Developmental Toxicity Testing for Biopharmaceuticals

Placental Transfer Considerations

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Placental Transfer Considerations

- Type of Molecule
  - Small molecular weight drug or chemical (<1000 Da)
  - Large molecular weight protein (non-antibody) or peptide (mwt >1000 Da)
  - Antibody (mwt 150,000 Da)
- Species
  - Human, Non-Human primate, Rabbit, Rodent

Selection of a Pharmacologically Relevant Species for Developmental Toxicity Testing

- The NHP is not the default species for developmental toxicity testing of biopharmaceuticals
- Rats and rabbits are the default species for developmental toxicity testing (ref ICH S5 (R2) and Draft ICH S6 (R1) addendum)
- NHPs should only be considered when rodents and/or rabbits are not pharmacologically or biologically relevant species

Considerations For Using Rodents versus Non-Human Primates for Developmental Toxicity Testing of Antibodies

Placental Transfer

- In primates, IgG antibodies are transported across the placenta during the fetal period
- In rodents, antibodies are transported across the yolk sac during the embryonic and fetal periods

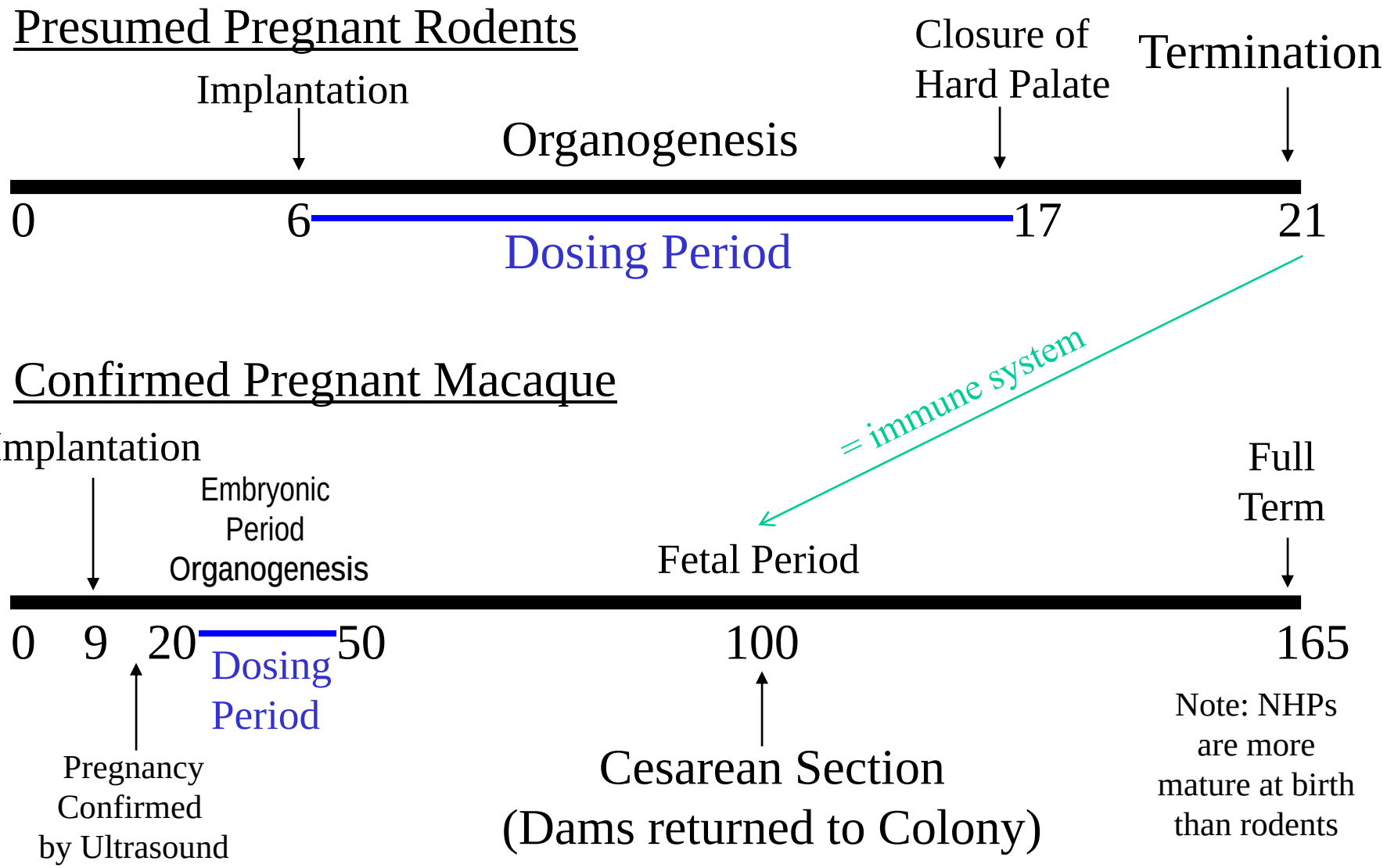
Milk Transfer

- In primates, antibodies secreted in milk are not absorbed across the neonatal gut
- In rodents, antibodies secreted in the milk are absorbed across the neonatal gut

Considerations for Developmental Toxicity Testing – Study Type

- Embryo/fetal development studies (ICHS5 R2)
  - Generally conducted in rats and rabbits
  - Evaluates potential fetal structural abnormalities following exposure of the mother (and potentially also the embryo) during the embryonic period i.e., period of major organogenesis
- Pre and Postnatal Development studies (ICHS5 R2)
  - Generally conducted in rats only
  - Evaluates potential structural and functional consequences in the pup following exposure of the mother (and potentially also the embryo/fetus) during the embryonic, fetal and lactation periods.

Comparison of Rodent and Non-Human Primate Embryofetal Developmental Study Designs



But What About Human Antibodies?

- Human infants acquire antibodies from their mothers during gestation and lactation **– mostly during gestation**
- IgG antibodies are transported from maternal serum to the fetus by receptor (FcRn) mediated placental endocytosis
- IgA and IgM antibodies are not transported across the placenta
- IgA and IgM antibodies are generated locally and act locally at mucosal surfaces
- IgA antibodies generated in the mammary gland and IgG antibodies, are secreted in human breast milk but are not absorbed across the gut

