Ajinomoto Co. @ Lab
Central Kick-off Event
March 27, 2025

It is nice to meet you!

REGENERATIVE MEDICINE

Katie Kilgour

Account Representative, Regenerative Medicine

Hajime Ohnuki

Manager, Regenerative Medicine

BIOLOGICS AND SMALL MOLECULE SOLUTIONS, GENE THERAPY

Kazu Takumi

VP of Global Coordination Officer, Forge Biologics

Magdalena Tyrpien

Chief Business Officer, Forge Biologics

CORPORATE VENTURE CAPITAL, HEALTHCARE

Yoichiro Miwa

Investment Director, Ajinomoto Corporate Venture Capital

MEDICAL NUTRITION

Rick Jentis

President, Ajinomoto Cambrooke

INNOVATION STRATEGY

Robert Morfino

Director of Innovation Strategy

Tomo Koyama

Associate Director, Innovation Strategy

Yasushi Noguchi

Senior Director, Innovation Strategy

Lab | Central

AJINOMOTO

BIO•PHARMA SERVICES

Innovative platform technologies for drug manufacturing and development

Magdalena Tyrpien
Kazu Takumi

27TH MARCH, 2025

Ajinomoto Bio-Pharma Services: Specialized CDMO Experts

About Aji Bio-Pharma

- Proven track record of clinical to commercial cGMP manufacturing
- Over 40 years of CDMO experience
- Bio-Pharma operations in 4 countries
- 1,800+ employees

AJINOMOTO BIO•PHARMA SERVICES | THE POWER TO MAKE

Innovation is Our Origin and Key Word

Commercialized AJI-NO-MOTO® in 1909 from amino acids (umami ingredients) contained in kelp dashi.

Dr. Kikunae Ikeda,
Discoverer of the umami taste

Our founding aspiration

Contribute to society through food

Commitment to improve the nutrition of Japanese people with umami

Saburosuke Suzuki II,
Founder of the Ajinomoto Group

Now

The Original
AJI-NO-MOTO®

Co-creation of social and economic value through our business

ASV(Ajinomoto Group Creating Shared Value)

Innovation

✖

Commercialization

↓

Innovative Product

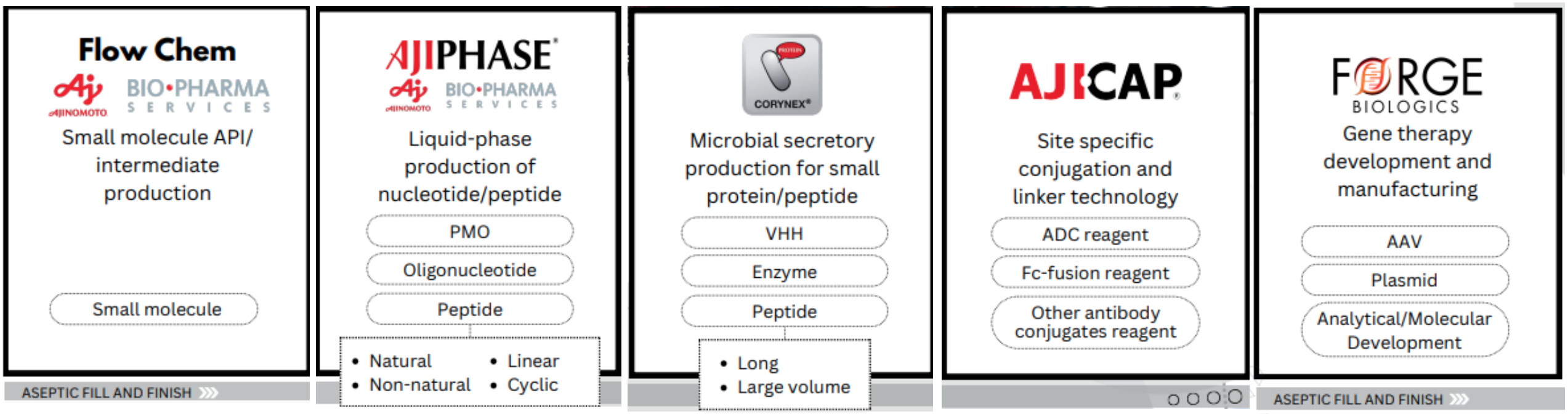
↓

Eat Well, Live Well.

AJINOMOTO

Innovative technologies for manufacturing and drug development

Through innovative technologies, Aji Bio-Pharma Services ***differentiates*** itself as a CDMO and ***embodies*** what customers need.



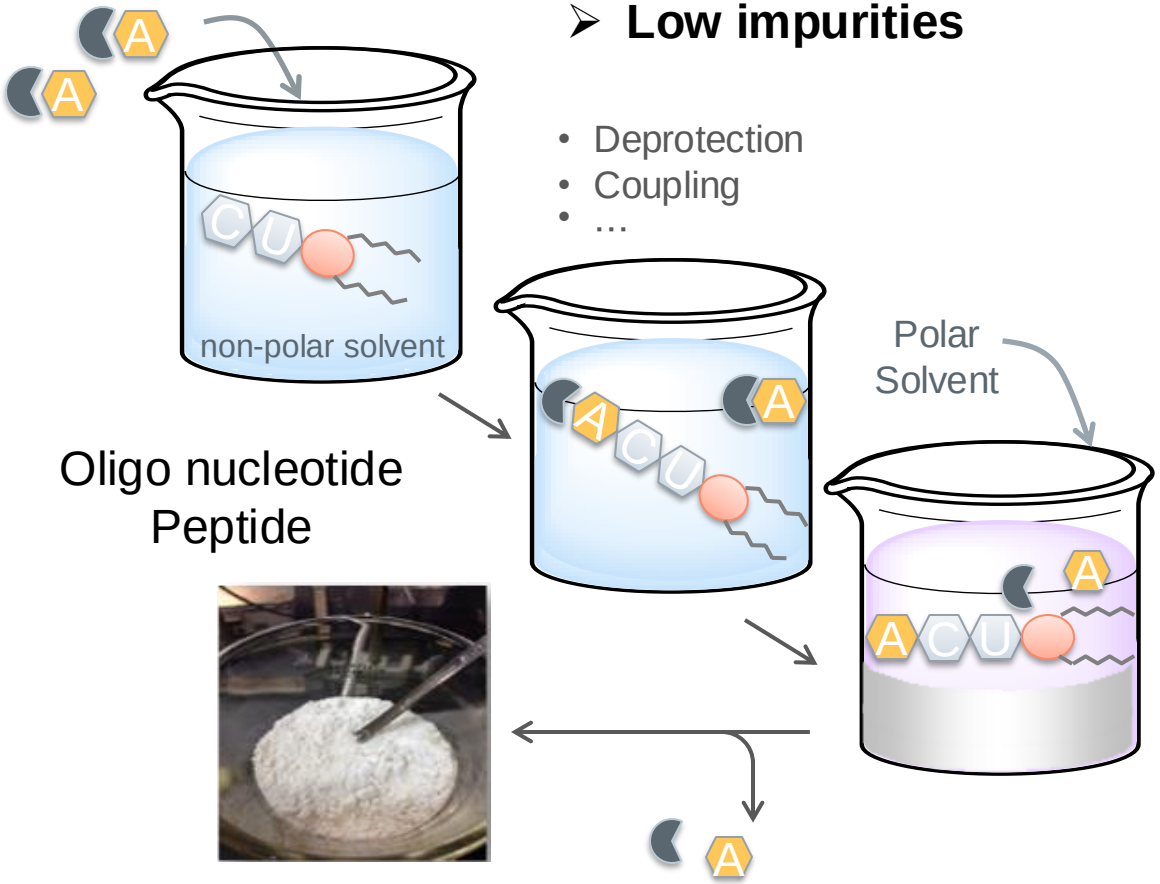
Progress of Our Technologies Utilized for Client Project

AJIPHASE®

Commercialized!

Values for Customers

- **Large amount production**
- **High yield**
- **Low impurities**



Oligo nucleotide
Peptide

Excess Reagents
Byproducts

CORYNEX®

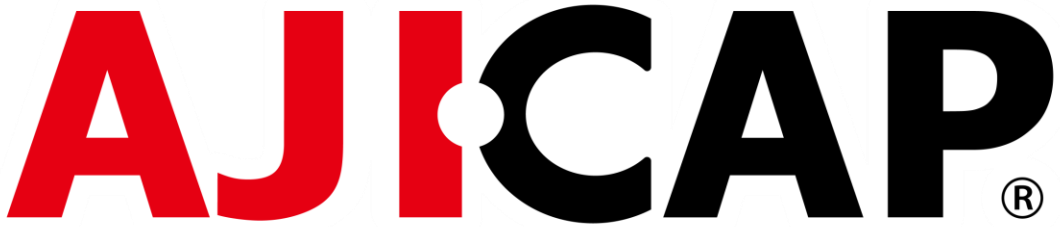
Values for Customers

- **No Endotoxin, High yield**
- **High-throughput**

***E. coli* (inclusion body)**	**Corynex®**
CELL CULTURE	CELL CULTURE
HARVEST (CELL)	HARVEST (SUP.)
LYSIS	No need to LYSIS
REFOLDING	No need to REFOLDING
COLUMN 1	COLUMN 1
COLUMN 2	COLUMN 2
COLUMN 3	No need to Remove Endotoxin
Low Recovery 5~8%	High Recovery 40%~

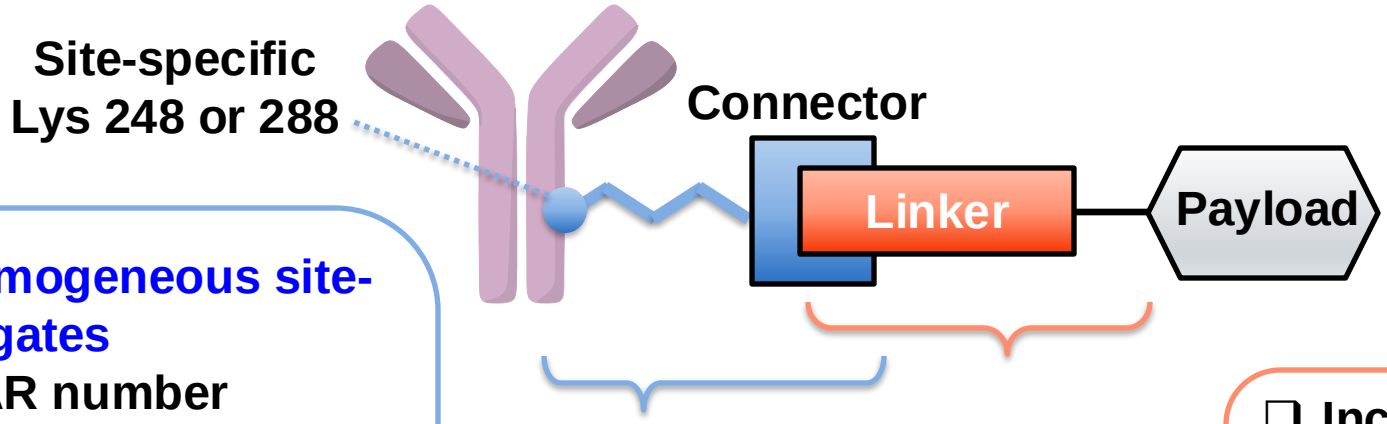
In Phase-2!

