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Screening for novel L-type amino acid transporter 1 (SLC7A5) inhibitors using a fluorescent amino acid

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ABSTRACT

L-type amino acid transporter 1 (LAT1) facilitates the transport of neutral amino acids with bulky side chains, including many essential amino acids that activate the mechanistic target of rapamycin (mTOR), thereby promoting cell proliferation. Inhibition of LAT1 suppresses abnormal cell growth, such as in cancer and polycystic kidney disease. Fluorescent probes are essential tools for monitoring transport activity and screening for novel inhibitors. We discovered that the fluorescent amino acid (*S*)-2-Amino-3-(9-oxo-9,10-dihydroacridin-2-yl) propanoic acid hydrochloride (H-Ala (2-Acd)-OH • HCl) is specifically transported by LAT1 in Ca9-22 cells and is effective for drug screening. The transport of H-Ala (2-Acd)-OH • HCl was inhibited by the LAT1-specific inhibitor JPH203 and by excess leucine, a natural LAT1 substrate. In contrast, the structurally similar fluorescent amino acid (*S*)-2-Amino-3-(12-oxo-5,12-dihydrobenzo [*b*] acridin-2-yl) propanoic acid hydrochloride (H-Ala (2-Bacd)-OH • HCl) exhibited minimal cellular uptake. Using H-Ala (2-Acd)-OH • HCl and Ca9-22 cells, we screened over 10,000 compounds and identified several potent LAT1 inhibitors.

1. Introduction

L-type amino acid transporter 1 (LAT1) is a heterodimeric transporter that forms a functional complex with 4F2hc via a disulfide bond [1]. In healthy individuals, LAT1 mRNA expression is predominantly found at blood-organ barriers such as the brain, testis, and placenta, as well as in rapidly proliferating cells including bone marrow and embryonic cells [1,2]. LAT1 is upregulated in various cancer types, particularly those with high malignancy [3], and its expression correlates positively with cancer aggressiveness and negatively with patient survival [4,5]. As well as cancer cells, we have recently reported that LAT1 is highly expressed in the case of autosomal dominant polycystic kidney disease (ADPKD) [6]. According to expression pattern and function of LAT1, it seems to be a critical therapeutic target for these cancer and ADPKD diseases.

BCH (2-Aminobicyclo [2.2.1]heptane-2-carboxylic acid) is a known LAT1 inhibitor, although it also affects related transporters such as LAT2, LAT3, and LAT4, which are primarily expressed in normal tissues. JPH203 was developed as a LAT1-specific inhibitor for anticancer therapy and does not inhibit other LAT family transporters [7]. While JPH203 effectively inhibits leucine uptake, higher concentrations are required to suppress cell growth, indicating a need for the development of more potent LAT1 inhibitors.

LAT1 activity is commonly measured by the uptake of radiolabeled amino acids using Xenopus laevis oocyte expression systems or stably transfected cell lines. Although highly sensitive, these methods are not ideal for high-throughput screening. In this study, we aimed to establish a screening system for LAT1 inhibitors using a fluorescent amino acid probe and to identify novel LAT1 inhibitory compounds.

2. Materials and methods

2.1. Drugs

Fluorescent amino acids H-Ala (2-Acd)-OH • HCl and H-Ala (2-Bacd)-OH • HCl were obtained from Watanabe Chemical Industries, Ltd. (Hiroshima, Japan). An LAT1-specific inhibitor JPH203 ((S)- 2-amino-3-(4-((5-amino -2- phenylbenzo [d] oxazol-7-yl) methoxy) -3,5- dichlorophenyl) propanoic acid), was purchased from TargetMol (Wellesley Hills, MA). Chemical libraries were provided from Drug Discovery Initiative, The University of Tokyo.

