English translation for reference purposes only

FY2020 3 Q Financial Results



(TSE4883) Modalis therapeutics Corporation

Corporate and Technology summary

November 5 , 2020

In case of any discrepancy, the Japanese version shall prevail

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1. Financial Highlights

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PL & Business Result

(Million Yen)

	FY2020 3Q	FY2020 Outlook	FY2019
Operating revenue	340	1,100 or over	644
Operating expenses	508	750 or over	487
R&D	348	550 or over	303
SGA	159	200 or over	183
Operating income	△168	350 or over	157
Ordinary income	△209	300 or over	146
Profit	△214	250 or over	140

Operating revenue

・Earning development milestone income for license(MDL-202), a new upfront payment(MDL-206), and collaborative R&D milestone income for three pipelines .

・Earning Operation revenue almost as planned, progress towards license agreement including MDL-101

Operating expenses

・R&D and SGA were as planned

・R&D and SGA increased year on year as business progressed

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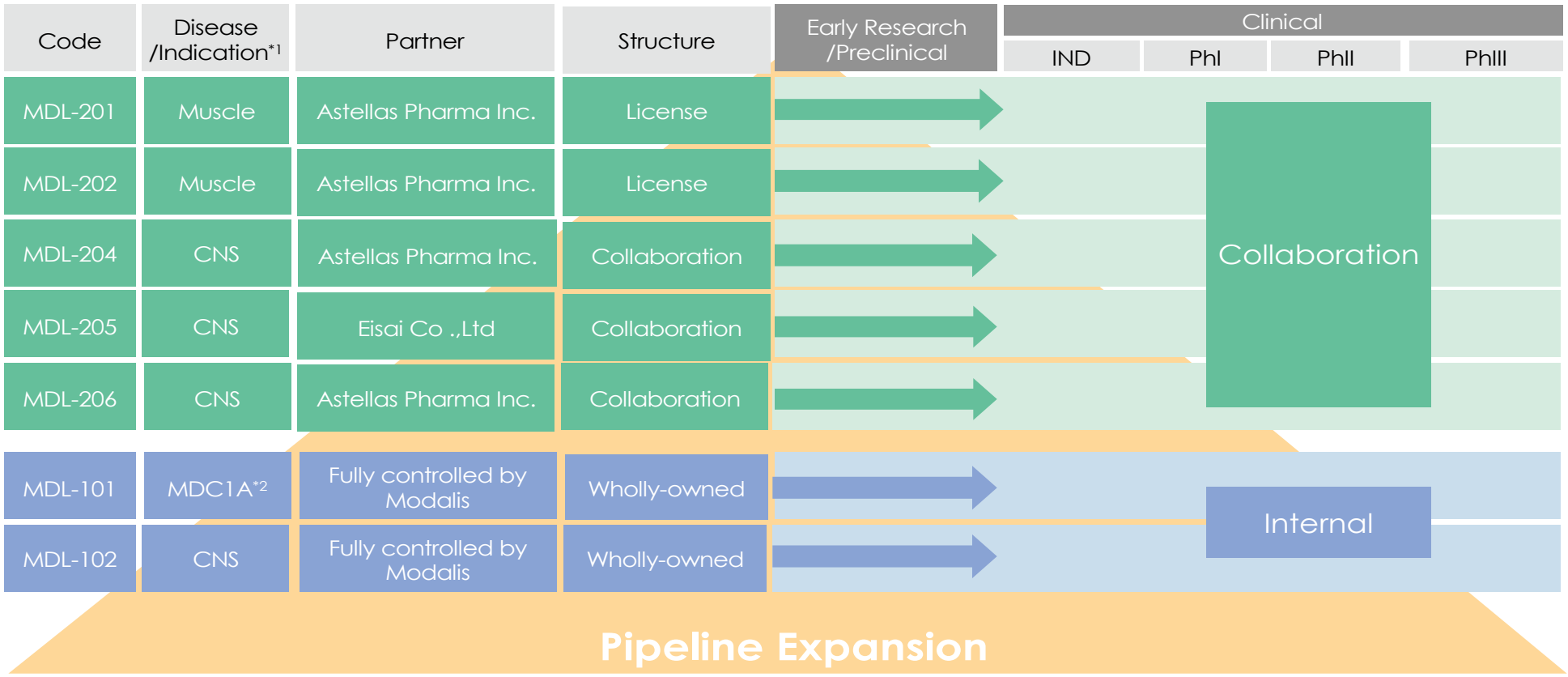
Pipeline



*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

Pipeline

- MDL101: Started non-human primates studies
- Even in the COVID-19 pandemic, pipeline progress is going well.

BS & Financial Position

(Million Yen)

	FY2019 (A)	FY2020 3Q (B)	(B)－(A)
Current assets	3,874	5,646	1,771
Cash & deposits	3,857	5,618	1,760
Non-current assets	63	833	770
Right to use patent	—	783	783
Total assets	3,938	6,480	2,542
Current liabilities	91	43	△47
Non-current liabilities	4	8	3
Total liabilities	95	52	△43
Total net assets	3,842	6,428	2,585
Total liabilities and net assets	3,938	6,480	2,542
Capital adequacy ratio	97.6%	99.2%	

- Stable financial base, High Capital adequacy ratio
- Obtained access to CRISPR/Cas9 foundational IPs from Editas Medicine, Inc

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2. Key Topics

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 Doundna, 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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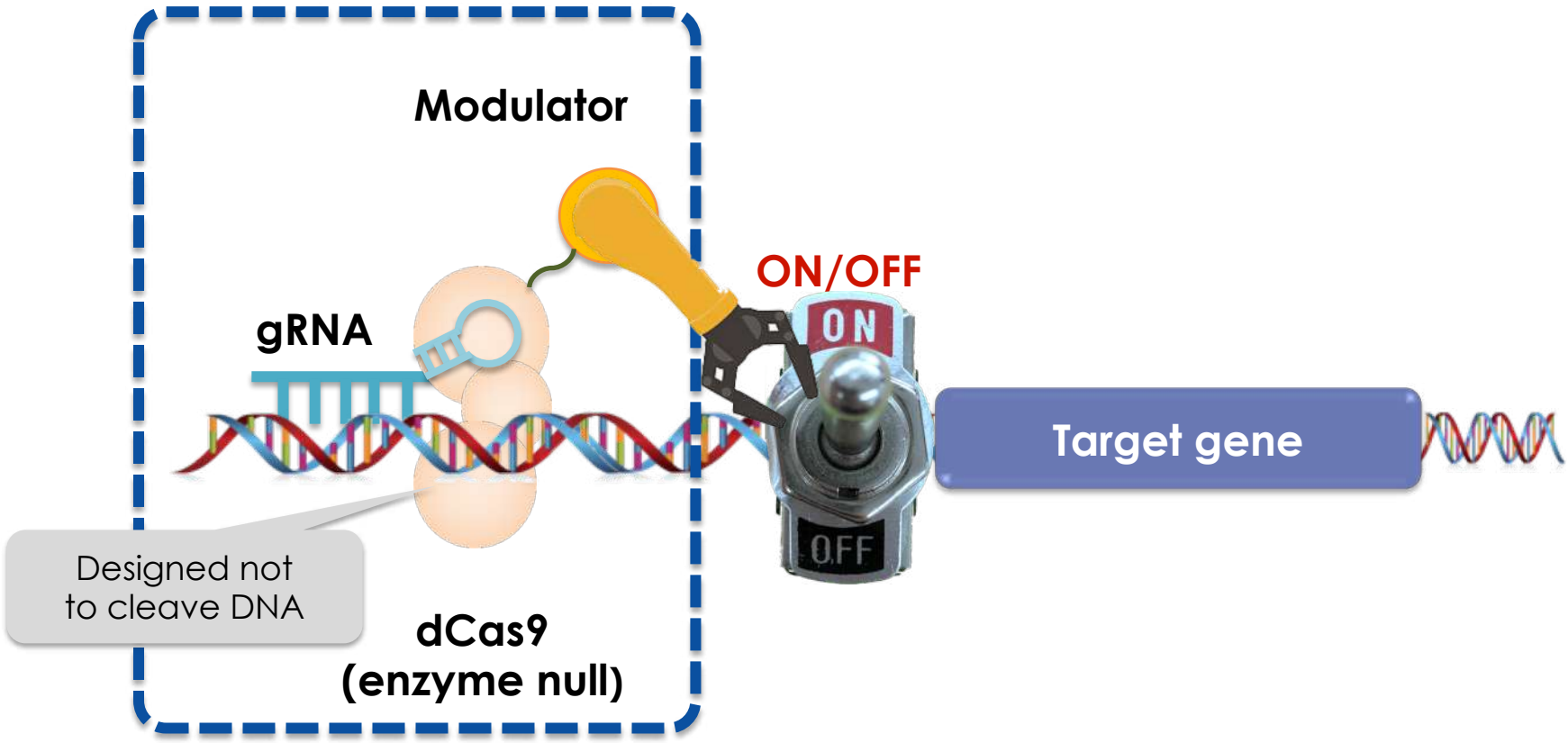
Non-cleaving CRISPR = CRISPR-GNDM®

Enables treatment of genetic disorders by controlling ON/OFF switch

CRISPR-GNDM (Guide Nucleotide-Directed Modulation) platform



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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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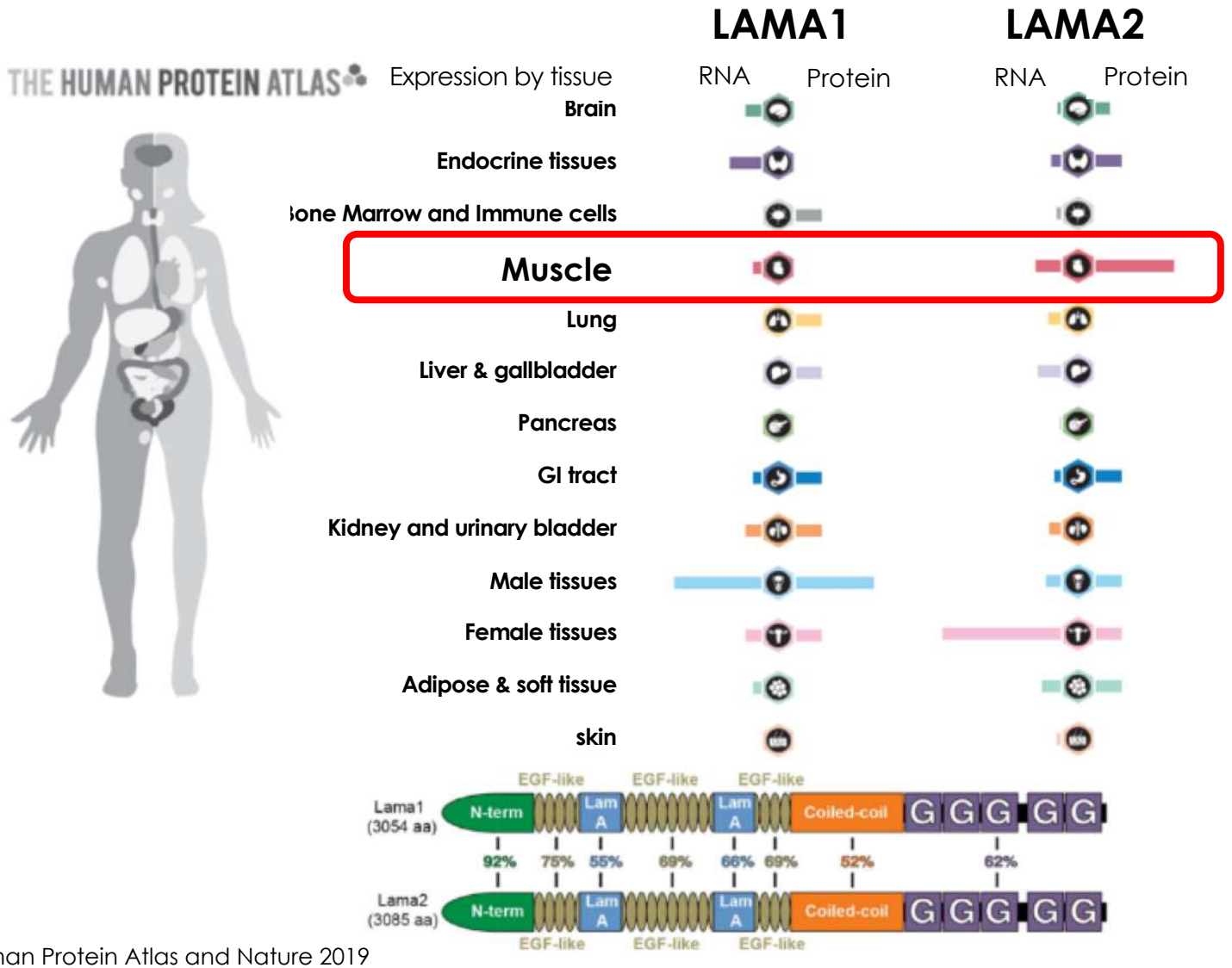
LAMA2 has a sister gene, LAMA1

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



Source: Human Protein Atlas and Nature 2019

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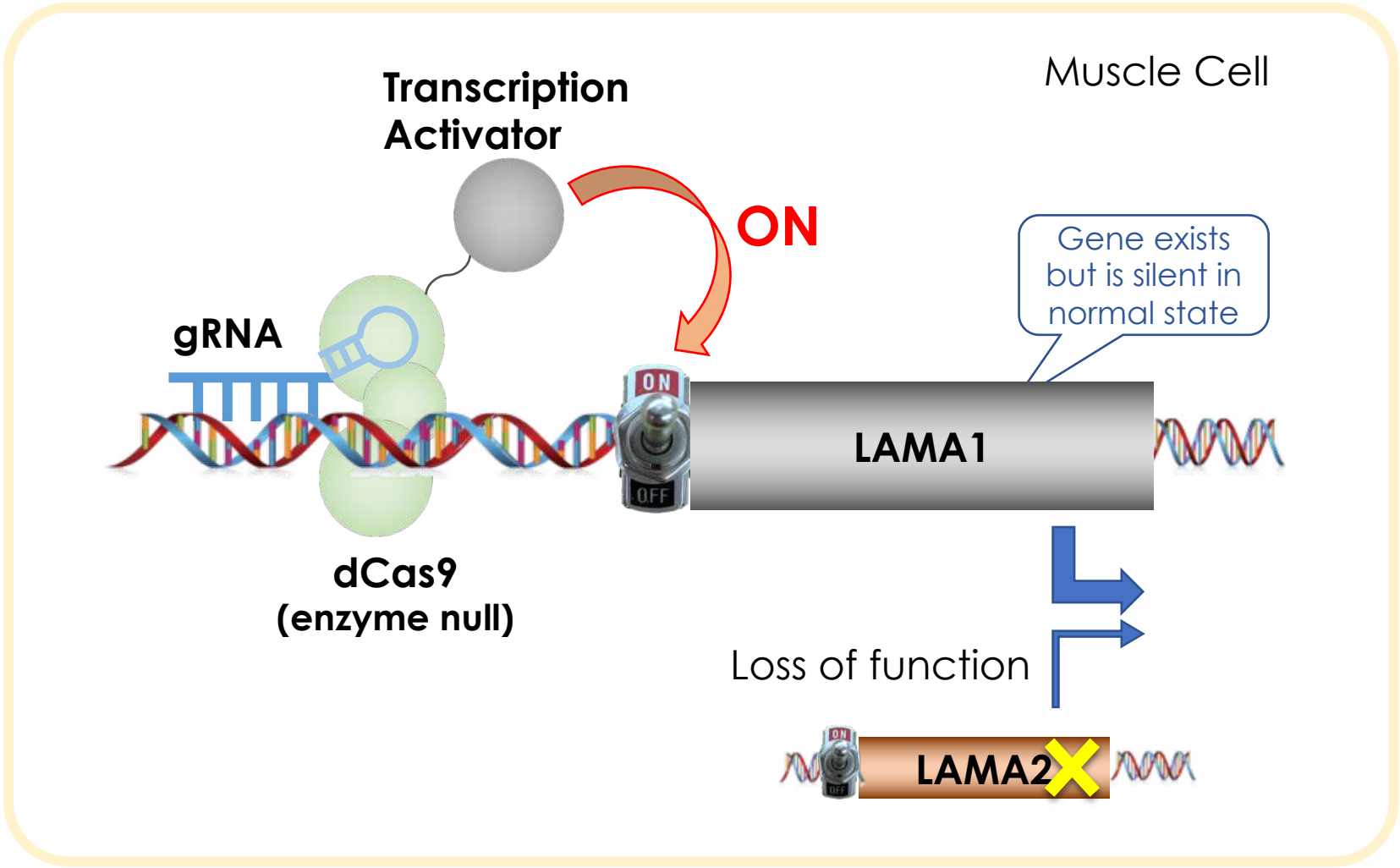
How GNDM cure MDC1A

