Identification of Bioactive Small Molecules altering Endometrial Receptivity and Embryo Implantation In Vitro and In Vivo

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Background and Aims: Implantation remains a major impediment to success in in vitro fertilization (IVF) treatments. The endometrial receptivity window in humans is limited to the mid-secretory phase of the cycle. Modulating endometrial receptivity using pharmacological agents represents a potential strategy to improve implantation rate and IVF outcomes.

Method: A high-throughput spheroid attachment assay using BeWo cells and receptive Ishikawa endometrial epithelial cells was utilized to screen the Library of Pharmacologically Active Compounds (LOPAC), comprising 1,280 bioactive small molecules. Lead compounds enhancing attachment were validated in non-receptive endometrial lines (HEC-1B, AN3CA). Their effective concentrations and cytotoxicity were determined. Their effects on embryo implantation were evaluated by transcervical injection into mouse uterus on 1.5 days post-coitum (dpc) and examining implantation sites on 5.5 dpc and 18.5dpc.

Results: Screening identified 255 up-regulators and 173 down-regulators of spheroid attachment. Three lead molecules (L, O, and P) significantly enhanced attachment in non-receptive HEC-1B and AN3-CA cells. Conversely, Molecule J reduced attachment in receptive Ishikawa and RL95-2 cells but increased attachment in non-receptive HEC-1B and AN3CA cells. These four molecules all significantly elevated implantation sites in the mouse model compared to the control in 5.5dpc and 18.5dpc (n=10-15).

Conclusion: Three molecules were found to increase spheroid attachment and embryo implantation in vivo and in vitro. Another molecule J reduced the spheroid attachment in receptive cell lines while increasing attachment in the non-receptive cells and in mouse model. Four identified pharmacological agents that can modulate endometrial receptivity and augment embryo implantation in mice, representing potential adjuvants to improve implantation and IVF success rates. [This study is partially supported by the CRCG and GRF grants 15162211 and 17120720 to KFL]