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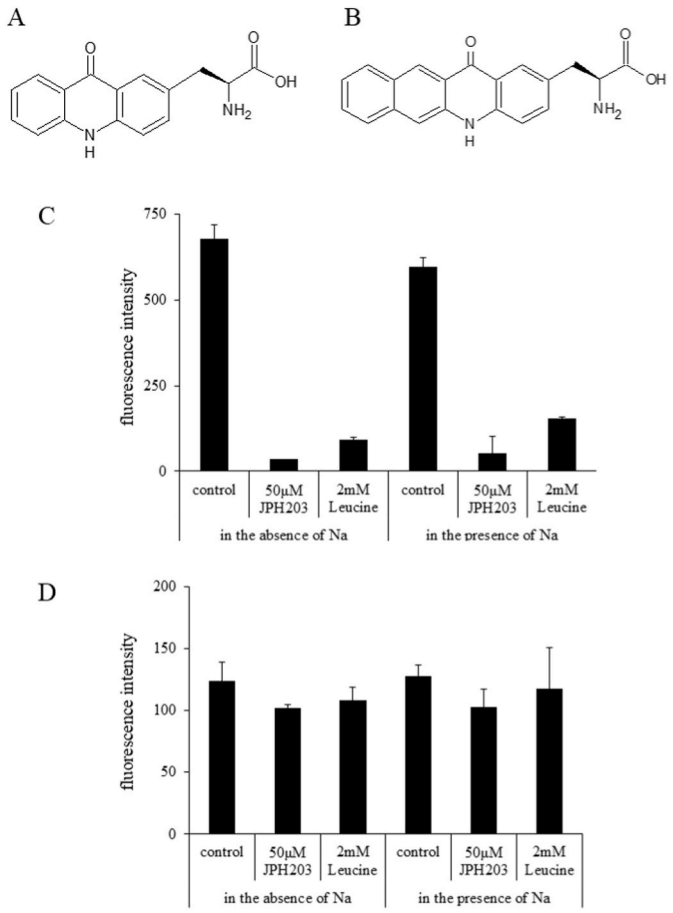

Fig. 1. Structure of fluorescent amino acids and their uptake. Chemical structures of H-Ala (2-Acd)-OH (A) and H-Ala (2-Bacd)-OH (B) are shown. Uptake of these fluorescent amino acids into Ca9-22 cells was measured using H-Ala (2-Acd)-OH (C) or H-Ala (2-Bacd)-OH (D). Cells were pre-incubated with 50 μM JPH203 or 2 mM leucine for 10 min followed by incubation with 100 μM H-Ala (2-Acd)-OH (C) or 50 μM H-Ala (2-Bacd)-OH (D) for 30 min. Intracellular fluorescence intensities were measured. Data are presented as mean ± SD (n = 4).

