The Human Placenta Project

*and the **importance** of placenta research*

Presentation to OHSU Summer Course

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Human Development is a Complex Process

Mom's Environment Matters

INPUTS:

imprinting

Environmental endocrine disruptors

nutritional/metabolic status during pregnancy

infection

alcohol

depression

medications

genetics

stress

maternal nutritional history

placental size, shape, surface area and degree of invasion

epigenetics

air pollution

cigarette smoke

microbiome

inflammation

prior pregnancy outcome

Paternal factors

Immune system

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POTENTIAL ADVERSE CONSEQUENCES:

Preeclampsia

cognitive impairment

cardiovascular issues

placental insufficiency

IUGR

preterm birth

stillbirth

metabolic disorders

life expectancy

A Major Role for the Placenta

The placenta has many critical functions, such as:

- Bringing nutrients and oxygen to the fetus
- Producing hormones to support fetal development
- Removing harmful waste
- Providing Immune Protection
- Providing a Physical Barrier to Mom's Blood

Problems with the placenta can lead to serious consequences, such as:

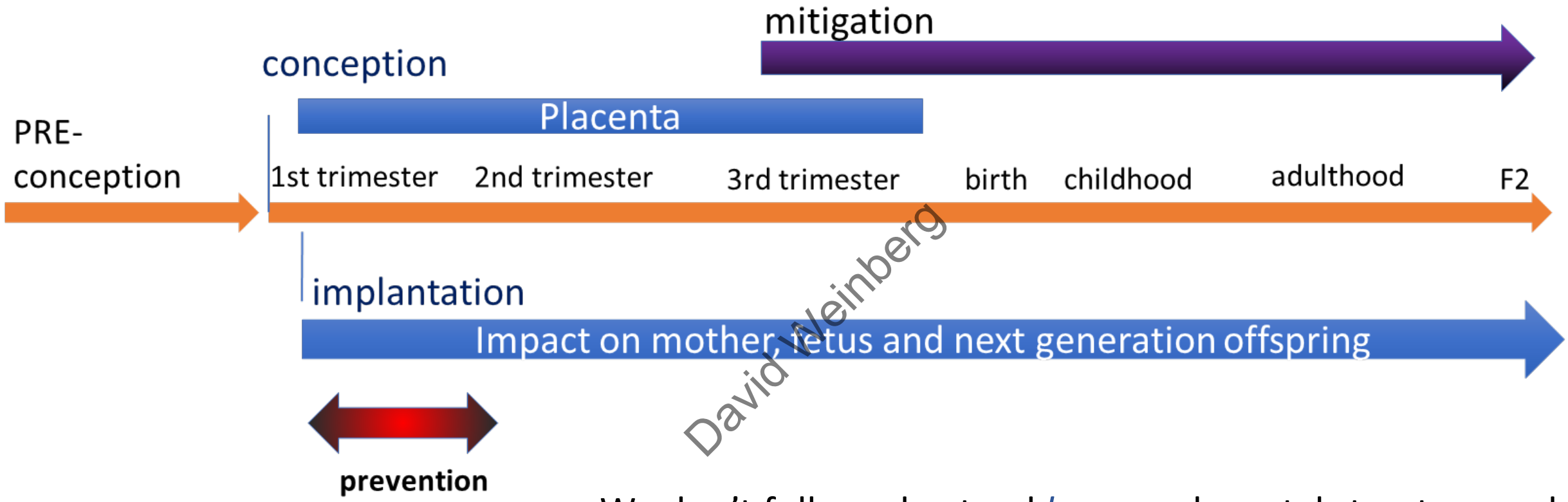
Preeclampsia

Gestational Diabetes

Preterm Birth and growth restriction

Stillbirth

Opportunities to change outcome



- We don't fully understand *human* placental structure and function across gestation (***it is constantly changing!)***
- What constitutes "normal" is unclear
- How placental dysfunction leads to long-term consequences (DOHAD) for both baby and mom is unknown

The Human Placenta Project

launched in 2014

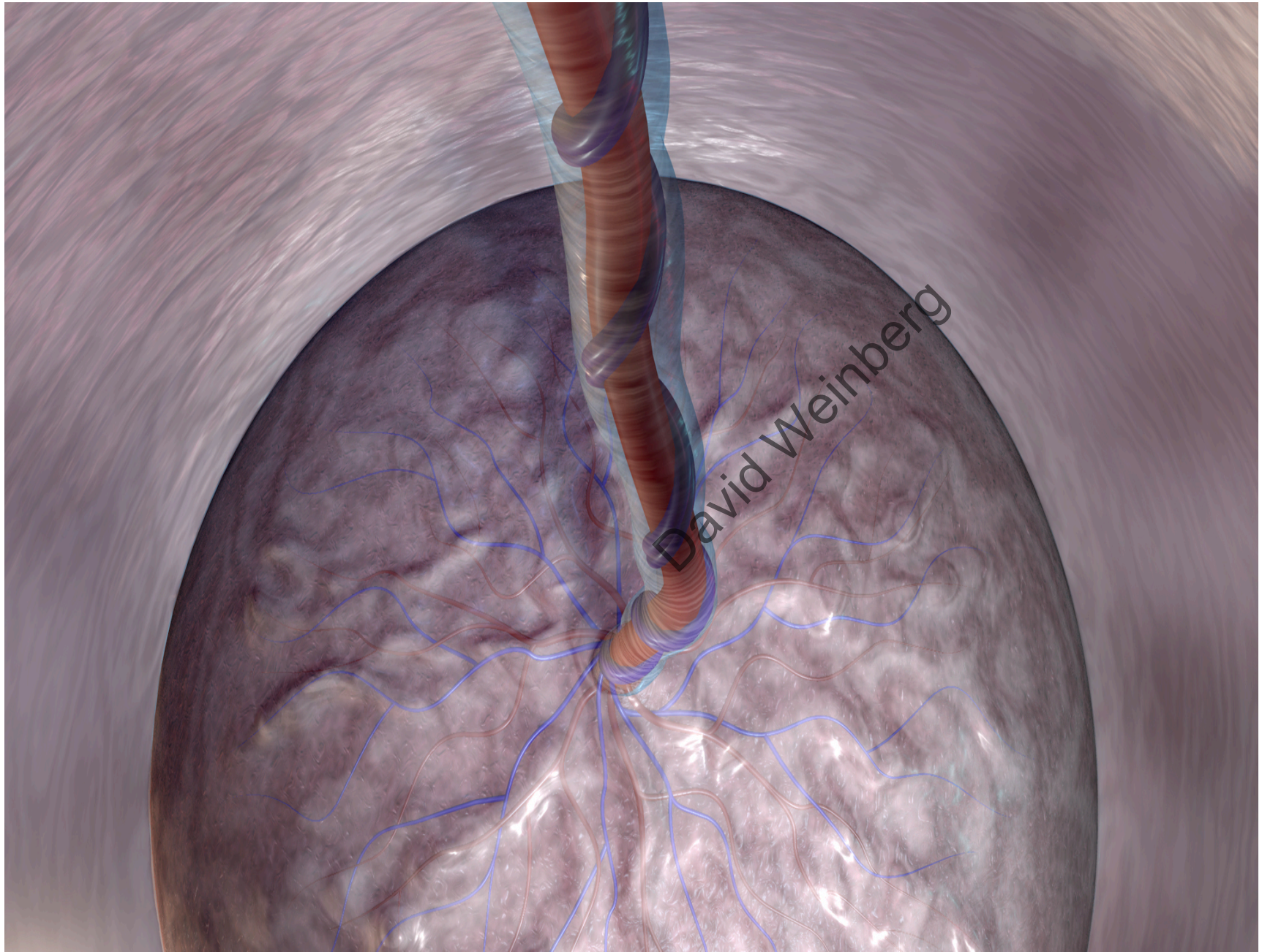
Goals:

