Orchard Bio Inc.

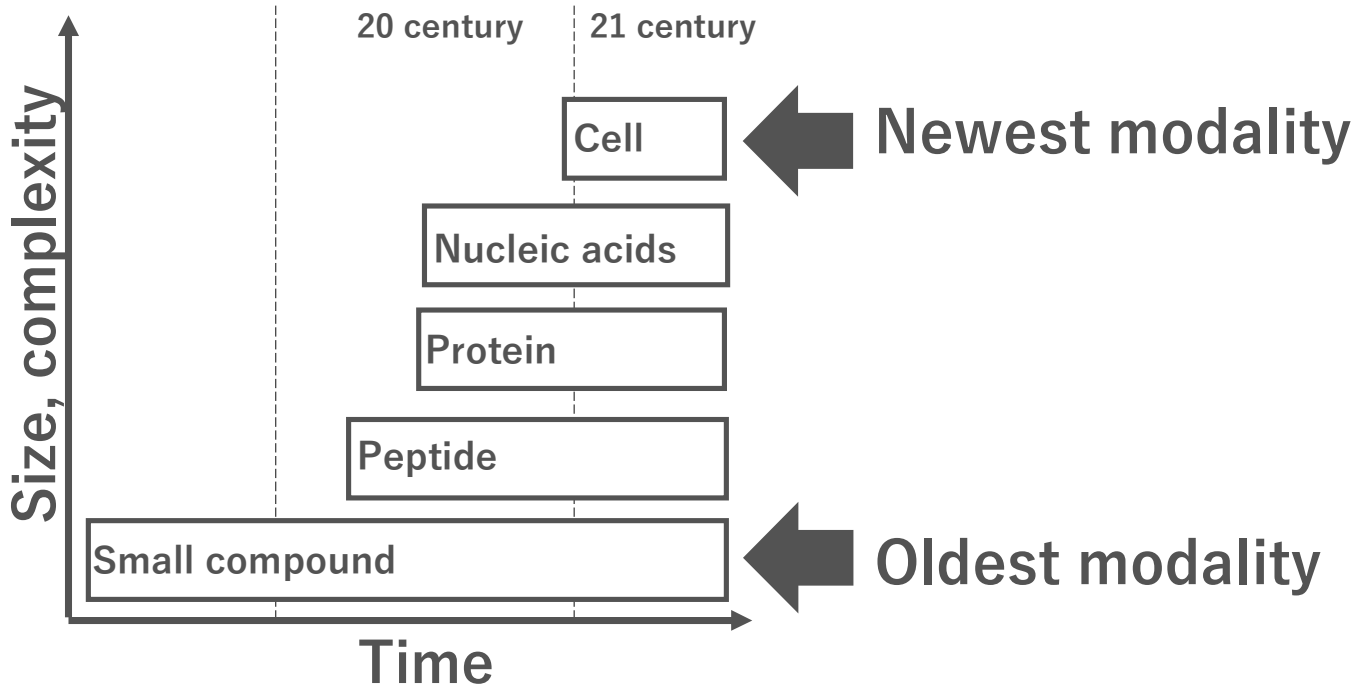
New concept of Cell Therapy with “hAP cell” :

Combination of conventional pharmaceutical and living cell

Orchard Bio

History of pharmaceutical development

After 20 century, more complex modalities are developed



Problems of cell therapy product

Important players of regenerative medicine, but still immature,

- Higher manufacturing cost
  Extensive facilities and controls are necessary in the manufacturing processes
- Less efficacy
  Intrinsic cellular functions are decreased along the manufacturing processes
- Uneven efficacy
  Even same cell types give rise to the inconsistent efficiencies from doner to doner

Problems of small compounds (drugs)

- Almost all of possible basic molecular structures are already revealed

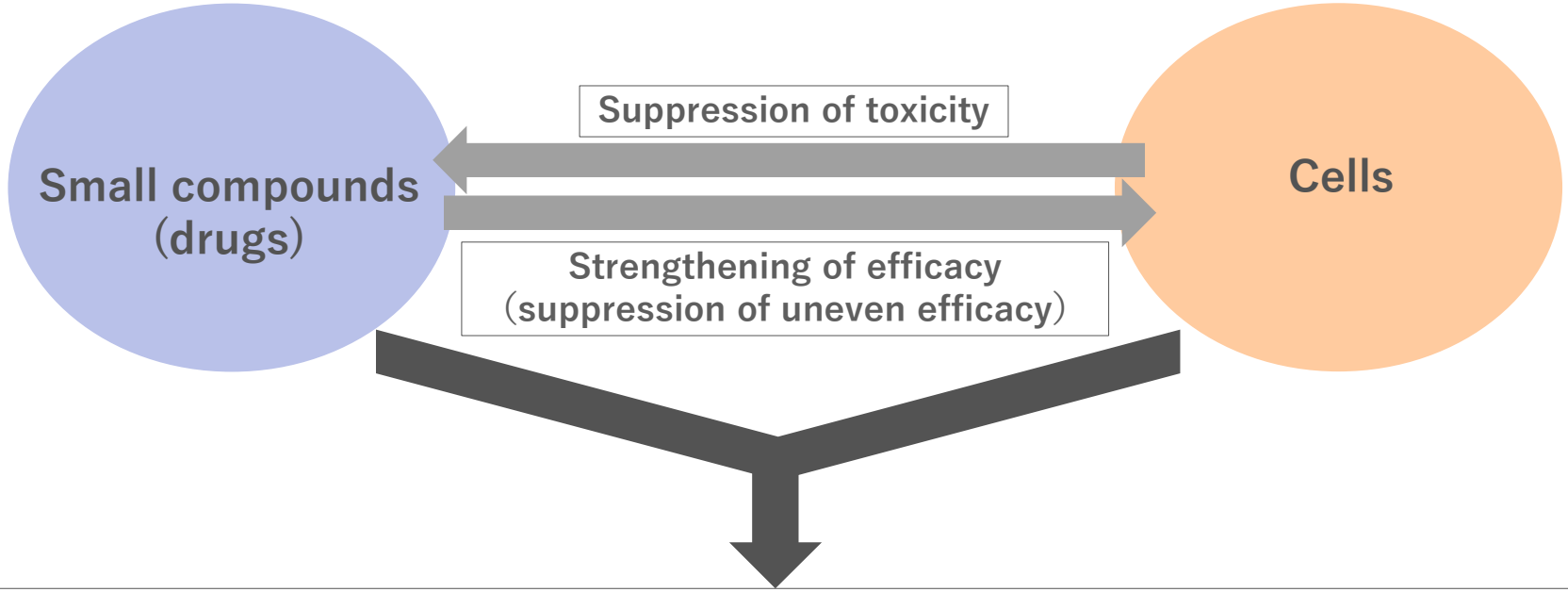
Current approach: utilization of the existing compounds

