

Biofunctional Synthetic Chemistry Laboratory  
Chief Scientist: Katsunori Tanaka (Ph.D.)



**(0) Research field**

CPR Subcommittee: Chemistry, Biology

**Keywords:** Molecular imaging, diagnosis/therapy, biofunctional molecules, glycan, therapeutic in vivo synthetic chemistry

**(1) Long-term goal of laboratory and research background**

Although many efficient bond-forming reactions have been developed in the field of synthetic organic chemistry, their utility typically fails to translate in complex mixtures present in cellular or living biosystems. As such, only a handful of effective labeling or conjugation methods in biosystems are readily available. To address this issue, we are synthetically exploring the unique reactivity of conjugated imines for their potential in novel chemical reactions. The benefit of this approach is that since a large part of amine-containing biomacromolecules are biosynthesized through imine chemistry, imine-mediated chemical reactions will not face the same challenges that classical synthetic organic chemical reactions face within living systems. In parallel to this work, our studies have also shown that the unique reactivity of imines could be involved in pathways that regulate biologically important processes.

Besides usage in methods of labeling or conjugation, the novel reactivity of imines, in combination with other advanced metal-catalyzed transformations, could alternatively be used in the multi-step synthesis of biofunctional molecules within living biosystems. Through a concept we refer to as “Therapeutic In Vivo Synthetic Chemistry”, we aim to develop an adaptable system where a cascade of organic transformations can be directly executed at target regions within the body during predefined times to generate a bioactive molecule that elicits a localized biological effect. Towards this goal, we are analyzing, with the use of molecular imaging, the complex “pattern recognition” mechanisms of natural glycans in vivo and applying the glycan-based interactions to direct various linked biomolecules to desired organs and tissues.

**(2) Current research activities (FY2019) and plan (until Mar. 2025)**

1. Localized therapy by in vivo metal-catalyzed reaction

We achieved the selective recognition of the target cells, even in vivo, by applying the “pattern recognition mechanism” of the glycoclusters. We used the glycoclusters as delivery system to carry the transition metal catalysts to cancer regions, in order to perform the desired organic transformation towards anticancer molecules (Fig. 1). We would synthesize various drugs and biologically active natural products to generalize our concept, “Therapeutic In Vivo Synthetic Chemistry”.

2. Chemical transformation of toxic substance to diagnostic molecule

We succeeded in transforming the acrolein, which can be selectively and with significant amounts produced in the cancer, to the diagnostic molecules in vivo. Thus we performed the sequential reactions in the cancer specimens, which were taken during the breast cancer surgery, to diagnose various kinds of cancer within 5 minutes and with very simplified operation (Fig. 2). The method, named “Click-To-Release” has already successfully used in the clinical studies, and could be used soon in the hospitals worldwide. We would use such endogenous acrolein to synthetically convert to the therapeutic molecules to treat the cancer in vivo.

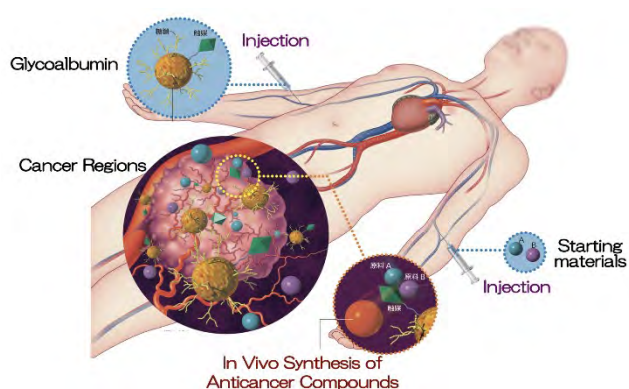


Fig. 1 Localized cancer therapy by in vivo metal-catalysis.

