

# **Initiatives in Drug Discovery Research**

***Reshape research framework, aim for further innovation***

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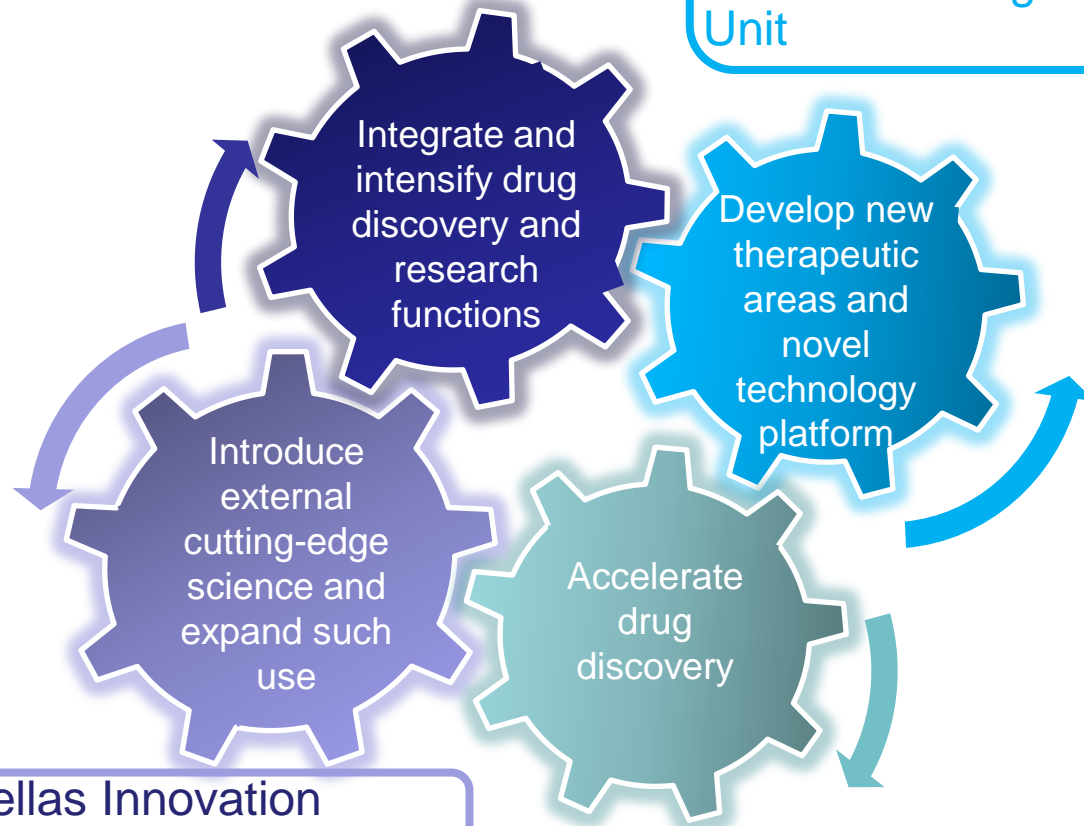
Actual financial results may differ materially depending on a number of factors including adverse economic conditions, currency exchange rate fluctuations, adverse legislative and regulatory developments, delays in new product launch, pricing and product initiatives of competitors, the inability of the company to market existing and new products effectively, interruptions in production, infringements of the company's intellectual property rights and the adverse outcome of material litigation.

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# Reshape Research Framework

- Reorganize Drug Discovery Research functions
- Develop *Network Research System*

