English translation for reference purposes only

FY2022 1Q
Financial Results



In case of any discrepancy,
the Japanese version shall prevail

MODALIS

Modalis therapeutics Corporation

(TSE : 4883)

May 9, 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

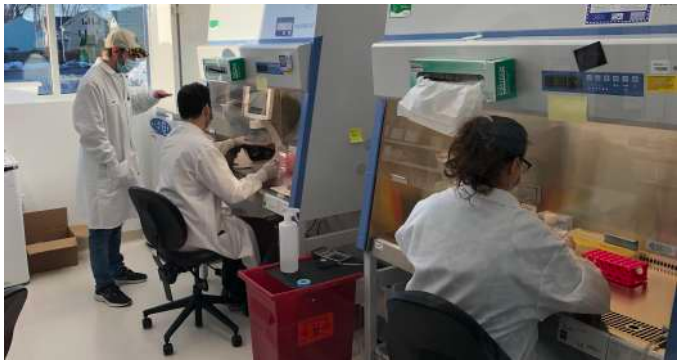












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Corporate Philosophy

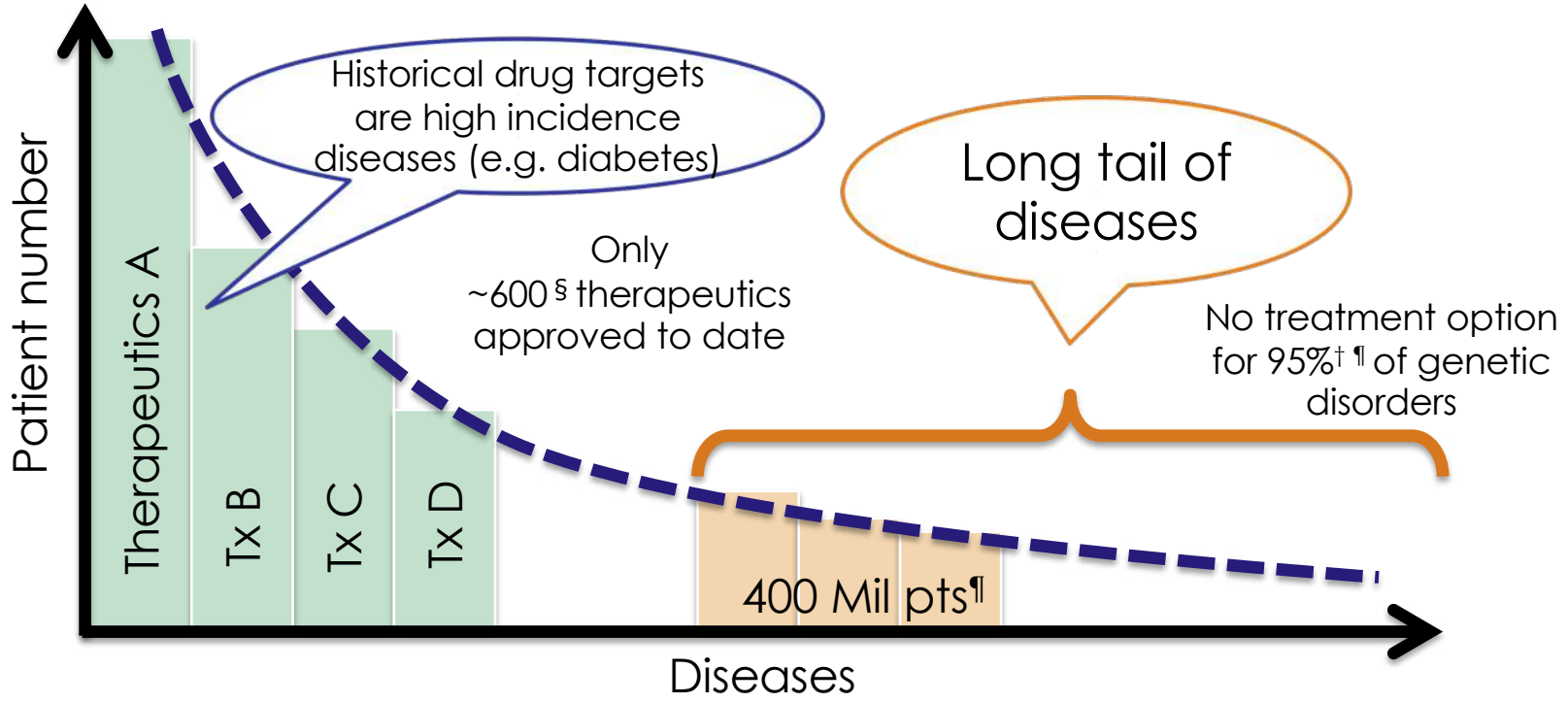
Every life deserves attention

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)

	FY2021 1 Q (A)	FY2022 1 Q (B)	(B)－(A)
Operating revenue	0	40	40
Operating expenses	253	507	254
R&D	184	442	258
SGA	69	65	(4)
Operating income	(252)	(466)	(214)
Ordinary income	(245)	(443)	(198)
Profit	201	(438)	(639)

