

Kyowa Kirin R&D Meeting

December 5, 2022

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These uncertain factors include, but are not limited to, potential risks of the business activities in the pharmaceutical industry in Japan and overseas, intellectual property risks, risk of side effects, regulatory risks, product defect risks, risks of changes to the prices for raw materials, risks of changes to market prices, as well as risks of changes to foreign exchange rates and financial markets.

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Vision

Our New Vision toward 2030

Kyowa Kirin will realize the successful creation and delivery of life-changing value that ultimately makes people smile, as a Japan-based Global Specialty Pharmaceutical company built on the diverse team of experts with shared passion for innovation.

Provide pharmaceuticals for unmet medical needs

We are focused on developing medicines for diseases where there is a clear patient need for new options. We make full use of multiple therapeutic modalities, including biotechnology such as antibody technology, and beyond, building on our Kyowa Kirin established strengths.

Address patient-centric healthcare needs

We will meet the needs of patients and society by providing value across the entire patient care pathway, delivering cutting-edge science and technology, grounded in our in-depth pharmaceutical knowledge and expertise.

Retain the trust of society

We pursue world-class product quality and operational excellence to grow our business in ways which build long-term trust with our stakeholders.



Research & Development Concept

Technology x Biology x OI

The Kyowa Kirin Group is aiming to build a competitive technology platform by enhancing and combining its drug discovery technologies and its drug discovery modalities. By matching that technology platform with disease-oriented science and by harnessing open innovation with partners that have specific strengths, we aim to develop completely new technologies or select efficient drug discovery targets to create life-changing value.

Technology

We will continue to evolve our antibody technology, while also pursuing the possibilities of other modalities and building a platform that leads to innovative new therapies.

Disease Biology

Continue to provide “Only-one value drug” for UMN, while utilizing the disease science* cultivated to date within KKC

* Nephrology, Oncology, Immunology & allergy, CNS

Open Innovation (OI)

Continue to work on collaborative research activities* with academia, startups and other partners, combine this with rapid access to start up information gained from investment in VC funds and CVC funds, and tap into external innovation through advanced OI activities

* Reenergize the San Diego research base

Create Life-changing value with clear competitive advantages

Today's Agenda

- **Toward the Creation of Pharmaceuticals for High Unmet Medical Needs**
 - From Our Investigational Products
 - KW-3357 (Preeclampsia)
 - KHK4951 (Tivozanib eye-drop)

- **Toward the Successful Creation and Delivery of Life-changing Value**
 - From Early-stage R&D Activities
 - Data-driven drug discovery - Collaboration with InveniAI
 - Deepening Kyowa Kirin's Antibody Technology - Collaboration with Synaffix
 - The pursuit of innovation with a long-term perspective - VC fund investment/CVC activities

Toward the Creation of Pharmaceuticals for High Unmet Medical Needs - From Our Investigational Products

- KW-3357 (Preeclampsia)
- KHK4951 (Tivozanib eye-drop)

Toward the Creation of Pharmaceuticals for High Unmet Medical Needs - From Our Investigational Products

- KW-3357 (Preeclampsia)
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Preeclampsia (Preeclampsia, PE)

- One of the forms of Hypertensive Disorders of Pregnancy (HDP)
- Poor prognosis for mothers and fetuses
 - Mothers: Brain, lung, liver, kidney, and other organ damage
 - Fetuses: High rate of perinatal mortality, fetal growth restriction, delivery rate of infants weighing less than 2500g, and NICU admission at birth
- Patients: 2.7% of the number of mother in Japan^{*1}, 2-5% globally (8-12% in Africa, etc.)^{*2}
- Causes: Placental dysplasia in early pregnancy, and imbalance of angiogenic and inhibitory factors after midpregnancy
 - Low antithrombin activity at diagnosis in patients with onset of disease before 34 weeks' gestation may be associated with high risk of early pregnancy termination^{*3}
- Standard of Care:
 - Early termination of pregnancy - poor neonatal prognosis and increased risk of complications
 - Antihypertensive drugs - may adversely affect the fetus and placental function
 - No drugs under company-sponsored development have been identified.

*1: Shiozaki A., Comparison of risk factors for gestational hypertension and preeclampsia in Japanese singleton pregnancies. J Obstet Gynaecol Res. 2013;39(2):492-9

*2: <https://www.figo.org/figo-releases-new-guidelines-combat-pre-eclampsia>

*3: Morikawa M. et al., Int J Gynaecol Obstet. 2019 Apr;145(1):62-69.

Serious disease, but effective treatment not yet established

KW-3357 Overview

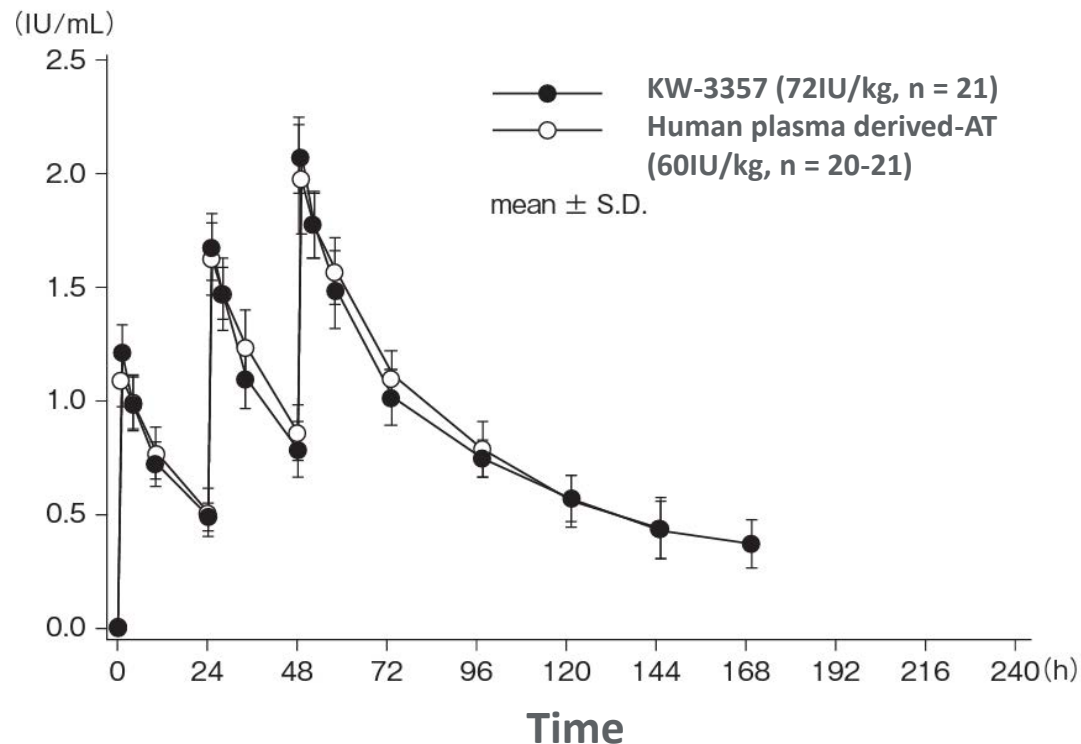
- Generic name: Antithrombin gamma
- Product name (in Japan) : ACOALAN® for Intravenous Injection 600, 1800
- Indication: Congenital antithrombin (AT) deficiency-based thrombogenicity and disseminated intravascular coagulation syndrome
- Ph3 study (KOUNO-TORI) underway for preeclampsia
- Features
 - A recombinant human AT pharmaceutical with an **amino acid sequence identical to that of human plasma-derived AT**
 - **Modification to the same type of glycans as human plasma-derived AT by POTELLIGENT® leads to its persistence comparable to that of human plasma-derived AT***
 - Manufactured with CHO cells, no other biogenic raw materials used = **Low risk of infection + Stable production**
 - Exhibits anti-inflammatory effects by binding to heparan sulfate in vascular endothelium and to molecules on neutrophils = **Potential to improve organ damage** in addition to anticoagulation

