A New Therapeutic Strategy against Hormone-Dependent Breast Cancer: The Preclinical Development of a Dual Aromatase and Sulfatase Inhibitor

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Abstract Purpose: The production of E2 is paramount for the growth of estrogen receptor–positive breast cancer. Various strategies have been used, including the use of enzyme inhibitors against either aromatase (AROM) or steroid sulfatase (STS), in an attempt to ablate E2 levels. Both these enzymes play a critical role in the formation of estrogenic steroids and their inhibitors are now showing success in the clinic.

Experimental Design: We show here, in a xenograft nude mouse model, that the inhibition of both enzymes using STX681, a dual AROM and STS inhibitor (DASI), is a potential new therapeutic strategy against HDBC. MCF-7 cells stably expressing either AROM cDNA (MCF-7AROM) or STS cDNA (MCF-7STS) were generated. Ovariectomized MF-1 female nude mice receiving s.c. injections of either androstenedione (A4) or E2 sulfate and bearing either MCF-7AROM or MCF-7STS tumors were orally treated with STX64, letrozole, or STX681. Treatment was administered for 28 days. Mice were weighed and tumor measurements were taken weekly.

Results: STX64, a potent STS inhibitor, completely blocked MCF-7STS tumor growth but failed to attenuate MCF-7AROM tumor growth. In contrast, letrozole inhibited MCF-7AROM tumors but had no effect on MCF-7STS tumors. STX681 completely inhibited the growth of both tumors. AROM and STS activity was also completely inhibited by STX681, which was accompanied by a significant reduction in plasma E2 levels.

Conclusions: This study indicates that targeting both the AROM and the STS enzyme with a DASI inhibits HDBC growth and is therefore a potentially novel treatment for this malignancy.
AROM and STS are postulated to play important roles in the etiology and maturation of ER+ breast cancer (see Fig. 1), as expression of these enzymes is detected in 60% to 70% (15, 16) and 90% (17, 18) of breast tumors, respectively. STS activity has been suggested to be much higher than the AROM complex (19), resulting in as much as a 10-fold greater amount of E1 originating from this route compared with the AROM pathway (20). Inhibition of AROM, with letrozole, exhibits clinical benefits in postmenopausal women with breast cancer (21, 22), and similarly, preclinical and clinical STS inhibition with STX64, also known as 667Coumate and BN83495, has been shown to achieve encouraging results (23–26). However, it would be an advantage to inhibit both AROM and STS activity in vivo and therefore maximize estrogen reduction (8).

Therefore, the development of a dual AROM and STS inhibitor (DASI) is an attractive target for the treatment of HDPC. Theoretically, a DASI should give a more complete depletion of available E2 levels than either inhibitor could achieve alone and could conveniently remain as a single orally effective agent. This multiple ligand with one-drug approach, as opposed to a multiple-drug approach, has various advantages. Clinical development of a multiple ligand, in terms of risks and costs involved, is no different from the development of any other single entity. Another advantage is that a single agent could aid the development and pharmaceutical strategies that go with a dual inhibitor (27). The DASI concept has been validated by the incorporation of the pharmacophore for STS inhibition into the known AI, YM511 (28), leading to the successful, highly potent inhibition of both AROM and STS in vitro and in vivo. Further work on the development of new classes of DASIs, which are structurally related to the established nonsteroidal AIs letrozole and anastrozole, has recently been published (29–31).

Consequently, the objective of the work presented here was to examine the in vivo potential of STX681, a potent DASI compound, in an immature rat pregnant mare serum gonadotropin (PMSG)-stimulated AROM model. This compound was then taken forward to preclinical evaluation in a mouse xenograft model using two breast cancer cell lines overexpressing the AROM and STS enzymes. To determine the AROM and STS inhibitory activity of STX681, plasma E2 levels were assessed in all models to show in vivo activity.

