Tackling preeclampsia and its aftermath: Innovative strategies to understand and treat the underlying pathology

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ALWAYS WAS
ALWAYS WILL BE

Priscilla Kincaid-Smith – Lessons from a Trailblazer

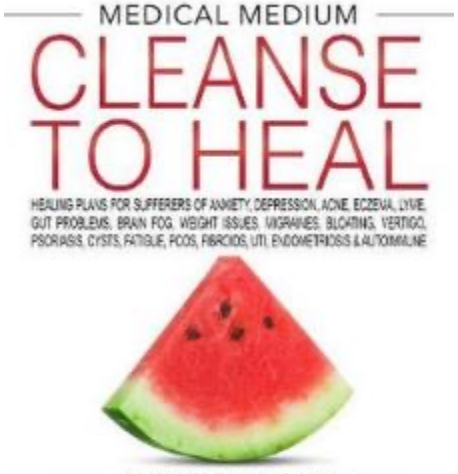
First Woman Professor at the University of Melbourne

Historical treatments for toxemia

Phlebotomies
1600s

Bleeding/purging
1800s

Colonic irrigation
1930s



Cleansing diets
1960s

Current treatment for preeclampsia: expectant management

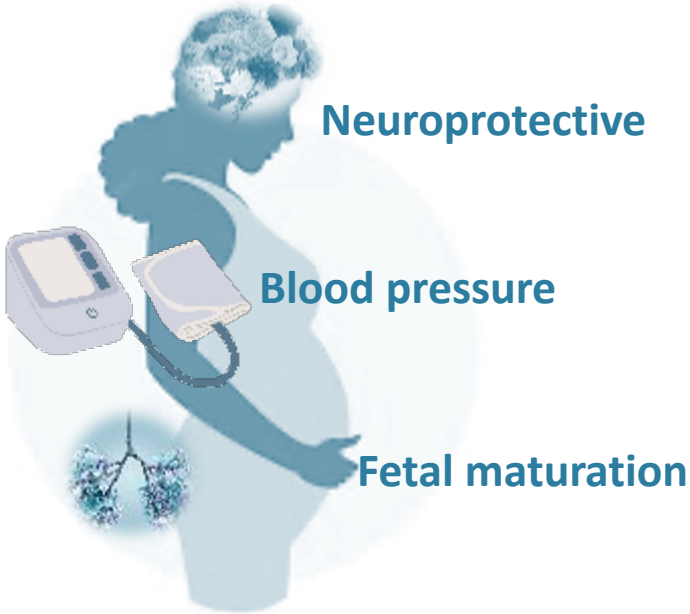


Table 2. Medications Used to Treat Preeclampsia

Magnesium sulfate
- Loading dose 4-6 g diluted in 100 mL normal saline IV over 15-20 min
- Continuous infusion 2 g/h

Labetalol
- 20 mg IV × 1 dose; if no response, increase to 40 mg and then to 80 mg at 10-min intervals until target BP is achieved (max dose 220 mg)

Hydralazine
- 5-10 mg IV every 15-30 min (max dose 30 mg)

Betamethasone
- 12 mg IM × 1 dose, then repeat in 24 h

Dexamethasone
- 6 mg IM × 1 dose, then repeat every 12 h for 3 additional doses

BP: blood pressure; IM: intramuscularly; max: maximum; min: minimum. Source: References 1, 3, 7.

From USpharmacist.com

Preeclampsia

Dysfunctional Placenta Oxidative stress/ischemia

anti-angiogenic / inflammatory factors

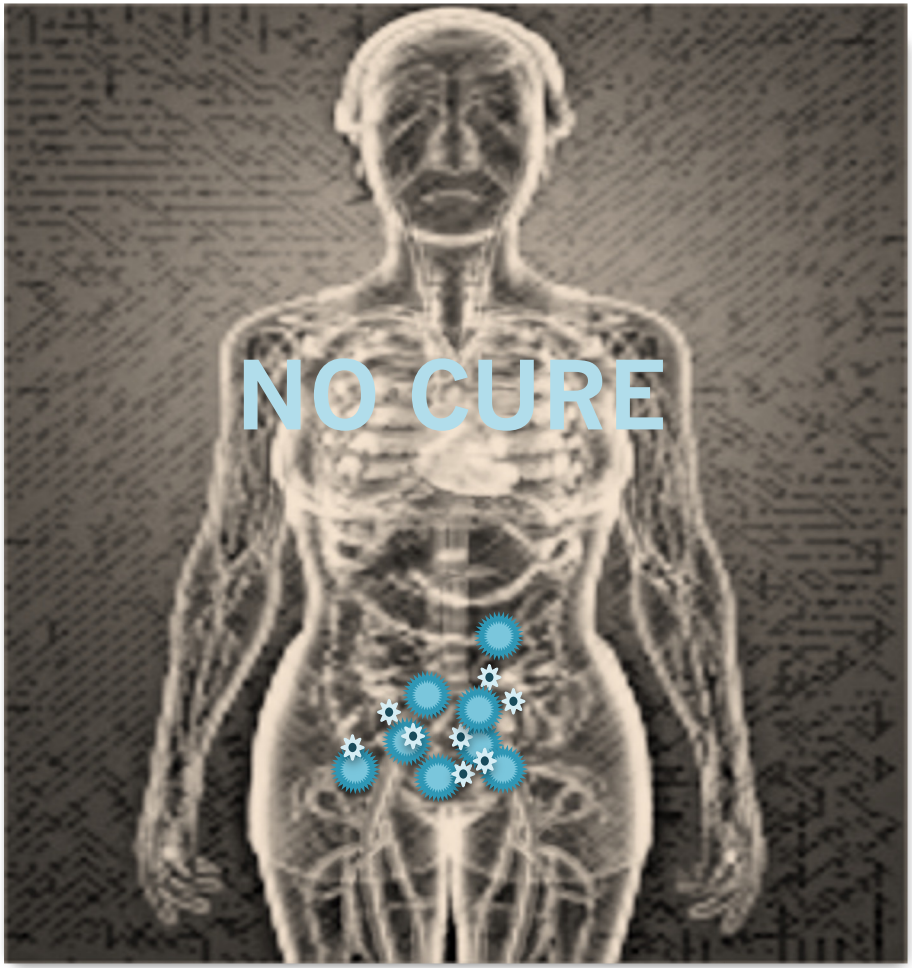
Maternal endothelial dysfunction

Preeclampsia

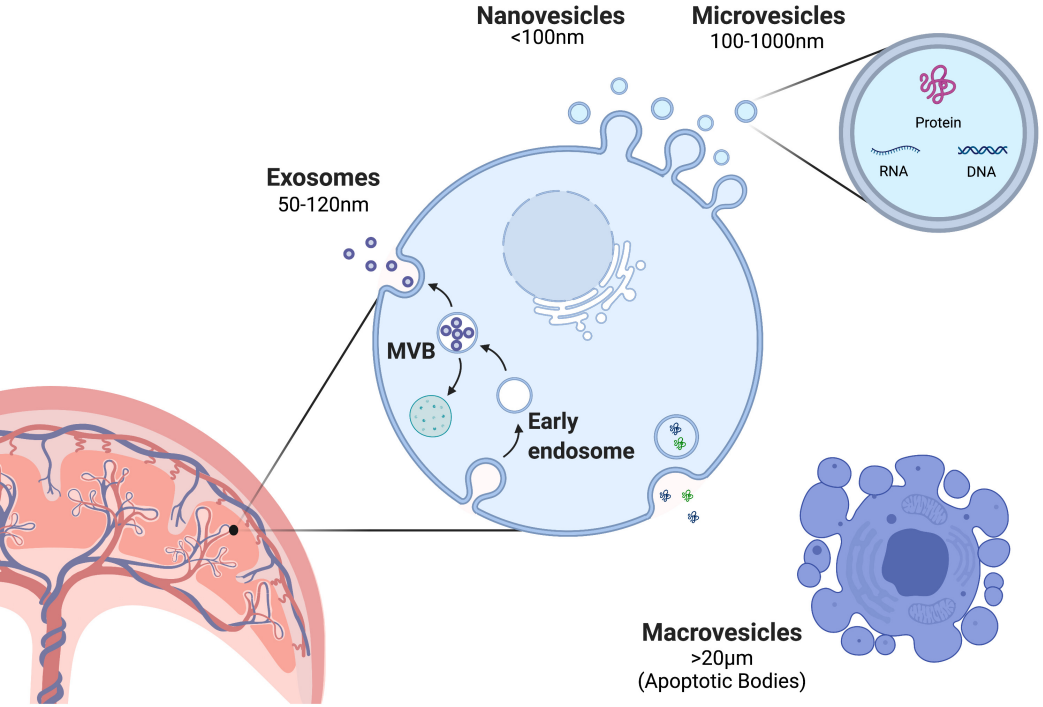
~~Dysfunctional~~
~~Placenta~~
~~Oxidative~~
stress/ischemia

~~anti-angiogenic~~ /
~~inflammatory~~
~~factors~~

~~Maternal~~
~~endothelial~~
~~dysfunction~~

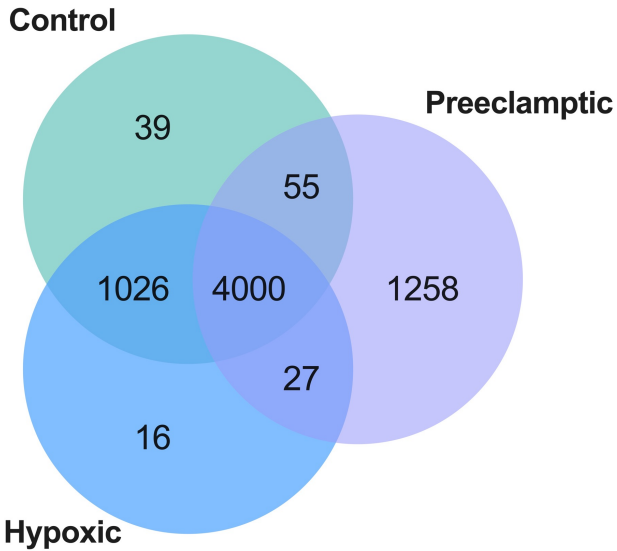


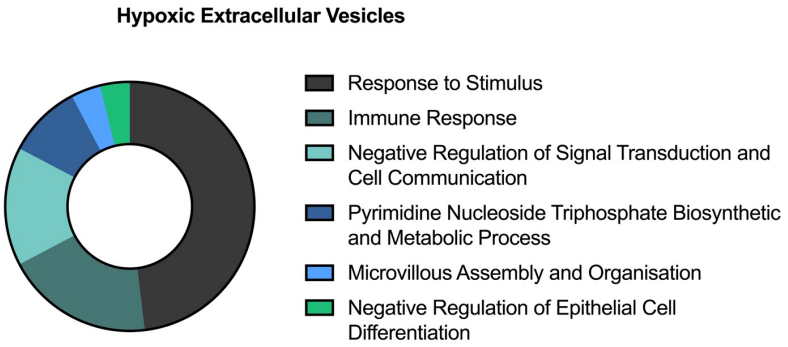
Extracellular Vesicles carry key physiological mediators

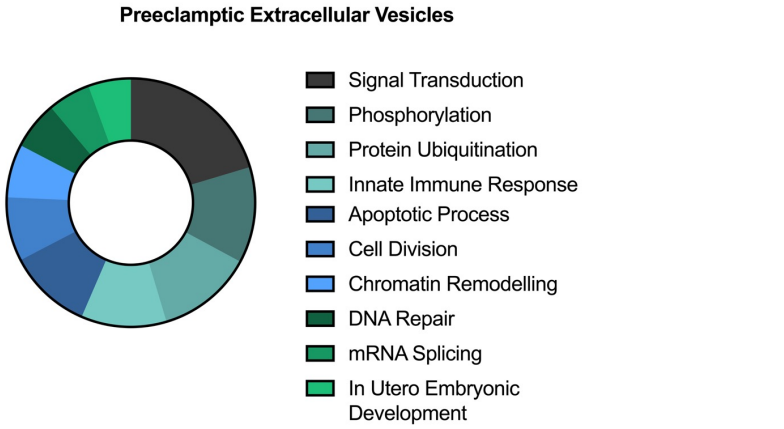


- Biophysiological actions on target cell
- Increased release of EVs across gestation

Is the cargo changed in preeclampsia and hypoxic placenta?







