INFRAFRONTIER

Industry & Innovation Workshop

28 & 29 June 2016 | Munich

INFRAFRONTIER
mouse disease models

IMPC
International Mouse Phenotyping Consortium

CONTENT

Welcome & Meeting Objectives

Dear colleagues,

As coordinator of INFRAFRONTIER and on behalf of the organising committee, it is with great pleasure that I welcome you to the INFRAFRONTIER IMPC Industry & Innovation Workshop, Munich, Germany.

The INFRAFRONTIER IMPC Industry & Innovation workshop aims at:

- Promoting INFRAFRONTIER and the IMPC resources and services, technology developments and translational research to industry,
- Presenting technological innovations relevant to INFRAFRONTIER and to the IMPC,
- Engaging with industry to discuss requirements and use of mouse models by Biopharma,
- Initiating new collaborations and new alliances with industry partners.

The workshop targets three important pillars:

- **Innovation** with several presentations on technology development by experts on genome editing technologies, proteomics, imaging and mouse reproductive biology,
- **Translational Research and Bioinformatics** covering distinct fields as metabolism, neurosciences, immunophenotyping and cancer model development,
- **Outreach** to European programmes such as the Innovative Medicine Initiative (IMI), EU projects and Research Infrastructures and to Industry

In addition, panel discussions on pertinent questions such as *'Impact of CRIRSPR technology, IT & Animal Welfare'* and *'Impact of rodents as models of human diseases'* and a networking session complete the workshop program.

I hope that the Industry & Innovation Workshop will meet your expectations and I wish you a successful and productive meeting.

Yours Sincerely,
Martin Hrabě de Angelis

Organising Committee: Ana de Castro and Michael Hagn

Agenda

TUESDAY 28 JUNE 2016	
12:00 – 13:00	Lunch
13:00 – 13:15	Welcome & INFRAFRONTIER Introduction Michael Hagn, Helmholtz Zentrum Munich, Germany
13:15 – 15:45	**Session 1: Technology Development I** **Chair: Radislav Sedlacek, Czech Center for Phenogenomics, Czech Republic**
13:15 – 13:45	International Mouse Phenotype Consortium: Future Challenges & Knockout Mouse Program Mark Moore & Colin Fletcher, IMPC & National Institutes of Health, USA
13:45 – 14:15	Mouse genetics and the CRISPR/Cas9 revolution Ralf Kühn, Max Delbrück Center for Molecular Medicine, Germany
14:15 – 14:45	CARD's Kaizen Strategy for Mouse Reproductive Technology Toru Takeo, Kumamoto University, Japan
14:45 – 15:15	Replacing Immunoassays with MS-based Technology: Quantitative Proteomics Kits Enabling Deep Molecular Phenotyp ing of the Mouse Christoph Borchers, Genome BC Proteomics Centre, Canada
15:15 – 15:45	Coffee Break
15:45 – 16:45	**Session 2: Panel Discussion -** ***Impact of CRISPR technology on repositories, IT & animal welfare*** **Introductory presentation & Chair: Lluis Montoliu, CNB-CSIC, Spain** Panel members: Terry Meehan, Ramiro Ramirez-Solis, Lauryl Nutter
16:45 – 18:15	**Session 3: Technology Development II** **Chair: Raija Soininen, University of Oulu, Finland**
16:45 – 17:05	Automated Multi-Dimensional Metabolic & Behavioral Phenotyping of Mouse and Rat Models of Human Disease Harm J. Knot, TSE Systems, Germany
17:05 – 17:25	Informatics for the Capture, Analysis, and Dissemination of 3D Image Data Henrik Westerberg, MRC Harwell, UK
17:25 – 17:45	Gnotobiotic mouse models to study the role of the commensal microbiota on host physiology Stephanie Ganal, University of Bern, Switzerland
17:45 – 18:05	Ageing: MouseAge Ilaria Bellantuono & Paul Potter, University of Sheffield & MRC Harwell, UK
18:15 – 19:00	**Session 4: Networking**
20:00	DINNER Hofbräukeller am Wiener Platz

WEDNESDAY 29 JUNE 2016	
08:30 – 10:30	**Session 5: Translational Research** **Chair: Yann Herault, PHENOMIN-iCS, France**
08:30 – 09:00	Metabolic research Hans Häring, University of Tübingen, Germany
09:00 – 09:30	Multiparametric profiling of the immune system using flow and mass cytometry Bernard Malissen, Centre d'Immunophénomique, PHENOMIN-CIPHE, France
09:30 – 10:00	Genetic dissection of breast cancer development, therapy response and resistance in mouse models Jos Jonkers, Netherlands Cancer Institute, The Netherlands
10:00 – 10:30	Bridging the innovation gap – EATRIS ERIC and the ESFRI BMS infrastructure efforts to Improve patient outcomes Anton Ussi, EATRIS-ERIC, The Netherlands
10:30 – 11:00	Coffee Break
11:00 – 12:40	**Session 6: Industry & Innovative Medicines Initiative (IMI)** **Chair: Dimitris Kontoyiannis, BSRC Alexander Fleming, Greece**
11:00 – 11:25	Investigation of real-time PCR-based pathogen screening for monitoring mice in flexible film isolators Stephanie Durrand, Charles River, France
11:25 – 11:50	The Evolution of Preclinical Testing through Novel Humanized Precision Disease Models Maria Denis, Biomedcode, Greece
11:50 – 12:15	Finding Treatments for Metabolic Disease and its Complications Andrew Peterson, Genentech, USA
12:15 – 12:40	Preclinical Data Reproducibility and Model Validation in Neuroscience – the IMI Approach Thomas Steckler, Janssen Research & Development, Belgium
12:45 – 13:30	Lunch
13:30 – 14:30	**Session 7: Panel Discussion - *Impact of rodents as models of human diseases*** **Introductory presentation & Chair: Yann Herault, PHENOMIN-iCS** Panel Members: Hans Häring, Bernard Malissen, Andrew Peterson, Thomas Steckler
14:30 – 15:30	**Session 8: Translational Bioinformatics** **Chair: Sabine Fessele, INFRAFRONTIER GmbH**
14:30 – 14:50	A New Drug Target Identification and Prioritisation Web Platform Gautier Koscielny, GSK - Open Targets, UK
14:50 – 15:10	PhenoDigm and the IMPC: New insights into the genetics of rare disease Terry Meehan, EMBL-EBI, UK
15:10 – 15:30	Network Biology for Big Data Integration Fabian Theis, Helmholtz Zentrum Munich, Germany
Meeting Conclusions	
15:40 – 15:45	Meeting wrap-up & Outlook Michael Hagn, Helmholtz Zentrum Munich, Germany

Session 1: Technolgy Development

Mouse genetics and the CRISPR/Cas9 revolution
Ralf Kühn
Max-Delbrück-Centrum für Molekulare Medizin, Berlin, Germany

Within the last years the CRISPR/Cas9 system developed into a transformative technology in life and other sciences which now enables genetic engineering in virtually any species. In its natural configuration Cas9 associates with short RNAs which guide the nuclease to a selected target sequence in order to create a targeted DNA double-strand break (DSB). In eukaryotic cells such breaks are fixed by DNA repair mechanisms which frequently cause small deletions at the target site or enable the introduction of precise mutations from homology directed targeting vectors. In addition to its use for DSB induction, a increasing number of applications utilize nuclease-dead Cas9 as a specific DNA binding entity in combination with other protein domains which enable gene activation, repression, imaging or epigenetic modification. The immediate impact of CRISPR/Cas9 for mouse genetics is the simplicity of creating new knockout or knockin mutants directly in zygotes, without the requirement for ES cell manipulation and the production of germline chimaeras. Nevertheless, the design of optimized protocols for the delivery of Cas9 and guide RNAs into zygotes by microinjection or electroporation is under active development. Furthermore, in mice CRISPR/Cas9 opens new opportunities for genetic manipulation in somatic tissues such as the use of Cas9 transgenic lines for cancer research and its application in vivo or ex vivo for the correction of genetic lesions by gene therapy.