BIO•PHARMA SERVICES | THE POWER TO MAKE


AJICAP®

AJICAP® Technological Overview

➢ **AJICAP® technologies enable to prepare a wide variety of antibody conjugates including ADCs**



- ❑ Generating homogeneous site-specific conjugates
- ❑ Controlling DAR number
  - ✓ DAR1, 2, 4, 8, 10
  - ✓ DAR2+2, 8+2 (dual payload)
- ❑ Simple operation
  - ✓ Not requiring column purification
  - ✓ >90% yield from naked antibodies
  - ✓ Succeeded in 60 g scale preparation under GMP

AJICAP® Conjugation × AJICAP® Novel linker

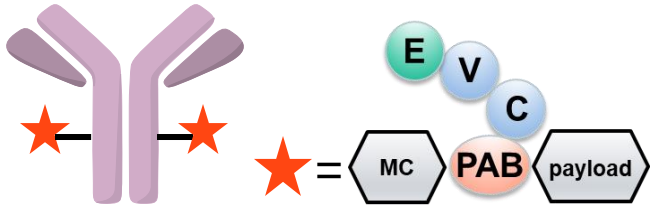
AJICAP® Technology

- ❑ Increasing stability
- ❑ Increasing hydrophilicity
- ❑ Cleaved by cathepsin B
- ❑ Applied to various payloads

Enhancing therapeutic window due to increasing the stability of the resulting conjugates through AJICAP® technologies

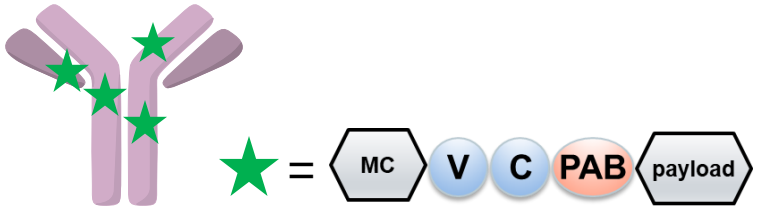
Biological Property of AJICAP® ADCs

AJICAP® DAR2 ADC
(AJICAP® conjugation + AJICAP® linker)

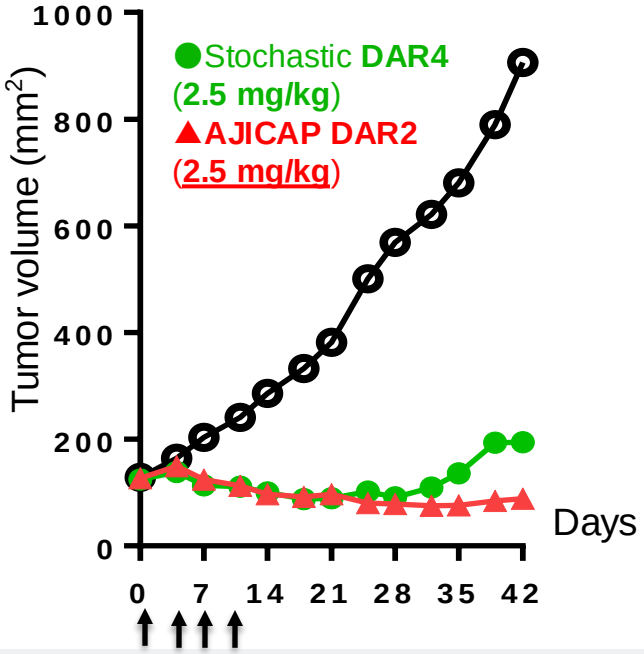


VS

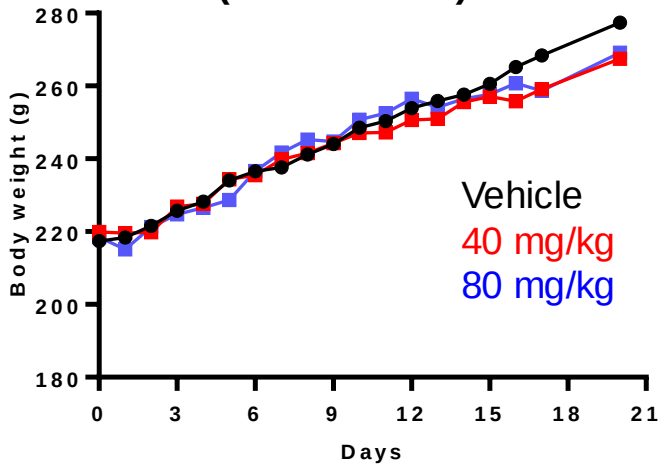
Stochastic DAR4 ADC
(Random conjugation + VC linker)



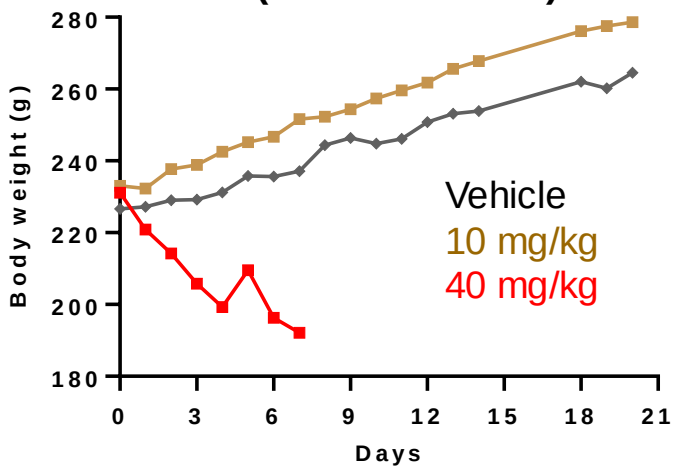
➢ **Efficacy study**
(AJICAP ADC vs Stochastic ADC)



➢ **Body weight change in TOX study**
(AJICAP ADC)



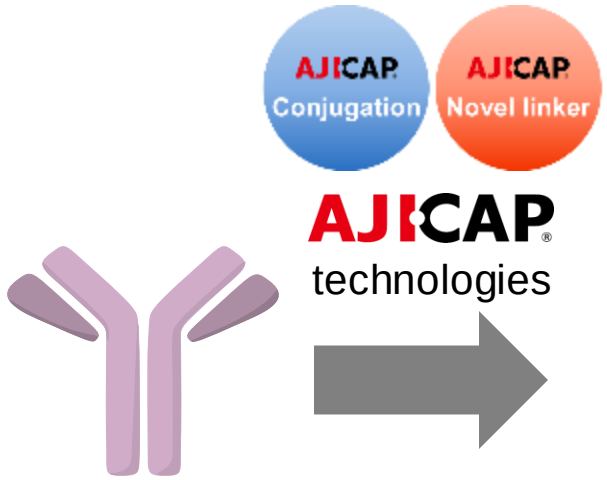
➢ **Body weight change in TOX study**
(Stochastic ADC)



AJICAP® ADC shows better biological profile than traditional DAR4 ADC

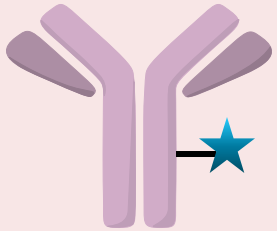
AJICAP® Technology Overview

➢ **AJICAP® technologies enable production of various DAR conjugates (DAR1, 2, 4, 8, and more).**



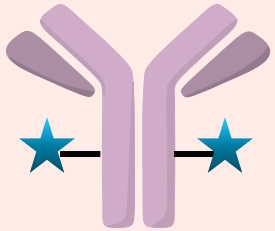
The combination of AJICAP® conjugation and linker technologies enables the production of various DAR conjugates (DAR1, 2, 4, 8, and more).

DAR1

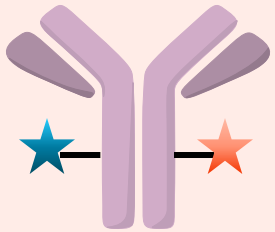


Asymmetric DAR1

DAR2

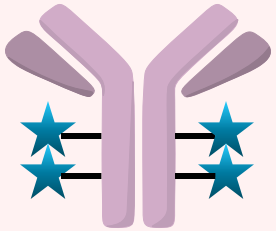


Symmetric DAR2

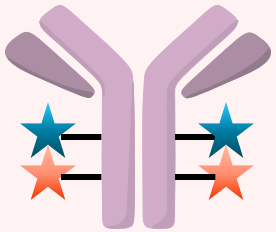


Asymmetric DAR2
✓ Dual MOA

DAR4



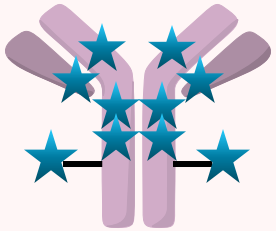
DAR4



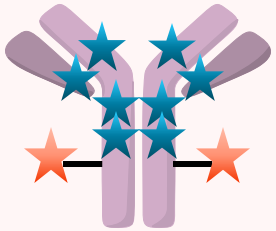
DAR2+2
✓ Dual MOA

DAR8+

DAR8 (reduction)