Bianca Fato
PhD Student

Prevention of preeclampsia with aspirin

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 17, 2017 VOL. 377 NO. 7

Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia

Daniel L. Rolnik, M.D., D
Catalina de Paco
Mandeep Sing
Walter Plasencia, M.D.,
Sveinbjorn

THE LANCET

Volume 395, Issue 10220, 25–31 January 2020, Pages 285-293

Articles

Low-dose aspirin for the prevention of preterm delivery in nulliparous women with a singleton pregnancy (ASPIRIN): a ebo-

of Bhalachandra S
MD [b], Jean Okitawutshu MD
, Abigail Mwapule BPH [e],
arlo MD [f], Javier Chicuy MD
[g], Lester Figueroa MD [g], Prof Ana Garces MD [g], Prof Nancy F Krebs MD [h], Saleem Jessani MBBS [i] ...
Farnaz Zehra

Decreased incidence of pre-term preeclampsia

No decrease in term preeclampsia

Very limited preclinical exploration/understanding of mechanisms of action

New generation antiplatelet agents

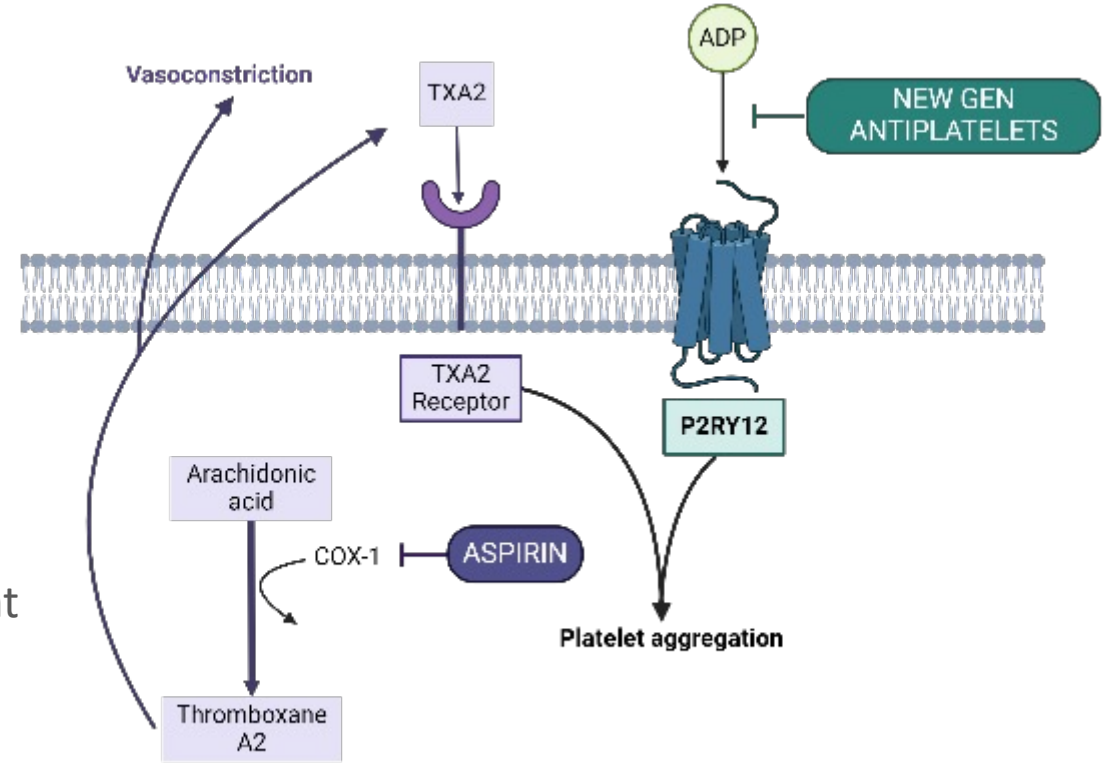
Clopidogrel, Prasugrel and Ticagrelor

(Category B/C drug)

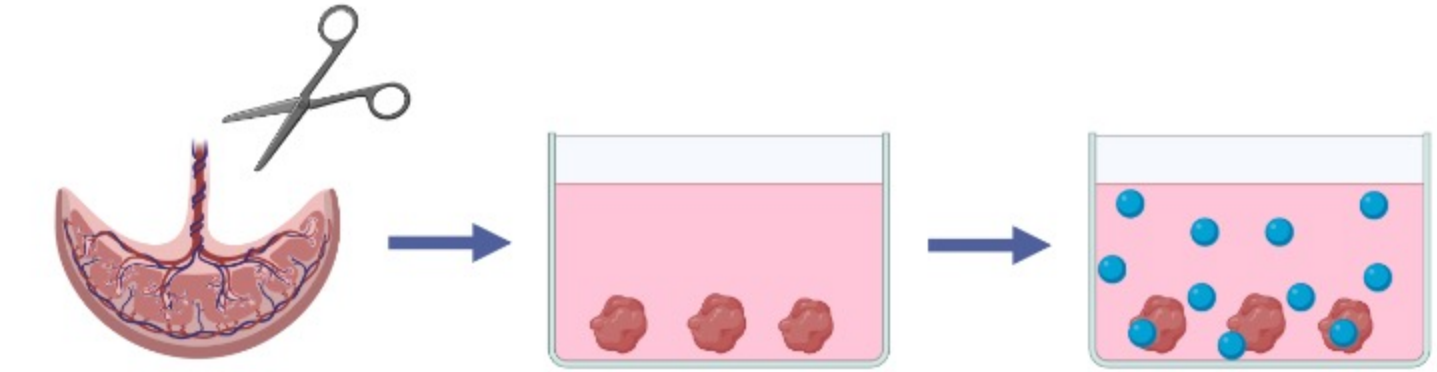
Oral antiplatelet – block blood clot formation

- protect against *oxidative damage* and have *anti-inflammatory* properties
- enhance *vasorelaxation* and prevent *endothelial dysfunction*

Multifaceted approach to prevent preeclampsia



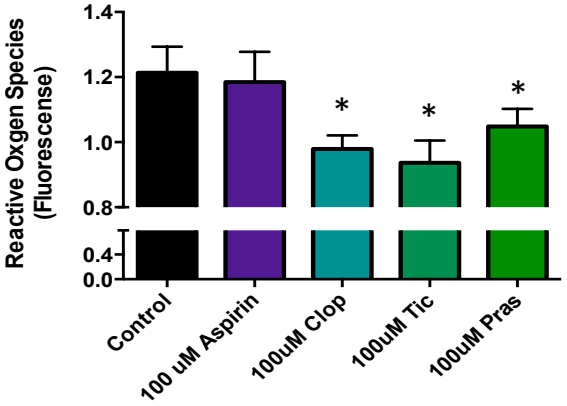
Exploration old and new generation antiplatelet agents

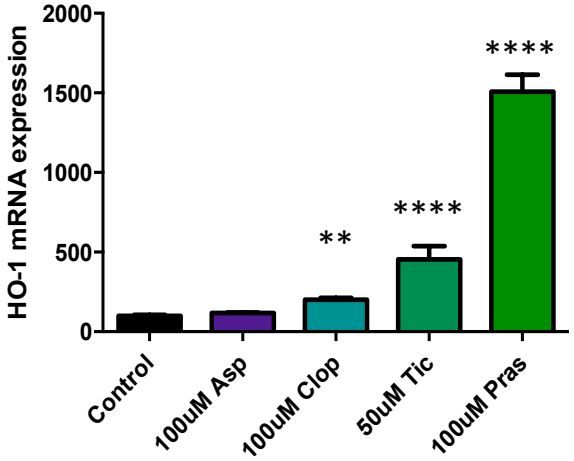


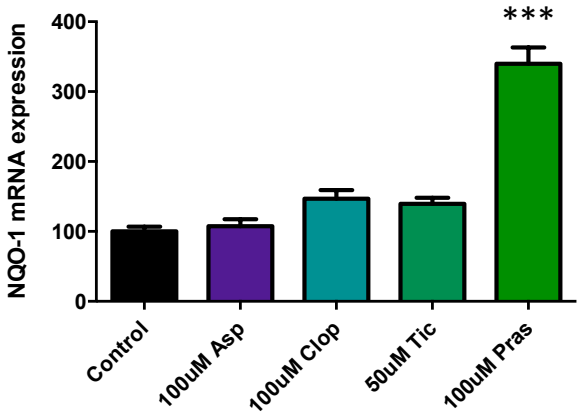
- Oxidative stress
- sFLT-1 and pro-inflammatory secretion

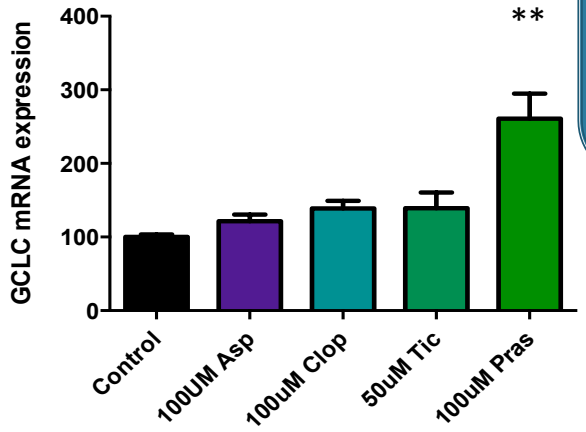
Created with Biorender.com

New generation antiplatelet agents enhance placental cytoprotective antioxidants and oxidative stress









Treatment with new generation antiplatelets in first trimester placenta

–

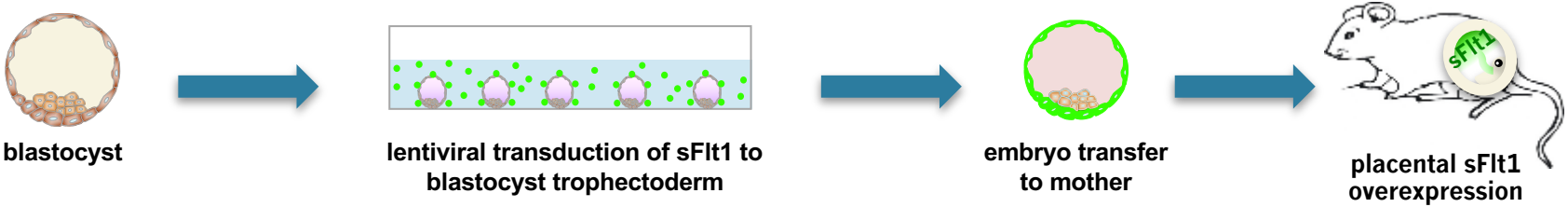
also enhanced antioxidant cytoprotection

New generation antiplatelet agents decrease placental release of anti-angiogenic sFlt-1

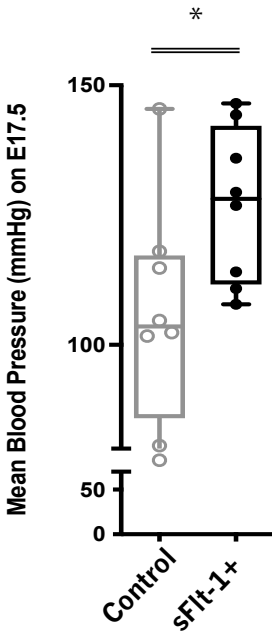
sFLT-1 anti-angiogenic factor associated with preeclampsia

Treatment of first trimester cytotrophoblast also reduced sFLT-1 and increased VEGF

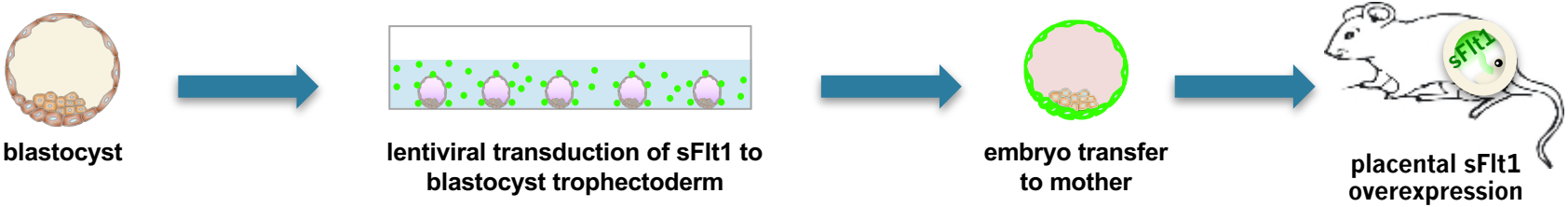
New generation antiplatelet effects in a sFlt-1 overexpression mouse model of preeclampsia