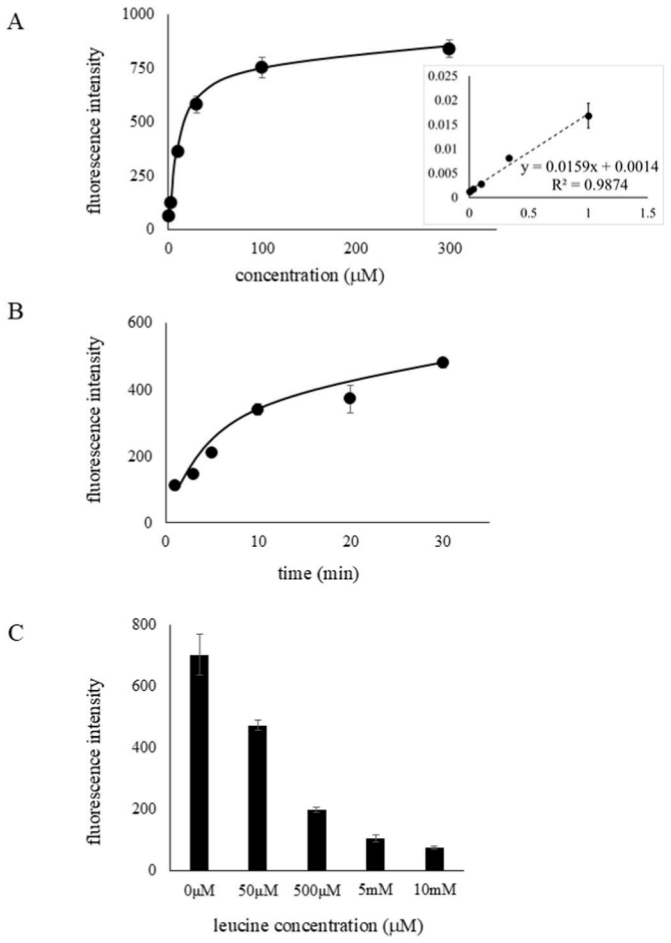

Fig. 2. Characteristics of fluorescent amino acid H-Ala (2-Acd)-OH uptake. The concentration dependence (A), time dependence (B), and leucine concentration dependence (C) of H-Ala (2-Acd)-OH uptake were measured. Data are presented as mean ± SD (n = 8).

2.2. Plasmid construction

The constructs of transporters were cloned by PCR from human kidney or human placenta cDNA libraries with In-Fusion® HD Cloning Kit (Takara Bio) according to the manufacturer's instructions. PCR primers were designed to share 15 bases of homology at PCR fragment and vector ends with the sequences encoding flag or HA epitope tags. These tags were fused to the N termini of transporters. The PCR fragments were subcloned into the EcoRV cleaved mammalian expression vector pcDNA 3.1 (−). All PCR primer sequences are available on request.

2.3. Cell culture and transfection

Ca9-22 cells were purchased from Japanese Collection of Research Bioresources (Osaka, Japan). This cell line was cultured in Eagle's Minimum essential medium (MEM) with 10 % fetal bovine serum (Life Technologies, Carlsbad, CA, USA), 100 units/mL penicillin, and 100 μg/mL streptomycin in a humidified incubator with 5 % CO_2 at 37 °C. Cells were transfected with 1 μg of cDNA3.1-transporters or pcDNA3.1 (Mock) for 48 h using Lipofectamine 3000 (Thermo Fisher Scientific, MA, USA) according to the manufacturer's instruction.

2.4. Fluorescent amino acid uptake

Cells were seeded on 96-well plates. The cells were washed three times with standard uptake solution (125 mM NaCl, 4.8 mM KCl, 1.3 mM $CaCl_2$, 1.2 mM $MgSO_4$, 25 mM HEPES, 1.2 mM KH_2PO_4 and 5.6 mM glucose, pH 7.4). For Na^+ f-free conditions, 125 mM choline chloride replaced NaCl. Cells were incubated with 100 μM fluorescent amino acid in uptake solution for 30 min. After washing three times with ice-cold uptake solution, the cells were solubilized with 0.1 M NaOH and fluorescence intensity was measured by a fluorescence microplate reader.

3. Results

3.1. LAT1-dependent uptake of fluorescent amino acids

Human head and neck squamous cell cancer lines, Ca9-22 was used because it is known that LAT1 is highly expressed and almost all of leucine uptake is taken through LAT1 [8]. We tried to use two kinds of fluorescent amino acids to monitor LAT1 transport activity. One was H-Ala (2-Acd)-OH (Fig. 1A) and the other was H-Ala (2-Bacd)-OH (Fig. 1B). Both compounds have amino acid structure which is amino group and carboxy group, and they have different side chain; tricyclic and tetracyclic. When H-Ala (2-Acd)-OH was used for uptake, a fluorescent amino acid was incorporated into cells and that was inhibited by LAT1 specific inhibitor; JPH203 or excess substrate; 2 mM leucine (Fig. 1C). This uptake exhibited sodium independence, consistent with