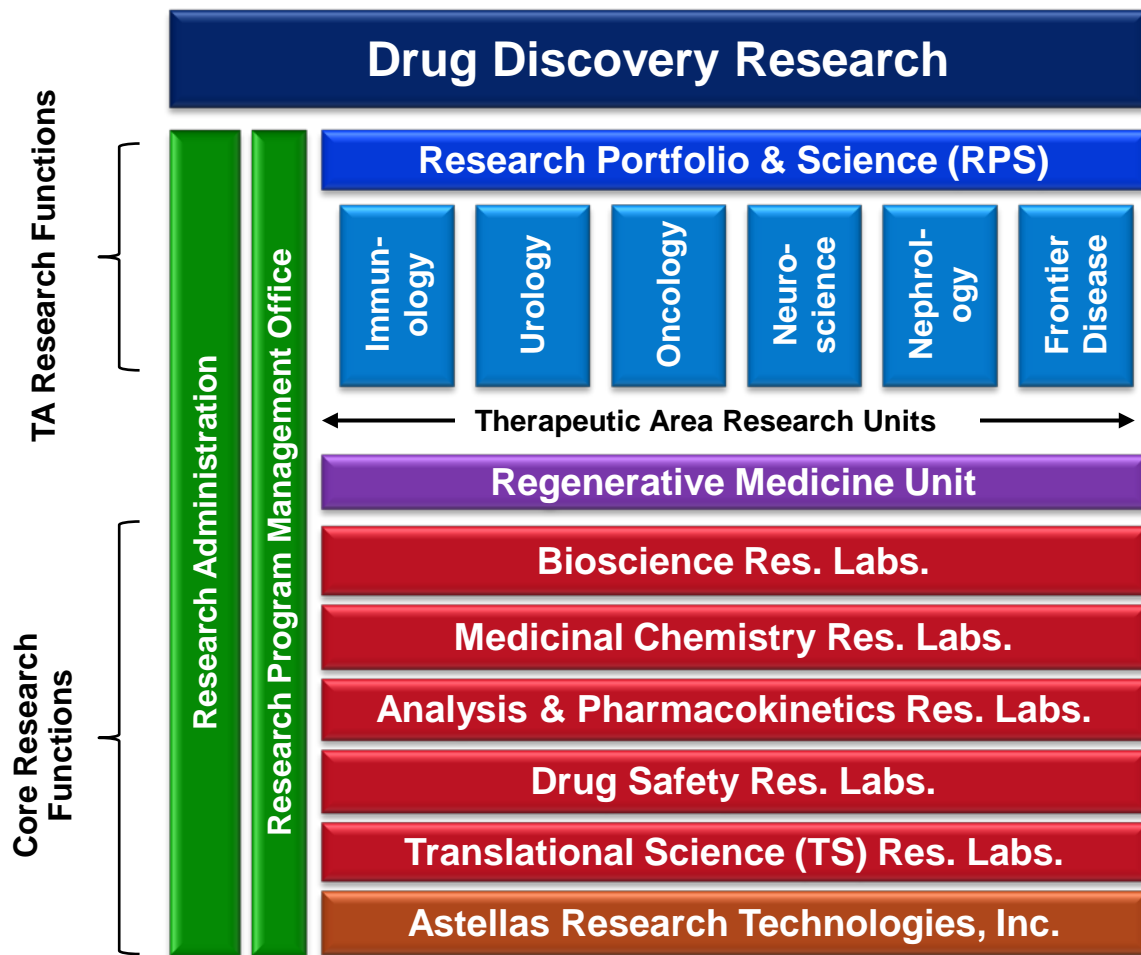
- Cooperate with various partners
- Expand activities of Frontier Disease Research
- Establish Regenerative Medicine Unit



- Establish Astellas Innovation Management

- Enhance research management
- Introduce multiple R&D pathways

# Restructure Organization



**RPS** possesses two important functions of managing research portfolio and fostering/capturing innovation. The latter is carried out in close coordination with Astellas Innovation Management..

Pharmacology Research Labs. was dissolved and restructured into **TA Research Units** which have enhanced autonomy and accountability








Translational Science-related scientific and managerial capabilities are integrated to form the new **TS Research Labs.**

TA: Therapeutic Area



# **Develop New Therapeutic Areas and Novel Technology Platform**

# Develop New Therapeutic Areas and Novel Technology Platform

Apply recombinant human proteins produced by transgenic silkworms to medicine	<ul style="list-style-type: none"> <li>• Collaboration for research with Immuno-Biological Laboratories</li> </ul> 
Advance novel therapies for diseases and medical conditions associated with muscle weakness	<ul style="list-style-type: none"> <li>• Collaboration for R&amp;D and commercialization with Cytokinetics</li> </ul> 
Discover and develop novel drugs that improve mitochondrial functions	<ul style="list-style-type: none"> <li>• Collaboration for R&amp;D with Mitokyne (with exclusive right to acquire the company)</li> </ul> 
Expand our commitment to regenerative medicine	<ul style="list-style-type: none"> <li>• Establishment of Regenerative Medicine Unit</li> </ul>
Develop RSV (Respiratory syncytial virus) vaccine	<ul style="list-style-type: none"> <li>• Strategic partnership with ClearPath, investing in development of vaccine</li> </ul> 
Discover and develop novel antibody-drug-conjugates (“ADCs”) in oncology field	<ul style="list-style-type: none"> <li>• Collaboration for next generation ADC with Ambrx</li> </ul> 
Seek more chance of innovation by diversifying compound sources	<ul style="list-style-type: none"> <li>• Compound library sharing partnership with Daiichi Sankyo (400 thousand compounds each other)</li> </ul> 
Collaborate with academia beyond individual corporate frameworks for discovery of novel CNS drugs	<ul style="list-style-type: none"> <li>• Participation in LIBD consortium</li> </ul> 



# Develop New Therapeutic Areas: Collaboration with Cytokinetics

**Conduct research/development collaborations with an aim to create new innovative drugs in the field of skeletal muscle diseases.**

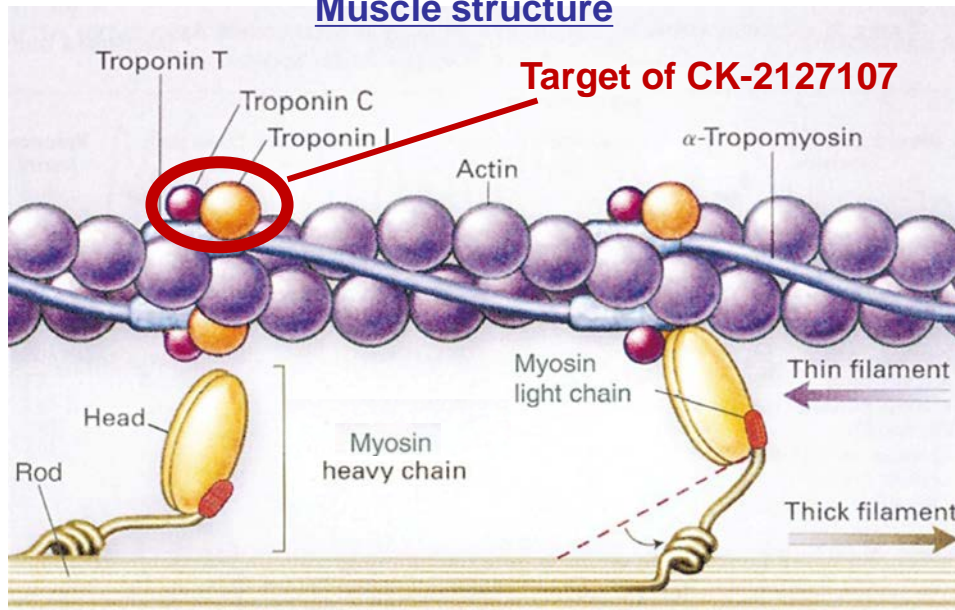
Skeletal muscle plays a role in various organs and sites in the body. Deterioration of its functions causes various diseases and symptoms.