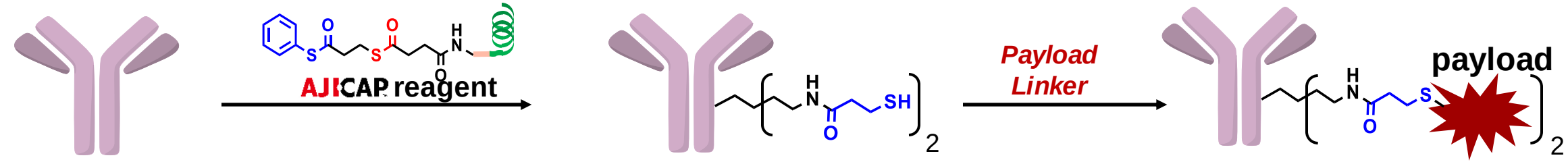


DAR10



DAR8+2
✓ Dual MOA

AJICAP® Conjugation

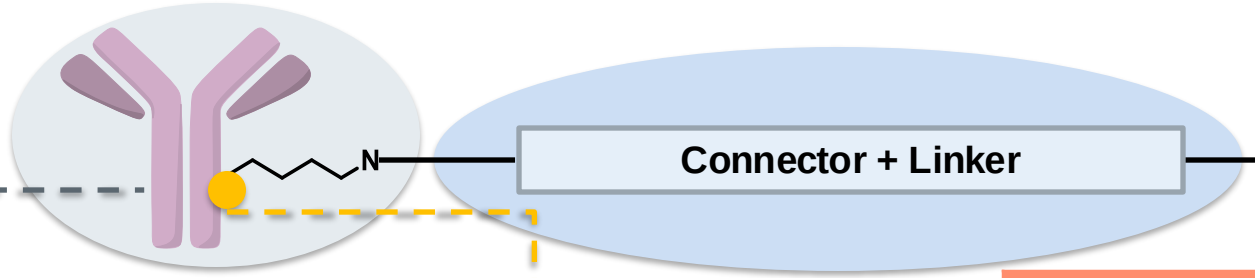


Native antibody

Site-specific functionalized Antibody

Site-specific ADC

- ✓ No Chromatography required
- ✓ High yield(>90%) from mAb can be achieved



Non-mutated mAb

Antibody	
hIgG1	hIgG4
hIgG2	Mouse, Rat antibody

Conjugation Site
Lys248
Lys288
Lys248 & 288

Payload / Toxins	
Small molecule	Nano particle
Protein/Peptide	Cell
Oligonucleotide	

- ✓ AJICAP® can provide flexibility
- ✓ No limitation for the Payload

FORGE BIOLOGICS

A member of Ajinomoto Bio-Pharma Services

FORGE BIOLOGICS
A member of Ajinomoto Bio-Pharma Services

A Leading Global Genetic Medicine CDMO

By the numbers

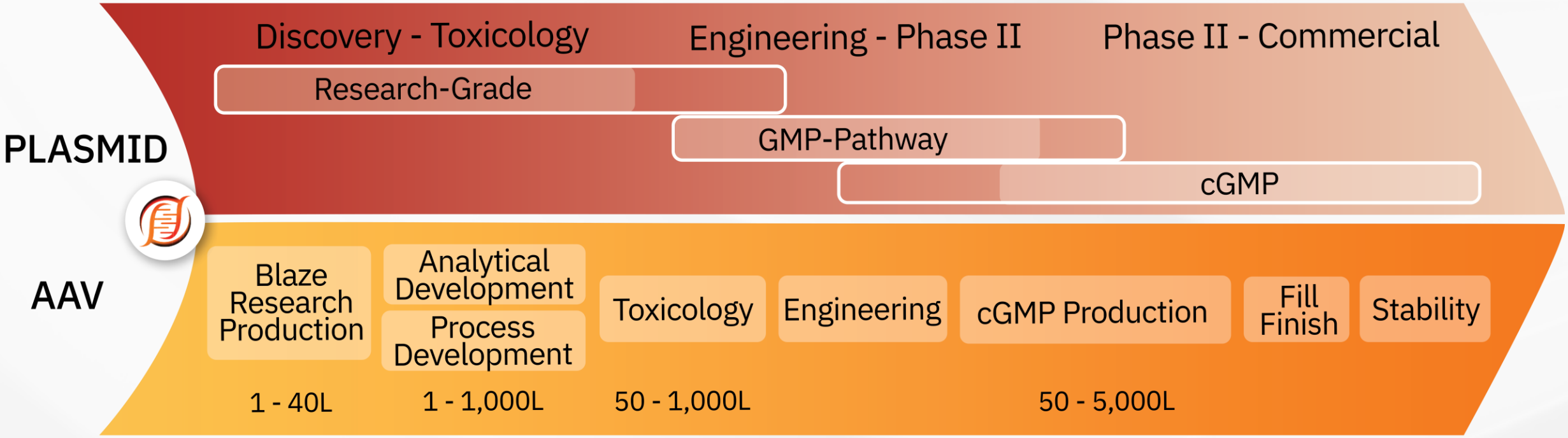
- 20 — cGMP Suites
- 1-5,000L — AAV Development & cGMP Production
- >20,000L — Bioreactor Capacity
- >370 — Employees

Our Facility, The Hearth:

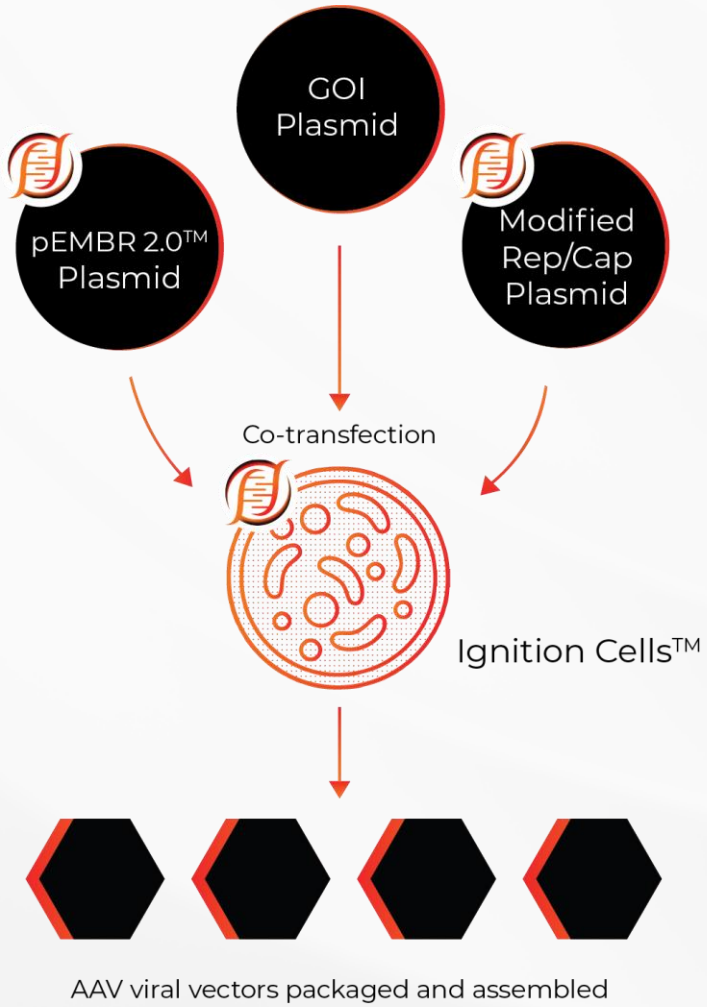
Forge is one of the **largest** AAV manufacturers in the world.

20 cGMP suites with 50L, 500L, 1,000L and 5,000L bioreactors

From **Discovery to Delivery** & Every Need in Between



Advanced Technologies



NEW! pEMBR 2.0™ Ad Helper Plasmid

- One of the smallest Ad helpers commercially available at 8.9kb
- Increases efficiency in manufacturing
- Improved safety profile–reduction in adenoviral components that are not necessary for AAV production
  - Reduced: VA RNA I, VA RNA II, Hexon Assembly & Precursor, E2A Region
  - Removed: 23kDa Endo-protease, DNA terminal protein, Fiber, L1-52/55K
- Forge specific intellectual property

NEW! Modified Rep/Caps

- Client-specific capsid sequence is incorporated into Forge's proprietary backbone plasmid
- Designed for safety and higher AAV yields
- No changes to protein sequences
- Patent pending

Ignition Cells™

- Suspension HEK293 mammalian cell line
- Royalty-free license for clients
- Well documented history with regulatory feedback
- Fully qualified Master Cell Bank and Working Cell Bank produced at Forge
- Optimized for robust transient transfection
- Capable of >90% full capsid post-enrichment, often with undetectable empty particles

What is the FUEL™ platform?

Forge's Advanced Technologies

- **NEW** pEMBR 2.0™ Ad Helper Plasmid
- **NEW** Modified Rep/Cap Plasmids
- Ignition Cells™

Optimization Packages

Flexibility for client-specific customizations through multiple packages designed for optimizing yield, recovery, regulatory success, and more

Proven Manufacturing Processes

~500 platform runs across all serotypes including novel

Why is Forge focused on manufacturing innovation?

As more gene therapy developers introduce new programs and work on more prevalent diseases, **manufacturing must keep pace**

Innovation and a focus on R&D is a key part to Forge and Ajinomoto's collaboration

Our goal with FUEL™ is to **deliver more efficient manufacturing solutions** so that we can support more programs and larger disease populations

All driven by our mission of **enabling access to life-changing therapies**

Thank You

We will be back here on 8th May with specialists!

Lab | Central

Ajinomoto Cambrooke

March 27, 2025

Our Vision

Ajinomoto Cambrooke will remain relentlessly committed to our patient communities through outstanding nutrition options and superior service.

