Future Drug Development by In Vivo Glycocarrier
-Therapeutic In Vivo Synthetic Chemistry-

Tokyo Institute of Technology
RIKEN

Katsunori Tanaka

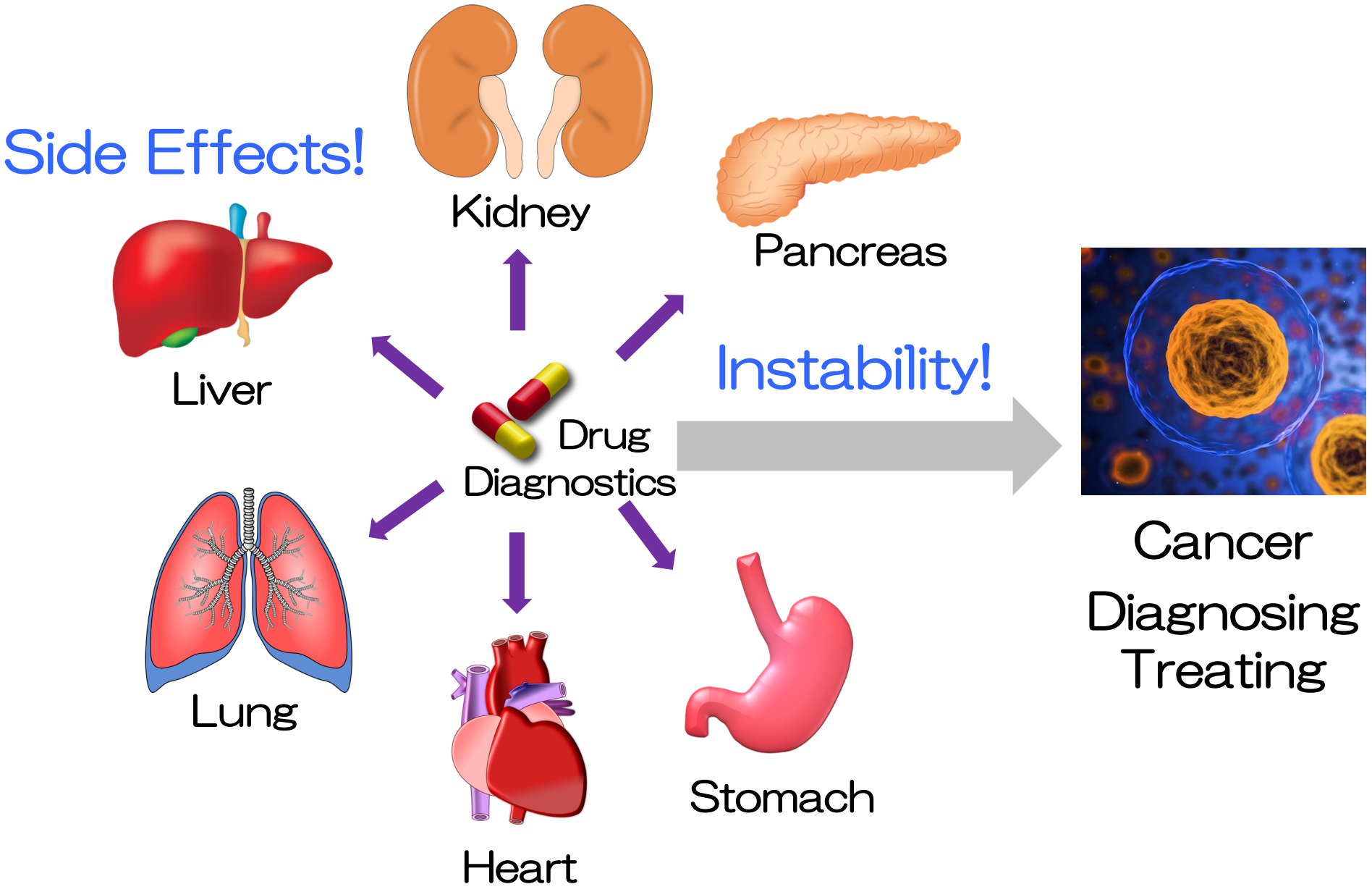
Research Concept

“On-site” Synthesis

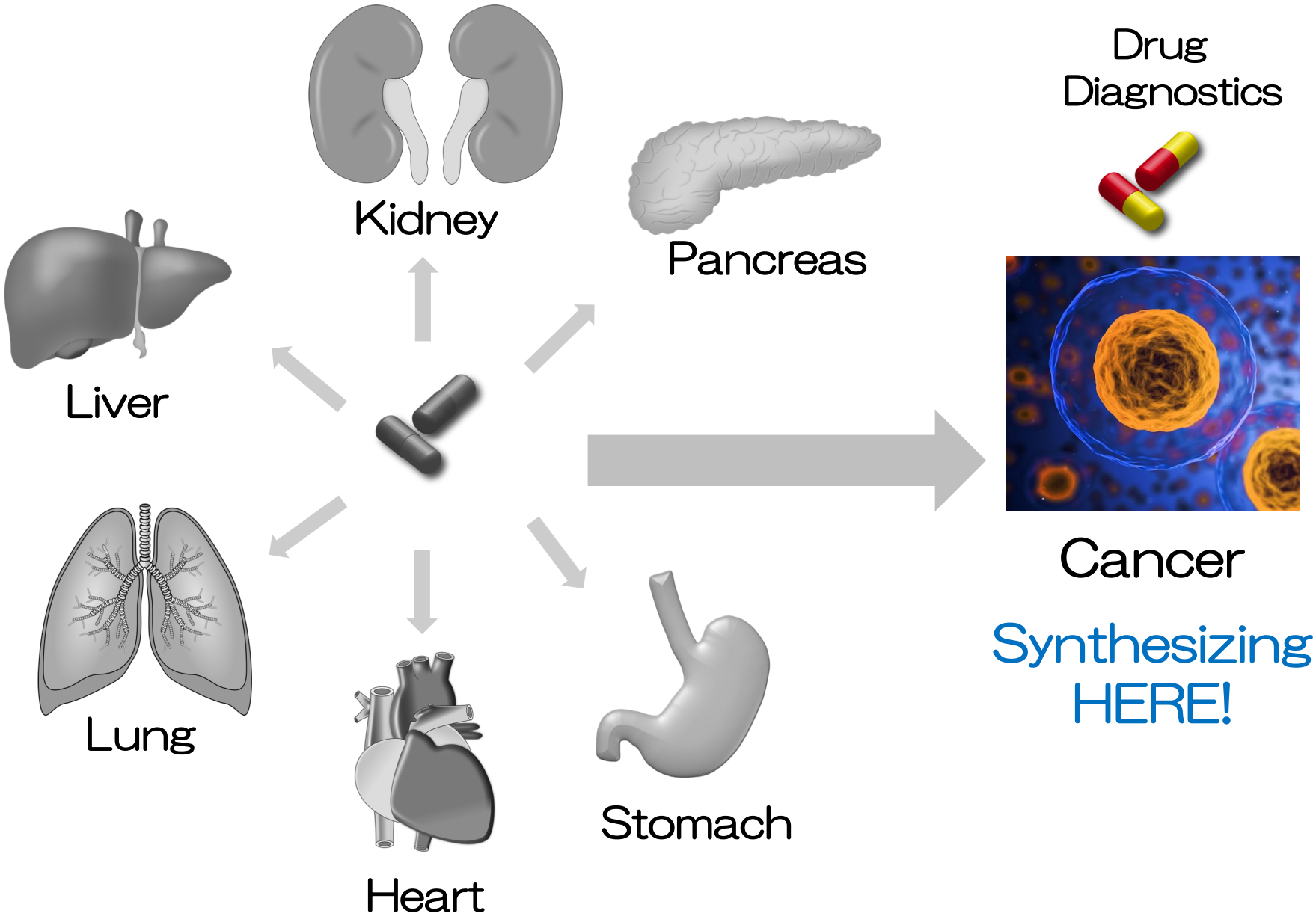
Synthesizing and Functioning “On-Site”

Chemical Biology, Drug Development, Plant Science,
Food Chemistry, Material Science...

Why Therapeutic In Vivo Synthetic Chemistry?



Why Therapeutic In Vivo Synthetic Chemistry?

