# Chugai R&D Meeting


## CHUGAI PHARMACEUTICAL CO., LTD.

12 December, 2023

# Important Reminders

This presentation may include forward-looking statements pertaining to the business and prospects of Chugai Pharmaceutical Co., Ltd. (the "Company"). These statements reflect the Company's current analysis of existing information and trends. Actual results may differ from expectations based on risks and uncertainties that may affect the Company's businesses.

Information regarding pharmaceuticals (including products under development) is included in this presentation, but is not intended as advertising or medical advice.

# Agenda

01 **Characteristics of Chugai's Research to Early Development**

Associate Vice President, Head of Translational Research Div.

**Tomoyuki Igawa Ph.D.**

02 **Chugai's Mid-size Molecule Drug Discovery**

Vice President, Head of Research Div.

**Hitoshi Iikura Ph.D.**

03 **Q&A**

# Characteristics of Chugai's Research to Early Development

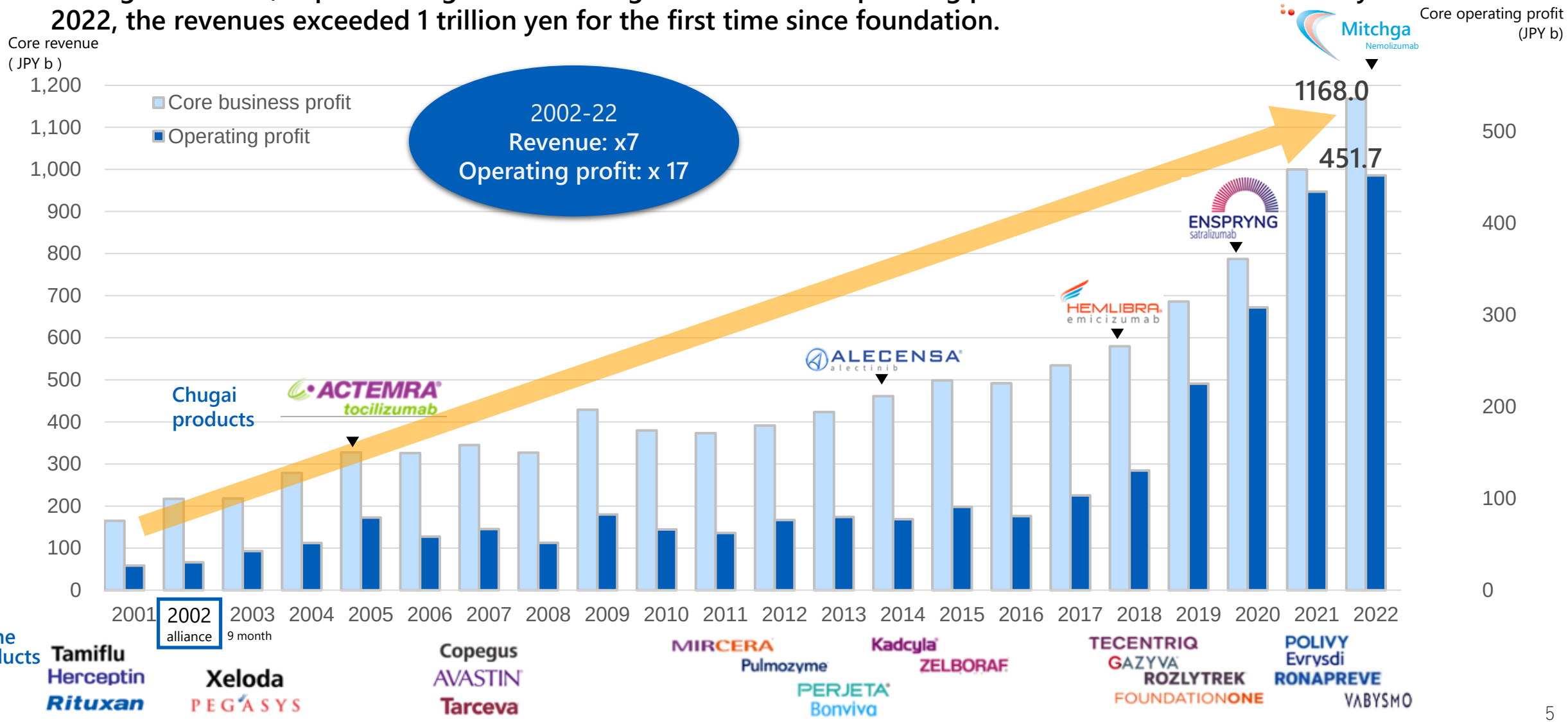
Tomoyuki Igawa Ph.D.
Associate Vice President, Head of Translational Research Div.

CHUGAI PHARMACEUTICAL CO., LTD.

12 December 2023

# Exponential Growth in Revenues Volume Trends

➢ **During 2017-2022, kept breaking the record-high revenues and operating profit for the sixth consecutive year. In 2022, the revenues exceeded 1 trillion yen for the first time since foundation.**




2012 and before: JGAAP, 2013 and beyond: IFRS Core, Revenues excluding OTC and diagnostics

 * Counting from 2003 to 2022. F1T and F1L are counted as one.

# Chugai R&D Principles

- ✓ “Technology-Driven” drug discovery
- ✓ “Quality-Centric” clinical candidates
- ✓ "Molecule-Centric/Biology-Driven" indication selection
- ✓ "Value Maximization" clinical development

- Chugai R&D has fostered a unique company culture and mindset over a long period of time.
- Chugai R&D principles reflect this culture and mindset.
- We will contentiously follow these principles and achieve higher R&D productivity.

# Chugai R&D Principles

## "Technology-Driven" drug discovery

- We develop unique and innovative modality technologies to make undruggable targets or MOAs druggable, and pursue drug discoveries that can only be accomplished by Chugai
- We apply proprietary technologies to a variety of targets or MOAs in any disease area where the idea can achieve a differentiated product and fulfill patients' unmet medical needs
- We conduct forward and reverse translational research into proprietary modality technologies, to improve the efficiency and success rate of our drug discoveries and clinical developments

## "Quality-Centric" clinical candidates

- We identify the highest quality drug candidates (in terms of activity, selectivity, DMPK, safety, stability, etc.) that are achievable using the latest technologies, without compromise
- We demonstrate clear differentiation points from competitors based on non-clinical experimental data and scientific evidence
- We persevere even for a decade until we succeed in achieving the highest quality possible, if the idea, when realized, is game-changing for patients
- We pursue the highest prediction accuracy for DMPK properties and safety, from non-clinical to human settings

# Chugai R&D Principles

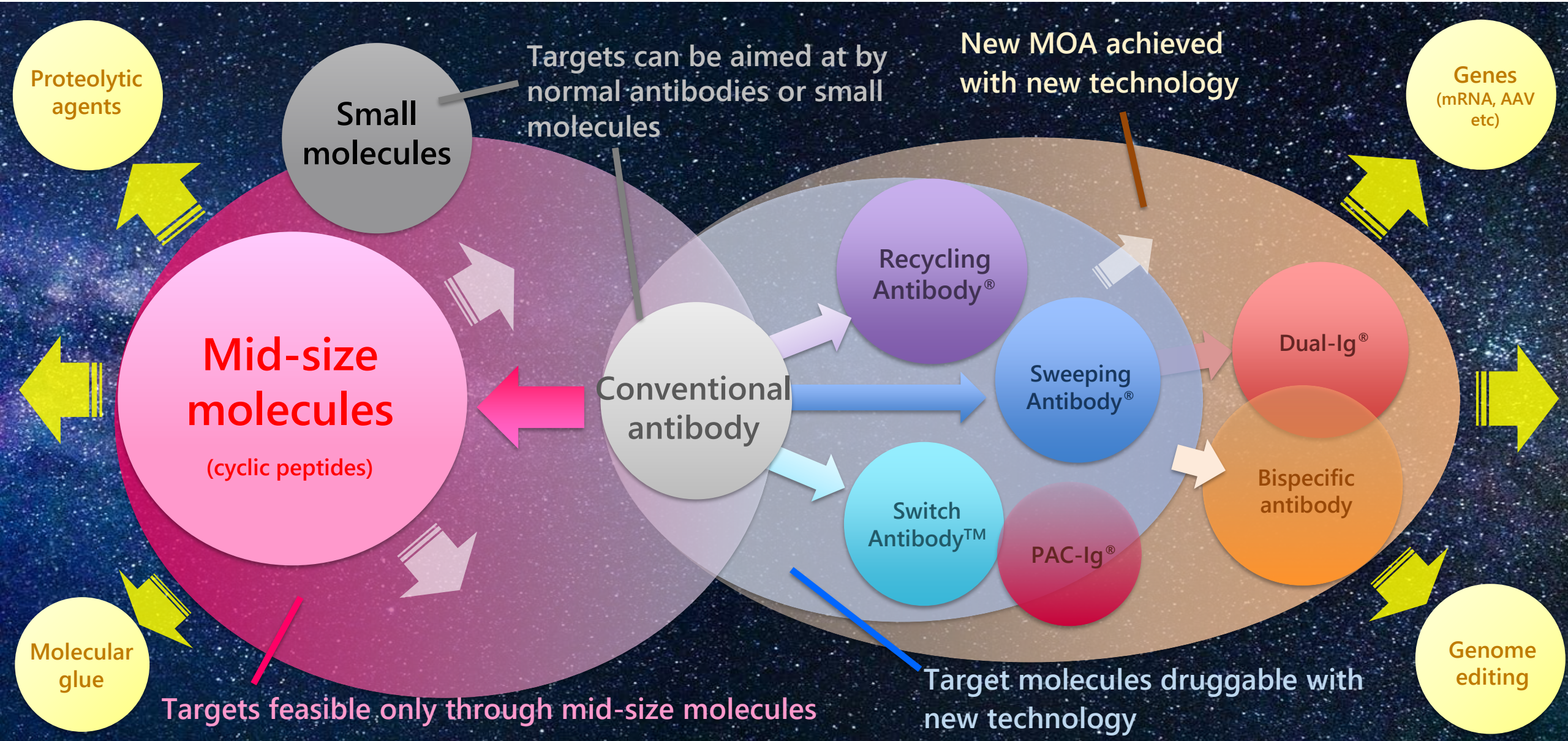
## "Molecule-Centric/ Biology-Driven" indication selection

- We select the right indications for each drug molecule based on the MOA of the molecule and the biology of the target, not restricted to a specific disease area
- We select indications that are based on the value that the product can potentially deliver to patients, rather than drug price and market size estimated prematurely at the early stage of clinical development
- We improve Go/No go decision accuracy by obtaining biological PoC data for our non-clinical hypotheses at the early stage of clinical development, to increase success rates in the later stage of clinical development.

## "Value Maximization" clinical development

- We maximize the value of each product across multiple disease areas, rather than its value in a single disease area, and seek a wide variety of opportunities beyond the focused disease area, through concurrent development in multiple indications from the early stage of clinical development
- We focus on generating key data in clinical studies and do not make prioritization or Go/No go decision of a project in the absence of scientific evidence, and continue the project as long as the science-based non-clinical/clinical data supports fulfilling patients' unmet medical needs
- We collaborate with partners or out-license to them when we lack our own expertise or resources to develop a project, and generate data to demonstrate the value of the product

# Drug Discovery only Achieved by Chugai through Technology-Driven Drug Discovery



# Long-term Continuous Investment in New Technology Development that Support Technology-driven Drug Discovery is the Best Way to Continuously Create Innovation

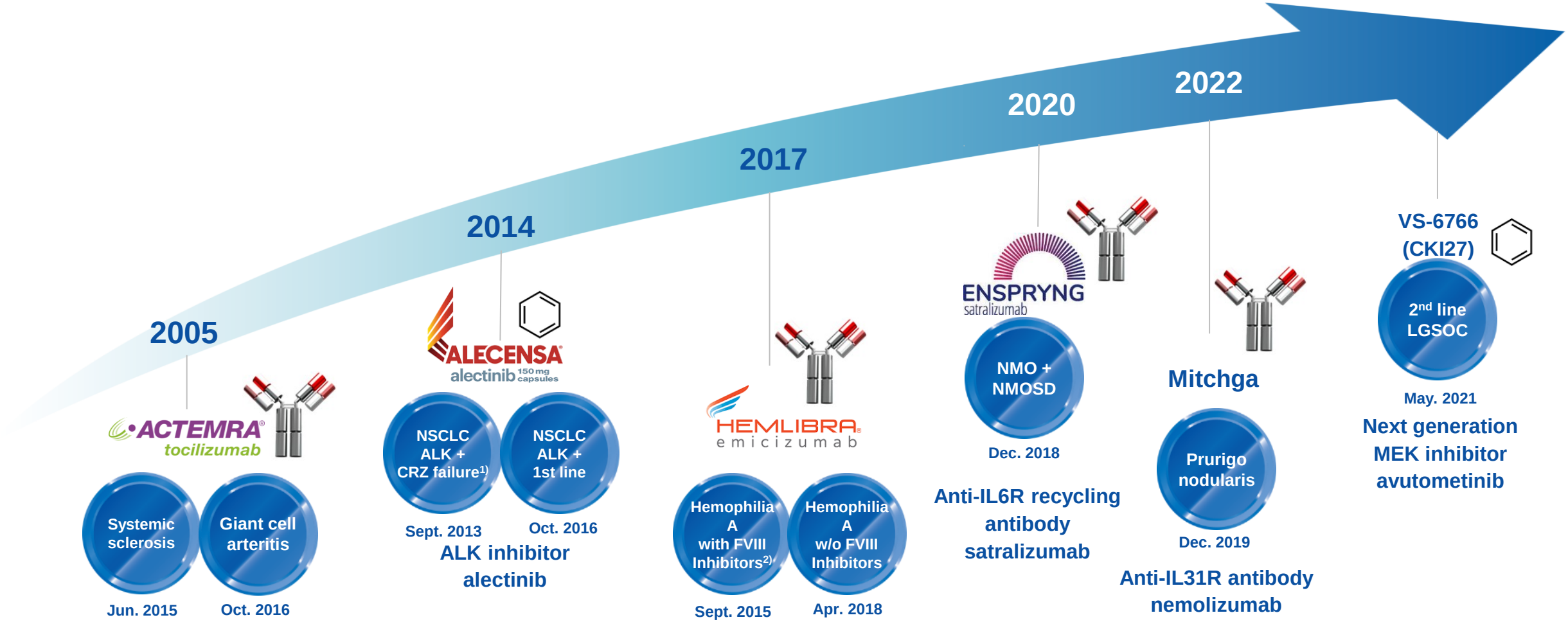

△ Adding to the Chugai's Development Portfolio

☆ Verifying technical PoC in clinical studies

# PoC verified by other companies

# Nine indications for six products receive US FDA Breakthrough Therapy designations

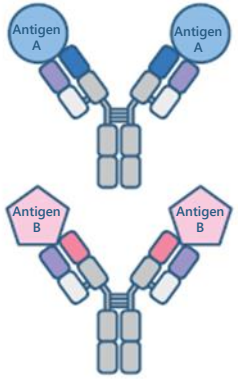
As of December 12, 2023




1) Progressed on or intolerant to crizotinib.
2) For prophylaxis, 12 years or older.

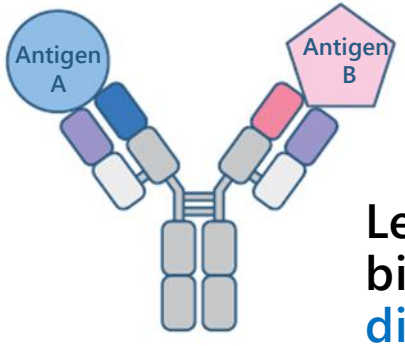
# HEMLIBRA® Was Created through Chugai's Unique Mindset, Barrier-free Handling of Disease Areas

Normal antibody structure

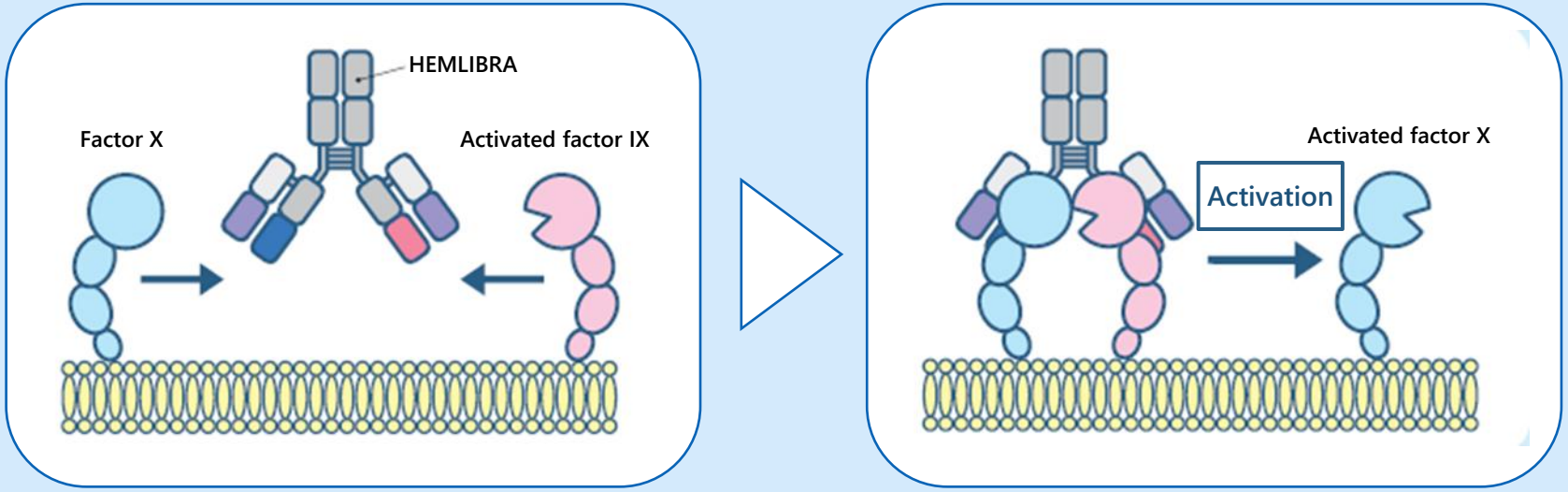



Left and right arms bind to the **same antigen**

Bispecific antibodies



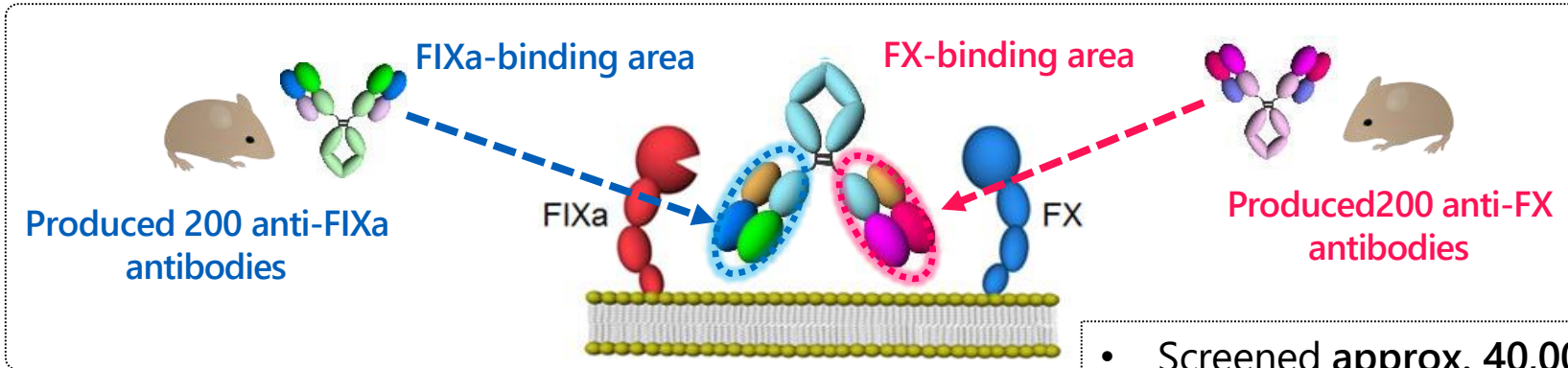

Left and right arms bind to the **different antigens**




HEMLIBRA binds factor IX and factor X to coagulate blood.