CARD's Kaizen Strategy for Mouse Reproductive Technology

Toru Takeo & Naomi Nakagata
Division of Reproductive Engineering, Center for Animal Resources and Development (CARD), Kumamoto University, Kumamoto, Japan

The Center for Animal Resources and Development (CARD) was established as a mouse resource bank at Kumamoto University in 1998. Since then, we have produced and archived over 2,600 strains of genetically engineered mice and improved a number of reproductive techniques, building a robust research infrastructure for the use of genetically engineered mice in the scientific community. The cryopreservation of embryos and sperm is a useful and efficient method of archiving a large number of mouse strains. In vitro fertilization makes it possible to mass produce embryos and mice. It is easier to transport cold storage of fresh embryos and sperm than ship live animals or cryopreserved samples. We have continuously enhanced the quality of reproductive techniques and encouraged effective sharing of valuable mouse resources archived in mouse repositories worldwide. Recently, we achieved the production of 100 oocytes from a single C57BL/6 mouse donor oocyte through the combined administration of inhibin antiserum (IAS) and equine chorionic gonadotropin known as the ultra-superovulation or IASe method.

Improving mouse reproductive techniques can assist in the provision of a robust and efficient system of preservation, production, and supply of genetically engineered mice for the scientific and industrial community. In addition, the system using mouse reproductive technology can contribute to implement the 3R principle (replacement, refinement, and reduction) of animal experiments. CARD has therefore put into practice its kaizen strategy of continuous improvement in mouse reproductive technology, and this has been adopted as a national project of the Advanced Research and Development Programs for Medical Innovation in the Japan Agency for Medical Research and Innovation to accelerate drug discovery through effective medical research using mouse models of human disease.

In this lecture, I shall describe the history of mouse reproductive technology development at CARD.

Replacing Immunoassays with MS-based Technology: Quantitative Proteomics Kits Enabling Deep Molecular Phenotyping of the Mouse

Christoph Borchers
Genome BC Proteomics Centre, Canada

Mice are the most commonly used mammals in health research. Because of their key role in drug development and biomedical research, the number and diversity mouse models continue to expand at an unprecedented rate. However, new mouse models require extensive validation to determine if they are a meaningful representation of human disease and thorough characterization in order to yield new insights into health and disease, suggest treatment approaches, and facilitate drug development. Determining the concentration of a wide variety of proteins in biofluids and tissues of mice is an important way of assessing these models, but present methods can only study 10s to 100s of proteins at a time, even though it is estimated that there are >16,000 proteins expressed in mice. This means that we are currently very limited in the amount of information we can obtain in a given study. Moreover, many potentially important proteins are completely ignored because of a lack of tools to study them.

A more comprehensive approach is crucial in order to move the field forward. In this project, we will take the crucial first steps toward whole proteome quantitation in mice by developing new mass spectrometry (MS)-based technology for rapid analysis of 3000 mouse proteins in a single sample. By developing quantitative assays for 3000 proteins, we will transform quantitative proteomics from a very targeted approach with limited scope to one capable of accessing a significant portion (~20%) of the mouse proteome. The new MS test will be formatted as an easy-to-use kit that can be applied by researchers worldwide in their own laboratories for their own studies. Furthermore, we will publish reference ranges that will help researchers interpret the data they obtain from running the kits. By offering the ability to simultaneously obtain accurate concentration measurements for a large number of proteins in a simple and widely applicable format, this technology will disrupt the use of immunoassays and Western blot for mouse phenotyping applications. Launching this new approach will extend scientific reach for a more in-depth and complete picture of how the full complement of proteins in the genome is involved in health and disease.

Session 3: Technology Development II

Automated Multi-Dimensional Metabolic & Behavioral Phenotyping of Mouse and Rat Models of Human Diseases

Harm J. Knot
TSE Systems, Germany

Based on our metabolic screening platform PhenoMaster and our behavioral screening platform IntelliCage we have developed new technologies to significantly enhance these individual platforms as well as develop an integrated concept system termed PhenoWord. New developments in metabolic screening with emphasis on gnotobiotics , use of germ-free animals in metabolic screening will be discussed. Extension of our flexible gas sensor technology with added sensors for hydrogen, methane and volatile organic substances to integrate microbiota activity screening will be presented.
I will provide an overview on where we are today with the technology to monitor metabolism and how this technology can be used to enter and advance other fields of research such as cognitive/ behavioral, cancer and cardiovascular research. I will discuss current challenges using metabolic monitoring equipment and how our next generation equipment and software, including metabolic and energy balance simulation might look like. I will also present the current status, using a combinatorial approach, of our PhenoWorld concept.

Informatics for the Capture, Analysis, and Dissemination of 3D Image Data

Henrik Westerberg
Biocomputing, MRC Harwell
Harwell Campus, Oxfordshire, OX11 0RD, UK

The goal of the International Mouse Phenotyping Consortium (IMPC, www.mousephenotype.org) is to functionally characterise every mouse gene using standardised phenotyping tests. Around 35% of the analysed knockout lines are embryonic or perinatal lethal or subviable. These lines go through the embryonic phenotyping pipeline which contains a large 3D Imaging component consisting primarily of OPT at E9.5 at micro-CT at E14.5-E15.5 and E18.5.
What is also required to go hand in hand with the biological phenotyping pipeline are the software tools to capture, store, display, analyse, and annotate 3D image data. At MRC Harwell, as part of the MPI2 consortium, we have been developing software tools in conjunction with the IMPC embryo working group at each stage of the data processing pipeline process in order to aid our partners but also to put forward new ideas in how best to maximise the utility of this data. This talk will outline the software tools we have developed and will go into some detail how it is possible to automatically annotate (derive phenotypic ontological associations) from 3D data.

Gnotobiotic mouse models to study the role of the commensal microbiota on host physiology
Andrew J. Macpherson & Stephanie C. Ganal-Vonarburg
Maurice Müller Laboratories (DKF), Universitätsklinik für Viszerale Chirurgie und Medizin, Inselspital, University of Bern, Switzerland

A vast number of bacteria, viruses, and fungi inhabit the inner and outer body surfaces, such as the intestine, the airways and the skin, of all healthy mammals. They are referred to collectively as the commensal microbiota. The remarkable impact of commensal microbiota on the mucosal and systemic immune systems became apparent in the last decade. It is now believed that changes in microbiota composition as a consequence of "Western" lifestyle, such as hygiene and nutrition, significantly contribute to the rising incidence of autoimmune and allergic diseases, including inflammatory bowl disease, type I diabetes, multiple sclerosis and asthma. But also non-immunological disorders such as obesity and autism have been linked to the commensal microbiota.
In order to study the impact of the microbiota on host physiology and to understand the underlying molecular pathways, axenic and gnotobiotic mouse models are nowadays routinely used. In the Clean Mouse Facility at the University of Bern, we breed a great number of mouse lines under germ-free and gnotobiotic conditions and we have the possibility to re-derive further strains upon request. Our gnotobiotic models range from simple mono-colonizations with known gut commensals and a model of transient colonization of germ-free mice with a commensal E. coli strain, to more complex model microbiotas harboring 10-20 commensal bacteria. In our experiments, we analyze different functional aspects of host immunity as well as the metabolic profile of both host and microbes using metabolomic mass spectrometry analysis in order to understand how microbial products penetrate the host and alter its physiology.
Interestingly, there is evidence that exposure to certain microbes during early childhood is an important factor in shaping the immune system and the health of the infant. Delivery mode (natural, caesarian section), feeding regime (breast milk, formula-fed), and living environment (countryside, city) significantly alter the infants gut microbiota and can be connected to autoimmune and allergic disease prevalence. We have recently shown that the microbial shaping of the mammalian immune system not only starts after birth when the newborn gets colonized but already before birth by signals derived from the maternal microbiota. This early life period is called the "window of opportunities".
Future challenges in the field of microbiota research will be to better define the importance of microbial influences early in life on the susceptibility to various diseases. Further, it will be more and more important to establish novel model floras, which best possible mimic a "healthy gut microbiota" and which are stable over many generations and can be used to standardize experiments among different laboratories.