For those with chronic health conditions requiring daily dietary therapy we elevate quality of life by creating superior, great tasting solutions and sustained competitive advantage

Helping people **Eat Well, Live Well**

OUR FOCUS

Our Patients | **Our Products** | **Our People**

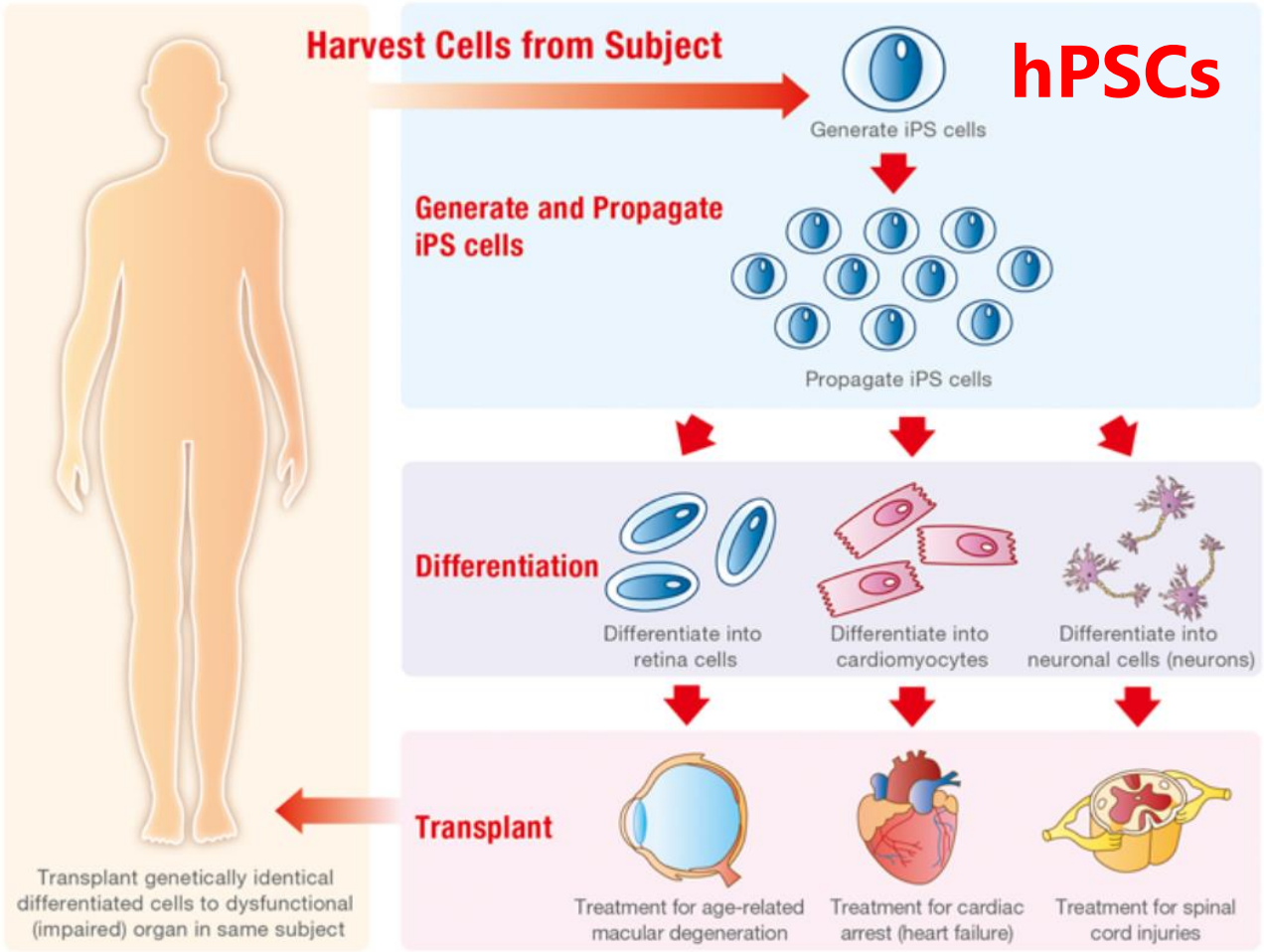
Lab | Central

Advancing Drug Discovery
The Role of Organoid Manufacturing

Ajinomoto Health and Nutrition North America, Inc.

March 27, 2025

What are human pluripotent stem cells (hPSCs)?



hPSCs include;

- **Induced pluripotent stem cells (iPSCs)**
- **Embryonic stem cells (ESCs)**

Cell Therapy

Drug Screening

StemFit & StemFit Purotein

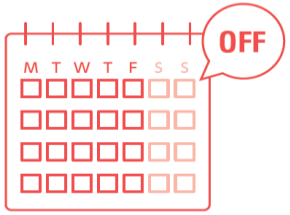
StemFit™ Basic03 GMP

StemFit™ Basic04CT GMP

StemFit™ For Differentiation GMP

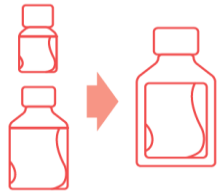
StemFit Purotein™

Animal-Origin Free (AOF)



Weekend-Free Feeding

Single-Cell Expansion



One Bottle Composition

Today’s topics

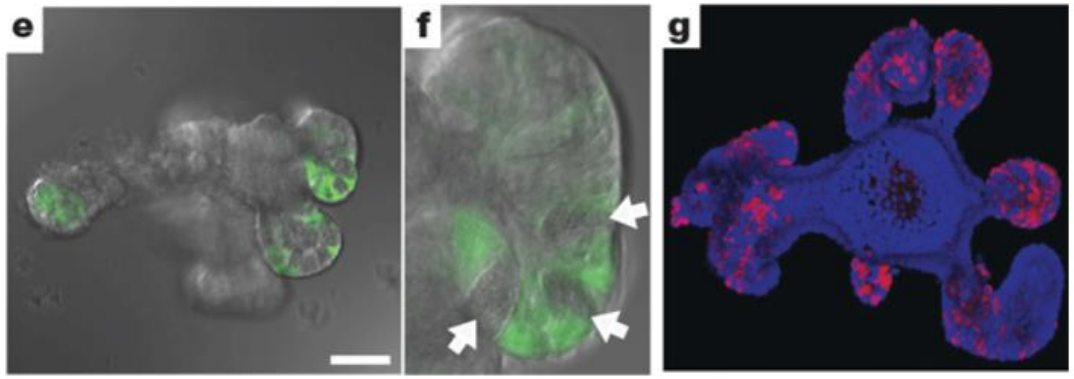
1. Drug Screening with Organoids
2. Future Clinical Applications
3. Importance of Ancillary Material for Safety and Quality

Today's topics

1. **Drug Screening with Organoids**
2. Future Clinical Applications
3. Importance of Ancillary Material for Safety and Quality

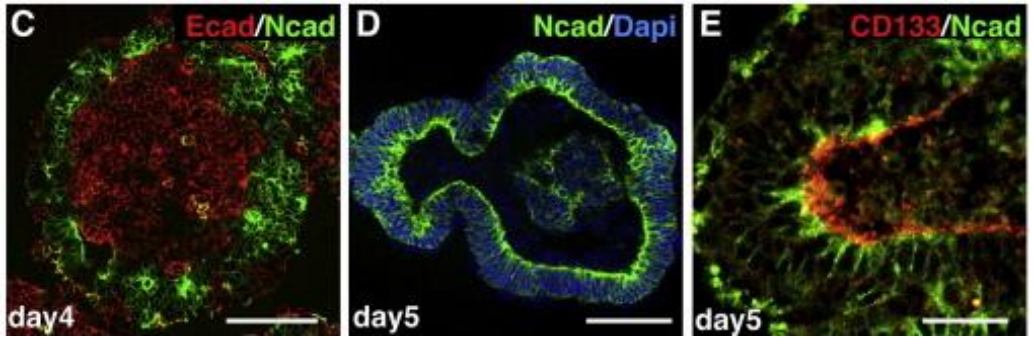
What is an Organoid and how it is used

Tissue derived intestinal organoid by Prof. Hans Clevers

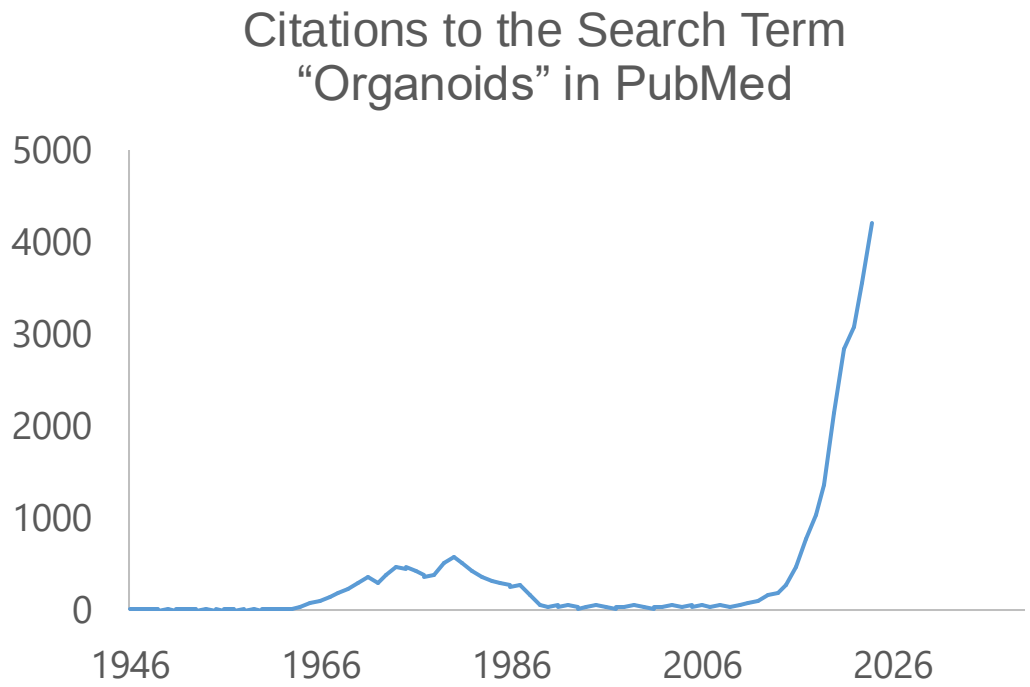


Sato, T. et al. Nature 459, 262–265 (2009).

hPSC derived brain organoid by Dr. Yoshiki Sasai



Eiraku, M. et al. Cell Stem Cell 3, 519–532 (2008)