* It is known that ATs produced with conventional methods shows low-persistence due to the additions of glycans that are different in type from human plasma-derived AT.

The persistence of KW-3357 is comparable to human plasma-derived AT

* From Interview Form of ACOALAN® for Intravenous Injection 600, 1800
https://www.info.pmda.go.jp/go/pack/6343444D1021_1_09/

Plasma AT activity



Pharmacokinetics Parameter (plasma AT activity)

Dose	C _{max, 3rd} (IU/mL)	AUC _{48-t} ^{a)} (IU·h/mL)	K _{el} ^{b)} (1/h)	t _{1/2} (h)
KW-3357 72IU/kg (n=21)	2.08 ± 0.17	98.71 ± 13.94	0.0101 ± 0.0032	81.82 ± 50.07 ^{b)}
Human plasma- derived AT 60IU/kg (n=20)	1.98 ± 0.23	98.99 ± 19.82	0.0130 ± 0.0038	58.02 ± 18.52 ^{b)}
Ratio(%) ^{c)} 90%CI ^{d)}	105.7 100.3-111.3	100.5 91.5-110.4	75.5 61.3-93.1	132.4 107.5-163.0

a) t = Final Measurement Point

b) n = 18

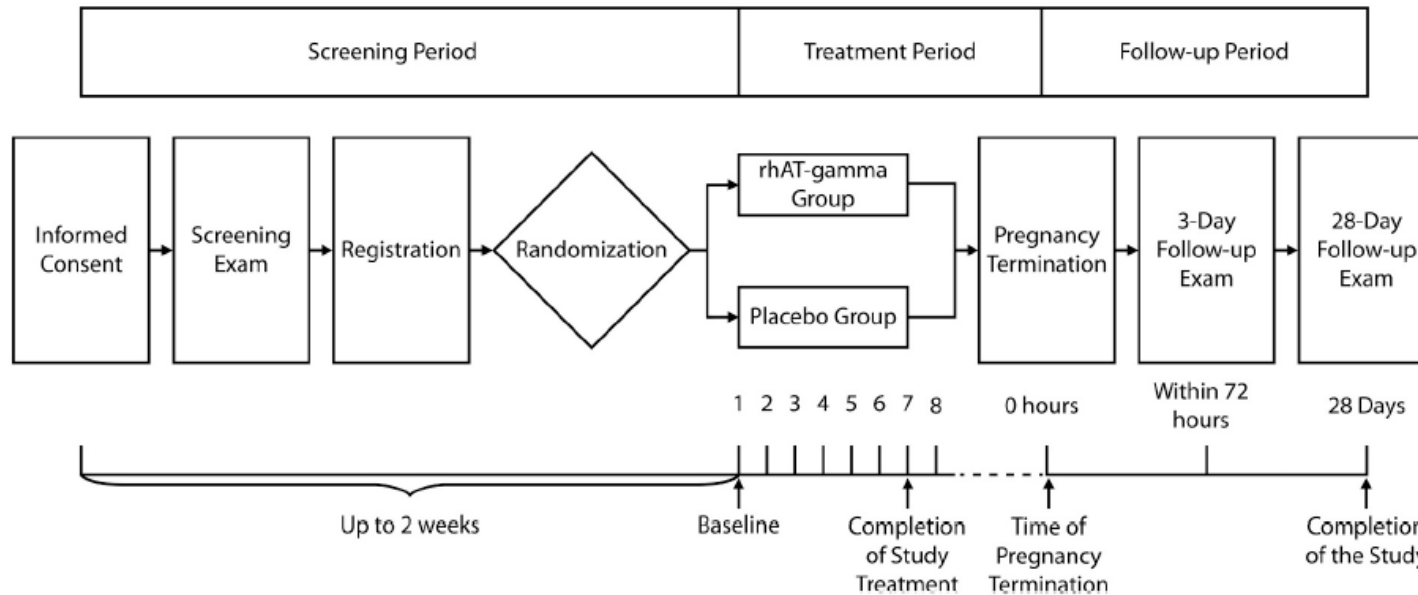
c) Ratio of KW-3357 to Plasma-derived AT

d) Calculated by inverse transformation of the log-transformed value of the difference between treatment groups

KW-3357 administered at 1.2 times the dose of human plasma-derived AT, achieving the same level of plasma AT activity
Persistence comparable to human plasma-derived AT was observed

Ph3 Test (KOUNO-TORI) Overview

S Saito, K Takagi, J Moriya, et al, Contemp Clin Trials. 2021
ClinicalTrials.gov Identifier: NCT04182373



Main inclusion criteria:

- ✓ Pregnancy between 24 weeks 0 days and 31 weeks 6 days
- ✓ Severe preeclampsia nephropathy
- ✓ AT activity less than 100%

Main Exclusion Criteria:

- ✓ Patients who are judged to require immediate delivery

Target number of patients: 180 (KW-3357 : placebo = 1 : 1)

Scheduled completion of the study: Jul. 31, 2023

Primary endpoint: Days of maintaining pregnancy

Secondary endpoints: Presence or absence of achievement of 28*, 32, or 34 weeks of gestation

Maternal: blood coagulation factors (AT activity, platelet count change, etc.)

