History of CCR4 Research

--From my personal point of view-

Takashi Ishida, M.D., Ph.D.

Director, Ishida Family Clinic

I have been engaged in research on CC chemokine receptor 4 (CCR4), hematological malignancies, and tumor immunology under the mentorship of Prof. Ryuzo Ueda (currently, Designated Professor, Nagoya University Graduate School of Medicine), together with many excellent collaborators. In this column, I would like to discuss the current status and further directions of our studies on CCR4.

CCR4 is a chemokine receptor selectively expressed on T cells during a limited stage of maturation in the thymus, and on specific functional subsets of mature $CD4^+$ T cells such as Th2 and regulatory T (Treg) cells after thymic selection (**Figure 1**). Around 2003, leading Japanese researchers such as Prof. Kouji Matsushima and Prof. Osamu Yoshie made significant observations in this field. Based on their important work, we reported that CCR4 is expressed on tumor cells from most patients with adult T-cell leukemia/lymphoma (ATL) (**Figure 2**) (1). Subsequently, we reported that CCR4 is also expressed on some subsets of mature T-cell neoplasms other than ATL, such as PTCL-NOS

(peripheral T-cell lymphoma, not otherwise specified) with unfavorable prognosis, Mycosis Fungoides, or Sezary Syndrome (subtypes of cutaneous T-cell lymphoma [CTCL]) (2). Furthermore, a defucosylated chimeric anti-CCR4 monoclonal antibody (mAb) mediated potent CCR4-specific antibody-dependent cellular cytotoxicity (ADCC) against CCR4-positive primary tumor cells together with autologous effector cells in several patients with mature T-cell neoplasms including ATL (**Figure 3**) (3). In this context, a fundamental framework for novel antibody immunotherapy targeting CCR4 to treat mature T-cell neoplasms was established, based on a series of studies including the use of humanized immunodeficient mice, in which autologous human immune cells were engrafted and functioned as ADCC effector cells (**Figure 4**) (4, 5).

These promising preclinical results prompted us to conduct a phase I clinical trial of mogamulizumab, a defucosylated humanized anti-CCR4 mAb (6), for patients with relapsed CCR4-positive PTCL, including ATL. This study demonstrated good tolerability, predictable pharmacokinetics, and preliminary evidence of potent antitumor activity, resulting in a recommended dose of 1.0 mg/kg for subsequent clinical trials (7). Accordingly, a multicenter phase II study demonstrated that mogamulizumab monotherapy showed clinically meaningful antitumor activity in patients with relapsed ATL, with an acceptable toxicity profile (8). Based on this study, mogamulizumab (brand name: POTELIGEO® Injection) received the world's first regulatory approval in Japan in March 2012, for the treatment of patients with relapsed or refractory CCR4-positive ATL. In a subsequent multicenter phase II study of mogamulizumab

monotherapy in patients with relapsed PTCL or CTCL, this antibody exhibited clinically meaningful antitumor activity with an acceptable toxicity profile (9). As a result, mogamulizumab received approval for the additional indication of relapsed or refractory CCR4-positive PTCL and CTCL in Japan in March 2014. Next, a multicenter, randomized, phase II study was conducted to examine whether the addition of mogamulizumab to mLSG15, a dose-intensified chemotherapy, further increases efficacy without compromising safety of patients with newly diagnosed aggressive ATL (10). As a result of this study, mogamulizumab received approval for the additional indication of chemotherapy-naive CCR4-positive ATL in December 2014.

Research that bridges basic scientific observations and clinical applications is referred to as translational research. As described here, the development of mogamulizumab exemplifies this process. Reciprocally, reverse translational research, where clinical findings are brought back to the laboratory, and fundamental biological mechanisms are clarified, is also important. In this context, we reported an ATL patient suffering from severe fatal skin disease, SJS/TEN, during mogamulizumab treatment **(Figure 5)**. There was a durable significant reduction of the $CD4^{+}CD25^{high}FOXP3^{+}$ T cell subset in the patient's PBMC, and the affected inflamed skin almost completely lacked FOXP3-positive cells **(Figure 6)** (11). Because CCR4 is highly expressed on $CD4^{+}CD25^{high}FOXP3^{+}$ effector Tregs, this implied that mogamulizumab functions as a Treg-depleting agent. Indeed, analyses of patients' paired sera before and after mogamulizumab treatment confirmed that this antibody elicits

autoantibodies with cytotoxic activity against skin cells such as keratinocytes or melanocytes, possibly associated with Treg depletion (12). This represents a clear example of reverse translational research. On the other hand, within the cancer microenvironment, Tregs play a critical role in creating a favorable environment for cancer cells to survive despite host immune recognition and potential attack. Thus, therapies targeting Tregs are now being recognized as a promising strategy in cancer immunotherapy, and the challenges of employing mogamulizumab against solid malignant tumors are currently under investigation.