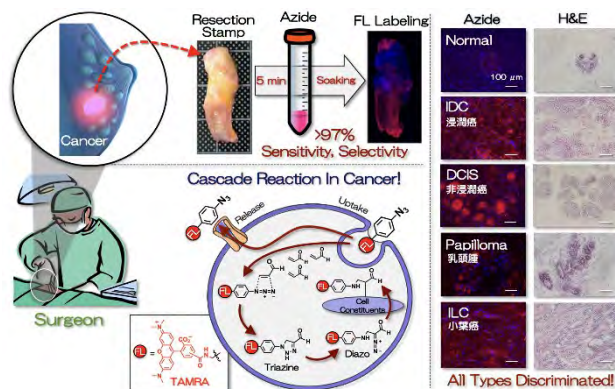


Fig. 2 Intraoperative diagnosis by cascade reaction in human cancer.

### (3) Members

#### (Chief Scientist)

Katsunori Tanaka

#### (Special Postdoctoral Researcher)

Ambara Pradipta, Kenward Vong

#### (Postdoctoral Researcher)

Katsumasa Fujiki, Shogo Nomura,  
Ahmadi Peni, Igor Nasibullin,  
Tsong-che Chang, Tomoya Yamamoto,  
Kayo Nakamura

#### (Technical Staff)

Sayaka Urano, Motoko Fujii

#### (Visiting Scientist)

Satoru Tamura, Takefumi Murase,  
Koji Morimoto

#### (Research Part-time Worker)

Yasuko Egawa, Arisa Kishimoto

#### (Assistant)

Masayo Ohara

as of March, 2020

### (4) Representative research achievements

1. "An artificial metalloenzyme biosensor can detect ethylene gas in fruits and Arabidopsis leaves", K. Vong, S. Eda, Y. Kadota, I. Nasibullin, T. Wakatake, S. Yokoshima, K. Shirasu, K. Tanaka, **Nature Commun.**, 10, 5746 (2019).
2. "Biocompatibility and therapeutic potential of glycosylated albumin artificial metalloenzymes", S. Eda, I. Nasibullin, K. Vong, N. Kudo, M. Yoshida, A. Kurbangaliev, K. Tanaka, **Nature Catal.**, 2, 780-792 (2019).
3. "Cascade reaction in human live tissue allows clinically applicable diagnosis of breast cancer morphology", T. Tanei, A. R. Pradipta, K. Morimoto, M. Fujii, M. Arata, A. Ito, M. Yoshida, E. Saigitbatalova, A. Kurbangaliev, J.-I. Ikeda, E. Morii, S. Noguchi, K. Tanaka, **Adv. Sci.**, 6, (2019).
4. "211At-Labeled immunoconjugate via a one-pot three-component double click strategy: Practical access to  $\alpha$ -emission cancer radiotherapeutics", K. Fujiki, Y. Kanayama, S. Yano, N. Sato, T. Yokokita, P. Ahmadi, Y. Watanabe, H. Haba, K. Tanaka, **Chem. Sci.**, 10, 1936-1944 (2019).
5. "The core fucose on an IgG antibody is an endogenous ligand of Dectin-1", Y. Manabe, R. Marchetti, Y. Takakura, M. Nagasaki, W. Nihei, T. Takebe, K. Tanaka, K. Kabayama, F. Chiodo, S. Hanashima, Y. Kamada, E. Miyoshi, H. P. Dulal, Y. Yamaguchi, Y. Adachi, N. Ohno, H. Tanaka, A. Silipo, K. Fukase, A. Molinaro, **Angew. Chem. Int. Ed.**, 58, 18697-18702 (2019).

## Supplementary

Dr. Tanaka holds concurrent roles as a Chief Scientist at the RIKEN and as a Professor at the Tokyo Institute of Technology. Tanaka group also collaborates with his research groups in RIKEN, i.e., RIKEN/Kazan joint laboratory (Biofunctional Chemistry Laboratory) and RIKEN Baton Zone program (GlycoTargeting Research Group), to achieve the “Therapeutic In Vivo Synthetic Chemistry”.



RIKEN Cluster for Pioneering Research



Tokyo Institute of Technology



RIKEN/Kazan (Russia) Joint Laboratory



RIKEN Baton Zone program (GlycoTargeting Research Group)

## Laboratory Homepage

[https://www.riken.jp/en/research/labs/chief/biofunct\\_synth\\_chem/index.html](https://www.riken.jp/en/research/labs/chief/biofunct_synth_chem/index.html)

<http://www.apc.titech.ac.jp/~noritanaka/>