The “Decoding Embryonic Lethal Phenotypes In Knock-Out Mouse” (DELPHIKOM) project

Olivia Wendling, Fabien Pertuy, Didier Hentsch*, Hugues Jacobs, Mohammed Selloum, Patrick Reilly, Tania Sorg, Manuel Mark* and Yann Hérault

Institut Clinique de la Souris-ICS-MCI, PHENOMIN, CNRS UMR7104, INSERM U964, Université de Strasbourg, 1 rue Laurent Fries BP 10142 Parc d’Innovation 67404 Illkirch, France;
* IGBMC, CNRS UMR7104, INSERM U964, Université de Strasbourg, 1 rue Laurent Fries BP 10142 Parc d’Innovation 67404 Illkirch, France;

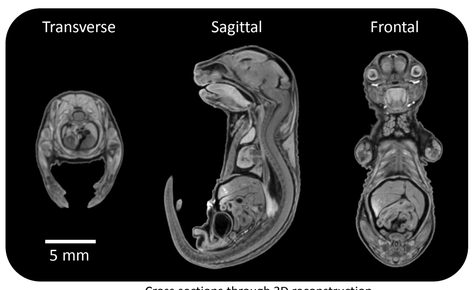
Strategy of embryonic phenotyping at ICS/phenomin - New 3D imaging technologies

The goal of the IMPC (18 research institutions) is to discover functional insight for every gene by generating and systematically phenotyping 20 000 knockout mouse strains. IMPC revealed that 35 % of mouse lines are lethal during embryonic development or before weaning. At ICS/ phenomin , on the 96 lines we are currently studying , 12 lines are subviables (13/15 %) and **42 lines are lethal in utero or around birth (43% lines)**

