Developing molecularly targeted therapeutics for severe preeclampsia

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Background: Preeclampsia is one of the most serious complications of pregnancy, responsible for 60,000 maternal deaths annually and far greater numbers of neonatal losses. In this condition, factors are released from the placenta into the maternal circulating, causing widespread endothelial dysfunction and severe maternal organ injury. Soberingly, there is no treatment other than delivery of the fetus. If severe preeclampsia occurs when the fetus is very preterm, clinicians are often forced to deliver the fetus to save the mother. Unfortunately, this inflicts prematurity to the fetus, which can then lead to major complications such as cerebral palsy, chronic lung disease and death. Hence, drugs that can quench the disease process of preeclampsia could allow the pregnancy to continue longer until the fetuses is more mature in gestation and ready to be delivered. Such a drug could save the lives of many mothers and fetuses.

Key pathophysiological steps in preeclampsia (PE) are 1) release of anti-angiogenic factors sFlt-1 and soluble endoglin (sEng) 2) oxidative stress and 3) maternal endothelial dysfunction. Any drug that can counter these important pathophysiological effects may be an effective therapeutic approach to treat preeclampsia.

We are performing functional studies in primary human tissues, screening candidate drug approaches to block these important pathological processes. Most of our work has focused on the therapeutic potential of proton pump inhibitors (PPIs) in order to counter these pathophysiological effects. We have also been screening other drug approaches, including short blocking peptides, neutralizing antibodies, and nanoparticle targeted delivery of siRNAs targeting sFlt-1.

Methods: Our overall strategy in screening candidate molecularly targeted drugs involves functional studies using primary human tissues: 1) primary trophoblast (placental tissues) 2) primary human umbilical vein endothelial cells (HUVEC), 3) uterine microvascular cells and 4) placental explants, obtained from women with severe preeclampsia. We have been examining whether the candidate drugs we are screening are able to cause the following: 1) block sFlt1/sEng production 2) up-regulate heme-oxygenase-1 (HO-1) expression and Nrf2 translocation (endogenous anti-oxidant defences) and 3) decrease endothelial dysfunction (modelled by adding TNFα or PE patient serum to endothelial cells).

Results: We have found PPIs to be an exciting therapeutic candidate for Preeclampsia. They dose-dependently reduce mRNA expression and protein secretion of sFlt1 and sEng in all cell types. The decrease was potent: for example, the top dose of esomeprazole of only 100 μM decreased sFlt1 release from trophoblast by 50%, and release sEng by 90%. Importantly, PPIs markedly reduced sFlt-1 production (and increased HO-1) when added to placental explants from women with severe PE.

All PPIs induced a highly significant dose dependent increase in HO-1 mRNA and protein in all tissues, a potent anti-oxidant protein. PPIs also induced nuclear translocation of the master antioxidant transcription factor, Nrf2, and upregulated Nrf2 regulated genes. PPIs rescued both TNFα and PE serum induced endothelial dysfunction (quenching leukocyte adhesion and attenuating VCAM1 and endothelin-1 expression). Furthermore, PPIs blocked TNFα-induced disruption of endothelial tube formation (both in HUVECs and uterine microvascular cells).

Conclusions: PPIs potently decrease sFlt1/sEng release, switch on anti-oxidant defences and quench endothelial dysfunction. Widely prescribed for gastric reflux during pregnancy, they represent an exciting novel candidate therapeutic to treat severe preeclampsia. On the basis of these preclinical studies, we are implementing a randomized placebo controlled trial in South Africa, using the proton pump inhibitor esomeprazole to treat severe preeclampsia.

Other novel molecular targeted approaches to treat preeclampsia (*e.g.* small peptides, neutralizing antibodies and nanoparticle delivery of siRNAs) may also be of value as candidate therapeutic approaches, but require further experimental evaluation.