**Materials and Methods**

*Compounds.* The synthesis of STX64 has been published elsewhere (32). Letrozole was synthesized at the University of Bath. The DASI compound STX681 (Fig. 2) was synthesized according to Woo and colleagues (29). All compounds exhibited spectroscopic and analytic...
incubator; the overexpressing cell line medium was further supple-

3-fold increase in AROM activity with no increase in STS activity when

Conversely, MCF-7AROM cells showed an 11-fold increase in STS activity and no increase in AROM activity

generation of MCF-7 cells overexpressing STS cDNA (MCF-7STS)

has been previously published (23, 24). Cells overexpressing AROM

1640 (Sigma) and cultured at 37°C (33–35). All cells were grown in 10% serum-supplemented RPMI

Cell culture. MCF-7 wild-type cells (MCF-7 WT) were purchased

in ice-cold PBS (pH 7.4) containing 250 mmol/L sucrose and supernatants were prepared by centrifugation

Centrifugation (2,000 × g, 4°C for 10 min). Aliquots of tissue supernatants were incubated with [6,7-3H]E1S (4 × 10^5 dpm; Perkin-Elmer) and adjusted to a final concentration of 20 μmol/L with unlabeled E1S (Sigma). [4,14C]E1 (1 × 10^5 dpm; Perkin-Elmer) was included in the reaction mixture to monitor procedural losses. Samples were incubated for 60 min at 37°C, after which the product E1 was separated from E1S by partition with toluene. An aliquot of toluene was removed and 3H and 14C radioactivity was measured by liquid scintillation spectrometry. The mass of E1S hydrolyzed was calculated from the 3H counts detected corrected for procedural losses. A protein measurement was also obtained for the tissue using the Bradford assay method. Results are determined as nmol product formed/h/mg protein and expressed as the percent inhibition or activity compared with the control.

AROM biochemical assay. For AROM activity, [1β,3H]androstenedione (2-3 nmol/L, 30 Ci/mmol; Perkin-Elmer Life Sciences) was incubated with JEG-3 cells for 1 h in the presence or absence of inhibitor. The product E1 was separated using dextran-coated charcoal at 4°C for 2 h, and remaining radioactivity was measured by scintillation spectrometry.

In vivo tumor growth model. Ovariectomized, athymic, female MF-1 nude mice (nu-/nu-) were purchased from Harlan at 6 to 8 wks of age (approximately 20-25 g in weight). All experiments were carried out under conditions that complied with institutional guidelines. Animals were kept in a 12-h light/dark cycle and given food and water ad libitum. Ovariectomized animals were chosen as they have been shown to have similar serum estrogen levels to those of postmenopausal women (38, 39). Mice received s.c. injections of E2S (50 μg/50 μL/mouse) or A4 (100 μg/50 μL/mouse) 24 h before cell injection. E2S was chosen to stimulate MCF-7STS tumor growth rather than E1S as this avoids the

Table 1. The AROM and STS activity and tumorigenicity of MCF-7WT, MCF-7STS, and MCF-7AROM cells

<table>
<thead>
<tr>
<th>Enzyme activity (fmol/h/10^6 cells)</th>
<th>In vitro cell line</th>
<th>In vivo tumor size after 42 d (mm^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MCF-7WT</td>
<td>MCF-7STS</td>
</tr>
<tr>
<td>STS</td>
<td>39.4 ± 1.5</td>
<td>438.7 ± 72.1</td>
</tr>
<tr>
<td>AROM</td>
<td>10.26 ± 4.2</td>
<td>8.8 ± 2.1</td>
</tr>
<tr>
<td>Stimulated with:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E2S (50 μg)</td>
<td>241.7 ± 32.3</td>
<td>240.7 ± 34.9</td>
</tr>
<tr>
<td>A4 (100 μg)</td>
<td>Did not grow</td>
<td>Did not grow</td>
</tr>
</tbody>
</table>
need for the liberated E1 to be converted to E2 by the MCF-7 cells, which only have low 17β-hydroxysteroid dehydrogenase type 1 activity (40). Monolayers of MCF-7 cells were removed by trypsinization, and the resultant cell suspension was centrifuged for 5 min at 1,000 × g and then resuspended in ice-cold Matrigel (BD Biosciences). Five million wild-type MCF-7 cells (MCF-7_WT), or MCF-7_STS cells, or 10 million MCF-7_AROM cells were injected s.c. into the right flank of the animal. A4 (100 μg/50 μl 10% ethanol:90% propylene glycol) was injected s.c. daily or E2S (50 μg/50 μl 10% ethanol:90% propylene glycol) was injected s.c. on alternate days until the end of the study. When tumors reached 70 to 100 mm3, mice were randomly divided into five treatment groups of 10: vehicle (10% tetrahydrofuran:90% propylene glycol), STX64 (10 mg/kg), letrozole (0.5 mg/kg), a combination of STX64 and letrozole (10 and 0.5 mg/kg, respectively), or STX681 (20 mg/kg). The dose of letrozole has previously been shown to be efficacious in this model (41-43). All compounds were given orally for 5 d a week for 28 d. Throughout the study, mice were weighed and tumor measurements were taken on a weekly basis. Tumor volumes were calculated using the formula (length × width2 / 2). At the conclusion of dosing, animals were terminated and their tumors and livers were removed for AROM and STS activity measurements. Cardiac blood samples were also taken for the measurement of plasma E2 concentrations.