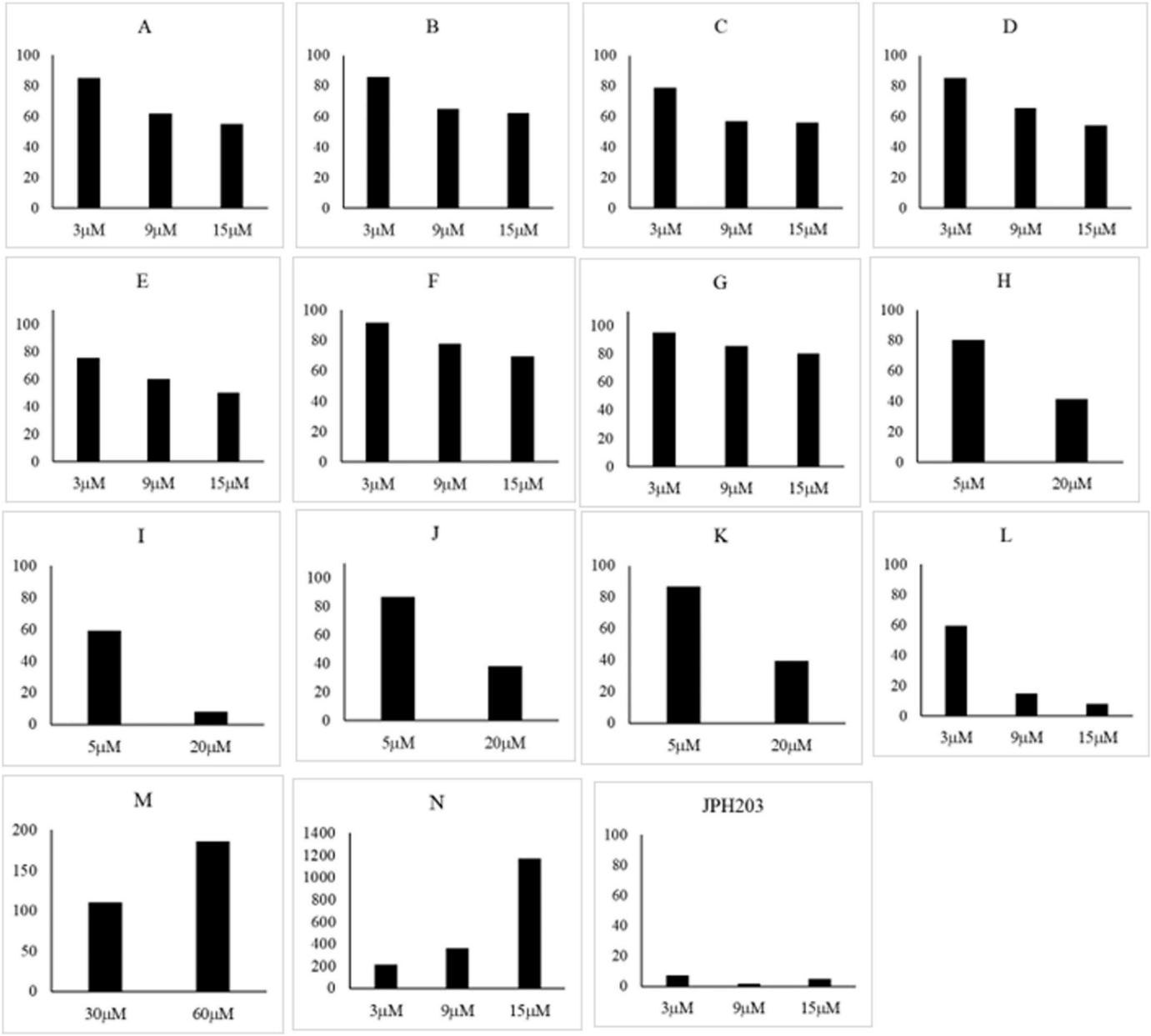

Fig. 3. Partial screening results for LAT1 inhibitors. After the initial screening, compounds that affected fluorescent amino acid uptake were re-evaluated at two to three different concentrations. The chemical structures labeled A to N are shown in Supplemental Fig. 4.

the known activity of LAT1. On the other hand, When H-Ala (2-Bacd)-OH was used, no significant uptake was detected neither in the absence nor presence of sodium (Fig. 1D). The small amount of fluorescence uptake was observed, however it did not inhibit by both JPH203 and excess leucine. For the further study, H-Ala (2-Acd)-OH was used for screening.