- Develop a deep understanding of human placenta development and function across pregnancy
- Enable safe, non-invasive, real-time assessment of human placenta development and function across pregnancy

How:

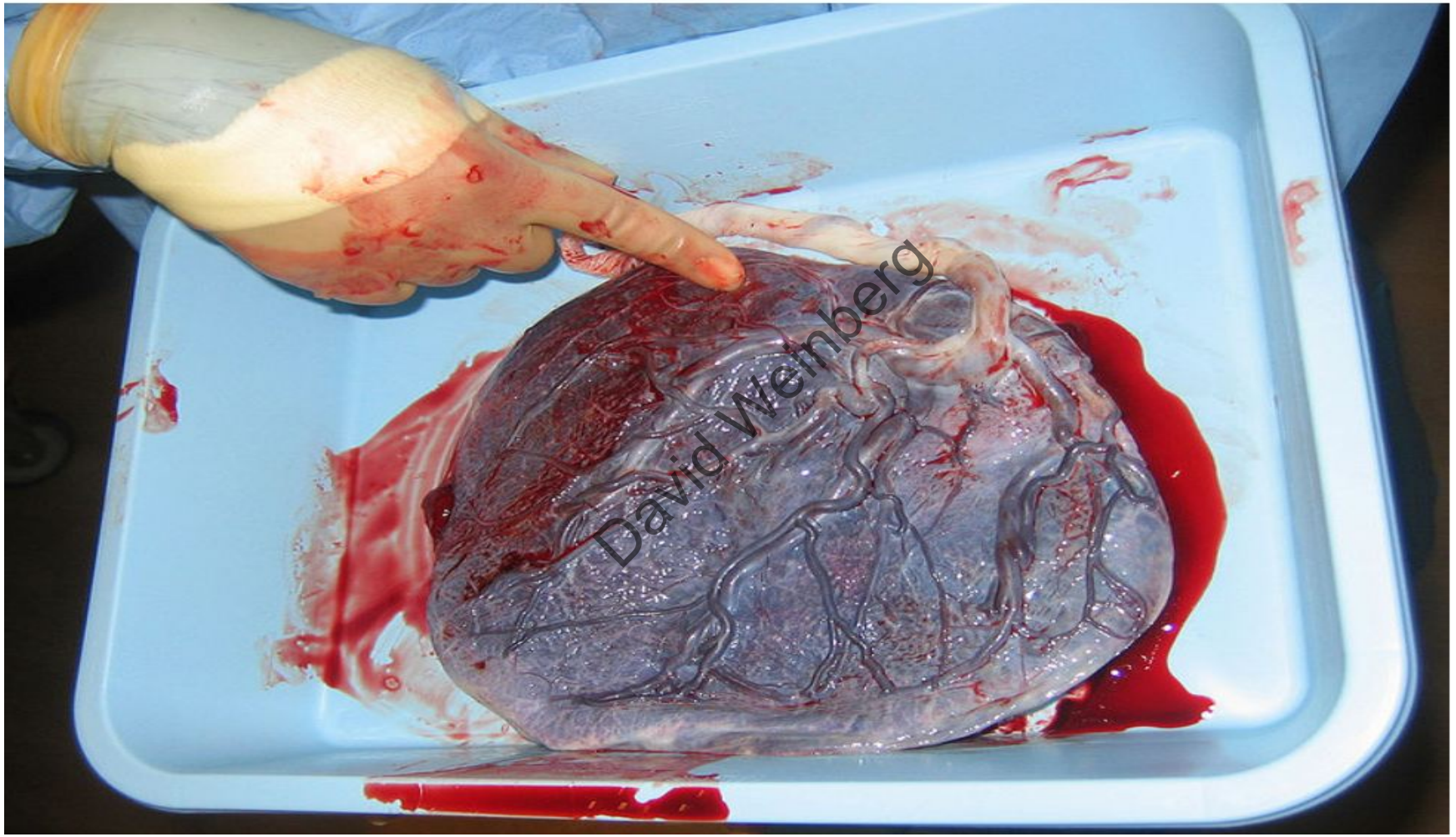
- Funding Announcements that enable multi-disciplinary teams with a directed focus on technology development
- Continued funding of basic placenta research to develop the mechanistic understanding necessary to understand the placenta's role in DOHAD and to make technology development possible.

