Development of therapeutics for preeclampsia

Hudson researchers have identified a molecule linked to preeclampsia development in women. This molecule represents a novel target for the development of urgently needed therapeutics for this disease.

Our team of world-leaders in placental biology and disease have established that the cytokine IL11 plays a role in the pathogenesis of early-onset preeclampsia. Increased levels of IL11 have been associated with the development of disease symptoms, and treatment to normalise levels of this molecule may be a novel therapeutic strategy.

Summary

Preeclampsia is the most common medical complication of pregnancy, affecting 5-8% of pregnancies. It is a major cause of fetal and maternal morbidity and mortality.

Preeclampsia can have severe outcomes for mother and baby, and failure to manage or diagnose the disease can be life-threatening. Preeclampsia and associated complications are responsible for approximately 15% of maternal deaths, and up to 20% of the 13 million preterm births worldwide each year.

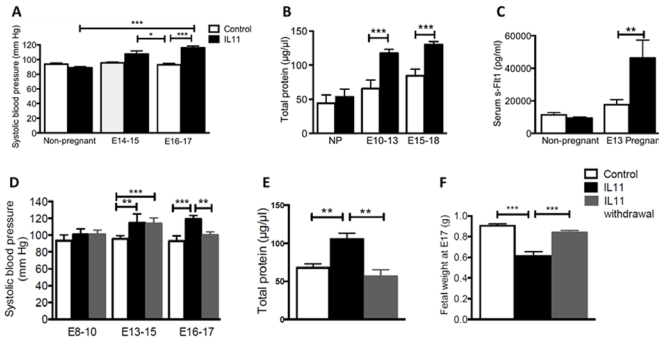
Characterised by high blood pressure and proteinuria, other symptoms include headaches, abdominal pain, shortness of breath and nausea. Early-onset preeclampsia (before 32 weeks' gestation) is the most severe and difficult to treat form of the disease, affecting 4 per 1000 pregnancies and associated with poor outcomes. As the only current treatment for preeclampsia is delivery of the baby and placenta, either by labour induction or Caesarean section, early-onset preeclampsia can result in very or extremely premature birth.

Despite years of research, we still do not have a clear understanding of the underlying causes of preeclampsia. This has hindered the development of potential therapeutics and improved management strategies. Researchers at Hudson Institute have found that levels of the cytokine interleukin-11 (IL11) are higher in women who go on to develop preeclampsia. They have also shown that IL11 plays a role in the development of preeclampsia symptoms, and have identified it as a potential therapeutic target.

The two defining symptoms of preeclampsia have traditionally been high blood pressure and proteinuria. Our team have found that the administration of IL11 leads to development of these preeclampsia symptoms in an in vivo murine model. Halting the administration of IL11 resulted in a reversal of symptoms, suggesting that the use of an agent to normalise IL11 levels may be a method to prevent or ameliorate symptoms of preeclampsia.

Key data

To model elevated levels of IL11, as is seen in women with preeclampsia, mice were administered a physiologically-relevant amount of IL11 on embryonic days 10-17 (E10-E17).



Our team found that administration of IL11 to pregnant mice resulted in increased blood pressure and proteinuria, but had no effect on non-pregnant mice. Systolic blood pressure levels increased by 20% in IL11-treated pregnant mice (A), but was not affected in non-pregnant mice. Total urinary protein also significantly increased in pregnant mice given IL11, but was unchanged in non-pregnant mice given IL11 (B). Levels of sFlt1, a validated biomarker of preeclampsia in women, were also significantly elevated in a pregnancy-specific manner in response to IL11 (C), *p<0.05, ** p<0.01, *** p<0.001.

Withdrawal of IL11 treatment mid-gestation led to a reduction of blood pressure in the model (D), and a decrease of total urinary protein (E). Fetal weight was also significantly increased at late gestation, after cessation of IL11 treatment, compared to mice that received IL11 throughout (F), ** p<0.01, *** p<0.001.

Applications

There have been no therapeutic advances in the management of preeclampsia for nearly 50 years. Standard treatment is currently delivery of the baby and placenta, with supportive management used to delay delivery or mitigate symptoms where possible.

Coupled with the use of IL11 as a screening biomarker for the development of early-onset preeclampsia, women at risk of developing disease could be identified and then treated to prevent or ameliorate symptoms of preeclampsia – such as through normalising levels of IL11 to prevent disease progression.

Unmet market need

Preeclampsia is estimated to cost the US healthcare system more than USD2 billion per year in short-term costs, with the incidence of disease increasing in the population over the last three decades. Pre-eclampsia is estimated to affect more than 8 million women worldwide every year, with 70 000 maternal deaths. The costs associated with preterm delivery are substantial, with very preterm (28-31 weeks) and extremely preterm (<28 weeks) births costing around 40 and 100 times a term pregnancy, respectively.

Despite the introduction of first-trimester screening tests in some markets, the lack of effective follow-on therapeutic options to treat or delay disease progression has resulted in debate over the usefulness of such testing. The value of currently available screening tests for preeclampsia is also limited by their low positive predictive value, and improved biomarkers are needed to improve their utility. Ultimately, while improved screening will allow for better patient management, there is a clear and urgent unmet need for novel therapeutics in this space.

IP position

PCT/AU2016/050883 filed September 2016 – 'A method of treatment and prophylaxis'.

Publication

Winship et al. (2015) Interleukin 11 alters placentation and causes preeclampsia features in mice. Proc Natl Acad Sci USA. 112(52):15928-33.

Contact us

e: commercialisation@hudson.org.au
t: +61 3 8572 2528
w: http://hudson.org.au/commercialisation/

Development pathway

To date we have demonstrated efficacy in in vitro models, including with human patient samples, and an in vivo murine model. An IL11 inhibitor used in mice has demonstrated that hypertension and proteinuria can be reversed. Modification of the IL11 inhibitor has also demonstrated that it does not does not pass through the placenta to the fetus, thereby reducing any potential effects on the developing fetus. This modification strategy can be applied to a myriad of other therapeutics used during pregnancy, or that are currently unable to be used in pregnancy due to potential toxic effects on the fetus.

The next stage is to further validate IL11 as a treatment option for preeclampsia. Our team have developed a novel in vivo preeclampsia model for testing potential therapeutics, and identified IL11 as a novel screening marker for early-onset preeclampsia (see separate fact sheets). They welcome opportunities for co-investment, licensing or collaboration to further develop a therapeutic for preeclampsia.

Hudson Institute of Medical Research

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- Cancer
- Endocrinology and metabolism
- Fetal, infant and child health
- Immunology and infectious diseases
- Reproductive health and biology
- Women's health

Opportunities for collaboration and partnership

Partnership opportunities include:

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