⇒ Aim for the development of skeletal muscle activators that will improve these symptoms.

[Progress]

- Fast skeletal muscle troponin activator CK-2127107  
Phase I study showed dose-dependent pharmacokinetics and high tolerability
- Joint research of follow-up compounds is also progressing smoothly

## Muscle structure



Actin (filament) and  
regulatory complex

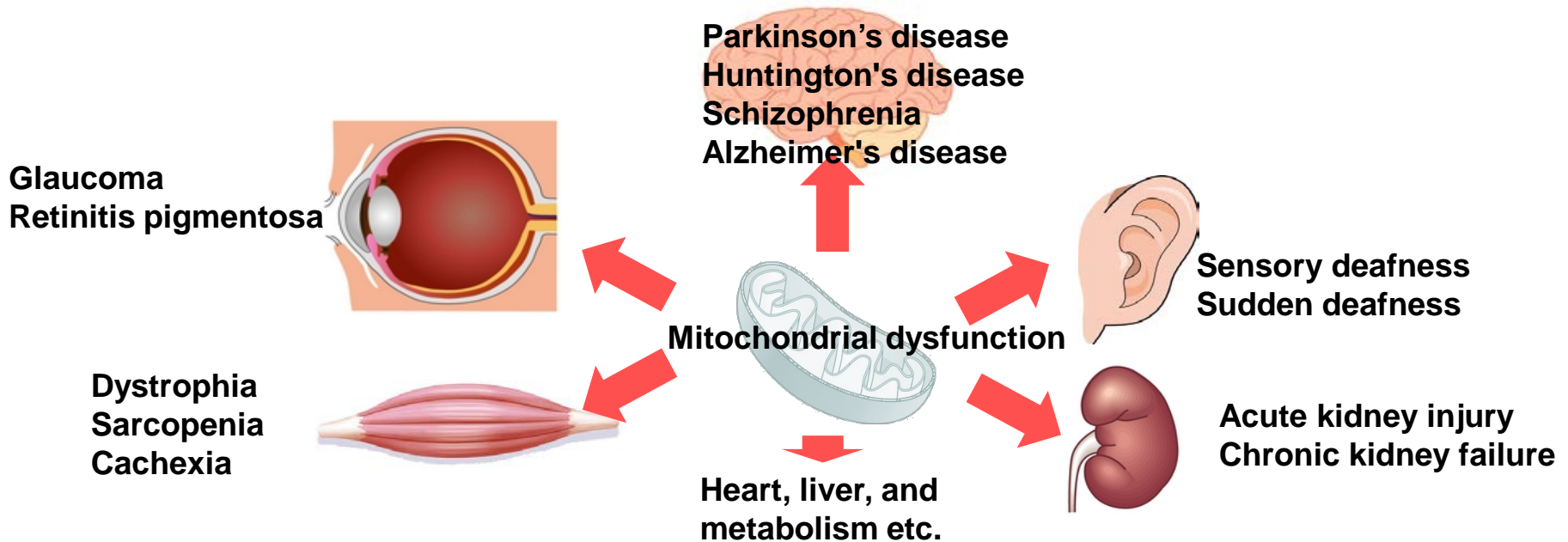
Myosin

Adapted from  
KAMISAGO et al.,  
*New England Journal of Medicine*;  
Volume 343 Number 23 : 1695

# Develop New Therapeutic Areas: Collaboration with Mitokyne

**Conduct research/development collaborations with an aim to create innovative new drugs and establish the leading position in the mitochondria-related diseases field**

**Mitochondrial dysfunction may cause various diseases**



## **Mitokyne Profile:**

- Mitokyne has completed set up and has initiated research activities.
- Its scientific advisors include a Nobel prize laureate Dr. Horvitz.
- Nature Biotechnology selected the company as one of the Innovative startups 2013





