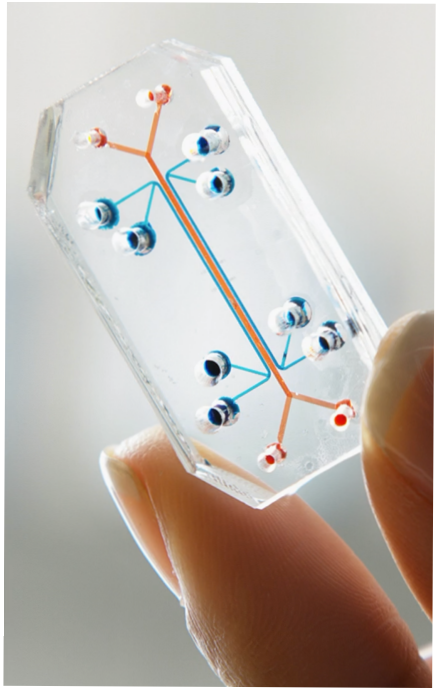
Discovery of a New Horizon

-Flow Chemistry to Human on a Chip-

Literature Seminar #2
19/6/2014
Takaya Ukai (M1)



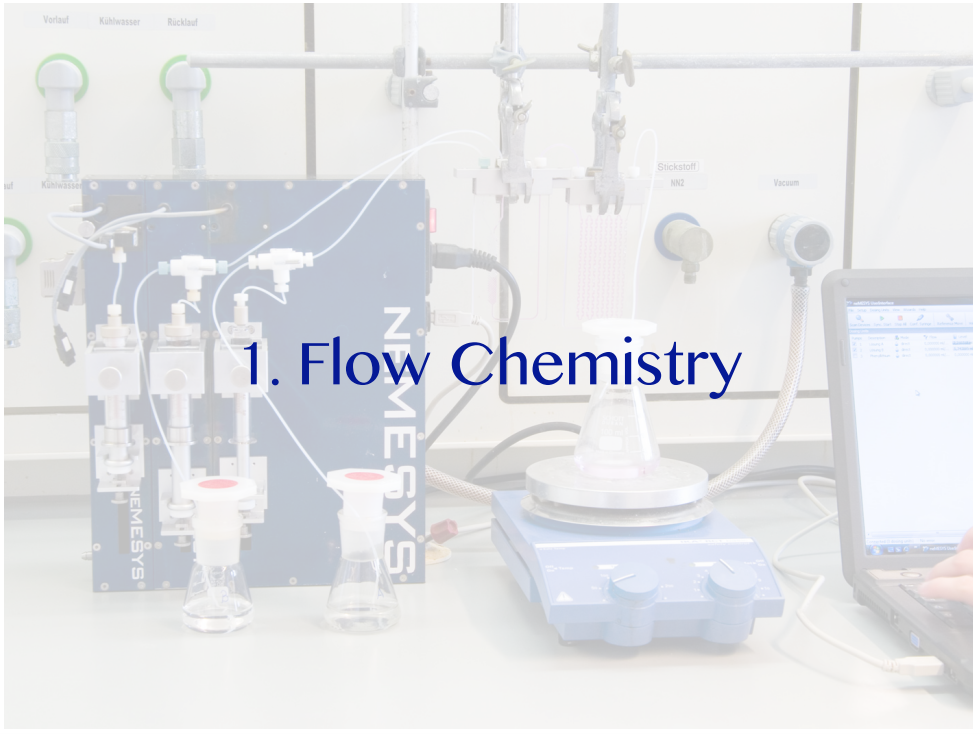
Technology

Value ⇒ **Function**

Function × **Concept** / **Technology**

⇒ **?** **Innovation**

Contents



1. Flow Chemistry

Goal of This Chapter

Hi! This is Akane! I will help you to follow the discussion. In this chapter, let's understand the "Functions" of Flow Chemistry. And that's it!

Assistant: Akane Hozuki
(a forensic scientist)

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First of All…

What is Flow Chemistry?