⇒exploring novel target molecules

⇒suppression of toxicities, for example by using DDS

Approach of Orchard Bio

Complement of each problem in the combination of drugs and cells

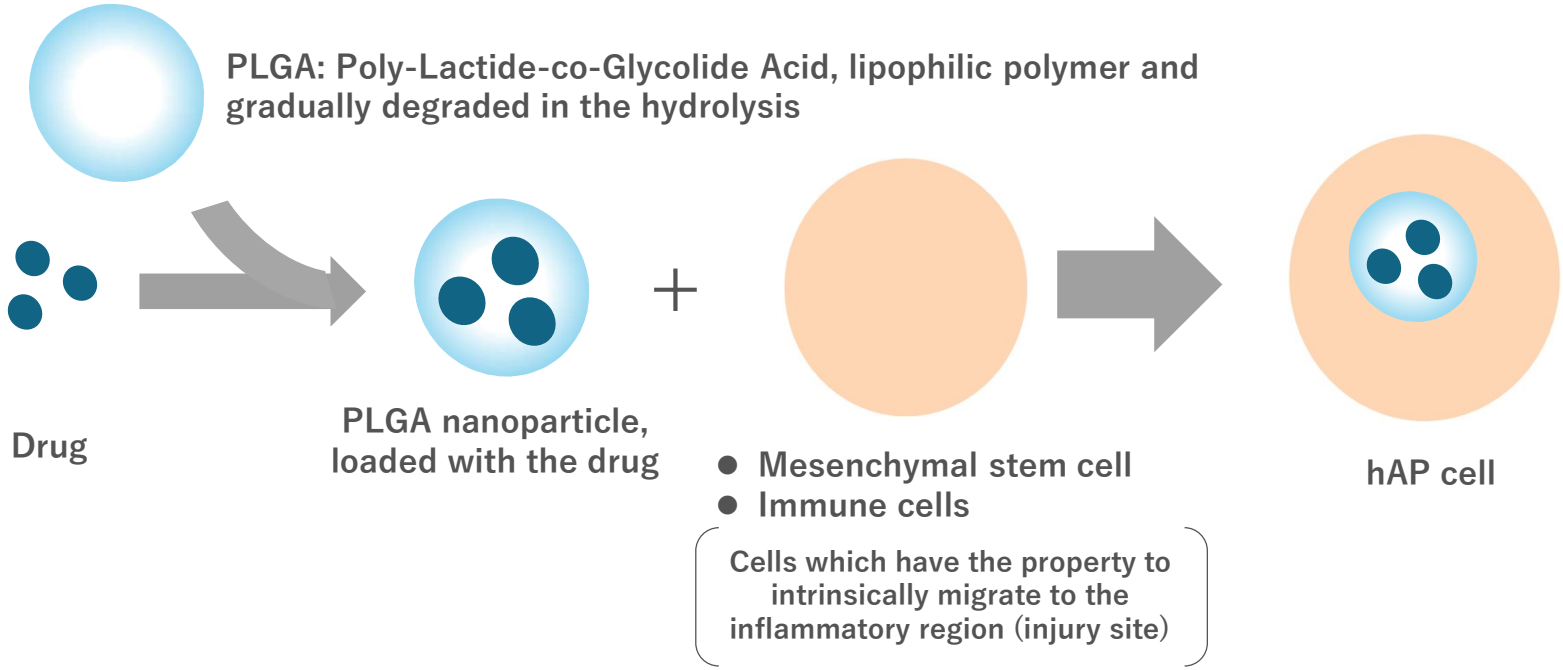


Combinational pharmaceutical composing of drugs and cells
＝hAP cell

hAP cell: holding Active Pharmaceutical Ingredient cell

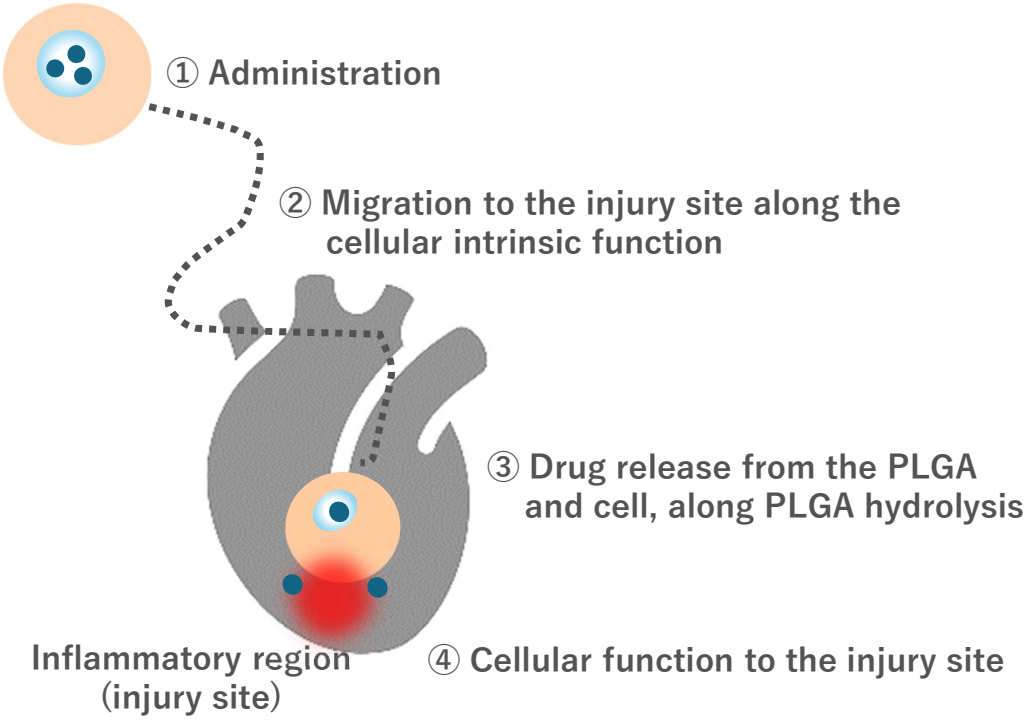
Manufacturing process of the hAP cell

PLGA nanoparticles loaded with the drugs are incorporated to the cell



Function of the hAP

Living cells are used as API and also as DDS for the inside drug



Advantage for the drug

Cellular DDS function enables to reduce the dose, resulting in the suppression of the toxicities

Advantage for the cell

Release of inside drugs provides another therapeutic effect in addition to the cellular function

Comparison of competitors

As cell therapy product or as DDS for drugs

Comparison as cell therapy product

	Cost	Efficacy	Uneven efficacy
Normal cell	△	△	×
CAR-T cell*	××	○	○
hAP cell	△○	○	○