Fetus: BPS (Biophysical Profile Score), etc.

Neonatal: birth weight, prognosis of 28 days post-termination, etc.

* With respect to presence or absence of achievement of 28 weeks of gestation, participants who were included at less than 28 weeks' gestation will be evaluated.



KOUNO-TORI
study

Toward the Creation of Pharmaceuticals for High Unmet Medical Needs - From Our Investigational Products

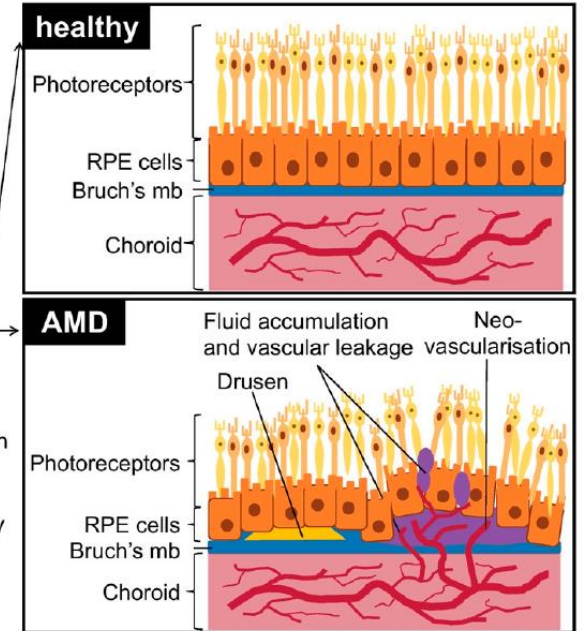
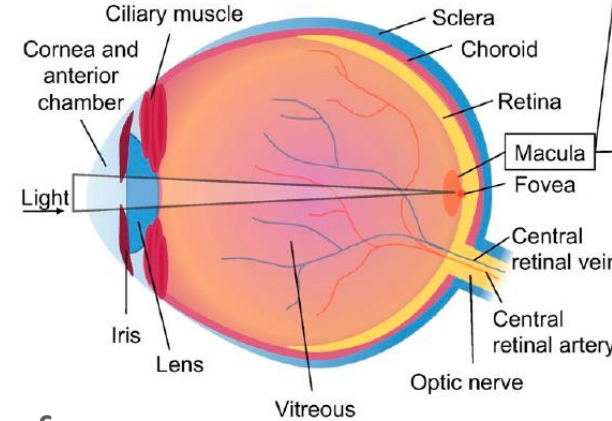
- KW-3357 (Hypertensive nephropathy of pregnancy)
- KHK4951 (Tivozanib eye-drop)

Neovascular age-related macular degeneration (nAMD)

- A disease in which the macula is affected by abnormal choroidal neovascularization
- Rapidly progressive, causing significant vision loss
- Number of patients treated with drugs
 - Japan: approx. 200,000
 - Global: approx. 1.6 million
- Cause: Aging causes deposition of waste products in the macular retina, which stimulates the production of VEGF from retinal pigment epithelial cells
- Standard of Care:
 - Intravitreal injection of anti-VEGF drugs

Because of the highly invasive nature of the treatment, there is high medical needs for non-invasive treatment methods.

J Ophthalmol. 2015;2015:820605.

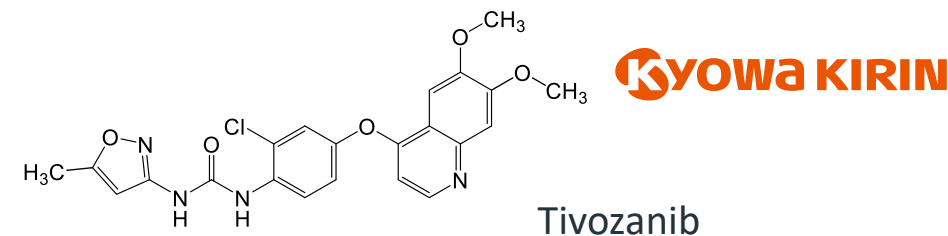


Intravitreal injection

Lancet 2012; 379: 1728-38



KHK4951: Tivozanib Eye-drop



- The active ingredient, tivozanib, is a VEGFR inhibitor discovered by Kyowa Kirin.
- Our Partner* markets tivozanib under the brand FOTIVDA® (oral formulation) for renal cell carcinoma in the U.S., Europe, etc.

* Developed by AVEO oncology and EUSA Pharma, approved in EU (2017) US (2021); AVEO markets in US, EUSA in EU/NZ/South Africa/UK.

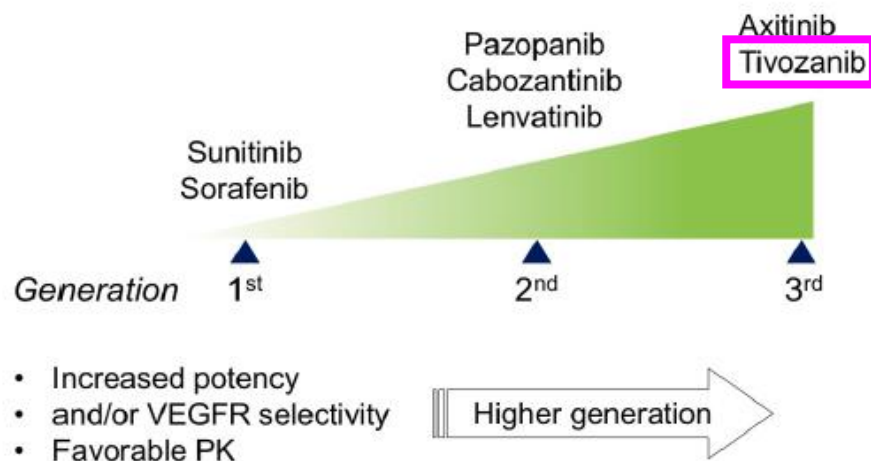


Fig. 1. Classification of selective (tivozanib, axitinib, and pazopanib) and non-selective (sorafenib, sunitinib, cabozantinib and lenvatinib) VEGFR-TKIs.