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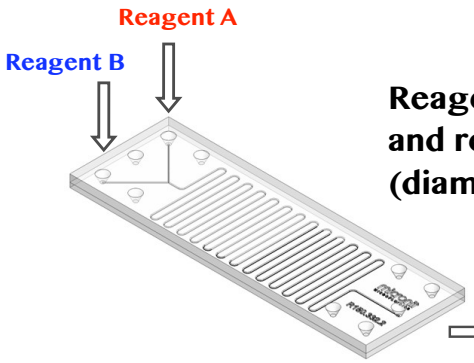
Reaction on a Chip

Flow Chemistry
= "Reaction on a Chip"

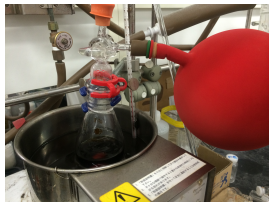


Reagents are mixed together and react in an ultra narrow tube (diameter: 100~500 μm)

⟹ **Product**

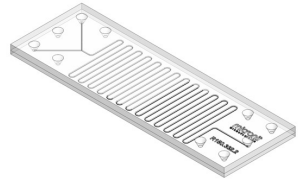
Difference from Flask and Tank

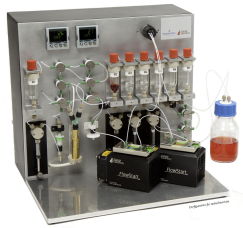
"Batch" System



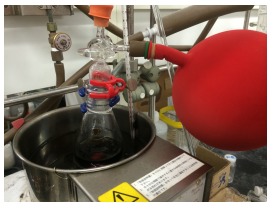
VS

"Flow" System

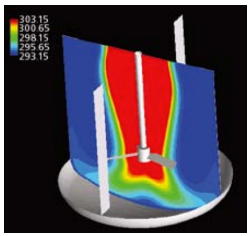




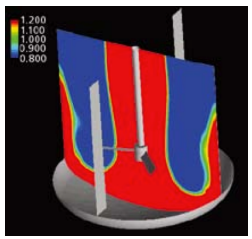
Batch System



- Scale ⇒ Size of the vessel
- Each process ⇒ Separated
- Heat ⇒ Poorer with Scale↑
- Mixing ⇒ Poorer with Scale↑



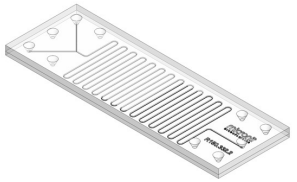
Heat distribution

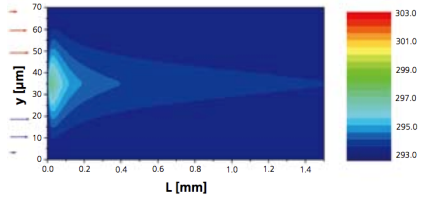


Mixing efficiency

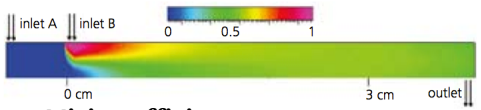
Flow System

- Scale ⇒ "Time" of Experiment
- Each process ⇒ Connected
- Heat ⇒ Almost homogeneous
- Mixing ⇒ Almost homogeneous

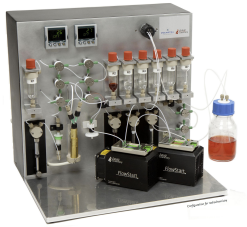




Heat distribution



Mixing efficiency



And then…

What can we do with Flow System?

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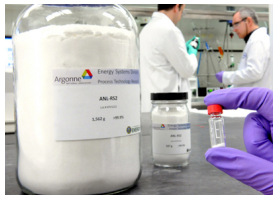
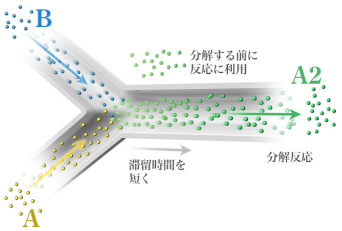
Advantages of Flow System

- **Scale Control**



- **Reaction Control**



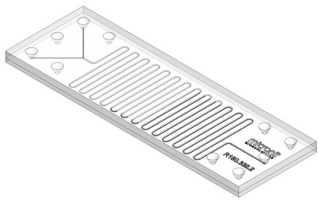
- **Connectable System**

- **Multistep Synthesis**

Scale Control

Production [g/min] = Flow Rate [mL/min]
× Concentration [mol/L]
× MW [g/mol]
× Yield [%] × 10^{-3}

