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PRIME

**Priorities for mouse functional genomics research across Europe:
Integrating and strengthening research in Europe**

Instrument: Coordination Action

Thematic Priority: Life sciences, genomics and biotechnology for health

**Deliverable No.'s 09 and 13
Report of networking meetings**

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RE	Restricted to a group specified by the consortium (including the Commission Services)	
CO	Confidential, only for members of the consortium (including the Commission Services)	

PRIME

Deliverable No. 9: Report of networking meetings held – aims and main conclusions

***EuroPhenome* - 7th – 8th September 2006 - Munich**

One of the current challenges in mouse functional genomics is to determine the function of every gene in the genome. The mouse research community in Europe is undertaking this by setting up high-throughput screening of knock-out mouse lines to determine the resulting phenotype. A key part of this endeavour is having suitable database systems to store the data from the phenotyping tests so that data from different clinics can be added, there is easy access to the whole research community and the data is well presented and easy to search.

The phenotyping data will be obtained in the EUMODIC project, which was funded in the last call of FP6 and started February 2007. Four mouse clinics (German Mouse Clinic (at HMGU), Mouse Clinical Institute (MCI/ICS), Wellcome Trust Sanger Institute and The Harwell Mouse clinic (MRC MGU) will perform the phenotyping. Prior to the start of the project, members from the clinics and their bioinformatician met under the auspices of EuroPhenome on 7th and 8th September 2006 in Munich to establish the range of data that would be collected and possible systems to use (see agenda at Appendix 1). Presentations were given (on day 2) on local systems (LIMS) used for data capture in the various clinics, the format for the EuroPhenome database and ways to search and analyse the data (phenostat). There was also the opportunity to discuss coordination with the secondary phenotyping partners, breeding and welfare issues.

This was a valuable meeting and enabled the bioinformatics to lead the phenotyping effort rather than the more usual situation where the data is collected and grows organically before systems are put in place to store and process it logically.

***InterPhenome* – 9th September 2006 – Munich**

As well as the European initiative to perform high-throughput phenotyping, there are a number of other initiatives worldwide where large amounts of phenotype data are being collected. The International Phenome or InterPhenome committee was established by PRIME to bring these bioinformaticians together. The meeting on 9th September in Munich was attended by bioinformaticians from Europe, USA and Japan. The various institutes were given the opportunity to describe their phenotyping programmes and associated databases. There was a session to compare the two main mouse ontologies being developed (PATO and Mammalian Phenotype Ontology). The European resource of phenotype screen (EMPreSS) and its associated database (EuroPhenome) were presented in detail. A report of the meeting is given in Appendix 2.

As a result of this meeting the group wrote a paper on the integration of mouse phenotype data resources published under their fuller name of the Mouse Phenotype Database Integration Consortium.

Reference: J. Hancock *et al.*: Mouse Phenotype Database Integration Consortium: Integration of Mouse Phenome Data Resources, Mammalian Genome, Volume 18, 157-163 (2007). See Appendix 3.

The authors include representatives from:

- MRC Mammalian Genetics Unit, Harwell, UK
- Wellcome Trust Sanger Institute, Cambridge, UK
- BSRC Fleming, Greece
- The Jackson Laboratory, USA
- Mammalian Genetics & Genomics Group, Oak Ridge National Laboratory, Oak Ridge, Tennessee, USA
- MRC Human Genetics Unit, Edinburgh, UK
- Institute of Experimental Genetics, GSF National Research Center for Environment and Health, Germany
- Department of Genetics, University of Cambridge, UK
- Institut Clinique de la Souris, France
- RIKEN Genomic Sciences Center, Japan
- Helmholtz-Zentrum für Infektionsforschung GmbH, Braunschweig, Germany
- University of Manchester, UK
- European Bioinformatics Institute, Wellcome Trust Genome Campus, UK
- Mouse Biology Unit, EMBL Monterotondo, Italy
- Department of Physiology, Development and Neuroscience, University of Cambridge, UK
- Computing Laboratory, Oxford University, UK
- MRC Mary Lyon Centre, Harwell, UK

PRIME has also established a website (<http://www.interphenome.org>) and a bulletin/information exchange site (or wiki) to act as a central coordinating site for the InterPhenome group. This has open access so that members of the mouse community not currently represented can comment and take part in the group's activities.

InterPhenome - 23rd February 2007 – Barcelona

The InterPhenome group met again on 23rd February 2007 in Barcelona. This meeting included representatives from RIKEN, EuroPhenome, The Jackson Laboratory and MGI. This meeting was focused on discussing the formats for describing a phenotyping procedure (SOP), e.g. purpose of the screen, technical requirements, procedure, etc.. The full report of this meeting can be seen in Appendix 4. These have subsequently been used to establish a schema for PPML (Phenotyping Procedure Mark-up Language (http://www.interphenome.org/ppxml/ppml_v1_3.html) that is published on the InterPhenome website (see Appendix 5 for an example from the published schema).

PRIME Open Meeting: EuroMouse II - 5th – 6th July 2007 – Heathrow

The second PRIME open meeting (called EuroMouse II) was held on 5th and 6th July in Heathrow, UK. This was a later date than originally scheduled. This enabled the wider European mouse research community to be updated on the outcome of the Brussels workshop on “The future of research in mouse functional genomics” and discuss the resulting priorities.

EuroMouse II also covered a wide range of areas on mouse functional genomics, including: mutagenesis approaches and technologies; phenotyping archiving and dissemination; the mouse proteome; expression and molecular phenotyping; the role of industry; and databases, informatics and systems biology. Representatives of the EC-

funded projects that attended the meeting were also given the chance to present on their projects in a poster session and during talks on day 2 of the meeting. See Appendix 6 for agenda of the meeting.

The PRIME SAG meet during the meeting to discuss the conclusions from these sessions and priorities identified. As a result a new PRIME position paper was drafted (see report for deliverables 10 and 14).