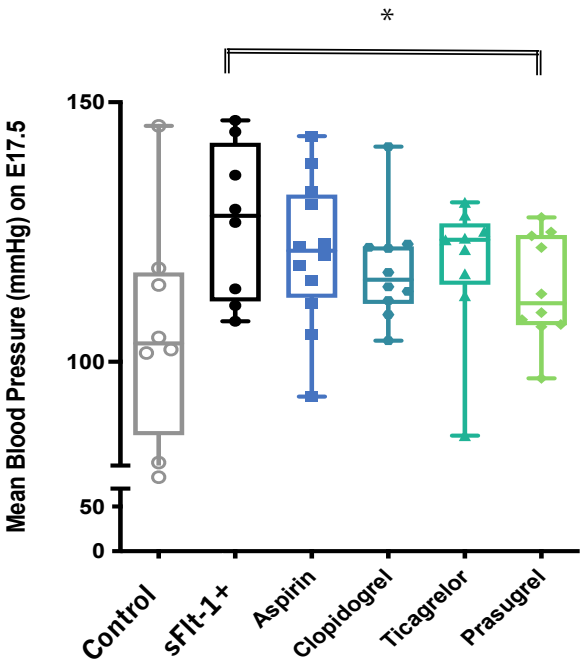
Dr. Natalie Binder

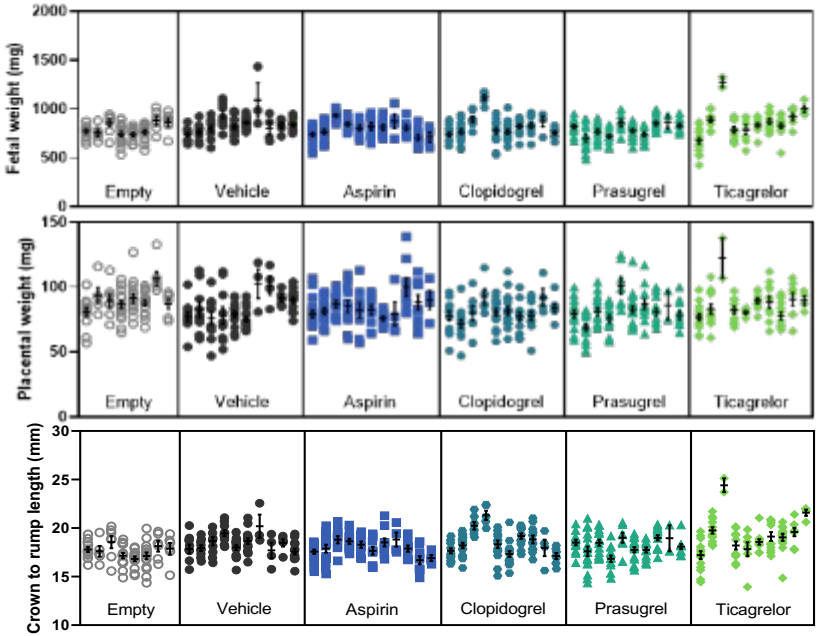


New generation antiplatelet effects in a sFlt-1 overexpression mouse model of preeclampsia

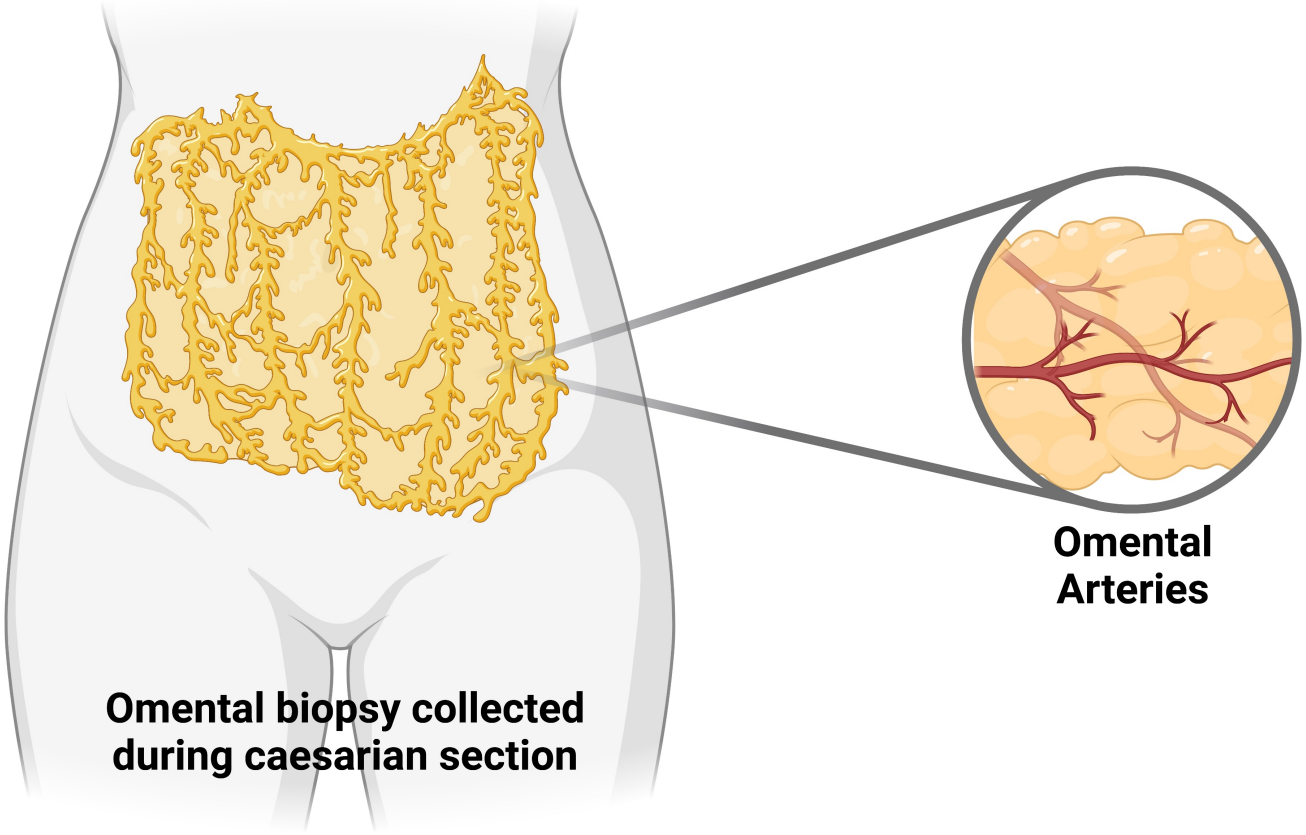


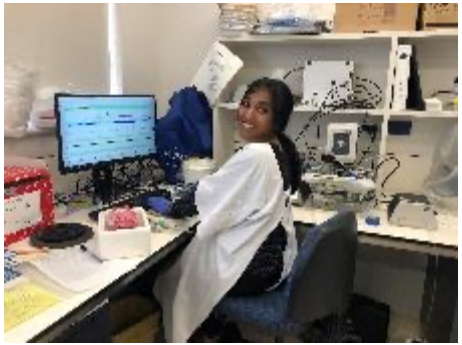
Dr. Natalie Binder





Measuring whole vessel function and response to therapies

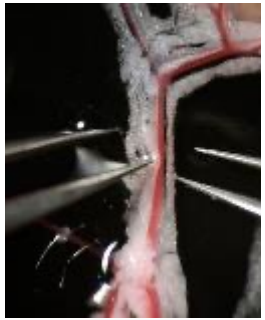


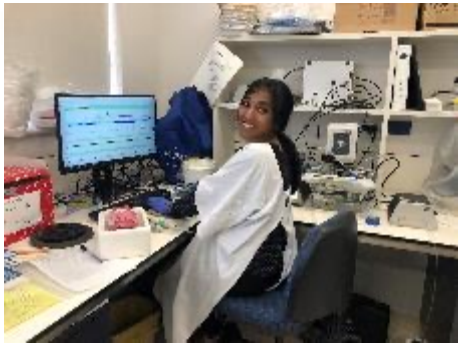


Dr Natasha de Alwis

Measuring whole vessel function and response to therapies

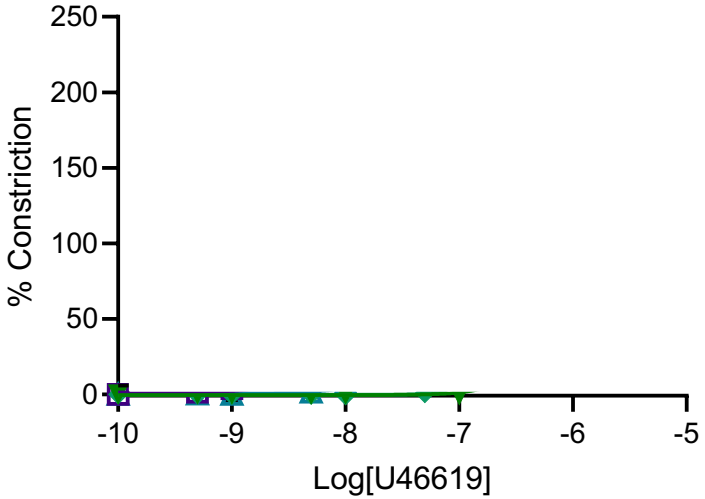
Dissect vessels → Mount vessels + stretch

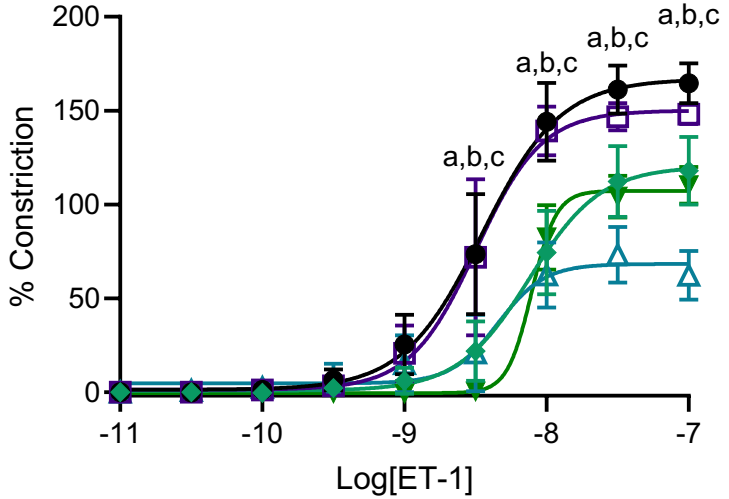




Dr Natasha de Alwis

Can new generation antiplatelet agents reduce vasoconstriction in arteries from preeclamptic pregnancies?

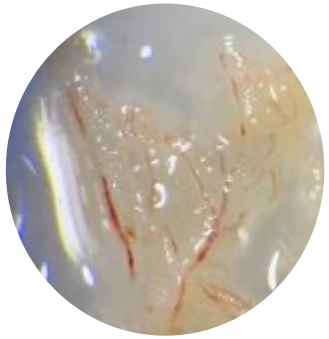


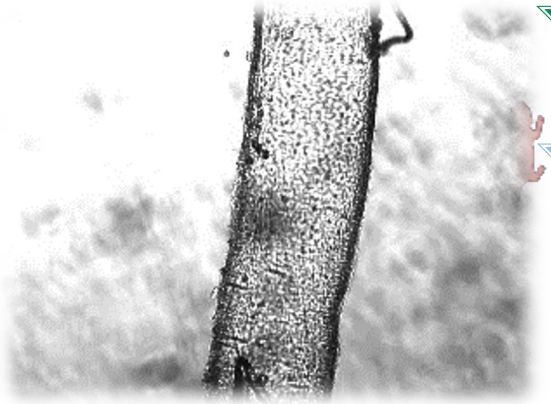


Ctrl Asp Clop Pras Tic

*Significant results: **a** – ctrl vs clop, **b** – ctrl vs pras, **c** – ctrl vs tic. Mean±SEM, n=4-6 patients*

New generation antiplatelet agents have distinct benefits over aspirin; mitigating key pathogenic aspects





- Oxidative stress
- sFLT-1 and pro-inflammatory secretion
- Endothelial dysfunction
- Blood pressure in two mouse models
- Reduced vasoconstriction and enhanced vasorelaxation human vessels from pregnancy

Hunt for drugs safe in pregnancy that can halt pathogenesis of preeclampsia

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Use of Proton-Pump Inhibitors in Early Pregnancy and the Risk of Birth Defects

Björn Pasternak, M.D., Ph.D., and Anders Hviid, Dr.Med.Sci.

