English translation for reference purposes only

FY2021 Corporate Presentation

The switch  is the Key

(TSE4883) Modalis therapeutics Corporation

Corporate and Technology summary

In case of any discrepancy, the Japanese version shall prevail

February 12 , 2021

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1. Corporate Overview

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Corporate Overview(As of end December 2020)

Modalis Therapeutics is a biotech company to develop CRISPR-based gene therapies

Name	Modalis Therapeutics Corporation (Ticker symbol: 4883)
Foundation	Jan 2016
President CEO	Haru Morita
HQs	3-11-5 Nihonbashi-Honcho, Nihonbashi-Lifescience-Bldg.2 7F Chuo-ku, Tokyo 103-0023 Japan
US subsidiary	Modalis Therapeutics Inc. (51 Moulton st. Cambridge MA)
Business	Drug Development
Common stock	2,707,320 thousand yen
Outstanding share	28,515,600 common stock
Number of employee	22 (including 8 PhD) (4 in Japan, 18 in US)

Date	History
Jan 2016	Founded in Tokyo as EdiGENE Corporation
Apr 2016	Established 100% owned US subsidiary EdiGENE Inc. (Now Modalis Therapeutics Inc.)
Apr 2017	Entered into research collaboration with **Astellas** Pharma Inc.
Dec 2017	Series A round from **FUJIFILM** Corporation and 8 other companies through third-party allotment
Dec 2017	Expanded research collaboration with **Astellas**
Jan 2019	HQs moved to new facility
Mar 2019	Established license agreement on a genetic disorder with **Astellas** Pharma Inc.
Mar 2019	Cambridge Lab moved to the new facility
Aug 2019	Company name changed to Modalis Therapeutics
Sep 2019	Established 2nd license agreement on a genetic disorder with **Astellas** Pharma Inc.
Nov 2019	Entered into research collaboration with **Eisai** Inc.
Apr 2020	Entered into a license agreement with **Editas Medicine**, Inc to obtain access to foundational CRISPR IP.
Aug 2020	Listing on Mothers, Tokyo Stock Exchange (Ticker symbol: 4883)

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Modalis' 6 strengths

In the right time, the right place, with the powerful technology and the best brightest

GTx and Gene Editing, the "next big thing"

- **Expected Strong market growth** after the dawn period
- Huge opportunities of **100s monogenic disorders**

Leading non-cleaving CRISPR company

- The **precision** of gene editing but even **safer** as it doesn't cut DNA
- **unique IP position** with access to CRISPR foundational IP

Diversified and scalable pipelines

- Solid discovery process and predictable clinical outcome
- **5** on-going collaboration pipelines with large pharma companies and **3** internal pipelines

Pharma Partnerships

- Collaboration with **3** multinational pharma companies
- Total milestone of the 2 out license programs worth **>$350M**

Hybrid pipeline model

- Hybrid of earlier cash flow from **collaboration pipeline** and upside potential from **Internal pipeline**
- Came to **ordinary profits positive** in FY2019

Strong team

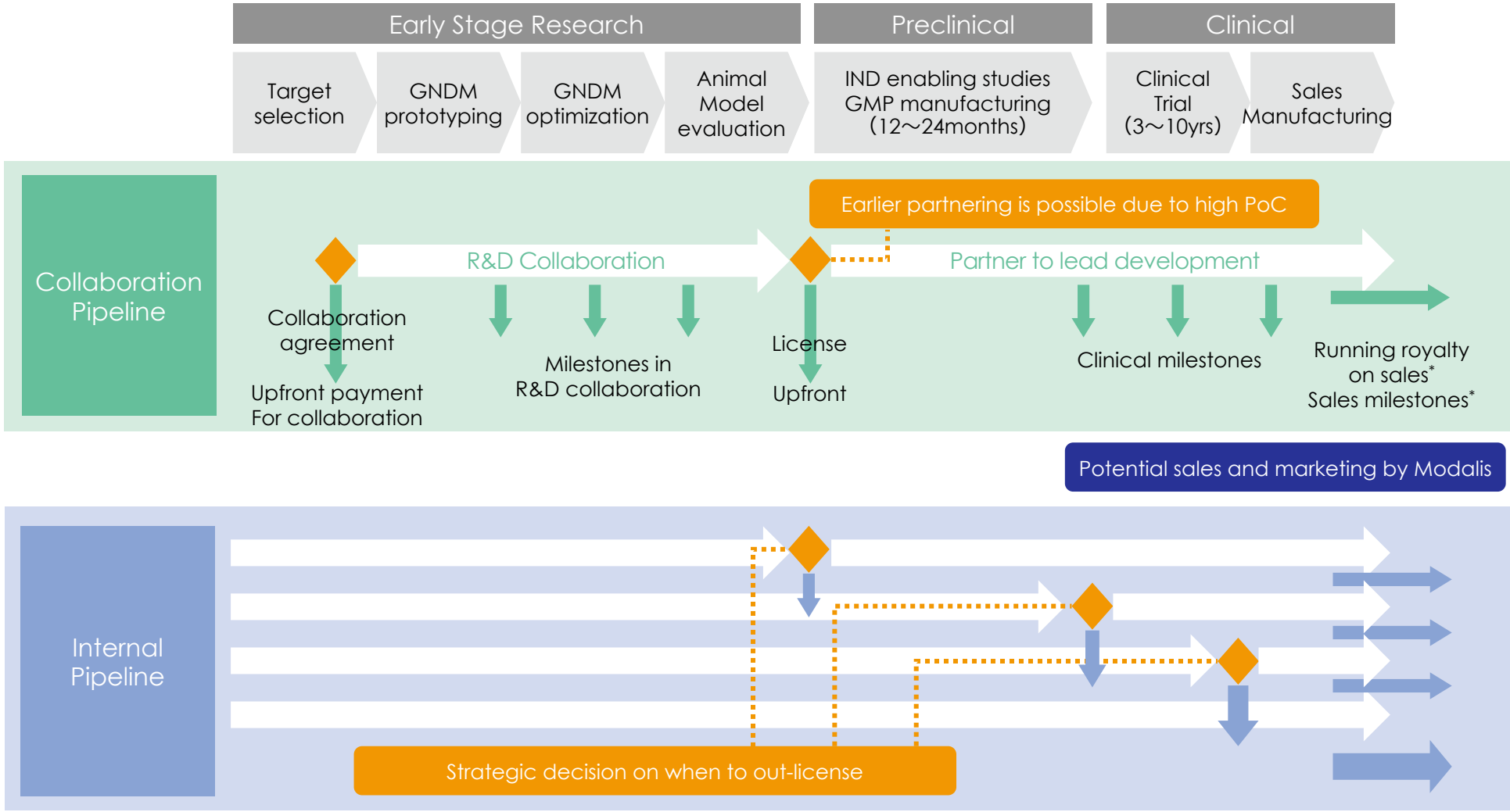
- Combination of seasoned management and talented scientists from all over the world

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Business Model

Hybrid of own pipeline and collaboration pipeline



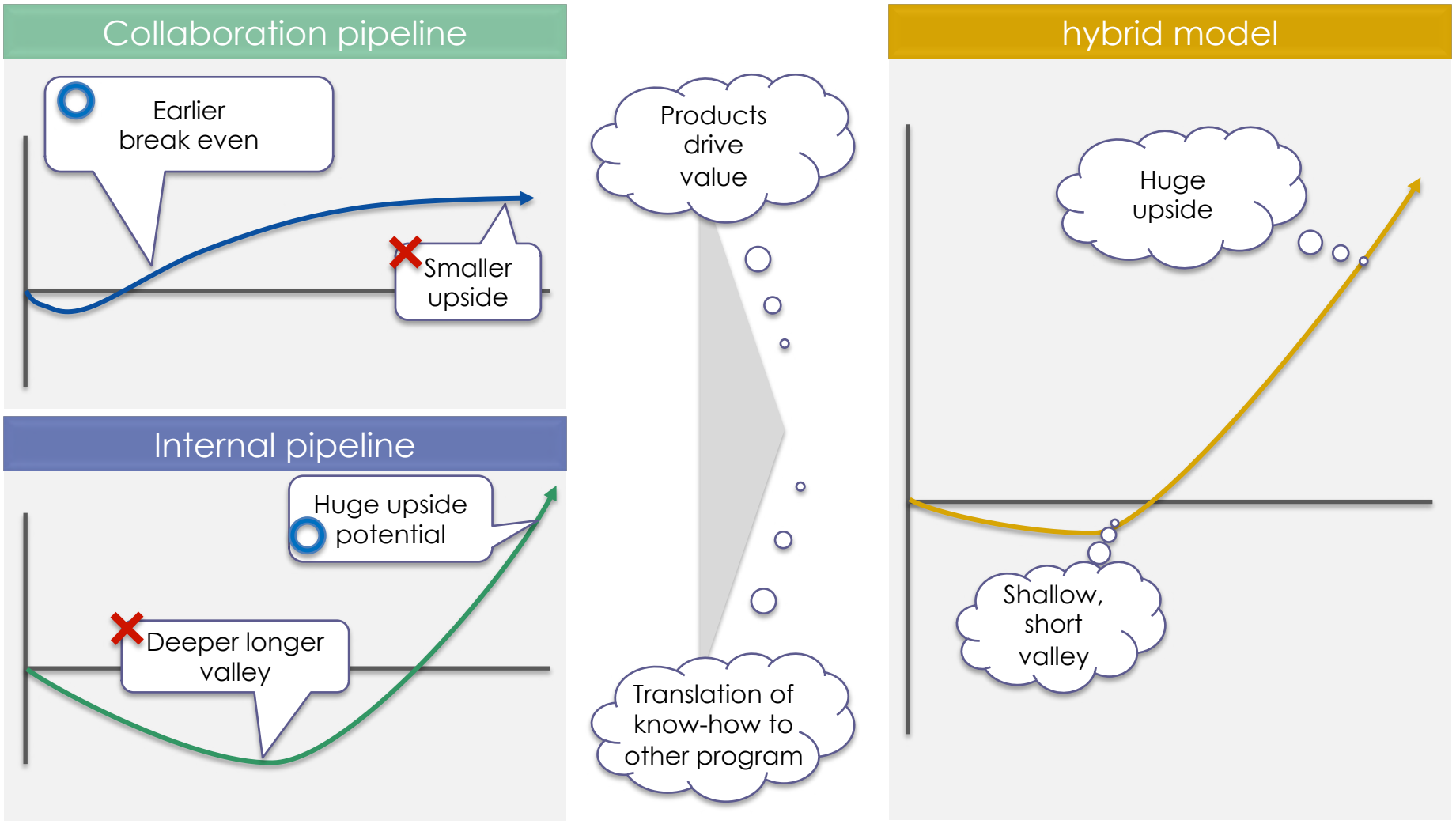
* future plan

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Modalis is pursuing a hybrid model

Combination of upside from internal pipelines and earlier cash stream from collaboration pipelines



* The above is only an image and does not suggest or guarantee our future performance.

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Risk - profit share model

While collaboration model brings earlier cash, internal pipeline has higher profit with higher risks

Collaboration pipeline

Upfront
+
Development M/S
+
Sales M/S



CoGs and Sales expenses

Royalty payment*

Partner's share

Modalis' share

Internal pipeline



CoGs and Sales expenses

Royalty payment*

Modalis' share

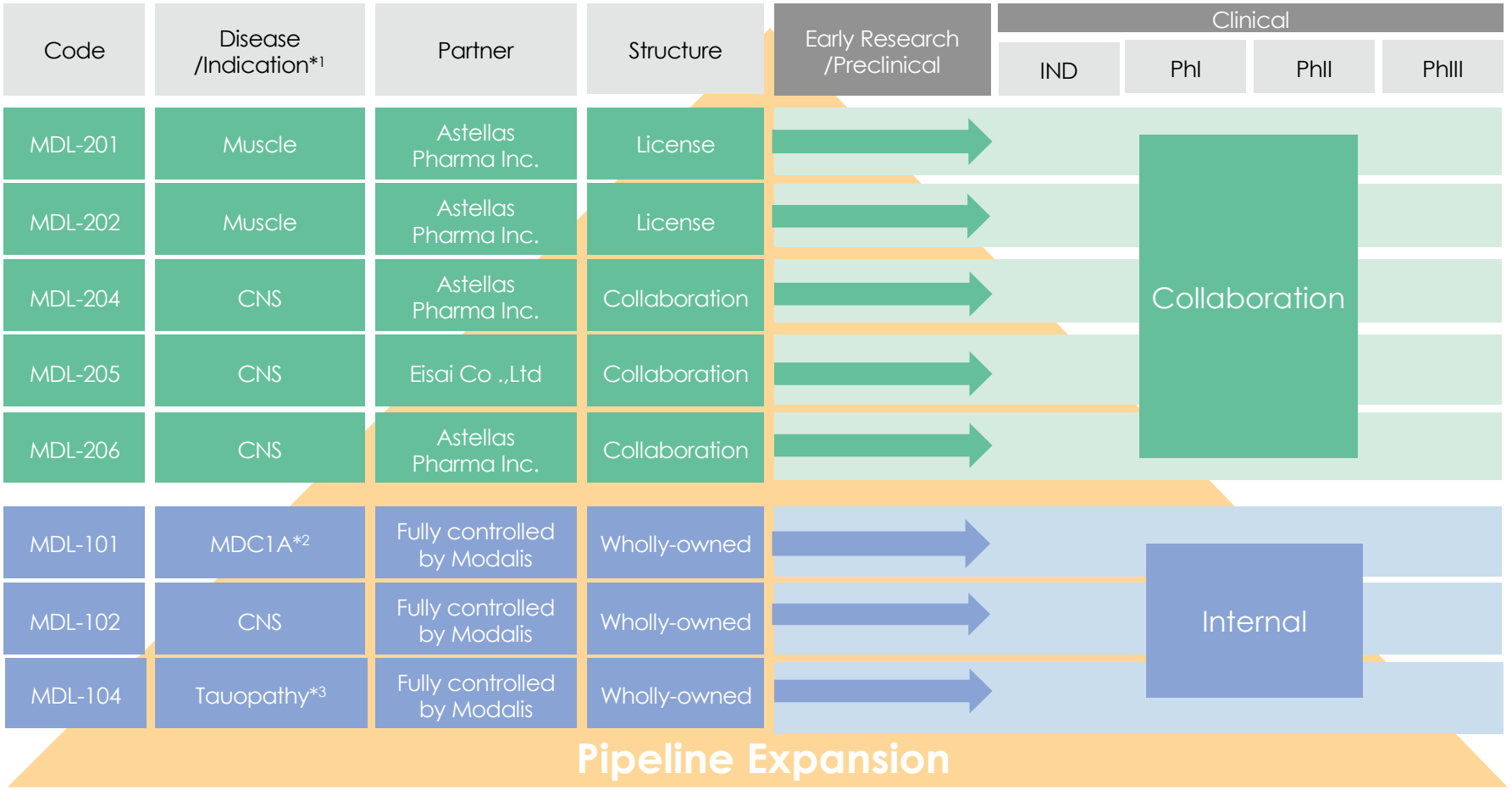
Modalis' sales

* : As a consideration for the licensed in intellectual property, a certain percentage of sales after market launch is paid to the intellectual property holding organization.