The brochure “The Mouse as a Model of Human Disease” (see report for deliverables 11 & 15 for information on the brochure) was launched at the EuroMouse meeting. There was a lot of interest in the brochure. As a result, 700 copies have been ordered and distributed by individuals and projects represented in it.

In order to bring together the information on the EuroMouse projects PRIME has established the internet site www.euromouse.eu. Summaries of the EuroMouse projects are presented on the site as well as an electronic version of the brochure.

International Mouse Phenotyping Consortium first meeting – 26th – 27th November 2007 – Rome

An international mouse phenotyping consortium (IMPC) has been established by PRIME. The first meeting was held in Rome on 26th and 27th November 2007. The aim of the meeting was to discuss the formation of the consortium to promote and coordinate global large-scale mouse phenotyping efforts; to consider the scientific goals in the next five years; to establish the necessary coordination mechanisms to achieve the scientific goals, including interactions with other consortia and to develop an operational plan that considers funding and infrastructure requirements. The agenda of the meeting and list of attendees are given in Appendix 7. The full report of the meeting can be found in the joint report for Deliverables 10 and 14.

Note: Meetings of the Science Advisory Group (SAG) and Training Group are covered in the joint report for Deliverables 10 and 14.

Merck, Artemis, Charles River, Novartis, AstraZeneca, GSK, Sanofi-Aventis, Velocigen and Devgen

Appendix 1
EuroPhenome Meeting
Munich, 7 and 8th September 2006

EuroPhenome Meeting Day 1: 1° and 2° phenotyping

7th September 2006

Agenda

- 10:00 *Arrival tea and coffee*
- 10:15 – 10:20 **Welcome**
Martin Hrabé de Angelis, GSF, Munich
- 10:20 – 10:40 **EMPreSSslim - Steve Brown**
Agreement on EMPreSSslim pipelines
QC on 1° data. Minimum standards for QC. Central QC before data goes live?
- 10:40 - 11:00 **Databases - John Hancock**
EuroPhenome and tracking database
Time frame for entry of data into EuroPhenome
- 11:00 - 13:00 **EMPreSSslim clinic - meetings of workgroups**
Agreement to EMPreSSslim SOPs
Discussion on parameters measured from each SOP. Agreement on minimum set of data to be entered in EuroPhenome
Identification of metadata that should be recorded for each of the EMPreSSslim SOPs
Identification of data values that would make secondary partners interested in receiving the lines for secondary phenotyping
Analysis or reports on 1° phenotyping results by 2° partners
- 13:00 - 14:30 *Lunch*
- 14:30 - 15:00 **2° phenotyping**
Supply of frozen lines to secondary partners
Recording of data in EuroPhenome. Should all secondary data be entered in EuroPhenome? If so what should be the timeframe for data enter/release to public
Agreement on authors for 2° phenotyping data. Should 1° phenotypers who identified the model be authors?
- 15:00 - 15:30 *Tea and Coffee*
- 15:00 - 15:30 **Breeding**
Identification of animal house and handling metadata (with an SOP)
- 15:00 - 15:30 **Animal welfare**
Animal welfare advisory committee
Supply of documentation for national regulations
SOP for animal welfare observations
- 15:30 - 15:45 Meeting recap (Meeting closes 16:00)

16:00 - 17:00 PRIME SAG meeting - PRIME SAG by invitation

EMPRESSslim clinic - workgroups and WP leaders

Day 1: 11.00 - 13.00

WG2 - Ann-Marie Mallon

WP2.1 Clinical chemistry - Béatrice Desvergne

WP2.2 Cardiovascular - Ludwig Neyses

WG3 - John Hancock

WP2.3 Respiratory - Bernard Ryffel

WP2.4 Infection - Werner Müller

WG4 - Chris Duran/Hilary Gates

WP2.5 Behaviour - Sabine Hölder

WP2.6 Sensory - Ian Jackson & Steve Brown

WG 5&6 - Simon Greenaway

WP2.7 Skeletomuscular – Helmut Fuchs

WP2.8 Pathology & Cancer - Leticia Quintanilla-Fend

WP2.9 Imaging - Marc Janier

EuroPhenome Meeting Day 2: Phenome data capture

8th September 2006

Agenda

10:00 *Arrival tea and coffee*

Session 1: Phenome data capture

10:15 – 10:30 **Introduction - data capture**
John Hancock, MRC Mammalian Genetics Unit, Harwell

10:30 -11:00 **Progress with EuroPhenome**
Ann-Marie Mallon, MRC Mammalian Genetics Unit, Harwell

11:00 - 12:00 Centre updates (15 minutes each)

12:00 – 13:00 **Open Discussion – other requirements**

13:00 - 14:00 *Lunch*

Session II:

14:00 – 14:10 **Phenome data interface**
Introduction – data interface
John Hancock, MRC Mammalian Genetics Unit, Harwell

14:10 – 14:25 **Europhenome interface**
Simon Greenaway, MRC Mammalian Genetics Unit, Harwell

14:25 – 14:40 **Phenostat**
Eli Reuveni, EMBL, Monterotondo

14:40 – 15:00 **Final discussion and recap**

15:00 – 17:30 **PRIME Resources report**

Appendix 2

International Phenome Meeting

Munich, 9th September 2006



International Phenome Meeting

Munich, 9th September 2006



The following action points arose from the discussions:

- EMPReSS SOPs should be annotated using PATO as well as MP terms.
Action: Arrange meeting with George plus Duncan & Kirsty at Harwell. Teleconference mid-Oct to report back.
- Complete initial work on SOP formats between Harwell & MPP ASAP and broaden discussion to other sites (esp. RIKEN).
- Data exchange
 - Draft core data model
 - Basic XML based on this - use our XML plus PhenoXML
 - Agreement on mode of data exchange
 - Look at Functional Genomics Object Model
- Use wiki to disseminate results

A publication is in preparation and will be completed as soon as possible.