GNDM upregulation of LAMA1 gene in skeletal muscle

CRISPR-GNDM targeting LAMA1



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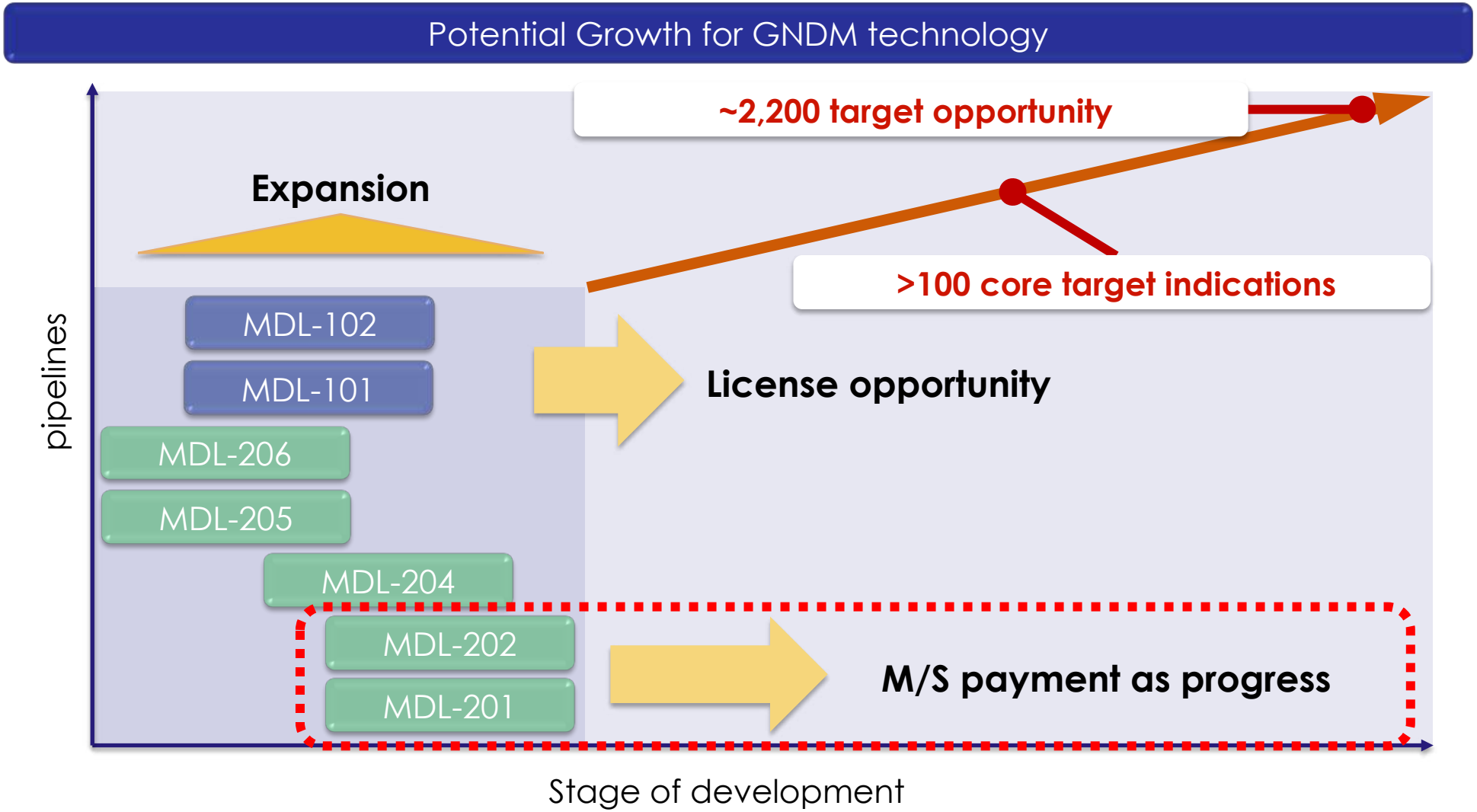
3. Growth Strategy

Growth Strategy
opportunity expands two dimensionally



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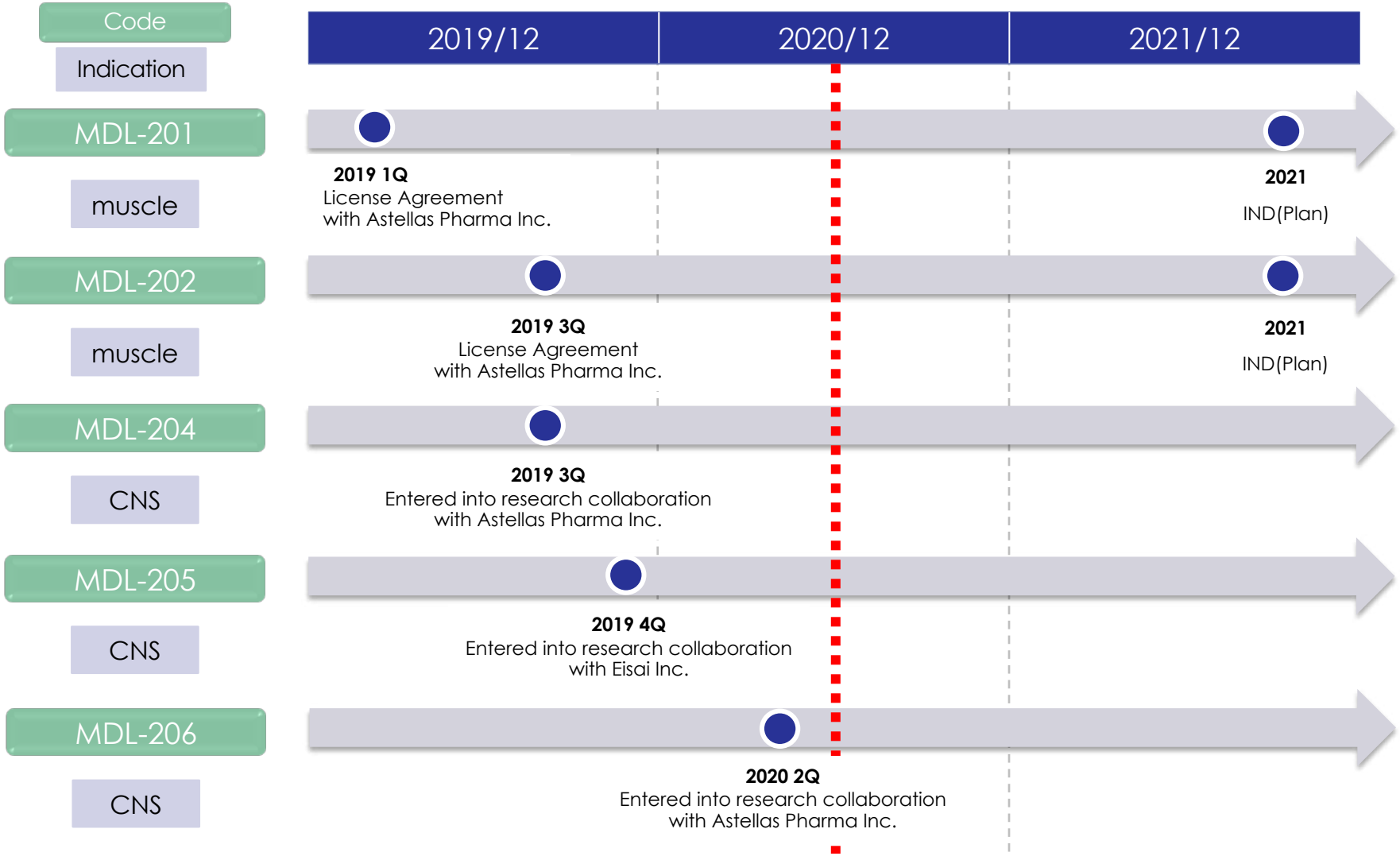
Collaboration pipeline

Achieved and expected Milestone events*



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

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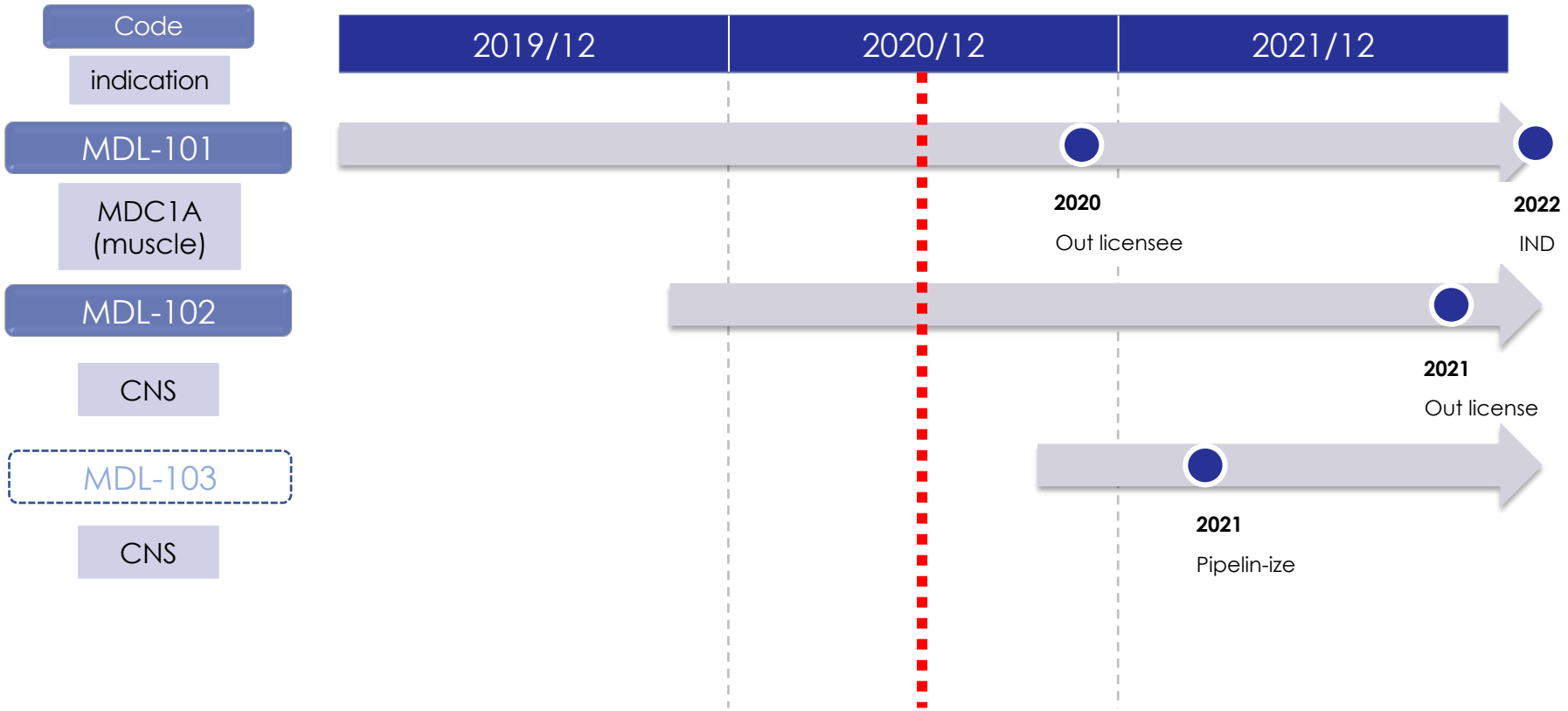
Internal pipeline

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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Reference

Corporate Overview

Our Features and Strong points

Business Model

Appendix

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Corporate Overview

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Corporate Overview(As of end September 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	2,700,697 thousand yen
Outstanding share	28,090,000 common stock
Number of employee	21 (including 8 PhD) (4 in Japan, 17 in US)
Award	J-STARTUP（2018）

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**
Jun 2018	Selected as a **J-Startup** program, an elite program funded by the Japanese government.
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 **2** 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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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)

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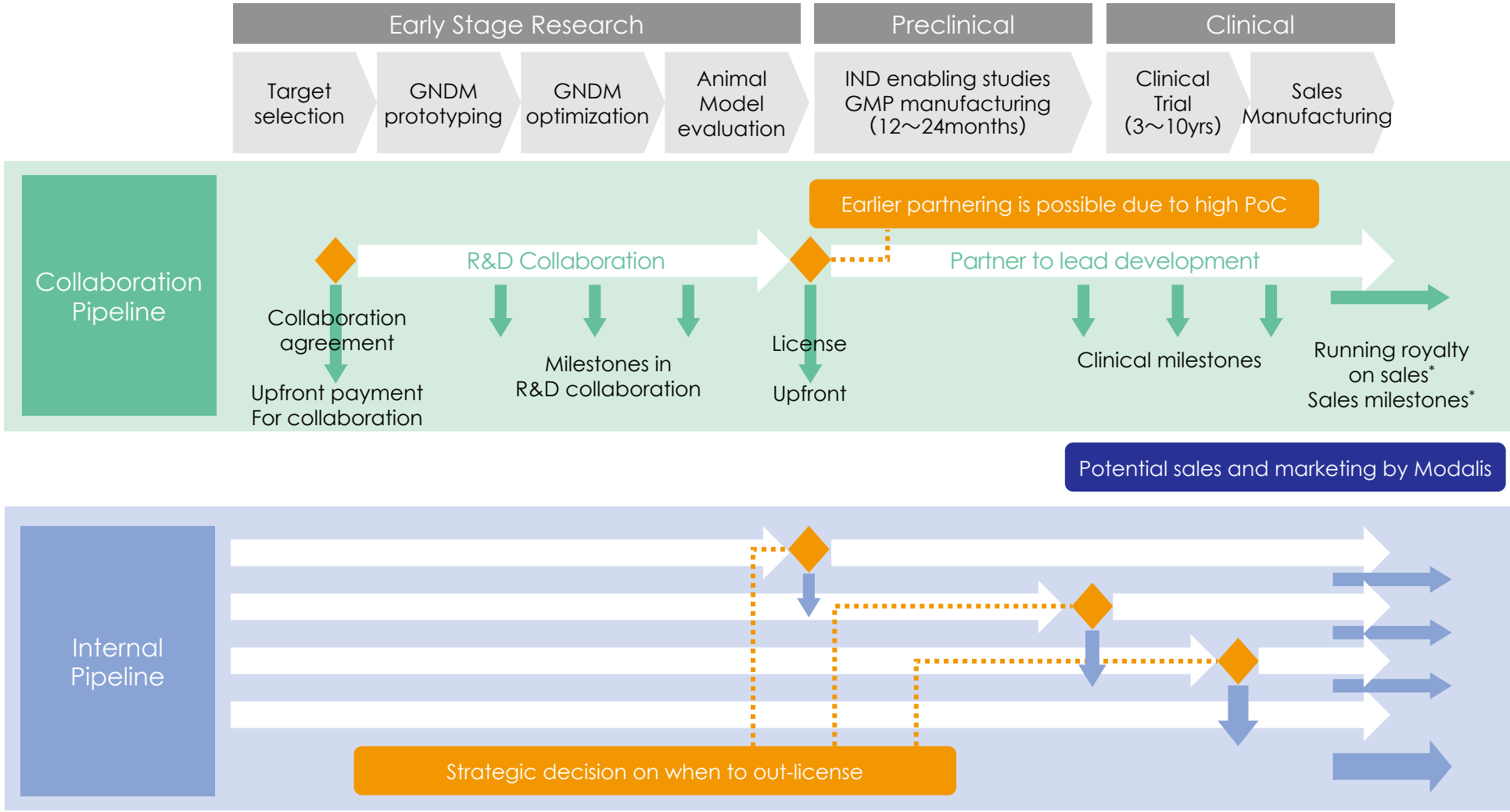
Business Model

