FDA Public Workshop

Evaluation of Immunosuppressive Effects of In Utero Exposure to Drugs and Biologic Products

White Oaks Campus

Silver Spring, Maryland

Nonclinical Evaluation of Placental Transfer and Immunotoxic Potential:

In Vivo Animal Assessments

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Disclosure

- The author is employed by Exponent (a science, engineering and technology consulting firm)
- The author has no financial or other interests that pose a conflict of interest

Outline of Presentation

- What is a placenta?
- Understanding the rodent inverted yolk sac placenta
- Placental transport of immunoglobulins in rodents and humans
- Can safety tests inform placental research?
- Is there a “best” placental model?

What is a placenta?

Placenta

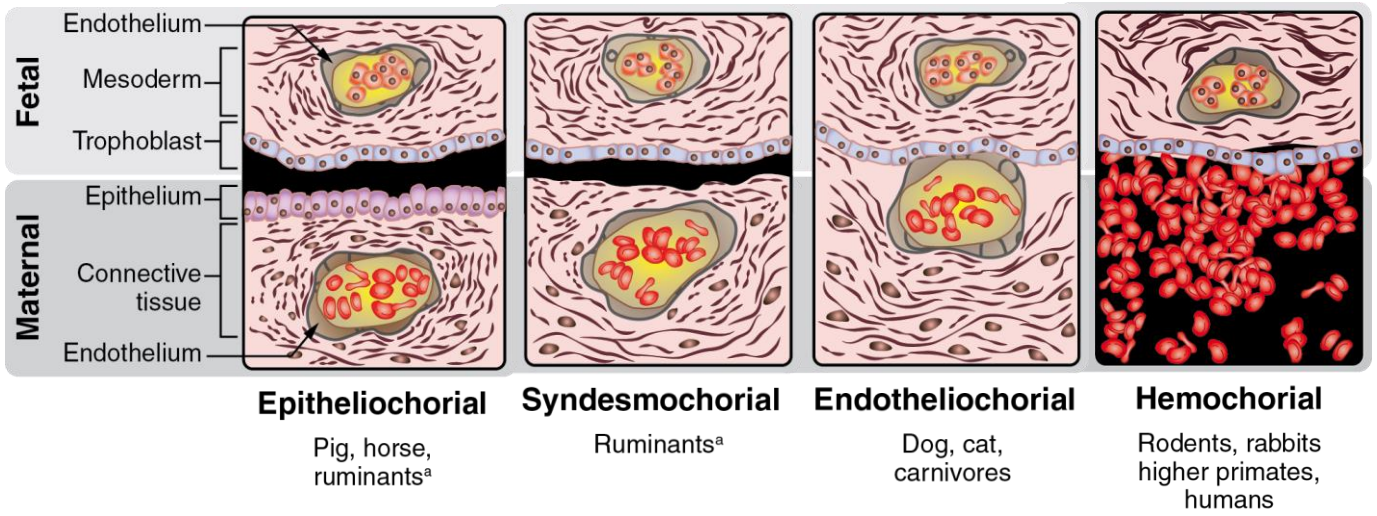
Any apposition of embryonal to parental tissues for the purpose of physiological exchange

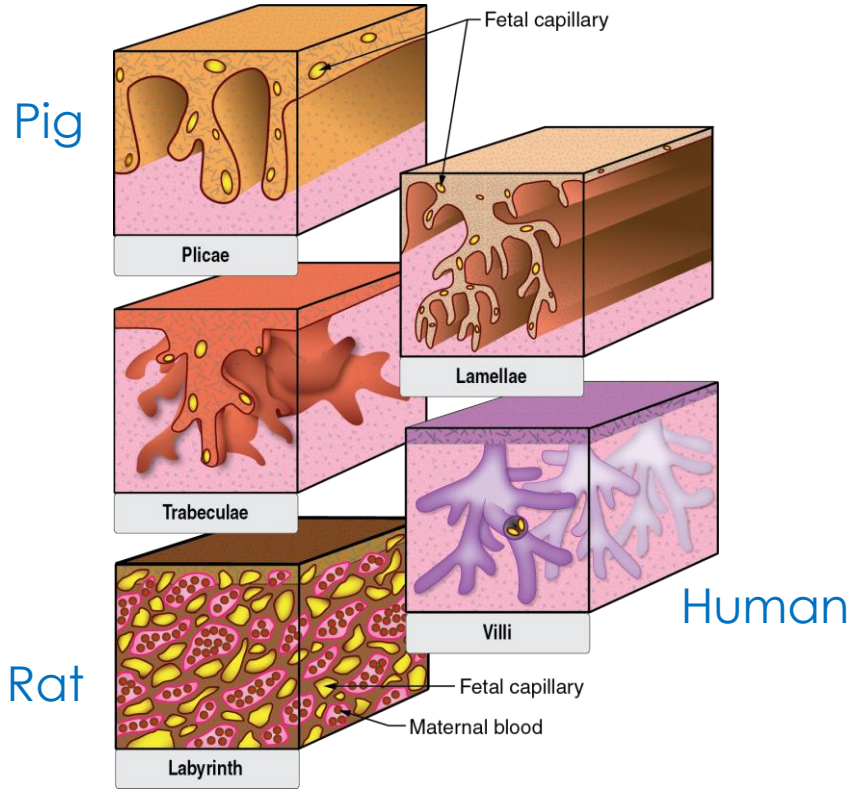
A Unique Organ

- Composed of tissues from 2 different individuals
- Temporary – but of critical importance
- Morphology and physiology evolve dramatically with age