Operating revenue

・Earning collaborative R&D milestone income

Operating expenses

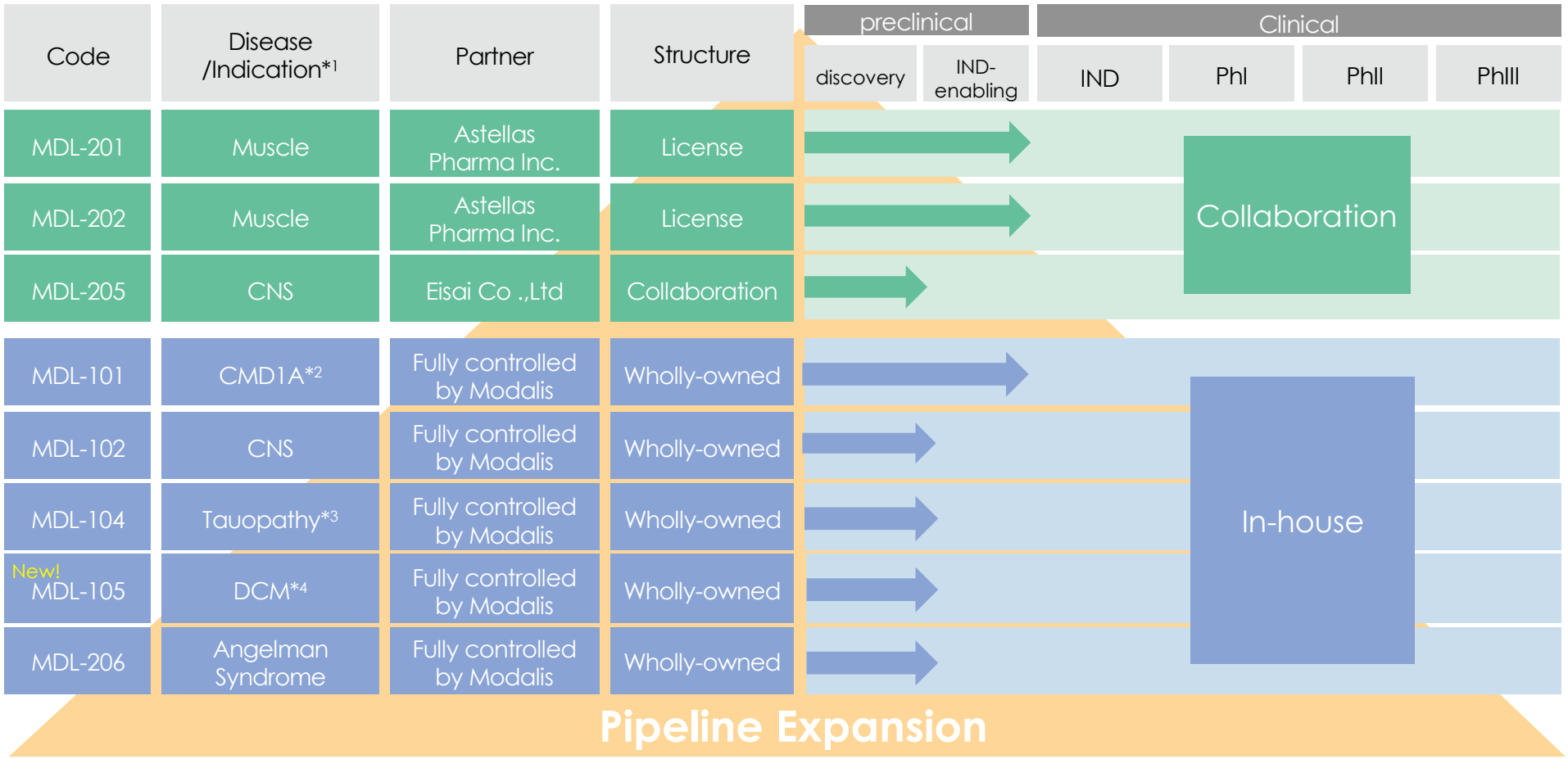
・R&D increased year on year as business progressed(primarily in personnel expenses, research material expenses, rent fee and expenses for conducting clinical trials of MDL-101)

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 1Q (B)	(B) – (A)
Current assets	5,067	4,573	(494)
Cash & deposits	4,936	4,404	(532)
Non-current assets	1,002	1,051	49
Property, plant and equipment	223	295	72
Right to use patent	704	689	(15)
Total assets	6,069	5,624	(445)
Current liabilities	181	171	(10)
Non-current liabilities	339	327	(12)
Total liabilities	520	498	(22)
Total net assets	5,549	5,126	(423)
Total liabilities and net assets	6,069	5,624	(445)
Capital adequacy ratio	91.4%	91.2%	

- 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 4Q/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
  - Continues 2nd NHP study
  - Prep for INTERACT meeting and the meeting was accepted by FDA
  - Further optimization of GNDM cassette and locking in final construct (codon usage, cassette orientation, etc.)
  - Hired Director, Translational Research
- Next steps:
  - INTERACT meeting (Jul)
  - Filing pre-IND meeting (by end 2022)
  - Continue IND enabling GLP tox and PK/PD

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Summary of other R&D activity

- Other pipelines
  - Add MDL-105 as a new pipeline
    - Targeting Titin gene to treat DCM
  - Achieved research milestone of MDL-205 with Eisai and agreed to extend research collaboration period

- Other
  - 6 articles will be presented at ASGCT*(May 16 - 19th @D.C.)

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

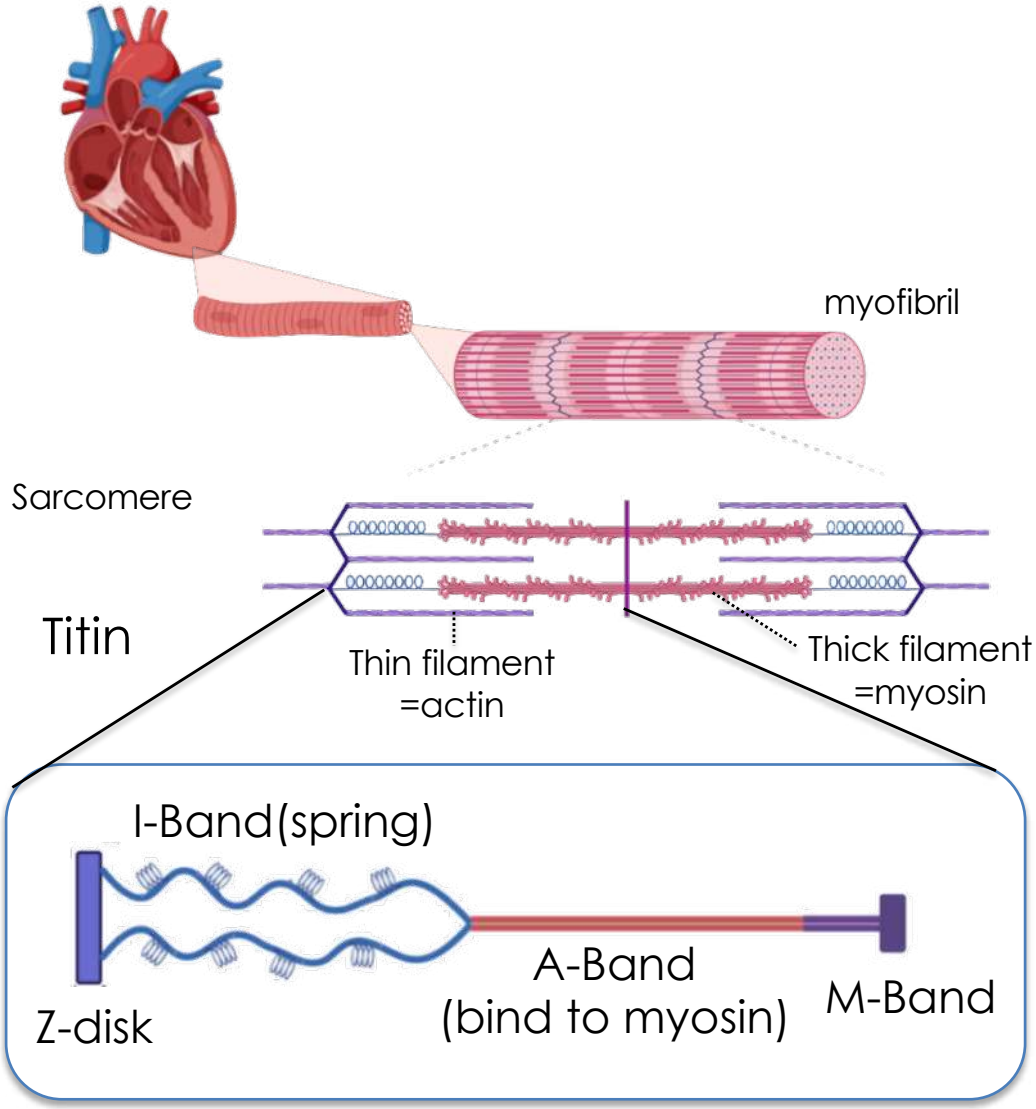
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TTN is the largest human protein - which is too large for AAV packaging

