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ABSTRACTS

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Reprogrammed Induced-Pluripotent-Stem Cells (iPSCs) Encoded With Anti-GRP78 shRNA Induces Apoptosis After a Gene-Silencing Bystander Effect Circumventing Vinorelbine-Induced Angiogenesis, and Metastatic Spread in Advanced Gastro-Intestinal Stromal Tumors (GIST)

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Background: Vinorelbine-tartrate in advanced GIST cells induces tumor relapse with enhanced angiogenesis and metastasis by inducing an innate cancer cellular stress response, which enhances the expression of GRP78 that blocks cell death or apoptosis increasing growth, and spread of GIST due to chemoresistance. We aim to circumvent this chemoresistant mechanism with the use of induced pluripotent stem cells encoded with antisense GRP78 shRNA.

Methods: We generated induced pluripotent stem cells(iPSCs), which we infected them with a DNA vector that encoded an RNA molecule of 67 nucleotides. The sequence of this small hairpin RNA (shRNA) is designed to suppress the GRP78 gene. GIST cells were obtained from patients, and they were implanted in animal models, which were treated with vinorelbine-tartrate.After tumor relapse, there was induction of enhanced angiogenesis, and metastasis. These chemoresistant tumor cells were treated with the induced pluripotent stem cells, which were encoded with shRNA against GRP78.

Results: Post-treatment, stem cells encoded with anti-GRP78 shRNA converted dicer into a siRNA molecule generating a long lasting RNAi silecing effect of GRP78, which spreads to adjacent tumor cells inducing a gene silencing bystander effect (GSBE). Capillary growth into the tumors were blocked, while VEGF and bFGF were downregulated. PKG was upregulated inhibiting b-catenin. Integration of endothelial precursor cells and tumor cells was blocked inhibiting growth of mosaic blood vessels. This leads to inhibition of tumor spread or metastasis, while the existing tumors die from lack of nutrients/oxygen, and a waste disposal pathway. TEM exhibited induction of type I PCD or apoptosis in tumor cells leading to a bystander killing effect. Thus, anti-GRP78 induced pluripotent stem cells (iPSCs) circumvented vinorelbine induced angiogenesis, and metastasis eradicating chemoresistant GIST cells.

Conclusions: Vinorelbine-tartrate induced angiogenesis, and metastatic spread in GIST are circumvented with induced pluripotent stem cells (iPSCs) encoded with anti-GRP78 shRNA, which induces apoptosis after a gene silencing bystander effect (GSBE).