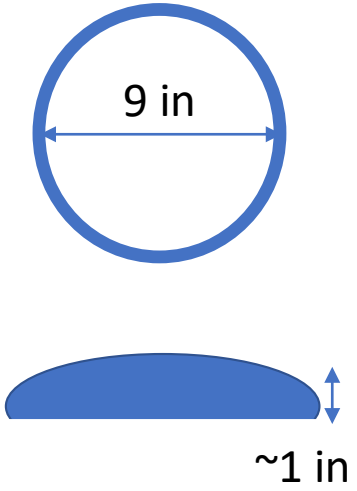
Fetal view of the placenta from above

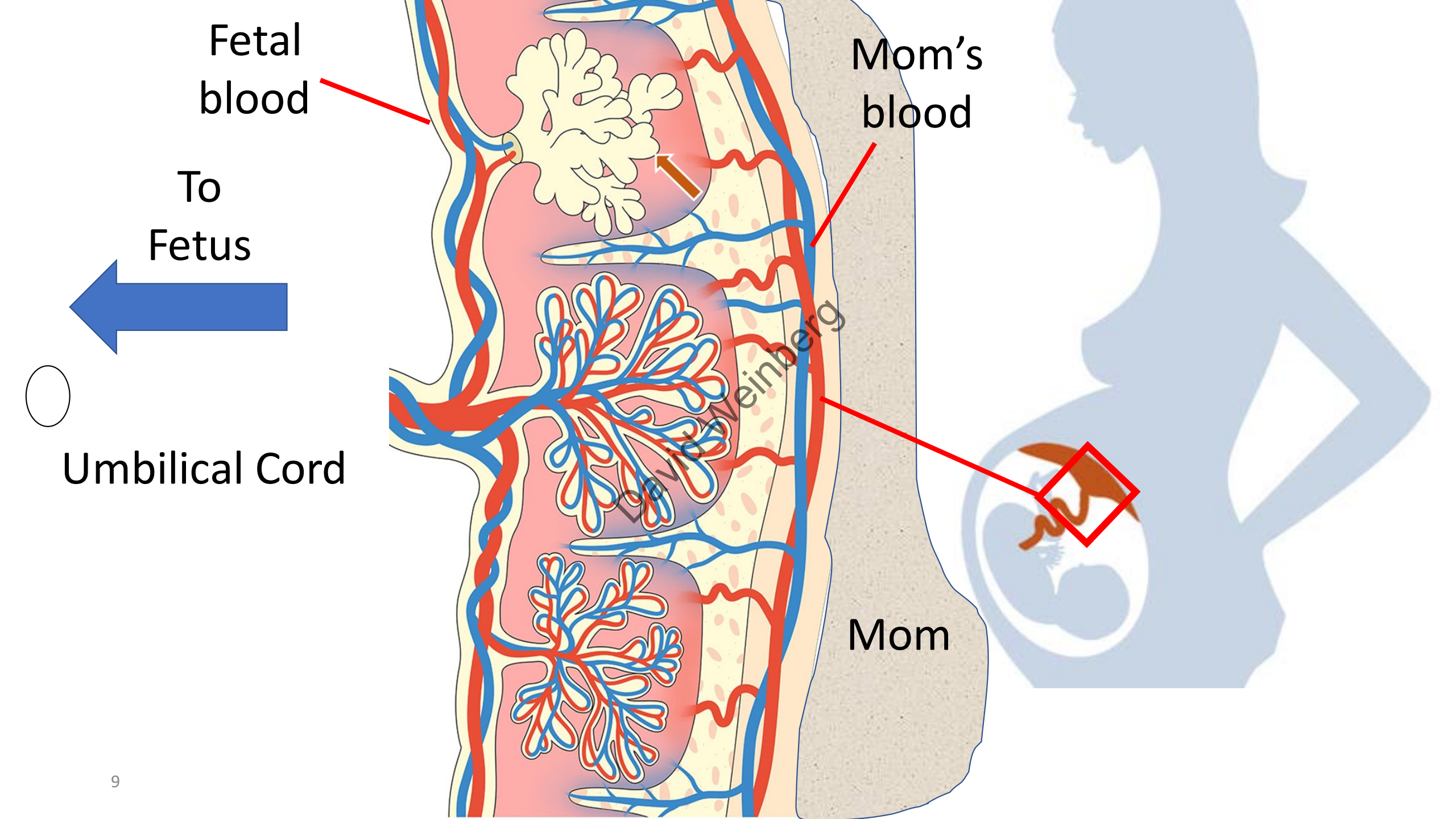


Credit: Joel B. Floyd Jr.

The Placenta As We Know It






Fetal blood
To Fetus
Umbilical Cord
Mom's blood
Mom
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A Maternal-Fetal-Placental Ecosystem

Communication in multiple directions

- Maternal/placental
- Placental/immune
- Microbial?/placental

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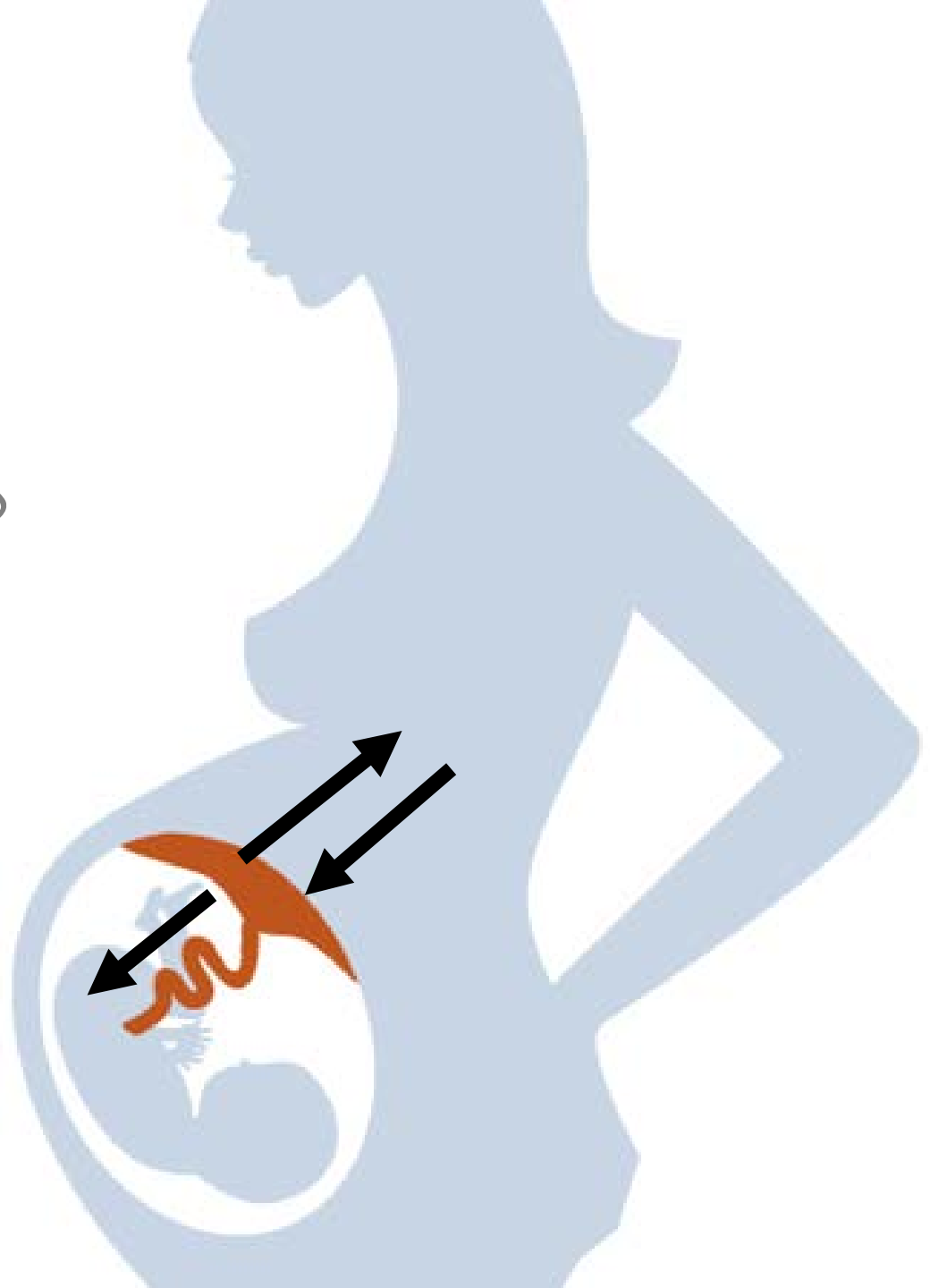


