Is the experience with cloning in mice and cattle relevant to other species ?

What are the abnormalities and their likely causes?

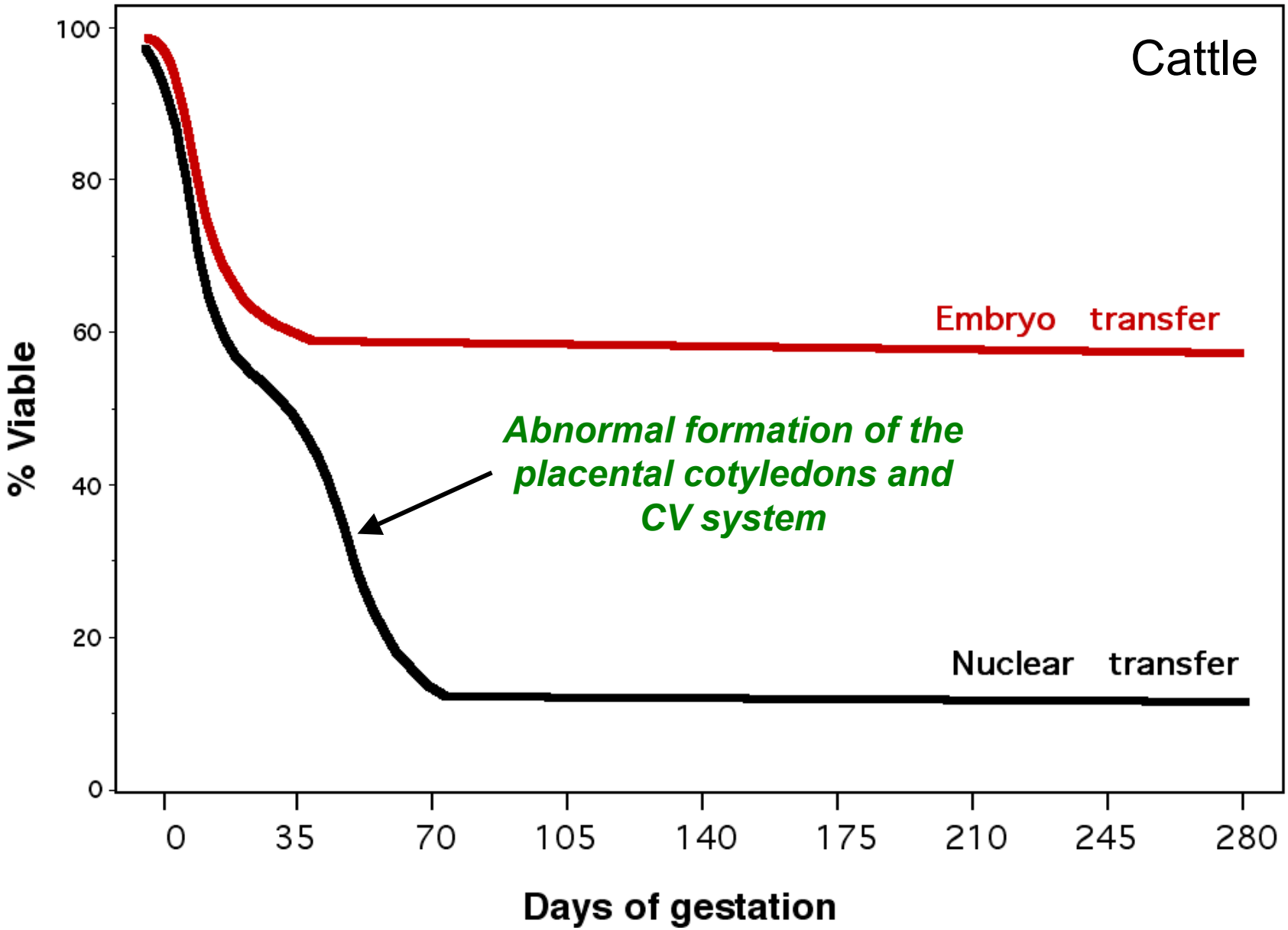
Is embryonic development similar among species?