The next meeting of the group would be a working meeting to discuss one of the major areas discussed by the group, most likely a standard format for SOPs

Agenda

09:15	Arranged departure from hotel
10:00	<i>Arrival tea and coffee in building 23</i>
10:15 – 10:25	Introductory Comments Steve Brown, MRC Mammalian Genetics Unit, Harwell
10:25 - 10:35	Meeting Introduction John Hancock, MRC Mammalian Genetics Unit, Harwell
<i>Session 1 – Data Exchange</i>	
10:35 – 10:50	Phenome Portal Ann-Marie Mallon, MRC Mammalian Genetics Unit, Harwell
10:50 – 11:05	MGI Cynthia Smith, Jackson Laboratory
11:05 – 11:20	RIKEN Hiroshi Masuya, RIKEN
11:20 – 11:35	MPD Molly Bogue, Jackson Laboratory
11:35 - 12:00	Discussion

Session 2 – Ontologies

- 12:00 – 12:15 **Update on PATO**
George Gkoutos, University of Cambridge
- 12:15 - 12:30 **Update on Mammalian Phenotype Ontology**
Cynthia Smith, Jackson Laboratory
- 12:30 – 12:45 **Testing PATO and MP**
Kirsty Lee, MRC Human Genetics Unit, Edinburgh
- 12:45 - 13:00 **General Discussion**
- 13:00 - 14:00 *Lunch*

Session 3 - SOP formats and XML

- 14:00 – 14:15 **EMPreSS**
Andy Blake, MRC Mammalian Genetics Unit, Harwell
- 14:15 - 14:30 **SOP Formats - EMPreSS and Phenome**
John Hancock, MRC Mammalian Genetics Unit, Harwell
- 14:30 - 15:00 **Discussion**
- 15:00 - 15:15 *Tea and Coffee*
- 15:15 - 15:45 **Position statement - consideration of draft manuscript for publication**
- 15:45 – 16:30 **Open discussion - next steps**
- 16:35 Arranged return to hotel

Appendix 3

InterPhenome publication in Mammalian Genome

J. Hancock *et al.*: Mouse Phenotype Database Integration Consortium: Integration of Mouse Phenome Data Resources, *Mammalian Genome*, Volume 18, 157-163 (2007).

giving rise to the idea that large-scale phenotyping centers need to be established, alongside the experimental resources, to generate mutations and knockouts in all mouse genes (reviewed by Brown et al. 2006). There need to be public data resources that collect phenotypic data on both mutant mice and wild-type inbred strains to allow quantification of natural trait variation and whether a given observation in a given mutant line deviates significantly from expectation given the genetic background upon which the mutation was analyzed. To compare results obtained by different centers, collections of well-characterized and reproducible protocols for mouse phenotyping, such as the EMPReSS resource (<http://www.empress.har.mrc.ac.uk>) developed by the EU-funded EUMORPHIA consortium (Brown et al. 2005), need to be in place. These data resources should be openly available via the worldwide web and should be linked to other genomic and functional genomic resources to allow a thorough understanding of the phenotypes, how they were measured, and deeper analysis of molecular processes that underlie any given phenotype. It should also be possible to make the data seamlessly accessible through web interfaces, allowing joint mining and analysis of the data. This requires the establishment of well-structured, curated, open source, and appropriately funded databases and portals to provide this information to the mouse community.

A characteristic problem of biological databases is the emergence of different databases containing similar but not identical data at different sites internationally. The classic example of this and its eventual resolution are the GenBank, EMBL, and DDBJ sequence databases which eventually developed a data-sharing model whereby all three databases effectively merged (Brunak et al. 2002). What follows are the conclusions of two discussion meetings held in Barcelona on 25 February 2006 and in Munich on 9 September 2006, which initiated a process of integrating as far as possible the current (and future) mouse phenotype resources.

Current resources

For the discussion of current resources we distinguish three types of data: data characterizing a wide range of phenotypes in established mutant mice compared with their normal controls, data collected as phenotypic screens to discover new mutations produced via mutagenesis (organized either as formal databases or presented via web sites), and data characterizing normal phenotypic parameters across inbred strains (Fig. 1). These distinctions are somewhat artificial, reflecting our inability to experi-

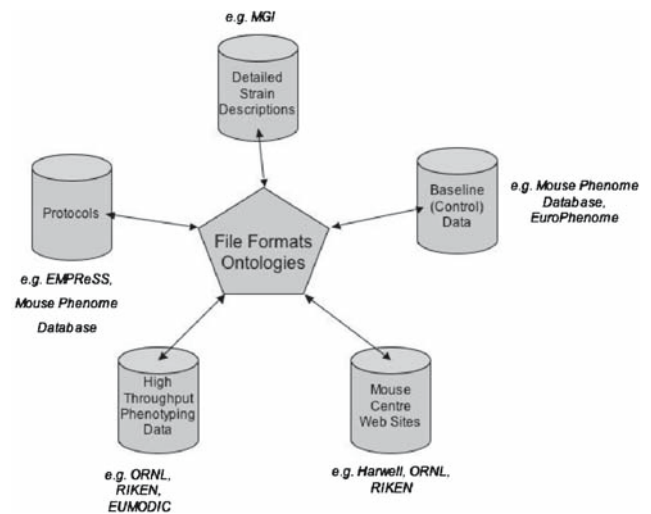


Fig. 1. Phenotype data resources. We can distinguish a variety of types of resource-holding data on mouse phenotypes. These range from the detailed descriptions held by the Mouse Genome Informatics group through quantitative data on the normal phenotypes of inbred lines held at the Mouse Phenome Database and in Europhenome, through to descriptions of high-throughput phenotyping studies such as EUMODIC and summary descriptions of individual mutant lines held at a number of sites. Knowledge of the protocol used to derive data is also essential. To unify these data we will require a common description vocabulary, in the form of ontologies and a common means of representing the data itself and the underlying protocols for transfer between databases and between databases and analysis applications.

mentally measure all phenotypes in all mice, both technically and practically, and our need to analyze data from the perspective of mutations and normality.

