Tocilizumab: Humanized Anti-human Interleukin (IL)-6 Receptor Monoclonal Antibody

○ Yoshiyuki Ohsugi, Masayuki Tsuchiya(Chugai Pharmaceutical Co. Ltd.), and Tadamitsu Kishimoto(Graduate School of Frontier Bioscience, Osaka University)

Tocilizumab is a humanized anti-human interleukin (IL)-6 receptor antibody which is a highly efficacious drug for Castleman's disease, developed and launched in Japan in 2005. This is the only anti-Castleman's disease drug currently available, as well as the sole IL-6 inhibitor in the world. It has also remarkable efficacy in treating patients with rheumatoid arthritis and systemic onset juvenile idiopathic arthritis. Therefore, BLA (Biologic license application) was submitted to the Japanese authority as an additional indication in April 2006.

In late 70's, we found that intrinsic polyclonal B-cell activation induced auto-antibody production, resulting in spontaneous development of autoimmune kidney disease in NZB/NZW F1 mice which resembled human SLE. However, in spite of our vigorous effort, the factor responsible for this B-cell activation remained unidentified for many years.

In 1986, Kishimoto's group at Osaka University, after their long term investigation regarding T-B cell interaction in antibody production, cloned a gene coding for B cell stimulatory factor-2 (BSF2/IL-6), which was a T cell-derived soluble factor to differentiate B cells into antibody forming plasma cells.

Further studies have demonstrated that IL-6 is a multifunctional cytokine: It induces activated T cells; acts on hepatocytes to induce acute phase reactants such as CRP and fibrinogen; and decreases serum albumin level. Moreover, it has been clarified that IL-6 is responsible for all the chronic autoimmune inflammatory disease-like symptoms such as fatigue, anorexia, fever, auto-antibodies, increase in ESR, and increase in CRP, which developed in a patient with cardiac myxoma. Based on these findings, we decided to develop tocilizumab (humanized anti-human IL-6 receptor monoclonal antibody) as an anti-autoimmune disease drug in collaboration with Osaka University.

As expected, clinical studies have shown that tocilizumab improves fatigue, fever, anorexia, and anemia in Castleman's disease. Furthermore, there were similar abnormal

symptoms shared among Castleman's disease; systemic onset juvenile idiopathic arthritis; and rheumatoid arthritis. This led us to test the efficacy of tocilizumab for these two diseases. Due to significant clinical efficacy, tocilizumab is expected to be the first choice of rheumatoid arthritis therapy. Clinical studies are now on-going worldwide in the patients with rheumatoid arthritis in 41 countries.