Finally, I would like to mention the role of *CCR4* gain-of-function (GOF) mutations **(Figure 7)**. Approximately 30% of ATL cases and around 7% of Sézary Syndrome samples harbor *CCR4* GOF mutations, highlighting their importance in mature T-cell tumorigenesis. In a retrospective analysis of ATL patients treated with mogamulizumab, we reported that the presence of *CCR4* GOF mutations correlated with significantly better overall survival **(Figure 8)** (13). Importantly, this finding has been confirmed in a prospective clinical trial (14). This indicates that the presence or absence of *CCR4* GOF mutations is a crucial factor in providing the most suitable treatment strategy for ATL patients. Clarifying the clinical significance of *CCR4* GOF mutations in CTCL and in novel CCR4-targeted approaches such as CAR-T cell therapy or antibody-drug conjugates remains a key challenge for the future.

In this column, I have summarized a part of the history and insights of CCR4 research, established together with my mentor Prof. Ueda and many good collaborators across generations, from my own perspective **(Figure 9)**.

Mogamulizumab, developed in Japan, is now an approved treatment for mature T-cell neoplasms in 58 countries and regions as of September 2024. I have been given the opportunity to contribute to this journey of CCR4, and it is sincerely a source of both happiness and pride for me as a clinical physician and a basic researcher. Currently, I am devoted to community medical practice as a family physician, striving to utilize the fruits of cutting-edge science and evolving clinical evidence, in order to contribute to the true well-being of each patient. I still continue to further refine my knowledge and practice in pursuit of patients' health and happiness.

Acknowledgments

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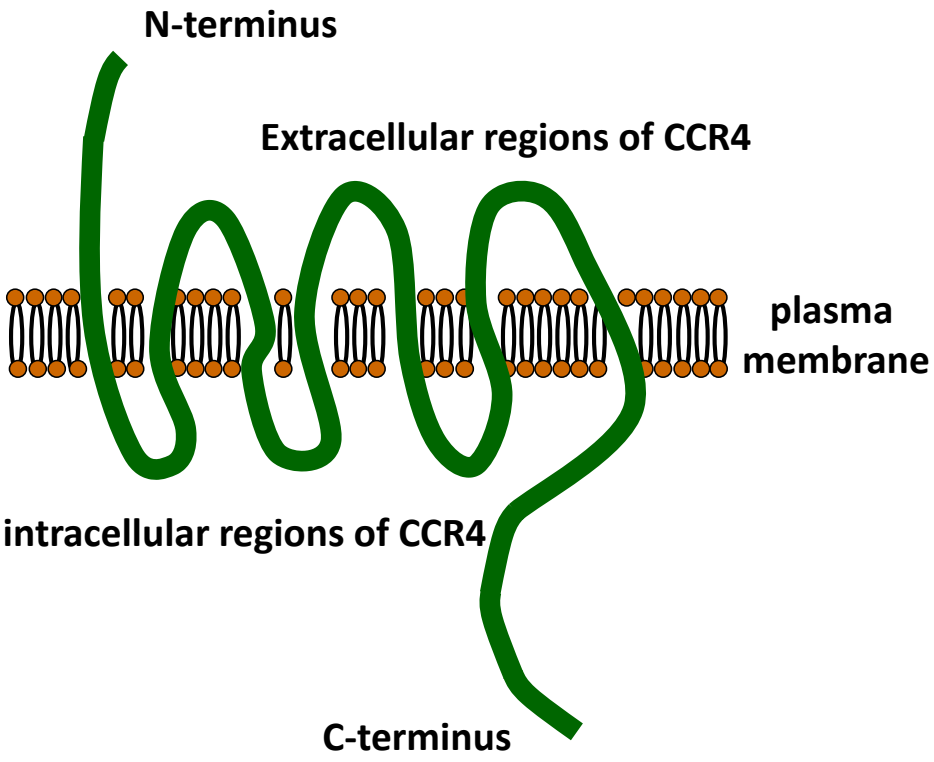

Figure 1. CCR4 protein. CCR4 is a 7 transmembrane G protein-coupled receptor and consists of 360 amino acids. C-C motif chemokine ligand 17 (CCL17)/TARC and CCL22/MDC are ligands of CCR4. The *CCR4* gene is located on chromosome 3p24.

