The Post Delivery Placenta: From Biowaste to Biotherapeutics Engine

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Background
The causes of Necrotizing Enterocolitis (NEC) are not well understood, but the concentration of risk in very low birth weight infants suggests that inadequate exposure to swallowed amniotic fluid may be a contributing factor. Amniotic fluid derives almost all its growth factor constituency from placental cyto- and syncytio-trophoblasts and Hoffbauer cells. An acellular extract of the post-delivery, term placenta (HPEx) was tested to demonstrate the feasibility of repurposing the generative engine of pregnancy into a biotherapeutics resource and remove it from the bio-waste stream.

Design
To demonstrate that HPEx acts as amniotic fluid does in the womb, human jejunal stem cells were cultured with increasing physiologically relevant concentrations of HPEx. Cell count, type and confluency were determined. Cells were then exposed to LPS and IL-6, TNF-a and IL-10 secretion was quantified. Expanding upon the *in vitro* data an *in vivo* model of NEC was utilized. Twelve piglets (gestational day 105, delivered via C-section) were assigned to either control (n=3, iv nutrients) or HPEx (n=9, iv nutrients and 1.5ml/kg/hr HPEX by OG tube) groups, and received the designated treatment for the first 48 hours of life. All piglets also received an oral formula from 48 to 96 hours of life. Outcomes included clinical and histologic evidence of NEC and survival.

Results
In initial *in vitro* testing, an "inverted U" dose response to HPEx with significant increases in cell number and confluency were observed compared to serum control. The cell types observed varied based on the dose of HPEx administered. Lower doses showed more enterocytes and Paneth cells, while intestinal stem cells and Goblet cells were equally present over the range of doses exposed. HPEx blunted LPS induction of IL-6 and TNF-a and increased IL-10 concentrations in a congruent fashion to its effects on proliferation, etc. Maximum effects in all outcomes were at total protein concentrations equivalent to amniotic fluid. The pre-mature piglets treated with HPEx showed no clinical or histologic NEC. Published control treatments for this model demonstrate a 40-70% incidence of NEC. The lone surviving control piglet developed histological NEC, yielding a 33% incidence of the disease. The HPEx group had double the survival rate of the control group (67% versus 33%).

Conclusions
Term, post-delivery placentae are an abundant and renewable biotherapeutics resource. These results demonstrate that HPEx is beneficial to intestinal stem cells and a viable candidate for preventing NEC in premature humans.