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Pipeline



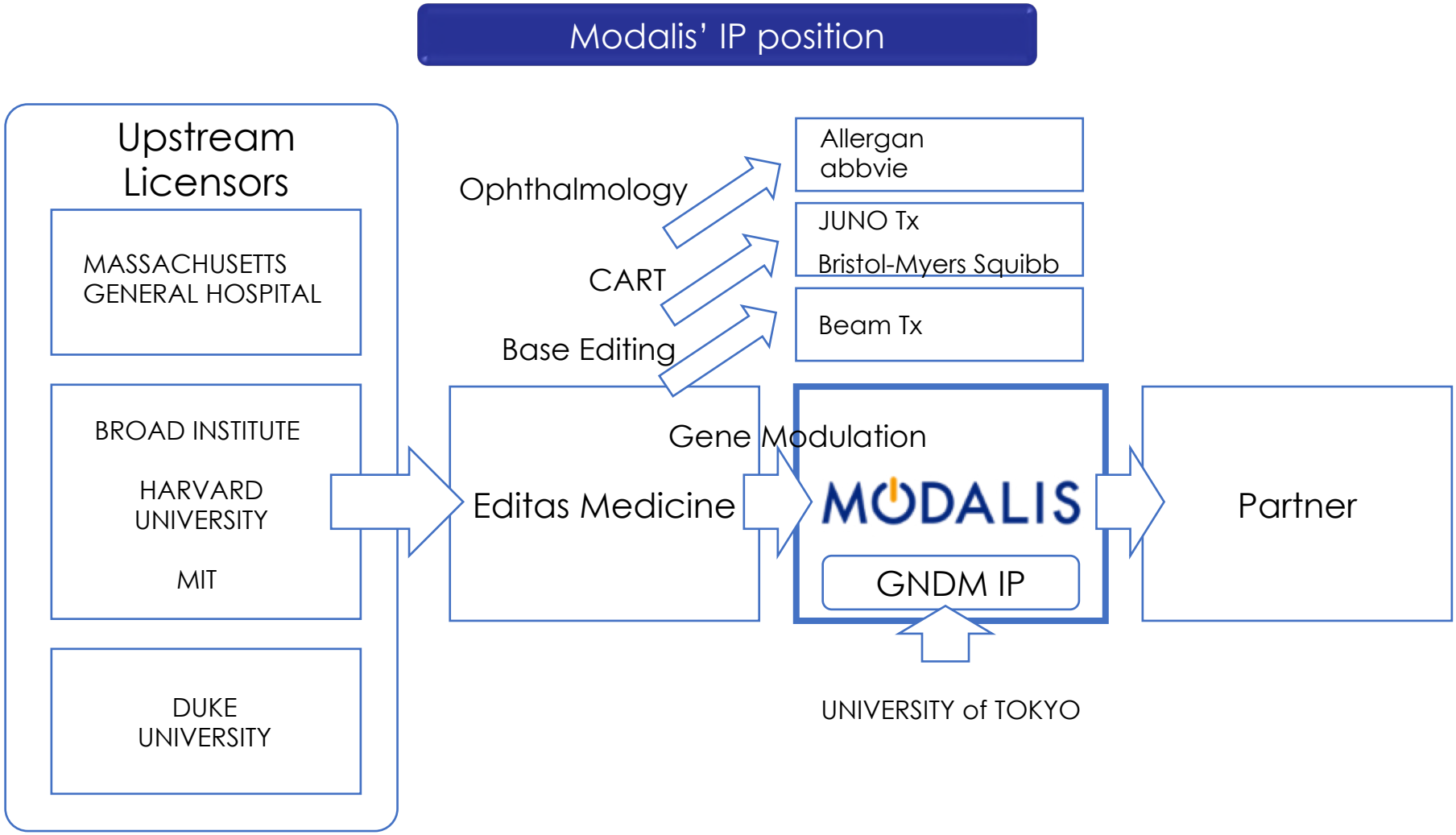
*1: We have adopted a strategy of withholding specific indications until the patent application is published for competitive reasons.
*2: MDC1A=Merosin-deficient congenital muscular dystrophy type 1A
*3: Tauopathy belongs to a class of neurodegenerative diseases involving the aggregation of tau protein.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

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IP position

Established IP with foundational CIRPSR IP from Broad and engineered Cas9 from Univ of Tokyo

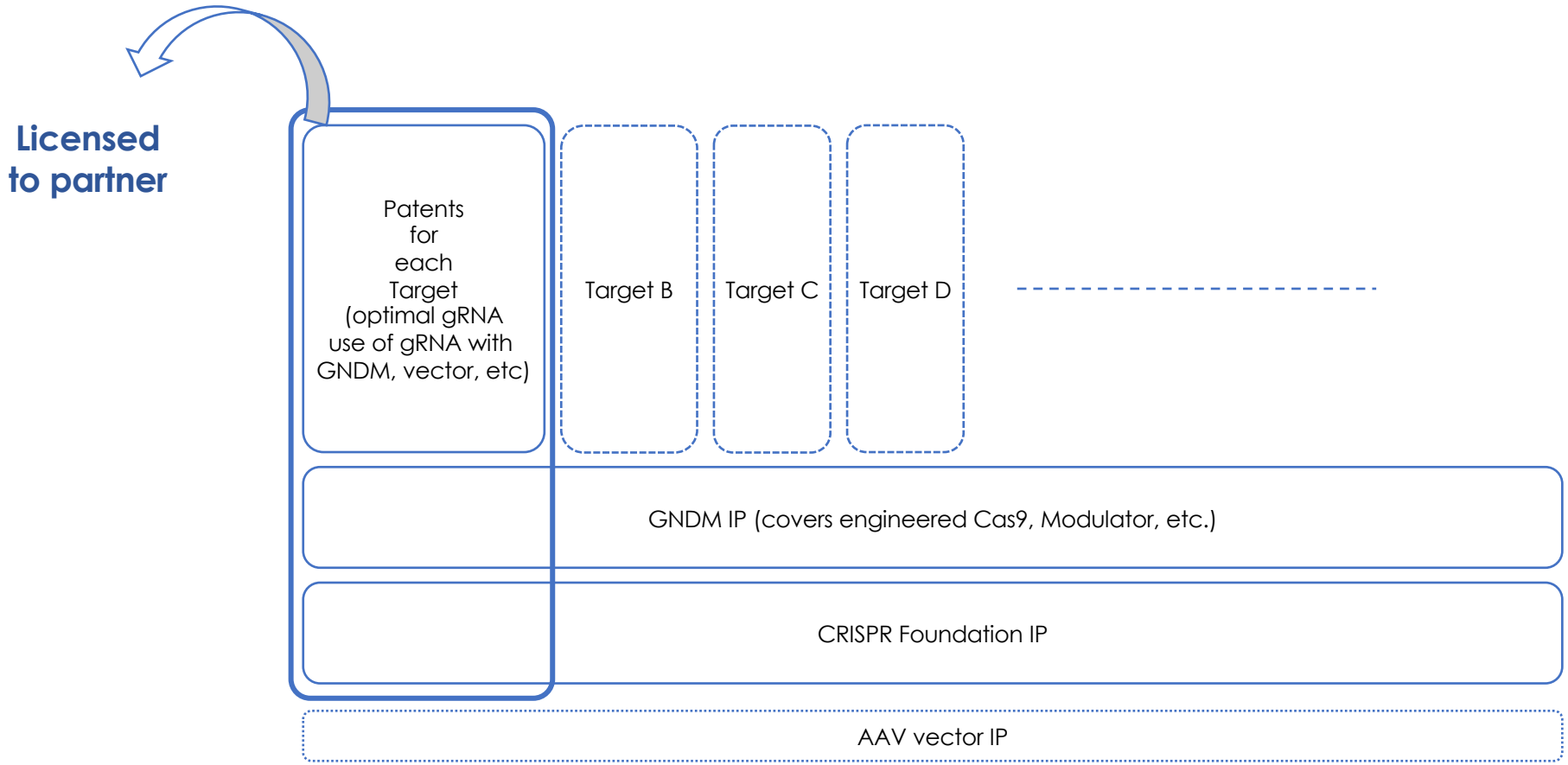


Source : disclosed information by each company

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Each product will be protected by multiple layers of IP



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Management Team and Board of Directors
Seasoned team



Co-founder, President, CEO, and Chair of the board
Haru Morita

- REGiMMUNE, Founder, President and CEO
- Y's Therapeutics, Booz Allen and Company, Kyowa-KIRIN



Board member, founding scientist
Osamu Nureki Ph.D

- Professor, Department of Biological Sciences, Graduate School of Science, The University of Tokyo
- Purple Ribbon medal (Shiju-Hou-shou)



SVP, Chief Technology Officer
Tetsuya Yamagata, M.D. Ph.D

- Glaxo Smith Kline, Tempero Pharmaceuticals
- Joslin Diabetes Center, Harvard Medical School



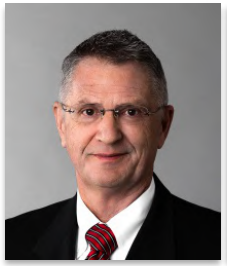
Board member
Hideki Takeda

- President, Medical Patent Research
- Healios KK former president, Fujisawa (merged into Astellas)



VP, Chief Financial Officer
Naoki Kobayashi, MBA

- Former CFO at Oncolysbiopharma, Hatena, and Argens
- Deloitte Tohmatsu, Daikyo Real estate



Board member
Joseph S. McCracken, DVM

- Roche Head of Global license, Genentech, Sanofi

Board member, Audit committee
Miyuki Shimane

- Chugai Pharma

Board member, Audit committee, CPA
Teruhisa Tajima

- President Tajima CPA office
- Corporate Auditor (Quantum Biosystems, OncoTherapy, Prism Bioscience)

Board member, Audit committee, Attorney at Law
Toshio Furuta

- Representing attorney, Clair Law Firm
- Corporate Auditor (NetYear Group, Canbas, Zenrin DataCom)

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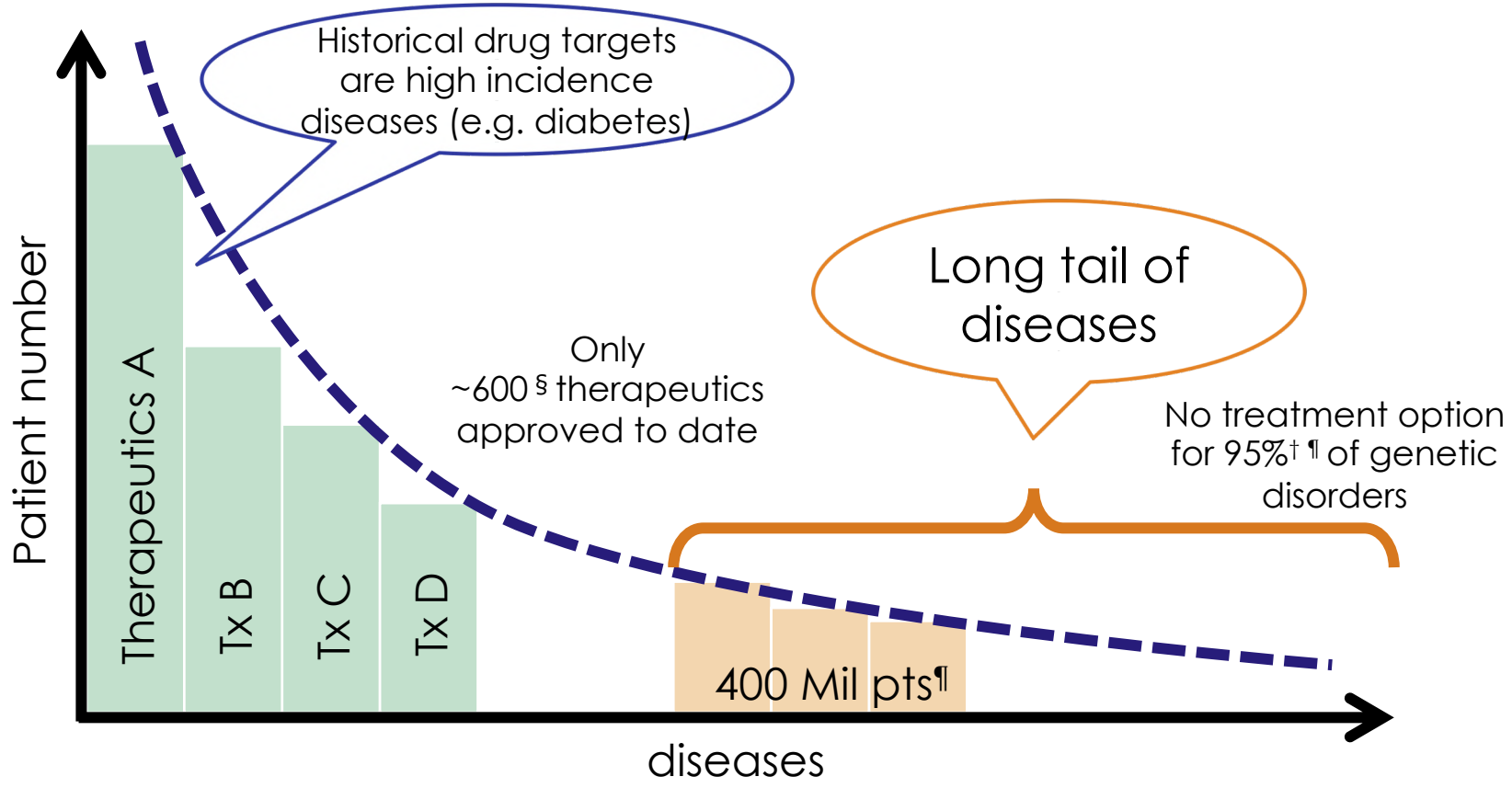
2. Gene Therapy and Gene Editing

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To target "long tail" of diseases, innovation is needed

Among 10,000* human disorders ~7,000#are orphan disease and 80%†are genetic disorders