Scale does not depend on volume but on time



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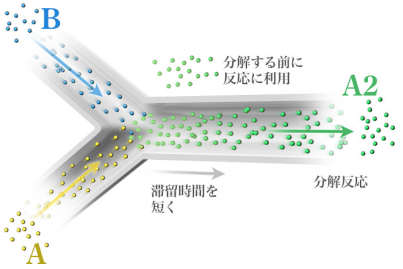
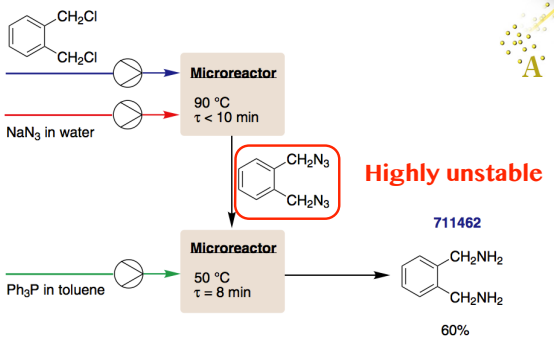
yt-engineering

Aldrich ChemFiles. Vol. 9, No.4, Microreactor Technology

Reaction Control

Controllable Factors:
- **Temperature (Heat Exchange)**
- **Pressure**
- **Dispersion, Mixing**
- **Reaction time (Retention time)**

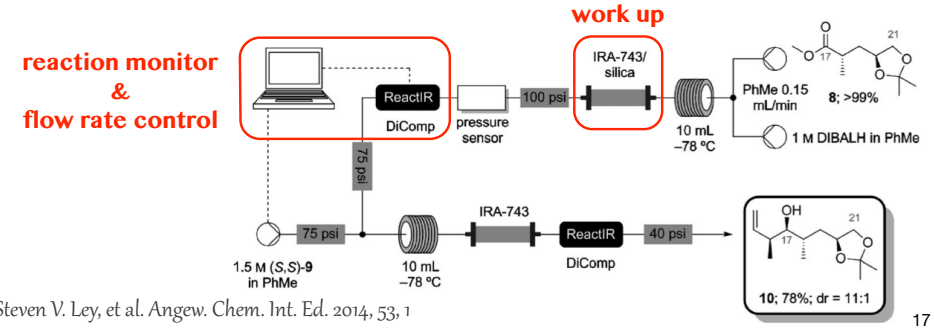




Kopach, M.; Murray, M.; Braden, T.; Kobierski, M.; Williams, O. Org. Process Res. Dev. 2009, 13, 152-160.

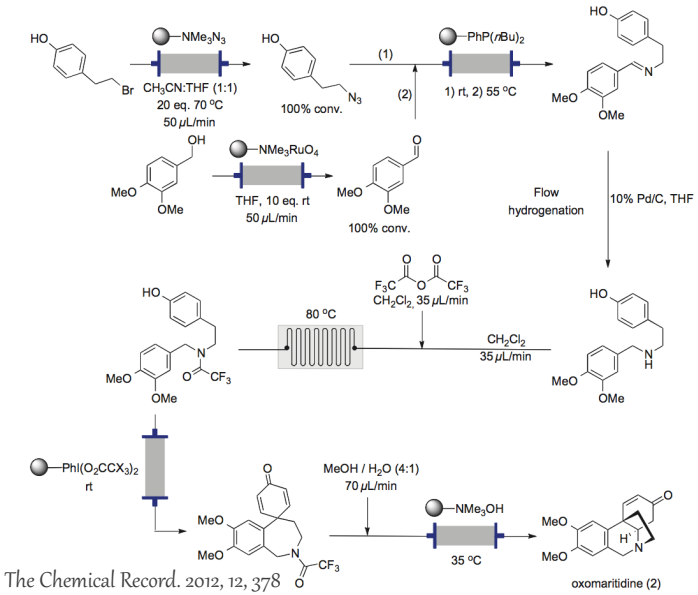
Connectable System

Connectable Apparatuses:
- **Column (short pad)**
- **FLLEX (liquid separation)**
- **ReactIR (reaction monitoring)**
- **HPLC (analysis)**
- **NMR (analysis)**



Steven V. Ley, et al. Angew. Chem. Int. Ed. 2014, 53, 1

Multistep Synthesis



Steven V. Ley. The Chemical Record. 2012, 12, 378

Disadvantages of Flow System

Weak Points:
- **Clogging (viscosity, large particulate)**
- **Gas evolution (shortens retention time)**
- **Pulsating flow**
- **Corrosion of microreactor**

Did you get it?
It's OK if you grasp the points!

