English translation for reference purposes only

FY2022
Business Plans and
Matters Related to High Growth Potential



(TSE：4883)

In case of any discrepancy, the Japanese version shall prevail

Modalis therapeutics Corporation

March 29 , 2022

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1. Corporate Overview

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













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Every life deserves attention

Corporate Philosophy

Every life deserves attention

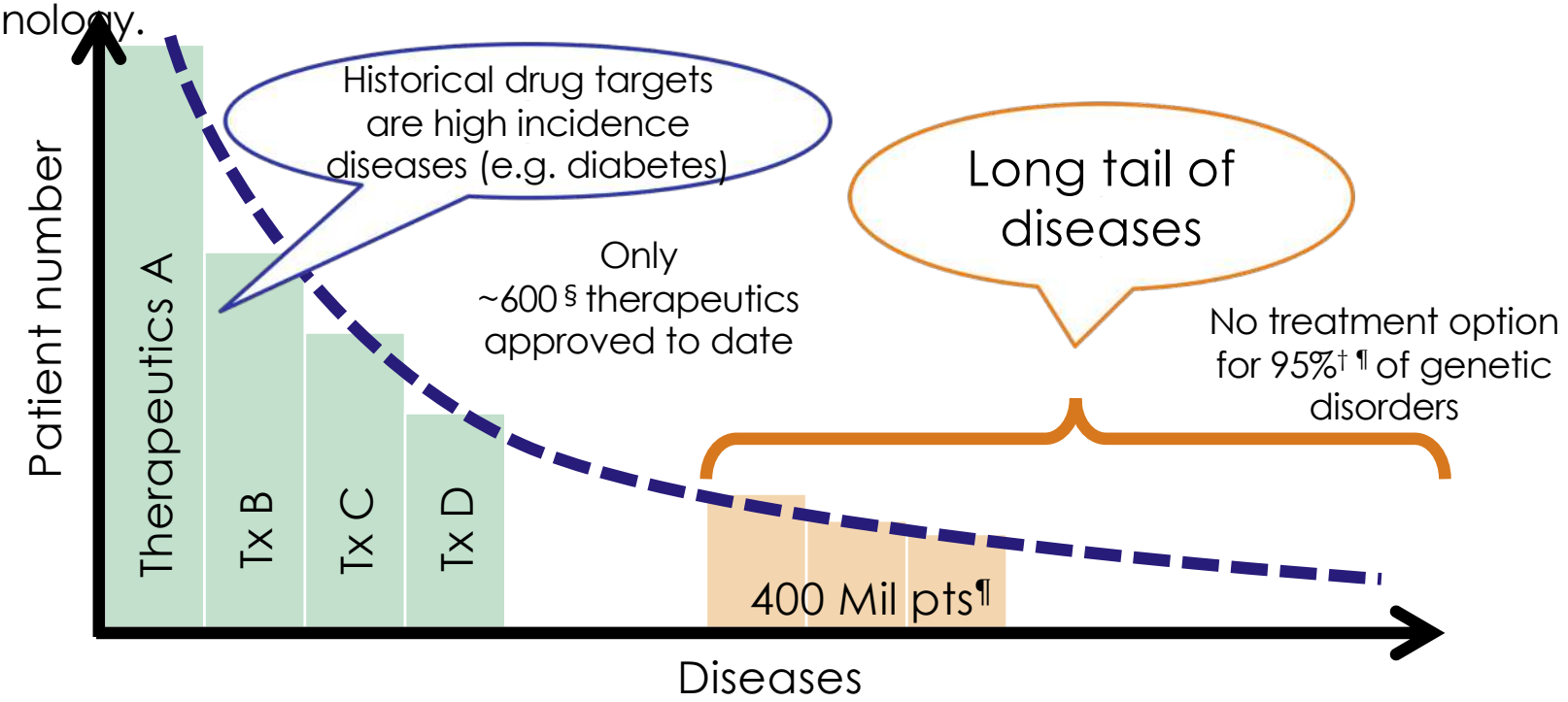
The company group, through drug discovery using the core platform technology "non-cutting CRISPR technology" (CRISPR-GNDM ® technology) to invent therapeutics targeting rare genetic disorders. True to our corporate philosophy of "every life deserves attention," we hope to contribute to society by giving 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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Corporate Overview (As of end Sep 2021)

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. (43 Foundry Avenue, Waltham, Massachusetts)
Business	Drug Development
Common stock	2,744,447 thousand yen
Outstanding share	28,967,500 common stock
Number of employee	27 (including 12 PhD) (4 in Japan, 23 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	Expanded research collaboration with **Astellas**
Mar 2019	Established license agreement on a genetic disorder with **Astellas** Pharma Inc.
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)
Oct 2021	Lab moved to To Waltham MA, which is adjacent to Cambridge

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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
- **3** on-going collaboration pipelines with large pharma companies and **4** in-house pipelines

Pharma Partnerships

- Collaboration with **3** multinational pharma companies
- Aggregated milestone of the 2 out license programs worth **>$350M** (MDL201,MDL202)

Hybrid pipeline model

- Hybrid of earlier cash flow from **collaboration pipeline** and upside potential from **In-house pipeline**

Strong team

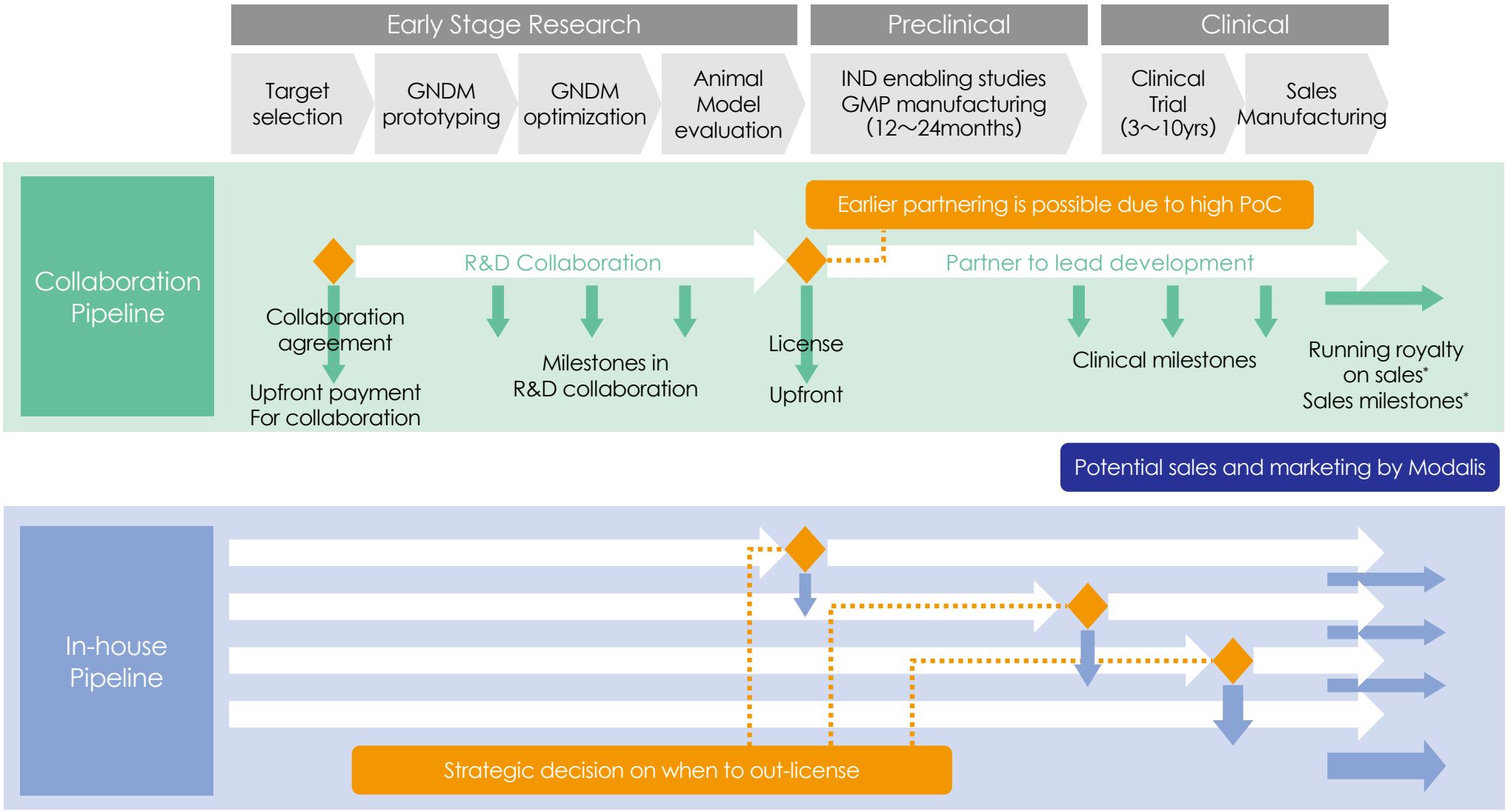
- Combination of seasoned management and talented scientists from all over the world

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Business Model

Hybrid of own pipeline and collaboration pipeline

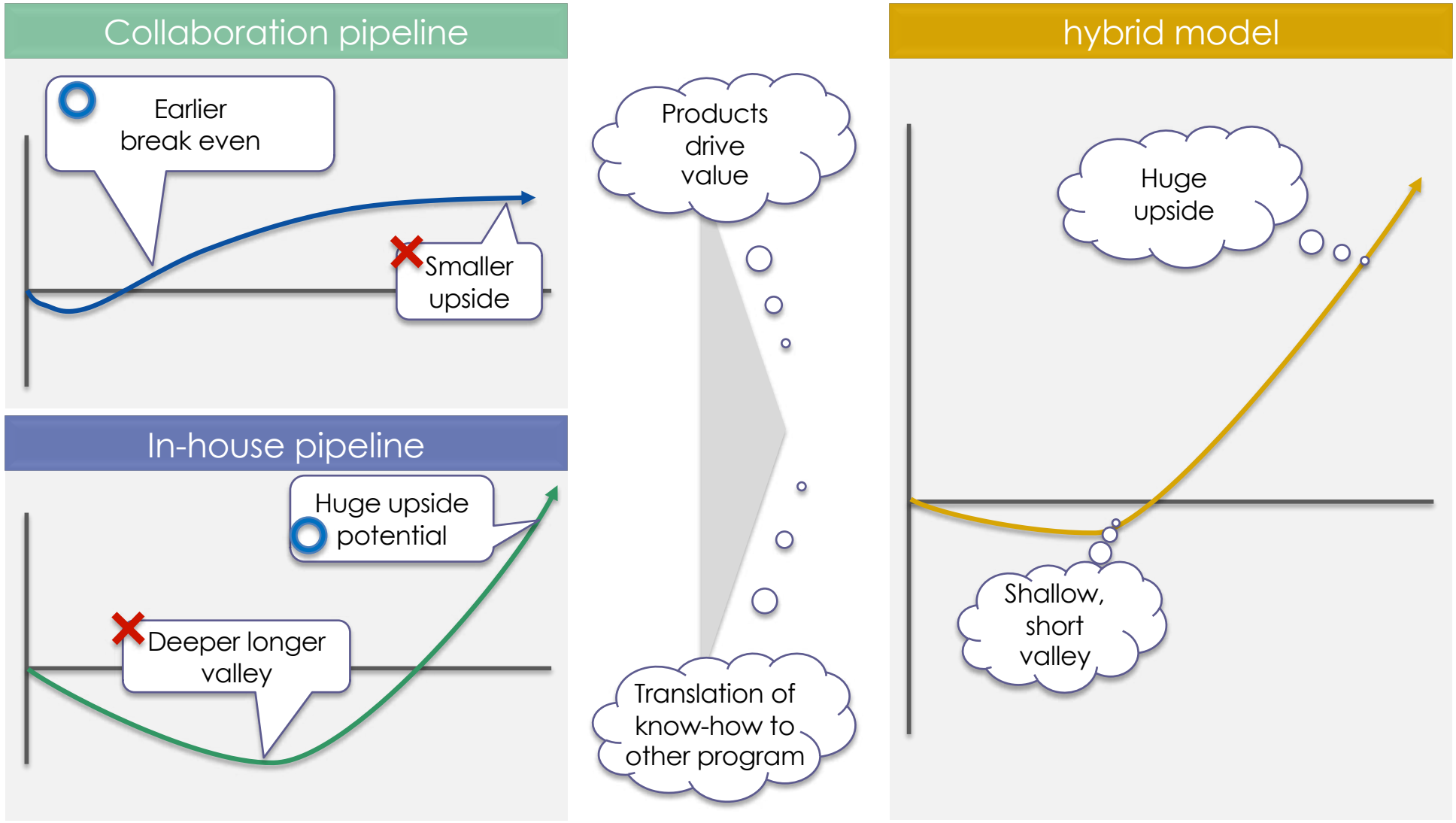


* future plan

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Modalis is pursuing a hybrid model

Combination of upside from in-house pipelines and earlier cash stream from collaboration pipelines

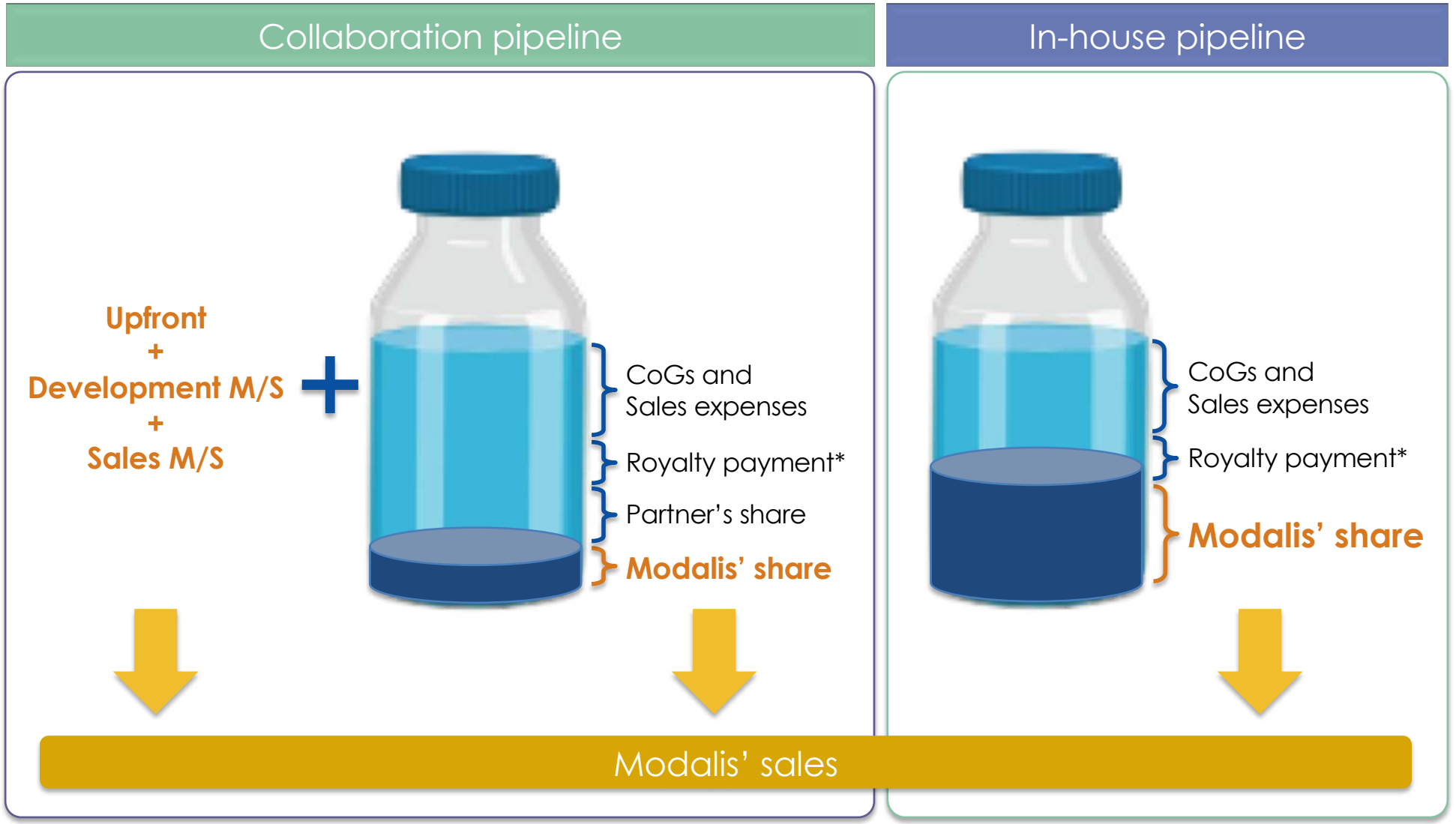


* The above is only an image and does not suggest or guarantee our future performance.