# Develop Novel Technology Platform: Initiative for Regenerative Medicine

**Regenerative Medicine Unit established in April 2014**

## ■ Mission

In the field of regenerative medicine and **cell therapy**,

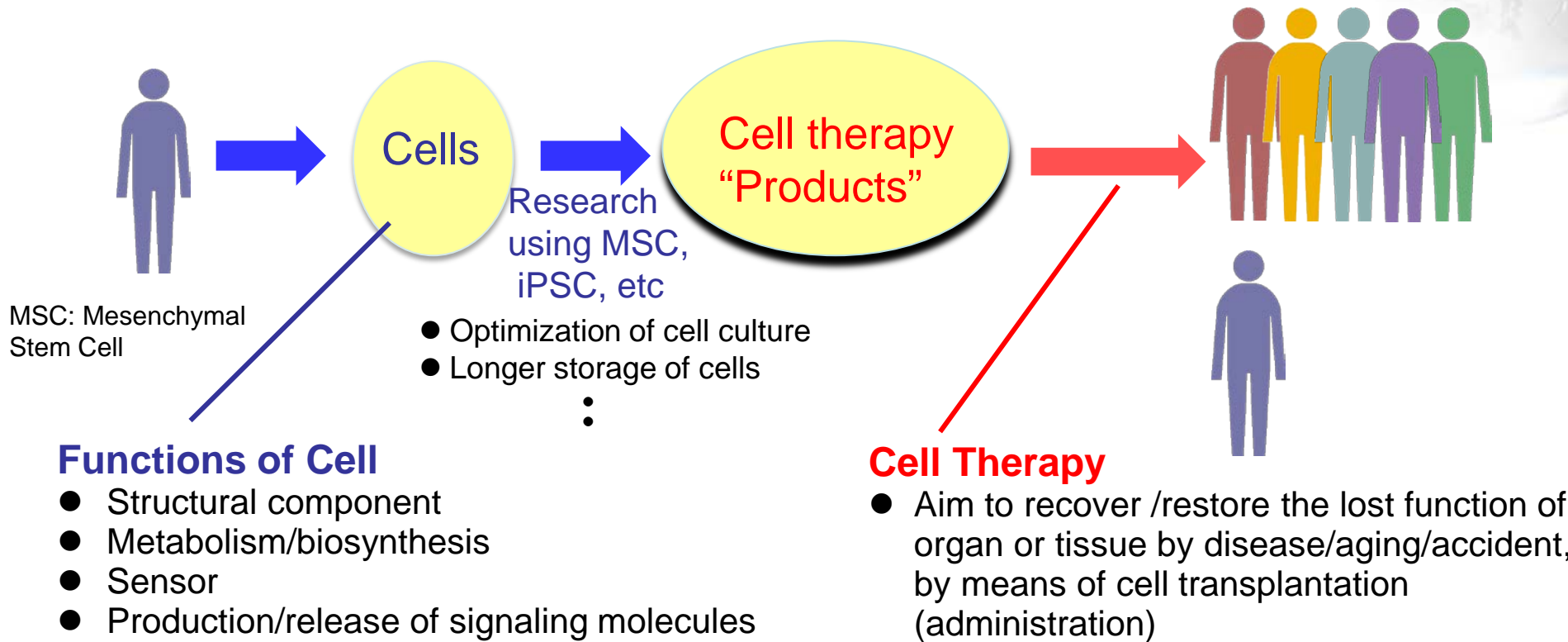
- ✓ Generate product candidates with competitive superiority
- ✓ Establish and maintain technology platform
- ✓ Bear the hub function as the core research unit in Astellas

## ■ Organization/management structure

- ✓ Direct reporting to Head of Drug Discovery Research
- ✓ Start with core research members of approximately 20
- ✓ Plan to expand along with the progress of the research

# Concept of Cell Therapy and Target of Astellas

<Expecting its multifunctionality that small compounds or biologics cannot display>



## Cell therapy Astellas targets

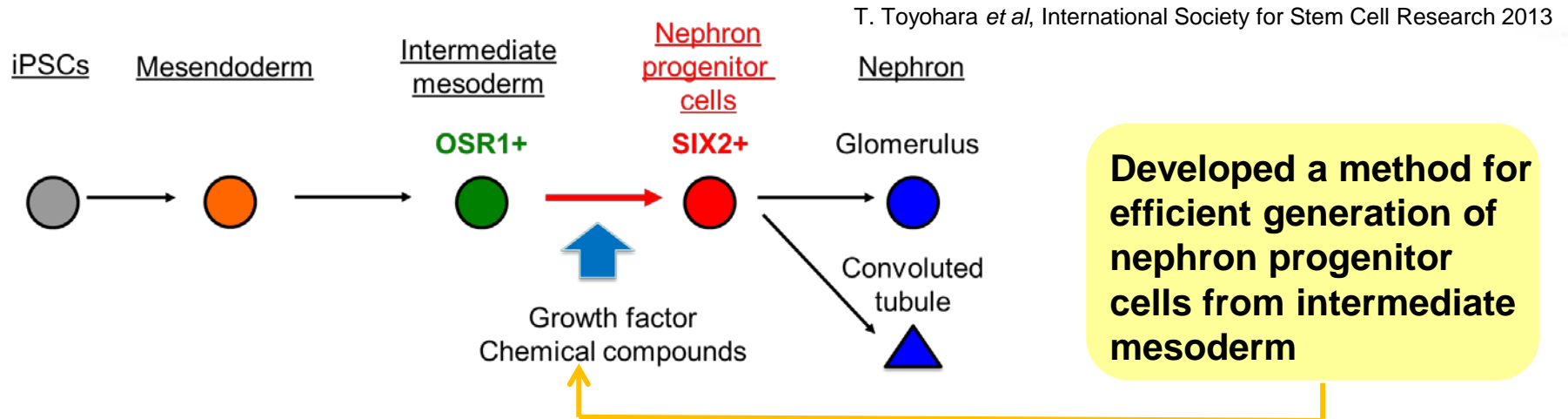
- Target indications:** Those with high unmet medical need such as cardiovascular diseases & cancer
- Short-Mid term goal:** Recovery of function by paracrine effects of transplanted cells  
**initiate a clinical study in a few years at the earliest.**
- Long term goal:** Recovery of function by transplanted cells themselves