Hybrid of own pipeline and collaboration pipeline



* future plan

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Our Features and Strong points

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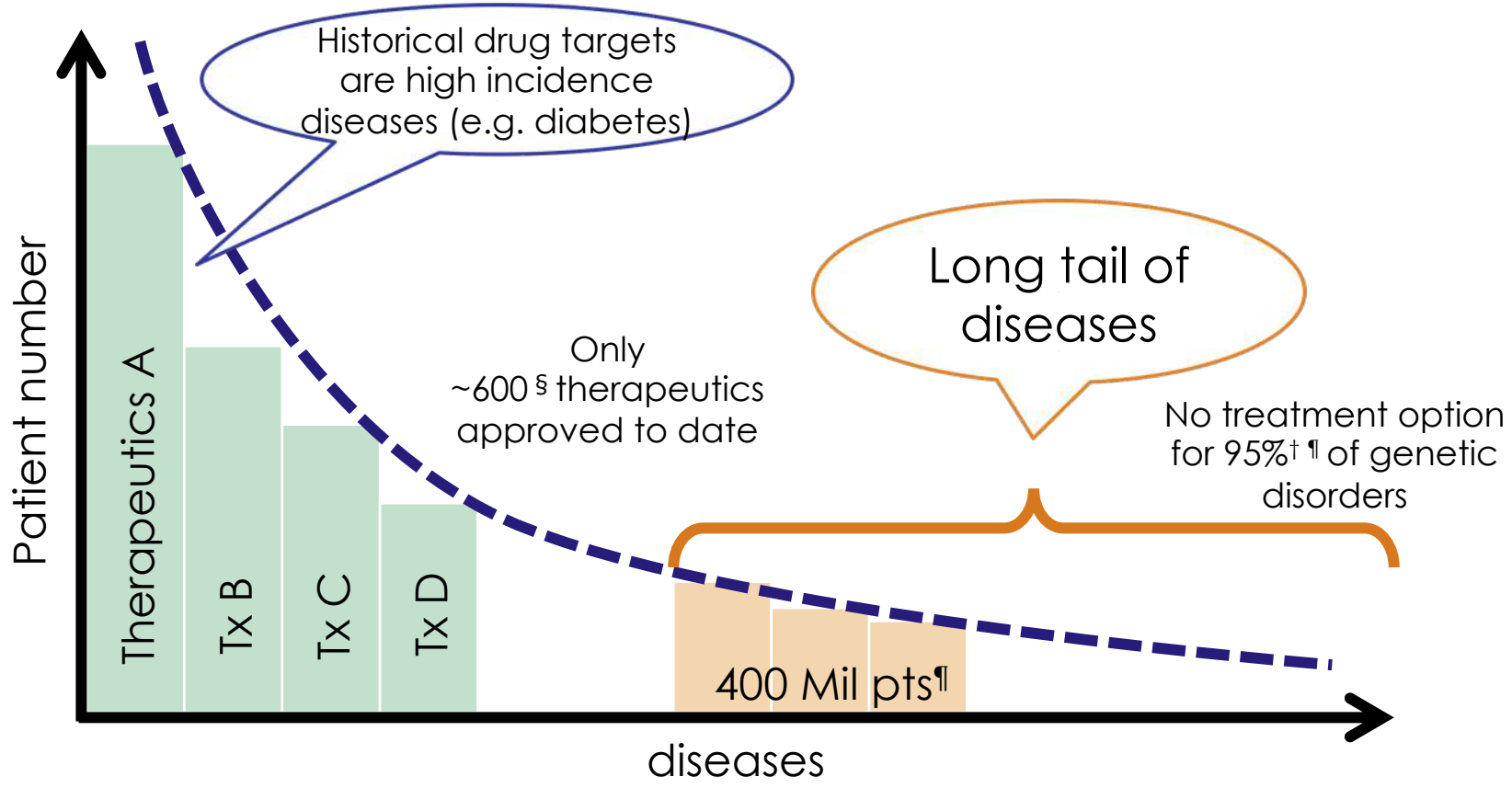
To target "long tail" of diseases, innovation is needed

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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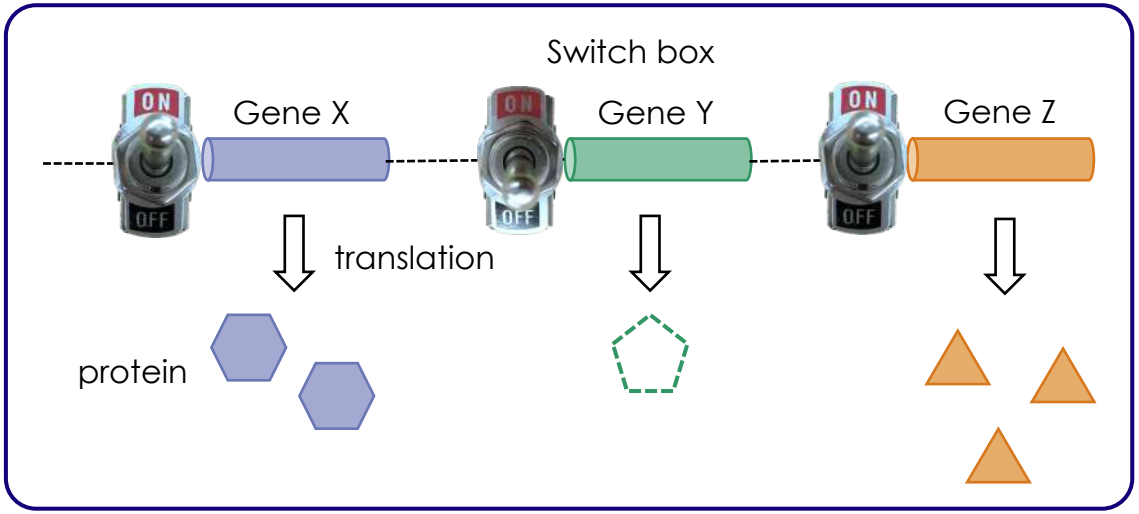
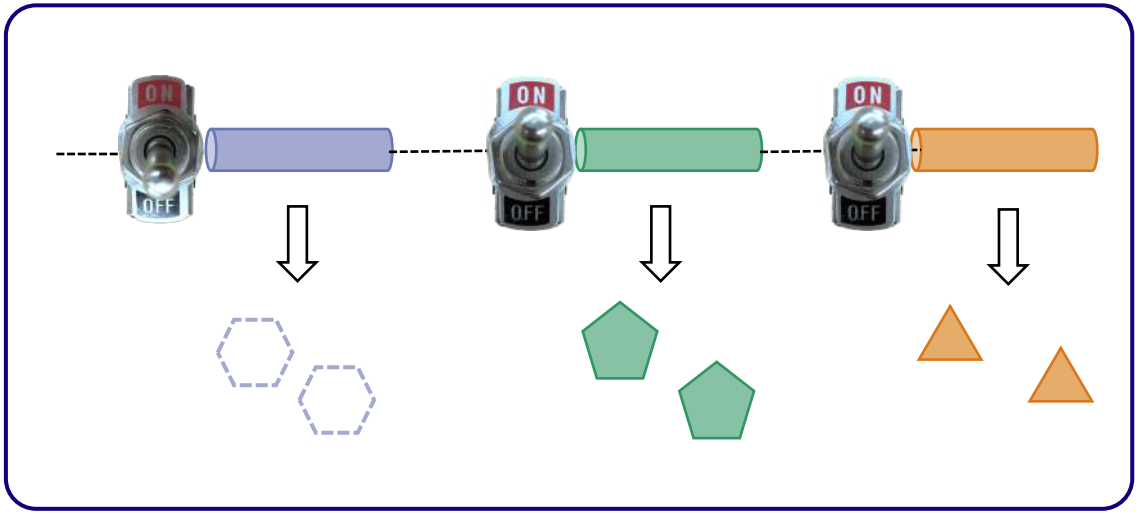
How multiple cell types are created from the same DNA code

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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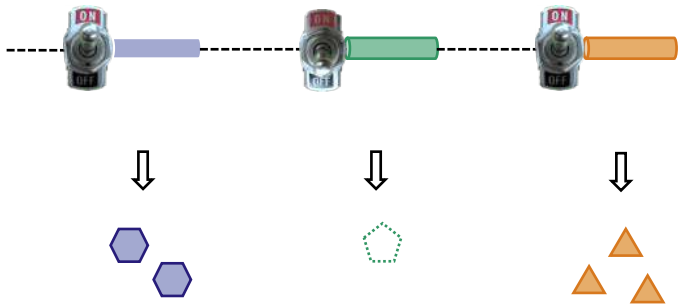
3 types of genetic disorders

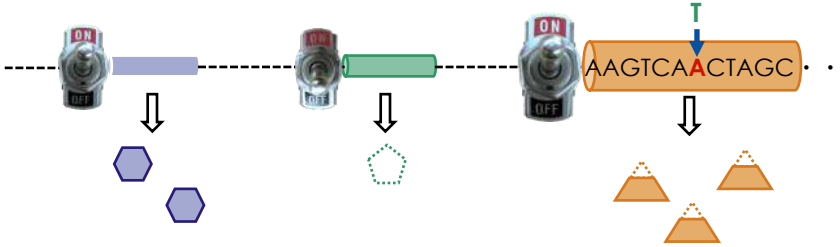
An error in the code or in switching can cause disorders

Normal state

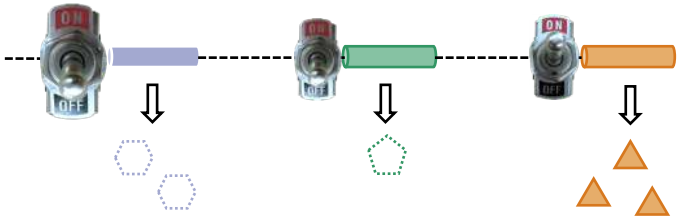


Switches control which, when and how much protein is expressed

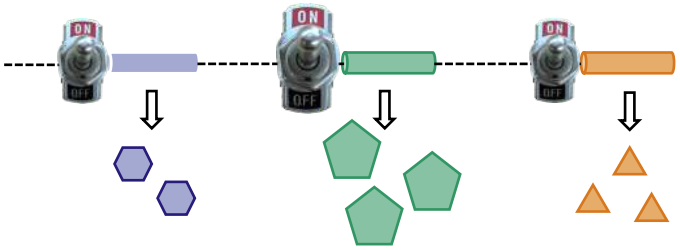
Error in the code results in a **non-functional protein**



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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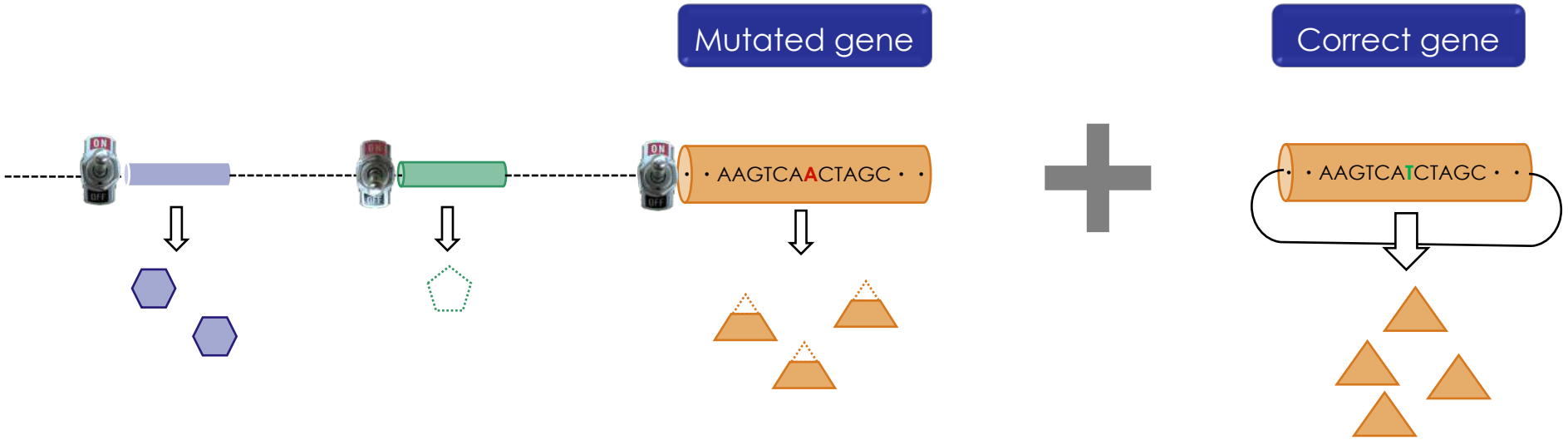
Classical gene therapy

Replaces a mutated gene by inserting a correct gene exogenously



Overwrite of missing gene

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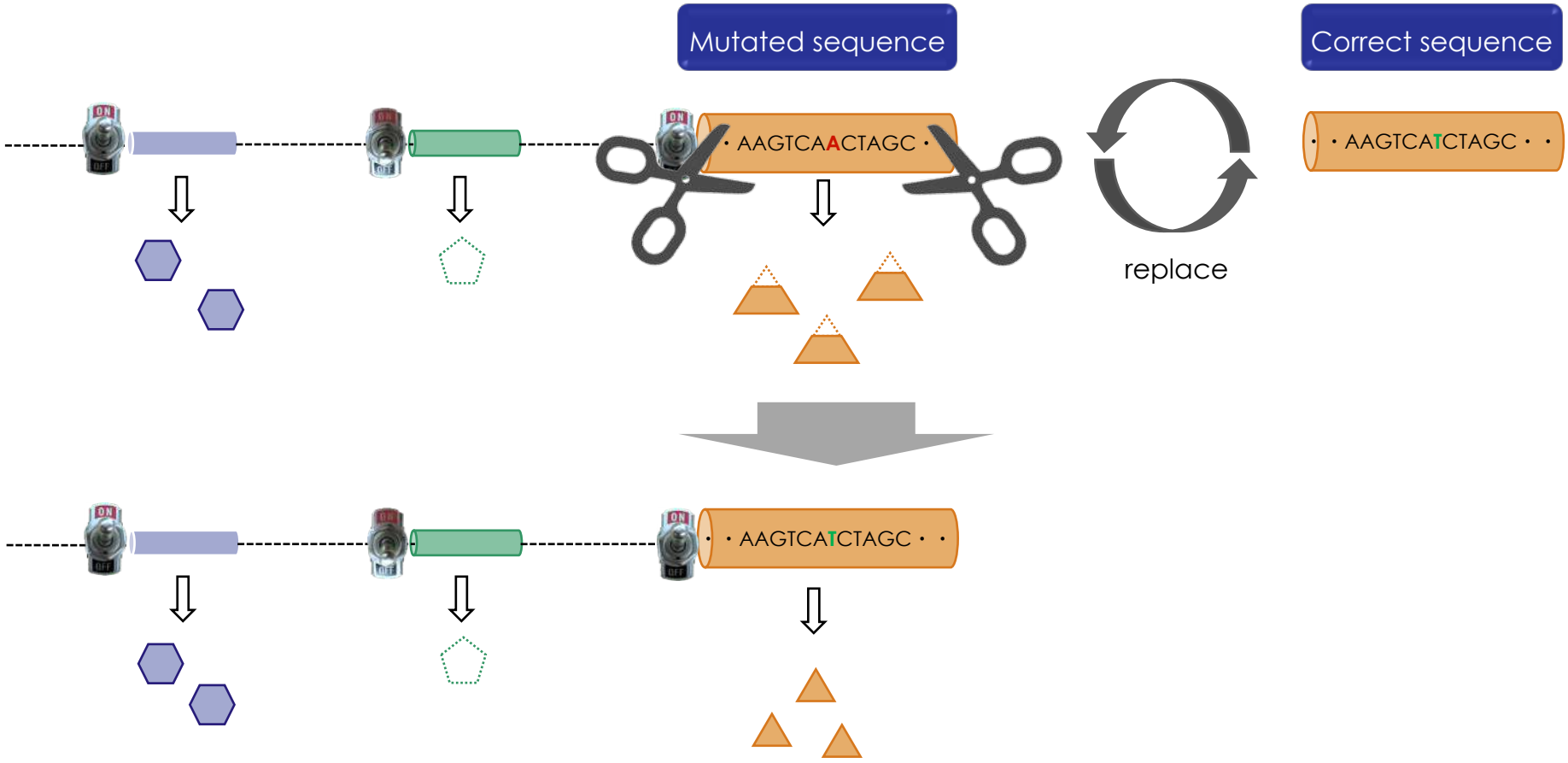
Gene Editing