Characterizing phenotypes in mutant mice compared with normal controls. The Mouse Genome Database (MGD, <http://www.informatics.jax.org>) aims to integrate data on all phenotypic mutations known in the mouse (Eppig et al. 2005; Blake et al. 2006). Data are gathered from the scientific literature and direct submissions from individual researchers and mutagenesis centers. Data are annotated with Mammalian Phenotype (MP) Ontology terms (Smith et al. 2005) to enable integrated searches for phenotypes across all mouse mutations. Key to the context of the phenotype is the genotype, comprising the allelic composition of mutations carried by a particular mouse cohort and the genetic background on which the phenotypes were analyzed. In addition, MGD has recently made available phenotypic data on a set of knockout mice created and characterized by Deltagen Inc. and Lexicon Genetics Inc. that are being deposited in public repositories for research use as part of the NIH-funded mouse repa-

triation process (see <http://www.nih.gov/science/models/mouse/deltagenlexicon/factsheet.html>). These mutants are also integrated into MGD and annotated with MP terms to make them searchable in the context of all other known mouse mutants. As of September 2006, over 66,100 annotations to MP terms had been curated to over 17,500 genotypes.

Data from phenotypic screens to discover new mutations. A number of major phenotyping centers present information via their web sites about mutants discovered during their mutagenesis screens. Examples include the Harwell (<http://www.mgu.har.mrc.ac.uk/mutagenesis/access/>), Baylor College of Medicine (<http://www.mouse-genome.bcm.tmc.edu/ENU/MutagenesisProj.asp>), Oak Ridge National Laboratory (<http://www.bio.lsd.ornl.gov/mgg/resources.html>), and RIKEN (<http://www.gsc.riken.go.jp/Mouse/>) resources (see http://www.informatics.jax.org/mgihome/other/phenoallele_commun_resource.shtml for a more complete listing). Summary information on mutant lines is primarily prepublication data or data on lines that are made available to the mouse community for further experimentation. This summary information is typically provided in the form of a free-text description of the main features of the mutant phenotype. This information, while useful to researchers browsing a particular web site, could be made more useful for computational integration through community adoption of standard vocabularies to describe phenotypes (see section on Ontologies below). MGD has integrated many of these mutations into their phenotypic data and provided MP annotations to facilitate searching and computational analysis of these mutations. Potentially these mutagenesis center databases also contain underlying phenotype data on individual mice as well as summary information, although this is not usually made available.

The phenotypic characteristics of inbred mouse lines. Databases containing characteristics of inbred strains of mice are becoming an increasingly important resource for mouse geneticists. These databases serve two major purposes. First, they provide baseline data for the characterization of mutation effects. Well-established and robust estimates of trait values are critical to successful detection of extreme alterations. Second, they allow comparison and genetic correlation of complex traits across diverse populations. Currently there are several significant resources that contain data characterizing normal parameters among inbred mouse strains. Examples of this growing body of resources include the Mouse Phenome Database (Grubb et al. 2004) based at The Jackson Laboratory, MuTrack at the

Oak Ridge National Laboratory (Baker et al. 2004), the EuroPhenome database (Mallon et al., unpublished) based at MRC Harwell, PhenoSITE at RIKEN, and GeneNetwork at the University of Tennessee (Chesler et al. 2004).

The Mouse Phenome Database (<http://www.jax.org/phenome>) is the database of the Mouse Phenome Project (Bogue and Grubb 2004), which aims to gather quantitative phenotype data on a large set (up to 40) of standard inbred strains. The aim of collecting data from a large number of strains is to provide broad coverage as a community resource and to allow mining of the data for correlations between phenotypic measures across strains. A feature of the database is that each data collection is associated with a protocol that describes how the data were generated. The project also provides online analysis tools to allow identification of correlations within its data set.

GeneNetwork (<http://www.genenetwork.org>), encompassing WebQTL, is a database of genotypes and complex phenotypes ranging from gene expression to behavior in standard inbred strains and six panels of mouse recombinant inbred strains, including the two largest sets (BXD and LXS) of approximately 80 strains each. Rat and *Arabidopsis* populations are also represented. Approximately 1500 phenotypes spanning the 25-year history of these strains are incorporated in this public resource, many of which were retrieved from the literature. All phenotypes are integrated with an analytic engine for basic statistics and multivariate and genetic analyses (Chesler et al. 2004). Phenotype records in this database reference the publications from which they are drawn. Integration to other phenotype resources is a key step in enhancing the usefulness of this resource.

Data currently in EuroPhenome (<http://www.europhenome.org>) result from applying the standardized operating procedures (SOPs) making up EMPReSS (Brown et al. 2005; Green et al. 2005) to four inbred mouse strains. EMPReSS is a set of standardized and validated SOPs for large-scale mouse phenotyping. EuroPhenome data are validated across a number of phenotyping laboratories. EuroPhenome also contains data from experiments that produce qualitative and quantitative data and is essentially protocol-centered. There is a plan to build on EuroPhenome to include phenotyping data on knockout mouse lines produced by the EU-COMM project (<http://www.eucomm.org/>) during the EUMODIC program (<http://www.eumodic.org/>).

The MuTrack system (Baker et al. 2004) (<http://www2.tnmouse.org/mutrack/stats/Statistics.php>) was developed for the Tennessee Mouse Genome

Consortium's effort in the NIH Neuromutagenesis Program (Goldowitz et al. 2004), and it is still in use today for a variety of studies of complex phenotypes. The database contains trait data for several hundred phenotypes, including common inbreds, consomics, 80 BXD recombinant inbreds, hybrids, and over 60,000 mutagenized mice, including ENU mutants and several knockout lines. SOPs are used for phenotypic data acquisition. This publicly accessible database is an excellent example of one that can be made significantly more valuable to the community with a standard in place for the reporting of these protocols.

PhenoSITE (<http://www.gsc.riken.go.jp/Mouse/phenotype/top.htm>) provides baseline phenotype data for three inbred strains and their F₁ hybrids. Data were generated by analyses using a comprehensive phenotyping platform developed in the mouse mutagenesis program in RIKEN GSC. SOPs of the phenotyping platform are also posted on the web site. PhenoSITE also contains phenotype annotation of ENU-induced mutant mouse strains generated in RIKEN GSC. The annotation is based on multiple ontologies such as MP and mouse adult gross anatomy.

