



# JFCR39, a panel of 39 human cancer cell lines, and its application in the discovery and development of anticancer drugs

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## ABSTRACT

Over the past few decades, panels of human cancer cell lines have made a significant contribution to the discovery and development of anticancer drugs. The National Cancer Institute 60 (NCI60), which consists of 60 cell lines from various human cancer types, remains the most powerful human cancer cell line panel for high throughput screening of anticancer drugs. The development of JFCR39, comprising a panel of 39 human cancer cell lines coupled with a drug-activity database, was based on NCI60. Like NCI60, JFCR39 not only provides disease-oriented information but can also predict the action mechanism or molecular target of a given antitumor agent by utilizing the COMPARE algorithm. The molecular targets of ZSTK474 as well as several other antitumor agents have been identified by using JFCR39 and some of these compounds have since entered clinical trials. In this review, we will describe human cancer cell line panels particularly JFCR39 and its application in the discovery and/or development of anticancer drug candidates.

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## 1. Introduction

Discovery and development of new anticancer drugs require a reliable predictive preclinical model to test drug efficacy. Such models mainly include human cancer cell lines propagated in culture or as xenografts in mice, and genetically engineered mouse models of human carcinogenesis.<sup>1</sup> The need for high throughput and low cost means that only the cultured human cancer cell line model is applicable in both drug discovery and drug development. The other models are generally used only in the drug development process.<sup>1</sup> Indeed, cultured human cancer cell lines have been widely used for decades as a disease-oriented screening model for new anticancer drugs. In the past ten years, development of molecular-targeted anticancer drugs has been a great success (e.g., development of imatinib). These drugs are generally designed to target oncogene-encoding-proteins specifically or far more expressed in cancer cells. Genomic heterogeneity has been frequently reported to exist across the patient population with the same pathological cancer type, and some oncogenes have been known to play a key role in tumorigenesis. In order to match the 'right' drugs to the 'right' patient, a predictive biomarker is required for molecu-

lar-targeted drugs. Cell line panels of a certain cancer type have been used to discover these predictive biomarkers.<sup>2</sup> As an example, PIK3CA mutation and EGFR amplification have been demonstrated to be predictive biomarkers of a PI3K inhibitor GDC-0941 by use of a large panel of breast cancer cell lines with or without PIK3CA mutation and EGFR amplification.<sup>2</sup> Recently, a huge panel named CMT1000 (Center for Molecular Therapeutics1000), which currently consists of 1200 human cancer cell lines, was established for the development of molecular-targeted drugs against various cancers. This panel of cell lines is expected to evaluate the sensitivity of inhibitors targeting EGFR, ERB2, MET, PDGFR, ALK and BRAF kinases.<sup>1</sup>

NCI60 (National Cancer Institute 60),<sup>3</sup> which was developed in the late 1980s and consists of 60 cell lines from various human cancer types, remains the most powerful human cancer cell panel for high throughput screening of anticancer drugs. In addition to the disease-oriented screening of anticancer drugs, which was the original aim for establishment of NCI60, another function of this cancer cell line panel system is the prediction of action mechanism of antitumor agents. This latter function contributed to the development of bortezomib, an inhibitor of proteasome that was approved in 2003 by the US Food and Drug Administration (FDA). Compared with NCI60, JFCR39 (Japanese Foundation for Cancer Research 39) is a more compact system with a reduced number of cell lines. Nonetheless, JFCR39 retains the functional capability of NCI60.

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## 2. JFCR39, an informatic anticancer drug discovery and development system

The development of JFCR39 in the early 1990s was based on the NCI60 system with some modification.<sup>4,5</sup> Like NCI60, this system consists of a human cancer cell line panel coupled with a drug-activity database. The JFCR39 panel utilizes 30 cell lines in NCI60 together with 6 cell lines of stomach cancer of which the incidence is high in Japan, and 3 breast cancer cell lines (HBC-4, HBC-5, and BSY-1) established in JFCR (Japanese Foundation for Cancer Research) (see Table 1).<sup>4,5</sup> Genomics on each cell line of JFCR39 has been recently reported.<sup>6</sup>