Abnormal Development of Cloned Murine and Bovine Embryos

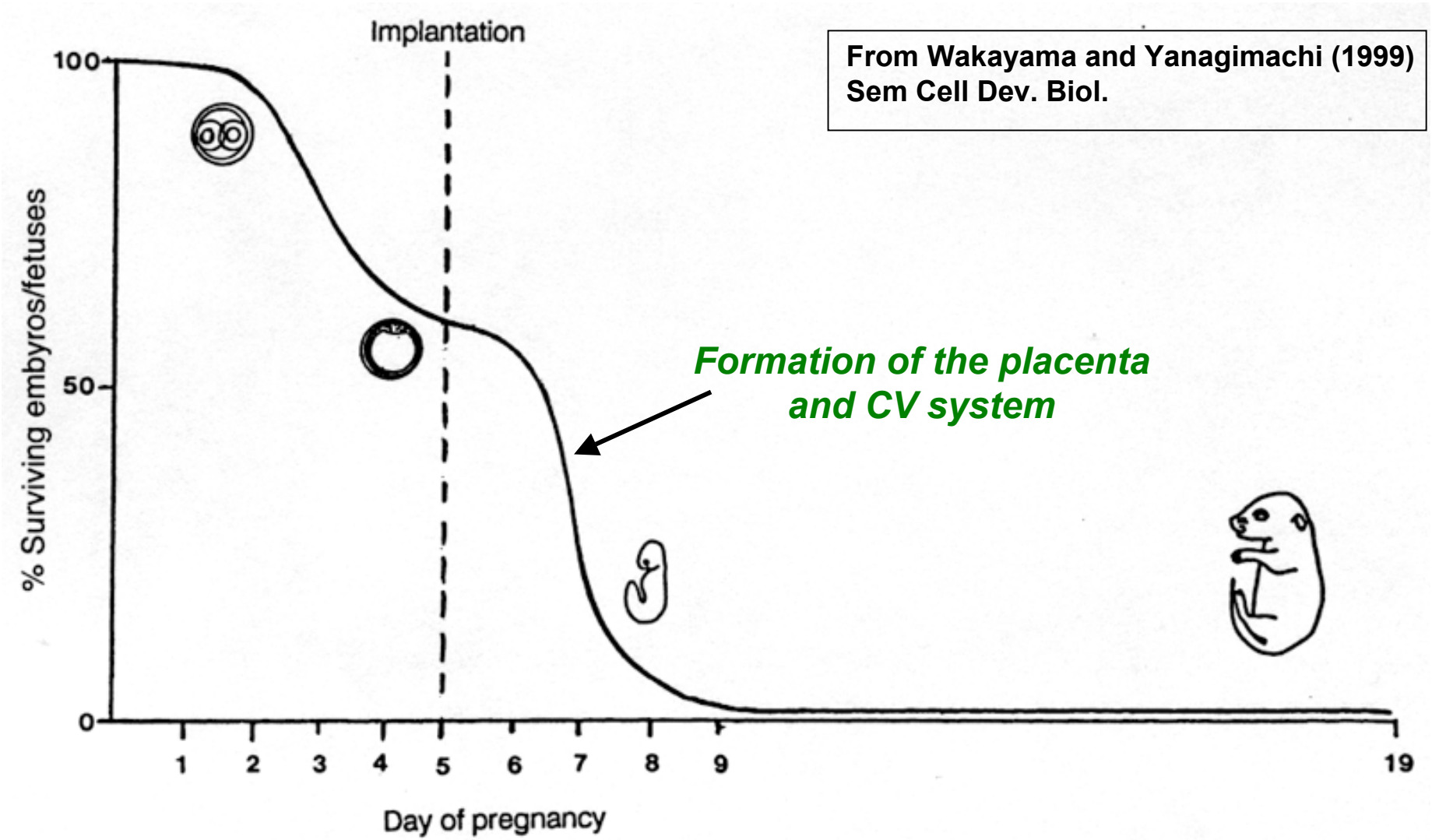
- "Large Offspring Syndrome"
  - Congenital anomalies
  - Fetal overgrowth
  - Placental hypertrophy

