The Wonderful World of the Placenta…

…How it Works, What Can Go Wrong, and using Nanomedicines to Fix It

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Learning Objectives

- Discuss the placental structure and function in humans
- Articulate how a poorly functioning placenta can cause pregnancy complications such as pre-eclampsia, fetal growth restriction, and stillbirth
- Analyze the risks involved in using medicines during pregnancy while exploring approaches to help reduce these risks.

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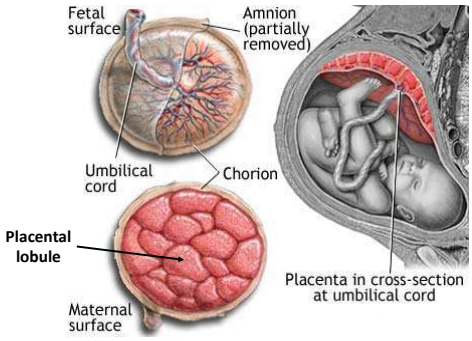
The placenta: basic structure and function



- Nutrient and oxygen transport
- Waste removal
- Barrier to infection and toxic substances
- Produces hormones

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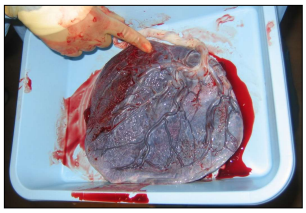
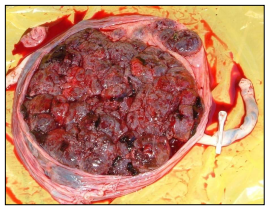
The placenta: "gross" anatomy





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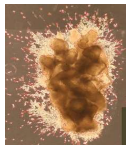
The placenta: microscopic anatomy

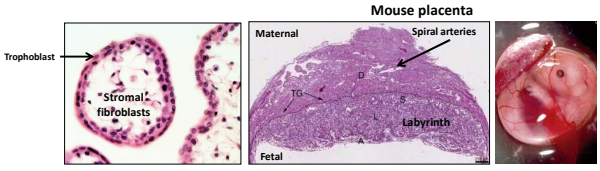
First trimester placenta

Gilbert-Barness et al. (2014). The Placenta. Handbook of Pediatric Autopsy Pathology. Springer NY



Cultured in the lab

Mouse placenta



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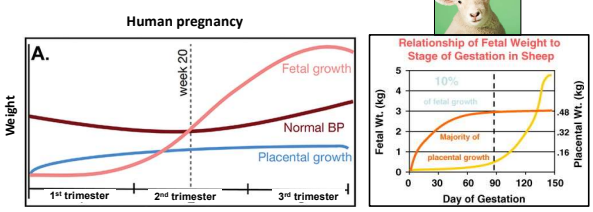
Fetal growth depends on placental growth



Adapted from Hollegaard et al. (2013) PLOS ONE 8(2): e56821

Redmer et al. (2004) Domestic Animal Endocrinology 27(3): 199-217

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Why should we study the placenta?

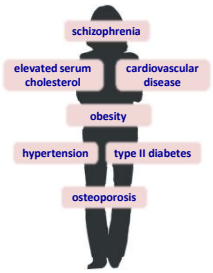
Infertility (10-15% of couples)

- Miscarriage 1:4 pregnancies

Pregnancy complications

- Preterm birth <37 weeks (10%)
- Fetal growth restriction (7%)
- Pre-eclampsia (7%)
- Macrosomia > 4kg (1-10%)
- Stillbirth (5.8%)

Short term consequences



Long term consequences: development programming

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The placenta: what can go wrong

- Many pregnancy complications are linked to poor placental growth and/or function
- A placenta may be:

Too small	→	give drugs to promote growth
Bad at transporting nutrients	→	give drugs to aid nutrient exchange
Not receiving enough blood	→	give drugs to increase blood flow
Aging prematurely	→	give drugs to mend the damage

We know that improving placental function helps the baby to grow better…so let's make medicines to treat the placenta!

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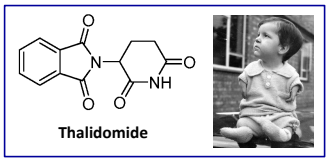
Why is it so difficult to make new medicines for pregnant women?



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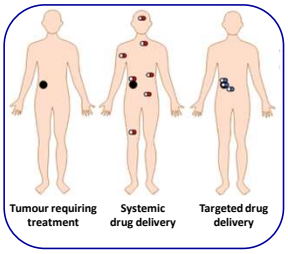
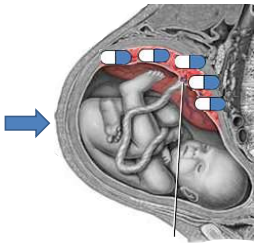
How can we address these problems?

Lessons from tumour drug delivery…





Adapted from Vrettos et al. (2018) *J. Org. Chem.* 2018, *14*, 930.

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How do we achieve targeted drug delivery?

<u>Targeted drug delivery</u>

…when a drug is selectively delivered <u>only to its site of action</u> and not to any other cells or tissues

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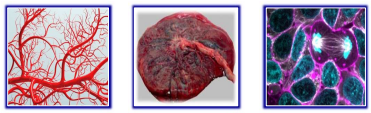
How does it work?

- We can target specific sites within the body, if we know their postcode



Blood vessels | Organs | Cells

- The drug is "hidden" in an envelope, so it only acts at its final destination → Fewer side effects!
- Less drug is needed overall, but the local concentration is higher → More effective treatment!