Like NCI60, one important function of JFCR39 is to evaluate the in vitro drug efficacy and provide disease-oriented information based on the differential growth inhibition activity of a certain antitumor agent against the 39 cancer cell lines. Inhibition of cell growth is assessed by the sulforhodamine B (SRB) assay, which determines the change in total cellular protein of the cells following 48 h of treatment with the antitumor agent.<sup>7–9</sup> The molar concentration of the agent needed for 50% growth inhibition (GI<sub>50</sub>) of each cell line in JFCR39 is then obtained.<sup>9,10</sup> A graphical representation (or ‘fingerprint’) for the differential growth inhibition against the cells in the JFCR39 panel is finally plotted based on a calculation that uses a set of GI<sub>50</sub> values.<sup>11</sup>

Another function of the JFCR39 is to predict the action mechanism or molecular target of an antitumor agent. The action mechanism of a drug candidate can be predicted by comparing its fingerprint with those of reference compounds (including anticancer drugs and chemical tools with known mechanisms) in our drug-activity database using the COMPARE algorithm, because the fingerprint represents the whole inhibition profile of the growth-related targets in the cells.<sup>5,9</sup> The COMPARE analysis is carried out by calculating the Pearson correlation coefficient (*r* value) between the GI<sub>50</sub> mean graphs of two compounds X and Y using the following formula:  $r = (\sum(x_i - x_m)(y_i - y_m)) / (\sum(x_i - x_m)^2 \sum(y_i - y_m)^2)^{1/2}$ , where  $x_i$  and  $y_i$  are Log GI<sub>50</sub> of the two compounds, respectively, for each cell line, and  $x_m$  and  $y_m$  are the mean values of  $x_i$  and  $y_i$ , respectively ( $n = 39$ ).<sup>9,11</sup> The *r* value is then used to determine the degree of similarity, that is, the higher the *r* value is, the greater the similarity of X with Y. Generally, an *r* value of more than 0.6 between two agents suggests they might have a similar action mechanism, whereas a value of >0.8 suggests they have the same mechanism of action. Interestingly, we recently found that the difference of *r* value between 0.6 and 0.8 might reflect

the different target specificity between two phosphatidylinositol 3-kinase (PI3K) inhibitors.<sup>12</sup>

## 3. Application of JFCR39 in the discovery and development of anticancer drugs

### 3.1. FJ5002

We have been searching for new anticancer drug candidates in our database by using JFCR39 COMPARE analysis-guided assay. As an example, FJ5002 (CAS number 147366-40-3, Fig. 1) was discovered as a potent telomerase inhibitor in 1999.<sup>13</sup> To search for a potent telomerase inhibitor in our drug-activity database, we used berberine, a compound which weakly inhibits telomerase with an IC<sub>50</sub> of 37 μM, as a seed compound. The COMPARE analysis with JFCR39 generates a list of top 20 compounds with *r* values of more than 0.6. Then we determined their telomerase inhibitory activity and found MKT077 was a more potent telomerase inhibitor (IC<sub>50</sub>: 5 μM) than berberine. We then performed another round of COMPARE analysis by using MKT077 as a seed compound. Subsequently, another list of top 20 compounds exhibiting higher *r* values than 0.6 was produced. An assay of their telomerase inhibitory activity led to the discovery of FJ5022 as a more potent telomerase inhibitor than MKT077. FJ5002 inhibits telomerase with an IC<sub>50</sub> of 2 μM, causes population-doubling dependent changes characterized by progressive telomere erosion, increased chromosome abnormalities and senescence/crisis-like features in long-term cultivated U937 cells.<sup>13</sup>

### 3.2. Pladienolide B

The JFCR39 system can be used to determine the action mechanism or molecular target of an antitumor agent. Of course, prediction of a molecular target depends on whether there is a reference compound with the same molecular target in the database. If not, we can predict that the compound has a novel molecular target, which is different from that of current drugs or chemical tools. Pladienolide B is one such example.<sup>14</sup>