Access to mutant and inbred strains. In addition to accessing data about mutant and inbred strains, the strains themselves must be physically accessible to the research community for further experimentation. The International Mouse Strain Resource (IMSR, <http://www.imsr.org>) is a searchable online database of mouse strains and stocks available worldwide, including inbred, mutant, and genetically engineered mice (Strivens and Eppig 2004). Here, repository sites and consortia and individual laboratories that distribute mouse resources as live stock, cryopreserved embryos or gametes, or embryonic stem (ES) cell lines can list their available holdings. Users can search the IMSR by one or more of the following parameters: strain name or accession identifier, type of strain (e.g., congenic, inbred), state in which the mice exist (live, cryopreserved embryo, sperm or ovary, or ES cell line), gene or mutant allele of interest or gene or allele accession identifier, mutation type (e.g., deletion, transgenic), and repository location (either limiting one's search to a particular set of repositories or a continental location). From a search results page, IMSR users can locate their strain(s) of interest, link to detailed strain information available from the holding repository, link to the holding repository for inquiries or to order mice, and link to the Mouse Genome Database phenotype data for each mutant allele carried by a given strain. All major public

repository sites contribute their listings to IMSR, which currently contains listings from 16 repositories and repository consortia, comprising 24 repository sites in the U.S., Canada, Europe, Japan, and Australia.

These major repositories have recently formed an international organization, the Federation of International Mouse Resources (FIMRE, <http://www.fimre.org>), with the goals of coordinating repository centers to meet research demand for genetically defined mice and ES cell lines, establishing consistent high-quality animal health standards, providing genetic verification and quality control for mouse resources, and providing training to enhance utilization of cryopreserved resources (FIMRe Board of Directors 2006).

Essential components for integration of mouse phenotype databases

We have identified three main issues that need to be addressed to enable and support the integration of mouse phenome resources internationally:

- Data description standards (ontologies and vocabularies). The need to store phenotype data in a human-comprehensible and computationally accessible ontologic structure drove the development of the MP (Smith et al. 2005). The need to capture individual data measurements on individual mice has given rise to the EAV (Entity + Attribute + Value) approach (Gkoutos et al. 2005) and its derivative, the EQ (Entity + Quality) approach (http://www.bioontology.org/wiki/index.php/PATO:Main_Page), making use of PATO (the Phenotypic Quality Ontology). Although these systems represent different perspectives on the description of phenotype information, cross-referencing of terms between these ontologies is a goal. In addition, there is a need to standardize on other vocabularies that provide supporting data for phenotypic information and to identify any new ontologies that may be required.
- Phenotyping protocols. Several web sites, including those for the Mouse Phenome Database, EMPReSS, MuTrack, and PhenoSITE, make phenotyping protocols available. There is a need for developing standard vocabularies for naming protocols and the common data elements within them to foster global understanding of methods and to provide a single framework allowing protocols to be searched and shared across sites and used in annotation of phenotype data.
- Data exchange technologies. It will be necessary to develop a common data format for exchange of phenotype data that should be linked to informa-

tion on protocols used to obtain the data. This will allow data to be exchanged between databases and analysis tools to import data from the different databases and carry out analysis over this wider data set.

Ontologies. Ontologies are widely used to represent genomic and functional genomic information (Bodenreider and Stevens 2006). A confounding factor for phenotype data is the evolution of ontologies that are of different character, yet not orthogonal (e.g., Gkoutos et al. 2005; Smith et al. 2005). For example, different types of knowledge representation require different levels of granularity: In some cases summary information is adequate, in others a more detailed approach is required. It is important that studies to evaluate currently available ontologies be carried out in collaboration with major centers for ontologic research such as NCBO (National Center for Biomedical Ontology), NCOR (National Center for Ontological Research), and ECOR (European Centre for Ontological Research). It will also be important to study ontologies for traits not covered by either of these approaches, and it remains to be established whether all the necessary vocabularies and ontologies needed to represent phenotype information are currently available (for example, to describe housing and handling conditions, or welfare status, which can affect the results of phenotyping experiments). In the medium to short term, the community will need to investigate means of cross-referencing MP and EAV/EQ-based ontologic descriptions. In the longer term, these approaches may converge to produce a unitary phenotype ontology. Finally, as the protocol used is a critical factor in determining the results obtained, there is a need to investigate the utility of linking protocols or protocol types into an assay vocabulary (Gkoutos et al. 2005), which provides information on the relatedness of different protocols from the perspective of the phenotypic attributes they measure.

Protocols and minimum information for a phenotyping experiment. In addition to EMPReSS, MPD, MuTrack, and PhenoSITE, a number of other web sites also host protocol collections. Protocols are central to the acquisition and comparison of phenotyping data and can potentially be used both in data acquisition software as a direct means of specifying the information to be reported from any given experiments and as a means of specifying formally the units of measurement and reasonable ranges of the data collected. During the design of the EMPReSS database (Green et al. 2005), a basic XML

schema was developed that allowed the consistent description of SOPs developed during the EUMORPHIA project. We propose to take this as the basis for the development of a more comprehensive XML schema that will allow the representation of all the information needed to describe a phenotyping protocol. A natural offshoot of this process is to consider what is the minimum set of information needed to describe a phenotyping experiment, by analogy with the MIAME criteria developed for microarray data sets (Brazma et al. 2001). In addition to the protocol used, it is clear that variables such as mouse strain (or genetic composition), mutation type, gene mutated (where known), housing conditions (possibly including history), feeding regime, and handling conditions will need to be recorded. We have set up a working group to develop these general ideas into a more formal framework.