# Persisting Research and Uncompromising Stance for Quality Led to Creation of HEMLIBRA®

2002
Start of research




2006
Acquired lead antibodies

- Screened **approx. 40,000** bispecific antibodies and acquired lead antibodies
- Studied **more than2,000** modified antibodies

**Multidimensional optimization of lead antibodies**

- ✓ Increase the FVIII-mimetic activity
- ✓ Improve pharmacokinetics (prolongation of half-life in blood)
- ✓ Improve physicochemical properties
- ✓ Reduce immunogenicity
- ✓ Improve production efficiency of antibody

*Sampei et al. PLoS One 8 e57479 (2013)*

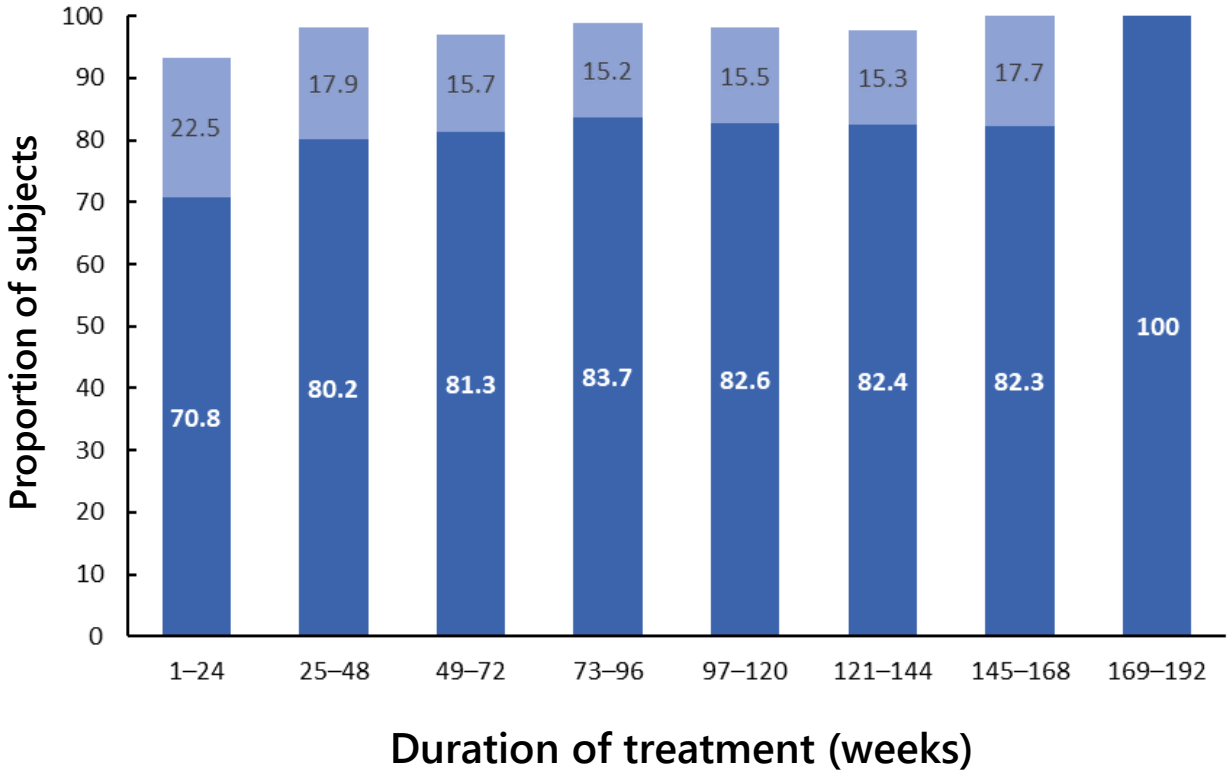
2010
Acquired antibody for development

**Creation of HEMLIBRA: humanized anti-FIXa/FX bispecific $IgG_4$**

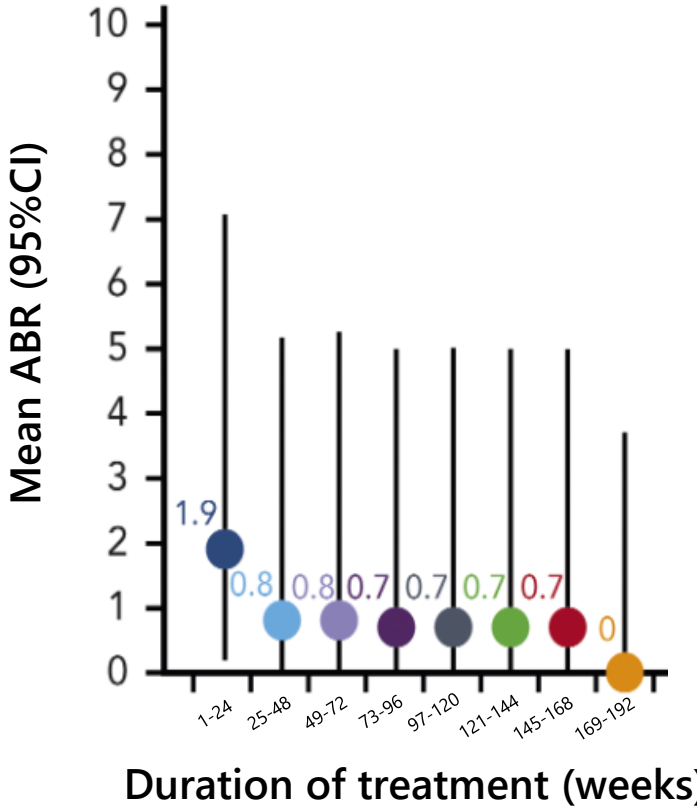
# HEMLIBRA® Creates New Value in Hemophilia Treatment

Long-term administration of HEMLIBRA data showed that as the administration went longer, bleeding requiring treatment were getting to zero.

**Proportion of subjects experienced 0 or 1-3 bleedings requiring treatment**




**Annualized bleeding rate (ABR)**

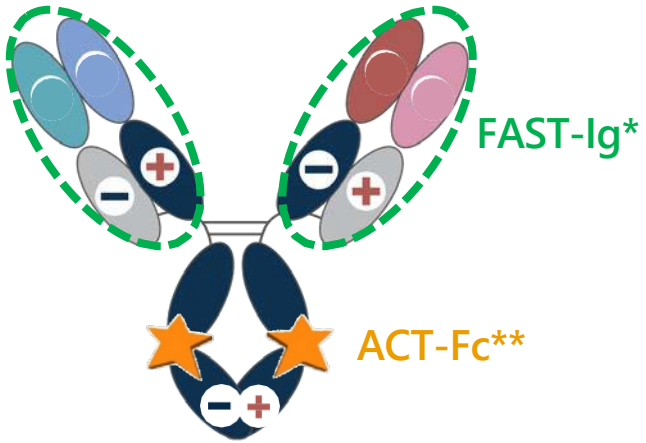



Collaghan et al, *Blood 2021; 137(16): 2231*

# A Next-generation Hemophilia Drug NXT007 Was Created by Applying Newly-developed Technology and Is under Development

## Mechanism of Action

NXT007 acts on blood coagulation Factor IXa (FIXa) and Factor X (FX), enhances FX activation catalyzed by FIXa, and promotes blood coagulation reactions by arranging FIXa and in a spatially suitable position(similar to HEMLIBRA).




Source: PEGS Boston, 2014 (partially modified)

## Target profile

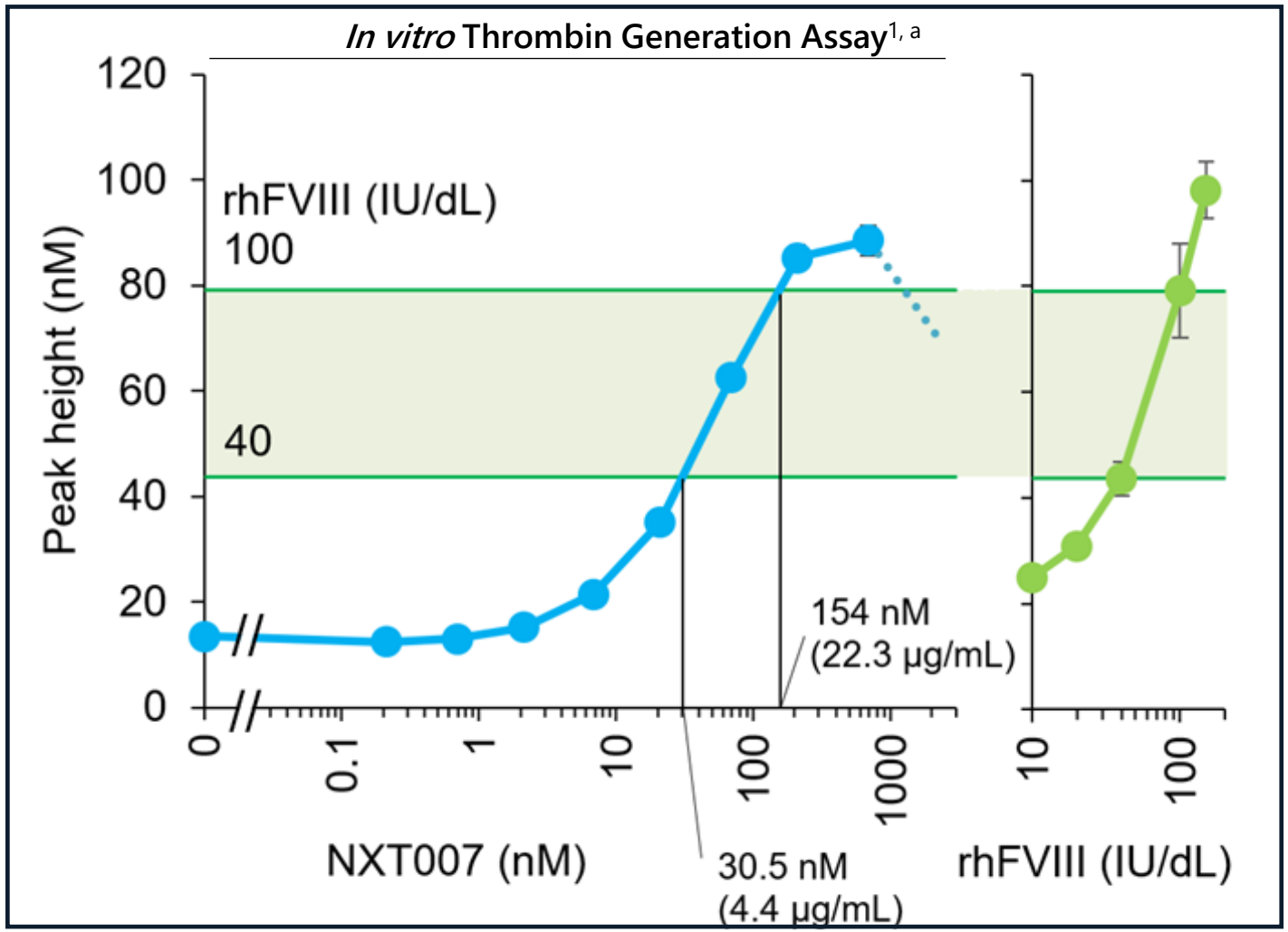
- Blood coagulability equivalent to healthy adults/children
- Improved convenience at administration

## Major new technologies applied in the development of NXT007

- COSMO
  - Multidimensional optimization system of molecules. Evaluate multidimensionally approx. 1300 antibodies produced for each lead antibody.
- FAST-Ig™
  - Technology to control charged interactions between H chain and L chain to enable improved industrial productivity of bispecific antibodies
- ACT-Fc®
  - Technology expected to improve PK profile

* Four-chain Assembly by electrostatic Steering Technology – Immunoglobulin
** Antibody Clearance controlling Technology – Fc region

# NXT007 Demonstrated Possibility of Maintaining Blood Coagulability Equivalent to Healthy Individuals in People with Hemophilia A



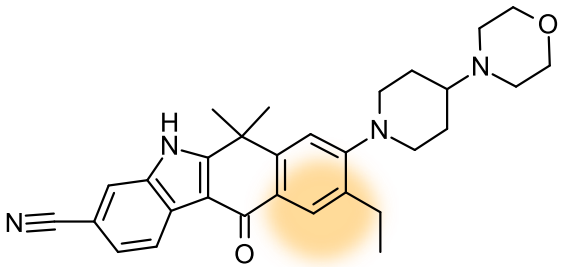

Non-clinical research data (*in vitro*)

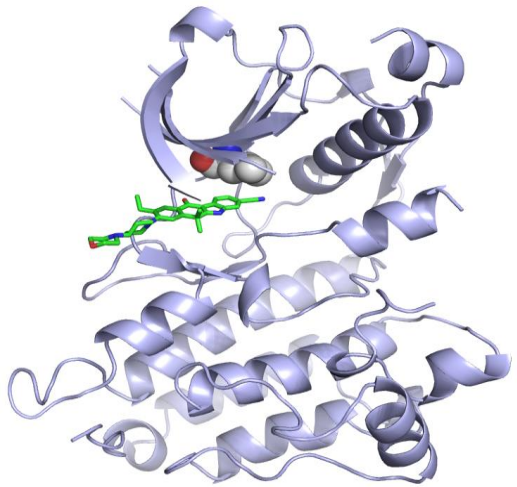
**Normal blood coagulability**

[1] *Yuri Teranishi-Ikawa et. al Journal of Thrombosis and Haemostasis 2023* (partially modified)
[a] tissue factor triggered

# Alectinib (ALECENSA®) Is the Result of Our Commitment to Quality

- Chugai-created ALK inhibitor
- Approved for the treatment of ALK fusion gene-positive non-small cell lung cancer in more than 70 countries including Japan, the United States, and Europe
- Added high selectivity by design based on target structure information



Kinoshita et al.
*J. Med. Chem.*
**2011**, *54*, 6286.

In vitro Enzyme Inhibition Activity

| Tyr kinase | $IC_{50}$ (nM) | Ser/Thr Kinase | $IC_{50}$ (nM) |
|---|---|---|---|
| ALK | 1.9 | AKT1 | >5,000 |
| ALK F1174L* | 1.0 | AKT2 | >5,000 |
| ALK R1275Q* | 3.5 | AKT3 | >5,000 |
| INSR | 550 | AuroraA | >5,000 |
| KDR | 1,400 | CDK1 | >5,000 |
| ABL | >5,000 | CDK2 | >5,000 |
| EGFR | >5,000 | MEK1 | >5,000 |
| FGFR2 | >5,000 | PKA | >5,000 |
| HER2 | >5,000 | PKCα | >5,000 |
| IGF1R | >5,000 | PKCβ1 | >5,000 |
| JAK1 | >5,000 | PKCβ2 | >5,000 |
| KIT | >5,000 | Raf-1 | >5,000 |
| MET | >5,000 | | |
| PDGFRβ | >5,000 | | |
| SRC | >5,000 | | |

* Hotspot activating point mutations in neuroblastoma

Sakamoto et al.
*Cancer Cell*
**2011**, 19, 679.