Cancer Treatment Reviews 84 (2020) 101966

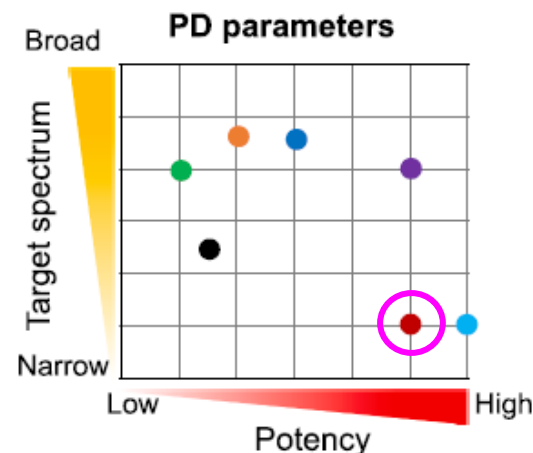


Fig. 3. Overview of VEGFR-TKI pharmacodynamics and pharmacokinetics.

Tivozanib has high VEGFR selectivity and potent inhibitory activity to VEGFR

Background to date

KHK4951

Kyowa Kirin Bought Back
Tivozanib for its Non-
Oncology Rights from
AVEO



Ph1 study started
(Japan, nAMD)



Ph1 study
Last Patient Out



December 2006

December 2015

August 2019

April 2020

March 2021

2022 and Beyond!



Kirin Brewery Out-
licenses KRN951* to
AVEO

EUSA Pharma Acquires
European Marketing
Rights from AVEO

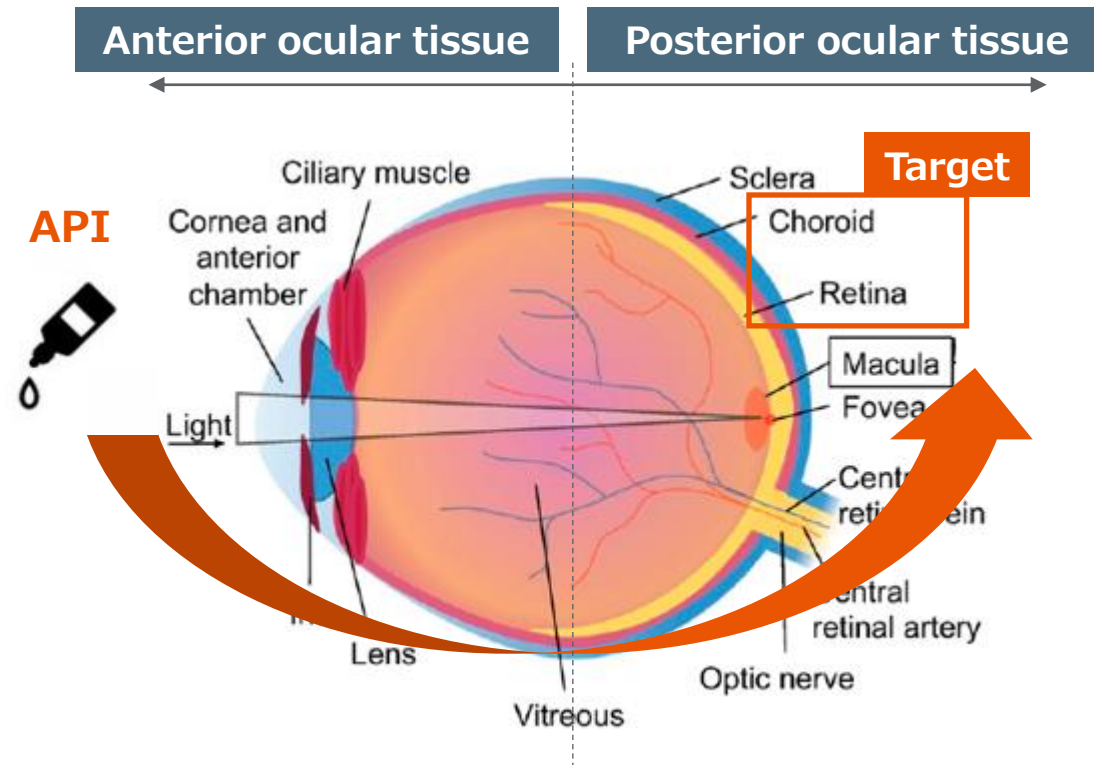
AVEO Receives Approval
in the U.S.
(Renal Cell Carcinoma)

*Development Code of Tivozanib
Oral administration

FOTIVDA®

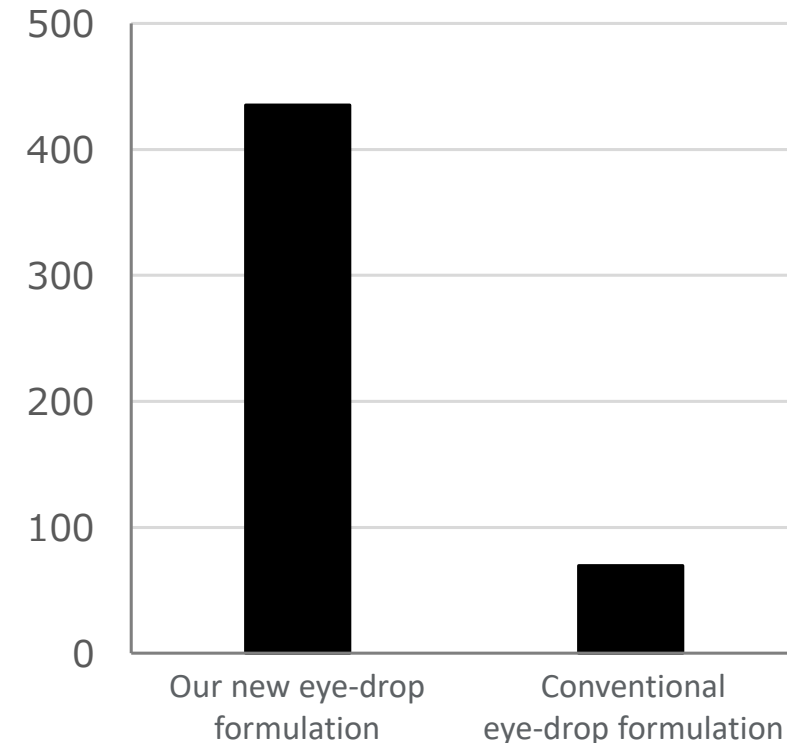
Our Proprietary New Eye-drop Formulation

Drug concentration in posterior ocular tissue after topical instillation of tivozanib eye-drop to rats



J Ophthalmol. 2015;2015:820605. (partially modified).

Concentration in posterior ocular tissue (ng/g)



New eye-drop formulation developed by Kyowa Kirin enables efficient delivery of API to posterior ocular tissues.