Ageing: MouseAge

Ilaria Bellantuono[1] & Paul Potter[2]
[1] MRC Arthritis Research UK Centre for Integrated Research into Musculoskeleta Ageing (CIMA) Department of Oncology & Metabolism, The University of Sheffield, Sheffield, UK
[2] Mammalian Genetics Unit, MRC Harwell, Oxfordshire, UK

The number of people over the age of 65 is predicted to double in the next 50 years with consequent increase in the incidence of age-related chronic diseases. Up until now, research has focused predominantly on single diseases often with a focus on mortality as the main endpoint. However, over 60% of the over 65 has more than one disease at the same time. In addition 50% of over 80 develop frailty, which displays a progressive accumulation of deficits with severe decline in health and function. Current treatments are ineffective and costly when targeting multimorbidity and frailty. There is a need to identify new interventions in addition to the single disease model. Recent advances have shown that drugs targeting fundamental mechanisms of ageing are able to prevent or delay age-related tissue dysfunction as a group rather than one at a time and boost resilience in murine models. However, testing of these drugs, and indeed testing interventions in ageing models in general, to support clinical translation presents many challenges both in know-how, tools and infrastructure. There is currently a clear lack of well characterised ageing models, models of frailty and multimorbidity, of meaningful, standardised testing conditions and agreed endpoints that facilitate the transition to clinical testing across European centres. In addition studies on aged animals are resource intense, they take a long time and are costly. Here we present two initiatives which aims at addressing these challenges and are interconnected. The COST Action MouseAge is funded by the European programme Horizon 2020 and aims at defining endpoints, standardising methodologies, as well as centralising information, models and technologies for the assessment of interventions in preclinical mouse models relevant to ageing and age-related disease. It was launched in January 2015 and involves 24 European countries and approximately 200members to create a critical mass of cross-disciplinary scientists, clinicians, industrial partners and representative of regulatory bodies to reach consensus on ways to test preclinical interventions in ageing mice. It aims to consolidate current best practice across leading European institutions and researchers worldwide, and centralise infrastructure to speed up testing of interventions. It also provides a platform to help train the next generation of scientists and clinicians. MouseAge encourages the participation of researchers from COST countries and is keen to liaise with organizations with similar or complementary expertise worldwide. The second initiative is the Shared Ageing Research Materials biobank (ShARM), which is funded by the Wellcome trust and provides ready access to tissues from aged mice by collecting surplus tissues from that would otherwise be discarded. They are stored in a biorepositiory together with a larger amount of information including diet and health status. The biobank provides rapid access to aged tissues, reducing the number of aged animals used, thus accelerating research and reducing costs. ShARM has also an online database which provides details of living colonies which can be accessed by researchers upon request for bespoke collections and a collaborative environment for discussion and knowledge exchange, particularly on animal welfare.

Session 5: Translational Research

Multiparametric profiling of the immune system using flow and mass cytometry

Bernard Malissen, Marie Malissen & Hervé Luche
Centre d'Immunophénomique, PHENOMIN-CIPHE, Marseille, France

The immune system is composed of many cell types that function in a concerted manner to protect us against infectious agents. In recent years, it has been recognized that T cells have the ability to eliminate cancer cells. Therapeutic antibodies (checkpoint inhibitors) blocking the functions of inhibitory molecules expressed at the T cell surface have become standard treatment for metastatic melanoma, leading to a revival in the study of T cells. The immune system can be considered as a 'fluid connective tissue' and this permits to isolate its components via mild extraction procedure and to subject them 'ex vivo' to a cell-profiling technology called flow cytometry, in which fluorescent proteins are attached via specific antibody to defined proteins expressed at the surface of immunocytes so that combinations can be easily detected and the cells scored or sorted. By relying on objective mathematical principles to define cellular clusters, automated analyses have recently increased the reproducibility of flow analysis by circumventing manual gating. They also simplified the visualization of the multidimensional datasets, which is particularly important when analyzing mass cytometry dataset involving more than 30 markers simultaneously measured per cell on sample made of several thousands of cells. The Immunophenotyping CIPHE Core Facility has the unique ability to phenotype all the cellular components of the immune system under normal and pathological conditions (inflammation, infection, cancer) by using advanced multiparametric flow and mass cytometry approaches involving over 200 quantitative parameters. It provides a broad range of instruments and services for the analysis and isolation of cells based on fluorescent and rare earth-metal labeling. It contributes to the current ongoing global efforts to profile the transcriptional landscape of various immune cells (Immgen2) and the immune-phenome of the mouse spleen (PHENOMIN/IMPC). It also aims at defining at the system-level and in an unbiased and comprehensive manner the mode of action of the checkpoint inhibitors used in cancer immunotherapy.

Genetic dissection of breast cancer development, therapy response and resistance in mouse models

Jos Jonkers
Netherlands Cancer Institute, Amsterdam, The Netherlands

My lab is focused on the genetic dissection of human breast cancer through the use of genetically engineered mouse models and patient-derived tumor xenograft models. For this, we have developed mouse models for BRCA1- and BRCA2- associated hereditary breast cancer and E-cadherin mutated invasive lobular carcinoma (ILC). We have used these models to (1) investigate genotype-phenotype relations in mammary tumorigenesis; (2) identify genetic changes underlying breast tumorigenesis; (3) study mechanisms of therapy response and resistance.
Our mouse models for BRCA1-deficient breast cancer develop tumors that are characterized by genomic instability and hypersensitivity to DNA-damaging agents and PARP inhibitors. Nevertheless, none of these drugs are curative: tumors grow back after drug treatment and eventually become resistant. Using a combination of functional in vitro screens and in vivo studies, we have found that therapy resistance of BRCA1-mutated tumors can be induced by several mechanisms, including genetic reversion, activation of drug efflux transporters, hypomorphic BRCA1 activity, and rewiring of the DNA-damage response. Therapy resistance of BRCA1-methylated tumors is driven by loss of BRCA1 promoter methylation or by de novo BRCA1 gene fusions created by intrachromosomal genomic rearrangements.
Using forward and reverse genetics in our mouse models of ILC, we have shown that mutations in fgfr2 or PI3K pathway components (pik3ca, Akt or Pten) strongly cooperate with E-cadherin loss in tumorigenesis, leading to development of mammary tumors that closely resemble classical ILC. We have also used in vivo insertional mutagenesis screens to identify mutations that cause resistance to FGFR inhibitors in E-cadherin mutated mammary tumors with overexpression of FGFR2.
To accelerate in vivo evaluation of candidate drivers and drug resistance genes, we have developed novel methods for rapid generation of germline and non-germline breast cancer models. Using embryonic stem cells (ESCs) derived from our conditional mammary tumor models, we can quickly introduce additional gain- and loss-of-function alleles and generate novel tumor models by blastocyst-injection of the manipulated ESCs. Using intraductal injection of CRISPR vectors in mammary tumor models with conditional expression of Cas9, we can test candidate tumor suppressors by in vivo gene editing.

Bridging the innovation gap – EATRIS ERIC and the ESFRI BMS infrastructure efforts to improve patient outcomes

Anton Ussi
EATRIS-ERIC, The Netherlands

The process of translating novel biological insights into effective interventions is a highly complex highly undertaking, requiring significant dedicated expertise and infrastructure. The hope generated by the revolution in biology stemming from the unravelling of the human genome and subsequent explosion of a variety of 'omics fields was not met with an increase in effective medical interventions.
While 2014 and 2015 saw a welcome continuation of the recent increase in new drug approvals by the EMA and FDA, the development path from discovery to market remains long, complex and costly. Development failure rates remain stubbornly high. Concomitant to this reality is the continuing trend that industry is substantially reducing its research investments in the early phases of translational research and development.

The field of translational science is a highly multi-disciplinary enterprise, tasked with gaining a fuller mechanistic understanding of both disease process and the mode of action that a would-be therapeutic would utilise to modulate its effects. This is a move away from more empirical methods of development, and is in part a response to increasing scrutiny from regulators, who are more and more requiring that developers show (a) understanding of the mechanisms behind their investigational drugs, and (b) increasing onus on the ability to stratify potential responders from non-responders ex ante on the basis of companion diagnostic tests.
Due to these developments in the field, the development pipeline finds itself in a transitional stage, where developers are trying to validate tools that can support in discriminating early in the R&D process which drug candidates have high potential versus those that will fail, as well as significant resources deployed to identify and validate potential biomarkers for patient stratification and prognostication. Regarding the former, the so-called "Fail Early" paradigm can be seen below. It is in this biology-driven, technology-rich area that academia is proving to be a significant driver of productivity, both in terms of novel tools for development, as well as in the very interventions that ultimately will transition along the pipeline towards the patient.