Materno-fetal Transfer Is Major Function of Placentae

- Efficiency of transfer is affected by
  - Increase in circumference of placental base
  - Modifications of interface to increase surface area
  - Decrease in Layers and thickness of layers between maternal and fetal blood



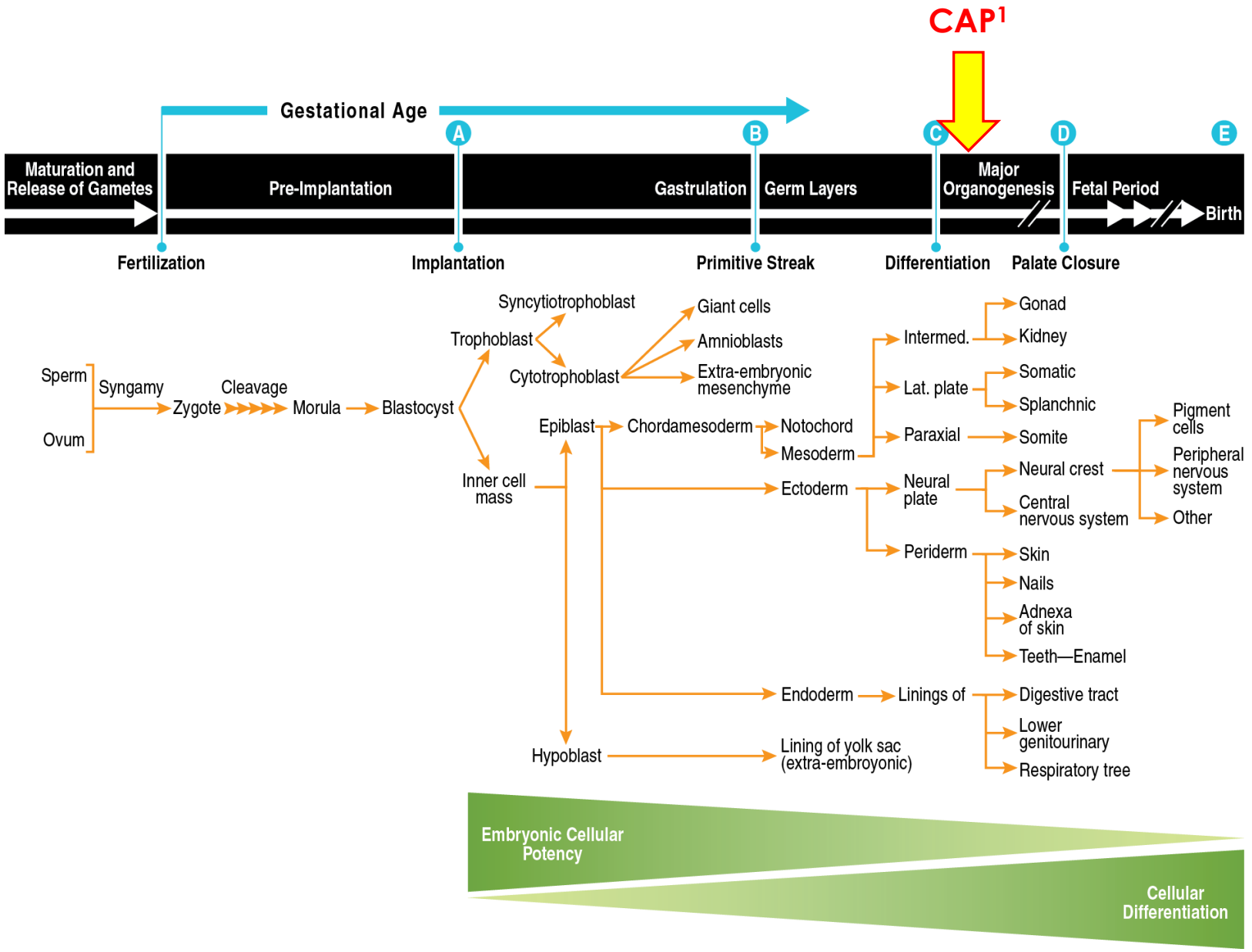


- Presence of receptors/carrier molecules

Regardless of morphological differences, the role of all placentae is materno-fetal exchange

However, these differences are important, and must be taken into consideration for appropriate extrapolation to humans

Conceptual Roadmap of Embryonic Development



DeSesso (2012) in Developmental and Reproductive Toxicology 3rd Ed, RD Hood Ed, Informa Press