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Risk - profit share model

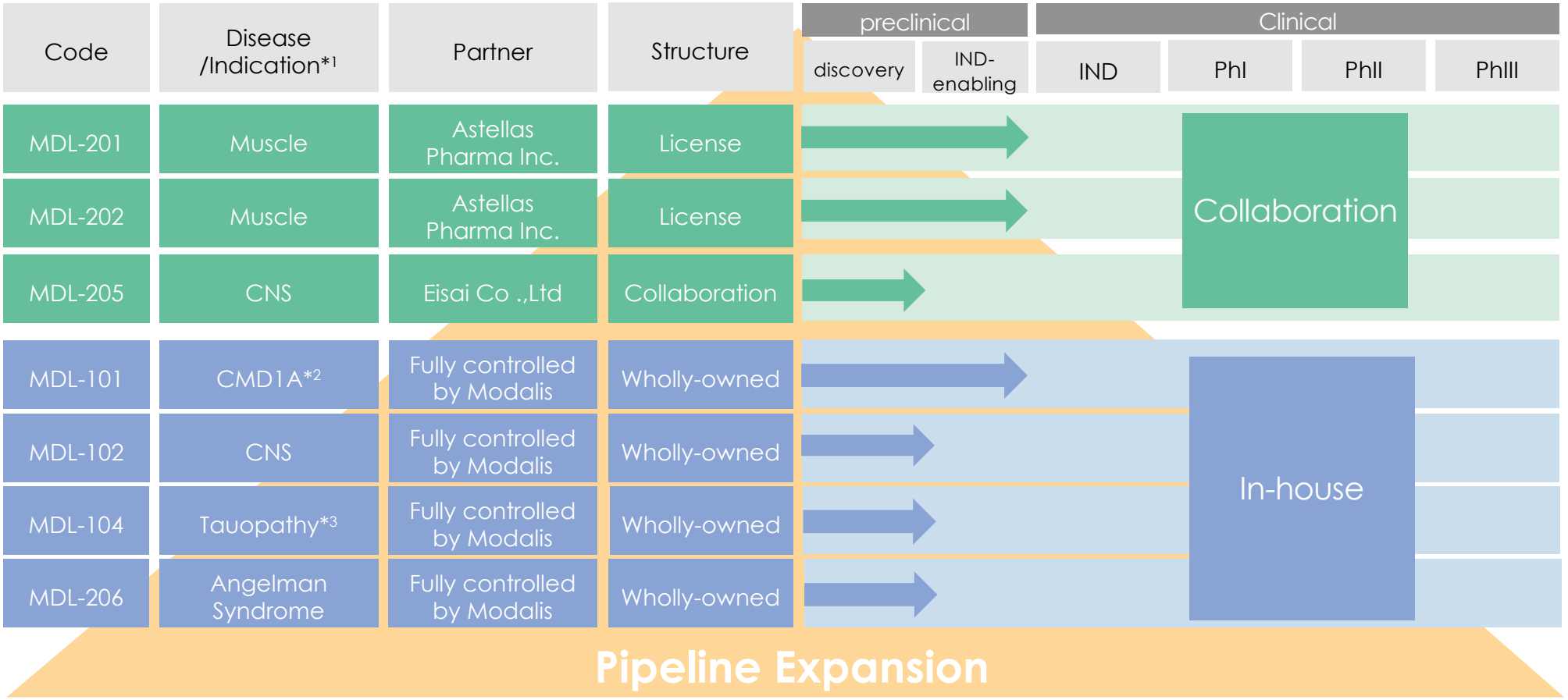
While collaboration model brings earlier cash, In-house pipeline has higher profit with higher risks



* : 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

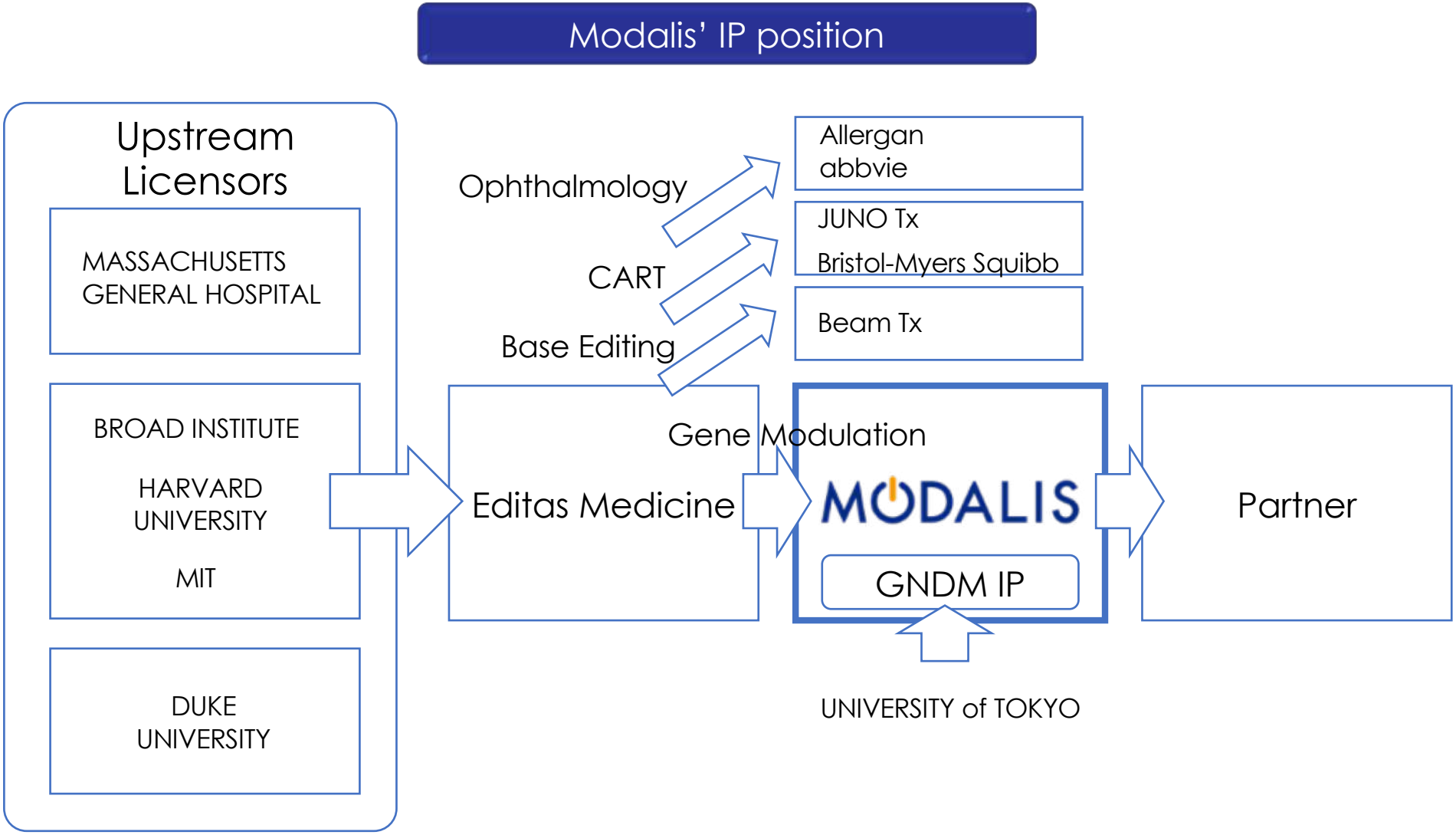


*1: We have adopted a strategy of withholding specific indications until the patent application is published for competitive reasons.
*2: CMD1A=Congenital muscular dystrophy type 1A
*3: Tauopathy belongs to a class of neurodegenerative diseases involving the aggregation of tau protein. Correlation with Alzheimer's disease has been suggested.

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IP position

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

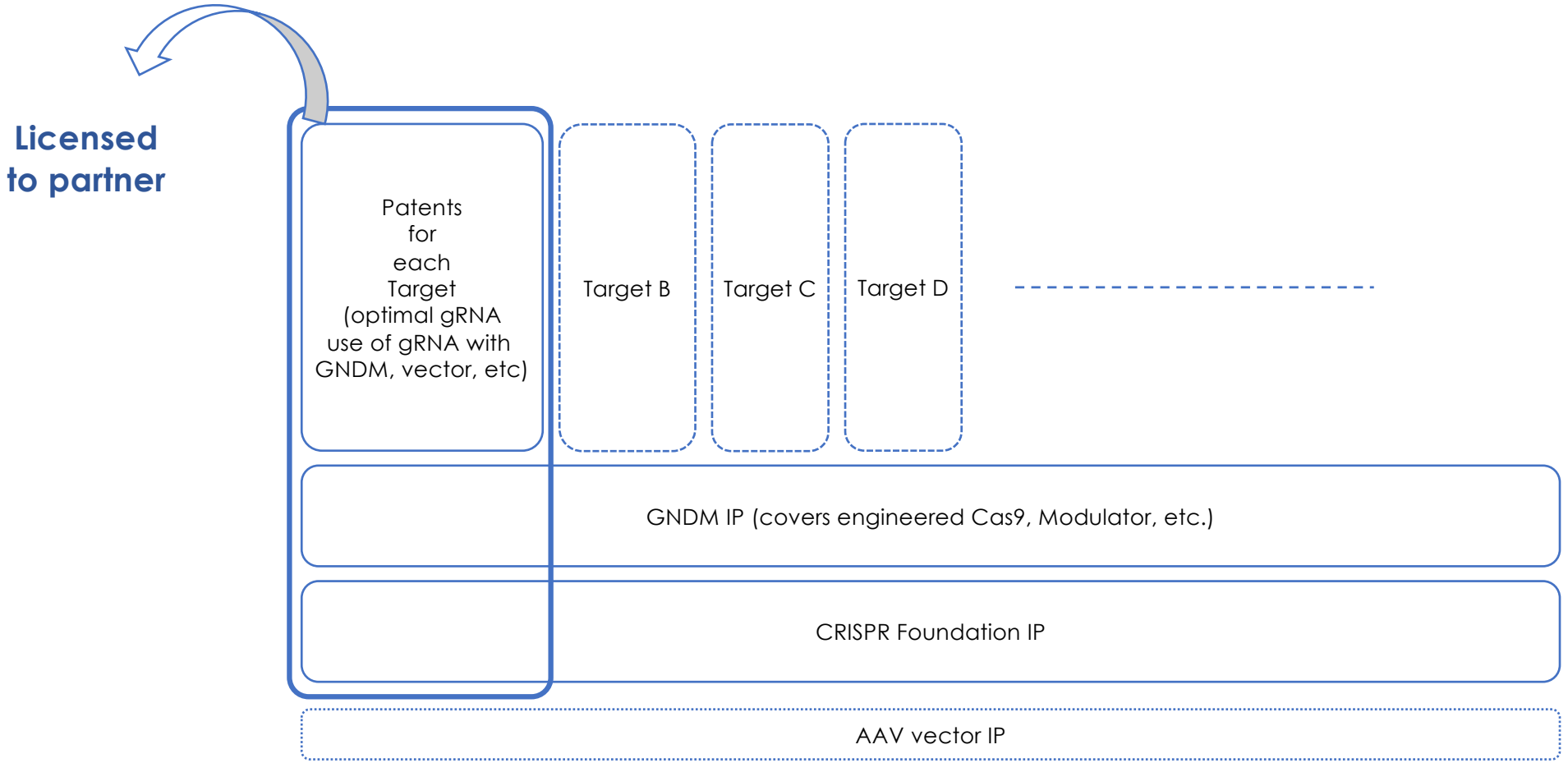


Source : disclosed information by each company

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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

Executive Officers



SVP, Chief Technology Officer

Tetsuya Yamagata, M.D. Ph.D

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



VP, Chief Financial Officer

Naoki Kobayashi, MBA

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



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 of Directors



Board member

Hideki Takeda

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



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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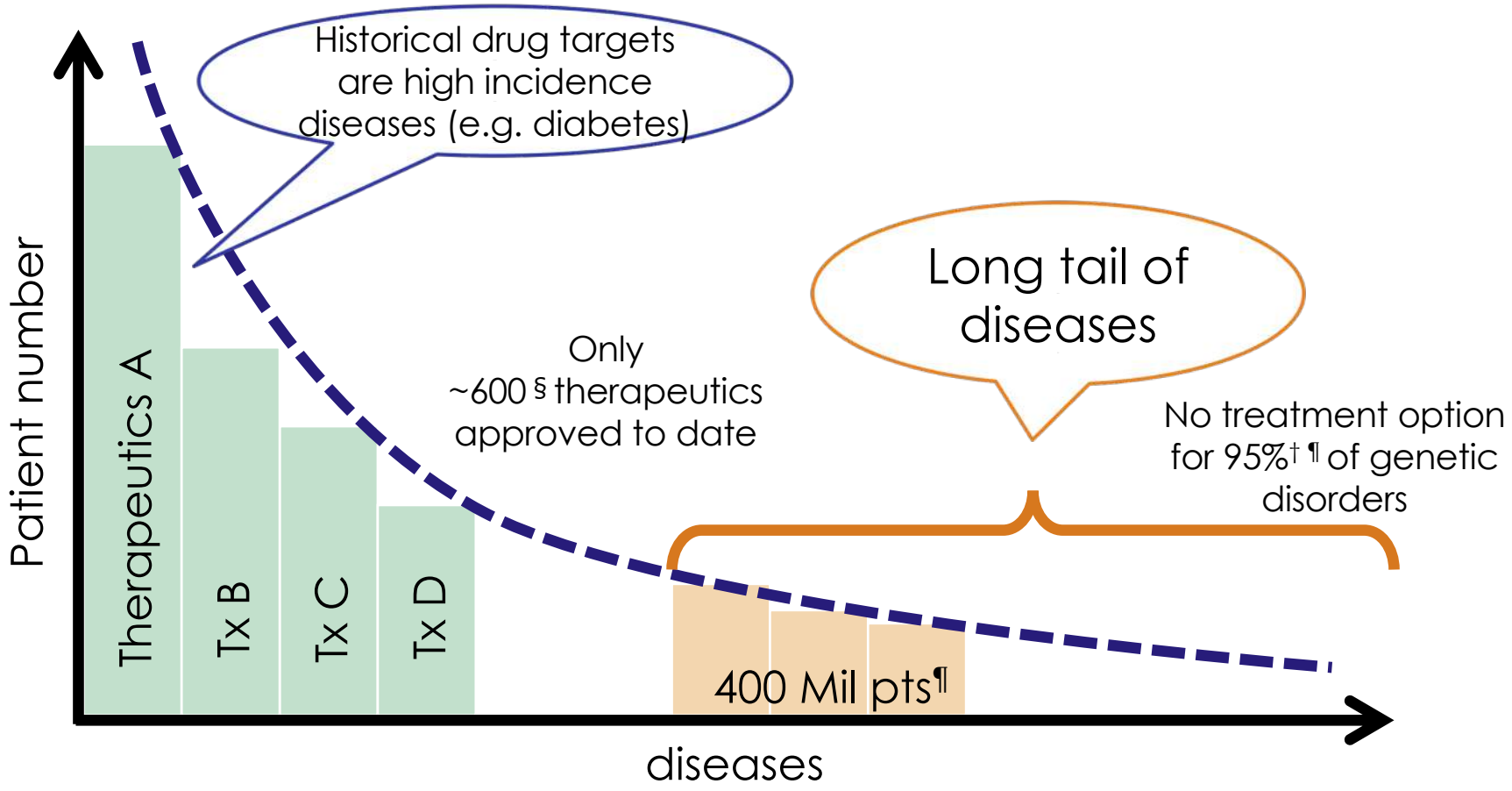
2. Gene Therapy and Gene Editing

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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

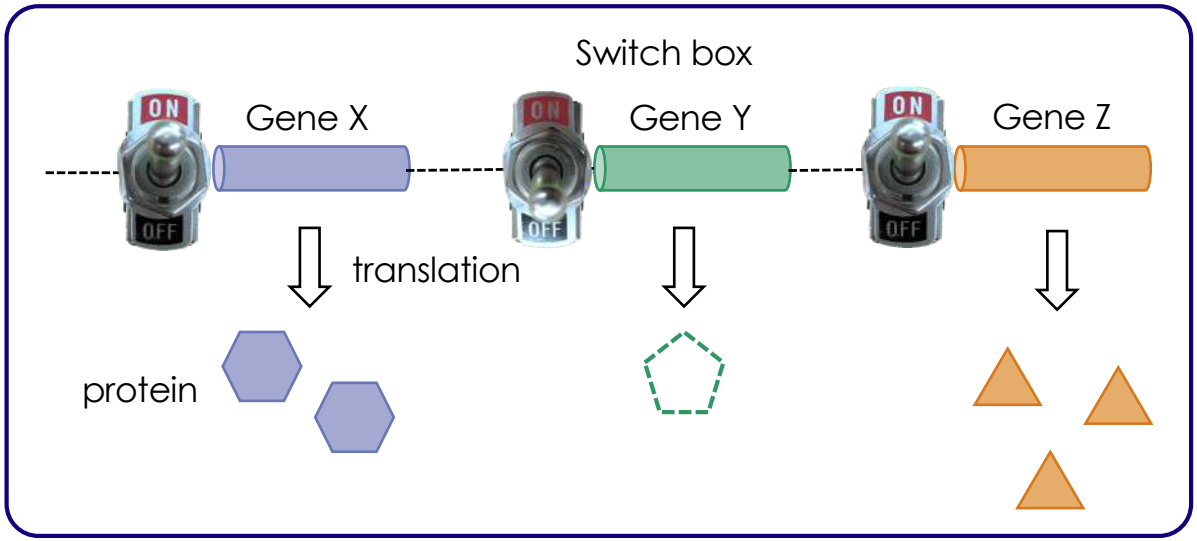
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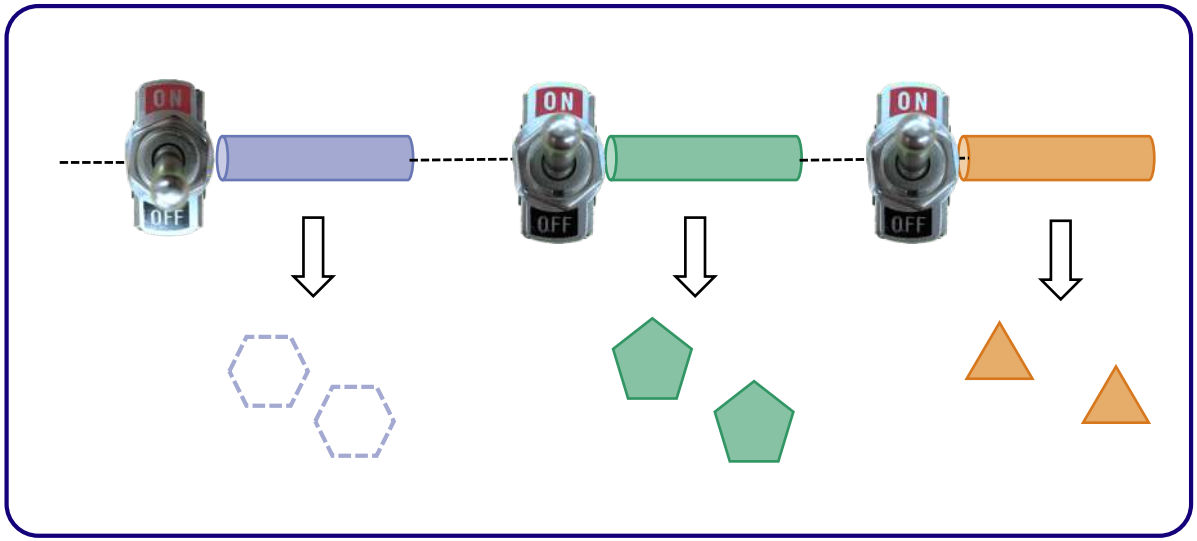
How multiple cell types are created from the same DNA code

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**

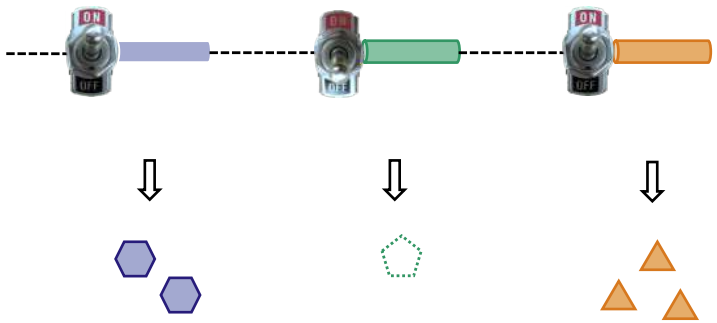
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3 types of genetic disorders

