IC-3Rs 2021
Symposium booklet

7 & 8 OCTOBER 2021

IC-3Rs
INNOVATION CENTRE
3R ALTERNATIVES

IC-3Rs can expand its activities thanks to:

the **Chair Mireille Aerens** and

the generous support of the **Brussels Region**, Animal Welfare under Minister Bernard Clerfayt

General Data Protection Regulation (GDPR) note:

All participants of the symposium may be contacted for future events. If you do not wish to be contacted, please inform us at info@IC-3Rs.org

Leerstoel **Mireille Aerens**
voor de ontwikkeling van proefdiervrije methoden

The IC-3Rs platform could be created thanks to **Mireille Aerens** and the **Chair Mireille Aerens for the Development of Alternative methods.**

Mireille Aerens was a very friendly person with a warm heart, not only for humans, but also for animals. In 2015, she created the **'Chair Mireille Aerens for the Development of Alternative Methods'** with **Vera Rogiers** as chairholder. As the dedicated founder of the chair, Mireille Aerens closely followed up the 3R-research of young scientists. In 2017, she helped to launch the IC-3Rs platform at the VUB.

Mireille sadly left us on 30 March 2020 at the age of 86. We lost a very dear and loyal friend, and will definitely continue her life's work at the VUB. She made this possible in her last will, wherein she maintained her support for animal-free studies within the research group IVTD. Thanks to her personal engagement, the Mireille Aerens Chair and the IC-3Rs platform will continue and grow for many years to come. This beautiful gesture reflects her attitude to life.

We will all remember her exceptional kindness and generosity.

IC-3Rs 2021 Symposium

HUMAN-RELEVANT MODELS FOR DRUG RESEARCH AND DEVELOPMENT

ONLINE **7+8 OCTOBER 2021** **13.30 -16.30**

Thursday 7 October 2021

13.30 **Welcome by Vera Rogiers** and introduction of Bernward Garthoff, moderator of the afternoon

13.45 **Non-clinical testing of human medicinal products: challenges and opportunities for regulatory acceptance of 3Rs**

SONJA BEKEN, Coordinator non-clinical evaluators, senior GMP inspector at the Federal Agency for Medicines and Health Products, Brussels, BE

14.15 **The relevance of animal models and alternatives in nonclinical safety testing and human risk assessment for pharmaceuticals**

ROBERT MADER, Senior Principal Scientist ROCHE Pharma Research and Early Development, ROCHE Innovation Center, Basle, CH

14.45 - 15.00 Short Break

15.00 **Hope for *in vitro* alternatives in developmental and reproductive toxicology?**

GIEL HENDRIKS, CEO Toxys, The Hague, NL

15.30 **Human-relevant models: the case of Alzheimer's and Parkinson's disease**

LIESBETH AERTS, Senior Researcher Biomedical Sciences-Science Communicator KUL/VIB-Infopunt Proefdieronderzoek, BE

16.00 **Q&A** Live moderation by Bernward Garthoff

IC-3Rs 2021 Symposium

HUMAN-RELEVANT MODELS FOR DRUG RESEARCH AND DEVELOPMENT

ONLINE 7+8 OCTOBER 2021 10.30 -16.30

Friday 8 October 2021

10.30 Special Q&A Poster session Live moderation by Joery De Kock

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13.30 Welcome back by Vera Rogiers, moderator of the afternoon

13.40 Organ-on-chip JANNY VAN DEN EYNDEN-VAN RAAY, Managing Director at hDMT, Organ-on-Chip Consortium, Eindhoven, NL

14.05 Species differences in the mechanism of action of drugs on the thyroid function THOMAS STEGER-HARTMANN, Head of Investigational Toxicology, Bayer Pharmaceuticals, Berlin & Wuppertal, DE

14.30 - 14.45 Short Break

14.45 Stem cells as source of human target cells
MUSTAPHA NAJIMI, Senior Research Associate at the Laboratory of Pediatric Hepatology & Cell Therapy at the UCL, Brussels, BE

15.10 Human self-testing of experimental drugs? Vaccines in pandemic times CHRISTA THÖNE-REINEKE, Professor and Head of Institute, Veterinary specialist in Laboratory Animal Science and Physiology, University of Berlin, Chair of the Scientific Committee for the Bf3R, Berlin, DE

15.35 RE-Place: the central database for Replacement Methodology for which Expertise exists in Belgium BIRGIT MERTENS, Senior Researcher Risk and Health Impact Assessment at Sciensano, Brussels, BE

