Axcelead Global Webinar #1

– Driving innovative drug discovery through integrated high-throughput screening platform –

August 17,2022
4pm/PT, 7PM/ET

Axcelead Drug Discovery Partners, Inc.

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Drug Discovery Partners

Agenda

1. Company Overview

Speaker: Yoshinori Ikeura, PhD
CEO, Axcelead Drug Discovery Partners, Inc.

2. Driving innovative drug discovery through integrated high-throughput screening platform

Speaker: Tomohiro Kawamoto, PhD
Senior Director of Discovery Biology,
Axcelead Drug Discovery Partners, Inc.

Company Overview

Yoshinori Ikeura, PhD

Axcelead Drug Discovery Partners Inc.

August 17, 2022

AXCELEAD Drug Discovery Partners

We are Solution Provider in the drug discovery space from Japan

General information

- Established in 2017 as Takeda spin-out company and became a fully independent company on April 1, 2019
- Number of employee: 270 (as of July 2022)
- Location: Shonan Health Innovation Park (Former Takeda Shonan Research Center)
- Contract more than 170 organizations (as of July, 2022)

CEO: Yoshinori Ikeura, Ph.D

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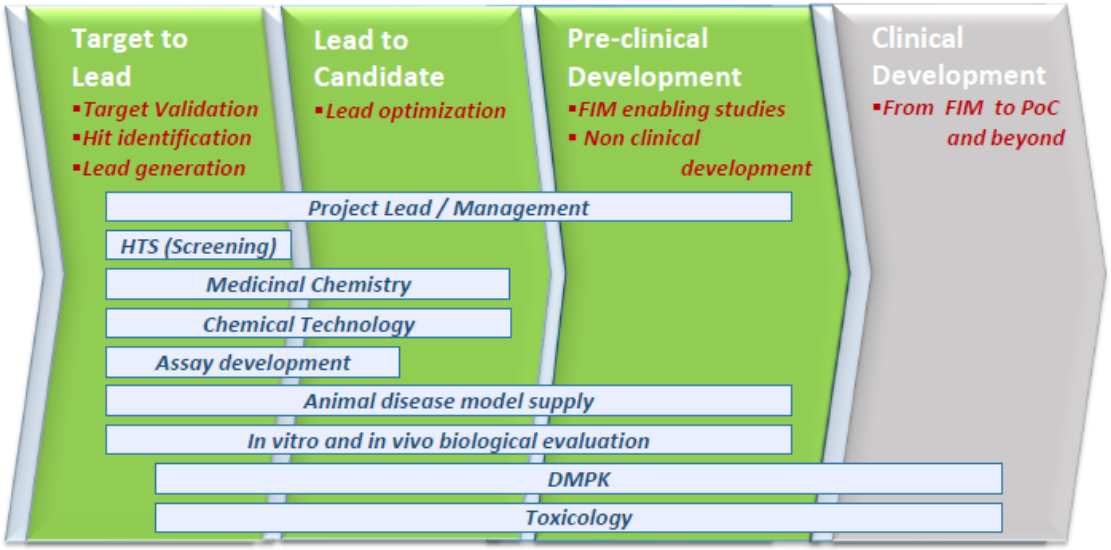
Highlight of Axcelead

// **The spin-out of Takeda Pre-Clinical R&D capability, inheriting its unique and proprietary drug discovery platform, "People", "Infrastructure" and “Legacy Data"**

Scientific leadership team

// **Full Capabilities for small molecule & peptide drug discovery: from early stage exploration studies to optimization of candidate and even a bridge process to clinical development.**



// **Partnership for new technologies and strong relationship with Japanese government**

New modalities and technology

- **FUJIFILM/ FCDI** — iPS cell
- **PassPort TECHNOLOGIES** — Transdermal drug delivery
- **FRONTEO** — AI
- **LAP&P** — PKPD modelling & simulation
- **Schrödinger** — Computed chemistry
- **SPERA PHARMA** — CMC
- **創晶 SOSHO** — Crystallization of protein
- **T-CiRA** — iPS cell, regenerative medicine
- **ERS GENOMICS** — Transgenic animals/cell
- **Croit** — All japan library
- **PhoenixBio** — Chimeric mouse w/ humanized liver

Japanese government & bio industry

- *Japan Agency for Medical Research and Development (AMED)*
- *Pharmaceuticals and Medical Devices Agency (PMDA)*
- *Japan Pharmaceutical Manufacturers Association*
- *Japan Bioindustry Association etc*

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Our strength is to generate the candidate

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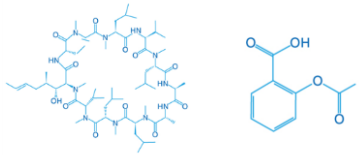
Legacy Data

Jump start utilizing Takeda legacy data

Hit Identification

Hit compounds identified by our HTS capability

Customers' seeds



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One site, fully integrated

	Lead generation	Lead optimization	Candidate Selection
Screening	In vitro evaluation	In vitro evaluation	
Chemistry	Design and Synthesis	Design and Synthesis	non-GxP bulk. (API synthetic route)
Biology	In vitro Pharmacology	In vivo PD	Efficacy in disease model
DMPK	HT-ADME	HT-ADME PK/PD	Human PK. PK/PD
Safety	In vitro toxicology	In vitro toxicology. In vivo toxicodynamics.	In vivo toxicology

Integrated Drug Discovery capability inheriting from Takeda Pharmaceuticals

- **Pharma Scientists**
- **Knowledge Experience**
- **Legacy Data**

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Target Identification/ Validation

Biology platform:

- Omics
- Bioinformatics (single cell/single nucleus analysis etc)
- Histopathology (Visium, mIHC etc)
- KO/KI animals
- Pharmacology etc

Candidate Selection

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IND enabling study

IND

GLP tox study, DMPK

- 100+ IND 20+ NDA
- Network with PMDA/FDA

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Axcelead Global Webinar #1

Driving innovative drug discovery through integrated high-throughput screening platform

Tomohiro Kawamoto, PhD

Axcelead Drug Discovery Partners Inc.

August 17, 2022

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Outline

- Key factors for hit identification
  - High quality and diverse library
  - Hit identification platform
- Approach to drugging unknown targets
  - Phenotypic screening using iPS cells
  - Target deconvolution
- Capabilities on drugging undruggable targets
  - Targeted protein degradation
  - RNA targeted drugs

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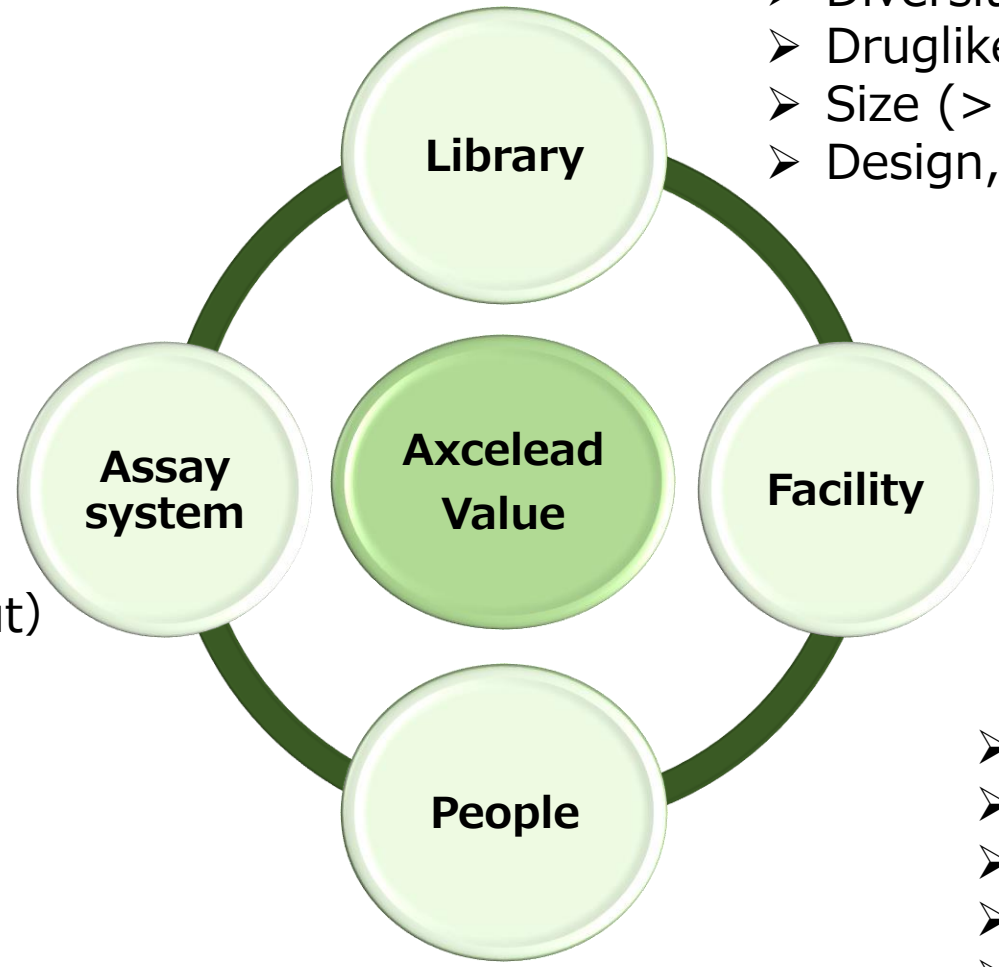
Key Factors for Hit Identification

- Diversity
- Druglikeness
- Size (>1.0 million)
- Design, Synthesis, Purchase



- Quality, Speed, Cost
- Throughput
- Robustness
- Disease relevancy
- Phenotypic rule of three (Cell X Stimulant X Readout)
- Profiling
- Data analysis

- Robotics
- Plate readers
- Dispensers
- Systems
- Maintenance

- Knowledge, Skill, Experience
- Expertise
- Strategy planning
- Problem solving ability
- Reliability
- Communication
- Collaboration

- ***Axcelead provides comprehensive hit identification services through our integrated platform***

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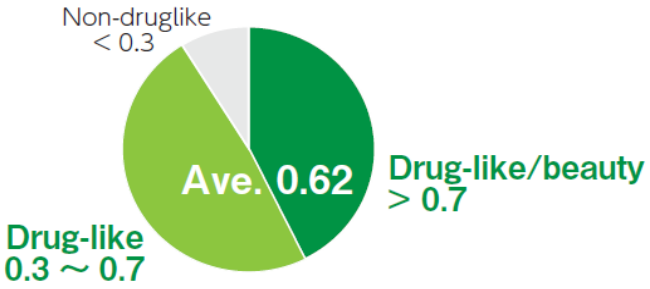
Axcelead Compound Library

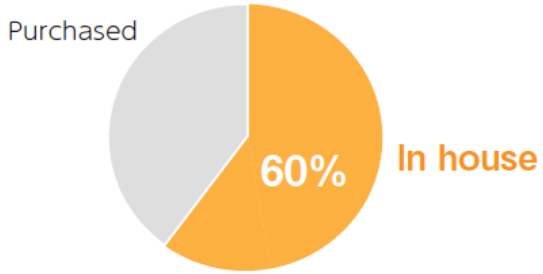
>1,500,000 Compounds

Quality

Lead likeness
QED: Quantitative Estimate of Drug-likeness



In-house compounds



Library sets for HTS

■ **Diversity libraries**
- Single library 129,000 compounds
- Pooled library 500,000 compounds (Standard 320,000 cpds)

■ **Focused libraries** 41,000 compounds
- Libraries for target classes (Kinase, GPCR, Protease, PPI, etc.)
- Macrocyclic
- RNA
- Covalent
- Extended rule of 5
- Natural product
- Annotation

➢ Biologically annotated library is available for phenotypic screening
➢ We are also able to construct a focused library selected from 1.5 million compounds library by virtual screen