- High embryonic mortality
  - Mice: 95 - 98%
  - Bovine: 75 - 98%

Significant Embryonic Losses Associated with Cloning

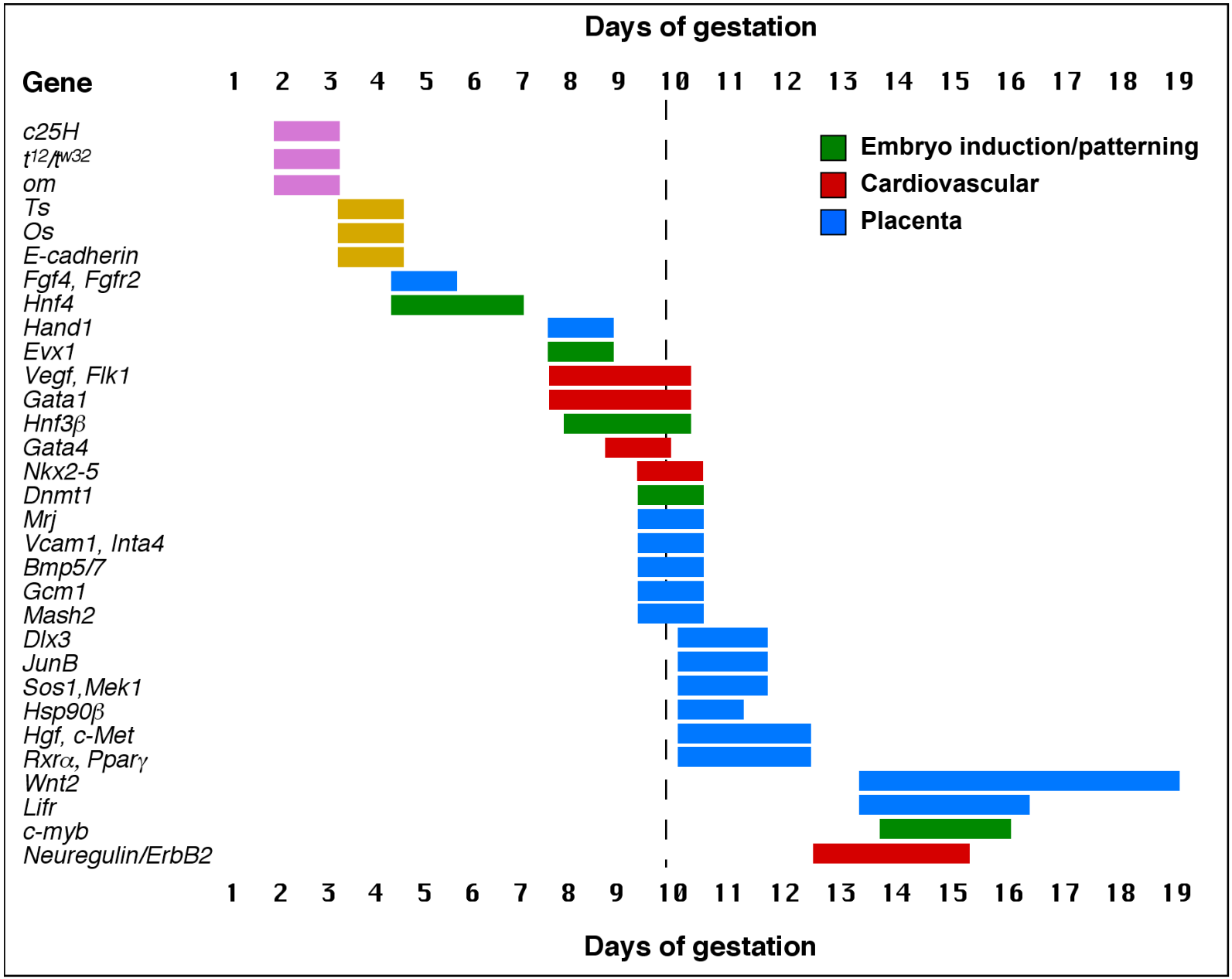


Embryonic Losses Associated with Cloning in Mice



From Wakayama and Yanagimachi (1999) Sem Cell Dev. Biol.