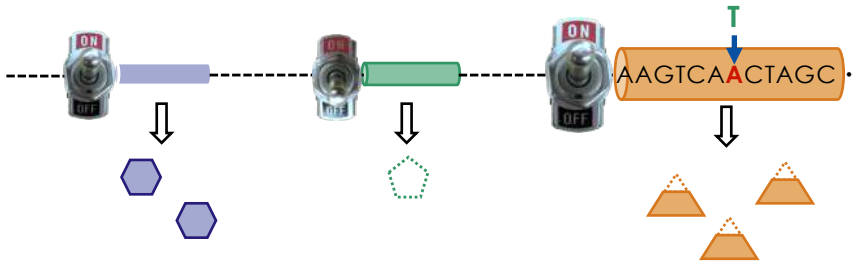
An error in the code or in switching can cause disorders

Normal state

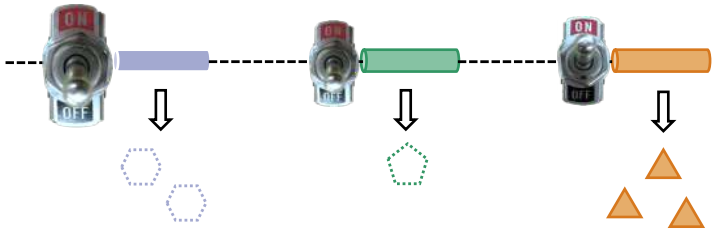


Switches control which, when and how much protein is expressed

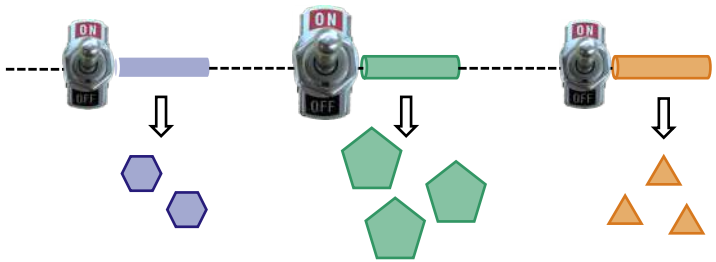
Error in the code results in a **non-functional protein**



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

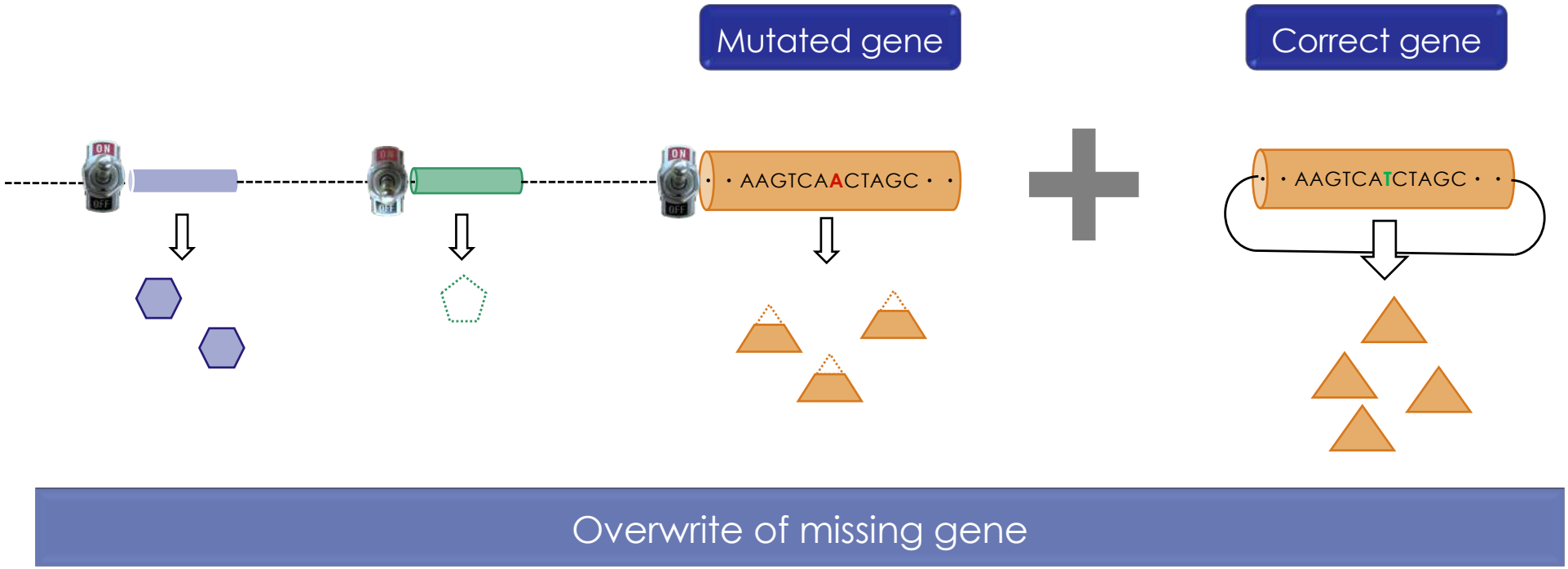


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Classical gene therapy

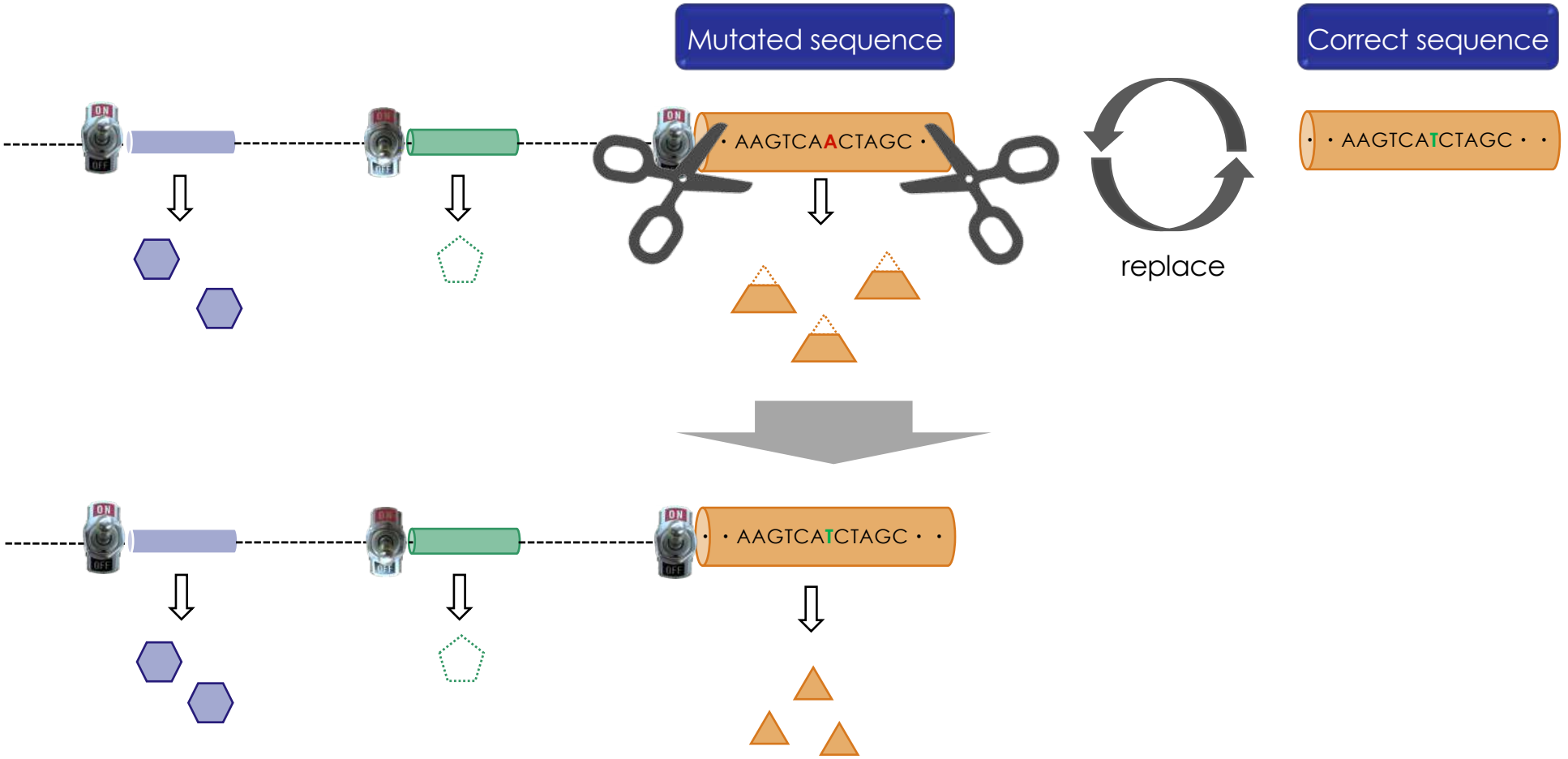
Replaces a mutated gene by inserting a correct gene exogenously



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Gene Editing

Replaces mutated DNA with correct DNA by cleaving DNA



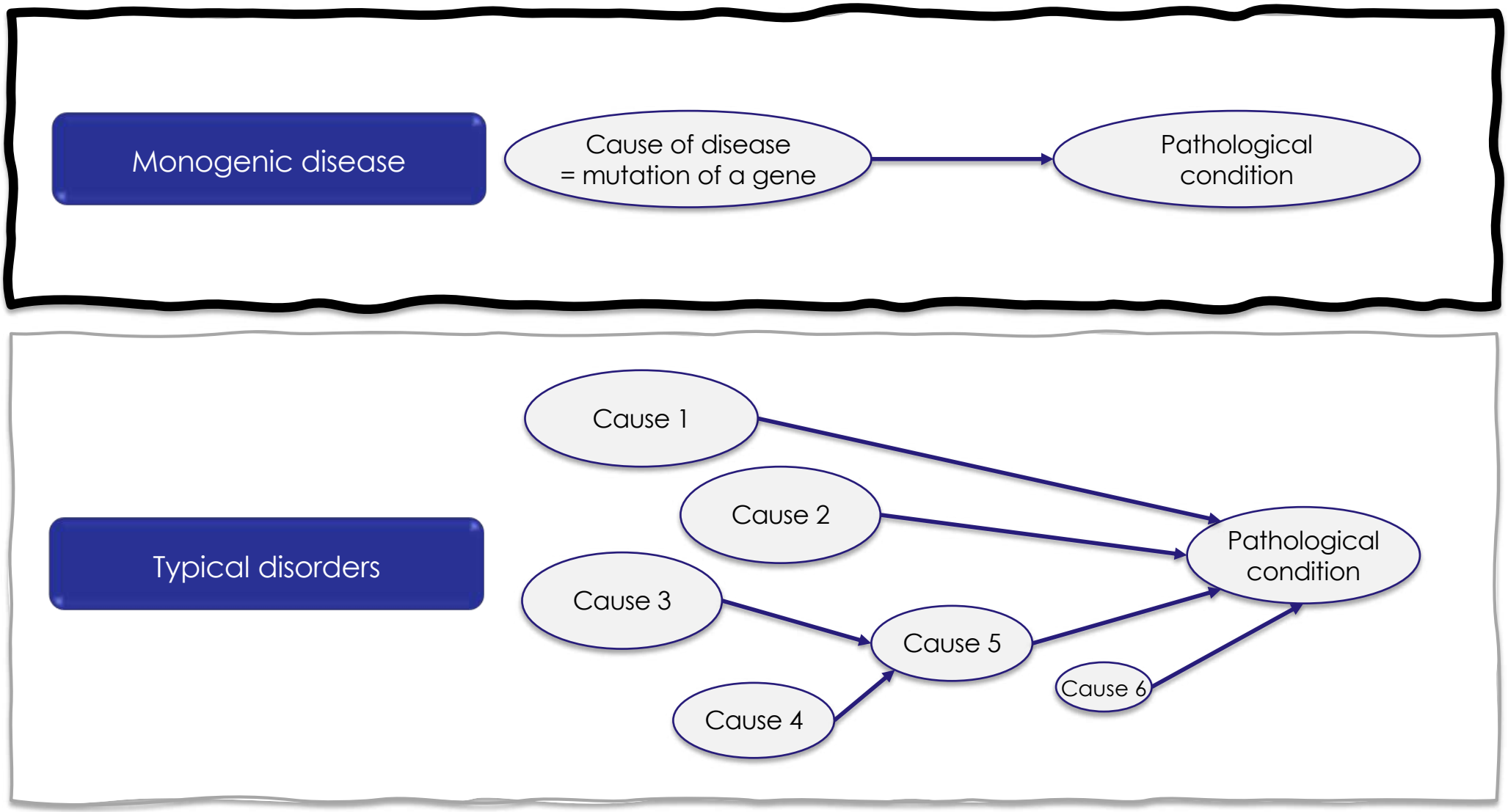
However, cleaving DNA increases risk of cancer

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Monogenic Diseases

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



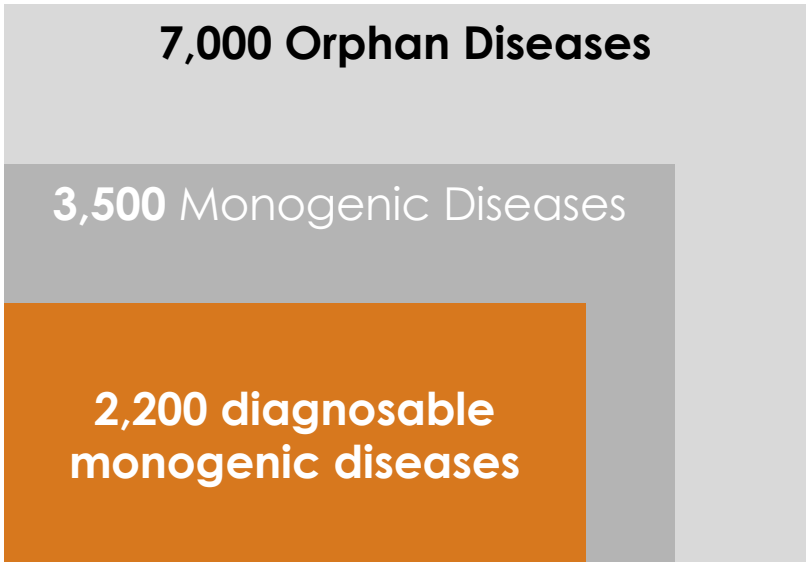
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Untapped opportunities in monogenic disorders

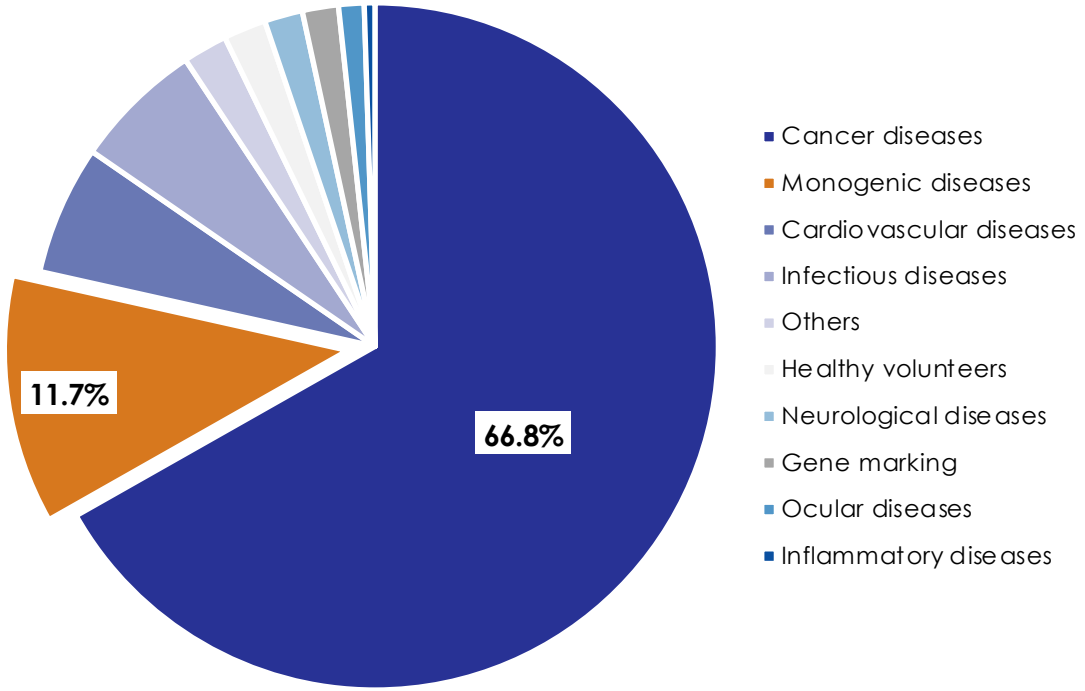
Limited number of drugs are approved or in clinical development for monogenic disorders

Monogenic Disease



Source: Discovery Medicine

Breakdown of GTx clinical trials (1989~ Worldwide)



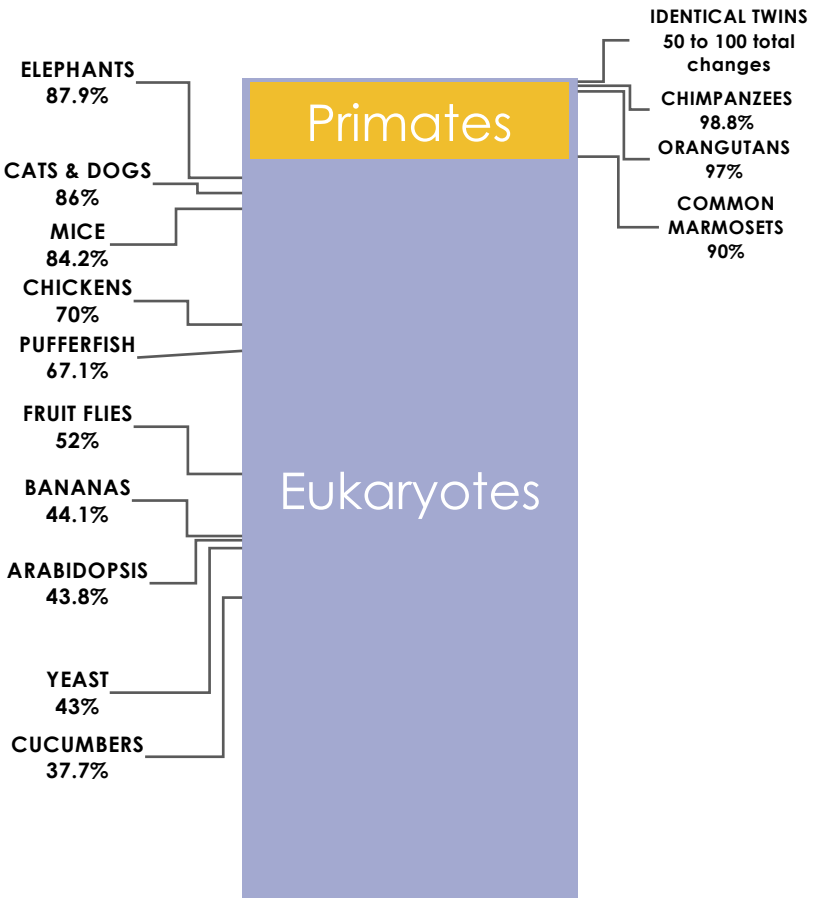
Source: The Journal of Gene Medicine (2019)

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Why GTx outcome is predictable?