# Result of Research in Regenerative Medicine:

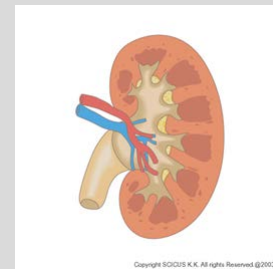
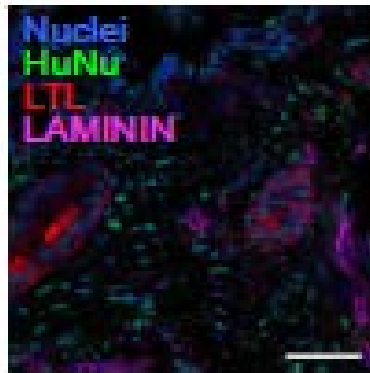
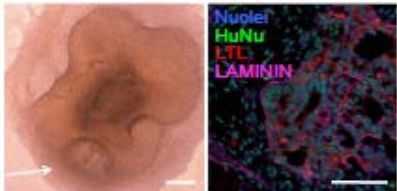
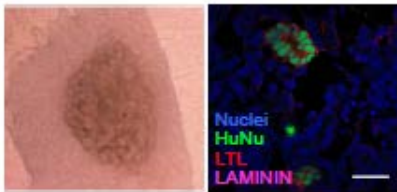
## Research Collaboration with CiRA, Kyoto Univ. for Kidney Regeneration

CiRA: Center for iPS Cell Research and Application

**Efficient generation of nephron progenitor cells from iPSC**  
**Progress for drug evaluation, disease model generation and cell therapy**



*In vitro* 3-D culture(Left) *in vivo* (Right)  
renal tubule specific protein was expressed and  
renal tubule-like structure was formed



### Nephron

Nephron is the functional unit of kidney, which has glomerulus and renal tubules. There are about 1 million nephrons in a kidney.

# Develop Novel Technology Platform: Strategic partnership with ClearPath for Vaccine

Develop vaccine business through creative business scheme



RSV  
Corporation

Develop **vaccine**  
**for RSV**



Manage/Operate

In-license

- Up-front payment
- Milestone payments
- Royalty

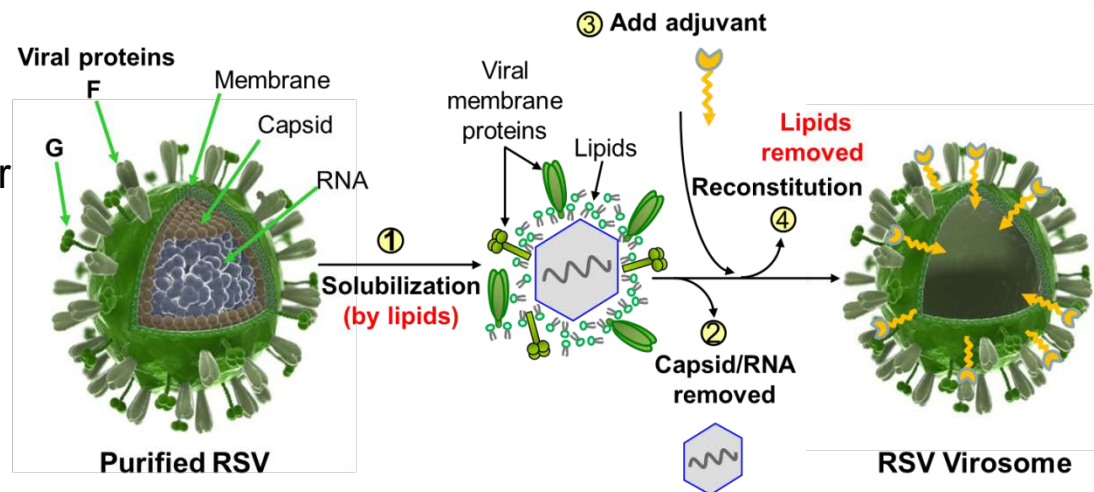
Robust  
experience of  
vaccine clinical  
development



**MYMETICS**  
Cutting-edge  
virosome  
vaccine  
technology

## Virosome: Membrane nanoparticle containing natural surface proteins without genetic material

- Powerful immune responses similar to a normal virus infection due to similar structure to natural RSV
- Enhancement of immune responses by the incorporation of an adjuvant
- No risk of infection due to lack of genetic material