＊CAR-T cell: Chimeric Antigen Receptor-T cell, T cells that artificially express specific membrane antigens are artificially expressed in T cells. The application is currently limited in cancer therapy

Comparison as DDS

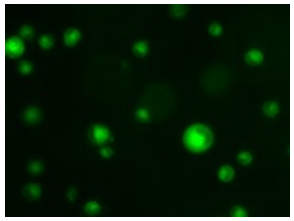
	Delivery	Gradual release	Suppression of toxicity
ADC**	○	△	△
Nano*** particle	△ ×	○ △	○
hAP cell	○	○	○

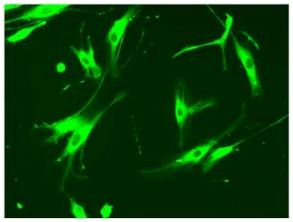
＊ADC: Antibody Drug Conjugate, The application is currently limited in cancer therapy
＊＊＊ Nanoparticle: Liposomes or lipid-soluble nanoparticles, etc. Attempts to improve delivery to the ntargets are underway

Characteristics of hAP cell

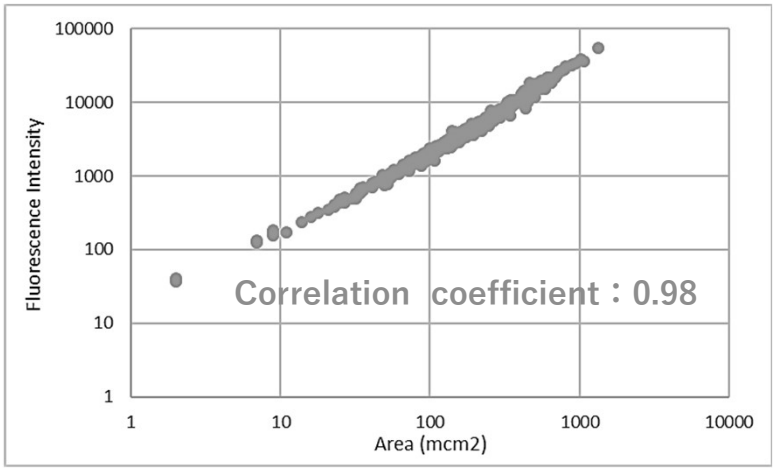
Incorporation of the PLGA nanoparticles into the cells

Incorporation of Coumarin6-loaded PLGA nanoparticles into the MSCs

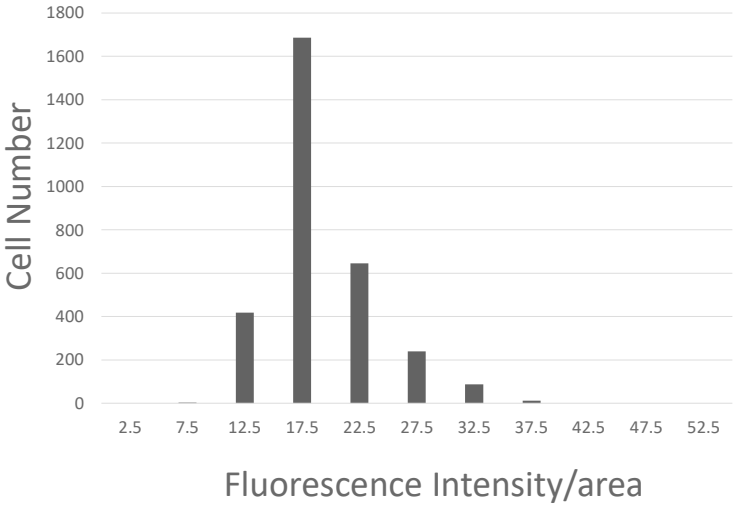




Plot of FI/Cell and the cellular sizes



Distribution of FI/cellular size



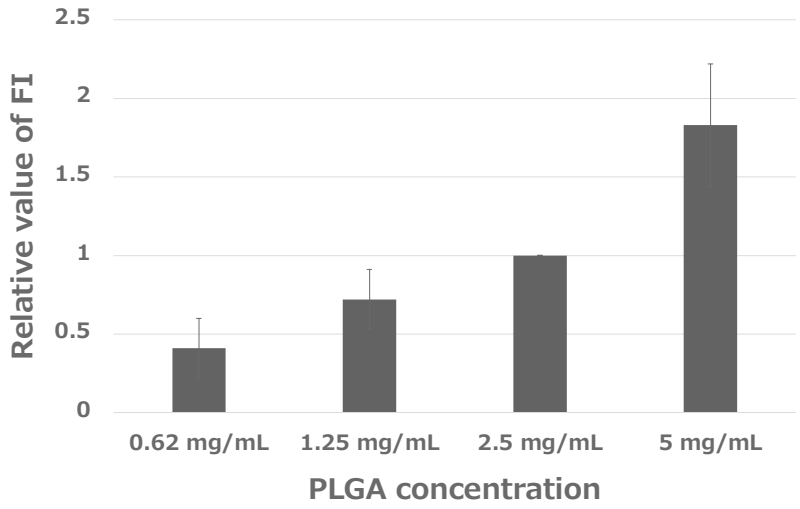
PLGA nanoparticles are incorporated into the cells according to the cellular sizes