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





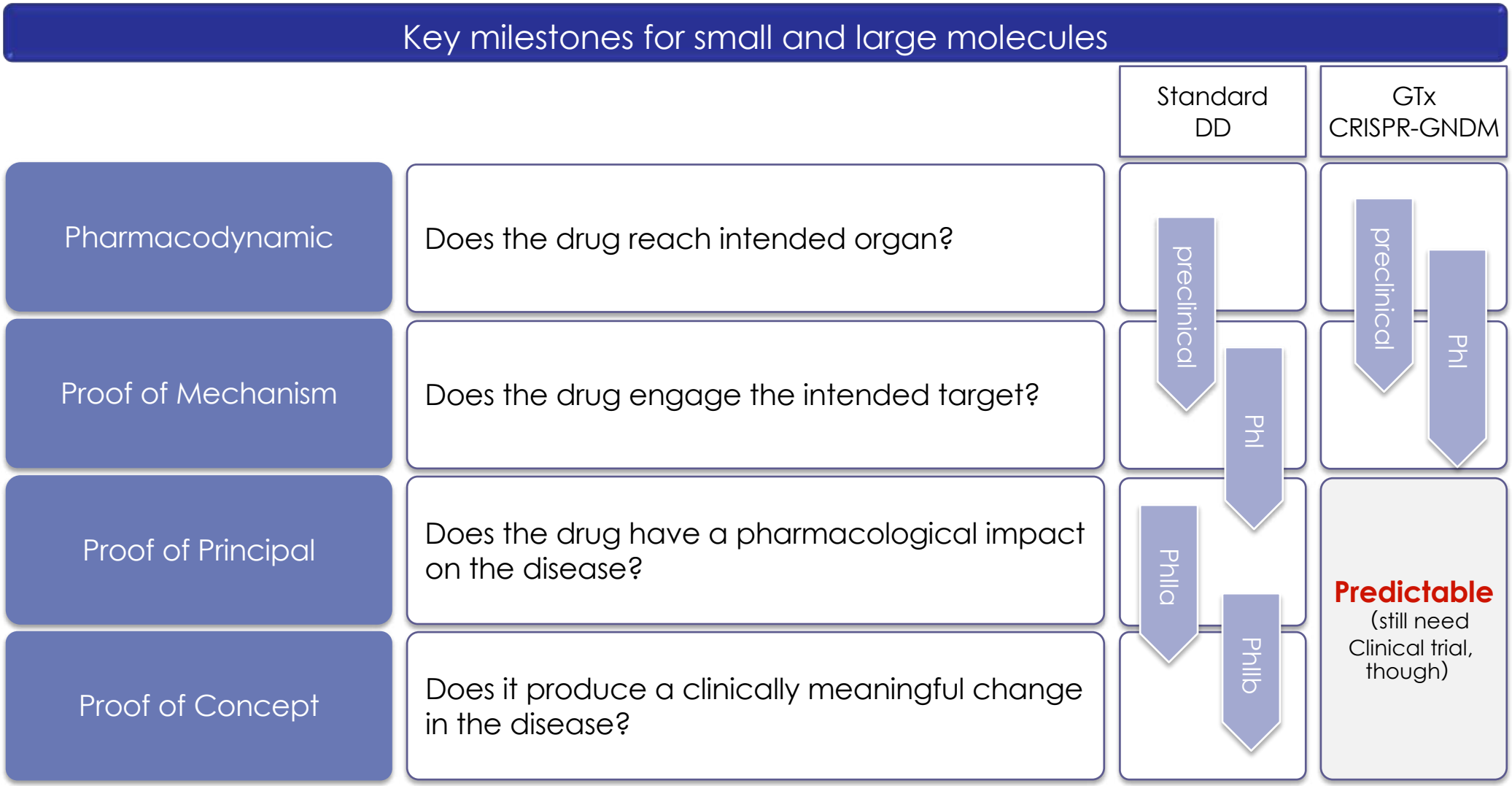
Humans share 40% of their genes with cucumbers

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)

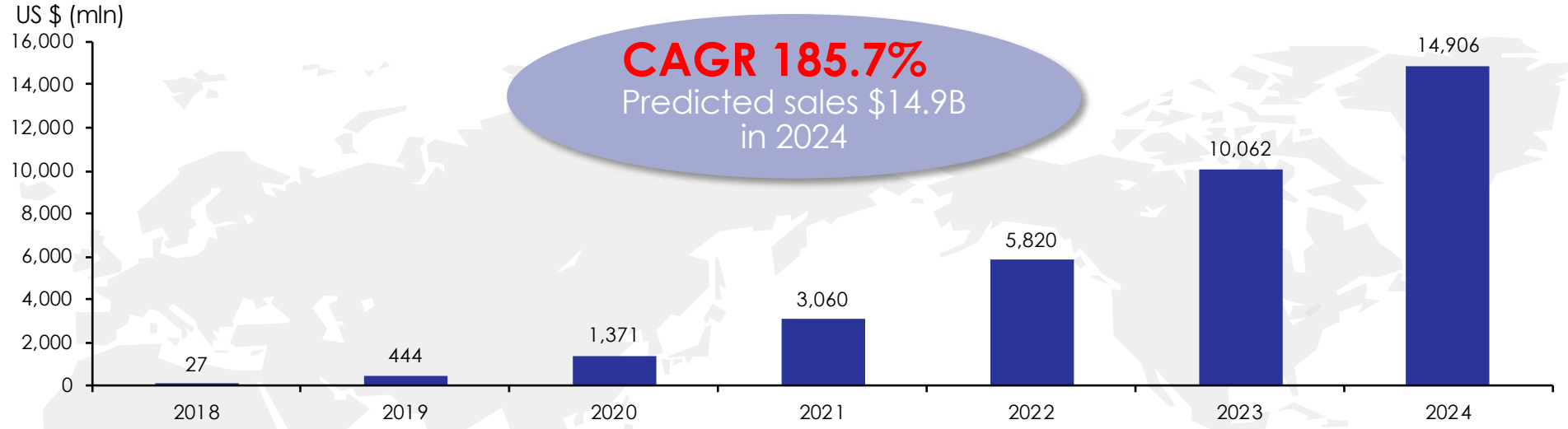
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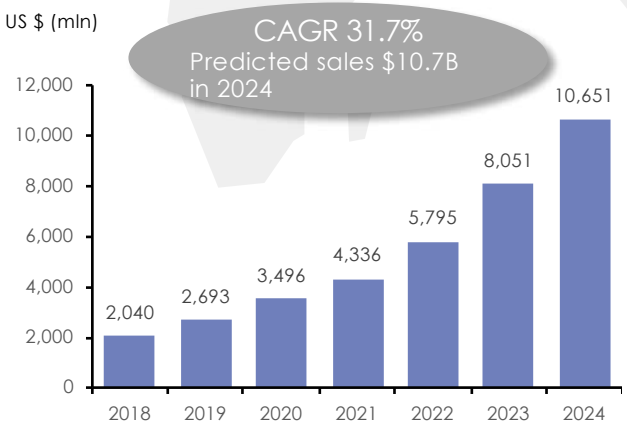
Sales growth of pharmaceutical modalities

GTx is growing faster than other modalities

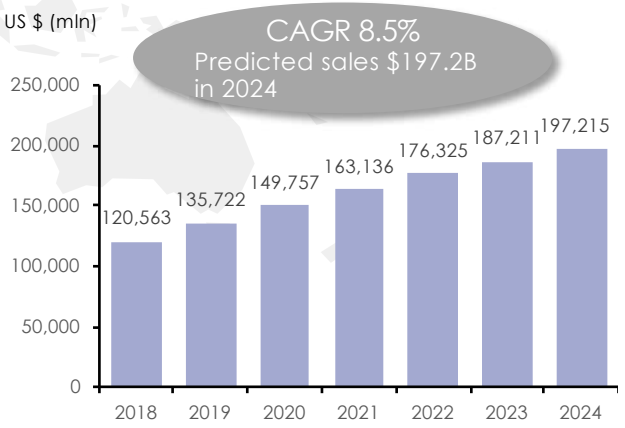
Predicted sales of Gene Therapy (WW)



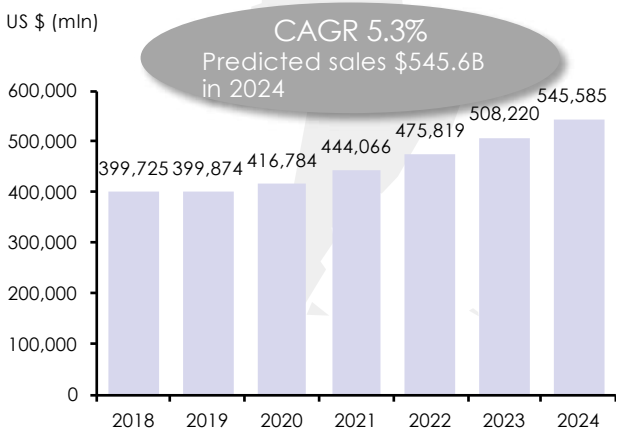
DNA&RNA therapeutics



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

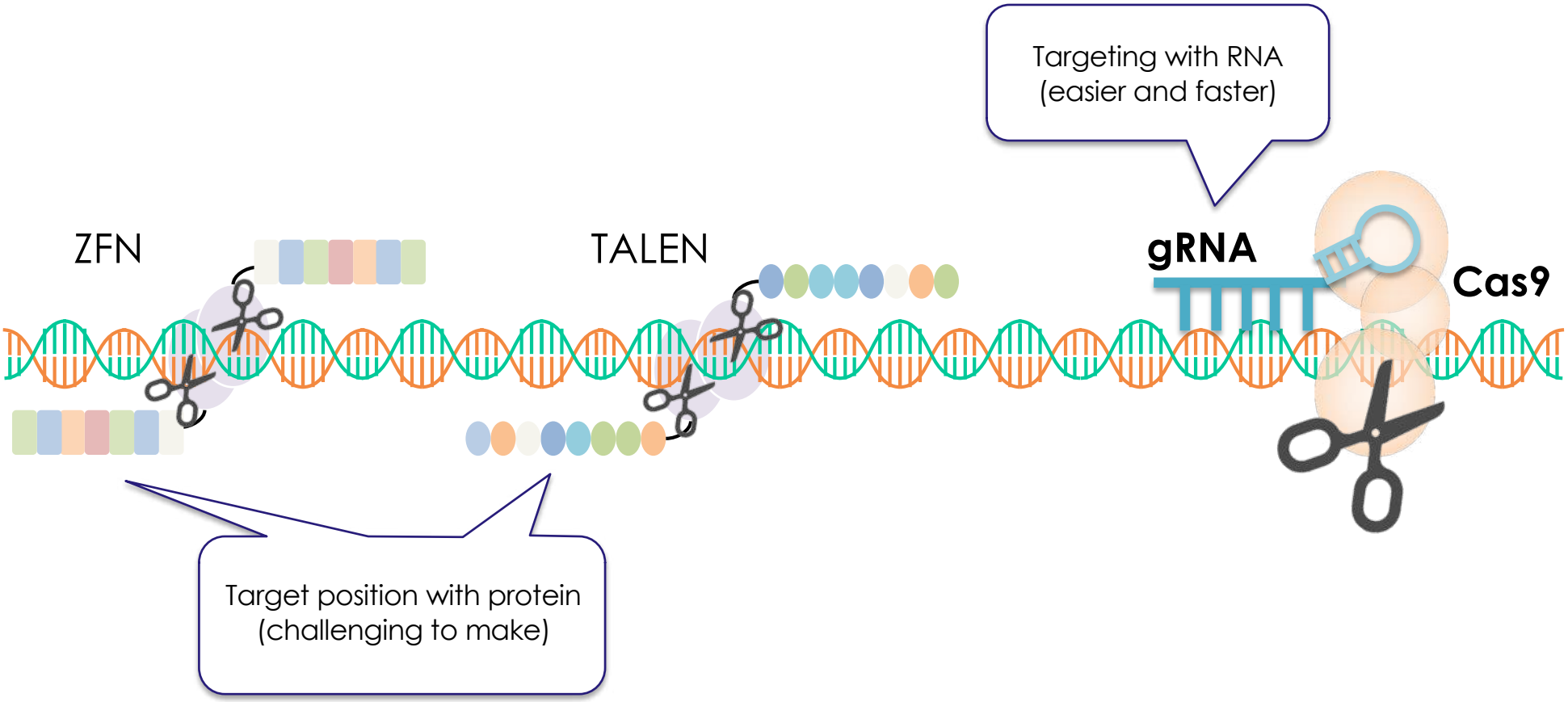
Faster and higher throughput due to limited variable region which is easily synthesizable as gRNA

Old gene editing technologies

ZFN

TALEN

CRISPR

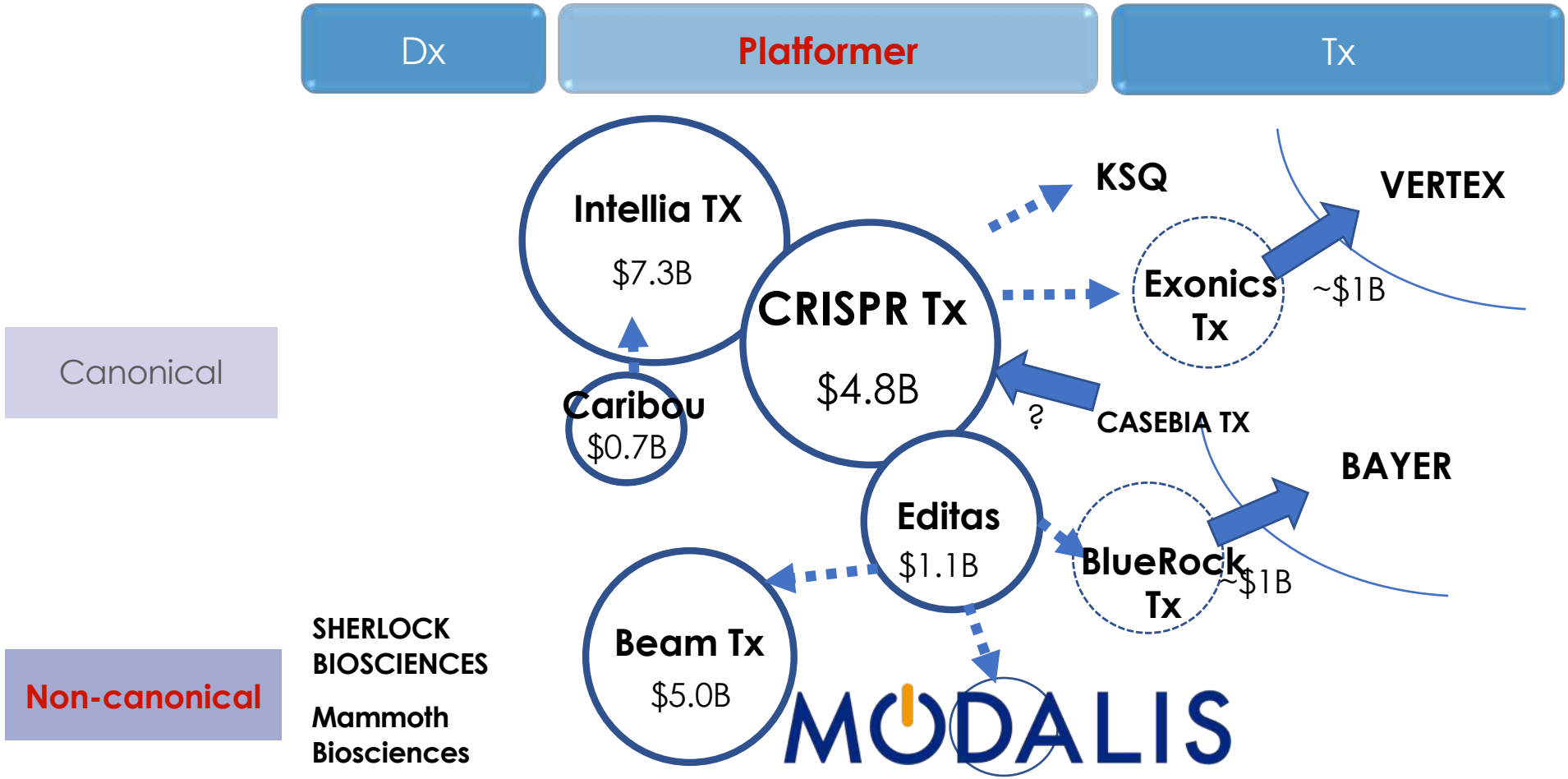


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Major players in CRISPR field

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



Source: stock info. The figures represent market cap as of Feb 15th ,2022 or value at the time of acquisition.
Dotted circle represent acquired companies

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Market size

Drug price and patient number of marketed gene therapies

Trade Name (proper name)	cost	Indication	Manufacturer	Patient Population	US market size (mil USD)*
Kymriah (tisagenlecleucel)	$475k	B-ALL	Novartis	1.6 per 100,000 (6500 new cases per yr in US)	< 3,000
Yescarta (axicabtagenecilole ucel)	$373k	NHL	Kite Pharma (Gilead)	3.8 per 100,000 (7500 new cases per yr in US)	< 2,800
Lxturna (voretigeneneparvo ec-rzyl)	$850k	RPE65	Spark Therapeutics	2 per 100,000	< 1,700
Strimvelis (GSK2696273)	$648k	ADA-SCID	GSK	0.5-0.1 per 100,000	< 324
Glybera (alipogene tiparvovec)	$1.2M	LPLD	uniQure	0.1 per 100,000	< 120

*estimated from prevalence

market size = Drug price x patient number
As drug price is hard to be estimated until we see its clinical benefit, it is hard to estimate market size, which is the function of drug price
On the other hand, it is possible to go beyond $1B in US or $2B in WW unless it is ultra orphan

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3. CRISPR-GNDM® and its advantages

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Gene Modulation is CRISPR 2.0



"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."

