# 学位論文審査結果の要旨

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（学位論文審査結果の要旨）

Quantitative Phenotyping-Based *In Vivo* Chemical Screening in a Zebrafish Model of Leukemia Stem Cell Xenotransplantation

著者らは論文において下記の内容を述べている。

Zebrafish-based chemical screening has recently emerged as a rapid and efficient method to identify important compounds that modulate specific biological processes and to test the therapeutic efficacy in disease models, including cancer. In leukemia, the ablation of leukemia stem cells (LSCs) is necessary to permanently eradicate the leukemia cell population. However, because of the very small number of LSCs in leukemia cell populations, their use in xenotransplantation studies (in vivo) and the difficulties in functionally and pathophysiologically replicating clinical conditions in cell culture experiments (in vitro), the progress of drug discovery for LSC inhibitors has been painfully slow. In this study, we developed a novel phenotype-based in vivo screening method using LSCs xenotransplanted into zebrafish. Aldehyde dehydrogenase-positive (ALDH+) cells were purified from chronic myelogenous leukemia K562 cells tagged with a fluorescent protein (Kusabira-orange) and then implanted in young zebrafish at 48 hours post-fertilization. Twenty-four hours after transplantation, the animals were treated with one of eight different therapeutic agents (imatinib, dasatinib, parthenolide, TDZD-8, arsenic trioxide, niclosamide, salinomycin, and thioridazine). Cancer cell proliferation and cell migration were determined by high-content imaging. Of the eight compounds that were tested, all except imatinib and dasatinib selectively inhibited ALDH+ cell proliferation in zebrafish. In addition, these anti-LSC agents suppressed tumor cell migration in LSC-xenotransplants. Our approach offers a simple, rapid, and reliable in vivo screening system that facilitates the phenotype-driven discovery of drugs effective in suppressing LSCs.

本研究において張は白血病幹細胞移植ゼブラフィッシュを用いて、腫瘍サイズ・転移のphenotype-basedな*in vivo*スクリーニングシステムの開発に成功した。よって本論文は、新たな抗白血病幹細胞作用をもつシーズ化合物の探索研究で学術上極めて有益であり、学位論文として価値あるものと認めた。

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