Interventions aiming to treat fetal growth restriction
and
the EVERREST EU-project

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Fetal Growth Restriction

- Complicates ~8% of pregnancies (severe 1:500)
- Major cause of perinatal mortality & morbidity
- No effective treatment
- Outcome dependent on gestational age
- Early-onset severe IUGR associated with **reduced uterine blood flow**

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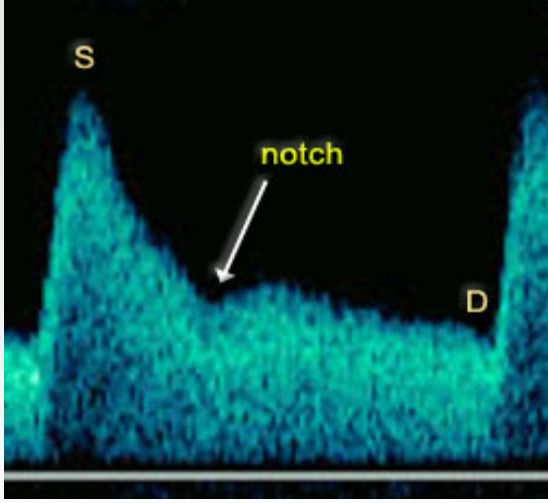
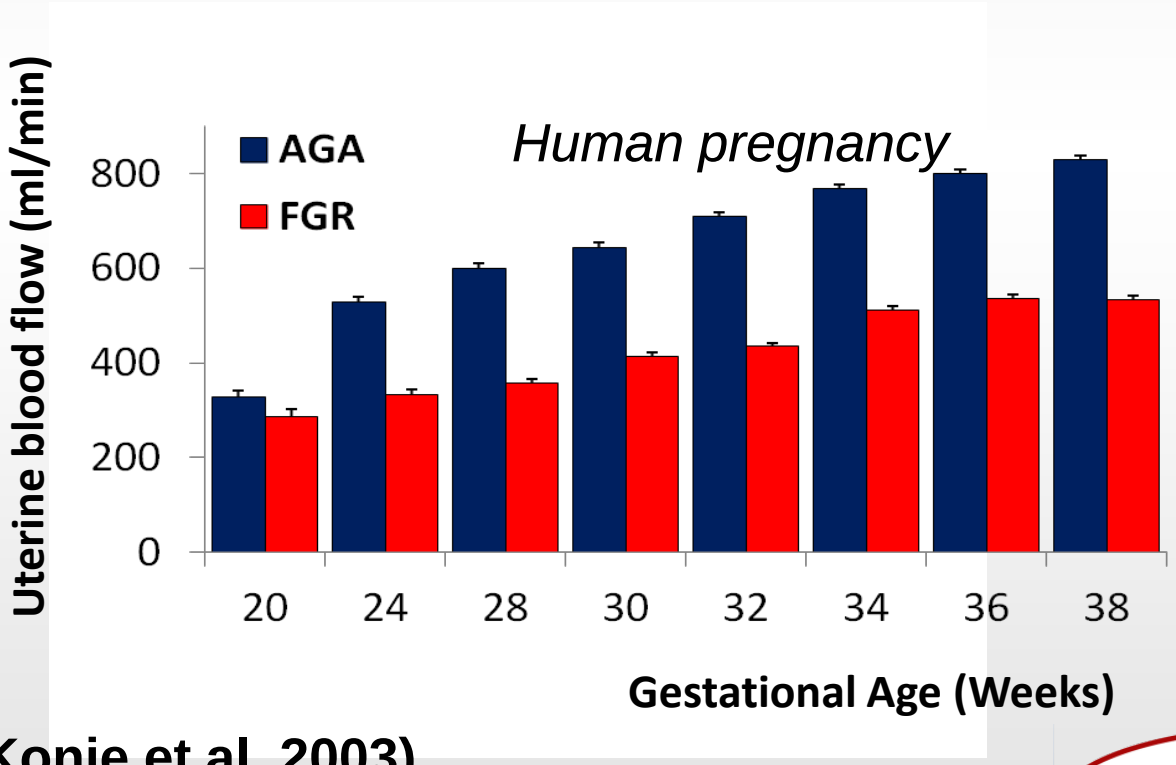
Uteroplacental perfusion

Uteroplacental blood flow is proportional

to fetal size

Uteroplacental insufficiency





(Konje et al. 2003)