Concentrations of IgG in Human Fetal versus Maternal Serum with Gestational Age

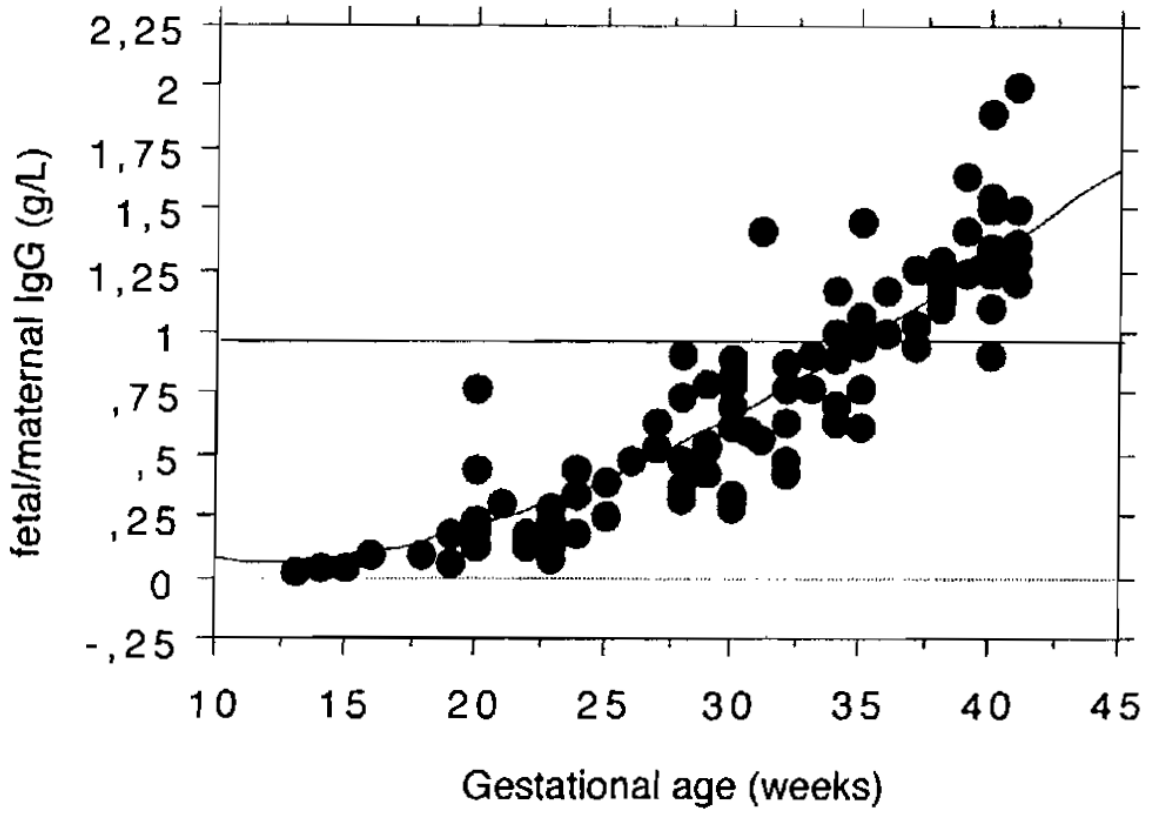
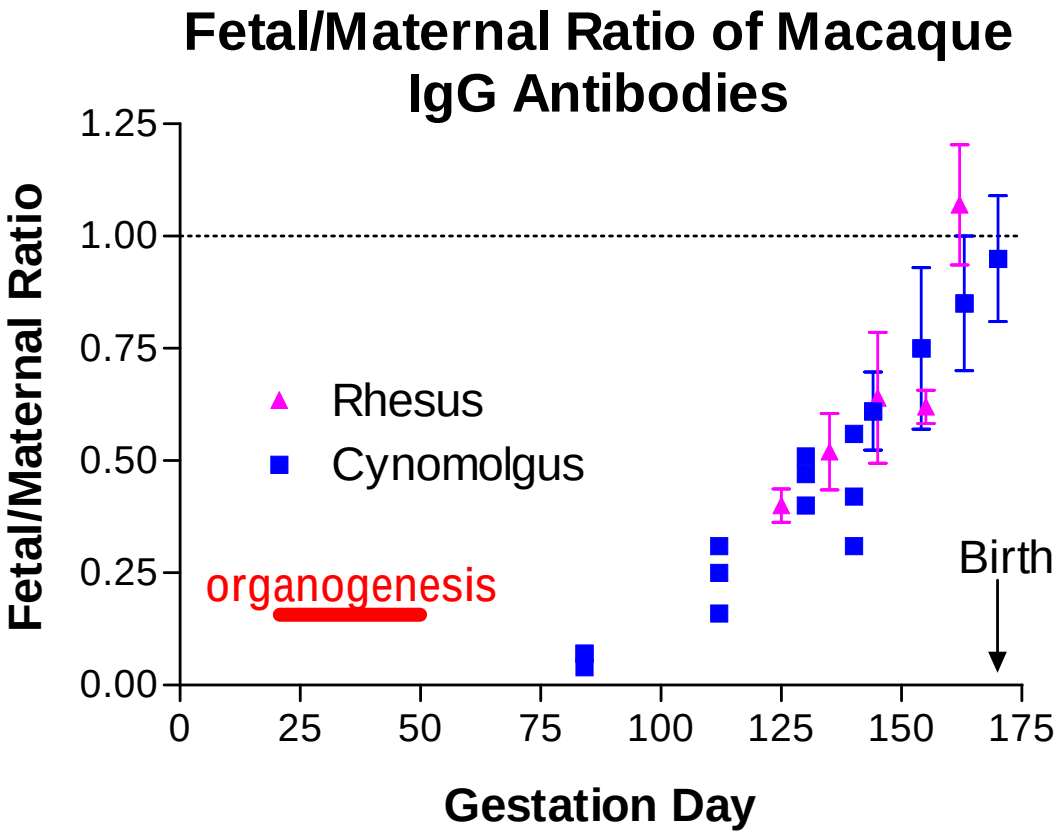


Fig. 3. The relationship between fetal/maternal (f/m) IgG ratio and gestational age (GA), based on 258 measurements of paired samples from six publications, and the regression analysis. f/m IgG = 0.399 – 0.059*GA + 0.003*GA^2 – 2.065^{-5}*GA^3; $R^2 = 0.67$.

