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Y.C. LU, C.H. CHUANG, W.W. LIN, T.L. CHENG

Autologous hinge as a universal antibody lock enhance the selectivity and safety of antibody drug

Key words: on-target toxicities, "antibody lock", Remicade

On-target toxicities caused by systemic administration of antibody drugs limit their application. Here, we "copied" the hinge region as a universal "antibody lock" and "pasted" it on the antigen binding site of the monoclonal antibody drug infliximab (Remicade) by linking with a disease-specific protease substrate to generate pro-Remicade which can be selectively activated at the disease site. The binding of pro-Remicade was 395-fold weaker than Remicade, and could be completely restored after activation with protease. The antibody lock also markedly prevented the neutralizing effect of an anti-idiotypic antibody induced by long-term drug administration to rheumatoid arthritis patients. In mice model, selectively activated pro-Remicade provided equivalent serum half-life and therapeutic efficacy comparable to Remicade while reducing on-target toxicities to maintain the immunity against *Listeria* infection. Moreover, the spatial-hindrance-basedantibody lock was successfully applied to several antibodies. The universal antibody lock may revolutionize the development of antibody drugs to achieve disease site-specific therapy.

LU Yun-Chi, *CHENG Tian-Lu – Professor, Director (Graduate Institute of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan, Department of Biomedical Science and Environmental Biology, Kaohsiung Medical University, Kaohsiung, Taiwan), CHUANG Chih-Hung - Assistant Professor (Department of Medical Laboratory Science and Biotechnology, College of Health Sciences, Kaohsiung Medical University, Kaohsiung, Taiwan), LIN Wen-Wei (Department of Laboratory Medicine, School of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan). *E-mail: tlcheng@kmu.edu.tw

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