**Conclusions:** Exosomal HMGB1 from TNBC could target Tim-3 ligand on lung macrophages and accelerate glycolysis and lactate production to induce PD-L1$^{+}$-TAMs, suppressing CD3$^{+}$CD8$^{+}$ T lymphocytes immunity and generating a pre-metastasis immune-suppressive niche.

**Legal entity responsible for the study:** The authors.

**Funding:** Top Talent of Changzhou "The 14th Five-Year Plan" High-Level Health Talents Training Project.

**Disclosure:** All authors have declared no conflicts of interest.

https://doi.org/10.1016/j.esmoop.2024.103087

## 82P VRTX531: A potent inhibitor of USP1 for treatment of BRAC1/2mut and HRD+ cancers

U.K. Surampudi[1], P.K. Bhavar[1], P.P. Sarma[2], A. Kshirsagar[2], V.M. Bokka[2]

*[1]Drug Discovery, VRise Therapeutics Inc., Cambridge, MA, USA; [2]Drug Discovery, VeGen Therapeutics Private Ltd., Hyderabad, India*

**Background:** Breast cancer accounts for the highest cancer incidence and second highest cancer-related mortality among women in the United States. Breast Cancer is often molecularly characterized by mutations in the BRCA1/2 Gene, which are the master regulators of genomic stability and are essential for accurate DNA double-strand break (DSB) repair by homologous recombination (HR). Although, targeted therapies, such as the administration of poly (ADP-ribose) polymerase (PARP) inhibitors, can effectively eliminate mutated BRCA1/2 tumors, the development of resistance in patients eventually highlights the need for innovative therapeutic strategies. USP1 is a protease in the ubiquitin-specific protease (USP) subfamily that plays a crucial role in modulating DNA damage response (DDR) pathways. USP1 is a key promoter of metastatic breast cancer, making it a therapeutically relevant target to improve patient outcomes.

**Methods:** Inhibitory effect of the VRTX531 on USP1/UAF1 activity was assessed using Ub-Rho 110 biochemical assay. Colony Formation Assay was performed in BRCA1$^{MT}$ / HRD$^{+}$ human breast cancer cell line MDA-MB-436. Combination synergy of VRTX531 with PARP inhibitors was evaluated in-vitro using both the cell proliferation and Colony Formation Assay.

**Results:** VRTX531 is a novel, potent and selective inhibitor of USP1 with an IC50 of $<$50 nm in biochemical assay and demonstrated nM potency across a broad range of tumor lineages, including MDA-MB-436. VRTX531 was found to be having low intrinsic clearance and desirable oral bioavailability. In combination studies with first and second-generation PARP inhibitors, VRTX531 demonstrated robust synergy.

**Conclusions:** VRTX531 exhibited profound activity alone and in combination with PARP inhibitors in BRCA1/2 mut and HRD+ tumours and is currently ongoing late-preclinical studies.

**Legal entity responsible for the study:** VRise Therapeutics Inc.

**Funding:** VRise Therapeutics Inc.

**Disclosure:** P.P. Sarma: Financial Interests, Institutional, Full or part-time Employment: VRise Therapeutics Inc. V.M. Bokka: Financial Interests, Institutional, Other: VRise Therapeutics Inc. All other authors have declared no conflicts of interest.

https://doi.org/10.1016/j.esmoop.2024.103088

## 83P Boron-doped alginate carbon-nanogel exhibits superior anti-metastatic effect on breast cancer by cell cycle arrest and actin dysfunction

S. Sarkar[1], B. Unnikrishnan[1], C-Y. Wang[1], C-J. Lin[1], A. Anand[2], R-H. Shih[1], L.E. Hean[1], C-C. Huang[1]

*[1]Department of Bioscience and Biotechnology, National Taiwan Ocean University, Keelung City, Taiwan; [2]Department of Biomedical Engineering, Chang Gung University, Taoyuan City, Taiwan*

**Background:** Metastasis is widely recognized as the primary contributor to mortality in cancer-related cases; however, the precise mechanisms responsible for this phenomenon have yet to be fully elucidated. The potential of natural compounds, particularly polysaccharides and polyphenols, as medicines with anti-tumor and anti-metastasis effects has attracted increasing attention in recent years. Therapeutic efficacy may be improved by the use of nanomaterials that can be controlled and used as delivery systems. In our findings, we employed boron-doped alginate carbon nanogels Bor$_{(5)}$/Alg-240-CNGs that demonstrate a higher degree of efficacy in suppressing the migration and invasion of cancer cells in triple-negative breast cancer (TNBC).

**Methods:** Migration assays, invasion assays, cell attachment assays, microcolony analyses, and cell cycle analyses are used to assess the anti-metastatic properties of Bor$_{(5)}$/Alg-240-CNGs *in vitro*. Different types of breast cancer cells and normal cells were tested for their sensitivity to Bor$_{(5)}$/Alg-240-CNGs in order to learn more about their biocompatibility. The DCFH-DA assay and apoptosis analysis were then performed to examine anti-cancer activity further. *In vivo*, these nanomaterials were used to cure 4T1-induced tumors in BALB/c mice. Finally, proteomics provided much-needed insight into how exactly these nanomaterials produce their anti-metastatic actions.

**Results:** In our findings, we employed Bor$_{(5)}$/Alg-240-CNGs that demonstrate a higher degree of efficacy in suppressing the migration and invasion of cancer cells in TNBC and also TNBC-dependent cell cytotoxicity due to ROS induced apoptosis. Further *in vitro* mechanisms show Bor$_{(5)}$/Alg-240-CNGs induce cell cycle arrest and F-actin disorganization which is an essential factor for paralyzing migration. In the *in vivo* study, therapy with Bor$_{(5)}$/Alg-240-CNGs resulted in an 86.16 % decrease in the number of metastatic lung nodules compared to the untreated group. The overall mechanism was further validated using proteomics.

**Conclusions:** Finally, Bor$_{(5)}$/Alg-240-CNGs have the potential to be a cost-effective, inventive, and unique nanodrug with many targets for cancer treatment.

**Legal entity responsible for the study:** The authors.

**Funding:** Ministry of Science and Technology of Taiwan.

**Disclosure:** All authors have declared no conflicts of interest.

https://doi.org/10.1016/j.esmoop.2024.103089