# Possibility of Reduced Frequency of Acquired Resistance by Higher Target Inhibition

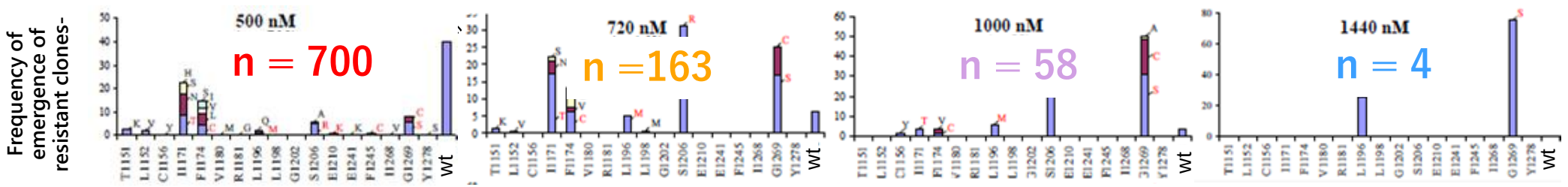
- ✓ The *in vitro* efficacy and clinical exposure ratio of alectinib is 6.8 fold higher than that of crizotinib, and the high selectivity of alectinib results in stronger inhibition of ALK.

| ALK Inhibitors | Cell-growth inhibition H2228[1] | Clinical Pharmacokinetics | | | Ratio |
|---|---|---|---|---|---|
| | (1) $IC_{50}$ (nM) | $AUC_{0-\tau}$ (ng.h/ml) | Clinical dose (mg) | (2) Mean concentration calculated from $AUC_{0-\tau}$ (nM) | (2)/(1) |
| Crizotinib | *170* | 4608[2] | 250, b.i.d. | 853 | **5.02** |
| Alectinib | *30* | 4970[3] | 300, b.i.d. | 1031 | **34.4** |

6.8 fold

- ✓ Greater inhibition of ALK at higher concentration of crizotinib reduces the emergence of resistant clones.

Crizotinib Concentration



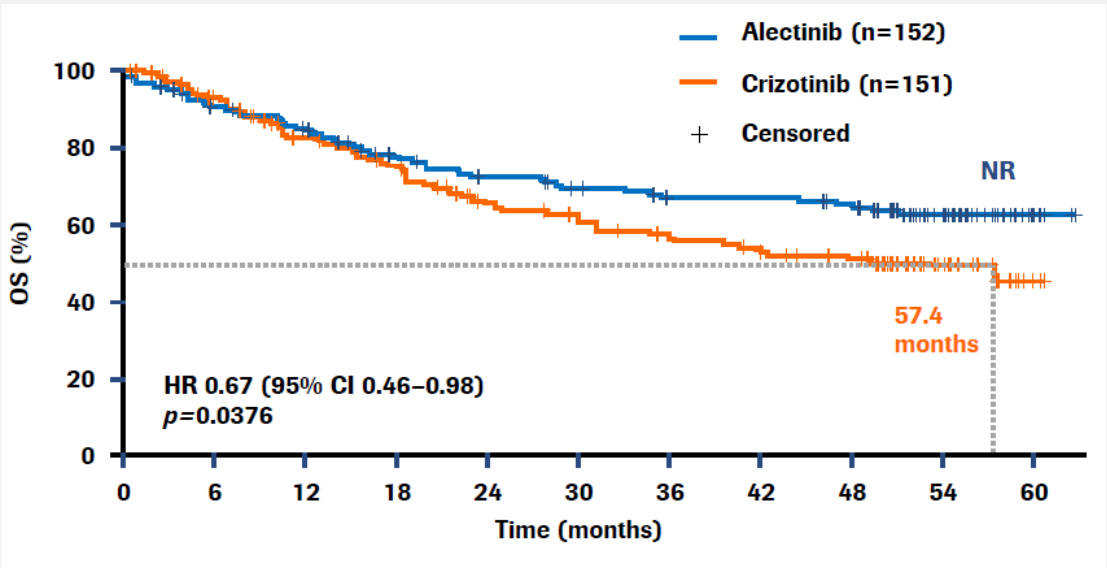

Resistance Induction Study in Ba/F3 Cells Expressing EML4-ALK by Treatment with N-Ethyl-N-Nitrosourea in the Presence of Various Concentrations of Crizotinib[4]


1) Isozaki et al., *Cancer Res.*, **2016**, *76 (6)*, 1506
2) Xalkori PMDA interview form
3) alectinib interview form
4) Zhang et al., *Chem. Biol. Drug. Des.* **2011,** *78*, 999

# ALECENSA® Is Expected to Further Contribute to Treatment of ALK-positive Lung Cancer

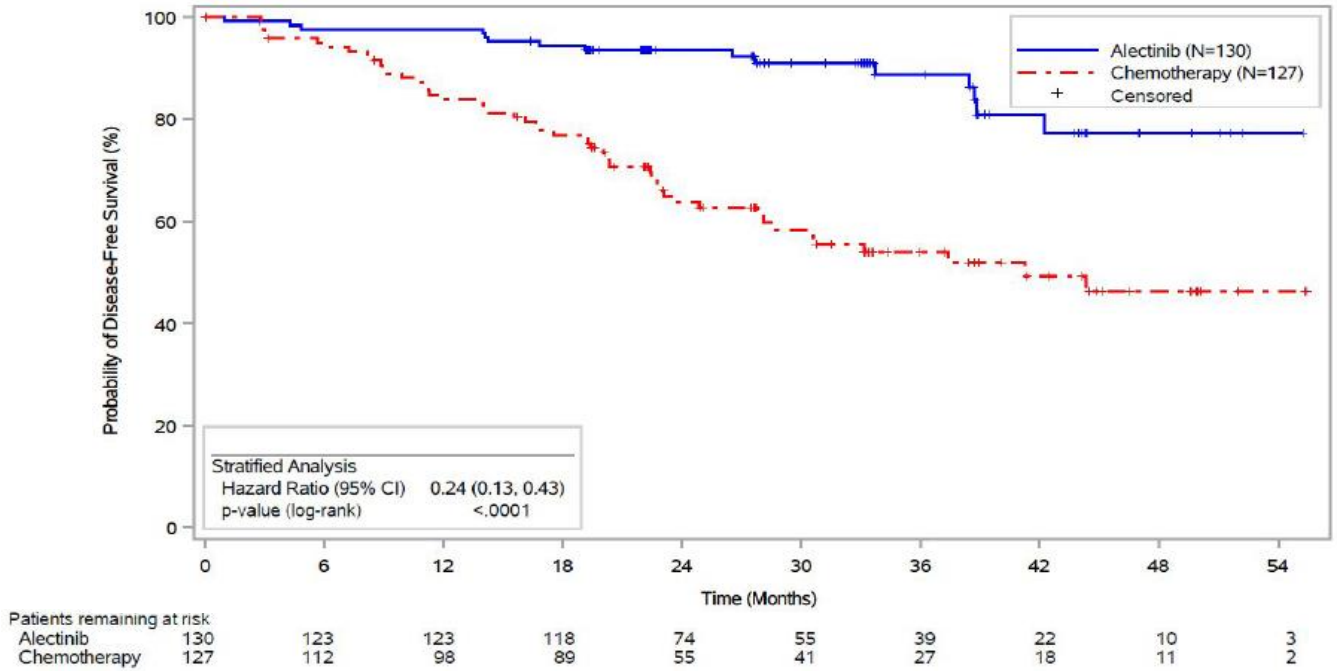
## P3 ALEX Study

- Alectinib demonstrated OS superiority and good tolerability over crizotinib
- Five-year survival rate exceeded 60%




## P3 ALINA Study

- As an adjuvant postoperative treatment for patients with completely resected Stage IB-IIIA ALK-positive NSCLC, ALECENSA reduced the risk of recurrence or death by 76% compared to chemotherapy




Data cutoff: November 29, 2019; OS: overall survival; ASCO: American Society of Clinical Oncology; NR: not reached.

Dose in ALEX study: 600 mg of alectinib twice daily
Approved dose in Japan: 300 mg of alectinib twice daily

Source: ASCO20 Virtual Roche Analyst Event (partially modified)

Source: FYE DEC 2023 3Q Financial Results Briefing (October 24, 2023)

# Maximize the Product Value by Developing Multiple Indications Simultaneously at Early Stage after Identifying Non-clinical Concepts in Clinical Environment

CHUGAI
Roche Roche Group

**Gradually adding indication after the launch** → **Being developed for multiple diseases simultaneously before approval** → **Preparing for simultaneous development of multiple indications from Phase 1**

## ACTEMRA® (tocilizumab)

**9** Indications
Approved

Since its launch in June 2005, indications have been added mainly for immune diseases. In September 2023, indication for cytokine release syndrome induced by cancer therapy was added.

## Crovalimab

**4** Indications
Under development

- Paroxysmal nocturnal Hemoglobinuria (submitted for approval/global)
- Atypical hemolytic uremic syndrome (P3)
- Sickle cell disease (P2)
- Lupus nephritis (P1)

## GYM329

**2** Indications
Under development

- Spinal muscular atrophy (P2/3)
- Facioscapulohumeral muscular dystrophy (P2)

## ENSPRYNG® (satralizumab)

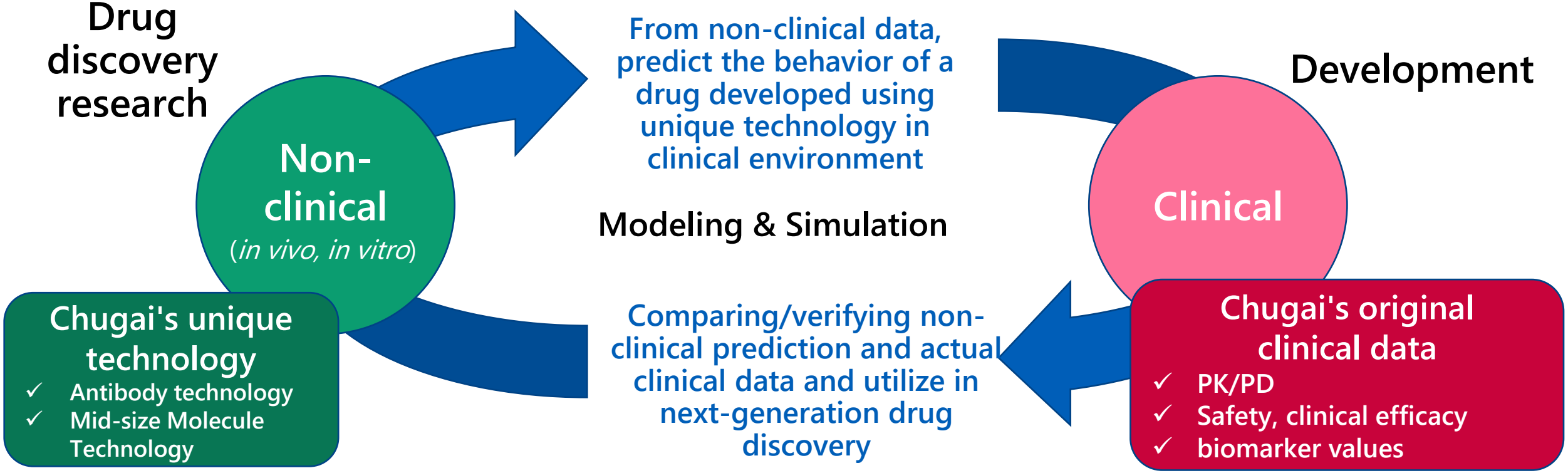
**4** Indications
Under development

- Generalized myasthenia gravis (P3)
- Anti-myelin oligodendrocyte glycoprotein antibody-associated diseases (MOGAD) (P3)
- Autoimmune encephalitis (AIE) (P3)
- Thyroid eye disease (P3)
  (Currently launched for treatment of neuromyelitis optica spectrum disorder)

## RAY121

In October 2022, P1 study was started. P1a study is ongoing. P1b study for simultaneous development of multiple indications is being prepared.

# Enhance Speed/Success Probability/Competitive Superiority in R&D by Increasing Human Prediction Technology in Unique Modality Technology




Through this cycle, we aim to improve speed/success probability/ competitive superiority of R&D.

# Toward Achieving “TOP I 2030”

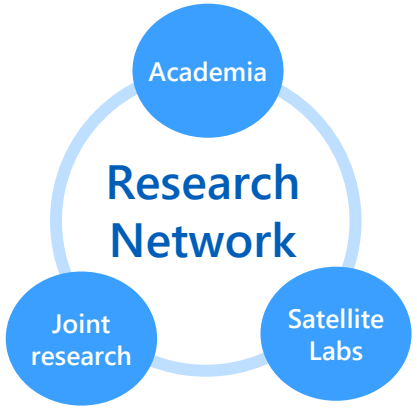
Disease-causing molecules (regardless of disease areas)

Selecting appropriate drug discovery target

Developing innovative drug creation technology

- Next-generation antibody technology
- Small molecule drug discovery technology
- Mid-size molecule drug discovery technology

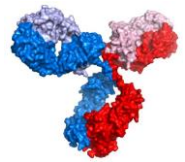
**“Technology-Driven” drug discovery**



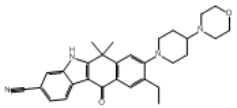

**“Quality-Centric” clinical candidates**

**"Molecule-Centric/Biology-Driven" indication selection**

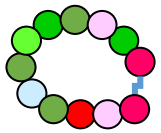
**"Value Maximization" clinical development**



Next-generation antibodies



Small molecules



Mid-size molecules

**"Doubling R&D output" "Launch global in-house products every year"**

# Chugai's Mid-size Molecule Drug Discovery

Hitoshi Iikura Ph.D.
Vice President, Head of Research Div.

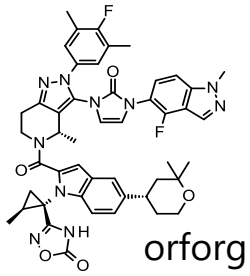
CHUGAI PHARMACEUTICAL CO., LTD.

12 December 2023

# High-profile Mid-size Molecular Research

CHUGAI
Roche Roche Group

## (1) Beyond small molecule drugs (Beyond Rule of 5)

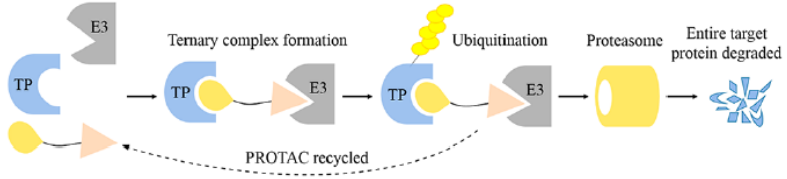


orforglipron*

## (2) Nucleic acid medicine

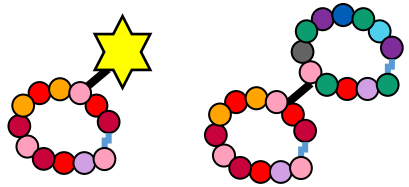
## (3) Cyclic peptides

## (4) PROTAC




*ACS Med. Chem. Lett.* 2020, **11**, 237

* The worldwide development and commercialization rights have been licensed out to Eli Lilly and Company



**Peptide-drug conjugate, multi-peptides**

- Disease site-specific drugs

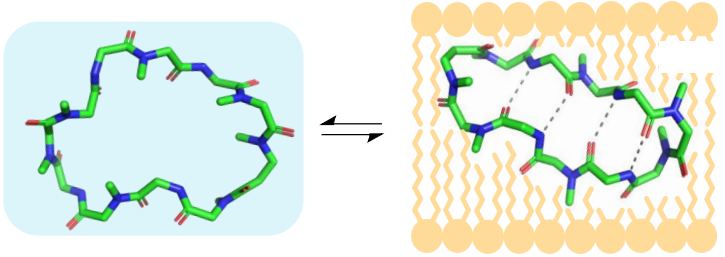
PeptiDream

**Antibody mimic**

- Orally ingestible antibodies
- Aiming at higher penetrability than antibodies

Ra Pharma and MERCK

*J. Mec. Chem.* 2020, **63**, 13796
*J. Mec. Chem.* 2021, **64**, 16770
*ACS Med. Chem. Lett.* 2022, **13**, 1379



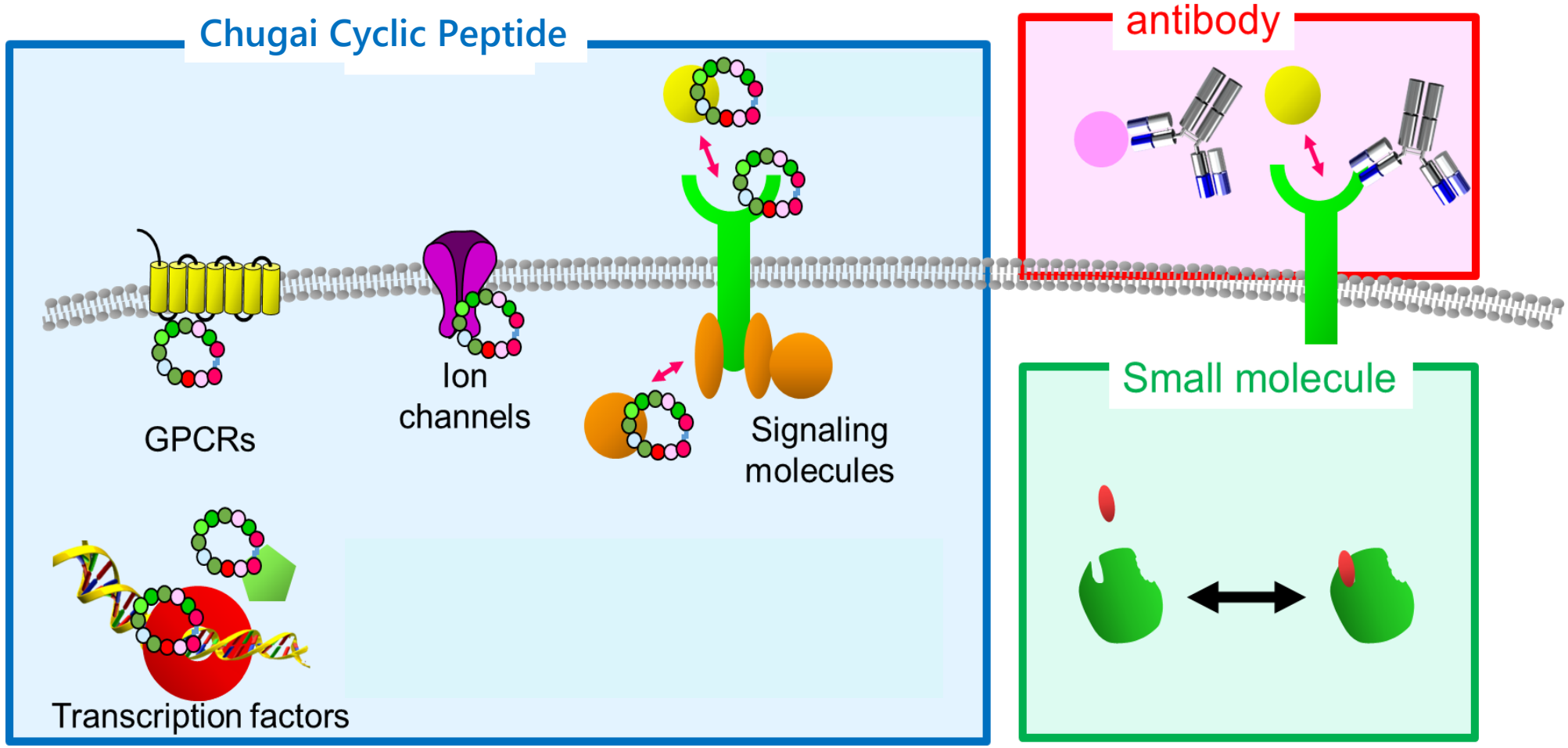
**Intracellular transferring peptides**

- Drug discovery difficult even using antibodies or small molecules

Chugai

*J. Am. Chem. Soc.* 2023, **145**, 24035
*J. Am. Chem. Soc.* 2023, **145**, 16610
*J. Med. Chem.* 2022, **65**, 13401