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Hit Identification in Axcelead

➢ ***Axcelead offers high quality hit compounds with sophisticated strategies***

Strategy planning
Target assessment
Target product profile
Strategy
Screening cascade

Assay development
Preparation of materials
(Recombinant proteins,
Stable cell line)
Selection of assay systems
Miniaturization

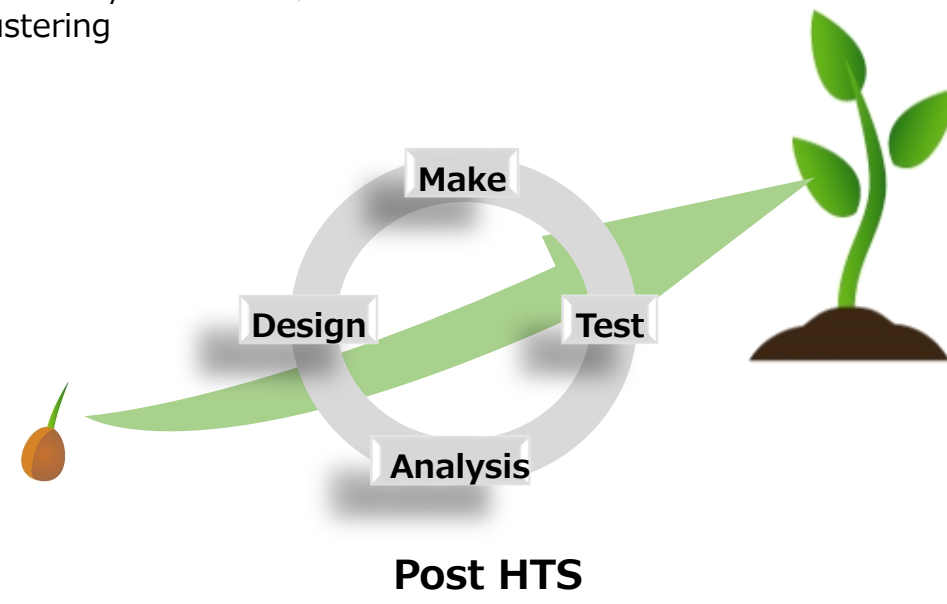
Primary HTS
Pilot screening
Library selection
Adaptation of robotics

Counter Assay
Elimination of false positives

Hit selection
Determination of EC/IC50
Structural clustering
Purity check

Post HTS
Profiling
MOA/Selectivity/Species
Biophysical analysis
Cell-based assays
ADMET

Toward Lead generation
Hit expansion
Evaluation of related compounds
Synthesis (Parallel/Custom)
SAR analysis



Post HTS

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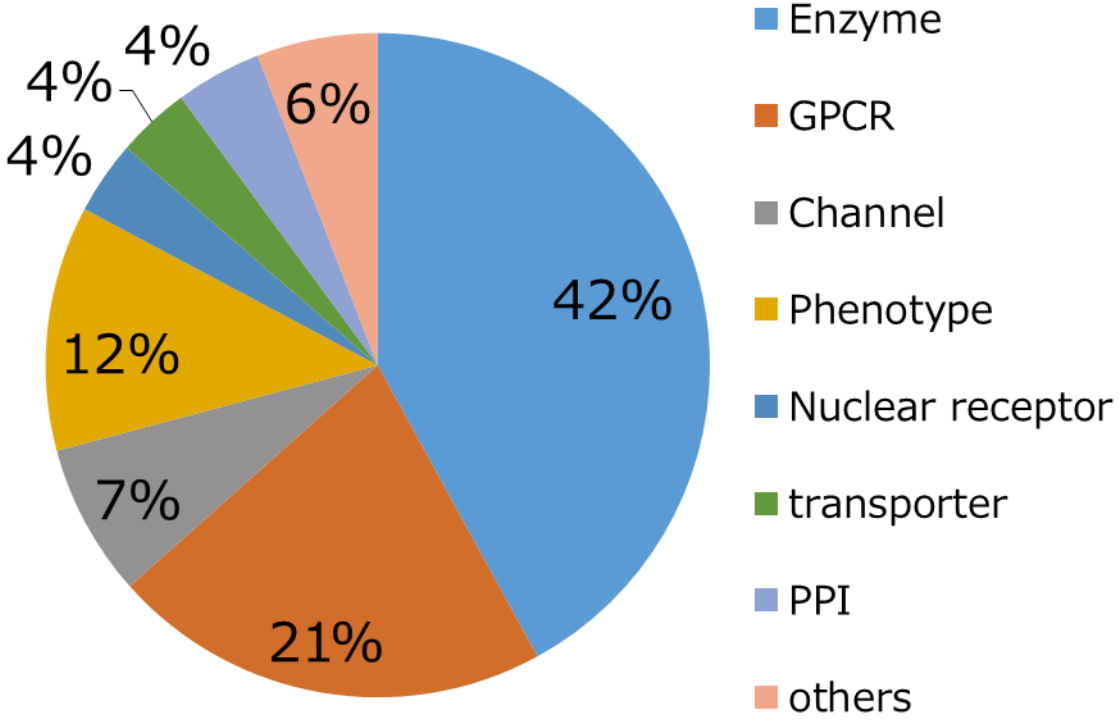
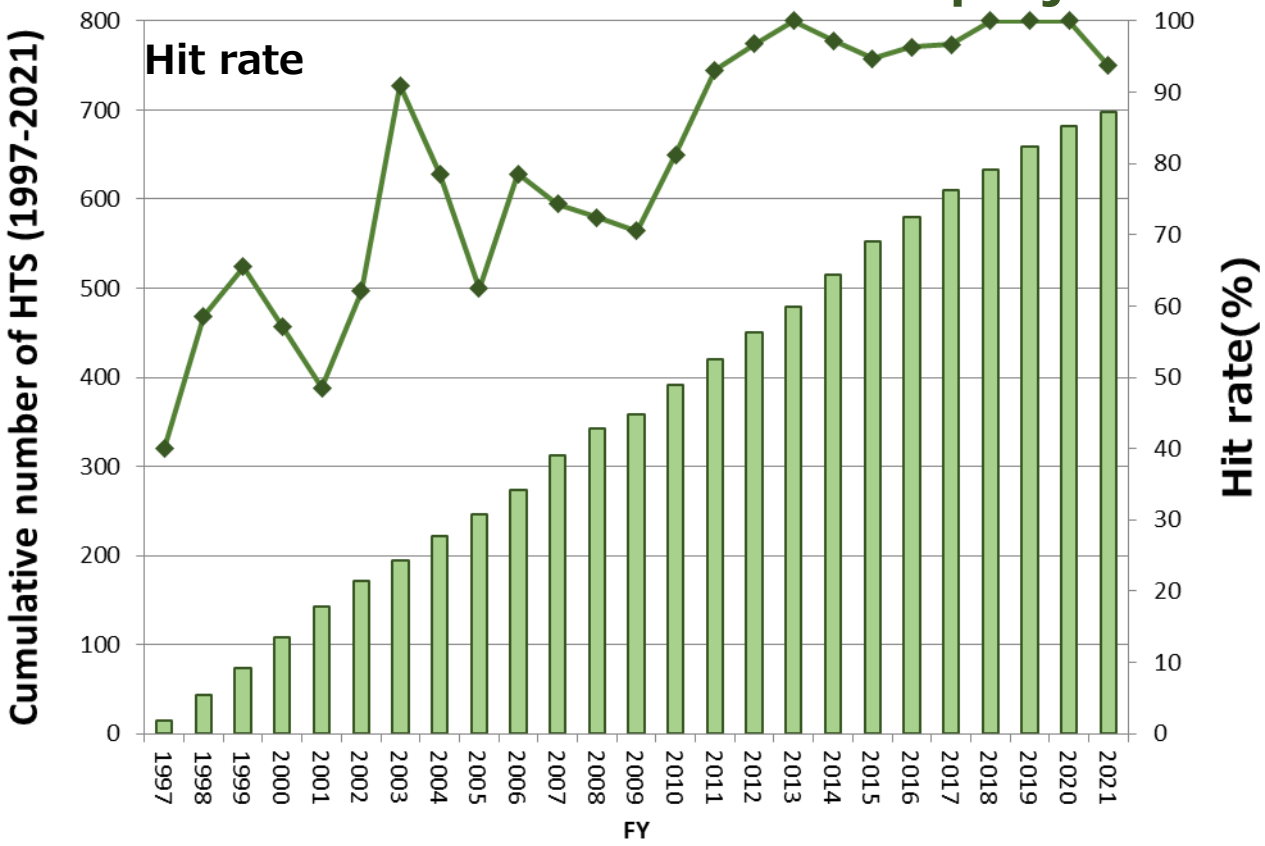
Track Record of HTS Campaigns

Target class



698 projects



- ***We have successfully completed around 700 HTS campaigns for various target classes with high hit rates***

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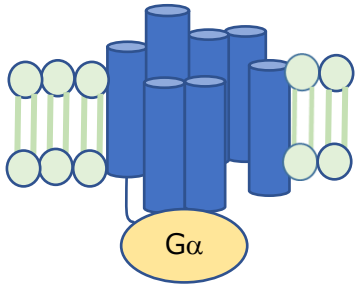
Target-based Assay Platform

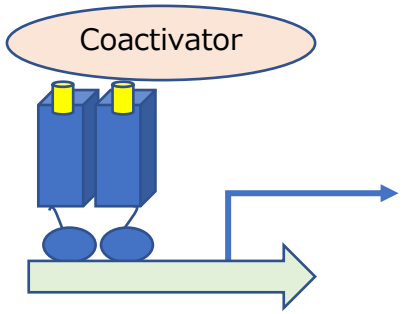
GPCR

- cAMP assay
- Ca^{2+} flux assay
- Reporter gene assay
- Arrestin/Internalization assays
- Binding assay
- Impedance assay



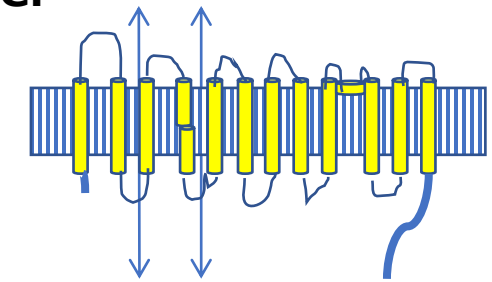
Nuclear receptor

- Binding assay
- Cofactor recruitment assay
- Reporter gene assay
- Nuclear translocation assay



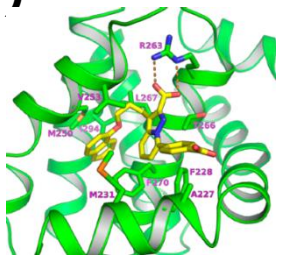
Ion channel / Transporter

- Ion influx assay
- Membrane potential
- Electrophysiology
- Substrate uptake
- Binding



PPI (protein-protein interaction)

- TR-FRET/Alpha screen assay
- ELISA
- NanoBit/BRET
- Two-hybrid assay
- Biophysical assay



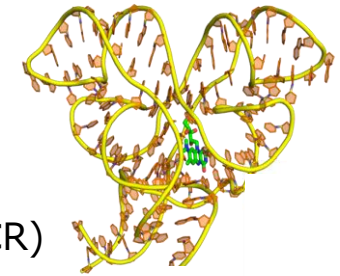
J Med Chem **56** 9635–45 (2013)

Enzyme

- Luminescence, Absorbance, Fluorescence, TR-FRET
- Alphascreen, ELISA
- Radiometric assay
- Label-free assay (e.g. Rapidfire-MS)
- Coupling assay
- Global kinase panel

Nucleic acid

- Biophysical assay (e.g. ASMS)
- Fluorescence probe binding
- FRET
- Cell-based assay (Reporter gene, RT-qPCR)