Pladienolide B (see Fig. 1) is a 12-membered macrolide isolated from *Streptomyces platensis* Mer-11107 by scientists of Eisai. This compound exhibits potent growth inhibitory activity against various cell lines including those resistant to chemotherapeutic drugs like camptothecin, and induces cell cycle arrest at both G1 and G2/M. Favorable in vivo antitumor activity of pladienolide B iv was also shown on xenograft models such as WiDr and BSY-1. To investigate the molecular target of pladienolide B, COMPARE analysis was carried out by use of our JFCR39 system. However, there were no compounds in our reference list with an *r* value greater than 0.6, suggesting pladienolide B has a novel molecular target or mechanism.<sup>14</sup> Based on this interesting finding, continuous efforts were made to investigate the molecular target of pladienolide B. Finally, by use of <sup>3</sup>H-labeled, fluorescence-tagged and photoaffinity/biotin (PB)-tagged chemical probes, splicing factor SF3b was demonstrated to be the target protein of this agent.<sup>15</sup> Currently, a derivative of pladienolide B, E7107, is under evaluation in clinical trials for cancer treatment.

### 3.3. MS-247

The first example of the use of JFCR39 to determine a molecular target was for the synthetic compound MS-247 (see Fig. 1).<sup>9</sup> COMPARE analysis predicted that this compound might target topoisomerase because an *r* value of 0.683 was shown for correlation with CPT-11, a well known topoisomerase inhibitor. Such a prediction was then demonstrated by the result that MS-247 inhibited the topoisomerase-induced conversion of supercoiled DNA to nicked

**Table 1**  
Cell lines in JFCR39 panel

Cancer	Number of cell lines	Cell line
Lung	7	NCI-H23, NCI-H226, NCI-H522, NCI-H460
Stomach	6	A549, DMS273, DMS114
Ovarian	5	<u>St-4</u> , <u>MKN-1</u> , <u>MKN-7</u> , <u>MKN-28</u> , <u>MKN-45</u> , <u>MKN-74</u>
Renal Melanoma	2	OVCAR-3, OVCAR-4, OVCAR-5, OVCAR-8, SK-OV-3
Colon	5	RXF-631L, ACHN
Breast	5	LOX-IMVI
Brain	6	HCC-2998, KM-12, HT-29
Prostate	2	HCT-15, HCT-116
		<i>HBC-4</i> , <i>BSY-1</i> , <i>HBC-5</i>
		MCF-7, MDA-MB-231
		U251, SF-268, SF-295, SF-539, SNB-75, SNB-78
		DU-145, PC-3

The cell lines underlined are stomach cancer cell lines with high incidence in Japantyped and those in italics are established in JFCR.