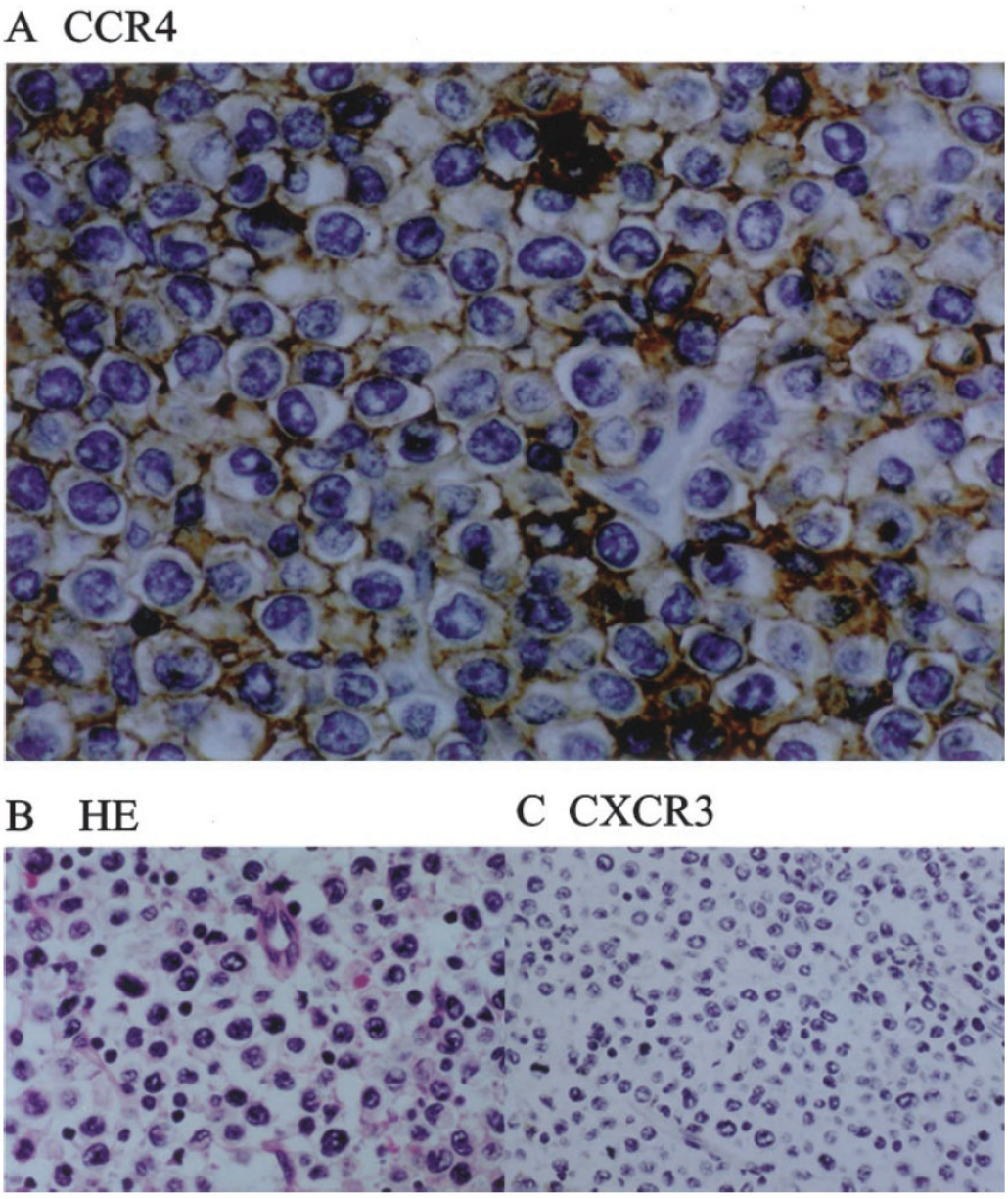

Figure 2. A representative lymph node finding of a patient with lymphoma type ATL (A) The majority of tumor cells stain for CCR4. Most cells show membrane staining and granular cytoplasmic staining (CCR4 immunostaining). **(B)** Proliferation of large atypical cells with irregular and pleomorphic nuclei. This case was classified as pleomorphic large cell type (H&E staining). **(C)** The same tumor cells of this case are negative for CXCR3 (CXCR3 immunostaining). (**Reproduced from Reference 1)**