Ph1 Study Synopsis (ID: 4951-001)

ClinicalTrials.gov Identifier: NCT04594681

Cohort	Dosing		Subjects	No. of steps	No. of subjects / step
	Cohort 1*	Single administration KHK4951:Placebo=6:2	Healthy volunteers Japanese/White	5	8
	Cohort 2*	3W administration KHK4951:Placebo=6:2	Healthy volunteers Japanese/White	6	8
	Cohort 3**	3W administration KHK4951 only	nAMD patients Japanese	3	6~10
Endpoint	• Primary endpoint: Assessment of safety and tolerability - Adverse events, Laboratory test, Vital signs, General physical exam, 12-lead electrocardiogram - Ophthalmic exam (Visual acuity, IOP, Slit-lamp exam, Fundus exam, OCT) • Secondary endpoints: Assessment of pharmacokinetics and efficacy ➤ Pharmacokinetics (Serum KHK4951 concentration, Pharmacokinetic parameters) ➤ Efficacy ✓ CST (Central subfield retinal thickness) ✓ BCVA (Best corrected visual acuity) ✓ Retinal morphological change with OCT (SRF, IRF, sub-RPE fluid, Dry macula, SHRM) ✓ Total area of CNV lesion and leakage with FA				

*Randomized, double-masked, placebo-controlled, dose escalation

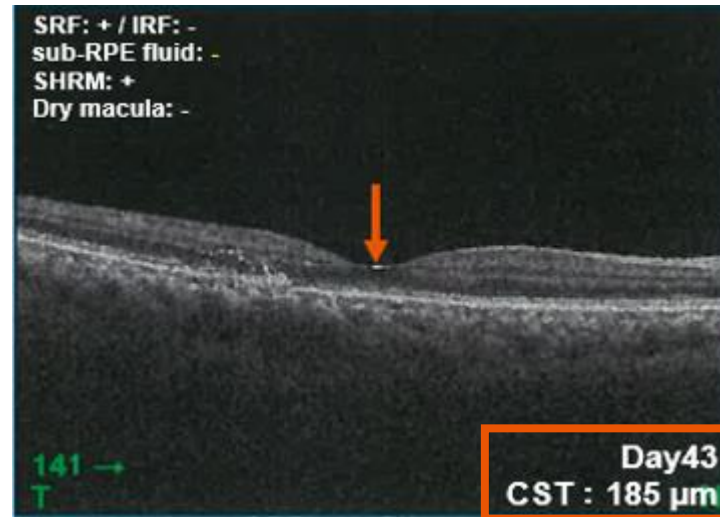
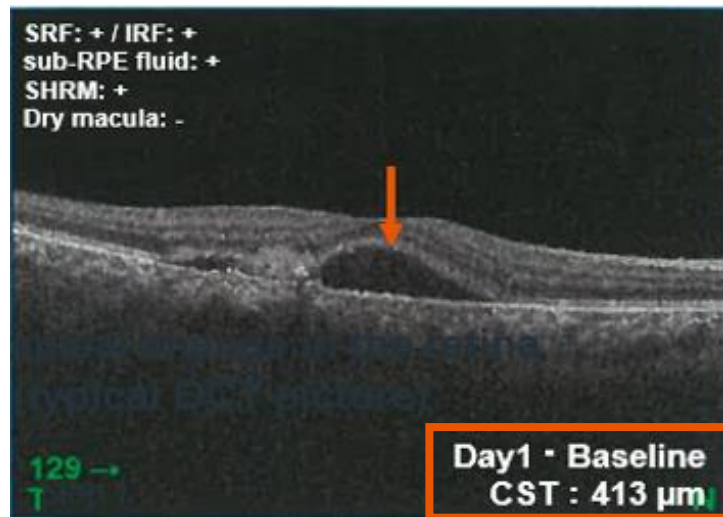
**Open, dose escalation

Ph1 study results (ID: 4951-001)

- Achieved Last Patient Out
- Safety, pharmacokinetics, and pharmacodynamic data are under analysis
- Received positive feedbacks from global KOLs in discussion regarding the Ph1 data

Anatomical changes of retina: OCT (Optical Coherence Tomography) image

Note: This is an example where KHK4951 was found to be effective



Step 2

Treatment naïve

PCV / Occult with No Classic CNV

In preparation for a publication
of the Ph1 data

* CST: central subfield retinal thickness

A Ph2 study in Japan and US (+α) is currently under preparation.

Toward the successful creation and delivery of Life-changing value - Early-stage R&D Activities

- Data-driven drug discovery - Collaboration with InveniAI
- Deepening Kyowa Kirin's Antibody Technology - Collaboration with Synaffix
- The pursuit of innovation with a long-term perspective - VC fund investment/CVC activities

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Collaboration with InveniAI to date

1.

2018: Started collaboration

Explore new indications for existing pipelines

2022:

Obtaining new insights into target molecules and disease mechanisms of action suggesting efficacy by confirming preclinical POC

2.

2020: Expanding collaboration

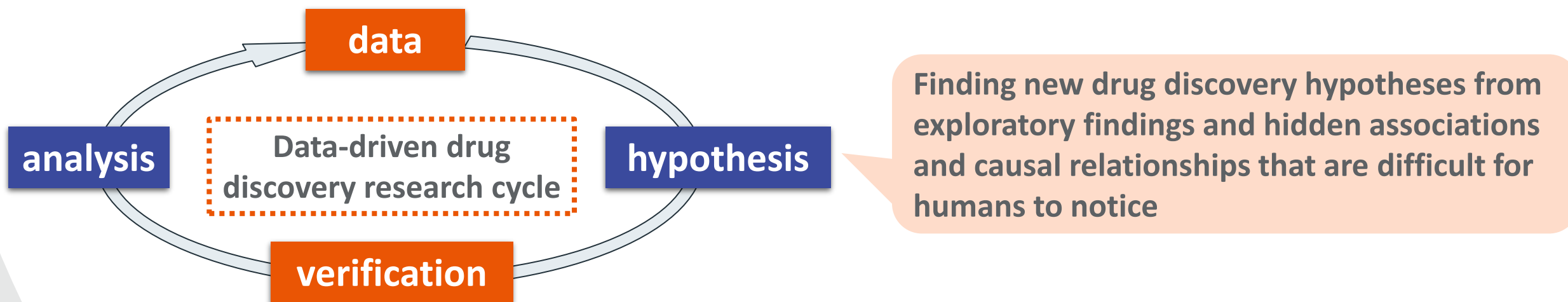
Target exploration for next generation antibody technology

3.