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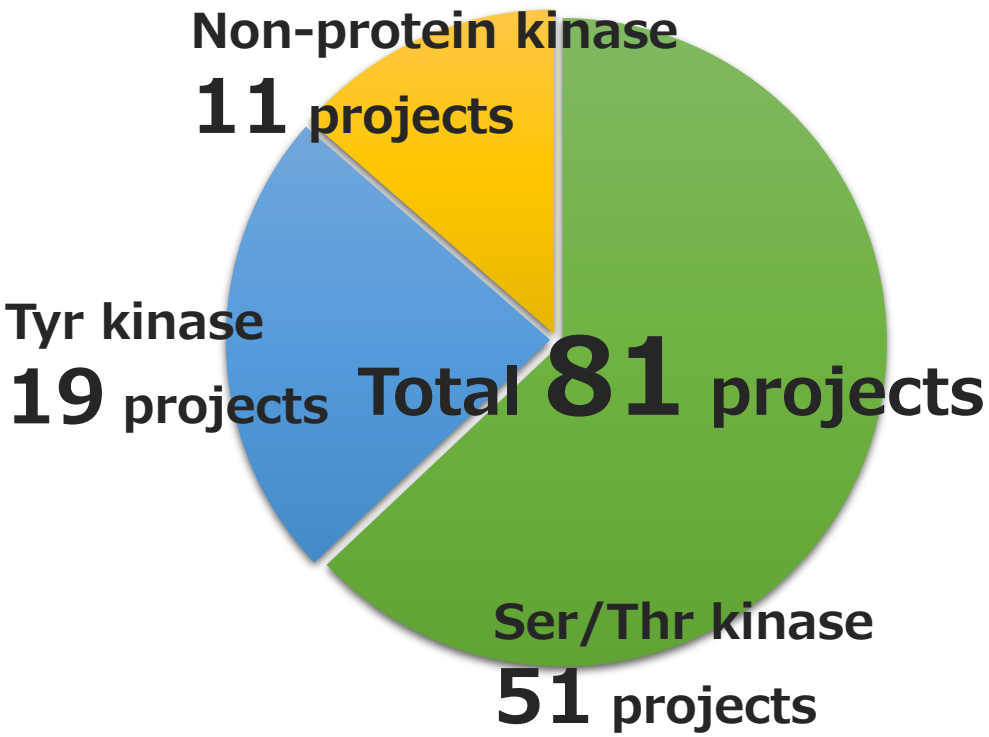
Kinase Platform

Kinase HTS track records



Full range of assay/HTS platform

Assay / HTS
- Enzyme activity assay (TR-FRET, Glo, Radiometric isotope, RapidFire-MS)
- Binding assay (Kinase tracer, AS-MS)

Profiling
- Internal Kinase Panel assay
- Molecular MoA analysis
  - Binding kinetics analysis
  - Substrate competition
- Cell-based assay

Biophysics
- SPR, ITC, TSA
- Crystal structure analysis

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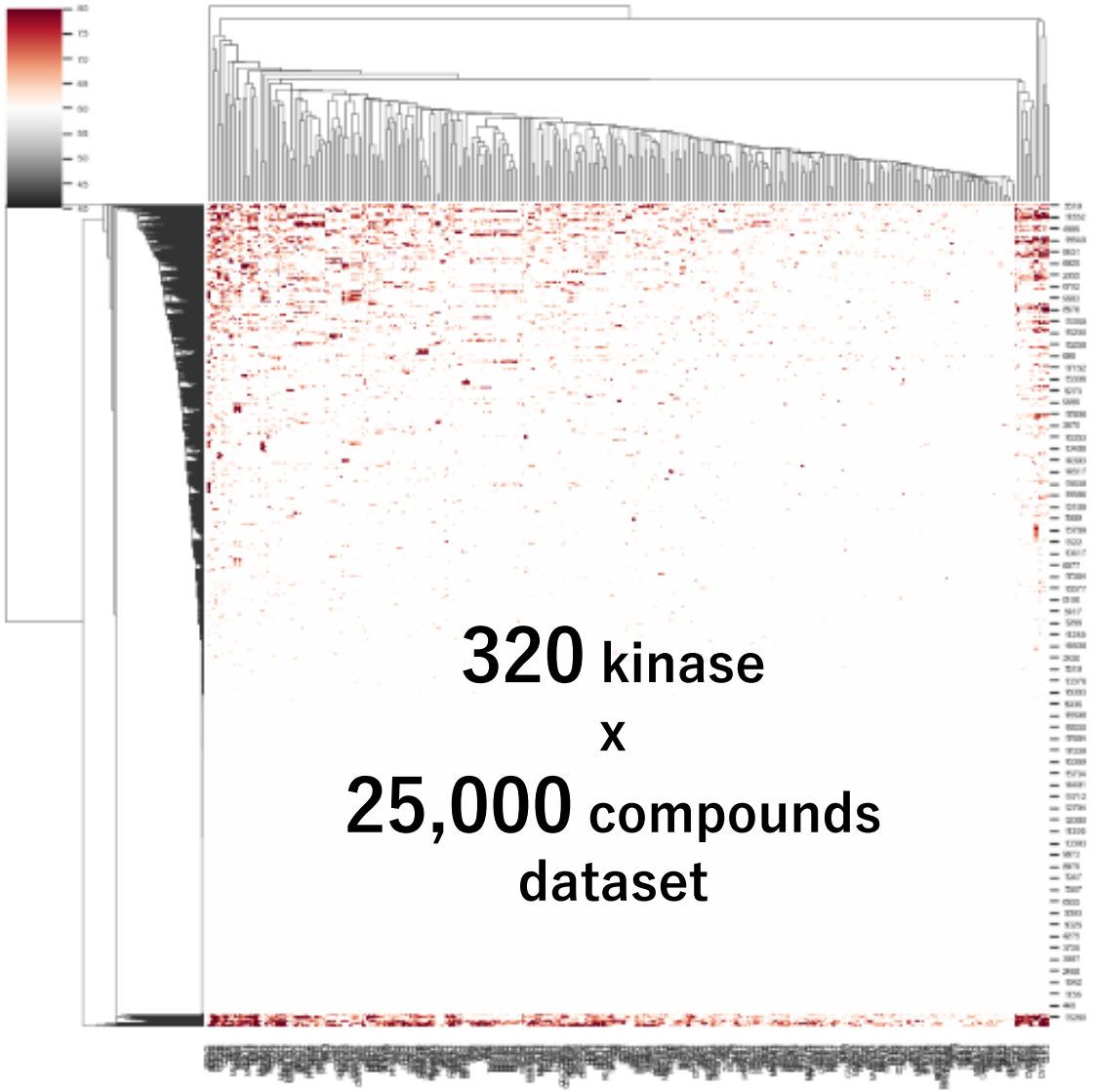
Original Selective Kinase inhibitors



A-SKIP (Axcelead Selective Kinase Inhibitor Profiler) for > 120 kinases

- ***Axcelead has original selective kinase inhibitors (A-SKIP) through our global kinase panel consisting of >300 kinases.***
- ***We can accelerate your drug discovery with our assets as an integrated drug discovery service***

***A-SKIP criteria**

- **Selectivity Score<=5% (>300 kinase)**
- **highest pIC50>=7.5**
- **Num of (pIC50>=7.5) <=4**

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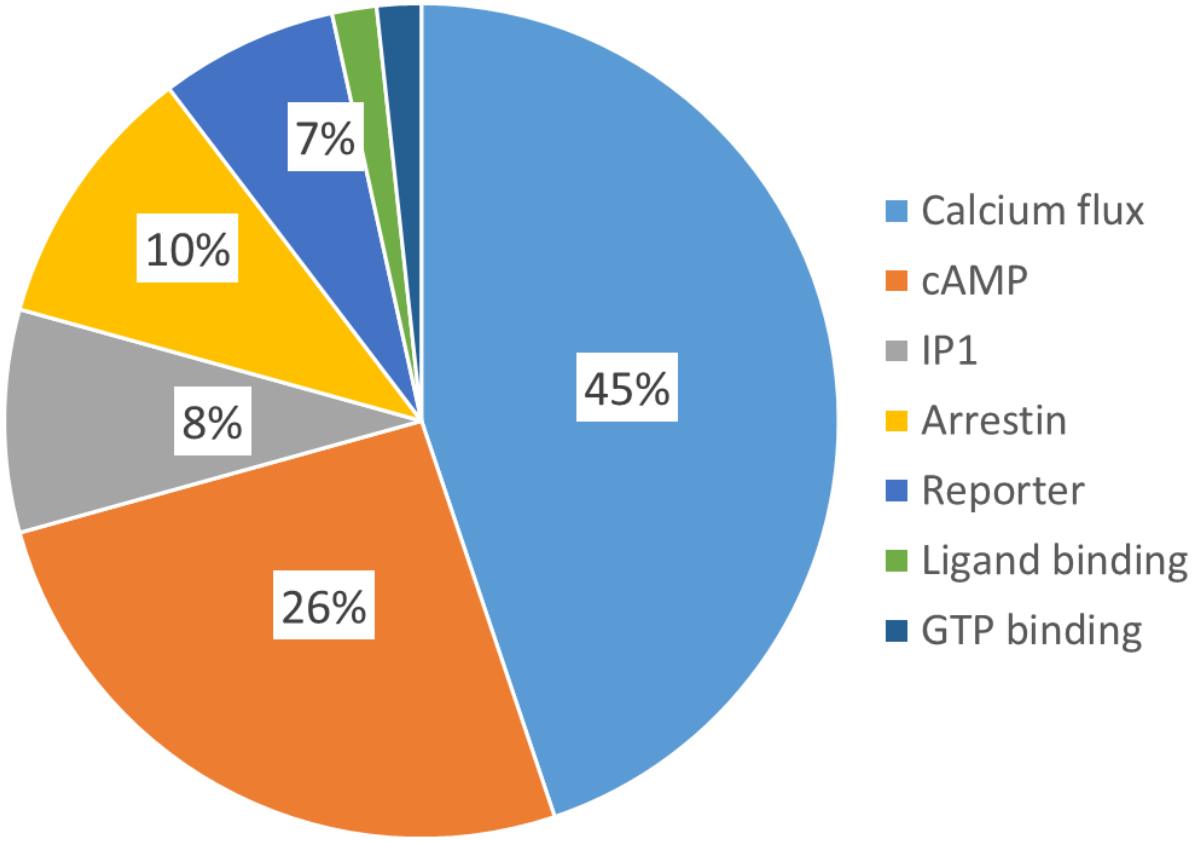
Discovery of GPCR Biased Ligands

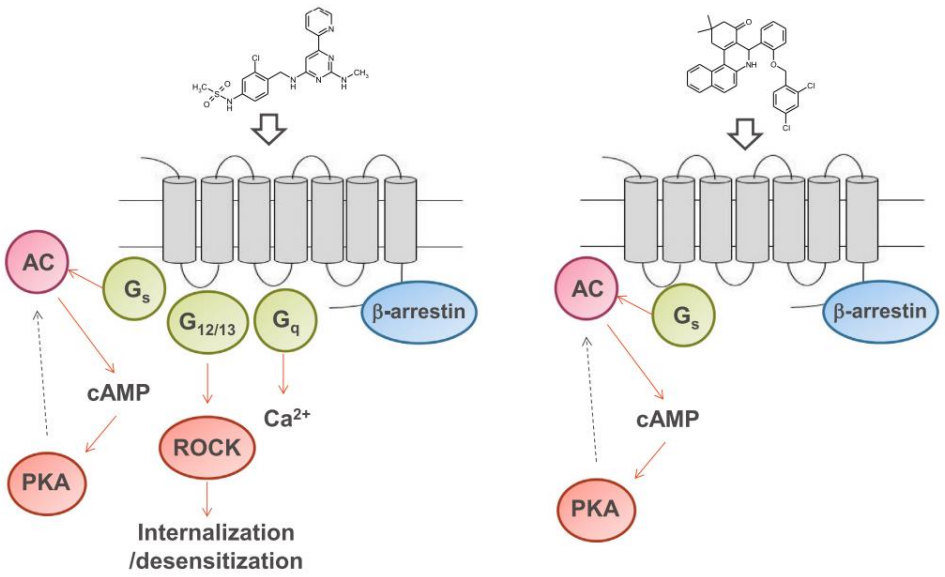
Track record of primary assays in HTS campaign targeting GPCRs