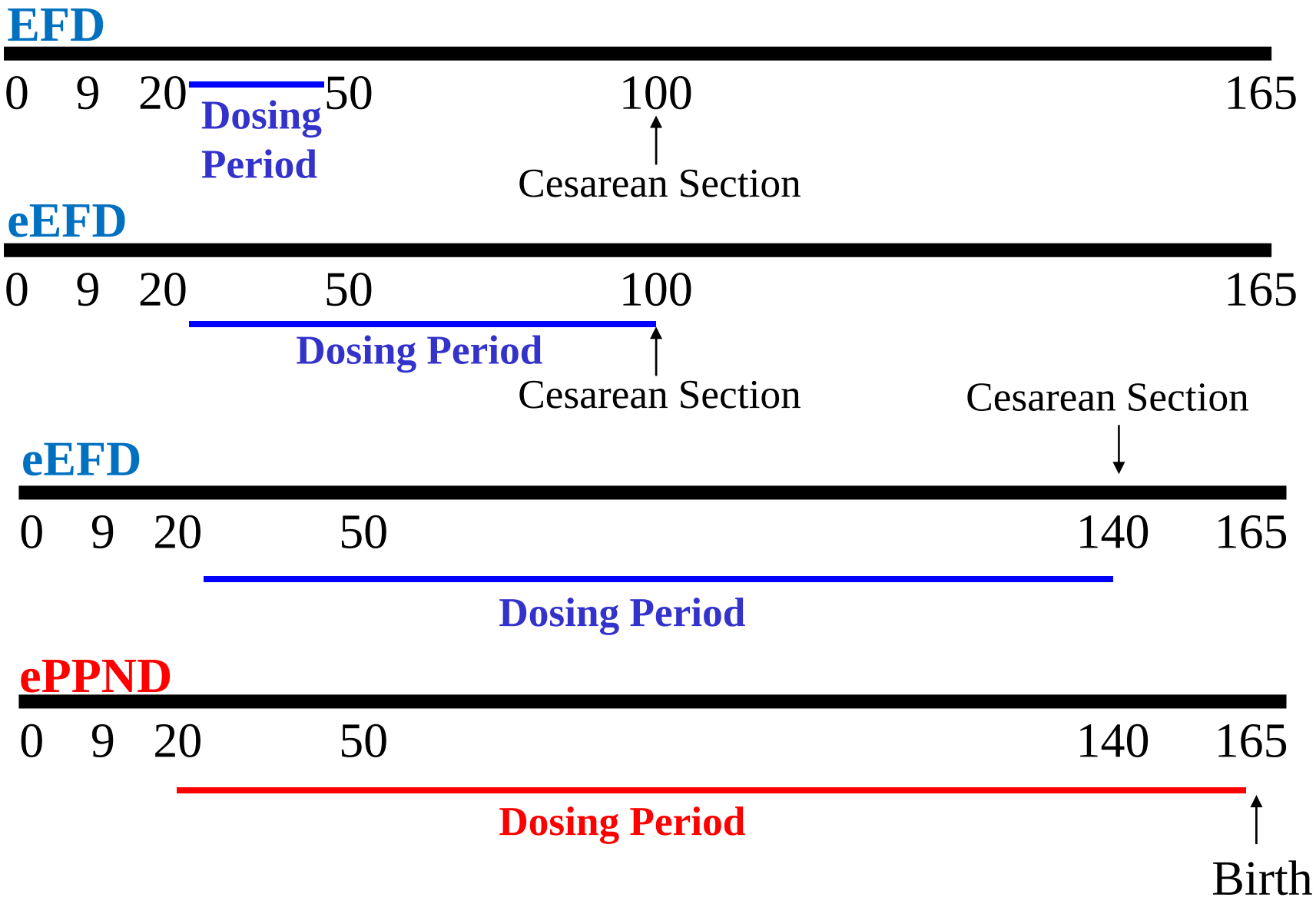
Palfi and Selbing, AJRI 39: 24 – 26,1998

The Timing of Increased Fetal Exposure to IgG is Similar for Macaques and Humans i.e., During the Fetal Period