-Jennifer Doudna, Nobel Prize Winner on CRISPR
Source: "Fresh Off Her Nobel Prize Win, Jennifer Doudna Predicts What's Next for CRISPR"

CRISPR-GNDM®

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

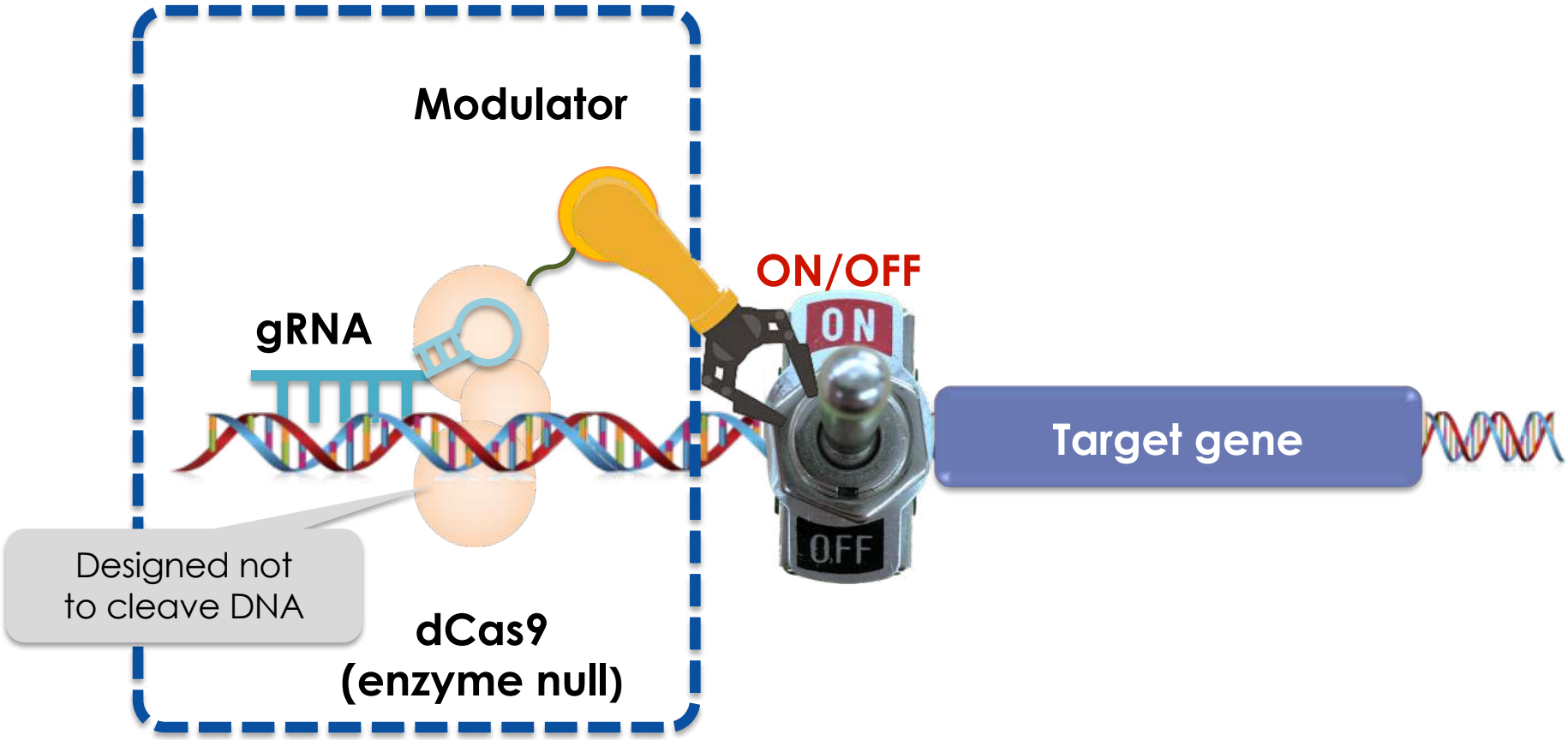
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Non-cleaving CRISPR = CRISPR-GNDM®

Enables treatment of genetic disorders by controlling ON/OFF switch

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

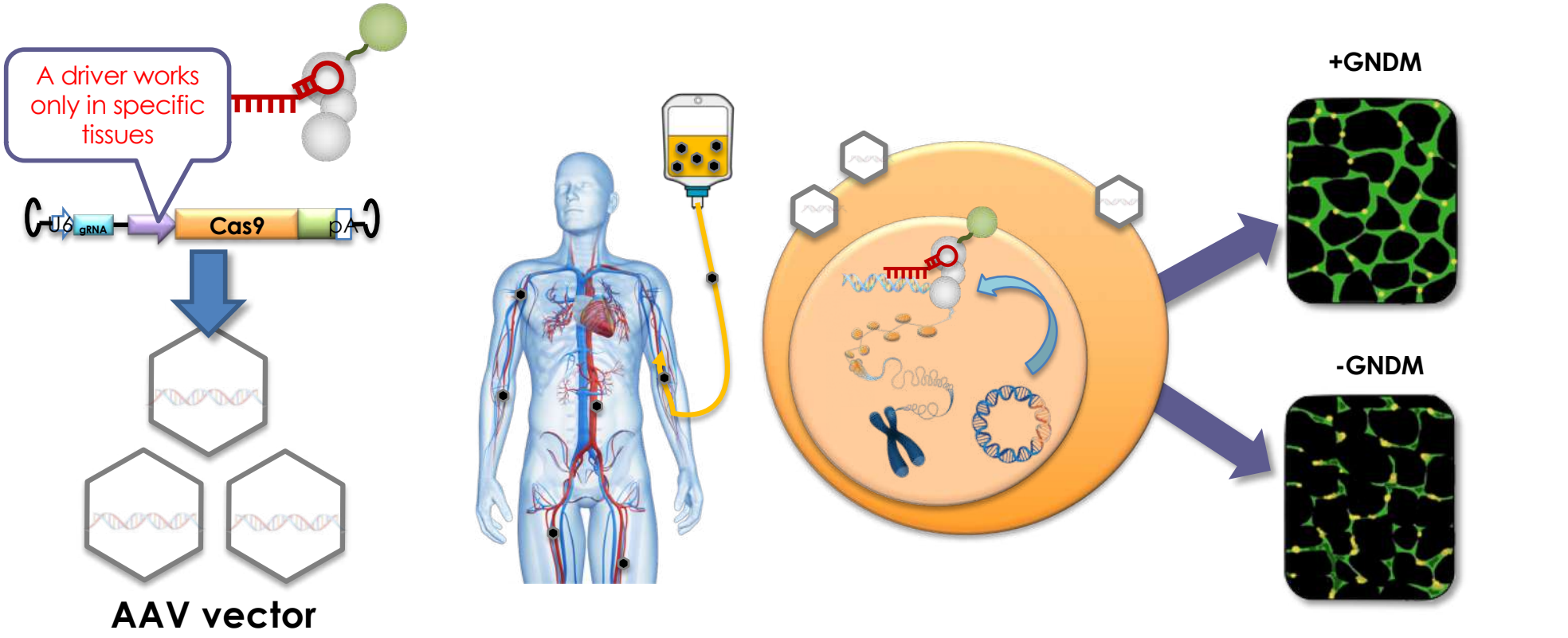


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Delivery of CRISPR-GNDM® to target

Use AAV vector to deliver GNDM to target cell

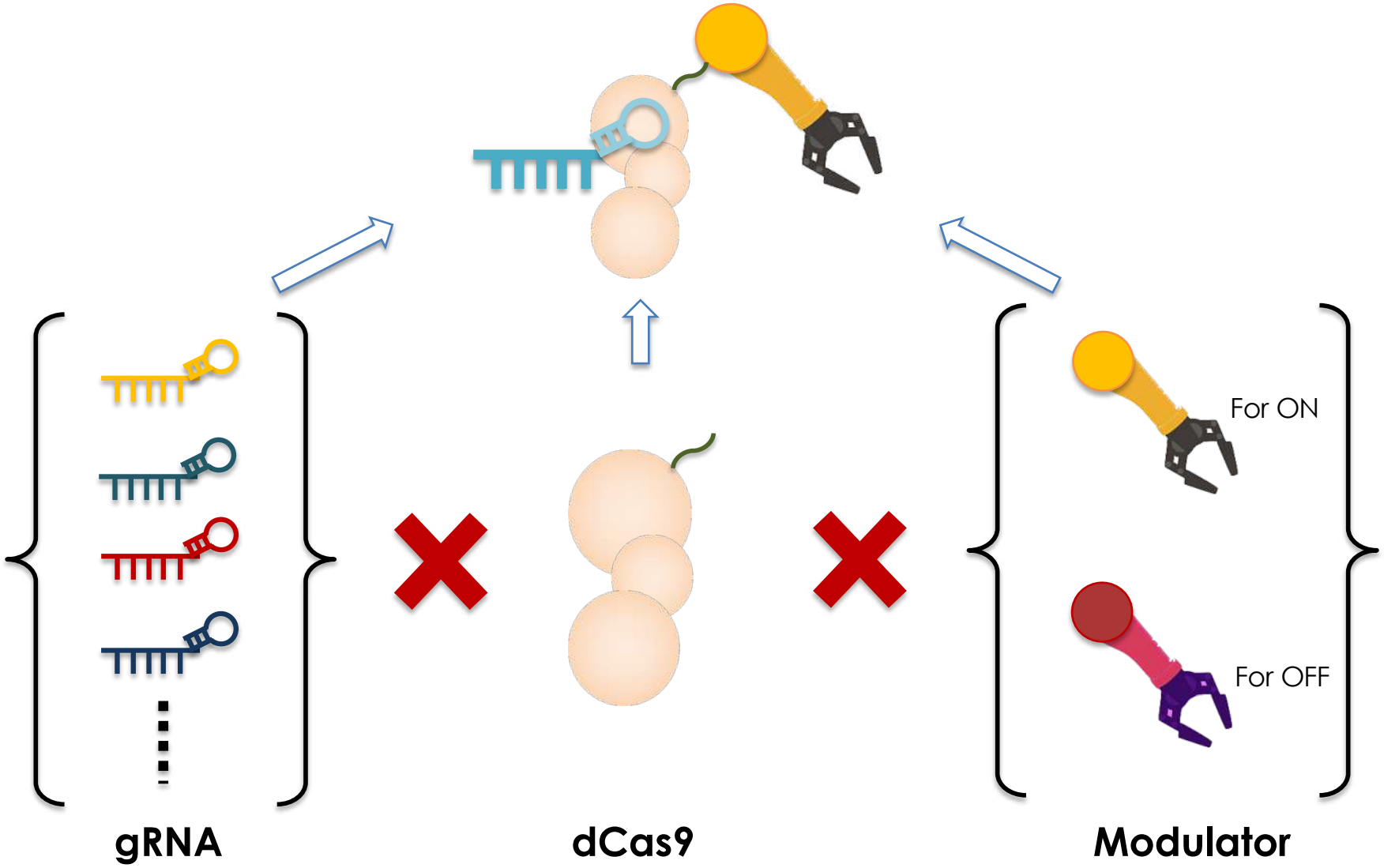


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Scalability of GNDM

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

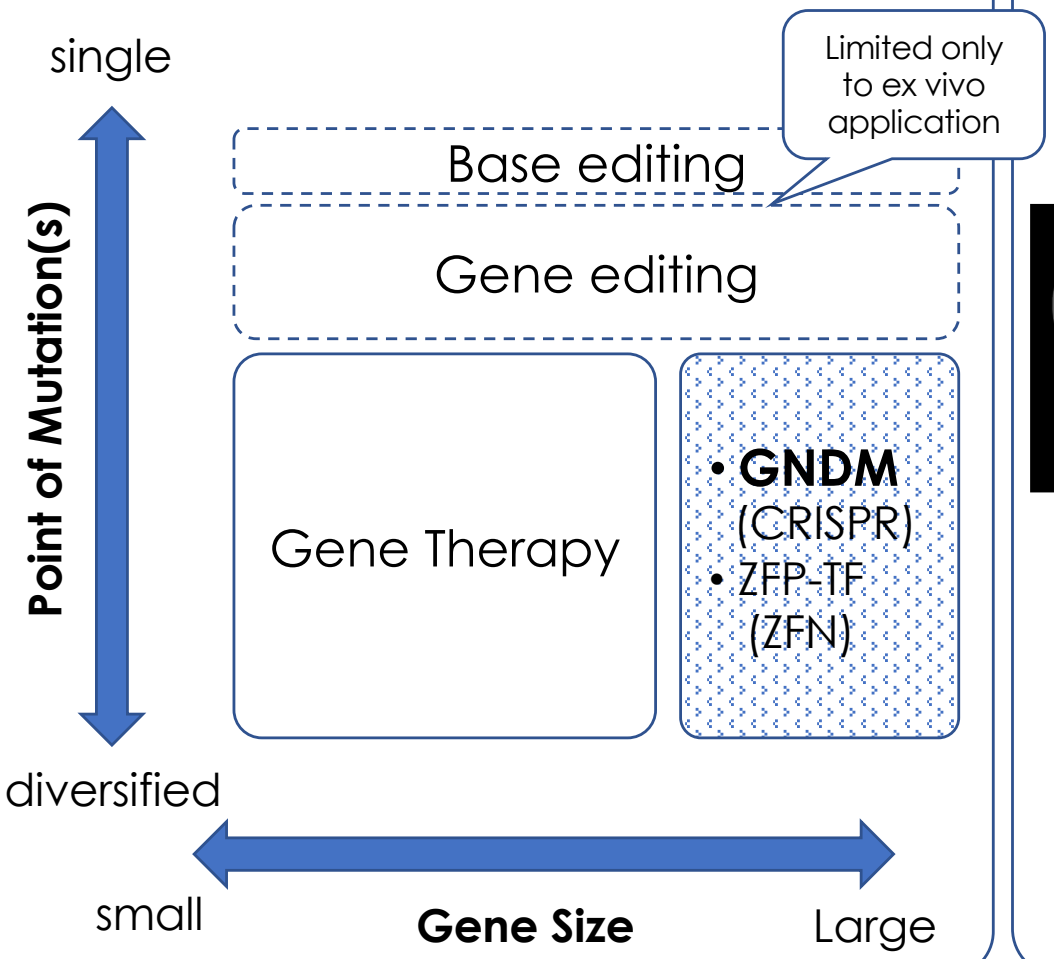


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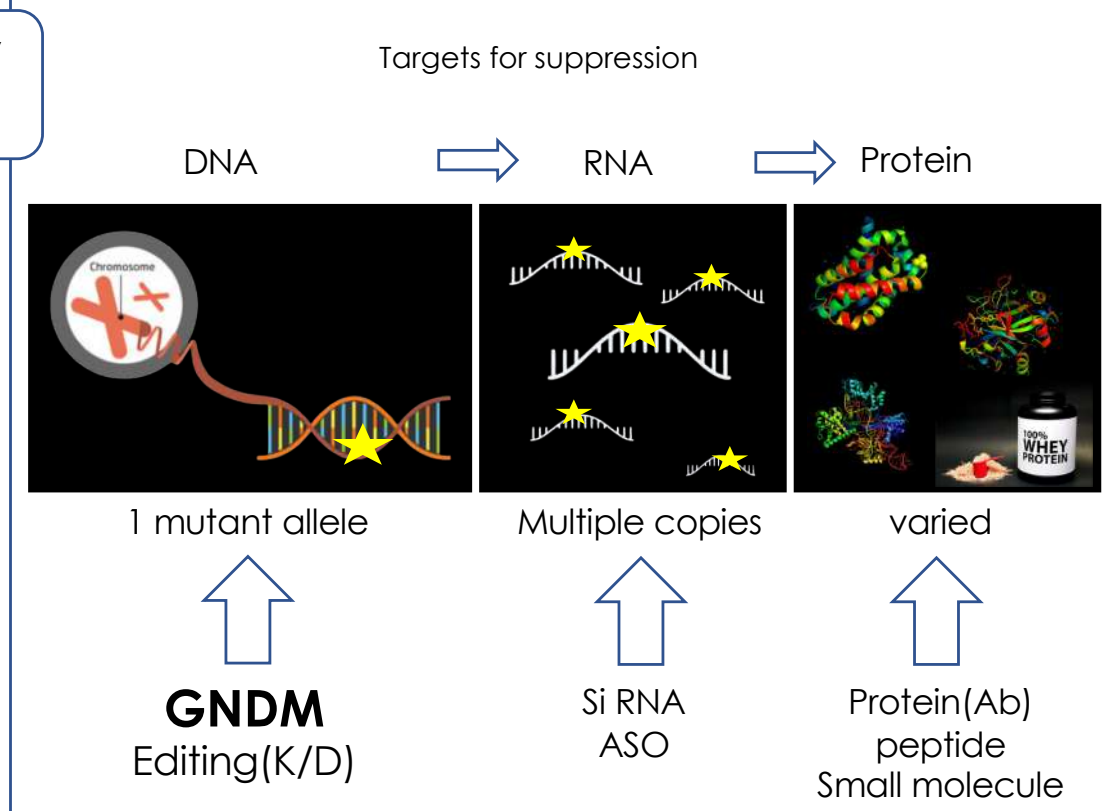
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GNDM is efficient approach both for LoF and GoF mutation

In LoF disorders



In GoF disorders



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

K/D: Knock-down

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Uniquely positioned even in the CRISPR field

Positioning in CRISPR and Editing Company

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

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4. Key Topics
   MDL-101 for CDM1A
   MDL-104 for Tau
   MDL-206 for Angelman Syndrome
   Sets new target area and incubate a few pipelines

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4. Key Topics

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Summary in R&D

- MDL-101
  - IND enabling study on going
    - Pilot Tox and PK/PD for designing GLP studies
  - Preparing for interaction with FDA
    - File INTERACT meeting (1Q)→Scheduled to be held in July 2022.
    - 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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Other business topic

- 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

- Relocated US operation as of Oct 20*
  - To Waltham MA, which is adjacent to Cambridge
  - Substantially upgraded and expanded from the Company's prior facility to have 13,000sqf (1,200 ㎡)size that accommodates process development function as well as expanded discovery group.
  - Can accommodate up to 40~50 people level.