16.00 Q&A Live moderation by Vera Rogiers

VUB IC-3Rs INNOVATION CENTRE 3R ALTERNATIVES

www.IC-3Rs.org

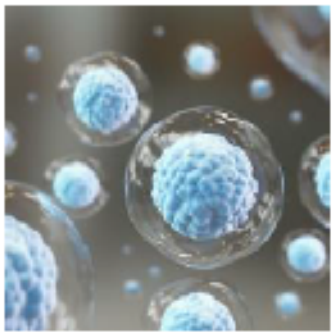
BIO Clustermanagement NRW GmbH

www.bioclustermanagement.de | info@bioclustermanagement.de

BIO Clustermanagement NRW GmbH

Who we are:

- Founded 2011 in Düsseldorf
- Closely connected to BIO.NRW – the official biotechnology network of the German Federal State of North-Rhine Westphalia (NRW)
- Supporting BIO.NRW by various means, e.g. business operations
- Focusing on the development of the life science industry in NRW and beyond

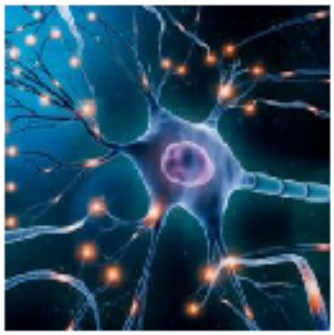


What we do:

- Project management
- Business event organization, such as the annual Business Angel Congress
- Preparation of business studies
- Tailor-made market and technology studies
- Mediation of qualified business coaches
- Organizing symposia, workshops & specialized meetings, also in areas such as alternatives to animal experimentation

Current activities:

- Catalyzer in the EIT Health Bridgehead program; supporting startups and SMEs to successfully enter the Chinese or European market



SYMPOSIUM MODERATORS

ROGIERS, VERA

Prof. Dr. Emeritus
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Vrije Universiteit Brussel (VUB)
Laarbeeklaan 103, 1090 Brussels, Belgium

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EDUCATION

Pharmacist (University of Ghent, 1974)
Doctor in Pharmaceutical Sciences (Vrije Universiteit Brussel, 1980)
Master in Applied Toxicology (University of Guilford, UK, 2000)
European Registered Toxicologist (since 2010)

BIOGRAPHY

After many years of leading the department of *In Vitro* Toxicology and Dermato-Cosmetology at the VUB in a successful way, Emeritus professor in Toxicology Vera Rogiers is actually still teaching dermato-cosmetics at the VUB and the University of Ghent. She also gives a limited number of lessons to the University of Namur and the Université Libre de Bruxelles. She yearly organizes international courses on Cosmetics and Risk Assessment. She is the Director of the Innovation Centre-3Rs (IC-3Rs) at the VUB and of the scientific Chair Mireille Aerens, both with focus on replacing experimental animals by novel technologies. At the EU level, she is co-chair of the Scientific Committee on Consumer Safety (SCCS) and member of the Mirror group of the European Partnership on Alternative Approaches to Animal Testing (EPAA). Her main research activity was many years situated in the development of *in vitro* models as an alternative to the use of experimental animals. Actual focus is on the differentiation of human skin-derived stem cells to functional hepatic cells and their application for drug discovery and the detection of drug-induced liver injury. She has been promoter of 33 doctoral theses, is author or co-author of >380 publications in international peer reviewed scientific journals and is editor of several scientific books. She is an often-invited speaker (>350) and participated in the organization of more than 60 international congresses. She has coordinated 2 EU research projects and was partner in several FP6, FP7 EU and Horizon 2020 research projects concerned with *in vitro* methodology development. Of the obtained scientific results, several patents have been filed. Throughout her carrier she received several international scientific awards for her pioneering role in *in vitro* Experimental Toxicology.