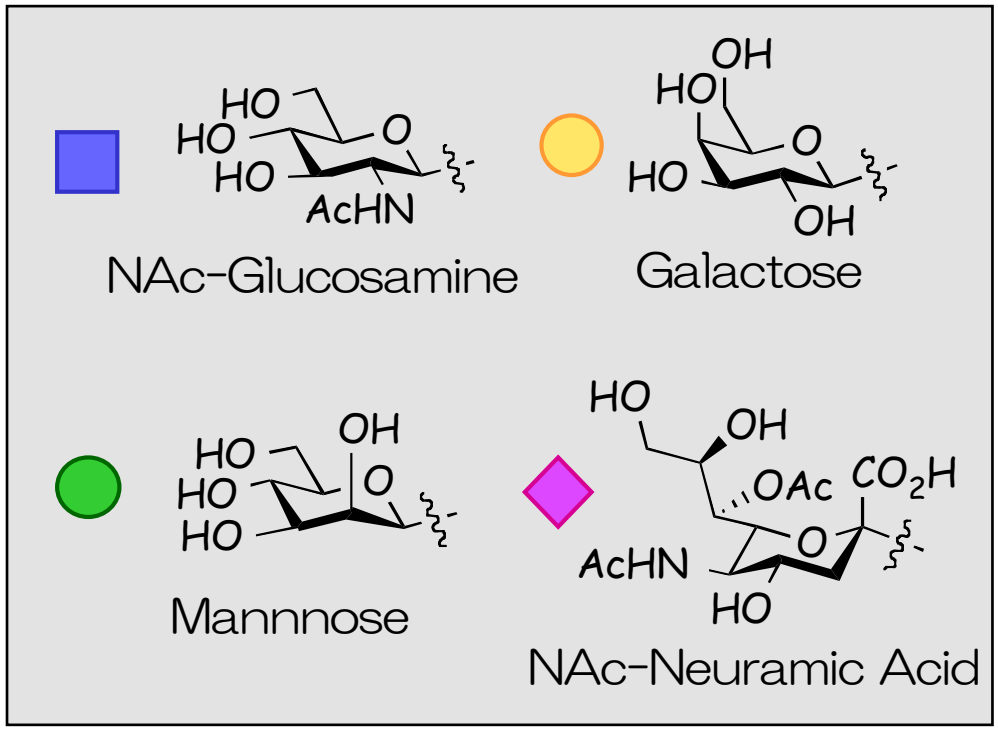


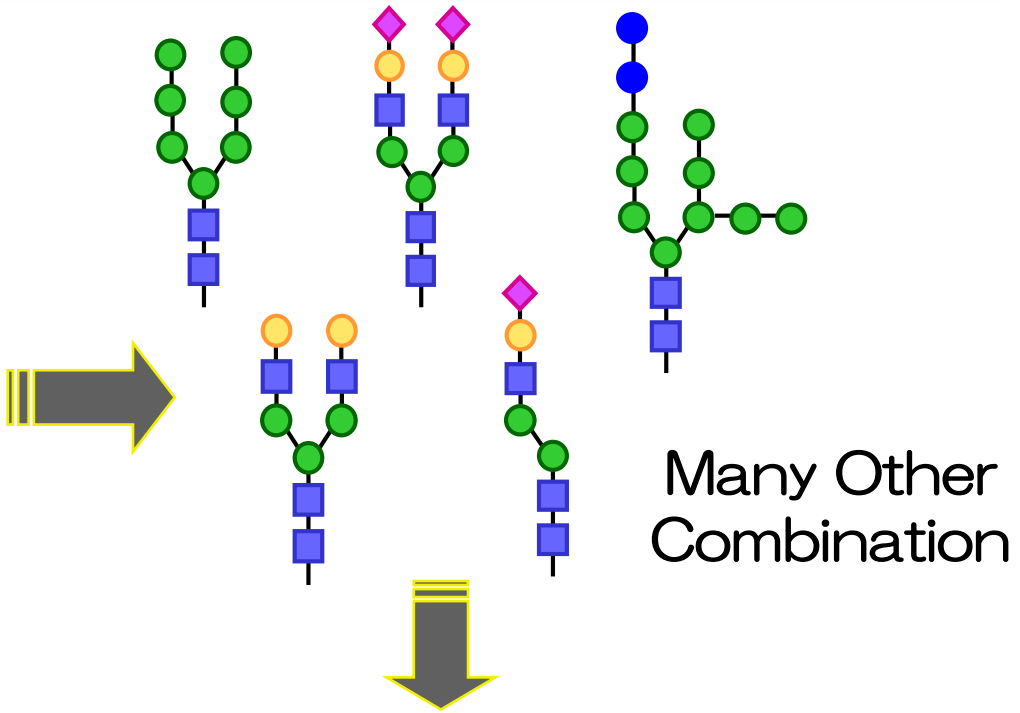
Two Strategies

In Vivo Metal-Catalyzed Synthesis

In Vivo Chemical Metabolite Transformation

Mono-, Poly-Saccharides to Glycocluster

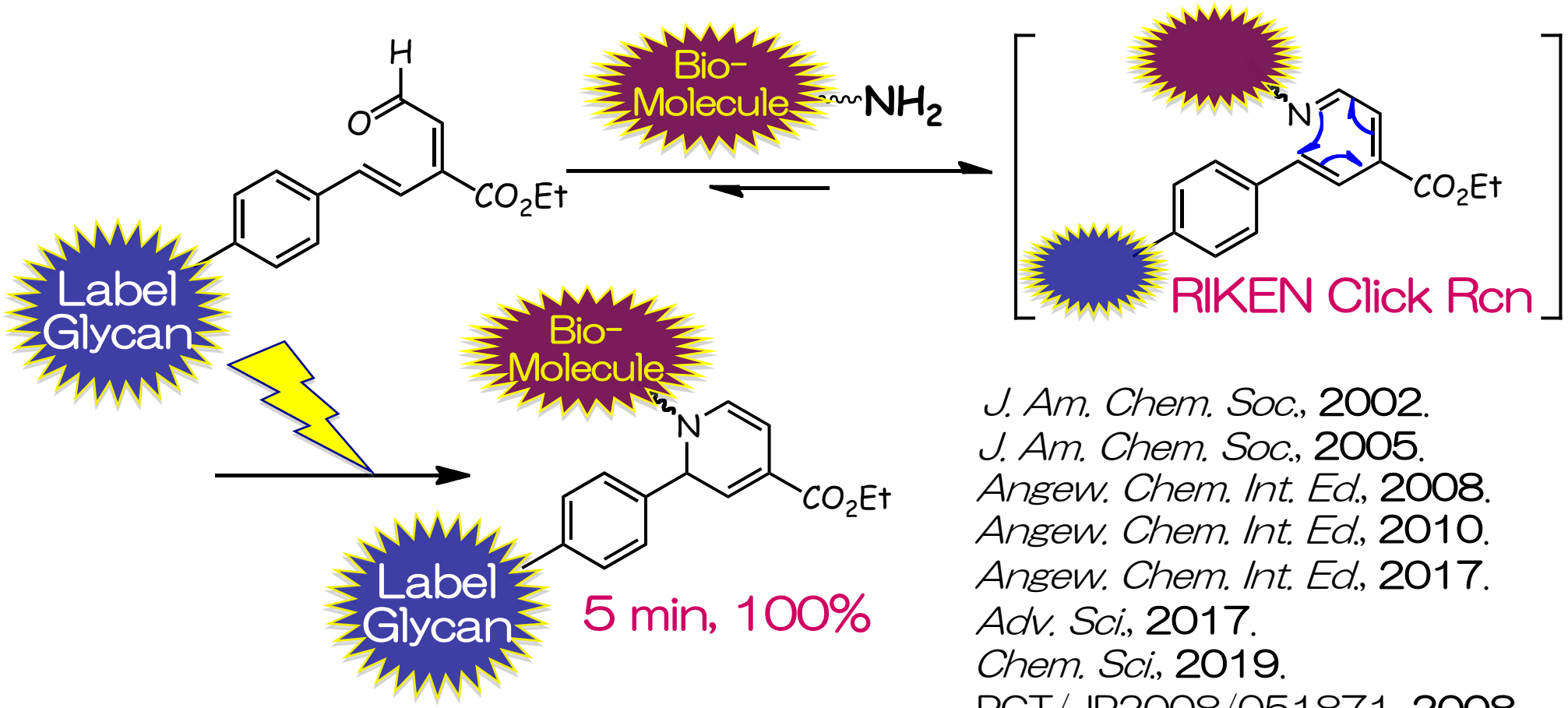




Glycocluster!

New In Vivo Targeting by
Glycan Heterogeneity Through
Pattern Recognition

RIKEN Click Reaction (6π-Azaelectrocyclization)

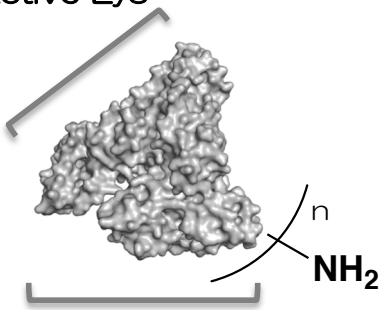


J. Am. Chem. Soc., 2002.
J. Am. Chem. Soc., 2005.
Angew. Chem. Int. Ed., 2008.
Angew. Chem. Int. Ed., 2010.
Angew. Chem. Int. Ed., 2017.
Adv. Sci., 2017.
Chem. Sci., 2019.
PCT/JP2008/051871, 2008.
PCT/JP2013/1614079, 2013.
Encyclopedia of Reagents for Organic Synthesis, 2019.