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MDL-101 for CMD1A

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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:

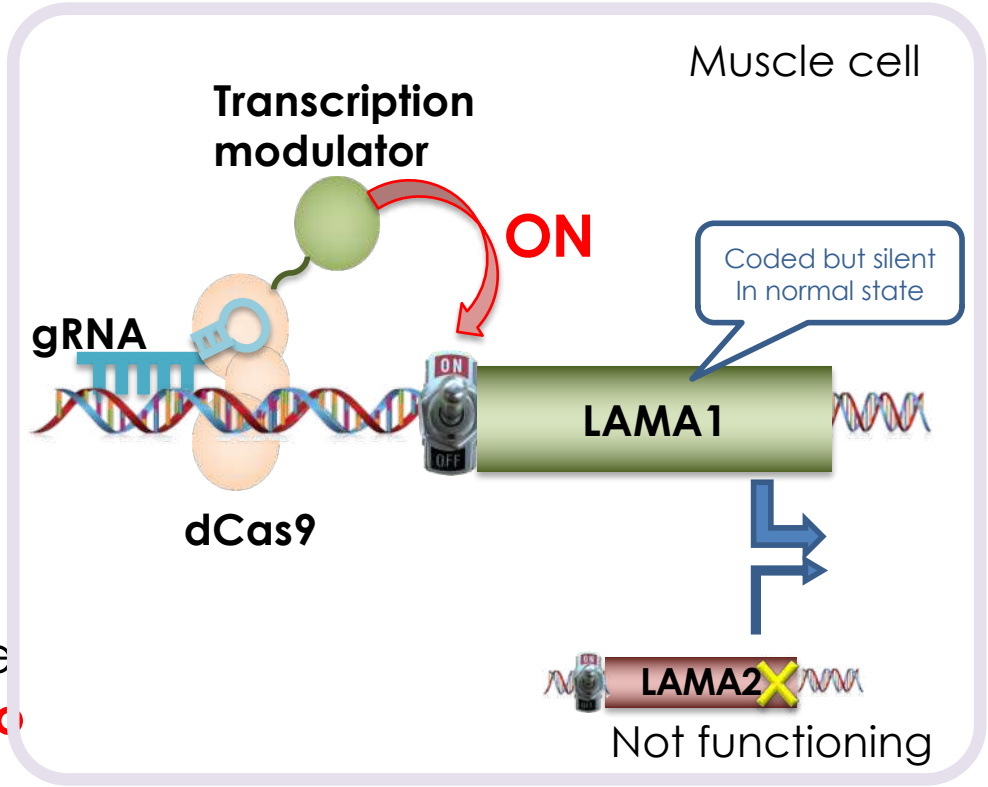
Severe muscle weakness;
Lack of muscle tone (hypotonia);
Little spontaneous movement;
Joint deformities (contractures);
Heart problems and seizures.

- Life expectancy:

Because of the serious health problems that occur in this form of the disorder, many affected individuals **do not survive past adolescence**.

- Genetic cause: **LAMA2** mutation

CRISPR-GNDM® targeting LAMA1

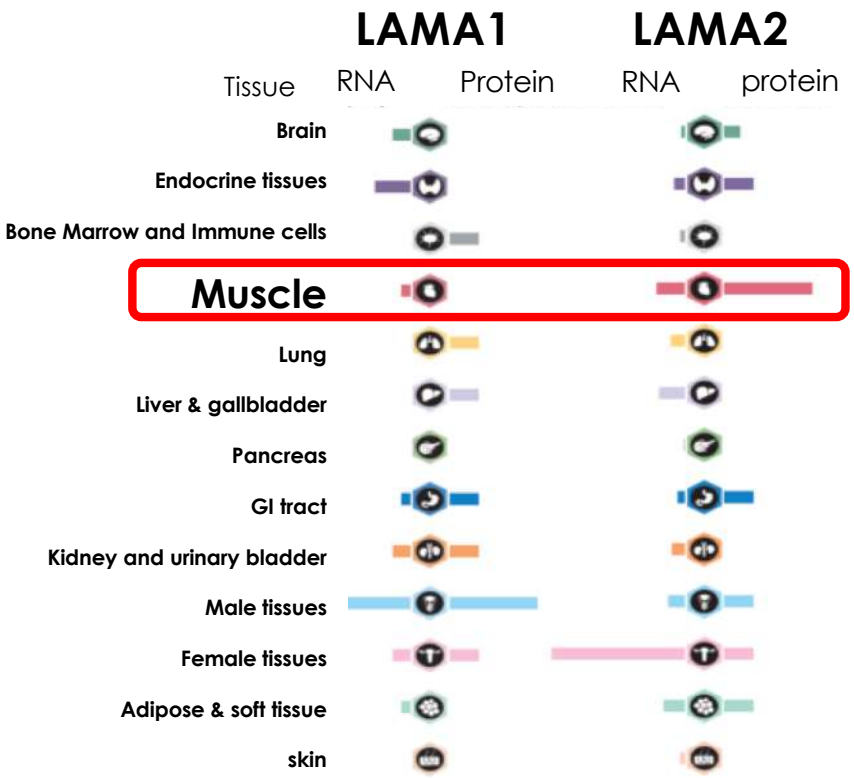


*Orphanet

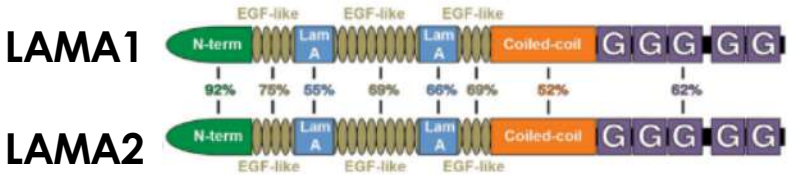
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By activating the sister gene, LAMA1, GNDM compensates missing function of LAMA2

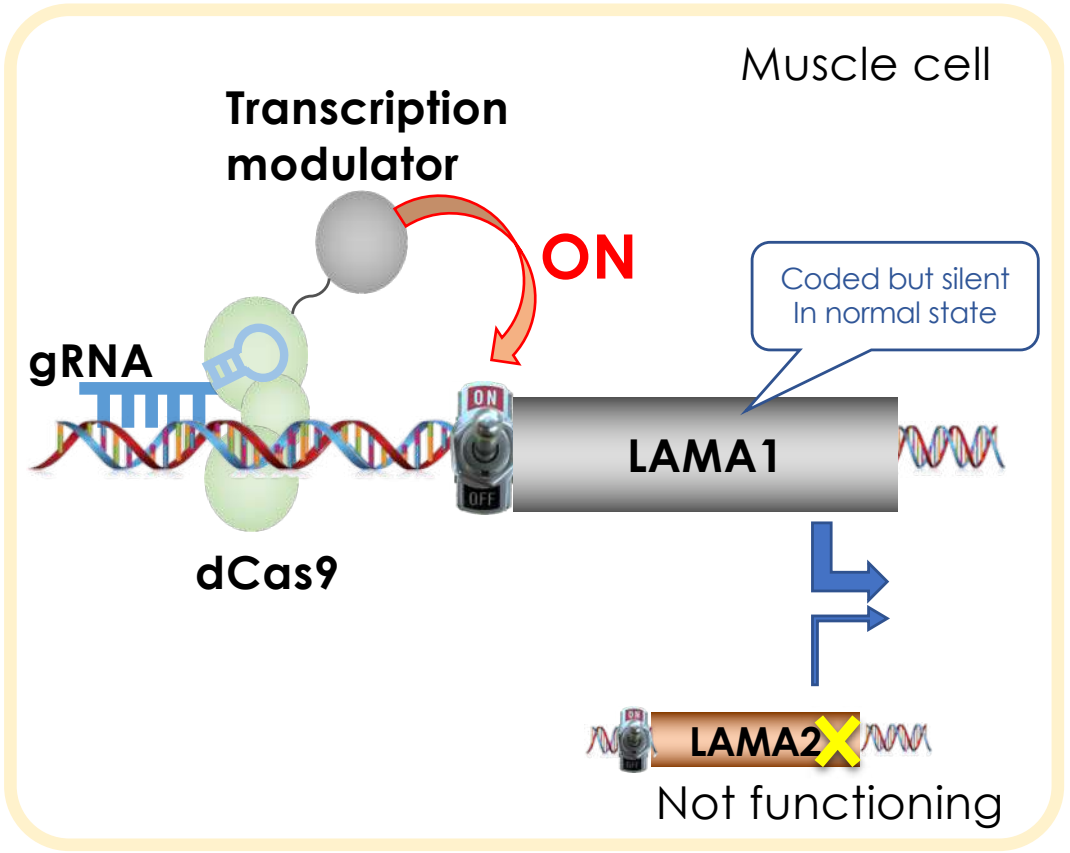
Exspression pattern of LAMA1and LAMA2 by tissues



Protein structure of LAMA1 and 2



CRISPR-GNDM® targeting LAMA1

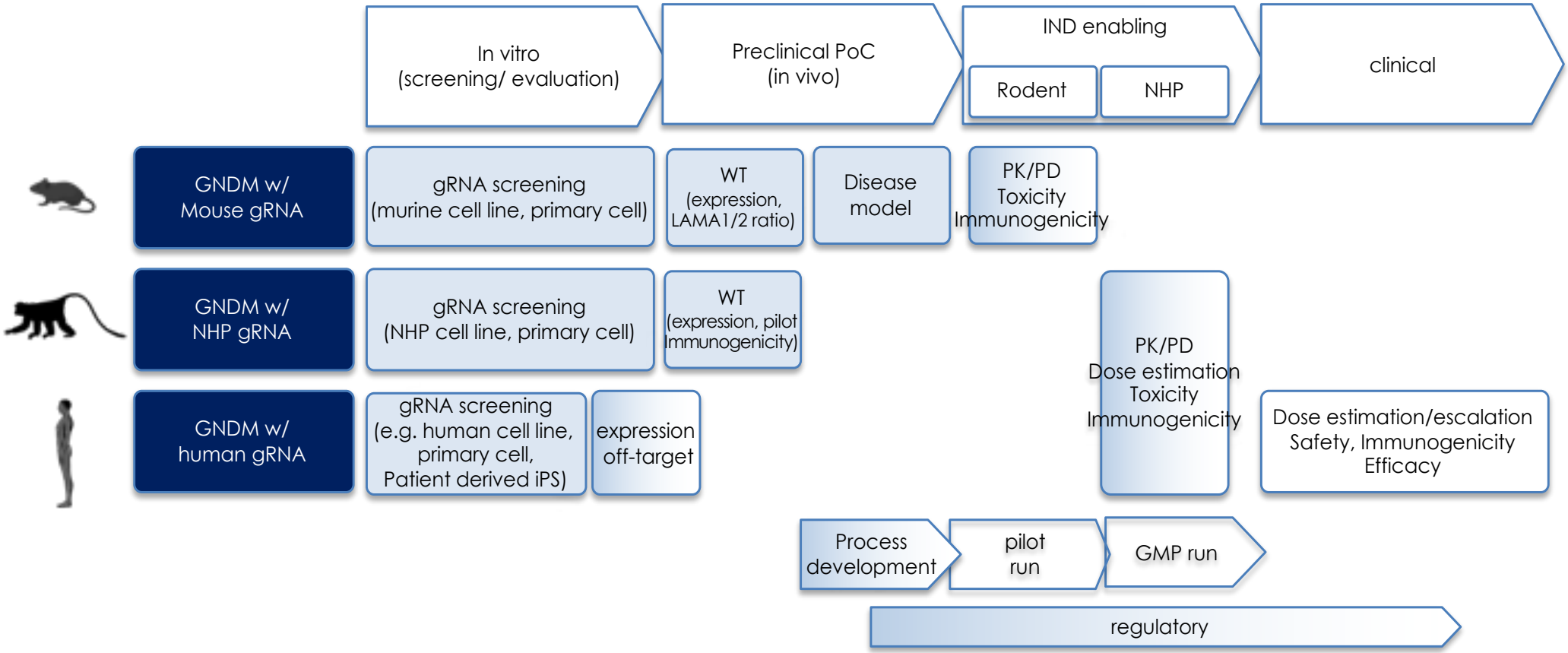


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Conducting IND enabling studies as well as process development

Path to clinic for CRISPR-GNDM®



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Summary of MDL-101

- Statue Summery
  - 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
  - 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.)

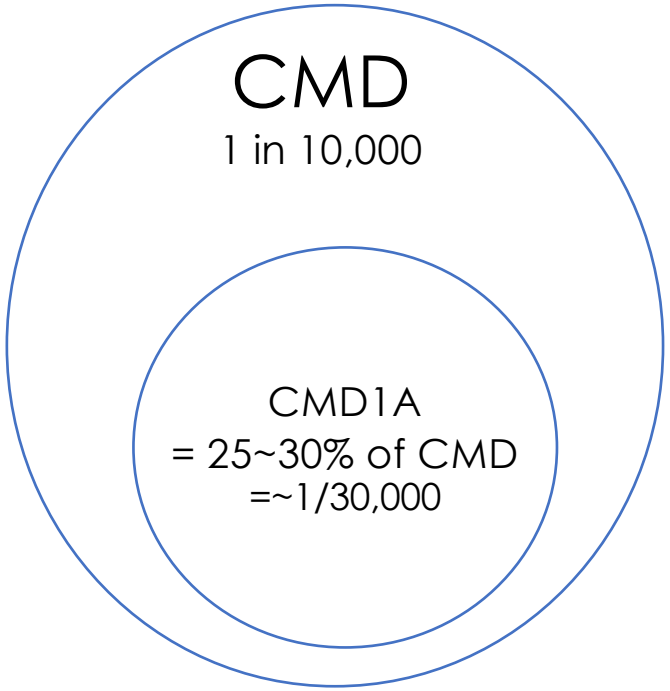
- Next steps:
  - INTERACT meeting and pre-IND meeting
  - IND enabling GLP tox and PK/PD

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Prevalence of CMD1A

- Exact prevalence of CMD1A is still unknown but...
  - The prevalence of congenital muscular dystrophies (CMD) has been estimated between
    - 1-9/100,000
  - CMD1A is about ~30% of CMD:
    - **~1/30,000** with regional variation



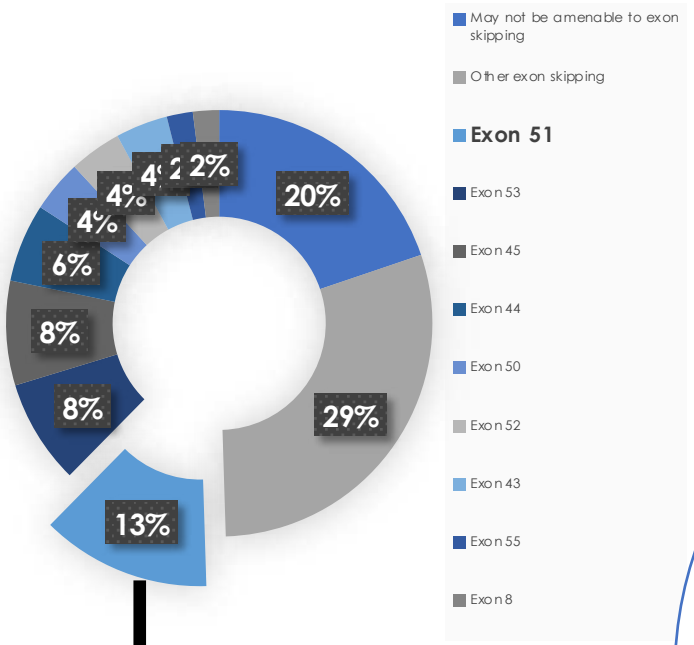
CMD: congenital muscular dystrophy

Source: orpha.net

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CMD1A is about the same size to DMD caused by Exon 51 mutation



DMD
=1 in 3,500#

exon51
=~13% of DMD*
=~1/27,000

CMD
1 in 10,000

CMD1A
= ~30% of CMD
=~1/30,000#
=10,000 in US

DMD: Duchenne muscular dystrophy

*https://www.cureduchenne.org/cure/exon-skipping/
#Source: www.orpha.net

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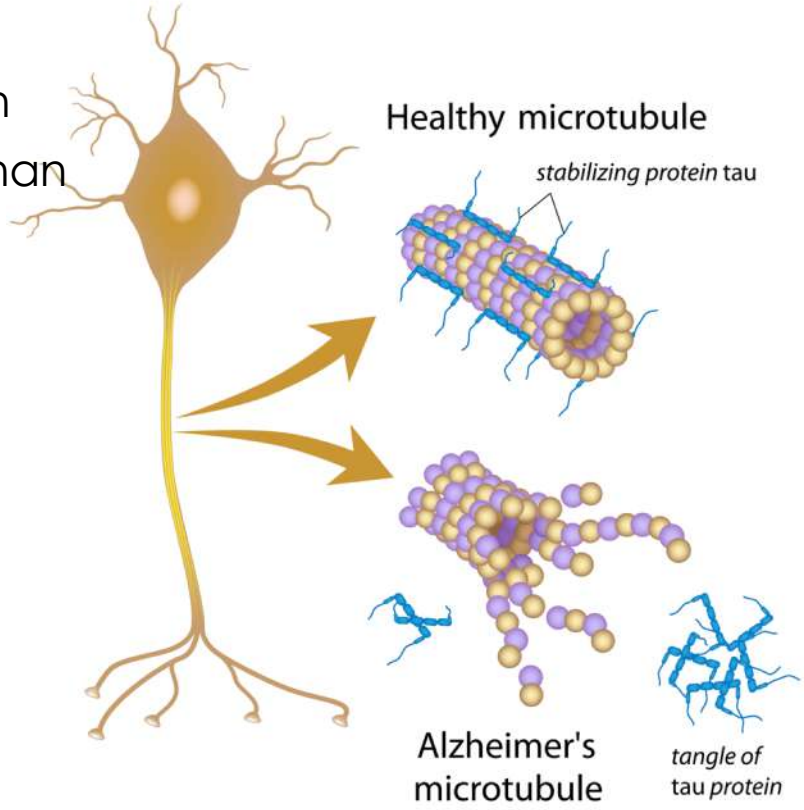
MDL-104 for Tau

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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