EATRIS ERIC was created to defragment the substantial European efforts in this field, with the mission to improve productivity of the translational R&D pipeline, by providing high quality research services to public and private research entities. An integral part of this mission is to collaborate with complementary infrastructures, such as INFRAFRONTIER, in order to jointly discover, validate and disseminate high value tools and more predictive models for the drug and diagnostics development process. An excellent example of collaborative efforts to this end are embodied in CORBEL, a multi-infrastructure Horizon2020 project aiming at delivering integrated, user driven services in biomedical research in the European Research Area.

Session 6: Industry & Innovative Medicines Initiative (IMI)

Investigation of real-time PCR-based pathogen screening for monitoring mice in flexible film isolators

Stephanie Durrand
Charles River, France

PCR panel-based pathogen screening has become more economically feasible because sample types can be pooled to some degree and there is a potential to reduce or eliminate sentinels and the associated husbandry, shipping cost, and multiple traditional screening methods. To address pathogen screening for thousands of flexible film isolators within our facilities, we proposed considering the use of real-time (rt) PCR-based pathogen screening for replacement or partial replacement of sentinel use. Based on a pilot study using flexible film isolators containing either pet shop mice or rats, we identified optimal sample types for the detection of a large array of rodent pathogens. To further investigate alternative isolator monitoring, we designed a larger study to compare rtPCR-based screening of direct sampling and environmental samples with contact sentinels screened by traditional methods in 13 isolators containing genetically modified mice. Direct PCR sampling included pooled feces and body swabs and pooled environmental sampling included an exhaust port and floor swab. In this investigation, contact sentinel use and rtPCR equally detected MNV and S. aureus; however, there were minor to substantial false-negative findings by sentinels use for all other agents detected. Both direct sampling and environmental sampling detected most agents by rtPCR, except Pneumocystis and Cryptosporidium which was found only in the environmental samples. Average estimated target copy numbers was highest by direct sampling for Helicobacter, Campylobacter, S. aureus, K. pneumoniae, P. mirabilis, P. pneumotropica, Murine norovirus, Spironucleus, and Entamoeba, but highest by environmental samples for K. oxytoca, P. aeruginosa, and fur mites. We conclude that PCR testing of non-invasive samples in combination with environmental samples improves the detection of infectious agents of mice maintained in flexible film isolator over sentinel use by traditional screening methods.

The evolution of preclinical testing through novel humanized precision disease models

Maria C. Denis & Niki Karagianni
Biomedcode Hellas SA, Vari, 16672, Greece

In the search for novel cures for human disease, the preclinical phase of drug development is of critical importance and its translational value depends heavily on the use of carefully selected animal models that faithfully recapitulate key features of the complexity of the human disease. The importance of this selection is highlighted by the number of clinical studies that have failed to reproduce preclinical data because they were derived from poorly selected animal models.
A concentrated effort focusing on the search for novel cures stems from the Be The Cure (BTCURE) which is an Innovative Medicines Initiative (IMI)-funded consortium aiming to combine academic and industrial resources to develop new therapies against rheumatoid arthritis.
In total 37 partners, 24 academic and 14 industrial, from all over Europe participate in an effort to enhance basic understanding of rheumatoid arthritis pathogenesis and therapeutic development. This combined effort tackles both patient and animal model derived findings aiming to align animal models to different aspects of human disease, standardize procedures and interpretation of data arising from commonly used RA animal models and generate new RA animal models. By combining human and mouse data, the consortium aims to systematically generate, archive and validate data on treatment responses to existing and developing drugs in animal models and align them to different subsets of human disease, thus creating a comprehensive “pathogenesis map” for RA.
Through a fruitful collaboration both with academic and industrial partners, Biomedcode has contributed in the BTCURE effort by standardizing animal model-related operating procedures and generating novel humanized arthritis preclinical platforms required by pharmaceutical partners for the evaluation of novel human therapeutics. By combining the Collagen Antibody Induced Arthritis (CAIA) protocol with a human TNF transgenic mouse (Tg1278TNFKO) and a human TNF-TNFR1 transgenic mouse (Tg1278TNFKOhTNFR1KI), Biomedcode has developed a fast, highly reproducible and sensitive model for the evaluation of human therapeutics targeting the TNF-TNFR1 pathogenic pathway. Moreover, Biomedcode has characterized in detail spontaneous humanized models of arthritis revealing that in addition to closely recapitulating the human pathology these models also develop arthritis related comorbidities thus offering a unique multidimensional disease environment that allows the evaluation of human therapeutics in a context that closely mimics the complexity of the human disease.
The translational value of preclinical work is unquestionable but there is currently a pressing need to evolve the animal models we use to more closely reflect the human condition and the heterogeneity of the human disease that is an orchestrated process affecting simultaneously multiple organs and systems. The generation, characterization, validation and standardization of such models offers invaluable tools in the study of common disease mechanisms as well as the identification and validation of novel diagnostic and therapeutic targets and the evaluation of novel therapeutics for multiple indications. Biomedcode supports such efforts by developing mouse models humanized for key pathogenic players including TNF, TNFR1, IL17, RANKL in multiple models of chronic inflammatory conditions including arthritis, IBD, osteoporosis, spondyloarthritis, psoriasis and others and works towards the better understanding of the complexity of the human disease through the analysis of relevant multidimensional models.

Finding Treatments for Metabolic Disease and its Complications

Andrew Peterson
Department of Molecular Biology, Genentech, USA

Metabolic dysregulation affects a very significant fraction of the world's population where it profoundly increases the incidence of diabetes, heart disease, liver disease and cancer. The diabetic state is one in which the incidence of all of the other associated diseases is even more dramatically increased and where additional and specific diseases flare up in the eye and kidney. Our efforts to discover new treatments have been focused in two areas; broadly correcting metabolic dysregulation in individuals who are at the most significant risk of complications and in a separate approach, identifying opportunities to prevent or treat the specific microvascular complications that lead to blindness and kidney failure in in patients with diabetes.

The endocrine hormone Fgf21 is able to significantly improve metabolic dysregulation in rodents and primates by binding to a receptor/co-receptor complex of FgfR/βKlotho. In treated animals LDL cholesterol is reduced, HDL cholesterol and adiponectin are increased, hyperglycemia is corrected and weight loss occurs. To capture these beneficial activities in a drug-like molecule we have created an antibody molecule that mimics the activity of Fgf21 by simultaneously recognizing FgfR and βklotho molecules on the surface of adipocytes. This provides potent Fgf21-like activity with dramatically improved selectivity and half-life.

Our efforts to find therapeutic opportunities to treat diabetic microvascular disease use genetics to identify pathways and targets in human patients. We are carrying out studies in collaboration with hospitals and clinics in India with large patient populations to use clinical databases to build risk models that allow us to identify patients with the greatest genetic risk for microvascular disease. Gene discovery studies in these patients are allowing us to identify intrinsic pathways and pathobiological mechanisms that damage the retina and nephron in response to hyperglycemia.