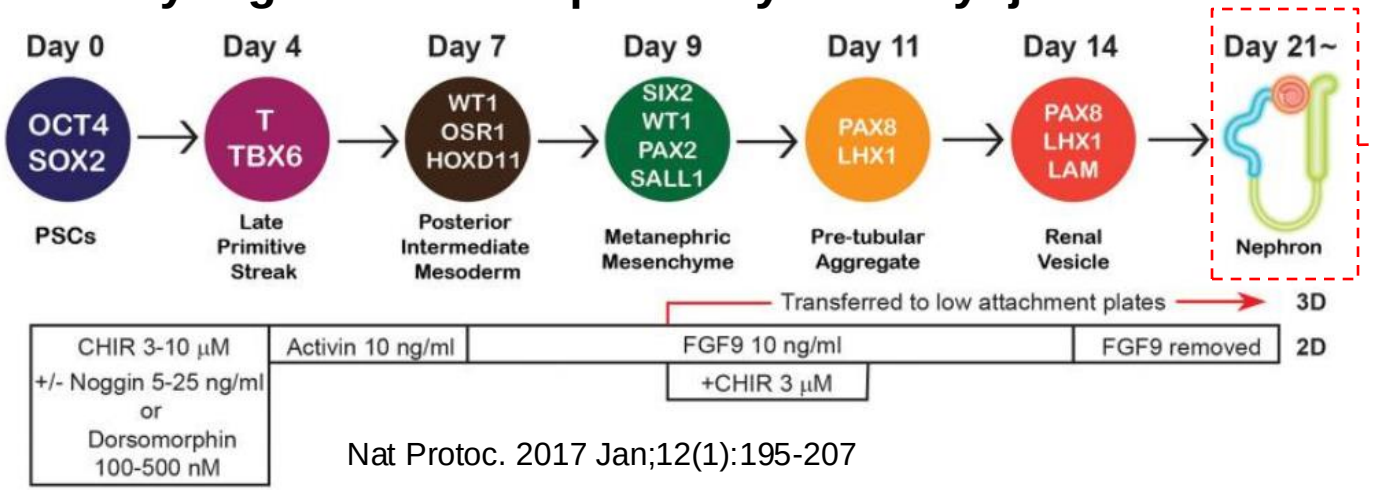


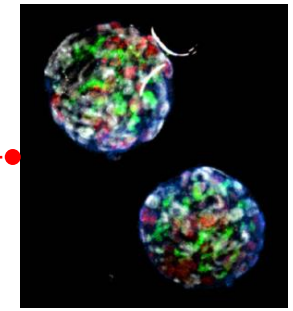
Advantages of Organoids

- 3D structure that mimics actual tissue
- Culturable
- Application to pathology models

Case Study #1: hPSC-derived kidney organoids

Kidney organoid development by Prof. Ryuji Morizane

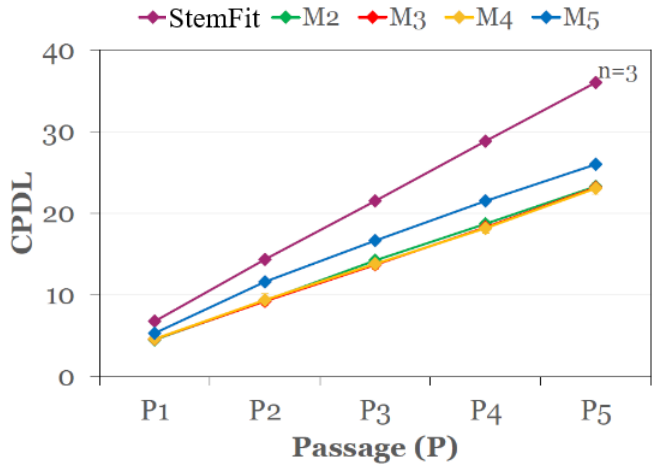




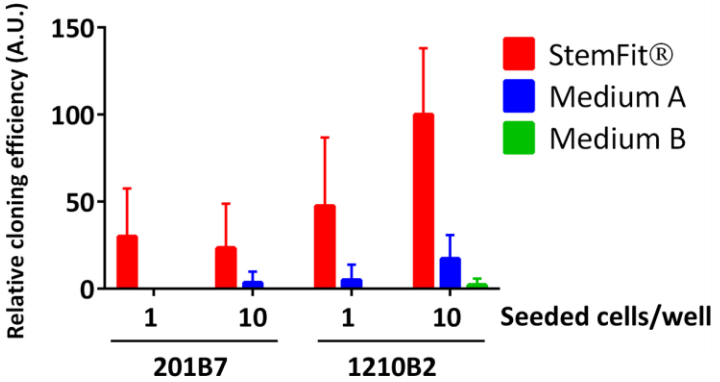
Nat Protoc. 2017 Jan;12(1):195-207

hPSC growth profile and cloning efficiency (ratio of correct clones)

Growth



Cloning

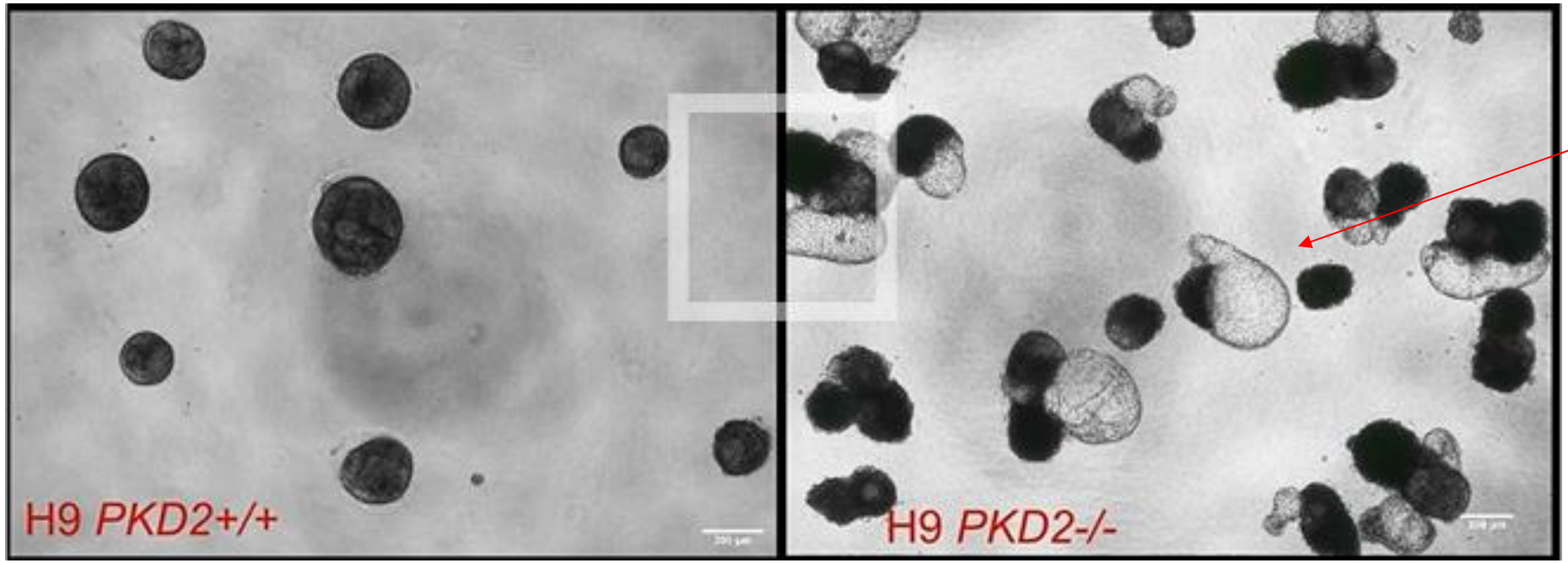


Internal data

- Organoid development is complex.
- It is critical to start with a uniform distribution of hPSC at Day 0.
- High quality growth and differentiation media ensures its correct development.
- “Cell viability and cloning efficiency were high, which contributed to the efficiency of genome editing” by Prof. Morizane

Case Study #1: Polycystic Kidney Disease (PKD) model for drug screening

PKD model by Dr. Cheng Jack Song and Prof. Andrew McMahon

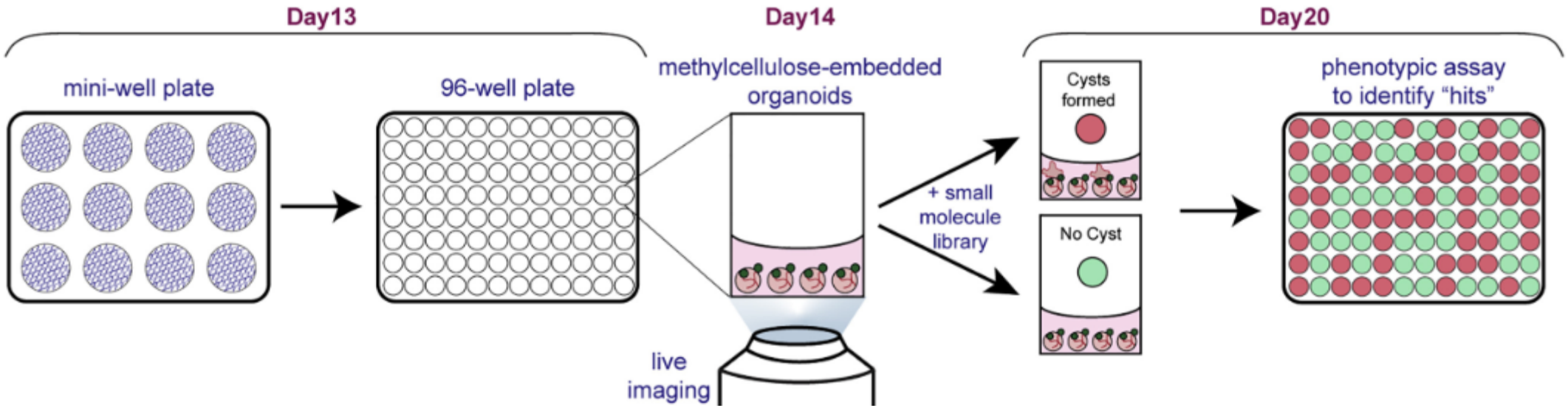


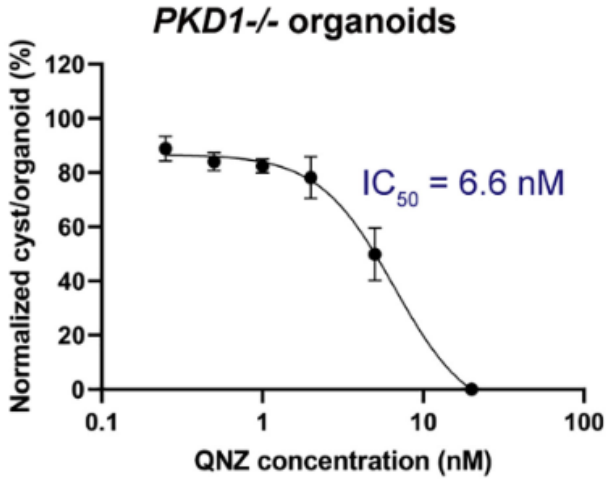
Cyst formation

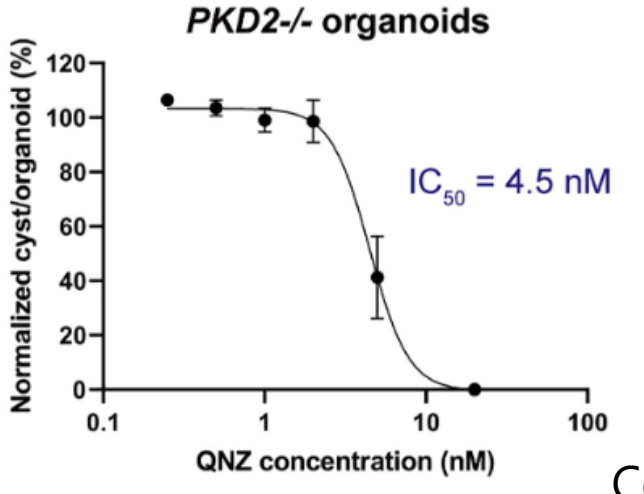
A PKD2 mutant was introduced in the organoid to trigger the formation of cysts, replicating a diseased tissue.