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)

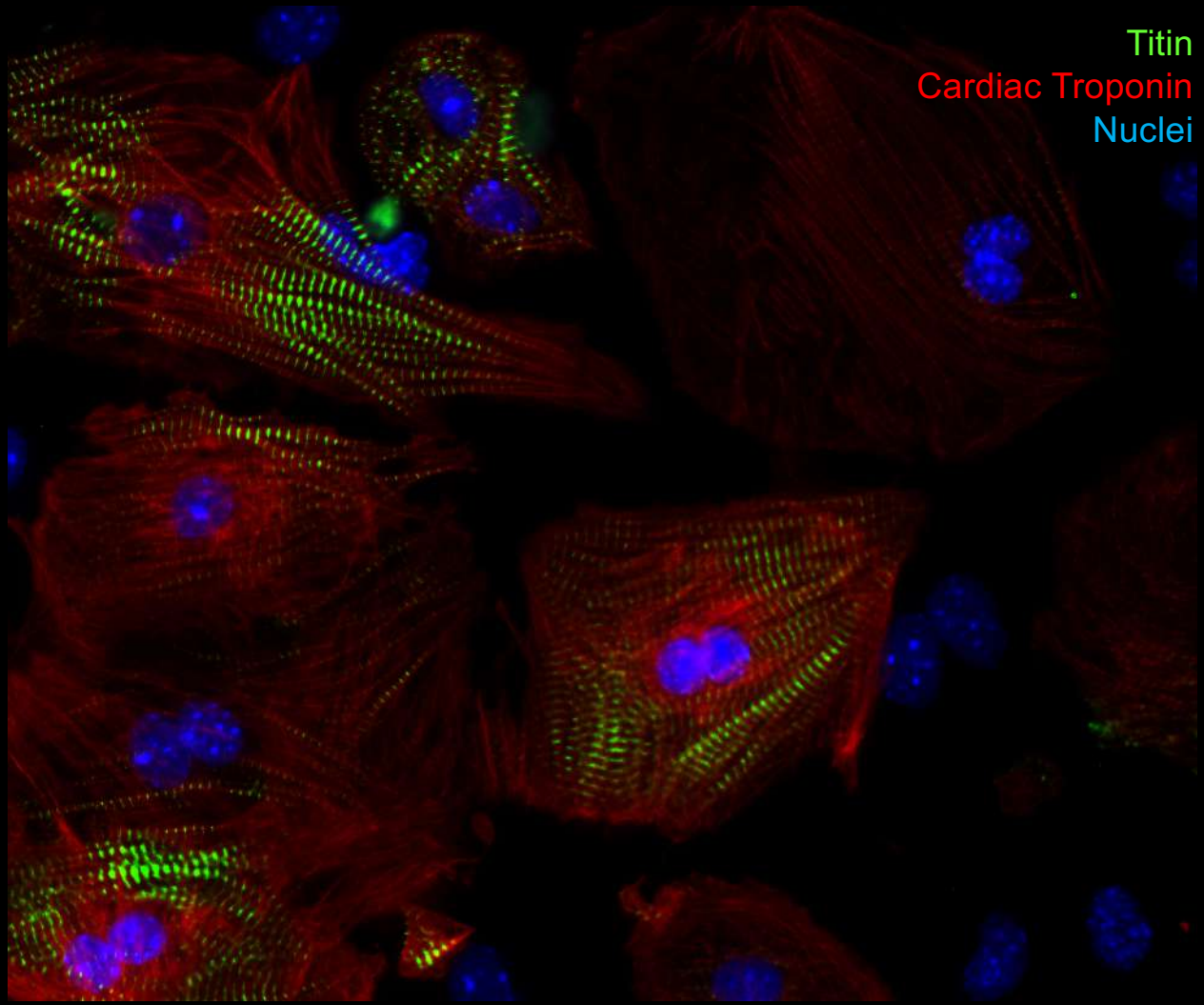


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Ttn protein

ex vivo cardiomyocytes, Day 10



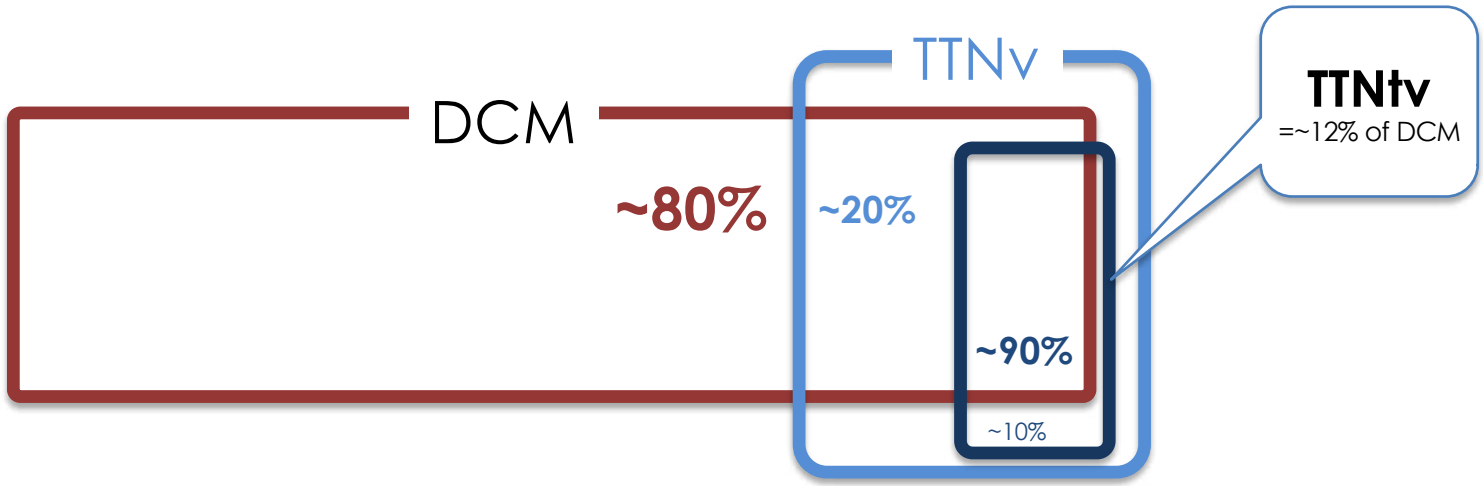


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TTNtv are highly penetrant in DCM patients

- 87.5% (7/8) in patients > 40 yr (PMID: 33941202)
- >95% (n=37) in patients > 40 yr (PMID: 22335739)
- Important to identify TTNtv carriers prior to DCM onset