Scalable efficient approach is required to tackle the divided population

Source: *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

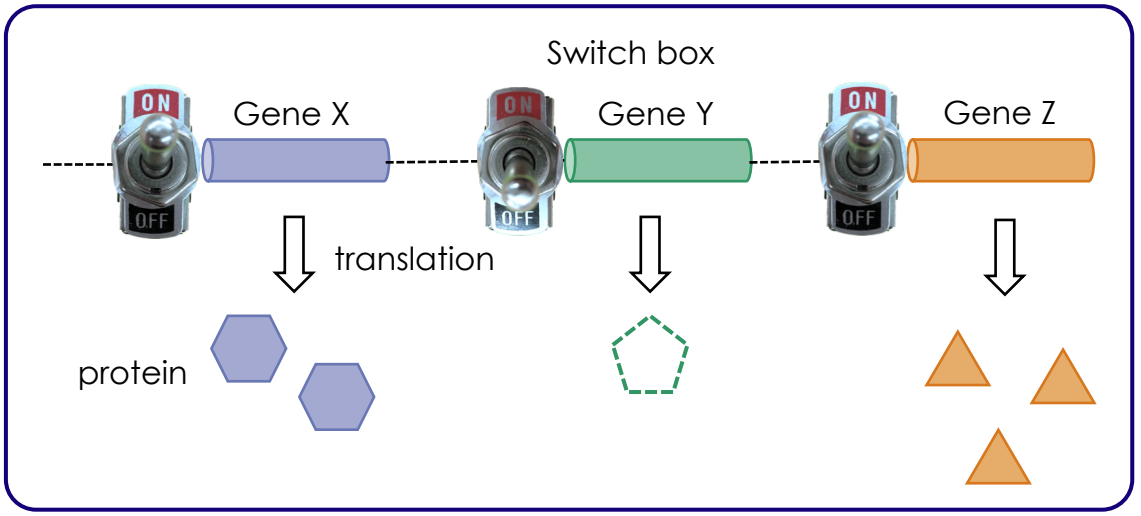
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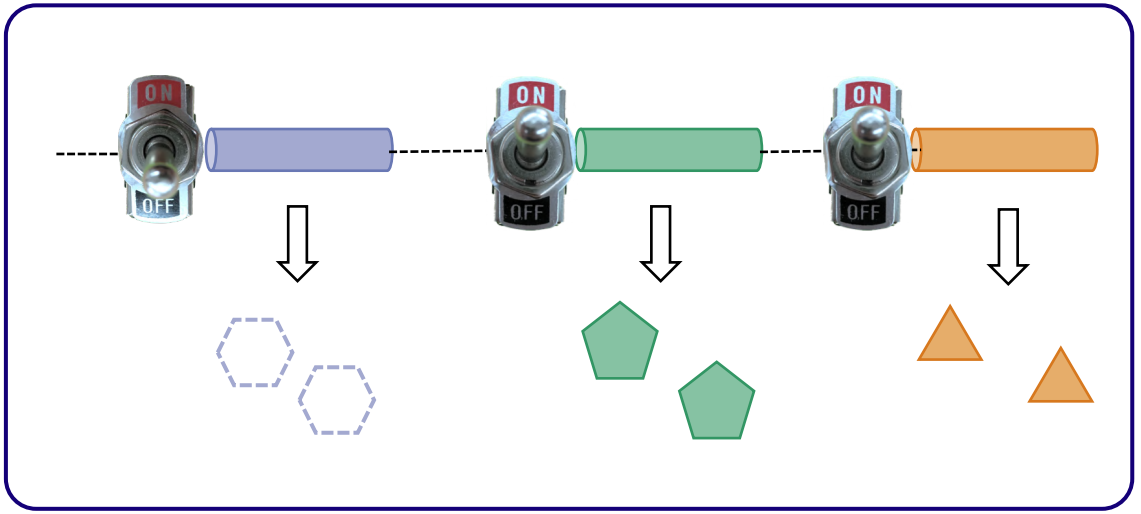
How multiple cell types are created from the same DNA code

Each of 20,000 genes have ON/OFF switches that control cell type specific expression

Cell A



Cell B



- There are **37.2 Trillion cells** in our body
- **200 cell types** in our body have the same DNA code despite differences in appearance and function
- Differences in cell types and their states are controlled by ON / OFF switches of the expression of **20,000 genes** coded by **3 billion bases of DNA**

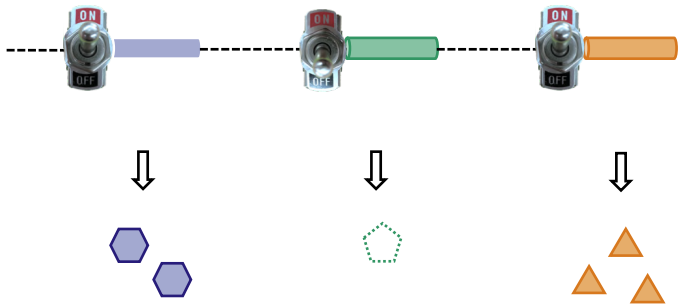
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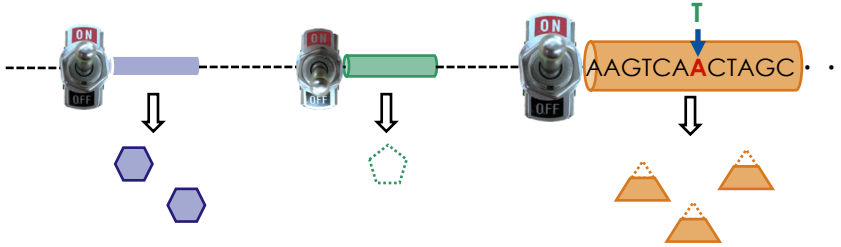
3 types of genetic disorders

An error in the code or in switching can cause disorders

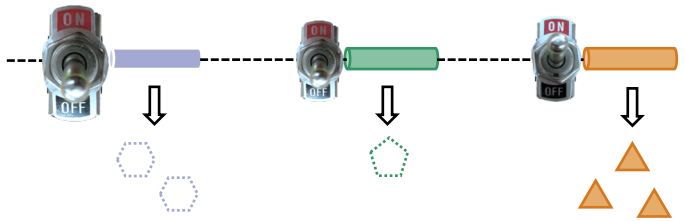
Normal state



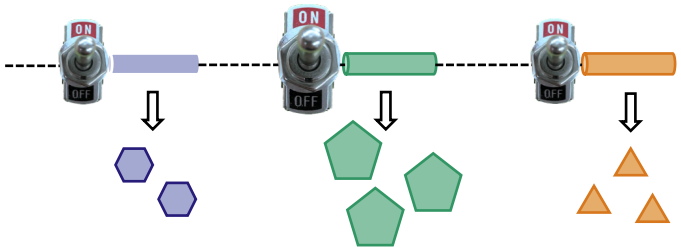
Error in the code results in a **non-functional protein**



A **required protein** is not supplied due to being witched OFF due to a switching error



An **un-necessary protein** is produced by a switching error



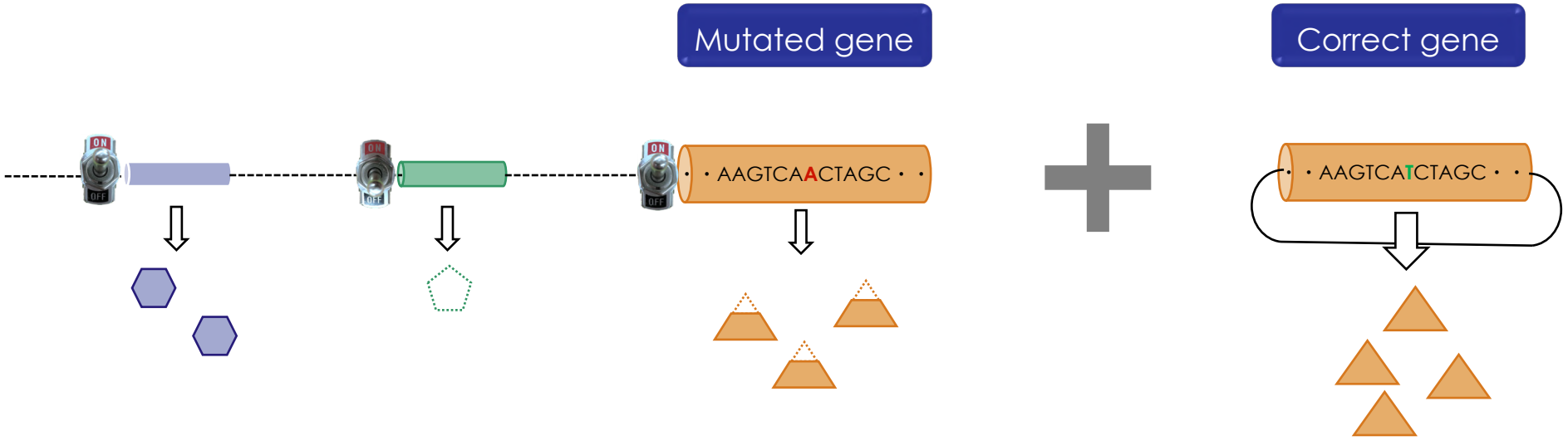
Switches control which, when and how much protein is expressed

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Classical gene therapy

Replaces a mutated gene by inserting a correct gene exogenously



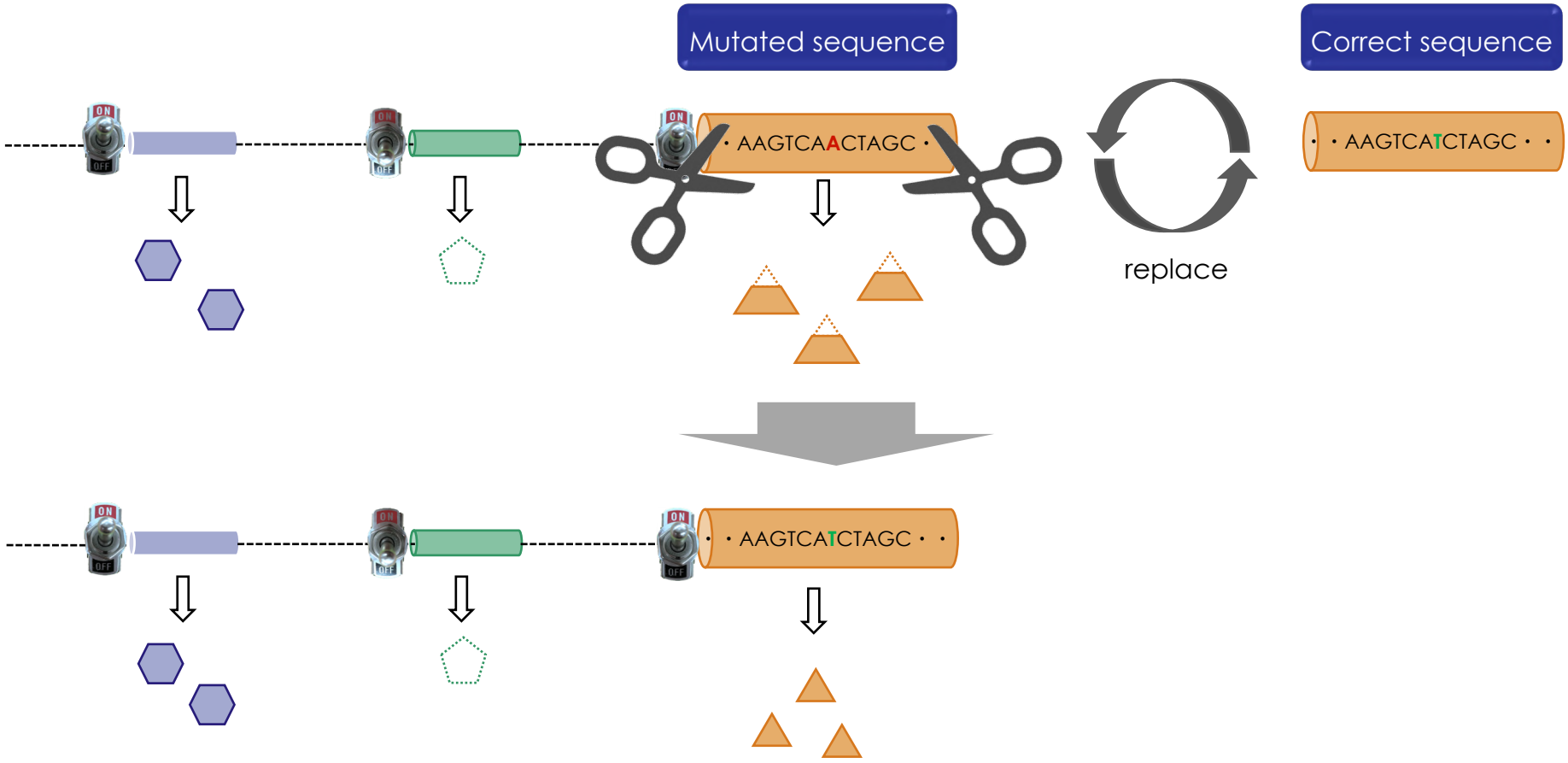
Overwrite of missing gene

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Gene Editing

Replaces mutated DNA with correct DNA by cleaving DNA



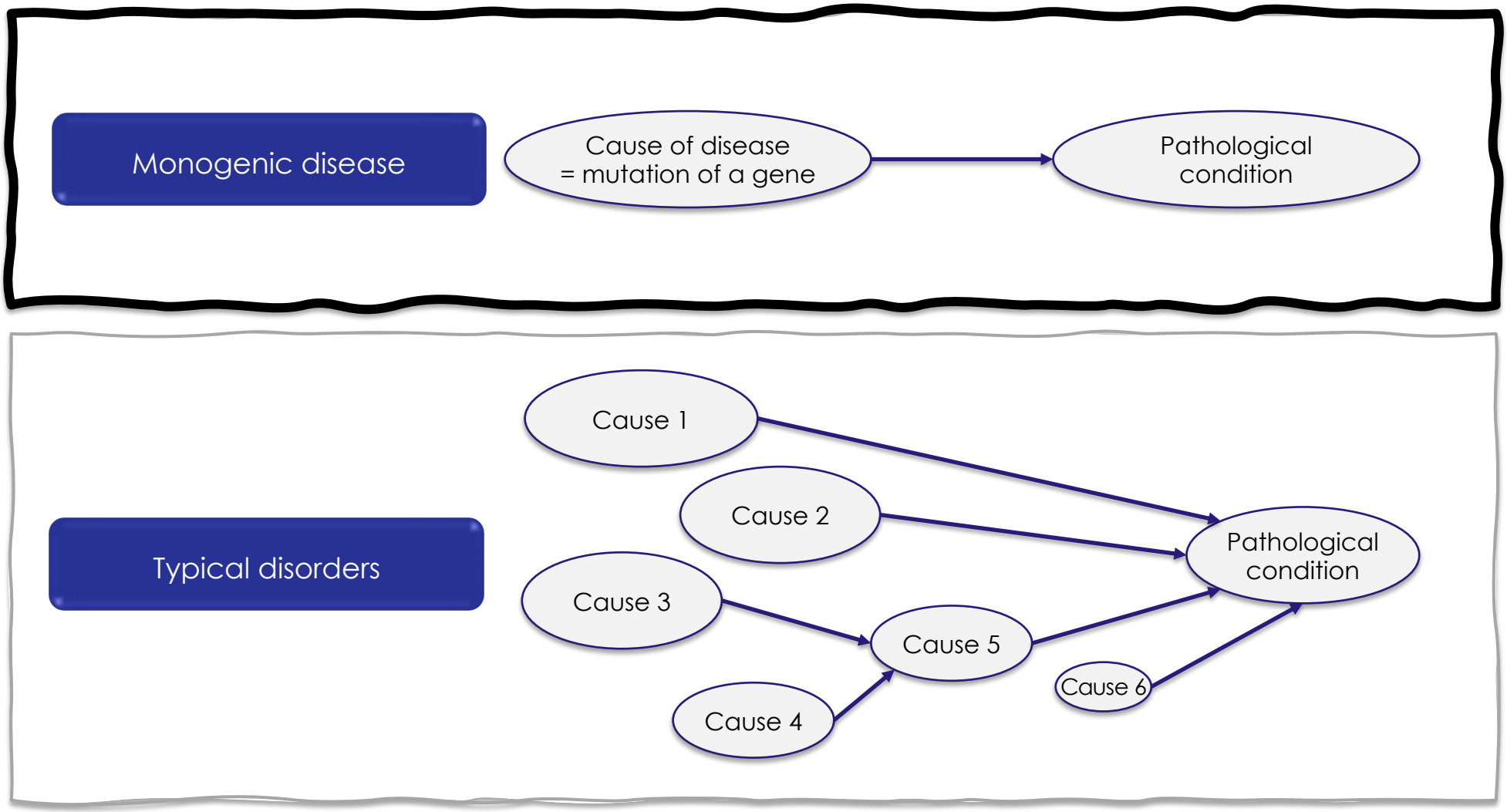
However, cleaving DNA increases risk of cancer