Embryonic Lethal Mutations in Mice



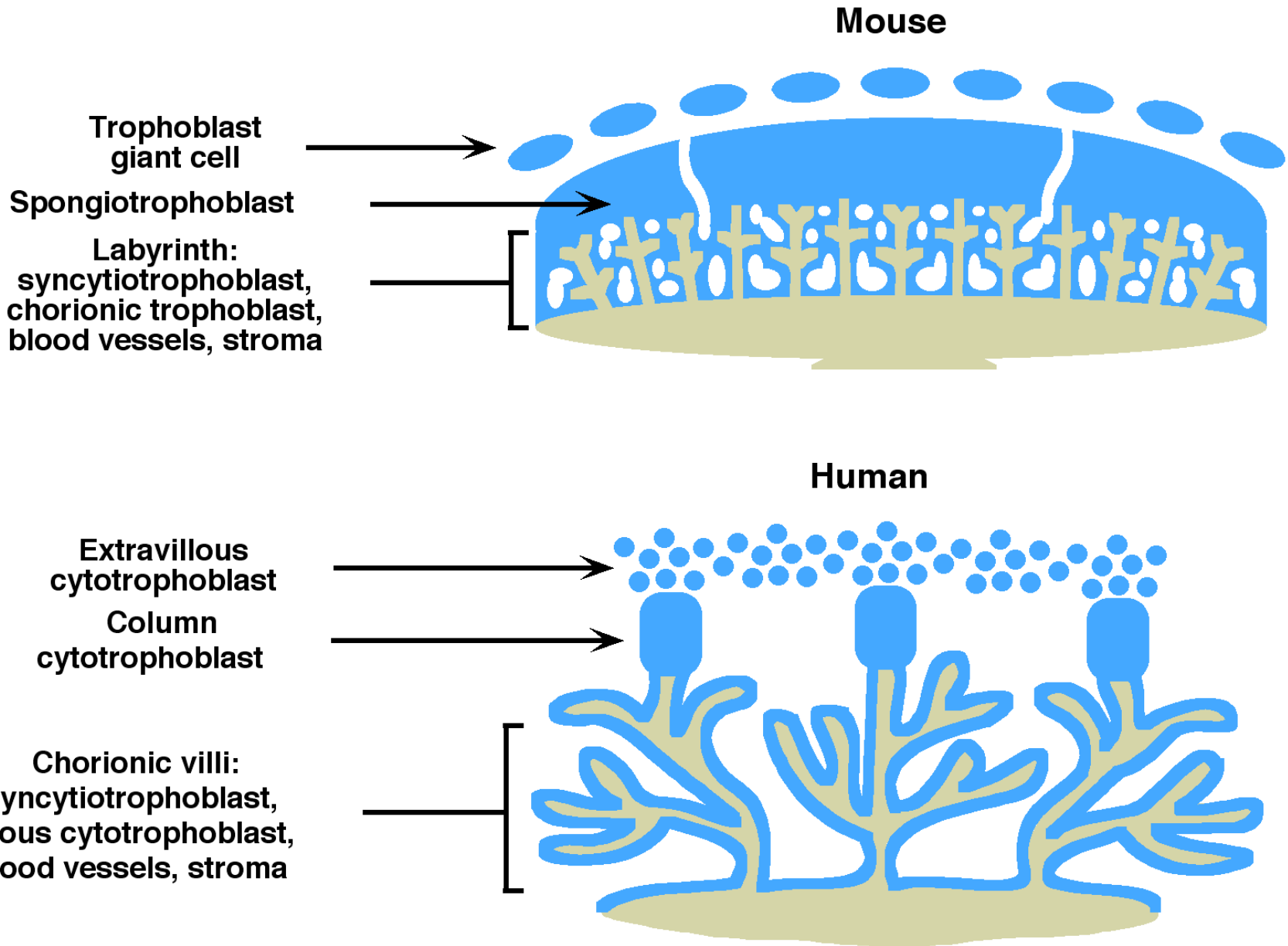
Is the experience with cloning in mice and cattle relevant to other species ?

- **Likely causes of abnormalities ?**

  - abnormal *placental development* is implicated in both early and late complications

