Development of novel antitumor active drug for leukemia cells with simplified natural products

(1Graduate School of Informatics and Engineering, University of Electro-Communications, 2Center for Neuroscience and Biomedical Engineering, University of Electro-Communications, 3Stem Cell Project, Tokyo Metropolitan Institute of Medical Science, 4Graduate School of Medical and Dental, Tokyo Medical and Dental University, 5 Graduate School of Science, Department of Biological Science, Tokyo Metropolitan University) ○Tomoya Higashi,1,2 Chihiro Yoshida,1,2 Yoshifumi Hachiro,1,2 Chihiro Nakata,3,4 Takuya Yagi,3,4 Adusa Takechi,3,5 Nobuo Kitada,1,2 Takahiko Hara,3,4,5, Shojiro Maki,1,2

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T-cell derived acute lymphoblastic leukemia (T-ALL) is an aggressive type of leukemia with poor prognosis. We have identified two fungi-derived active compounds, 44D-L008 and 31D-F005, using high throughput screening (HTS). T-ALL-derived CCRF-CEM, but not Burkitt lymphoma-derived Raji, were killed in the presence of low concentrations of these compounds. 44D-L008 and 31D-F005 share a common chemical structure.

In this study, we synthesized several 44D-L008 and 31D-F005-related compounds and evaluated their anti-tumor activities in CCRF-CEM and Raji. we succeeded in synthesizing a compound Ra#61 that shows higher growth inhibitory activity on CCRF-CEM cells than identified natural compounds by HTS [1]. IC₅₀ value of Ra#61 for CCRF-CEM was 68 nM. In addition, we performed similar tumor cell viability tests on another leukemia cell lines. We found that Ra#61 had the similar level of antitumor activity in HL-60, THP-1, and TF-1 as CCRF-CEM. To investigate whether Ra#61 induces apoptosis via an endogenous pathway, phenotypic changes of Ra#61 treated CCRF-CEM cells were examined. We found that mitochondrial membrane potential of CCRF-CEM was rapidly lost by Ra#61 treatment. In in vivo tests using immune-deficient mice transplanted with CCRF-CEM, Ra#61 showed a tumor growth-suppressing effect. In conclusion, Ra#61 is a novel anti-leukemia compound that is potentially effective not only for T-ALL but also for another type of leukemia.