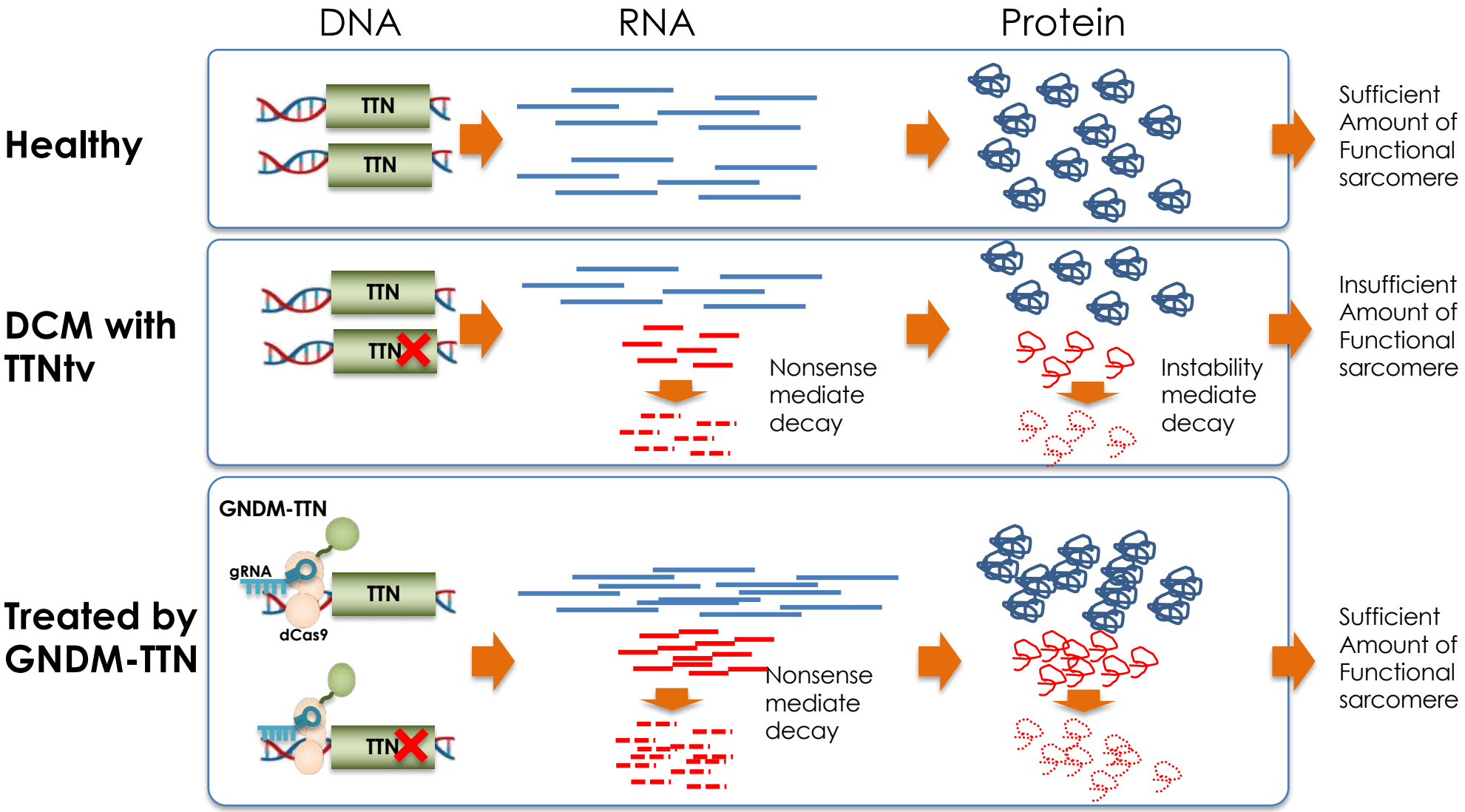


TTNtv: TTN truncating variant

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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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6 papers to be presented at ASGCT

- Novel single AAV vector treatment for Congenital Muscular Dystrophy type 1A (MDC1A) using CRISPR-GNDM® technology
- NGS based evaluation of AAV genome integrity for improved production and function
- Utilizing CRISPR-GNDM® mediated gene activation of the extra-large gene titin for the treatment of dilated cardiomyopathy and other titinopathies
- Blocking SNHG14/UBE3A-ATS lncRNA Transcription with Dead Cas9 (CRISPR- GNDM®) Can Un-Silence Paternal UBE3A in an Angelman Syndrome Mouse Model
- Evaluation of Cas9 mediated immune response effect on long term transgene expression in WT mice and NHPs without immune suppression
- Robust suppression of Tau by CRISPR-GNDM® system for treatment of Tauopathies

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Other updates on business

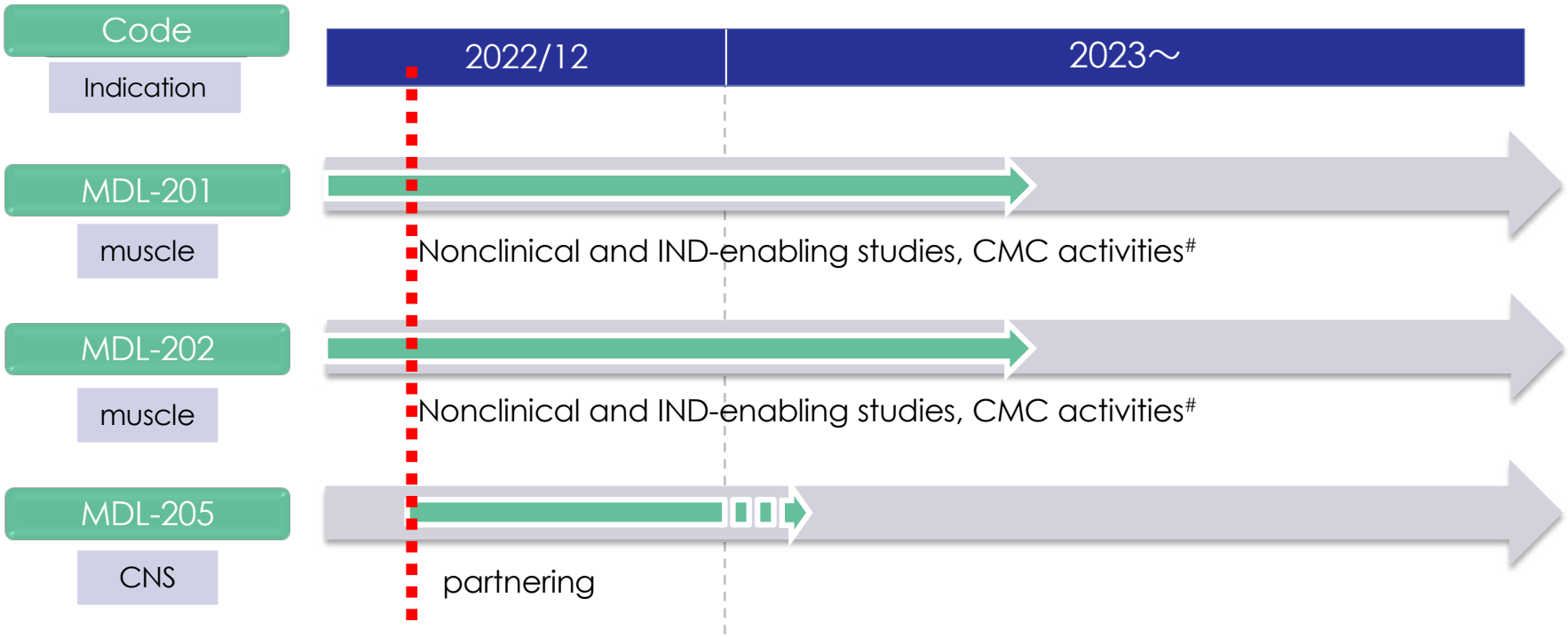
- Progress on intellectual property
  - CRISPR patent ruling on the second interference with UC Berkeley favors Broad Institute (Feb)
  - A patent co-filed with Astellas titled 'Method for treating muscular dystrophy by targeting utrophin gene' was granted in Japan (May)