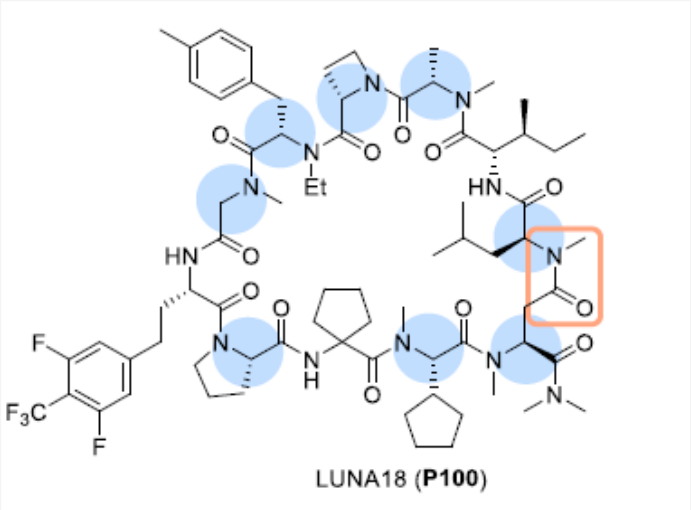
# Establishing a Drug Discovery Platform for Intracellular Tough Targets That Are Challenges to Be Targeted by Small Molecules and Antibodies

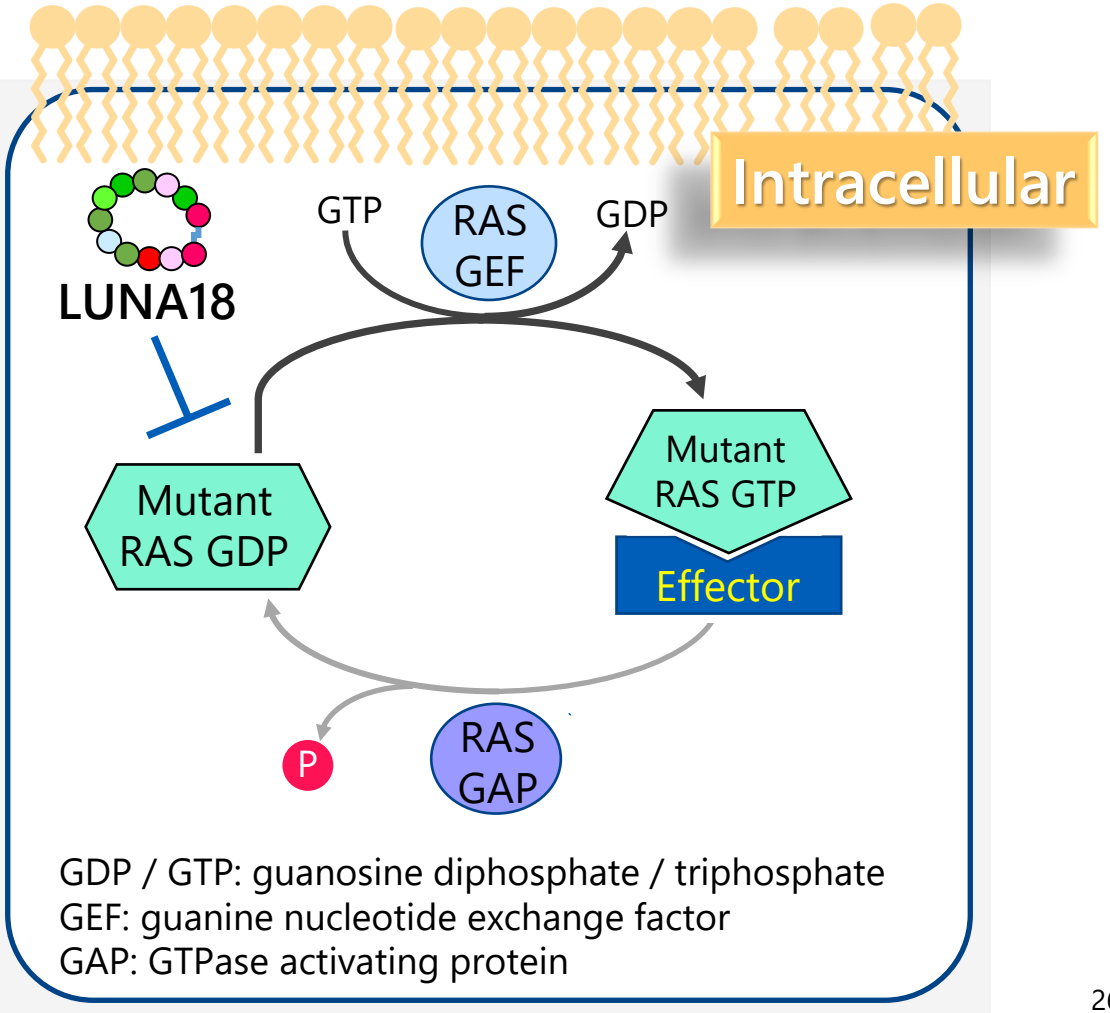


# The First Clinical Trial from Mid-Size Molecule Technology (October 2021)

## Novel cyclic peptide, LUNA18

- Orally available cyclic peptides
- Inhibits protein-protein interaction between RAS and GEF (inhibits RAS activation)
- Inhibits tumor cell growth for various RAS alterations (mutations or amplifications)

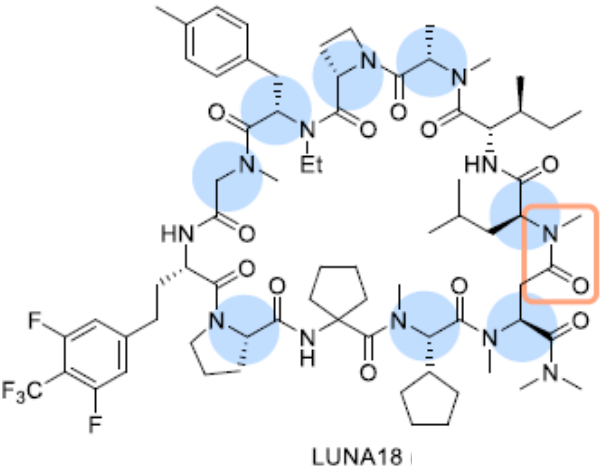


# LUNA18: Orally Available pan-RAS(GDP) Inhibitor (Phase 1 Study on-going)

*J. Am. Chem. Soc.* 2023, **145**, 24035

## *In vitro* efficacy




Binding affinity to N-, H-, K-Ras: around 50 pM

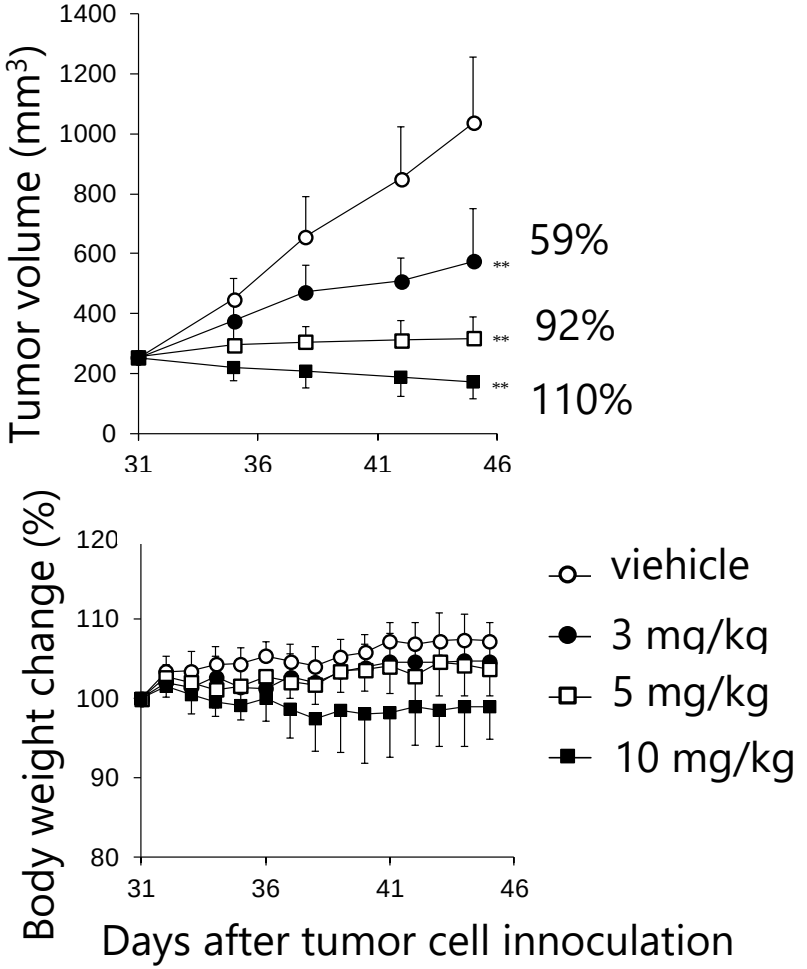
| Cell line | Genetic alterations | Cell IC50 (nM) (n = 6) |
|---|---|---|
| NCI-H2122 | KRAS-G12C | 1.4 ± 0.28 |
| NCI-H441 | KRAS-G12V | 2.9 ± 0.73 |
| GSU | KRAS-G12D | 0.17 ± 0.015 |
| A-375 | RAS-WT | > 1,000 |

## Animals PK

| | LUNA18 |
|---|---|
| Mouse BA | 21% |
| Rat BA | 22% |
| Monkey BA | 26% |
| Dog BA | 47% |

## *In vivo* efficacy

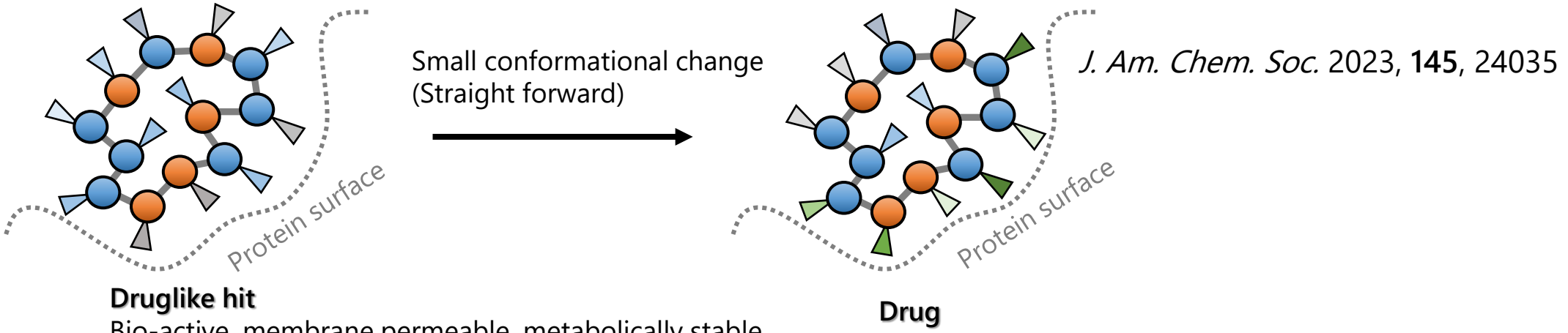
NCI-H441 (NSCLC)



# Our Strategy is to focus on obtaining “Druglike Hits”

- The reason for successful small molecule drug discovery lies in H2L from the Druglike hit (Rule of 5)
  (The reason why the development of peptide drug discovery is limited is the lack of knowledge of Druglikeness)
- We proposed the world's first Druglike Criteria for mid-size molecules and created a compound library consisting of Druglike molecules.

**Chugai**

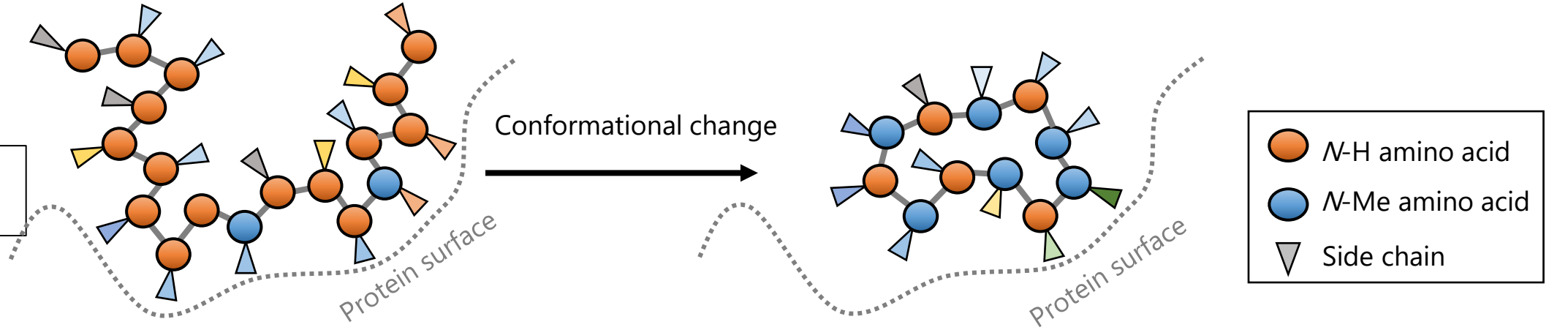



**Druglike hit**
Bio-active, membrane permeable, metabolically stable

**Drug**

*J. Am. Chem. Soc.* 2023, **145**, 24035

**Existing Peptide Drug Discovery**




**Non-druglike hit**

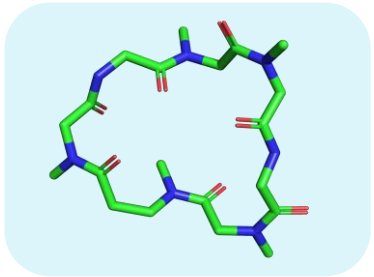
# Druglikeness of Cyclic Peptides

*J. Am. Chem. Soc.* 2023, **145**, 24035

| Rule of 5 | *Chugai's experimental data* |
|---|---|
| ✓MW < 500 | ✓MW up to 1500 |
| ✓CLogP < 5 | ✓CLogP >13 |
| ✓No. H-B acceptor <10 | ✓No. H-B acceptor-intraM HB <10 ? |
| ✓No. H-B donor < 5 | ✓No. H-B donor-intraM HB < 5 ? |

## Peptides with 7 amino acids

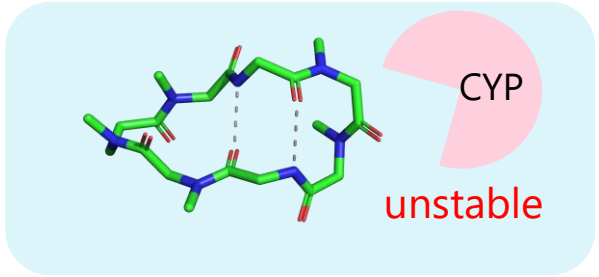
Hydrophilic peptide

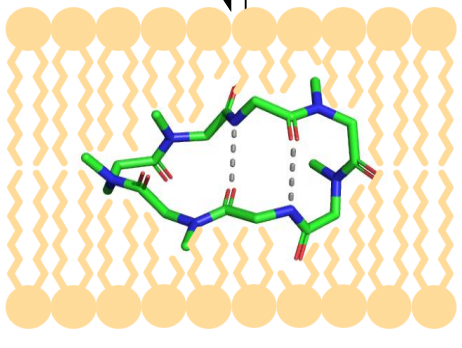


Rigid conformation

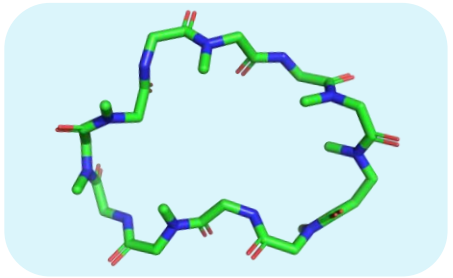


Hydrophobic peptide



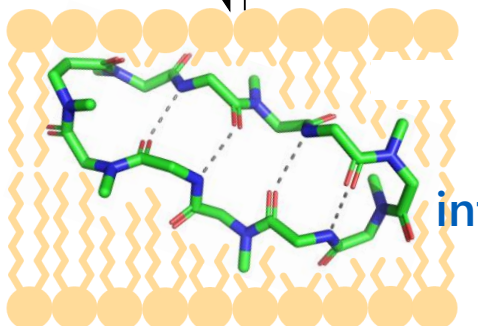



## Hydrophobic peptides with 11 amino acids



Metabolically stable
(polar group outside)

