Japan Academy Prize to:

Ryuzo Ueda
Designated Professor, Graduate School of Medicine,
Nagoya University
Emeritus Professor, Nagoya City University
Emeritus Professor, Aichi Medical University

for "Translational Research on Antibody Drug Development for Adult T-cell Leukemia and Lymphoma"

Outline of the work:

Dr. Ryuzo Ueda graduated from Nagoya University School of Medicine in 1969 and began clinical research, focusing on chemotherapy for leukemia. In 1976, he worked at the Sloan Kettering Cancer Institute in New York to study tumor immunology and conducted research to discover human tumor antigens.

Dr. Ueda conducted tumor antigen analysis (autologous-serum typing) to examine the reaction between kidney cancer patient serum and cultured cancer cells derived from the same patient, to find out whether the human body can recognize its cancer as a foreign substance. He was successful in identifying kidney cancer-specific antigens. Furthermore, he was a pioneer in identifying a human kidney cancer-specific antibody using a monoclonal antibody production method that had been newly developed. He was convinced that cancer immunotherapy targeting cancer-specific antigens is effective in cancer treatment, and hence he immersed himself in translational research (TR), from basic cancer research to clinical application, upon his return to Japan.

After returning to Japan in 1980, he initiated research on adult T-cell leukemia/lymphoma (ATLL) at the Aichi Cancer Center Research Institute. ATLL is an incurable leukemia caused by the human T-cell leukemia virus type 1 (HTLV-1), which was discovered in 1977 by Japanese researcher Dr. K. Takatsuki. There is an ATLL endemic region in southwestern Japan. At the time, there were no effective treatments for ATLL.

Since the late 1990s, Dr. Ueda's laboratory at Nagoya City University School of Medicine has been involved in pathological analysis of more than 100 ATLL patients specimens along with the mouse monoclonal antibody, developed by Dr. K. Matsushima and his colleagues. They observed an elevated expression of the chemokine receptor 4 (CCR4) molecule on the surface of ATLL cells in more than 90% of patients diagnosed with ATLL. They identified CCR4 to be a specific marker molecule for ATLL and also a factor responsible for the poor prognosis of ATLL patients, and further identified it as an optimal target molecule for ATLL tumor treatment.

Since the year 2000, Dr. Ueda has been actively engaged in ATLL TR in collaboration with a company. During his tenure, the company successfully produced antibodies with high

potency and antibody-dependent cell cytotoxicity (ADCC) by developing a technology known as the Poteligio technology, involving the removal of sugar chains from the Fc (fragment crystallizable) region of antibodies. Dr. Ueda's laboratory was the first in the world to demonstrate that after administration of this fucose-depleted chimeric anti-CCR4 antibody, lymphocytes from ATLL patients were able to destroy their own ATLL cells in vitro.

Dr. Ueda then directed the company to formulate a humanized anti-CCR4 antibody as a therapeutic antibody drug. After verification of the activity, safety, and stability of the antibody by the company, Dr. Ueda's group initiated a first-in-human trial to administer the antibody (mogamulizumab) to ATLL patients. In the phase 1 trial, the drug was administered to 16 CCR4-positive relapsed or refractory cases. As a result, the trial was safe and two ATLL patients achieved complete remission (CR), and three patients achieved partial remission (PR), resulting in an overall response rate (ORR) of 31%. Based on the results of the phase 1 trial, Dr. Ueda's group immediately initiated a phase 2 clinical trial involving 26 patients with relapsed ATLL. The results of this trial were amazing, with eight patients achieving CR and five patients achieving PR, resulting in an ORR of 50%.

These clinical trials resulted not only in the creation of Japan's first self-created anti-cancer antibody drug in 2012, as an orphan drug for recurrent ATLL, but also in the first simultaneous approval of the first companion diagnostic drug in Japan. In Japan, this drug was approved in 2014 for expanded indications to treat untreated ATLL, relapsed CCR4-positive peripheral T-cell lymphoma (PTCL), and cutaneous T-cell lymphoma (CTCL). Overseas, in 2018, the drug was approved by the U.S. Food and Drug Administration and the European Medicines Agency for the treatment of mycosis fungoides (MF), relapsed and refractory skin lymphoma, and Sézary syndrome (SS).