**Plasma E2 measurement.** Blood taken from mice was collected into heparinized tubes and centrifuged at 13,000 rpm for 1 min to remove erythrocytes. The plasma was collected and stored at -20°C until assayed. Plasma E2 levels were measured using a Coat-A-Count Estradiol RIA kit (Diagnostic Products Corp.) according to the manufacturer’s instructions. The intra-assay coefficient of variation for these measurements of plasma E2 concentrations by this method was <10%

**Statistical analysis.** A one-way ANOVA followed by a Bonferroni’s multiple comparison test was done to determine statistical significance on most data sets. Where only two groups are compared, a Student’s t test was applied. All values are represented as the mean ± SE.

**Results**

**Inhibition of AROM and STS activity in vitro.** The potency of STX681 as an AROM and STS inhibitor was initially tested on JEG-3 cells. Using this assay, the IC50 value for STX681 was 0.82 nmol/L for AROM inhibition and 39 nmol/L for STS inhibition. The IC50 value of STX64, a potent STS inhibitor, against STS activity in this cell line is 0.5 nmol/L, whereas the IC50 value for letrozole against AROM activity is 0.89 nmol/L.

**Cell proliferation.** To establish the effects of STS inhibition, AROM inhibition or DASI on breast cancer cell growth, MCF-7_STS and MCF-7_AROM cells, in phenol red–free medium supplemented with charcoal-stripped serum, were stimulated with 10 nmol/L E2S or 10 nmol/L A4. These cells were also treated with STX64, letrozole, and STX681 and cell proliferation over 72 h was assessed using a Coulter counter. MCF-7_STS cell growth was approximately double when in E2S-supplemented medium compared with cells in SFBS medium alone (Fig. 3A). STX64, STX64 with letrozole, and STX681 inhibited this proliferation by 32%, 38%, and 46%, respectively. Letrozole had no significant effect. Complete cell growth inhibition (i.e., similar to cells grown in SFBS) was not obtained, as E2S in the medium is not particularly stable and can break down to E2 (44). MCF-7_AROM cells grown in 10 nmol/L A4 proliferated by 39% compared with cells in SFBS alone (Fig. 3B). In these studies, letrozole, STX64 with letrozole, and STX681 significantly inhibited this proliferation by 74%, 35%, and 67%, respectively. As expected, STX64 had no significant effect on this A4-stimulated cell growth.

**Inhibition of PMSG-induced plasma E2 levels in vivo.** Immature female rats injected s.c. daily with a dose of 200 IU PMSG exhibited a maximal increase in plasma E2 concentration of 320.3 ± 97.4 pg/mL after 4 days (Fig. 4A). E2 levels were elevated on days 1, 2, 3, and 4 compared with control. Therefore, in all future studies using this model, animals received daily s.c. injections of 200 IU PMSG for 4 days. In the same animals, the liver STS activity was also assessed and indicated that PMSG had no effect on the activity and regulation of this enzyme (Fig. 4B). To confirm that the PMSG-induced plasma E2 levels were produced via the AROM pathway, an oral dose response to letrozole was undertaken where letrozole inhibited PMSG-induced plasma E2 levels at concentration as low as 0.01 mg/kg (Fig. 4C).