GARTHOFF, BERNWARD

CEO at BIO Clustermanagement NRW GmbH

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EDUCATION

Veterinary Medicine (Hannover University, 1974)

Doctor in Veterinary Medicine (1975)

Board certified pharmacologist and toxicologist (1984)

Lectureship for pharmacology (Ruhr-University of Bochum)

Variety of major positions in research and development at Bayer AG (1976 - 2009)

BIOGRAPHY

Dr. Bernward Garthoff is the CEO of the BIO Clustermanagement NRW GmbH. Before, he was the Biotechnology Representative for the Federal State of North Rhine-Westphalia, Germany, and chair of the Biotech Cluster BIO.NRW. Prior to that, he held several positions in the pharmaceutical and plant protection business of Bayer in Germany, the USA and Japan. In 1994, Dr. Garthoff had joined the top management of Bayer's Crop Protection Business, managed the integration process associated with the acquisition of Aventis CropScience and was member of the Board of Management of Bayer CropScience AG. He is member of the Boards of several foundations and until recently Supervisory Board member of Rottendorf Pharmaceuticals GmbH. He has also been chairman of the German Association of Biotechnology Industries (DIB), a member of the Private Sector Committee of CGIAR (World Bank) and of the EuropaBio Board. He has been a member of ESAC, of ecopa, co-chair of EPAA and of the German foundation/ platform for alternatives "set". He serves in diverse committees of the Federal Ministry of Agriculture of Germany dealing with animal welfare.

DE KOCK, JOERY

Professor
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EDUCATION

Pharmacist (Vrije Universiteit Brussel, 2006)

Doctor in Pharmaceutical Sciences (Vrije Universiteit Brussel, 2012)

BIOGRAPHY

Joery De Kock graduated in 2006 as Pharmacist from the Vrije Universiteit Brussel (VUB) and obtained his PhD in Pharmaceutical Sciences in May 2012 under the mentorship of Prof. Vera Rogiers. During his PhD, he managed for the first time to differentiate so-called human skin-derived precursor cells (hSKP) into hepatic cells. These hSKP-derived hepatic cells (hSKP-HPC) have provided a solid basis for multiple successful follow-up PhD projects over the last years. He is since 2017 a full-time Tenure Track professor affiliated to the Faculty of Medicine and Pharmacy at the research group of In Vitro Toxicology and Dermato-Cosmetology (IVTD) and was previously a postdoctoral research fellow of the Research Foundation Flanders (FWO) from 2012 until 2017. From 2016 to 2018, he was a visiting researcher at the Institute of Biotechnology of the RWTH Aachen University in Germany. During this period he acquired expertise in state-of-the-art directed protein evolution technology. His ongoing research uniquely combines gene and stem cell therapy with directed protein evolution technology in order to develop next generation medicines to cure inborn errors of liver metabolism.

POSTER PITCHES

PARTICIPANT POSTERS

The abstracts and poster pitches are available at the expo area from Thursday 7 October onward and throughout the entire duration of the symposium. **A dedicated Poster Pitch session is held on Friday 8 October at 10h30 CEST.**

During this session, each poster pitch is displayed. After each pitch, a LIVE Q & A is organised with the presenter.

Presenter	Pitch subject
Anna Michalaki	*In vitro toxicity of Helleborus extract*
Arturs Abols	*Cyclic olefin copolymer and Off-stoichiometry thiol-ene polymer hybrid gut on a chip development*
Carla Carolina Munari	*Skin model platform with melanoma as one important tool in the study of new therapeutic approaches*
Chloé Bars	*Bioactivation capacity of the zebrafish embryo model*
Kirsten Deridder	*Lung tumor spheroids for onco-immunological research*
Ellis Michiels	*Pancreatic cancer organoids*
Fien Meeus	*3D tumor models and real-time cell imaging to optimize CAR-T cell therapy*
Jeffrey Aalders	*A cost-effective platform to generate cardiospheres from co-cultured cardiomyocytes and cardiac fibroblast for disease modelling*
Julia Kapr	*In vitro disease modeling*
Léa Hiéronimus	*Mice innate-like B-1 lymphocytes accumulate in the lungs and promote particle-induced granuloma formation in vitro and immune responses beside macrophages*
Libera Fresiello	*In silico-in vitro cardiovascular simulator*
Maria Rocchi	*Use of a cardiovascular hybrid simulator as a support decision system for ventricular assist device therapy*
Sigrid Verhelst	*Large scale toxicoepigenetics on histones: a mass spectrometry-based screening assay applied to developmental toxicity*
Victoria de Leeuw	*Connecting professionals with TPI.tv*

SPEAKERS

AERTS, LIESBETH

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EDUCATION

MSc in Biosciences Engineering (KU Leuven, 2009)
MSc in Clinical Neurosciences (UCL, 2010)
PhD in Biomedical Sciences (KU Leuven, 2015)

BIOGRAPHY

Liesbeth Aerts is a science communicator at VIB, specialized in neuroscience. She trained as a molecular neuroscientist, completing her PhD on the molecular mechanisms of Parkinson's disease, and transitioned to clinical research during her postdoc at the Dementia Collaborative Research Centre at UNSW Sydney, where she analysed data from human cohorts to improve the detection of and care for dementia.