GPR39 positive allosteric modulators

Library: >600,000 cpds at 3μM
Primary assay: FRET (cAMP), PAM mode

Gs biased



Biochemical Pharmacology 140 (2017) 105–114

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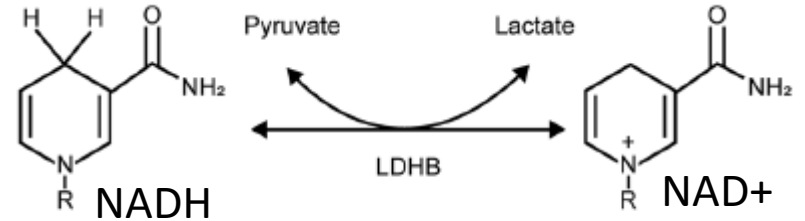
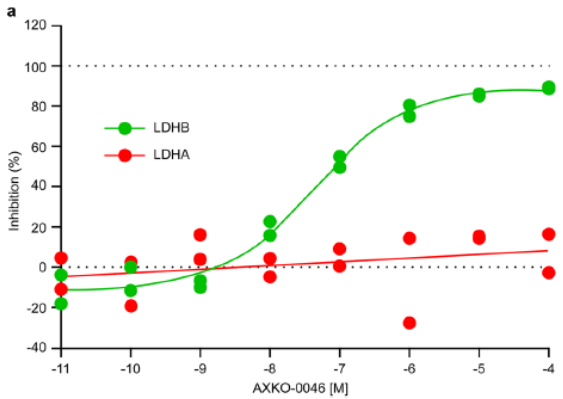
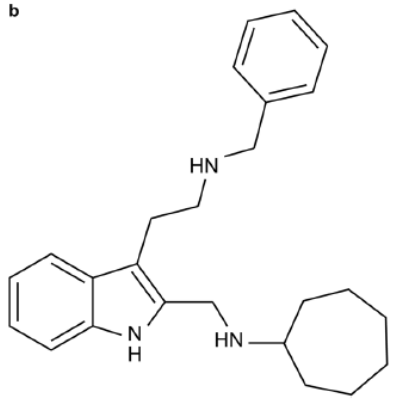
Discovery of Enzyme Inhibitors using Rapidfire-MS

LDHB







HTS cascade

Primary screening (ca. 370,000 compounds)

- Diversity pooled library 10 μM, N=1
- Enzyme assay with Rapidfire-MS

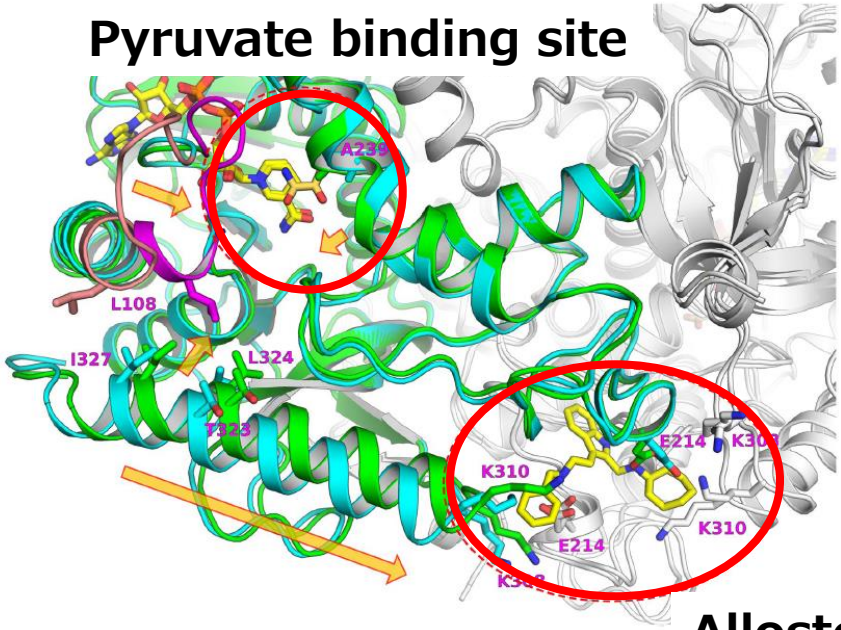
Deconvolution assay (ca. 800 cpds)

- Positive compounds from primary screening 30 μM, N=1

Dose response test

- 4-5 dose, N=2
- Selectivity test (LDHB/LDHA)
- Clustering
- Purity check
- Evaluation of related compounds

Hit compounds



Sci.Rep 2021 11:21353

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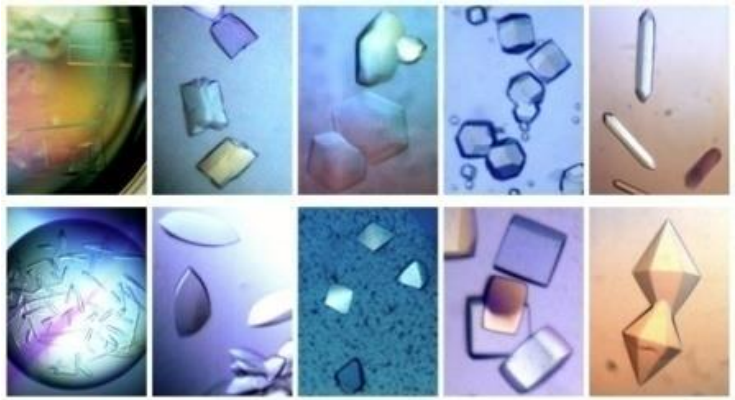
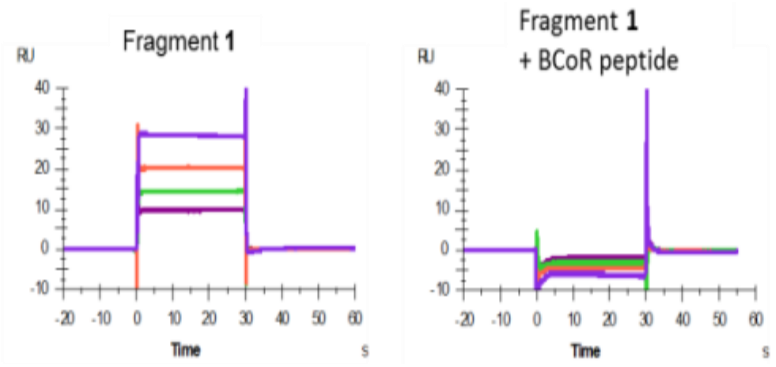
In vitro Assay Platform for Profiling

- Biochemical assay (Potency/Selectivity/Species difference for SAR)
- Mode of action/ Kinetics analysis and Profiling assay
- Cell-based assay (Cellular target engagement, Cellular function etc.)
- Biophysical analysis for target-compound interaction assay
  - AS-MS, TSA, NMR, ITC, SPR, X-ray crystallography

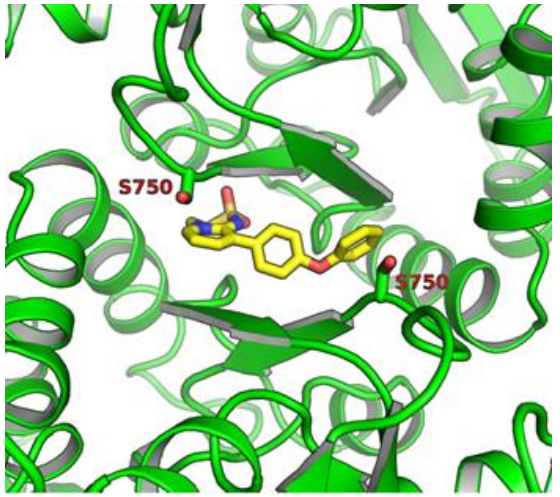


Competition experiment



Kinetics assay with SPR

Thermodynamics assay with ITC



X-ray crystallography

Neuropsychopharm **44** 961–70 (2019)

- ***We can drive drug discovery by using various technologies led by multidisciplinary teams***

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Outline

- Key factors for hit identification
  - High quality and diverse library
  - Hit identification platform
- **Approach to drugging unknown targets**
  - Phenotypic screening using iPS cells
  - Target deconvolution
- Capabilities on drugging undruggable targets
  - Targeted protein degradation
  - RNA targeted drugs

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Drug Discovery Strategy

Strategies	Materials	Pros	Cons
Target-based Drug Discovery (TDD)	Recombinant protein, Nucleic acid, Cell	■ High throughput ■ Robust screening cascade has been established ■ Structure–based approach is possible	■ Hit compounds may not show efficacy in cell-based assay ■ Shortage of druggable target molecules
Phenotypic Drug Discovery (PDD)	Cell, Tissue, Organ	■ Not need to know molecular targets of a disease ■ Possibility to discover hit compounds with unique MOAs ■ Novel biological discovery	■ Low throughput ■ Low stability and robustness of assay system ■ Target deconvolution and MOA analysis can be challenging

➢ ***Axcelead has both capabilities of TDD and PDD and provides the best solution***

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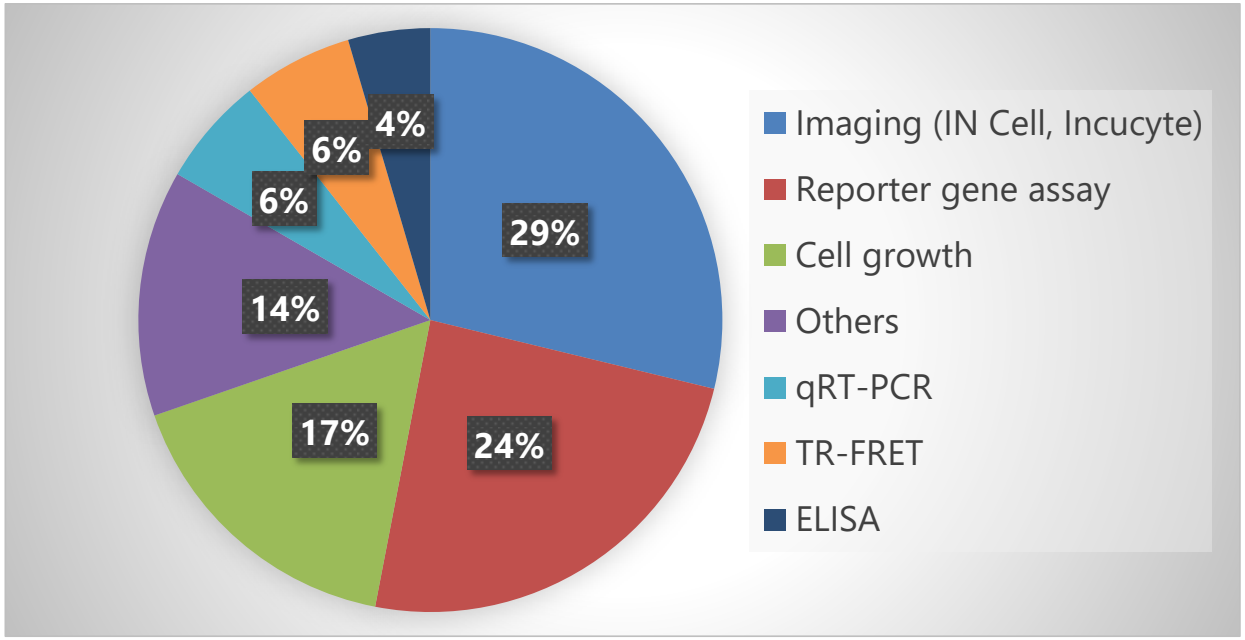
Track Record of Phenotypic Screening