- Progress on 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
MDL-205 has achieved MS and collaboration is extended

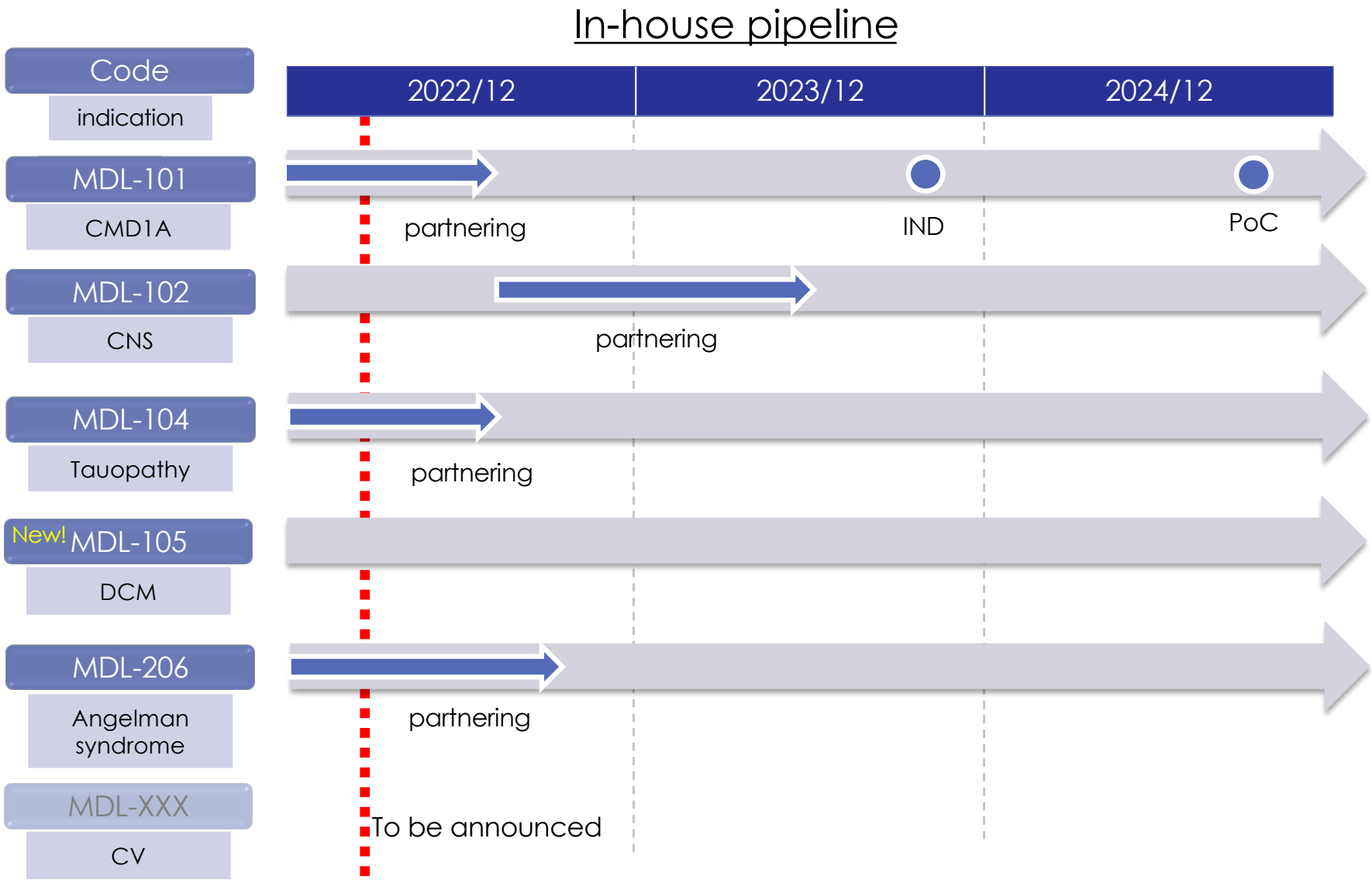
Collaboration pipeline



*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



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

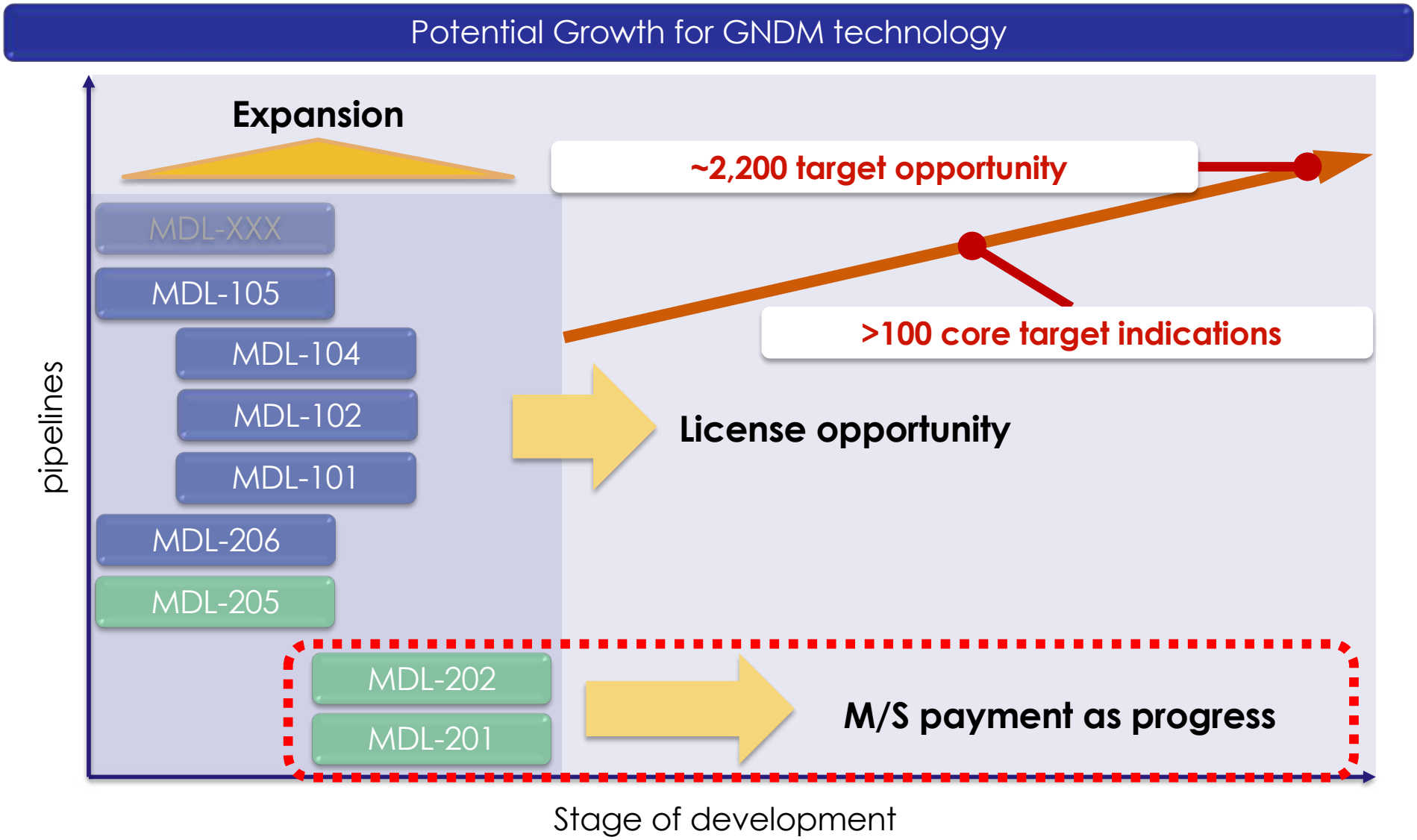