Flexible conformation

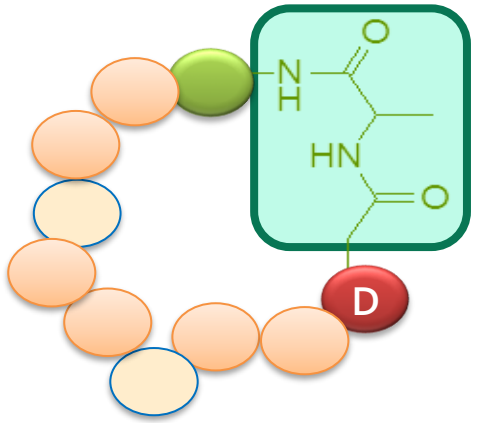


Membrane permeable
(polar group neutralized by intramolecular hydrogen bonding)

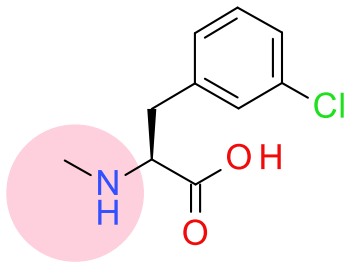
# Defining “Druglike” Cyclic Peptide

*J. Am. Chem. Soc.* 2023, **145**, 24035

**Cyclic peptides with 9-11 amino acids,**
**more than half should be *N*-alkylated, etc,.**

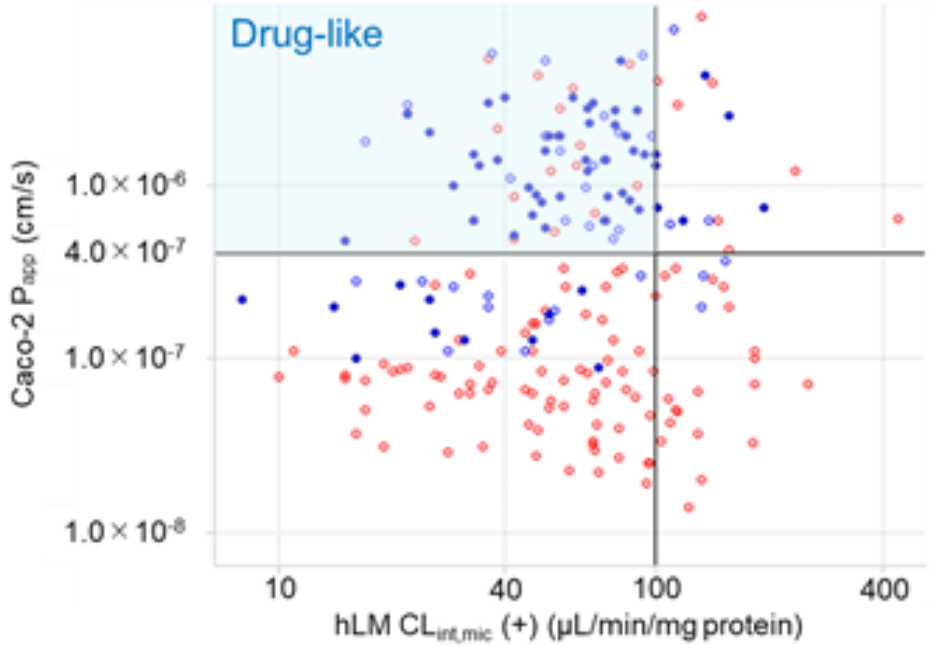



✓ *N*-alkylated amino acids (unnatural amino acids)




✓ Acceptable metabolic stability by appropriate ring size, and our cyclization methodology

✓ Compatibility of membrane permeability and metabolic stability is a key for “drug-like” peptides




| | 1st campaign ClogP < 12.9 or *N*-alkyl < 6 ○ | 1st + 2nd campaign ClogP ≥ 12.9 & *N*-alkyl ≥ 6 ○ + ● |
|---|---|---|
| drug-like (hLM-Caco-2) | 15/116 13% | 63/95 66% |

# Development of General Synthetic Method of *N*-Alkyl Rich Drug-like Peptides

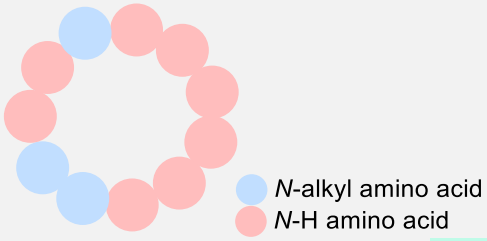
- Enabled **parallel synthesis** of **random** and **highly *N*-alkylated** compounds that could not be achieved by conventional methods.
- One researcher can synthesize more than 500 compounds per year. **We promote** almost **all mid-size molecule drug discovery using the same synthetic method.**

*J. Med. Chem.* **2022**, *65*, 13401

## Conventional solid-phase parallel peptide synthesis

Even a sequence containing 2-4 *N*-Me amino acids per 11 residues is difficult to synthesize

Drug discovery by conventional methods is unrealistic.




Synthesis success rate: 54%
Mean yield: 18%
Mean purity: 55%

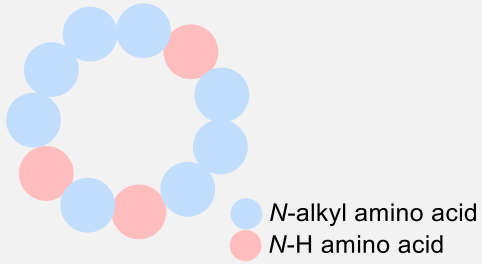
7 *N*-Me amino acids→ almost 0% success

Too many "similar impurities" makes purification difficult

Identified and overcame 3 challenges

## Established general synthetic method

Almost all of drug-like peptides containing 5-8 *N*-Me amino acids in 11 residues can be synthesized!



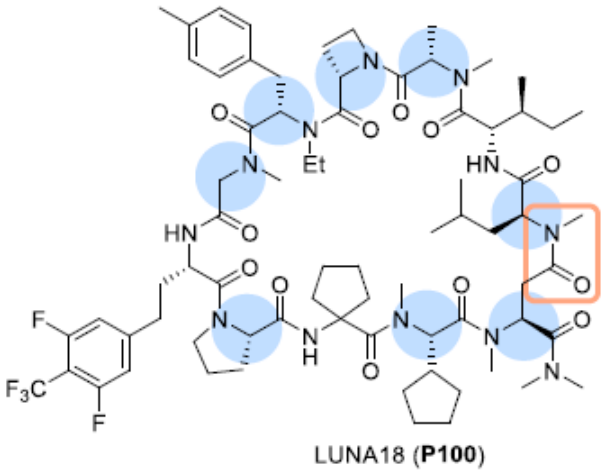

Synthesis success rate: 100%
Mean yield: 31%
Mean purity: 97%

Parallel synthesizer synthesize efficiently

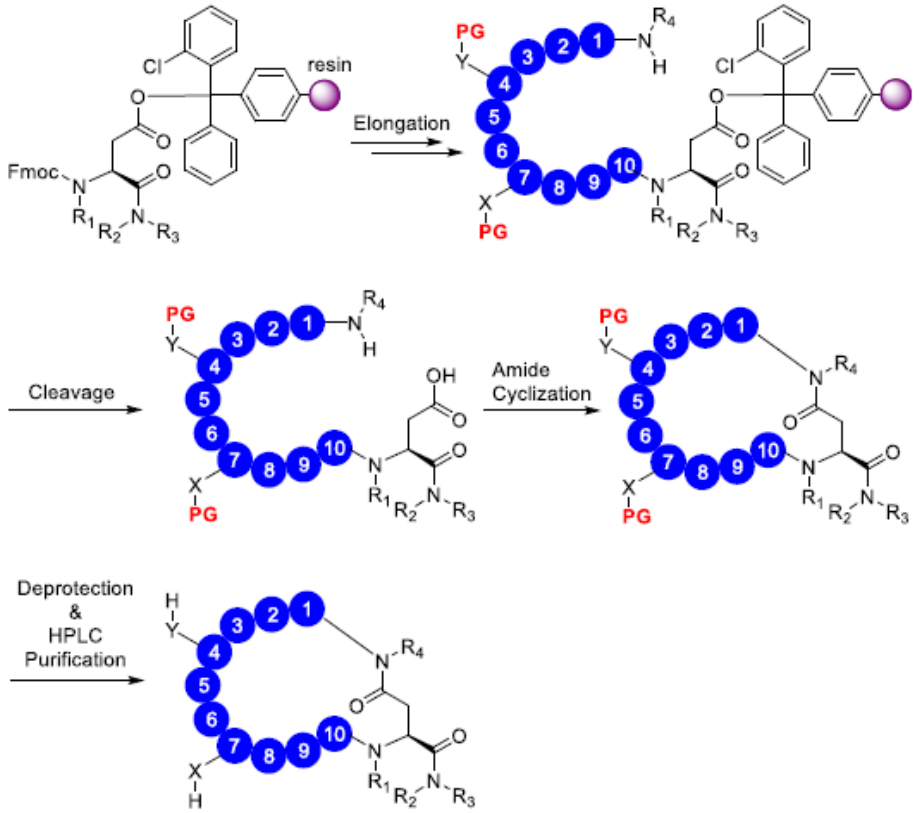
# Development of General Synthetic Method of *N*-Alkyl Rich Drug-like Peptides

J. Med. Chem. 2022, 65, 13401

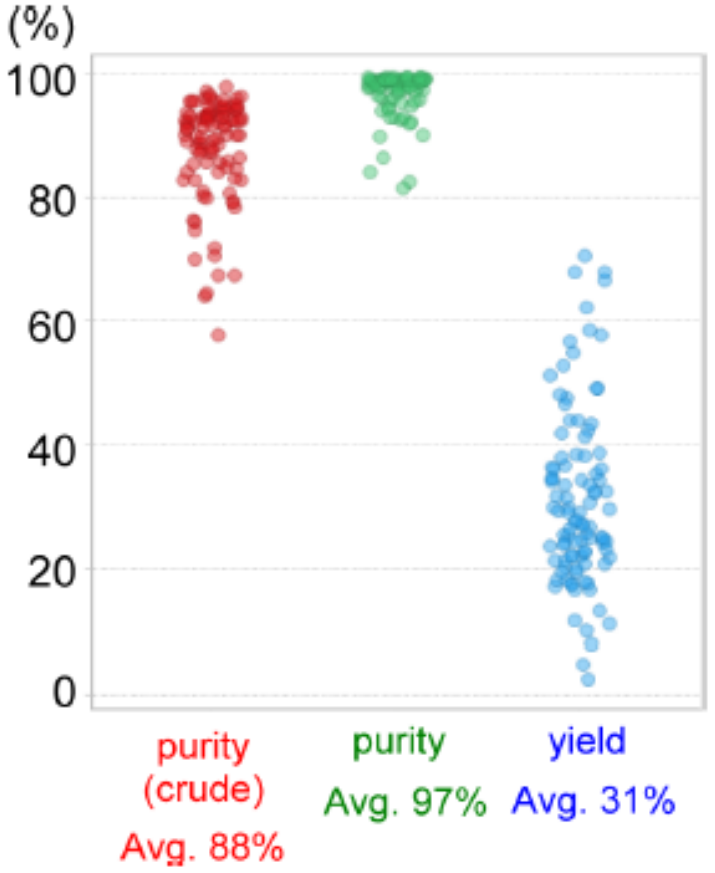
## *N*-alkyl rich cyclic peptides



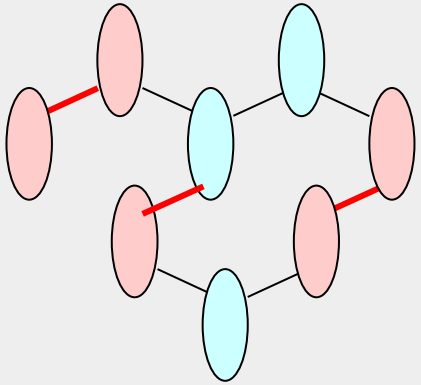

## Solid phase synthesis method




## Yield and purity of 100 peptides with various sequences

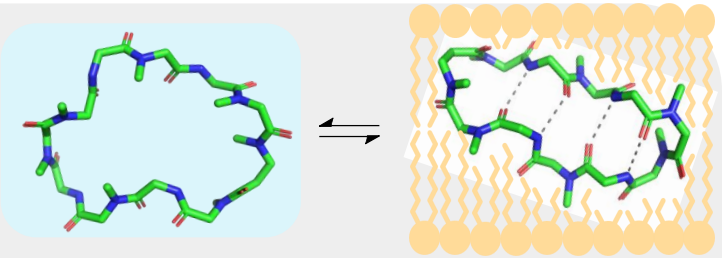


# Construction of Cyclic-peptide Drug Discovery Tech. by Fusing Medicinal Chemistry and Biotechnology



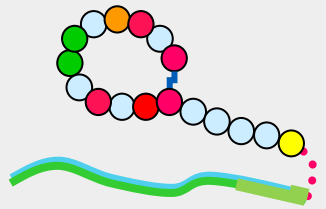
**Chemistry:**

Identifying criteria for Drug-likeness



**Biotechnology:**

Library construction, obtaining Drug-like hits



Without major structural changes

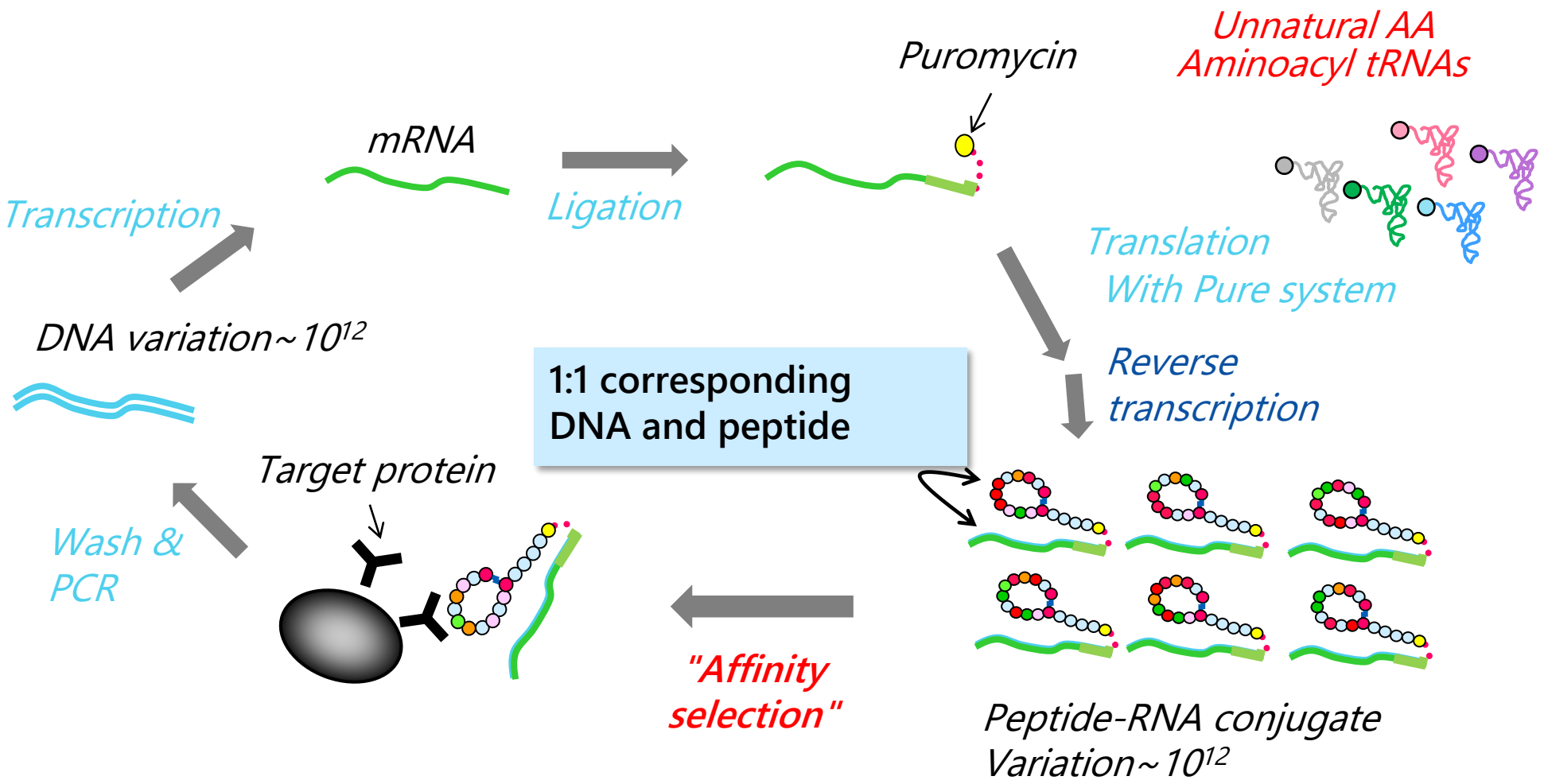
**Products**

**Chemistry:**

Creation of lead compounds from hit Compounds

Creation of clinical products by optimizing lead compounds

# Drug-like Peptides with $10^{12}$ Diversity Could Be Achieved by mRNA Display



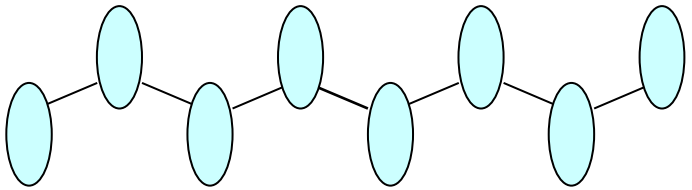
# PURESystem: Translating Non-natural Amino Acids by Biotech

mRNA AUGUUGCCGG...