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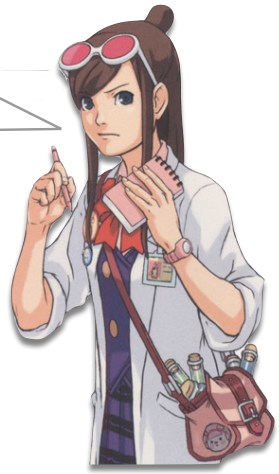
Aldrich ChemFiles. Vol. 9, No.4, Microreactor Technology

What to Do Next?

Let's consider Values and Functions of Flow Chemistry!



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Flow Chemistry

Value ⇒ Function

Values

Value = Advantages (usually)

- Scale Control
- Reaction Control
- Connectable System
- Multistep Synthesis

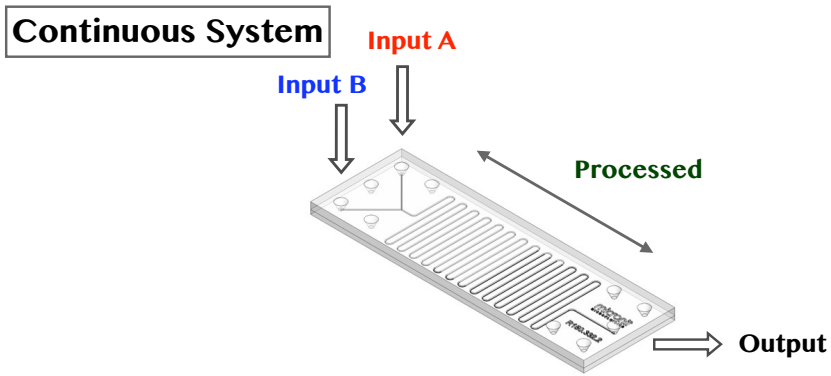
⇒ Value for **Organic Chemists**

Point: Find out the Value for people who are engaged in that field

Functions

Point: Consider what kind of Functions are essential for the Values

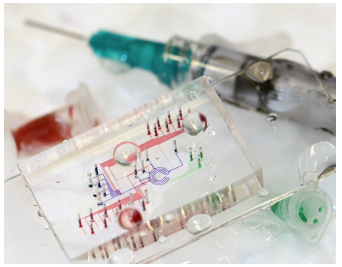
① **Inputs are continuously processed and outputted**

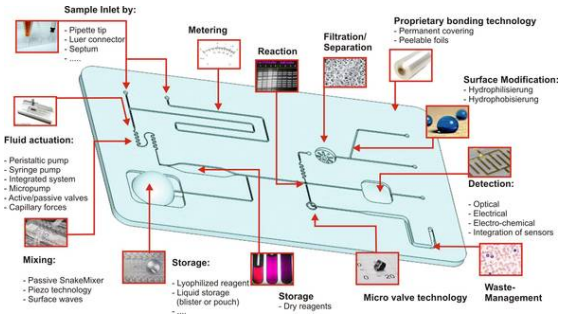


Functions

Point: Consider what kind of Functions are essential for the Values

② **Construction, fabrication and production of micro scale system**

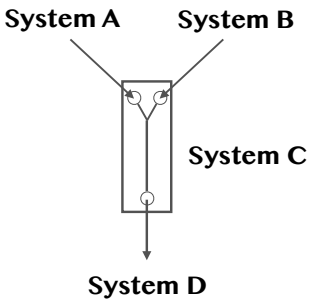




Functions

Point: Consider what kind of Functions are essential for the Values

③ Flow channels are connectable and recombinable



Are These Functions Enough?

Functions:

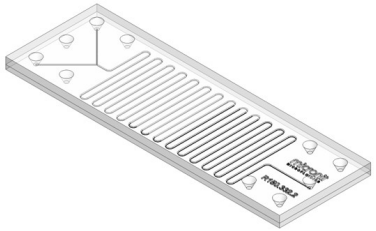
① Inputs are continuously processed and outputted

② Construction, fabrication and production of micro scale system

③ Flow channels are connectable and recombinable

Values:

- **Scale Control ⇒ ①**
- **Reaction Control ⇒ ②, ③**
- **Connectable System ⇒ ③**
- **Multistep Synthesis ⇒ ①, ③**



Flow Chemistry

Value ⇒ **Function**

Free from Organic Chemistry

Function × **?** × **?** ⇒ **?**

Innovation?

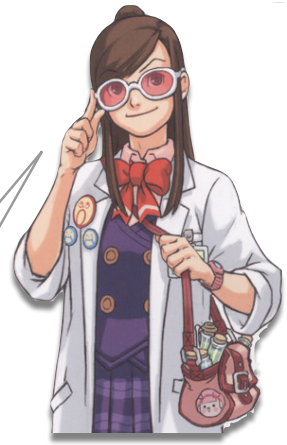
What to Combine with?