# Develop Novel Technology Platform: Ambrx Next-Generation ADC (“Antibody-Drug Conjugate”)

**Introduce new ADC technology with increased blood stability**

## Conventional ADC

Conjugate drug on natural amino acid residues of antibody

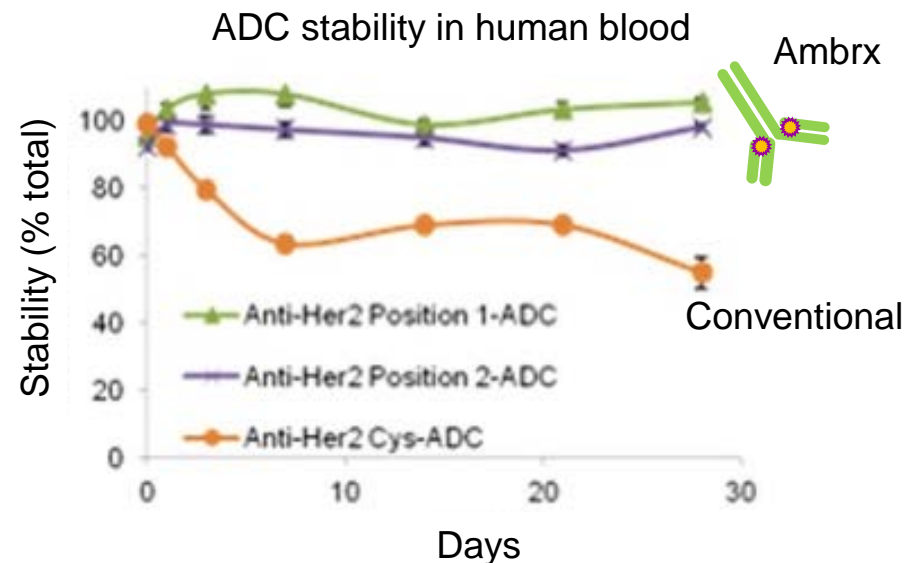
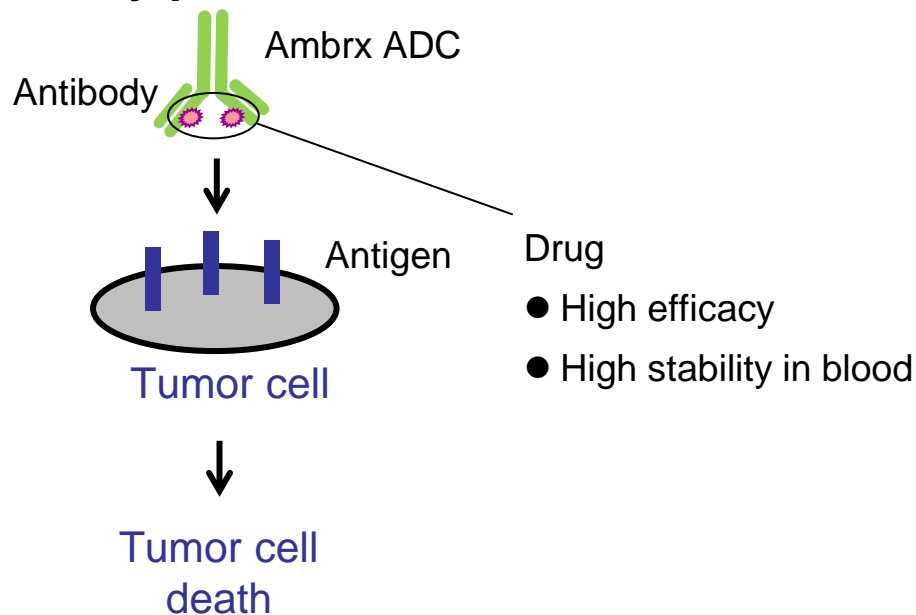
- Non-specific conjugation

## Ambrx ADC

Incorporate non-natural amino acids into antibody and conjugate drug to the sites

- Site specific ADC → high efficacy
- High stability in blood → low side effects

**Ambrx ADC is expected to be an anti-cancer drug with more efficacy and better safety profile**



Jackson D. *et. al.*, *PLoS One*. 2014;  
(reported by Agensys and Ambrx)