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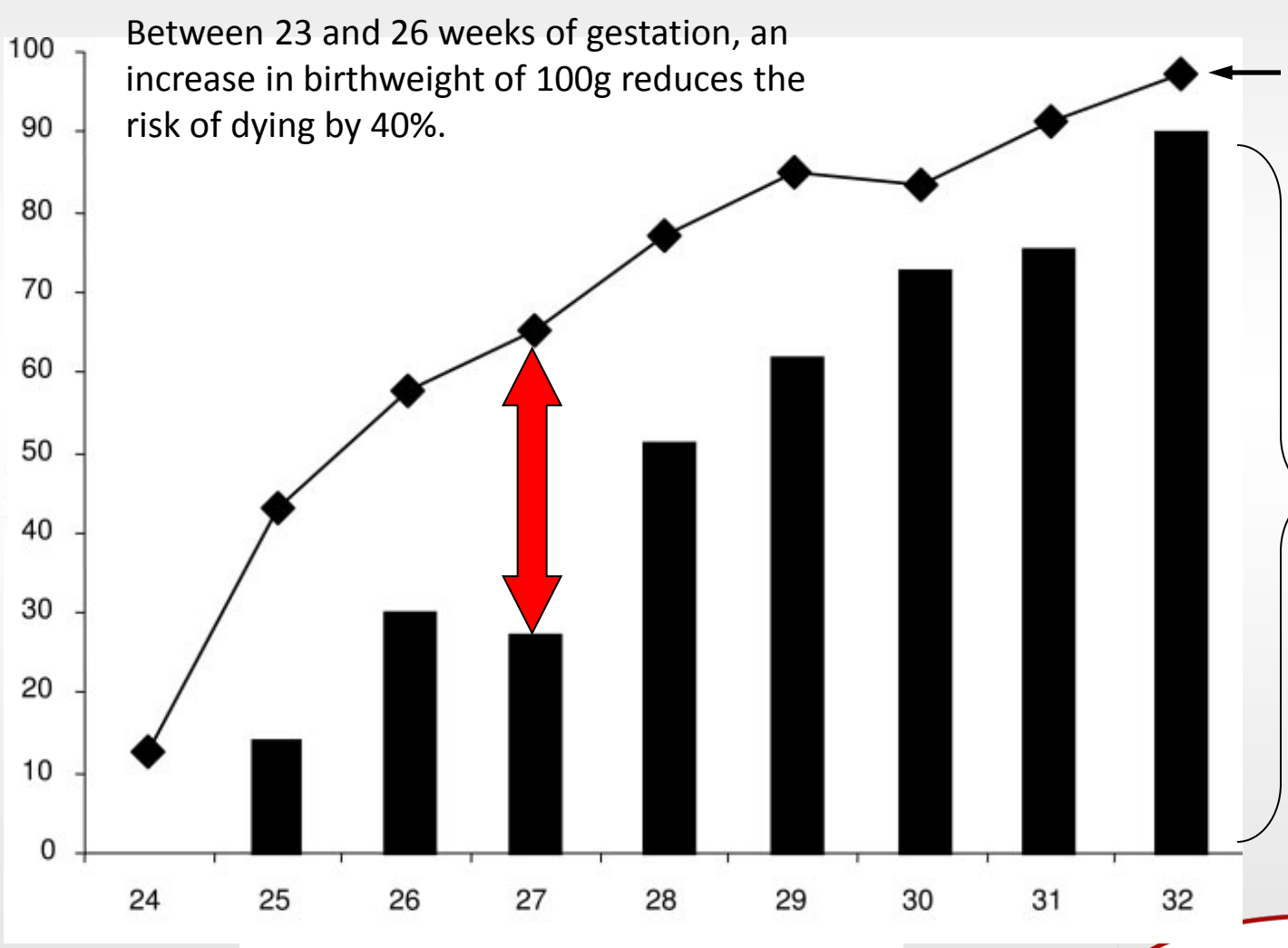
Neonatal outcome in fetal growth restriction



Baschat et al 2007

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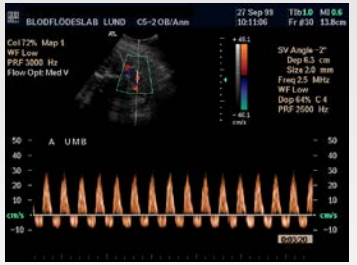
Very preterm IUGR – high survival:

- Lund / Malmö 90%
- TRUFFLE study 94 %

HOWEVER

- both the short-term and long-term morbidity is considerably high !

- cognitive impairment
- behavioural disturbances
- reduced lung function
- changes in cardiovascular function



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Early-onset IUGR

Postnatal growth stimulation of IUGR infants difficult.

It is desirable to improve fetal growth and to prolong pregnancy.

Need for intrauterine therapy.

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Therapies that do not work

- Bedrest
- Maternal oxygen supplementation
- Maternal nutritional supplements
- Low-dose aspirin
- β-mimetics (RCTs show no effect)
- Calcium channel blockers
- Plasma volume expansion
- Vitamin C

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Interventions aimed at increasing uterine blood flow

L-arginine (aminoacid, nitric oxide donor)

- Maternal intravenous infusions
- L-arginine readily available and safe in pregnant women, however, conflicting data on increase in birth weight
- Currently not recommended for treatment of IUGR

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Interventions aimed at increasing uterine blood flow

Sildenafil citrate (nitric oxide donor)

- Temporary smooth muscle relaxation in vessels
- Works in animal models and tested in humans
- In severe, early-onset IUGR thrice daily maternal treatment with 25 mg sildenafil until delivery = ↑ AC growth velocity
- Randomized controlled trial data required

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Growth hormone treatment

- Animal models
- Maternal and fetal supplementation
- Risk of adverse effects (hydranencephaly in fetuses)

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Insulin-Like Growth Factor-1 (IGF-1)

- Implicated in regulation of normal placental function and of appropriate fetal and postnatal growth

- Anabolic effect, stimulates substrate uptake and inhibits protein breakdown

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IGF-1 treatment

Maternal

Guinea pigs

- Increased placental mass and functional capacity of placenta = ↑ fetal growth
- Significant effects on maternal physiology

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IGF-1 treatment

Fetal infusion

Sheep and non-human primates

- Increased aminoacid utilization and alteration in fetal protein accretion
- Adequate substrate supply necessary for effective tissue growth
- Organ specific increases in growth, however no significant effect on body size and growth

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IGF-1 treatment

Intra-amniotic

Sheep

- Increased total fetal growth rate and organ growth in growth restricted fetal sheep
- Up-regulates placental amino acid transporters
- Promising approach (?)

