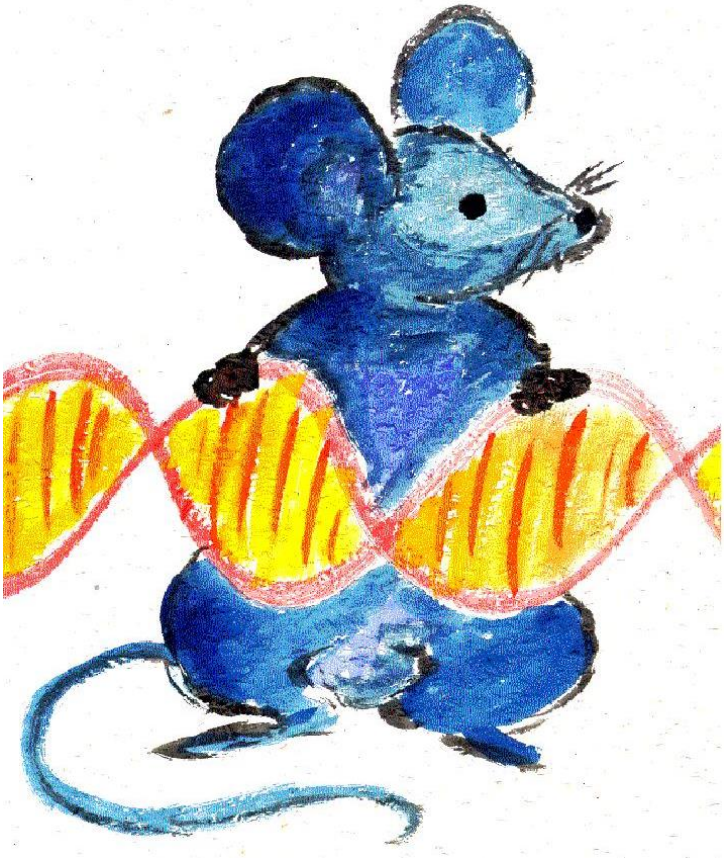
10th Workshop on Innovative Mouse Models



June 19-21, 2019

Leiden University Medical Center
Albinusdreef 2, 2333 ZA Leiden
The Netherlands

IMM2019 – Workshop report

Name of the event: 10th Workshop on Innovative Mouse Models (IMM2019)

Location of the event: Leiden University Medical Center (LUMC) – Lecture Hall 1, Leiden, The Netherlands

Dates: June 19-21, 2019

Website: www.immworkshop.nl

Organizing Committee:
Anna Gandaglia, The Netherlands Cancer Institute, Amsterdam
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Topics
CRISPR/Cas9, genome editing, base editing, HITI: basic biology and applications
lssDNA, Tild, ES cells
Microbiome impacting colony management
Imaging
Mouse models vs organoids and organ-on-chip models

Sessions
Keynote Lecture 1
Session 1: Novel in vivo applications of CRISPR/Cas9 technology (I)
Session 2: How to make mice in the CRISPR era?
Keynote Lecture 2
Discussion on 'How to make mice in the CRISPR era'
Session 3: Microbiome→Impact on colony management
Session 4: Novel in vivo applications of CRISPR/Cas9 technology (II)
Session 5: Imaging and phenotyping
Session 6: Debate: Are mice essential or obsolete in fundamental and/or translational research?
Discussion on 'mouse models versus organoids and organs-on-chips'

IMM2019 – Workshop report

On June 19-21, 2019, the 10th Workshop on Innovative Mouse Models (IMM2019) was held at the Leiden University Medical Center (LUMC), Leiden, The Netherlands.
As in the previous editions of this biannual event, the primary goal of the IMM2019 was to bring together a diverse group of scientists interested in all aspects of advanced mouse experiments within current ethical standards, including key developers of emerging technologies as well as researchers who wish to apply and assess these new approaches.
The workshop encouraged an in-depth and unvarnished discussion of novel developments in the field of mouse modeling in an informal way with a series of presentations from 18 invited speakers and 4 presenters of selected abstracts. This, together with the lively poster discussions (with stand-up tables and posters surrounding the area dedicated to breaks and lunches), represented a unique opportunity for young researchers to share their experiences with a highly specialized audience. This international and open context gave all the participants the possibility to receive/give interesting input on technical and ethical questions related to mouse modeling.

The Workshop on Innovative Mouse Models this year reached its 10th edition. To celebrate this important achievement, the organizers of the IMM2019 decided to open the Workshop one evening earlier on Wednesday June 19 with a great Keynote Lecture by **Hellmut Augustin** (German Cancer Research Center, Heidelberg, Germany) reviewing the state-of-the-art of current preclinical tumor model research and its limitations (especially considering the systemic nature of tumors) and by proposing possible solutions to overcome some of the mentioned issues.

Thursday June 20 started with the first part of the session on 'Novel in vivo applications of CRISPR/Cas9 technology', a topic that of course dominated also this edition of the Workshop on Innovative Mouse Models. **Lukas Dow** (Weill Cornell Medicine, New York, NY, USA) showed us how to optimize and exploit CRISPR/Cas9 base editing to generate new mouse models in order to study the consequences of single nucleotide variants (SNVs) on tumor initiation and progression. **Reza Kalhor** (Harvard Medical School, Boston, MA, USA) told us about using the CRISPR system and multiple genomically-integrated homing guide RNAs (hgRNAs) to generate combinatorial DNA barcodes to perform early developmental lineage tracing in mammalians. In this session we also had the opportunity to hear two brief oral presentations from selected abstracts. **Amine Bouchareb** (University of Oxford, Oxford, United Kingdom) illustrated us side-by-side comparisons of zygote microinjections versus electroporation for delivery of the CRISPR/Cas9 machinery for generation of mouse models. He demonstrated that, compared to microinjection, electroporation results in higher rate of embryo survival and of mutagenesis, which could be further increased by using embryos derived from Cas9 expressing mothers. **Lydia Teboul** showed the results of a new pilot for the use of long-read sequencing for validation of increasingly complex alleles generated by using the CRISPR/Cas9 system. This study uncovered unwanted/unexpected variants as a result of CRISPR/Cas9 application and highlighted the importance of an extensive validation at early stages of the mutagenesis process.