Novelty

Feasibility

Conception Approaches:

- Forced Creation
- Affinity Search
- Competence Link



This time, let's do "Affinity Search" !
What has high affinity with chemistry?
Can it be a friend with the functions?

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Affinity Search

Flow Chemistry ⇨ **Organic Chemistry**

- **Engineering**

Material, Polymer,
Solar Energy,
Fuel Chemistry, etc

- **Physics**

Quantum Physics,
Thermodynamics,
Nuclear Chemistry, etc

- **Biology**

Biochemistry,
Chemical Biology,
Photosynthesis,
Metabolism,
Cellular Biology, etc

(Ideal: Indiscriminate trial)

Flow's Function × Cellular Biology

⇨ Human on a Chip

2. Human on a Chip

Goal of This Chapter

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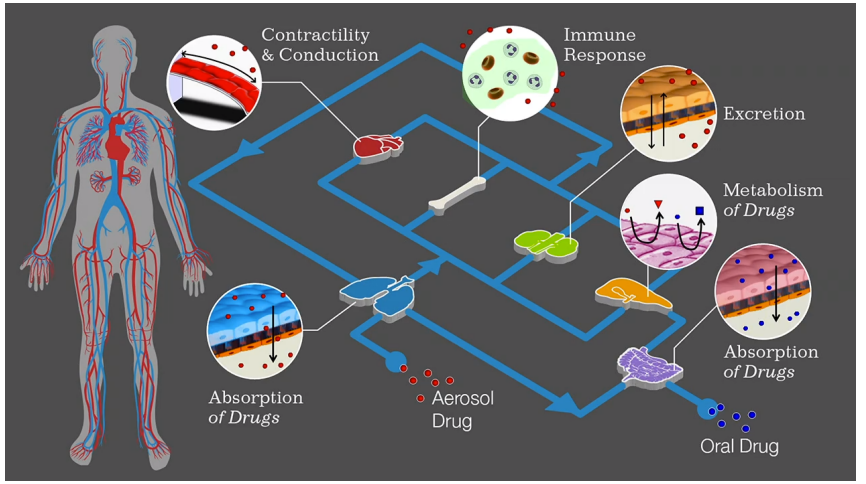
Human on a Chip - Destination -



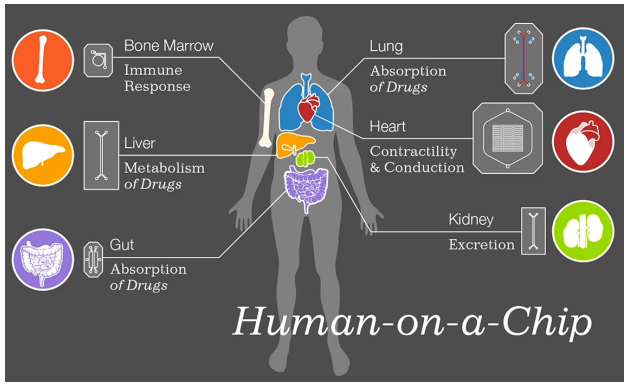
Fully replicate human body functions on a microsystem

Human on a Chip - Potential -

Microsystem which replicates human body compartments utilizing Microfluid technics

⇨

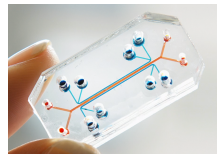
New assay platform for drug discovery, tailor-made medicine, safety test, etc…



Replacement of Animal Testing

	Animal Testing	Human on a Chip
Feeding Cost	High (not manufacturable)	Low (manufacturable)
Length of Trial	Long	Short
Validity	Insufficient (cross-species)	Sufficient (patient-specific)

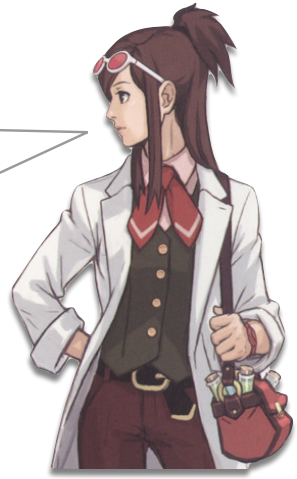
⇨



A. Schober, et al. Lab on a Chip. 2013, 13, 3471

What Is Necessary?