E18,5

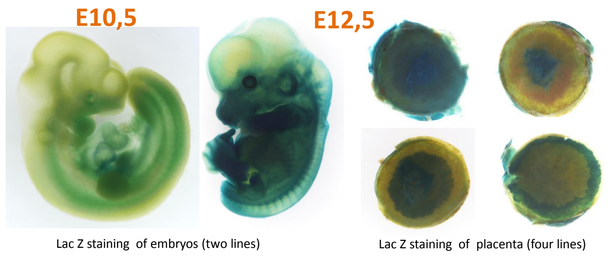
3D reconstruction

3D display of the skeleton



Cross sections through 3D reconstruction

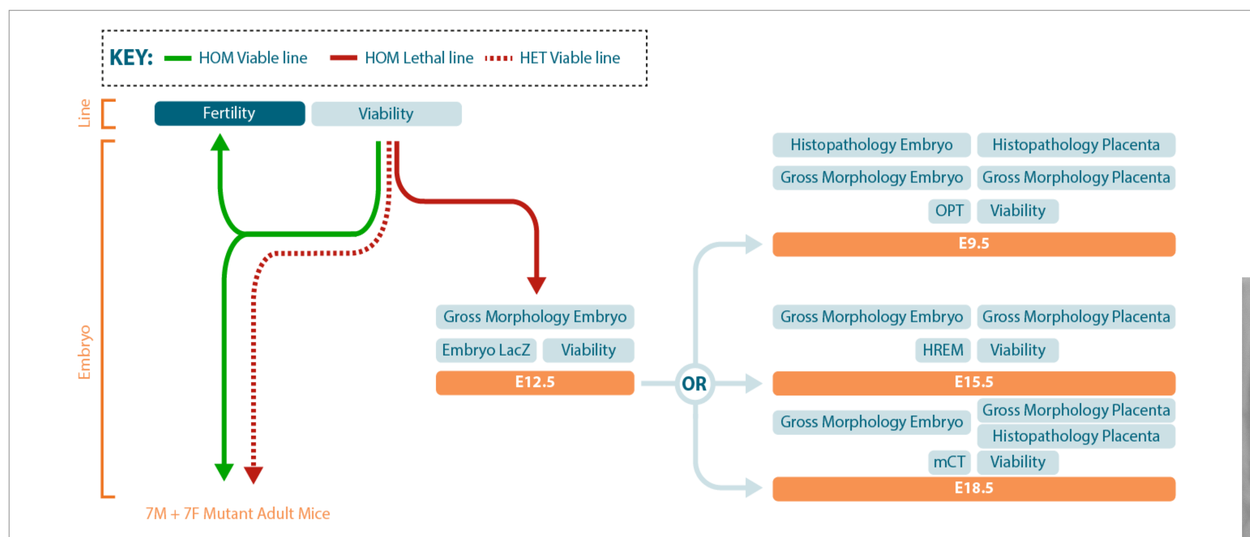
E10,5 E12,5



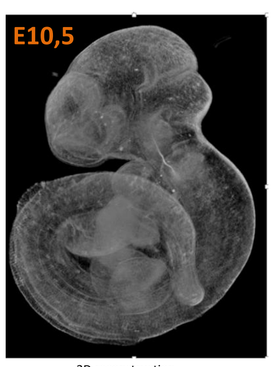
Lac Z staining of embryos (two lines) — Lac Z staining of placenta (four lines)

The LacZ KnockIn constructs of the lines, permits to determine the expression patterns of the genes by detection of the *LacZ* product

Micro-CT has become an option to image mouse embryos since protocols are available to provide contrast to soft tissues (e.g. Lugol). ICS/MCI has acquired a Quantum Fx µCT high-speed *in vivo* system for adult and embryonic phenotyping.



E10,5



3D reconstruction

Under development

3D data automatic volumetric analysis under development

Under development

E15,5

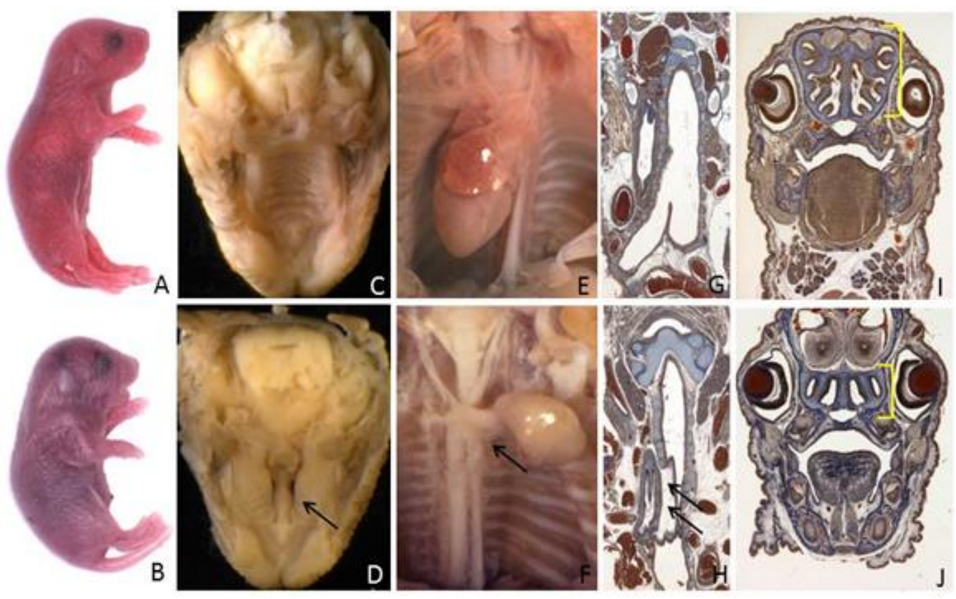
HREM raw images

3D reconstruction

OPT (Optical Projection Tomography) follows the principle of micro-CT for analyzing the anatomy and study gene expression pattern of mouse embryos at stage E12 or younger. We implemented the technology at the ICS/MCI with the help of the IGBMC imaging center and Dr. Mark Henkelman, Toronto Center for Phenogenomics.

HREM (High Resolution Episcopic Microscopy) is an interesting alternative to histology. The technology is based on optical block-face imaging and permits to give high resolution images. Dr Timothy Mohun, (MRC, London) who co-invented HREM, helped us in implementing the system at the ICS/MCI in cooperation with the IGBMC imaging center.