Structurally Well-Defined Glycoclusters by RIKEN Click Reaction

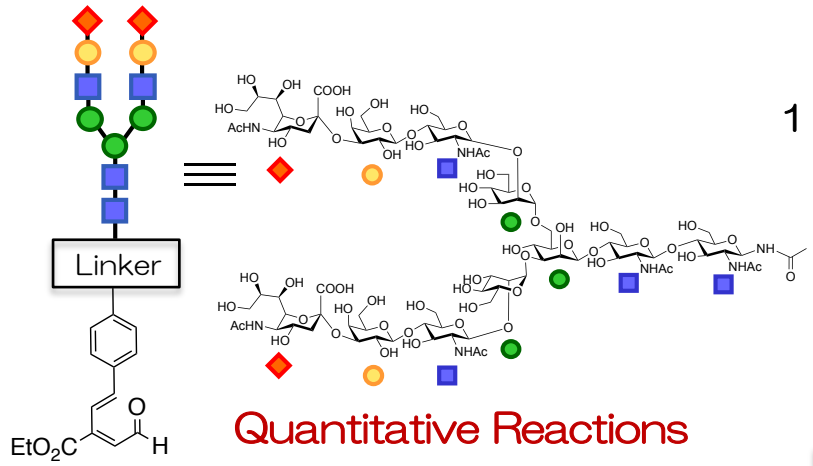
(A) Glycocluster Containing
One Kind of Glycan

Most Reactive Lys



2nd Reactive Lys

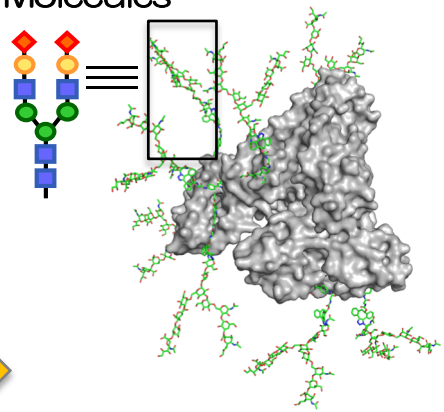
Serum Albumin
(30 Reactive Lys)



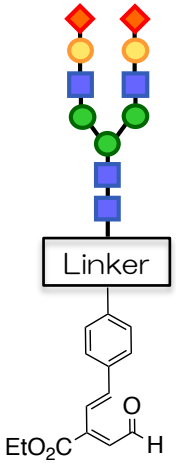
Quantitative Reactions

Conjugation with 10 Glycans

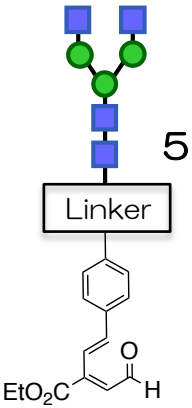
10 Molecules



(B) Glycocluster Containing
A Few Kinds of Glycans



1) 1st Glycan Conj.



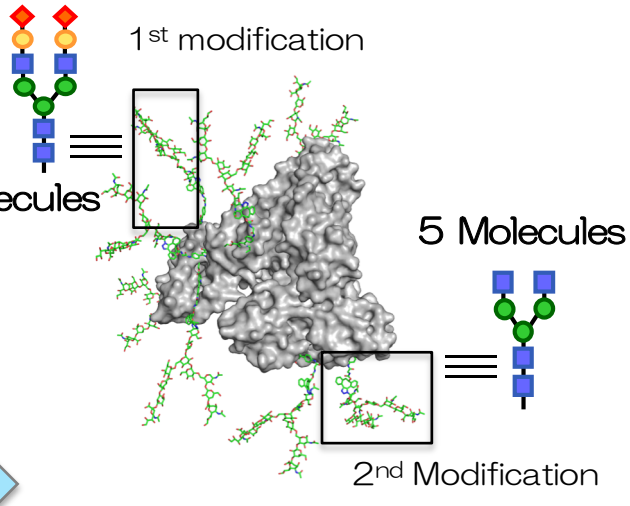
2) 2nd Glycan Conj.

Sequential Reaction from Highest Lys

1st modification

5 Molecules

5 Molecules



2nd Modification

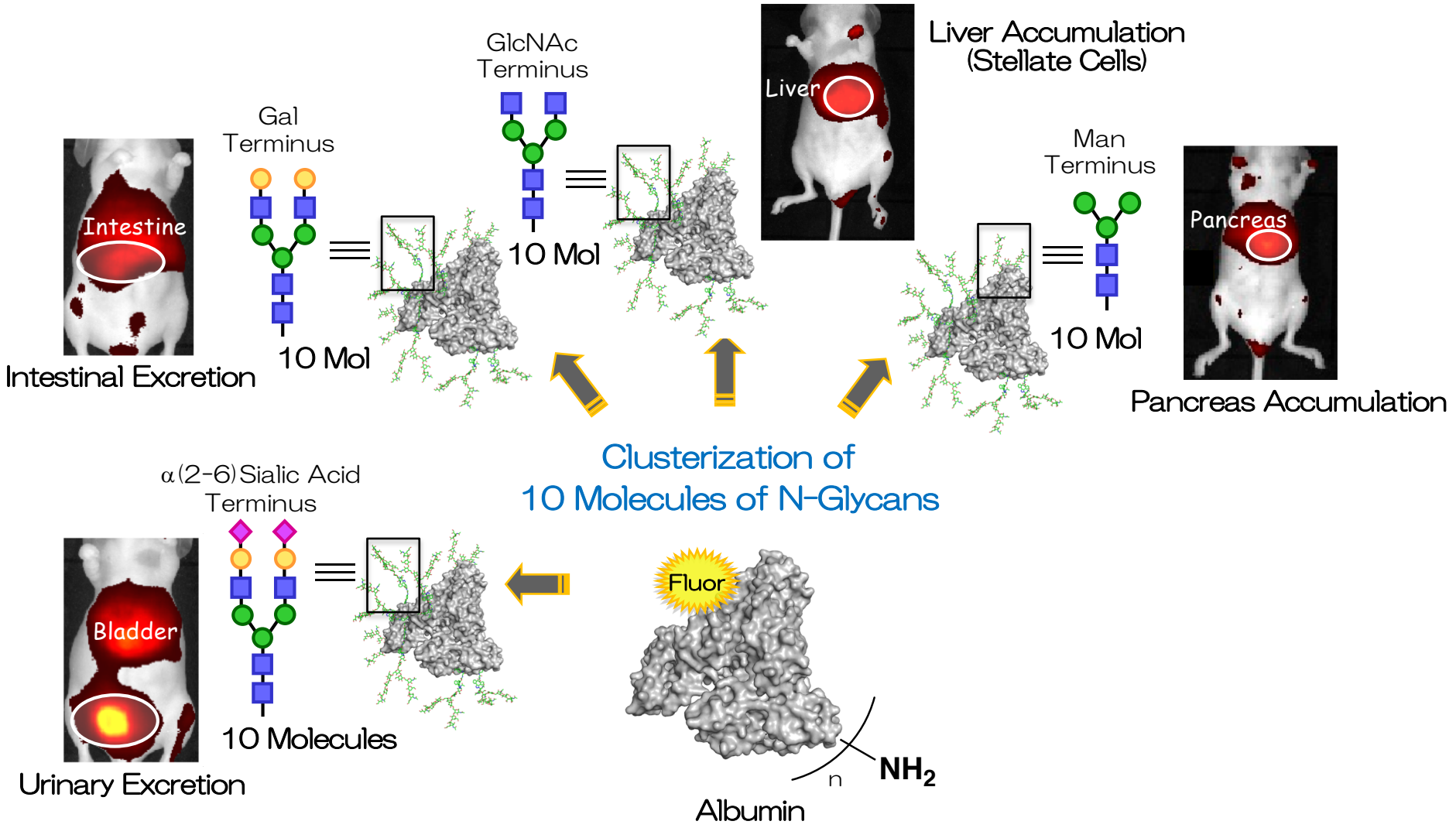
Structurally Well-Defined
Glycocluster with Two Glycans

α(2,6)-Sialic Acid
α(2,3)-Sialic Acid
NAc-Glucosamine
Galactose
Monnose

Sci. Rep. **2016**, *6*, 21797; *Adv. Sci.* **2017**, *4*, 1600394.

N-Glycan Dependence on In Vivo Kinetics and Biodistribution

Noninvasive Fluorescent Imaging 1-2 h After Intravenous Injection



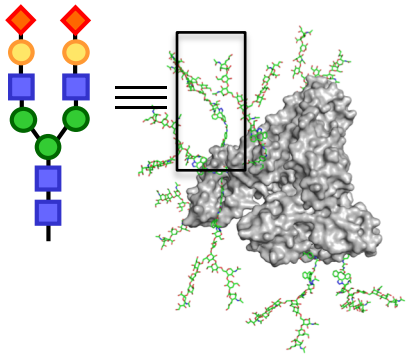
Sci. Rep. 2016, *6*, 21797.