Characteristics of hAP cell

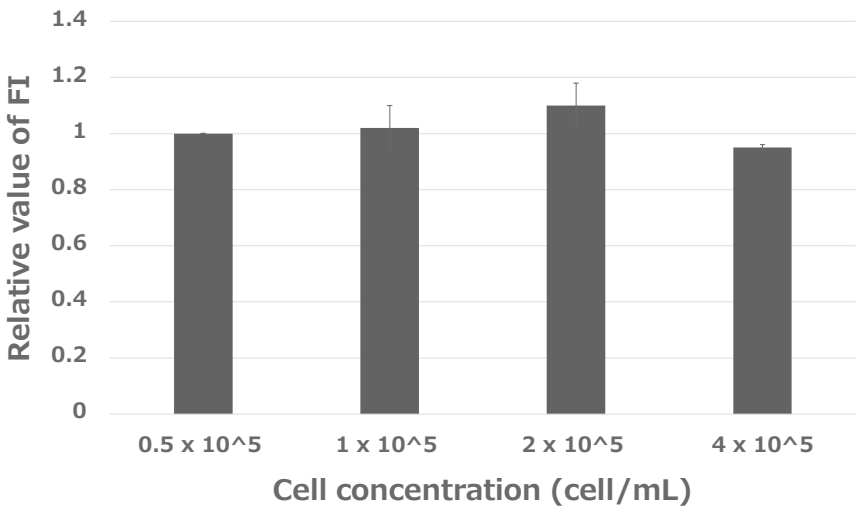
Influence of the concentrations in the manufacturing process

Incorporation of Coumarin6-loaded PLGA nanoparticles into the MSCs

Influence of the PLGA nanoparticle concentration



Influence of the cellular concentration



The drug contents in the hAP cell are dependent on the nanoparticle concentration but not on the cell concentration

Characteristics of hAP cell

Robustness of the drug contents in the same manufacturing process

Incorporation of Minoxidil-loaded PLGA nanoparticles into the MSCs

Test number	Drug contens
Test-1	45.7ng/10^5 cells
Test-2	52.5ng/10^5 cells
Test-3	46.1ng/10^5 cells
Test-4	41.8ng/10^5 cells
Test-5	36ng/10^5 cells
Test-6	40.8ng/10^5 cells

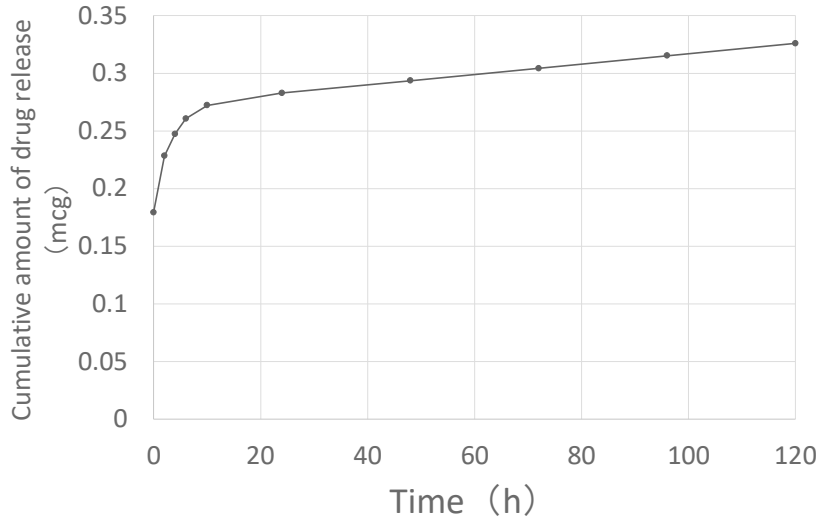
Average	43.82
SD	5.63
CV	12.85

The drug content in each hAP cell lot is consistent in the same manufacturing processes