Some examples of lines presenting neonatal lethality

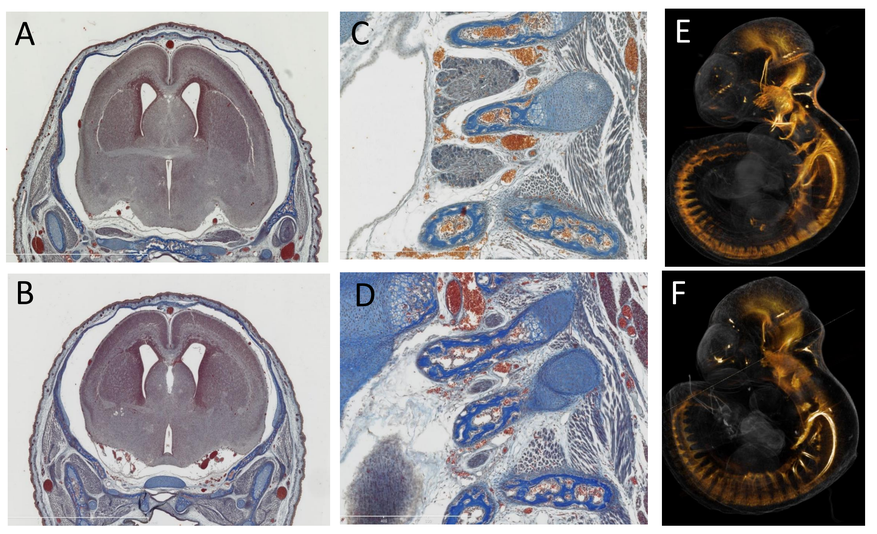


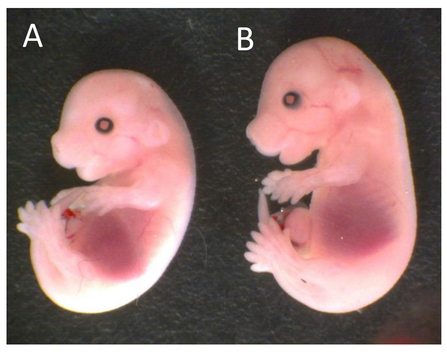
Abnormalities of *Kdm8* knockout mice at stage E18.5. A, C, E, G, I: WT fetuses; B, D, F, H, J: mutant fetuses. A, B: external views of fetuses during the “viability test”. C to F: photomicrographs of the palate and heart taken during necropsy. G to J: histological sections of the trachea and the nasal cavities. *Kdm8* knockout mice are growth-retarded. They are unable to breath and remain cyanotic. They display micrognathia, tracheal cartilage abnormalities, cleft palate, retro-oesophageal subclavian artery, and hypoplasia of ethmoid turbinates.

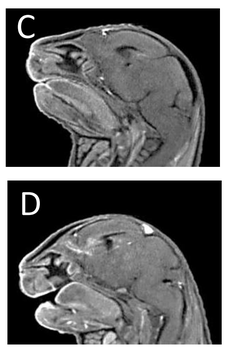
Discover PHENOMIN:

Contact ICS:

Abnormalities of *Tubb3* mutant mice at stage E18.5 and E10.5. A, C, E, : WT fetuses; B, D, F : mutant fetuses. A- D: histological sections of the head and the vertebral column. E, F : OPT 3D reconstruction of E10,5 embryos stained with an anti-neurofilament staining. At E18,5, Tubb3 mutant mice don’t move during the pinching test, they are unable to breath and remain cyanotic. They display a severe hypoplasia of trigeminal ganglions and dorsal root ganglia, an absence of anterior commissure to cross the midline. A E10,5, tubb3 mutants display cranial nerves abnormalities.







Abnormalities of *Nxn* knockout mice at stage E15.5 and E18,5. A, C: WT fetuses; B, D : mutant fetuses. A, B: external views of fetuses at E15,5. C, D: sagittal cross sections through micro CT 3D reconstruction. *Nxn* mutants display facial hypoplasia and cleft palate.

Abnormalities of *Grhl3* knockout *mice* at stage E18.5. A, D: WT fetus; B, C, E : mutant fetus. A, B: micro CT 3D reconstruction, D, E: frontal cross section through 3D reconstruction, C: external view. They display spina bifida, smooth skin, pyelocaliceal dilation in the kidney.