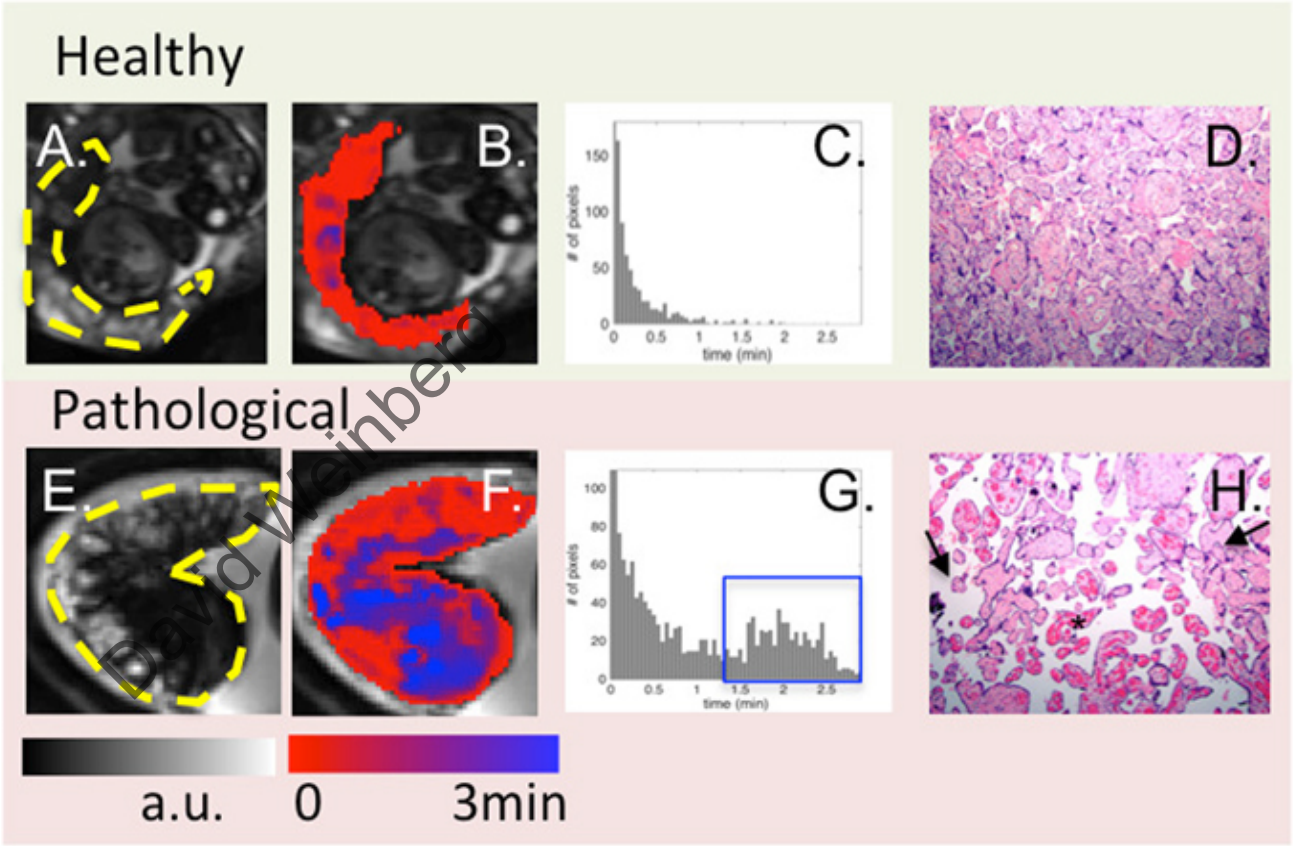
Adapting Technologies Already In Use in Pregnancy

- Blood Draws
- Imaging

Applying Cutting-edge MRI Technologies to Placental Assessment

Blood Oxygen Level Dependent (BOLD) MRI

- Advanced motion correction
- Connecting placental function to outcomes



From left to right: BOLD images, TTP maps, histogram of TTP distribution and histology (10X). One control (top) is compared to one case with abnormal placental pathology (bottom). Yellow dashes in A and E outline the placenta. For healthy subjects, TTP values were short and placental histology was normal. For pathological cases, TTP values were longer and less uniform (blue regions in (**F**) and blue box in (**G**)). Arrows in H point to avascular villi and the star identifies chorangiosis.