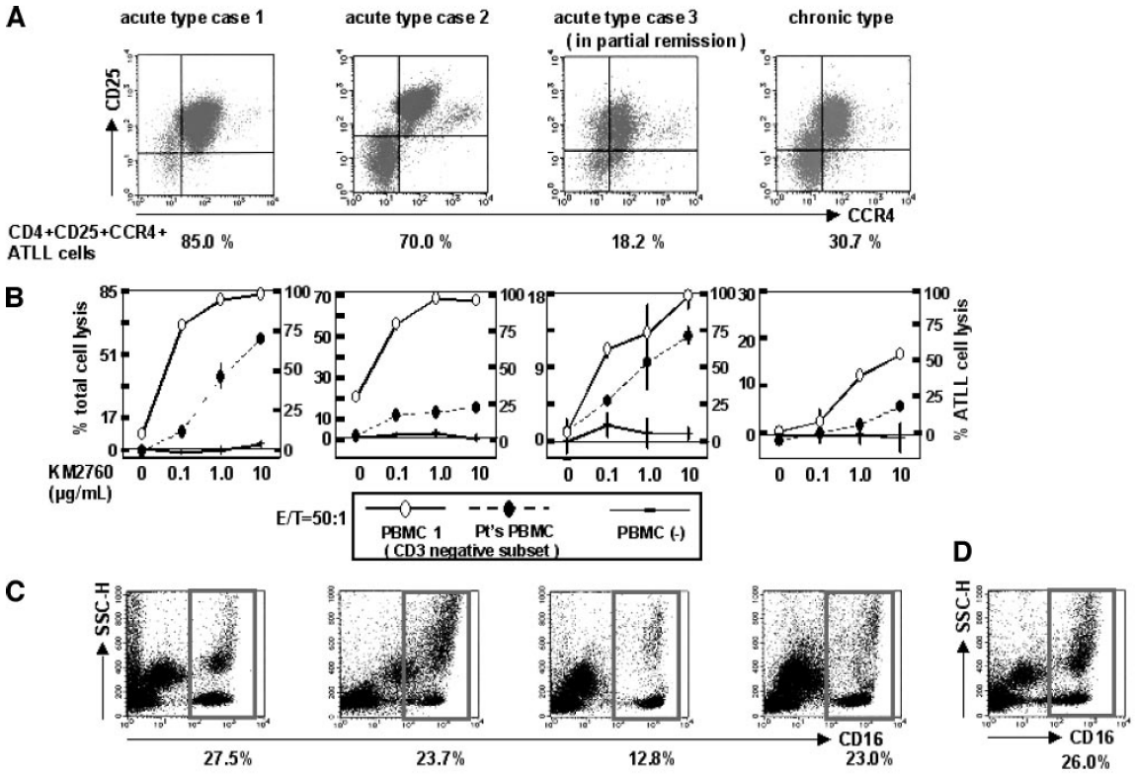

Figure 3. A defucosylated chimeric anti-CCR4 monoclonal antibody (mAb), KM2760, induced ADCC against ATL cells obtained from patients tested in an autologous setting. (A) Target ATL cells used in this study. Freshly isolated PBMCs from four patients with ATL were sorted into a CD3-positive (containing ATL cells) subset and used as ADCC target cells. The percentage of CD4+CD25*CCR4+ cells (as ATL cells) among the CD3-positive subset is indicated below. **(B)** KM2760-induced ADCC activity mediated by autologous effector cells. KM2760-induced ADCC against the CD3-positive subset was measured in the presence of the CD3-negative subset at an E:T ratio of 50:1. All experiments were done in triplicate, and the percent cell lysis is presented as the average ± SD. **(C)** Autologous effector cells used in this study. The remaining CD3-negative subsets (containing NK cells and monocytes) of patient's PBMCs were used as autologous ADCC-effector cells. The percentages of CD16+ cells are indicated below each flow cytometry panel. **(D)** Allogeneic effector cells as controls. A CD3-negative subset was also isolated from a healthy adult volunteer (PBMC 1) and used as control allogeneic ADCC-effector cells. The percentage of CD16+ cells is indicated below the panel. (**Reproduced from Reference 2)**