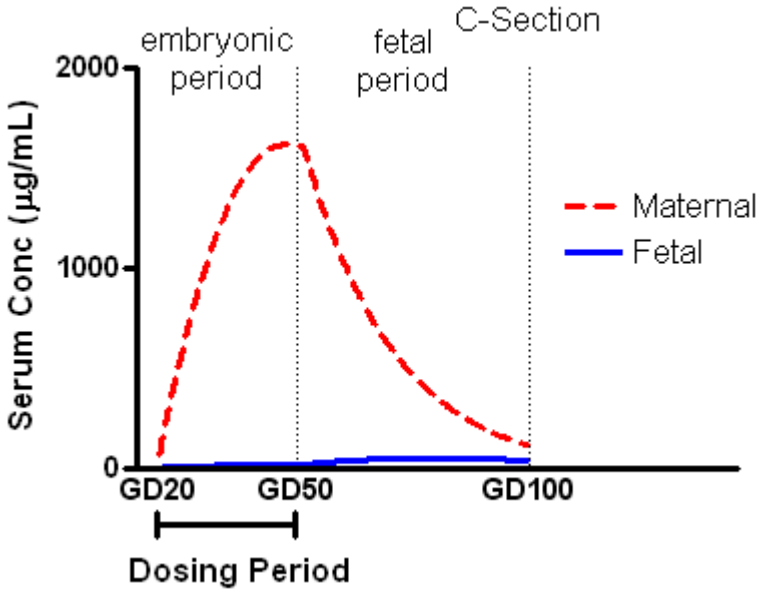


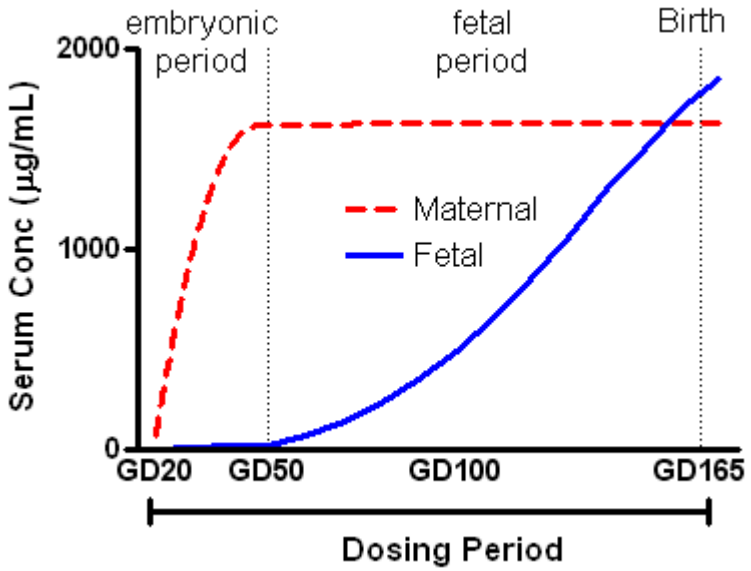
Cynomolgus Data from Fujimoto et al., 1983
Rhesus Data from Coe et al., 1993

