**Project Title:** Role of hypoxia/oxidative stress in pre-eclampsia  
**Code:** NCS14

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<thead>
<tr>
<th>Host School/ Institute</th>
<th>Address: Level 10, Kolling Building B6. Royal North Shore Hospital E25, St Leonards, NSW 2065</th>
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**Project Type:** Laboratory based  
**Project Category:** Reproduction

**Project Keywords:**  
1. Pregnancy  
2. oxygen  
3. trophoblasts  
4. pre-eclampsia

**Project Description:**  
Human placentation requires adequate placentation, which is the result of precisely coordinated differentiation and proliferation of villous trophoblasts and migration and invasion extravillous invasive cyto-trophoblasts (CTB). Defective CTB invasion results in the inadequate establishment of uteroplacental blood supply and ultimately the two most common and serious medical complications of human pregnancy, fetal growth restriction (FGR) and pre-eclampsia (PE). The resulting placental microenvironment in PE and FGR is characterized by hypoxia and oxidative stress which are implicated in the development of these disorders. This proposal examines the potential roles for maladapted responses to low oxygen to promote PE, a uniquely human condition.

**Specific Hypothesis:** Our hypothesis is that CTB migration/invasion/differentiation in normal human pregnancy is regulated by changes in the local oxygen gradient, and that abnormal regulation of oxygen sensing promotes deficient CTB invasion in PE. The primary objective of the proposal is to understand how oxygen sensing in CTB works and how it goes wrong in PE/FGR. Specifically, the aims are:

**Aim 1:** To determine the alterations in oxygen sensing/response occur during pre-eclampsia. We will examine changes in the expression of Oxygen sensing and responsive proteins, and markers of oxidative injury, in tissue sections and protein lysates from normal and PE pregnancies.

**Aim 2:** Does the regulation of oxygen responses change in a microenvironment that mimics PE? We will examine expression of oxygen sensing and response proteins in CTB cells lines in normoxia and hypoxia and determine the effect of serum from normal and PE pregnancies on expression.

**Aim 3:** To determine whether perturbations in oxygen sensing molecules effect CTB function. We will examine in vitro the functional oxygen sensing and response mechanisms of CTB function. Thus aim will use PCR, cloning, mammalian cell culture and transfection, and assays of cellular function (including growth, survival and migration/invasion).

The proposed studies will correlate deficiencies in the oxygen sensing apparatus with functional aspects of CTB migration and have the potential to vastly improve our understanding of normal human placentation and of the disturbances that result in PE. This knowledge will provide a basis for specific therapies to correct the poor placentation observed in PE and manipulate the clinical course of disease.