Development of novel inhibitors of the serum/glucocorticoid induced kinase (SGK) family to address limitations of AKT/PI3K/mTOR inhibitors in breast cancer

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BACKGROUND

- The phosphatidylinositol-3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) signaling pathway is one of the most commonly activated pathway in cancer.
- > 40% of estrogen receptor positive (ER+) breast cancer tumors harbor activating mutations in the alpha subunit of PI3K (*PIK3CA*).
- Several PI3K/AKT/mTOR inhibitors have been developed, however, they have been limited due to various feedback and crosstalk mechanisms amongst different members of the pathway as well as dose limiting toxicities.
- The **S**erum and **G**lucocorticoid Induced **K**inase (SGK) family is involved in maintaining PI3K/AKT signaling in cancer resistance and thus represent an attractive therapeutic target.

Similarities between AKT and SGK families

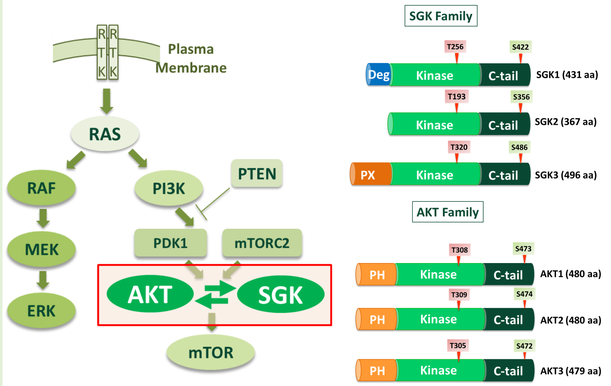
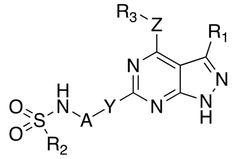


Figure 1: Schematic of PI3K/AKT/mTOR signaling. LEFT: Upon activation of a receptor tyrosine kinase (RTK), the proliferation signal is propagated from the plasma membrane to the nucleus. The AKT and SGK families share the same upstream activating kinases PDK1 and mTORC2, and the same downstream effectors such as TSC2, FOXO3, and GSK3B (not shown). RIGHT: SGK1, 2, 3 have extensive homology with the AKT family of kinases, including similar domain structures. Legend: Deg: degradation domain , PH; pleckstrin homology domain, PX: phox homology domain.

DEVELOPMENT OF NOVEL SGK INHIBITORS



Novel ATP-competitive inhibitors of the SGK family were developed with improved drug-like properties as well as improved potency and selectivity towards SGK1.

Table 1: Summary of selected Thryv compounds

	EMD638683	GSK650394	Thryv selected compounds
MW (g/mol)	364	382	506 - 553
cLogP	1.5	5.58	1.81 - 3.52
TPSA (Å^2)	99	66	112 - 130
SGK-1 (IC_{50} nM) [20 µM ATP]	54 - 116	23 - 109	0.3 – 67.4
Whole-cell SGK-1 (IC_{50} nM)	>75,000	686	3 – 279
Kinase-Select > 50%@10 µM	0	13	0 - 15

> 400 compounds were synthesized and tested for their affinity and selectivity towards the SGK family and selected compounds are summarized here.

IN-CELL TARGET ENGAGEMENT OF SGK1 INHIBITORS

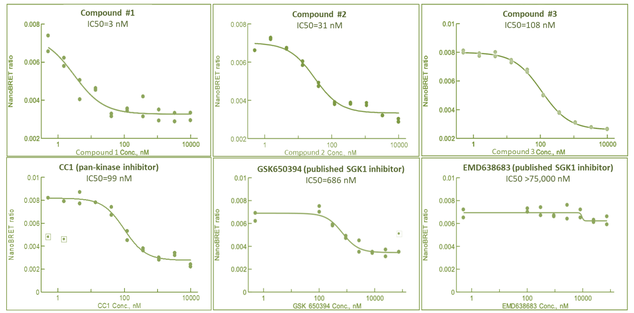


Figure 2: Potent inhibition of SGK1 in HEK293 cells. The NanoBRET SGK1 kinase target engagement assay (Promega) was used to test the potency of Compounds # 1, 2, and 3 to inhibit SGK1-NanoLuc in transiently transfected HEK293 cells. These compounds were significantly more potent to inhibit SGK1 compared to the CC1 pan-kinase and previously published SGK1 inhibitors GSK650394 and EMD638683.