[1]Chorioallantoic Placenta

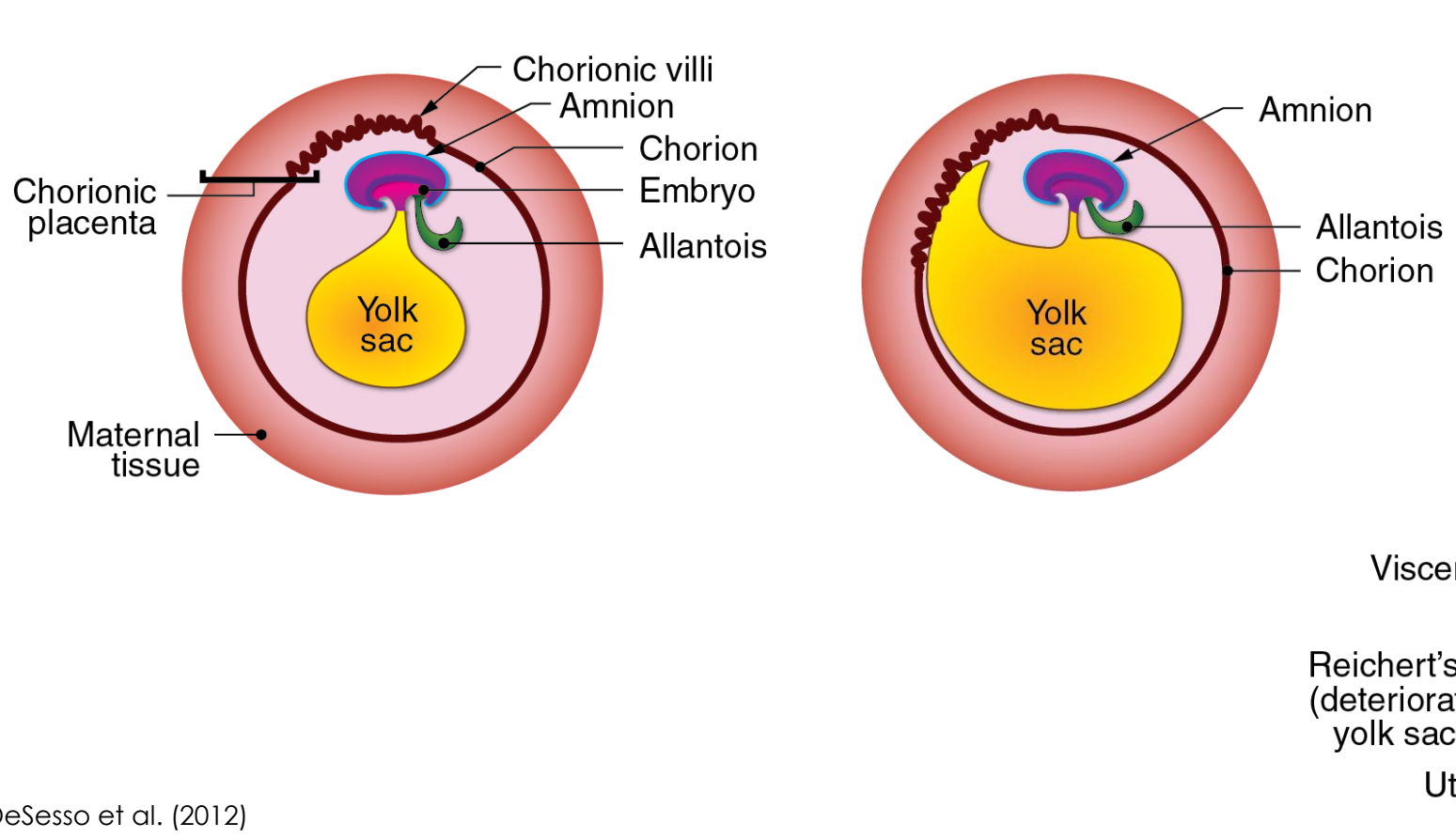
Understanding the rodent inverted yolk sac placenta

Chorioallantoic Placenta (CAP) Develops Late in Organogenesis of Rodents

	Gestational Milestone[1] (in gestational days)					
Species	**A**[2] Implantation	**B** Primitive Streak	**C** Early Differentiation	**CAP**	**D** Organogenesis Ends	**E** Usual Parturition
Hamster	4.5–5	7	8	—	13	16
Mouse	5	6.5	9	9.2	15	19–20
Rat	5–6	8.5	10	11.5	17	21–22
Rabbit	7.5	7.25	9	12.5	19	30–32
Guinea Pig	6	12	14.5	—	~29	67–68
Monkey	9	17	21	~23	~44–45	166
Human	6–7	13	21	28	~50–56	266