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3. Growth Strategy

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Growth Strategy

opportunity expands two dimensionally

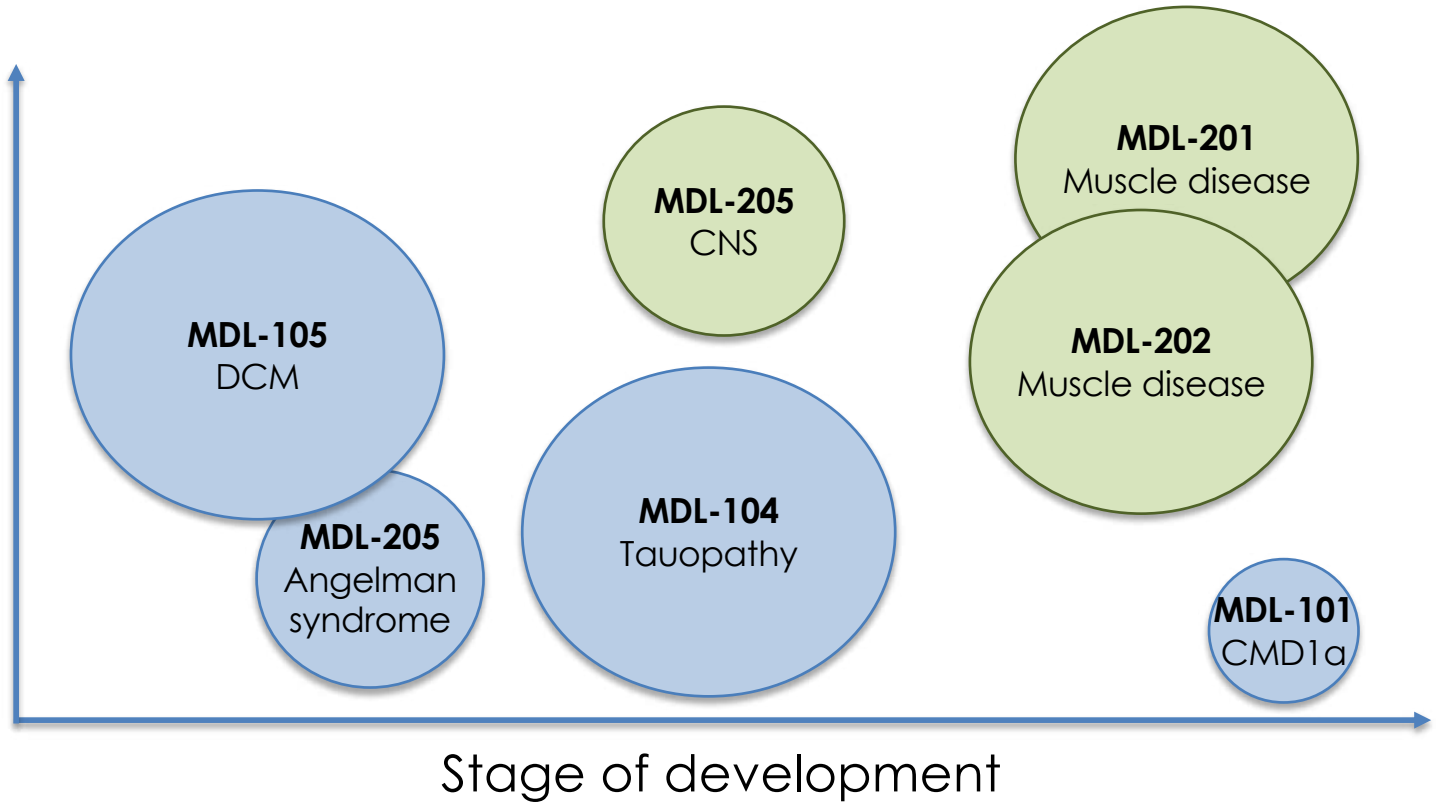


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Large indication programs follow MDL-101 which paves the clinical path