Preclinical Data Reproducibility and Model Validation in Neuroscience – the IMI Approach
Thomas Steckler
Janssen Research & Development, Beerse, Belgium

Reproducibility and relevance of research findings represent the pillars of the scientific method. For drug discovery and preclinical drug development, as well as basic science, robust data and scientific rigor are key drivers for decision making, determining the validity of hypotheses, patent strength, time-to-market and consequently knowledge gain and availability of new treatments to patients. Recent publications report challenges with the robustness, rigor, and/or validity of research data, which may impact decisions about whether to proceed to preclinical testing as well as conclusions on the predictability of preclinical models. Agencies funding research, publishers, academia, industry and the public rely on robust, reproducible, and valid data and any potential challenges in this area are of concern. Higher failure rates due to non-reliable scientific data increase the risks and costs associated with Research and Development (R&D) and may hamper the successful translation of innovation to novel treatments for patients. While these issues impact all research areas, some areas seem to be more challenging than others, e.g., Neuroscience. Public-private partnerships pursued under the umbrella of the Innovative Medicines Initiative (IMI) started to address the issues of preclinical data reproducibility in the Neuroscience field, e.g., the PharmaCog, NewMeds and EU-AIMS consortia, and more recent initiatives have a complete focus on the topic of data quality. In this presentation the pertinent issues with preclinical data quality and factors contributing to the specific challenge in Neuroscience will be highlighted, and the strategies taken by some of the IMI initiatives that aim to address those issues will be discussed.

Session 7: Translational Bioinformatics

A New Drug Target Identification and Prioritisation Web Platform

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We have designed and developed a data integration and visualisation platform that provides evidence about the association of potential drug targets with disease. Currently integration of such evidence is mostly carried out by specialist bioinformaticians using complex tools. The platform is designed to enable biomedical researchers who need to discover a biological target for a new therapy to identify and prioritise targets for follow up. The platform supports either a target-centric workflow to identify diseases that may be associated with a specific target, or a disease-centric workflow to identify targets that may be associated with a specific disease, allowing users to flexibly transition between workflows. Targets may be a protein, protein complex or RNA molecule, and we integrate evidence through the target gene. Phenotypes are integrated through the Human Phenotype and Mammalian Phenotypes ontologies, diseases are integrated through the Experimental Factor Ontology, which contains ontologies across biomedical domains that classify rare and common diseases and their phenotypes. We derive evidence of association between a target and a disease from multiple public domain expert-reviewed and data-driven resources including germ-line and somatic genetics, known drugs, gene expression profiling, reaction pathways, murine genetic models and the biomedical scientific literature, partnering across several cross-disciplinary teams. The association between a target and a disease is scored using a data-driven approach that incorporates data-specific terms for the observed frequency, the experiment confidence and the likely strength of the effect. The platform provides bespoke visualisations of association evidence from a target or disease perspective and an approach based on facets and filters to refine the set of interesting associations by strength, data type or properties of the target or disease (e.g. presence in a reaction pathway, therapeutic area). In addition to evidence displays, we provide aggregated target- and disease-specific information including graphical displays served via JavaScript plugins from the data providers. In designing and developing the platform we employed a user-centred design process, and tested extensively through usability workshops, interviews and reviews with a panel of scientists enrolled as beta testers.

The platform uses a JSON schema for data exchange, python scripts for quality control and analysis of the data, Virtuoso for ontology lookup, ElasticSearch for data audit, indexing and querying. A REST API serves the web front end written in the AngularJS framework and is publicly accessible to retrieve the data presented in the web platform.

Access: https://www.targetvalidation.org

PhenoDigm and International Mouse Phenotyping Consortium: New insights into the genetics of rare disease

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Whole exome- and genome-sequencing is accelerating the discovery of gene variants associated with rare diseases. While hundreds of novel disease-associated genes have been characterised, the identification of disease causing mutations is challenging due to the large number of rare variants within a patient population and the lack of knowledge for the function of most genes. PhenoDigm is a resource developed to prioritise candidate rare disease variants using semantic algorithms developed by the Monarch Initiative that compares clinical features of a human disease with the phenotypes associated to model organisms. The broad-based phenotyping of new knockout mouse strains by the International Mouse Phenotyping Consortium (IMPC) greatly contributes to these methods by associating phenotypes to thousands of poorly characterised genes. PhenoDigm overlap scores of mouse models to human disease are provided on the IMPC web portal, mousephenotype.org, and are used in prioritising candidate disease candidates from patient exomes with the Exomiser tool. In this talk I will highlight these resources and demonstrate how they are being incorporated into exome analysis pipelines including the UK 100,000 Genomes project.

Network biology for big data integration

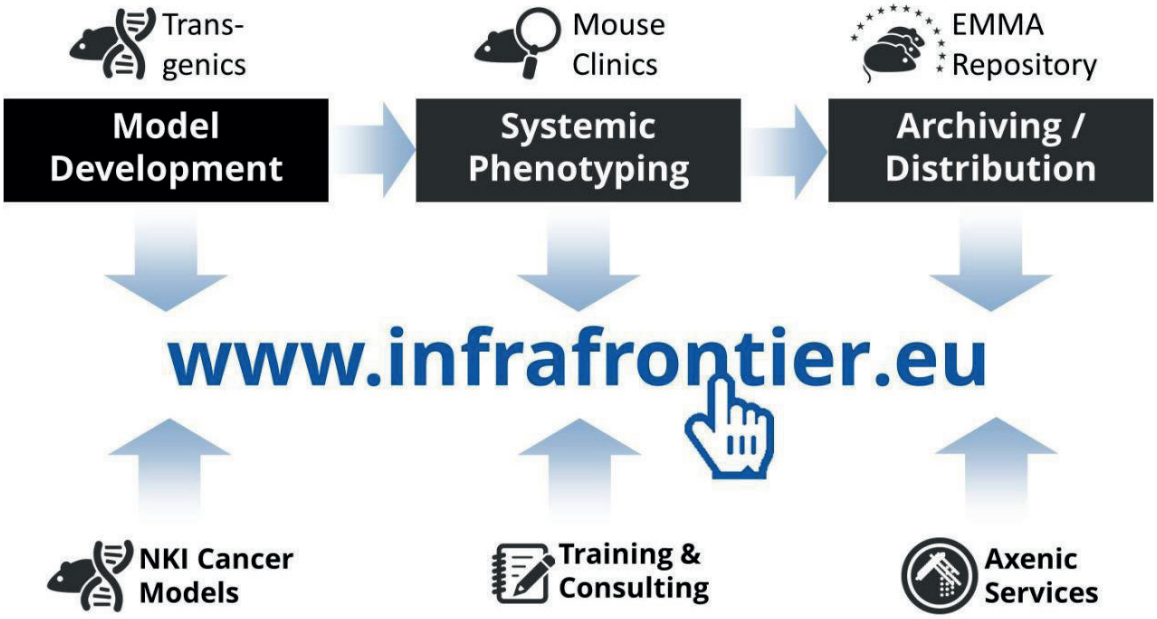
Fabian Theis
Institute of Computational Biology, Helmholtz Zentrum München, Germany

In modern high-throughput biomedicine, huge and complex data sets are being generated, in particular from the 'omics and imaging fields. The analysis and integration of these data sets is daunting but crucial not only for research but also for envisioned clinical use e.g. for precision medicine. Big data is a challenge both for infrastructure as well as for analysis. In this talk I will focus on the latter, showing that network biology is an ideal tool for multi-omics data integration and analysis. Networks consist of nodes typically representing certain molecules and edges describing interactions of those, such as regulation, coexpression or complex formation. I will describe how to use networks to integrate data in population cohorts from multiple omics-level, in particular a graphical model for metabolomics and genetics data, and will finish with a mouse multi-organ metabolomics study.

INFRAFRONTIER

mouse disease models

INFRAFRONTIER is the pan European Research Infrastructure for generation, systemic phenotyping, archiving and distribution of mouse diseases models providing access to first class tools and data for biomedical research. Specialized services as generation of germ-free mice and training in state-of-art cryopreservation and phenotyping technologies complete the INFRAFRONTIER service portfolio.
All resources and services offered by INFRAFRONTIER can be accessed via the INFRAFRONTIER webportal.



www.mousephenotype.org • @IMPC

IMPC

International Mouse Phenotyping Consortium

An open-access encyclopedia of mouse gene function

The IMPC is **creating** 20,000 knockout mouse strains on a single background strain, **characterizing** each through a standardized phenotyping protocol, **connecting** the data to existing mouse and human genomic databases, and **cataloguing** it online for use by researchers worldwide.