3.2. Kinetics of fluorescent amino acid, H-Ala (2-Acd)-OH uptake

Dependency of concentration and time in fluorescence uptake was observed (Fig. 2A and B). Fluorescence amino acid uptake increased in a concentration-dependent and time-dependent manner. According to Lineweaver–Burk plot, Km and Vmax values for the fluorescence amino acid uptake were 11.4 μM and 714.3 (fluorescence intensity).

Inhibition of fluorescence amino acid uptake with leucine, which is one of the LAT1 substrate, was measured with concentration dependency (Fig. 2C). The uptake of fluorescence was inhibited in a manner dependent on leucine concentration.

3.3. Fluorescent amino acid uptake by other amino acid transporters

It was sure that LAT1 specifically transported H-Ala (2-Acd)-OH. Then, we tested whether other amino acid transporters, which transport neutral amino acid such as leucine, can transport H-Ala (2-Acd)-OH (Fig. S1). Each transporter was transfected into the cells and fluorescence amino acid uptake was measured in the presence of JPH203 to exclude influence of endogenous LAT1. LAT2/4F2hc, y^+LAT1/4F2hc, y^+LAT1/4F2hc, LAT3, LAT4, BAT1/rBAT, ASC1/4F2hc, xCT/4F2hc and ATB^{0+} were tested. None of them incorporated the fluorescent amino acid, so uptake of H-Ala (2-Acd)-OH would be specific substrate of LAT1.