Replaces mutated DNA with correct DNA by cleaving DNA



However, cleaving DNA increases risk of cancer

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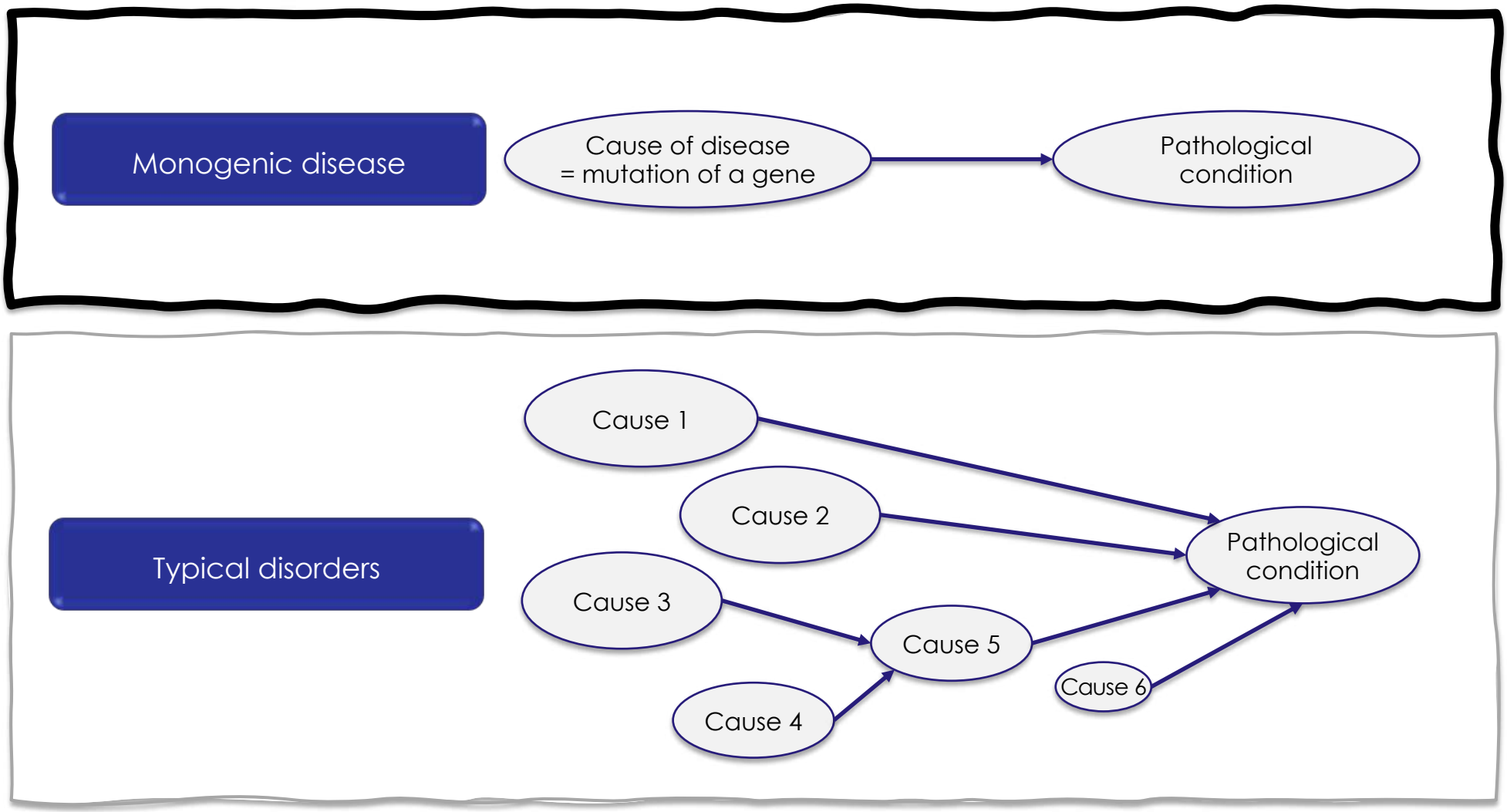
Monogenic Diseases

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



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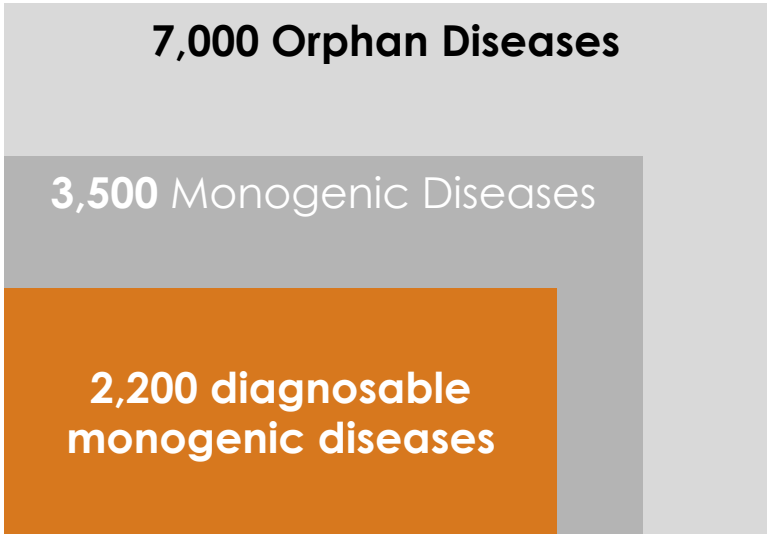
Untapped opportunities in monogenic disorders

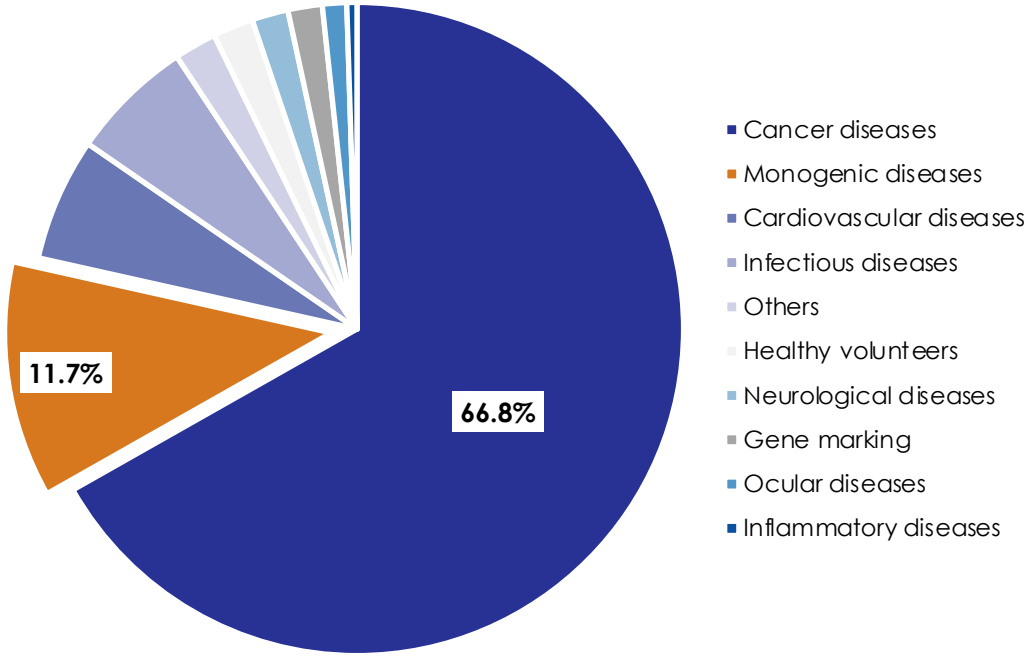
Limited number of drugs are approved or in clinical development for monogenic disorders

Monogenic Disease



Source: Discovery Medicine

Breakdown of GTx clinical trials (1989~ Worldwide)



Source: The Journal of Gene Medicine (2019)

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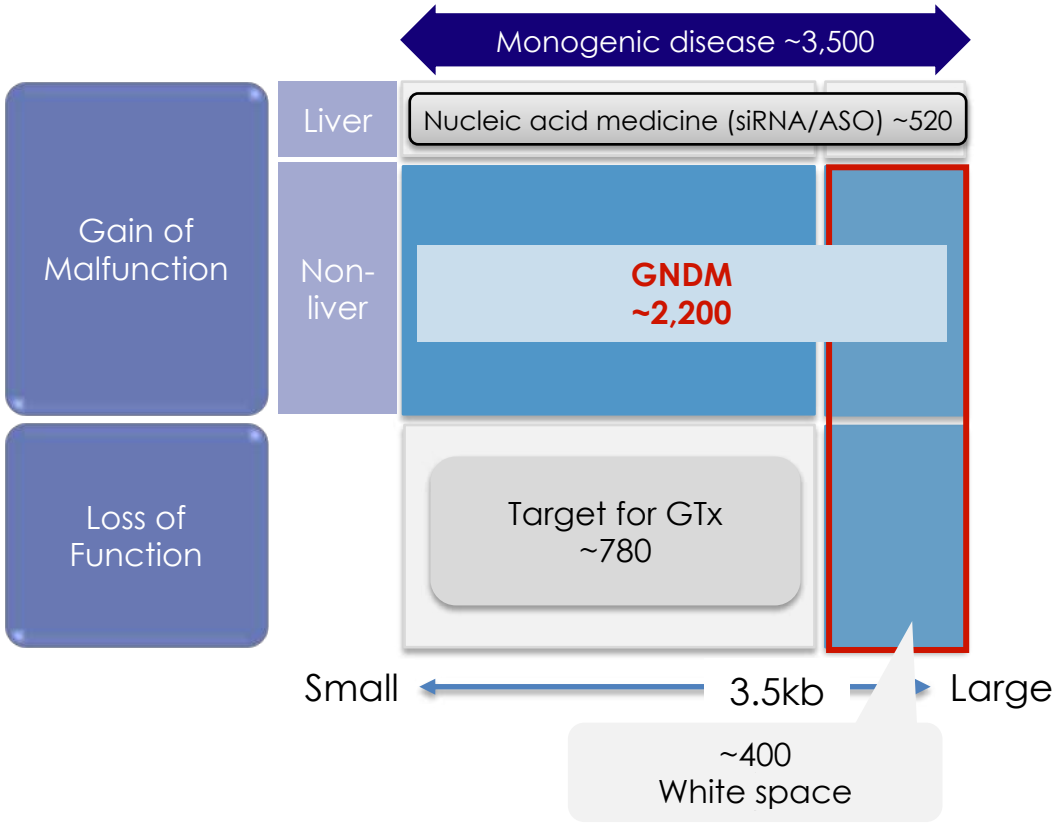
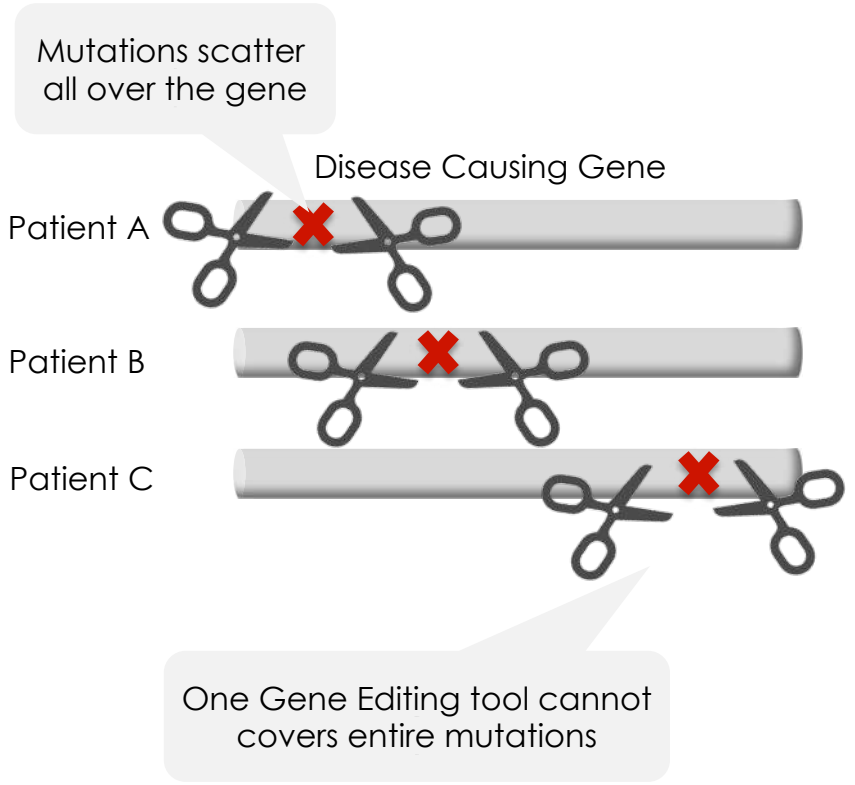
Target diseases of GNDM

GNDM enable us to reach differentiated genetic targets

Targets of GNDM



Limitation of Gene Editing



GNDM enable us to approach differentiated targets which cannot be reached by other gene therapies or gene editing