Characteristics of hAP cell

Kinetics of the drug release from the hAP cells

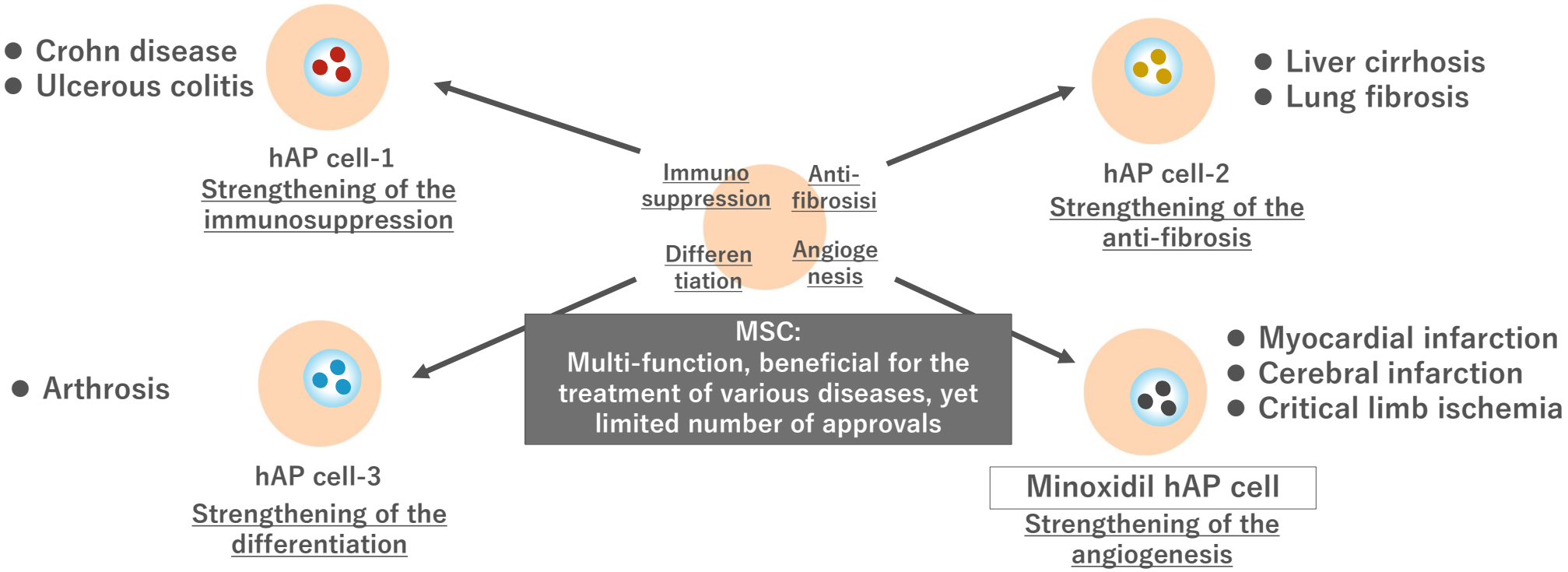
Drug release from statin hAP cell



The drug release become stable after 12 hours and is constantly maintained at least for 5 days

Application of the hAP cell-1

Strengthening of efficacy in Mesenchymal Stem cell (MSC)

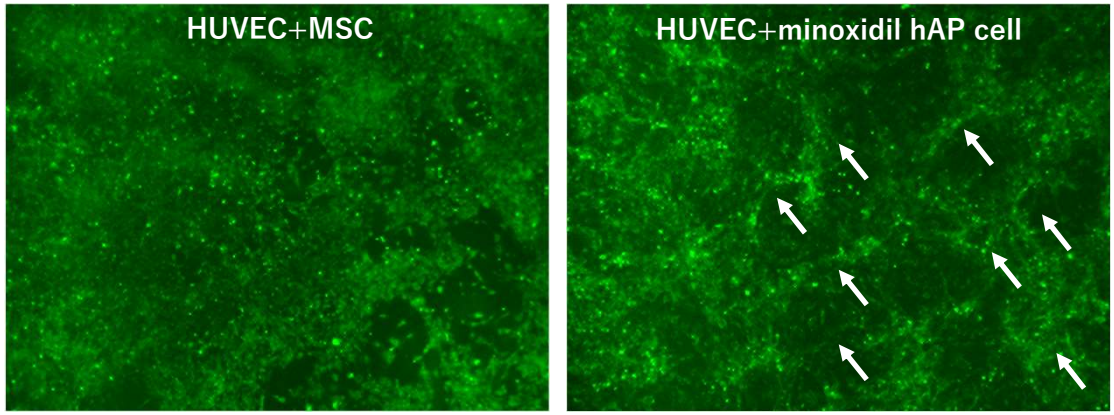


Minoxidil hAP cell

Drug: minoxidil
Cell: MSC

Availability of the Minoxidil hAP cell

- It is found that minoxidil, known to have vasodilatory property, exhibit enhancement of HUVEC angiogenesis in the presence of MSC
- Minoxidil hAP cell configuration enable to drastically reduce minoxidil dose to enhance HUVEC angiogenesis, beneficial to suppress minoxidil toxicity



Angiogenesis (the formation of blood vessel-like structures) was confirmed after 48 hours of co-culturing with fluorescently labeled HUVEC (Human Umbilical Vein Endothelial Cell).

Clinical target

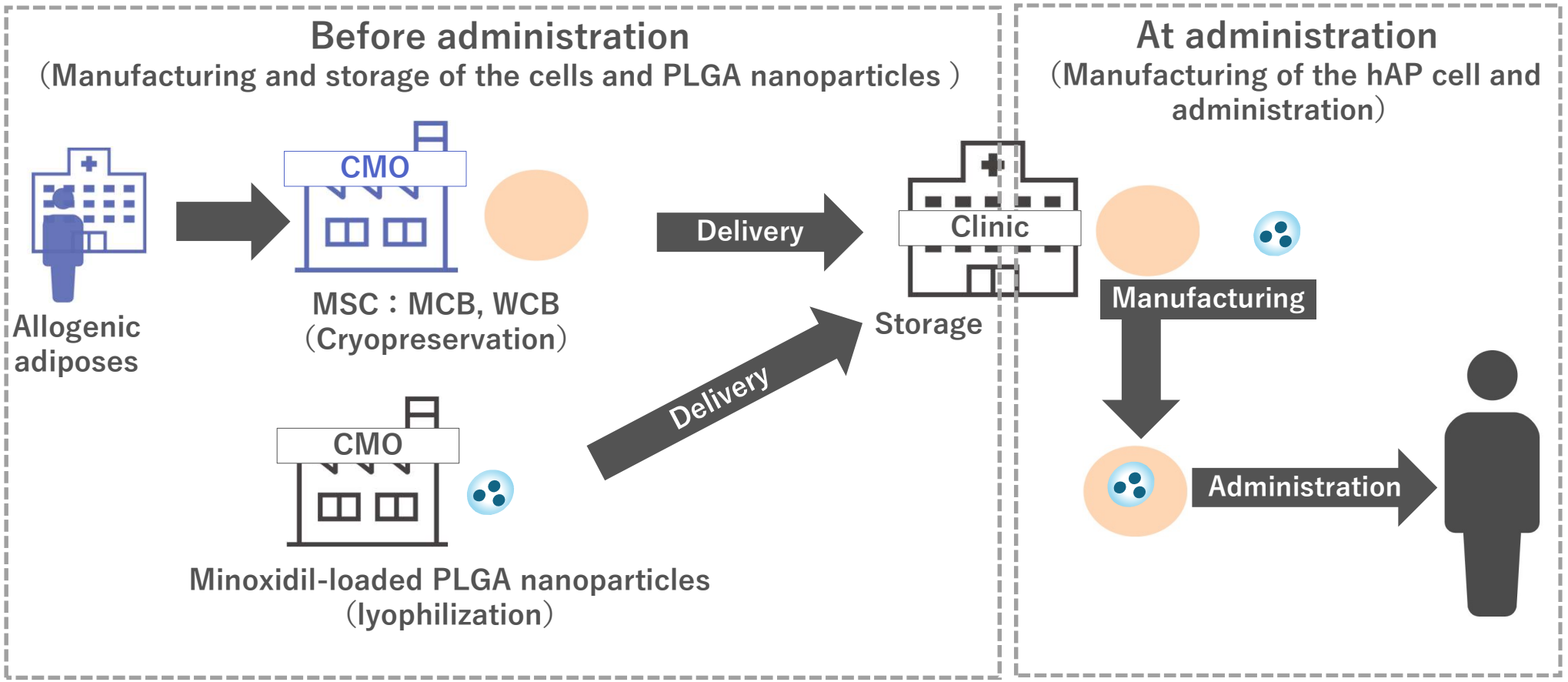
Therapy to ischemic diseases, using the hAP cells with the allogenic MSCs

