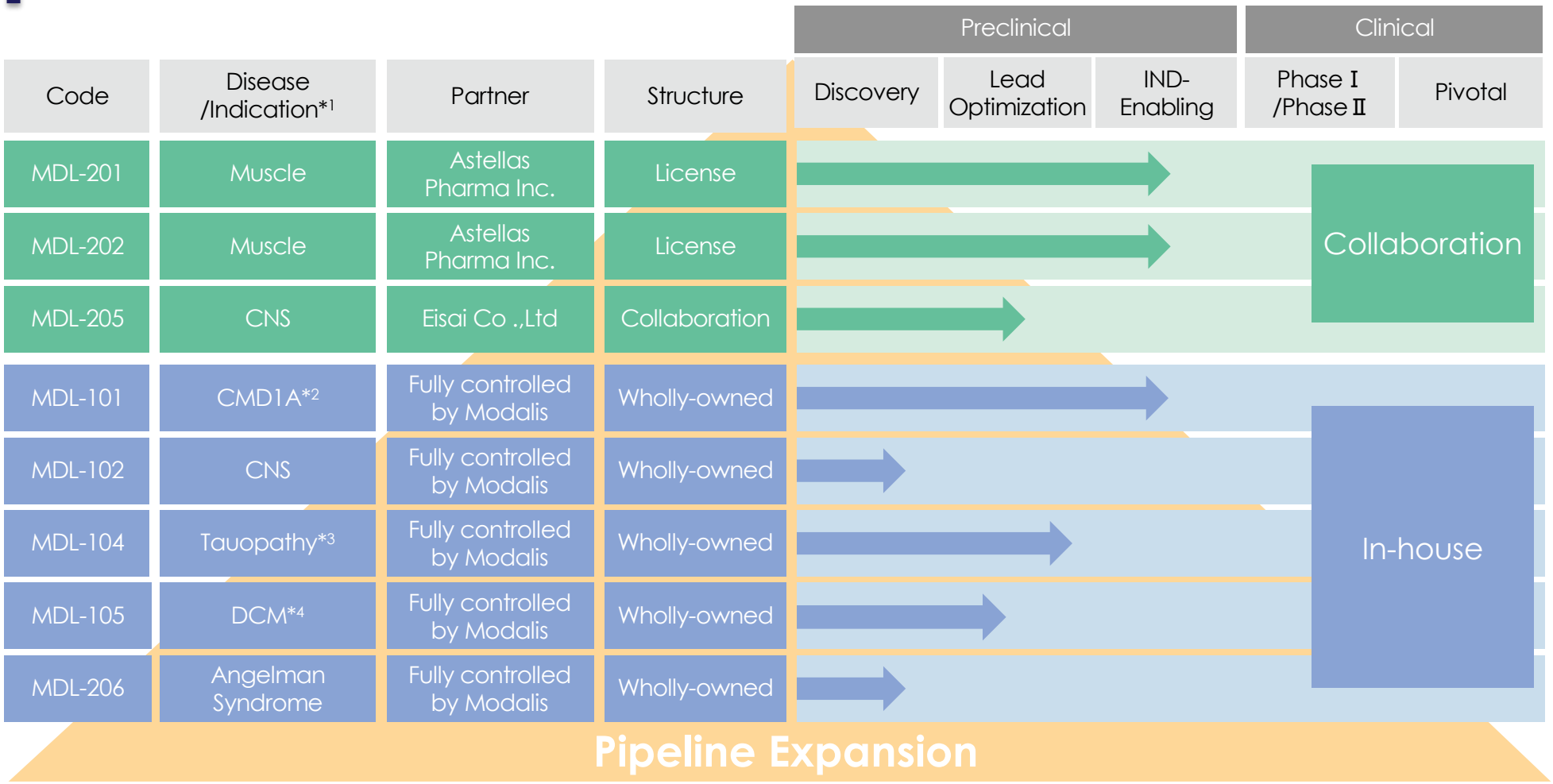
・R&D increased year on year as business progressed(primarily in personnel expenses, research material expenses, rent fee, expenses for conducting clinical trials of MDL-101 and yen depreciation against US dollar)

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 = 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.
*4: DCM = Dilated cardiomyopathy

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BS & Financial Position

(Million Yen)

	FY2021 (A)	FY2022 3Q (B)	(B) – (A)
Current assets	5,067	3,803	(1,264)
Cash & deposits	4,936	3,681	(1,255)
Non-current assets	1,002	1,083	81
Property, plant and equipment	223	349	126
Right to use patent	704	657	(47)
Total assets	6,069	4,886	(1,183)
Current liabilities	181	285	104
Non-current liabilities	339	317	(22)
Total liabilities	520	602	82
Total net assets	5,549	4,284	(1,265)
Total liabilities and net assets	6,069	4,886	(1,183)
Capital adequacy ratio	91.4%	87.6%	

- Stable financial base, High Equity ratio
- Increased property, plant and equipment such as research equipment due to the expansion of the laboratory of the US subsidiary

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2. Key Topics

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Summary of MDL-101

- Reported by 2Q/2022
  - 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 is ongoing in collaboration with a CDMO.
  - Had the INTERACT meeting with FDA
- Progress thereafter
  - The capsid* is changed (as announced in Sep 15th news release)
  - Preparation of additional monkey study for finalization of improved capsid
  - Revision of the manufacturing process as the capsid changed
- Next steps:
  - Filing pre-IND meeting (mid-2023)
  - Continue IND enabling GLP tox and PK/PD
  - Continue process development and pilot productions for GMP campaign

*capsid :Refer to P14(Describe the relationship with the AAV vectors)

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Previously shown

INTERACT* Meeting summary

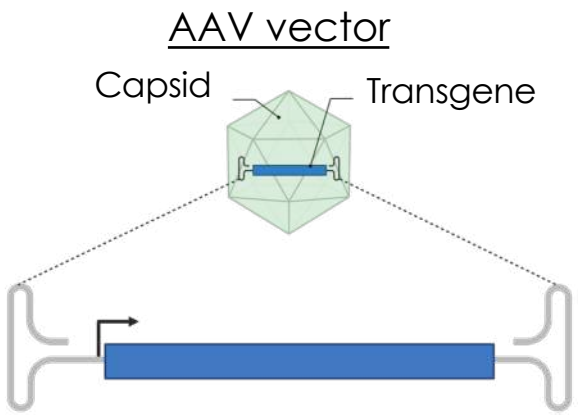
- Held in Mid July
- Non-binding
- Modalis provided development summary and questions to FDA and FDA answered to them in writing and follow them up in a web meeting.
- Primary agenda includes
  - Manufacturing process and method to assess clearance of the resulted product
  - Compatibility among samples used in animal studies and clinical trials
  - Species selection for the GLP studies
  - Using surrogate products for animal studies
- FDA responses were found to be within Modalis' expectations and under control