Hypertension. 2017 Mar;69(3):457- 468

Preeclampsia

Proton Pump Inhibitors Decrease Soluble fms-Like Tyrosine Kinase-1 and Soluble Endoglin Secretion, Decrease Hypertension, and Rescue Endothelial Dysfunction

Kenji Onda,* Stephen Tong,* Sally Beard, Natalie Binder, Masanaga Muto, Sevvandi N. Senadheera, Laura Parry, Mark Dilworth, Lewis Renshall, Fiona Brownfoot, Roxanne Hastie, Laura Tuohey, Kirsten Palmer, Toshihiko Hirano, Masahito Ikawa, Tu'uhevaha Kaitu'u-Lino, Natalie J. Hannan

Reduced sFlt-1 and inflammatory pathways in preeclampsia models

Attenuated hypertension

(mouse model sFlt-1-e15a placental overexpression)

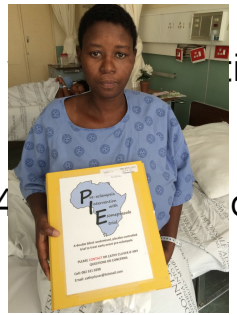
Reduced endothelial and vascular dysfunction

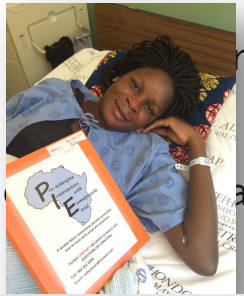
PIE study

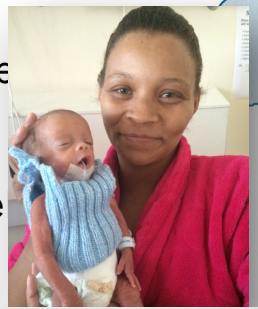
(**P**reeclampsia **I**ntervention with **E**someprazole)

Phase II randomised placebo controlled trial

120 participants







en Tong
n Walker
Mol
Hannan

PE study

ion with Esc

American Journal of Obstetrics and Gynecology
Volume 219, Issue 4, October 2018, Pages 388.e1-388.e17

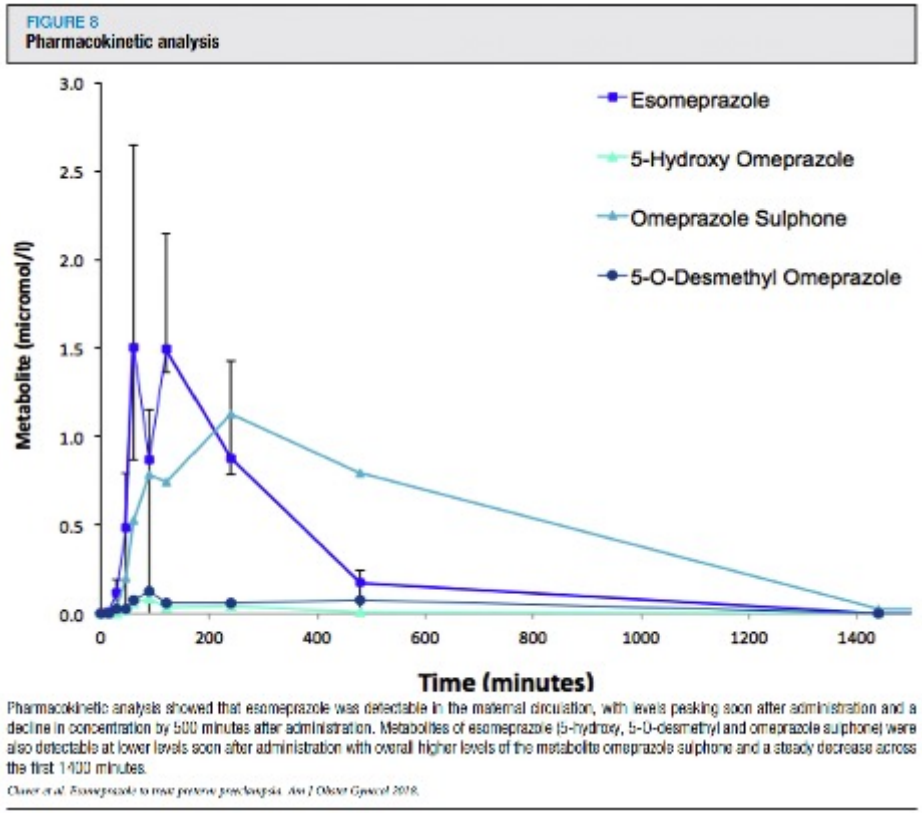
Original Research

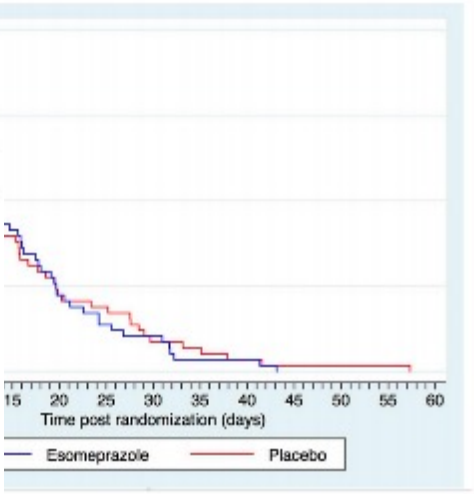
Obstetrics

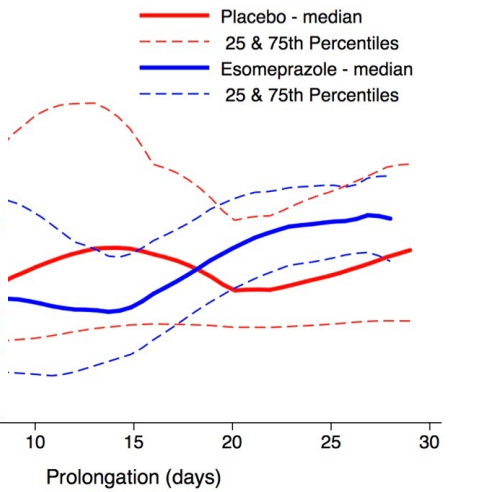
Esomeprazole to treat preterm preeclampsia placebo controlled tri

Presented at the Society for Maternal-Fetal Medicine 28th
Dallas, Texas.

Catherine A. Cluver MMed [a d], Natalie J. H
Richard Hiscock MBBS [f], Sally Beard BSc [d e], Ben
David R. Hall MD [a], Eric H. Decloedt MMed [b], Mc
Megan Rensburg MMed [c], Pawel Schubert MPhil







Cluver et al. AmJOG, 2018

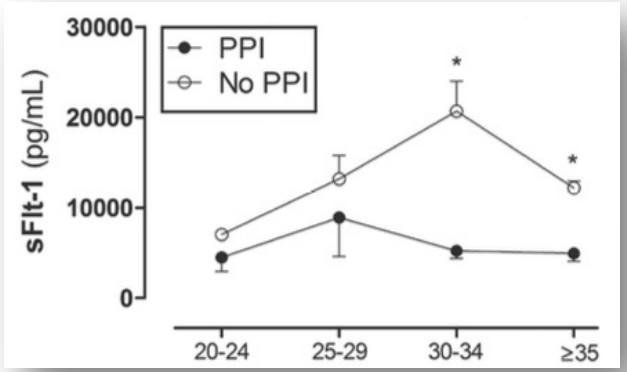
Can you stop the run away train? Is prevention better than cure?

Original Article

Low Soluble Fms-Like Tyrosine Kinase-1, Endoglin, and Endothelin-1 Levels in Women With Confirmed or Suspected Preeclampsia Using Proton Pump Inhibitors

Langeza Saleh, Raaho Samantar, Ingrid M. Garrelds, Anton H. van den Meiracker, Willy Visser, A.H. Jan Danser

Hypertension 2017



Prevention of preeclampsia with esomeprazole

Phase II randomised trial:

Women at high risk for preeclampsia
Aspirin vs. Aspirin + Esomeprazole

Primary Outcome:

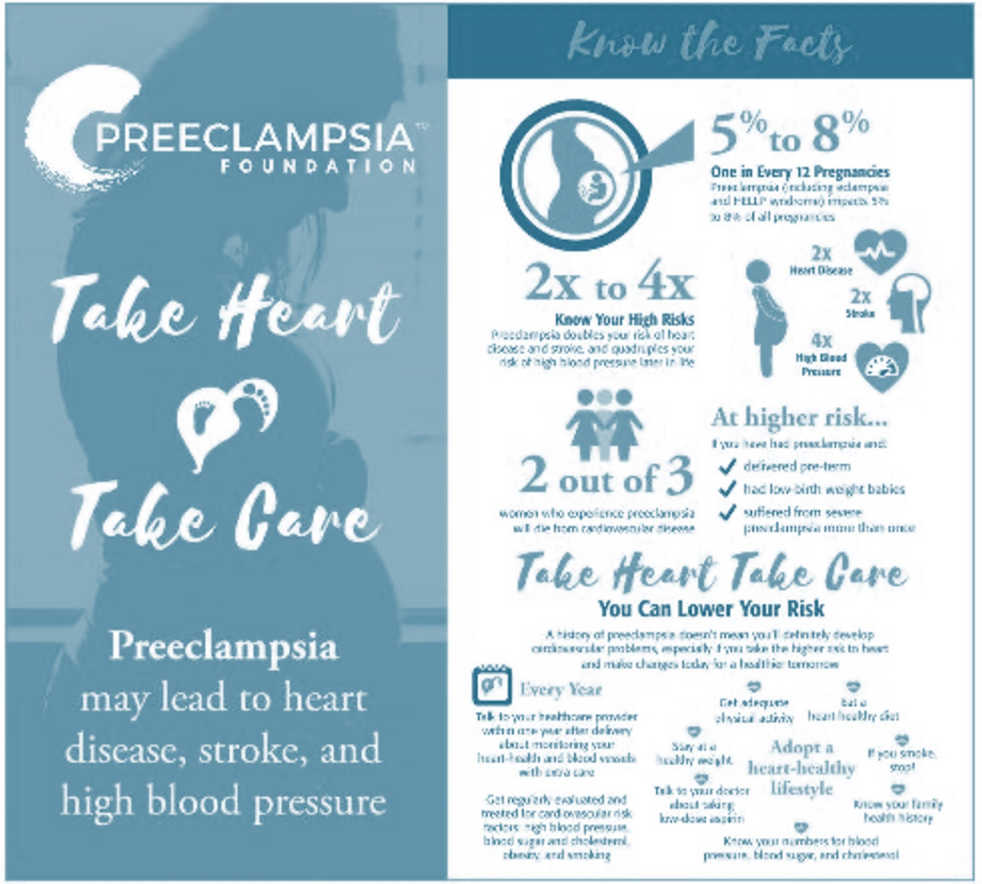
Reduction Mean arterial pressure at 36 weeks gestation

Secondary Outcomes:

1) Reduction in sFlt-1 concentrations at 36 weeks gestation
2) Reduction in severity of proteinuria at 36 weeks gestation
3) Prolong pregnancy
4) Increase in fetal birth weight

The aftermath of preeclampsia: moving on from admiring the problem

>2 - 4-fold ↑ risk of CVD



A mother's risk of future cardiovascular disease following preeclampsia: is early detection and prevention possible?