Track record for >70 PDD programs

Assay methods



Assay methods	Usual screening library size
Imaging	100K compounds
Reporter gene assay	400K compounds
Cell growth Incl. synthetic lethality	400K compounds 3200 compounds
qRT-PCR	30 K compounds
TR-FRET	100K compounds
ELISA	100K compounds
POI-HiBit screening (for degrader screening)	100K compounds

➢ ***We can propose the best screening strategies according to your needs***

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Phenotypic Screening using iPS Cells

FUJIFILM Cellular Dynamics

Aβ uptake assay in iCell® Microglia AD TREM2

HTS cascade

Primary screening (c.a. 4000 compounds)

- Biologically annotated compounds, > 3,000 cpds
- 3 μM, N=1
- Phagocytosis assay and cytotoxicity (CellTiter-Glo® Luminescent Cell Viability Assay)

⇩

Reproducibility test (350 compounds)

- Positive compounds from primary screening
- 3 μM, N=1
- Phagocytosis assay and cytotoxicity (CellTiter-Glo® Luminescent Cell Viability Assay)

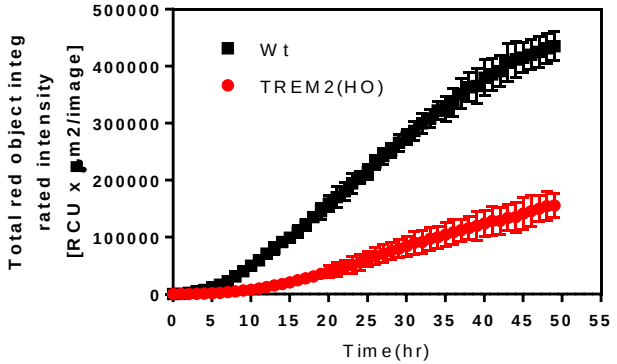
⇩

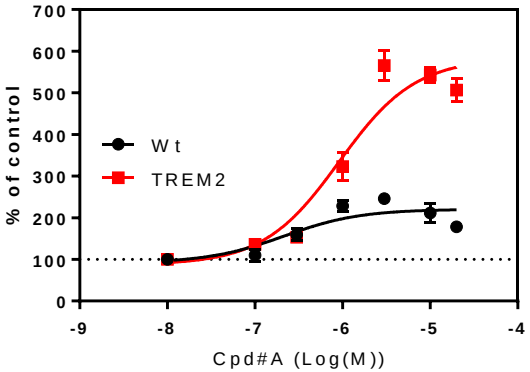
Dose response test (24 compounds)

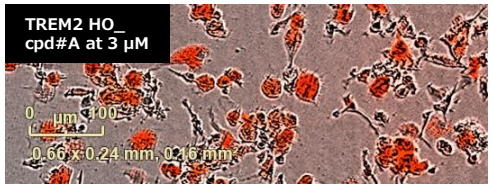
- Selected compounds from reproducibility test
- 6 dose, N=2
- TREM2 mutant and WT
- Phagocytosis assay and cytotoxicity (CellTiter-Glo® Luminescent Cell Viability Assay)

⇩

Hit compounds







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MOA Analysis Using Annotation Library

Hit compounds from annotated library

Target candidates
- Kinase A
- GPCR B
- Nuclear receptor C

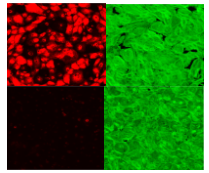
Predict MOAs for other hit compounds

Search if we have other Kinase A inhibitors with different chemical structures
in our internal compound library

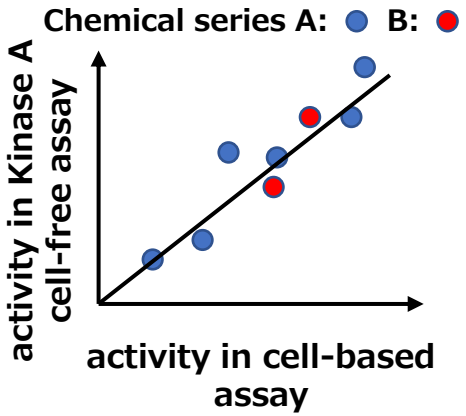
Compounds X and Y are Kinase A inhibitors, but have different chemical structures

Hit Compounds X from screening

Compounds Y from Our library



Both compounds induce the same phenotypic outcomes ?

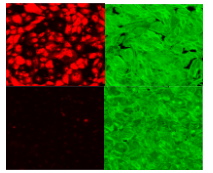


Both activities correlate well?

Kinase A could be a possible drug targets to modulate the phenotype

Validation study

Genome-editing tools
si/shRNA
CRISPR/Cas9



Same phenotypic outcomes as Kinase A inhibitors?

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Target Deconvolution

Target deconvolution

- *Phenotypic screening*
- *Target-unknown drugs*

Annotation analysis

Chemical proteomics

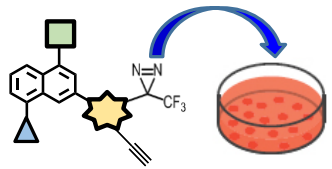
Finger printing

- *Target based drug discovery*
- *Drug repositioning*

Direct target fishing

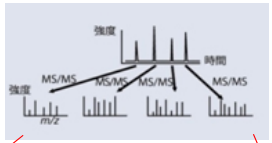
1. Probe design & synthesis

2. Probe labeling & isolation



➢ Photoaffinity labeling

3. LC-MS/MS analysis

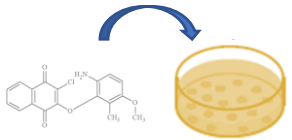


MKWVTFISLL FLFSSAYSRG VFRRDAHKSE VAHRFKDLGE
ENFKALVLIA FAQYLQQCPF EDHVKLVNEV TEFAKTCVAD
ESAENCDKSL HTLFGDKLCT VATLRETYGE MADCCAKQEP
ERNECFLQHK DDNPNLPRLV RPEVDVMCTA FHDNEETFL

4. Biological/ biochemical target validation

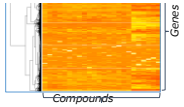
Target/ pathway prediction

1. Compound treatment



2. NGS (AmpliSeq) & gene signature analysis

3. Search compound with similar gene signature



➢ Public database (in service)
➢ AXL original database (in plan)

4. Biological target validation

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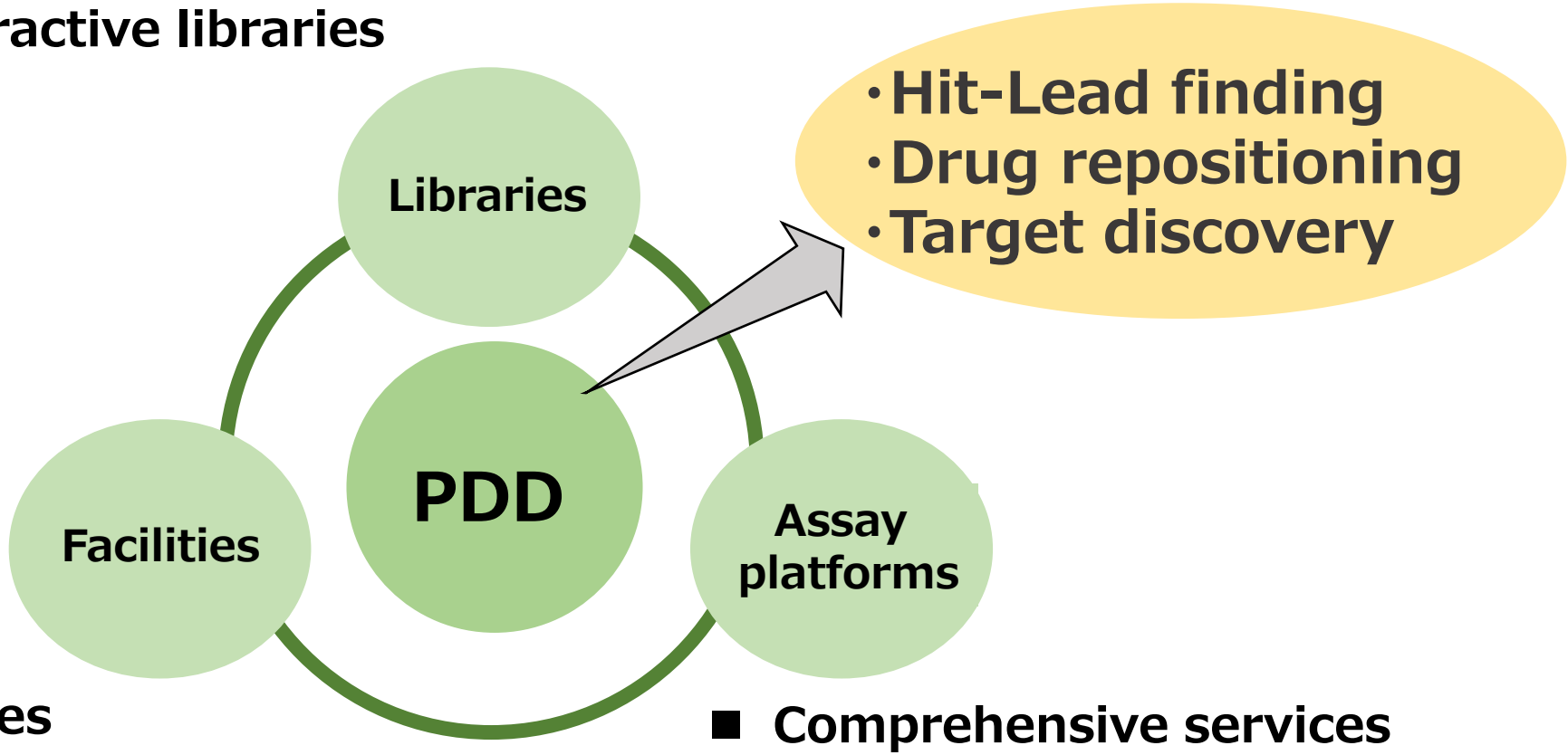
Phenotypic Drug Discovery (PDD) in Axcelead

■ High quality and attractive libraries

・Diversity
・Biological annotation
・FDA approved
・Focused



■ Cutting edge facilities

・Automation system
・Wide rage of devices
  Envision
  Incell6000
  qRT-PCR system etc.
・BSL2 laboratory

■ Comprehensive services

・Cell construction
・Assay platforms
・Target discovery with Crispr Cas KO screen
・MOA analysis
・Biochemistry and Biophysics
・Target deconvolution

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Outline

- Key factors for hit identification
  - High quality and diverse library
  - Hit identification platform
- Approach to drugging unknown targets
  - Phenotypic screening using iPS cells
  - Target deconvolution
- Capabilities on drugging undruggable targets
  - Targeted protein degradation
  - RNA targeted drugs