INHIBITION OF SGK1 CELLULAR TARGET

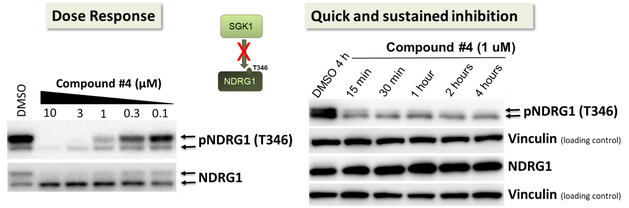


Figure 3: Inhibition of NDRG1 phosphorylation by SGK1 inhibitors in cells. NDRG1 is a direct target of SGK1 and incubation of cells with an SGK1 inhibitor (Compound #4) results in its dose and time-dependent inhibition of phosphorylation.

INCREASED SGK1 SIGNALING WITH PI3K INHIBITION

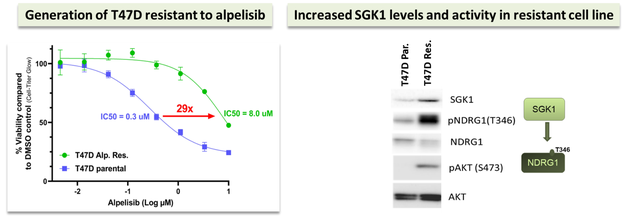


Figure 4: Increased SGK1 protein levels and signaling upon resistance to alpelisib. LEFT: Generation of resistant T47D breast cancer cells by continuous incubation with increasing concentrations of alpelisib. RIGHT: Alpelisib-resistant cells show increased SGK1 protein and phosphorylation of its substrate NDRG1 (similar to previously published[1]).

SYNERGISTIC COMBINATION OF SGK + AKT INHIBITORS

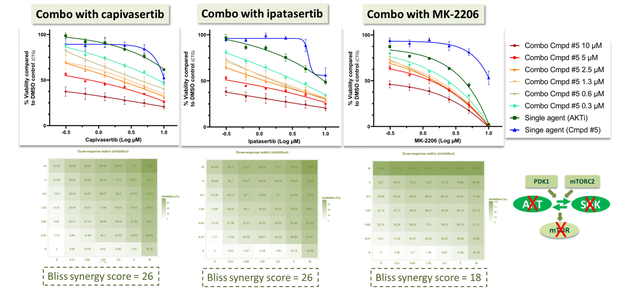


Figure 5: Combination of SGK and AKT inhibition is synergistic. JIMT-1 breast cancer cells (resistant to AKT, PI3K and HER2 inhibitors) were treated with single agent as well as combinations of different AKT inhibitors and the SGK inhibitor Compound #5 for 7 days. Bliss synergy index are shown below as well as a representation of the inhibited pathway.

SYNERGISTIC COMBINATION OF SGK + PI3K INHIBITORS

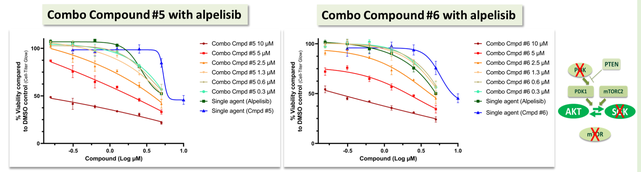


Figure 6: Combination of SGK and PIK3CA inhibition is synergistic. JIMT-1 cells were treated with single agent as well as combinations of alpelisib and Compounds #5 or #6 for 7 days. Schematic of the inhibited pathway is shown on the right.

COMBINATION OF SGK with PI3K/AKT INHIBITORS

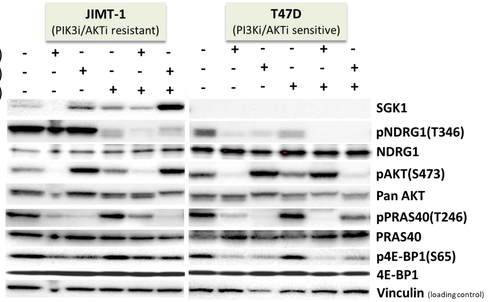


Figure 7: Combination of SGK and AKT inhibition results in further reduction of PI3K/AKT signaling. JIMT-1 cells were treated with 1 uM of each single agent as well as in combinations for 4 hours.

CONCLUSIONS

- Novel potent and selective inhibitors of SGK1 with improved drug-like properties were developed.
- Inhibition of SGK1 was synergistic with inhibitors of PI3K and AKT signaling in a model of resistance to existing breast cancer therapies.
- Combinations of SGK1 with PI3K/AKT/mTOR inhibitors could be an effective therapeutic strategy to increase their efficacy and delay the development of resistance.

REFERENCE AND CONTACT

[1]Toska, E. et al. 2019 *Cell Rep.*, *27*(1), 294-306

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