**STX681 inhibits AROM and STS activity in vivo.** Once the PMSG-stimulated immature female rat model had been validated, it was used to determine the effect of STX681 on both AROM and STS activity. As previously shown, daily s.c. injections of PMSG (200 IU) over 4 days resulted in a maximal E2 production. In this experiment, PMSG resulted in an increase in plasma E2 concentrations to 595.5 ± 95.27 pg/mL (Fig. 4D). Daily oral dosing of STX64 at 10 mg/kg did not significantly affect E2 levels (430.3 ± 45.51 pg/mL). However, letrozole (0.1 mg/kg) and STX681 (10 mg/kg) both significantly inhibited plasma E2 production, reducing levels to 107.8 ± 12.6 pg/mL (P < 0.001) and 285.9 ± 33.4 pg/mL (P < 0.001), respectively, compared with vehicle-treated mice. In the same animals, liver STS activity was not affected by PMSG injection or letrozole (Fig. 4E). However, both STX64 and STX681 completely inhibited STS action. This indicates that in female rats, STX681 is a potent, orally bioavailable DASI in vivo. These results validate this model for its use on the in vivo assessment of DASI compounds.

**Tumorigenicity of MCF-7 cell lines.** There has been much interest in the importance of A4 and E2S in the growth of MCF-7 breast cancer xenografts. However, to date, there have been no studies to examine the effects of these two substrates on the tumorigenicity of MCF-7_WT, MCF-7_AROM, and MCF-7_STS growth in vivo. Therefore, these three cell lines were inoculated into female nude mice, which were given s.c. injections of either A4 (100 μg daily) or E2S (50 μg thrice weekly). Table 1 summarizes the results along with the enzyme activity of each of the cell lines investigated. Previous work has shown that both MCF-7_WT and MCF-7_STS cells are capable of forming xenografts when inoculated into female ovariectomized mice given E2S injections (23). This was confirmed in the present study where MCF-7_WT and MCF-7_STS xenografts reached 241.7 ± 32.3 mm3 and 240.7 ± 34.9 mm3 after 42 days of E2S stimulation. However, in the present study, both these xenografts did not grow when given daily A4 stimulation. In contrast, animals bearing MCF-7_AROM cells developed tumors when given either E2S or A4, reaching a volume of 269.9 ± 53.5 mm3 and 165.1 ± 11.5 mm3, respectively. This suggests the importance of the STS pathway in tumorigenesis. Furthermore, letrozole, given orally at 0.5 mg/kg, failed to inhibit the growth of MCF-7_AROM xenografts stimulated with E2S (data not shown).

These results correspond to the enzyme activity of the cell before inoculation; MCF-7_WT and MCF-7_STS cells had minimal AROM activity, suggesting their limited ability to convert A4 into E1 (Table 1). However, all three cell lines had detectable STS activity, allowing the synthesis of E2 from E2S.
Surprisingly, despite an increase in STS activity, the xenografts derived from MCF-7STS did not increase in size at a greater rate compared with the MCF-7WT cells. This supports data previously published where both these tumor types developed at similar rates (23).

**STX681 inhibits A4-stimulated MCF-7AROM tumor growth.** As previously shown, STX681 exhibited the ability to inhibit both PMSG-induced E2 production via the AROM pathway and liver STS activity in the rat. The next step was to examine whether this compound could attenuate the growth of breast tumors overexpressing the AROM enzyme or STS enzyme. Consequently, MCF-7AROM and MCF-7STS breast cancer cells were inoculated into female ovariectomized nude mice to form xenografts. The animals were given either A4 (for MCF-7AROM-bearing xenografts) or no hormone (for MCF-7STS xenografts) to stimulate tumor growth.

**Fig. 3.** The effect of STX64, letrozole, and STX681 on hormone-stimulated breast cancer cell growth in vitro. A, the proliferation of MCF-7STS cells, in SFBS supplemented with E2S (10 nmol/L), was inhibited by STX64, STX64 with letrozole, and STX681. B, the proliferation of MCF-7AROM cells, in SFBS supplemented with androstenedione (10 nmol/L), was inhibited by letrozole alone, STX64 with letrozole, and STX681. Columns, mean (n = 3); bars, SE. *P < 0.05; **P < 0.001, compared with controls.

**Fig. 4.** The effect of a STS inhibitor (STX64), AI (letrozole), and a DASI (STX681) on PMSG-induced plasma E2 concentrations and STS activity in the immature rat. A, PMSG caused a maximal increase in rat plasma E2 levels after 4 d of treatment. B, PMSG had no effect on rat liver STS activity. C, PMSG-induced plasma E2 concentrations are inhibited in a dose-dependent fashion by letrozole in the rat. D, letrozole (0.1 mg/kg) and STX681 (10 mg/kg), but not STX64 (10 mg/kg), inhibit PMSG-induced plasma E2 production in the rat. E, in the same animals, STX64 and STX681, but not letrozole, inhibited liver STS activity. Columns, mean (n = 3); bars, SE. ns, not significant. *P < 0.05; **P < 0.01; ***P < 0.001, compared with controls.
mice) or E2S (for MCF-7STS–bearing mice) s.c. injections to stimulate tumor growth.