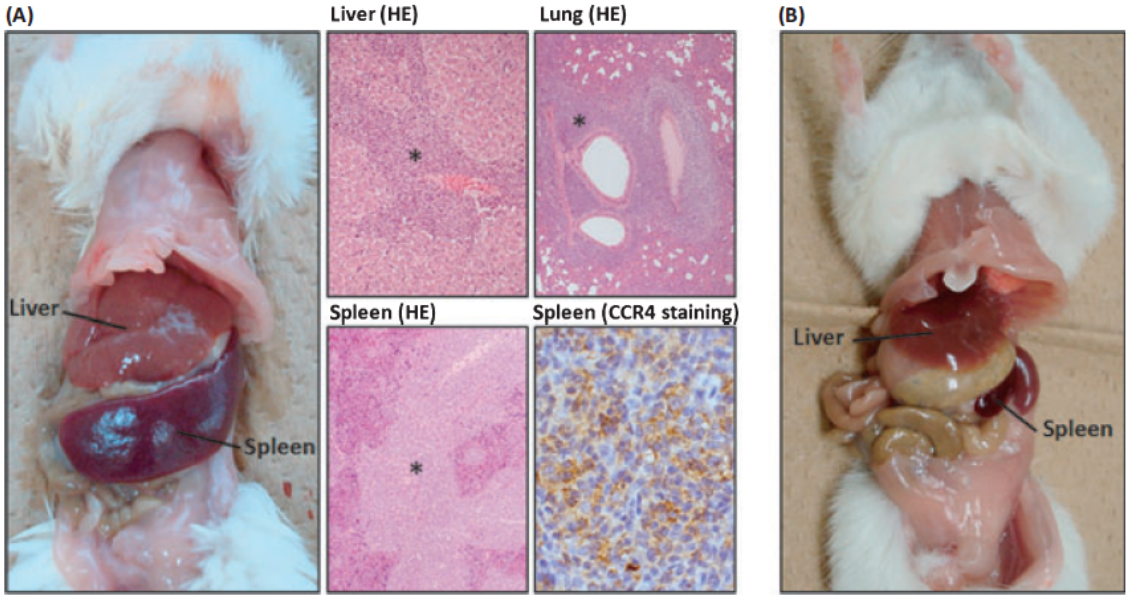

Figure 4. Macroscopic observations and histological findings of a primary ATL cell-bearing NOD/Shi-scid, IL-2Rγnull (NOG) mouse (A) Primary ATL cell-bearing NOG mouse. Both the liver and spleen of a NOG mouse are enlarged. Immumohistological analysis revealed that the liver, lung, and spleen were infiltrated by CCR4+ ATL cells and the normal architecture of each organ was destroyed. Asterisks indicate tumor infiltrating regions. **(B)** In contrast, a primary ATL cell-bearing NOG mouse treated with the therapeutic anti-CCR4 mAb has no morbid lesions detectable macroscopically.