2021: Expanding collaboration

- New drug research collaborations signed on several new drugs
- Access to AlphaMeld® and AI Innovation Lab
- Interaction with AI experts team begins

1. Exploration of new indications for existing pipelines



The same approach is being applied for other pipelines

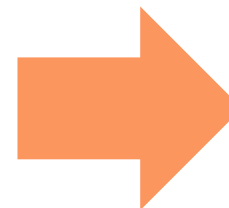
2. Target Exploration for Next Generation Antibody Technology



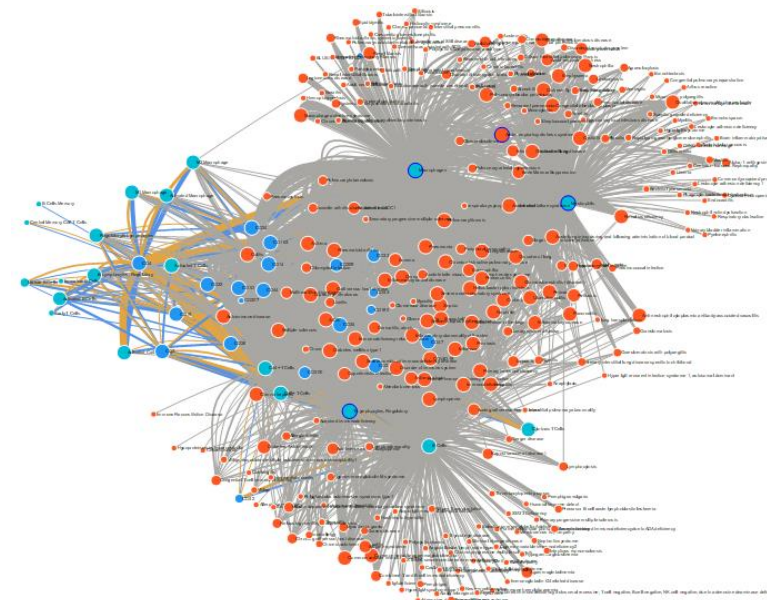
Bispecific antibody technology



AI analysis and search for combinations of two target molecules and optimal diseases

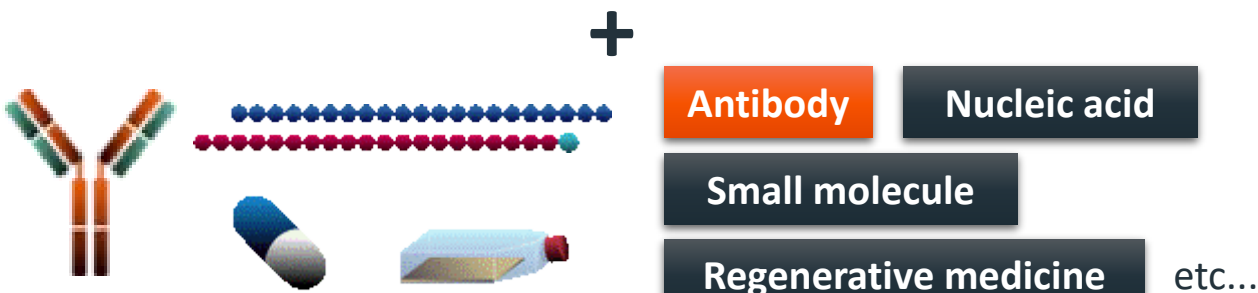


Extracts information/hypotheses that are difficult to be noticed
Significantly streamlines the research for optimal target diseases



An example of target molecule and disease discovery through comprehensive analysis

AI Drug Discovery Technology Platform



Aiming to accelerate pipeline creation with our technology x AI drug discovery

The approach will be applied to more than just antibodies

3. Expanding collaboration for implementation of AI drug discovery capabilities

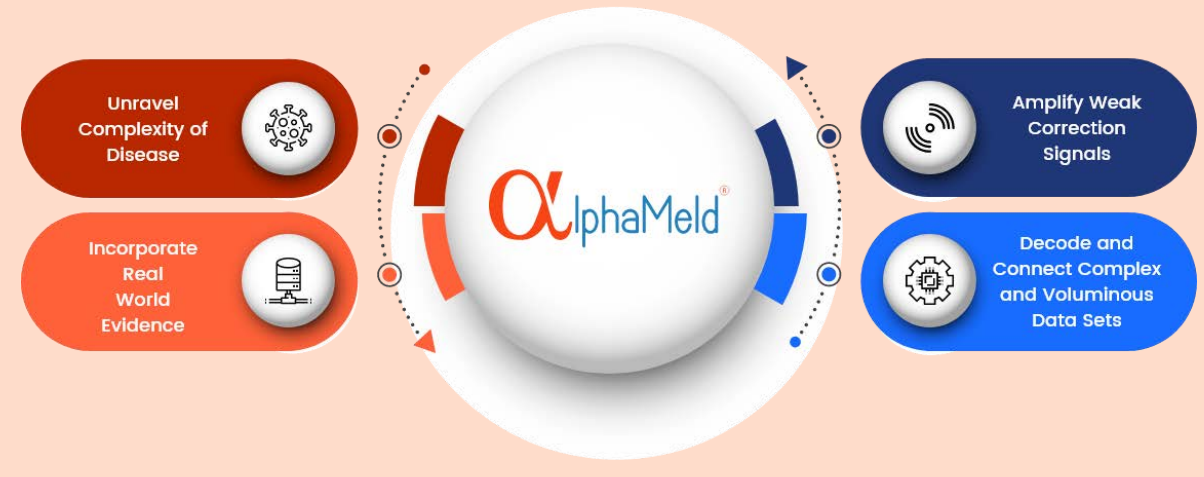


Close interaction between AI experts from InveniAI and Kyowa Kirin's researchers

Implementation of AI drug discovery function is one of the most important issues for DX in pharmaceutical companies

We continue to take the challenge for the successful creation and delivery of Life-changing value by combining biotechnology and digital technology

AlphaMeld® used directly by Kyowa Kirin researchers



Accumulating experience in operating AI platforms to implement functions from both software and hardware perspectives

Toward the successful creation and delivery of Life-changing value - Early-stage R&D Activities

- Data-driven drug discovery - Collaboration with InveniAI
- **Deepening Kyowa Kirin's Antibody Technology - Collaboration with Synaffix**
- The pursuit of innovation with a long-term perspective - VC fund investment/CVC activities

Kyowa Kirin's Antibody Drug Discovery Cycle



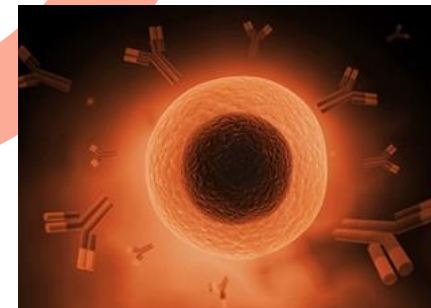
etc...