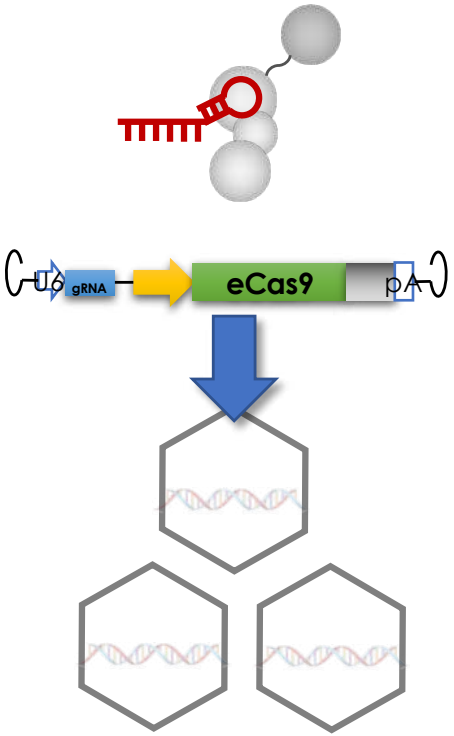


Source: Congdon EE, Nature Review Neurology 2018 "Tau-targeting therapies for Alzheimer disease"

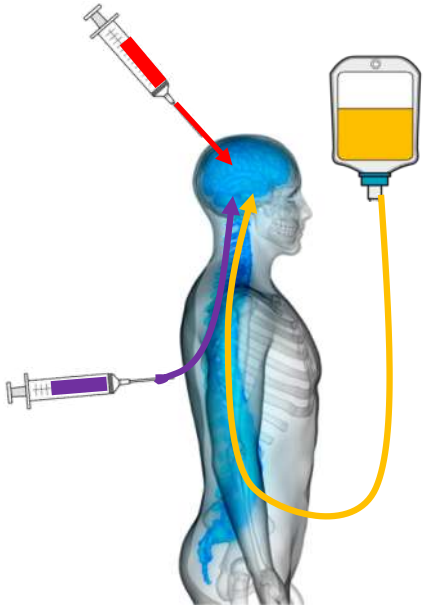
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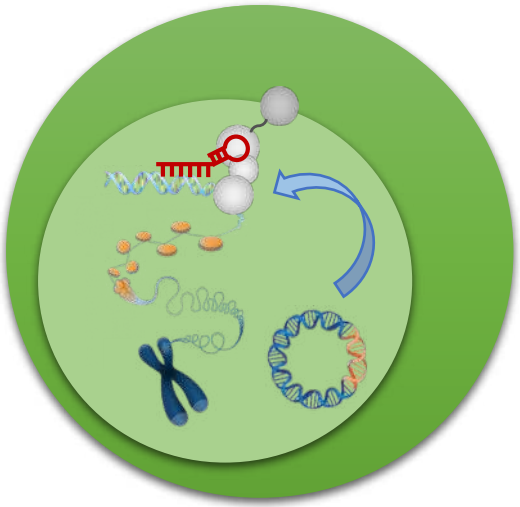
Single-administration of AAV - CRISPR-GNDM® to lower all tau forms at DNA level



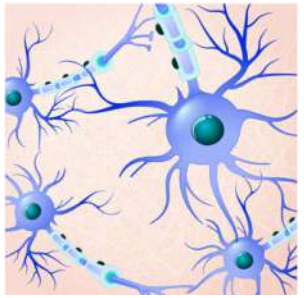
AAV vector



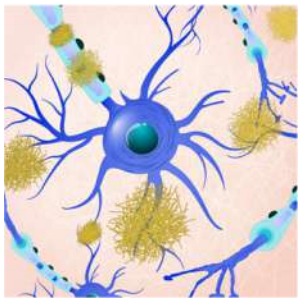
Non-integrating Virus vector



+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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Status of pipeline and the next steps

- Status
  - Confirmed Tau suppression by GNDM-Tau in mice.
  - Filed patent with optimal human gRNAs.
- Next steps
  - Evaluate functional improvement with disease model mice.
  - Optimizing capsid and administration route.

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MDL-206 for Angelman Syndrome

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What is Angelman syndrome

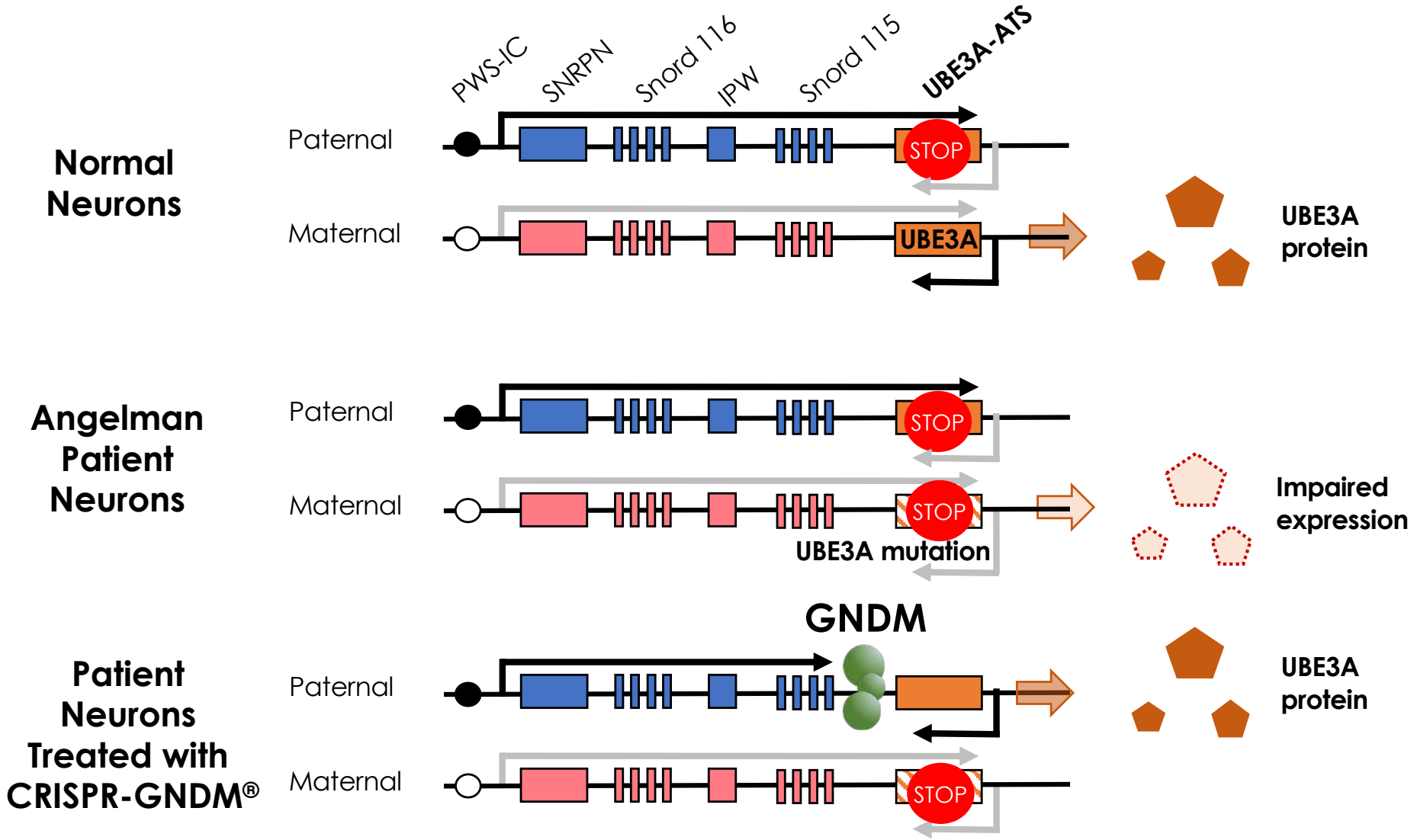
- Angelman syndrome (AS) is a rare neuro-genetic disorder that occurs in **one in 15,000 live births** or **500,000 people** worldwide.
- It is caused by a loss of function of the **UBE3A gene** in the 15th chromosome derived from the mother.
- Angelman syndrome shares symptoms and characteristics with other disorders including **autism**, **cerebral palsy** and **Prader-Willi syndrome**.
- People with AS have developmental problems that become noticeable by the **age of 6 – 12 months**. Other common signs and symptoms usually appear in early childhood like **walking and balance disorders**, **gastrointestinal issues**, **seizures** and **little to no speech**.

Source: Angelman Syndrome Foundation

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By blocking ATS transcript, GNDM un-silences UBE3A expression



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Status of pipeline and the next steps

- status
  - Established animal PoC in a disease model mice with a CRISPR-GNDM® based molecule

- Next steps
  - Assess its superiority over products developed by other modalities, such as antisense therapeutics, regular gene therapies, and small molecules.
  - Concurrently, Company looks for a partner

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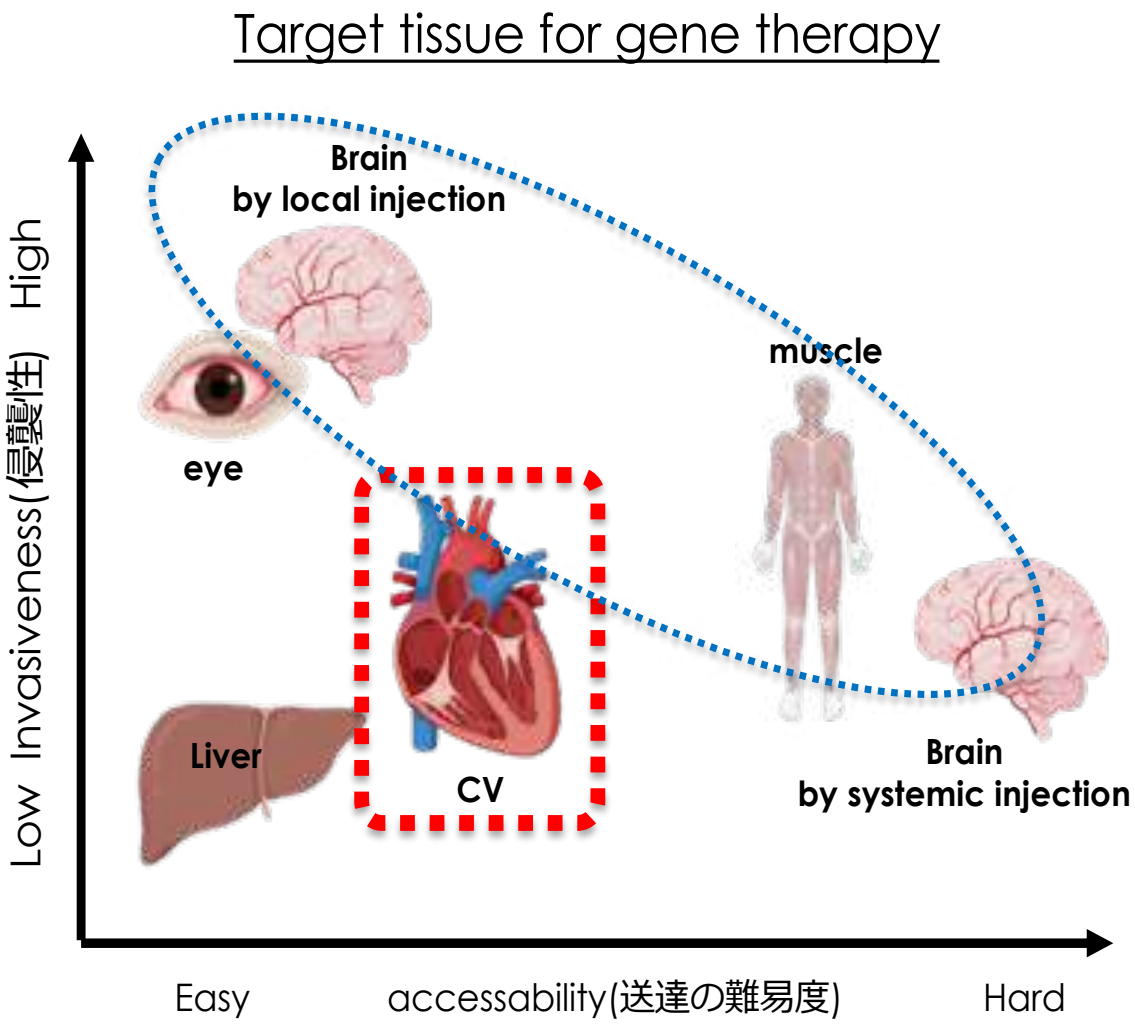
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4 . Sets new target area and incubate a few pipelines

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CV is our next horizon

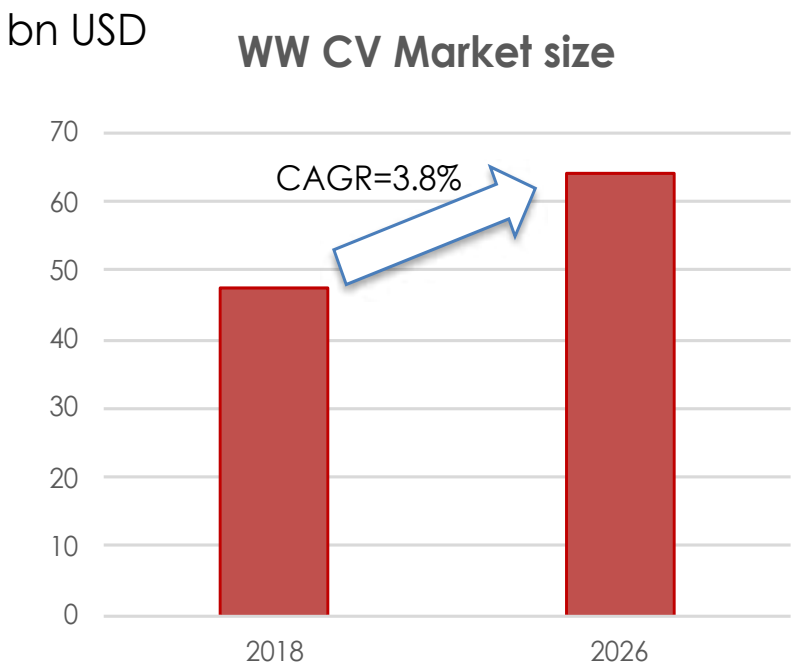


- Modalis has focused mainly on CNS and muscle disease area
- Our accumulated know how allow us to explorer new disease area
- CV is one of the reachable tissue by AAV systemic injection

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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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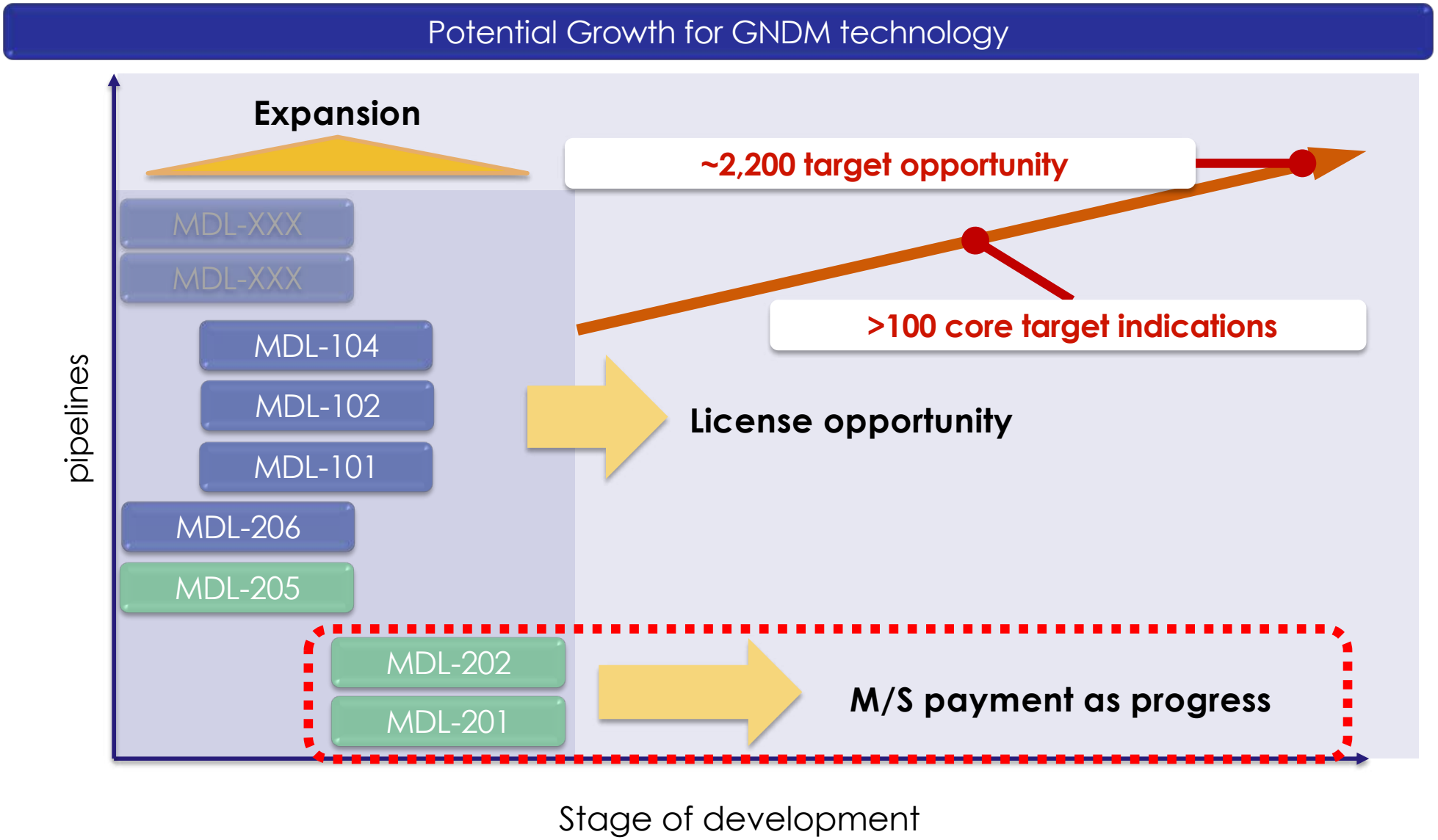
5. Growth Strategy

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Growth Strategy

opportunity expands two dimensionally



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Advantages of GNDM in our business

- **Unlimited upside potential**
  - >100s potential indication that GNDM is superior to the other technologies