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Monogenic Diseases

Gene therapies for monogenic disorders are expected to have higher probability of success due to simplicity of mechanism



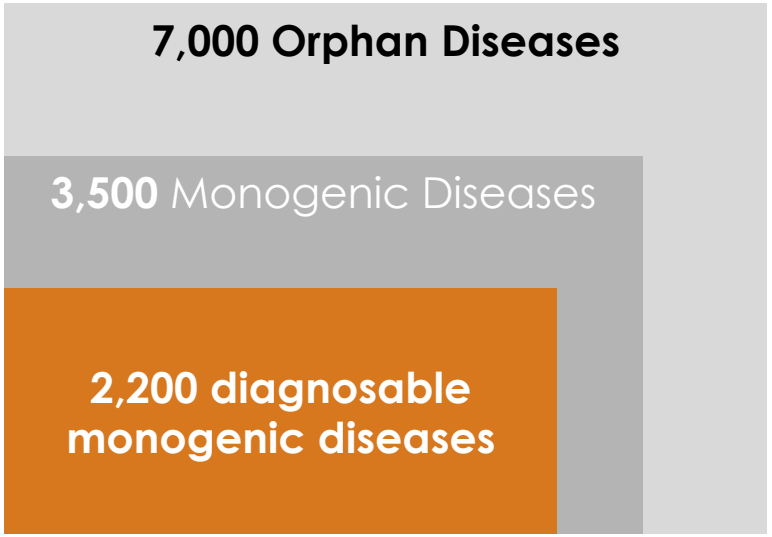
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Untapped opportunities in monogenic disorders

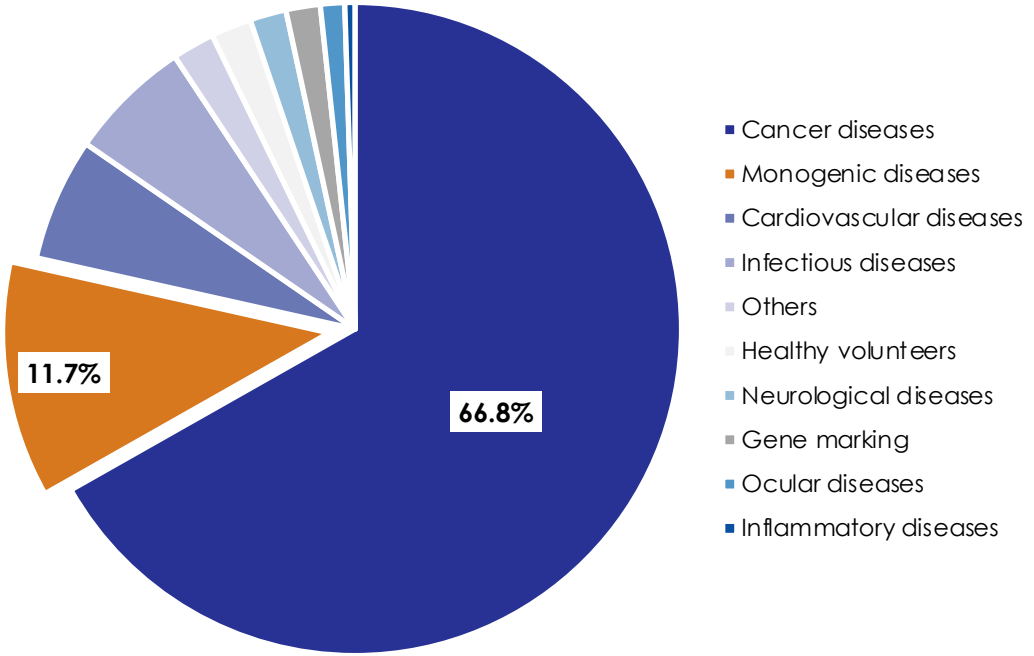
Limited number of drugs are approved or in clinical development for monogenic disorders

Monogenic Disease



Source: Discovery Medicine

Breakdown of GTx clinical trials (1989~ Worldwide)



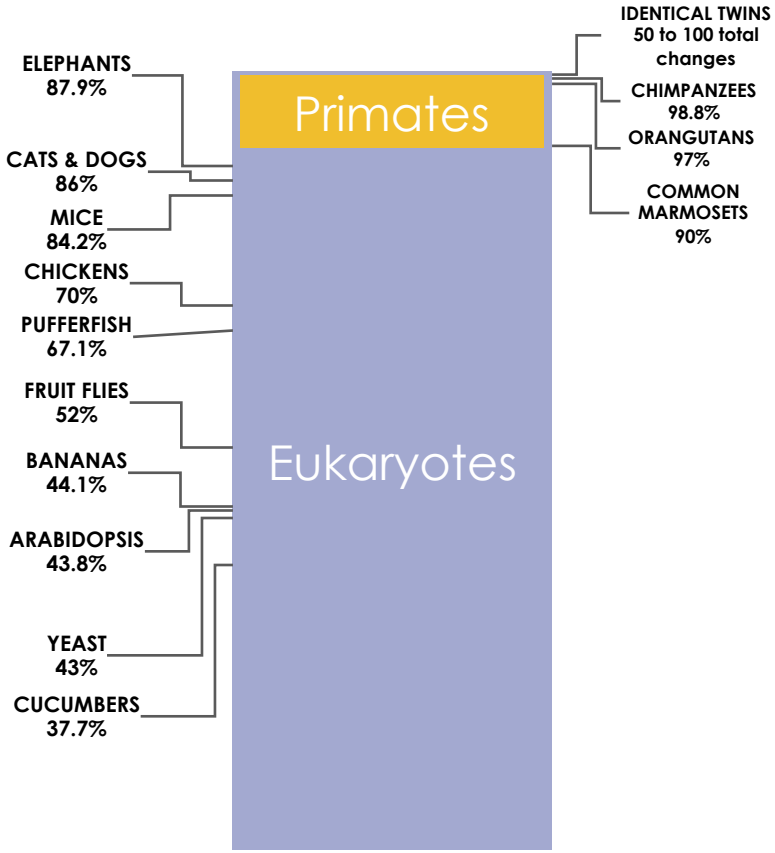
Source: The Journal of Gene Medicine (2019)

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Why GTx outcome is predictable?

Genetic machinery (OS) is common in eukaryotes while genetic codes differ





Humans share 40% of their genes with cucumbers

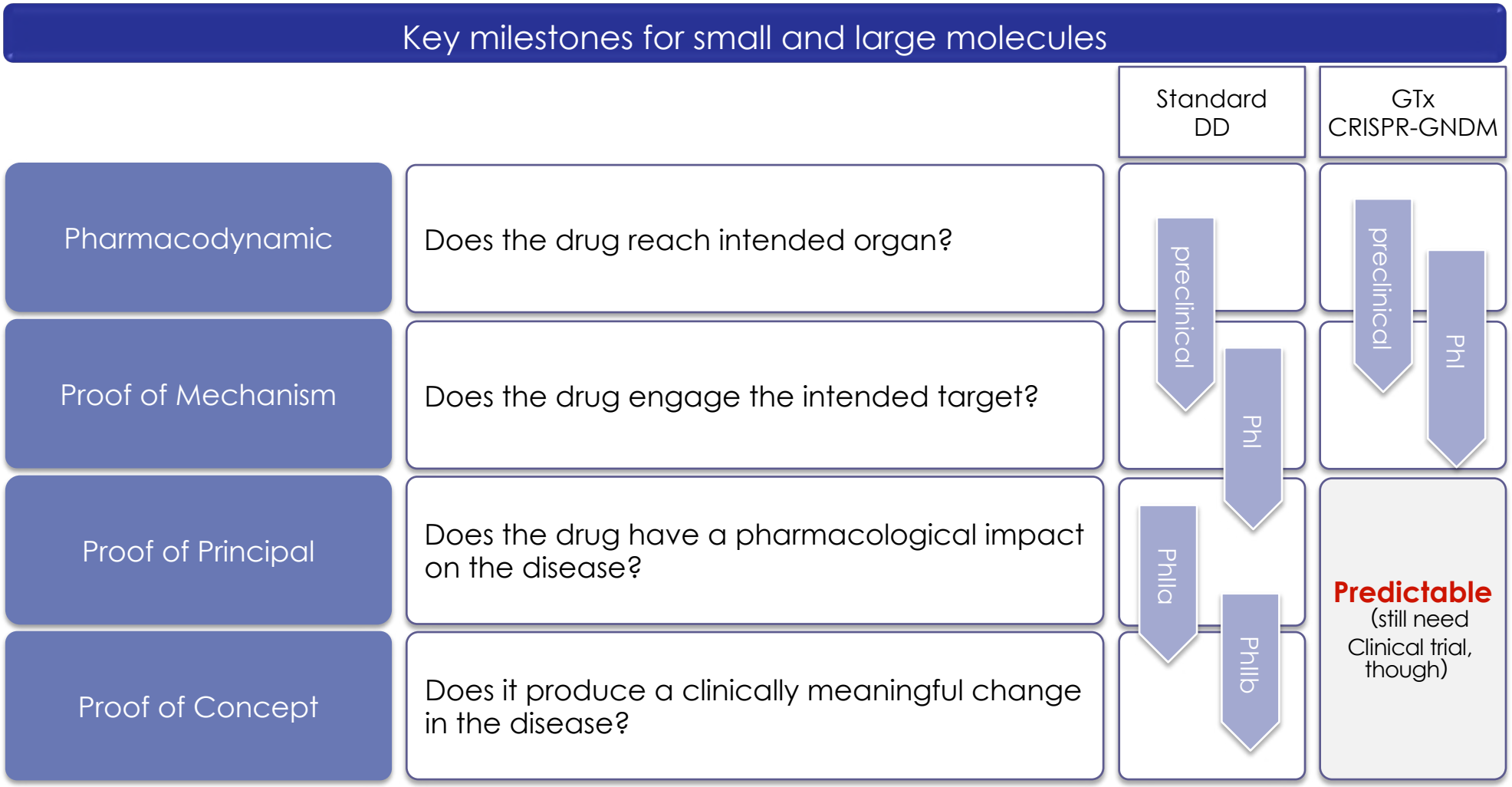
Source : Datascope

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Major hurdles in drug development

PoP and PoC are predictable in GNDM prior to human testing



Source : Nature Biotechnology volume 30, p596–599 (2012)

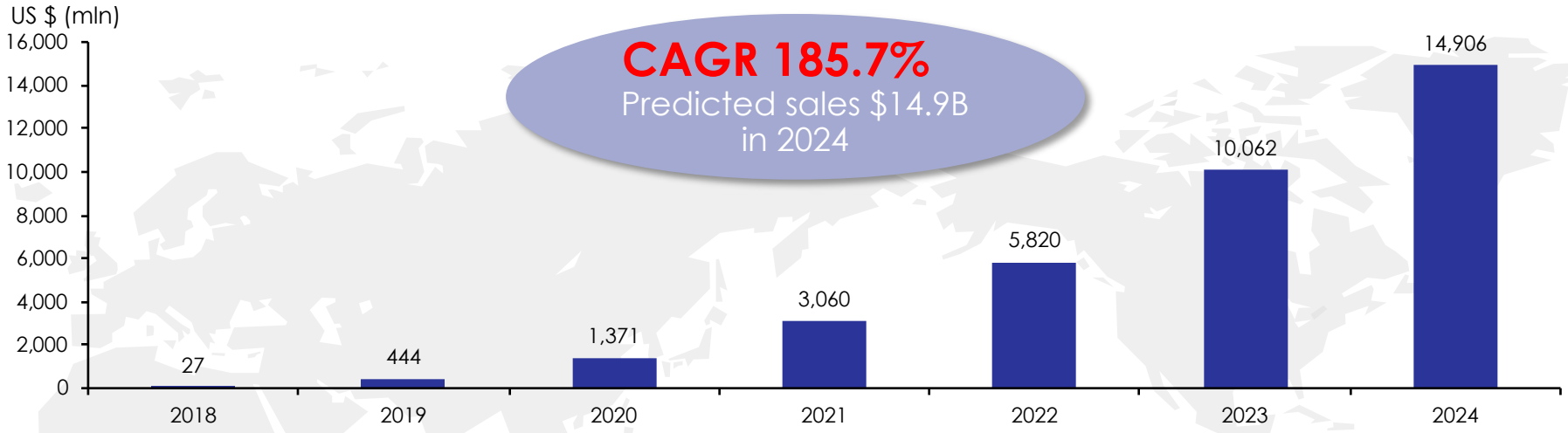
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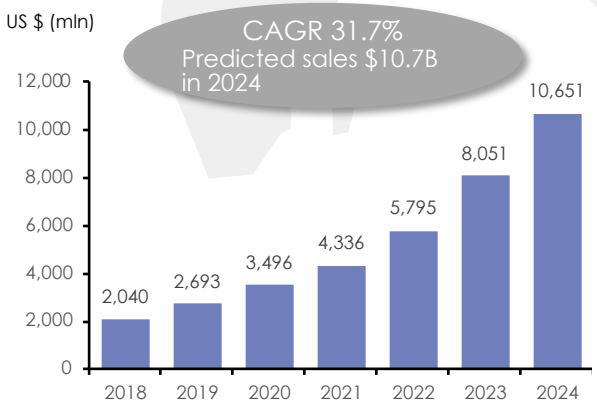
Sales growth of pharmaceutical modalities

