The small molecule SCO-101 mediates re-sensitization of Irinotecan resistant colorectal cancer cells and is currently being tested in clinical trials

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ABSTRACT

Resistance to anti-cancer drugs represents the main cause of cancer-related deaths.

Thus, re-sensitization of chemotherapy resistant cancer cells constitutes a highly unmet medical need.

Scandion Oncology's lead candidate, SCO-101, is a small molecule drug with oral administration that has passed 4 Phase I clinical trials demonstrating excellent PK and favourable safety profile.

In SN38 (active metabolite of irinotecan) resistant colon cancer cells[1] SCO-101 re-sensitize the cells to SN38. Flux assays shows that SCO-101 inhibits the activity of ABCG2/BCRP, and protein analysis show that SCO-101 causes degradation of ABCG2/BCRP. In silco docking predicted SCO-101 to bind in the part of ABCG2/BCRP where also SN38 binds. SRPK1 was identified as a SCO-101 target in a kinase screen and two different SRPK1 inhibitors re-sensitize the cells to SN38.

Scandion Oncology has reported the outcome of the first part of the ongoing Phase II clinical CORIST trial with irinotecan resistant metastatic CRC patients (www.clinicaltrials.gov/ct2/show/NCT04247256?term=scandion&draw=2&rank=2).

OBJECTIVES

To identify mechanisms of action for SCO-101 mediated re-sensitization of SN38 resistant colon cancer cells.

RESULTS

SCO-101 synergize with SN38 to re-sensitize SN38 resistant HT29 colon cancer cell

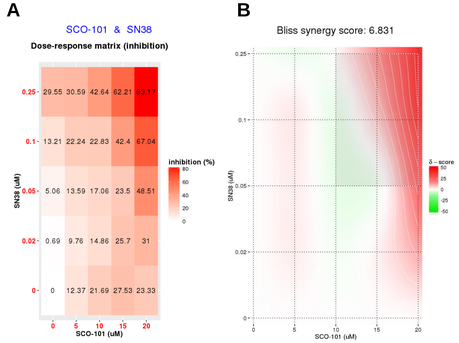

Figure 1
Synergistic combinatorial effects of SCO-101 and SN-38 in HT29 SN38 resistant colon cancer cells

Exposure to SCO-101, SN-38 or the combination for 72h and cell viability evaluation by MTT assay.
A) Dose-response matrix demonstrating a 83% inhibition of cell viability by 20 µM SCO-101 combined with 0.25 µM SN38.
B) Bliss synergy score was calculated by SynergyFinder2.0[2] and a score >10 demonstrates synergy. The most synergistic area score was 13.9 demonstrating synergy between SCO-101 and SN38

Dose response of SCO-101 to accumulate a fluorescent ABCG2 substrate and to degrade ABCG2

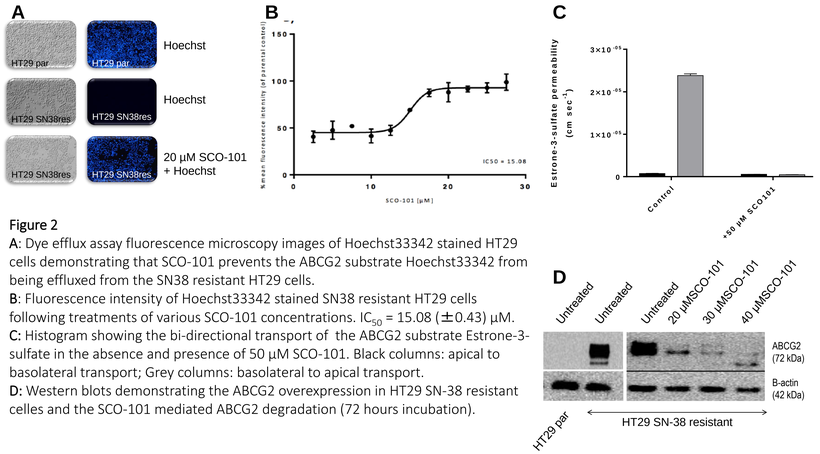

Figure 2
A: Dye efflux assay fluorescence microscopy images of Hoechst33342 stained HT29 cells demonstrating that SCO-101 prevents the ABCG2 substrate Hoechst33342 from being effluxed from the SN38 resistant HT29 cells.
B: Fluorescence intensity of Hoechst33342 stained SN38 resistant HT29 cells following treatments of various SCO-101 concentrations. IC_{50} = 15.08 (±0.43) µM.
C: Histogram showing the bi-directional transport of the ABCG2 substrate Estrone-3-sulfate in the absence and presence of 50 µM SCO-101. Black columns: apical to basolateral transport; Grey columns: basolateral to apical transport.
D: Western blots demonstrating the ABCG2 overexpression in HT29 SN-38 resistant celles and the SCO-101 mediated ABCG2 degradation (72 hours incubation).

RESULTS

SCO-101 inhibits the SRPK1 kinase and SRPK1 inhibition re-sensitizes HT29 SN38 resistant cancer cells

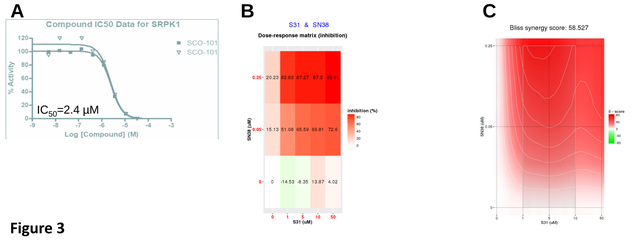

Figure 3
A: SCO-101 was screened in 2 kinase profilings and SRPK1 identified as a hit with an IC_{50} of 2.4 µM.
B: Dose-response matrix demonstrating a 89% inhibition of cell viability by 50 µM SPHINX31 (S31) combined with 0.25 µM SN38.
C: Bliss synergy score was calculated by SynergyFinder2.0[2] and a score >10 demonstrates synergy. The most synergistic area score was 39.2 demonstrating synergy between SPHINX31 and SN38.
Exposure to SPHINX31, SN-38 or the combination for 72h and cell viability evaluation by MTT assay.

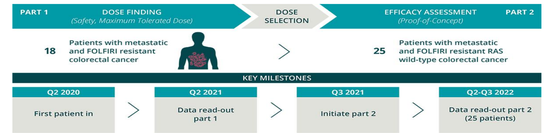

Figure 4
CORIST Study Design. In this Phase II study, patients with chemotherapy (FOLFIRI) resistant and metastatic colorectal cancer receive SCO-101 treatment together with the standard chemotherapy drug combination FOLFIRI. All patients enrolled in the trial have demonstrated acquired FOLFIRI resistance.

CONCLUSIONS

- SCO-101 synergize with SN38 to re-sensitize SN38 resistant HT29 colon cancer cells.
- SCO-101 inhibits the flux of ABCG2 substrates and caused a down regulation of the ABCG2 protein.
- SCO-101 inhibits the SRPK1 kinase and a SRPK1 kinase inhibitor (SPHINX31) synergize with SN38 to re-sensitize SN38 resistant HT29 colon cancer cells.
- SCO-101 is currently being tested in metastatic colorectal cancer patients with acquired FOLFIRI resistance.

REFERENCES

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2. Lanevski et al. SynergyFinder 2.0: visual analytics of multi-drug combination synergies. NAR, 2020 Vol. 48, Issue W1, P. W488–W493

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