Cancer Pattern Recognition by Heterogeneous Glycoclusters

Red : Strong
Purple : Moderate
Black : Weak

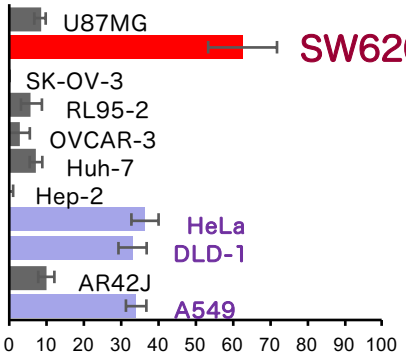
(Interaction with 11 Different Cell Lines)

10 Molecules



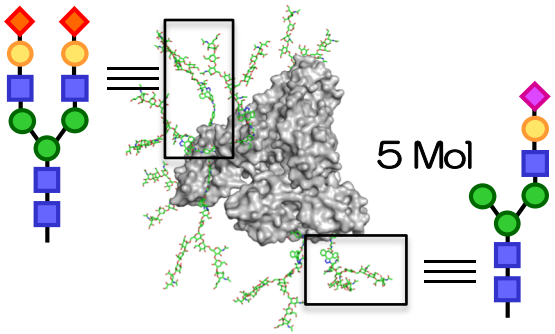
One-Kind of Glycan

Higher Interaction

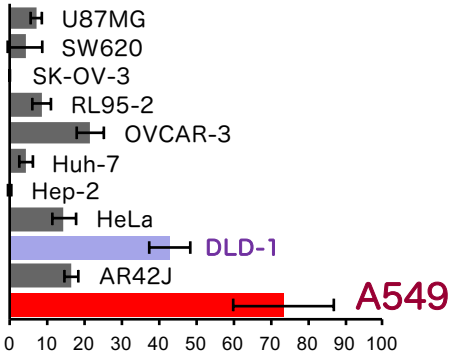


SW620 Colorectal Cancer

5 Molecules

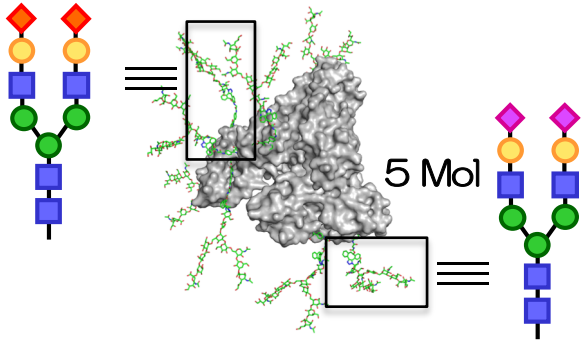


Two-Kinds of Glycans
(Heterogeneous Cluster)



A549 Lung Cancer

5 Molecules



Two-Kinds of Glycans
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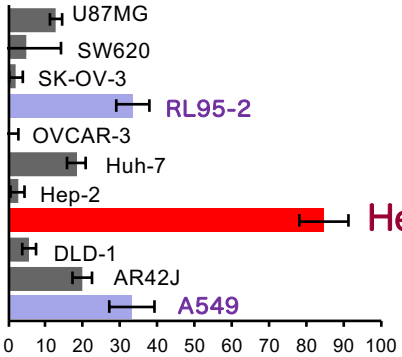
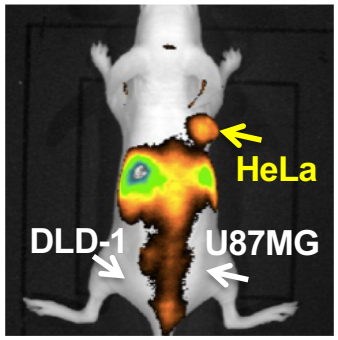


(Fluorescent Imaging in Cancer Implanted Mice)

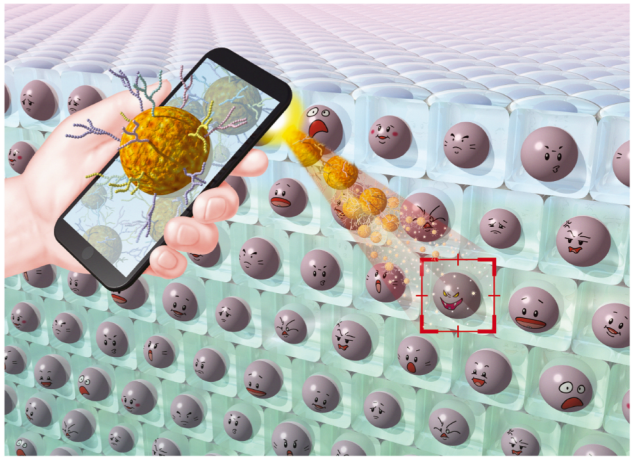


HeLa Cervical Cancer Both in Vitro and In Vivo

Fluor TAMRA (Cell Exp.),
Hilyte Fluor 750 (Mice Exp.)

Chem. Commun. 2018, *54*, 8693.

Glycan Pattern Recognition Exists!



Showcasing research from the laboratory of Professor Katsunori Tanaka, RIKEN, Saitama, Japan.

A viable strategy for screening the effects of glycan heterogeneity on target organ adhesion and biodistribution in live mice

This work is the first study for glycocluster libraries to uncover the importance of glycan pattern recognition for cell-specific binding, *in vivo* kinetics and targeting.

As featured in:

See Katsunori Tanaka *et al.*, *Chem. Commun.*, 2018, 54, 8693.

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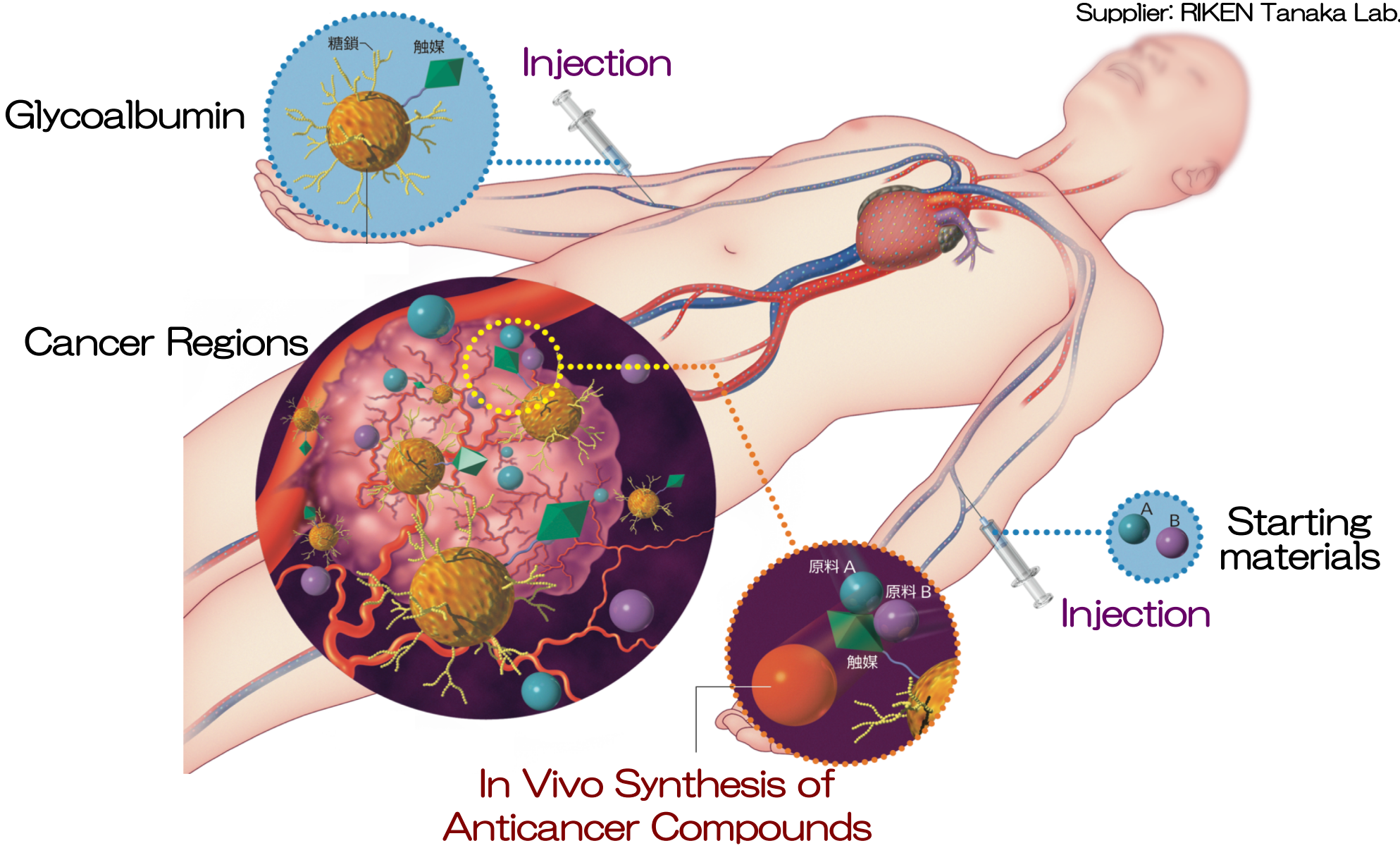
東京工業大学 Tokyo Institute of Technology

RIKEN 理化学研究所

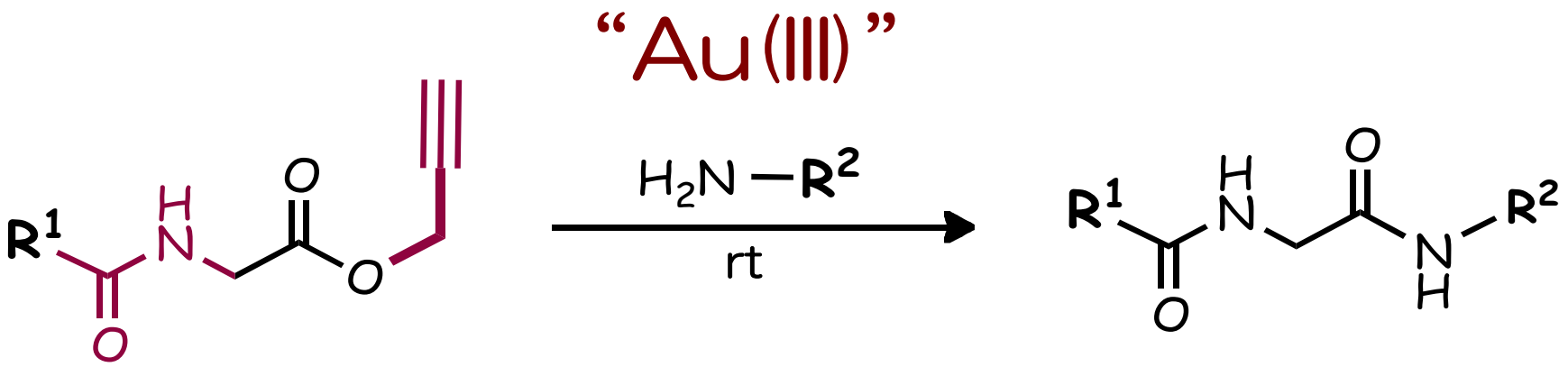
In Vivo metal Catalyzed Reaction

Supplier: RIKEN Tanaka Lab.