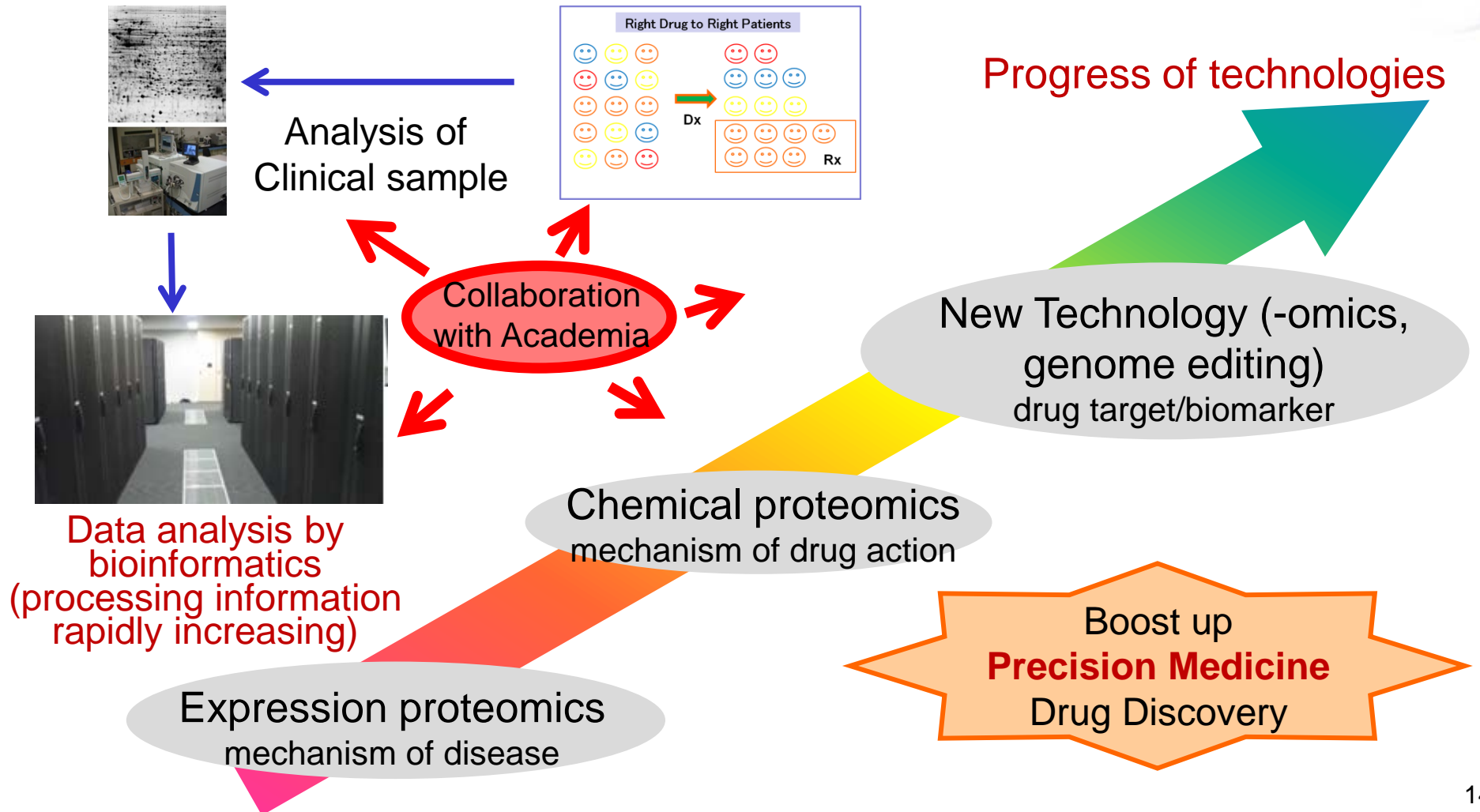




# **Initiatives in Technology Platform and Focus Therapeutic Areas**

# Initiatives in Technology Platform: Precision Medicine/ Omics

Using cutting-edge Omics technologies, gain insight of diseases and actively search for drug targets/biomarkers



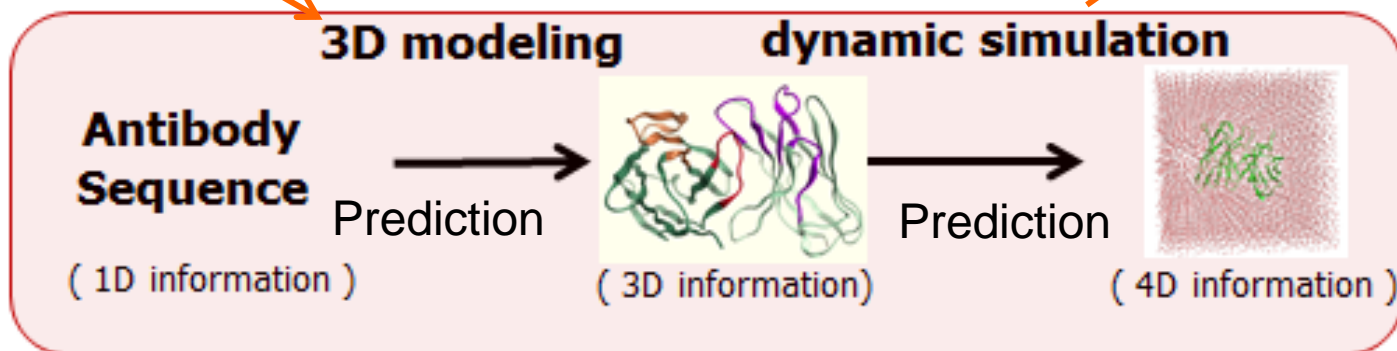
# Initiatives in Technology Platform: Antibody Drug Discovery and Structure Prediction

**Using cutting-edge IT technologies, increase accuracy  
of antibody structure prediction  
Promote creation of next generation antibodies**

Benefits from IT revolution  
and Big Data

Next generation antibody drug  
discovery

Development of antibody informatics



**IBC's 24th Antibody Engineering  
and Therapeutics**

**International competition of antibody  
structure prediction  
(The second competition in December 2013)**

- A team of Osaka University, National Institute of Biomedical Innovation, and Astellas predicted most correctly.