INTERACT : *INitial Targeted Engagement for Regulatory Advice on CBER Products*

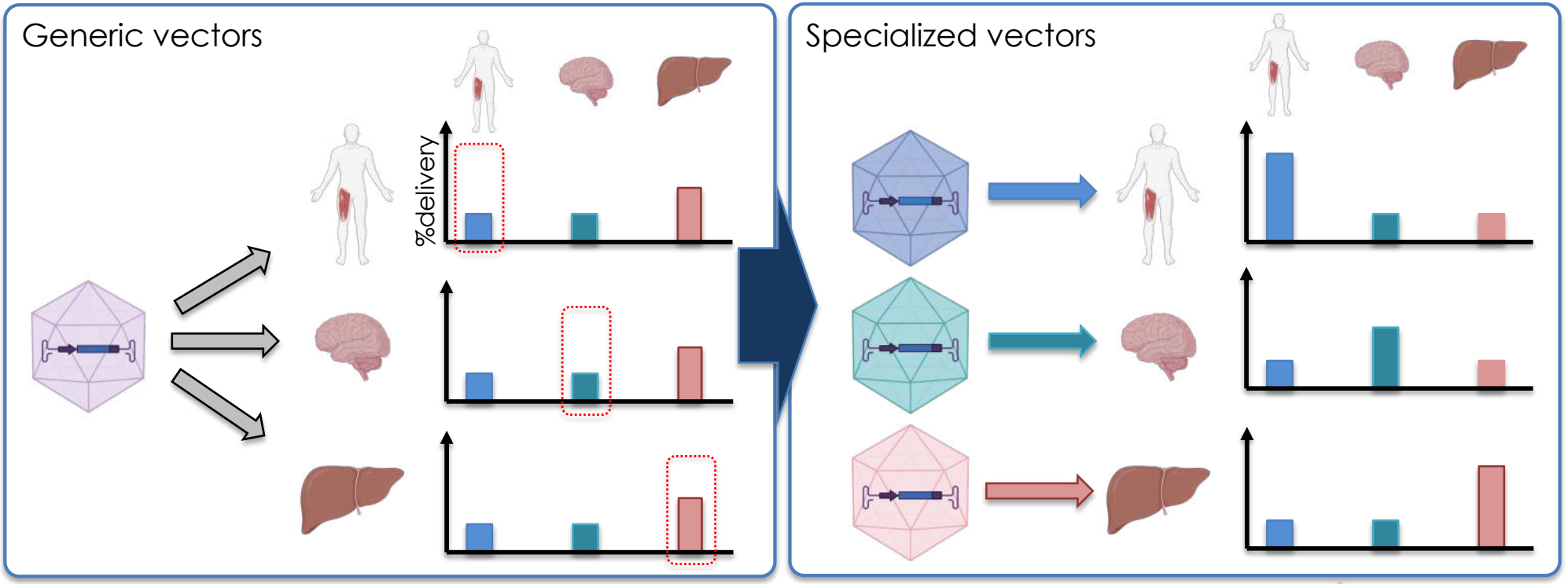
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Big innovations have been brought to AAV vectors recently