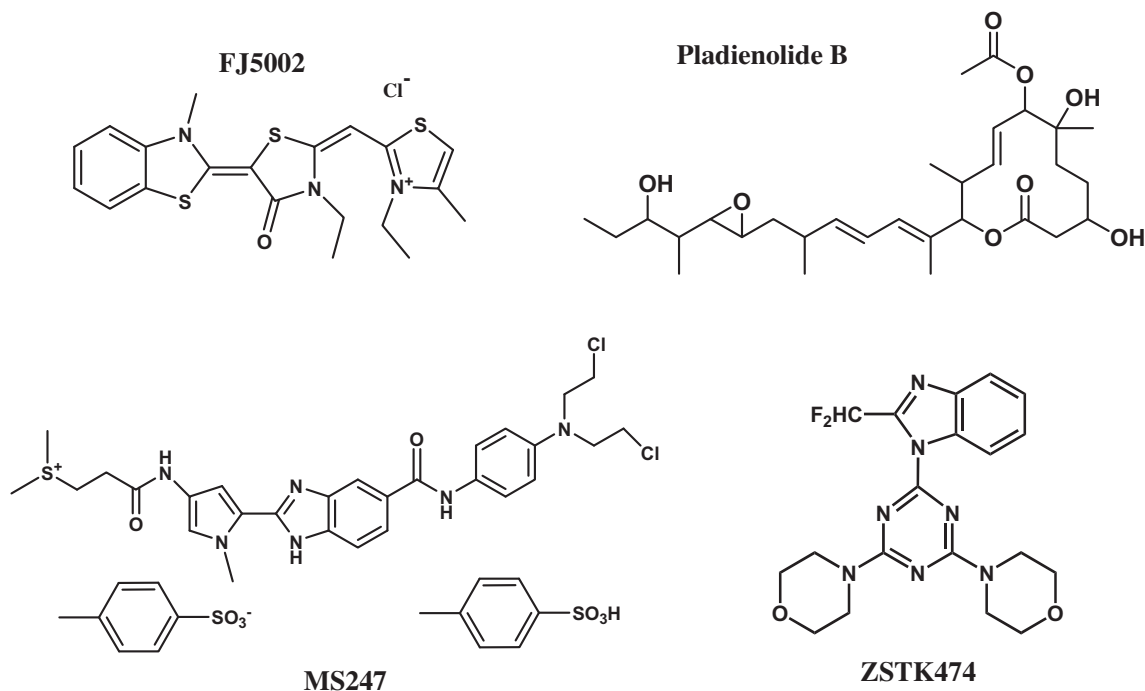


Figure 1. Chemical structures of the representative compounds identified by JFCR39.