Rationale

- ✓ **Strengthening of angiogenesis**
- ✓ **Repression of toxicity by reducing minoxidil dose**
- ✓ **Reasonable product price and appropriate timing of treatment by using allogenic MSCs**

Target indication：Critical limb ischemia (CLI), Cerebral infarction, Myocardial infatction, etc.

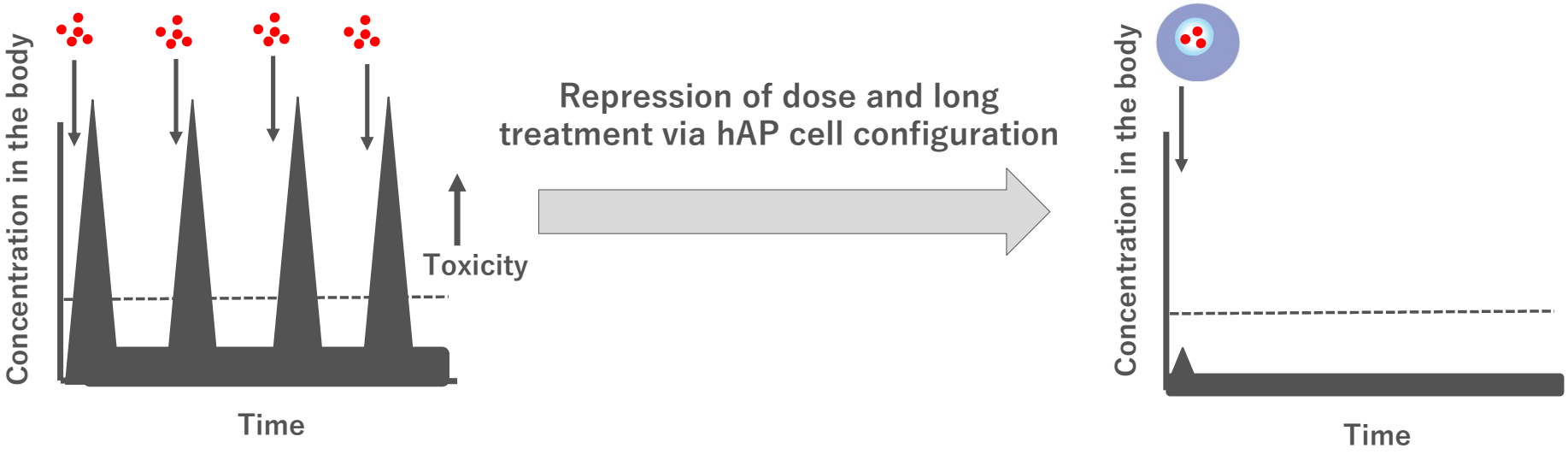
Clinical operation for the Minoxidil hAP cell



Application of the hAP cell-2

Optimal formulation of cyclosporine, high toxicity and low stability

Cyclosporine: strong immunosuppressive drug known to act to T cells. Pharmacokinetic monitoring is necessary because of its strong toxicity. Moreover twice in a day of dosing is required because of its severe instability in the body



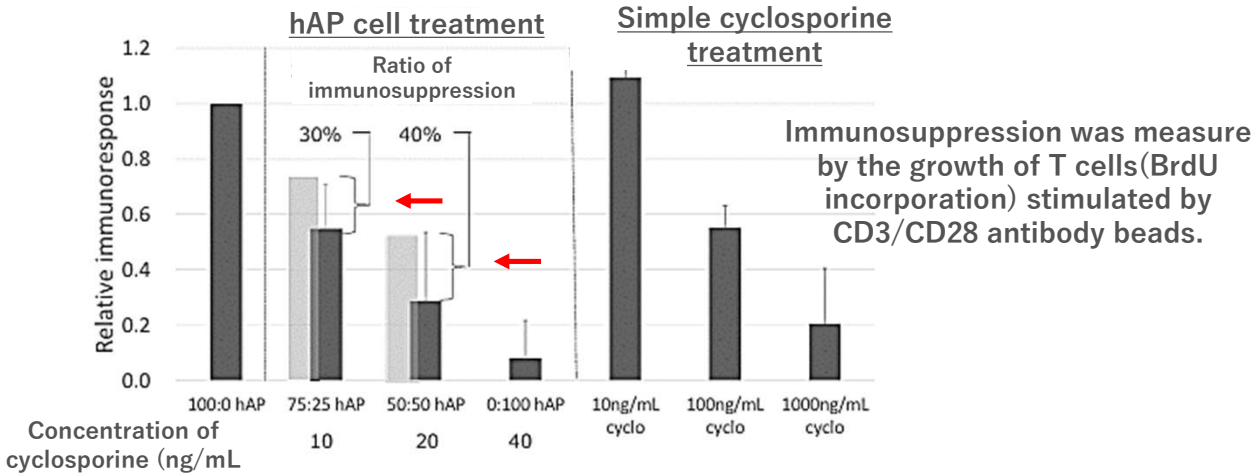
https://orchard-bio.jp/en-business/en-development/