Following the launch of the anti-CCR4 antibody, Dr. Ueda continues the physician-led drug development research to examine the optimal way to use this drug, as well as to clarify the mechanisms of recurrence and resistance development for this antibody drug.

As mentioned above, Dr. Ryuzo Ueda discovered a therapeutic target for ATLL and developed a therapeutic drug in collaboration with a pharmaceutical company. Furthermore, he supervised every step, right from the preclinical research to the clinical trials, and successfully launched Japan's first monoclonal antibody drug for cancer. He is an outstanding researcher who can be labeled as a role model for physician-scientists, as he has proved the clinical efficacy of the drug and successfully delivered an effective drug to ATLL patients around the world. This is a remarkable achievement in the history of cancer research and cancer treatment in Japan, and even today, Dr. Ueda continues to make several contributions to cancer immunotherapy and cancer TR.

List of Main Publications

1. Ishida T and **Ueda R.** Immunopathogenesis of lymphoma: focus on CCR4. **Cancer Sci.**, 2011; 102: 44–50. (review article)
2. Ishida T and **Ueda R.** Antibody therapy for Adult T-cell leukemia-lymphoma. **Int. J. Hematol.**, 2011; 94: 443–452. (review article)

3. **Ueda R.**, Shiku, H., Pfreundschuh, M., Takahashi, T., Li, I.T.C., Whitmore, W.F., Oettgen, H.F. and Old, L.J. Cell surface antigens of human renal cancer defined by autologous typing. **J. Exp. Med.**, 1979; 150: 564–579.
4. **Ueda R.**, Ogata, S., Morrissey, D.M., Finstad, c.L., Szkudlarek, J., Whitmore, W.F., Oettgen, H.F., Lloyd, K.O. and Old, L.J. Cell surface antigens of human renal cancer defined by mouse monoclonal antibodies: Identification of tissue-specific kidney glycoproteins. **Proc. Natl. Acad. Sci. USA.**, 1981; 78: 5122–5126.
5. **Ueda R.**, Tanimoto, M., Takahashi, T., Ogata, S., Nishida, K., Namikawa, R., Nishizuka, Y. and Ota, K. Serological analysis of cell surface antigens of null cell acute lymphocytic leukemia by mouse monoclonal antibodies. **Proc. Natl. Acad. Sci., U.S.A.**, 1982; 79: 4386–4390.
6. Motoi, T., Uchiyama, T., Hori, T., Itoh, K., Uchino, H. and **Ueda R.** Elevated serum-soluble interleukin-2 receptor (Tac antigen) levels in chronic myelogenous leukemia patients with blastic crisis. **Blood**, 1989; 74: 1052–1057.
7. Ishida T, Utsunomiya A, Iida S, Inagaki H, Takatsuka Y, Kusumoto S, Takeuchi G, Shimizu S, Ito M, Komatsu H, Wakita A, Eimoto T, Matsushima K and **Ueda R.** Clinical significance of CCR4 expression in adult T-cell leukemia/lymphoma: its close association with skin involvement and unfavorable outcome. **Clin. Cancer Res.**, 2003; 9: 3625–3634.
8. Niwa R, Shoji-Hosaka E, Sakurada M, Shinkawa T, Uchida K, Nakamura K, Matsushima K, **Ueda R**, Hanai N and Shitara K. Defucosylated chimeric anti-CC chemokine receptor 4 IgG1 with enhanced antibody-dependent cellular cytotoxicity shows potent therapeutic activity to T-cell leukemia and lymphoma. **Cancer Res.**, 2004; 64: 2127–2133.
9. Ishida T, Iida S, Akatsuka Y, Ishii T, Miyazaki M, Komatsu H, Inagaki H, Okada N, Fujita T, Shitara K, Akinaga S, Takahashi T, Utsunomiya A and **Ueda R.** The CC chemokine receptor 4 as a novel specific molecular target for immunotherapy in adult T-Cell leukemia/lymphoma. **Clin. Cancer Res.**, 2004; 10: 7529–7539.
10. Yamamoto K, Utsunomiya A, Tobinai K, Tsukasaki K, Uike N, Uozumi K, Yamaguchi K, Yamada Y, Hanada S, Tamura K, Nakamura S, Inagaki H, Ohshima K, Kiyoi H, Ishida T, Matsushima K, Akinaga S, Ogura M, Tomonaga M and **Ueda R.** Phase I study of KW-0761, a defucosylated humanized anti-CCR4 antibody, in relapsed patients with adult T-cell leukemia-lymphoma and peripheral T-cell lymphoma. **J. Clin. Oncol.**, 2010; 28: 1591–1598.
11. Ishida T, Joh T, Uike N, Yamamoto K, Utsunomiya A, Yoshida S, Saburi Y, Miyamoto T, Takemoto S, Suzushima H, Tsukasaki K, Nosaka K, Fujiwara H, Ishitsuka K, Inagaki H, Ogura M, Akinaga S, Tomonaga M, Tobinai K and **Ueda R.** Defucosylated anti-CCR4 monoclonal antibody (KW-0761) for relapsed adult T-cell leukemia-lymphoma: a multicenter phase II study. **J. Clin. Oncol.**, 2012; 30: 837–842.
12. Ogura M, Ishida T, Hatake K, Taniwaki M, Ando K, Tobinai K, Fujimoto K, Yamamoto K, Miyamoto T, Uike N, Tanimoto M, Tsukasaki K, Ishizawa K, Suzumiya J, Inagaki H, Tamura K, Akinaga S, Tomonaga M and **Ueda R.** Multicenter phase II study of mogamulizumab (KW-0761), a defucosylated anti-cc chemokine receptor 4 antibody, in patients with relapsed peripheral T-cell lymphoma and cutaneous T-cell lymphoma. **J. Clin. Oncol.**, 2014; 32:

1157–1163.

13. Ishida T, Jo T, Takemoto S, Suzushima H, Uozumi K, Yamamoto K, Uike N, Saburi Y, Nosaka K, Utsunomiya A, Tobinai K, Fujiwara H, Ishitsuka K, Yoshida S, Taira N, Moriuchi Y, Imada K, Miyamoto T, Akinaga S, Tomonaga M and **Ueda R.** Dose-intensified chemotherapy alone or in combination with mogamulizumab in newly diagnosed aggressive adult T-cell leukaemia-lymphoma: a randomized phase II study. **Br. J. Haematol.**, 2015; 169: 672–682.
14. Kurose K, Ohue Y, Wada H, Iida S, Ishida T, Kojima T, Doi T, Suzuki S, Isobe M, Funakoshi T, Kakimi K, Nishikawa H, Udono H, Oka M, **Ueda R** and Nakayama E. Phase Ia study of FoxP3+ CD4 Treg depletion by infusion of a humanized anti-CCR4 antibody, KW-0761, in cancer patients. **Clin. Cancer Res.**, 2015; 21: 4327–4336.
15. Sakamoto Y, Ishida T, Masaki A, Murase T, Yonekura K, Tashiro Y, Tokunaga M, Utsunomiya A, Ito A, Kusumoto S, Iida S, **Ueda R** and Inagaki H. CCR4 mutations associated with superior outcome of adult T-cell leukemia/lymphoma under mogamulizumab treatment. **Blood**, 2018; 132: 758–761.
16. Maeda Y, Wada H, Sugiyama D, Saito T, Irie T, Itahashi K, Minoura K, Suzuki S, Kojima T, Kakimi K, Nakajima J, Funakoshi T, Iida S, Oka M, Shimamura T, Doi T, Doki Y, Nakayama E, **Ueda R** and Nishikawa H. Depletion of central memory CD8+ T cells might impede the antitumor therapeutic effect of Mogamulizumab. **Nat. Commun.**, 2021; 12: 7280.