Source: Discovery Medicine、Science 2019

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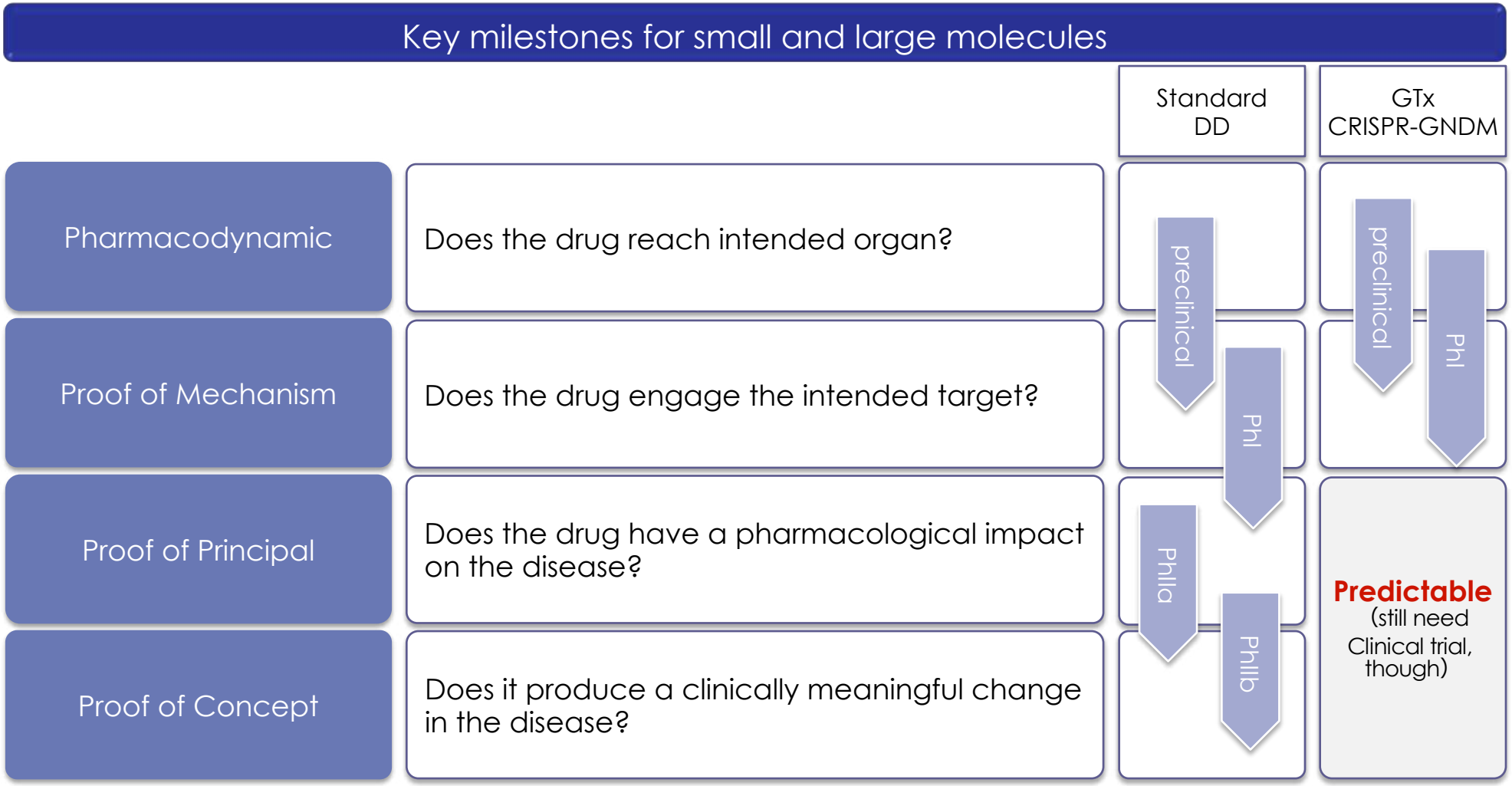
Major hurdles in drug development

PoP and PoC are predictable in GNDM prior to human testing



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

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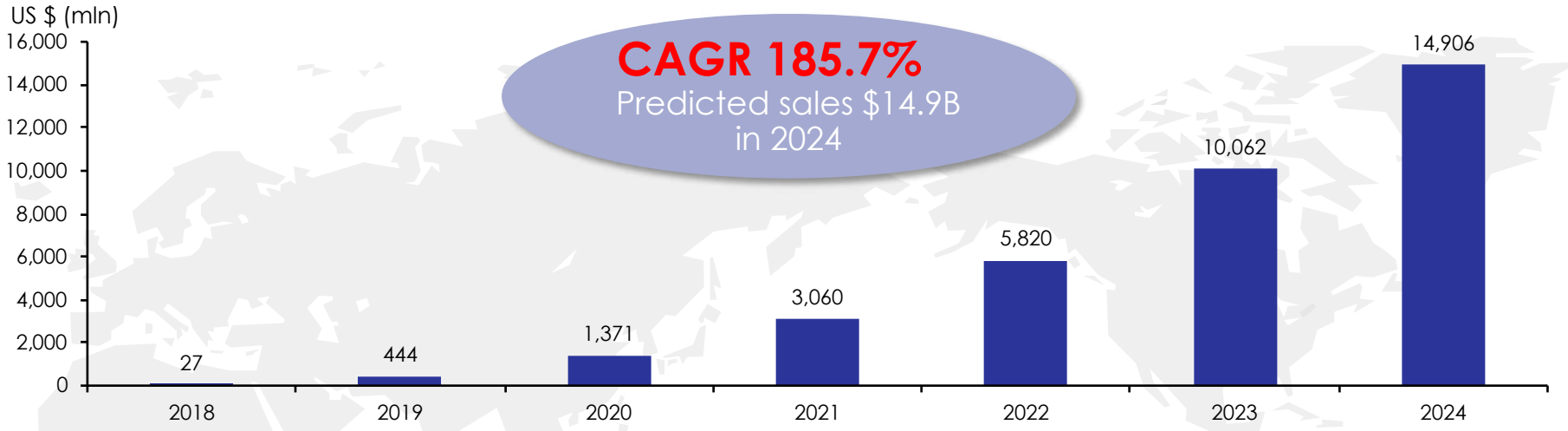
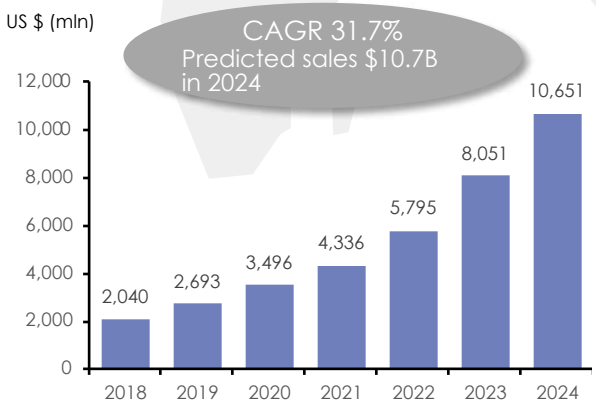
Sales growth of pharmaceutical modalities

GTx is growing faster than other modalities

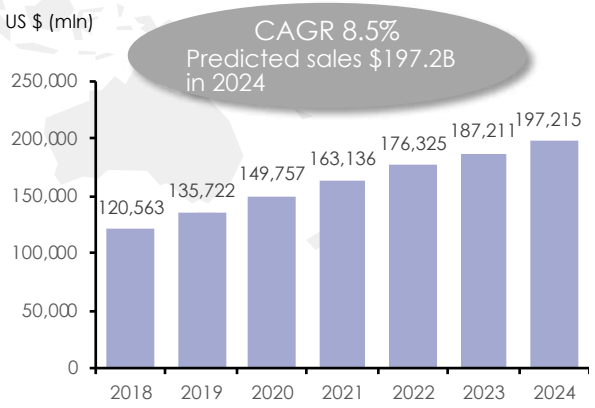
Predicted sales of Gene Therapy (WW)



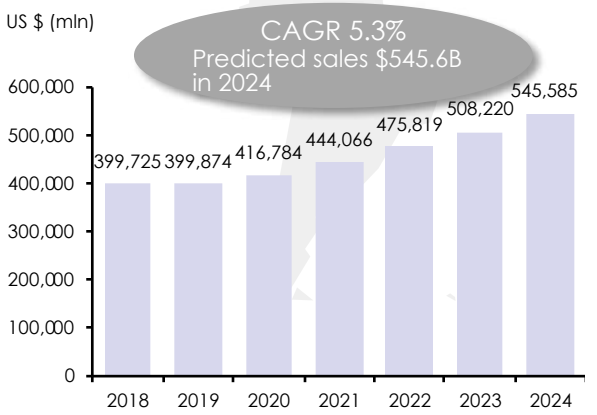
DNA&RNA therapeutics



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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Examples of GTx companies M&A

Acquisitions / investments in 2018-2019 deals ranged from millions to billions of US dollars

Name	Closing Date	Acquisition / investment	Deal total	Ref. (disclosed information by each company of GTx)
Astellas	2019/12	**AUDENTES Tx**	**$3.0 billion**	AT132: X-linked myotubular myopathy (XLMTM) AT845: Pompe disease AT702, AT751, AT753: Duchenne muscular dystrophy (DMD)
VERTEX	2019/6	**Exonics Tx**	**$1.0 billion**	Duchenne muscular dystrophy (DMD) myotonic dystrophy type 1 (DM1)
SAREPTA Tx	2019/3	**Myonexus Tx**	**$165 million**	MYO-101: limb-girdle muscular dystrophy 2E (LGMD 2E) MYO-102: limb-girdle muscular dystrophy 2D (LGMD 2D)
Biogen	2019/3	**Nightstar Tx**	**$800 million**	NSR-REP1: Choroid atrophy (Choroideremia) NSR-RPGR: X-linked retinitis pigmentosa (XLRP) NSR-ABCA4: Staggered disease
Roche	2019/2	**Spark Tx**	**$4.3 billion**	SPK-9001: Hemophilia B SPK-8011, SPK-8016: Hemophilia A SPK-7001: Choroid atrophy (Choroideremia)
NOVARTIS	2018/5	**AveXis**	**$8.7 billion**	Zorgensma AVXS-101（IT）: Spinal muscular atrophy type II（SMA Type 2） AVXS-201: Rett syndrome（RTT） AVXS-301: Amyotrophic lateral sclerosis（ALS）

Source : disclosed information by each company

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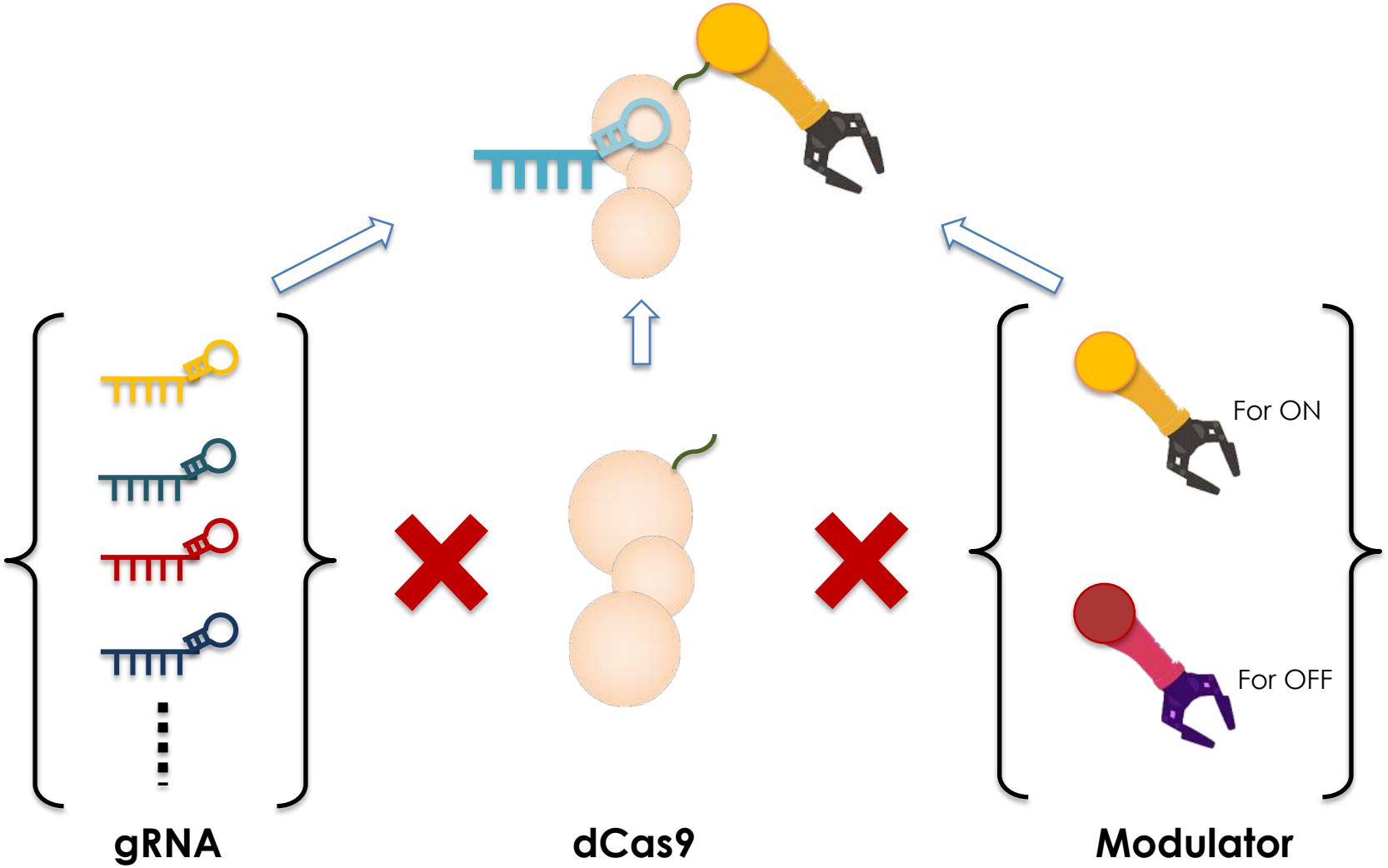
Scalability of GNDM

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



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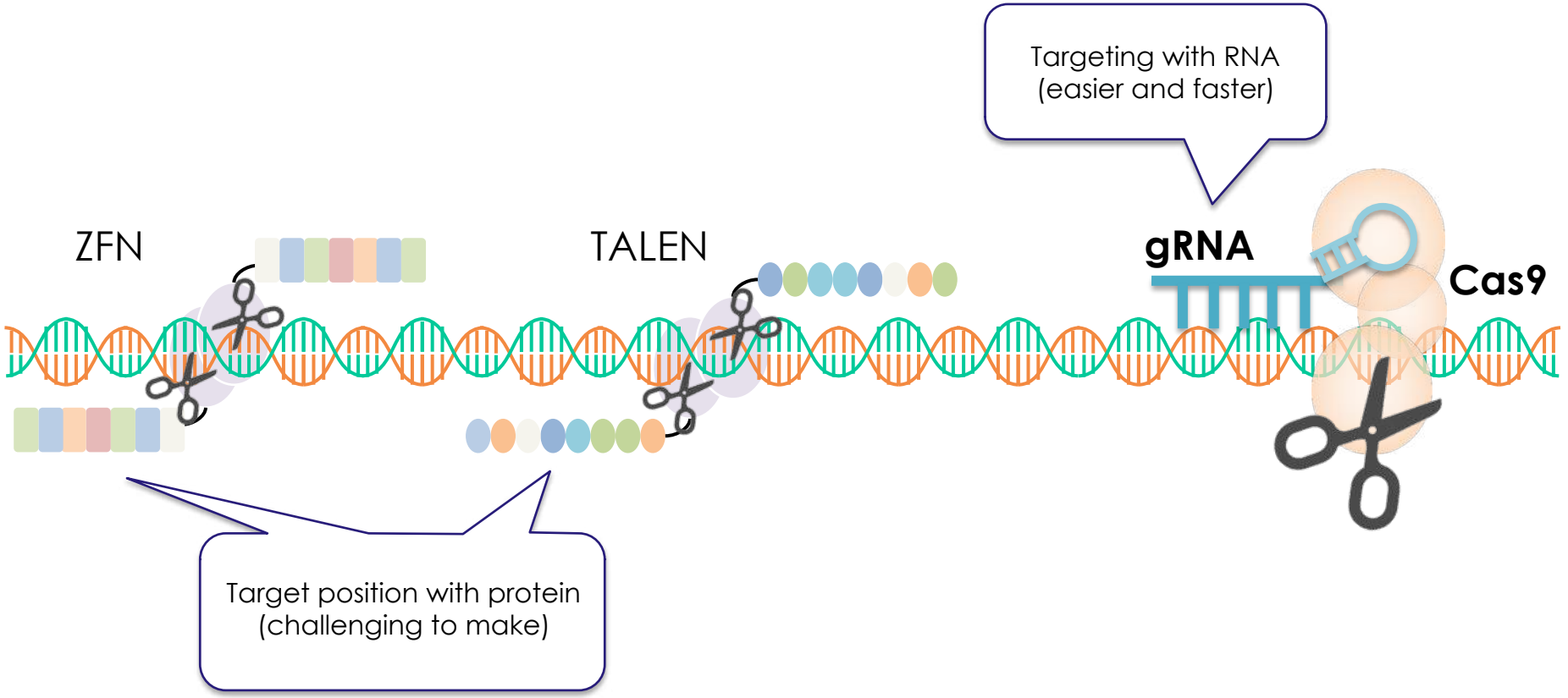
CRISPR is a novel gene editing technology