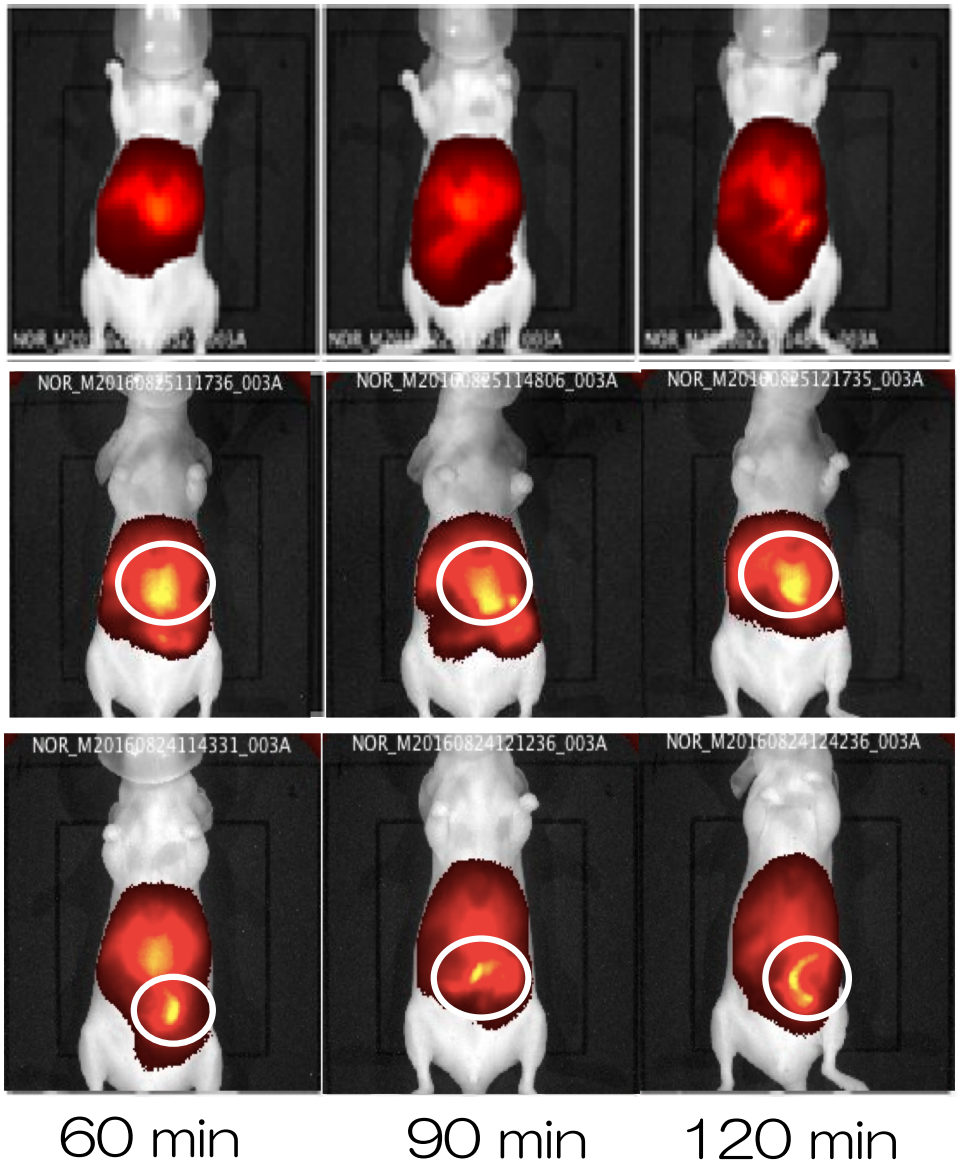
Nature Catal. 2019, *Nature Commun.* 2020.

Gold-Catalyzed Amide Bond Formation

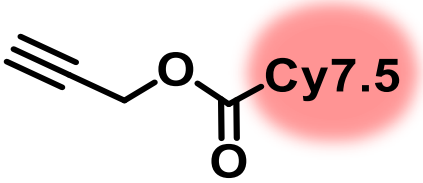


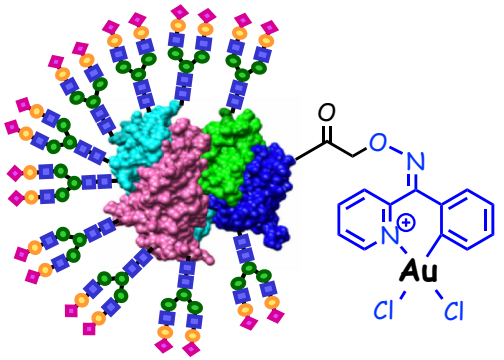
Chem. Eur. J. 2016, *22*, 18865-18872.
Chem. Commun. 2017, *53*, 8403-8406.
Angew. Chem. Int. Ed. 2017, *56*, 3579-3584 .
Chem. Eur. J. 2018, *24*, 10595-10600.

Organ-Selective Gold-Catalyzed Reaction



60 min　90 min　120 min





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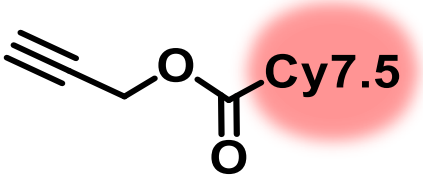
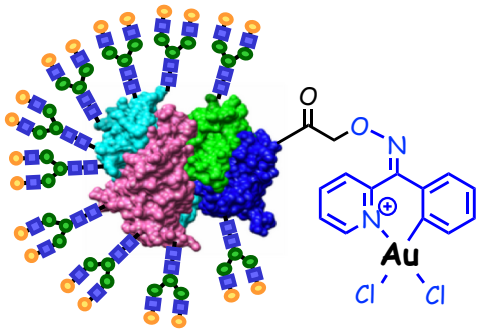


Liver Targeting Gold Catalyst



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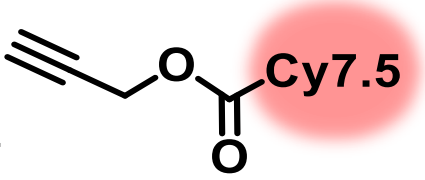
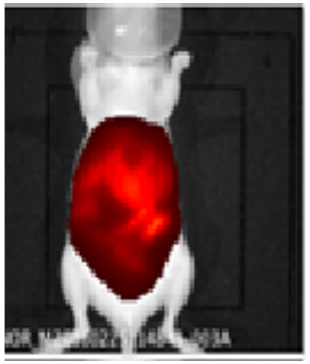


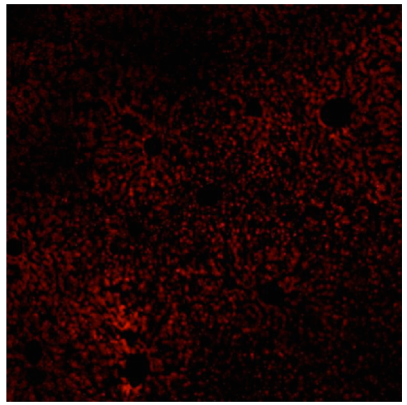
Intestine Targeting Gold Catalyst

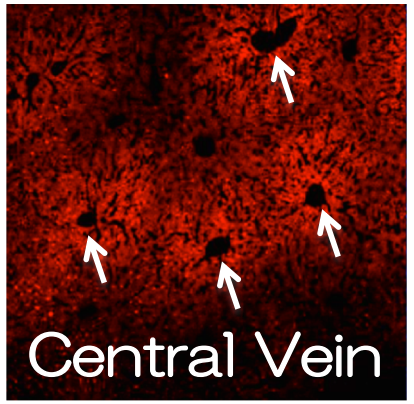
In Mice Gold-Catalyzed Amide Bond Formation

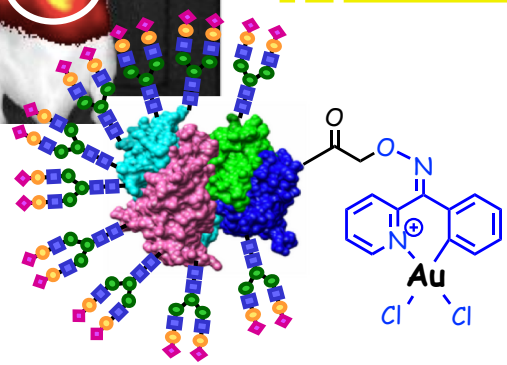


Dissection

Dissection







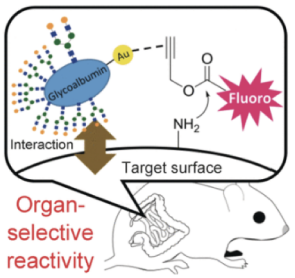
Amide Bond Formation at Glycan Target

Latest News

In-Mouse Catalysis

Organ-targeted metal-complex catalysis within living biological systems.
Address and deliver: A gold catalyst can be delivered to a target organ in a higher organism where it performs a chemical transformation visualized by bioimaging. This intriguing approach has been introduced by a Japanese team of scientists in the journal *Angewandte Chemie*. It could make organometallic catalysis applicable for therapy or diagnostics.