NHMRC Ideas Grant

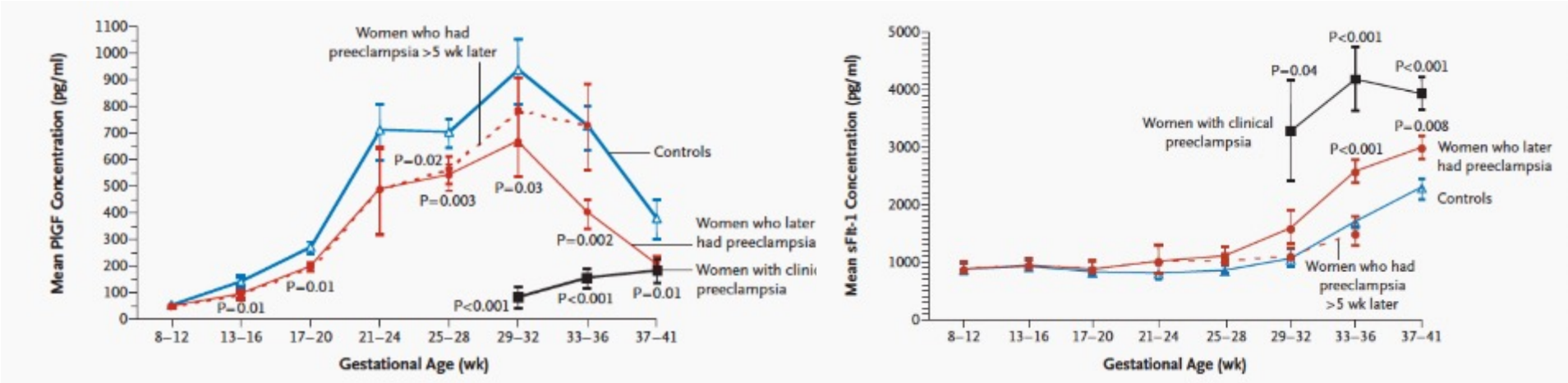
Circulating transcriptome & **cardiometabolic protein profile** following preeclampsia

combine these findings with non-invasive cardiovascular tests to determine diagnostic utility

BEYOND SMALL MOLECULE DRUGS TO TACKLE PREECLAMPSIA

Circulating markers of preeclampsia

⬇ PlGF: ⬆ sFlt-1



Levine et al, N Engl J Med. 2004 Feb 12;350(7):672-83

Reduce circulating sFlt1 to treat preeclampsia

Circulation

American Heart Association.

Pilot Study of Extracorporeal Removal of Soluble Fms-Like Tyrosine Kinase 1 in Preeclampsia

Ravi Thadhani, MD, MPH; Tuelay Kisner, MD*; Henning Hagmann, MD*; Verena Bossung, MD; Stefanie Noack, RN; Wiebke Schaarschmidt, MD; Alexander Jank, MD; Angela Kribs, MD; Oliver A. Cornely, MD; Claudia Kreyssig, MD; Linda Hemphill, MD; Alan C. Rigby, PhD; Santosh Khedkar, PhD; Tom H. Lindner, MD; Peter Mallmann, MD; Holger Stepan, MD; S. Ananth Karumanchi, MD; Thomas Benzing, MD

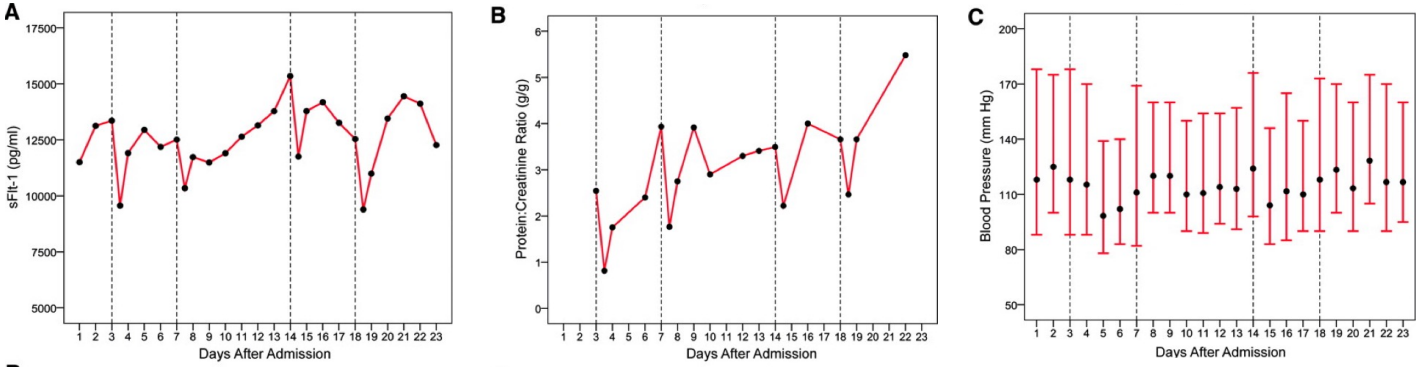
In vitro – 80-85% reduction in sFlt-1

What about in pregnant women?

Apheresis to remove sFlt1 to treat preeclampsia

35, primip, 27+4 admitted for pre-term preeclampsia
Blood pressure: 177/95 Protein creatine: 2.3

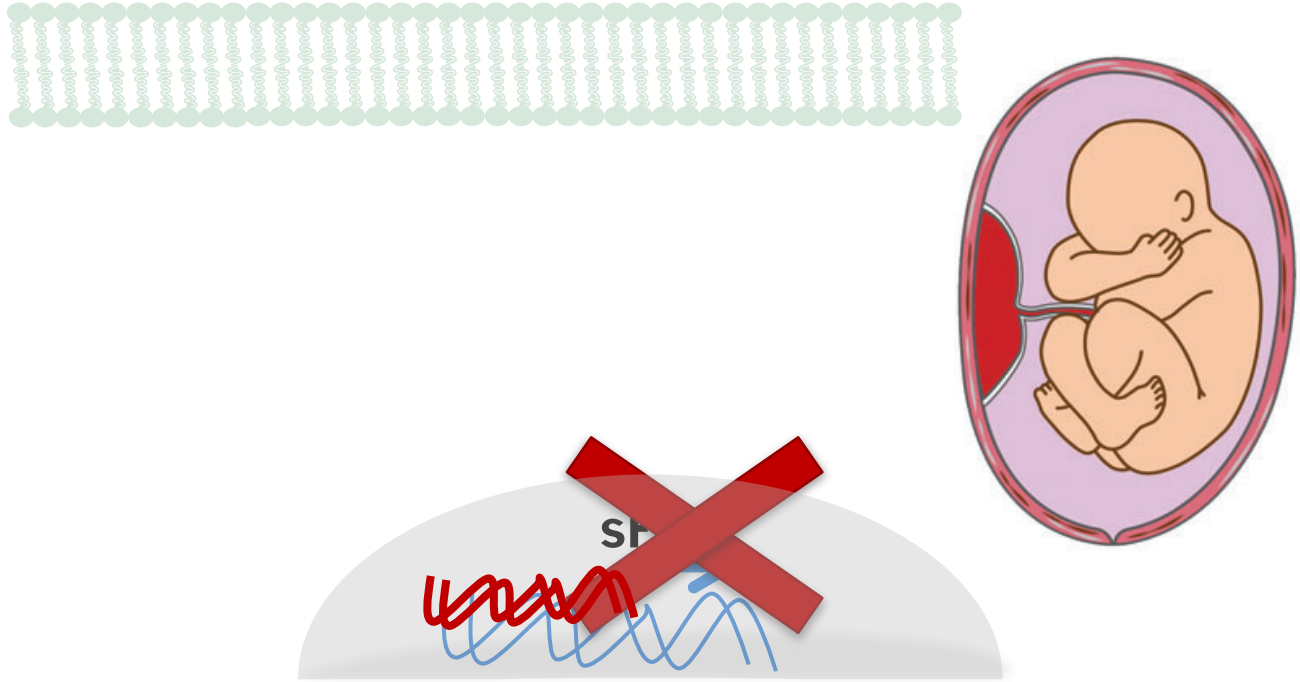
Circulating sFlt1 | Proteinuria | Blood pressure



Prolongation of 23 days; delivered at 30+6 weeks

Thadhani et al, 2011, Circulation

Block production of sFlt-1 by the preeclamptic placenta?



Directly block the production of sFlt1 to reduce to aberrant levels

Molecular Therapy
Nucleic Acids
Original Article

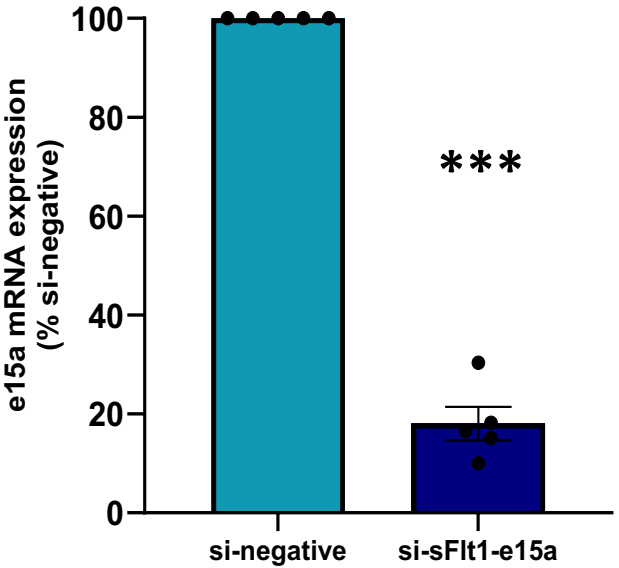
Chemical optimization of siRNA for safe and efficient silencing of placental sFLT1

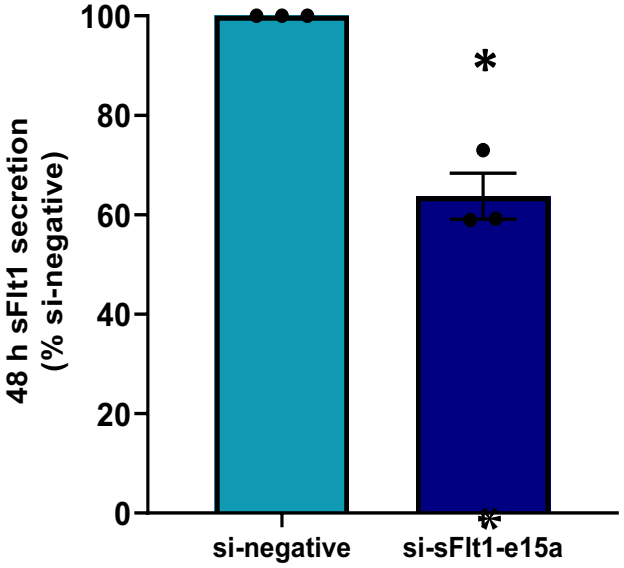
Sarah M. Davis,[1,7] Vignesh N. Hariharan,[1,7] Agnes Lo,[2,3,7] Nicholas McHugh,[1] Annabelle Biscans,[1] Julia F. Altermar and Anastasia Khvorova[1,6]

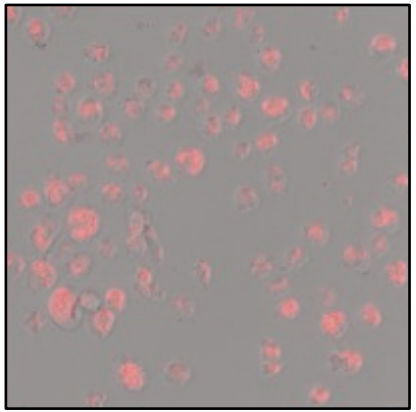
RNAi Modulation of Placental sFLT1 for the Treatment of Preeclampsia.