- 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

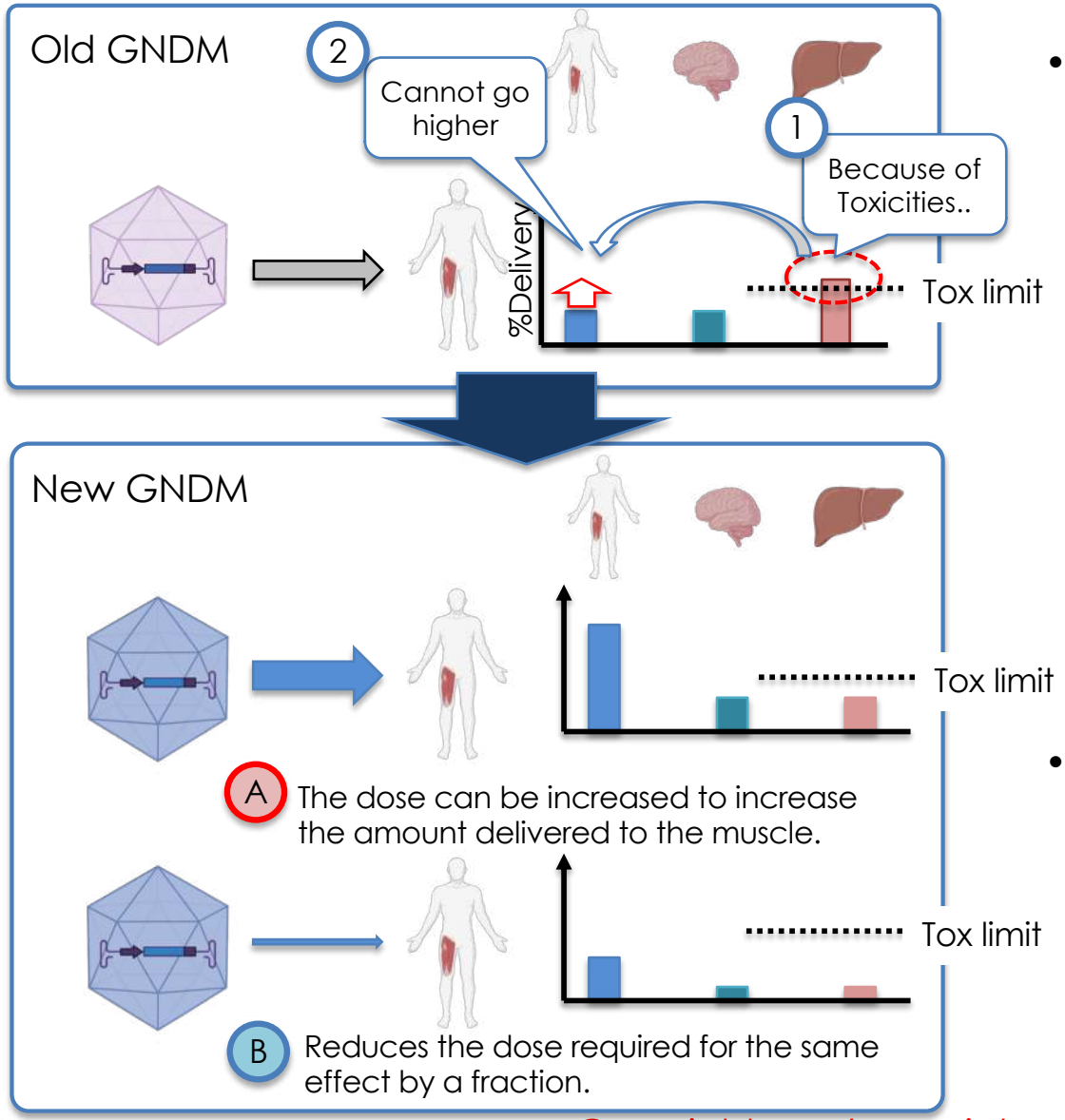


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Transition to specialized capsid is the need of the field and will be beneficial in the long run

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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Summary of other R&D activity

- Other pipelines
  - MDL-104 (Tau)
    - Optimizing the final vector for the potential clinical trial
    - Preparation of NHP study to confirm the final vector
    - Protocol development for the clinical trial
  - MDL-105 (TTN)
    - Got access to a disease model mice and initiated animal proof-of-concept studies

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Other updates on business

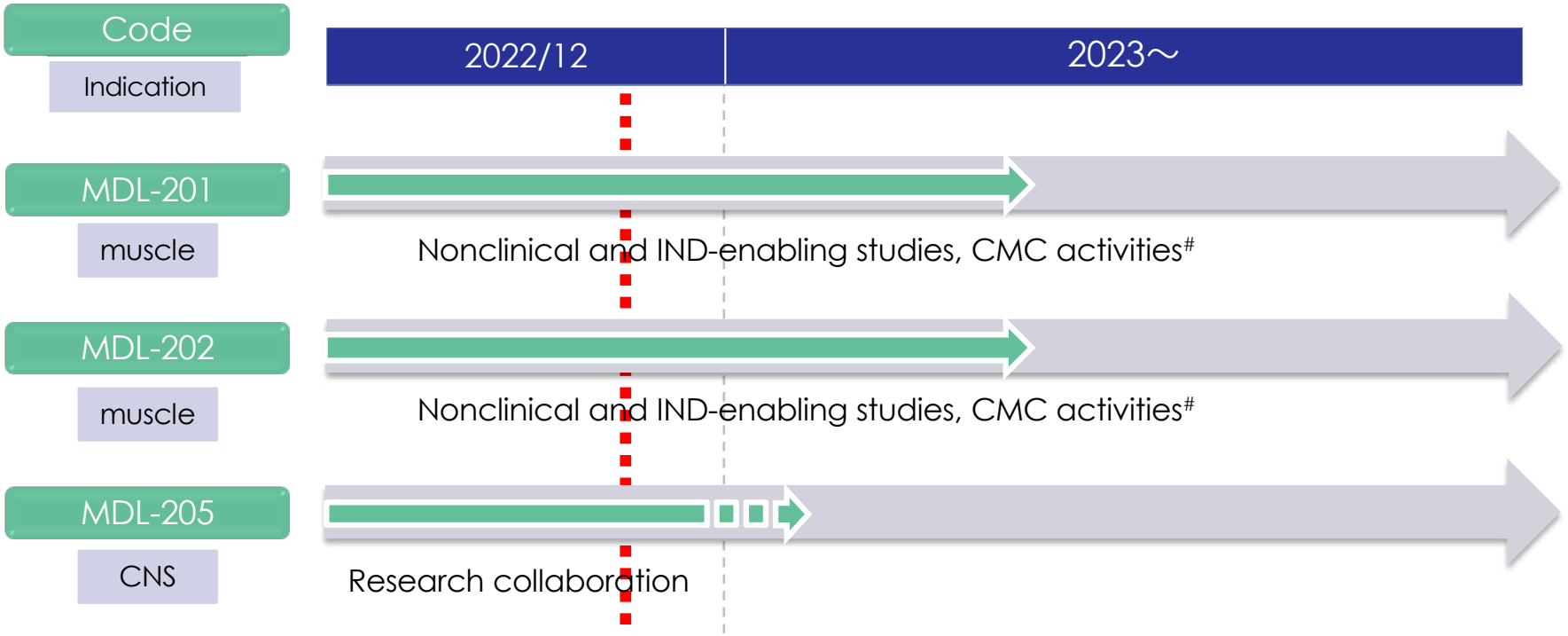
- Progress on intellectual property
  - On October 18, "METHOD FOR TREATING MUSCULAR DYSTROPHY BY TARGETING UTROPHIN GENE" was issued as US 11,473,071 B2 patent.

- Progress on partnering
  - MDL-101, 104, and 105: Partnering discussion ongoing with pharma/biotech companies
  - Research collaboration: In discussion with pharma/biotech companies on new targets

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Steady progress in IND enabling of 201 and 202
MDL-205 has achieved MS and collaboration is extended