Read more.



1st Example of Organ Selective Metal Catalysis

東京工業大学 Tokyo Institute of Technology　理化学研究所 RIKEN

Angew. Chemie., 2017 (Hot Paper).

Possibility to Use Metal Catalysts In Vivo

Pd, Cu NanoParticles
Prof. M. Bradley (U. Edinburgh)

Ru, Ir Artificial Metalloenzyme
Prof. T. Ward (U. Basel)

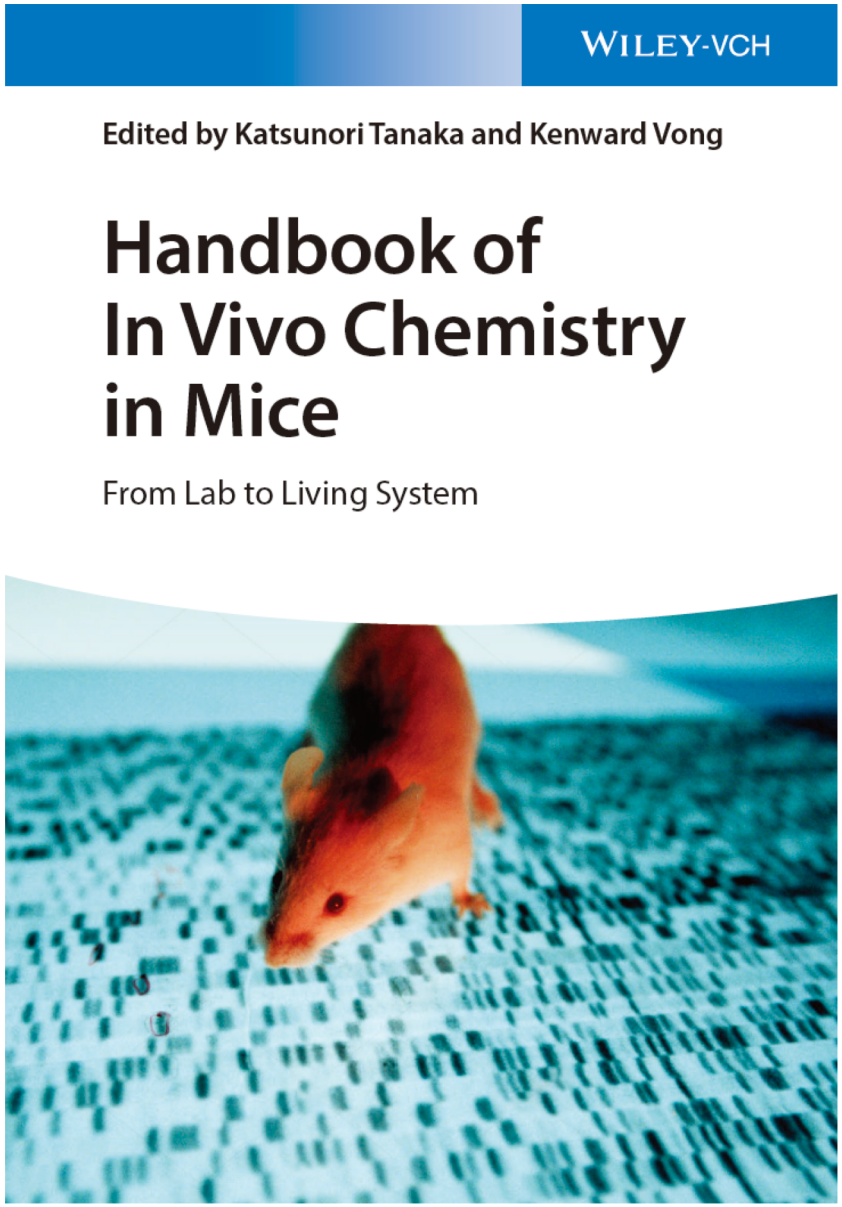
Live Cells E. Coli Zebrafish Embryo

(Problems)

1. Glutathione Inactivates Metal Catalysts!
2. How Metal Catalysts Can Be Carried to Target or Cancer?

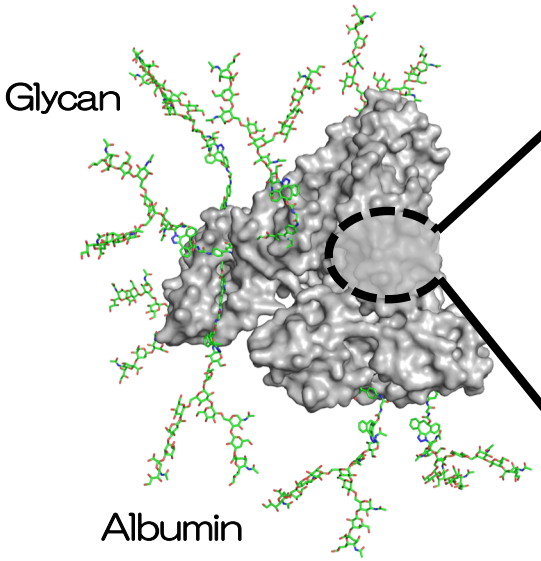
Currently NO Solutions!

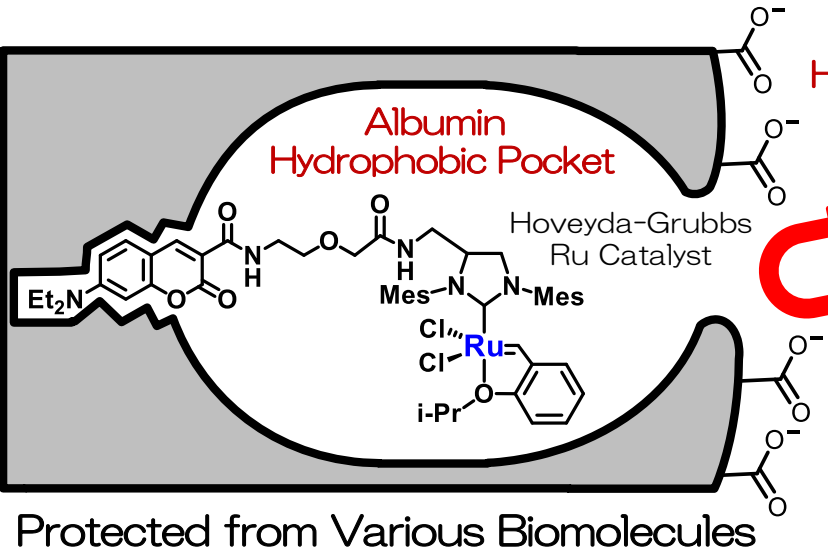
Possibility to Use Metal Catalysts In Vivo



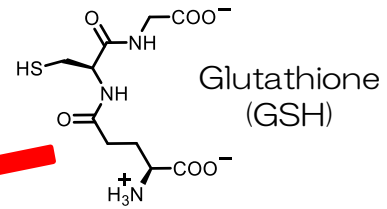
Introduction of Metal Catalysts to Glycoalbumins

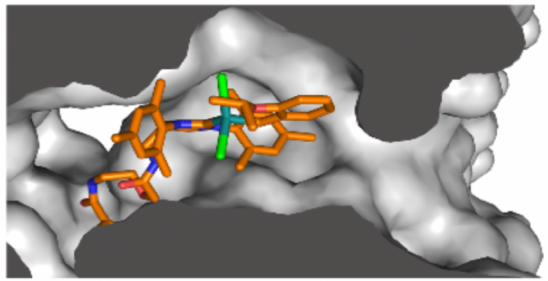
Rapidly Trafficking to target Organs or Cancer ➡ Metal Carriers in Mice