Anton A. Turanov[#1], Agnes Lo[#2,3], Matthew R. Hassler[#1], Angela Makris[#4,5,6], Ami Ashar-Patel[1], Julia F. Alterman[1], Andrew H. Coles[1], Reka A. Haraszti[1], Loic Roux[1], Bruno MDC Godinho[1], Dimas Echeverria[1], Suzanne Pears[4], Jim Iliopoulos[5], Renuka Shanmugalingam[4,5,6], Robert Ogle[7], Zsuzsanna K. Zsengeller[2,3], Annemarie Hennessy[4,5], S. Ananth Karumanchi[2,3,8], Melissa J. Moore[1,9], and Anastasia Khvorova[1,10]

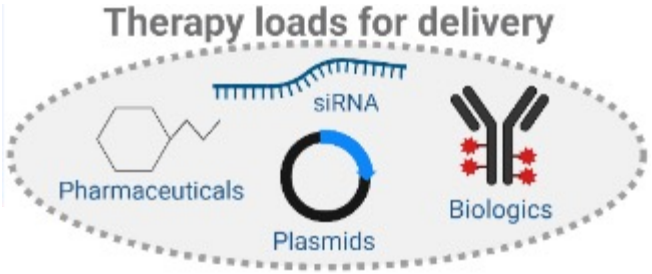
Silencing RNA reduces sFlt1 expression and release from human primary trophoblast







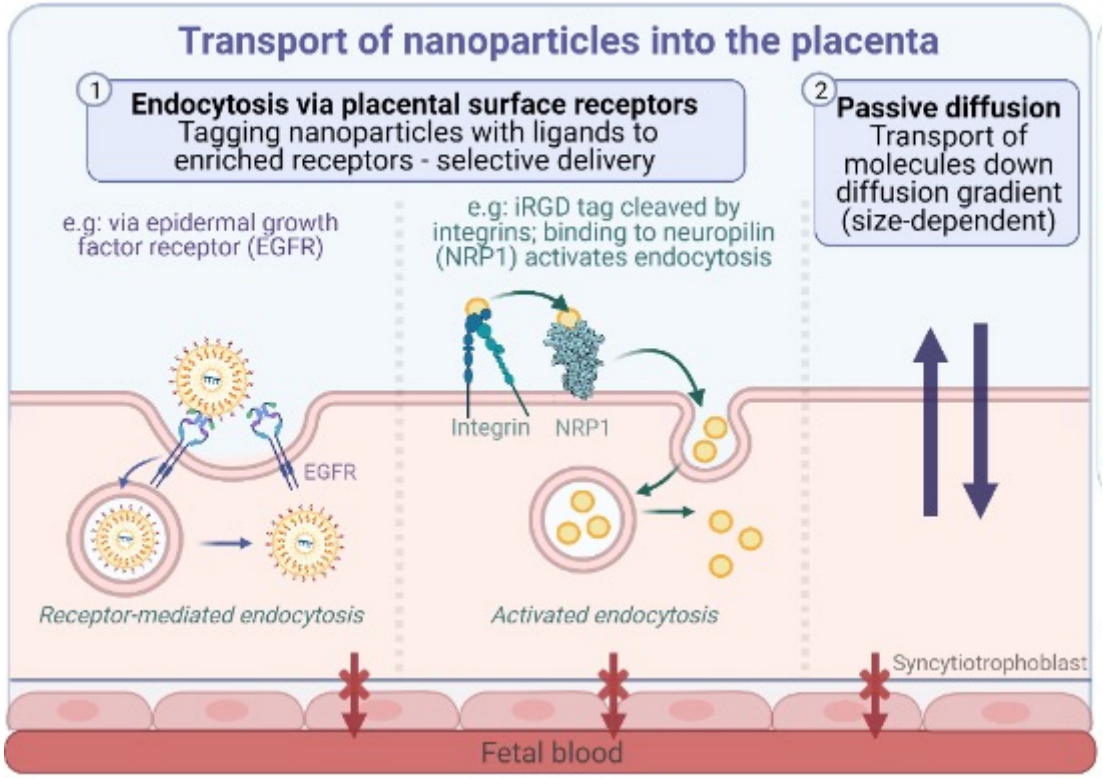
Nanomedicine in Pregnancy: the next frontier in the treatment of preeclampsia



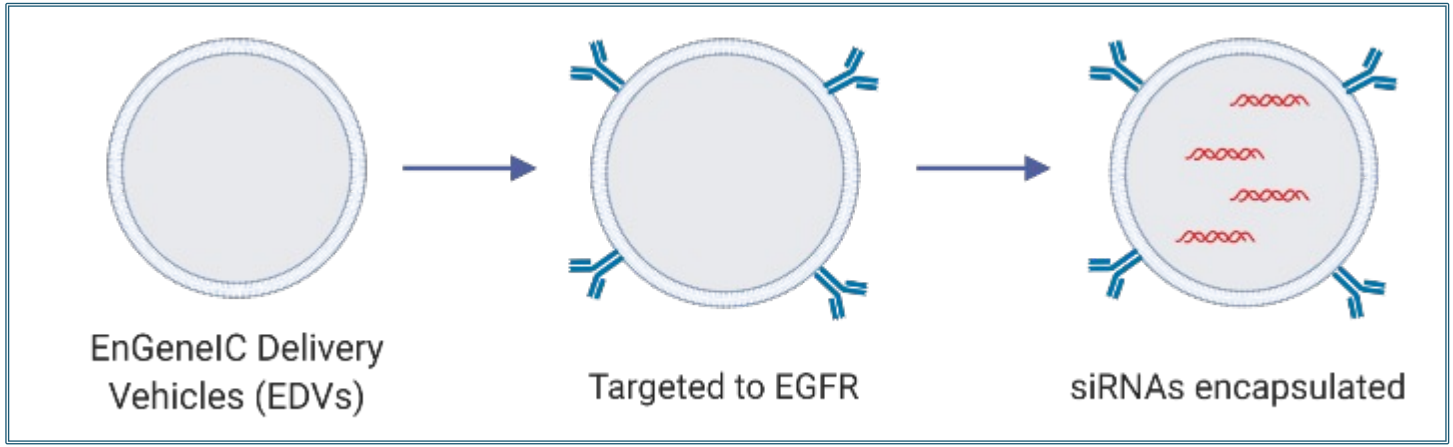
Lower therapeutic is required compared to systemic administration

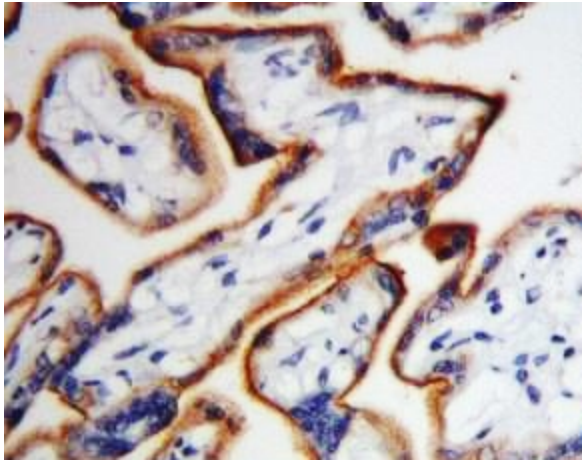
Therapeutic is protected from breakdown

Reduces patient side effects

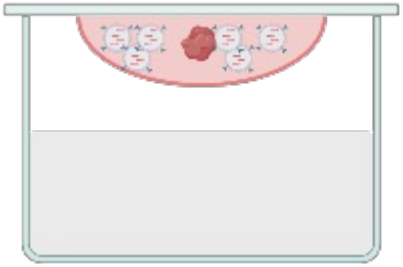


Pritchard et al., Hum Repro Update. 2021 2021 Feb 19;27(2):280-304;
de Alwis N et al., Trends Mol Med. 2021 Aug;27(8):824-825

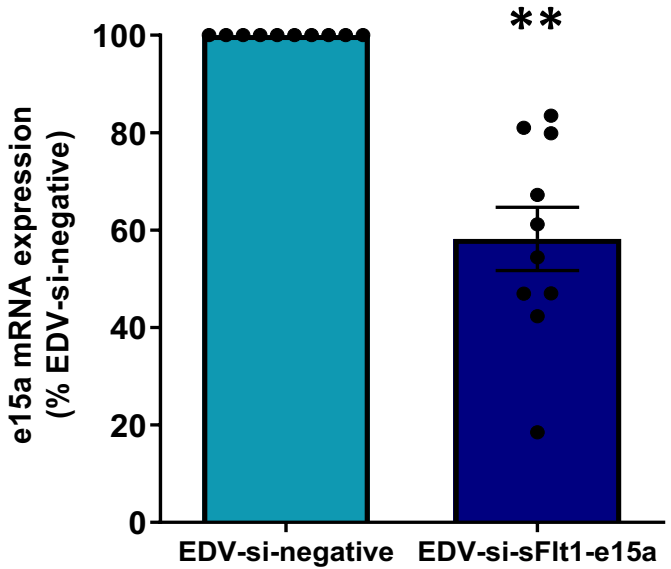

EnGeneIC Delivery Vehicles (EDVs)
Targeted to EGFR
siRNAs encapsulated

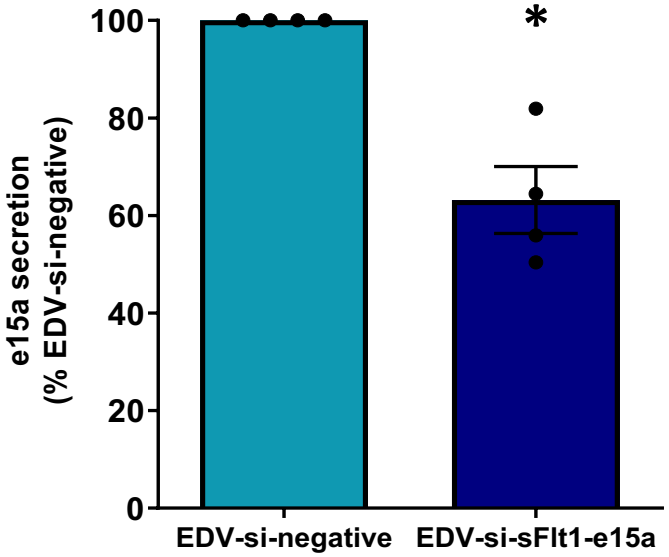


Nanoparticles to deliver silencing RNA to block sFlt1 release from the preeclamptic placenta

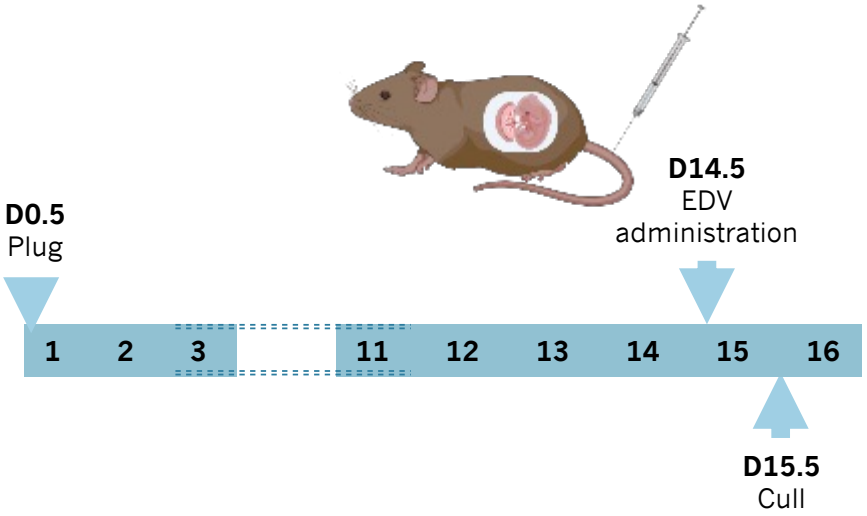


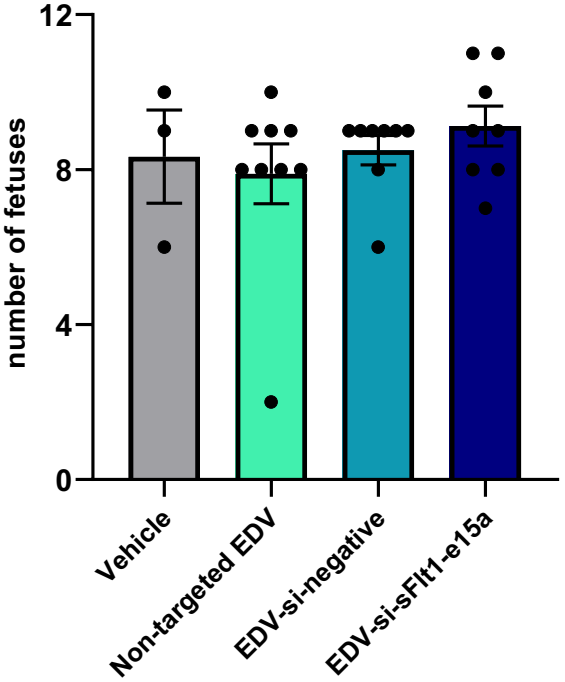
Placental explant tissue culture with EDVs