GTx is growing faster than other modalities

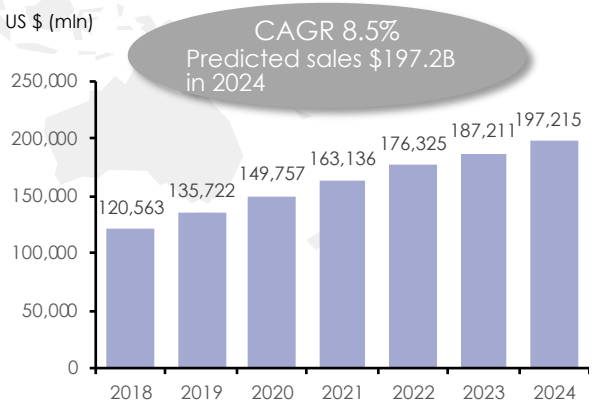
Predicted sales of Gene Therapy (WW)



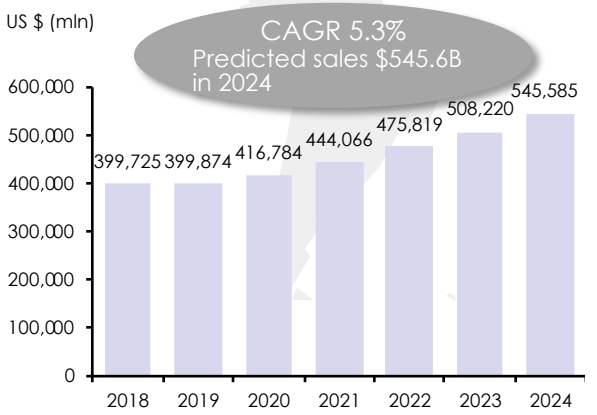
DNA&RNA therapeutics



Monoclonal antibody



Small molecule



Source : Evaluate Ltd (in Aug 2019 data) *CAGR=2018 to 2024. 2019 to 2024 are predicted sales

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CRISPR is a novel gene editing technology

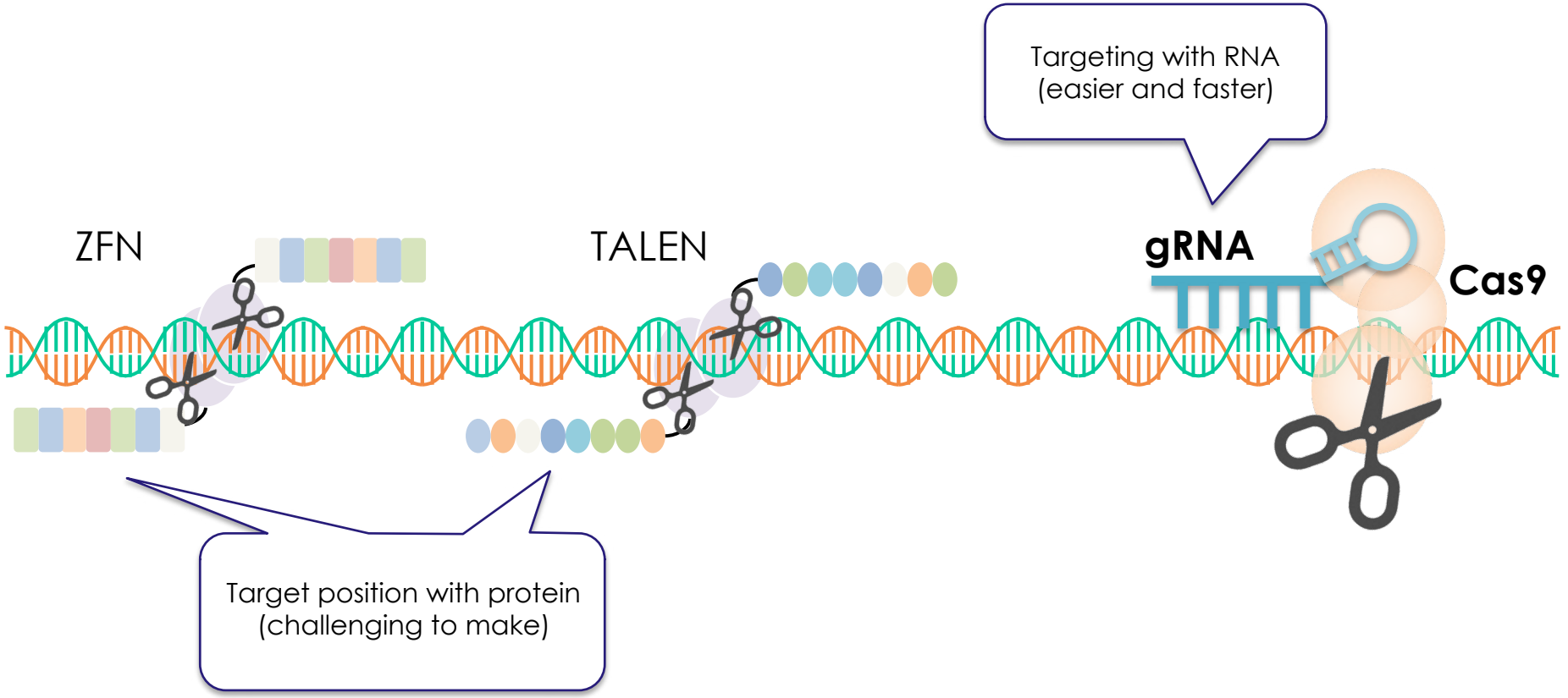
Faster and higher throughput due to limited variable region which is easily synthesizable as gRNA

Old gene editing technologies

ZFN

TALEN

CRISPR

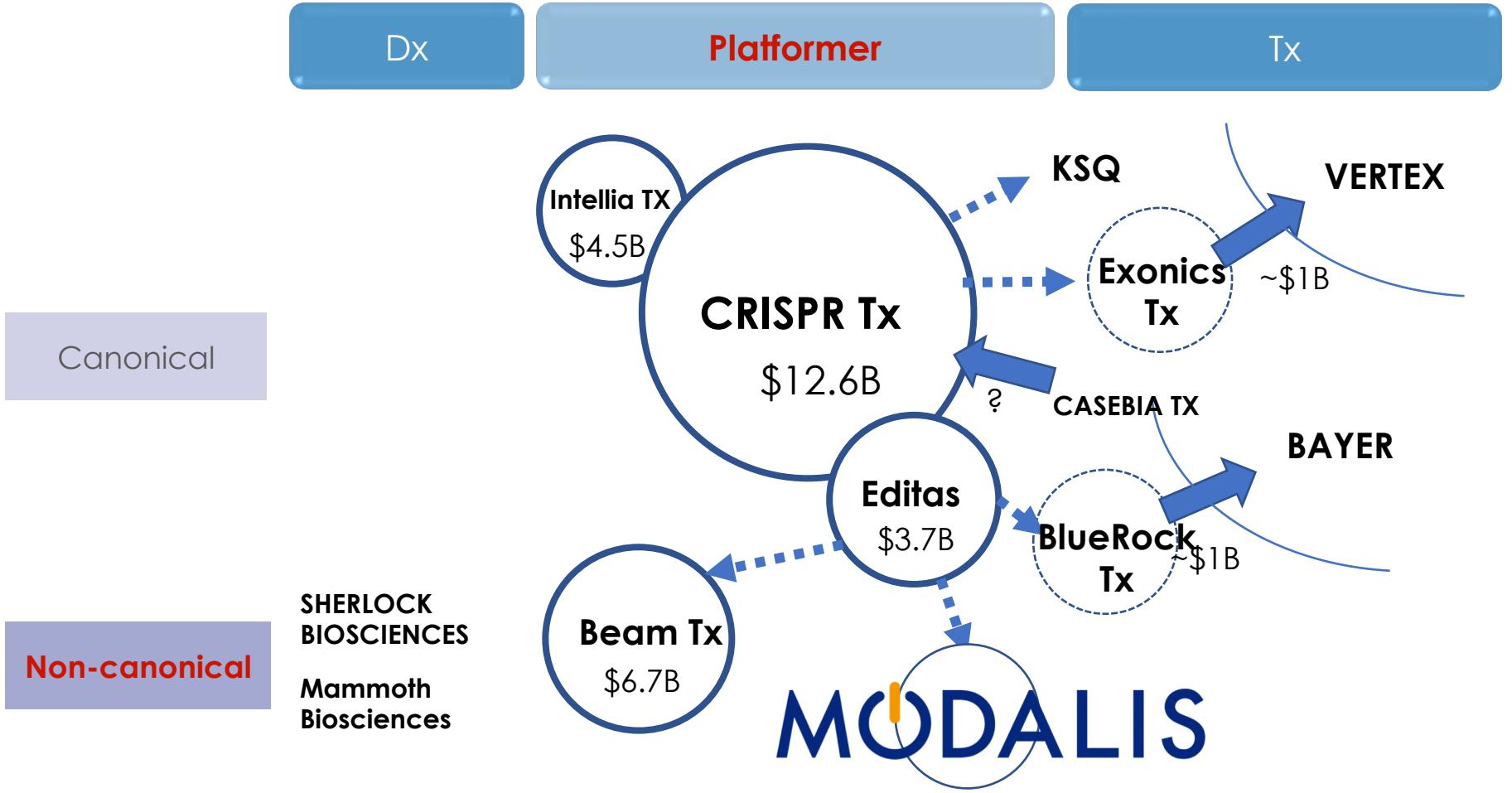


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Major players in CRISPR field

Modalis established unique position in CRISPR companies, most of which reached >$1B



Source: stock info. The figures represent market cap as of Feb 10th ,2021 or value at the time of acquisition.
Dotted circle represent acquired companies

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3. CRISPR-GNDM® and its advantages

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Novel prize 2020 is awarded to CRISPR/Cas9

On October 7, Royal Swedish Academy of Sciences announced 2020 Nobel Prize in chemistry is awarded to 2 scientist who contributed to CRISPR/Cas9 based gene editing

In an interview* to one of the two winners, Jennifer Doudna, she mentioned about CRISPR based gene modulation as follows.

Q: "What do you think is going to be the next big CRISPR advance?"

Doudna: "That's always a hard question. We've so much going on in the field. I think one interesting possibility is that **we'll see CRISPR being used not to edit genomes, or at least not to make permanent changes to genomes, but instead to regulate them, to control levels of human proteins that are produced from different genes.** This is a newer way of using the CRISPR technology. I think it has a lot of potential to allow control of cells that doesn't require actual permanent chemical changes being made to the DNA."

*Source: Interview on Future Human "Fresh Off Her Nobel Prize Win, Jennifer Doudna Predicts What's Next for CRISPR"

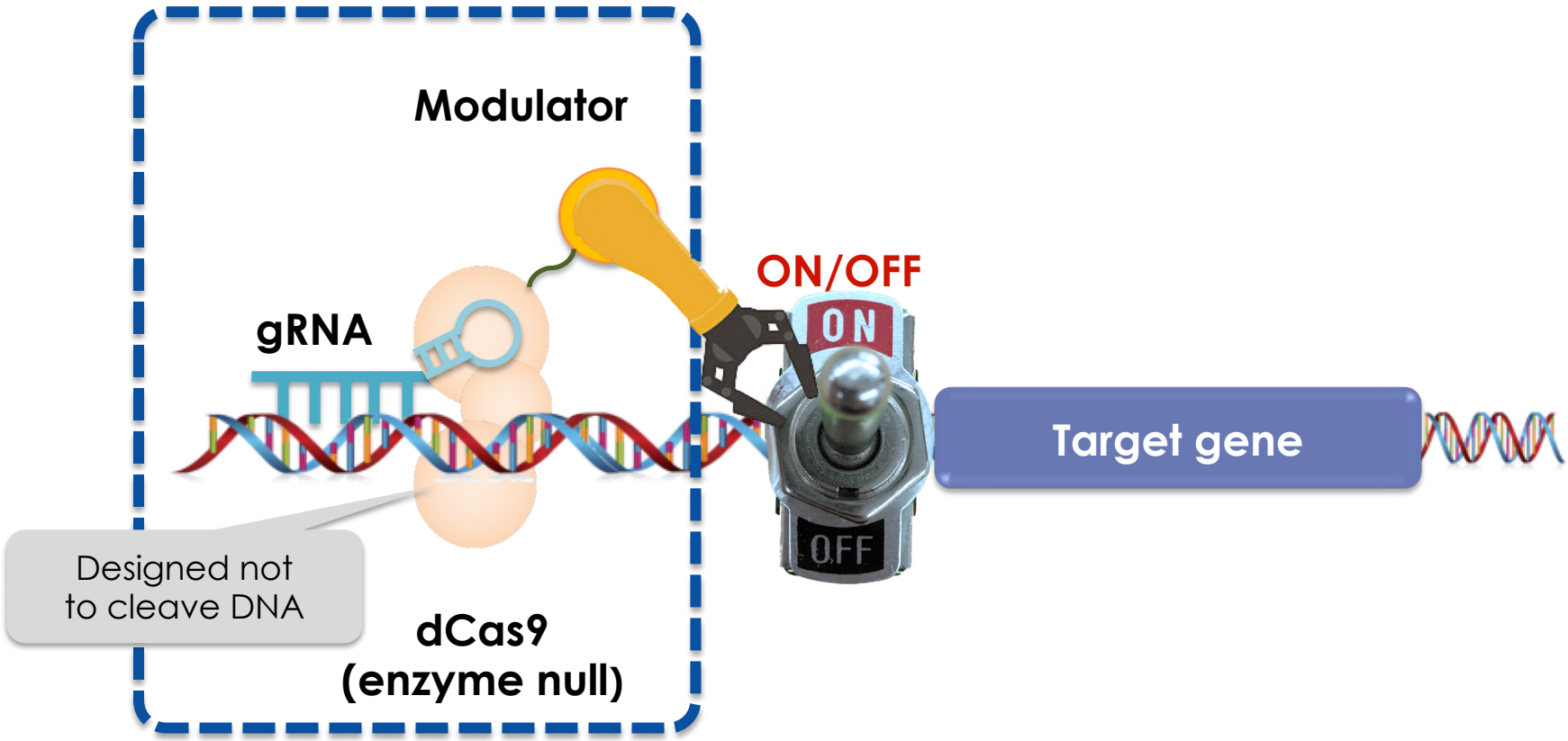
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Non-cleaving CRISPR = CRISPR-GNDM®