Explore the IMPC web portal to:

- **Search** by gene, phenotype, or anatomy for free access to IMPC data
- **Find** mouse models of human diseases, including rare diseases
- **Order** mice for your research

20,000 knockout mouse strains

18 research institutions

15 countries

5 national funders

4 continents

1 goal

Knockout Mouse Program
Colin Fletcher[1] & the IMPC Research Network
[1]National Institutes of Health, USA

The NIH funded KOMP project marks its 10th year in 2016. The project was envisioned as an effort to determine the phenotypes of a comprehensive set of null mutation in the mouse. The project was launched in 2006 with the support of 18 institutes and centers at NIH, and operated in conjunction with similar European efforts. The first iteration of the project, from 2006 – 2011, accomplished the task of creating a library of 9,000 knockouts in the form of embryonic stem cells. In 2011, the focus shifted to animate of live mice from this library and the broad phenotyping of the strains. The project has been renewed for an additional five years and intends to complete the phenotyping of over 5,500 knockouts by 2021. KOMP will be discussed in light of the larger genomics portfolio at NIH.

www.actualanalytics.com

Rodent behaviour analysis plays a vital role in drug discovery, in everything from the development of disease models through to safety pharmacology. Through the NC3Rs CRACK-IT Challenges (in **partnership** with AstraZeneca, MRC Harwell, University of Strathclyde, University of Edinburgh, and **The NC3Rs**), we have developed an innovative home cage analysis system that provides 24/7 monitoring of rodent behaviours in a group-housed environment that is beneficial from both data and welfare perspectives.

The Actual Home Cage Analysis system represents the newest and most exciting technology available in rodent behavioural research. Rodents in research labs live in small social groups in highly optimised plastic home cages where they thrive and grow. Inside such 'hotels' the animals eat, drink, sleep, interact and behave; yet this data is largely ignored due to technical challenges. Experimenter influence is a particularly difficult issue; even if the data capture itself can be automated, or controlled, the presence of the scientist during the experiment may have an influence. Instead the current system for characterising these rodents usually involves removing these animals from their home cage into singly housed, novel environments. The depth of analysis is limited to the designated hours of observation, meaning researchers obtain a limited snapshot of the rodents' activity and behaviour over short periods of time. However, the human manifestations of many central nervous system disorders are often characterised by multiple phenotypes, presented over longer periods of time. Monitoring rodents around the clock allows for the refinement of disease models and early phenotypes can be identified sooner and addressed accordingly, making studies more accurate and reducing the number of expensive failures in the later stages of the drug discovery pipeline.

The system is highly compatible with modern, high-density animal facilities. ActualHCA is installed seamlessly into unmodified IVC racks. To achieve spatial monitoring of individual location and detect animal activity, the home-cage is placed on a low profile base-plate that contains a 2D array of RFID antennae. Each of the antennae in the baseplate is designed to energise a small spatial area within the cage and read the identity of a tagged animal within that space. Video footage is shot from the side view and an infrared light source allows for 24/7 automated behaviour recognition.

The richness of the data provided by ActualHCA is unmatched by traditional methods. It allows researchers to obtain the maximum data possible per rodent as part of standard in vivo testing; according to the University of Strathclyde, ActualHCA delivers 90% more data with 50% fewer rodents than traditional observation methods.

Not only does this mean your organisation benefits from better experimental data, it also enables better compliance with the 3RS and **reduces safety-related project closures further up the drug discovery pipeline**.

Currently we are seeing exciting advances in numerous facets of research including Huntingdon's disease and Malaria. We work closely with world-class research facilities, if you would like to know more about our recent work and publications, contact us at: getintouch@actualanalytics.com

www.ayoxxa.com

Who we are
AYOXXA Biosystems GmbH is an international biotech company based in Cologne (Germany), with offices in Boston (USA) and Singapore. AYOXXA introduced patented LUNARIS™ beads-on-a-chip technology to analyse picogram amounts of proteins in precious biological samples. This innovative technology platform detects almost any biomarker, in multiplex and at any throughput. Thus, LUNARIS™ pushes the minimum required sample volume to single-digit microliter amounts and greatly expands the types and number of samples from which scientists can gain insights. AYOXXA offers a robust, precise and accurate protein detection all the way from basic to clinical research.

AYOXXA's focus areas include, but are not limited to
- Ophthalmology - Therapy monitoring and preclinical tool to analyze delicate samples taken from the eye
- Mouse-to-Man – Using data generated from small specimen efficiently, using fewer animals for scientific experiments
- Immunooncology (in the pipeline).

We make a difference
Unlock insights from **low-volume samples** - LUNARIS™ pushes boundaries in biomarker analysis by enabling quantitative and highly precise analyses of samples down to 3 µL.
Scale throughput to any need - LUNARIS™ BioChips comprise a modular system for **96/384 MTP format** that requires a single BaseFrame, but enables scaling experiments from 32 to 384 tests.
Integrate multiplexing into your routine - Processing and readout of LUNARIS™ assays were developed to accommodate your research in-house. However, for fieldwork or when readout equipment is not available, **BioChips once processed can be sent to AYOXXA for readout and analysis.**
Count on **accurate** results, every time - **Microbeads** are coated with antibodies and s**afely captured in microcavities** on the surface of the BioChips. This prevents bead aggregation or loss during assay procedure, increasing the reliability of your results.

Our offer:
Ready to use kits – AYOXXA offers a range of detection kits including all the components to start your multiplexing experiment immediately. Please find an overview of our products for key applications on www.ayoxxa.com/products.

Innovative multiplex assay development – Challenge AYOXXA's expertise in protein multiplexing: we design and develop assays and panels according to your individual needs.
Full service protein analysis on LUNARIS™ platform – Just send in your biosamples and you will receive a detailed report in less than 5 working days.

Readout services – Perform sample testing on your own then send your LUNARIS™ BioChips to AYOXXA for readout and analysis.

Partnerships
AYOXXA has the honor of participating in several outstanding international collaborations that drive clinical and translational discoveries. The consortium allows us to validate LUNARIS™ in clinical settings.
EYE-RISK consortium: This large European biomedical consortium brings together the expertise of highly reputable specialists from academia, clinics, a patient organization, Roche and AYOXXA as sole industry partners. The goal of EYE-RISK is to explore the role of different risk factors in the development of Age-Related Macular Degeneration (AMD).
AYOXXA will develop tests to compare biomarker profiles from AMD patients.
www.eyerisk.eu
Singapore Eye Research Institute: SERI is Singapore's national research institute for ophthalmic and vision research, one of the leading eye research institutes worldwide. Together with SERI, AYOXXA is measuring biomarker profiles in samples from Diabetic Retinopathy patients.
www.seri.com.sg
Collaborations with pharma and academia:
AYOXXA has established several partnerships with research groups in academia and in the pharmaceutical industry. We offer custom panel development up to full service protein analysis and readout services.

www.biomedcode.com

Biomedcode Hellas SA is a highly innovative Contract Research Organization (**CRO**) founded in 2006 as a spin-off company of the Biomedical Sciences Research Centre "Alexander Fleming". Biomedcode offers a diverse array of state-of-the-art preclinical evaluation platforms based on a unique collection of spontaneous and induced humanized mouse models that closely recapitulate the pathology and complexity of **human inflammatory diseases including Rheumatoid Arthritis, Osteoporosis, Intestinal Inflammation, Multiple Sclerosis, Psoriasis and others**. The proprietary **spontaneous and induced humanized mouse disease models** offered by Biomedcode in combination with technological platforms for comprehensive **phenotyping of disease progression** and **response to therapy** form the tools offered by Biomedcode for the accurate, reproducible and sensitive evaluation of human therapeutics.

Since 2006, Biomedcode has provided preclinical drug evaluation services to more than 80 pharmaceutical and biotech companies worldwide contributing in the preclinical evaluation of multiple human therapeutics including **novel biologics, biosimilars, biobetters and small molecules** while data generated by Biomedcode have been included in patent applications and contributed in several successful IND process applications.