Collaboration pipeline



*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

In-house pipeline



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

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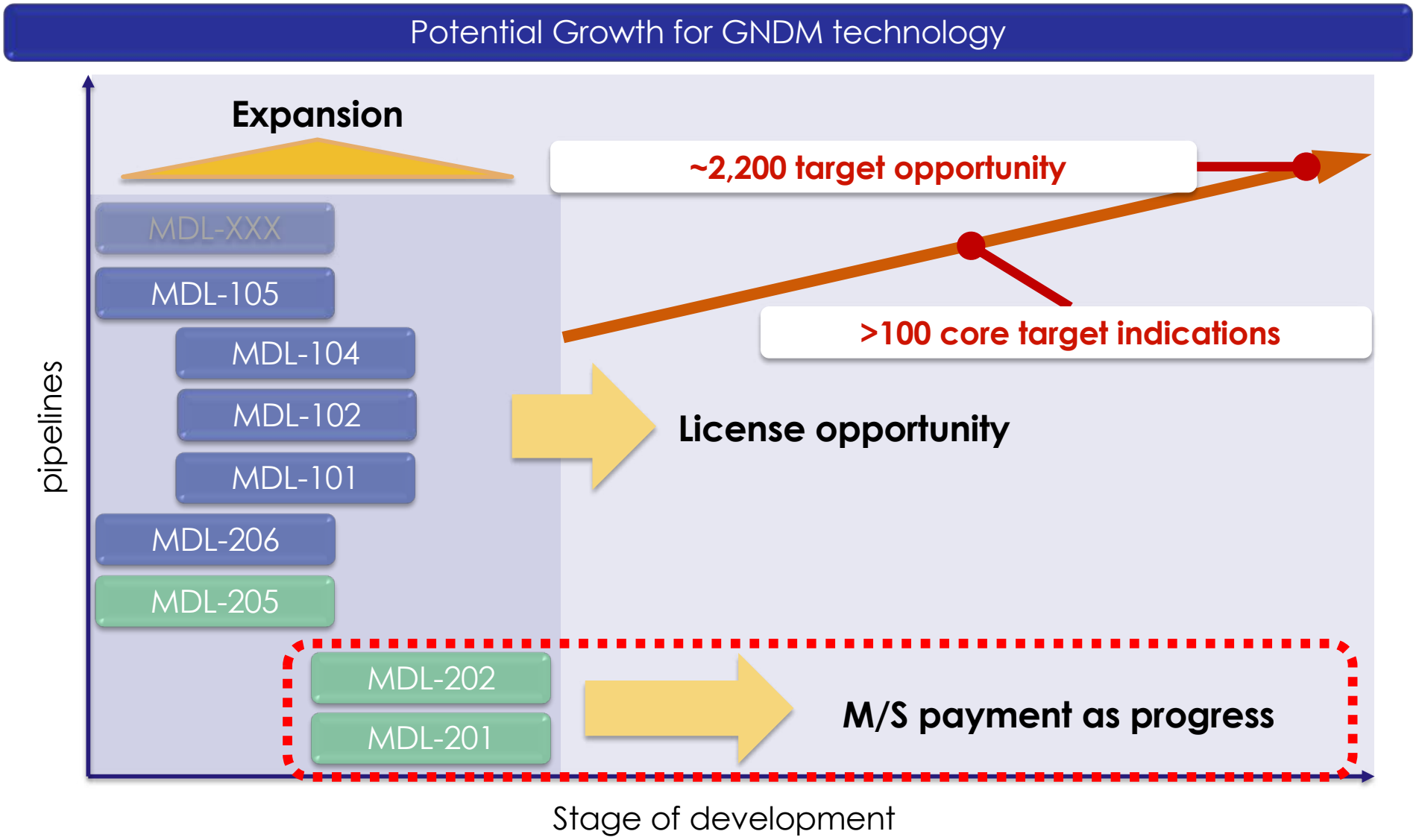
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3. Growth Strategy

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Growth Strategy

opportunity expands two dimensionally

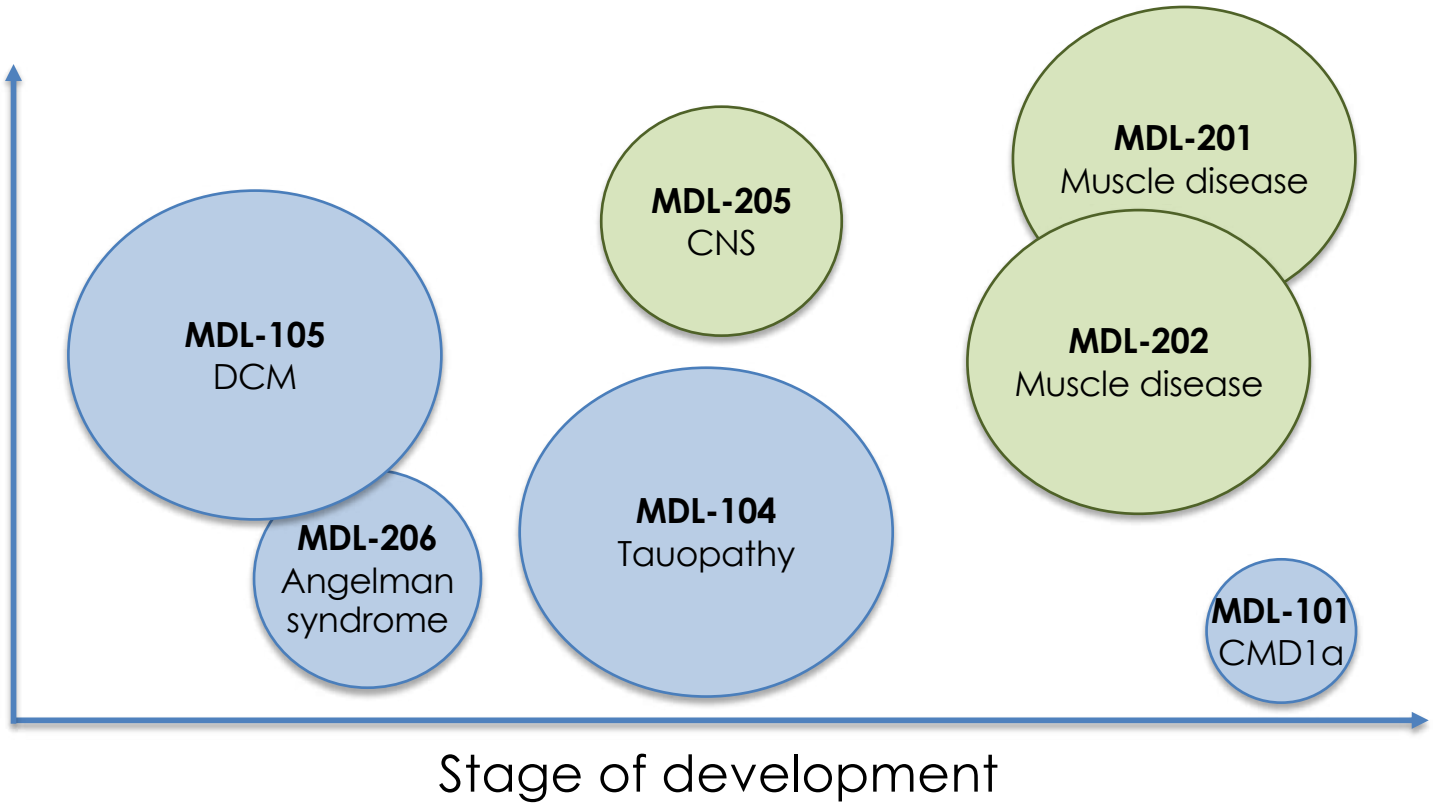


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Large indication programs follow MDL-101 which paves the clinical path