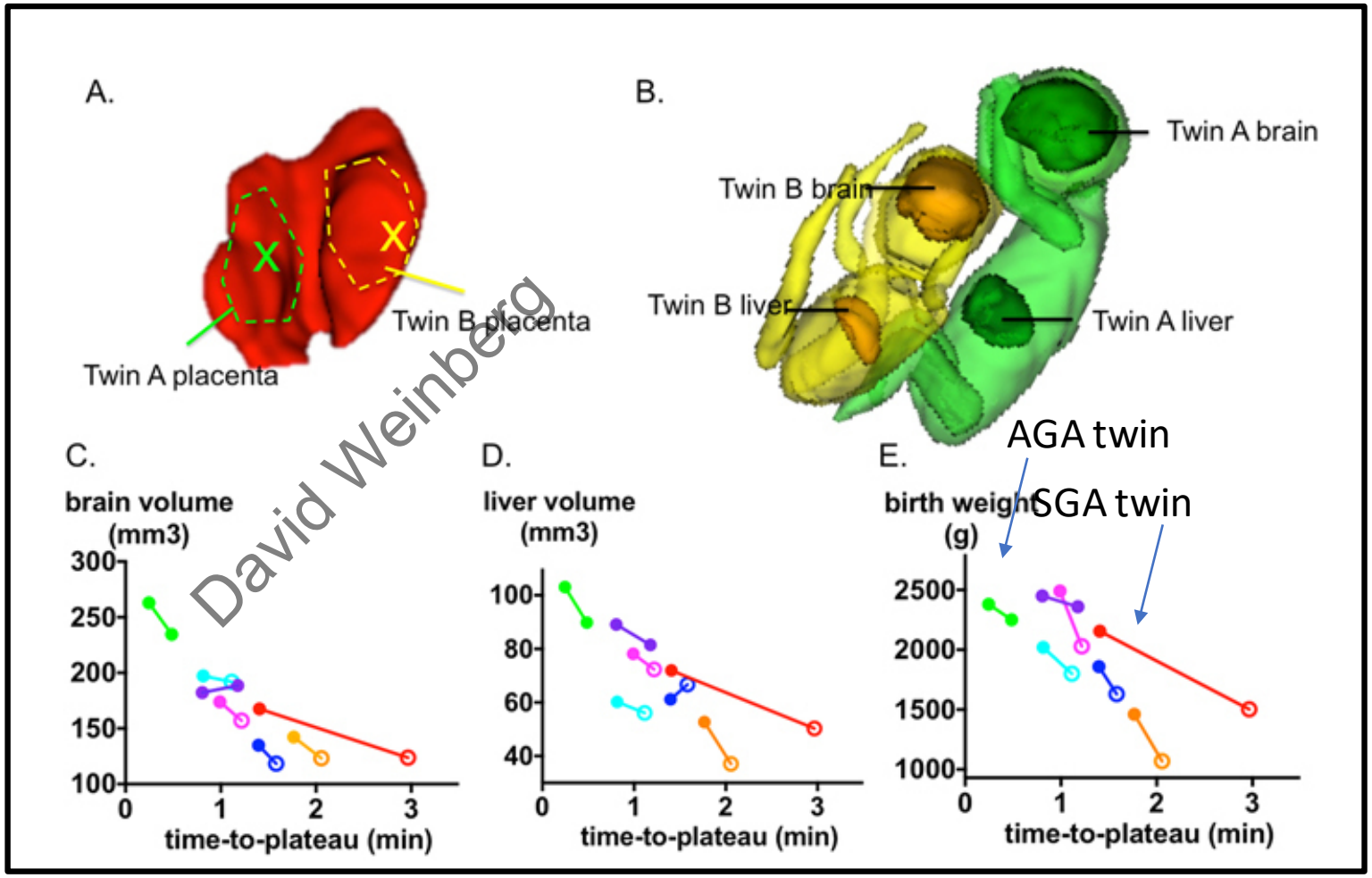
In Vivo Quantification of Placental Insufficiency by BOLD MRI: A Human Study. Science Reports 2017 7(1):3713

Ellen Grant, Harvard Medical School - HPP Grantee

Applying Cutting-edge MRI Technologies to Placental Assessment

Discordant monozygotic monochorionic, diamniotic twins

- Connecting placental function to outcomes

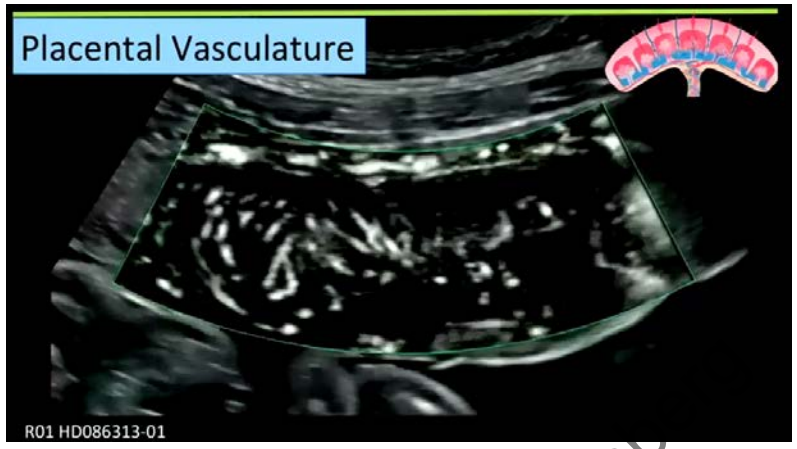


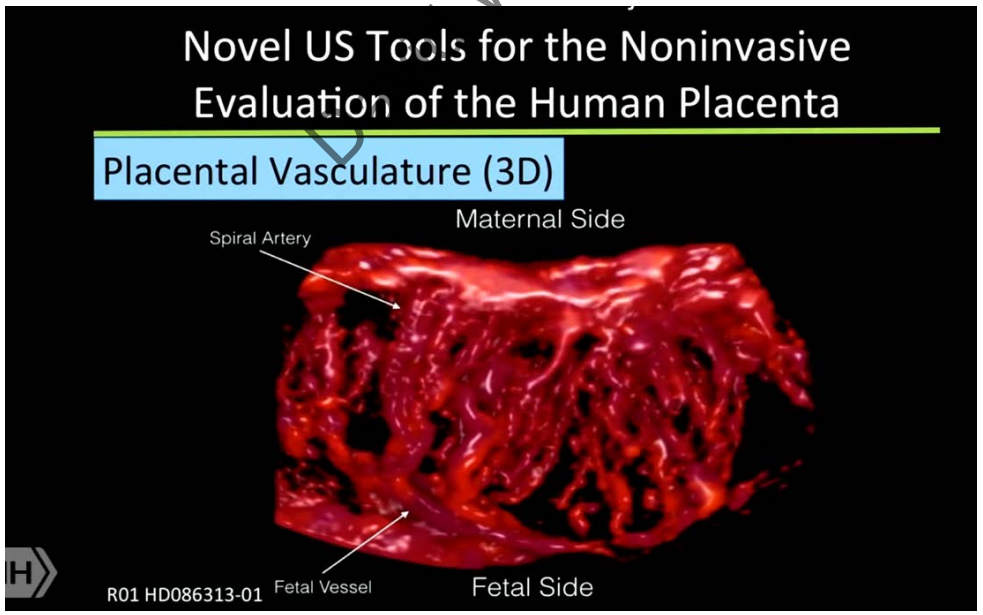
In Vivo Quantification of Placental Insufficiency by BOLD MRI: A Human Study. Science Reports 2017 7(1):3713