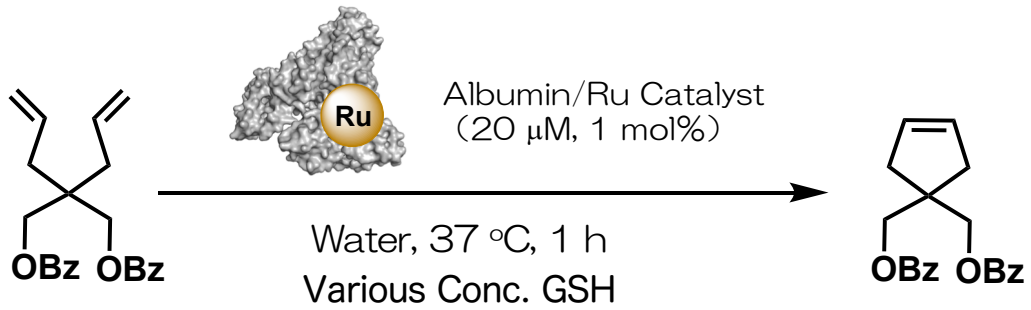


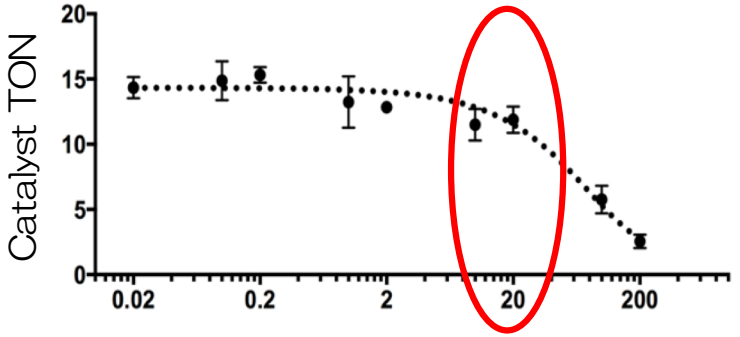


Hydrophilic GSH Cannot Enter!





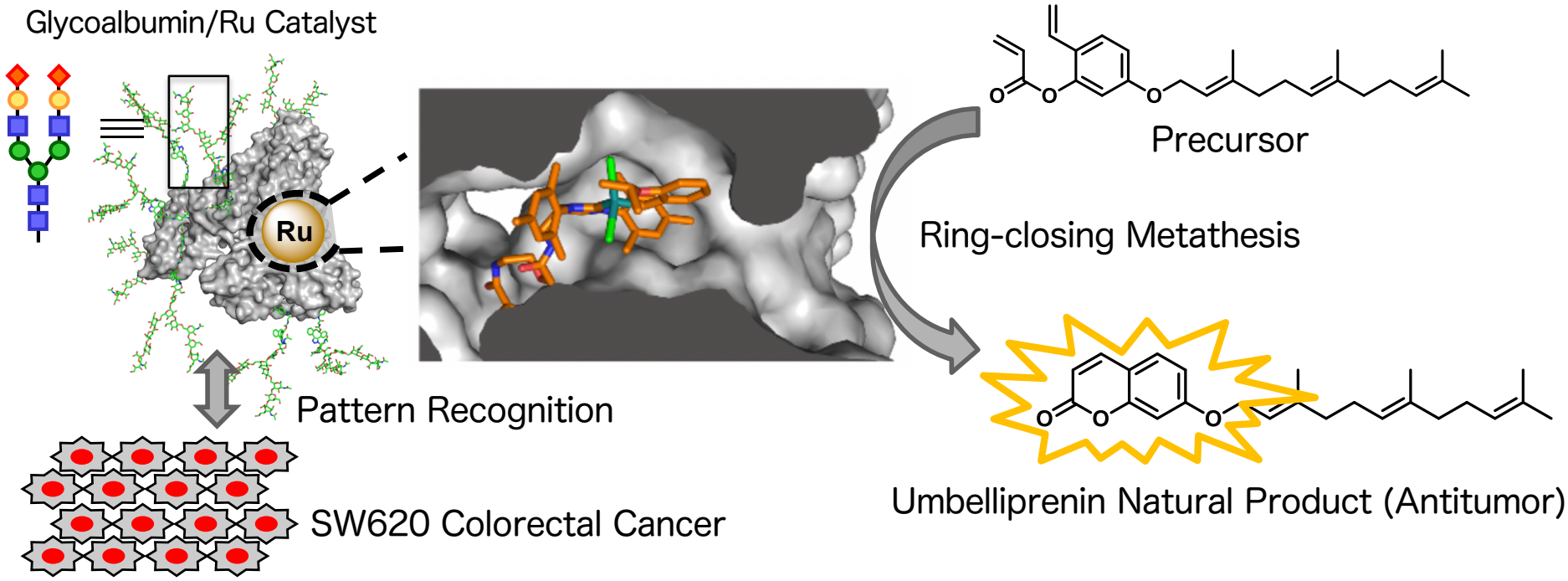


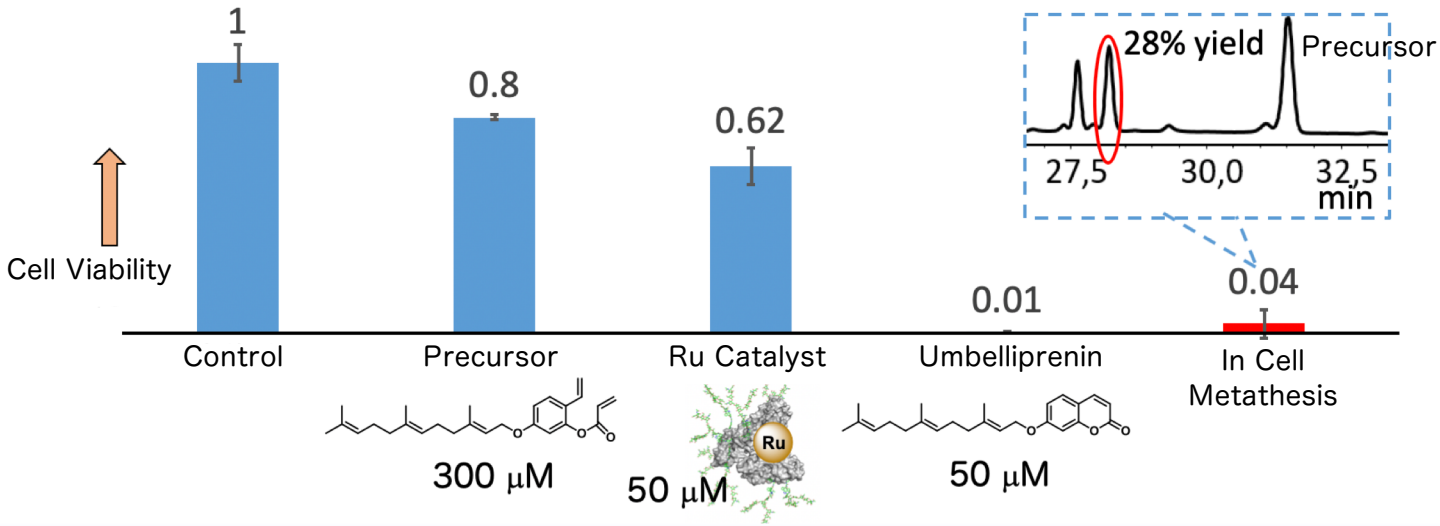


Metathesis Compatible at 20 mM (1,000 eq) of Glutathione

Nature Catal. 2019, *2*, 780.

Treatment of Target Cancer Cells by In Cell Metathesis



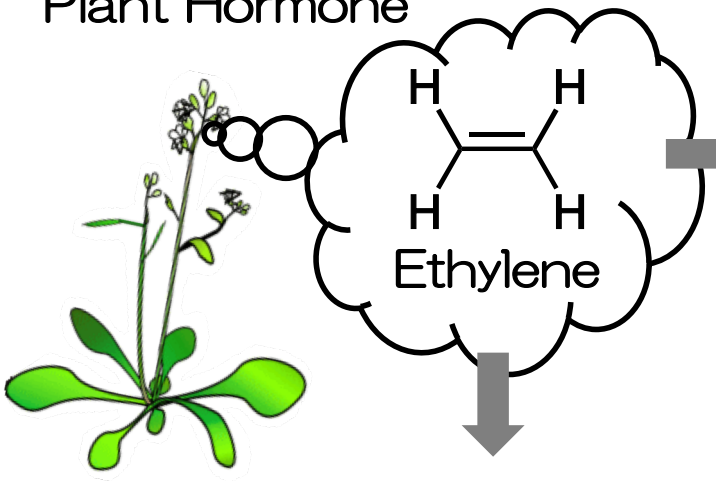


Nature Catal. 2019, *2*, 780.

Metathesis-Based Ethelene Sensor

Nature Commun. 2019, *10*, 5746.