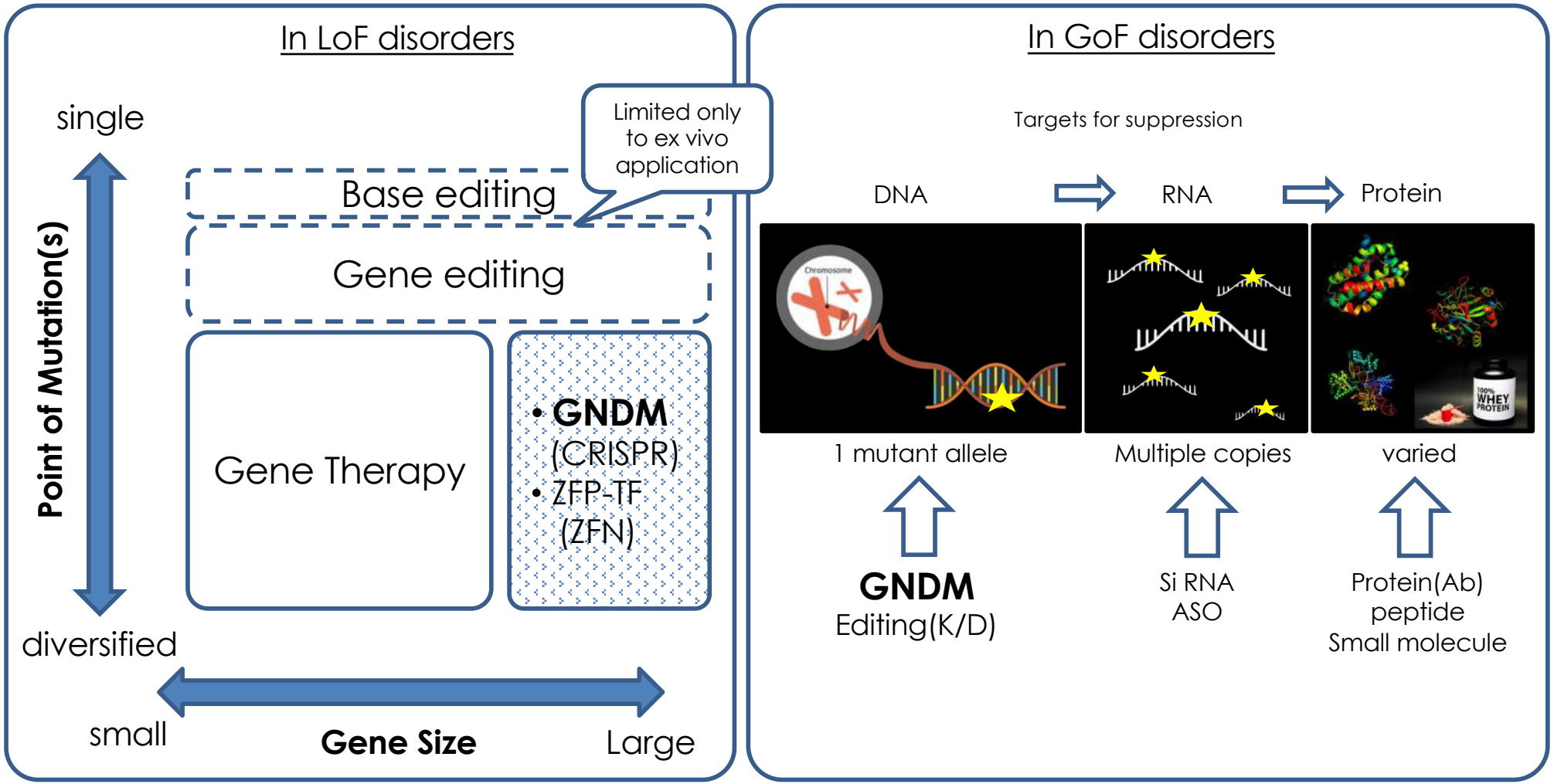
Modalis' pipelines and market size



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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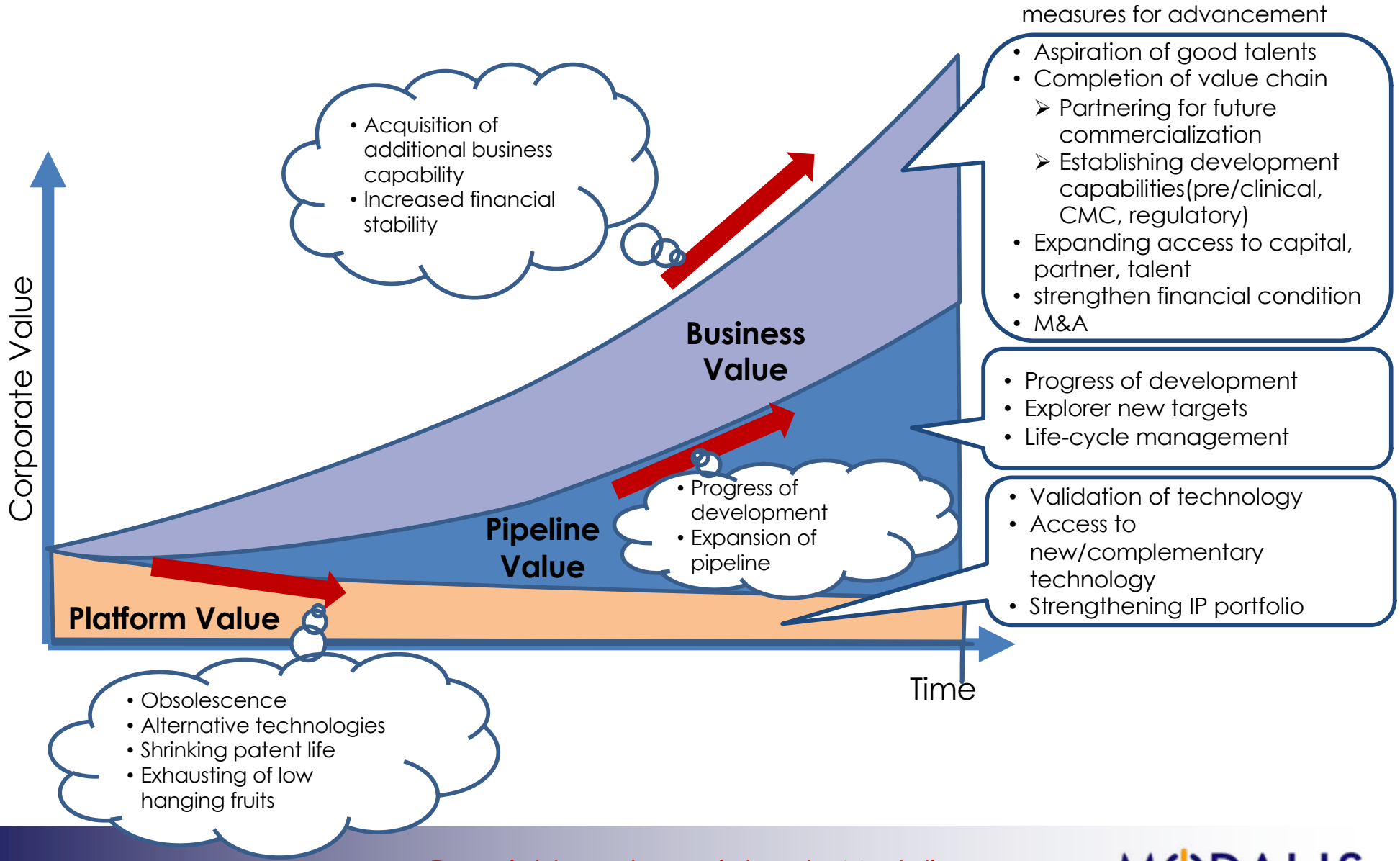
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Modalis is uniquely positioned within the CRISPR field

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

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Composition of Modalis' value and measures for advance



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4. Q & A

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Q1 What is the INTERACT meeting?