Cell Stem Cell. 2022 Jul 7;29(7):1083–1101.e7

Case Study #1: Evaluating the efficacy of a new compound using the organoid as a model



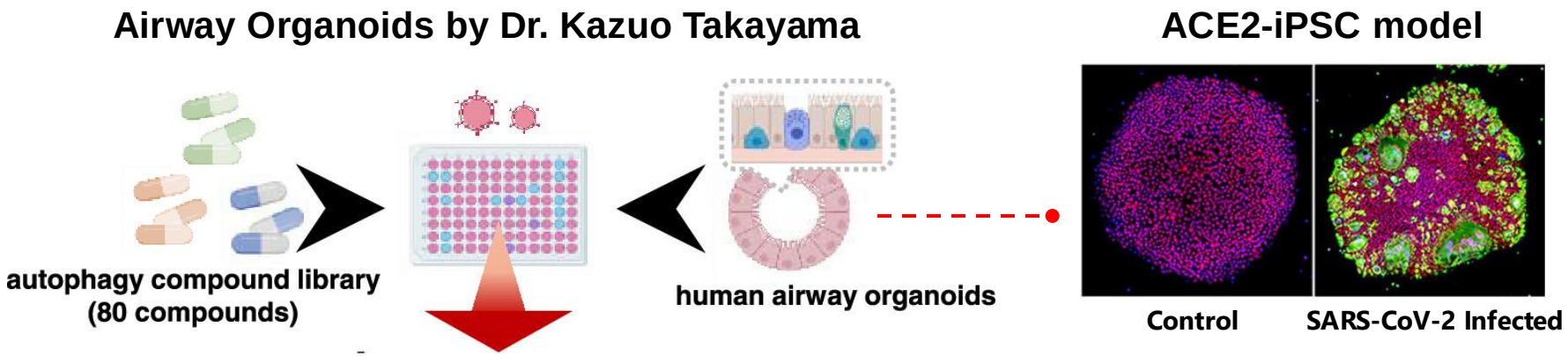


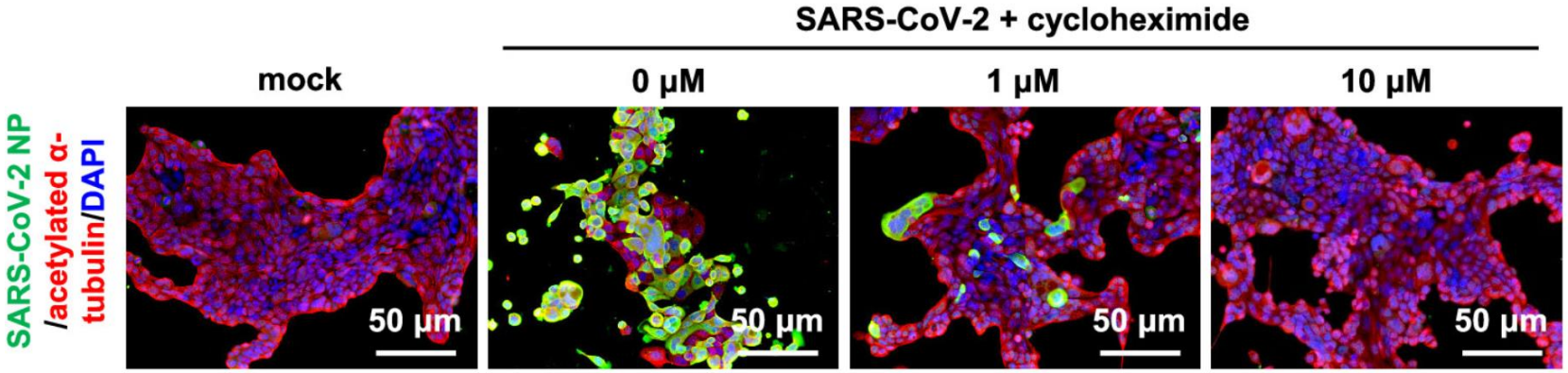


Quinazoline (QNZ) efficiently inhibited the cyst formation

Cell Stem Cell. 2022 Jul 7;29(7):1083–1101.e7

Case Study #2: Drug screening with iPSC-derived airway organoids





Approach

- Human airway organoids were infected with 6 variants of SARS-CoV-2
- 80 compounds were screened for performance
- **Cycloheximide** was identified as the most efficacious compound against SARS-CoV-2

Images courtesy of Dr. Kazuo Takayama

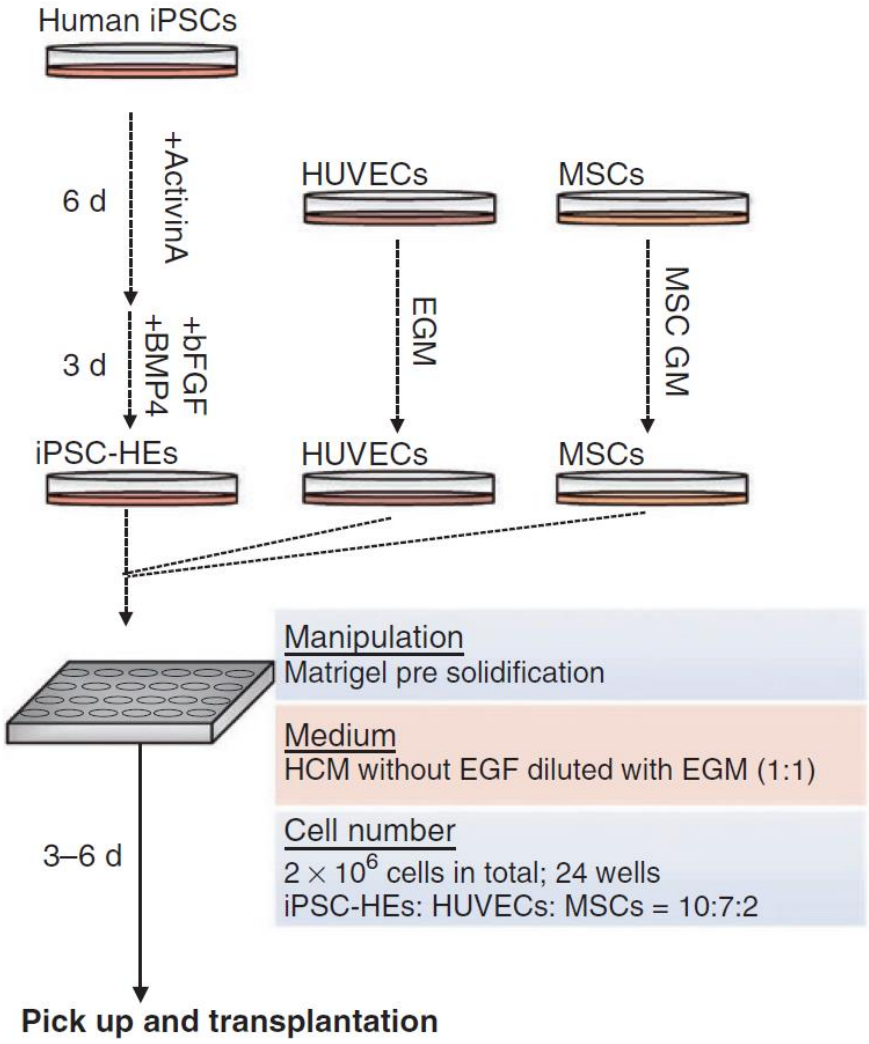
Mol Pharm. 2023 Apr 3;20(4):2276-2287

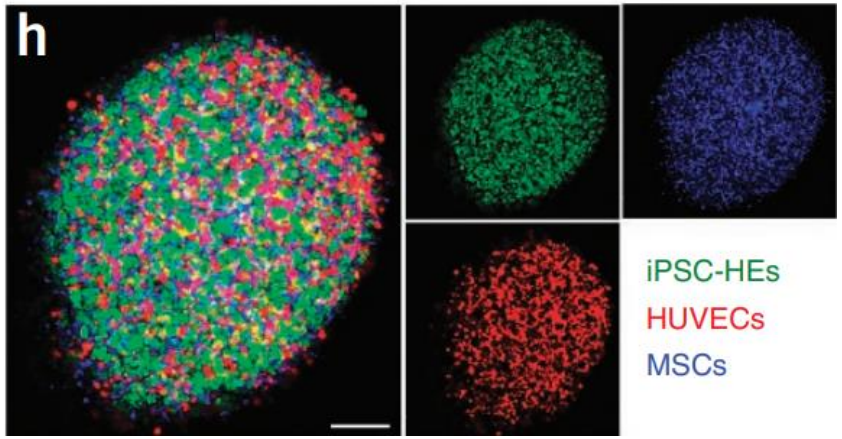
Today's topics

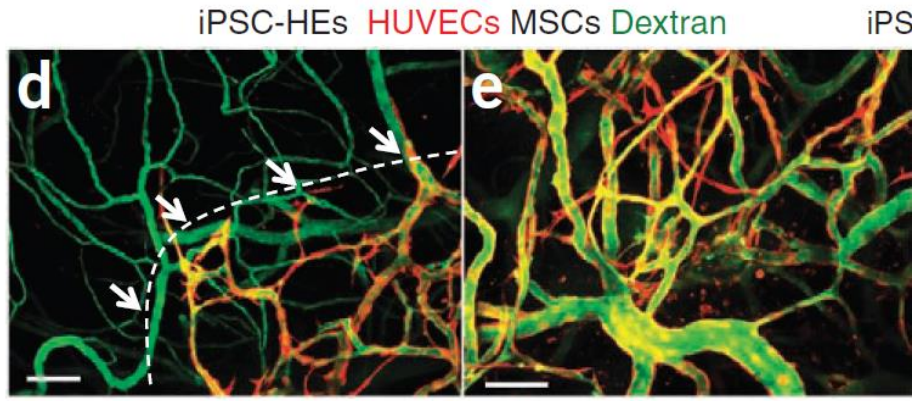
1. Drug Screening with Organoids
2. **Future Clinical Applications**
3. Importance of Ancillary Material for Safety and Quality