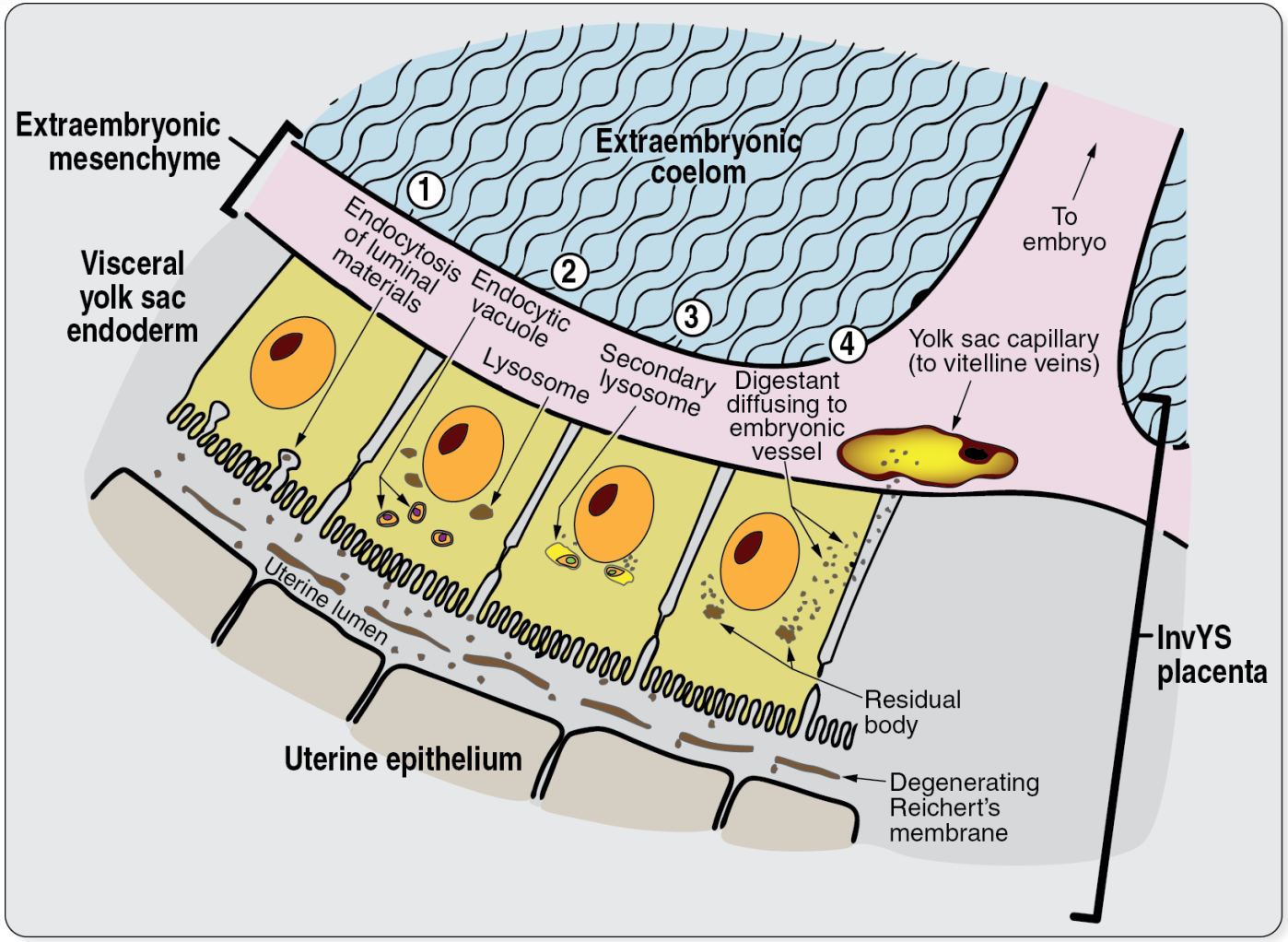
DeSesso (2012) in Developmental and Reproductive Toxicology 3rd Ed, RD Hood Ed, Informa Press

Rodent Inverted Yolk Sac Placenta



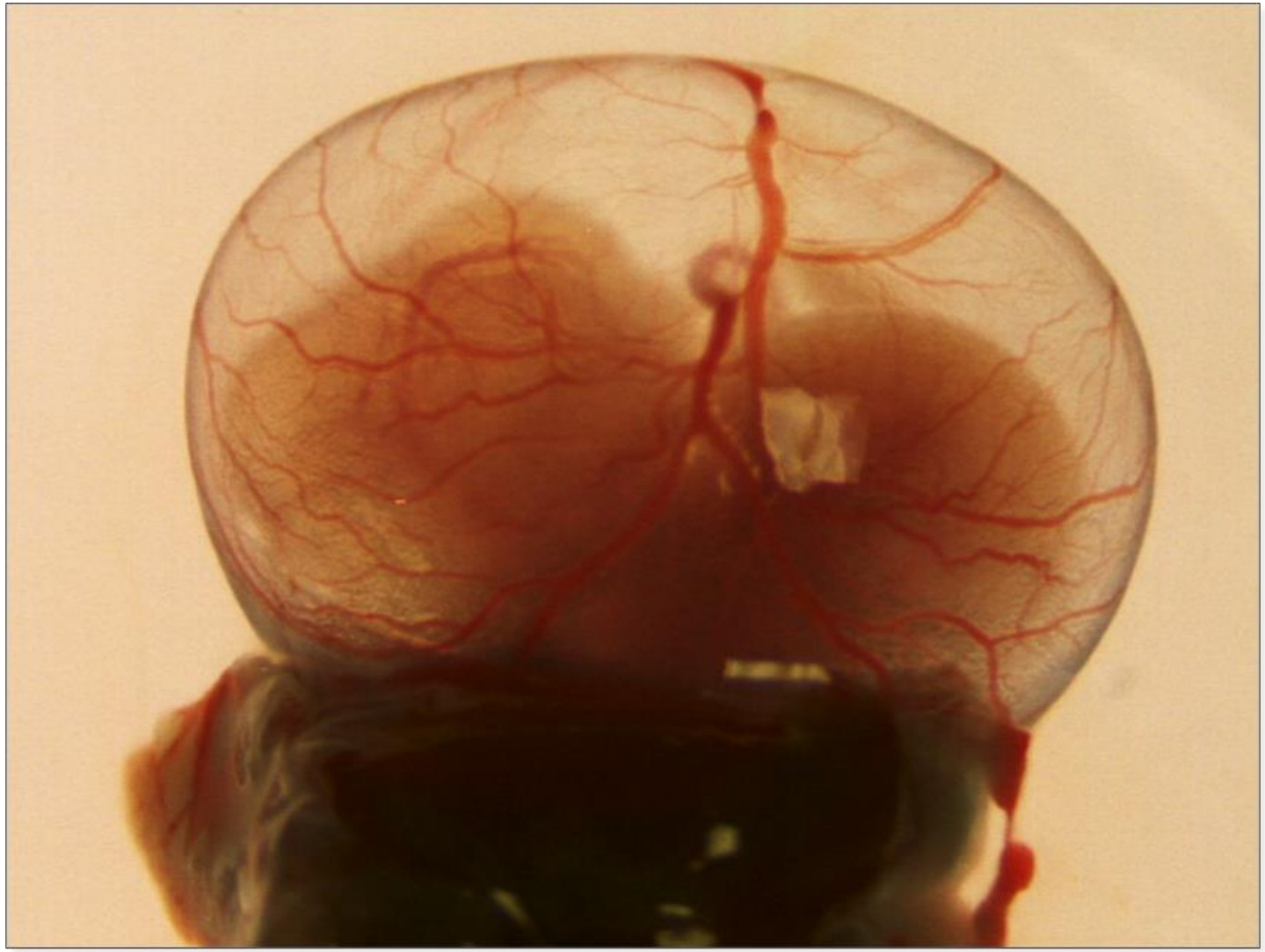
DeSesso et al. (2012)