Alternate Study Design Options for Developmental Studies in NHPs

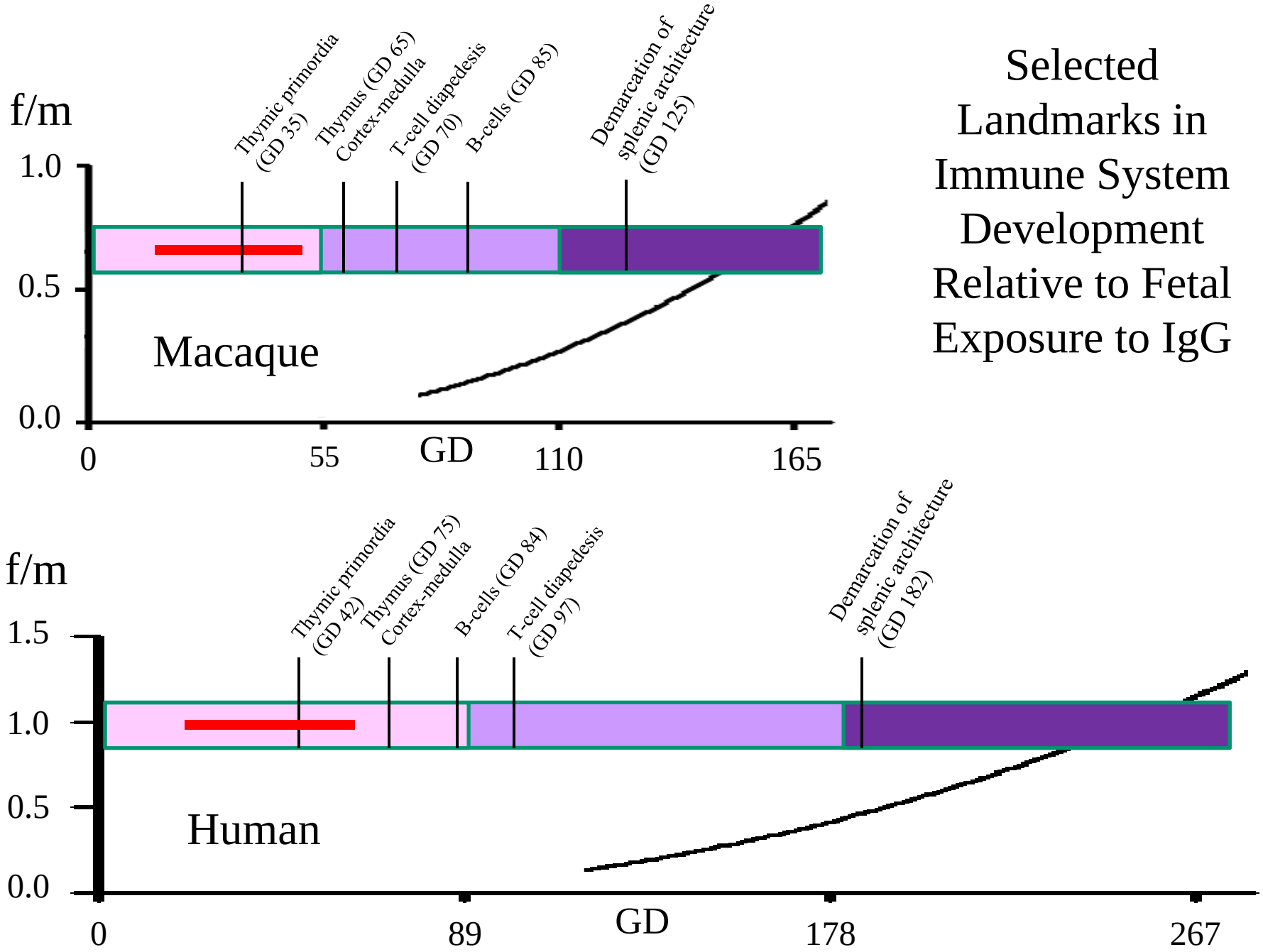


Extending Maternal Dosing into The Fetal Period Increases Fetal Exposure and Covers all Stages of In Utero Development





Assumptions for Fetal:Maternal exposure ratio:
1% on GD20-50, 30% on GD 100 and >100% at birth


Selected Landmarks in Immune System Development Relative to Fetal Exposure to IgG
f/m
1.0
0.5
0.0
Thymic primordia (GD 35)
Thymus (GD 65) Cortex-medulla
T-cell diapedesis (GD 70)
B-cells (GD 85)
Demarcation of splenic architecture (GD 125)
Macaque
0
55
GD
110
165
f/m
1.5
1.0
0.5
0.0
Thymic primordia (GD 42)
Thymus (GD 75) Cortex-medulla
B-cells (GD 84)
T-cell diapedesis (GD 97)
Demarcation of splenic architecture (GD 182)
Human
0
89
GD
178
267