Modalis' pipelines and market size

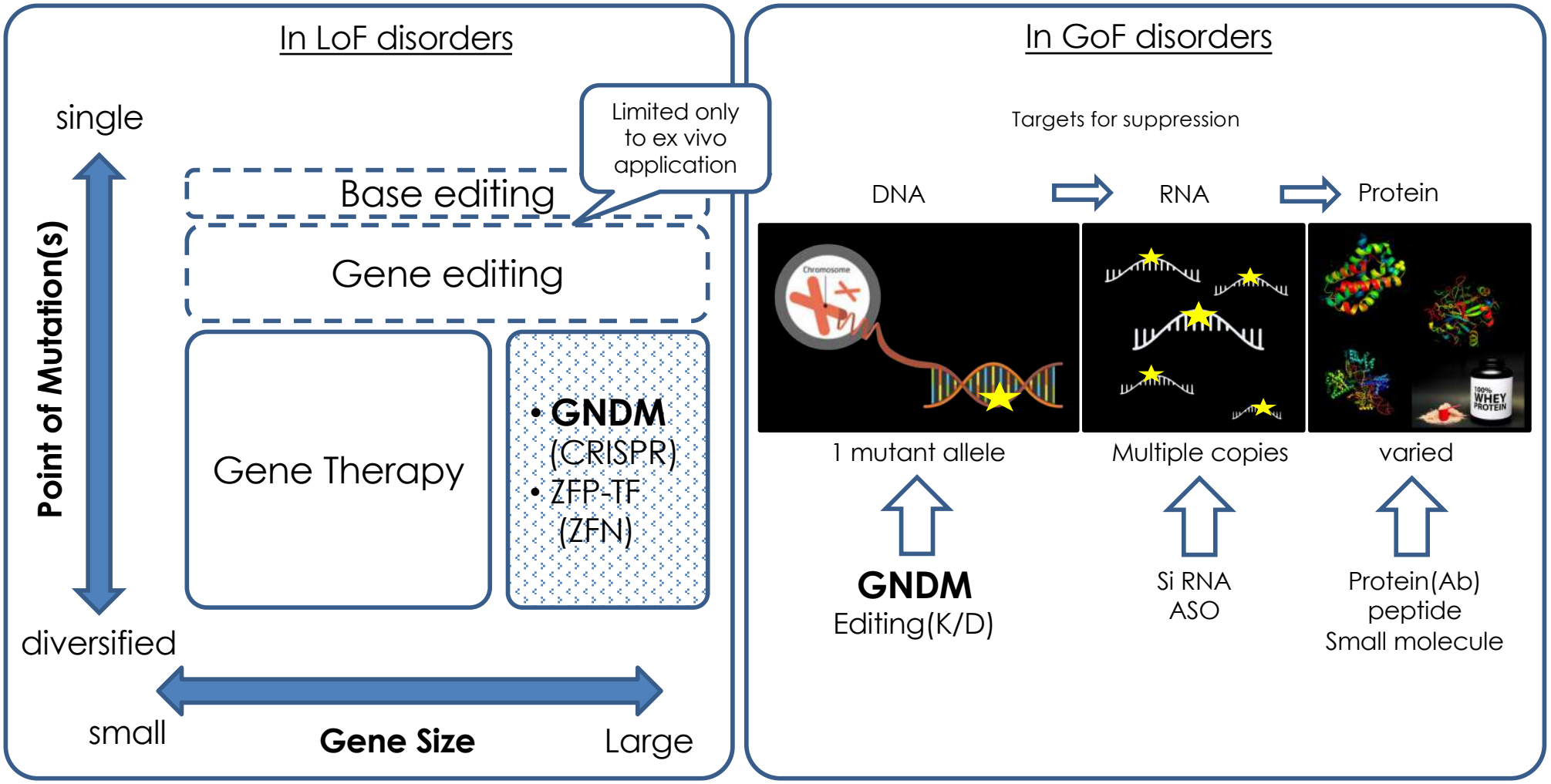


Size of circles represents an image of market size or patient number of each indication

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GNDM is efficient approach both for LoF and GoF mutation