Hmm, the goal is clear though… Then, why not consider what kinda basic researches are necessary to achieve that goal? Sorry for saying nothing special…



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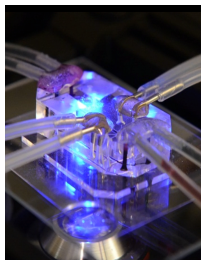
Prerequisite Basic Researches

Human on a Chip

⇩ **Break Down**

- **Precise replication of each organ**
- **Vascular system mimetic to connect each organ**
- **Same standard for tissue engineering**

Organ on a Chip



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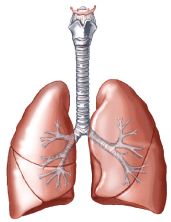

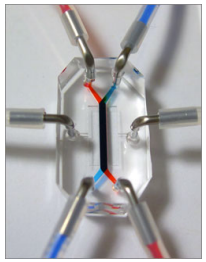

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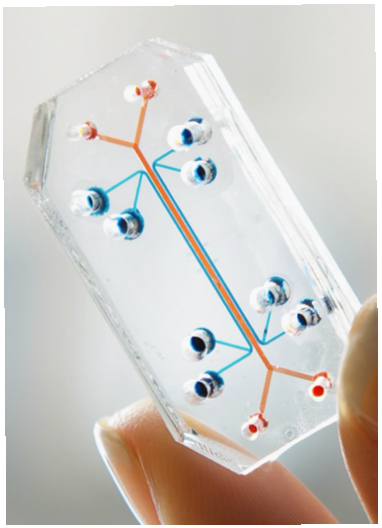
Micro organ composed of cells with organ-specific functions
(ex. epithelium, muscle, parenchyma, etc…)

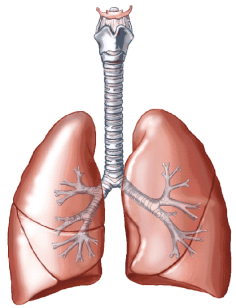
A. Schober, et al. Lab on a Chip. 2013, 13, 3471

First Example: Lung on a Chip



Essential Lung Functions:

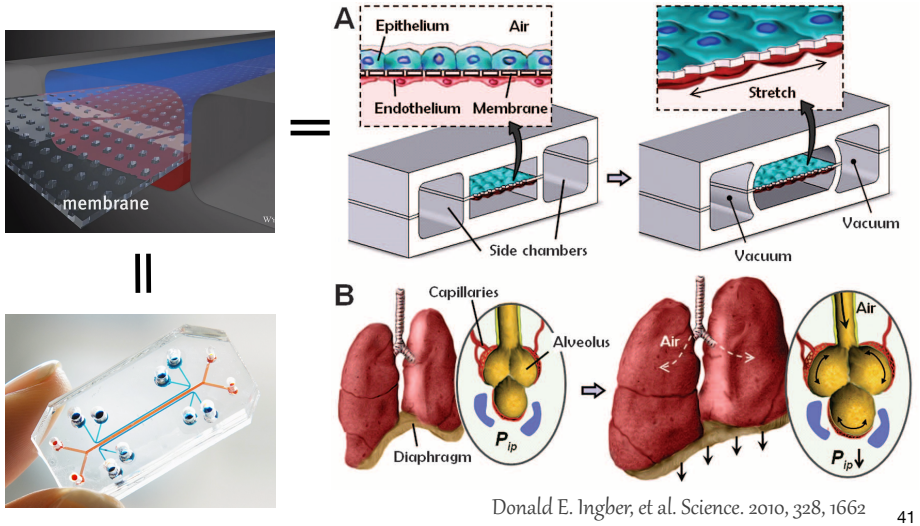
- **Alveolar cellular structure**
- **Contraction when breathing**
- **Inflammatory response**