Case Study #3: Vascularized liver organoids

Liver Organoids by Prof. Takanori Takebe and Prof. Hideki Taniguchi





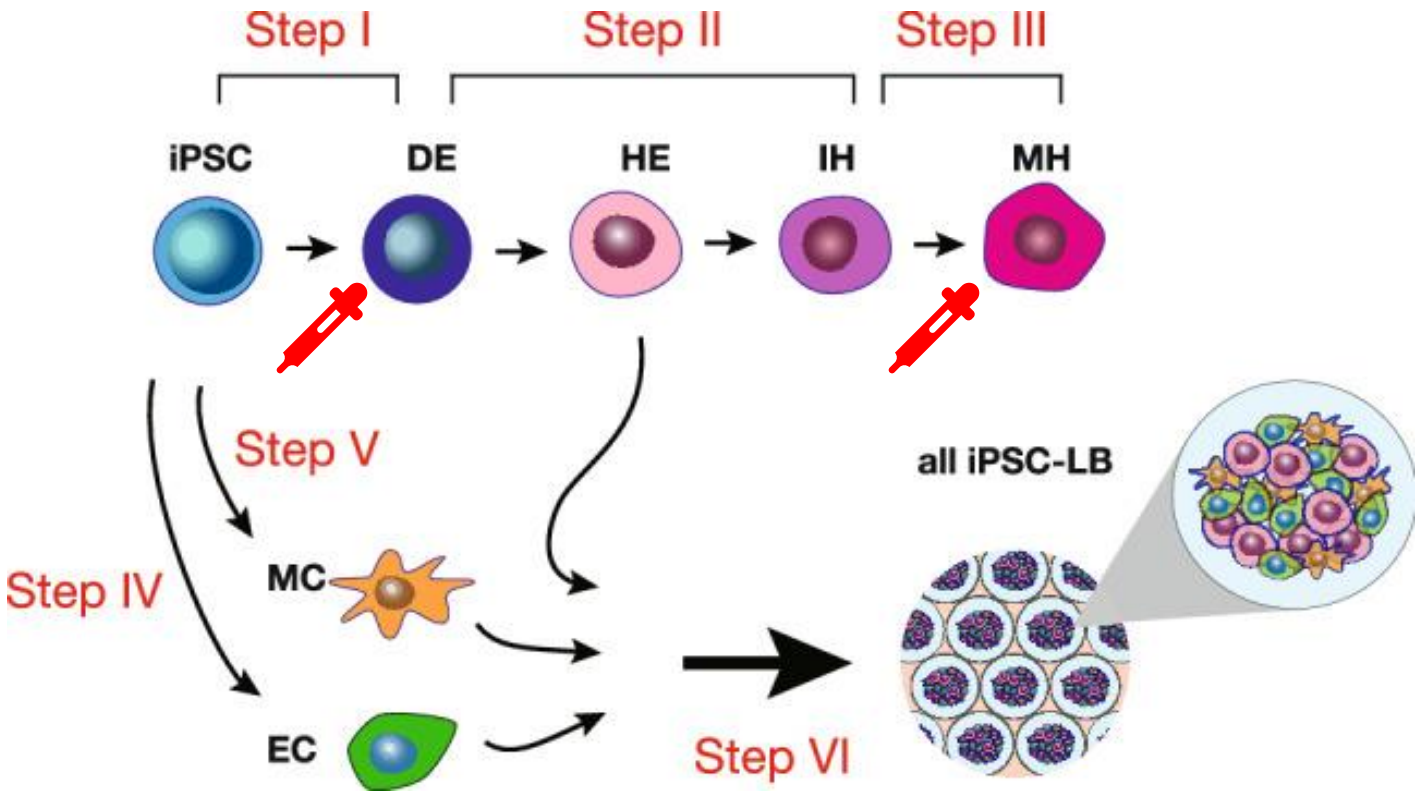


Approach

- Different cell types are combined to create a liver organoid.
- Liver organoid is transplanted into a mouse model.
- Die confirms correct vascularization of organoid in the model.

Nat Protoc. 2014 Feb;9(2):396-409

Case study #4: All iPSC-derived liver organoid



Sci Rep. 2020 Oct 21;10(1):17937.

Ajinomoto developed AOF supplement for differentiation

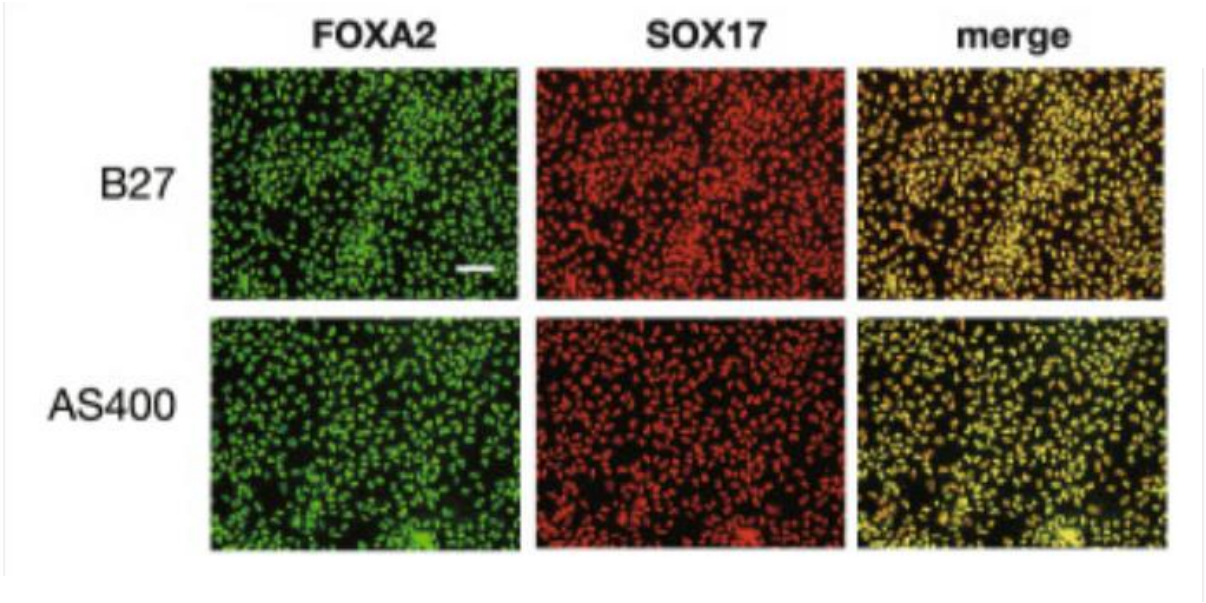
Approach

- Dr. Takebe and Dr. Taniguchi's group at the University of Cincinnati produced **all iPSC-derived liver organoids** by mixing iPSC-derived hepatocytes, mesenchymal cells, and endothelial cells,
- Ajinomoto collaborated with the researchers to develop an **animal origin-free (AOF)** supplement for liver organoid differentiation to optimize quality and differentiation performance.

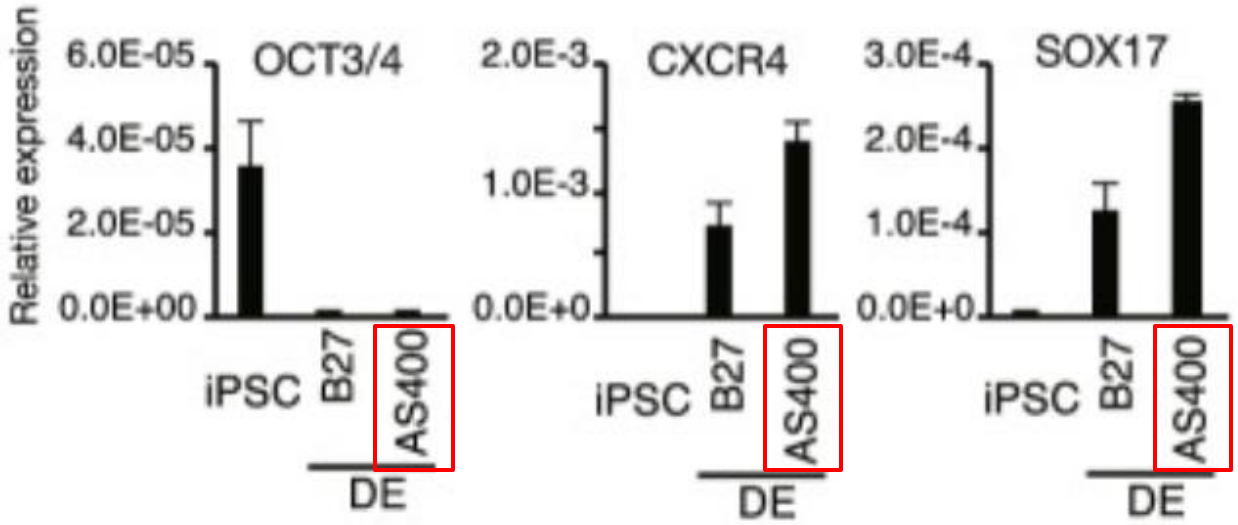
*AOF product does not contain any human or animal-derived ingredients