Ellen Grant, Harvard Medical School - HPP Grantee

Applying Cutting-edge Ultrasound Technologies to Placental Assessment

Superb Microvascular Imaging





- 15-16 weeks gestation – can visualize both fetal and maternal circulation
- Can count spiral arteries, fetal arterioles, and do quantitation with doppler techniques
- Generate a vascular index – the degree of vascularity for a given region of the placenta

Allows assessment of the overall health of the placenta

Alfred Abuhamad, (EVMS) and George Saade (UTMB) - HPP Grantee

Applying Cutting-edge Ultrasound Technologies to Placental Assessment: Superb Microvascular Imaging

Applied to Normal versus preterm births

Goals:
Normograms

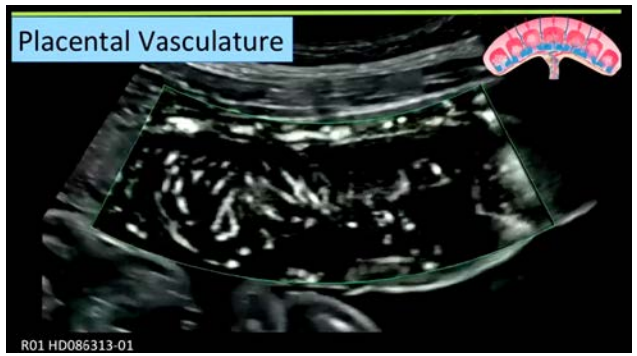
Selection of USEFUL clinical measurements

Development of a pregnancy index

Total Enrollment: **620**
Pregnancies for Normograms: **130**
Cases: **130**
Controls: **490**

8 ultrasound sessions from 12 weeks to 37 weeks

- Deep phenotyping:
  - Biometry
  - Vasculature – spiral arteries, Fetal arterioles
  - Tissue Density
  - Genetics
  - Calcification
  - Fetal Echo
  - Cell free RNA analysis
  - Placental pathology
  - Urine sample for phenol exposure study (with NIEHS)
  - Pregnancy outcome and maternal history data



Alfred Abuhamad, EVMS – George Saade UTMB HPP Grantee

Exosome Isolation of Placental Health

Cargo of miRNAs, lipids, proteins may reflect placental health

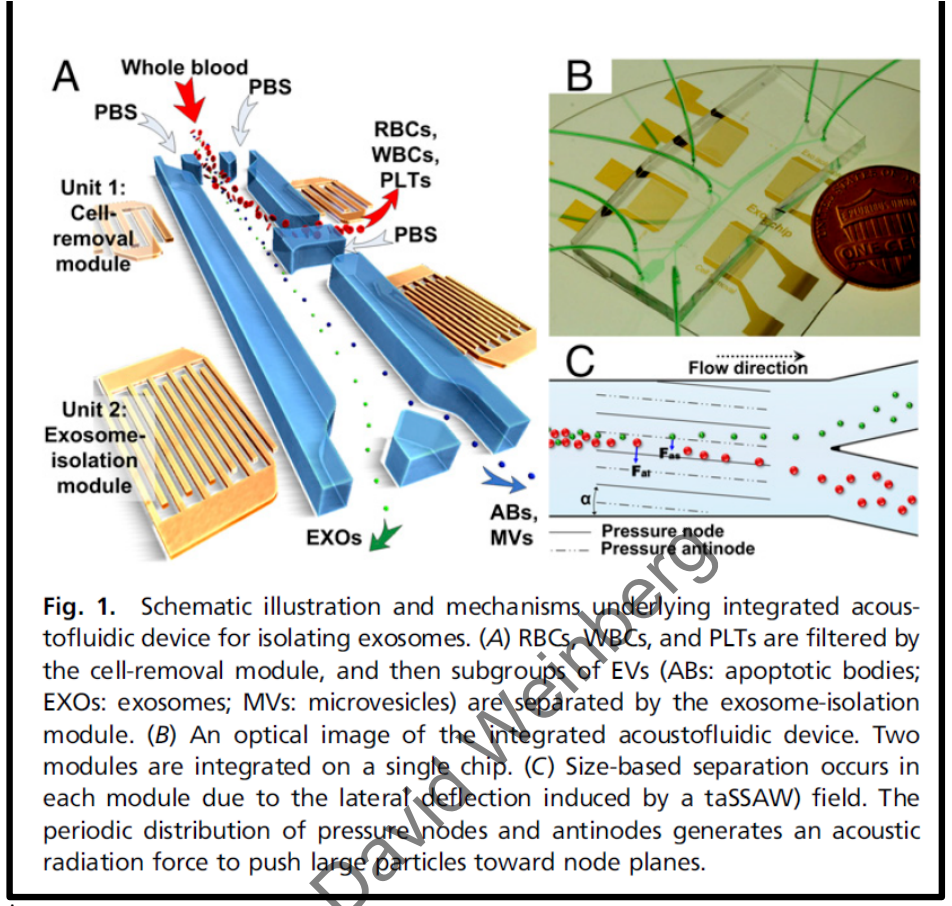


Fig. 1. Schematic illustration and mechanisms underlying integrated acoustofluidic device for isolating exosomes. (*A*) RBCs, WBCs, and PLTs are filtered by the cell-removal module, and then subgroups of EVs (ABs: apoptotic bodies; EXOs: exosomes; MVs: microvesicles) are separated by the exosome-isolation module. (*B*) An optical image of the integrated acoustofluidic device. Two modules are integrated on a single chip. (*C*) Size-based separation occurs in each module due to the lateral deflection induced by a taSSAW) field. The periodic distribution of pressure nodes and antinodes generates an acoustic radiation force to push large particles toward node planes.