Donald E. Ingber, et al. Science. 2010, 328, 1662

Lung on a Chip

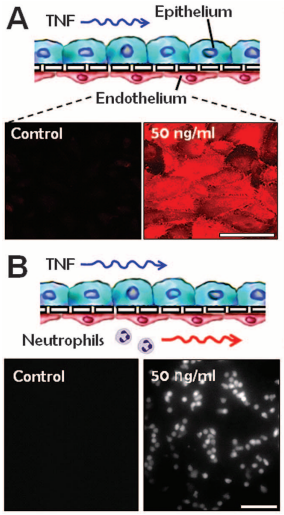
- **Structure, Contraction**



Donald E. Ingber, et al. Science. 2010, 328, 1662

Lung on a Chip

- **Inflammatory response**



***Jargons:**
TNF: Inflammatory cytokine
ICAM1: Lymphocyte trafficking signal

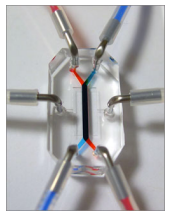
ICAM1 up-regulation

&

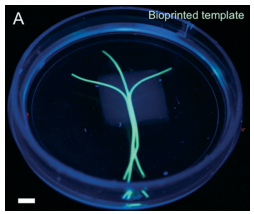
Neutrophils trapped

Donald E. Ingber, et al. Science. 2010, 328, 1662

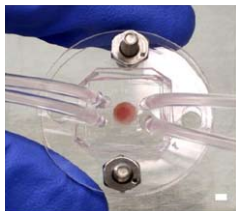
Other Organs & Tissues



Gut on a Chip*1



Vascular System*2



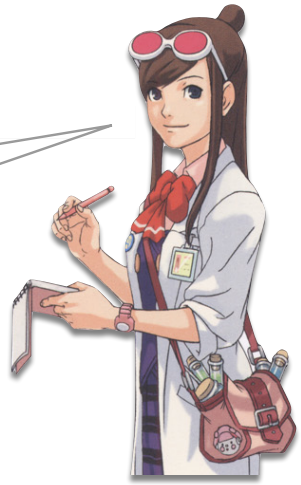
Bone marrow on a Chip*3

In spite of intensive researches, this field is still in its infancy

*1 Geraldine Hamilton, Donald E. Ingber, et al. Lab on a Chip. 2012, 12, 2165
*2 Ali Khademhosseini, et al. Lab on a Chip. 2014, 14. 2202
*3 Donald E. Ingber, et al. Nature Methods. 2014, 11, 663

In Conclusion…

Did you get it? Though this is just one good successful example, it's still helpful to consider "the reason for success", I think!



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3. Discovery of a New Horizon

Goal of This Chapter

In short, understand the whole thinking process for innovation.
But it's also crucial to figure out the limitation of this framework.
Anyway, we are not far off.
Let's run through toward the end!

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Flow Chemistry

Value → Function

Free from Organic Chemistry

Affinity Search

Flow's Function × Cellular Biology

→ Human on a Chip

Thinking Stream

Find the "interesting" and "novel" technology

⇩

Extract Functions from that technology

⇩

Look for the other field which has potential affinity

⇩

Combine them and break down to basic studies

Is This Framework Applicable?

Who needs it? How is it useful?
These questions are the keys probably…
but it's difficult, I know…hmm

Novelty

Feasibility

Conception Approaches:

- Forced Creation
- Affinity Search
- Competence Link

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Who benefits?

1. People involved in the Technology

Technology

2. People who have a Problem in their field

Problem

Novelty

3. People who want to do something Novel

How Useful?

1. People involved in the Technology

Technology

usually, but not novel

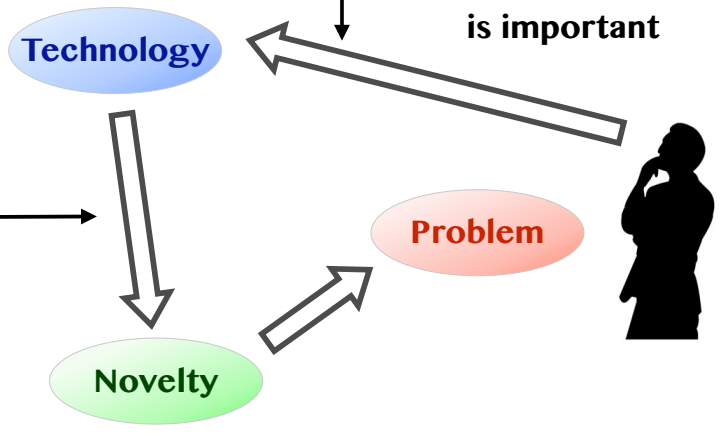
Problem

Novelty

If this process is "Forced Creation",
it becomes more likely to meet novelty

How Useful?