In addition to its preclinical services, Biomedcode maintains a highly active R&D programme that aims to generate, standardise and commercialize novel humanized preclinical evaluation platforms that are also used to identify disease pathways and biomarkers through pharmacogenomic and metabonomic approaches. Recently, Biomedcode has introduced activities that also cover disease induced phenotyping of genetically modified mouse models, repositioning approaches and the inclusion of comorbidities in the evaluation of test therapeutics. Through its research activities Biomedcode is a partner of choice in a number of national and European funded research activities thus strengthening its ties to the academic community and networks of innovative research.

www.criver.com

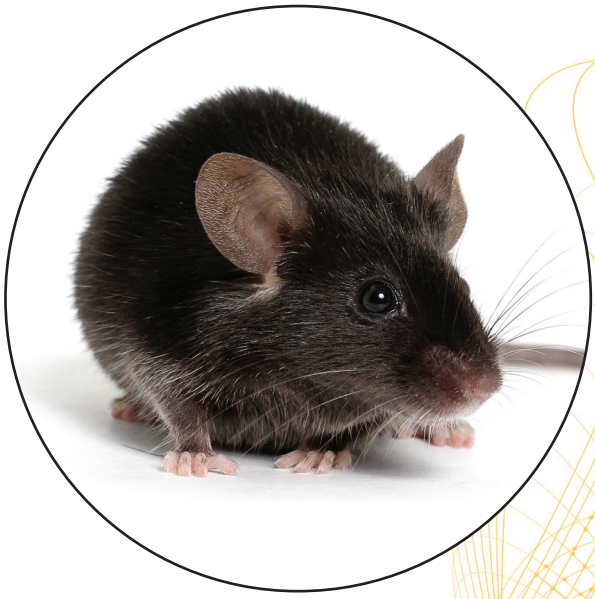
For more than 60 years, researchers worldwide have trusted Charles River as their source for the highest quality animal models and related services. Offering a broad selection of species and strains, we support today's most critical research with the timely delivery of study-ready, preconditioned and genetically engineered animals. Our leading scientists and global network of AAALAC-accredited vivaria and breeding facilities provide clients with accessible, expert management of outsourced colonies, biology services for line creation, maintenance and preservation, advanced diagnostics, and health monitoring to guarantee the long-term success of their work. Charles River is the official distributor of JAX™ mice in 29 European countries.

DSI™

About DSI

DSI is a pioneering biomedical research company focused on systems physiology and pharmacology. The recognized global leader in physiologic monitoring, DSI offers telemetry, instrumentation, software and services that help advance science.

Offering solutions tailored specifically to meet the unique research needs of customers as higher quality preclinical work will lead to better translation to the clinic.



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Fluidigm creates and manufactures innovative technologies and life-science tools designed to revolutionize biology through a relentless pursuit of scientific truth. Its core technologies are based on microfluidics and mass cytometry, and enable the exploration and analysis of individual cells, as well as the industrial application of genomics.

The company's **integrated fluidic circuits** (IFCs) offer rapid, efficient, highly parallel and reproducible analysis of up to hundreds of genetic markers across thousands of DNA samples in just hours, rather than days or weeks, all the way down to the level of the individual cell.
The Fluidigm microfluidic technology supports genomics-based applications such as **single-cell gene expression**, high-throughput SNP genotyping, protein expression analysis, digital PCR, mutant detection and more. Additionally, two of the company's instruments have proven to be workhorses within the life science industry: the **Biomark™ HD** and **C1™** systems.
In 2014, Fluidigm expanded into single-cell proteomics with its acquisition of technology leader DVS Sciences, the inventor of CyTOF®, a multi-parameter single-cell protein analysis system. The **Helios mass cytometer** analyzes antibody and metal complexes using an innovative method of atomic mass spectrometry, and solidifies Fluidigm's position at the leading edge of single-cell biology.

More than 400 people work for Fluidigm worldwide. The company works with more than 1,000 valued customers pioneering the field of single-cell biology or using applied genomics in industrial applications to improve and protect our food supplies, track samples in the world's largest biobanks and in general provide faster, more accurate, lower cost workflows to help improve people's lives.

Fluidigm is headquartered in South San Francisco, California, with sales and sales support operations from Beijing to Tokyo to Paris to San Francisco. Fluidigm conducts its Research and Development activities and manufactures its instruments, integrated fluidic circuits and reagents in its factories in South San Francisco, Singapore and Markham, Canada.

www.innoser.nl

InnoSer facilitates scientific biomedical research in a professional, efficient and responsible manner

There need to be a focus on accelerating biomedical research in Europe and promoting Europe as a centre of medical research innovation. Improved coordination and consolidation of excellent research across Europe and scientific input in biomedical research initiatives from the outset are vital to tackle the significant societal challenges in this domain. This means that science within Europe should choose to join forces by connecting networks, standardization, interoperability, reducing costs, and working transparently. Only then, Europe will be able to track the competition with America and Asia.

InnoSer is an important, relatively new player on the market that facilitates the European scientific biomedical research in an innovative, efficient, professional and responsible manner. InnoSer offers laboratory services in the field of genetically modified (genetically altered, GA) in vivo and in vitro models for biomedical research.
InnoSer's service portfolio includes: preclinical services, colony management, sanitation, cryopreservation and rederivation as well as generation and pathological analysis of GEMM research models. The services are local, well defined and under standardized conditions. InnoSer focuses entirely on professional support of researchers by field experts, keeping tight schedules and providing flexibility under highly attractive terms!

InnoSer's activities are based on the 4R's concept, Replacement, Reduction, Refinement and Responsibility. Corporate Societal Responsibility, or CSR,is the guiding principle in the company culture. InnoSer combines experience in commercial activities of a large state-of-the-art service facility for GA research models with expertise in the field of biomedical research. InnoSer is fully equipped to provide quality services and facilitate medical research while optimal conditions and animal welfare are part of the corporate culture.
Meanwhile, several research institutes and renowned researchers from the Netherlands and other European countries selected InnoSer as their preferred partner.
Moreover, our customer base is rapidly expanding.

Join InnoSer and you will also benefit from:

- local and distinctive presence
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Tecniplast, world leading company in the Lab Animal Industry since 1949, designs, manufactures and distributes patented equipment for vivaria. We offer the most complete related product portfolio ranging from IVC (Individually Ventilated Cages) systems, Bio containment and Bio exclusion IVCs, IVC monitoring, Analysis Systems, Aquatic solutions, Laminar Flow, Cage and Rack washers, Bedding Handling and Disposal systems, Decontamination and Automation, as well as a complete range of Accessories. Tecniplast has recently launched on the market the first **Digital Ventilated Cage (DVC™)**, enhancing the threshold in animal welfare, in users ergonomics and in management of Animal Lab Facilities.
Our constant investments in tooling, technologies, automation, production capabilities, stock availability, staff recruitment & training, the ISO certifications for quality (ISO9001) and environmental sustainability (ISO 14001) together with the management systems certifications, are a clear evidence of our commitment to provide customers with the most complete, reliable and relevant range of products.

We offer all-embracing solutions and services in Product Design, Ergonomic Planning, Environmental Responsibility, Space Planning, LEAN Audits and Budgetary Evolution. We support clients in installation, training and service with a direct presence in Italy, USA, France, UK, Germany, Australia, Japan and China, and worldwide with a network of 67 international representatives.

Tecniplast is committed as a contributor to a better society, investing time and efforts to promote the values that make us a center of excellence for Social Responsibility. We strive to achieve minimum environmental impact, while targeting also to Customer Satisfaction and good working condition for collaborators. Thus, as a tangible acknowledgment for these efforts, Tecniplast received the WCA certificate for the optimal working conditions of our employees. Our final aim is to produce environmentally-friendly products adopting ethical criteria, respecting human rights and the environment.

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http://www3.hilton.com/en/hotels/bavaria/hilton-munich-city-MUCCHTW/index.html

DIRECTIONS
From Munich Airport:
Take the suburban train S8 from "Franz-Josef Strauss" airport (MUC) towards Munich. The train station is between Terminals 1 and 2. Trains run at least every 20 minutes and the journey takes 35 minutes. Get off the train at the Rosenheimer Platz station with view to the driver's cabin and follow the signs to 'Gasteig'. The Hilton Munich City hotel is situated directly above the station. You do not even need to step outside the station, just follow the signs to "Gasteig" and take the elevator to the lobby.

