The DMDD consortium brings together scientists from across the UK developmental biology community, involving seven national research centres and with leading researchers in virtually every facet of mammalian embryo development.

Similar projects around the world

DMDD is only the UK part of a worldwide effort coordinated by the International Mouse Phenotyping Consortium (IMPC).

Similar work is already underway at the Toronto Centre for Phenogenomics - more will soon start in the USA, France and Japan.

Following receipt of the Wellcome Trust Strategic Award, the 5 year DMDD programme got underway in 2013.

Its aim is to study “embryonic lethal” mouse mutations, and begin to understand why their mutation has such profound effects on embryo development and survival.

Around two thirds of all embryonic lethal mutations have a direct impact on the developing embryo, causing major structural abnormalities.

Over the next 5 years, DMDD will study more than 200 embryonic lethal gene knockout lines produced at the Sanger Institute. We are using the latest 3D imaging and transcriptomics to identify embryo malformations and investigate their likely cause.

Some embryonic lethal mutations will affect the placenta (which supports embryo growth in the womb), so the structure of the placenta is being routinely examined.

In other cases, embryos may appear completely normal but will still die around birth because of more subtle defects affecting neural tissue. For these mutants, specialised imaging will be used to study the arrangement, distribution and connections of nerves.

The latest DNA sequencing resources of the Sanger Institute are being deployed to study the early embryo transcriptome of mutant lines, to identify key changes in gene expression caused by gene deletion. Together with the imaging data and the catalogue of abnormalities, this will provide a unique resource for developmental biologists and a new opportunity for clinicians studying developmental abnormalities.

All data generated by DMDD is freely available to the biomedical community and the DMDD website is launching in the first half of this year. This will go hand in hand with efforts to engage the developmental biology and clinical research communities, bringing them together to exploit a unique opportunity to better understand normal development and developmental disease.
Wax sections are being scored to identify any placental abnormalities which may be causing embryo malformations or compromise embryo development.

Myriam Hemberger
PLACENTAL HISTOLOGY

‘‘
Wax sections are being scored to identify any placental abnormalities which may be causing embryo malformations or compromise embryo development.

Myriam Hemberger
PLACENTAL HISTOLOGY

‘‘
We know from our zebrafish embryo studies that the latest sequencing techniques can identify how any mutation affects the transcriptome and provide clues about the molecular disruptions each mutation causes. Using the same approach in the mouse gives us an exciting way to study developmental abnormalities.

Derek Stemple
TRANSCRIPTOMICS

‘‘
We are using micro CT for non-invasive imaging, and HREM for higher resolution imaging. Both give 3D models with exquisite detail, enabling anyone to study embryo tissue architecture.

Tim Mohun
IMAGING

‘‘
Using a cocktail of antibodies gives us a powerful way to identify abnormalities in neural architecture and tissue arrangement in the brain and spinal cord.

Corinne Houart
PERINATAL LETHALS

‘‘
PROGRESS SO FAR

Delivering the DMDD programme is an enormous challenge, but we are making good progress:

- Each participating centre has tested and refined the analysis methods they will use
- Embryonic lethal lines have started to come from the mouse gene knockout project at the Sanger Institute and the first ones have been analysed
- A website capable of hosting and delivering terabytes of image data has been built
- A procedure for systematic phenotyping of malformations from image data has been created
- Custom software for annotating of 3D image data has been written
- A database of image data from over 100 wild-type embryos has been assembled to provide a comprehensive reference source

NEXT STEPS

As we build up the numbers of mutant lines analysed over the coming year, we aim to:

- Launch the DMDD website, providing access to all image data and phenotype annotations for every embryo analysed
- Pilot transcriptomics as a tool to identify candidate gene pathways disrupted in each mutant line
- Use the unique library of wild-type image data to explore important aspects of normal development such as heterochrony
- Pilot the use of automated computer analysis of embryo image data to assist in phenotyping
- Explore the possibility of providing arbitrary reslicing of 3D embryo image data online
- Provide the opportunity to download image data online
- Develop the novel software annotation tool DMDD has created to allow its use in a wider range of contexts by the research community

SHARING DATA

At the heart of the DMDD programme is the commitment to make the wealth of data generated freely and readily available to the biomedical community via a dedicated website, launching later this year.

This will include the ability to search by gene, phenotype or affected tissue, view all image data and access the transcriptome profile obtained for that mutation.

Image data from several embryos can be viewed simultaneously online, along with the phenotype data scored by anatomical experts.

Image stacks optimised for 3D modelling will also be available for download to encourage further study.

To offer all this, we have been developing a dedicated, user-friendly web interface that allows seamless, and realtime access to the vast amounts of data DMDD is collecting.

In the meantime, if you would like to look at any of the image data, take a look at our prototype website:

http://embryoimaging.org

If you want any for further study, we can ship this to you. You’ll find contact details on the last page.
Genes so far known to cause placental defects. The DMDD programme will identify others.

- Alleles analysed (pilot study & DMDD)
  - 100

- Mutant lines analysed (DMDD)
  - 8

- Wild-type embryos analysed
  - 193

- Mutant lines from pilot studies (data available)
  - 92

- Images on the website
  - ~150

- Wild-type embryos analysed
  - 1,874,507
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