Liesbeth Aerts is an advocate for openness on animal research and co-founded the vzw Infopunt Proefdieronderzoek, a communication platform dedicated to providing balanced information on the use of animals in biomedical research. As such, she coordinated the signing of a Belgian Transparency Agreement on Animal research, in which 18 Belgian universities, institutes and companies commit to open and transparent communication to the public about the role of animals, and animal-free methods, in their activities.

EXPERTISE

neuroscience, science communication, transparency

PRESENTATION:

PRESENTED BY: LIESBETH AERTS

HUMAN-RELEVANT MODELS: THE CASE OF ALZHEIMER'S AND PARKINSON'S DISEASE

Background: In light of the continued efforts to reduce, refine and replace animal testing in biomedical research (3R), we inventoried and evaluated non-animal methods currently in use for basic and applied research on Alzheimer's and Parkinson's disease (AD/PD), the two most common and most studied neurodegenerative diseases.

Aim: The aim of this study was to gather data on the current use and development of animal-free models and methods in this field, to inform the broader debate around replacement of animal research.

Methods: Publications that appeared between 2013 and 2018, combining a specific mention of (a) AD or PD, (b) a relevant biological endpoint to said disease, and (c) a method or model system (e.g. "cell model", "comput*" etc.) were retrieved. More than 13,000 abstracts were screened, of which approx. 70% were used animal-based methods or models. The remaining fraction described studies that develop, optimise or apply non-animal methods.

Results: For PD, methods based on human primary or stem cells represented the highest fraction (35%), followed by human/patient ex vivo tissue and body fluids (16%), biochemical assays (15%), human-derived immortalised cell models (14%) and computational/in silico methods (14%). For AD on the other hand, biochemical/cell-free models represented the most commonly used group of methods (27%), followed by human/patient ex-vivo models (22%) and computational models (18%). Among the studies that comprised animal research or animal-based model systems, the large majority made use of mice, or mouse-derived cells.

Conclusion: We compiled an inventory of non-animal methods comprised 568 different models, with detailed information about context and use. Answers to central questions "Why?", "How?" and "What?", as well as qualitative information related to the status, relevance and potential of a given method were compiled. As such, the inventory allows for straightforward browsing of existing published methods, which aims to contribute to 3R knowledge sharing and their increased adoption and acceptance in neurodegeneration research and related fields. At the same time, we argue that the role and scientific value of both animal and animal-free approaches are intertwined, and we highlight the need for better monitoring and more robust performance indicators of animal-free approaches.

BEKEN, SONJA

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EDUCATION

License (Master) in Biological Sciences (Vrije Universiteit Brussel, 1993)

Ph.D. in Pharmaceutical Sciences (Vrije Universiteit Brussel, 2000)

Master in Applied Toxicology (University of Surrey, UK, 2013)

BIOGRAPHY

Sonja Beken is the Coordinator of the Unit of non-clinical evaluators at the Belgian Federal Agency for Medicines and Health Products (FAMHP). This Unit is responsible for the evaluation of non-clinical data submitted to support all phases of drug development (e.g. marketing authorizations, clinical trials, EU/ national scientific advice, etc).

She is a Member of the Safety Working Party (Vice-Chair 2013-2016) and of the CVMP/CHMP Joint 3Rs Working Group (Chair 2011-2016) at the European Medicines Agency (EMA). She was the ICH Rapporteur for the revision of the S5(R2) Guideline (2014-2016).

Over the years, Sonja Beken has contributed to the direct identification of opportunities for regulatory implementation of 3R testing paradigms through her active involvement in large-scale international initiatives (EPAA, CAAT, ILSI HESI, NC3Rs, AIMBE & NIH, etc).

EXPERTISE

regulatory science, non-clinical drug development, (*in vitro*) toxicology and metabolism, alternative models to animal experiments (3Rs

PRESENTATION:

PRESENTED BY: SONJA BEKEN

NON-CLINICAL TESTING OF HUMAN MEDICINAL PRODUCTS: CHALLENGES AND OPPORTUNITIES FOR REGULATORY ACCEPTANCE OF 3Rs

Regulatory testing of human medicinal products is carried out to support first administration to humans; before carrying out clinical trials in even larger populations; before marketing authorisation or to control quality during production. Ethical and animal welfare considerations require that animal use is limited as much as possible. Directive 2010/63/EU on the protection of animals used for scientific purposes, unambiguously fosters the application of the principle of the 3Rs (Replacement, Reduction and Refinement) when considering choice of methods to be used.