- **Is placentation similar among mammalian species ?**

Comparison of the Mouse and Human Placenta



Invasive Trophoblast

Function: Endocrine, targeting maternal systems

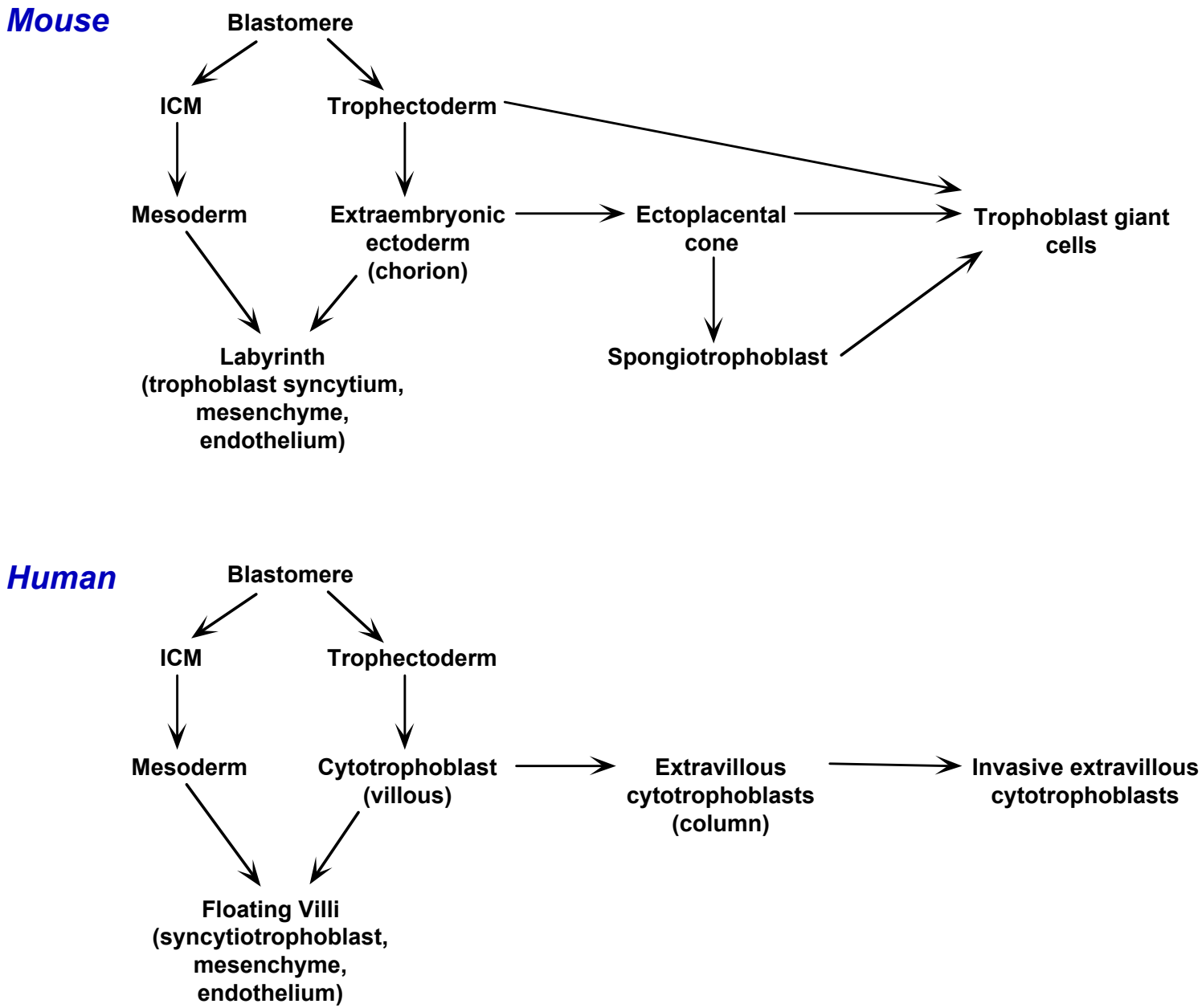
	Human	Mouse
Formal name	extravillous cytotrophoblast	trophoblast giant cell
Invasive	yes	yes
Proliferative	no	no
DNA content	polyploid (4N-16N)	polyploid (up to 1000N)
Vasodilator production	NO, CO, adrenomedullin	adrenomedullin
Angiogenic factor production	VEGF	VEGF, proliferin