Advantages of the ePPND Study versus Separate EFD and PPND Studies

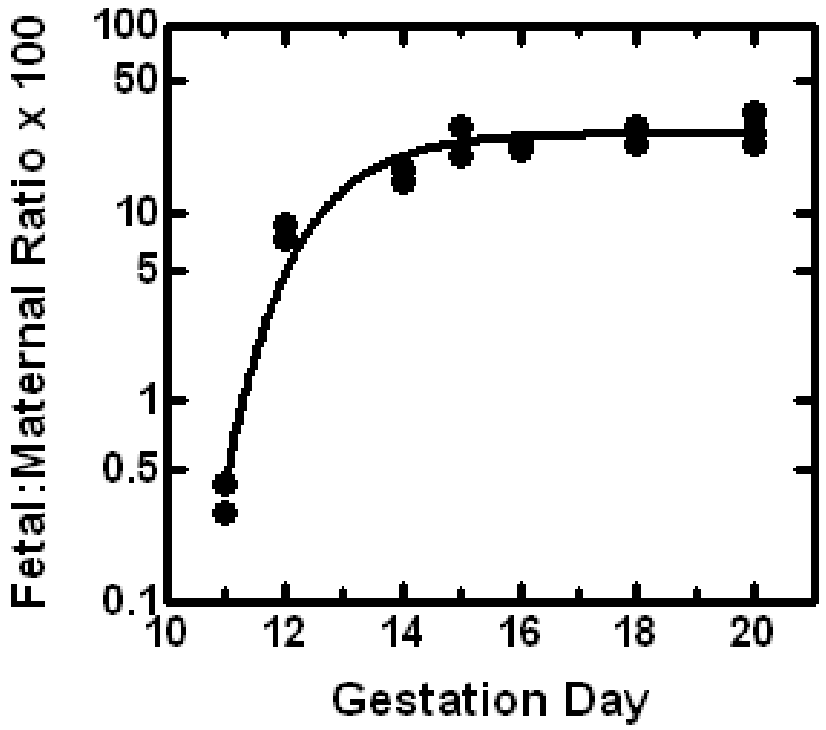
- Evaluates all stages of development in a single study
- Reduces the number of NHPs and number of studies needed for evaluating potential hazards to development
- Optimizes fetal exposure to better identify potential hazards

Testing of Human Therapeutic Monoclonal Antibodies in Rodents

What Do The Text Books Say About Rodent Antibodies?

- Infants acquire antibodies from their mothers during gestation and lactation – **mostly during lactation**
- IgG antibodies are transported from mother to the fetus by transfer across the yolk sac and by swallowing of amniotic fluid
- FcRn in fetal and neonatal gut absorbs antibodies from the amniotic fluid and from the milk

Ratio of Mouse Fetal Tissue Concentrations Relative to Maternal Serum Concentration of Human IgG