Isolation of exosomes from whole blood by integrating acoustics and microfluidics PNAS 114(40):10684 2017

- **Gentle, high yield approach**
- **Works for vesicles from any source circulating in blood**

Yoel Sadovsky and Tony Huang, HPP Grantees

Acousto-fluidics – Biotechnology *applied to the placenta and pregnancy*

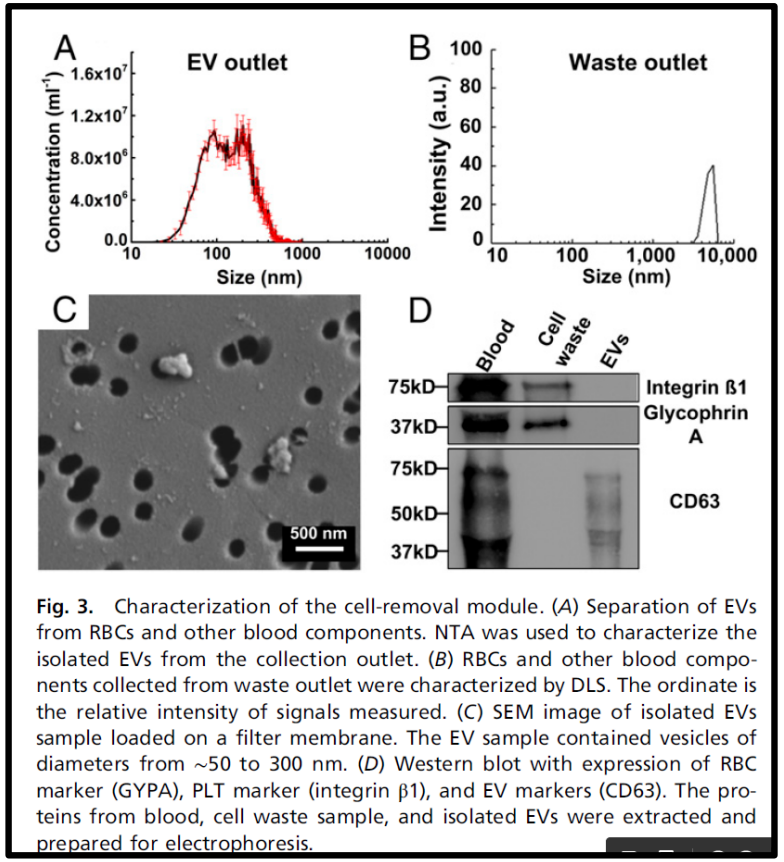


Fig. 3. Characterization of the cell-removal module. (*A*) Separation of EVs from RBCs and other blood components. NTA was used to characterize the isolated EVs from the collection outlet. (*B*) RBCs and other blood components collected from waste outlet were characterized by DLS. The ordinate is the relative intensity of signals measured. (*C*) SEM image of isolated EVs sample loaded on a filter membrane. The EV sample contained vesicles of diameters from ~50 to 300 nm. (*D*) Western blot with expression of RBC marker (GYPA), PLT marker (integrin β1), and EV markers (CD63). The proteins from blood, cell waste sample, and isolated EVs were extracted and prepared for electrophoresis.

HPP Investment and Advances

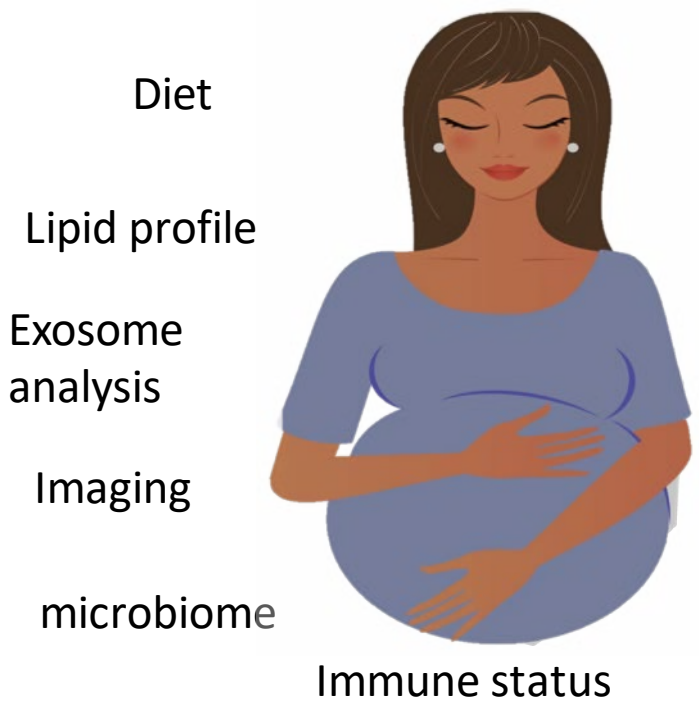
as of 2021

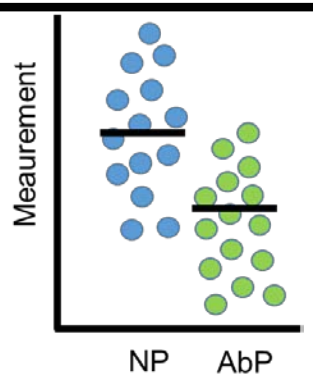
- ***>$91M*** over 7 years
- HPP investment is ***in addition*** to a large and continued investment in basic placenta research
- ***Hundreds*** of publications
- Some advances translate to other areas of research
  - E.g., rapid COVID-19 testing; novel approaches for isolating extracellular vesicles

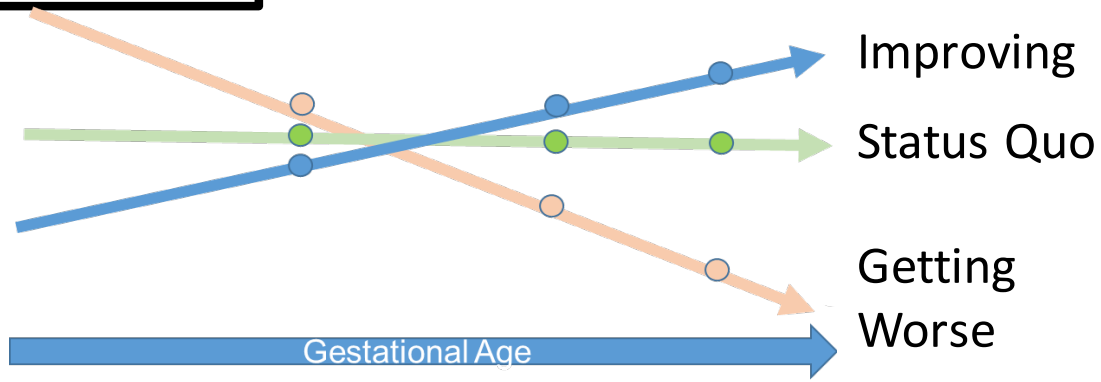
Many Challenges Remain

- Pathology may be multifactorial
- Associations often clearer in the aggregate
- Signals may be indications of normal compensation, not pathology
- Time/cost/risk-benefit issues related to increased testing (imperfect information)
  - ❖ We don't examine all placentas (range of variation of 'normal' is unknown)
- Clinical benefits unclear
- New technologies lack rigorous clinical confirmation
- Knowledge Gaps Remain