**Open
Innovation**

**Technology
Know-how
Production capacity
for antibody
development**

**New
generation
Antibody
Technology**

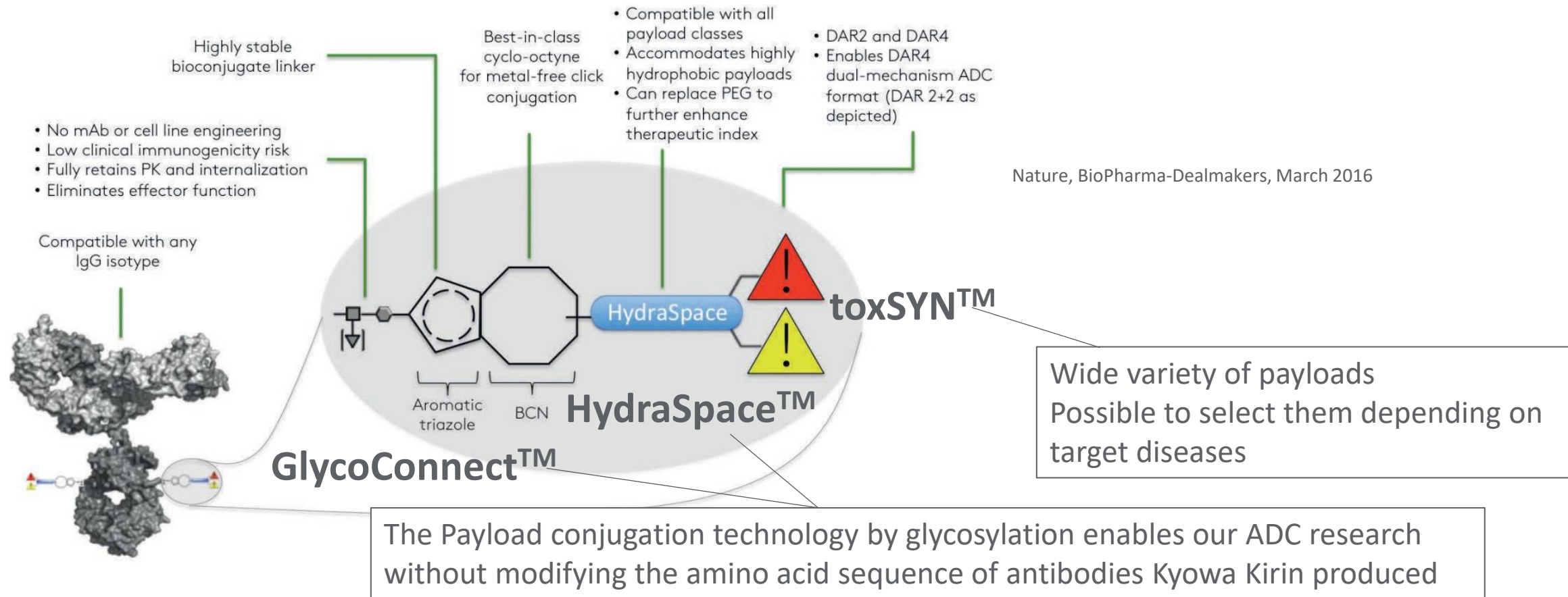
**In-house
Antibody
Library**



**Successful creation and delivery of
innovative antibody drugs**



Synaffix's ADC technology



These technologies fit our strength in antibody pipeline generation

License Agreement with Synaffix



August, 2021

June, 2022

Licensing agreement

Started ADC studies regarding two antibodies.

Expansion of agreement

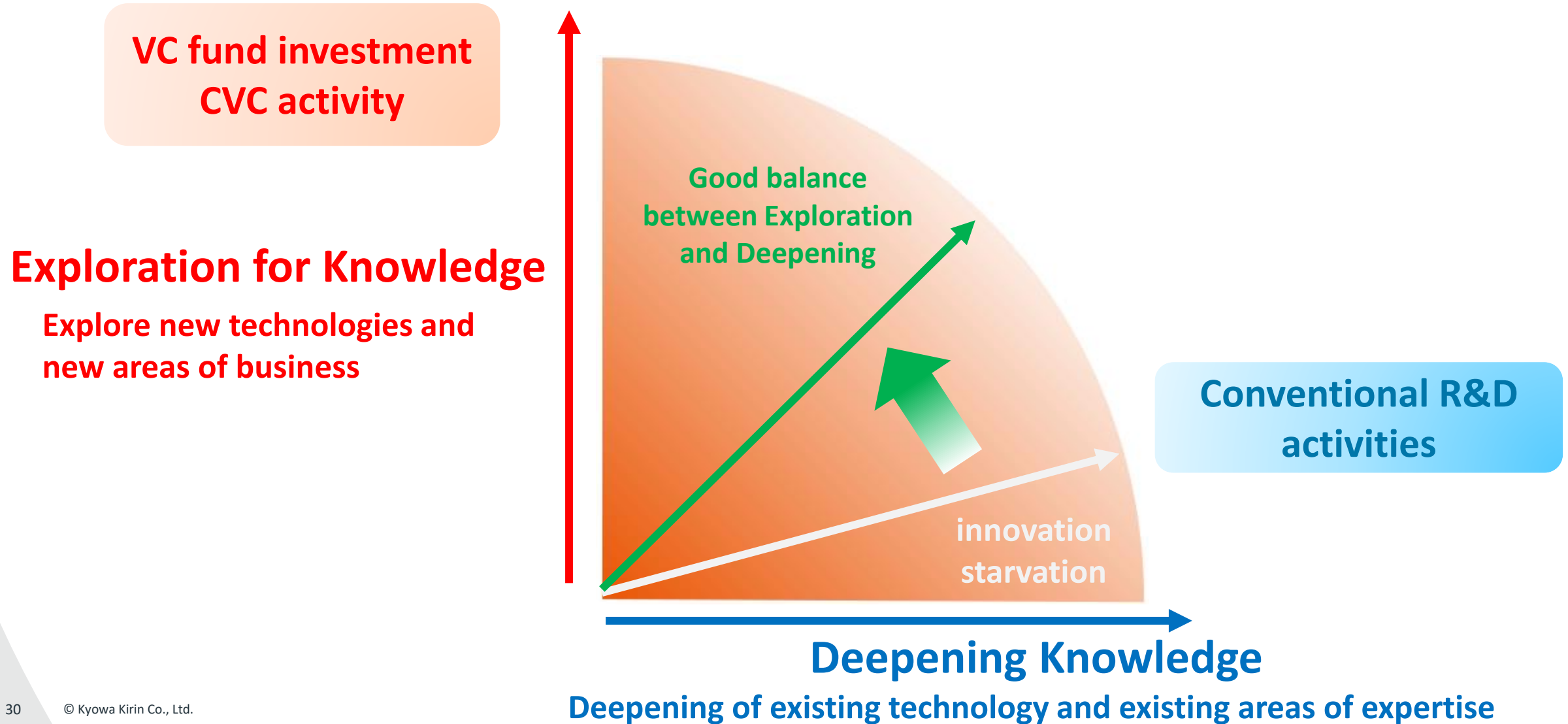
- One more antibody added
- Total of three ADC studies are currently underway