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Vascular Endothelial Growth Factor (VEGF)

Maternal uterine artery VEGF gene therapy

...and the EVERREST study

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VEGF → angiogenesis
vasodilatation
vascular protection

Vascular Endothelial Growth Factor

VEGF implicated in trophoblast invasion

Over-expression of sFlt1 in pregnant mice using adenovirus causes PE-like syndrome & IUGR

Pre-eclampsia

↓

sFlt-1 ↑

↓

VEGF ↓
PlGF ↓
endothelial dysfunction

IUGR

↓

Reduced endothelial derived vasodilatation

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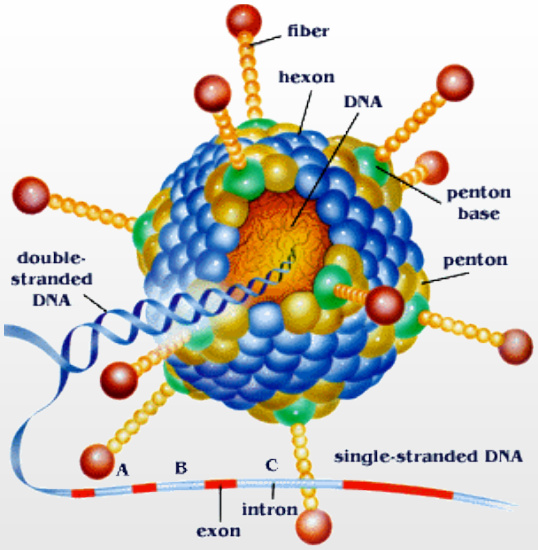
Gene therapy……

….uses genetic material as a drug delivery vehicle to facilitate the expression of therapeutic proteins



- ✓ Achieve targeted protein expression
  - Uteroplacental circulation
- ✓ Short term protein expression
  - Adenovirus vectors

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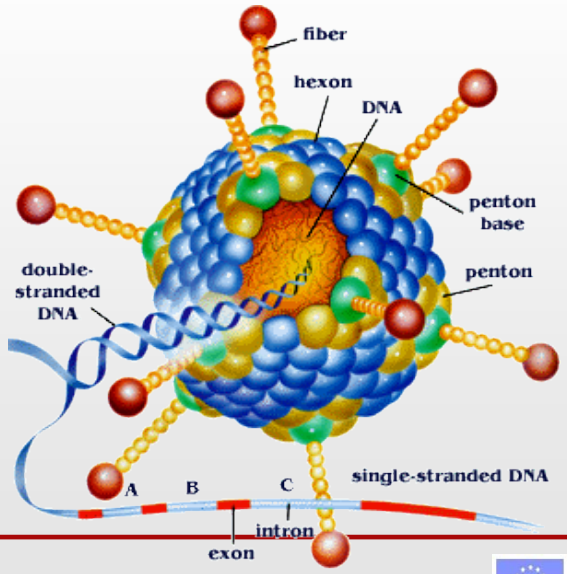
VEGF levels are reduced in fetal growth restriction

Sustained local levels of VEGF will treat fetal growth restriction



"Maternal growth factor gene therapy"