3.4. Screening of the LAT1 inhibitors

As H-Ala (2-Acd)-OH was specifically transported by LAT1, it was

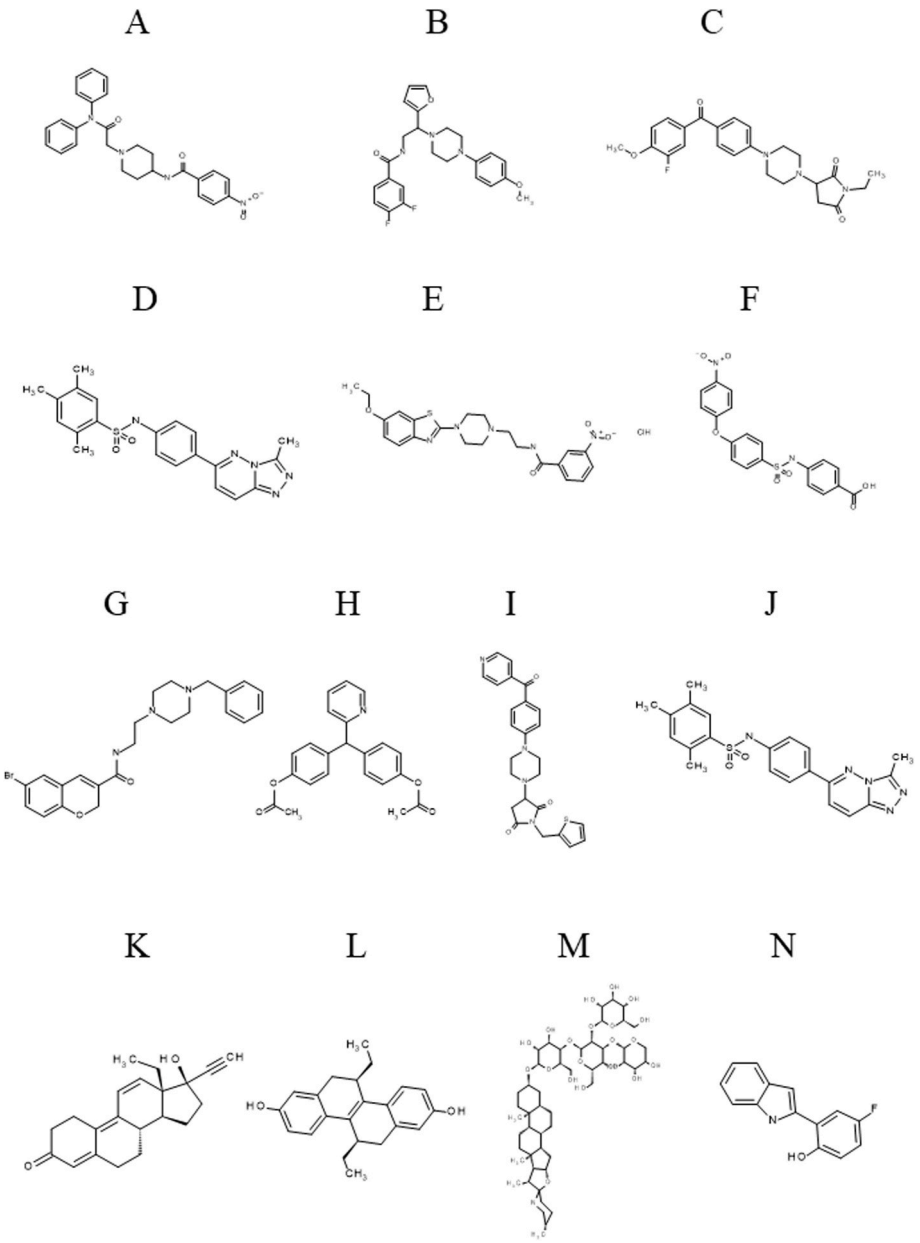

Fig. 4. The chemical structures that affected fluorescent amino acid uptake. The chemical structures labeled A to N in Fig. 3 are presented.

used for screening of the LAT1 inhibitors. A screening of more than 10,000 chemical compounds of validated library and core library from Drug Discovery Initiative, Graduate School of Pharmaceutical Sciences, The University of Tokyo was conducted. The results of the several compounds, which affected to LAT1 transport activity, were shown in Fig. 3 and their structure were listed in Fig. 4. Slight inhibited effects were seen in Fig. 3A–L. As showing in Fig. 3M, there was the chemical, which upregulated LAT1 activity. As shown in Fig. 3N, some compounds exhibiting fluorescence at the same wavelength as the fluorescent amino acid and capable of cellular uptake showed a marked increase in fluorescence, which was not suppressed by JPH203.

4. Discussion

Highly malignant cancers in general grow rapidly requiring energy (glucose) and biomolecular synthesis (amino acids and sugars for protein and nucleic acids) [9]. It has been reported that LAT1 is expressed in brain, spleen, colon, testis and placenta tested by high stringency Northern analysis from rat normal tissues [1]. Notably, it is also expressed in various cancer cells, especially highly malignant ones [10]. This cancer cell specific expression pattern can be used for diagnostic PET scan, where probes are substrates for LAT1 [11–14].

The amino acid transporter LAT1 is selectively upregulated in tumors and plays a critical role in the activation of mTOR, making it a highly promising target for the development of novel anticancer agents. Thus, LAT1 seems to be a good target for cancer therapy and many researchers including us have actually demonstrated that inhibition of LAT1 leads suppression of many kinds of cancers [7,8,15–19]. We have also recently demonstrated that the role of LAT1 in tumor-related endothelial cells by tumor cells injecting into endothelial cell–specific LAT1 conditional knockout mice ($Slc7a5^{fl/fl}$ Cdh5-Cre-ERT2) [20]. We have found that the shape of the tumor vasculature was normalized, and the size and numbers of lung metastasis was reduced. In addition, we have shown that LAT1 was highly expressed at the kidney with ADPKD and administration of excess BCAA to ADPKD model mouse have led exacerbation of cyst [6]. Therefore, it is considered that LAT1 is a very valuable target

for both cancer and ADPKD therapies. As its mechanism of action differs from that of currently available anticancer and ADPKD drugs, LAT1 inhibitors also hold potential as combination therapy agents.