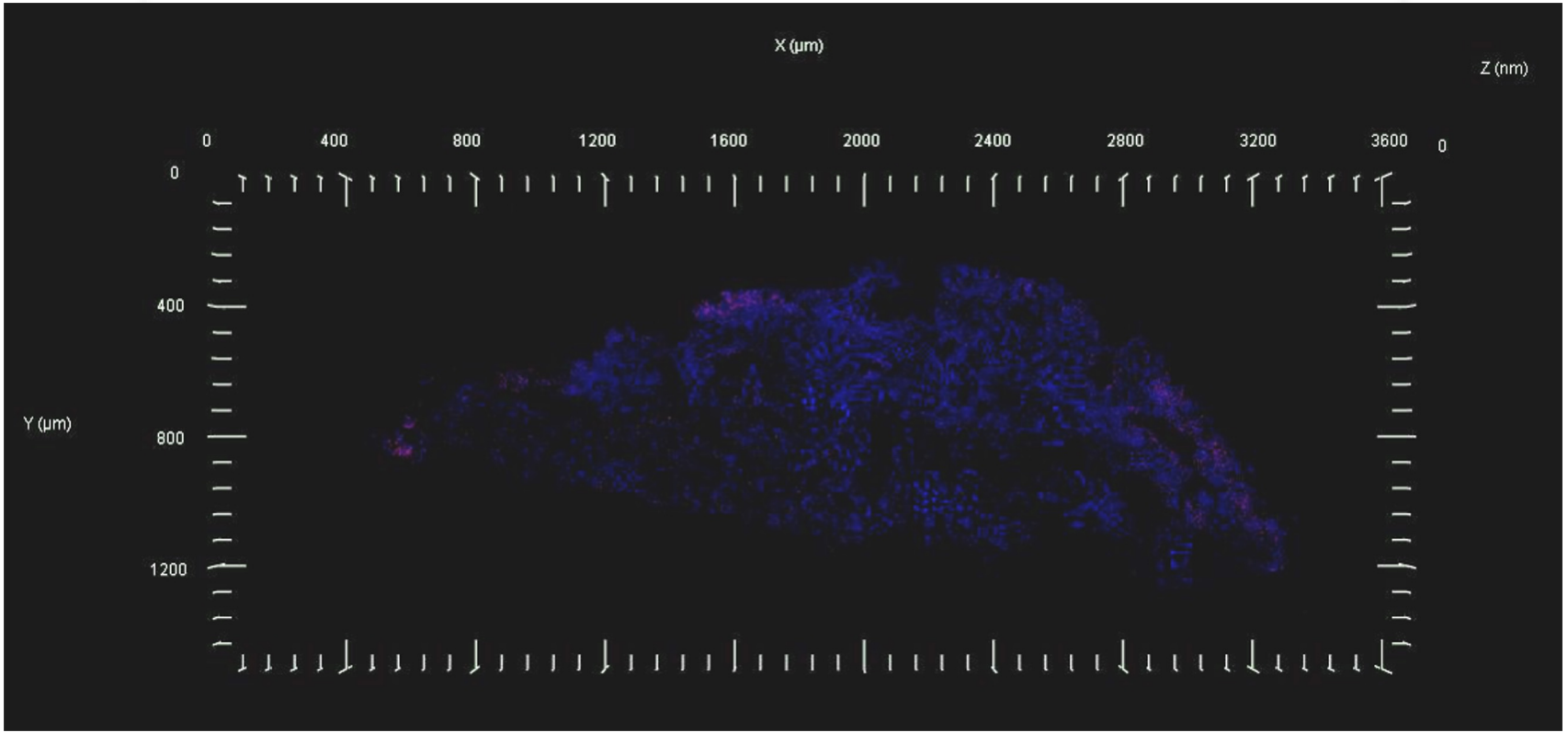


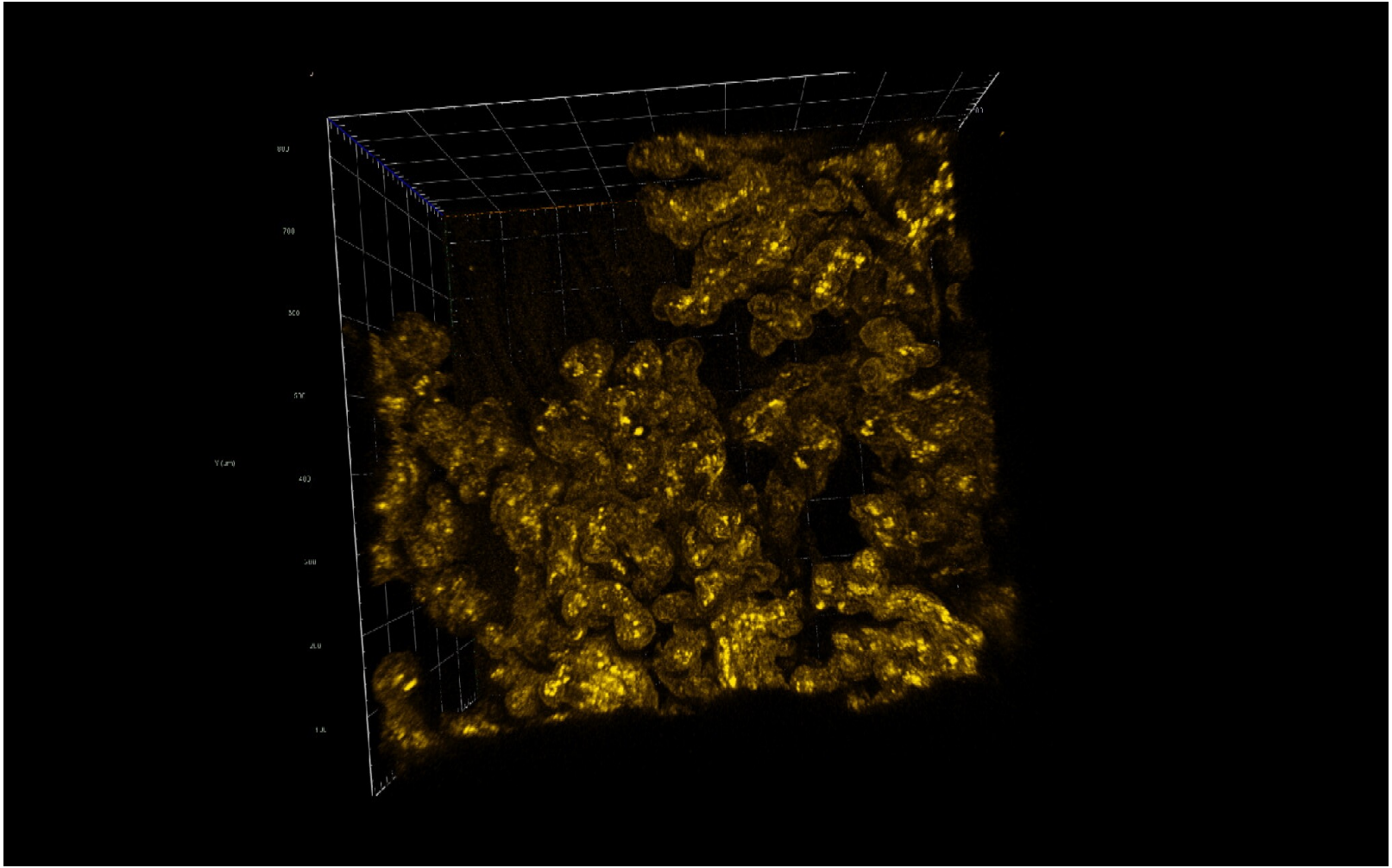
In vivo delivery of siRNA via nanoparticles to the mouse placenta



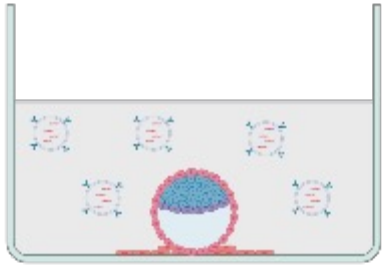


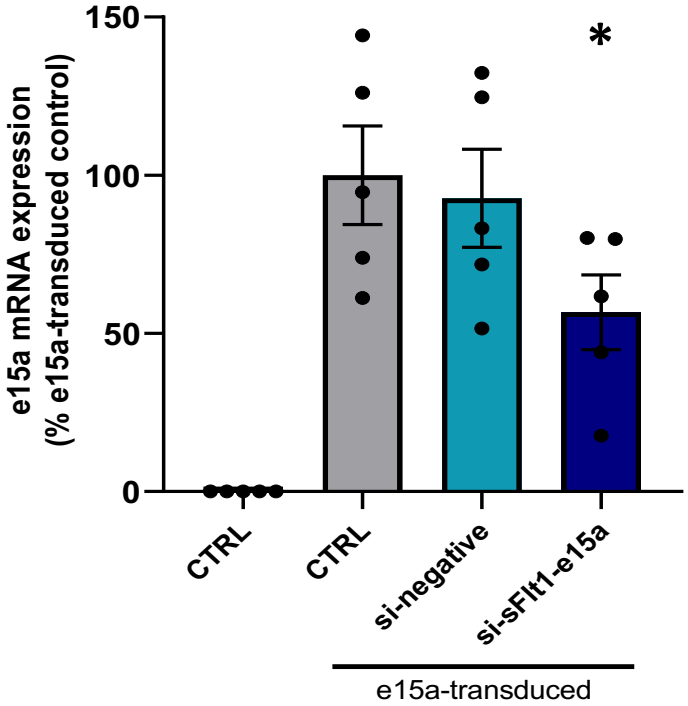
In vivo delivery to the mouse placenta

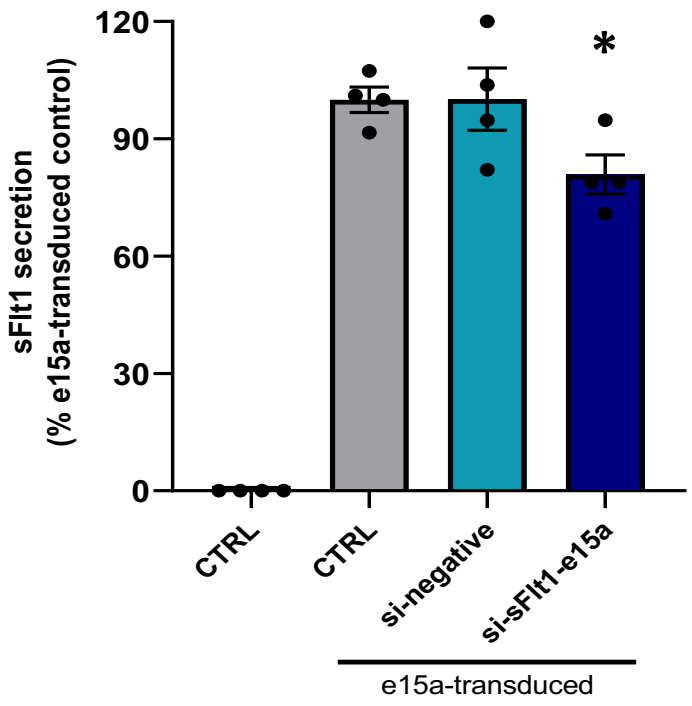




Nanoparticles to deliver siRNA to block sFlt1 production and release from mouse blastocyst