Session 2 was then dedicated to discuss 'How to make mice in the CRISPR era?'. Starting from recently published data on CRISPR off-targets events (Nat Methods 2018: 15(7):512-514), **Søren Warming** (Genentech Inc, South San Francisco, CA, USA) discussed how Genentech has implemented these findings.
Branko Zevnik (CECAD Cologne, Cologne, Germany) illustrated an easily adaptable electroporation approach developed for site-specific mutations of various mouse strains via CRISPR/Cas9. He showed

us the routine application of this protocol as well as possible modifications and limitations. Importantly, and in accordance with the data presented by Amine Bouchareb, electroporation appeared to be more successful than pronuclear injection. **Lin Wu** (Harvard University, Cambridge, MA, USA) gave an overview of their experiences with a large number of projects providing an important comparison of many variables in the CRISPR/Cas9 zygote workflow.

After lunch there was a second keynote by **Channabasavaiah B. Gurumurthy** (Nebraska Medical Center, Omaha, NE, USA). He gave an extensive overview of the development and possibilities of the *Easi*-CRISPR and *i*-GONAD techniques. Both are clearly important tools for the use of CRISPR/Cas9 in the generation of mouse models. His lecture was followed by a lively audience discussion about how different people use CRISPR in this, and where people see the important gaps and challenges in implementing this. Recurring themes were identifying the best techniques for knock-in of larger constructs, the practicalities of implementing new techniques in a facility and finding better ways of efficiently sharing real-life experiences with published techniques.

After an interactive and communicative coffee and poster session it was time for session 3 on the microbiome and its effect on colony management. Three talks illustrated that the microbiome has unjustifiably been ignored for too long in the use and interpretation of mouse models. **Arthur Liesz** (Ludwig Maximilian University of Munich, Munich, Germany) discussed the importance of the gut-brain axis for stroke, followed by **Floor Hugenholtz** (Amsterdam University Medical Center, Amsterdam, The Netherlands) discussing how mouse models can be used to study human intestinal microbiota research and **Els Robanus-Maandag** (Leiden University Medical Center, Leiden, The Netherlands) showed how changes in the gut microbiome can affect intestinal tumorigenesis in genetically modified mouse models. In all, this session made clear that the microbiome needs to be taken into account for many different, if not all, analyses of mouse models.

The first day was closed with the traditional walk through Leiden for the reception and buffet at the sunny terrace of Koetshuis De Burcht, as always a relaxing moment to get other participants of the meeting to know better.

Friday 21 June started with session 4, 'Novel in vivo applications of CRISPR/Cas9 technology part II'. **Keiichiro Suzuki** (Osaka University, Osaka, Japan) continued one of the themes of the discussion the previous afternoon by presenting his work on the HITI editing system. He was followed by **Ivo Huijbers** (The Netherlands Cancer Institute, Amsterdam, The Netherlands) who discussed how different techniques, including their ESC-based GEMM system, are used to accelerate cancer research and **Stefano Annunziato** (The Netherlands Cancer Institute, Amsterdam, The Netherlands) who spoke about his work on breast cancer modeling using somatic editing and *in vivo* base editing. **Natascha Gödecke** (Helmholtz Centre for Infection Research, Germany) closed this session with a talk about reversing transgene silencing through epigenetic means.

Session 5 continued with imaging and phenotyping of mouse models. It started with **Mark Henkelman** (Mouse Imaging Centre, Toronto, Canada) talking about their automated imaging / phenotyping pipeline. He was followed by **Jacco van Rheenen** (The Netherlands Cancer Institute, Amsterdam, The

Netherlands) who showed their work using intravital imaging to study (cancer) stem cells *in vivo* and **Mihail Todorov** (Ludwig Maximilian University of Munich, Munich, Germany) discussing tissue clearing-based imaging of small animals.

Finally, after the lunch and another opportunity to view and discuss the posters, the Friday afternoon was used for another 'first' this workshop with a debate on the question 'Are mice essential or obsolete in fundamental and/or translational research'. Three panel members discussed their thoughts on this question from different angles. **Yann Herault** (Institute of Genetics and of Molecular and Cellular Biology, Strasbourg, France) highlighted the insights they were getting from mouse models about the treatment of neurodevelopmental disorders, **Sylvia Boj** (Hubrecht Organoid Technology, Utrecht, The Netherlands) spoke about mouse and human organoids modeling a variety of diseases and **Christine Mummery** (Leiden University Medical Center, Leiden, The Netherlands) talked about organs-on-a-chip in cardiovascular disease. After this **Hellmut Augustin** kept the panel and the audience engaged in a lively discussion about the pros and cons of these three different model systems. The general feeling of both the panel and the audience was that animal models are still very important to address a host of fundamental and medical problems, in conjunction with *in vitro* systems.

After this discussion, the poster prize announcement and the closing remarks, IMM2019 was closed with some final drinks. The general opinion was that after 10 IMM workshops the meeting format is still alive and kicking, and people were already looking forward to the 11th IMM workshop in 2021.

Anna Gandaglia and Peter Hohenstein
(On behalf of the IMM2019 organizing committee)