SCO-101 is a novel oral drug that reverses antiestrogen resistance in breast cancer cells

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ABSTRACT

Breast cancer is the most frequent cancer diagnosed in women and 80% of all cases of breast cancer patients present with estrogen receptor (ER)-positive disease. Treatment with antiestrogens most notable tamoxifen and Fulvestrant (Faslodex) are effective for a large proportion of ER-positive breast cancer. However, antiestrogen resistance eventually arises in all patients with advanced disease. Thus, antiestrogen resistance represents a major problem in the clinical management of breast cancer patients and there is currently no treatment to overcome resistance to antiestrogens.

SCO-101 is an oral drug currently being tested in a Phase II clinical trial enrolling metastatic and chemotherapy resistant colorectal cancer patients with drug resistant disease (ClinicalTrials.gov Identifier: NCT04247256). In the current work, we investigated the potential of SCO-101 to act in combination with the antiestrogens tamoxifen or Fulvestrant in antiestrogen resistant breast cancer cell lines (MCF-7/LCC-2[1], MCF-7/LCC-9[2], T47D/TR1[3]) and - as a negative control - the ER negative MDA-MB-231 breast cancer cell line. Treatment effects were investigated by MTT cell viability assays. siRNA knock-down experiments and western blots were used to identify the mechanisms of Actions for SCO-101 in reversing anti-estrogen resistance.

SCO-101 only had minor inhibitory effects on cell viability when administered alone. Interestingly, when combining SCO-101 with tamoxifen or Fulvestrant in MCF-7 or T47D antiestrogen resistant breast cancer cells, an additive to synergistic inhibitory effect on cell viability was observed. In contrast to these results, SCO-101 in combination with antiestrogens had no effects on the triple negative MDA-MB-231 cell line, indicating the ER and/or or PR (progesterone receptor) are important for the effect of SCO-101 in antiestrogen resistant breast cancer cells. As SCO-101 has been described to target the volume-regulated anion channel (VRAC), in which LRRC8A is the essential subunit, we investigated whether knockdown of LRRC8A would impact the treatment outcome. No apparent changes in response to SCO-101 and antiestrogens were observed upon the knockdown. Additionally, the protein level of LRRC8A was examined upon treatment with antiestrogens +/- SCO-101 and the treatment did not alter LRRC8A protein expression. We also studied the effects of SCO-101 treatment on ER levels and found that SCO-101 did not significantly change the ER levels.

Our findings strongly suggest that SCO-101 interferes with antiestrogen resistance in breast cancer and we have recently received an EURECA Eurostars grant to further investigate the molecular mechanisms of action for SCO-101 in reversing antiestrogen resistance, to investigate drug response in 3D breast cancer models, and to conduct a Phase Ib dose escalation clinical trial with SCO-101 and Faslodex in patients with acquired antiestrogen resistant ER positive breast cancer.

OBJECTIVES

To investigate if SCO-101 can reverse antiestrogen resistance in breast cancer cells