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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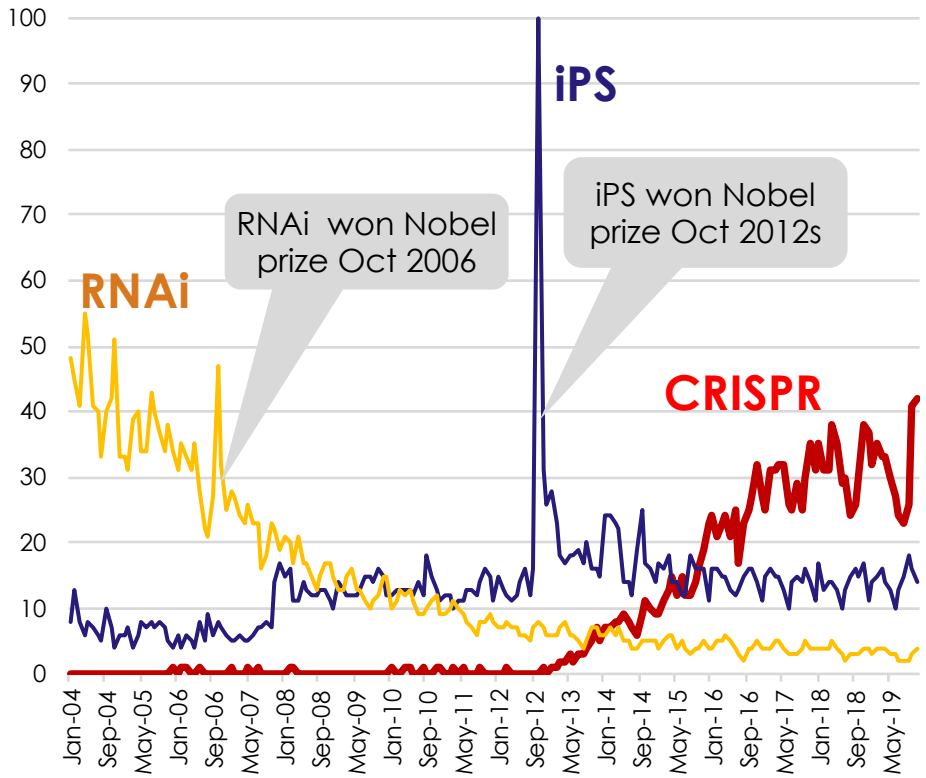
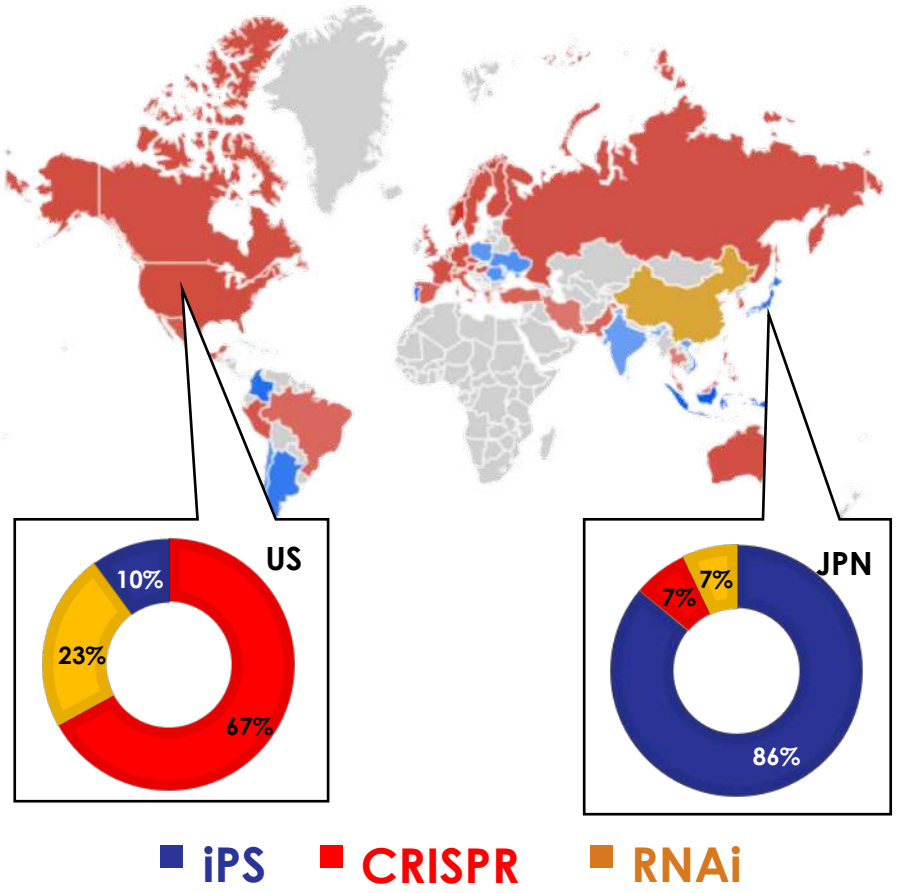
CRISPR gets more attention

Trends in Google keyword searches (world wide)



Geographic distribution of key word Google search (2005-2015)



Source : Google Trends
Note: Normalized by max of iPS at Oct 2012 as 100

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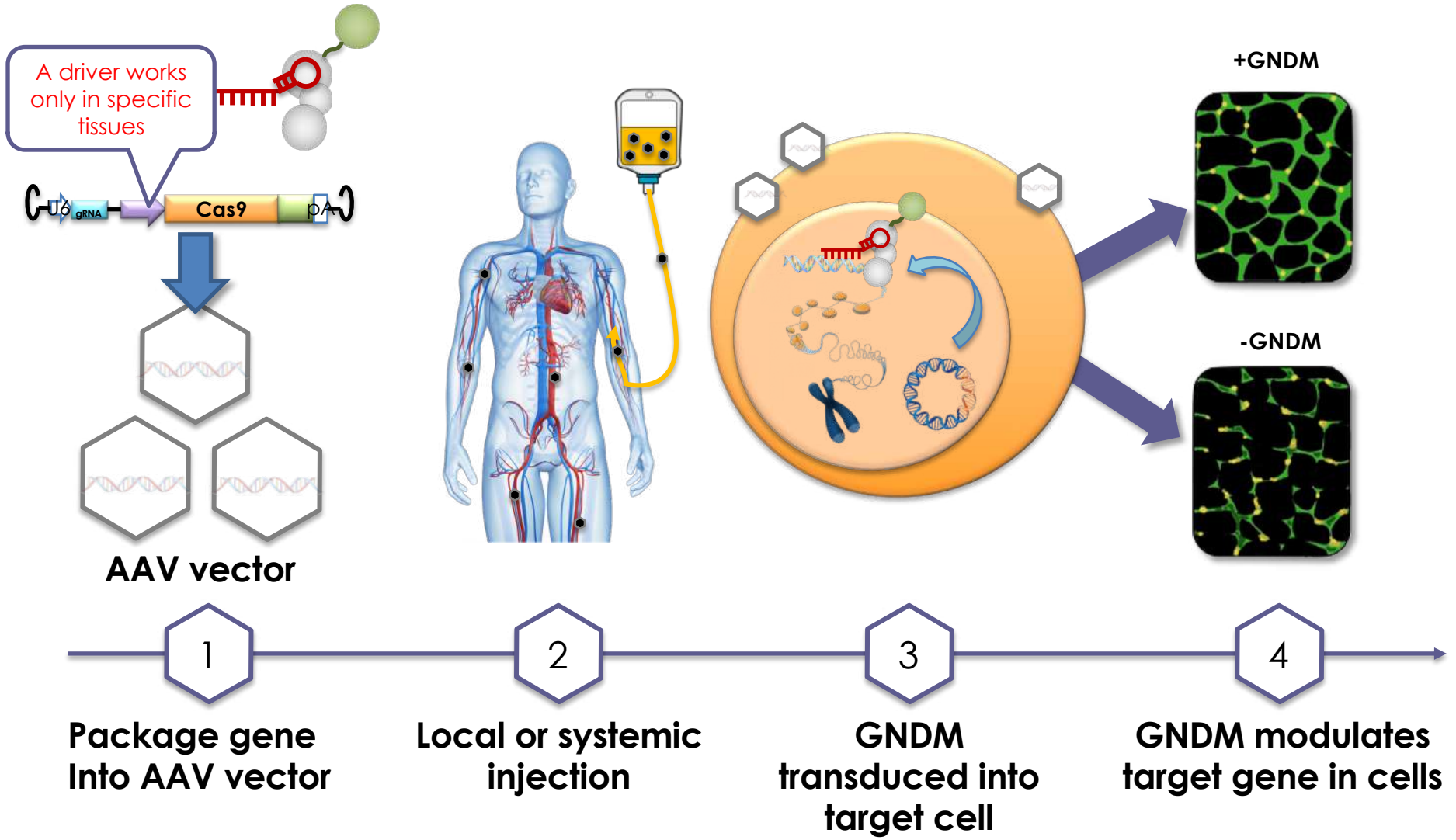
Delivery of CRISPR-GNDM® to target

Use AAV vector to deliver GNDM to target cell



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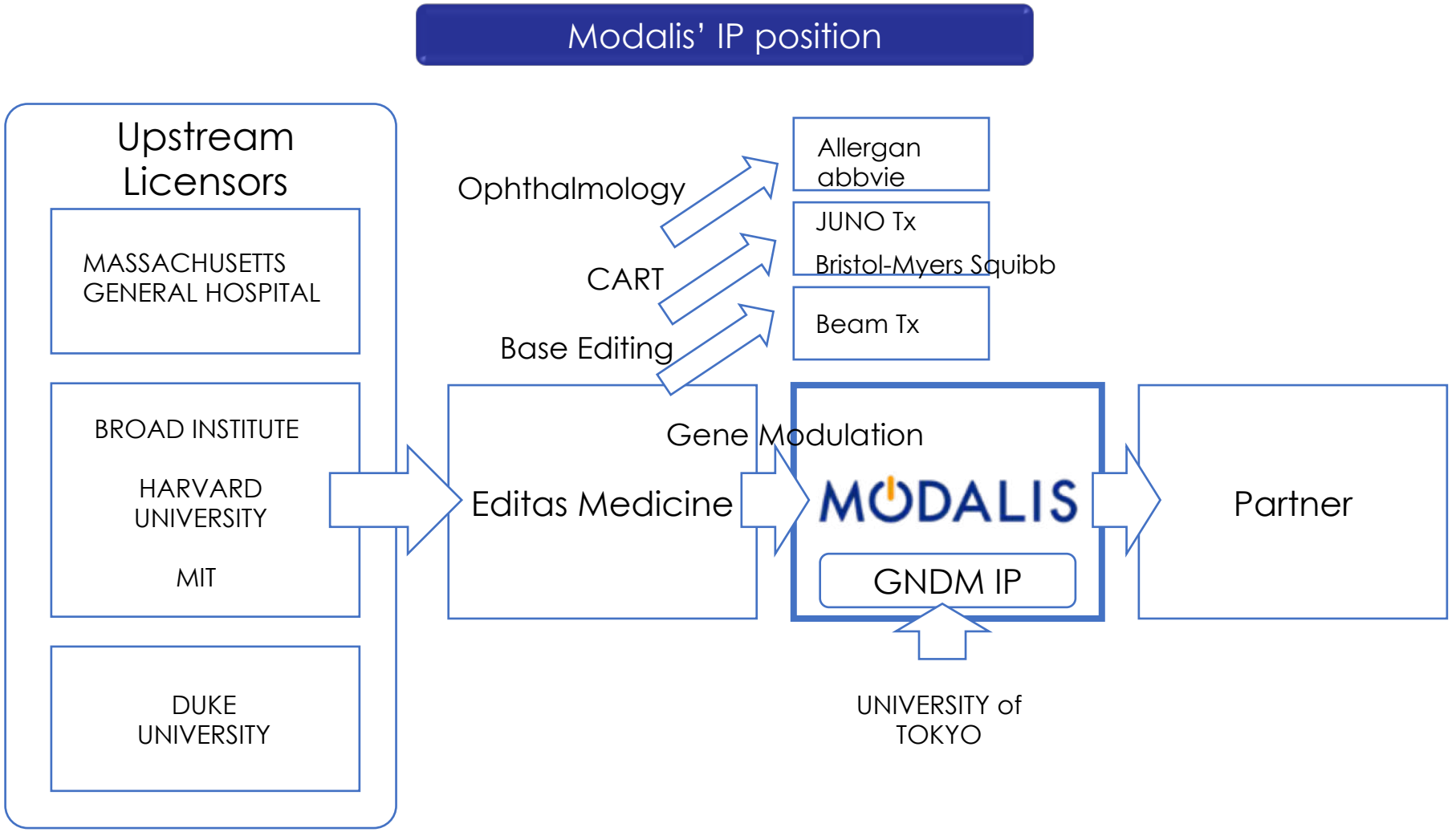
IP position

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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Business Model

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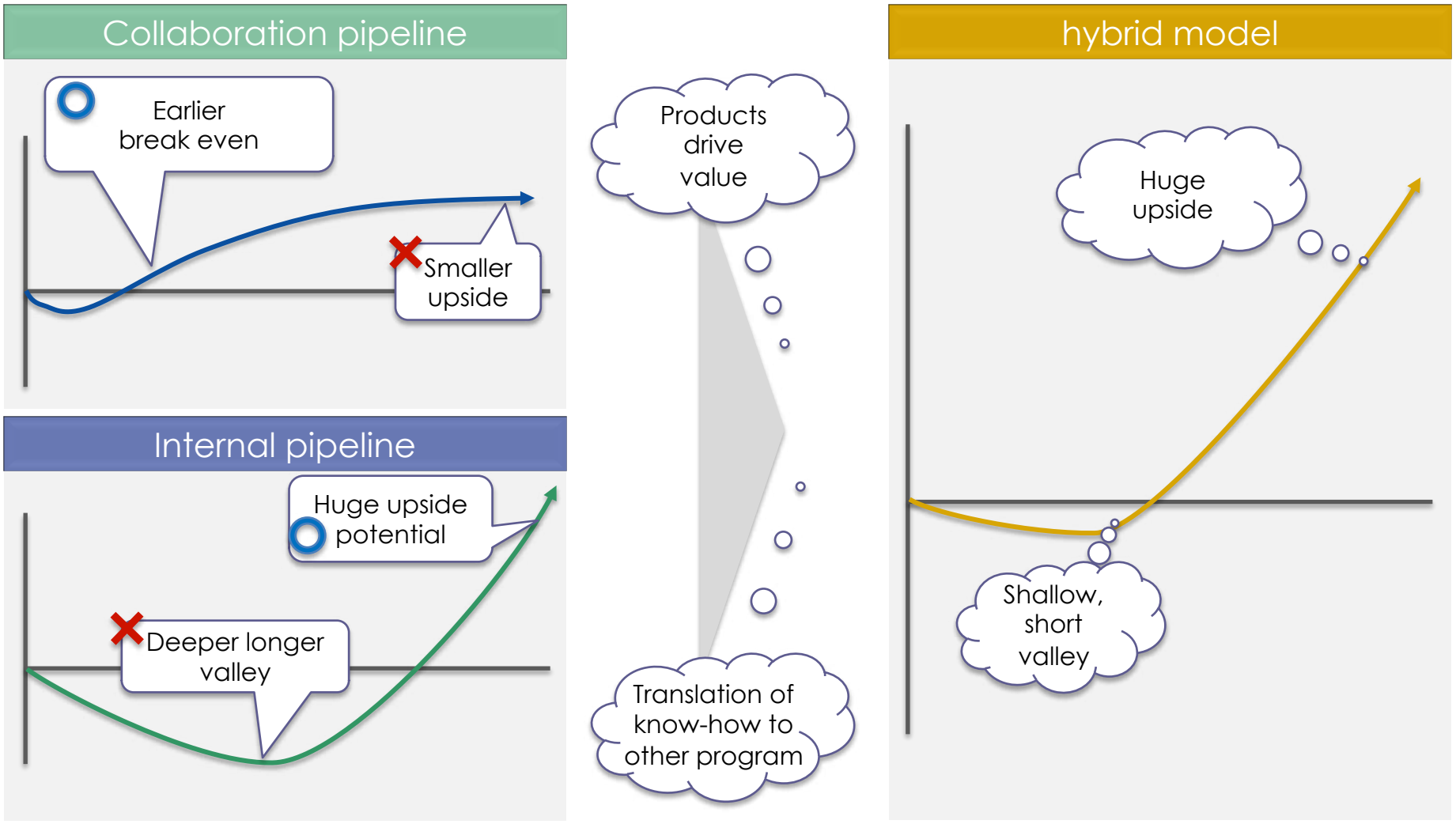
Modalis is pursuing a hybrid model