(**Reproduced from Reference 5)**

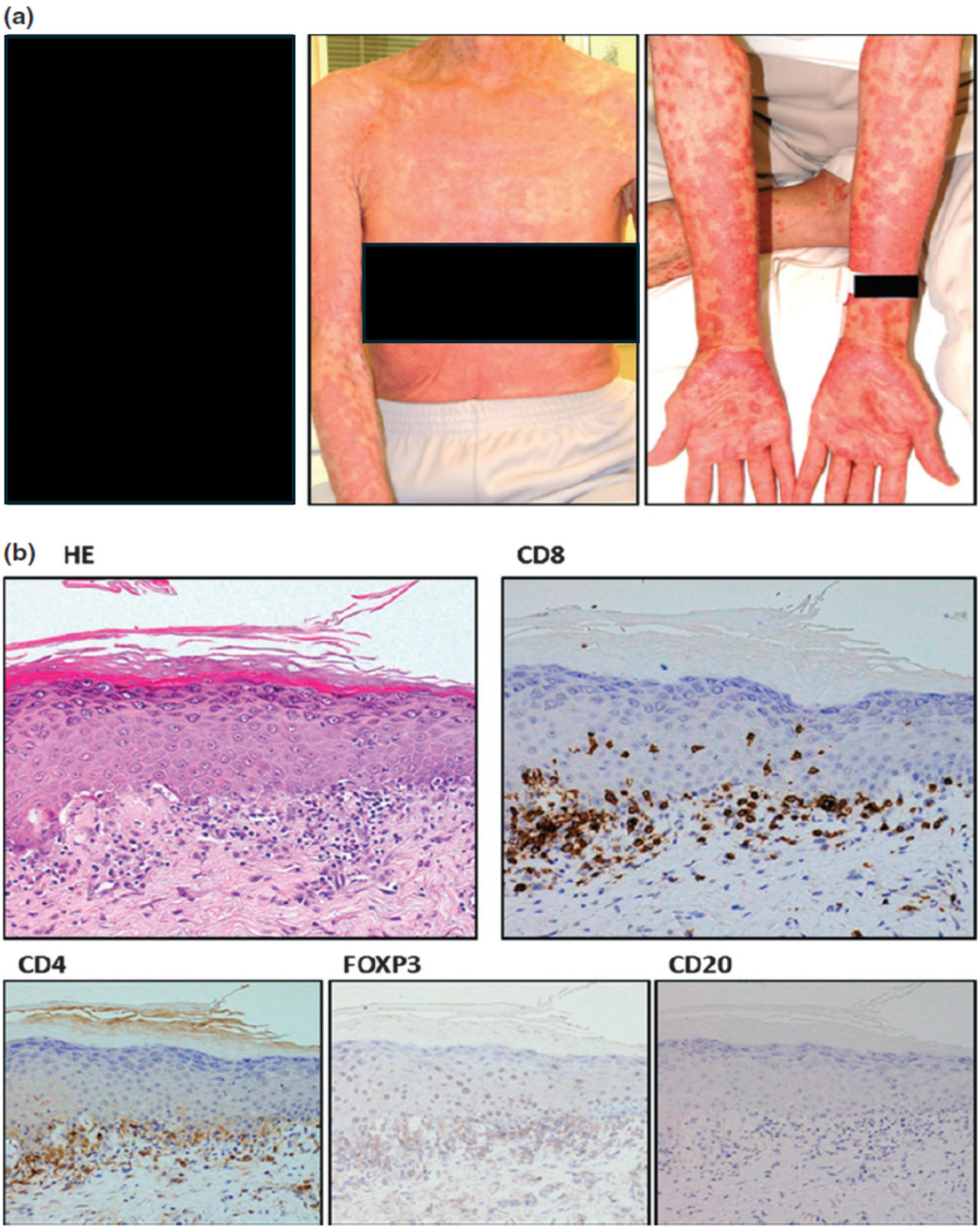

Figure 5. Macroscopic observations and histological findings of the patient's skin on the day she was diagnosed with Stevens–Johnson Syndrome (SJS). (a) Fulminant skin rashes including erythemas, scale-like plaques, vesicles, blisters and erosions are observed over many areas of the body. Her lips are swollen, and oral mucosa is erosive. **(b)** Corresponding skin biopsy showing liquefaction, degeneration and perivascular inflammation with dominant CD8-positive cells but almost no FOXP3-positive cells**.**