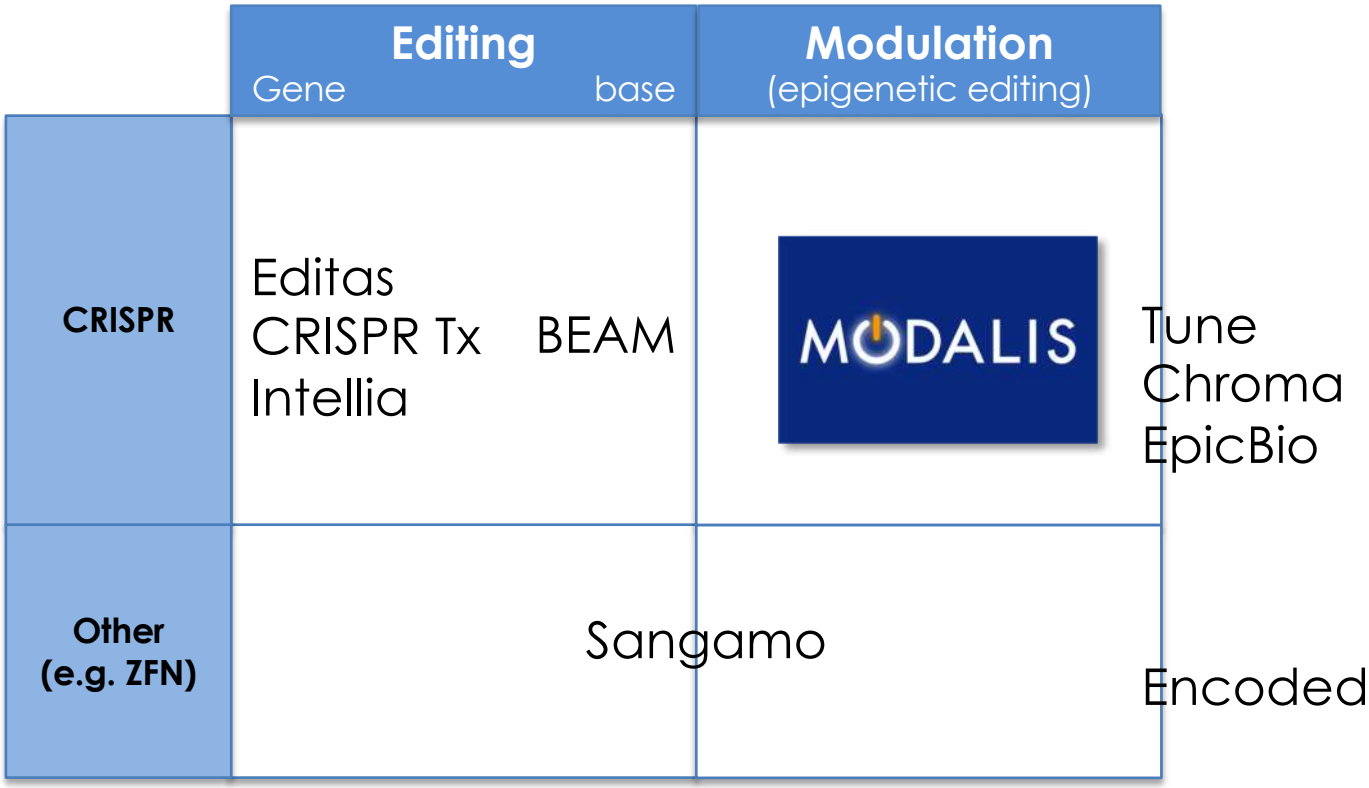


LoF: Loss of function
GoF: Gain of (mal)function

K/D: Knock-down

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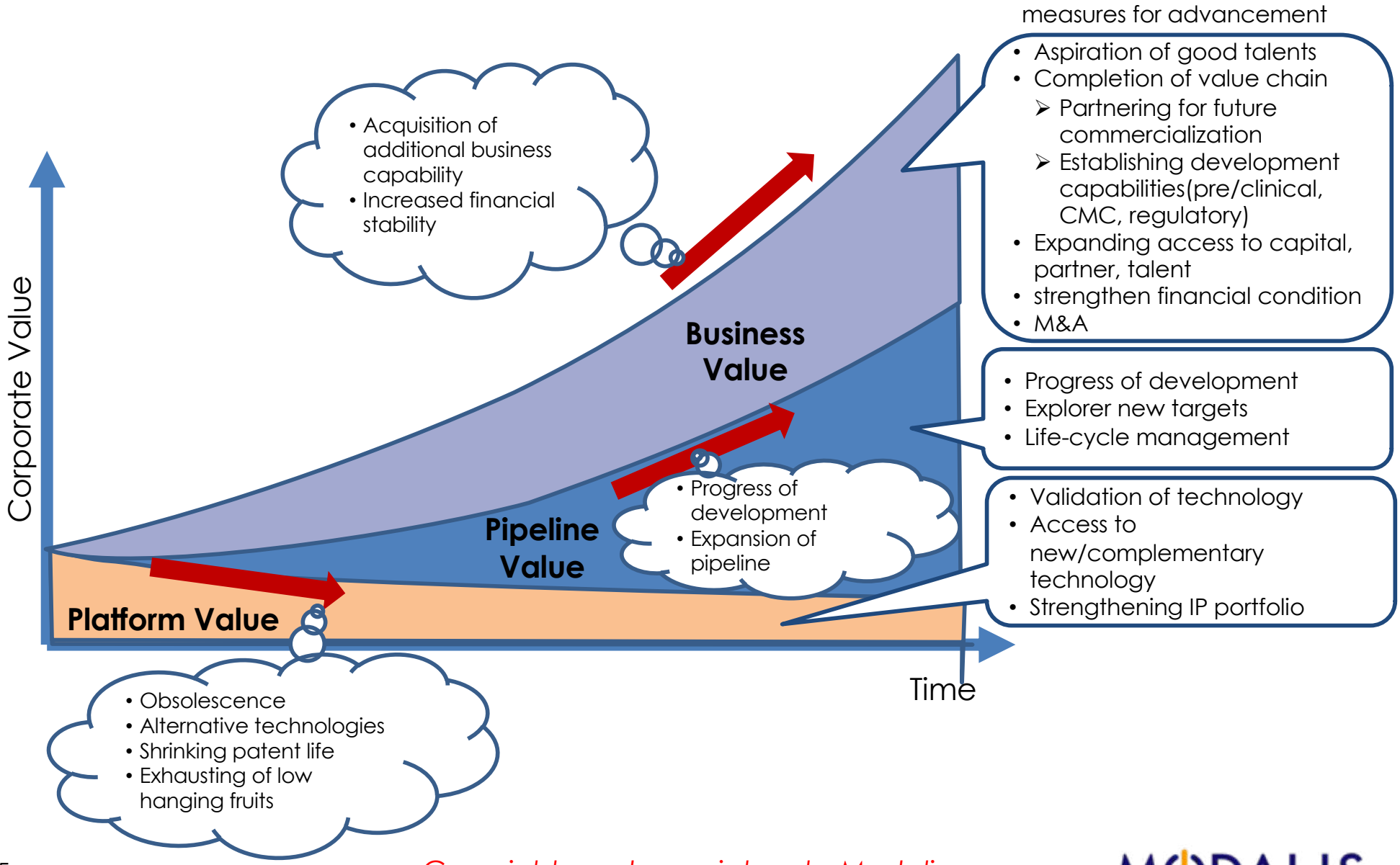
Modalis is uniquely positioned within the CRISPR field



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Composition of Modalis' value and measures for advance



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4. Q & A

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Q1 Why are most of the diseases covered by the pipeline in the muscular and the neuro area? Can you target cancer?

A) AAV (adeno-associated virus) vectors are currently the predominant delivery tool for gene therapy for genetic diseases. This is because of their superiority in terms of delivery efficiency and safety. On the other hand, the flip side of safety is that the virus does not replicate in the delivered cells, so the effect is attenuated each time the cells divide. Thus, the effect will not persist in cells that are actively proliferating.

For this reason, regardless of our technology, potential targets for gene therapy using AAV are limited to organs and tissues with relatively inactive cell proliferation, and as a result, cells such as muscle and central nervous system cells are often targeted, while blood cells and cancer cells are avoided.

Also, in the case of cancer cells, if the vector is not delivered to close to 100% of the cells, the effect will be temporary because growth will occur again from the undelivered cancer cells which will grow.