The application of all 3Rs is currently embedded in the drafting process of regulatory guidance both at the European and at International Conference on Harmonisation ((V)ICH) level. With respect to non-clinical testing requirements for human medicinal products, over the past years, new *in vitro* methods have been accepted for regulatory use via multiple and flexible approaches, either as pivotal, supportive or as exploratory mechanistic studies, wherever applicable. Whilst replacement of animal studies remains the ultimate goal, the application of all 3Rs need to be the focus. As such, approaches aiming at reducing or refining animal studies are and have been routinely implemented in regulatory guidelines, where applicable.

This presentation will provide a broad overview of the specific challenges and opportunities related to the regulatory acceptance of 3R methods for non-clinical testing of human medicinal products. In addition, the approach from the European Medicines Agency (EMA) to regulatory acceptance of 3Rs testing methods will be presented. Finally, the conclusions from the first EMA workshop on non-animal approaches in support of medicinal product development will be discussed and the experience gained from EU projects such as ORCHID, discussed.

HENDRIKS, GIEL

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EDUCATION

Master in Molecular Cell Biology, 1992-1998, Utrecht University, The Netherlands

Ph.D in Cell Biology, 1998-2003, Dept. of Cell Biology, Utrecht University Medical Center, The Netherlands

BIOGRAPHY

Giel Hendriks has a PhD in molecular biology from Utrecht University and worked for four years as a post-doctoral fellow in at Leiden University, studying the relationship between DNA damage and gene mutations. After this fundamental scientific projects he made a switch and worked for six years a senior scientist at the Leiden University Medical Center on the development of *in vitro* reporter systems to detect and understand the mechanisms of genotoxicity. During this period, he has been instrumental in the development of the ToxTracker assay.

In 2014, Giel obtained financing to start Toxys and to bring the ToxTracker assay to the market. In 2016, he attracted various investors that allowed Toxys to setup their own laboratory at the Leiden Bio Science Park. As CEO of Toxys, he worked to develop the company into an internationally recognised contract research organisation (CRO) in chemical safety testing for the pharmaceutical, cosmetics and chemical industry. A second financing round in 2020 boosted the development of new *in vitro* assays and further growth of the company. Toxys is valued for its scientific expertise and has various collaborations with different academic and industrial partners to develop innovative animal-free assays for toxicological research

EXPERTISE

in vitro toxicology, genotoxicity, developmental toxicity, mechanistic toxicity testing

PRESENTATION:

PRESENTED BY: GIEL HENDRIKS

REPROTRACKER: A NOVEL HUMAN STEM CELL-BASED BIOMARKER ASSAY FOR *IN VITRO* ASSESSMENT OF DEVELOPMENTAL TOXICITY

Testing for developmental toxicity according to the current regulatory guidelines requires large numbers of animals, making these tests very resource intensive, time-consuming and ethically debatable. Over the past recent years, several alternative *in vitro* assays have been developed, but these often suffered from low predictability and the inability to provide a mechanistic understanding of developmental toxicity.

To identify embryotoxic compounds, we developed a human induced pluripotent stem cell (hiPSCs)-based biomarker assay that was named ReproTracker. The assay is based on the differentiation of hiPSCs into functional cardiomyocytes and hepatocytes. Proper stem cell differentiation is investigated by morphological profiling and assessment of time-dependent expression patterns of cell-specific biomarkers. In this system, a decrease in the expression of the biomarker genes and morphology disruption of the differentiated cells following compound treatment indicated teratogenicity.

The ReproTracker reporter assay was validated with 22 well-established *in vivo* teratogens and non-teratogenic compounds during cardiomyocyte and hepatocyte differentiation. The *in vivo* teratogenic compounds (e.g., thalidomide and valproic acid) markedly disrupted morphology, functionality and the expression pattern of the biomarker genes in either one or both cell types. Non-teratogenic chemicals (e.g., folic acid and saccharin), generally had no effect on the morphology of differentiated cells, nor on the expression of the biomarker genes. Compared to the *in vivo* classification, the assay achieved high accuracy (91%), sensitivity (92%), and specificity (90%).