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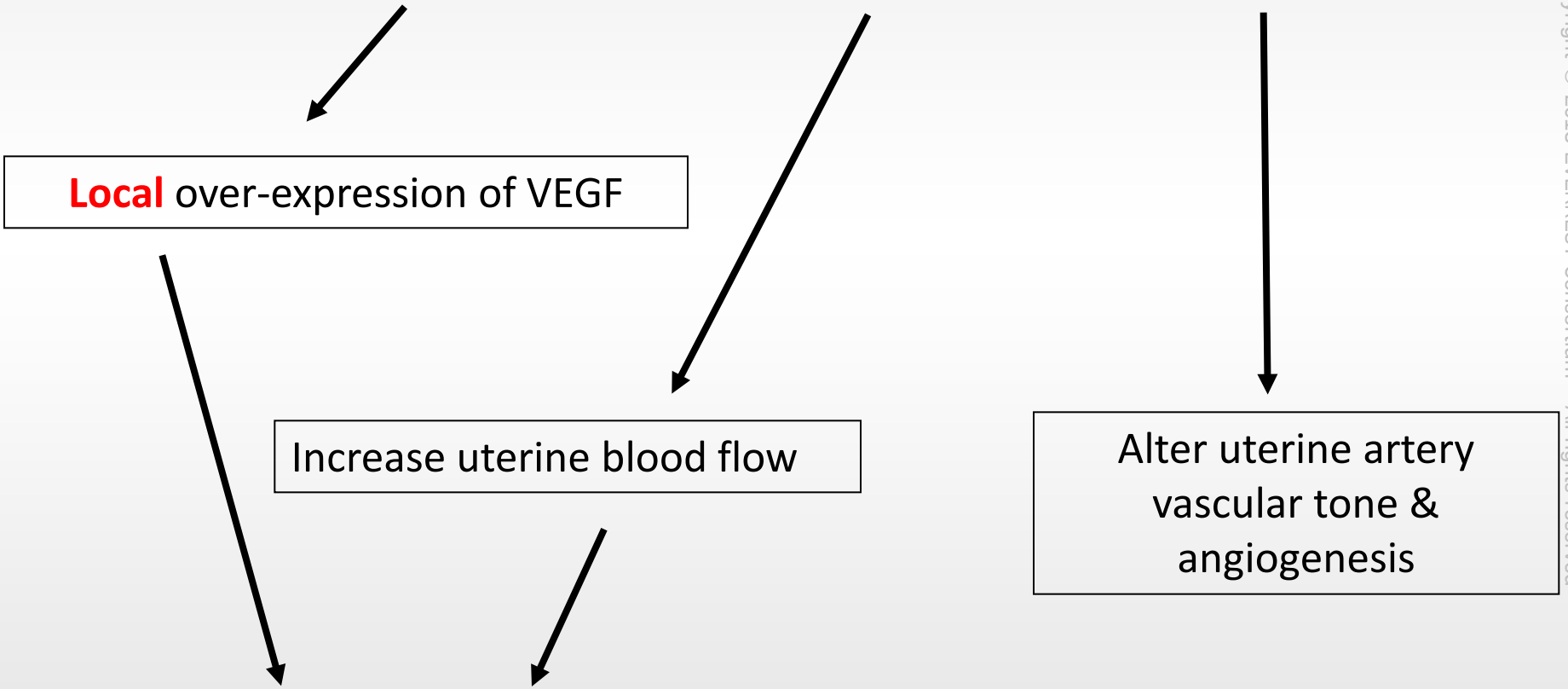
Hypothesis

Delivery of adenovirus containing VEGF gene to uteroplacental circulation



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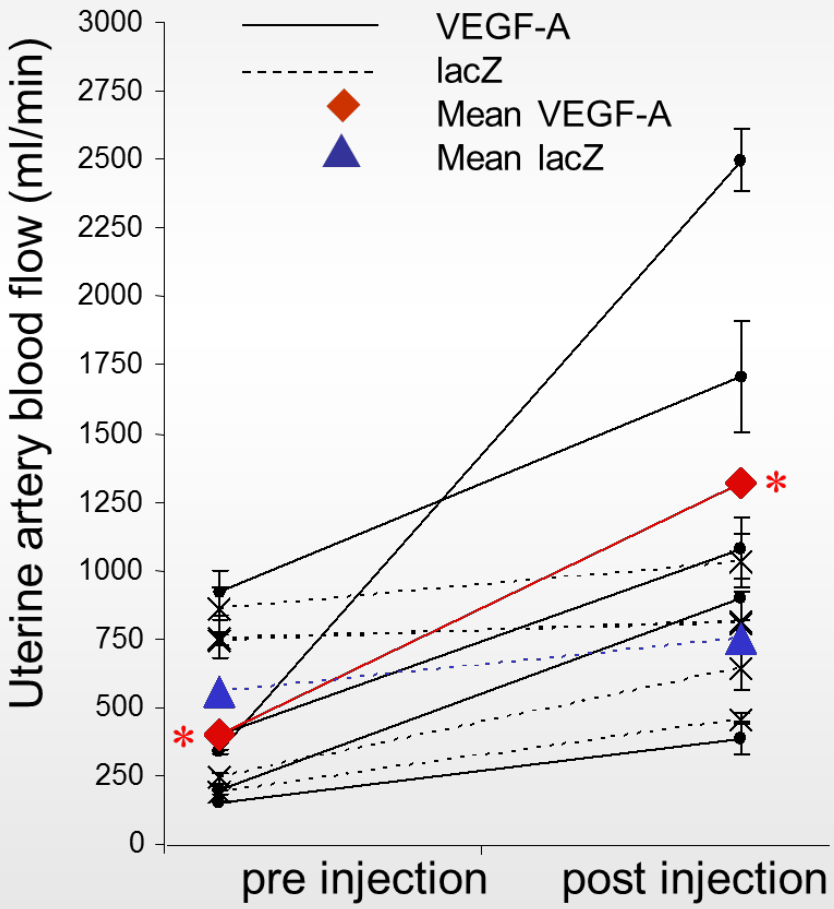
Short-term changes in uterine artery volume flow 4 – 7 days after vector injection



Mean ± SD	Before injection	After injection
VEGF-A	**408 ± 273**	**1321 ± 727**
lacZ	561 ± 281	755 ± 193