Plant Hormone

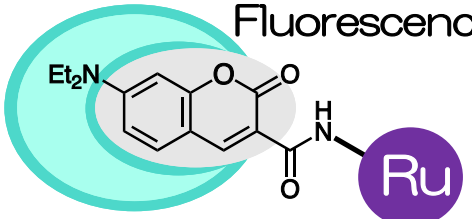


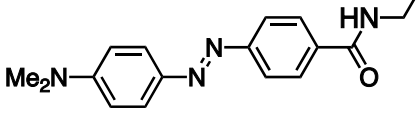
GC Analysis

Ru-Catalyzed Imaging

Albumin

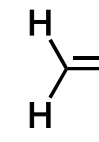
Fluorescence



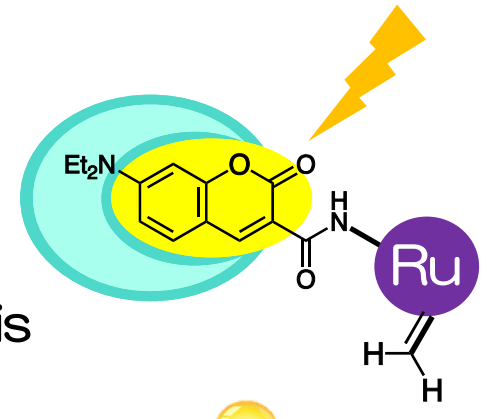


Quencher

OFF



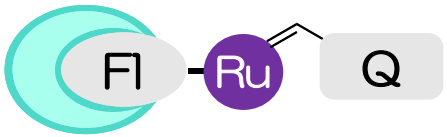
Metathesis



ON

A Whole Body Imaging

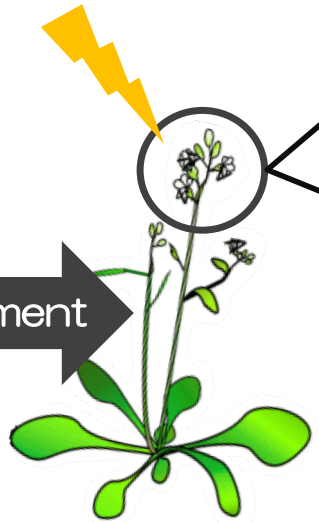
Ru/Alb-Probe



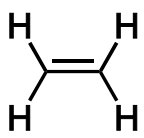
Ru/Albumin Complex

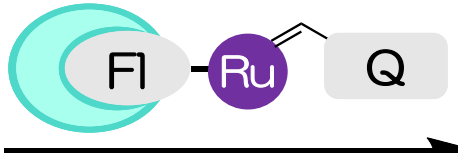
OFF

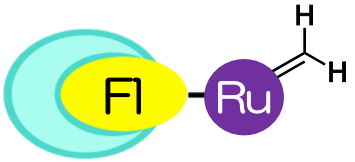
Treatment



Ethylene Production



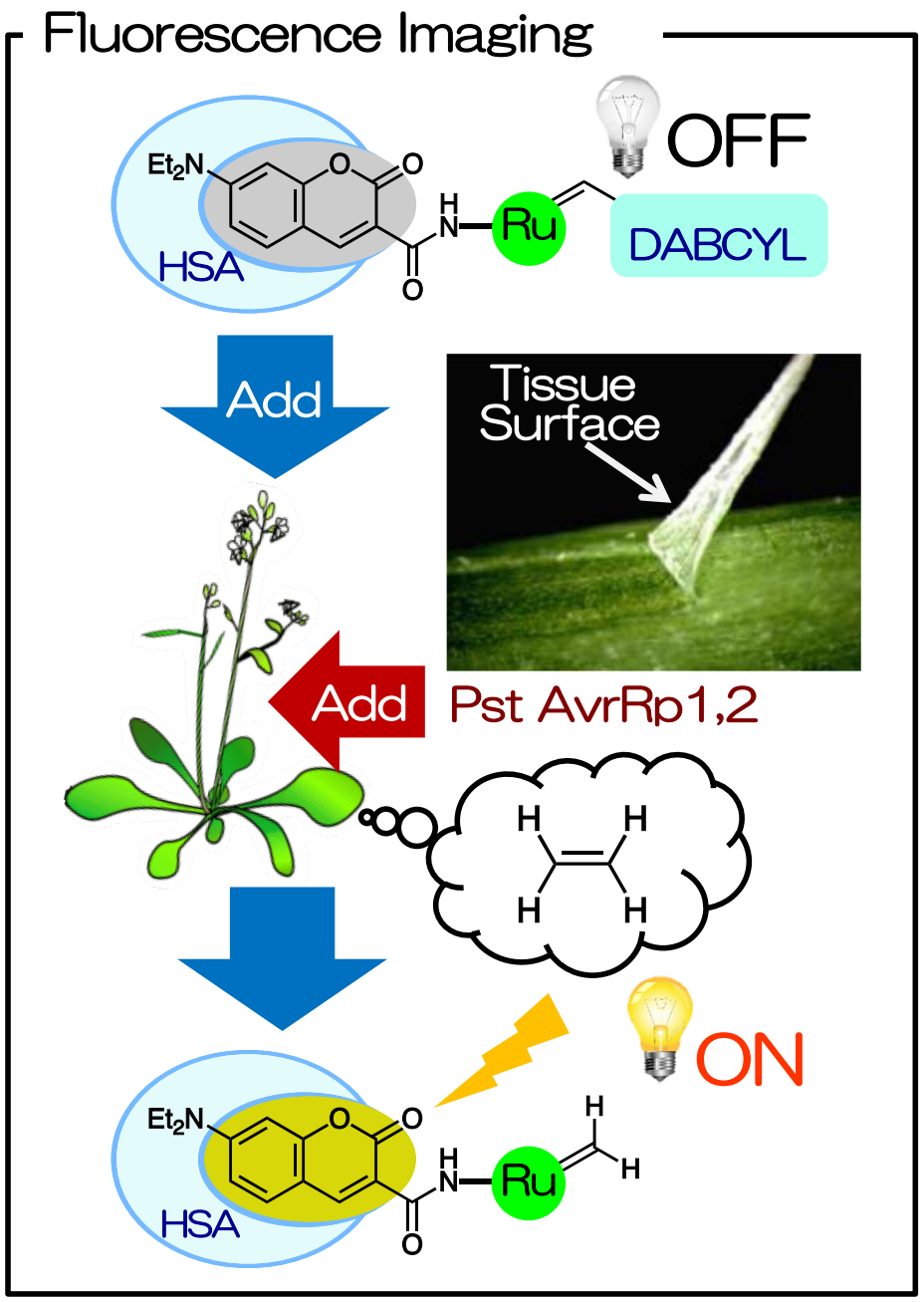


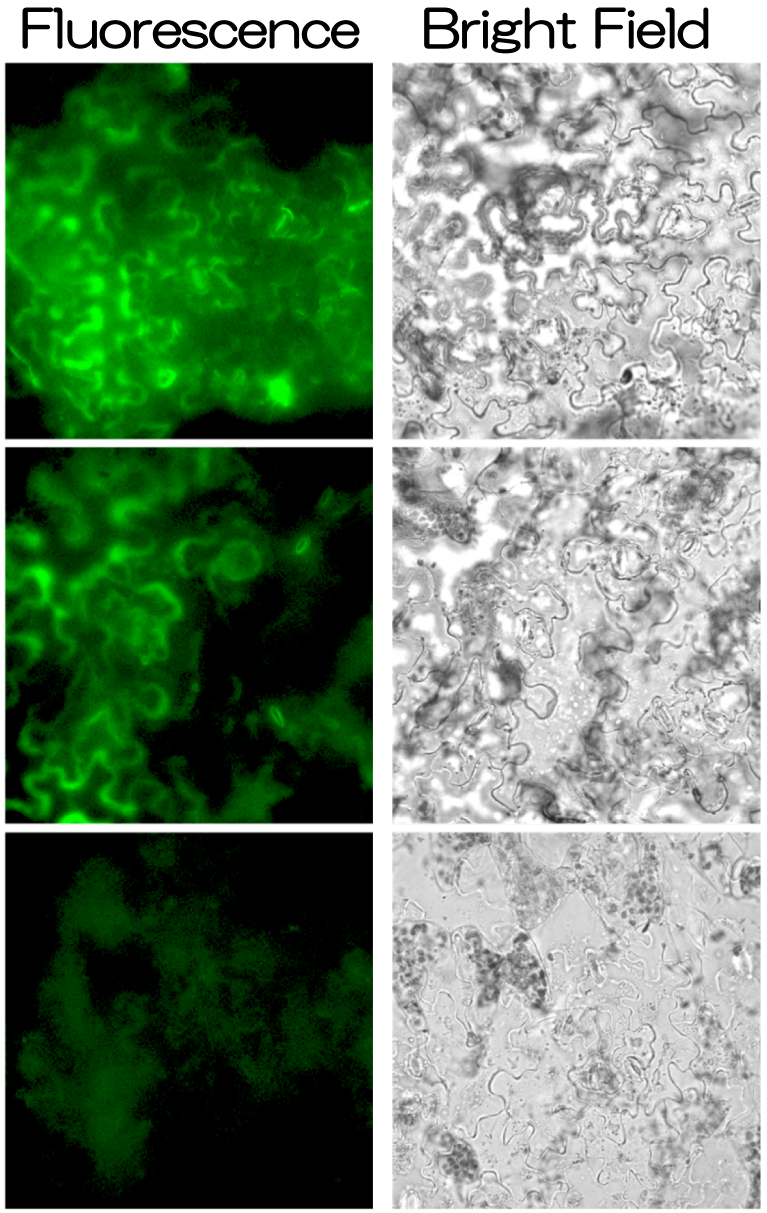


ON

Florescence Detection at C=C Production

Ethelene Sensor in Plant





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Research Concept

“On-site” Synthesis

Synthesizing and Functioning “On-Site”

Chemical Biology, Drug Development, Plant Science,
Food Chemistry, Material Science...