The pre-clinical stage studies are currently underway for creation of pipelines

Toward the successful creation and delivery of Life-changing value - Early-stage R&D Activities

- Data-driven drug discovery - Collaboration with InveniAI
- Deepening Kyowa Kirin's Antibody Technology - Collaboration with Synaffix
- **The pursuit of innovation with a long-term perspective - VC fund investment/CVC activities**

Approach to generate more innovations for long-term growth



Outline of Activities

VC Fund Investments

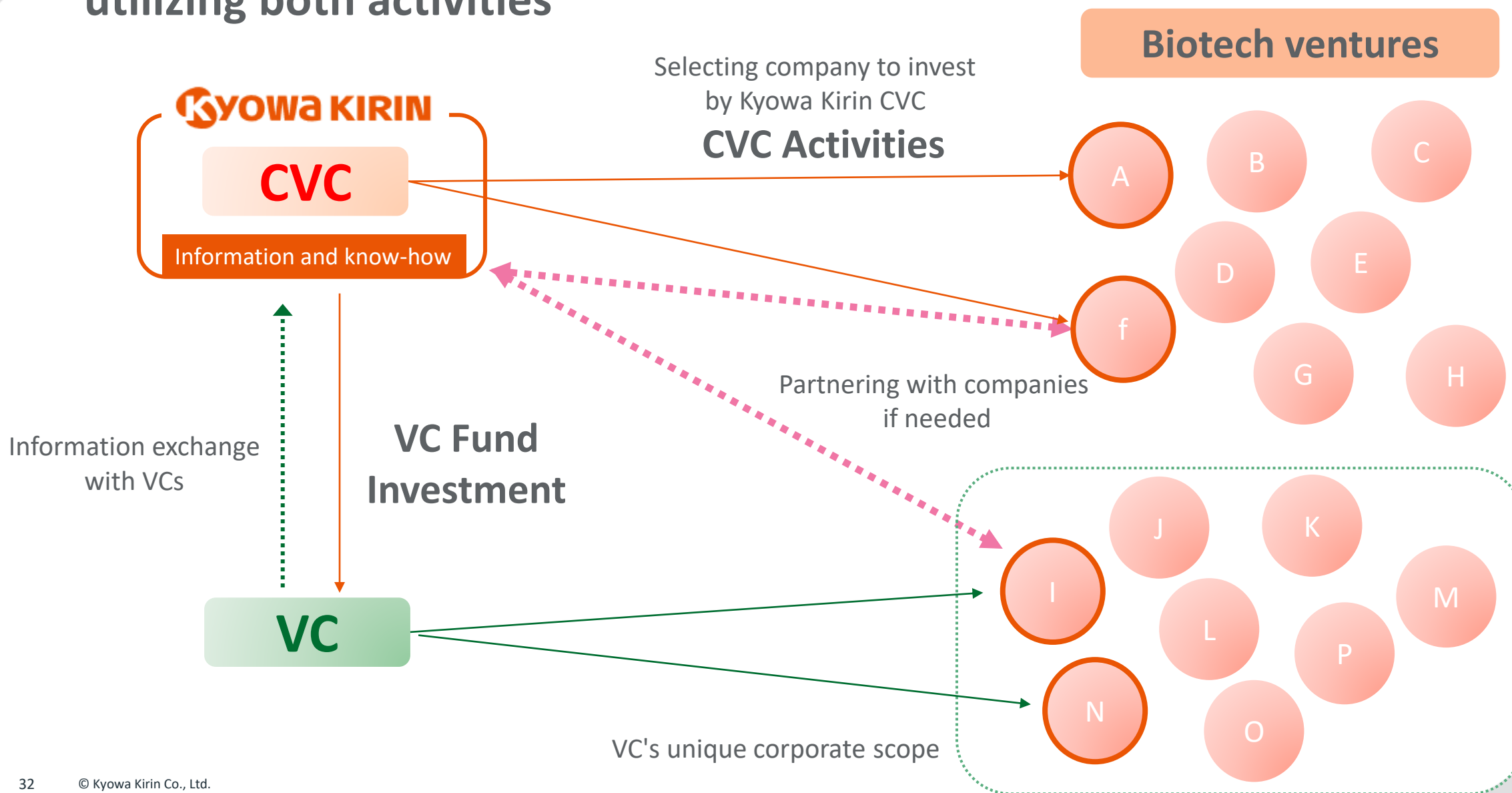
- To keep an eye out for the information related to drug discovery to search for innovative R&D seeds
- We have already invested in three companies to date and through this activity, a joint research agreement was signed with LUCA Science



CVC Activities

- To invest in companies from Kyowa Kirin's perspective while leveraging the experience in VC fund investments
- To enable direct communication with venture companies
- The dedicated team consisting of management and members in charge of practical operations was formed to ensure speedy decision-making and operations.

Exploration for a wide range of drug discovery research seeds utilizing both activities



Summary

- Toward the Creation of pharmaceuticals for High-Unmet Medical Needs
 - From Our Investigational Products
 - KW-3357 (Preeclampsia)
 - KHK4951 (Tivozanib Eye-drop)
- Toward Continuous Creation of Life-changing Value
 - From Early-stage R&D Activities
 - Data-driven drug discovery - Collaboration with InveniAI
 - Deepening Kyowa Kirin's Antibody Technology – Collaboration with Synaffix
 - The pursuit of innovation with a long-term perspective - VC fund investment/CVC activities

Kyowa Kirin will realize the successful creation and delivery of life-changing value that ultimately makes people smile