Data exchange. An essential requirement for exchange of phenotype data will be a standardized means (such as an XML schema) of describing phenotyping data. Current precursors of such a schema are PhenoXML (<http://www.reaper.lbl.gov/phenote/phenoxml.rnc>) and a schema being developed for transfer of phenotypic screen data to the EuroPhenome database by the EUMODIC consortium (<http://www.eumodic.org/>). A number of the established data resources containing mouse phenotype data contain different types of data held in different data structures. Our strategy is to facilitate the establishment of portals to make access to these various resources as seamless as possible. With this in mind, we are establishing an experimental web site (<http://www.interphenome.org>) that will initially provide links to individual sites providing access to mouse phenotype data. We will then start to implement a phased process of improving the integration of these data sources.

Potentially, the IMSR web site presents an accessible route through which to access phenotype data in the way we discuss here. However, there are other possibilities, e.g., RIKEN's search engine MusBanks (<http://www.omicspace.riken.jp/MusBanks/>), which overcomes the differences in phenotype description frameworks at different sites by directly searching the web pages of the original phenotype databases. MusBanks also inferentially connects arbitrary phenotypic keywords with the resources via text mining of MEDLINE, so as to suggest potentially undiscovered phenotypes remaining to be measured. Most likely, principles developed during the process outlined in this article will be usable by any number of sites wishing to access and analyze mouse phenotype data. Access to

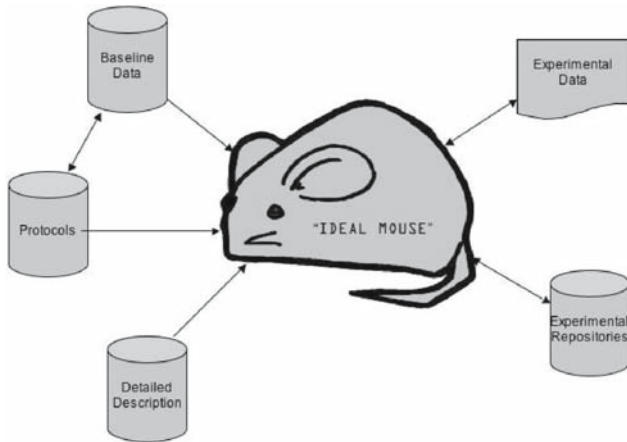


Fig. 2. The ideal mouse. For any given inbred line or mouse strain of defined genotype, data might be collected from various online sources to provide a summary of the phenotype of that line or strain in the form of a central tendency and a measure of variation. This would allow meta-analysis of phenotyping analyses carried out at different sites and the integration of similar data relating to different genetic backgrounds, facilitating mining of genotype/phenotype data sets for novel patterns of association. By collecting data from different sites, information on the reproducibility of particular measurements could also be gathered. The information could be updated continuously to maintain up-to-date information.

this information need not be restricted to conventional interfaces, e.g., it is possible to imagine interfaces similar to the visual interface used by the EMAP digital atlas of the embryonic mouse (<http://www.genex.hgu.mrc.ac.uk/Atlas/intro.html>). Another possibility is to present data in the form of an “ideal mouse,” which would summarize state-of-the-art knowledge of individual inbred lines derived using data extracted from various databases (Fig. 2).

Conclusions

The goal of linking phenotype to genotype in the laboratory mouse will be achieved only by a worldwide effort of mutagenesis, quantitative trait locus detection, and inbred strain profiling. These efforts provide us with converging insights into the role of the genome in trait variation, but the convergence only occurs if data can be combined and compared. It is therefore essential that information on mouse phenotypes be made available in an integrated manner to the mouse community internationally. With the advent of large-scale projects in these areas, it is vital that the mouse informatics community moves toward this goal as quickly as possible. We have initiated this process and aim to continue it with regular meetings to be held over the next few years with the goal of delivering an integrated portal

to mouse phenotype data. The only way such an initiative can succeed is by engaging as many members of the mouse community involved in these sorts of experiments as possible. We have established a web and wiki site (<http://www.interphenome.org>) to act as a central coordinating site for this project and we welcome input from members of the mouse community that we do not currently represent.

Acknowledgments

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Appendix 4

InterPhenome Meeting

Barcelona, 23rd February 2007



Conclusions from InterPhenome Mini-Workshop on Phenotyping Procedure (SOP) formats

Barcelona 23 February 2007

Attending were: Andrew Blake, Simon Greenaway, Joe Wood, Alison Walling, Hiroshi Masuya, Shigeharu Wakana, Molly Bogue, Hamid Meziane, Laurent Vasseur, Ann-Marie Mallon, Mandy Studley, Hilary Gates, Niels Adams, John Hancock

General Discussion

We considered what our aims were in designing an XML for phenotyping procedures. We decided that we needed something general with only limited prescriptiveness that could nevertheless be made more prescriptive for local use (e.g. EMPReSS).

A general point that arose during the detailed description of the content of the XML was that we should move away from using the term SOP as this was too specific. Consistent with usage at MPD we suggest using the term Phenotyping Procedure.

Discussion of Procedure Content

This was based on a draft document circulated to all participants and appended to this document.

In the following outline, compulsory elements are in **bold**.

Conclusions were as follows

- **ID** - a local identifier given by the originator allowing the origin of the procedure to be tracked
 - o Could be linked to a URL
- Edit history. Transformations applied to generate the current version from previous documents and their dates. To include the ID of the preceding document. Also allow comments on these edits - why were they needed?
- **Type** - there is a need to define whether a procedure is data-generating or not. This is needed because of the requirement to include parameters and units in data generating procedures.
- **Title** - all procedures should have a title
 - o Short or secondary title - these may be added if there is a name by which a procedure is commonly or often known but is not the full title of the procedure.
- **Source Information** - sources may either be a person or an institution, but some source must be identified.
 - o Contact. This should be strongly recommended. It may be the contact of an individual or an institution
- Documentation - this may be citation material, in which some sort of formal specification may be needed (authors, journal, year, pages) or some other form of documentation.