Enables treatment of genetic disorders by controlling ON/OFF switch

CRISPR-GNDM® (Guide Nucleotide-Directed Modulation) platform

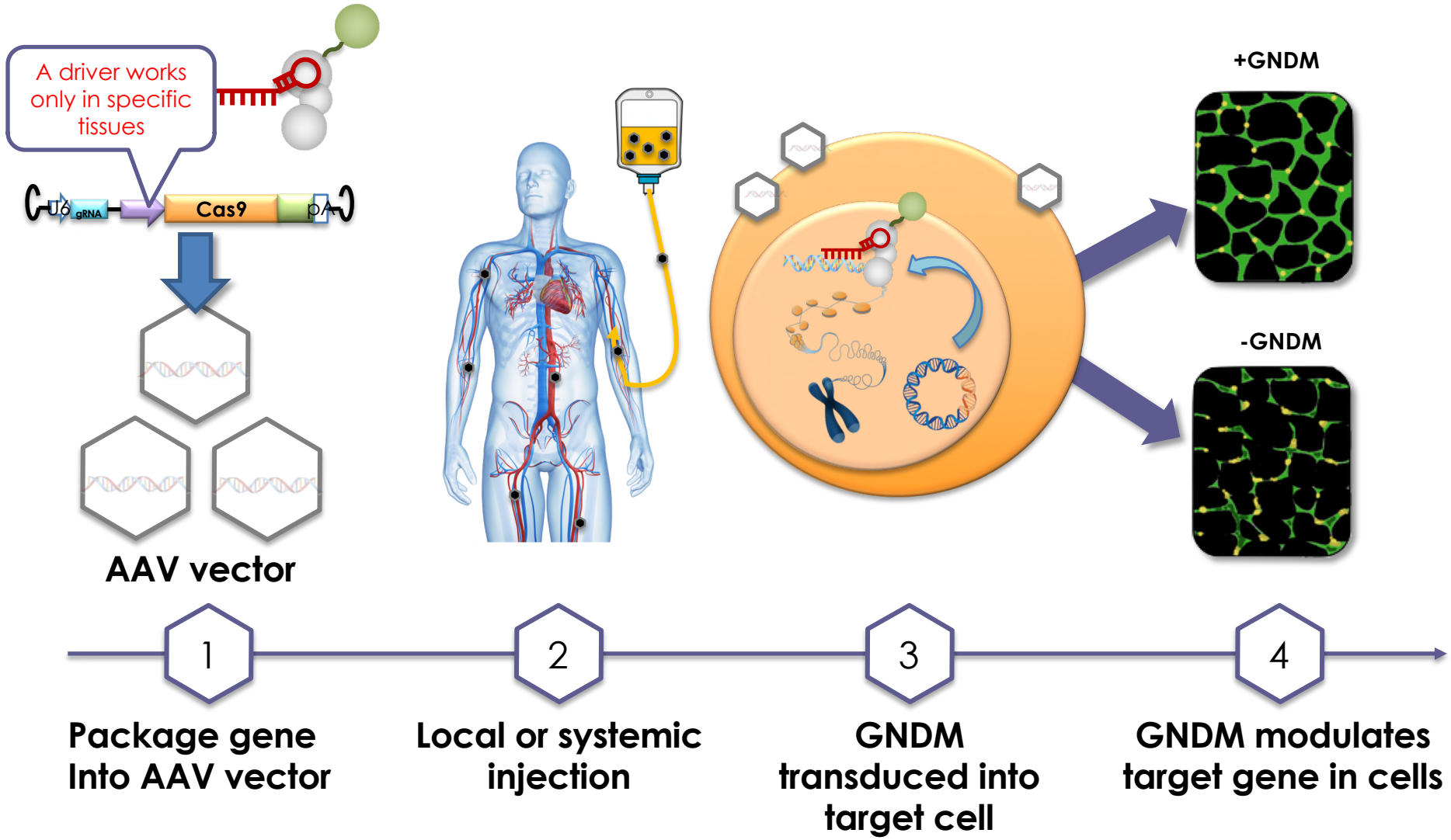


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Delivery of CRISPR-GNDM® to target

Use AAV vector to deliver GNDM to target cell

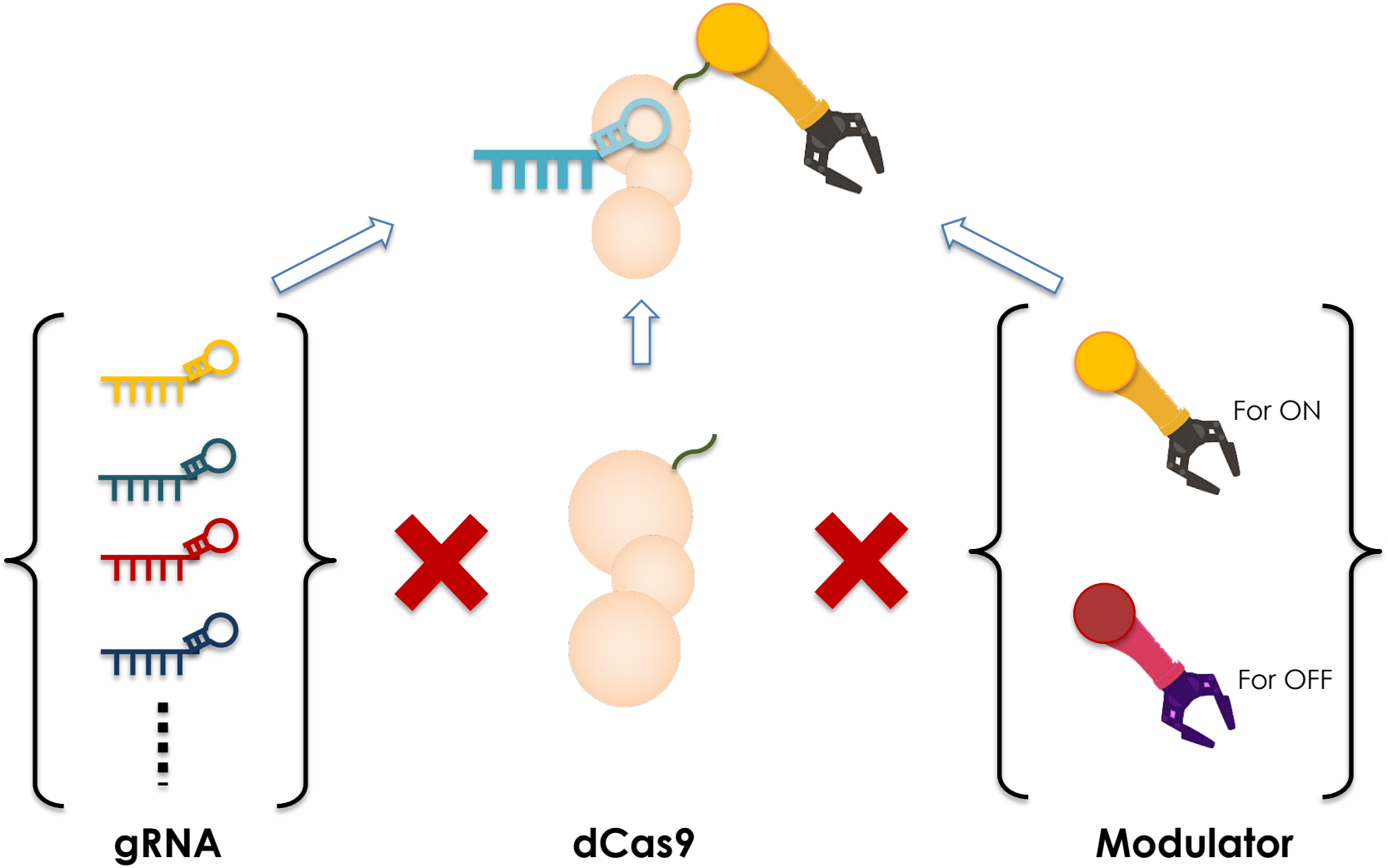


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Scalability of GNDM

gRNA is the only variable which is unique for each target. Other components are off-the-shelf to assemble.

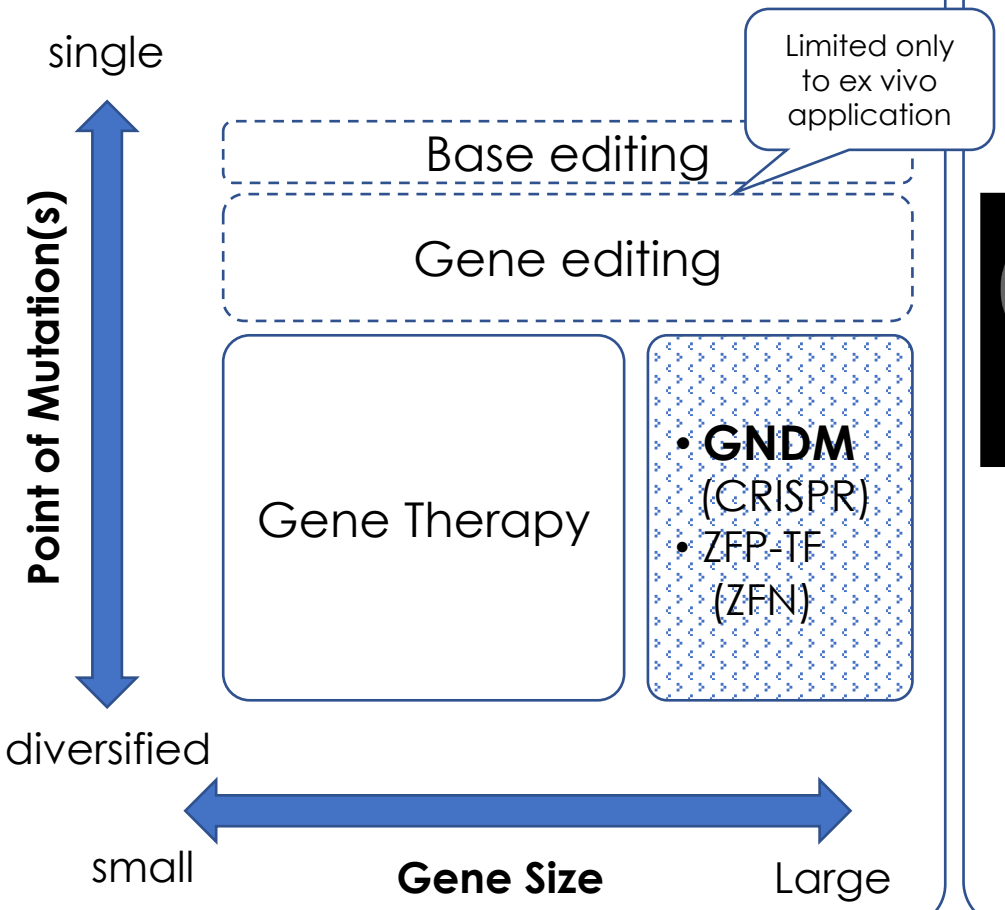


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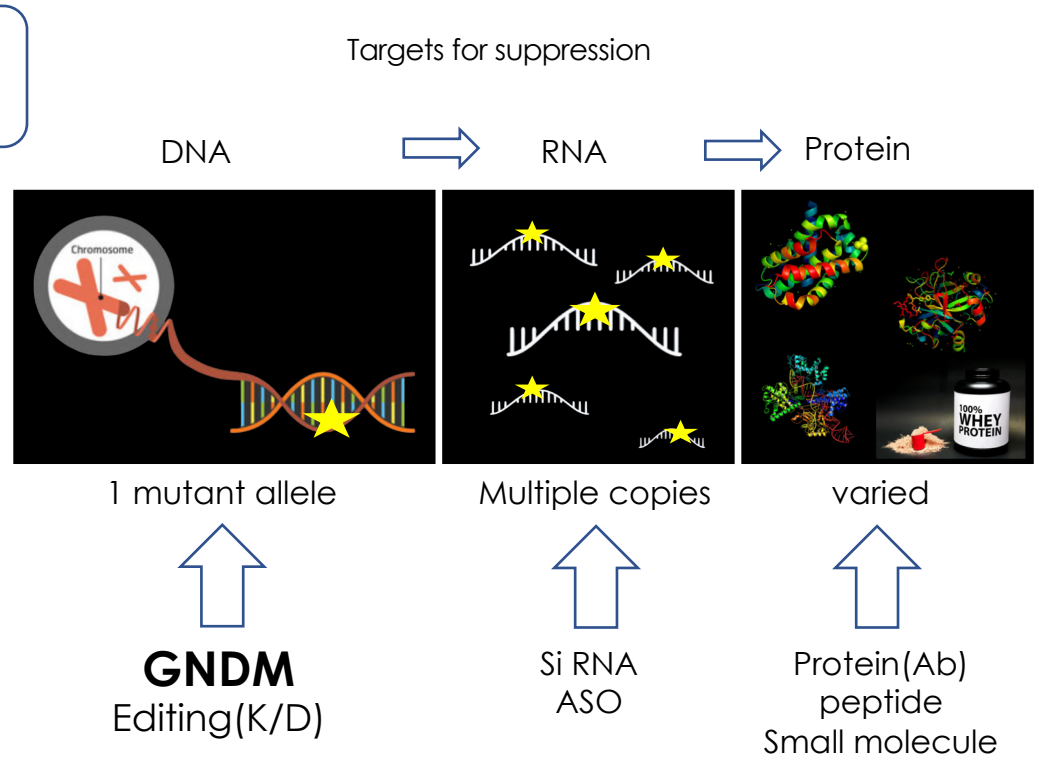
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GNDM is efficient approach both for LoF and GoF mutation

In LoF disorders



In GoF disorders

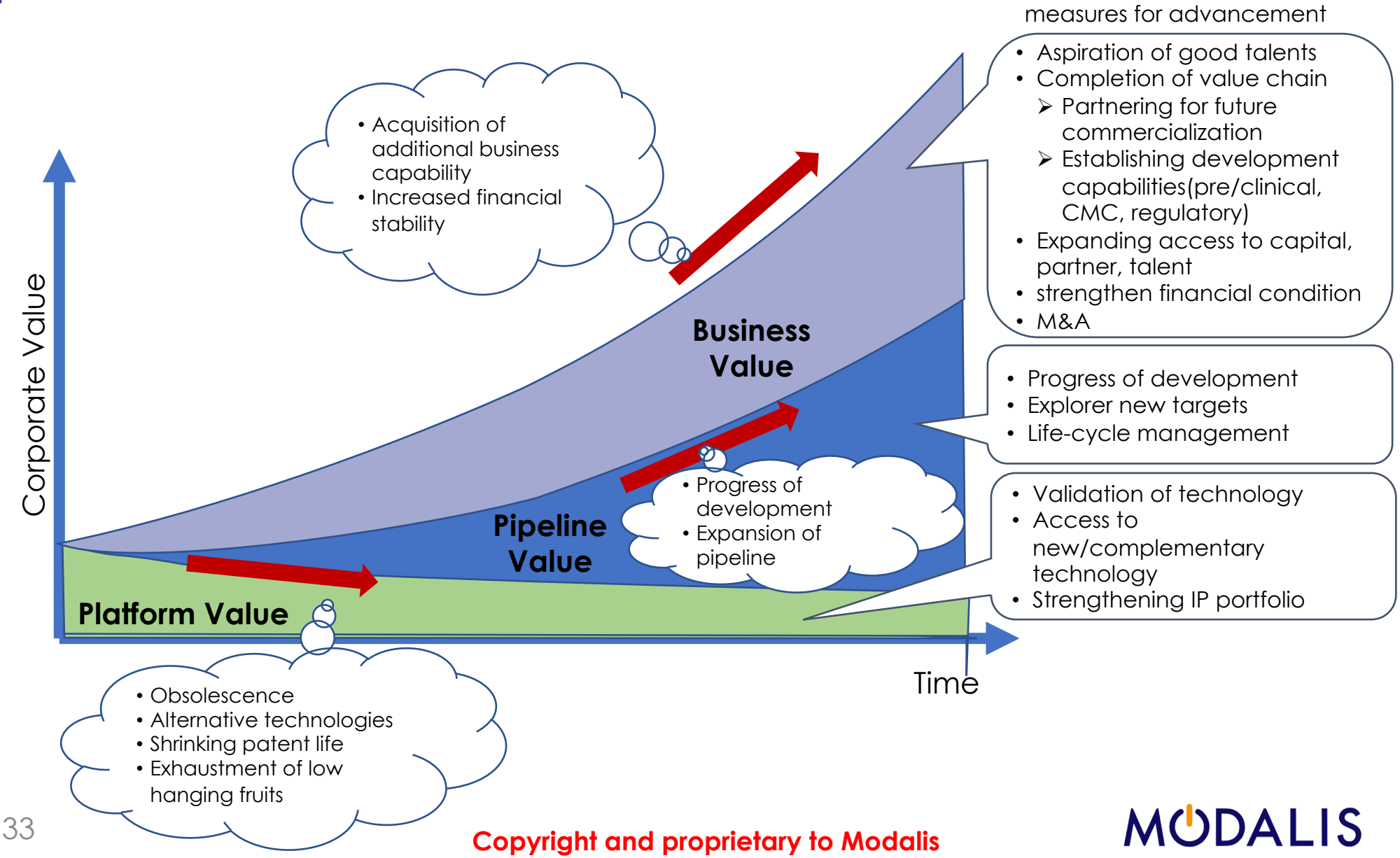


LoF: Loss of function
GoF: Gain of (mal)function

K/D: Knock-down

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Composition of Modalis' value and measures for advance