What is possible vs what is expedient







Placenta Research is still an NICHD Priority

HIGHLIGHTED

at the 2021 HPP Meeting

- It is impossible to fully understand DOHAD without understanding the placenta
- There are still many basic ***and*** translational research questions yet to be answered
- Understanding the placenta will require researchers across a broad range of disciplines
- Detecting placental issues is only the first step. Correcting problems in placenta development and function will be a major effort that will take time and effort.
- **NICHD has put the placenta as a key element** of the 2020 Strategic Plan for theme 3 *Setting the Foundation for Healthy Pregnancies and Lifelong Wellness*

"Expanded study of the placenta, including noninvasive methods to determine placental health in real time, will play a key role in this research area."

The Future of Placenta Research Will Depend upon the Next Generation of Researchers

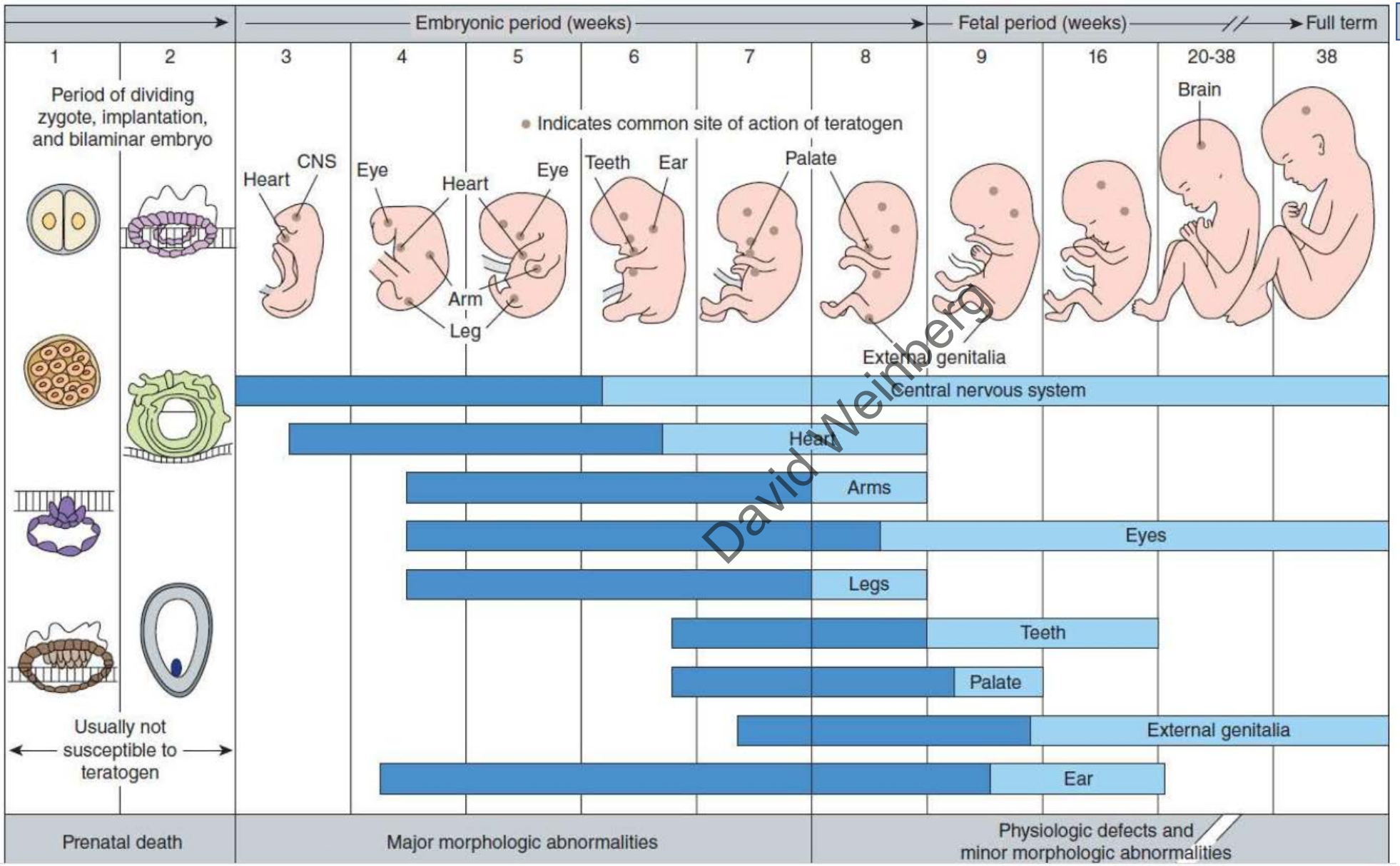
- **Will need** clinicians, cell biologists, immunologists, microbiologists, data scientists, bioengineers, radiologists, vascular biologists, pharmacologists, drug developers**, and more…**

- **Topics include**: modes of communication between mom, fetus and placenta; basic mechanisms of placenta development; mechanisms that underlie placenta dysfunction and potential targets for intervention; safe delivery vehicles for therapeutic agents; drug discovery for new therapeutics; validity of new models, regulation of nutrient transport and response to the environment; mechanisms underlying DOHAD in the face of environmental influences; regulation of drug transport across the placenta; biomarkers of placenta health across pregnancy; point of care technologies that may be used in low resource settings; the impact of stress on the maternal/fetal/placental ecosystem; the role of the microbiome; imprinting; paternal factors; impact of antiretroviral therapy, **and more…**

- ***There is plenty of room for new investigators!***

Thank you!

Setting the Stage



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