ReproTracker is a state-of-the-art *in vitro* assay that can identify the teratogenic potential of new chemicals and drugs with high accuracy and provide a signal as to the likely outcome of *in vivo* test systems. The assay can best serve as an early phase teratogen screening platform as alternative to animal testing outcomes.

MADER, ROBERT

Senior Principal Scientist
Toxicology Project Leader
Roche Pharma Research & Early Development
Roche Innovation Center Basel
Grenzacherstrasse 124
4070 Basel, Switzerland

EDUCATION

Pharmacist, LMU Munich 2000

Ph.D. in pharmacology, LMU Munich 2004

BIOGRAPHY

Robert Mader trained as a Pharmacist and got his Ph.D. in molecular pharmacology from the LMU Munich, Germany in 2004. In 2005, he joined NIBR, Novartis, Basel, first as a postdoc in the gastrointestinal disease area, followed by a laboratory head position in the musculoskeletal disease area, working on in vivo PK/PD. In 2007 he moved to Debiopharm SA, Lausanne, as a Project Toxicologist, responsible for planning and execution of safety assessments. He joined Roche pRED (Pharma Research and Early Development) in 2020 as a Toxicology Project Leader, responsible for the safety strategy and risk-benefit evaluation of novel therapeutics, ahead of clinical trials in humans. The reduction of use of animals to the necessary minimum is dear to his heart and a major component in his decision making process on the risk assessment strategy. He is participating in internal and cross-industry (EFPIA) workgroups on the subject of animal-free / animal-reduced risk assessment.

EXPERTISE

non-clinical drug development, regulatory risk assessment, early *in vitro* and in silico safety screening, mechanistic safety

PRESENTATION:

PRESENTED BY: ROBERT MADER

THE RELEVANCE OF ANIMAL MODELS AND ALTERNATIVES IN NONCLINICAL SAFETY TESTING AND HUMAN RISK ASSESSMENT FOR PHARMACEUTICALS

In terms of the application of 3Rs, Roche and other pharma companies are pushing the boundaries in terms of replacing, reducing and refining animal studies in the frame of regulatory safety assessments. The relevance of animal models for human risk assessment cannot be generalized and depends on several factors. Novel therapeutic approaches often lack such models and more human-relevant ways to assess safety are required. Animal studies are often of limited use in these cases, if at all. On the other hand, the predictive value of animal models for human safety is still very good for many drugs in development. Replacing them entirely or only partially in these circumstances is and will be hard to achieve in the foreseeable future. This presentation will provide a review of what would be required from alternative models to fully or partially replace animal studies for human risk assessment, as well as a case example where this can already be achieved today and one that exemplifies the challenges ahead.

MERTENS, BIRGIT

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EDUCATION

Master in Pharmaceutical Sciences (Vrije Universiteit Brussel, 2005)
Doctor in Pharmaceutical Sciences (Vrije Universiteit Brussel, 2010)
European Registered Toxicologist (since 2015)

BIOGRAPHY

Birgit Mertens is working as a senior scientist in the service 'Risk and Health Impact Assessment' of Sciensano. She is currently involved in different research projects related to (geno)toxicity testing of chemical and physical agents and the use of alternative methods to animal testing. Within this context, she is coordinating the RE-Place project together with Prof. Rogiers of the Vrije Universiteit Brussel. Furthermore, she is member of different (inter) national working groups in the domain of toxicology, with focus on the application of the 3R strategy and the assessment of public health risks. Dr. Mertens is National Coordinator of the Test Methods Programme both at the European and OECD level. She is also the Belgian contact point for the Preliminary Assessment of the Regulatory Relevance of Alternative Methods (PARERE) network. She is member of the Belgian scientific committee REACH and president of the Belgian Environmental Mutagenesis Society (BEMS). .

EXPERTISE

non-animal (geno)toxicity testing, 3R alternatives, test guidelines, risk assessment

PRESENTATION:

PRESENTED BY: BIRGIT MERTENS

RE-PLACE: DEVELOPMENT AND STATUS OF A BELGIAN DATA-BASE ON NEW APPROACH METHODOLOGIES

By applying 'New Approach Methodologies (NAMs)' based on (innovative) technologies such as computer modeling, high throughput testing and cell culture systems, the use of experimental animals in the life sciences can be reduced or sometimes even completely avoided. Due to the fast progress in the development of these technologies, up-to-date information on NAMs may be difficult to find and therefore limit their application. Bottom-up approaches such as local initiatives to map the available expertise on NAMs can help to stimulate the use of these methodologies. For this reason, the RE-Place initiative was launched in 2017, which aims to centralize the available Belgian expertise on NAMs in one database. To this extent, a template was first designed to collect the information of interest in a fast and consistent manner. Next, the template was embedded into a web-based application to facilitate the entry of information. This RE-Place online tool was then evaluated by experts in the field of NAMs during a pilot study, and based on their feedback, a revised version was launched to the public. During the development process, important aspects such as the user-friendliness, quality of submitted information, protection of personal data and intellectual property rights were all considered. Also hurdles such as incentives for collaboration were taken into account. All information collected with the RE-Place online tool is directly integrated in the open access RE-Place database. At present, the database already contains over 150 methods from various universities and research centers. These include methods in fundamental and translational research across various disciplines such as drug development, toxicology, immunology, neurology, and cancer research, but also methods used for regulatory applications. Overall, the RE-Place database can help to build trust in the use of NAMs and stimulate their further use and implementation in the long term.

The RE-Place project is financed by the departments of Animal Welfare from the Flemish and Brussels Capital region in Belgium.

NAJIMI, MUSTAPHA

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EDUCATION

Ph.D. in Cell and Molecular Biology (Université Pierre & Marie Curie, Paris VI, 1999)

BIOGRAPHY

Thanks to the support of the French Association for Research against Cancer, Dr NAJIMI joined in 1999, the UCLouvain as a visiting researcher in the laboratory of Pr Maloteaux. In 2003, he joined the team of Pr SOKAL to set up a platform of liver cells' culture with the aim to develop them for clinical use. Since then, he led the stem cell group. Thanks to an accumulated know-how of human liver cell populations and the way to isolate them, his research led to the discovery of intra-hepatic mesenchymal progenitor cells, subject of 200 citations and 4 granted patents. Dr NAJIMI has actively been involved in the production of their first clinical batches infused at Saint-Luc hospital in Brussels. He has supervised 16 PhD students and is member of Editorial Board of many journals. Dr NAJIMI has published more than 120 articles in peer-reviewed journals and 3 book chapters. He was invited as a speaker in numerous conferences.

Dr NAJIMI was scientific supervisor of the hepatocytes and hepatic stem cells banks at Saint-Luc Hospital. He is also co-scientific founder of Promethera Biosciences, for which he is currently Chief Scientific Officer and member of the scientific and medical advisory board.

EXPERTISE

cell therapy, mesenchymal stem cells, liver, ATMP

PRESENTATION:

PRESENTED BY: MUSTAPHA NAJIMI

STEM CELLS AS SOURCE OF HUMAN TARGET CELLS

It is well recognized that animal models, although having provided useful information on human diseases, diagnosis and prevention, do not accurately mimic human physiopathology. If appropriate human tissue can be obtained from accredited public and commercial biobanks as well as contract research organizations, several factors including substantial increasing scarcity of donated organs limit however the easy access to such material.

The discovery of both human embryonic and tissular stem cells as well as the demonstration of their potential to self-renew and to differentiate, have brought significant advances in the development of strategies modelling human diseases *in vitro* by using exclusively human cells. Besides reducing the reliance of animals in research, stem cell-based technologies have expanded the definition of human tissue, and have driven to the design and development of potentially safe and potent innovative therapeutic products. The subsequent knowledge in controlling the experimental conditions that maintain stem cells' survival, expansion and cryo-storage *in vitro*, has been considered as a significant technological improvement that may allow an unlimited access to this material. Mastering the composition of their extracellular environment components *in vitro* has also led to know more on stem cell differentiation potential and plasticity in the dish. This critical clue has provided useful information to learn more on human embryogenesis and organogenesis and hence attempting to mimic *in vitro* the sequence of molecular and cellular events that generate one or the other cell type. Those differentiated stem cells newly generated have been extensively investigated to enable the production of functional normal and diseased human tissues *in vitro*. Their use for drug screening, toxicology, and clinical cell replacement therapies is currently widely acknowledged to replace animal models, although the number of commercially available stem cell products is still low.

The proposed talk will provide the audience, an overview of the current status of stem cells biotechnological development as serious animals replacement *in vitro* systems, as well as the future directions of their use in manufacturing sophisticated functional tissues *in vitro* to address issues like long-term toxicity, and in efficiently designing therapeutic strategies for still untreatable defects.