Two way analysis of variance

*p < 0.005

David et al, 2008,
Human Gene Therapy

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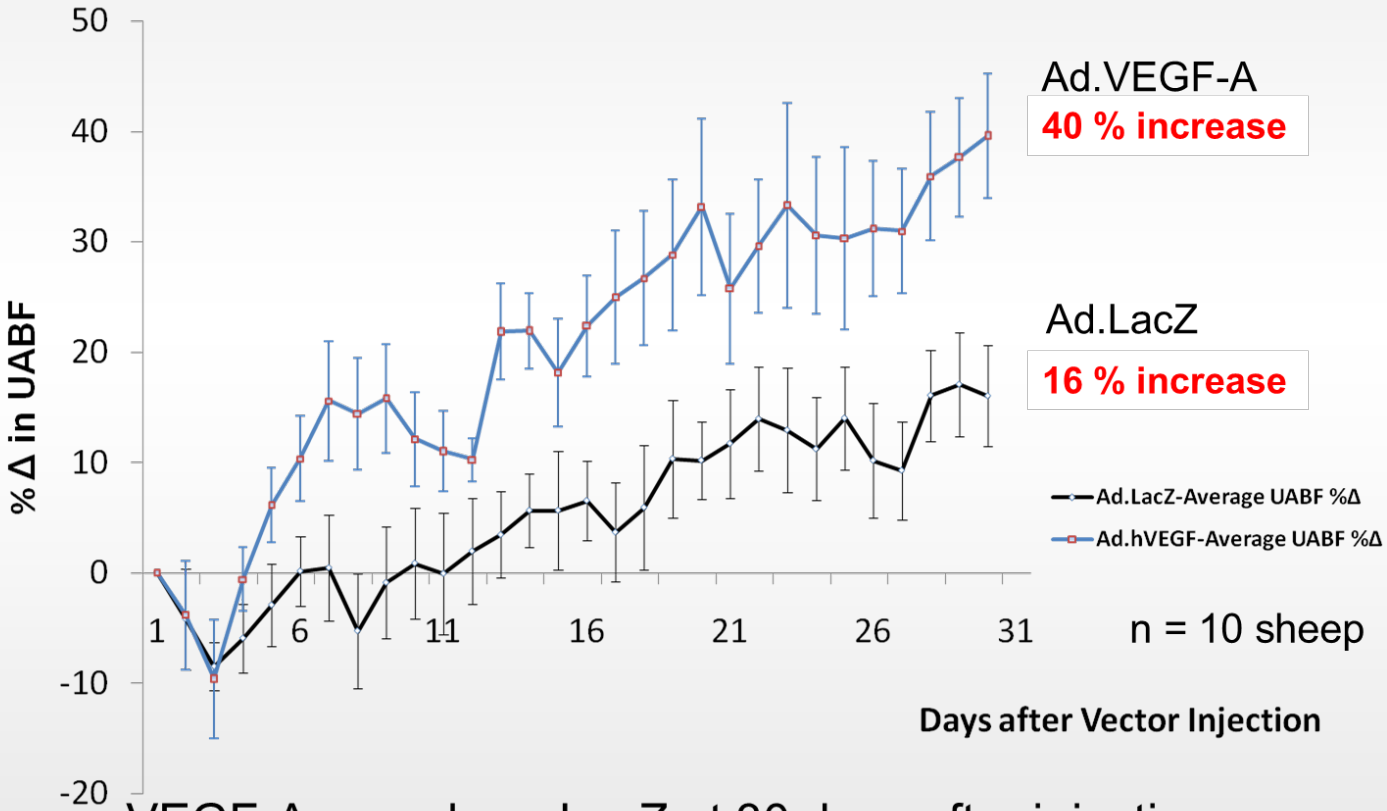
Long-term changes in uterine artery blood flow after vector injection



VEGF-A vessels vs LacZ at 30 days after injection

p=0.012 **Two-way ANOVA**

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Correcting growth restriction in animal models of IUGR