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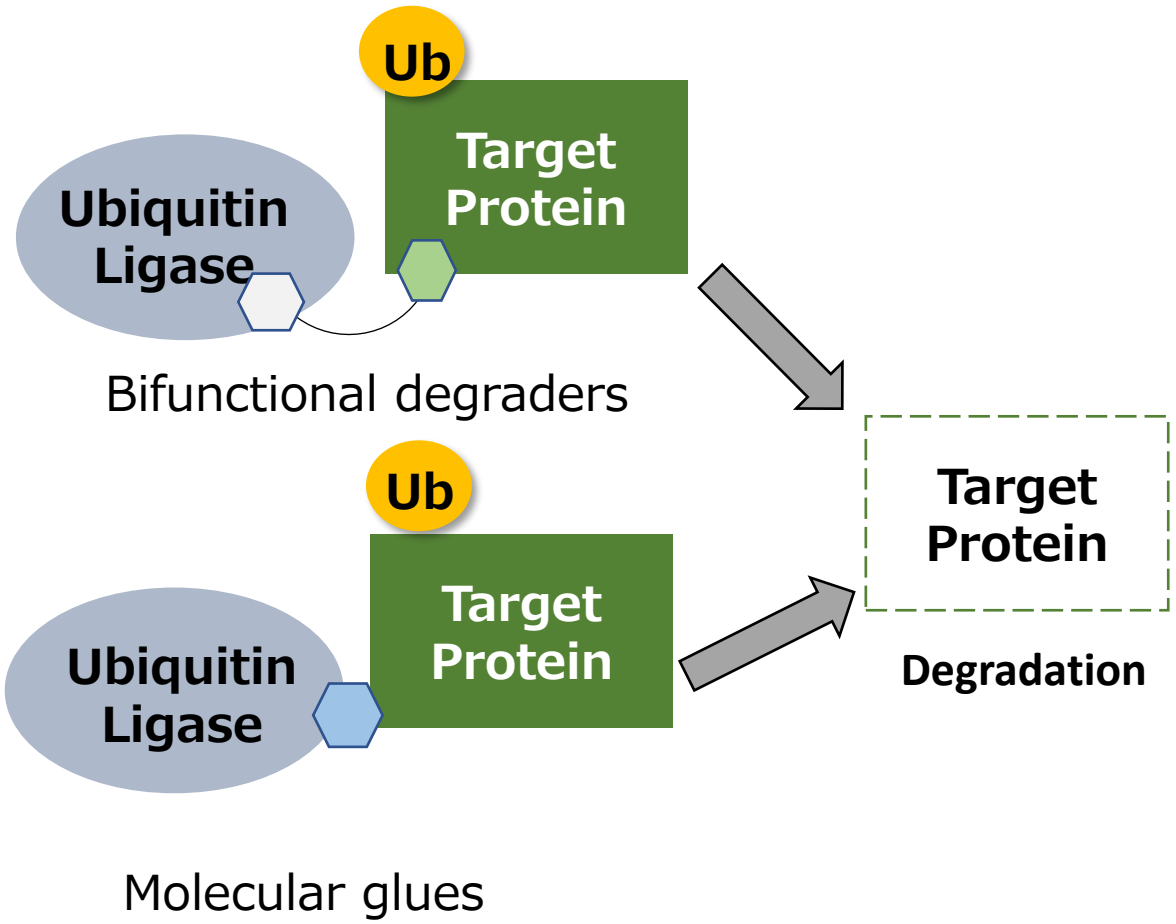
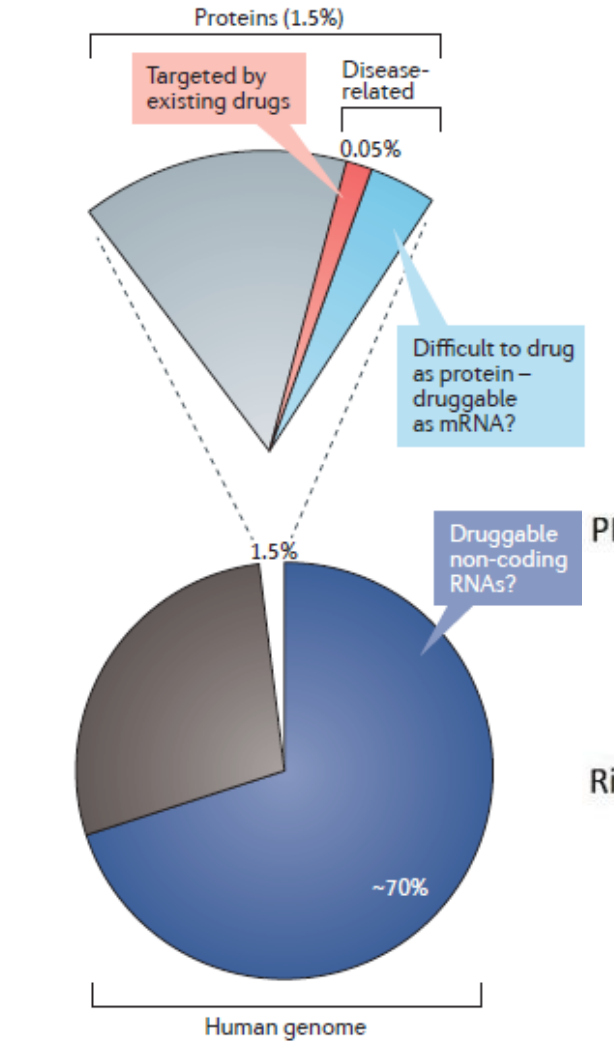
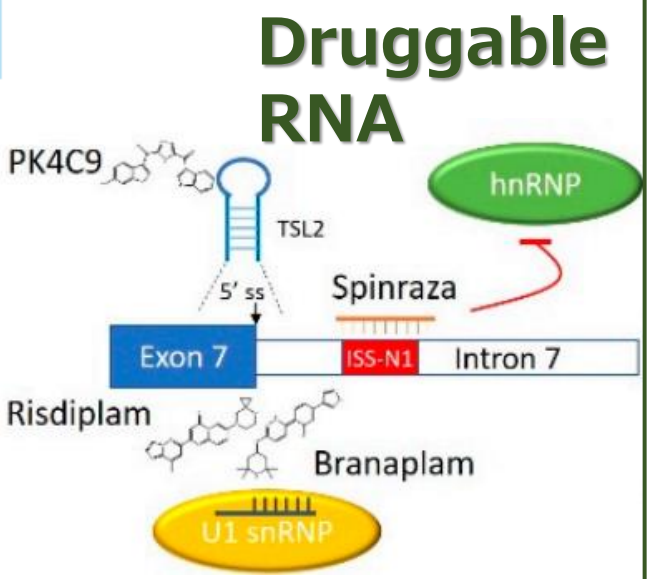
Recent Advances in Drugging Undruggable Targets

Targeted Protein Degradation



RNA targeted drugs





Nature reviews drug discovery 17 547 2018
Int. J. Mol. Sci. 21, 2996, 2020

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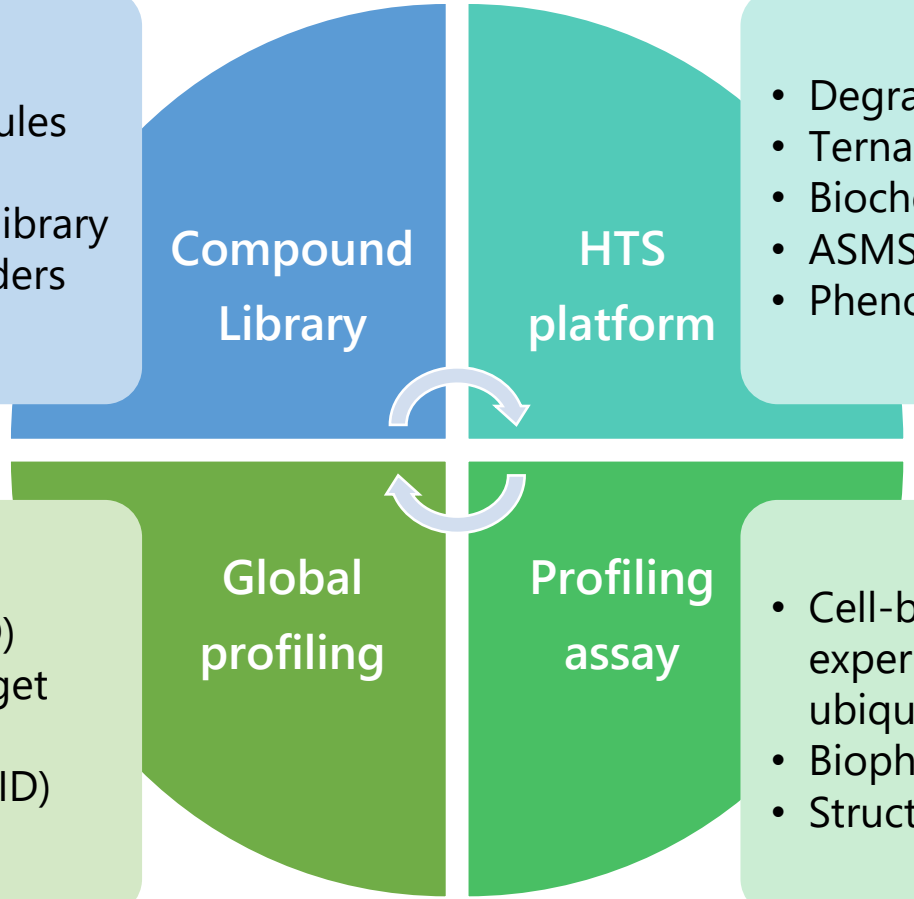
Targeted Protein Degradation Capabilities

Molecular Glue Library
- Targeting 27 TPD related molecules
- Reported compounds and their similar compounds from ADDP library
- Internally identified original binders for CRBN and three other E3



- Degradation assay (HiBit, ICC)
- Ternary complex formation assay
- Biochemical ubiquitination assay
- ASMS binder screening
- Phenotypic screening

- Proteomics (degradation target ID)
- Proximity labeling (interaction target ID)
- CRISPR screening (responsible E3 ID)

- Cell-based profiling by co-treatment experiments, degradation kinetics, IP, ubiquitination etc.
- Biophysics (SPR, ASMS, ITC)
- Structure biology (Xray-crystallography)

➢ Track record – **16** targeted protein degradation related HTS projects including internal Lead Generation program

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AXCELEAD Drug Discovery Partners

Discovery of Protein Degradation Inducers

HTS cascade

Primary screening (100,000 cpds)
Cell based assay
using Target X-Hibit knock-in cells