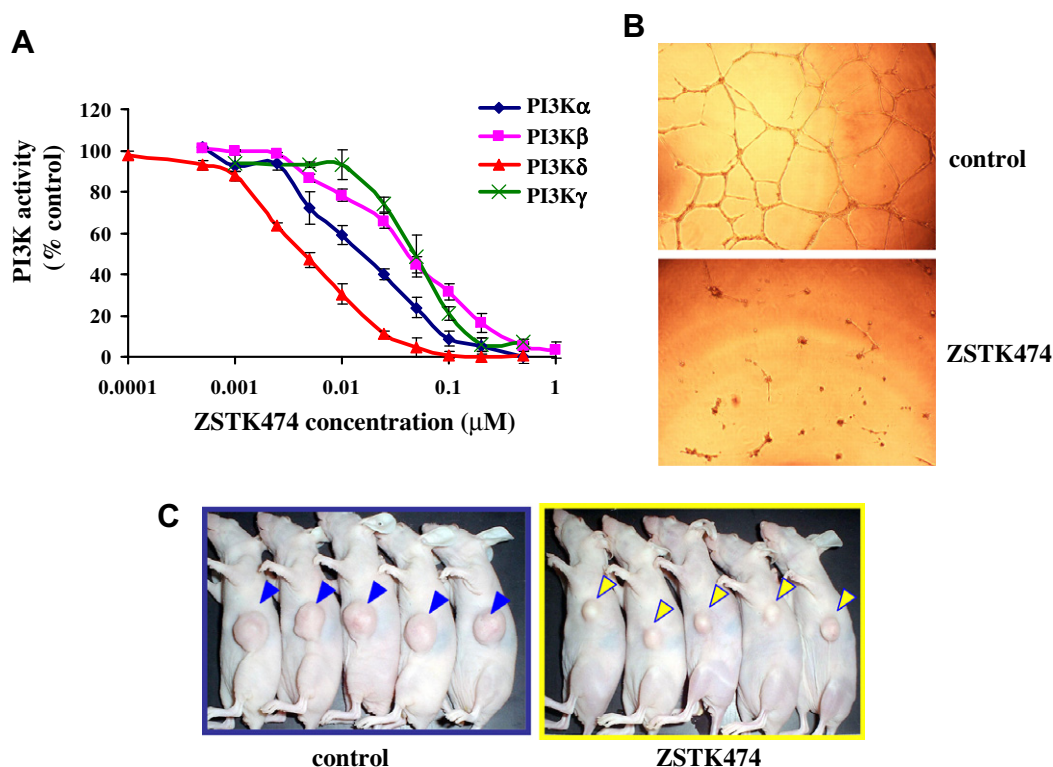
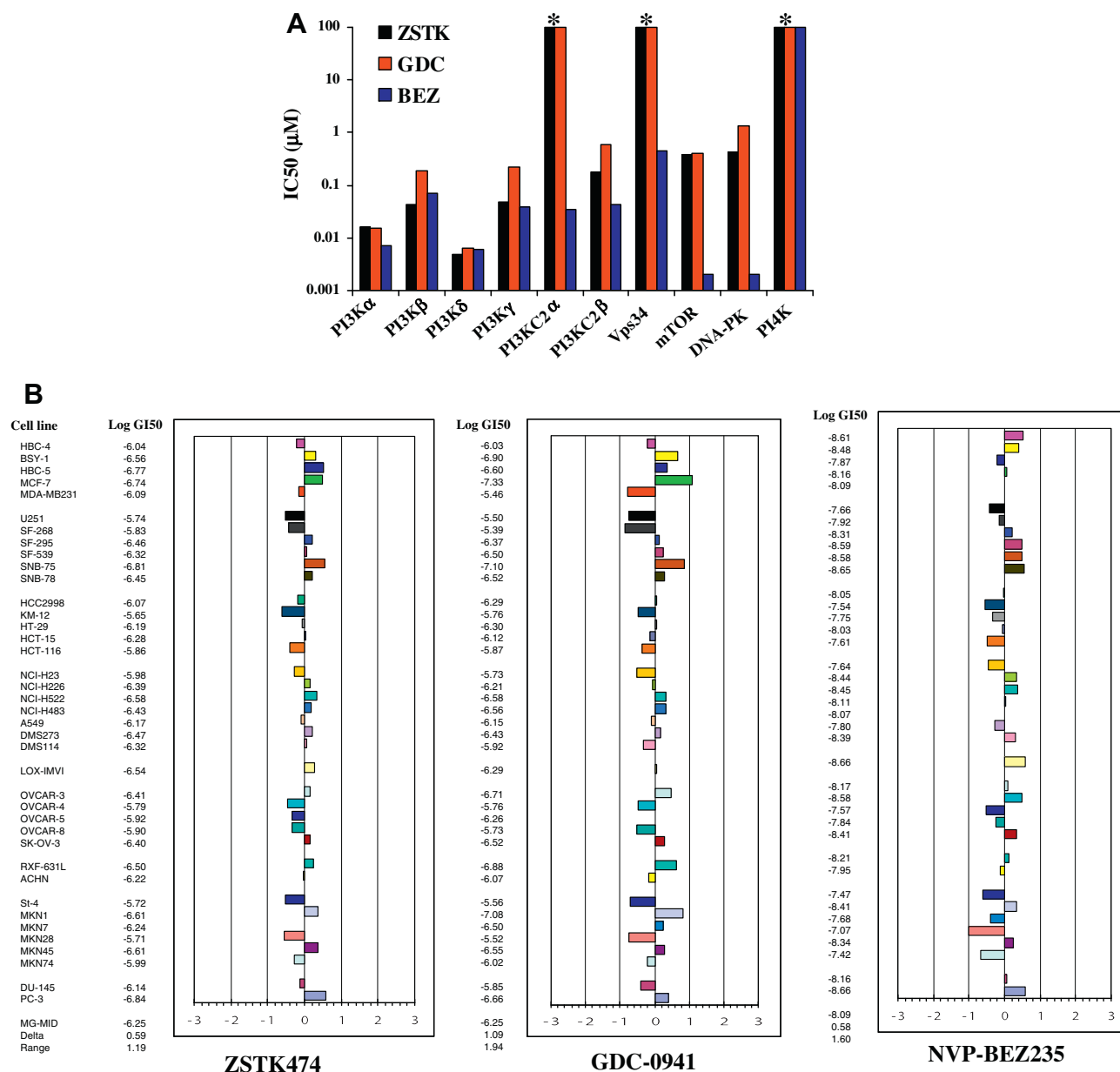


Figure 2. PI3K inhibition and antitumor activities of ZSTK474. (A) Inhibitory activity of ZSTK474 against class I PI3K isoforms. (B) In vitro antiangiogenic activity of ZSTK474. ZSTK474 (1  $\mu\text{M}$ ) inhibits tube formation by HUVEC (human umbilical vein endothelial cell). Quantitative data can be seen in previous report.<sup>23</sup> (C) In vivo antitumor efficacy of ZSTK474. Oral administration of ZSTK474 at 400 mg/kg to WiDr xenograft daily from day 0 to 26, except for days 6, 13 and 20, leads to obvious tumor growth inhibition. The pictures were taken on day 28.