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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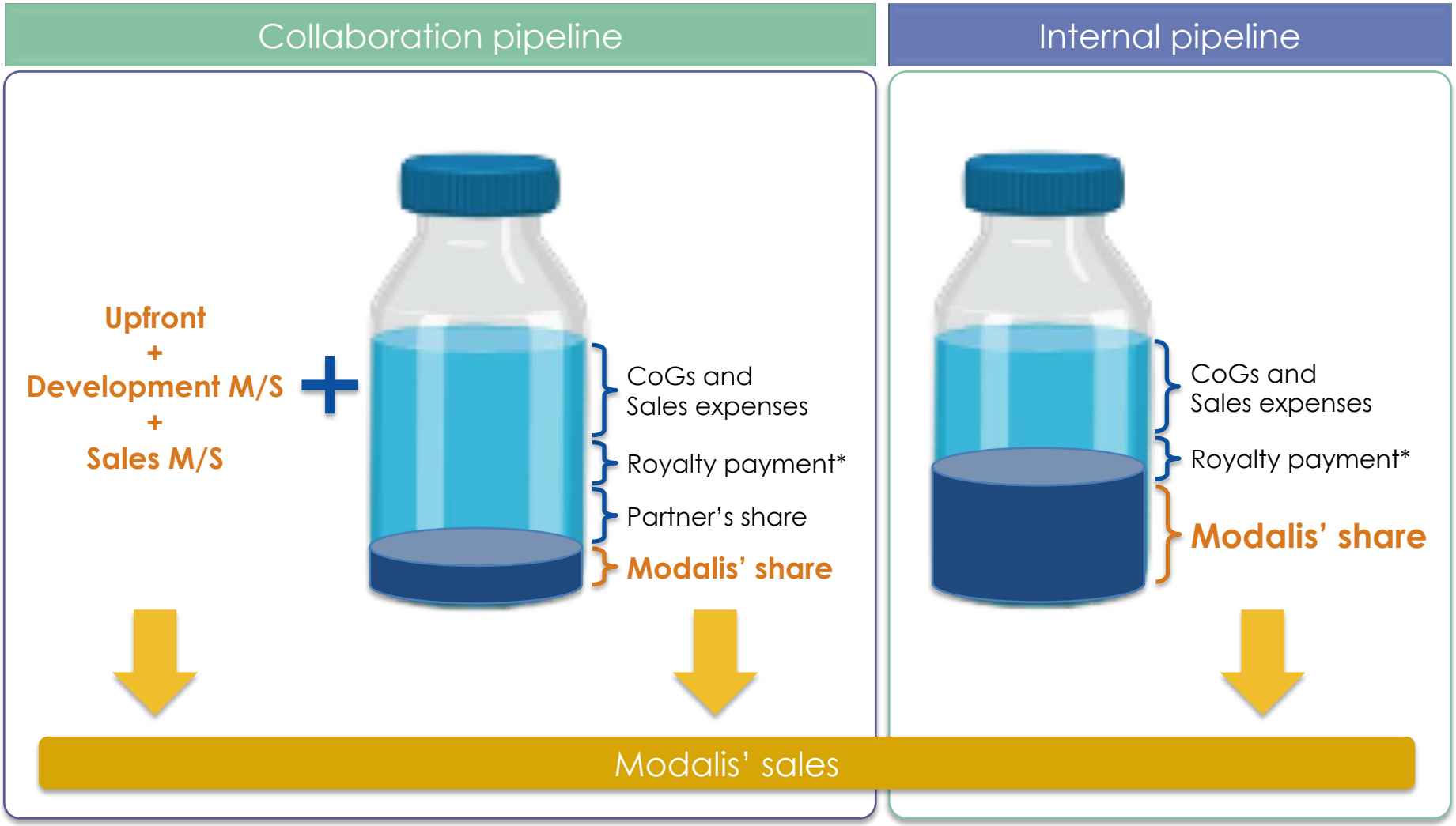
Risk - profit share model

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



* : 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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Landscape of Listed Bio-ventures in Japan

First listing with CRISPR platform company

Business Model

	Drugs / Therapies						
	Others	Small molecule	Protein / Peptide	Antibody	Regenerative / cellular medicine	Gene therapy / nucleic acid medicine	**Gene Editing (CRISPR)**
Drug discovery (Platformer)		**(4565) Sosei Group Mkt cap : 1,289B Yen**	**(4587) Pepti Dream Mkt cap : 6,345B Yen**				**MODALIS (4883) Modalis**
Drug discovery (Products)	Nano Carrier MED RX Oncolys BioPharma	CARNA BIOSCIENCES MEDICINOVA RaQualia CanBas DWTI Kubota Delta-Fly Pharma GNI SymBio Solasia	JCR OTS 3D MATRIX BrightPath Bio StemRIM Gene Techno Science	CHIOME Bioscience	SanBio Healios J-TEC CellSeed	Anges RIBOMIC	
analysis/contract processing services	SNBL HMT Phoenix Bio				Takara Bio MEDI NET REPROCELL CellSource		

Source: Prepared by Modalis Tx based on information disclosed by bio ventures listed from 1990 to date. The above chart classifies drugs and therapies based on main pipelines.
Market cap is as of Jun 24th

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Deal of CRISPR companies

3 editing companies have formed mega deal before entered into clinical trials

	Partner	Collaboration	Detail	Total deal size*
Editas Medicine Market Cap# : $1.7B (EDIT)	JUNO Tx Bristol-Myers Squibb	3 target in CART	Upfront $25M + R&D funding $22M + M/S $700M	$ 747M
	Allergan abbvie	5 targets in Ophthalmology Incl. LCA10	U/F $90M + MS・royalty	
Intellia Tx Market Cap# : $1.2B (NTLA)	NOVARTIS	CART and HSC	$10M（U/F）+ $20M（tech transfer） + $20M（R&D funding） + $230.3M（M/S / 1 product） + ~15%（royalty） $13M Equity investment	$ 293.3M
			& 14 DDS patent license from Novartis	
	REGENERON	Option for 10 liver target	$75M（U/F） + $135M（M/S / 1 product） + ~10%（royalty） $50M Equity investment@ IPO	$ 260M
CRISPR Tx Market Cap# : $4.5B (CRSP)	VERTEX	Option to 6 targets	$75M（U/F） + $30M（IP milestone） + $420M（MS / 1 target）+ royalty	$ 525M
	BAYER	JV	50:50 stake & $70M Equity investment	$ 405M
	CASEBIA	Hematology Blindness Heart	BAYER to CASEBIA $45M（U/F）+ $255M（R&D funding）	
			CASEBIAからCRISPR $15M（U/F）、$20M（when get IP）	

Source: S1 data and press release of each company. # As of end Jun 24th * Aggregated amount of U/F, milestones and equity investment

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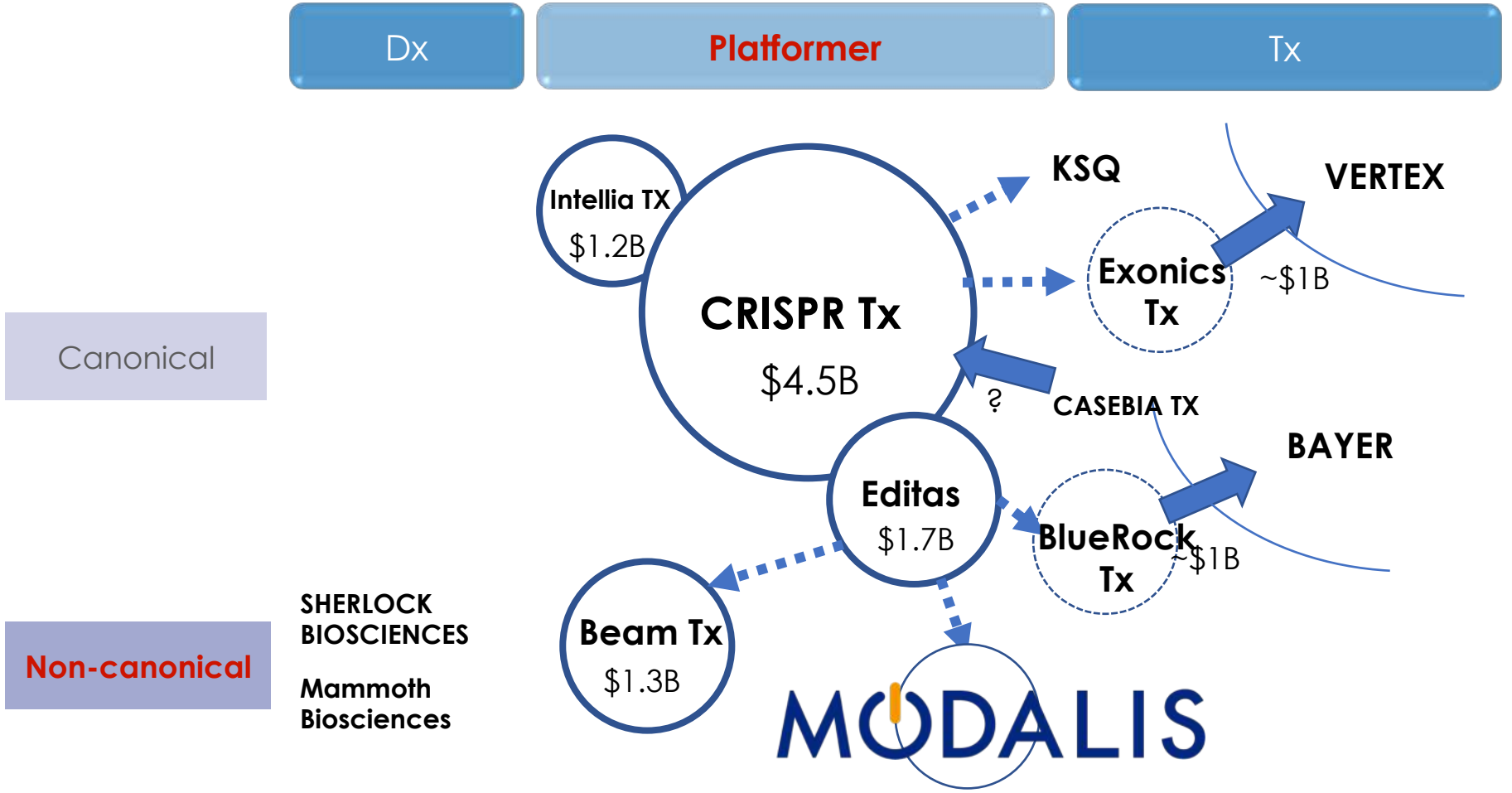
Major players in CRISPR field

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



Source: stock info. The figures represent market cap as of Jun 24th or value at the time of acquisition. Dotted circle represent acquired companies

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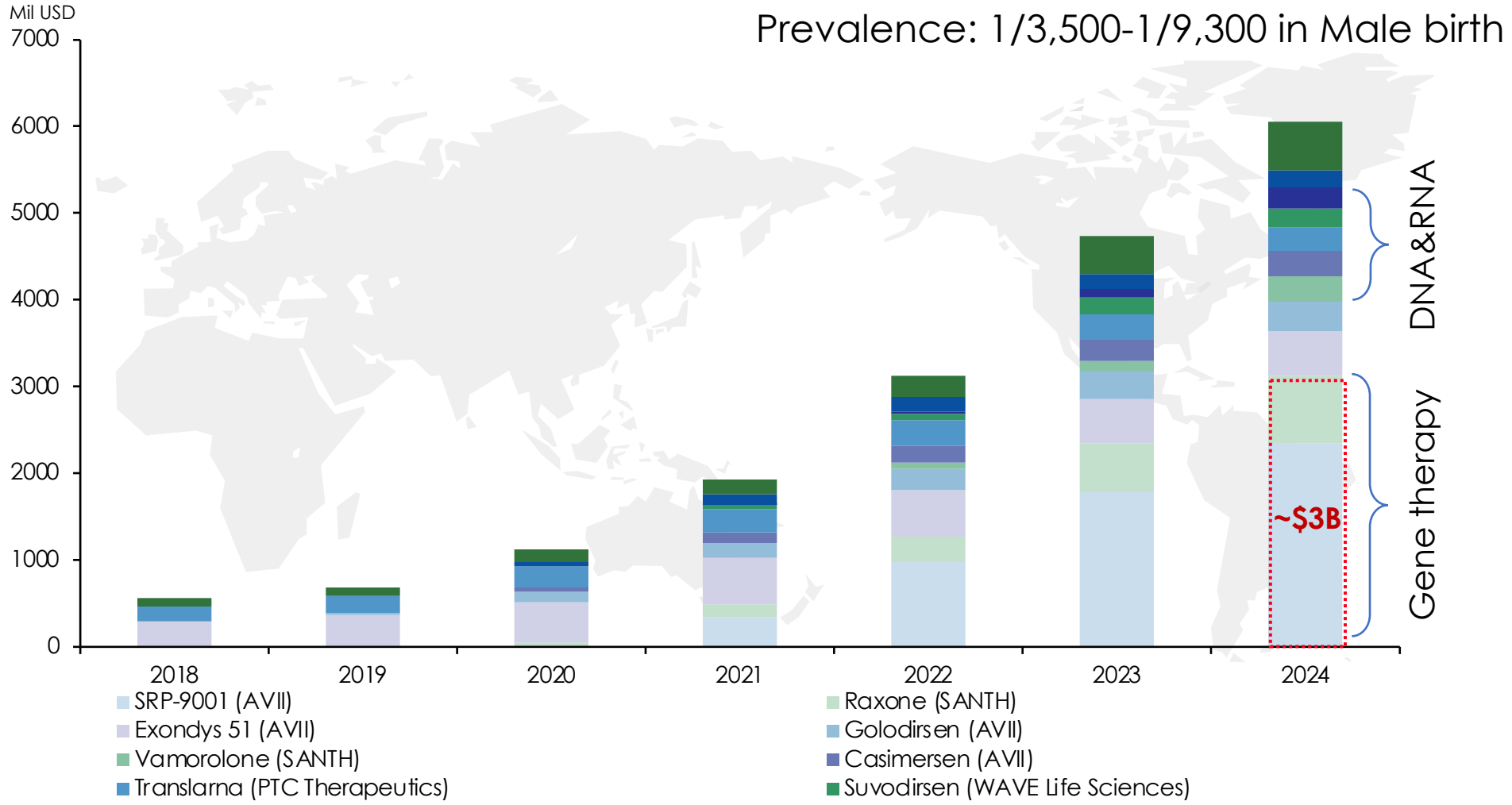
DMD market