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4. MDL-101 for MDC1A

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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

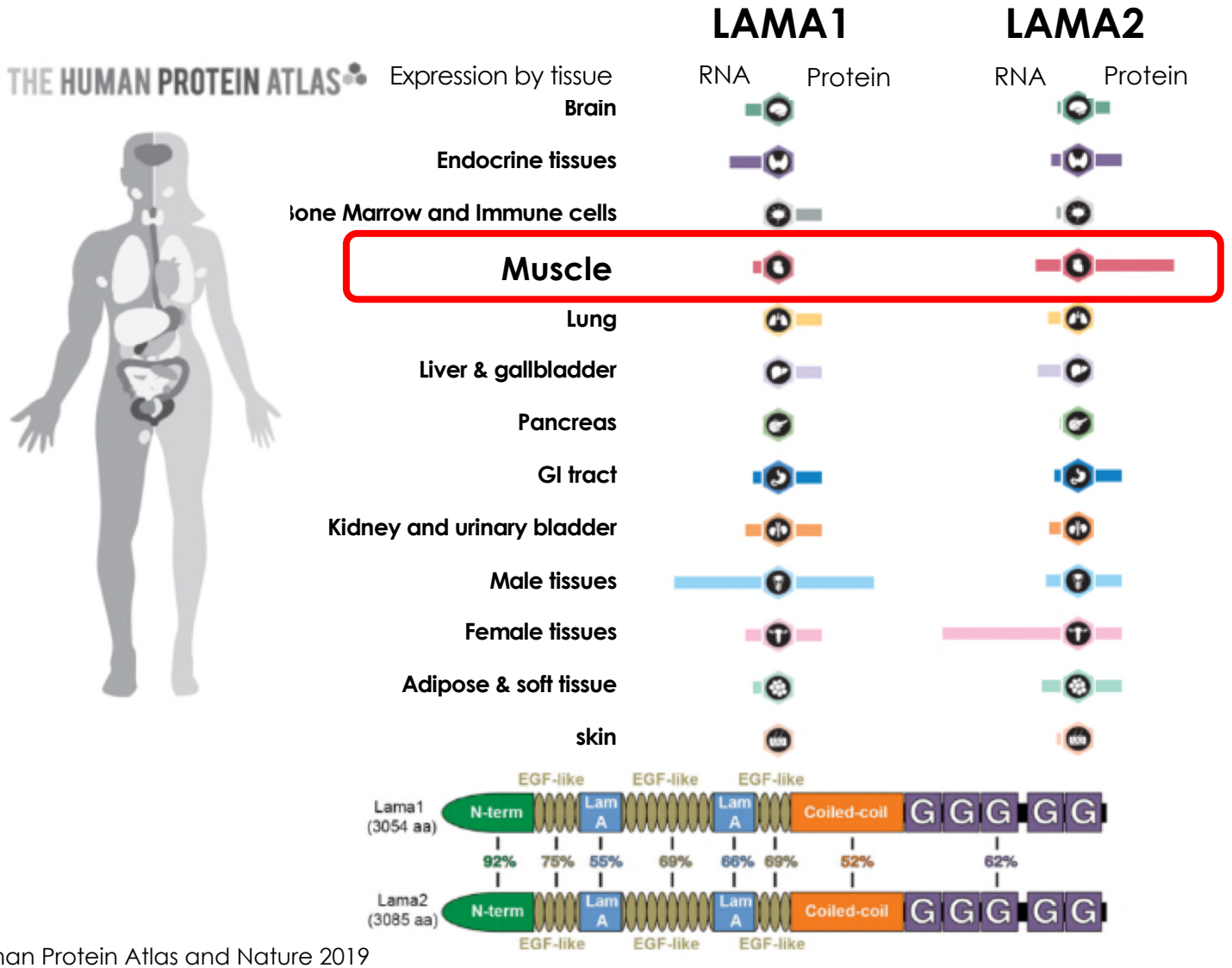
MDC1A: merosin- deficient congenital muscular dystrophy type 1A
*Orphanet

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LAMA2 has a sister gene, LAMA1

LAMA2 disfunction can be compensated by LAMA1 which is highly homologous to LAMA1



Source: Human Protein Atlas and Nature 2019

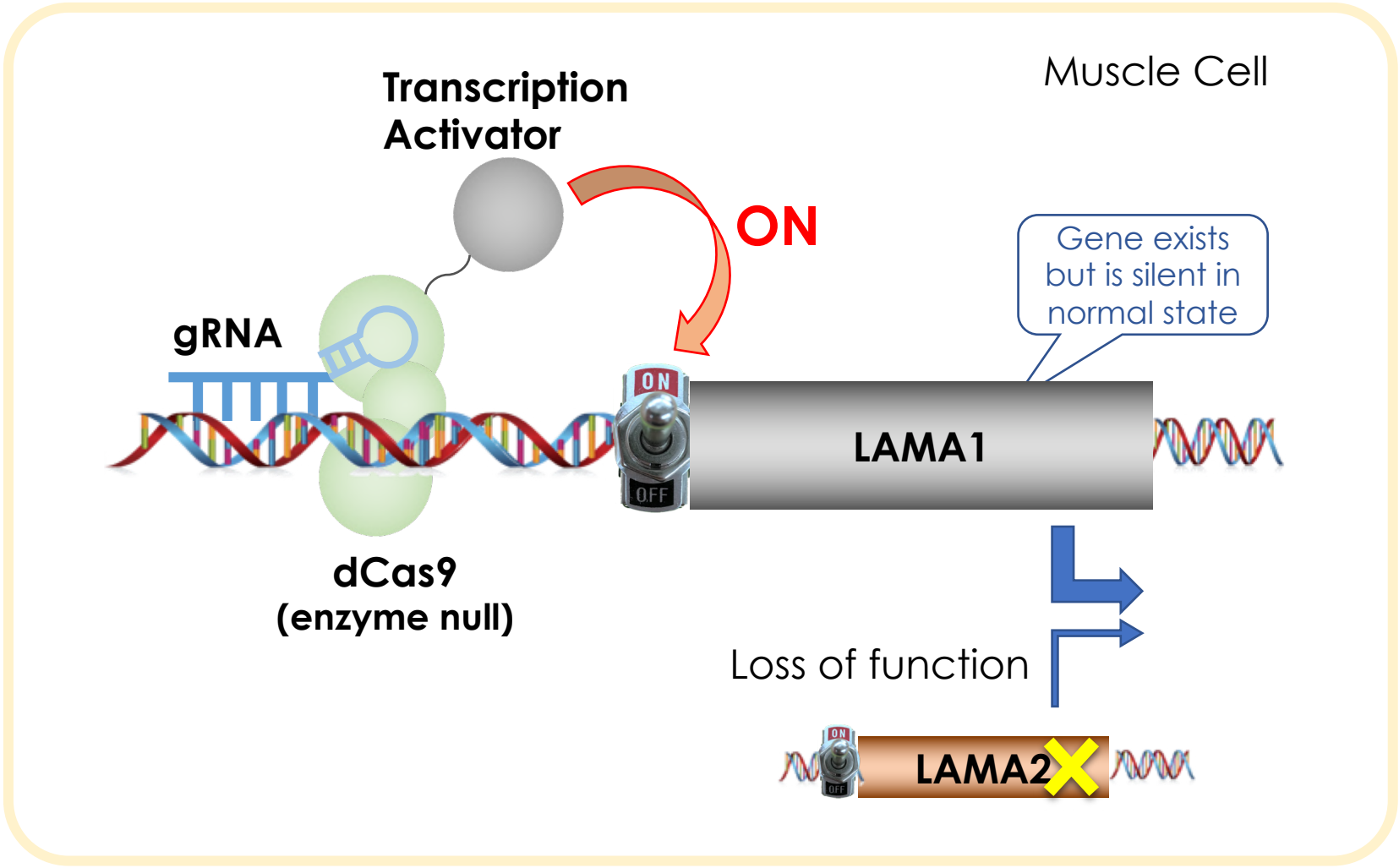
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How GNDM cure MDC1A

GNDM upregulation of LAMA1 gene in skeletal muscle

CRISPR-GNDM® targeting LAMA1

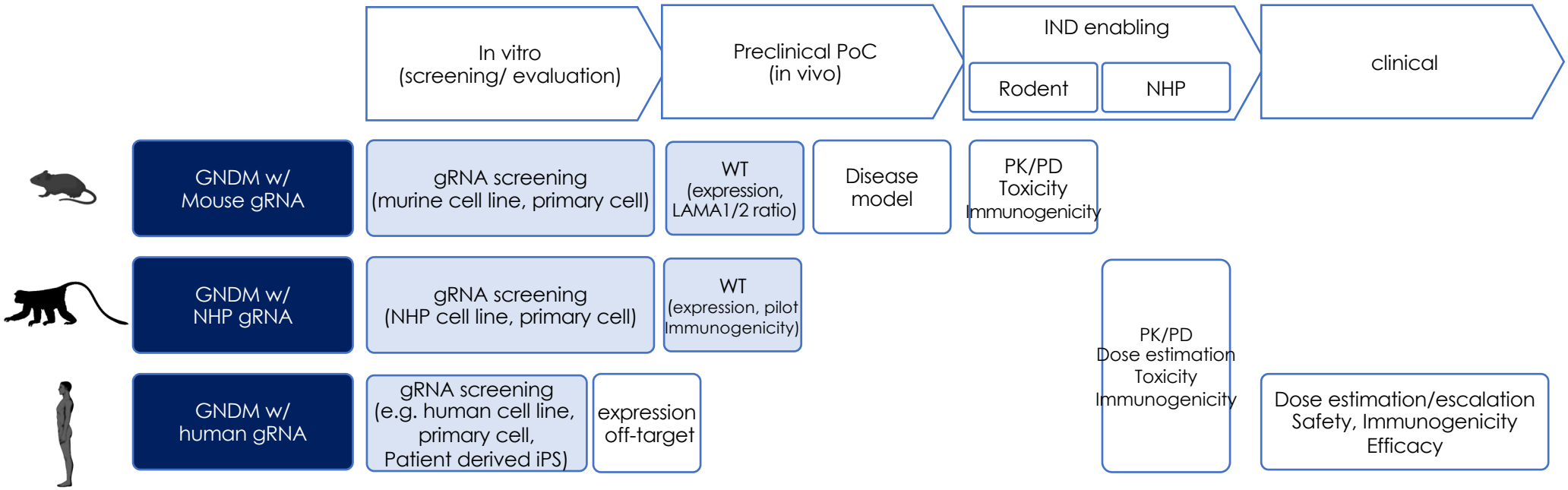


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Completed in vivo studies of MDL-101with encouraging outcome, moving towards to IND enabling studies

Path to clinic for CRISPR-GNDM®

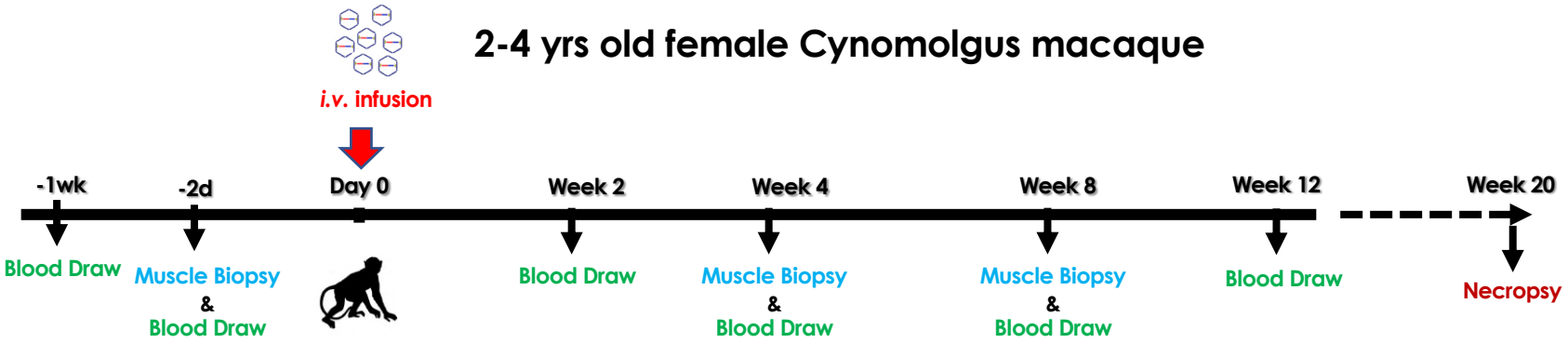


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Cynos studies with cGNDM-LAMA1 address immunogenicity concerns