⇩

Reproducibility test
- **Reproducibility and counter assays**

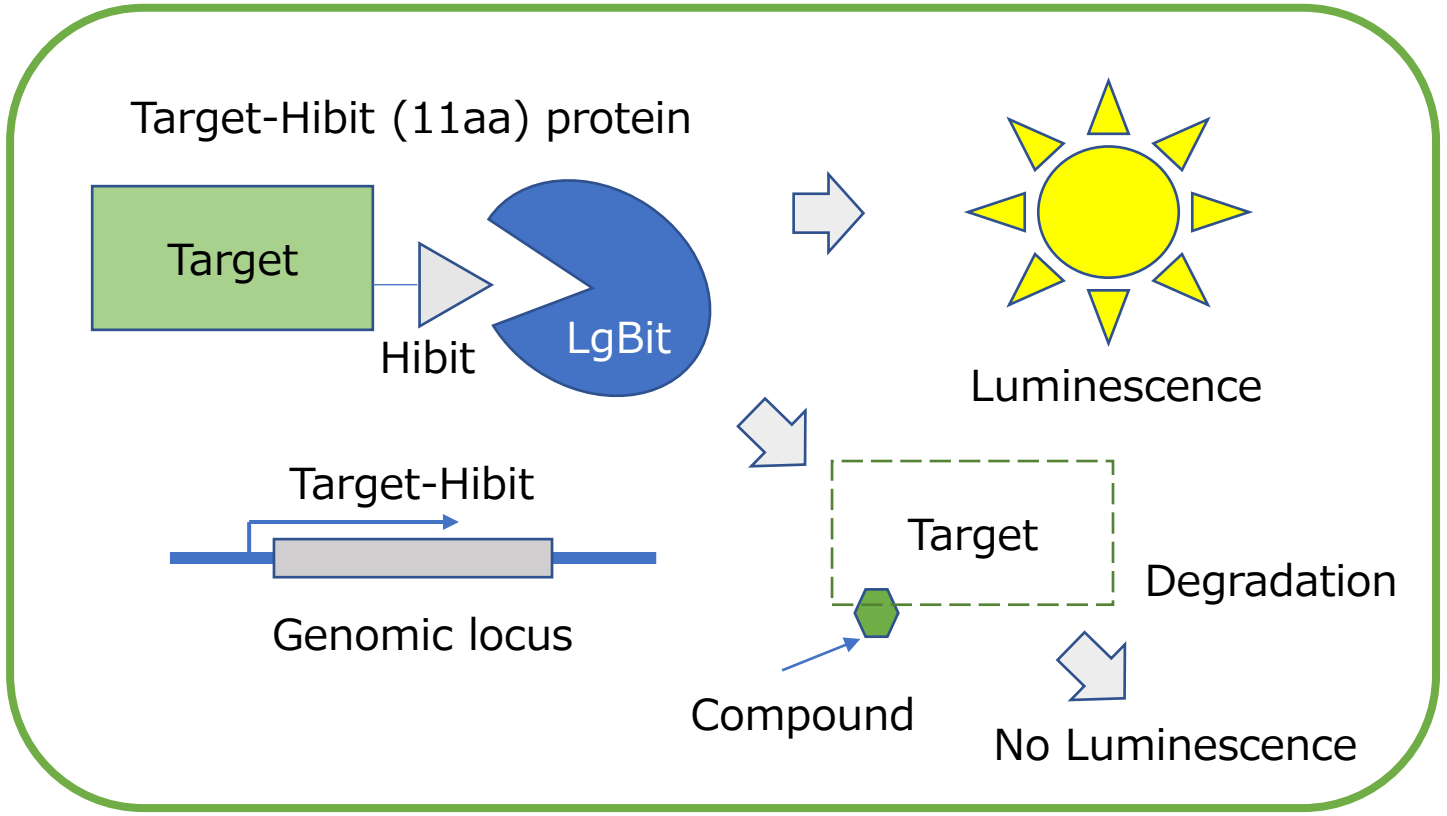
⇩

Dose response test
- **EC50 determination**
- **Selectivity test**
- **Cell toxicity test**
- **Purity check**
- **Clustering**

⇩

Hit compounds

HiBit system (Promega)



- **Detection of endogenous expression of targets**
- **Homogenous assay (High throughput)**
- **Luminescence based assay (Robustness)**

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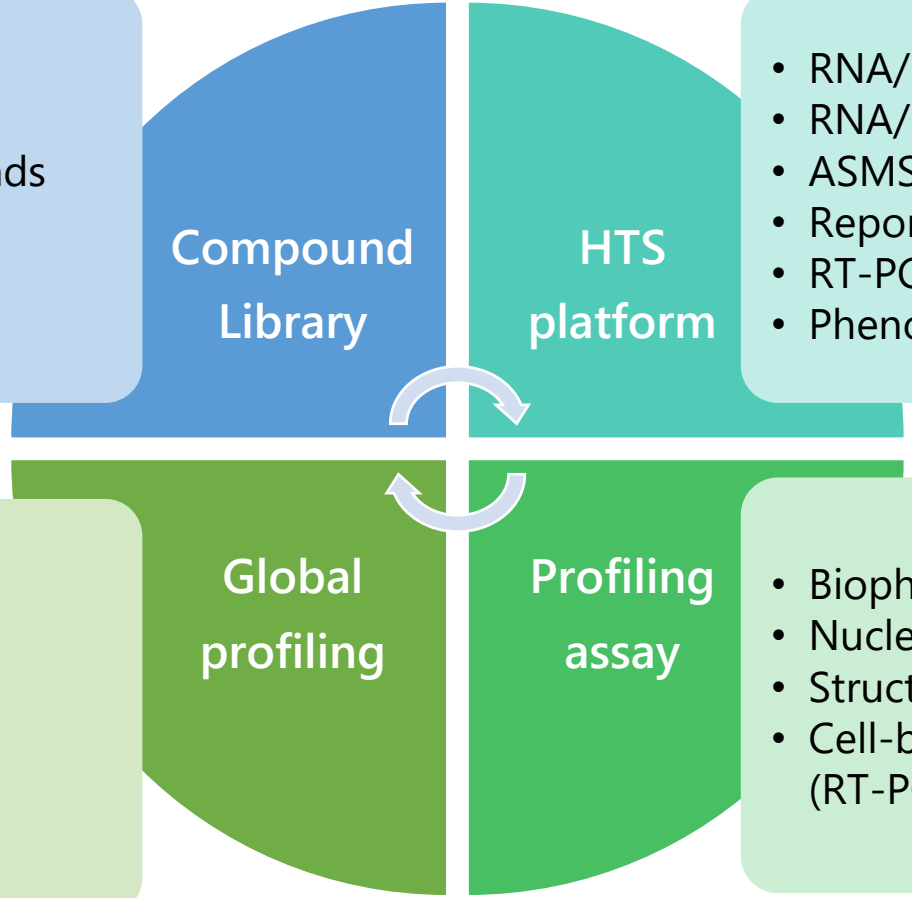
RNA Targeted Drugs Capabilities

Focused Library
- General RNA targeted compounds
- RNA splicing
- Virtual screen



- RNA/RNABP binding assay
- RNA/Fluorescence probe binding assay
- ASMS binder screening
- Reporter gene assay
- RT-PCR
- Phenotypic screening

- NGS (Expression, Splicing)
- Proteomics

- Biophysics （AS-MS, ITC, SPR）
- Nucleic acid binding
- Structure biology (Xray-crystallography)
- Cell-based assays
  (RT-PCR / Reporter gene / FISH etc.)

- Track record-15 RNA targeted drugs related HTS projects including internal Lead Generation program
- One Joint research with xFOREST and Kyowa Kirin is ongoing

xFOREST Therapeutics

KYOWA KIRIN

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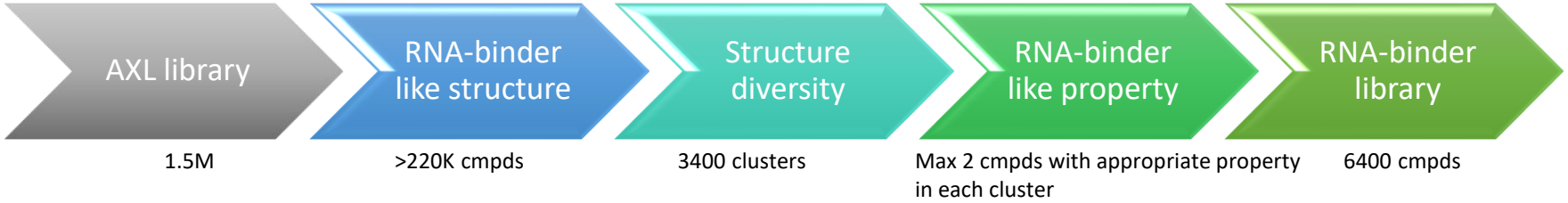
AXCELEAD Drug Discovery Partners

RNA focused Small Molecule Libraries

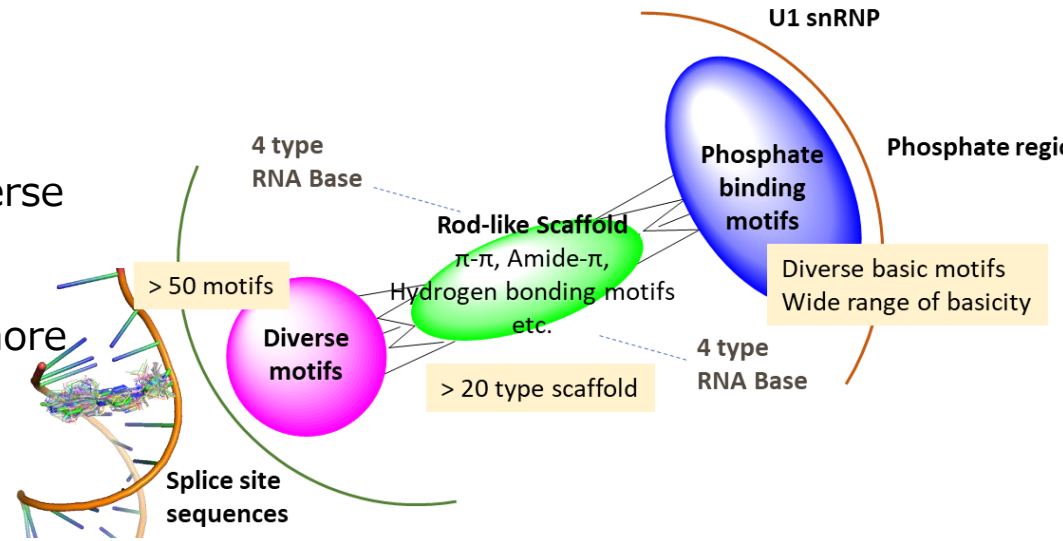
1. General RNA focused library

- **6,400** compounds selected from ADDP-1.5M library
- This library was selected by our multiple analysis of RNA-binders and RNA-cocrystal structure information, followed by prioritization of favorable physicochemical properties for RNA-binder and drug discovery
- We have some track records of hit compound discovery and higher hit ratio than other libraries



2. RNA splicing focused library

- Originally designed and synthesized **1,700** compounds
- The design concept is based on interaction patterns between diverse splice sites and snRNP
- All compounds designed by expertized medicinal chemists have high drug-likeness and diversity with splicing modulator pharmacophore
- This chemical space is rarely filled by commercially available compounds
- We have impressive track records of selective hit compound discovery and extremely high hit ratio for several targets



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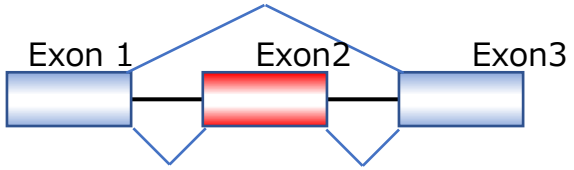
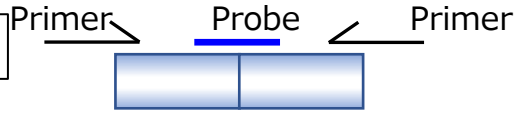
AXCELEAD Drug Discovery Partners

In-house study for splicing focused compound library

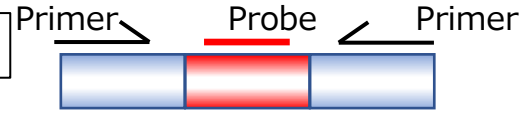
RNA splicing



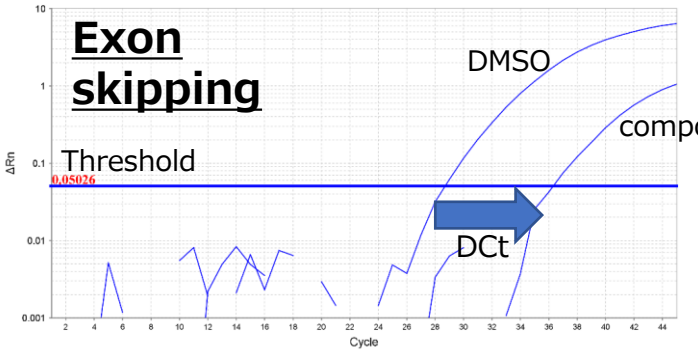
Exon skipping

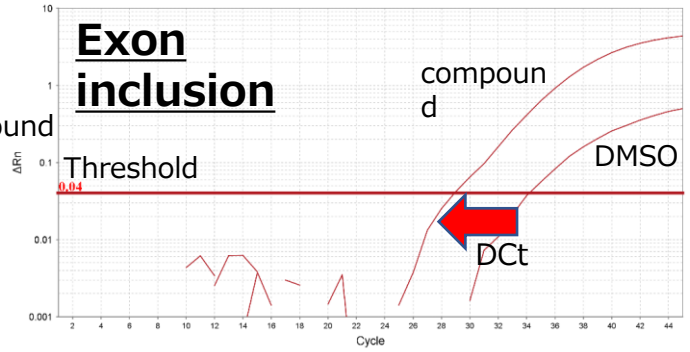


Exon inclusion



e.g.) RNA-focused library compound which increases Exon-inclusion RNA and decreases exon-skipping RNA (Gene A)