IUGR sheep: adolescent overfed ewe, Rowett Institute, Aberdeen

- efficacy, fetal growth, neonatal outcome and safety

IUGR guinea pig: maternal nutrient restriction model

- fetal growth, vector dose and safety

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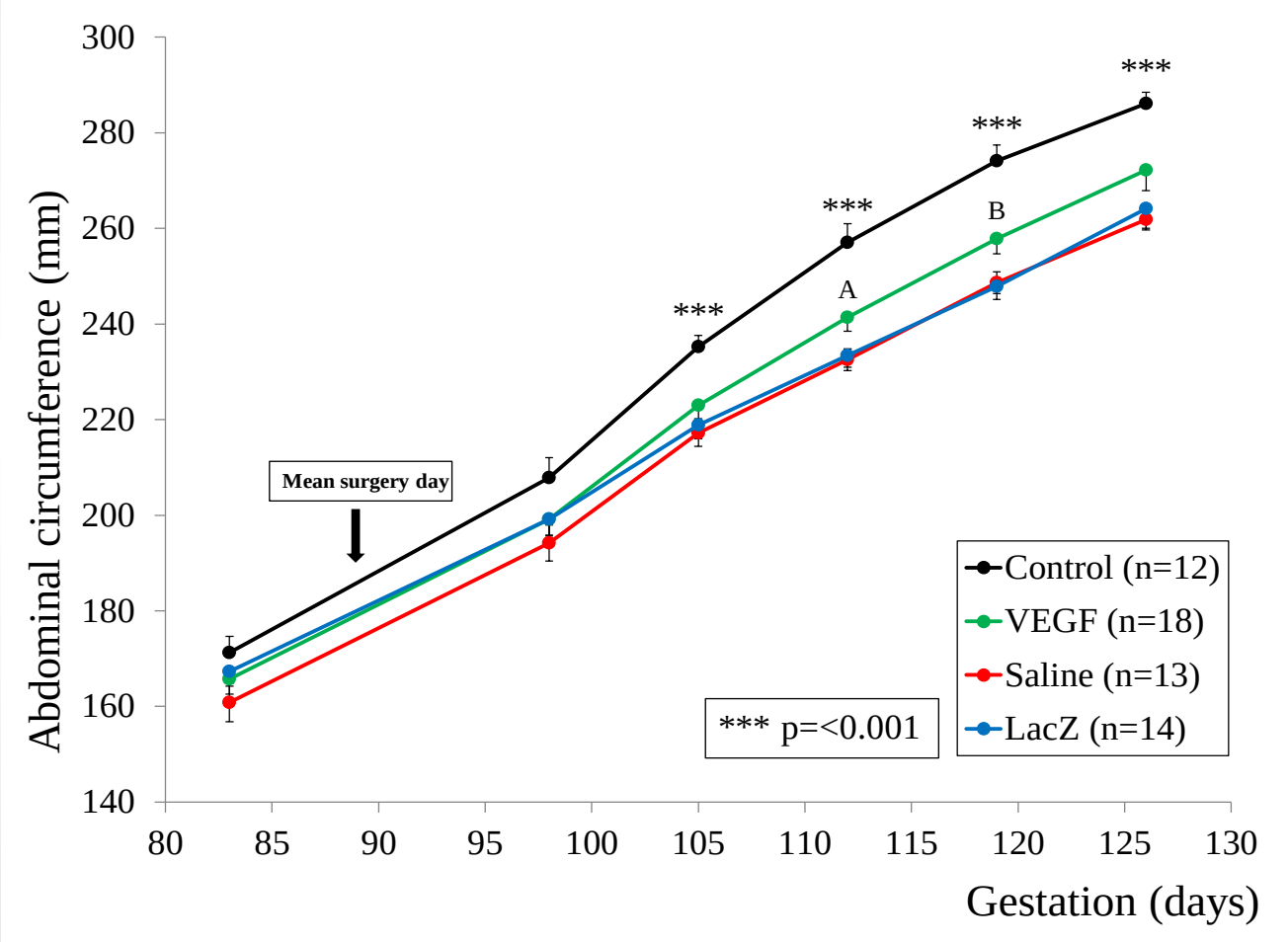
Fetal Growth Velocity - abdominal circumference



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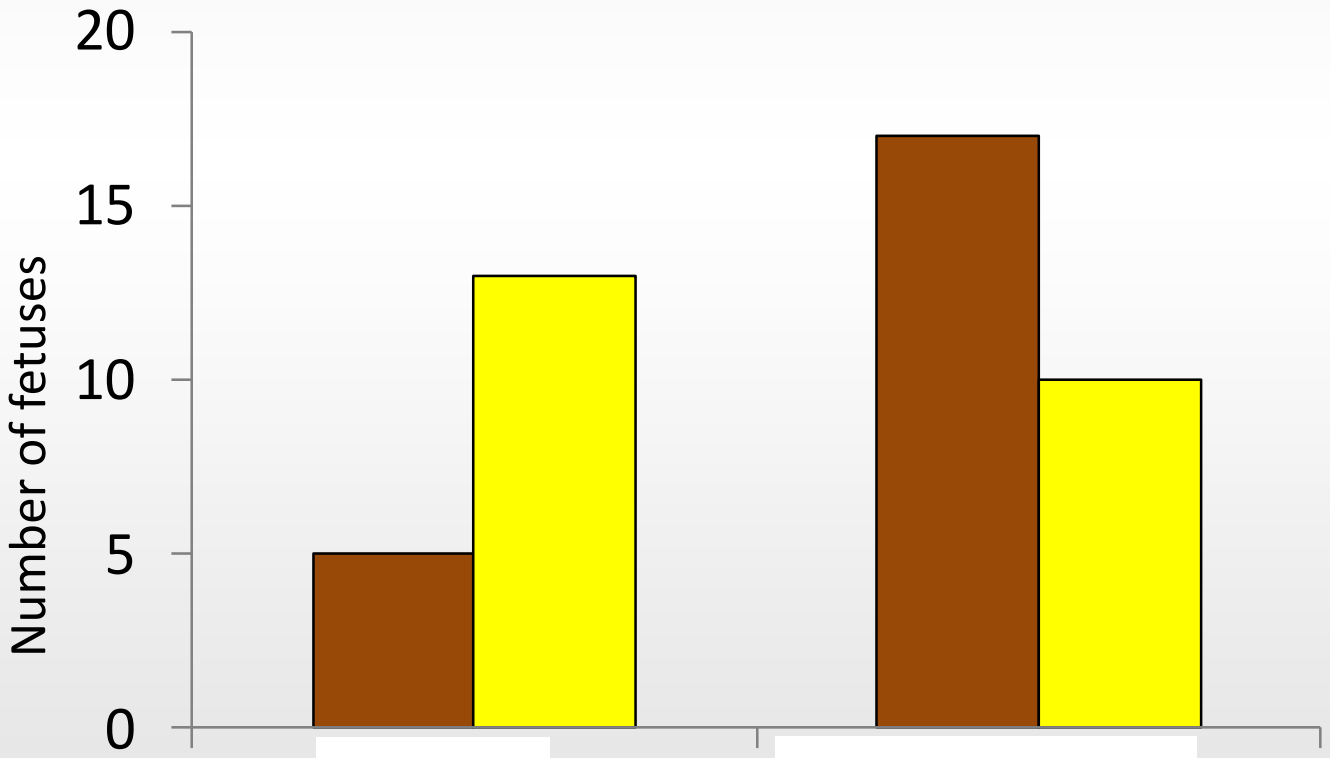
Proportion of very small sheep fetuses >2SD below control mean