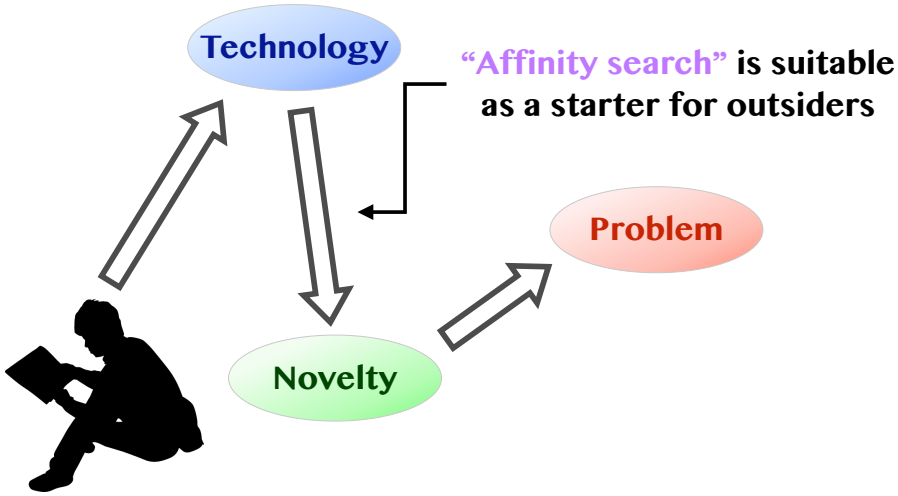
2. People who have a **Problem** in their field



For them, "Competence Link" is better to achieve feasible idea

How Useful?

3. People who want to do something **Novel**

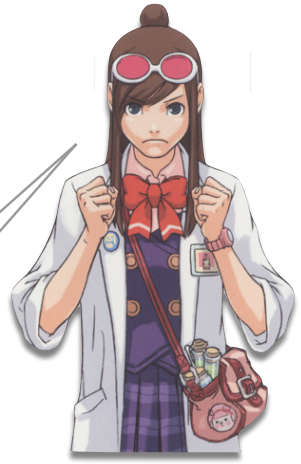


Limitation

Creation of a New Research Direction in …

○ New Research Realm (Blue Ocean)

× Existing Research Realm (Red Ocean)



It's difficult to meet all needs. Complementary process is necessary, and it's the next task!

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This is Just an Aside…

Why did we have to investigate the thinking process so intently?
It was abstract and complicated.
…So that I'm hungry.

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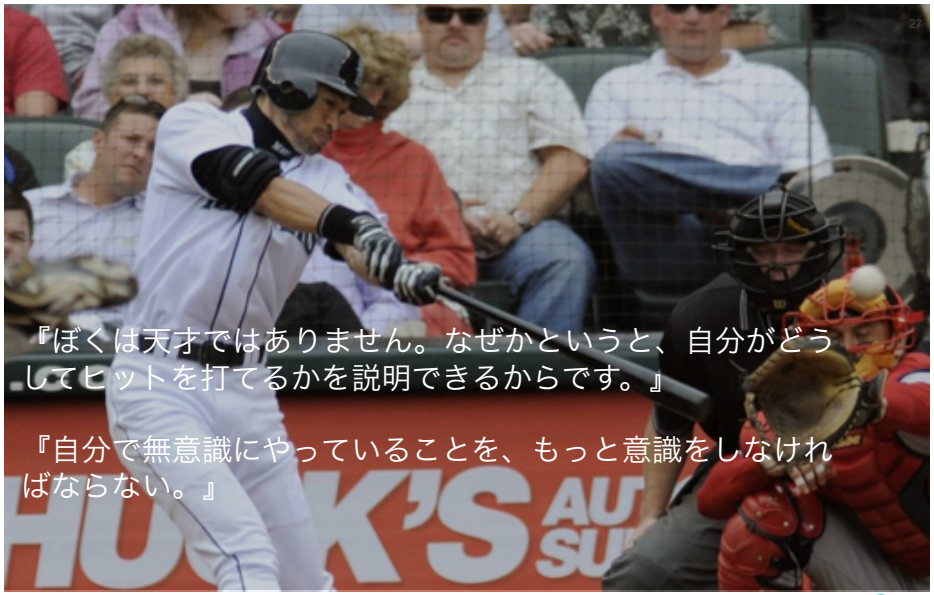
Meta Cognition

- Understand what you understand
- Understand how you understand
- Understand why you understand

⋮



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Special Thanks

- **Wyss Institute (Harvard University)**
  for providing Human on a Chip figures
- **i.school (the University of Tokyo)**
  for providing hints of the framework
- **CAPCOM**
  for dispatching a talented assistant
  (Akane Hozuki in "Gyakuten-Saiban")

Thank you very much!
See you next time!

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