Expected to be reaching $3B in 2024 driven by GTx



Source : Evaluate Ltd and Orphanet. 2019 to 2024 are predicted sales

DMD: Duchenne muscular dystrophy

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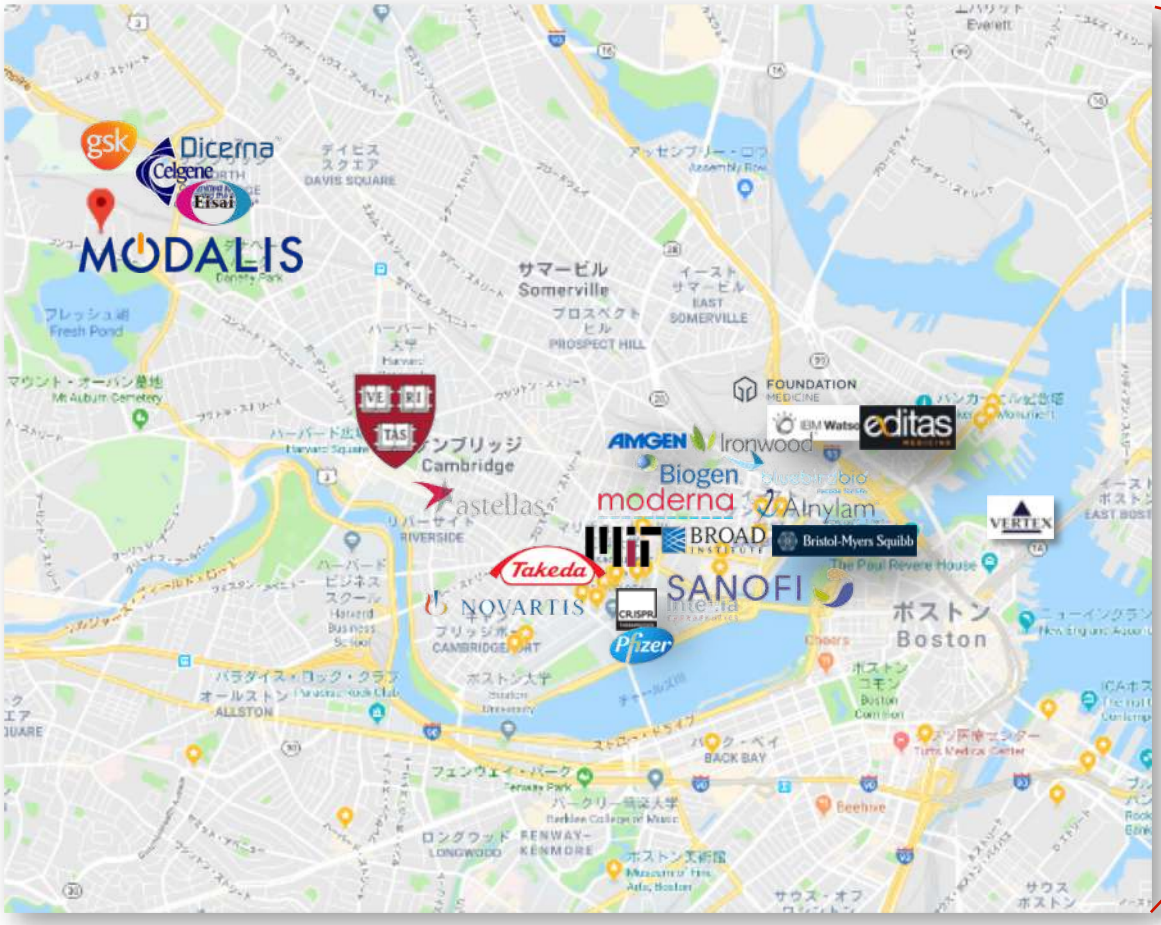
Appendix

Operated in Cambridge MA

The center of life-science







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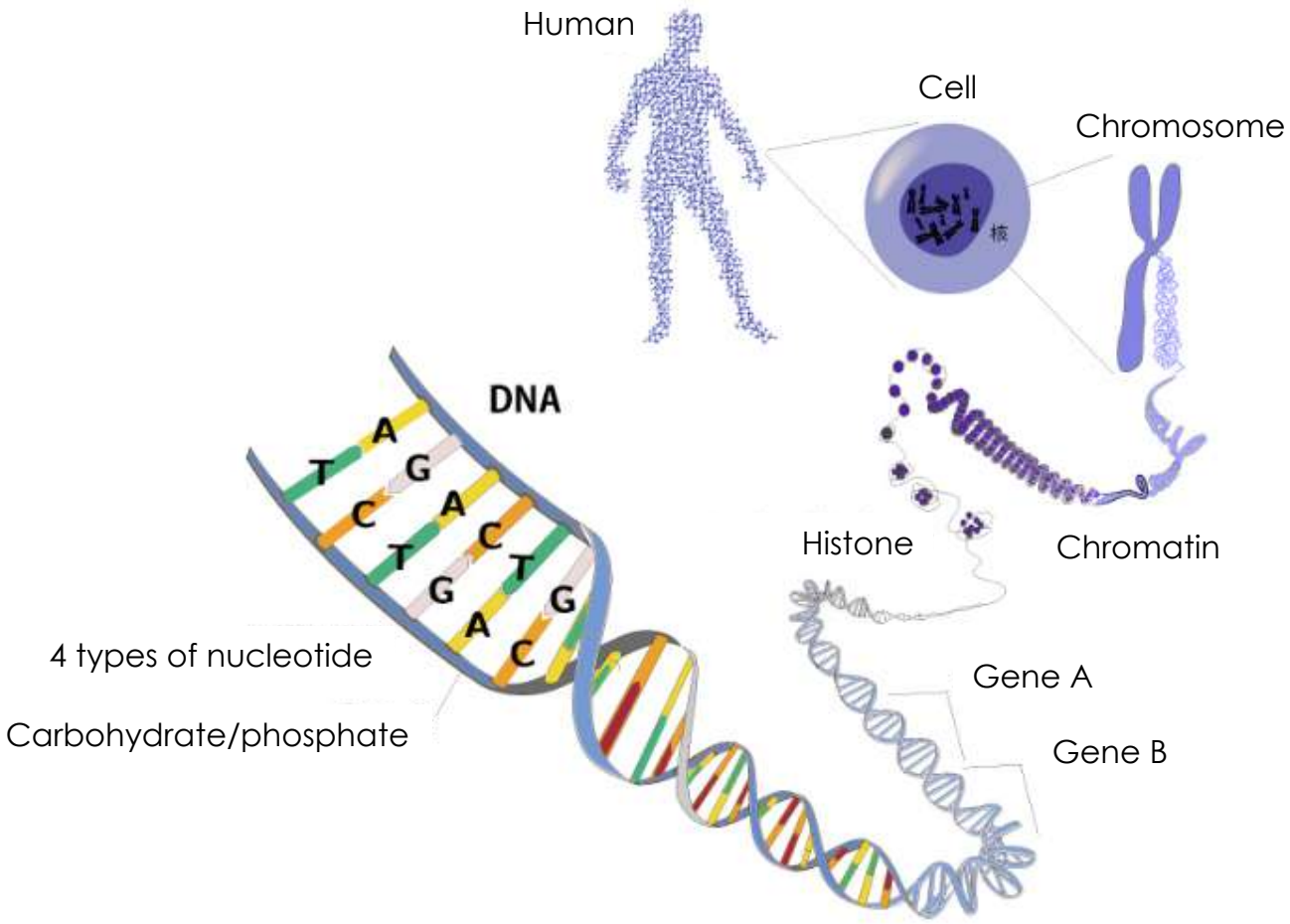
Genome, Gene, DNA

Gene is a meaningful unit (program) consisting of DNA (code) within the genome (system)



All cells in the body have the same DNA in all cell types

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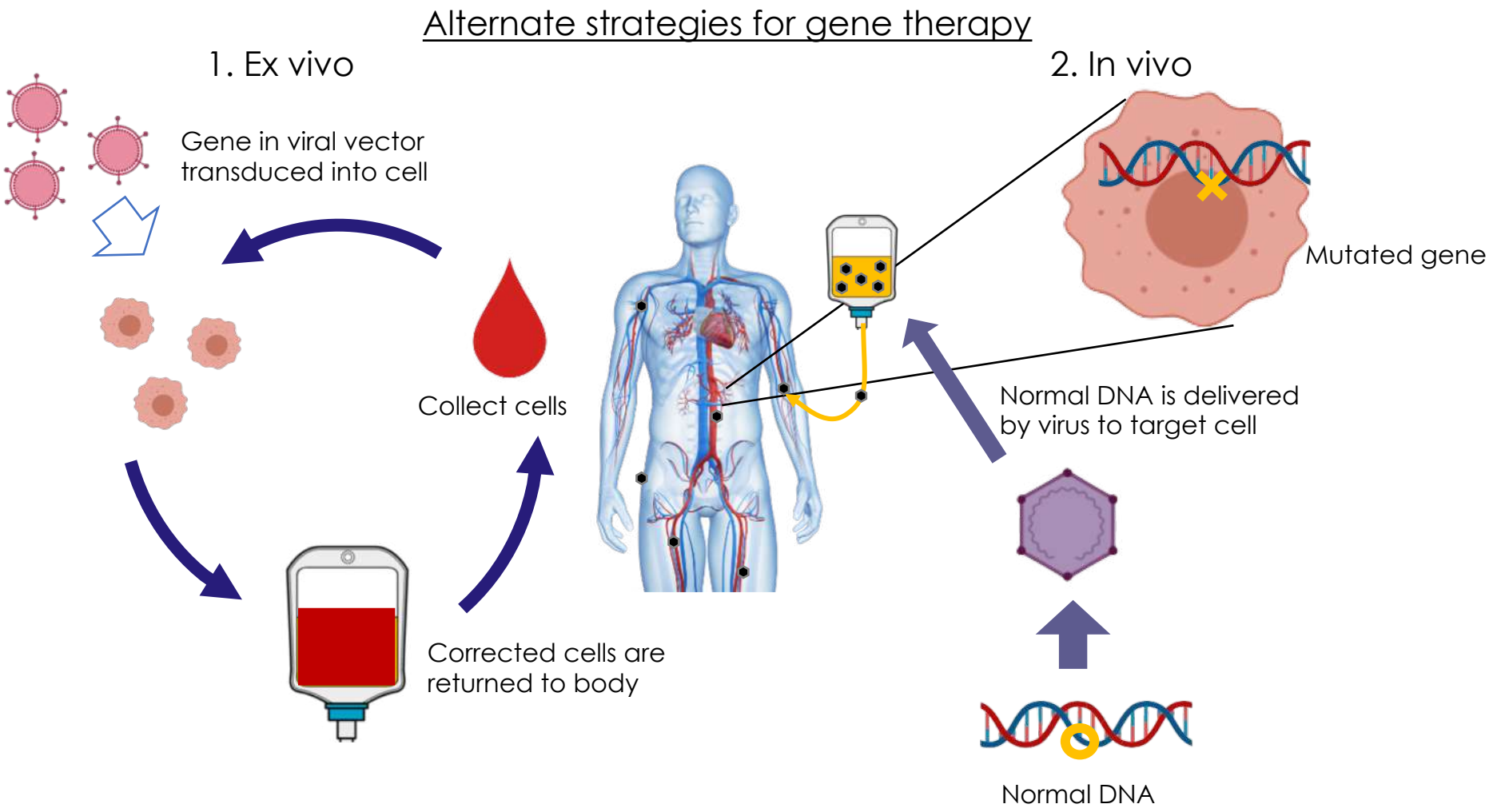
Delivery of gene therapy

Use of viral vector to deliver DNA to cell *ex vivo* or *in vivo*



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Comparison of GTx technologies

	Gene Therapy (broad sense)					
	GTx (narrow sense)	Gene Editing				
Basal technology	-	ZFN	TALEN	CRISPR	CRISPR	CRISPR
Molecule design	-	Complicated	Complicated	**Simple**	**Simple**	**Simple**
Mode	Gene Transduction	Gene Editing Gene modulation	Gene Editing	Gene Editing	Base Editing	Gene modulation
Delivery method	AAV/LNP	AAV	AAV	AAV/LNP	AAV/LNP	AAV
DNA cleaving	Yes	Yes	Yes	Yes	**No**	**No**
Max size of target gene	<~3.5kb	**No limit**	**No limit**	**No limit**	**No limit**	**No limit**
Companies	**AUDENTES Tx** **Spark Tx** **AveXis** **SAREPTA Tx** **REGENXBIO**	**Sangamo Tx**	-	**Editas Medicine** **Intellia Tx** **CRISPR Tx**	**Beam Tx**	MODALIS

Source: Modalis by public information

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Glossary（1/2）

Page	Word	Explanation
P6	CNS	Central Nervous System comprises the brain and spinal cord.
P6	MDC1A	A group of neuromuscular disorders that begin at birth or infancy and are characterized mainly by hypotonia, muscle weakness and muscle wasting. Caused by mutations in the LAMA2 gene. Inherited in an autosomal recessive manner.
P10	gRNA（guide RNA）	18-22nt RNA which is complementary (forming A-T or G–C pairs) and bind to target DNA sequence
P10	dCas9	Form of Cas9 enzyme which lacks activity to cut DNA
P33	GTx	Gene Therapy
P33	Gain of Malfunction	A type of mutation in which the altered gene product possesses a harmful molecular function or a harmful pattern of gene expression. Gain-of-function mutations are almost always Dominant or Semi-dominant
P33	Loss of function	Also known as inactivating mutations, which result in the gene product having less or no function
P33	siRNA	Small interfering RNA (siRNA) is a class of double-stranded RNA molecules, 20-25 base pairs in length, and operating within the RNA interference (RNAi) pathway. They interfere with the expression of specific genes with complementary nucleotide sequences by degrading mRNA after transcription thus preventing translation.

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Glossary（2/2）

Page	Word	Explanation
P33	ASO	A synthetic strand of nucleic acid (DNA, RNA or a chemical analogue) that binds to the messenger RNA (mRNA) produced by that gene and inactivates it, effectively turning that gene "off".
P38	ZFN（Zinc Finger）	Small protein structural motif that is characterized by the coordination of one or more zinc ions (Zn2+) which stabilize the structure. Engineered ZF arrays fused to a DNA cleavage domain (usually the cleavage domain of FokI) are used as a gene editing tool.
P38	TALEN	Transcription Activator-Like Effector Nucleases: restriction enzymes that can be engineered to cut specific sequences of DNA. They are made by fusing a TAL effector DNA-binding domain to a DNA cleavage domain.
P40	AAV vector	Adeno-associated virus (AAV) is a small virus that infects humans and some primate species. AAV is not currently known to cause disease and is used for delivery of gene therapy tools to cells for therapeutics.
P48	Duchenne muscular dystrophy(DMD)	Genetic disorder characterized by progressive muscle degeneration and weakness. One of nine types of muscular dystrophy. DMD is caused by an absence of *dystrophin*, a protein that helps keep muscle cells intact.
P51	Histone	Proteins found in eukaryotic cell nuclei that package and order the DNA into structural units.
P51	Chromatin	Complex of DNA and protein found in eukaryotic cells. Primary function is packaging very long DNA molecules into a more compact, denser form.
P52	Ex vivo / In vivo	Ex vivo: transduction of the therapeutic gene into patient-derived somatic cells, followed by subsequent transplantation back into the patient. In vivo: delivery of cargo (e.g. virus vector) and therapeutic components to body

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