(Control mean = 5084g , SD = 431g, -2SD cut-off = 4222g)



Severe FGR >2SD

Mild FGR <2SD

p = 0.033
(Fisher's exact test)

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Safety

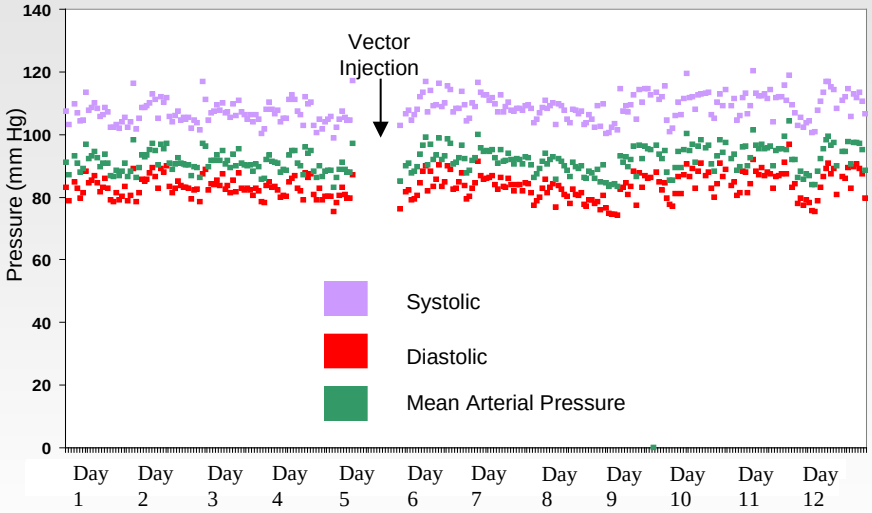
No significant changes in:

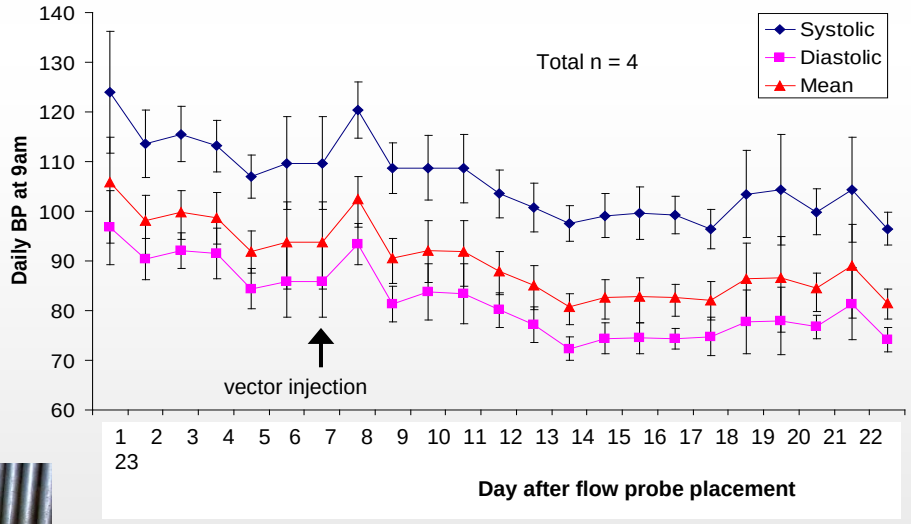
Maternal heart rate, blood pressure

Fetal heart rate, blood pressure

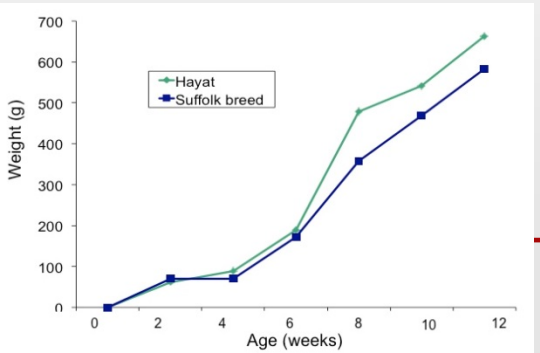
No vector spread

No fetal abnormalities





Abi-Nader et al, Lab Animals, 2011



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- Does vascular endothelial growth factor gene therapy safely improve outcome in severe early-onset fetal growth restriction?