(**Reproduced from Reference 11)**

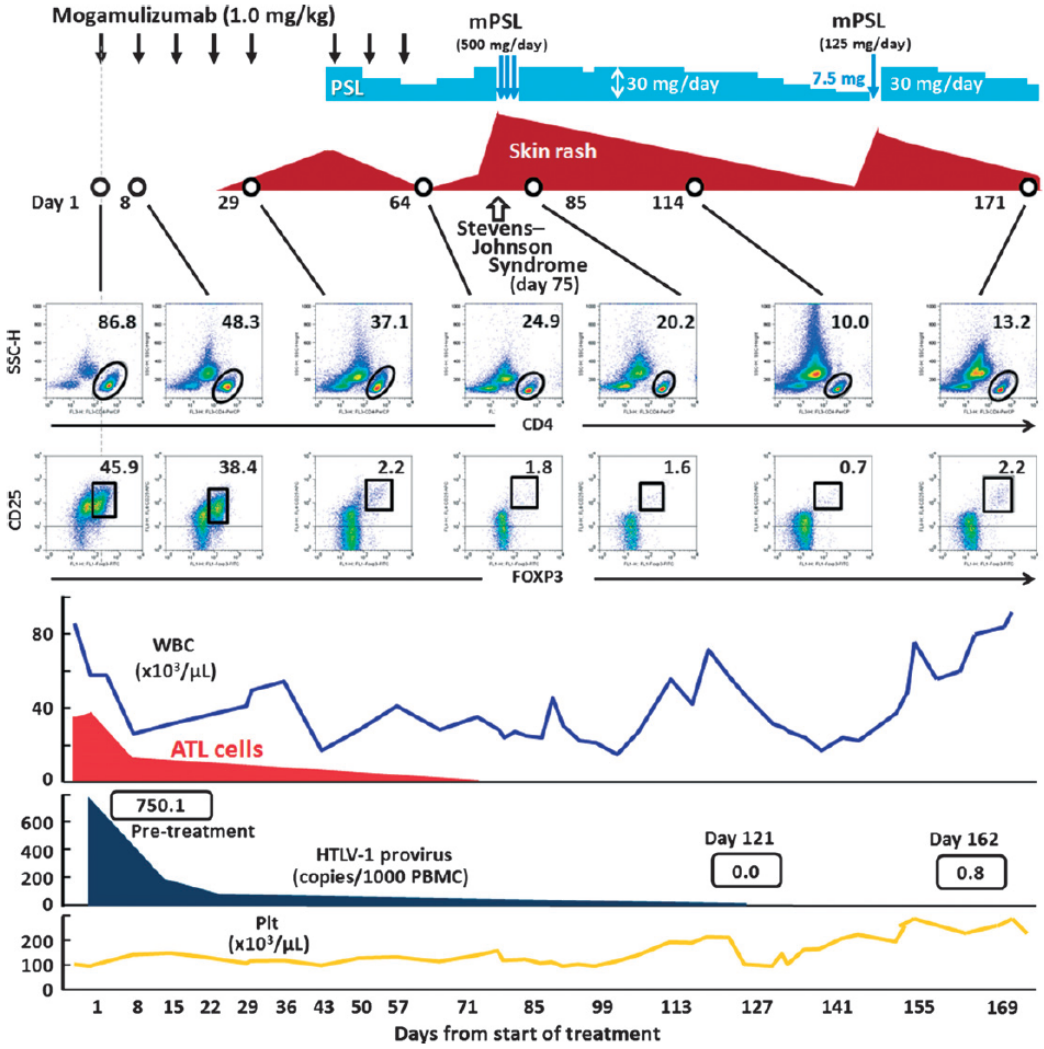

Figure 6. **Clinical course of an ATL patient receiving mogamulizumab monotherapy.** CD4, CD25 and FOXP3 expression by PBMC before, during, and after antibody treatment (middle panels). CD4-positive cells were gated as shown by the ovals (upper middle panels), and stained for FOXP3 and CD25 (lower middle panels). Before treatment, the majority of the patient's PBMC consisted of $CD4^{+}CD25^{+}$ ATL cells. Just before the 5th antibody infusion (day 29), around the time when her skin rash first appeared, the proportion of $CD25^{high}FOXP3^{+}$ cells among $CD4^{+}$ cells was reduced to 2.2%. Around the time of SJS onset, the proportion of cells in the Treg subset was further reduced. The proportion of $CD25^{high}FOXP3^{+}$ cells among CD4+ cells at days 64, 85 and 114 was 1.8%, 1.6% and 0.7%, respectively. The reduction of the Treg subset persisted until 4 months after the last of the eight antibody infusions (day 171). The HTLV-1 provirus load in PBMC pre-treatment, and at days 121 and 162 was 750.1, 0.0, and 0.8 copies/1,000 PBMC, respectively (lower second panels).
(**Reproduced from Reference 11).**

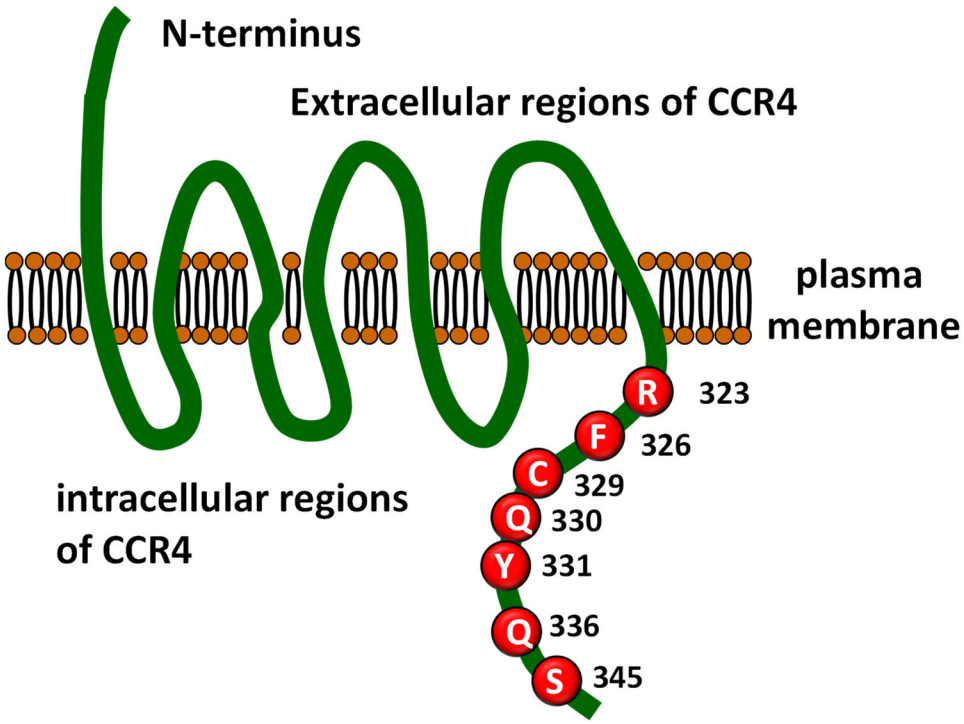

Figure 7. CCR4 protein in ATL. The CCR4 mutations in the c-terminus were determined to be gain-of-function, leading to increased cell migration toward CCR4 ligands by impairing receptor internalization.