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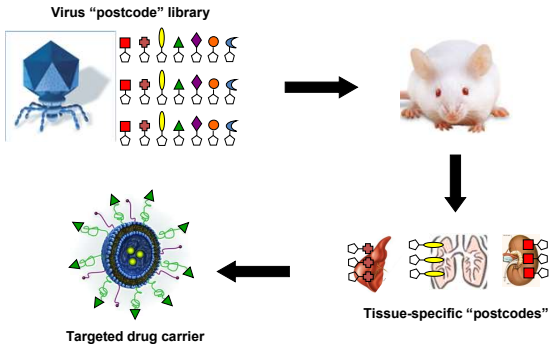
Discovering the placental postcode



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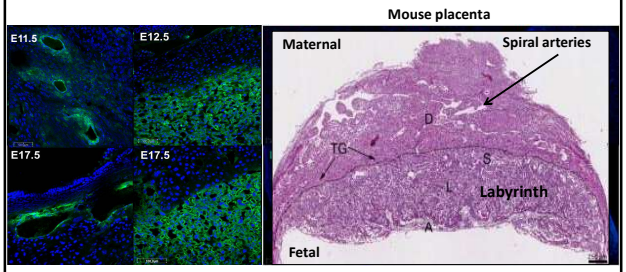
Postcode binding to mouse placenta



Fluorescent postcode (FAM-iRGD)

Nuclei

King at al. (2016). Science Advances. 2, 5, e1600349

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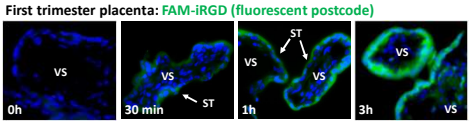
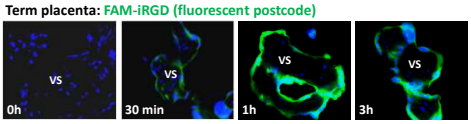
Postcode binding to human placenta

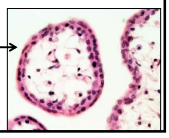
First trimester placenta: FAM-iRGD (fluorescent postcode)



Term placenta: FAM-iRGD (fluorescent postcode)



Placental trophoblast cells



King at al. (2016). Science Advances. 2, 5, e1600349

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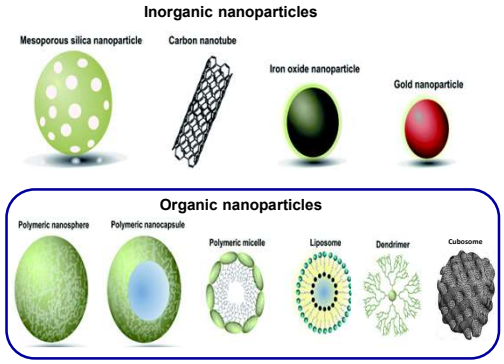
How do we make the envelope?



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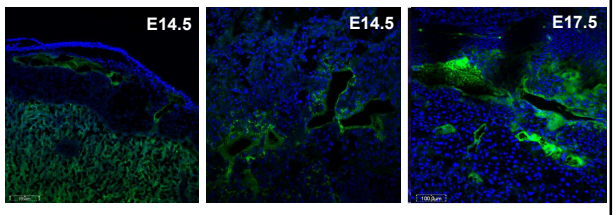
Attaching the postcode to the envelope

Iron oxide nanoworms (180nm)

Lipid micelles (15nm)



Postcode-labelled nanoworms

DAPI

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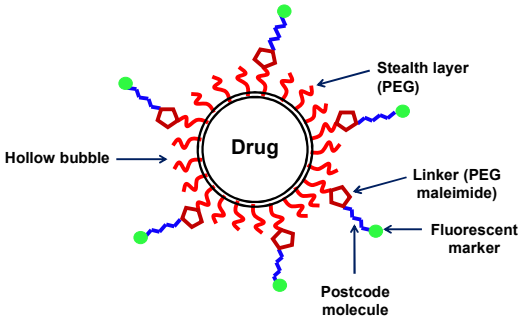
Final design of the nanomedicine



150-200 nanometers in diameter

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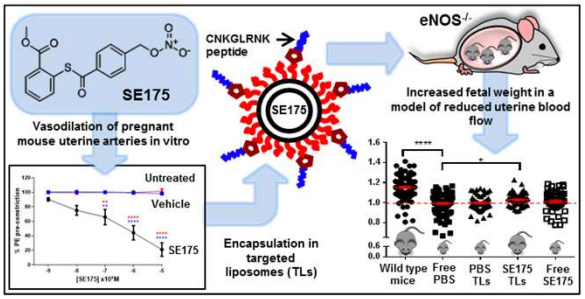
Targeted delivery of a drug to improve placental blood supply



Cureton et al. (2017) Selective Targeting of a Novel Vasodilator to the Uterine Vasculature to Treat Impaired Uteroplacental Perfusion in Pregnancy. Theranostics. 7, 3715-3731.

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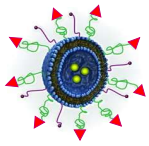
Targeted nanomedicines to improve pregnancy outcome

Targeted drug delivery



Mouse and human models

- [i] Improving placental growth and function
- [ii] Improving blood flow to the womb
- [iii] Controlling drug delivery in pregnancy

Treating placental disease

- Increased fetal / placental weights
- Enhanced placental nutrient transport
- Protection from oxidative stress
- Reduced side effects in mom and baby

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Consider donating your placenta for research!

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