Our aim

- To translate a novel gene medicine delivered to mothers, into the clinic, so as to improve fetal growth in severe early-onset fetal growth restriction

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- Reproductive toxicology
- Bioethics study
- First-in-woman phase I/IIa safety/efficacy study

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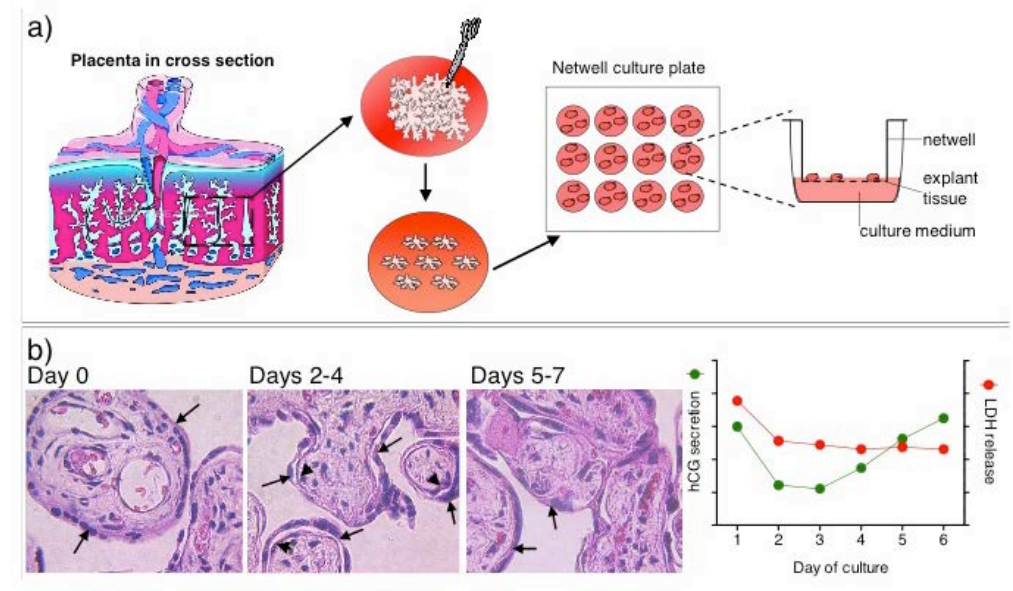
Human placenta toxicology studies



After regeneration of syncytiotrophoblast, placental villous explants are exposed to high dose adenovirus vector

Perfusion experiments in normal and IUGR human placentae with high dose adenovirus vector

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First-in-woman trial

First-in-woman trial

- 4 EU recruiting centres
  (London, Hamburg, Lund, Barcelona)
- Inclusion criteria:
  - Severe early-onset IUGR
  - ≥22 weeks of gestation
  - Uteroplacental insufficiency (abnormal blood flow)
  - Other causes of IUGR excluded
- Vector delivered via interventional radiology

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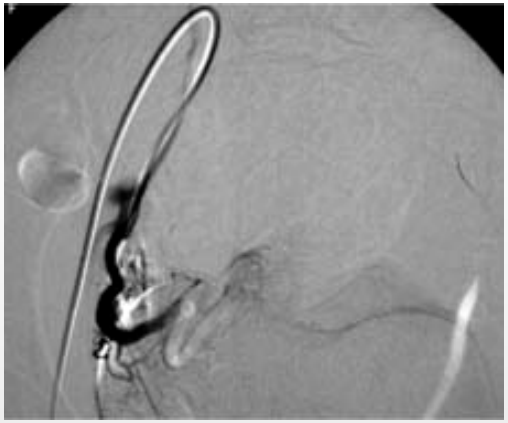
Treatment

- Vector instilled into uterine artery for 2 minutes using interventional radiology approach



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EVERREST outcome measures

Primary outcome

- Assessment of patient safety and tolerability

Secondary outcomes

- Uterine artery volume blood flow
- Abdominal and head circumference (ultrasound)
- Gestational age at delivery
- Birth centile
- Maternal blood pressure and proteinuria
- Composite clinical outcomes
- Myometrial artery contractility and placental phenotype

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Summary

- Local expression of VEGF in the uterine arteries
  - increases uterine blood flow
  - alters vascular reactivity
  - increases angiogenesis
  - improves fetal growth in IUGR pregnancies
  - without apparent maternal or fetal harm

- VEGF gene therapy promising as a therapy for severe early-onset IUGR

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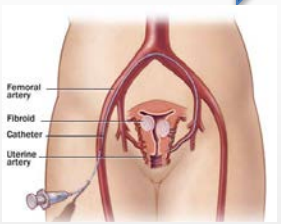
original idea

ethical & regulatory approval

Phase I/IIa safety/efficacy study

2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019



bioethics

Sup under the FP7 Programme

Thank you !

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UCL

Ark therapeutics

Queen Mary University of London

UNIVERSITY OF EASTERN FINLAND

Universität Hamburg

Universitätsklinikum Hamburg-Eppendorf

IDIBAPS

Institut D'Investigacions Biomèdiques August Pi i Sunyer

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University College London, UK

A David et al, Gene Therapy 2008
V Mehta et al, Gene Therapy 2011

original idea

Increase uterine artery blood flow short and long term
Relax uterine arteries
Increase endothelial nitric oxide synthase
Increase endothelial cell proliferation in uterine artery adventitia
No vector spread to fetus
No acute haemodynamic changes

2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019

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University College London, UK

D Carr et al, Hum Gene Ther 2014
V Mehta et al, PLoS One 2014

original idea

Increase fetal growth velocity
Mitigate “brain sparing”
No adverse events at delivery or up to 3 months postnatally
Planned clinical vector has similar effects

2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019

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