Cyclosporine hAP cell

Drug: cyclosporine
Cell: PBMC
Peripheral Blood Mononuclear Cell

Availability of the Cyclosporine hAP cell

- 1/10 of dose is sufficient for immunosuppressive activity in the hAP cell configuration
- At leaset 5 days of drug release from the hAP cell
- No need of cell cultivation in case PBMCs are used for the hAP cell manufacturing



Immunosuppression was measure by the growth of T cells(BrdU incorporation) stimulated by CD3/CD28 antibody beads.

Clinical target

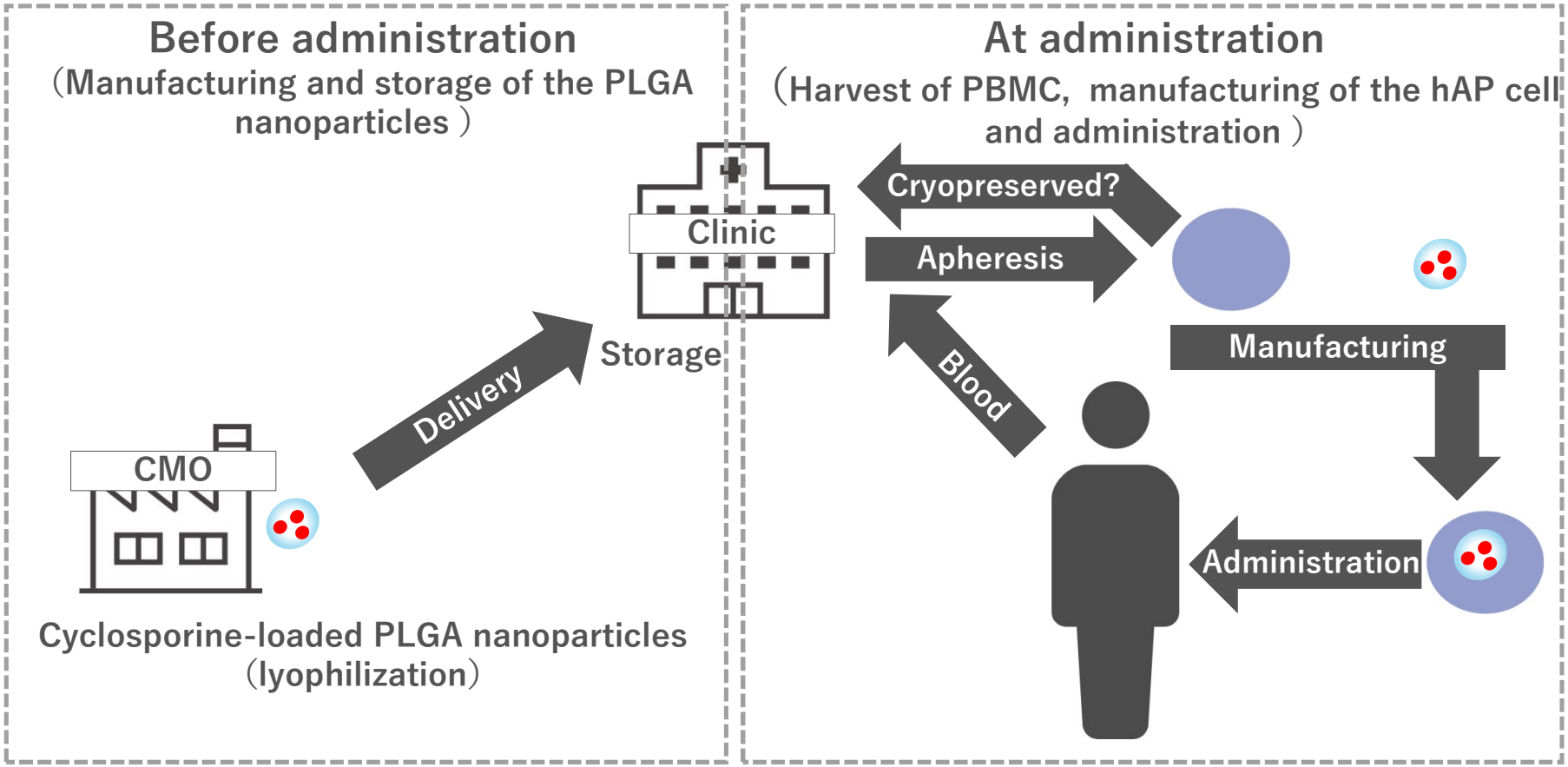
Therapy to autoimmune diseases, using the hAP cell with autologous PBMC

Rationale

- ✓ Long repeated treatment by reducing cyclosporine dose
- ✓ Reasonable product price by using non-cultivating cells

Target indication: Systemic sclerosis、Polymyositis、
Systemic lupus erythematosus, Chronic GvHD