Some gene and cell therapies target cancer, but in such cases, they do not target the cancer itself, but rather aim to increase cancer-killing cell activity by introducing genes into cancer-killing cells.

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Q2 What is the impact of the rise in US interest rates and yen depreciation of against the US dollar?

A) Rise in U.S. interest rates:
Because we have no debt, we are not directly affected by interest payments.

Yen's depreciation against the US dollar:
Since we have a laboratory in Massachusetts, US, where we conduct R&D, most of our payments are made in US dollars, so if the yen depreciates, our costs in Japanese yen will increase. On the other hand, if revenue is received on a dollar basis, the yen equivalent would increase, which would offset the future effect.

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Q3 During the second quarter, the UTRN patent was granted in the United States. Was it issued?

A) Yes, the patent was issued in October 2022.

As for the flow of patent examination, once a patent is granted, the patent is issued by paying the issue fee. Therefore, if there is an IR for a grant of a patent, we hope that you will understand that the patent will be granted over time.

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Q4 What are the “Key Audit Matters (KAM)” for the current fiscal year?

A) "Key audit matters (KAM)" are audit matters that the auditor determines to be of particular importance of the auditing company and are defined and described in the annual audit report.

The auditor makes a final judgment on the matters at the end of each fiscal year, so we are not in a position to tell what that will be for this year. That of last fiscal year was "Appropriateness of judgment on the necessity of recognition of impairment loss of non-current assets in the company’s gene therapy drug development business". Please refer to the following for details.

March 29, 2022 "Audit Report on Current Consolidated Financial Statements" (bit.ly/edinetE35518)

Generally speaking, non-current assets may be fully or partially impaired if it is determined that they cannot be capitalized according to certain accounting rules. (For your note, as of 3Q 2022, the recorded fixed assets includes tangible fixed asset of 349 million yen, intangible fixed assets of 657 million yen, and liabilities corresponding to intangible assets of -292 million yen).

Since impairment is an accounting matter, there is no actual cash out, and business value and these assets themselves do not disappear even it is applied

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Q & A
(Regarding Notice of transition of MDL-101 to an improved version disclosed on 2022/9/15)

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Q1 What is AAV? And what is the relationship between AAV and CRISPR-GNDM® ?

A) The Company's method of administering therapeutics is envisioned to deliver our proprietary CRISPR-GNDM® in an adeno-associated virus (AAV) vector to target cells in the body .

In other words, AAV is a delivery tool that delivers CRISPR-GNDM® to target cells.

For more information, see the following pages.

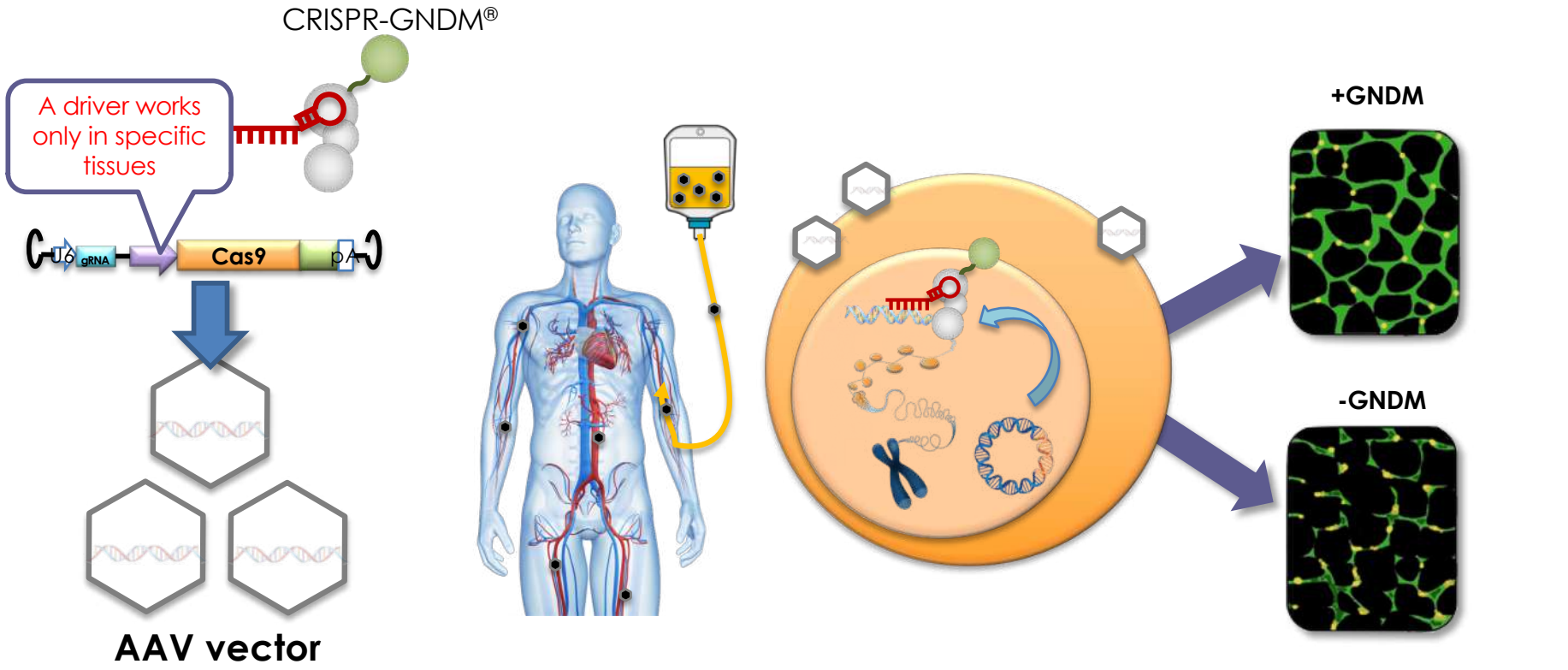
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Delivery of CRISPR-GNDM® to target

Use AAV vector to deliver GNDM to target cell



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Q2 What is the reason for changing the AAV capsid at this time? And What is the advantages of the improved AAV.