Pinocytosis and Process of Histiotrophic Nutrition



DeSesso et al. (2012)

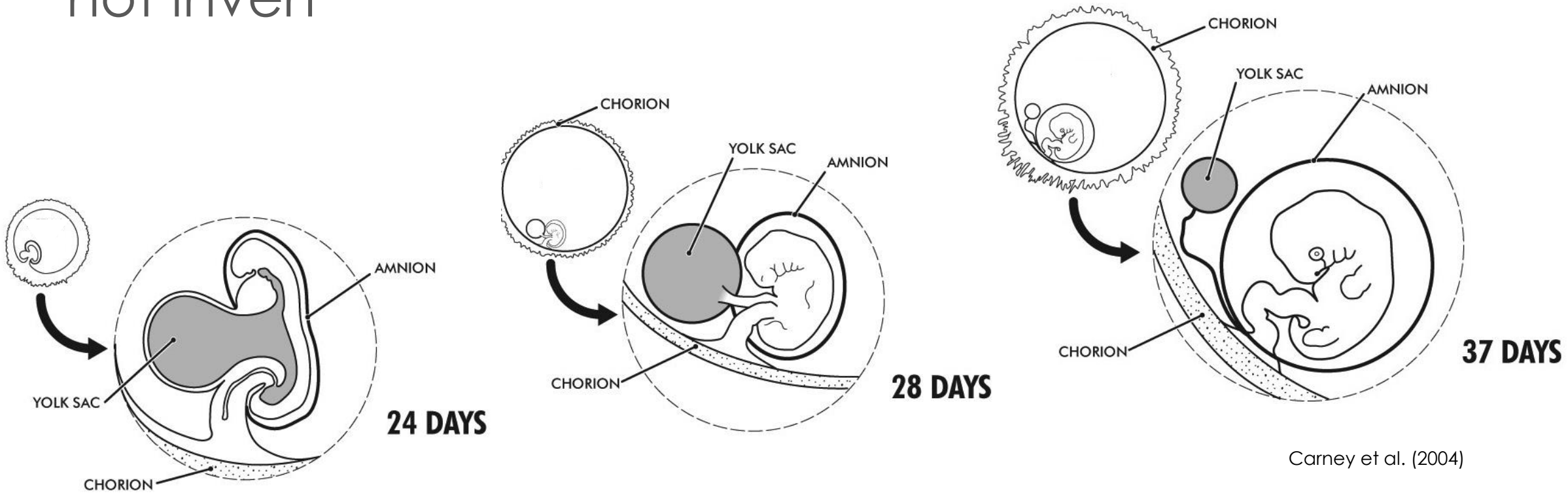
Day 13 Rat Conceptus



Courtesy of WIL Research

Human Yolk Sac Development

- Yolk sac never surrounds human embryo and does not invert



Carney et al. (2004)

- Nevertheless, pinocytosis is an important mechanism

Placental transport of Immunoglobulins in rodents and humans

Immunoglobulin G Structure

Fab

(Antigen Binding)