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

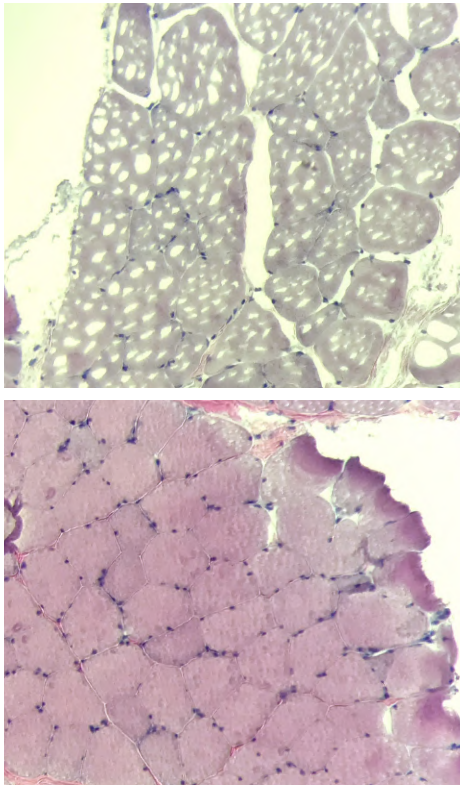


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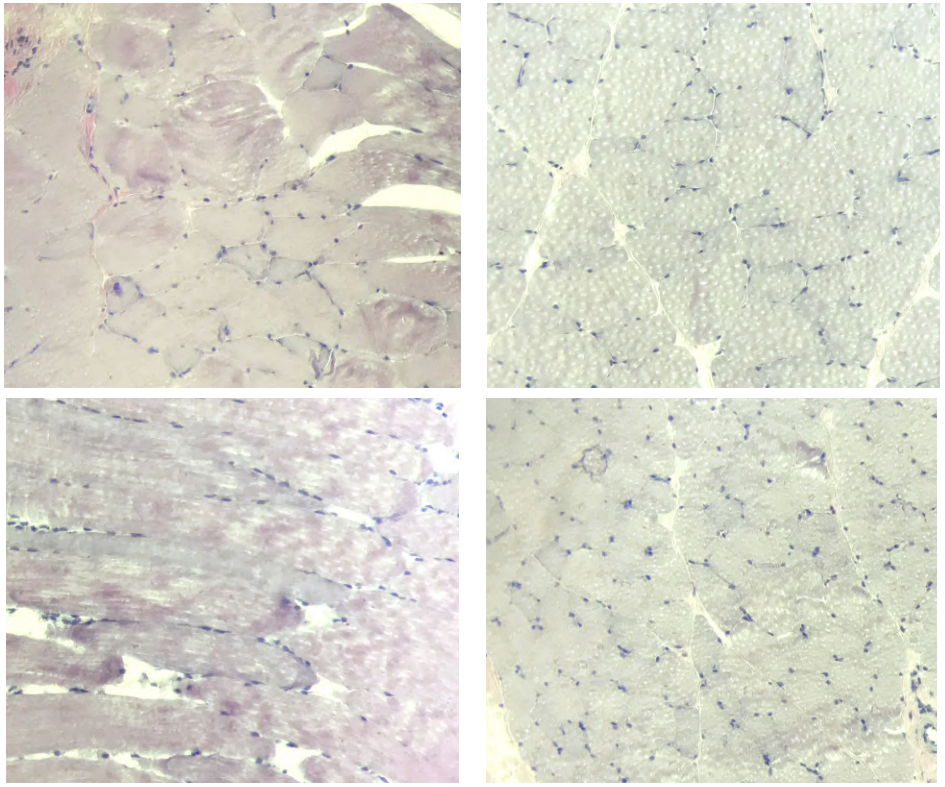
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No lymphocyte infiltration detected in AAV transduced muscle

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



Major potential concerns in animal study are eliminated

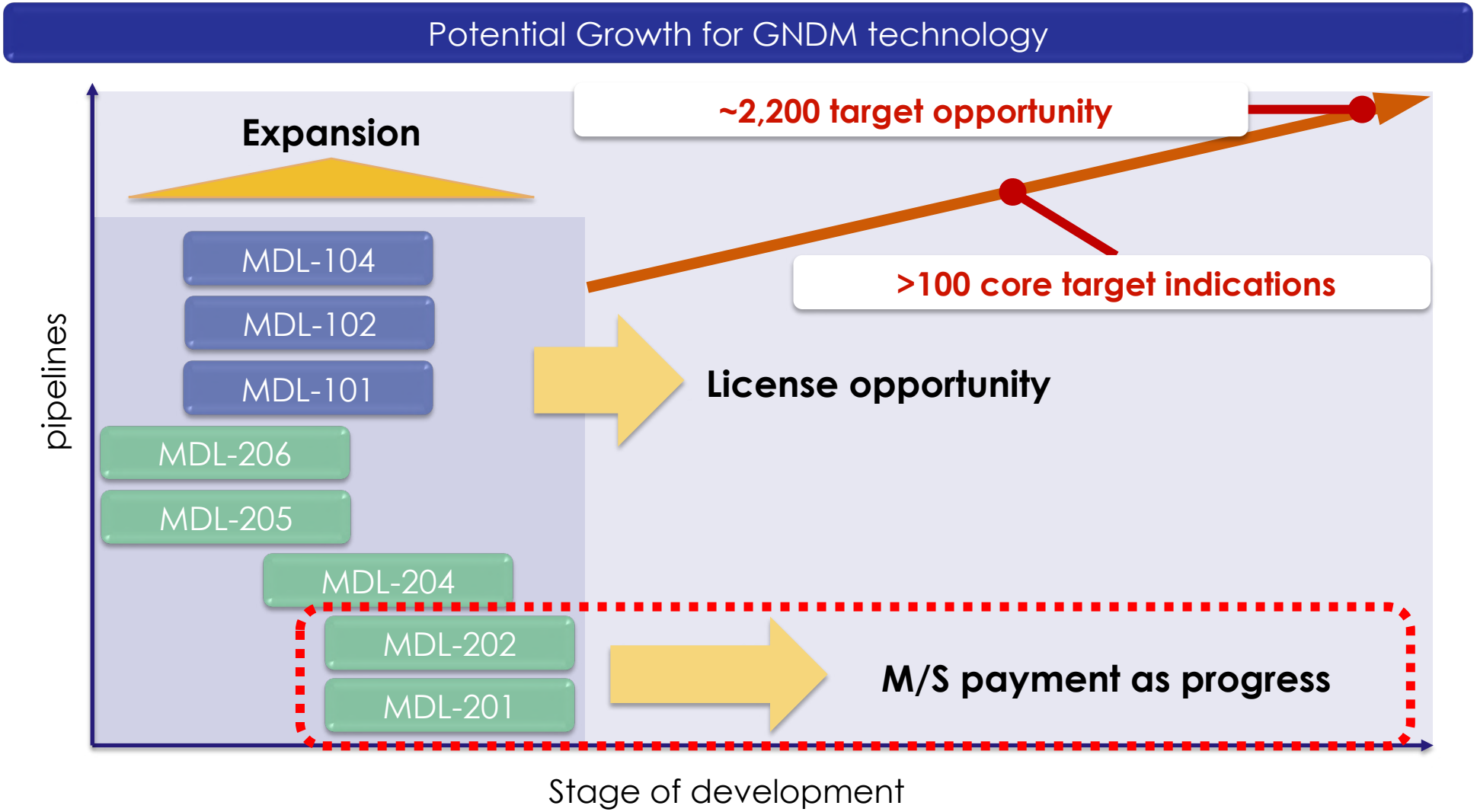
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5. Growth Strategy

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Growth Strategy
opportunity expands two dimensionally

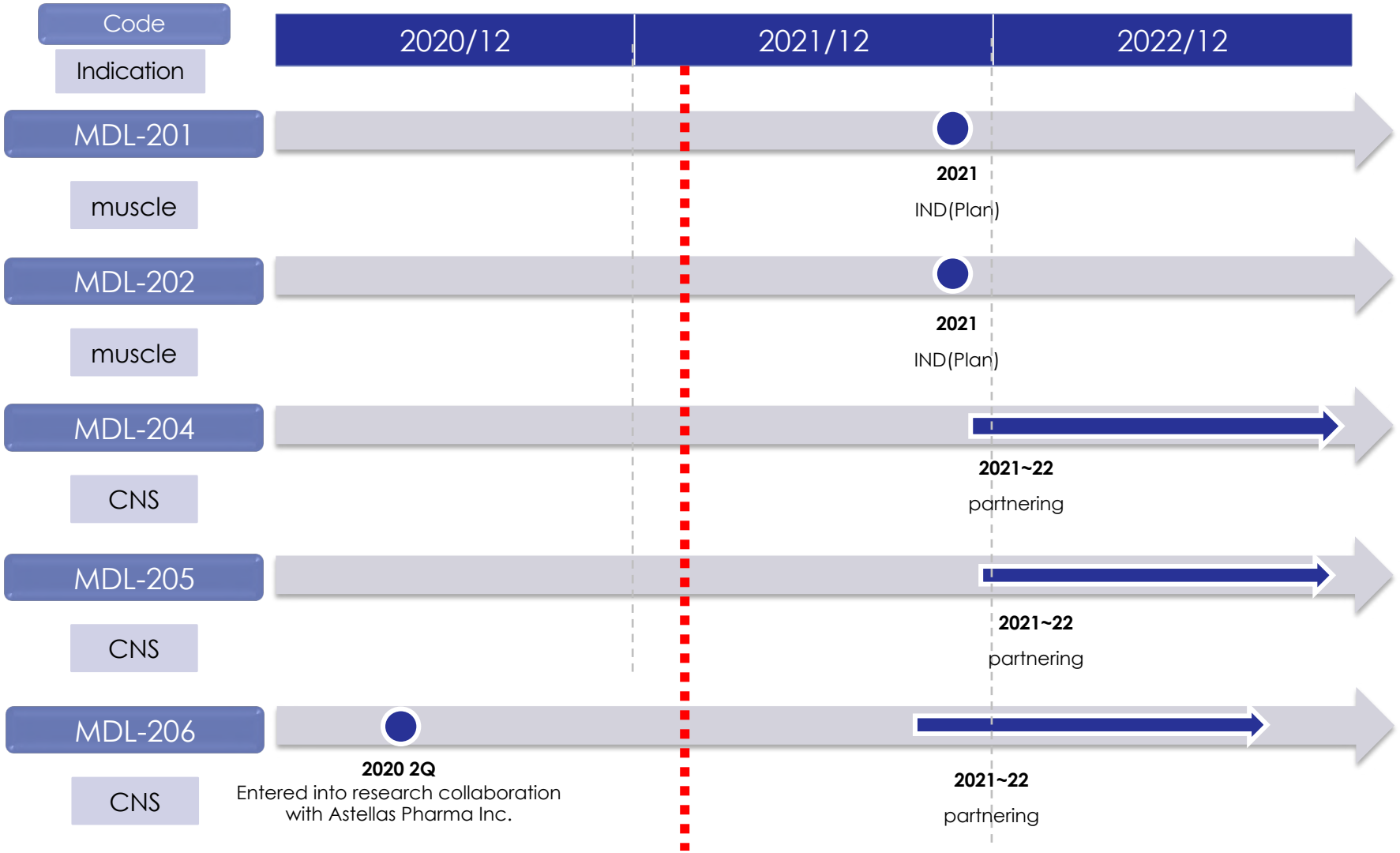


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Collaboration pipeline

Achieved and expected Milestone events*

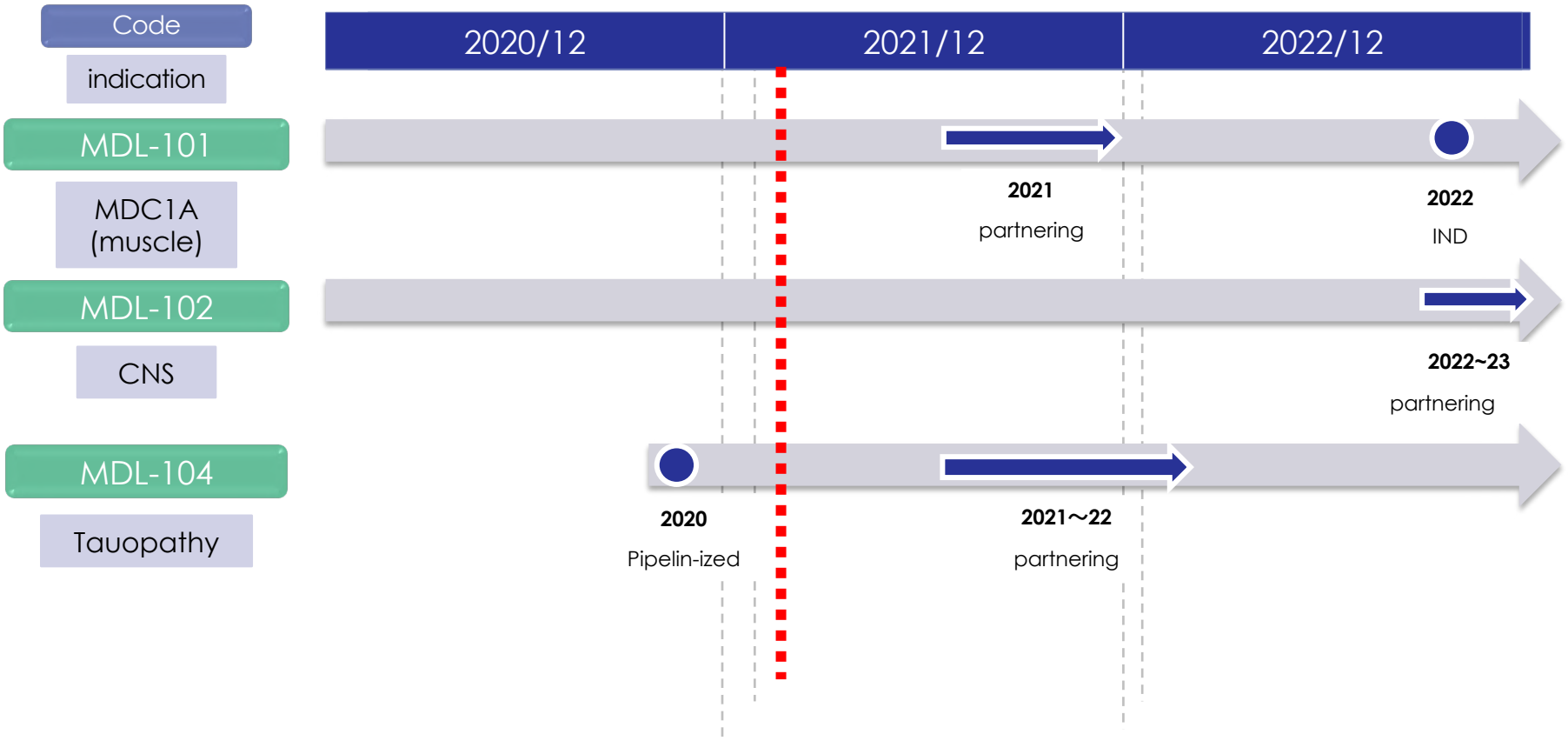


* Scheduled milestone events are informational in the future and subject to change

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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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Advantages of GNDM in our business

- Unlimited upside potential
  - >100s potential indication that GNDM is superior to the other technologies
- Bye-bye, one-in-millions
  - Predictable result and timeline based on experience and streamlined research process
- Scalable
  - Experience in one indication is easily transplanted into the other

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