- **Purpose** - A description of what the procedure aims to measure
 - o Associated ontology terms describing the measured entity (for example anxiety for open field, which is not measured by any particular parameter).
- Emergency Procedures - the term “Safety” was retired as it was not being used meaningfully in EMPReSS. However the possibility to add a description of what needed to be done in a procedure-specific emergency situation was needed.
- (Investigator) Notes - these are commonly used in EMPReSS and MPP.
- Quality control - how can the quality of the execution of the procedures be evaluated
- **Technical Requirements.** These may need to be related by AND or OR logical connectors.
 - o Equipment
 - o Consumables
- **Procedure.** A number of subheadings could be fitted under this general heading, although only Experimental Procedure is compulsory:
 - o Workflow (Order of Testing) - how this procedure might relate to others, including spaces after other procedures before this one should be carried out, and necessary or excluded preceding procedures
 - o Animal Husbandry. Aspects of husbandry essential for the procedure.
 - o Time and Capacity. Possibly two subheadings. How long it takes and what the throughput is.
 - o **Experimental Procedure**
 - o Procedural parameters, i.e. features of the procedure that may vary between experimenters and should therefore be reported, such as size of open field arena.
 - o Appropriate experimental controls
- **Parameters & Units of Measurement.** Compulsory for data-generating procedures.
 - o **Directly measured parameters**
 - o Calculated parameters that are reported as results of the procedure. These should contain information about how the value is calculated from the directly measured parameters.
 - o Ontology term(s) associated with each or all parameters defined in this section. Ontology terms to be referred to by ID (and by descriptor?)

Excluded: Scope, as we could not define what it means.



Appendix

Current Thinking on SOP Content

For Interphenome Mini-Workshop, Barcelona, February 2007

Fields in bold are absolutely required.

<i>Field</i>	<i>Comments</i>
Title	Required
Source Information	Author? Submitter?
Documentation	Citation Material; other Documentation. Need to distinguish? Needs to point to "permanent" URL.
Purpose	
Safety	Safety Requirements + Emergency Procedures. Optional but strongly recommended?
Notes	Optional but needs to be incorporated in XML. Need to consider how this is encoded.
Quality Control	
Animal Husbandry	Housing, Preparation/Acclimatisation. Optional.
Technical Requirements	Equipment, Supplies (=Consumables + Reagents?)
Procedure	Could contain: <ul style="list-style-type: none"> • Order of testing • Time & Capacity • Definitions • Experimental Procedure • Appropriate controls • Data Analysis
Parameters & Units of Measurement	Compulsory IF a data-generating SOP. Two types: <ul style="list-style-type: none"> • Directly measured • Calculated (encode formula or method of calculation)
EXCLUDED	
Scope	Not included as poorly defined
Sample Data	Can change so should be linked externally
Ontology mark-up	Can also change so should point to SOP. Does it point to Purpose or to Parameter?
History Review (Edit history)	Will be different at different sites - track externally.
QUESTION	
Is there a way to assign a UID? Is this necessary?	

Appendix 5

Example of the PPML schema

developed on the format agreed by the PRIME InterPhenome working group

Appendix 5: Extract of PPML developed according to the criteria agreed by the PRIME InterPhenome working group

See http://www.interphenome.org/ppxml/ppml_v1_3.html for full schema


Schema **PPML_v1_3.xsd**

schema location: **PPML_v1_3.xsd**
attribute form default: **unqualified**
element form default: **qualified**

Elements Complex types


procedure [contactType](#)
[dbreferenceType](#)
[descriptionType](#)
[documentationType](#)
[edithistoryType](#)
[equipmentType](#)
[experimentType](#)
[nameType](#)
[ontologyType](#)
[parameterType](#)
[pipelineType](#)
[procedureType](#)
[protocolType](#)
[purposeType](#)
[requirementsType](#)
[sourceType](#)
[titleType](#)
[xrefsType](#)

element **procedure**

procedure 


Describes one procedure that will form a single submission at a database


procedureType (extension)

 **attributes**


version

The version of the PPXML Schema

 **species**

source 

Description of the source of the entry, usually an organisation, but can be a person.

title 

Description of the title of the phenotyping procedure

purpose 

1..∞

A description of what the procedure aims to measure.

documentation 

Citation or supporting evidence material related to the phenotyping procedure


emergencyProcedures 

Description of what needs to be done in a procedure-specific emergency situation

pipelineDescription 

Description of the order of testing

 ... 


investigatornotes 

qualitycontrol 


Description of how the quality of the execution of the procedures can be evaluated

 **Time**


Description of how long the procedure takes

 **Capacity**


Description of what the throughput of the procedure is.

 **Controls**

Description of the appropriate experimental controls

Husbandry 

Description of the optimal husbandry conditions

Experiment 

Description of the methodology of the procedure

Appendix 6:

PRIME Open Meeting: EuroMouse II

5th – 6th July 2007

Heathrow

EuroMouse
Understanding human disease through mouse genetics
The European dimension

5th July, Heathrow
Agenda – 5th July 2007

(All sessions in Guggenheim)

Introduction

09:00 – 09:10 **Meeting aims**
Steve Brown, MRC Mammalian Genetics Unit, Harwell, UK

Session 1: Mutagenesis

09:10 – 09:25 **Mutagenesis approaches in the mouse**
Wolfgang Wurst, GSF, Munich, Germany

09:25 – 09:40 **Development and application of new mutagenesis technologies**
Allan Bradley, Wellcome Trust Sanger Institute, Hinxton, UK (tbc)

09:40 – 10:30 **Discussion**

10:30 – 11:00 ***TEA AND COFFEE***

Session 2: Phenotyping, Archiving and dissemination

11:00 – 11:20 **Large-scale phenotyping (EUMODIC)**
Steve Brown, MRC Mammalian Genetics Unit, Harwell, UK

11:20 – 11:40 **Large-scale mouse production and archiving**
Martin Hrabé de Angelis, GSF, Munich, Germany

11:40 – 12:30 **Discussion**

12:30 – 13:30 ***LUNCH***

Session 3: Mouse proteome, expression and molecular phenotyping

13:30 – 13:45 **Towards a mammalian interactome map**
Francis Stewart, Dresden University of Technology, Germany