Data in Fig. 5 show the effects of AROM and STS inhibition in mice bearing MCF-7AROM xenograft tumors. Treatment with letrozole, alone or in combination with STX64, or with STX681 successfully inhibited MCF-7AROM tumor growth (Fig. 5A). The tumors on vehicle-treated animals increased in volume by $213.1 \pm 18.4\%$ over the 28-day study period. Similarly, animals treated with STX64 had a $202.5 \pm 11.2\%$ enlargement of tumor burden. In contrast, letrozole, STX64 with letrozole, and STX681 treatment all resulted in a slight regression in tumor volume by $13 \pm 4.5\%$, $18.4 \pm 6.1\%$, and $12.3 \pm 4.9\%$, respectively. There have been no previous studies on the effects of regular daily dosing of STX681 in mice and examination of the mouse weights throughout the study indicated no ill effects (Fig. 5B).

On termination of this study, tumor and plasma samples were obtained from the mice. Tumors were weighed (Fig. 5C), which showed that STX64 did not reduce the MCF-7AROM tumor mass, whereas letrozole, alone and with STX64, and STX681 significantly reduced the final average xenograft weight compared with the vehicle-treated control. Plasma E2 measurements showed that these same treatment groups significantly reduced circulating E2 levels (Fig. 5D). E2 measurements were at $78.2 \pm 2.9$ pg/mL in vehicle-dosed animals administered s.c. with A4, STX64 treatment did not reduce this A4-stimulated plasma E2 concentration ($77.2 \pm 2.8$ pg/mL). However, a significant lowering of E2 was observed in mice treated with letrozole alone ($40.3 \pm 4.2$ pg/mL, $P < 0.001$), letrozole with STX64 ($36.3 \pm 2.7$, $P < 0.001$), and STX681 ($48.5 \pm 1.9$, $P < 0.001$) compared with vehicle-treated mice.

**STX681 inhibits E2S-stimulated MCF-7STS tumor growth.** Figure 6 shows the data obtained from the MCF-7STS side of the study. Daily oral dosing of STX64, or the combination of STX64 and letrozole, or STX681 all resulted in a significant inhibition of tumor growth (Fig. 6A). In vehicle-treated animals, tumors reached $274.1 \pm 41.6\%$ growth by day 28. In contrast, STX64 caused a $20.0 \pm 10.9\%$ tumor regression ($P < 0.001$, compared with control), STX64 and letrozole caused a $30.1 \pm 5.4\%$ regression ($P < 0.001$, compared with control), and STX681 treated tumors had only increased in volume by $4 \pm 11.8\%$ ($P < 0.001$, compared with control). Letrozole, however, failed to block E2S-stimulated xenograft growth and tumors were $229.9 \pm 22.6\%$ larger at day 28 compared with day 0. Note that the growth rate of the vehicle-treated MCF-7STS tumors is greater than the corresponding group bearing MCF-7AROM tumors (Fig. 5A). Examination of animal weights in this study also indicated that STX681 had no detrimental effects (Fig. 6B).

At the end of the study (day 28), tumor and liver tissue and plasma were collected. Final tumor weights were determined (Fig. 6C), indicating that STX64, the combination of STX64 and letrozole, and STX681 significantly reduced the xenograft tumor burden. Active enzyme analysis of these tumors (Fig. 6D) and of livers (Fig. 6E) indicated that these treatments completely attenuated STS activity in these tissues. Finally, measurement of plasma E2 levels showed a significant decrease in circulating E2 in the animals treated with STX64, alone or in combination with letrozole, and with STX681 (Fig. 6F). In all these assays, animals treated with letrozole were not significantly different from control.