Clinical operation for the Cyclosporine hAP



In-house pipeline

Each pipeline will be used for the appeal of hAP cell

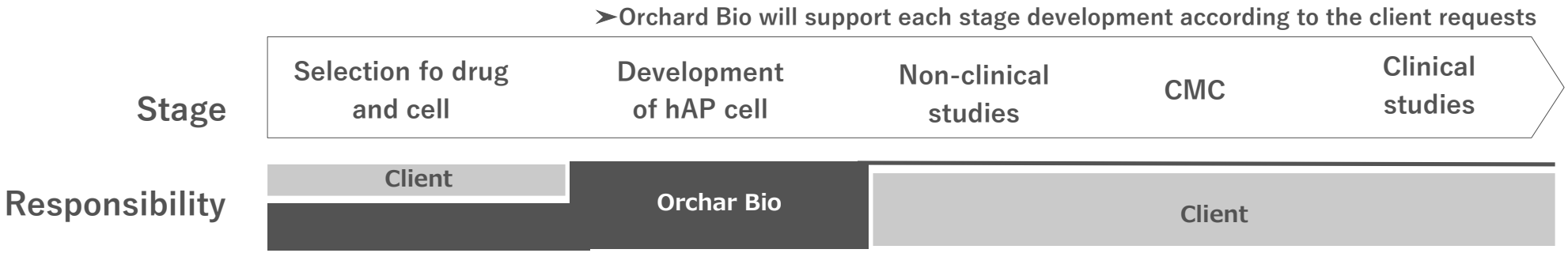
hAP cell type	Indication	Efficacy study		Safety study (non-clinical)	Clinical study
		in vitro	*in vivo*		
Minoxidil hAP cell	Ischemic diseases Alopecia	→	A collaboration has started with Foundation for Biomedical Research and Innovative at Kobe (FBRI)		
Cyclosporine hAP cell	Autoimmune diseases	→			
(X)hAP cell	Fibrosis	→	Screening for the selection of appropriate small compounds has started		
(Y) hAP cell	Cancer				

Future business plan

Business model：providing a platform to develop any hAP cells
Client：Pharmaceutical companies world wide

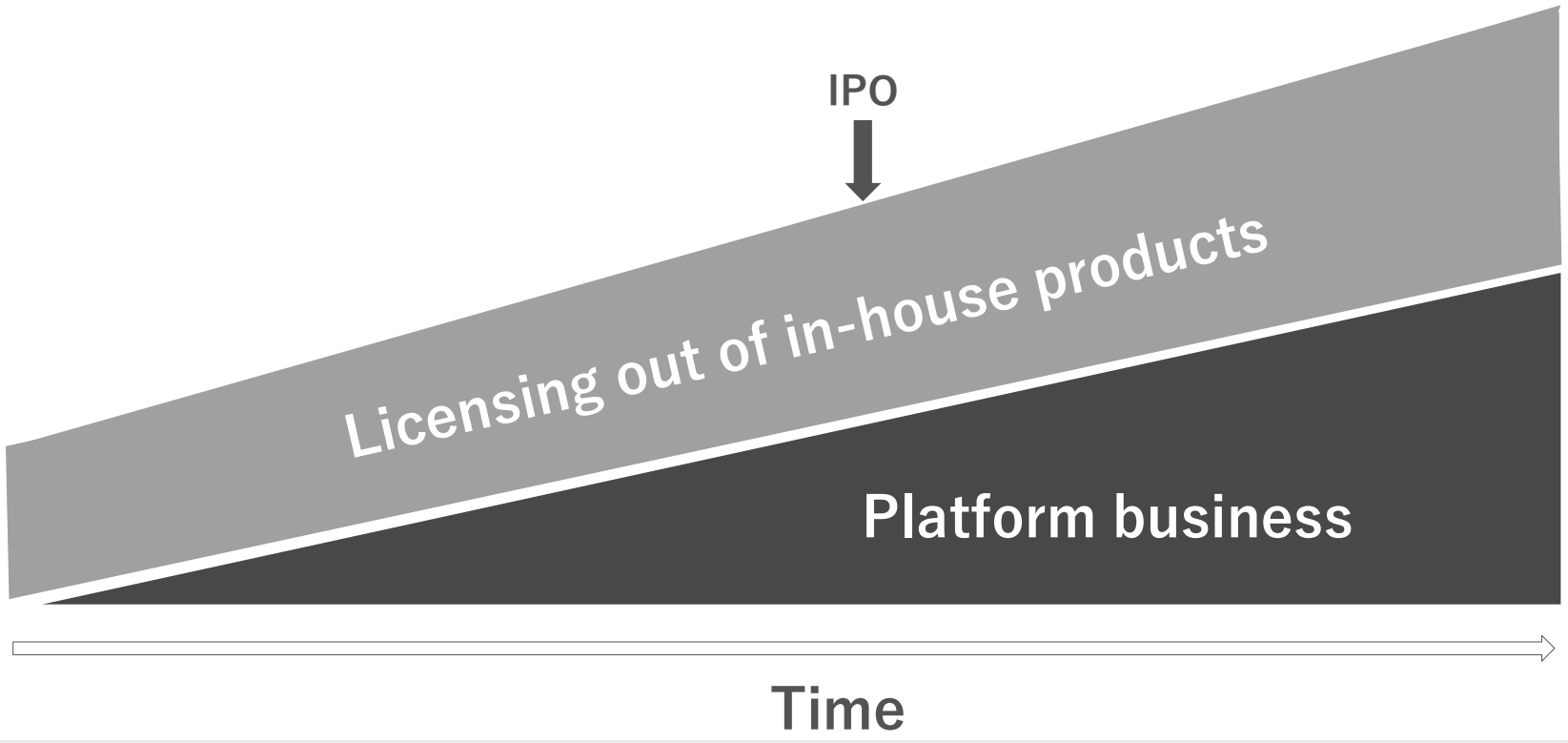
Orchard Bio takes responsibility mainly for constructing hAP cells, and the clients carry out other development stages.

- Enable to develop a lot of pipeline in the small manpower
- Enable risk hedge for each pipeline by increasing the number of the pipelines
- Revenue from contract fees, milestones, and post-sales royalties for each pipeline



Perspective

Promotion of licensing out of in-house products, Expand of platform business in the future



Patent information

Exclusive license right

- WO2016/076227：幹細胞機能増強用スタチン封入ナノ粒子製剤、並びにそれを含有する機能増強幹細胞及び その製造方法

➡ （precedent patent important for the start of hAP cell business）

Patent application in early 2024

- About utility of the hAP cells to reduce drug doses
- About vessels important in the manufacturing of the hAP cells

➡ （Critical patents in the hAP cell business）