13:45 – 14:00 **From Genotype to Phenotype**
Glauco Tocchini-Valentini, IBC CNR, Monterotondo, Italy

14:00 – 14:30 **Discussion**

Session 4: Translational research

- 14:30 – 14:45 **From mouse to medicine: the role of industry**
Björn Löwenadler, AstraZeneca, Mölndal, Sweden
- 14:45 – 15:00 **Discussion**
- 15:00 – 15:30 ***TEA AND COFFEE***

Session 5: Databases, informatics and systems biology

- 15:30 – 15:45 **The challenges in informatics – from mouse to man**
John Hancock, MRC Mammalian Genetics Unit, Harwell, UK
- 15:45 – 16:00 **Integration of European databases**
Ewan Birney, EBI, Hinxton, UK
- 16:00 – 16:30 **Discussion**

Session 5: The way forward

- 16:30 – 16:45 **FP7 and the way forward**
Christian Desaintes, European Commission, Brussels, Belgium
- 16:45 – 17:15 **Concluding discussion**
- 17:30 – 19:00 **Poster Session and project databases demonstration (internet café)**
- 20:00 ***Drinks on the lawn***

Agenda – 6th July 2007

(All sessions in Guggenheim unless stated)

- 10:00 – 10:10 **Introduction**
- 10:10 – 10:25 **Integration of data in a central 3-D database (EuReGene)**
Jamie Davies, University of Edinburgh Medical School, UK
- 10:25 – 10:40 **European databases for large-scale phenotyping and
integration with international phenome databases
(EMPreSS and EuroPhenome)**
John Hancock, MRC Mammalian Genetics Unit, Harwell, UK
- 10:40 – 10:55 **Understanding gene dosage imbalance in human health
(AnEUploidy)**
Mara Dierssen, Center for Genomic Regulation, Barcelona,
Spain
- 10:55 – 11:30 **TEA AND COFFEE**
- 11:30 – 11:45 **European Mutant Mouse Archive database (EMMA)**
Glenn Proctor, EBI, Hinxton, UK
- 11:45 – 12:00 **European Conditional Mouse Mutagenesis programme
database (EUComm)**
Wolfgang Wurst, GSF, Munich, Germany
- 12:00 – 12:15 **Large-scale gene expression analysis by RNA *in situ*
hybridisation (EUExpress)**
Graciana Diez-Roux, TIGEM, Naples, Italy
- 12:15 – 12:30 **Murine models of human immunological diseases
(MUGEN)**
George Kollias, BSRC “Alexander Fleming”, Vari, Greece
- 12:30 – 12:45 **From molecules to networks: Understanding synaptic
physiology and pathology through mouse models
(EUSynapse)**
Peter Seeburg, Max Planck Institute for Medical research,
Heidelberg, Germany
- 12:45 – 13:00 **Coordination and sustainability of international mouse
informatics resources (CASIMIR)**
Paul Schofield, University of Cambridge, UK
- 13:00 PRIME meeting closes
- 13:00 – 14:00 **LUNCH**

14:00 CASIMIR workshop (meeting room Kennedy on first floor)

Parallel session

10:00 – 11:00 PRIME SAG by invitation only (training room 1 on ground floor)

Appendix 7:

IMPC meeting agenda

Rome, 26th – 27th November 2007

IMPC meeting agenda

Rome, 26th – 27th November 2007

26th November 2007

09:00 – 09:15 *Introduction and meeting aims*
Steve Brown

Session 1: Current models and pilots for large-scale phenotyping initiatives

09:15 – 09:30 **The Jackson Laboratory**
Richard Woychik

09:30 – 09:45 **Toronto Centre for Phenogenomics**
Colin McKerlie

09:45 – 10:00 **RIKEN GSC and plans for a Japanese Mouse Clinic**
Shigeharu Wakana

10:00 – 10:15 **NIH-funded Mouse Mutagenesis and Phenotyping Center for Developmental Defects**
Monica Justice

10:15 – 10:30 **Australian Phenomics Network**
Adrienne McKenzie

10:30 – 11:00 *Tea and Coffee*

11:00 – 11:15 **The German Mouse Clinic**
Martin Hrabé de Angelis

11:15 – 11:30 **Sanger Mouse Genetics Programme - phenotyping**
Karen Steel

11:30 – 11:45 **MRC Harwell Mouse Clinic and EUMODIC**
Steve Brown

11:45 – 12:45 **Round table discussion – practicalities of establishing high-throughput phenotyping**
Led by Steve Brown and the speakers from this session

13:00 – 14:00 *Lunch*

Session 2: Standardisation of phenotyping methods

14:00 – 15:30 **Chairs:** Wolfgang Wurst & Steve Brown



Panel: Hiroshi Masuya, Mark Henkelman, Molly Bogue, Colin McKerlie

15:30 – 16:00 *Tea and Coffee*

Session 3: *Development of phenotyping technologies from the whole organism to the cell*

16:00 – 17:30 **Chairs:** Monica Justice & Lee Adamson

Panel: Tian Xu, Karen Steel, Adrienne McKenzie, Ian Jackson

27th November 2007

Session 4: Informatics issues: databases, standards for SOP formats and data exchange, ontologies

09:30 – 11:00 **Chairs:** Paul Schofield & John Hancock

Panel: Janan Eppig, Molly Bogue, Hiroshi Masuya, Moira O'Bryan

11:00 – 11:30 *Tea and coffee*

Session 5: *Development of infrastructures and funding*

11:30 – 13:00 **Chairs:** Martin Hrabé de Angelis & Phil Avner

Panel: Tian Xu, Monica Justice, Chris Goodnow, Glauco Tocchini-Valentini, Fatima Bosch

13:00 – 14:00 *Lunch*

Session 6: IMPC forward planning meeting and business plan

14:00 – 15:30 **Chair:** Steve Brown

15:30 – 16:00 *Tea and Coffee*



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