A) **IN**itial **T**argeted **E**ngagement for **R**egulatory **A**dvice on **C**BER produc**T**s (INTERACT) meeting is an informal non-binding consultation with the Center for Biologics Evaluation and Research (CBER) at FDA.
This in an opportunity for a sponsor (developer) that develops a cutting-edge product, to obtain consultation on innovative investigational products associated with unique challenges.
Considering recent low acceptance rate of the meeting, we believe our product is innovative enough to get attention of FDA.
The goal of the meeting for us is to clarify a path toward the clinic of not just MDL-101 but whole products based on CRISPR-GNDM® technology.

For more info, please visit FDA site
https://www.fda.gov/vaccines-blood-biologics/industry-biologics/interact-meetings

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Q2 What does the presentation at ASGCT mean to Modalis?

A) The ASGCT is the largest gene therapy-related scientific organization in the world with approximately 5,000 members.
Last year's annual meeting was held virtually but reportedly attended by approximately 6,800 people.
Every year, not only cutting-edge scientific findings are presented, but also pharmaceutical and regulatory aspects are discussed.
We believe that our presentation at this annual meeting is not only to showcase our progress, but also to share our knowledge with the academic community as part of our responsibility as a leader in Epigenetic Editing field.

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Q3 As the schedule of MDL-205 change, any push back in development?

A) MDL-205, which is being researched in collaboration with Eisai, is progressing well as evidenced by the milestone recognition recorded in 1Q. With the aim of further improving the PoS of the product, both parties have agreed to extend the collaboration period.

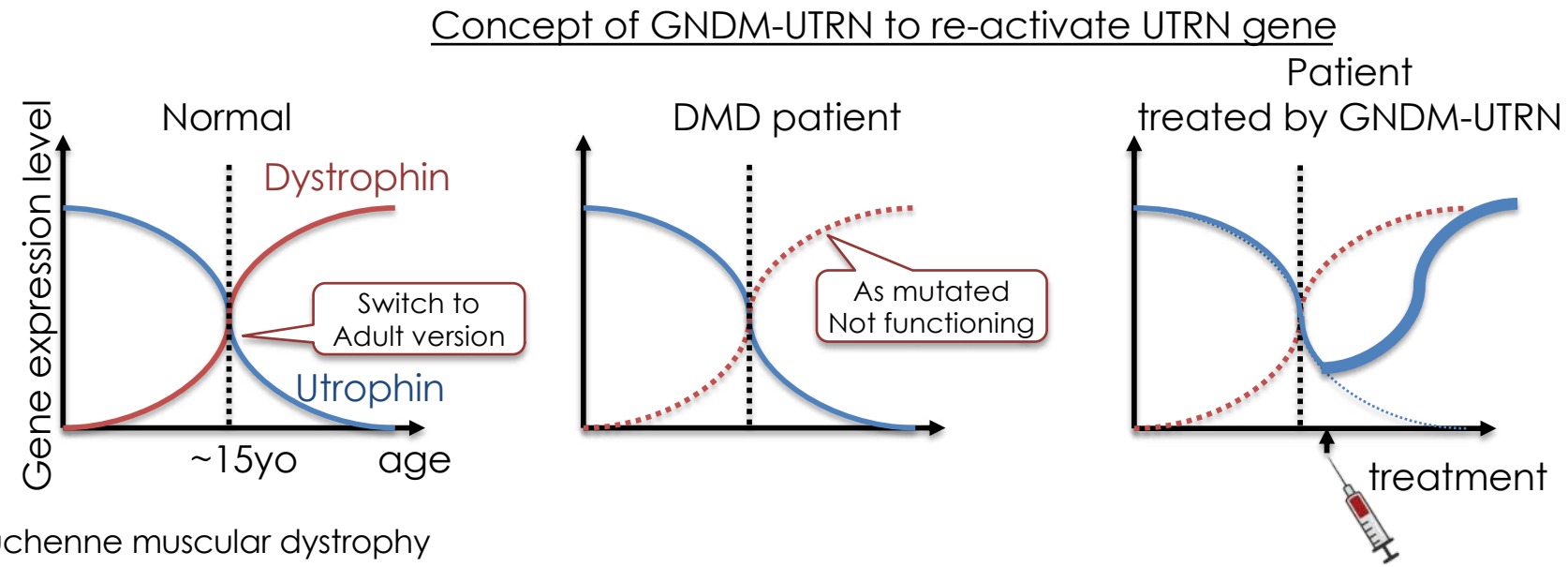
Due to agreement with Eisai, we are unable to disclose the additional extension period or any other status of the collaboration.

PoS: Probability of Success

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Q4 Can you elaborate a little more about the Utrophin patent?

A) This patent is for a therapeutic concept and molecules that uses GNDM technology to treat DMD. The treatment is based on a mechanism that supplements mis-functioning Dystrophin gene in patients by upregulating the expression of the fetal/juvenile form of the gene, Utrophin. The cDNA of the Dystrophin gene is 14 kbp, too large to be carried in an AAV vector, and this is a target that takes advantage of the GNDM, which is gene size agnostic. No disclosure is made for the collaboration program as to which patents correspond to which programs.



DMD: Duchenne muscular dystrophy

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Q5 How does Broad's victory in the U.S. patent interferences proceeding affect Modalis' business?

A) The U.S. Patent Office (USPTO) had been conducting an interferences (#106,115) between Broad Institutes (Broad) and the University of California, the University of Vienna, and Dr. Emmanuelle Charpentier (collectively, CVC), challenging the prior inventions in the U.S. On February 28, 2022, the USPTO Board of Appeals (PTAB) ruled that Broad's rights were not effectively interfered with in this interferences. On February 28, 2022, the PTAB ruled in favor of Broad, holding that there was no interference in fact with the interferences. The PTAB also rejected the CVC's argument in No. 106,048, which was also the subject of an earlier interferences proceeding.

This indicates that Broad's patent application for genome editing technology in eukaryotes, including humans, is valid in the United States.

As a result, the CRISPR foundational patents, which we have a right through the license agreement with Editas, will continue to be valid in our business areas and will continue to secure our business.

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Q6 Is there any impact of the draft guidance to gene editing product published by FDA in Mar?

A) This Draft Guidance reflects the FDA's findings in response to the recent progress of several genome-editing therapeutics to the clinical stage and is intended for companies primarily in preclinical stage.
The products we are developing are considered to fall under this category in a broad sense and we believe that the clarification of the hurdles to the start of clinical trials in this manner will make it easier for developers, including us, to plan preclinical strategies and to develop products.
We do not see any new hurdles in this guideline that we did not anticipate.

For more info, please visit FDA site.
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/human-gene-therapy-products-incorporating-human-genome-editing

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Q7 Is it fair to assume that the market size for diseases with small patient numbers is small?

A) The market size of rare diseases is estimated by multiplying the number of patients by the drug price. However, since there are no existing drugs that can be used as a reference, it is hard to estimate drug. In addition, drug prices tend to increase inversely correlated with the number of patients, and therefore, the number of patients and the market size are not necessarily correlated.

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