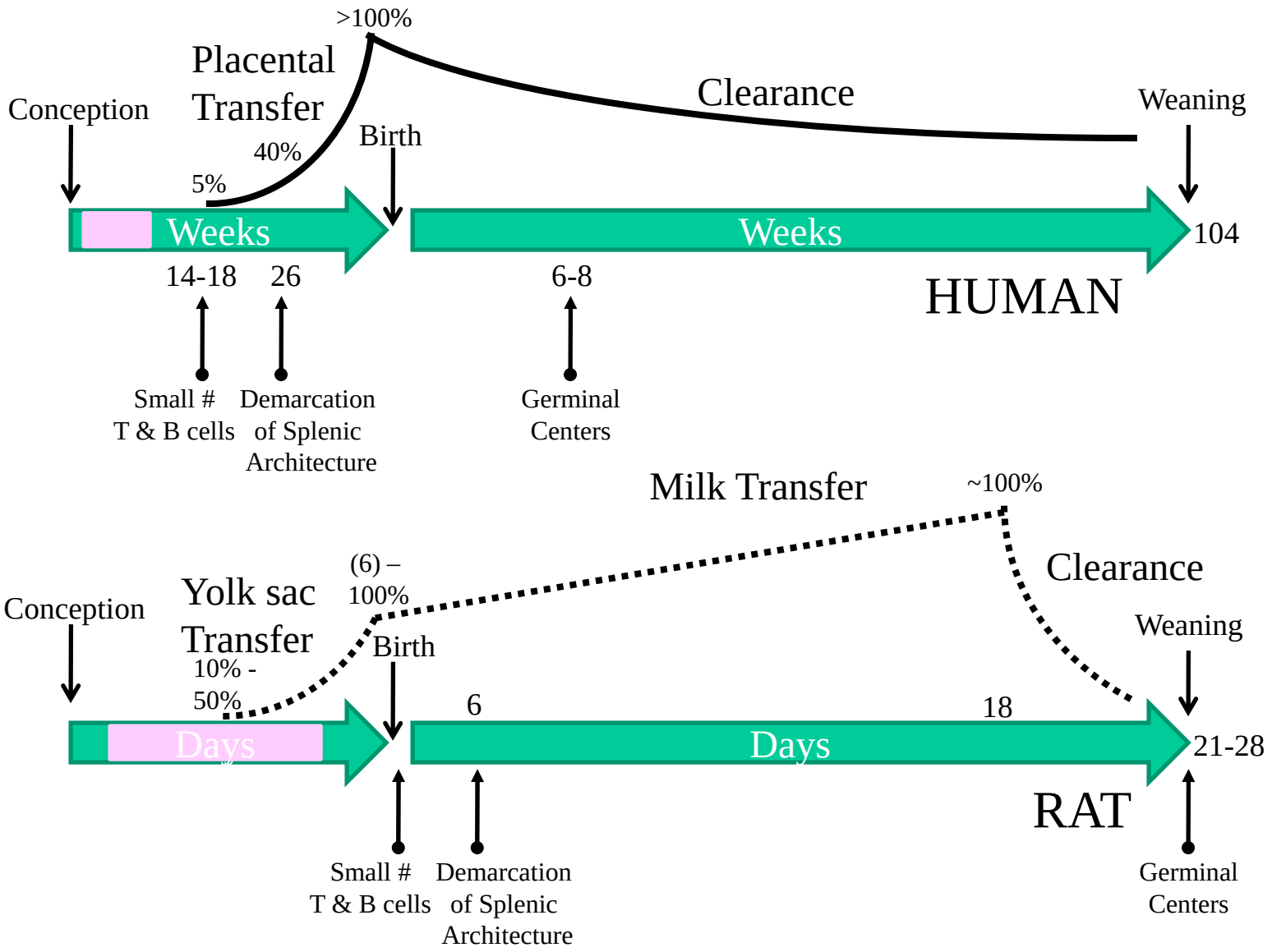
Fetuses were harvested 24 hr after dams received a single IV injection of human ^{131}I-IgG (Morphis and Gitlin, Nature 228:573, 1970)

Experience with IgG Antibodies in Rodent and Rabbits

Species (Period of Major Organo-genesis)	Human IgG1	Human IgG4	Mouse IgG2a	Rat IgG1	Rabbit IgG
Mouse (GD6-15)	-	-	54% GD14[1] 108% GD18[2]	36% GD18[7]	100% GD19/20[6]
Rat (GD6-17)	23% GD18[5] 30% GD21[8] 76% GD21[5]	39% GD18[3] 100% GD 21[3]	-	-	-
Rabbit (GD6-18)	< 1% GD19[4] 1.4% GD19[8] >100% GD29[4] 100% GD29[8]	7% GD20[3]	-	-	-

[1]Martin et al., *Int J Toxicol, 27:341–347, 2008*, [2]Clarke et al *Reg Toxicol Pharmacol 40: 219-226,2004*, [3] Martin et al., 2010a, [4] Martin et al., 2010b, [5]Centocor unpublished, [6]Mohanty et al., *J Reprod Immunol 84:133-144, 2010*, [7]*Actemra www.drugs@fda.gov*, [8]Novartis unpublished

Hypothetical Representations of Fetal Exposure Relative to Immune System Development in Humans and Rats Treated with an IgG Monoclonal Antibody During Gestation and Lactation



Recommendations

- Rodents or rabbits can be used for developmental toxicity testing to identify potential hazards
  - The differences between rodents and primates do not preclude the use of rodents but the differences do need to be understood
- When NHPs are the only relevant species a single ePPND study can be conducted
  - Study can be delayed until Phase III
  - Patients in Phase I and Phase II clinical trials take precautions to avoid pregnancy
  - The ePPND study can be conducted using a single treatment group only
- Rodent surrogate molecules or transgenic rodents can be used if scientifically justified

Relevant References

BioSafe White Papers

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