High hit rate

		Splicing focused library chemotypes													Hit rate
	5' splice site	A	B	C	D	E	F	G	H	I	J	K	L	M	
SMN2	GGA														15 / 80 (18.75%)
Gene A	AGA														9 / 80 (11.75%)
Gene B	TCA														10 / 80 (12.5%)

Selective hit compounds

|ΔCt|	> 3	3 ～ 1	1 >

Hit compound : |ΔCt| > 3

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AXCELEAD Drug Discovery Partners

Discovery of RNA Binders with HT-ASMS

HTS cascade

High-throughput Affinity Selection
Mass Spectrometry for FMN riboswitch RNA binders

Diversity Library: 140,633 cpds
General RNA focused Library: 6,400 cpds

FMN riboswitch RNA 5 μM
Compound conc.: each 0.5 μM

⇩

Reproducibility test

⇩

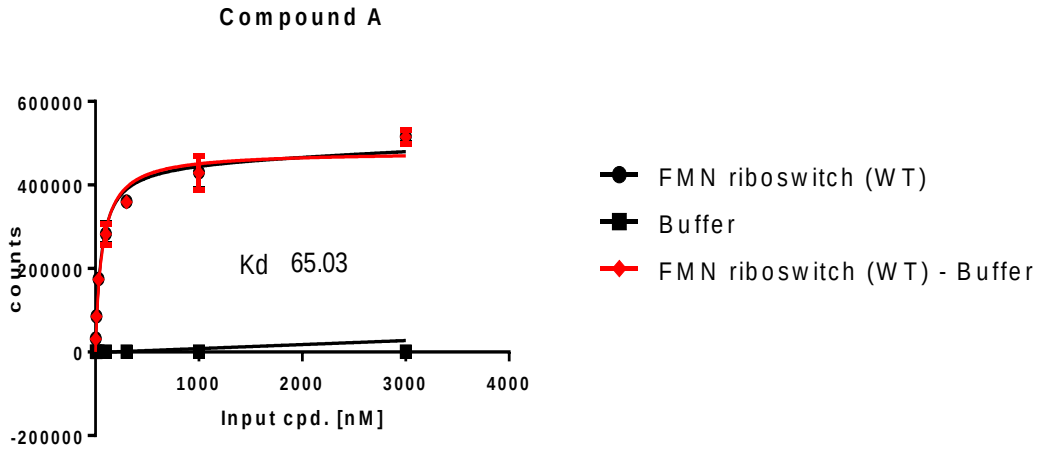
Counter Screen using scramble RNA

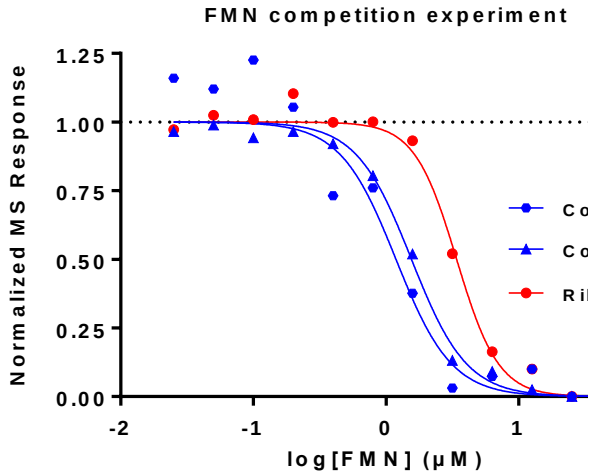
⇩

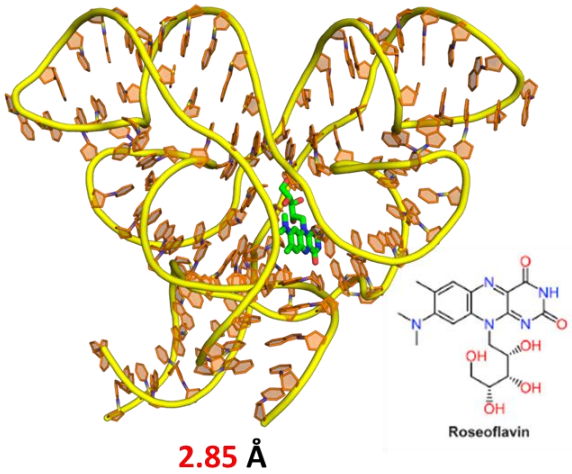
Confirmation assay
Diversity Library : 72 hits
RNA focused Library : 7 hits

⇩

Kd determination







In house data

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AXCELEAD Drug Discovery Partners

Post HTS Service

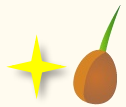
➢ **We strongly propose our Post HTS and Lead generation services to accelerate your drug discovery**

Target ID & Validation → Hit Identification → Hit Expansion (Post HTS) → Lead Generation → Lead Optimization → IND enabling study

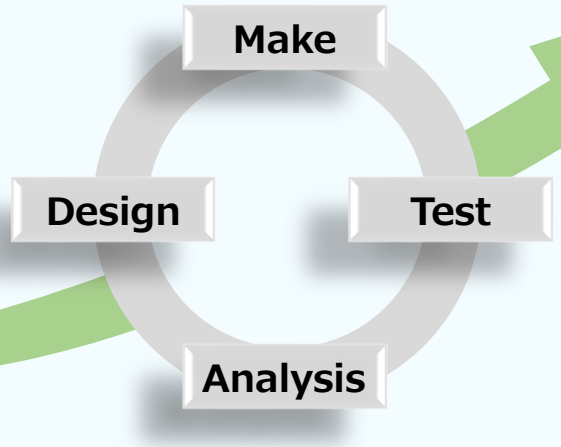
HTS

Screened from high-quality compound library

- Physicochemical property
- Number of related compounds in ADDP library



Quality Hit



DMTA cycle

Advanced Hit

Related Compound Assay Chemical synthesis for initial SAR study

- SAR information (Potency, Selectivity)
- ADME data

Advanced Hit

Extensive information enable smooth transition to LG stage

Accelerate Lead Generation

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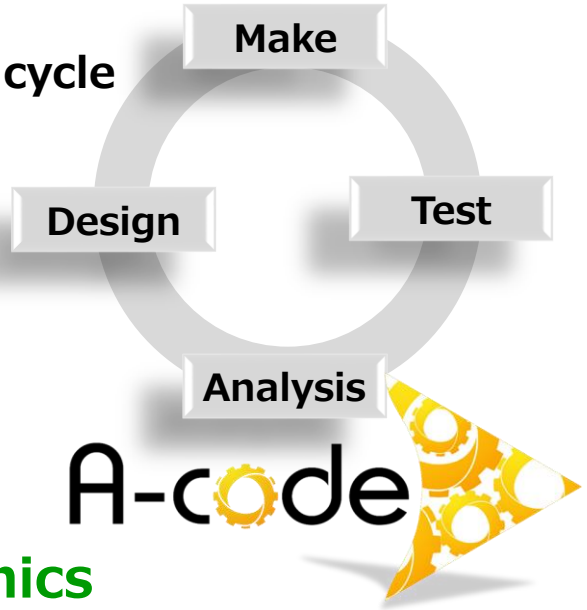
AXCELEAD Drug Discovery Partners

Axcelead high performance COmputing systems for Drug dEsign

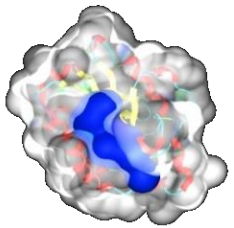
Hit Identification → Hit Expansion (Post HTS) → Lead Generation → Lead Optimization

DMTA cycle

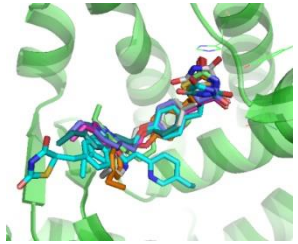


Pocket

Feasibility, Ligandability

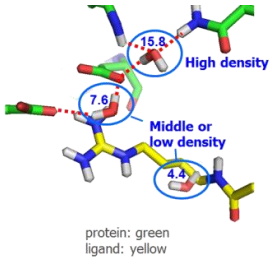


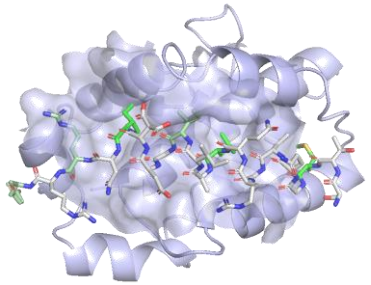
Docking model



Dynamics

MD simulation

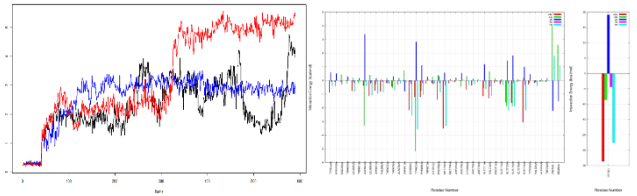




MMPBSA

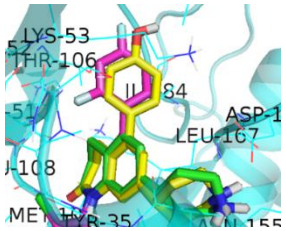
Prediction of IC50/EC50

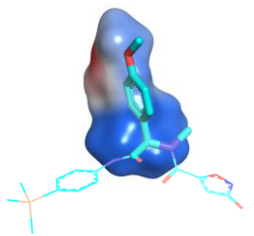
Molecular dynamics calculation

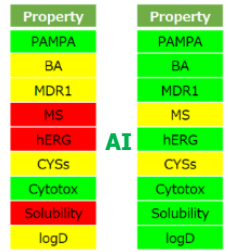


AutoDesign
Hopping
e-ADME

Multiple drug design tools

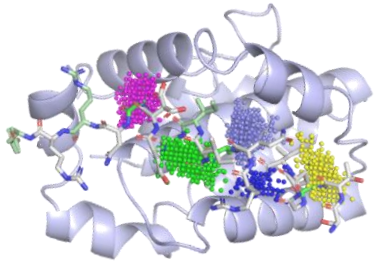






LigMap

Hot spot discovery



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AXCELEAD Drug Discovery Partners

Integrated HTS Platform

1. Attractive library

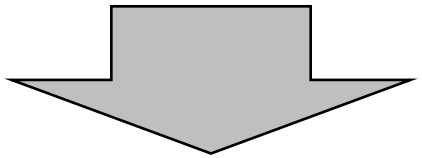
- Pharma origin, huge, high-quality and diverse library

2. State-of-the-art infrastructure

- Fully automated screening systems
- Comprehensive platforms covering diverse target classes and phenotypic screens

3. High quality and comprehensive services

- A proven track record of around 700 HTS campaigns for drug discovery
- Comprehensive services in hit identification including strategy planning, assay development, HTS and profiling
- Hit expansion and lead generation services by highly experienced medicinal chemists
- High-throughput-ADMET profiling services with extensive experience and sophisticated protocols



➢ ***We efficiently offer high-quality hit and lead compounds through our integrated HTS platform***

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Together
We can Create a Hopeful Future through Drug Discovery

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