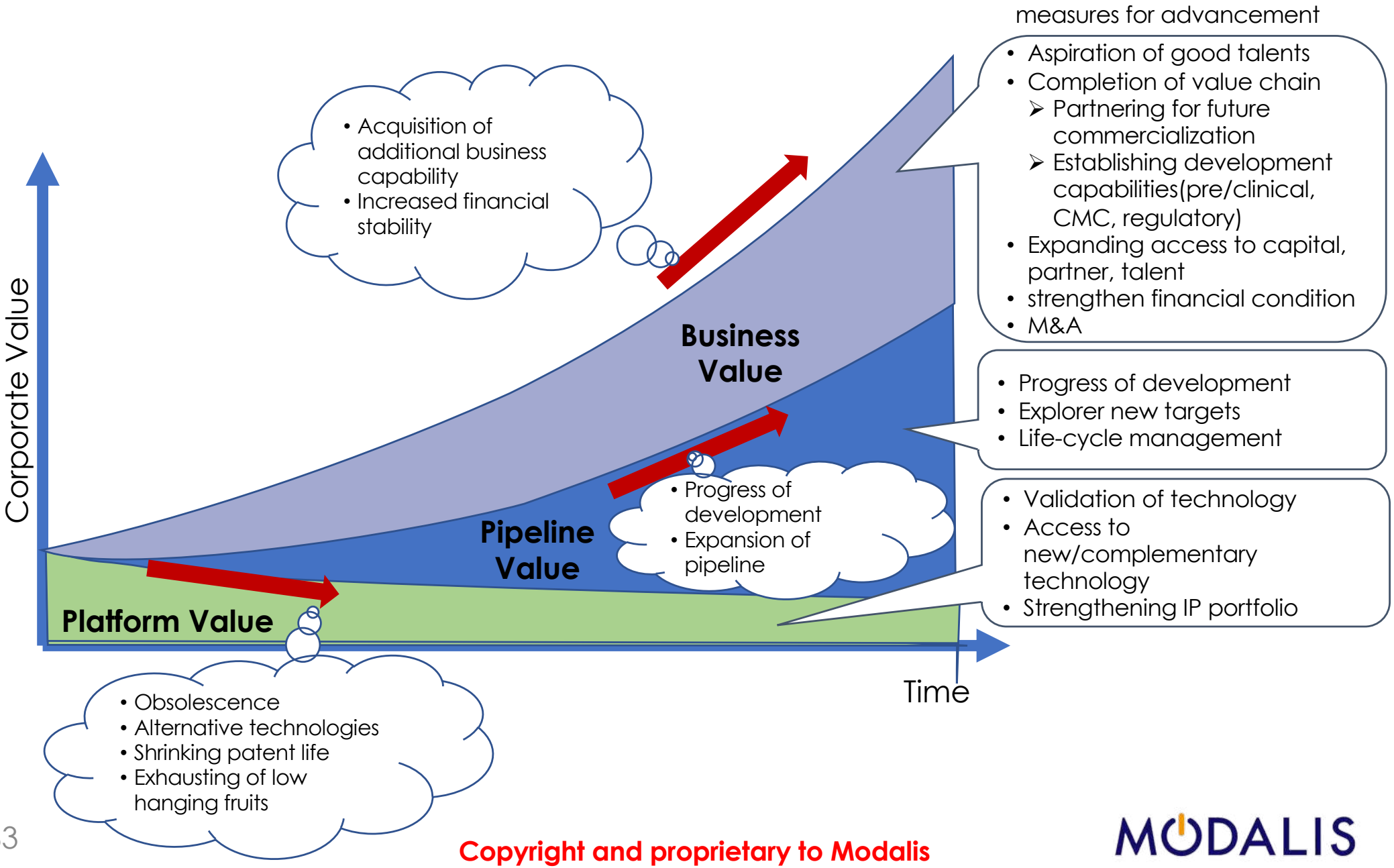
- **Bye-bye, one-in-millions**
  - Predictable result and timeline based on experience and streamlined research process

- **Scalable**
  - Experience in one indication is easily transplanted into the other

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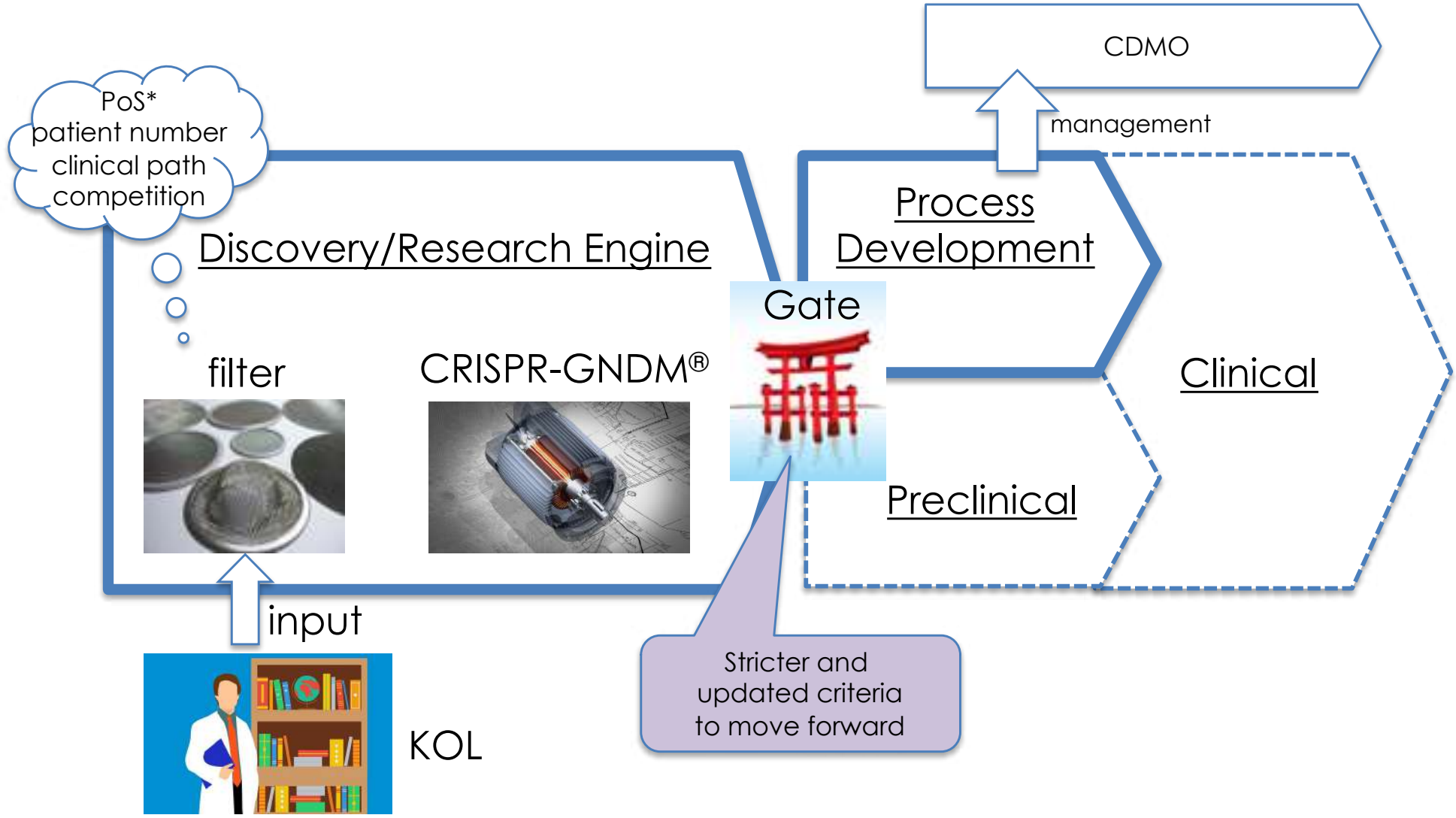
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Composition of Modalis' value and measures for advance



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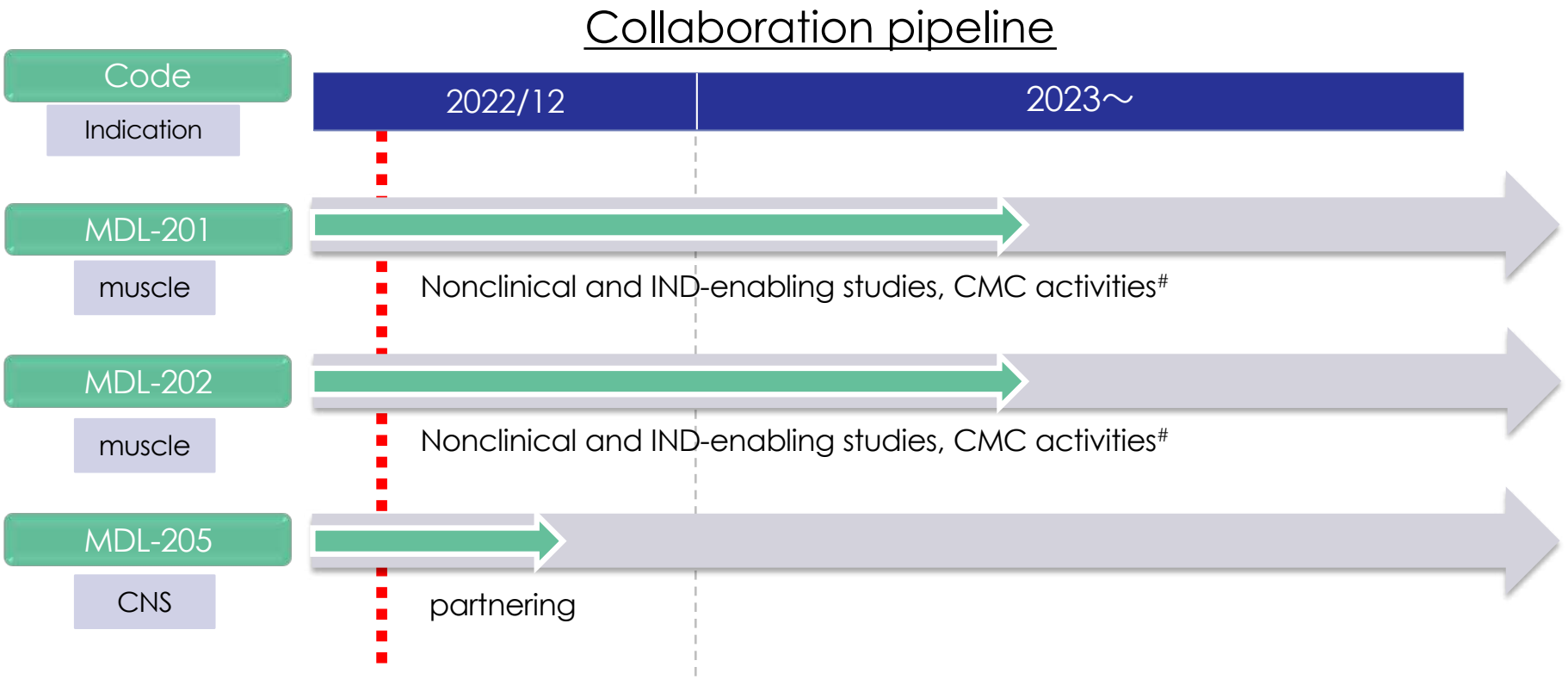
Upon transition from R to D, which cost time and money, stricter decision is made for higher ROI and better resource allocation.



PoS: Probability of success

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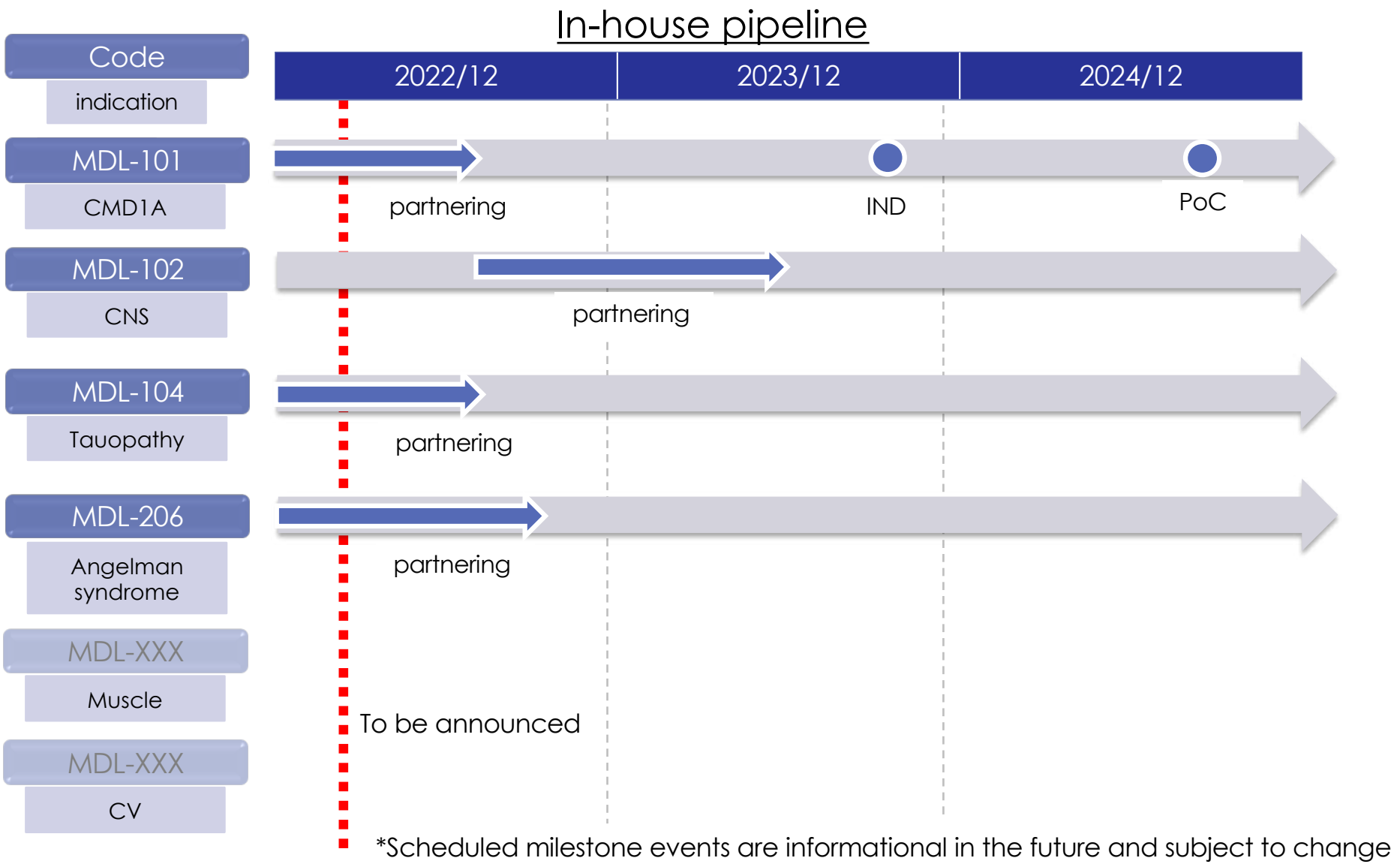
Steady progress in IND enabling of 201 and 202
Decision will be made on 205 in 1H 2022



*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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Partnering strategy

- We try to maximize the number of diseases that can be developed by CRISPR-GNDM®. On the other hand, given our limited resources, it is important for us to find partners with whom we can share risk/profit.
- Partnering will be undertaken when conditions and timing are deemed appropriate based on the value and business characteristics of each pipeline.
- Take an open stance on forms of partnering, including licensing, option deals, and co-development
- At the same time, we will negotiate the timing and scheme of the alliance in a manner that allows us to accumulate our own development know-how, with a view to improving the efficiency of future development and maximizing profits.

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Status summary

Collaboration pipeline

- MDL-201 and MDL-202: Astellas, which took over the whole development, has policy of not disclosing status until it becomes clinical program
- MDL-205: research collaboration is on going

In-house pipeline

- MDL-101:initiated 1) IND-enabling studies, 2) prep for FDA communications, and 3) process development for coming GMP manufacturing. At the same time, partnering discussion with multiple pharma/biotech on going.
- MDL-102: under the lead optimization
- MDL-104: additional animal studies on going while discussing potential partnering with multiple companies.
- MDL-206: Took over the whole right from Astellas to further develop by ourselves. Also exploring a new partner

New pipeline

- Partnership discussions are underway in several targets in the cardiac and muscular disease areas.

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6. Risk Information

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Known Risks and Preventative Measures（1）

Topic	Main Risks	Probability	Level of Impact	Preventative Measure(s)
(1) Risks related to the research and development of gene therapies	The risk of unforeseeable problems developing due to working with cutting-edge experimental medical treatments	Low	High	Constantly monitoring cutting-edge scientific technologies and related businesses, making pertinent judgements, taking appropriate actions
	Due to gene editing technology being a field with steady progress and rapid advancement, there is a possibility of new technologies appearing and risk of competing with other modalities	Low	High	Ensuring we are using the most up-to-date version of the underlying technologies in our research and subsequently monitoring new trends in technologies, and adopting necessary technologies as needed R&D will be carried out with priority given to pipelines with competitive advantage, and portfolio reviews such as discontinuation decisions will be made as needed for diseases for which competitive advantage cannot be maintained
(2) Risks related to the pharmaceutical industry	The risk of failure or decision to suspend development caused by a certain product or technology used in pharmaceutical development	Moderate	High	Regularly reviewing risk mitigation measures and making appropriate modifications to our portfolio when collaborating with partner companies and adding pipelines to our portfolio
(3) Risks related to execution of business activities	Due to the fact that execution and related decisions are driven by our partners, there is a possibility development is suspended and the risk of contract cancellation even if there are no failures during development	Moderate	High	Aiming to stabilize for the future and maximize profits through the stratification of our pipelines and strategically adding to our portfolio
	The risk of delays in the timeline if appropriate business coordination measures are not made regarding production that is entrusted to external parties, preclinical experiments, etc.	Low	High	Performing appropriate project management, concurrently negotiating with various candidate service providers, and securing a slot to prevent delays in the timeline

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Known Risks and Preventative Measures（2）

Topic	Main Risks	Probability	Level of Impact	Preventative Measure(s)
(4) Risks related to intellectual property rights	The risk that patents other than the originally introduced license will be required while the basic patent is in a disputed state.	Low	High	Striving to secure patents for each project (including the Company's own patents) and concurrently investigating the introduction of necessary patents
(5) Risks related to business performance, financial condition, etc.	The risk that recorded profits will not be stable, since profit is strongly influenced by the license agreements, milestones, etc.	Moderate	High	Using a hybrid model to stabilize for the future and maximize profits through the stratification of our pipelines and strategically adding to our portfolio
(6) Risks related to the company structure	The risk that we are unable to secure talented individuals who possess technical knowledge or skills for scientific research and development	Low	High	To attract talent, we are engaged in R&D that appeals to potential candidates and creating a favorable working environment in addition to adopting of a restricted stock unit system to recruit competitively
	The risk that negative gossip or rumors influence the public credibility of the Company group	Low	Moderate	Misinformation and rumors are taken seriously, and the Company maintains their position by the equitable, fair, and timely disclosure of information

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