From Munich Central Station:
Take the S-Bahn (S1-S4, S6-8) with direction "Marienplatz/Ostbahnhof" and take the exit "Rosenheimer Platz". At the platform, please follow the signs to the Hilton Munich City. The journey will take approximately 12 minutes.

Car Parking
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MEETING DINNER
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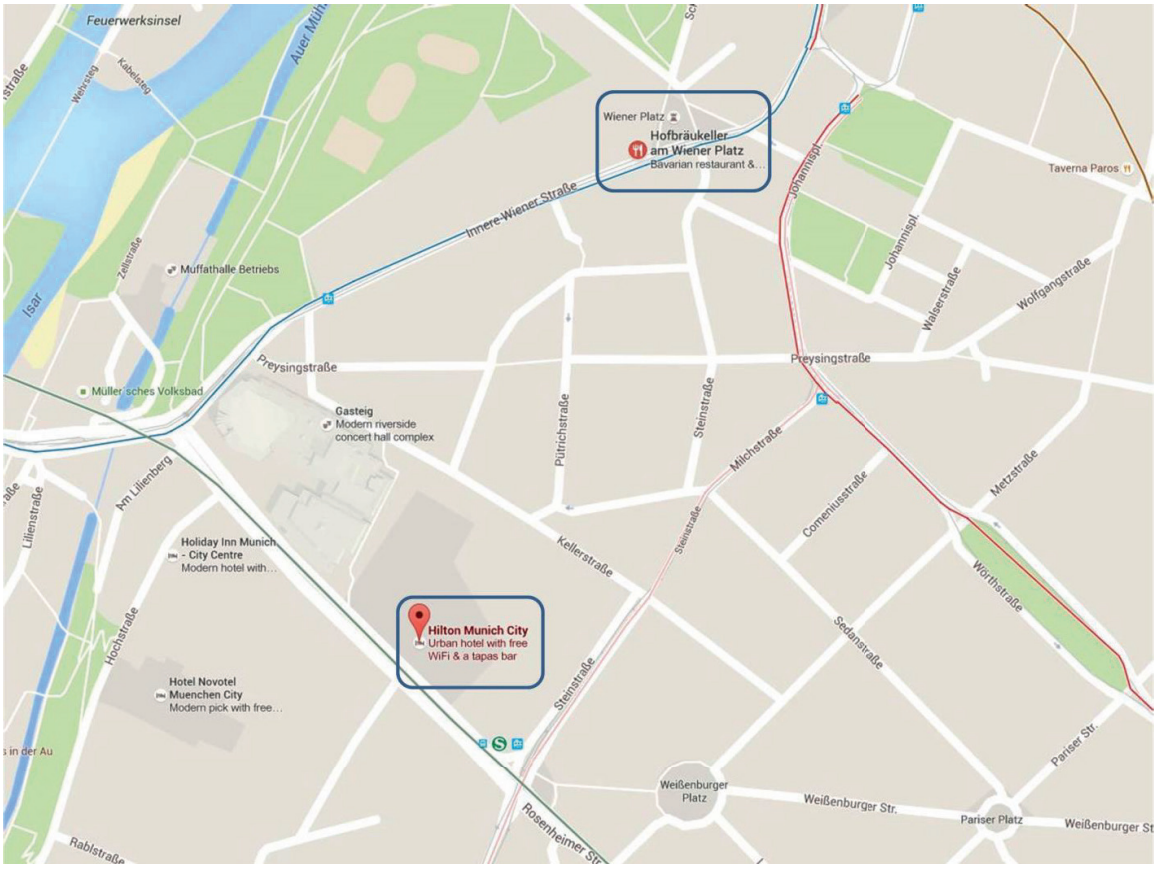
www.hofbraeukeller.de

LOCATIONS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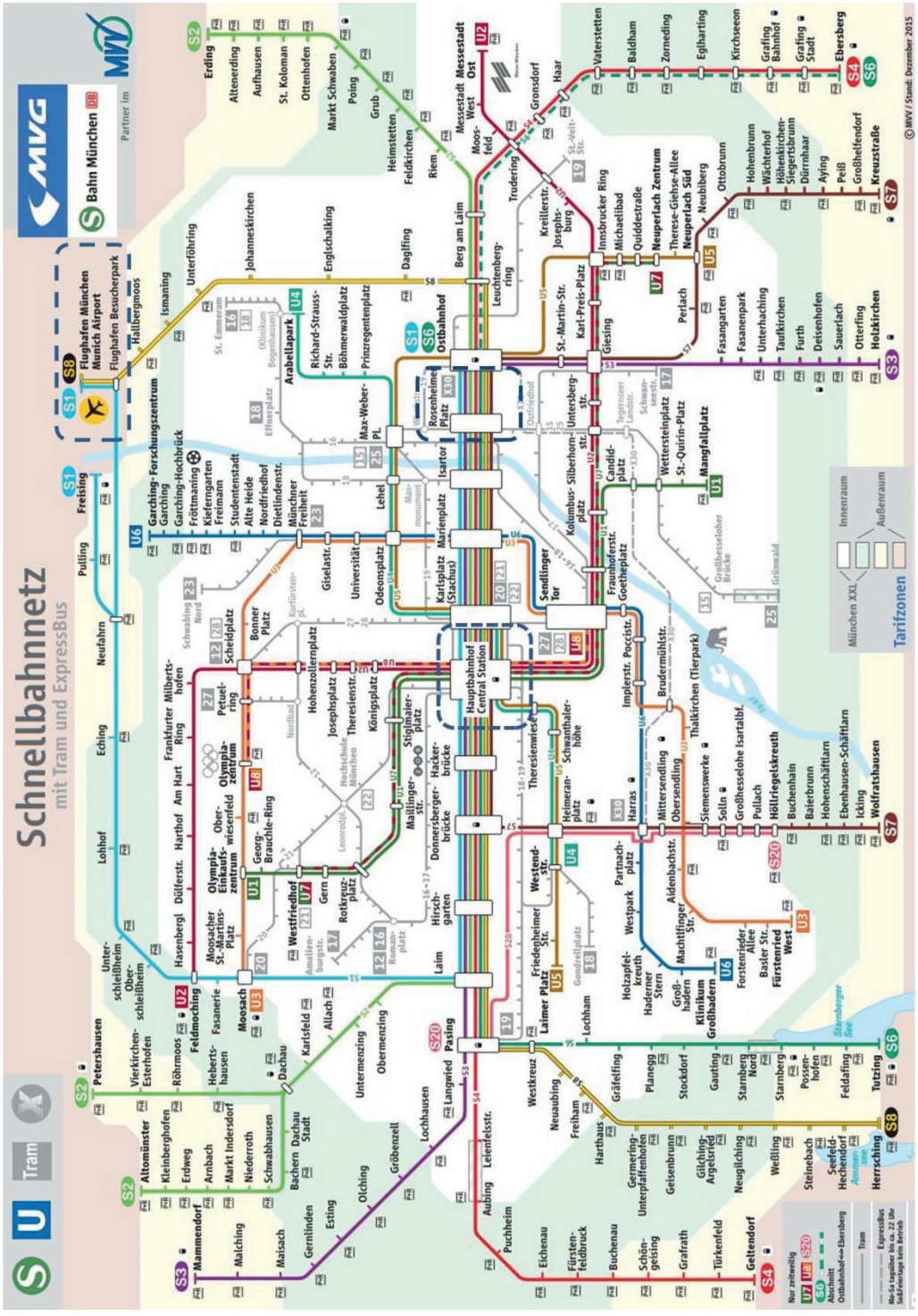
Steinstraße
Milchstraße
Johannisplatz
Walserstraße
Wolfgangstraße
Metzstraße
Comeniusstraße
Wörthstraße
Sedanstraße
Pariser Str.
Pariser Platz
Weißenburger Str.
Weißenburger Platz
Rosenheimer Str.
Rablstraße
Am Lilienberg
Lilienstraße
Holiday Inn Munich - City Centre
Modern hotel with...
Hilton Munich City
Urban hotel with free WiFi & a tapas bar
Hotel Novotel Muenchen City
Modern pick with free...
Hochstraße
Keller straße

MUNICH PUBLIC TRANSPORT



Notes

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