DNA.<sup>9</sup> In addition, MS-247 exhibited an average  $\text{IC}_{50}$  of 0.71  $\mu\text{M}$  for 39 cancer cell lines as well as inducing cell cycle arrest at G2/M phase and apoptosis at a concentration of 0.1  $\mu\text{M}$ .<sup>9</sup> Based on these

results, MS-247 was examined for the antitumor activity and found to exhibit potent in vivo antitumor efficacy on 17 xenografts derived from JFCR39.<sup>9</sup>



**Figure 3.** Similarity between JFCR39 fingerprints of PI3K inhibitors can be used to predict related target specificities. (A) Inhibition profiles of PI3K inhibitors ZSTK474, GDC-0941 and NVP-BEZ235 against PI3K superfamily members. The IC<sub>50</sub> values of the respective PI3K inhibitor for each kinase were used to plot the inhibition profile, \*: >100. ZSTK474 has a similar class I PI3K inhibitory specificity with GDC-0941, but different from NVP-BEZ235. (B) JFCR39 fingerprints of PI3K inhibitors ZSTK474, GDC-0941 and NVP-BEZ235. The ZSTK474 fingerprint exhibits a greater similarity to the fingerprint of GDC-0941, than that of NVP-BEZ235. Fingerprint indicates the differential growth inhibition pattern of ZSTK474 for the cell lines in the JFCR39 panel. The X-axis shows the difference in logarithmic scale between the mean of LogGI50 values for all 39 cell lines (MG-MID, expressed as 0 in the fingerprint) and the LogGI50 for each cell line in the JFCR39 panel. **Columns to the right of 0** indicate the sensitivity of the cell lines to a given compound and **columns to the left** indicate their resistance. MG-MID = mean of LogGI50 values for all 39 cell lines; Delta = difference between the MG-MID and the LogGI50 value for the most sensitive cell line; Range = difference between the LogGI50 values for the most resistant cell line and the most sensitive cell line.

### 3.4. ZSTK474

To date, the most successful application of JFCR39 has been the identification of ZSTK474 (CAS number 475110-96-4, Fig. 1) as a PI3K inhibitor. ZSTK474 is an s-triazine derivative that was originally synthesized by Zenyaku Kogyo as an anticancer drug candidate.<sup>16</sup> This compound showed the most promising antitumor efficacy among over 1500 synthesized analogues. However, the molecular target was unknown. In 2003, growth inhibitory activity of ZSTK474 was examined against the JFCR39 panel and its corresponding fingerprint was developed. COMPARE analysis was then carried out by comparing the fingerprint of ZSTK474 with those of

reference compounds in the JFCR39 drug-activity database. Interestingly, a high *r* value of 0.766 was found between the fingerprint of ZSTK474 and that of LY294002, a well known class I PI3K inhibitor.<sup>17</sup> We then predicted that ZSTK474 might also target class I PI3K. Class I PI3K is a family of four lipid kinase isoforms that phosphorylate phosphatidylinositol 4,5-bisphosphate (PIP<sub>2</sub>) to generate phosphatidylinositol 3,4,5-trisphosphate (PIP<sub>3</sub>), which plays an important role in various processes including cell growth.<sup>18–20</sup> To demonstrate that ZSTK474 really targets PI3K, we investigated the activity of the recombinant class I PI3K isoforms in the absence or presence of ZSTK474 by use of a homogeneous time-resolved fluorescence (HTRF) assay. Our results showed that ZSTK474