**Discussion**

There are significant advantages to using a single compound to affect two or more anticancer targets. This treatment strategy reduces the risk of drug-drug interactions in patients, which can lead to significant complications (27). More importantly, however, is that as tumors can develop resistance to single-targeted drugs, hitting a second target may overcome or circumvent that resistance. Furthermore, inhibiting two pivotal pathways could be valuable in cancers that may involve alterations in more
than one growth pathway. Modest results observed for AROM inhibition alone may be greatly enhanced when more pathways are blocked. The single-agent, dual-target approach has already shown significant success. Recently, there has been much interest in lapatinib (Tykerb), a compound that inhibits both epidermal growth factor receptor and HER2. Both these receptors are important targets of already approved drugs: trastuzumab targets HER2, and cetuximab, gefitinib, and erlotinib aim at EGFR. In fact, there is now a range of dual-targeted, even triple-targeted, agents in the preclinical and clinical pipeline (45).

The use of single-agent inhibitors against AROM in the treatment of HDBC is a recent and important clinical success. Letrozole and other AIs are now widely used therapeutically across the majority of the United States. Unfortunately, most women will relapse on these therapies with the development of AI therapy resistance (46), and consequently, there is still a need for new treatments (6). Recently, a phase I trial using the STS inhibitor STX64 showed a significant benefit for patients who had failed on tamoxifen and AIs, and this compound is now advancing into further trials (26). However, as breast cancer tissue is likely to contain elevated AROM and STS activities, there is a strong rationale in designing single compounds that target both these enzymes (15–18). This theory led to the synthesis of several DASI compounds by Woo and colleagues (28, 29). Therefore, in this study, one of these novel DASI compounds, STX681, was selected for preclinical experiments and was shown to inhibit both enzymes in an immature rat model stimulated with PMSG. Further studies showed, for the first time, that the inhibition of these enzymes can completely inhibit the growth of breast cancer xenografts overexpressing either AROM or STS. Significantly, letrozole failed to inhibit MCF-7 STS tumor growth, and conversely, STX64 failed to inhibit MCF-7 AROM tumor growth. Furthermore, STX681 is able to significantly reduce circulating E2 levels stimulated by either A4 or E2S. Finally, the results suggest that the STS pathway may play as important a role as AROM in the development of MCF-7 xenograft tumors.

STX681 was developed by incorporating the STS pharmacophore, a sulfamate ester group linked to an aryl ring, into a potent AI, YM511 (28–31). This created a potent DASI in vitro in the JEG-3 cell line whose AROM and STS activities are significantly elevated compared with most other cancer cells (37). However, the effects of a DASI on enzyme activity had not previously been examined. Therefore, an immature rat model was initially used to determine the oral bioavailability and potency of STX681 in vivo. After confirming that this model was suitable to examine both AROM and STS activity with the use of letrozole and STX64,
further studies showed that oral dosing of STX681 was able to significantly reduce PMSG-induced E2 production via the AROM pathway as well as inhibit rat liver STS activity. As expected, in these studies, letrozole alone had no effect on rat liver STS activity and STX64 alone had no effect on circulating plasma E2 concentrations.

The next step was to examine the effect of STX681 on the growth of breast cancer xenografts overexpressing either AROM or STS. However, before this was undertaken, it was vital to ascertain the effects of the substrates A4 and E2S on xenograft tumor growth in ovariectomized nude mice. Therefore, animals with MCF-7WT, MCF-7AROM, or MCF-7STS xenografts were given s.c. injections of the relevant substrates, and once tumors had reached 100 mm³, they were orally dosed with various compounds. Only STX681 was able to inhibit development of both these tumors, inhibit tumor AROM and STS activity, and lower plasma E2 concentrations.

Against MCF-7STS xenografts, STX64, the combination of STX64 and letrozole, and STX681 all inhibited tumor growth stimulated with E2S s.c. injections. Only letrozole failed in this model. Tissue activity data and plasma E2 levels confirmed that the STS inhibition resulted from STX64 and STX681 treatment. These data show the potent efficacy of STX681 against HDBC xenografts overexpressing either AROM or STS.

In conclusion, the use of a novel DASI, STX681, against HDBC is a potentially new and efficacious treatment for this malignancy. STX681 was able to abolish tumor growth, inhibit STS activity in liver and tumor samples, and significantly reduce circulating plasma E2 levels. The use of two compounds, a combination of an STS inhibitor and an AI, was also able to stop these cancer growths. However, there are many advantages in the use of a single agent with dual targets as a strategy for future clinical treatments. Therefore, STX681, a potent DASI, has therapeutic potential against breast cancer.

Disclosure of Potential Conflicts of Interest

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References

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