Catalytic Olefin Metathesis in Blood

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The rate of success of anticancer drugs in clinical trials is dismal, and many reasons for that have been proposed, including poor pharmacokinetics and drug bioavailability, unexpected systemic toxicity, a lack of efficacy, and drug resistance. Professor Katsunori Tanaka at the Tokyo Institute of Technology (Japan) and the RIKEN Institute (Japan) believes that a straightforward method to solve these problems is to directly synthesize therapeutic drugs at cancer sites, thereby not only avoiding unwanted side effects on healthy tissues but also allowing for a direct evaluation of drug therapeutic effects toward various cancers. "To minimize the burden on the body and maximize therapeutic effects, a method that is biocompatible and exhibits robust catalytic ability to produce the necessary amounts of drugs *in vivo* is desirable," added Professor Tanaka.

Recently, various transition-metal catalysts have been widely explored for uncaging prodrugs and synthesizing bioactive drugs in biological environments because they display remarkable catalytic reactivity in a myriad of chemical transformations.[1] Nonetheless, Professor Tanaka told SYNFORM that the method is difficult to apply *in vivo*, because blood cells and different metabolites, such as glutathione (GSH), tend to deactivate transition-metal catalysts. "The majority of these *in vivo* examples have involved nanocarriers with encapsulated transition metals, because the large surface-area-per-volume ratio of nanocarriers enables the loading of greater amounts of metal catalysts, thereby enhancing the reaction rates," said Professor Tanaka. He added: "However, these nanocarriers have been used in excess rather than in catalytic quantities to produce the required amounts of desired products *in vivo*, indicating that the blood environment substantially hindered their reactivity. A method that implements truly catalytic organometallic reactions in blood has not yet been reported."

Artificial metalloenzymes (ArMs) are the result of inserting transition-metal complexes into protein scaffolds of interest, which can impart enhanced biofunctionality to the anchored metal catalysts.[2] Professor Tanaka's group has recently developed a biocompatible ArM in which a Hoveyda–Grubbs complex, Ru-Cl, is anchored into a hydrophobic binding pocket of human serum albumin (HSA) (**ArM-RuCl**, Figure 1a) through the interaction of a coumarin moiety with the cavity.[3] Professor Tanaka said: "The negatively charged surface of HSA prevented the charged GSH from entering the metal-binding site, thus protecting the bound Ru catalyst even in the presence of GSH at concentrations as high as 20 mM in phosphate buffered saline (PBS) solution. However, the capacity of **ArM-RuCl** to catalyze ring-closing metathesis (RCM) was not high in blood."

Professor Tanaka emphasized that this new work showed that replacing the chloride ligands with iodide ones at the Ru catalyst of ArM dramatically improves its catalytic activity in blood (**ArM-RuI**, Figure 1a,b). "We found that just 2–5 mol% of the **ArM-RuI** could catalyze various types of olefin metathesis reactions in blood to synthesize a broad range of molecular scaffolds, including five- and six-membered carbocyclic and heterocyclic compounds, indole ring, and differently substituted naphthalenes in substantial yields (Figure 1b,c)," explained Professor Tanaka, who continued: "Furthermore, this work provided the first example of catalytic olefin cross metathesis in blood (Figure 1d). The results represent a new avenue for constructing a variety of molecules *in vivo* via olefin metathesis."

Professor Tanaka noted that the **ArM-RuI** also showed robust stability and catalytic reactivity for 24 hours in blood, adding: "In comparison with other known ArMs and metallic nanocarriers, **ArM-RuI** is the first that is shown to be able to carry out a highly efficient catalytic organometallic reaction in such a challenging biological environment. As a further demonstration (Figure 1e), we proved that the cyclic-Arg-Gly-Asp (cRGD) peptide-functionalized **ArM-RuI** with low dosages could still efficiently perform *in vivo* drug synthesis to inhibit the growth of implanted tumors in mice. This study significantly advances the field of transition-metal-catalyzed reactions, opening the door for the development of general metal-based ArMs for catalytic reactions, even in highly challenging media such as blood."

Professor Tanaka concluded: "Through combination with tailor-made drug delivery systems such as glycotargeting technology,[4] this ArM system in the future is expected to enable the synthesis of a variety of anticancer drugs only at cancer sites, for evaluation of drug efficacy and subsequent therapy in patients, without causing any side effects."