From early on the compound libraries enriched with amino acid backbone structures—potential LAT1 substrates—have been screened, and candidates with greater inhibitory potency have been selected based on structure–activity relationship (SAR) analysis. BCH (2-Amino-2-norbornanecarboxylic acid), which has amino acid structure, is an inhibitor of LAT1, but it has a major limitation in that it non-selectively inhibits all LAT family transporters. LAT2, a transporter homologous to LAT1, is expressed in normal cells and shares similar transport substrates. However, unlike LAT1, which was efficiently and competitively inhibited by the thyroid hormone T3, LAT2 exhibits minimal inhibitory activity by T3 [21,22]. Based on the structure of T3, Oda et al. first have developed LAT1 inhibitor, JPH203 (KYT-0353) [7]. They have shown that JPH203 has significant growth inhibitory effect on tumor cell growth both *in vitro* and *in vivo*. Kongpracha et al. also have developed LAT1 inhibitors, SKN compounds, based on the structure of T3 [23]. It has been shown that both SKN-103 and -104 have higher inhibitory effects than T3 and are non-transportable blockers of LAT1 rather than its substrate. SKN-103 exhibited inhibition of p70S6K, a downstream effector of mTOR signaling, and effectively suppressed the proliferation of cancer cells in both PANC-1 and H520 cell lines. Several inhibitors that are not based on the structure of T3 have also been identified. Dithiazoles and dithiazines compounds are expected to interact with the proteins through formation of disulfide bonds. It has been reported that 59 compounds based on dithiazoles and dithiazines scaffold are screened with the proteoliposomes system and several dithiazoles and dithiazines strongly inhibit LAT1 transport activity [24]. It has been also demonstrated that transport activity is recovered from inhibition after addition of disulfide reducing agent DTE. Furthermore, studies have also been conducted to search for inhibitors based on the structure of LAT1. Several LAT1 inhibitors have been discovered to date, and approaches such as antibody-based inhibition and nanoparticle-mediated delivery have also been explored [25]. Currently, only about two of these inhibitors have entered phase I or phase II clinical trials. Therefore, there remains considerable potential for the development of novel LAT1 inhibitors.

Conventional assays for evaluating LAT1 transport activity have relied on the use of radioisotope-labeled amino acids, which require complex handling procedures and are not suitable for large-scale screening of inhibitors. Here, we established a facile screening assay for LAT1 inhibitors employing fluorescent amino acids and cancer cell lines with elevated LAT1 expressions. Cancer cell lines, Ca9-22 exhibiting high LAT1 expression showed increased uptake of fluorescent amino acids, which was inhibited by the known LAT1 inhibitor JPH203 as well as by excess concentrations of the transport substrate leucine, thereby confirming that the fluorescent amino acid is specifically transported via LAT1. Using this system and a compound library, we conducted a screening and identified several compounds with inhibitory activity as well as others that conversely activated LAT1. Unfortunately, no compounds with inhibitory effects comparable to JPH203 were found. However, it is encouraging that compounds lacking an amino acid backbone have been identified, suggesting that further exploration based on these structures could lead to the discovery of more potent inhibitors.

CRediT authorship contribution statement

Toru Kimura: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Toru Tanaka:** Writing – review & editing, Supervision. **Hiroyuki Sakurai:** Writing – review & editing, Supervision, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Glossary

LAT, L-type amino acid transporter; BCAA, branched chain amino acids; ADPKD, autosomal dominant polycystic kidney disease; mTOR, mechanistic target of rapamycin; PET, positron emission tomography; T3, triiodothyronine.

Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbrc.2025.152768.

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