Barrier / Transport Trophoblast

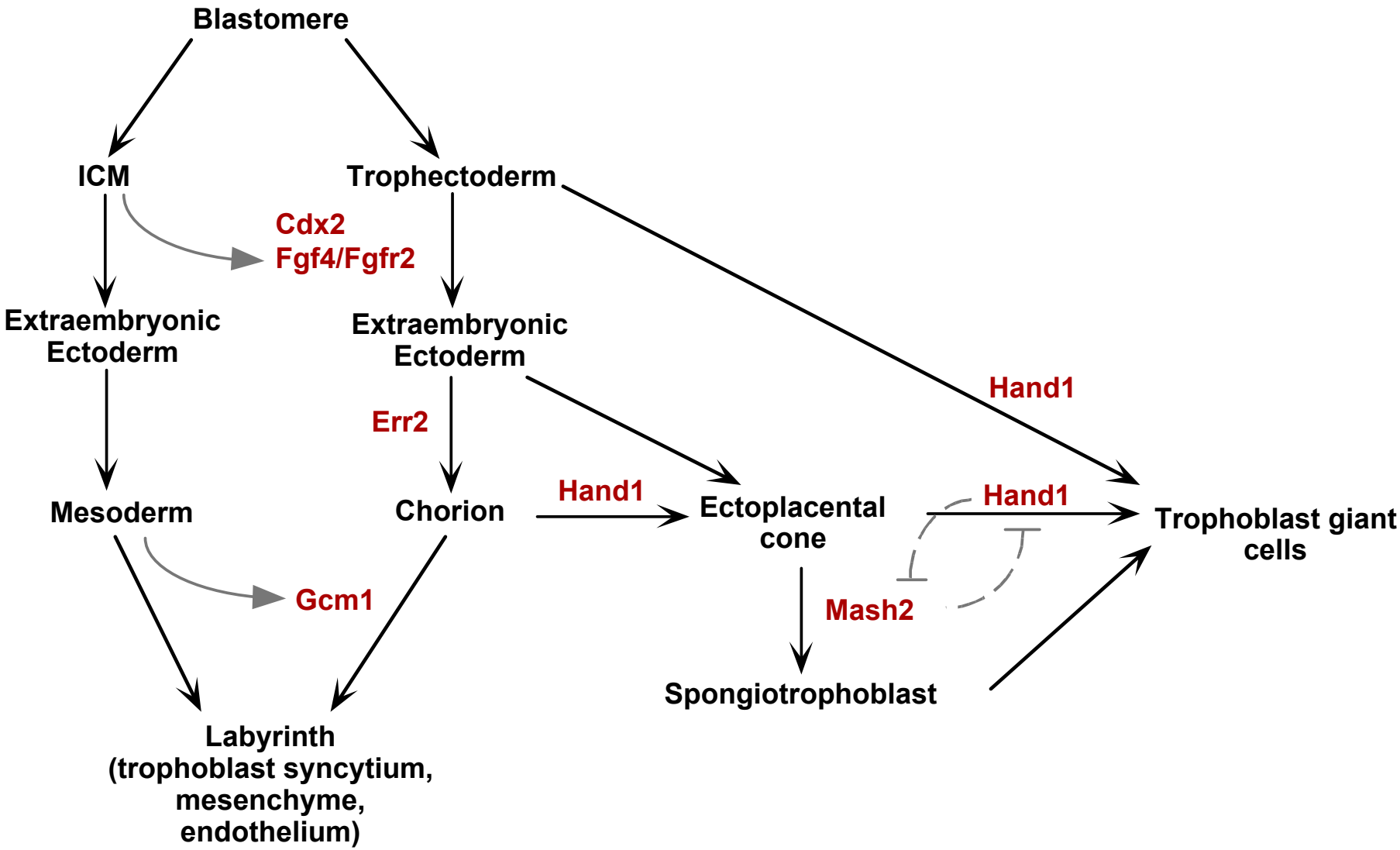
Function: Nutrient and gas exchange

	Human	Mouse
Formal name	chorionic villi	labyrinth
Haemochorial	yes	yes
Syncytiotrophoblast surface	yes	yes
formed by cell fusion	yes	yes
nuclear DNA content	diploid	diploid
Villi form by branching	yes	yes

Placental Development in Mice and Men



Regulation of Mouse Placental Development



Trophoblast subtype-specific gene expression in humans and mice

Gene	Humans	Mice
• *Id2*	villous cytotrophoblast	chorionic trophoblast
• *Gcm1*	syncytiotrophoblast & precursor	syncytiotrophoblast & precursor
• *Mash2*	column cytotrophoblast	spongiotrophoblast
• *Mmp9*	invasive cytotrophoblast	trophoblast giant cells

Imprinting and Feto-Placental Growth and Survival in Mice

Chromosome	Effect of UPD	Gene	Expressed Allele	Placenta Function	Human Expression
2 (proximal)	embryonic survival & fetal/placental growth	?			
6 (proximal)	embryonic survival & fetal/placental growth	?			
7 (distal)	embryonic survival & fetal/placental growth	*H19*	M	spongiotroph/glycogen cells	yes
		Igf2	P	spongiotroph/glycogen cells	yes
		Impt1	M	?	yes
		Kip2	M	giant cells, labyrinth	?
		Mash2	M	spongiotrophoblast	yes
11 (proximal)	fetal/placental growth	*Meg1/Grb10*	M	?	
12 (distal)	embryonic survival & fetal/placental growth	*Dlk*	M	?	
		Meg3/Gtl2	M	?	
18 (proximal)	fetal/placental growth	*?*			

Comparative Placental Development

- What's the same ?
  - General development, design (e.g., villous) and cell subtype composition
  - Genes regulating development

- What's different ?
  - Gross morphology (e.g., numbers and positions of cotyledons)
  - Some physiological (e.g., endocrine) and transport functions
  - Length of gestation

Comparative Development