RESULTS

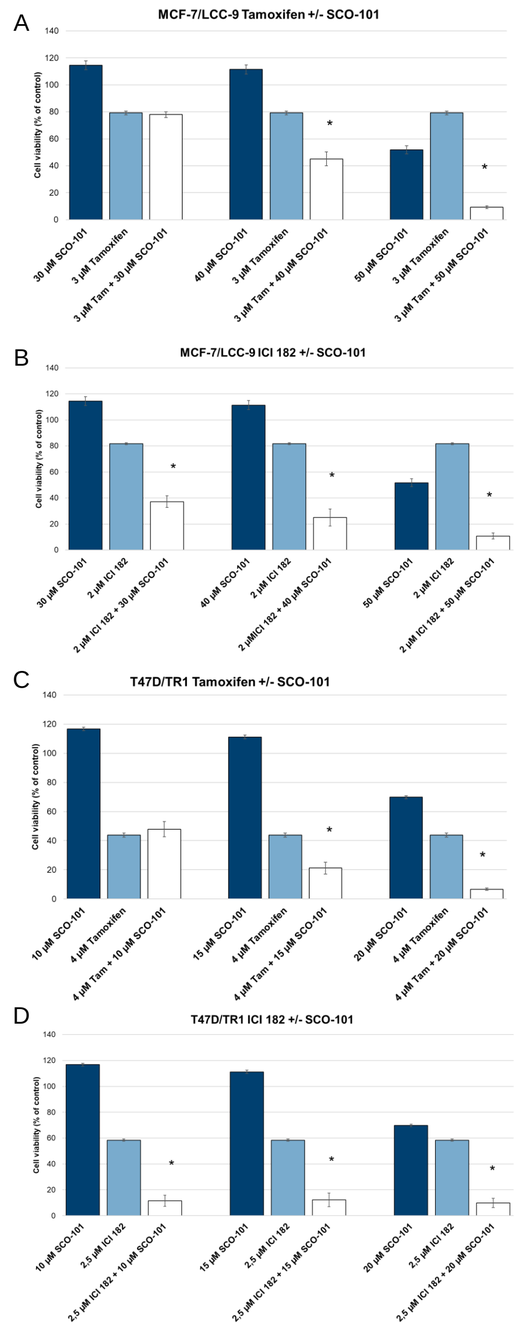

Figure 1. MTT cell viability assay on on anti-estrogen resistant ER positive breast cancer cells treated with antiestrogen +/- SCO-101 for 120h. The effects of combining anti-estrogens with SCO-101 is evident in the antiestrogen resistant LCC9 and T47D/TR1 cell lines.
A, B: Tamoxifen- and Fulvestrant (ICI 182,780) resistant MCF-7/LCC-9 cells treated with two anti-estrogens (Tamoxifen or Fulvestrant) +/- SCO-101 for 120 hours. Combinations marked with a star/asterisk were significantly different from either single treatments at p-value <0.05 in 5/5 experiments.
C, D: Tamoxifen resistant T47D/TR1 cells treated with either tamoxifen or Fulvestrant +/- SCO-101 for 120h. Combinations marked with a star/asterisk were significantly different from either single treatments at p-value <0.05 in 3/3 experiments.

RESULTS

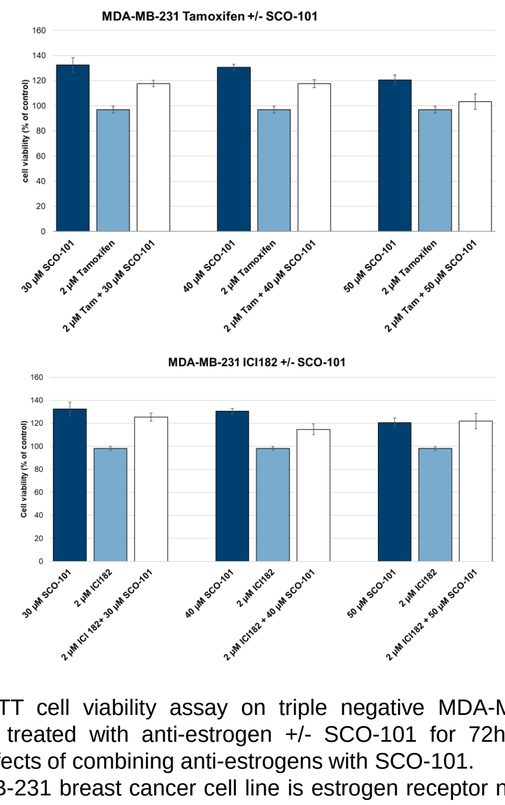

Figure 2. MTT cell viability assay on triple negative MDA-MB-231 breast cancer cells treated with anti-estrogen +/- SCO-101 for 72h. There is no significant effects of combining anti-estrogens with SCO-101.
The MDA-MB-231 breast cancer cell line is estrogen receptor negative and is included as a negative control.

CONCLUSIONS

- SCO-101 resensitizes the antiestrogen resistant cell lines; LCC and T47D (LCC2[1], LCC9[2] and T47D/2%[4] T47D-TR1[3], T47D/TR2[3]) to tamoxifen and Fulvestrant (Data not shown for LCC2, T47D/2% and T47D/TR2).
- The Mechanism of Action for SCO-101 was not the ion channel LRRC8A (VRAC) and also SCO-101 did not significantly change the ER levels.

Through a recently received an EURECA Eurostars grant we will further investigate

- Molecular mechanisms of action in reversing antiestrogen resistance
- Drug response in 3D breast cancer models
- The safety and efficacy of the combination of SCO-101 and Faslodex by performing a Phase Ib dose escalation clinical trial in patients with Faslodex resistant ER positive breast cancer.

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