Fc

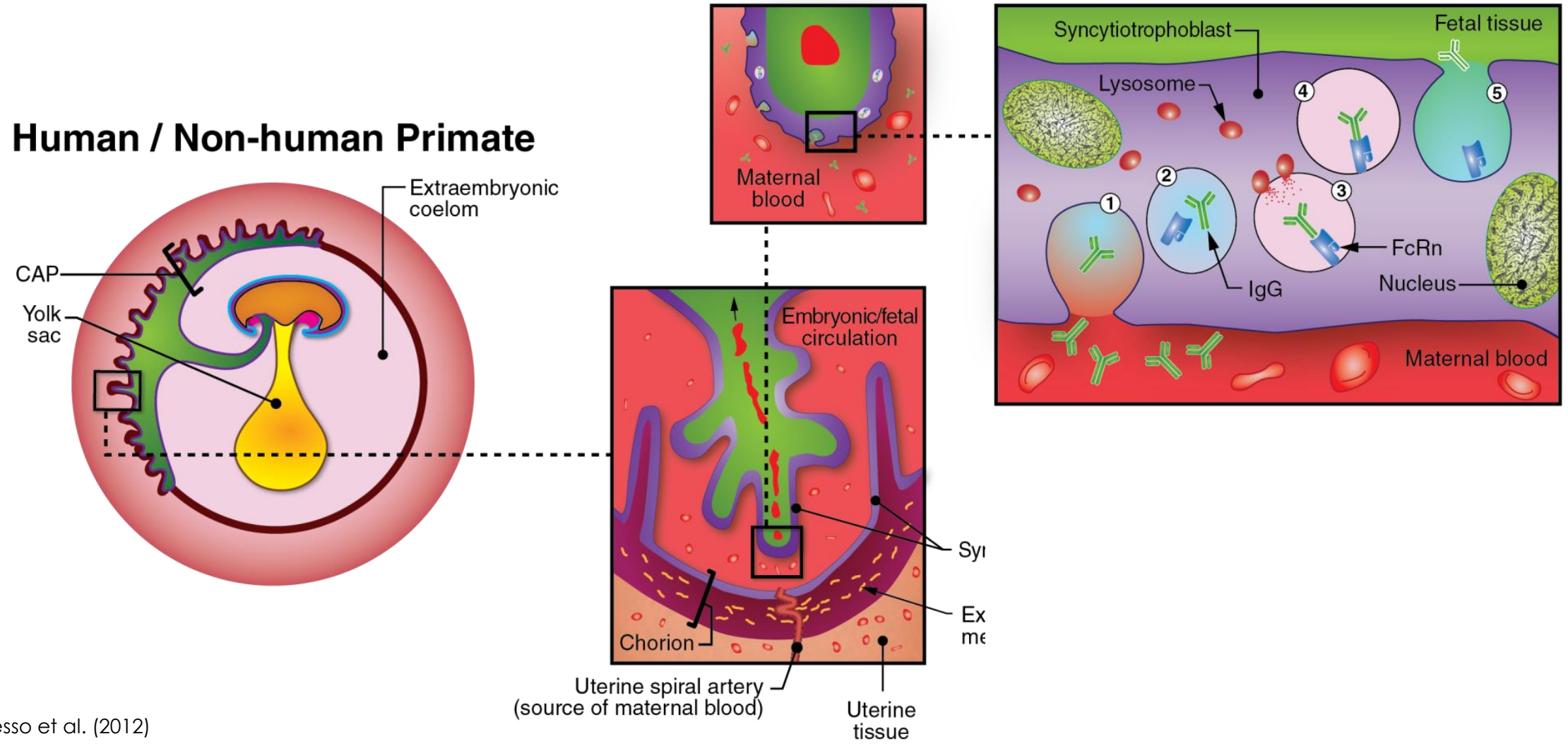
(Binds to Fc Receptors)

Light Chain

Heavy Chain

Molecular Weight ~150,000 Daltons

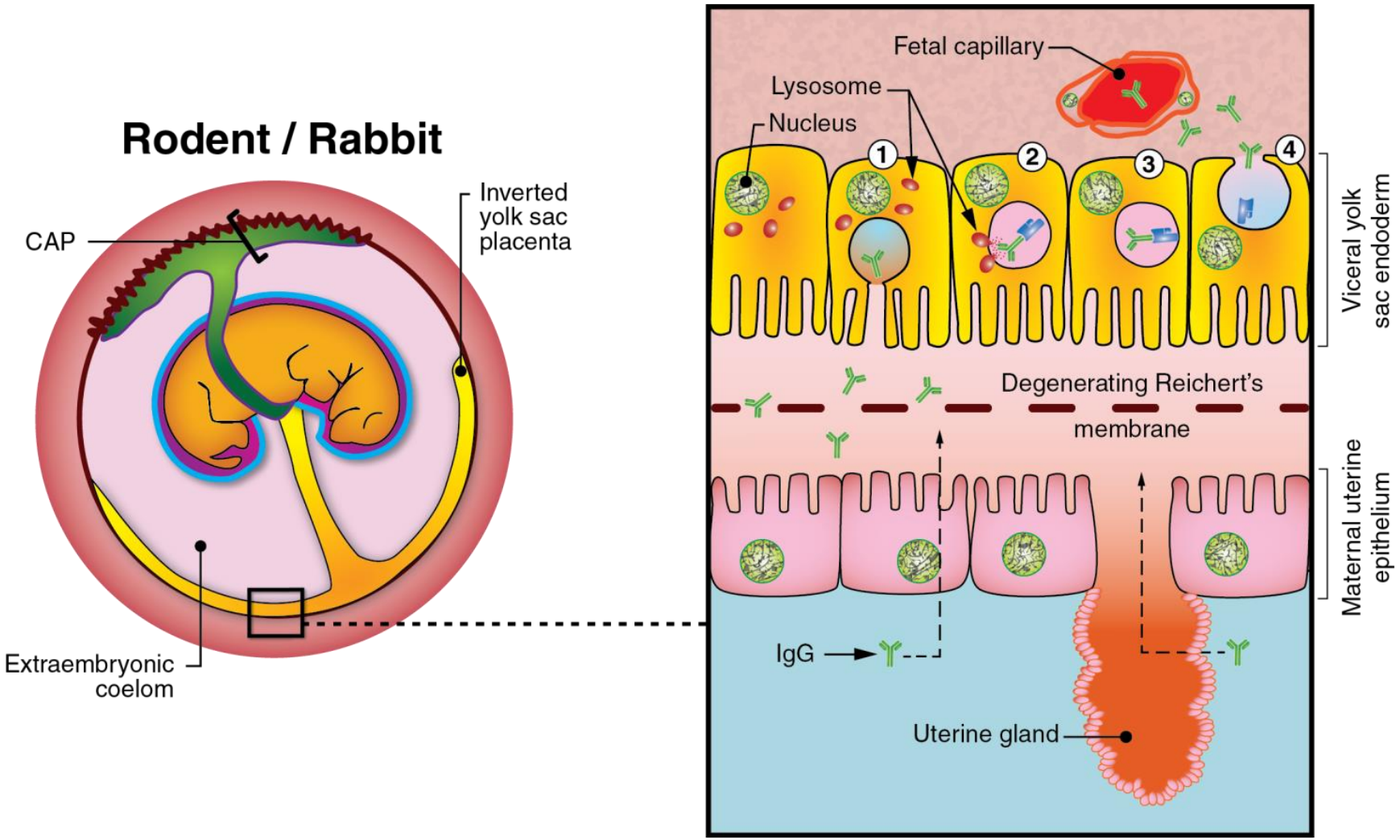
How Do Large Biomolecules (IgG) Get to Offspring?