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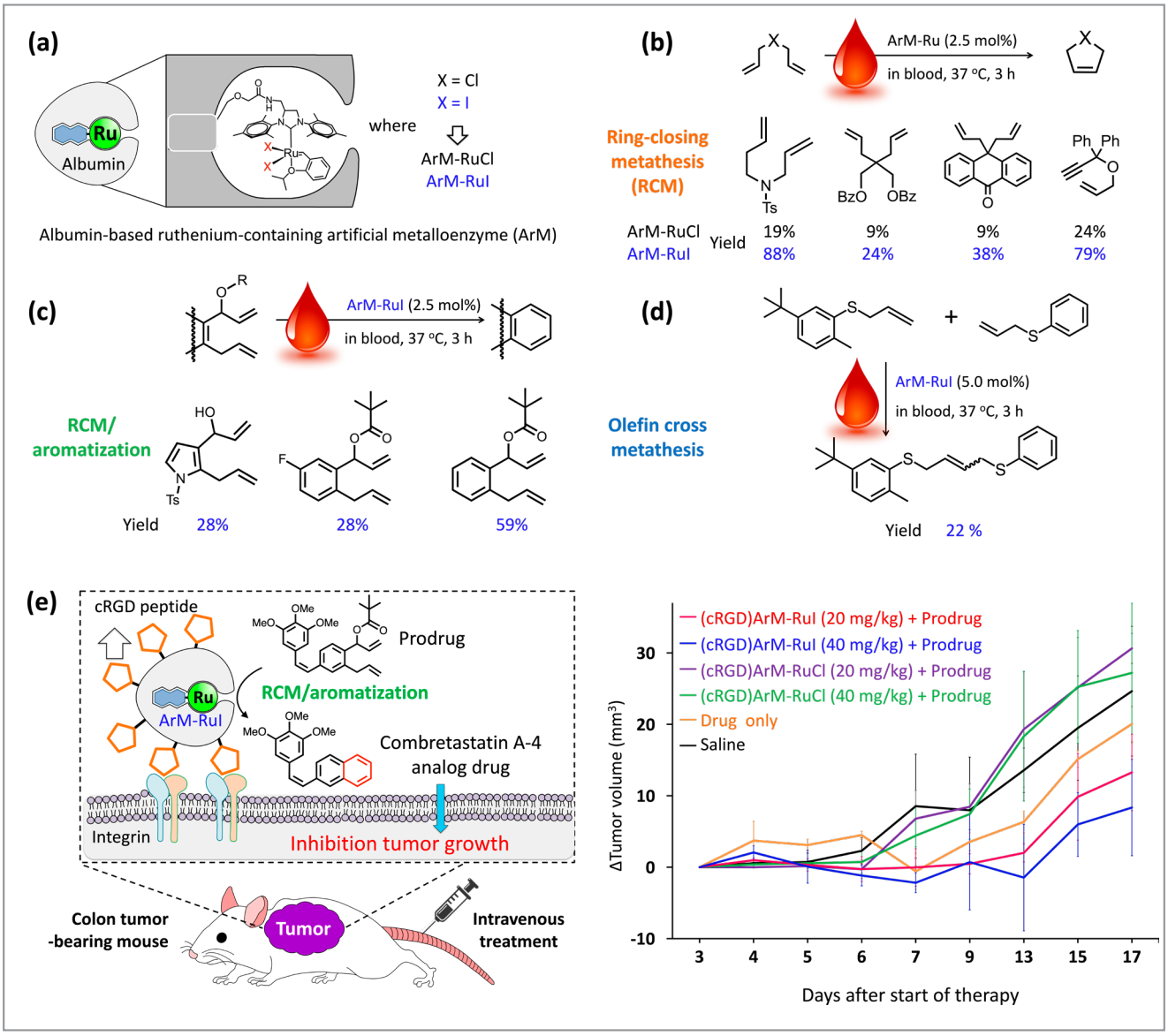

Figure 1 Catalytic olefin metathesis in blood and its anticancer application in vivo

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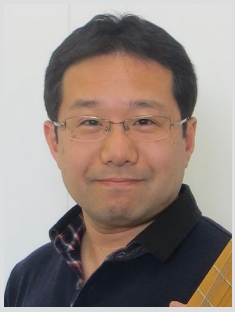

Prof. K. Tanaka

Katsunori Tanaka received his B.S. (1996) and Ph.D. (2002) in chemistry from Kwansei Gakuin University (Japan) under the guidance of Prof. Shigeo Katsumura. Following a postdoctoral stint with Prof. Koji Nakanishi at Columbia University (USA), he worked as an assistant professor in the group of Prof. Koichi Fukase at Osaka University (Japan). At present, he holds concurrent roles as a professor at the Tokyo Institute of Technology (Japan) and as a Chief Scientist at the RIKEN Institute (Japan). His research interests include organic synthesis, molecular imaging, *in vivo* synthesis, and natural products.

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