A) The success of gene therapy since the 2010s has been largely due to adeno-associated virus (AAV) vectors, which are considered relatively safe and have a low risk as not self-replicating in the body mor inserting into chromosomes after transduction into cells. This was a major safety advantage over the previous generations.
Early gene therapies using AAV were developed initially for applications that requires local administration such as ophthalmology, and the remarkable results of these therapies have led to the expansion of their use to muscle diseases that require systemic high-dose administration.
Currently, the pipelines of various companies for the treatment of Duchenne Muscular Dystrophy (DMD) are reaching to the late-stage clinical trials and regulatory submissions, and the results of clinical trials have led to discussions of various issues associated with large systemic dosing. To tackle these problems, academia and the pharmaceutical industry have developed improved AAV vectors with enhanced tropism to target tissues such as muscle, and several recently developed improved vectors have been confirmed to have more than 10-fold improved tropism and other characteristics compared to the conventional type. These profiles are expected to have a disruptive impact in terms of reduced toxicity in off-target organs such as the liver and lower manufacturing costs due to lower dosage requirements.
Under these circumstances, we have come to believe that the significance of continuing development with the current technology is largely lost and that ethical issues arise in administering products developed based on the old technology, which has concerns, when there are new technologies with higher safety standards.
We believe that products developed based on new technologies are superior in terms of efficacy, safety, manufacturing cost, and probability of success, and that although this may temporarily delay development in the short term, it will have a positive impact in the long term by increasing product and corporate value.

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Q3 Will modifying the MDL-101 AAV render the previous R&D effort useless?

A) No.

The GNDM molecule to be mounted on the improved version AAV capsid will be basically the same molecule as before, so the drug efficacy and safety data obtained to date will be extrapolatable.

Since GMP(Good Manufacturing Practice) manufacturing has not yet started, some process development will have to be redone to accommodate the new molecule, but we believe that this will require only minimal backtracking.

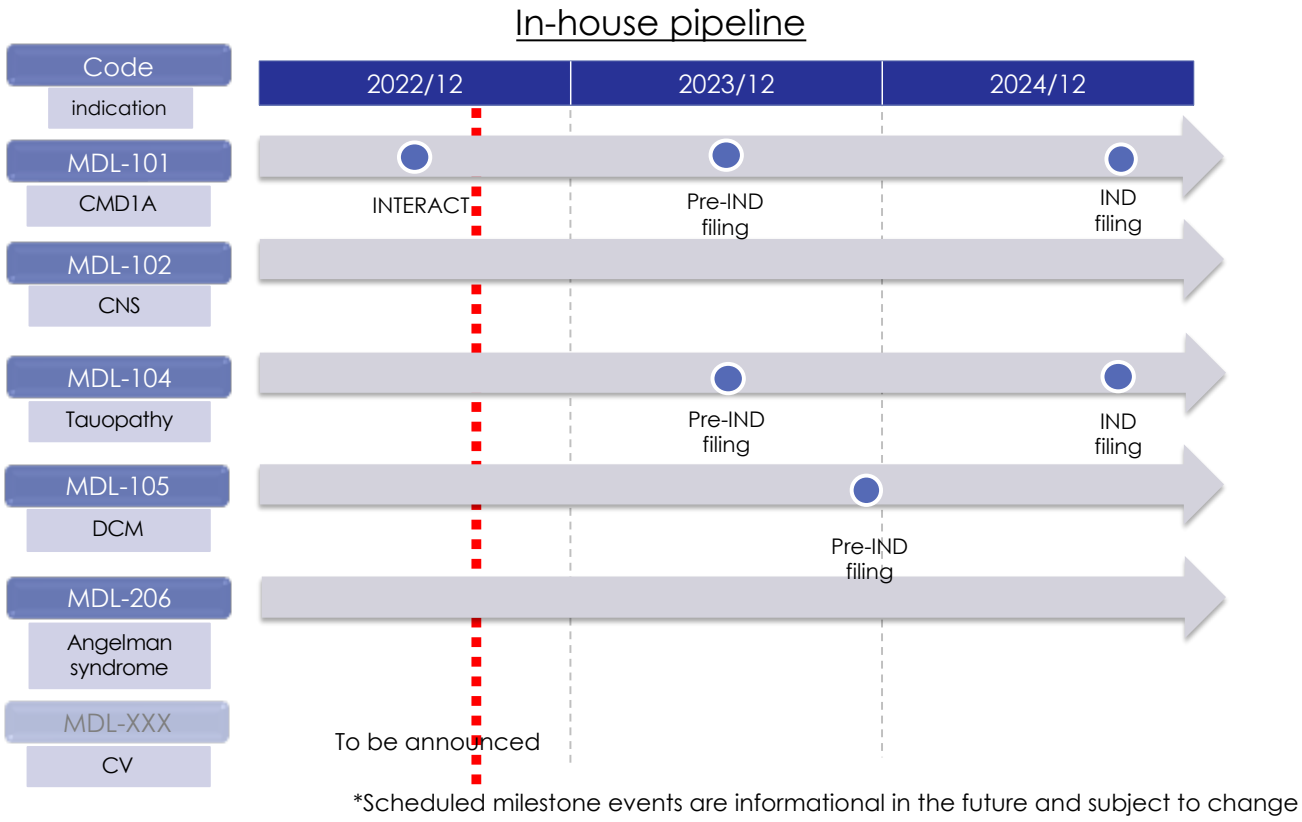
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Q4 Does this affect the license-out of MDL-101?

A) There may be some potential impact on the partnering schedule, but on the other hand, we believe that the improved MDL-101 configuration will be more strongly supported by the partners, so we believe that the results will be positive.



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Q5 Why company put higher priority on MDL-104, which has been a late starter?

A) Pipelines that require systemic administration, such as MDL-101, will be affected by the transition to improved AAV for the reasons described in Q1, but molecules that are intended for local administration to the CNS, such as MDL-104, MDL-205, and MDL-206, do not have the same risk.
When considering risk diversification of our pipeline portfolio, we believe it is reasonable to develop MDL-104 in parallel with MDL-101, as both have a different risk orientation.
Advantages of MDL-104 include: 1) local administration avoids systemic toxicity, 2) also local administration allows for much lower manufacturing of the clinically required dose, and 3) availability of humanized Tau mice that allows for direct estimation of clinical doses by mouse studies.
For the above and other reasons, the development timeline of MDL-104 could be shortened and becomes comparable to MDL-101 which will undergo improvements. As a result, we believe it makes sense to raise the priority of MDL-104

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Q6 Will Company continue to disclose each revision to the development plan?

A) It is our policy to disclose any significant changes in development plans through press releases or other means. In the case of ordinary revisions, our policy is to disclose such revisions in each quarter and at other times.

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