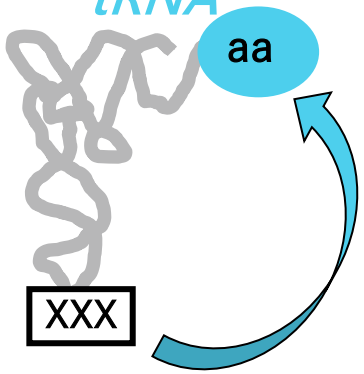
Universal genetic code

| | U | C | A | G | |
|---|---|---|---|---|---|
| U | Phe | Ser | Tyr | Cys | U |
| | | | stop | stop | C |
| | Leu | | | Trp | A |
| | | Pro | His | Arg | G |
| C | | | | | U |
| | | | Gln | | C |
| | | | | | A |
| | | | | | G |
| A | Ile | Thr | Asn | Ser | U |
| | | | | | C |
| | Met | | Lys | Arg | A |
| | | | | | G |
| G | Val | Ala | Asp | Gly | U |
| | | | | | C |
| | | | Glu | | A |
| | | | | | G |

Natural peptide



*Aminoacyl - tRNA*

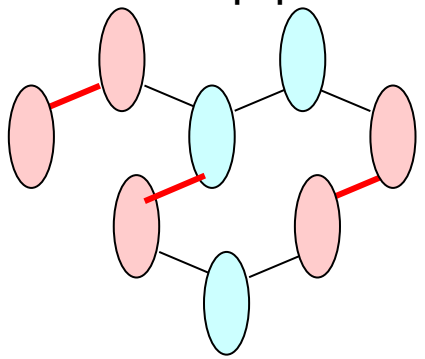



mRNA AUGUUGCCGG...

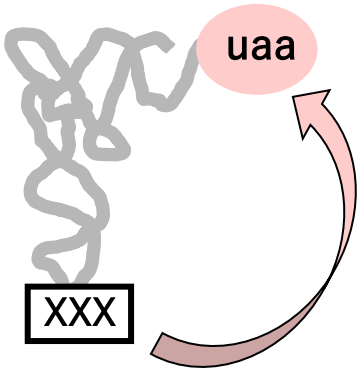
Reprogrammed genetic code

| | U | C | A | G | |
|---|---|---|---|---|---|
| U | Phe | Ser | Tyr | Cys | U |
| | uaa | | stop | stop | C |
| | Leu | | | Trp | A |
| | | Pro | uaa | Arg | G |
| C | | | | | U |
| | | | Gln | | C |
| | | | | | A |
| | | | | | G |
| A | Ile | uaa | Asn | uaa | U |
| | | | | | C |
| | Met | | Lys | Arg | A |
| | | | | | G |
| G | Val | Ala | Asp | Gly | U |
| | | | uaa | | C |
| | | | | | A |
| | | | | | G |

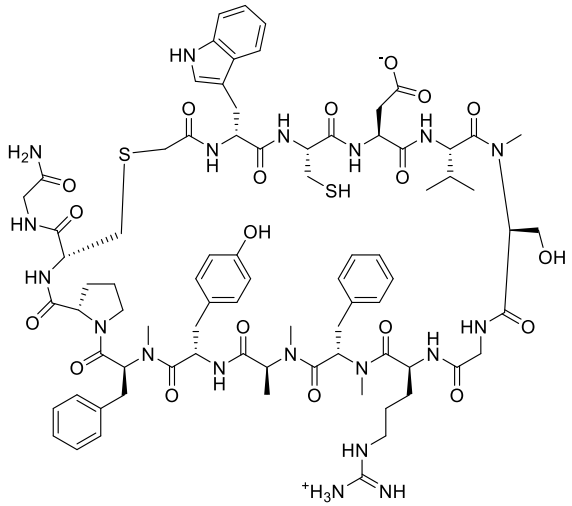
Unnatural peptide



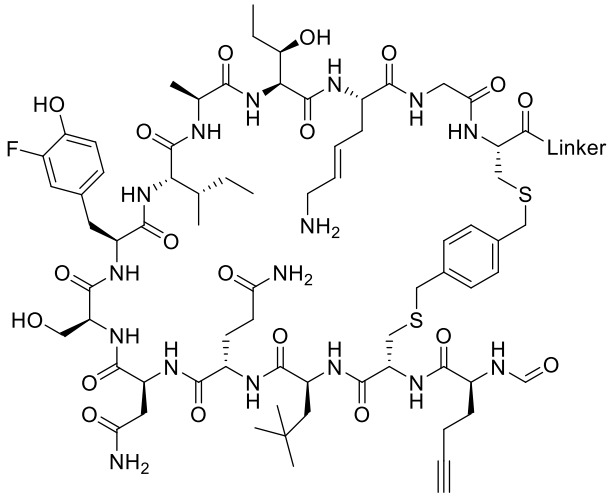
*Unnatural-aa(UAA)-Aminoacyl-tRNA*



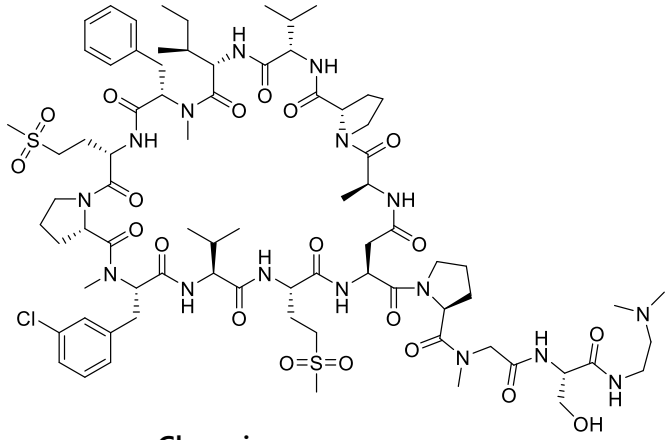
# mRNA Display Is Effective for Creation of Mid-size Cyclic Peptides



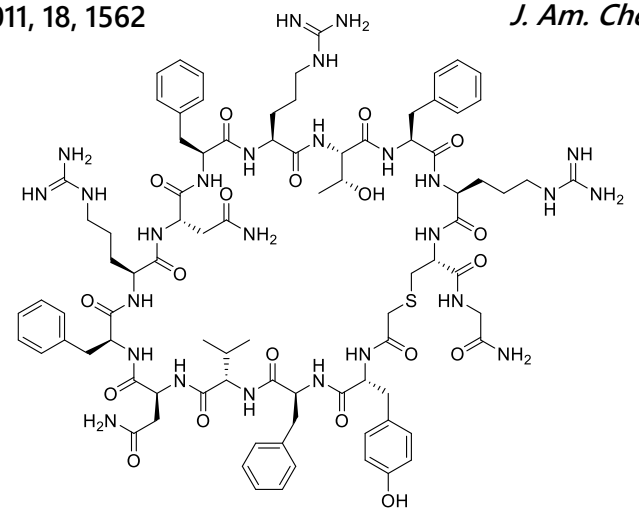
Prof. H. Suga et al.
E6AP inh.
*Chem. Biol.* 2011, 18, 1562



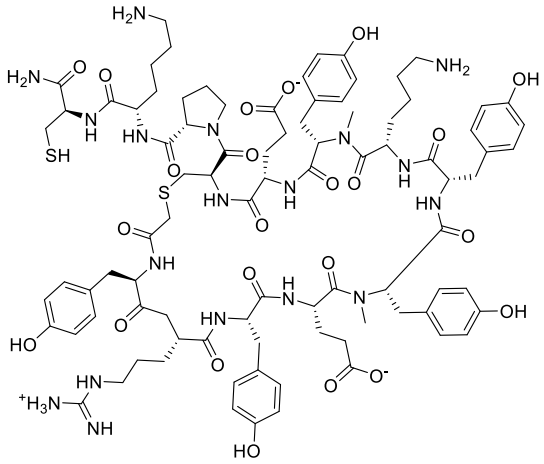

Prof. J. W. Szostak et al.
Thrombin inh.
*J. Am. Chem. Soc.* 2012, 134, 10469



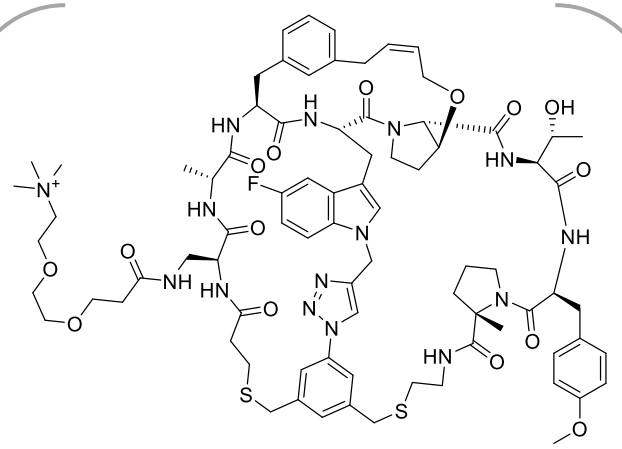
Chugai, our group.
IL-6R inh.
*WO2013100132* (2013)



Prof. H. Suga et al.
KRAS(G12D) inh.
*ACS Cent. Sci.* 2020, 6, 1753



Prof. H. Suga et al.
iPGM inh.
*ACS Chem. Biol.* 2022, 17, 2284

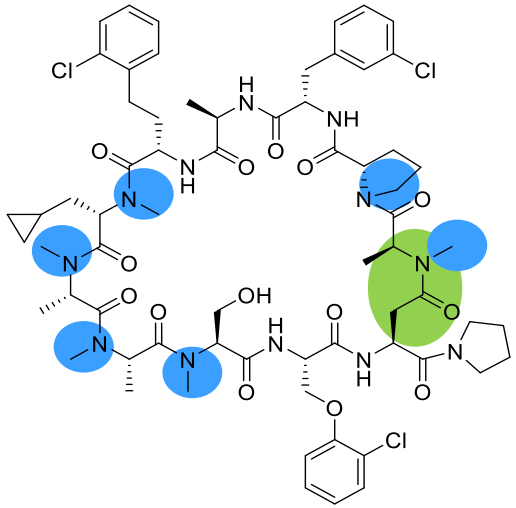


Dr. T. J. Tucker et al. (Merck)
PCSK9 inh. (chemically optimized)
2.9% oral BA w/ permeation enhancer
*J. Med. Chem,* 2021, 64, 16770

# Chugai Druglike Hit Generation Technology

- High diversity → Up to 36 of 64 possible codon is utilized in hit generation
- Highly *N*-Alkylated → modifying tRNA, and engineering ARS
- Reproduce Drug Scaffold → Druglike cyclization

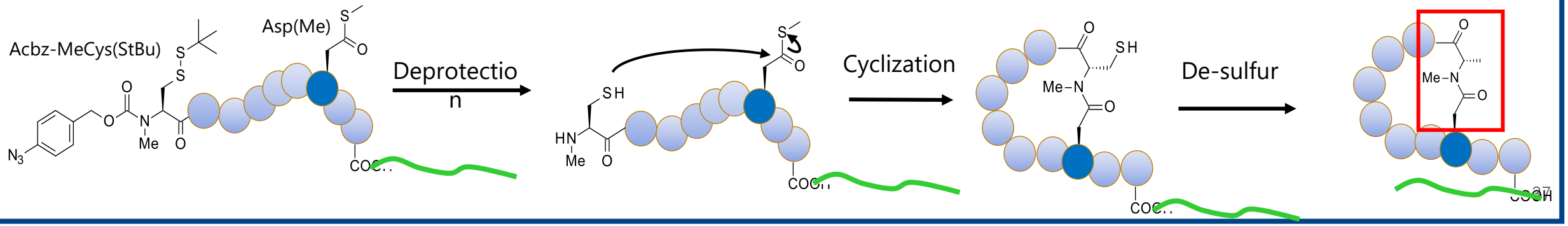
| | | | |
|---|---|---|---|
| Pro | MeGly | MeAla | MeVal |
| MePhe | MeAA(6) | MeAA(7) | MeAA(8) |
| MeAA(9) | MeAA(10) | MeAA(11) | D-MeAA(1) |
| AlGly(1) | AlGly(2) | AlGly(3) | CyAA(2) |
| CyAA(3) | CyAA(4) | Gly | Ile |
| Thr | L-AA(1) | L-AA(2) | L-AA(3)) |
| L-AA(4) | L-AA(5)a | L-AA(6) | L-AA(7) |
| L-AA(8) | L-AA(9) | D-AA(1) | D-AA(2) |
| D-AA(3) | b-Ala | AspSMe | MeAspSMe |



N-Alkyl, drug-like
N-H, drug-like
Non drug-like
Cyclization point

cyclization point

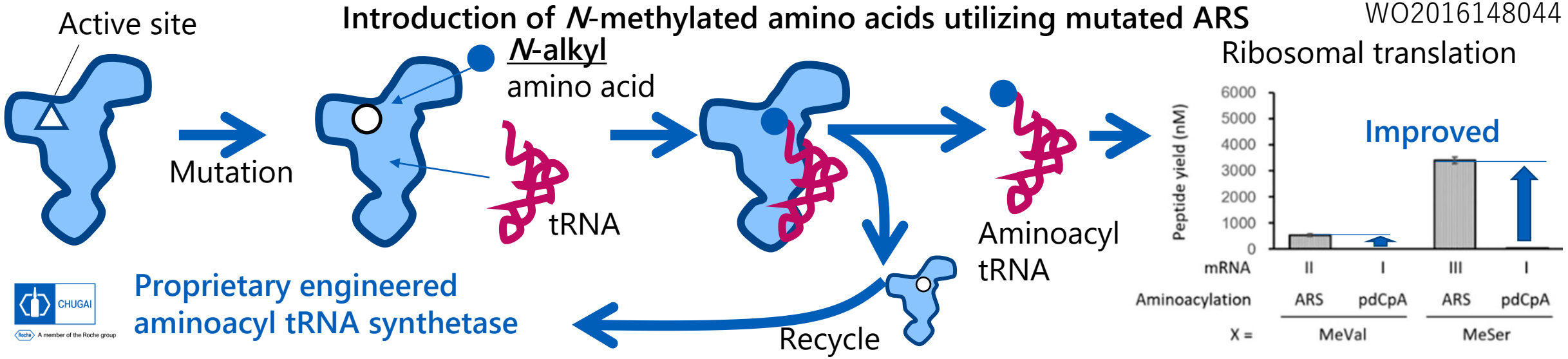
## Druglike cyclization by achieving specific chemical reactions in complex systems (e.g. in water, with proteins or nucleic acids)



# Representative Biotechnology in Mid-size Molecule Display Library

## Introduction of *N*-methylated amino acids utilizing mutated ARS

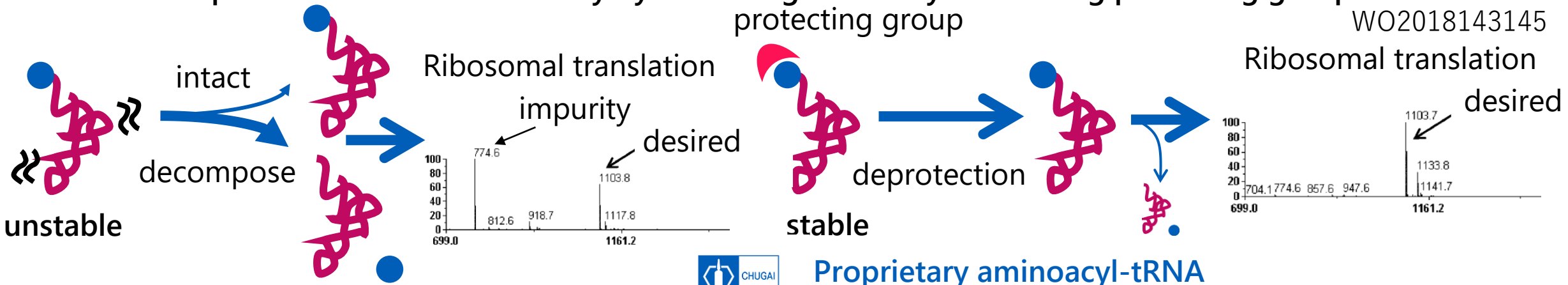
WO2016148044




Proprietary engineered aminoacyl tRNA synthetase

## Improved translation efficiency by stabilizing aminoacyl RNA using protecting groups

WO2018143145

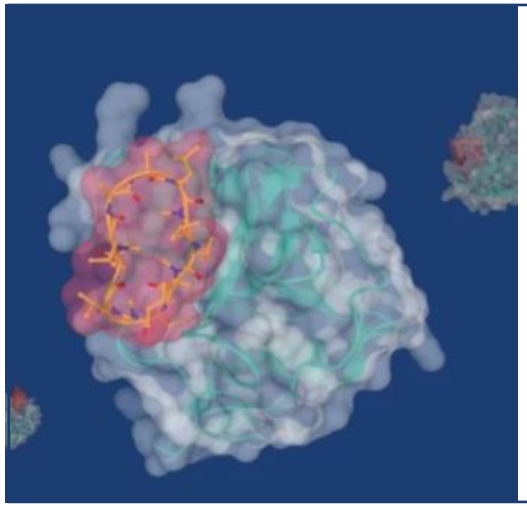



Proprietary aminoacyl-tRNA

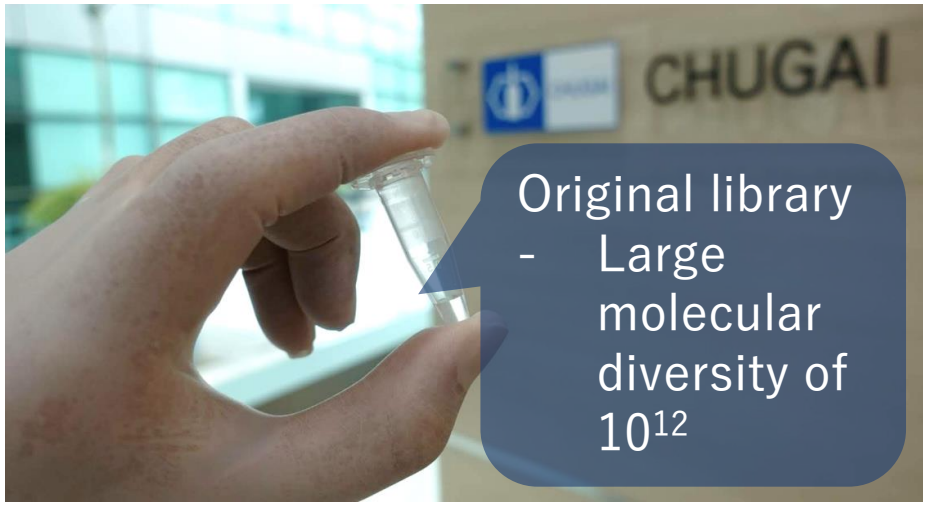
Mid-size molecule drug discovery

# Establishing a System That Allows Us to Screen More Than 20 Targets in a Year at CPR

HTS: High throughput screening
CPR: Chugai Pharmabody Research Pte. Ltd.