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mercy perinatal

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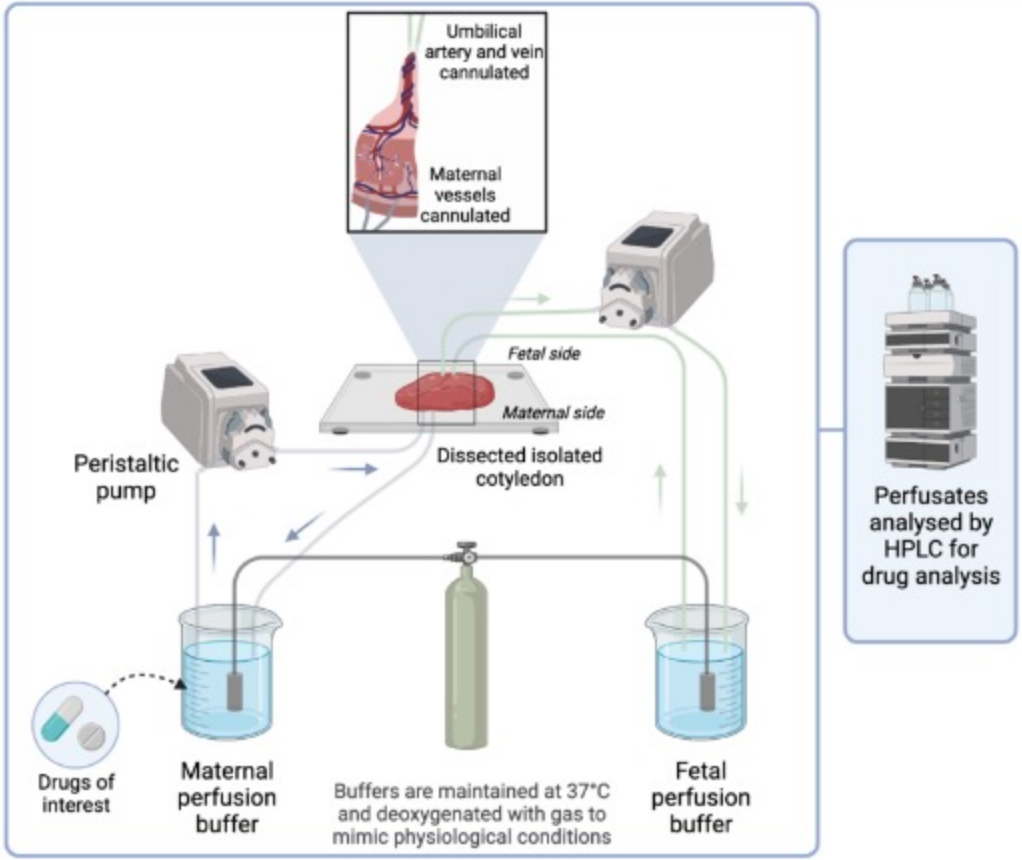
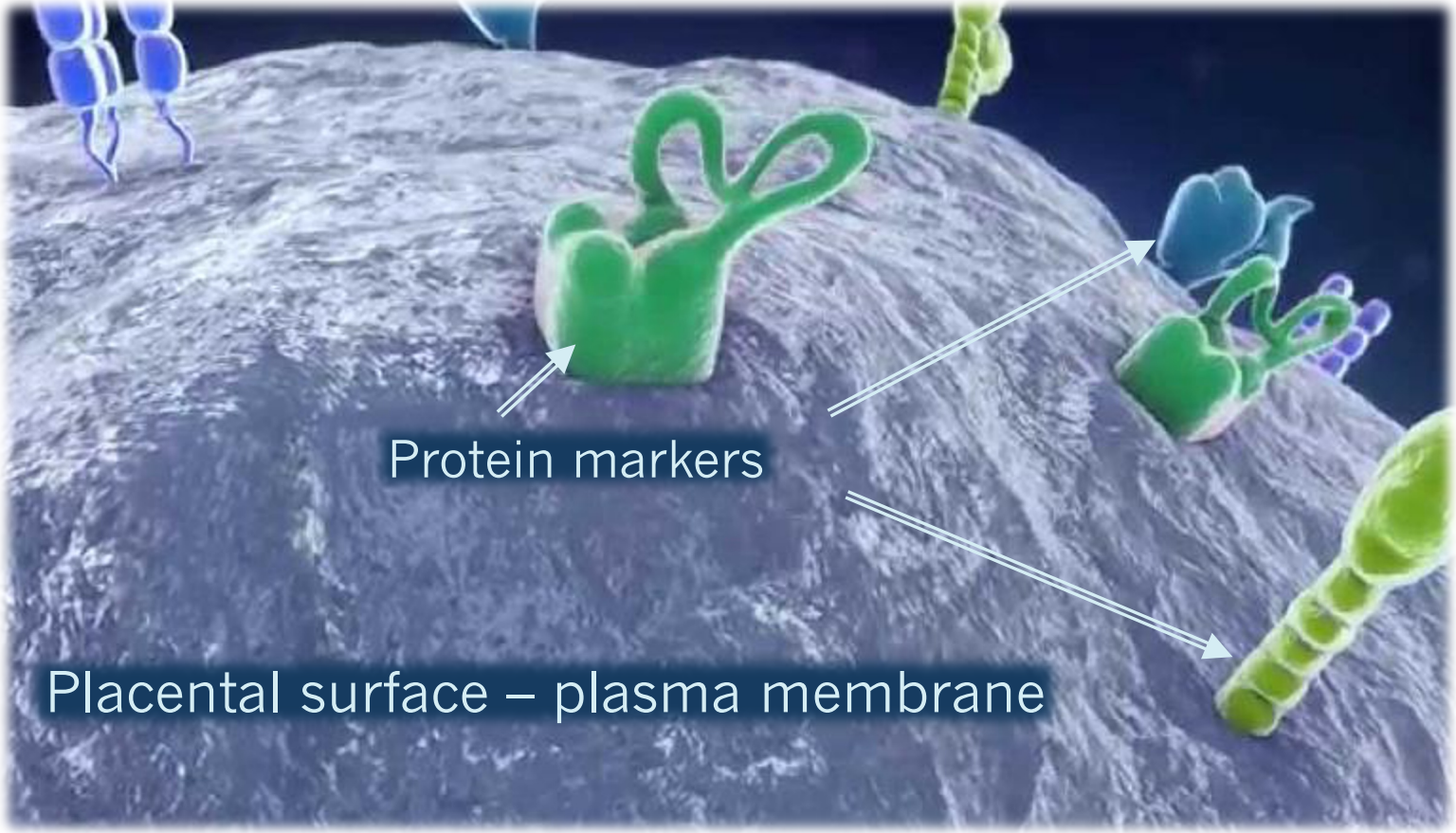
mercy perinatal

SOMANZ

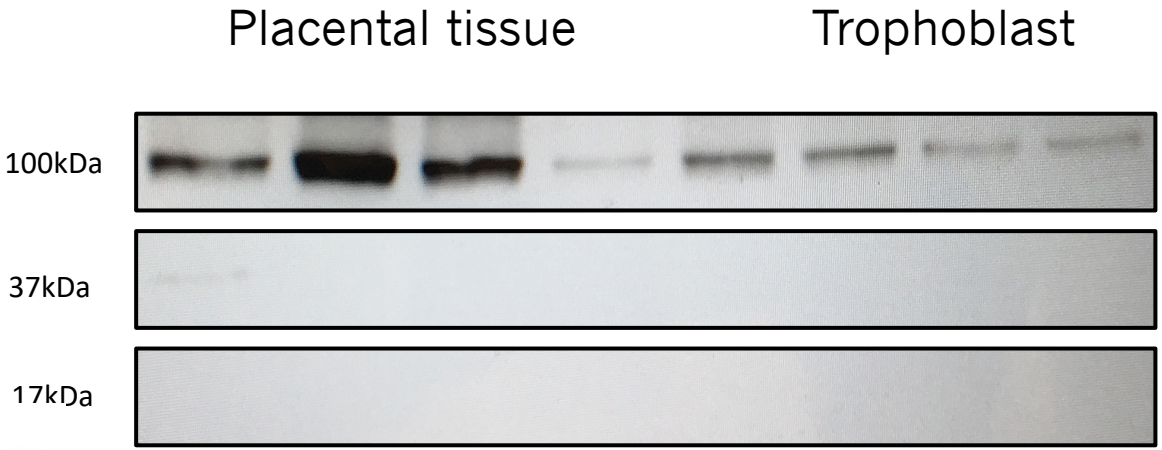
Dual placental perfusion model to evaluate where therapeutics go



Surface plasma membrane – rich in placental specific markers



Surface plasma membrane extraction – to enrich targeting

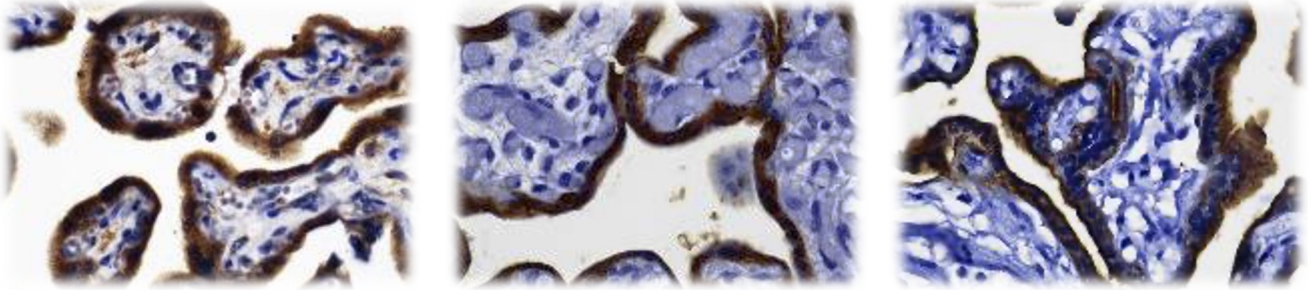


Sodium potassium ATPase
Plasma membrane marker

GAPDH
Cytosol marker

Histone H3
Nuclear marker

Proteomics – identify most abundant plasma membrane proteins



Nanoparticles to target RNAi to the preeclamptic placenta

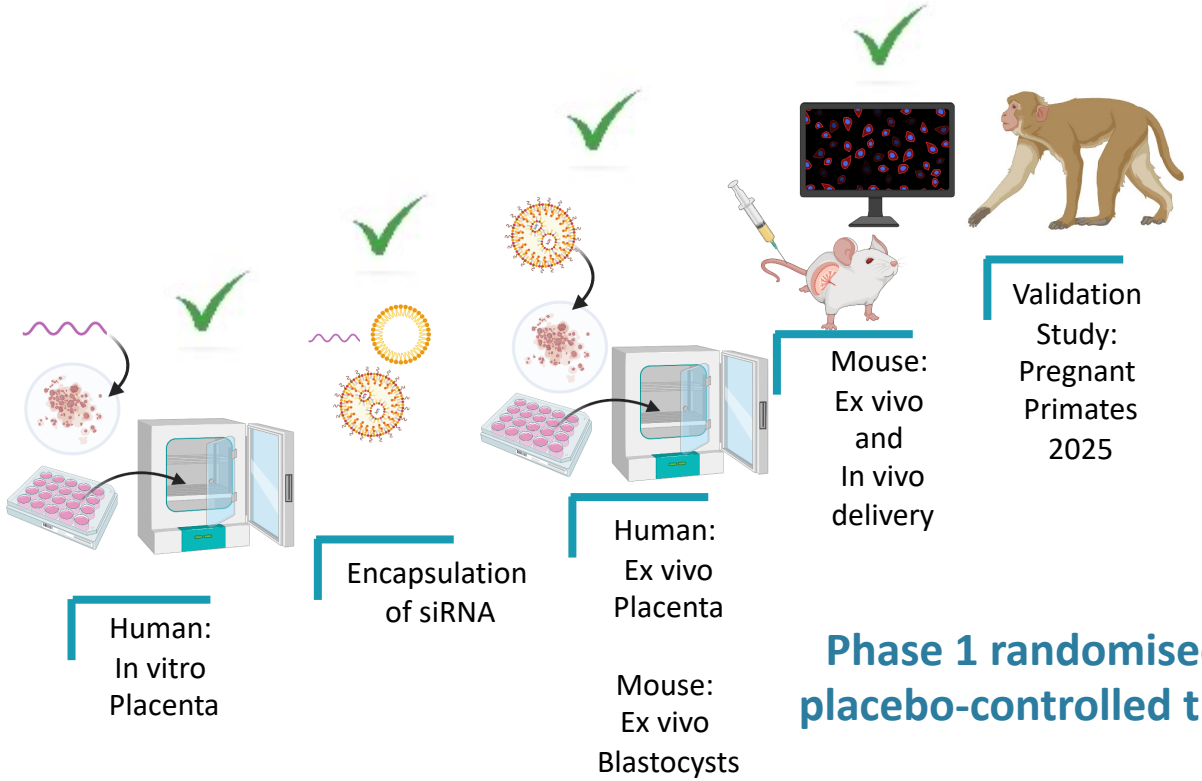
Developed RNAi to block sFlt1

RNAi taken up by placenta

Placental gene expression of sFlt1

Secretion of sFlt1

Delivery of RNAi to the mouse placenta



Human: In vitro Placenta

Encapsulation of siRNA

Human: Ex vivo Placenta

Mouse: Ex vivo Blastocysts

Mouse: Ex vivo and In vivo delivery

Validation Study: Pregnant Primates 2025

Phase 1 randomised placebo-controlled trial