DeSesso et al. (2012)

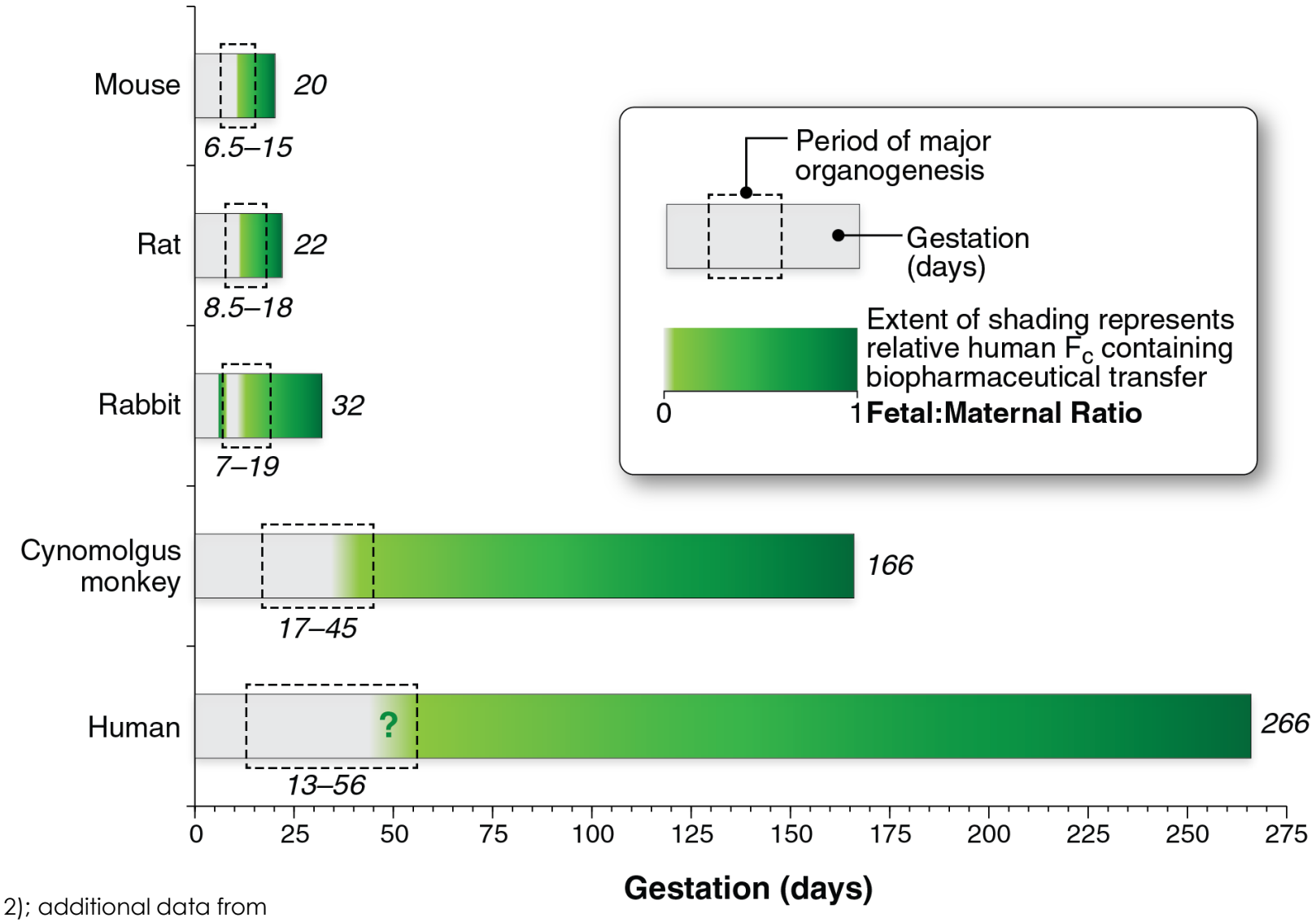
But rodent syncytiotrophoblast cells do not have FcRn receptors

How Do Large Biomolecules (IgG) Get to Rodent Offspring?