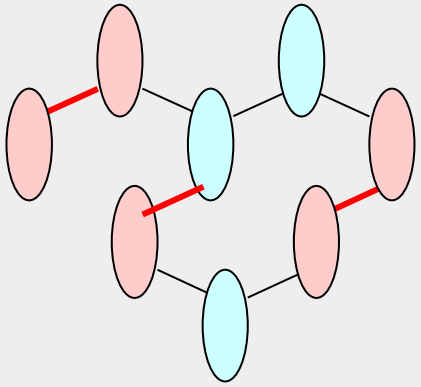
## Mid-size molecule
- Cyclic peptide
- Oral administration
- Membrane permeability


Original library
- Large molecular diversity of $10^{12}$

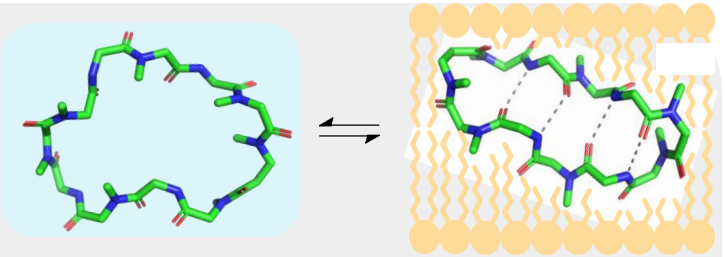
## High-throughput Screening platform
- Identify binders to many targets
- Semi-automated system

# Drug Discovery Platform through Fusion of Biotech and Chemistry



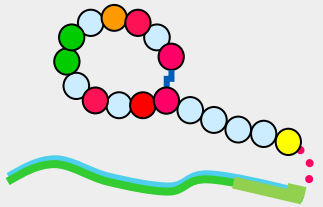
**Chemistry:**

Identifying criteria for Drug-likeness



**Biotechnology:**

Constructing library with drug-like $10^{12}$ compounds



**H2L without major structural transformation**

**Products**

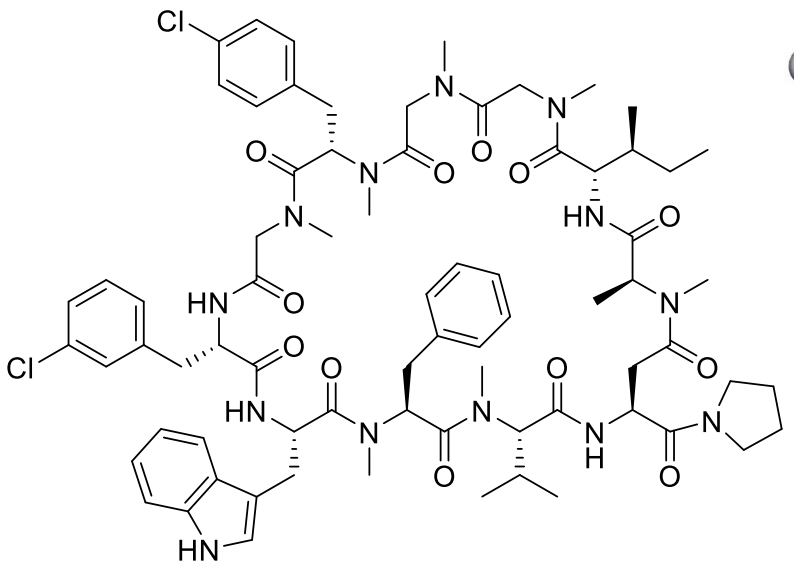
**Chemistry:**

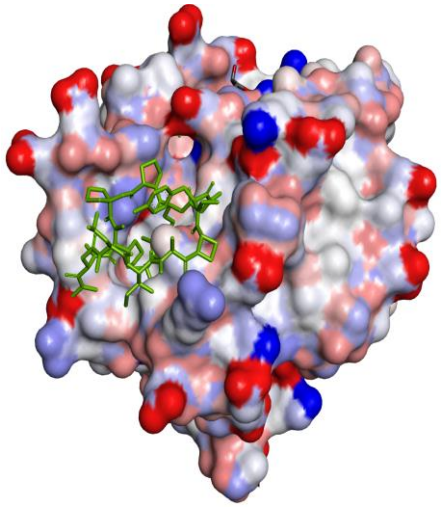
Creation of lead compounds from hit Compounds

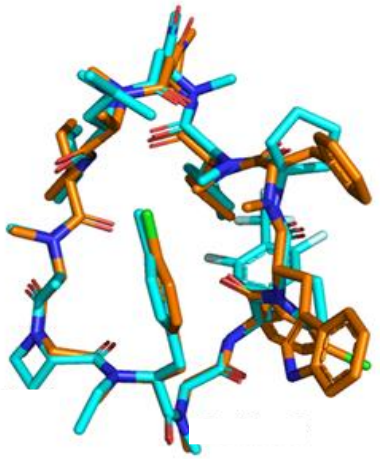
Creation of clinical products by optimizing lead compounds

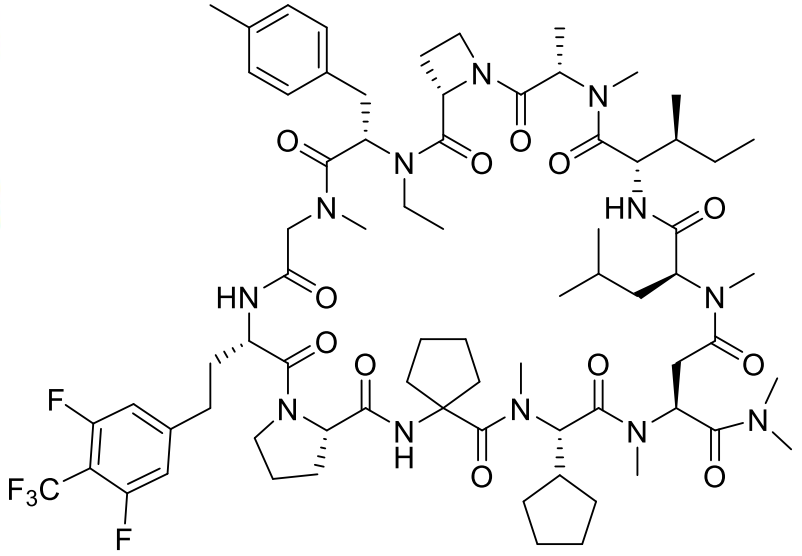
# Summary of hit to LUNA18

*J. Am. Chem. Soc.* 2023, **145**, 16610









**approximately 3 years**

**Panning Hit**

Cell $IC_{50}$ (AsPC-1) > 20,000 nM
$K_D$ (KRAS-WT) = 340 nM
Caco-$2_{papp}$ = 0.02 x $10^{-6}$ cm/s

**Cell active**

**vivo active**

**LUNA18**

Cell $IC_{50}$ (AsPC-1) = 1.4 nM
$K_D$ (KRAS-WT) = 0.035 nM
Caco-$2_{papp}$ = 2.3 x $10^{-6}$ cm/s

# Set up of Production Facilities

- Acquired advanced technologies for EHS as well as small-and mid-size molecule with high pharmacological activity
- Build a consistent in-house supply system from manufacturing process development and early clinical development to initial commercial production by 2025


| | | | | |
|---|---|---|---|---|
| Start of Operation | 2020 | 2003 | Dec. 2022 | Scheduled in Mar. 2025 |
| Total floor area | 4,925 $m^2$ | 5,417 $m^2$ | 6,190 $m^2$ | 10,250 $m^2$ |
| Total investment | 4.5 billion yen | 7 billion yen | 19.1 billion yen | 55.5 billion yen |

EHS: Environment, Health and Safety

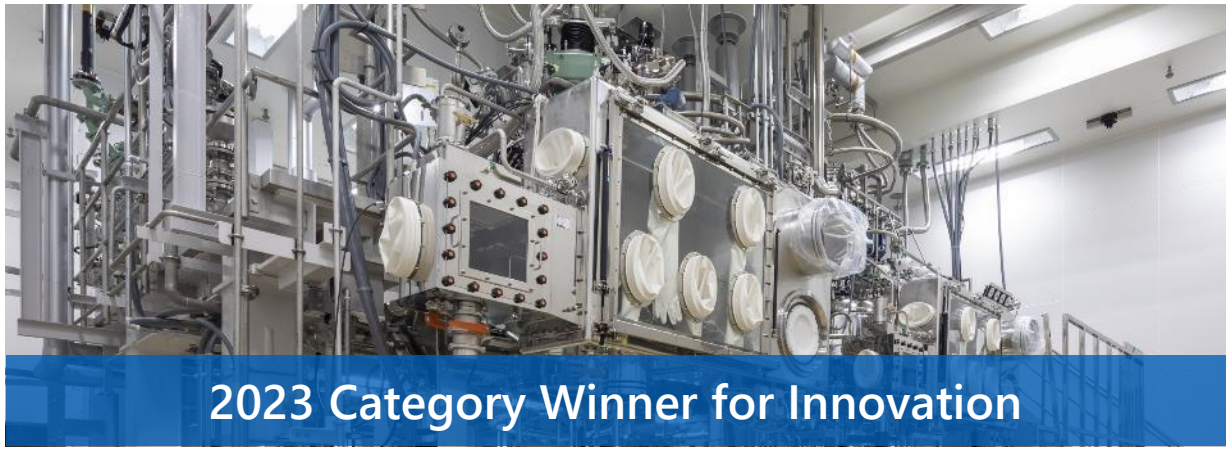
# FJ2: Facility Compatible with "Ultra-highly Active" Mid-size Molecules


- Introduced an "isolator" that can handle highly pharmacologically active and difficult compounds safely
- Achieve the highest global-level air containment with air concentration ≤0.05 μg/m$^3$
- Awarded "2023 Facility of the Year Awards" in the Innovation category by ISPE*

*ISPE; International Society for Pharmaceutical Engineering

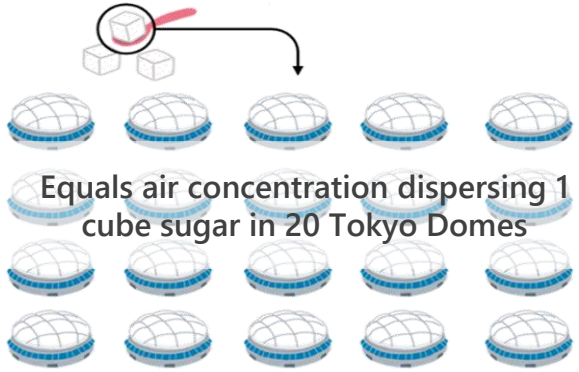
FOYA 2023
ISPE Facility of the Year Awards

CATEGORY WINNER
Innovation

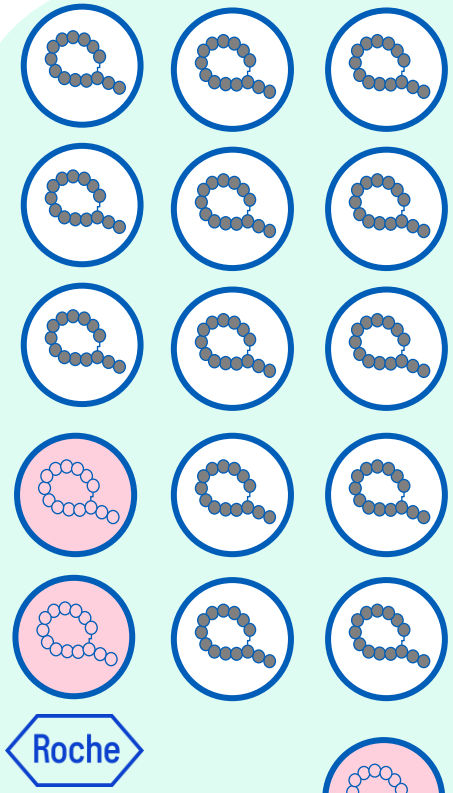


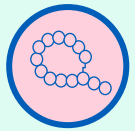

Awards ceremony
at ISPE Annual Meeting & Expo

Containment level ≤0.05 μg/m$^3$

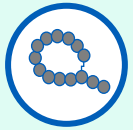



# December 2021: Mid-size Molecule Drug Discovery and Research Portfolio



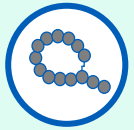



Univ. of Tokyo



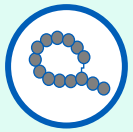
**Cancer**

- ✓ Intracellular
- ✓ Oral/injection



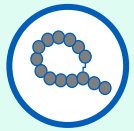
**Cancer**

- ✓ intracellular
- ・Cellular activity
- ✓ Oral



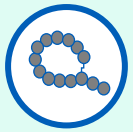
**Cancer**

- ✓ Intracellular
- ✓ Oral



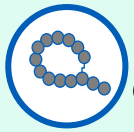
**Cancer**

- ✓ intracellular
- ・Cellular activity
- ✓ Oral



**Immune disease**

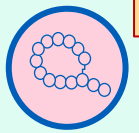
- ✓ Extracellular
- ・Cellular activity
- ✓ Oral



**Immune disease**

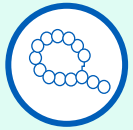
- ✓ extracellular
- ・Cellular activity
- ✓ Oral

Osaka univ.



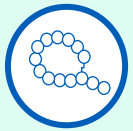
**Immune disease**

- ✓ intracellular
- ・Cellular activity
- ・Animal PD
- ✓ Oral



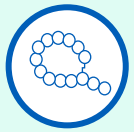
**Acute disease**

- ✓ intracellular
- ・Cellular activity
- ・Efficacy in animal
- ✓ Injection



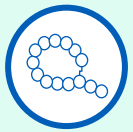
**Cancer**

- ✓ intracellular
- ・Cellular Activity
- ・Efficacy in animal
- ✓ Oral



**Cancer**

- ✓ intracellular
- ・Cellular Activity
- ・Efficacy in animal
- ✓ Oral



**Cancer**

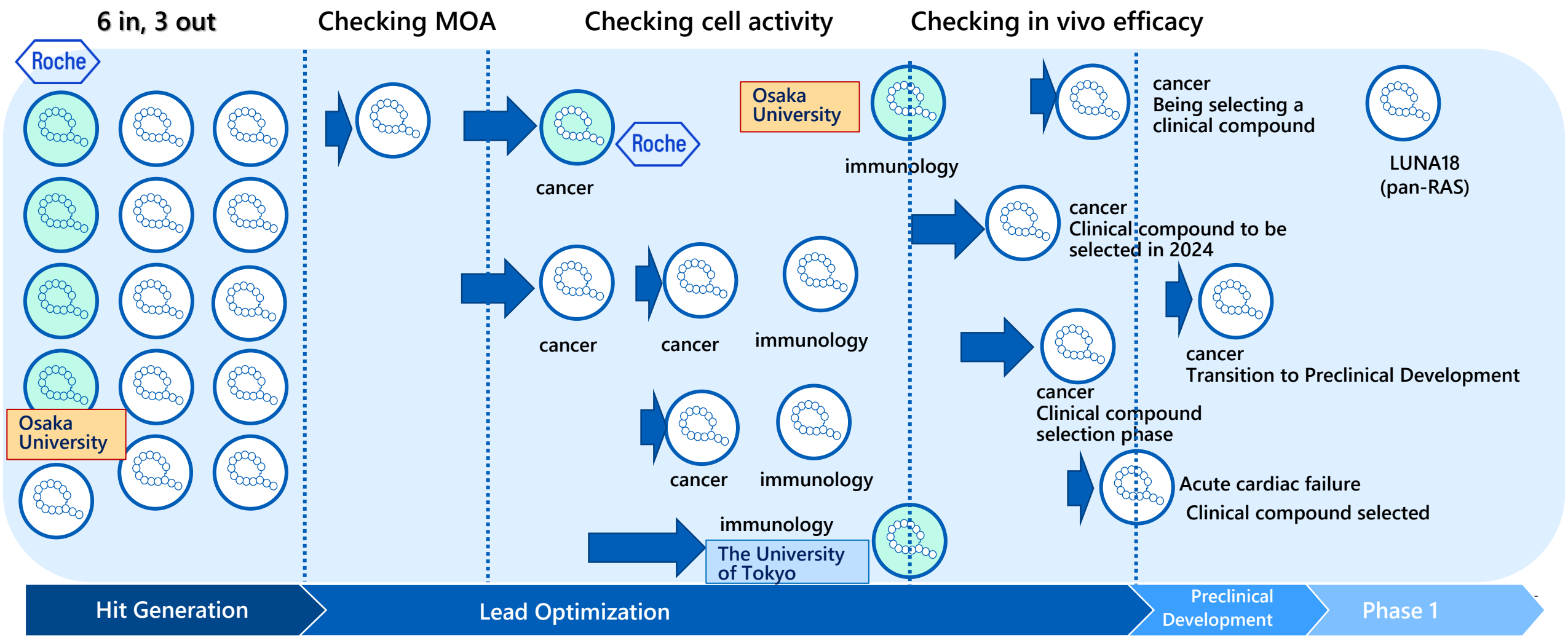
LUNA18
Pan-RAS inhibitor

- ✓ intracellular targets
- ・Cellular activity
- ・Efficacy in animal
- ✓ Oral

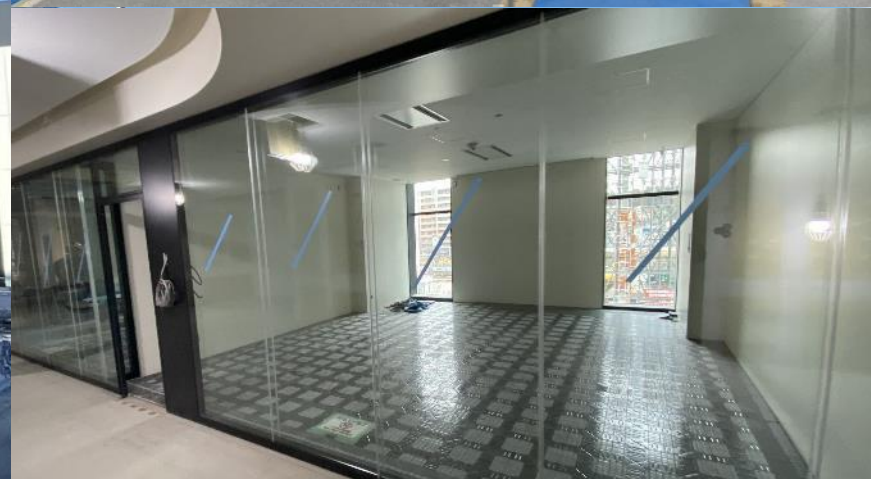
Lead Identification | Lead Optimization | Preclinical Development | Phase 1