Case study #4: We developed a customized differentiation media

Definitive Endoderm Differentiation



Key Differentiation Markers – OCT3/4, CXCR4, SOX17



Approx. 2x higher marker expression

Ajinomoto AOF supplement (AS400) successfully replaced B27 and enhanced the differentiation into definitive endoderm

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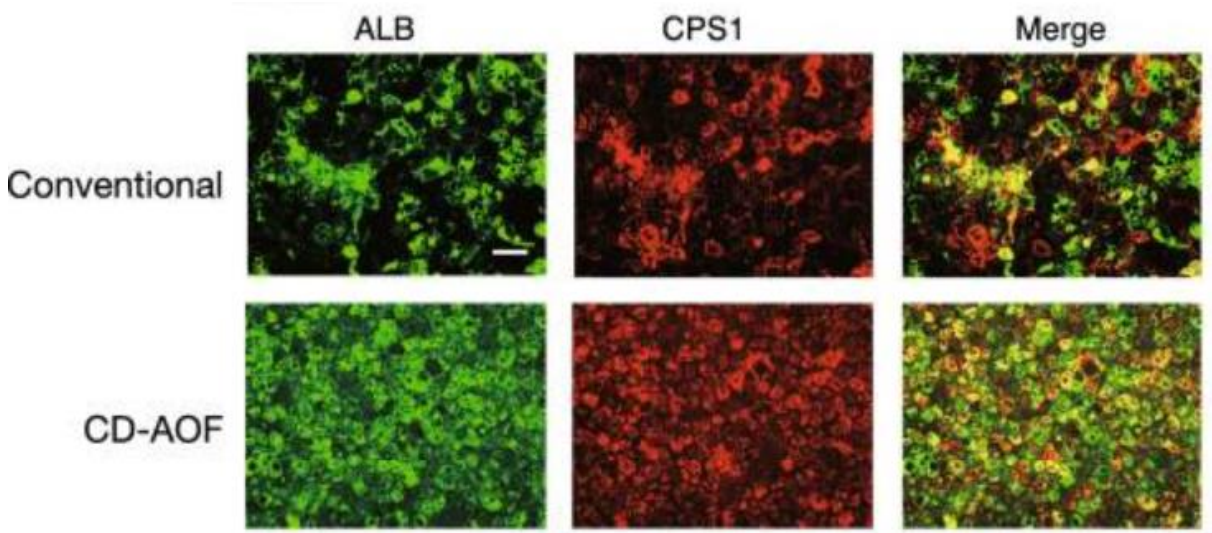
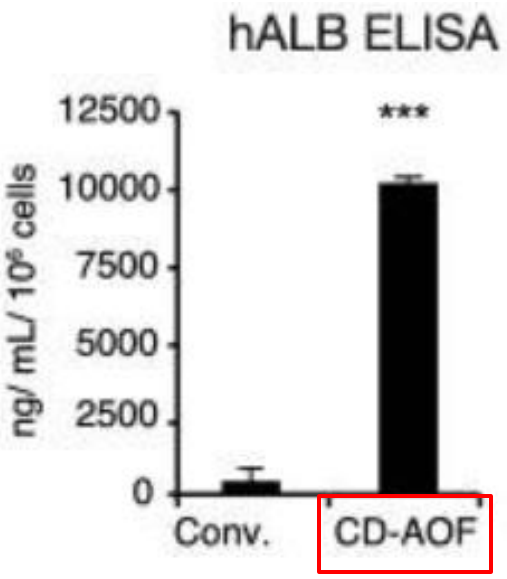
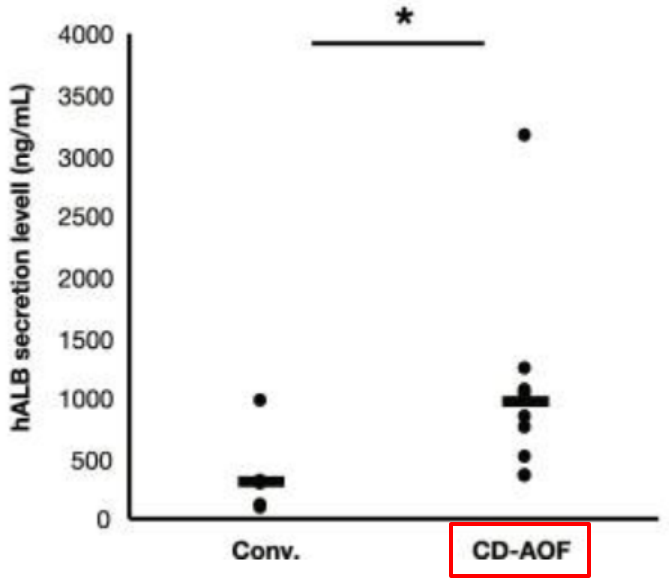
Case study #4: Customized media enhanced differentiation performance

Mature Hepatocyte





Liver organoids



The new AOF protocol improved the function of hepatocyte and liver organoid

*CD-AOF: Chemically Define-Animal Origin Free

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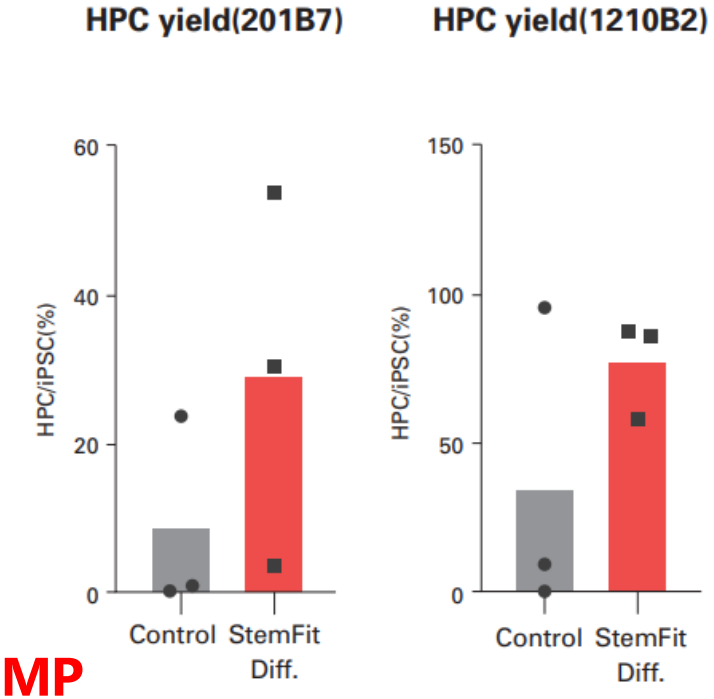
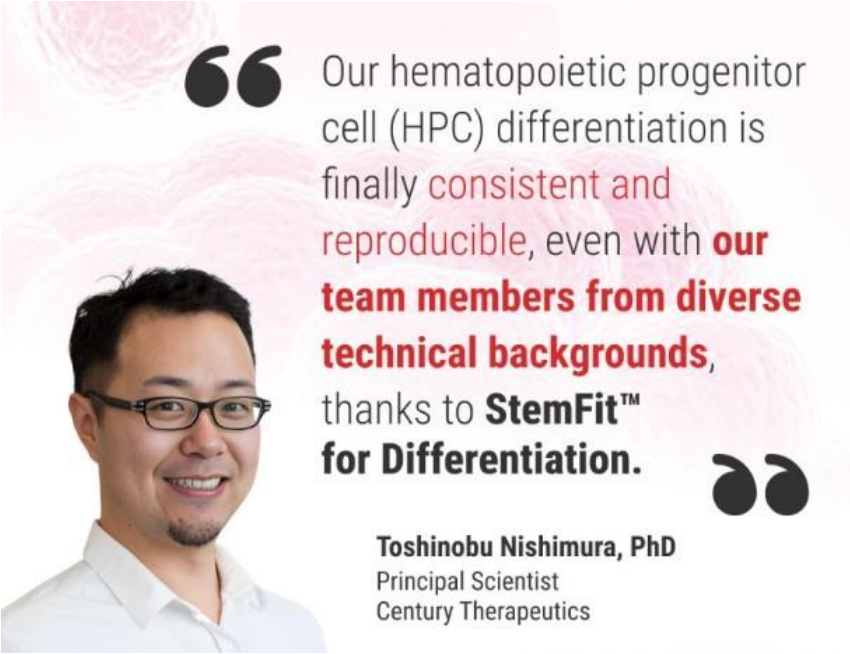
AS400 application for other cell types

StemFit For Differentiation GMP (AS400)





Today’s topics

1. Drug Screening with Organoids
2. Future Clinical Applications
3. **Importance of Ancillary Merial for Safety and Quality**

Guidelines for Ancillary Materials to ensure safety and quality

- ISO20399:2022 sets out the requirements and recommendations for both suppliers and users of ancillary materials (AMs) to ensure the safety and performance of the manufactured cell products. GMP should be considered in manufacturing AMs.

- USP1043 provides guidance on the development of appropriate qualification programs for AMs used in cell, gene, and tissue-engineered products. Appropriate guidelines (such as GMP) should be taken into account. Animal-derived materials are considered to be high-risk
- FDA published draft guidance for animal-derived materials used in cell & gene therapy.

- Standards for Biological Materials apply to all animal-derived materials, including those from humans.
- EP5.2.12 focuses specifically on materials extracted from various biological sources or produced by recombinant DNA technology and addresses risk assessment, manufacturing, and quality control.

GMP and animal-derived materials are key considerations for clinical use.

*Culture media and recombinant proteins are categorized into Ancillary materials (AMs) in the regulatory framework.

Animal-Origin free (AOF): Ajinomoto's approach

Issues related to animal-derived materials

- Animal components risk **zoonoses and immune reactions**. (Astori et al., 2016)
- Risk of **pathogen transmission** from human plasma material (Gröner, 2008)

- Animal derived products has **donor variations**. (Price, 2017)
- **Lot-to-lot variability** in BSA results in inconsistencies. (Ieyasu et al., 2017)

- Procuring the materials such as FBS and hPL has become a challenging task due to **their shortage**, and securing a good lot is always difficult.

Summary

- hPSC-derived organoids are potent tools for pathology modeling and drug screening
- Organoids are being explored as a potential future clinical application.
- GMP and animal-derived materials are key considerations for culture media in clinical use. Especially, animal origin-free (AOF) is more difficult to manufacture
- Ajinomoto provides GMP-compliant AOF media for hPSCs expansion and differentiation, ensuring consistent and high-quality cell manufacturing.