inhibits four PI3K isoforms potently, with IC<sub>50</sub> values of 16, 44, 5, 49 nM for PI3K $\alpha$ ,  $\beta$ ,  $\delta$ , and  $\gamma$ , respectively.<sup>21</sup> (see Fig. 2A) Docking analysis by using the crystal structure of PI3K $\gamma$ -LY294002 as a model suggested that ZSTK474 binds with PI3K in the ATP-binding pocket. Lineweaver–Burk plots also indicated that ZSTK474 inhibits PI3K by competing with ATP for a common binding site.<sup>21</sup> In vitro, ZSTK474 inhibited the growth of 39 human cancer cell lines with a mean GI50 value of 0.32  $\mu$ M,<sup>17</sup> and blocked cell cycle progression at G0/G1 phase in various human cancer cells without obvious induction of apoptosis.<sup>17,22</sup> Moreover, ZSTK474 displayed a potent antiangiogenic effect via two mechanisms: (i) inhibition of HIF-1 $\alpha$  expression and VEGF production in cancer cells, and (ii) blockage in the proliferation, migration, and tube formation of HUVECs (human umbilical vein endothelial cells). (see Fig. 2B).<sup>23</sup> Oral administration of ZSTK474 indicated obvious in vivo antitumor efficacy against various cancer xenografts (see Fig. 2C) at both early and advanced stages, without any obvious toxicity.<sup>6,22,23</sup> Given the favorable preclinical antitumor effect and safety, an investigational new drug application for ZSTK474 has been approved by the US FDA and the compound is in phase I clinical trials.<sup>4</sup>

We also investigated the application of JFCR39 for prediction of target specificity by using several PI3K inhibitors. In addition to four class I PI3K isoforms, we determined the activities of PI3K inhibitors ZSTK474, GDC-0941 and NVP-BE2235 against the kinases with a related structure or function (PI3K superfamily<sup>12</sup>): PI3KC2 $\alpha$  and PI3KC2 $\beta$  (class II PI3K), vacuolar protein sorting 34 (Vps34, Class III PI3K), mTOR and DNA-dependent protein kinase (DNA-PK) (Class IV PI3K), and phosphatidylinositol 4-kinase (PI4K). The IC<sub>50</sub> values were calculated and used to plot the inhibition profiles of each inhibitor. As shown in Figure 3A, ZSTK474 and GDC-0941 were found to be class I PI3K-specific PI3K inhibitors, by displaying selectivity over mTOR, DNA-PK, and other PI3K superfamily members. In contrast, NVP-BE2235 showed more potent activity against mTOR and DNA-PK than against class I PI3Ks,<sup>12,24</sup> suggesting the low selectivity for class I PI3K inhibition. We then compared the JFCR39 fingerprints of the three PI3K inhibitors (see Fig. 3B). Interestingly, ZSTK474 showed a more similar fingerprint with GDC-0941 ( $r = 0.863$ ), compared to that with BE2235 ( $r = 0.67$ ),<sup>12</sup> consistent with our biochemical assay results regarding inhibition of kinases belonging to the PI3K superfamily. Taken together, these results suggest that JFCR39 can be used to predict specificity for the molecular target of a certain antitumor agent. Furthermore, baicalein, a natural-product PI3K inhibitor we discovered from our SCADS library, also exhibits a different fingerprint to that of ZSTK474.<sup>25</sup> Baicalein is a flavonoid that inhibits various enzymes including 12-lipoxygenase.<sup>25</sup>

We recently reported a cluster analysis of 67 anticancer compounds, including PI3K/Akt/mTOR inhibitors, Mek inhibitors, and other conventional anticancer drugs, by use of their LogGI50s for each cell line of JFCR39,<sup>6</sup> further supported that JFCR39 could identify anticancer compounds with various targets.

#### 4. Conclusion

As a bioinformatics system, JFCR39 has made a significant contribution to the discovery and development of anticancer drugs. In particular, since the JFCR39 screening system became a key part of the program of Screening Committee of Anticancer Drugs (SCADS,

funded by the Ministry of Education, Science and Culture) of Japan,<sup>25</sup> JFCR39 has become a well known platform for the discovery of molecular-targeted anticancer drugs in Japan. Information from the JFCR39 system has facilitated the selection of many compounds for active development as anticancer drug candidates, some of which have entered clinical trials (e.g., ZSTK474).<sup>4,14</sup> The first molecular-targeted anticancer drug to be identified by JFCR39 is anticipated to enter the market in the near future.

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