# December 2023: Mid-size Molecule Platform Update

Aim for a consecutive portfolio in from 2023



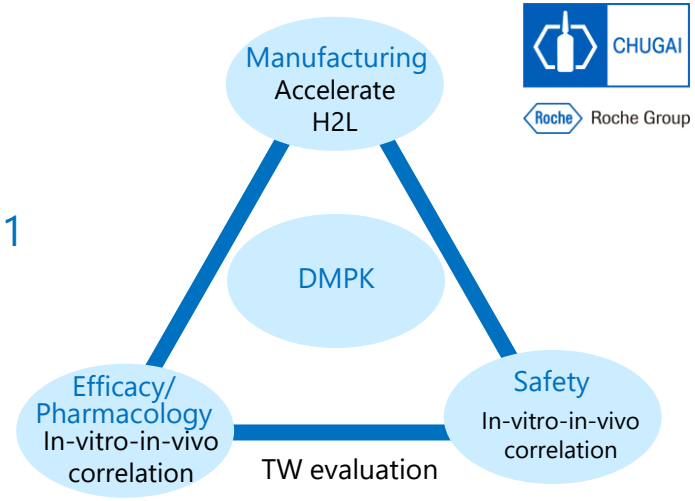
# Chugai Life Science Park Yokohama
# Full-scale Operation Started from April 2023



# Desilo: Streamlining through “Visualizing” Drug Discovery Process

- Any space that can decrease 20 FTE in the entire headquarters by increasing 3 FTE in 1 department ?
- Any solvable problem with “technology development” neglected?
  (Spending time on a project to overcome technical difficulties is acceptable)

CHUGAI
Roche Roche Group




**Streamline through “Discovering technology to see truth“**
- Strengthen in vivo predictive in vitro technology
- Predict monkey PK from mouse/rat PK
- Evaluate safety items in pharmacology studies

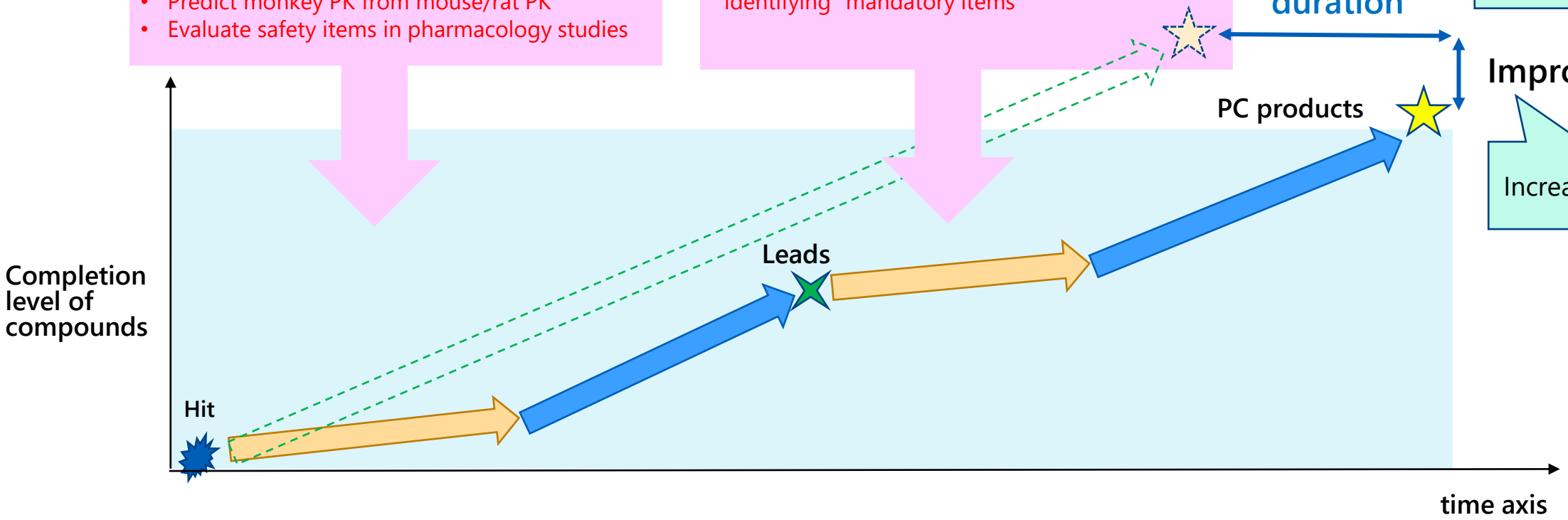
**Increase efficiency by management**
Minimize H2L activity duration without identifying “mandatory items”

**Shorten duration**

Reduce inputs

**Improve quality**

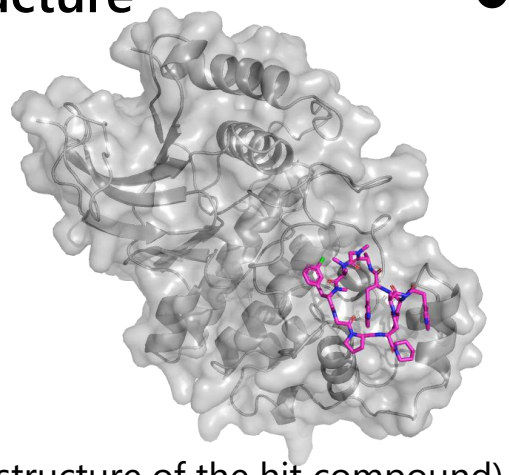
Increase outputs



# Hit to Lead: X-ray Structure, Cryo-Electron Microscopy, and Digital Utilization

- **X-ray crystal structure**

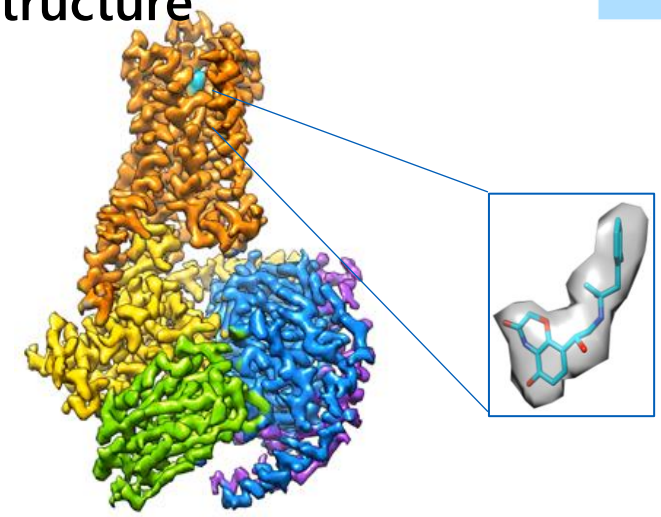
Synchrotron radiation



(crystal structure of the hit compound)

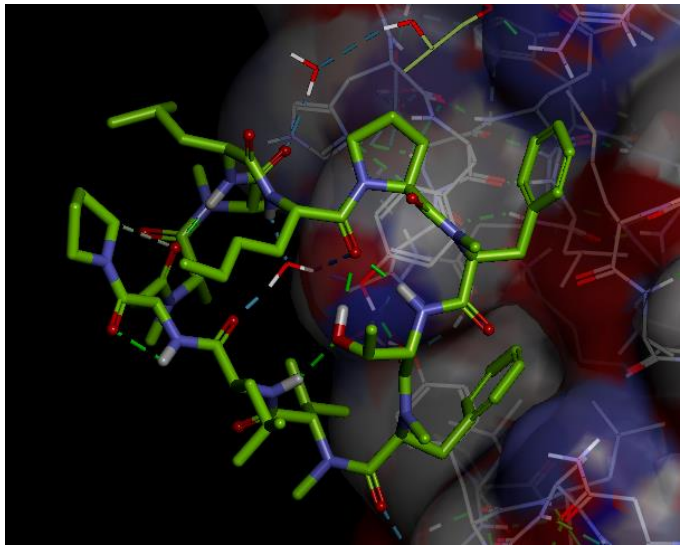
- **Cryoelectric structure**

Electron microscope



- **Digital utilization**

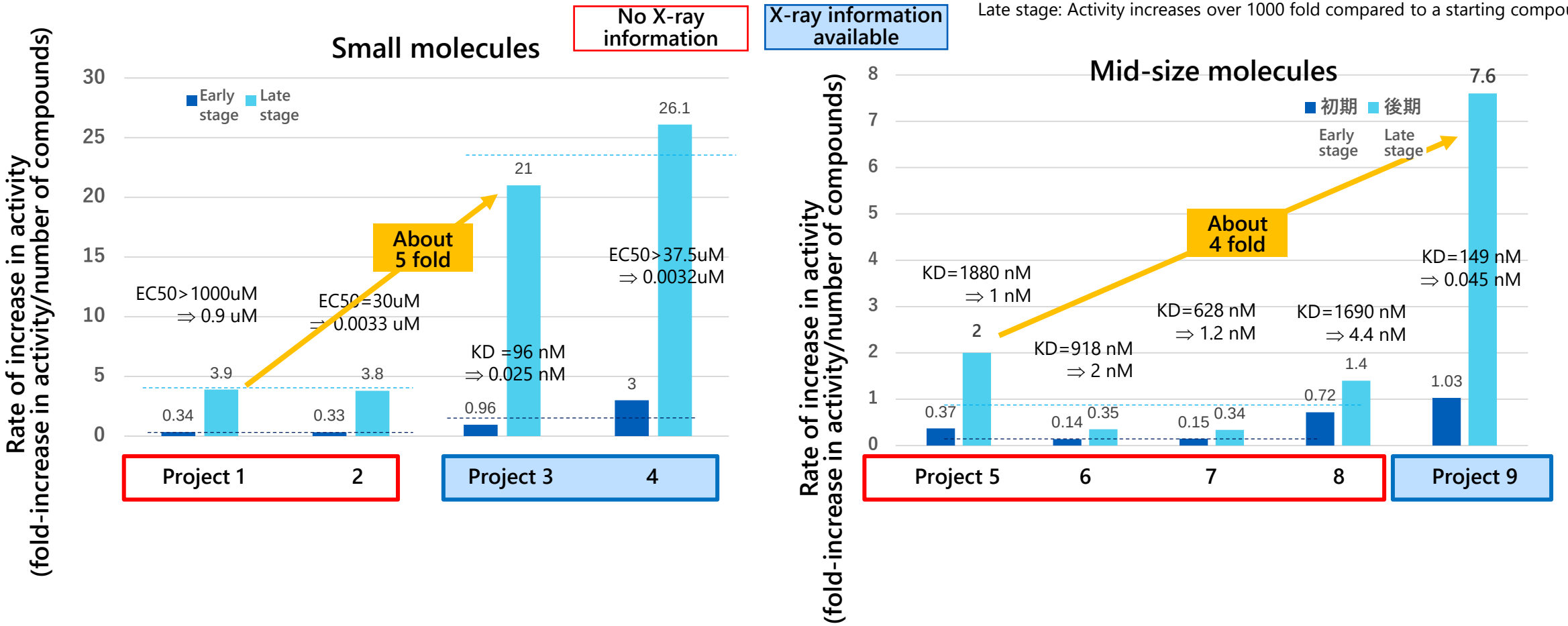
Chemical structural modification based on various in-house experimental data
・Simulation
・Prediction model



# With a 3D Structure, Number of Synthetic Compounds Can be Reduced to about 1/4

*Rate of increase in activity: If it reaches 100-fold increase in activity with 100 compounds from hit, it is calculated as 1.

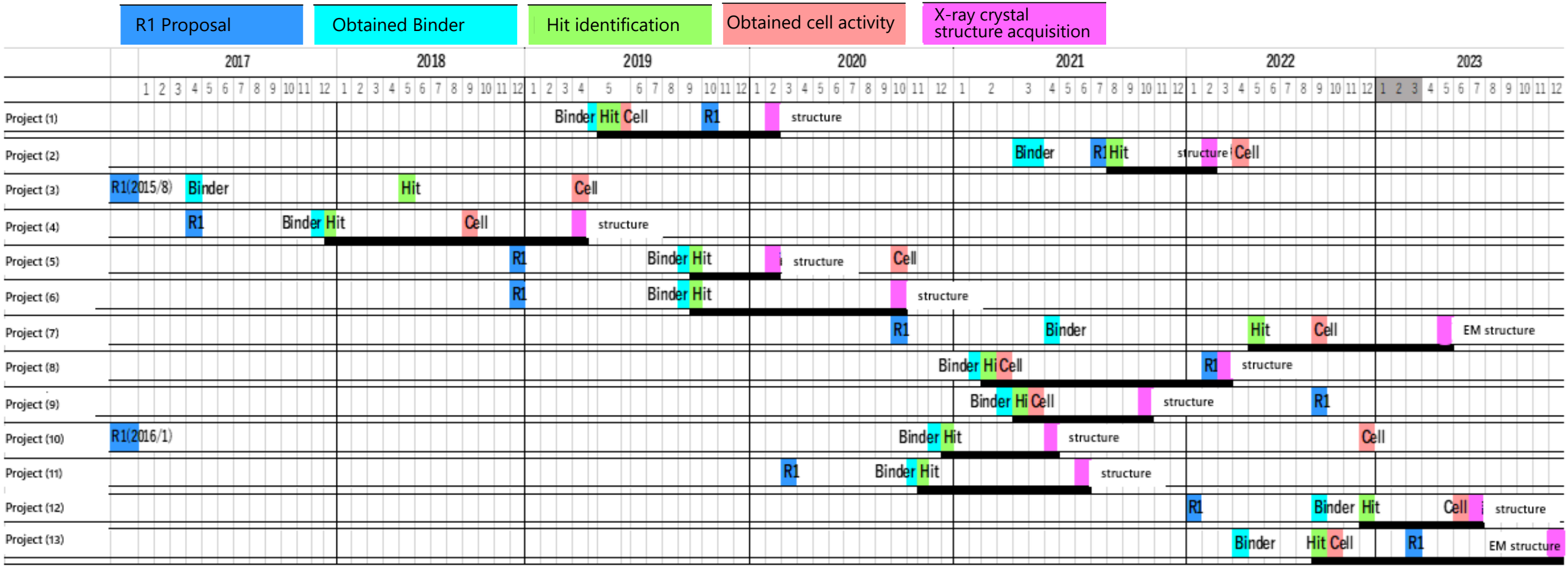
Early stage: Activity increases up to 100 fold compared to a starting compound
Late stage: Activity increases over 1000 fold compared to a starting compound



# Establish a System Can Acquire 3D Structure in an Average of 8 Months after Identifying Binder

CHUGAI
Roche Roche Group

**Reduced timelines with significant increase in number of applicable projects**
**From 2017: Mean 10.8 months ⇒ After 2021: Mean 7.8 months**




The period from January to March 2023 is deducted from the period because of downtime due to transfer.

## Established Protein Science Department in April 2021

**Protein Adjustment, Structural Analysis, Binding Kinetic Measurement, MOA Analysis**

# Chugai's Mid-size Molecule Drug Discovery

- **Focus on "Realization of Drug Discovery for Intracellular Tough Targets," which is difficult even with antibodies or small molecules**
- **Aim to establish a platform that enables consecutive drug discovery**
  - Identify a Druglike-area in the area with molecular weight exceeding 500
  - Develop a new fundamental biotechnology that enables to generate Druglike-hit
  - By having chemistry take charge of H2L, build a drug discovery platform that can provide commercial value through fusion of biotechnology and chemistry

## Number of patent applications 43

## Publication

Hit Generation: *J. Am. Chem. Soc.* 2023, **145**, 24035
Lead Optimization: *J. Am. Chem. Soc.* 2023, **145**, 16610
Synthesis: *J. Med. Chem.* 2022, **65**, 13401

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INNOVATION BEYOND IMAGINATION