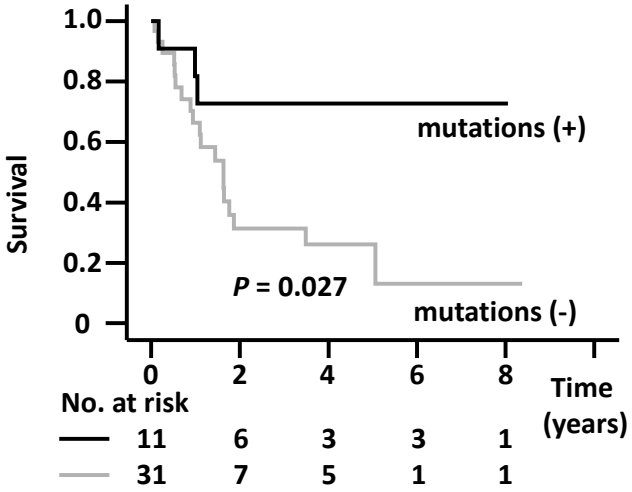

Figure 8. Overall survival according to *CCR4* GOF mutations. For patients who received mogamulizumab-containing treatments (but no allogeneic-HSCT), 5-year survival from the day of the first dose of antibody was 72.2% in those with CCR4 mutations, but only 26.2% in those without (P = 0.027)
(**Reproduced from Reference 13)**

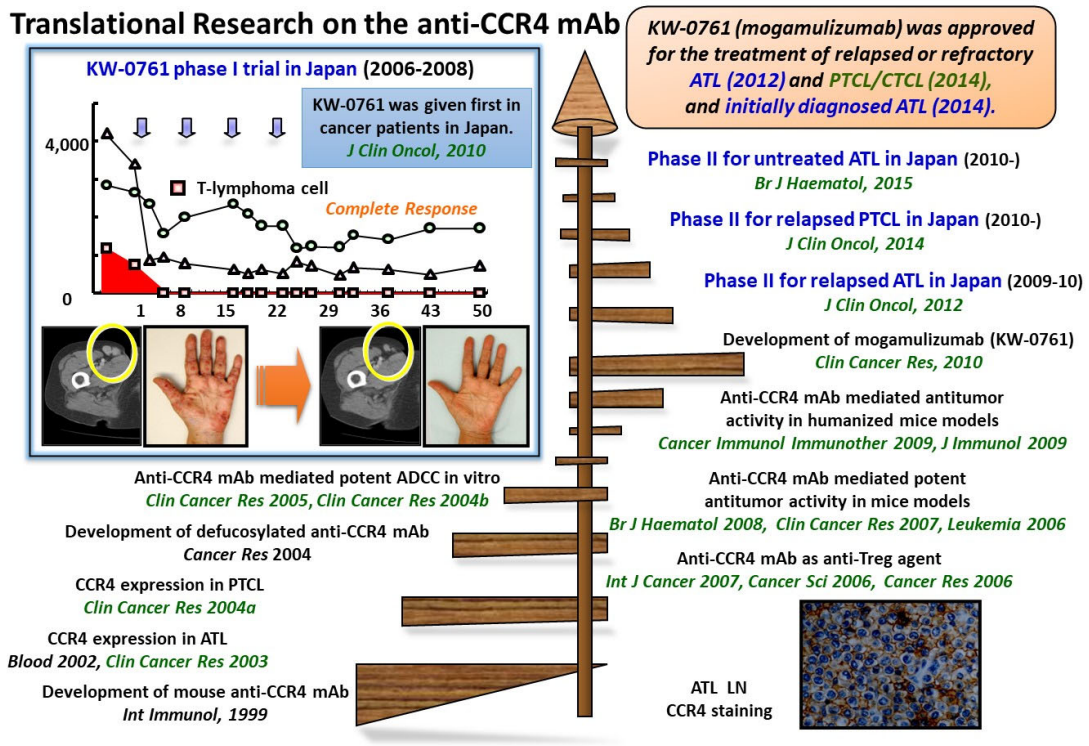

Figure 9. Translational Research on the anti-CCR4 mAb

Setember 18, 2025 Takashi Ishida