# Achievement in Oncology Research:

## ASP2215 (Novel FLT3/AXL Inhibitor)

**ASP2215, a FLT3/AXL inhibitor, showed potent antileukemic activity against AML with either or both FLT3-ITD and FLT3-D835 mutations.**

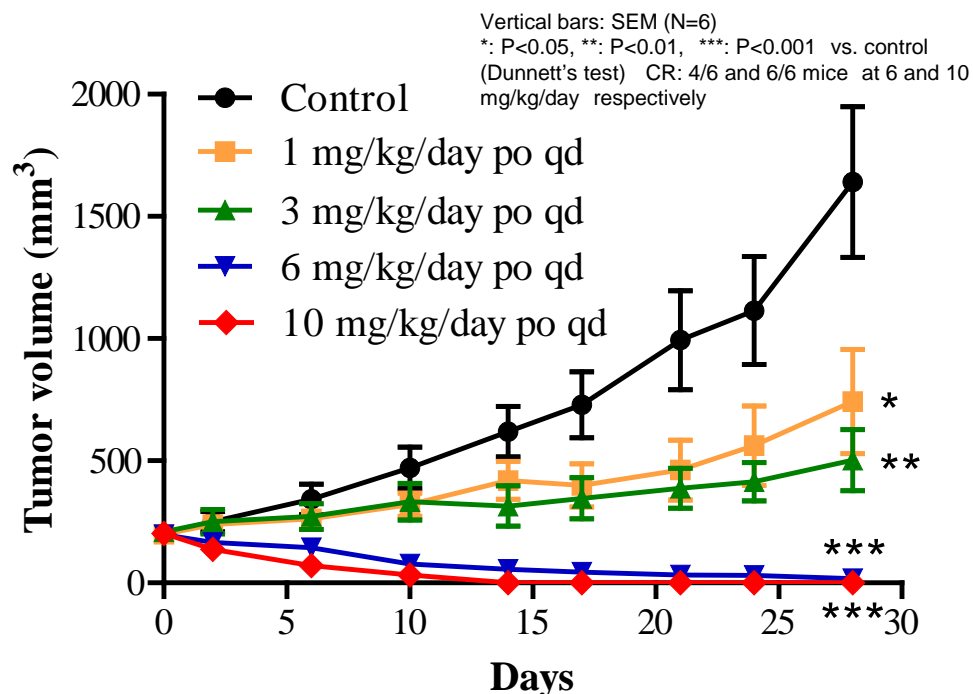
Mori *et al.*, 2014 ASCO Annual Meeting

### Kinase inhibitory profile

Kinase	IC <sub>50</sub> (nmol/L)
FLT3	0.29
LTK	0.25
ALK	0.42
AXL	0.70
TRKA	1.1
RET	1.8
ROS	1.5
MER	2.9
c-KIT	230

ASP2215 is a potent FLT3/AXL inhibitor.

### Antitumor activity of ASP2215 in mice xenografted with MV4-11 cells



ASP2215 induced complete remission in mice FLT3-ITD xenograft model at doses of 6 mg/kg and above.

# Achievement in Oncology Research: ASP8273 (Novel Mutant-Selective Irreversible EGFR Inhibitor)

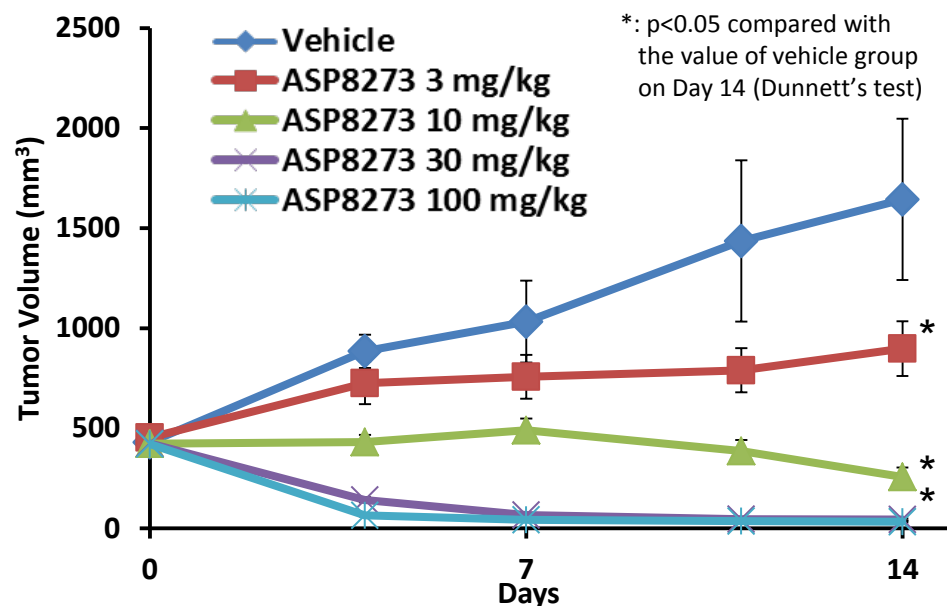
**ASP8273 showed antitumor activity in NSCLC xenograft model with EGFR T790M/L858R and higher affinity to these mutations than wild type.**

## Binding Affinity (KINOMEscan®)

EGFR	Kd (nM)
wild type	140
T790M/L858R	0.22

ASP8273 showed higher affinity to EGFR T790M/L858R than wild type EGFR.

## Tumor Regression



ASP8273 induced tumor regression in NSCLC xenograft model with T790M/L858R at doses of 10 mg/kg and above.



# Summary

## Reshape research framework, aim for further innovation

- More utilizing external resources with *Network Research System*
- Develop new therapeutic areas and novel technology platform
- Continue enhancing current technology platform and focus therapeutic areas