DeSesso et al. (2012)

Comparative Periods of Biopharmaceutical Transfer



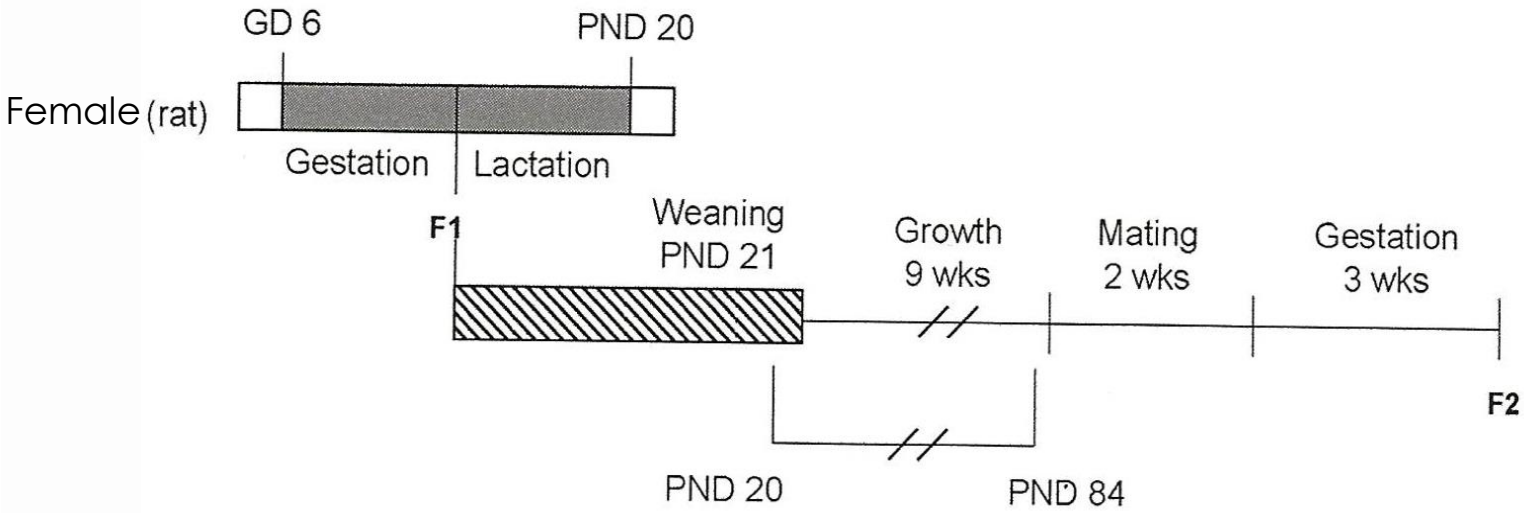
Based on figure from DeSesso et al. (2012); additional data from Bowman et al. (2013); Moffat et al. (2014)

Can safety tests inform placental research?

Safety Tests that Involve Placental Transfer

- Embryo-Fetal Development Tests (EFD)
- (Multigeneration) Reproductive Toxicity Tests
- Pre- and Postnatal Development Test (PPND)

Pre- and Postnatal Development Study (PPND) with Behavioral/Anatomical Measures



Behavioral/anatomic measures

- Motor activity
- Auditory startle
- Water maze/passive avoidance
- Developmental landmark
  - Vaginal patency
  - Preputial separation

Advantages of Pre- and Postnatal Development Study (PPND)

- Assesses functional consequences of mid to late gestational exposure
  - Relevant for risk assessment of monoclonal antibodies
    - Examination of pre-term fetuses not adequate to reveal possible adverse effects on functional development
    - Fetal exposure to maternal IgG increases as pregnancy progresses
  - Useful for understanding real-life exposures that cause effects
    - Helpful for setting exposure levels that can be used in mechanistic models to avoid using super-pharmacological exposures

Is there a "best" placental model?

General comments

- *In vivo* models
  - Incorporate ADME and vascular alterations not yet possible *in vitro*
- Non-human primates
  - Among apes
    - Chimpanzee placenta is nearly identical to human
    - Ethically untenable
  - Among old world monkeys
    - Rhesus is best studied (but problematic)
      - Bi-discoid placenta
      - Superficial implantation
      - Poor invasive potential
      - Prone to abortion
    - Not a particularly good choice

Reproductive and Placental Characteristics of Six Mammals

Characteristic	Human	Mouse	Rat	Rabbit	Guinea Pig	Mini Pig
Female adult weight	60 kg	20 g	280 g	3.5 kg	800 g	50 kg
Gestation Length (days)	266	19-20	22	32	64	115
Litter size	1	6 - 8	10 -16	5 - 8	2 - 4	6 - 8
Neonatal weight	3.3 - 3.5 kg	1.2 g	7 g	30 - 35 g	100 g	740 g
Placental shape	Discoid	Discoid	Discoid	Discoid	Discoid	Diffuse
Placental invasiveness	Hemomonochorial	Hemotrichorial	Hemotrichorial	Hemodichorial	Hemomonochorial	Epitheliochorial
Surface area modifications	Villi	Labyrinth	Labyrinth	Labyrinth	Labyrinth w/subplacental villi	Plicae
Fetal boundary layer in placenta	STB[1]	STB	STB	STB	STB	Cytotrophoblast
Site of FcRn	STB	Visceral endoderm of yolk sac	Visceral endoderm of yolk sac	Visceral endoderm of yolk sac	Visceral endoderm of yolk sac	Cytotrophoblast

[1] Synctiotrophoblast

Data from: Ramsey (1982); Aguilera et al (2022); DeSesso (2012); DeSesso et al (2012)

Summation

Conclusions

- Placentae have disparate anatomies, but common function
- The rodent inverted yolk sac placenta enables materno-fetal exchange early in gestation
- Among safety tests, PPND provides best ability to investigate health effects of immunoglobulins
  - If TK is performed it can inform dose-setting for *in vitro* tests
- Placental research is best considered as a tapestry wherein diverse tests in various systems contribute to our understanding of this complex organ
- There is no single "best" model

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