THÖNE-REINEKE, CHRISTA

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EDUCATION

Veterinarian (1994, Freie Universität Berlin)

Doctor theses, Institute of Molecular Medicine and Biochemistry (1994, Freie Universität Berlin)

Promotion Dr. vet. Med., (1997, Freie Universität Berlin)

Specialist in Laboratory Animal Science (2000, Veterinary Chamber Berlin)

Specialist in Physiology (2005, Veterinary Chamber Brandenburg)

Habilitation in experimental Pharmacology (2012, Charité-Universitätsmedizin Berlin)

BIOGRAPHY

Since 2014	Professor for Animal Welfare, Animal Behavior and Laboratory Animal Science, FU Berlin and Animal Welfare Officer
2006-2014	Assistant Leader and Animal Welfare Officer Forschungseinrichtung für Experimentelle Medizin, Charité Universitätsmedizin Berlin
2004–2006	Scientific Assistant, Center for Cardiovascular Research, Institute of Pharmacology, Center for Cardiovascular Research, Charité Berlin
2000–2003	Scientific Leader and Animal Welfare Officer of Max Rubner-Laboratory German Institute of Nutrition Bergholz-Rehbrücke
1994–2000	Research Scientist and Lecturer, Institute of Molecular Medicine and Biochemistry, Freie Universität Berlin

EXPERTISE

cardiovascular research, animal welfare, animal behavior and 3R

PRESENTATION:

PRESENTED BY: CHRISTA THÖNE-REINEKE

HUMAN SELF-TESTING OF EXPERIMENTAL DRUGS? VACCINES IN PANDEMIC TIMES

There is hardly any other area in our pluralistic society that is discussed as controversially as the area of animal experimental research. The demands range from "we must completely do without animal experiments" to "we will never be able to do without animal experiments".

All animal ethics positions largely agree that animals - as beings capable of suffering - must be considered morally for their own sake and that certain consequences for one's own actions must be derived from this. This insight has found its way into animal protection law based on EU Directive 2010/63.

German legislation requires adequate justification of the pain, suffering and harm inflicted on animals. For this reason, every scientist must demonstrate the ethical justifiability of the intended experiment in accordance with the principle of proportionality as part of the approval procedure for animal experiments. In particular, it must be demonstrated that there is no alternative method to achieve the objectives of the project. Furthermore, the indispensability of the project must be scientifically justified and assigned to a permissible purpose. The study design must use statistical methods to reduce the number of animals and their distress to the indispensable level. Animal husbandry and medical care must be ensured through permission to keep and breed animals within the framework of a culture of care. Ultimately, the expected gain in knowledge must be put in relation to the burden on the animals and must be ethically justifiable or even considered an ethical imperative or moral obligation. The scientist's proposal and statements are reviewed by the animal welfare officer and, if necessary, by the ethics committee of the respective institution. This is followed by a further review by the local authorities and the §15 Commission, in which ethics experts and animal welfare organizations are actively involved. After this review process, in which the responsible scientist is involved, the final review and approval by the local authorities takes place. As an example, consider the Corona virus pandemic. Research is mainly conducted on three different levels, the development of vaccines, and the development of new therapies and the extension of indications for existing active substances. To this end, almost 7,000 studies are being conducted, including more than 200 vaccine projects. Are mice suitable for Covid 19 research or would it be better to use appropriate animal models such as primates, ferrets or hamsters, or alternative methods? The rapid development of the vaccines approved to date is largely due to the animal-based basic research carried out in the past. For the approval of drugs and vaccines, animal experiments are required by law to prove efficacy and safety. Against this background, it is unethical to test vaccines on oneself or to use unapproved vaccines. Against this background, it must be taken into account that ethical concepts and attitudes of society can change over time. Therefore, a high degree of transparency and honesty in science is necessary.

VAN DEN EIJNDEN-VAN RAAIJ, JANNY

Managing director hDMT, Dutch Organ-on-Chip Consortium
Aanschot 85, 5629 GZ Eindhoven, The Netherlands

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EDUCATION

Biochemist (Radboud University Nijmegen, 1981)

PhD in Biochemistry (Radboud University, 1985)

BIOGRAPHY

Janny van den Eijnden-van Raaij is managing director of hDMT, the Dutch Organ-on-Chip Consortium. She obtained her PhD as a biochemist at Radboud University Nijmegen in 1985. She then became group leader at the Hubrecht Institute Utrecht focusing on stem cells and growth factors in embryonic/ tumour development. In 2003 she became managing director of the Comprehensive Cancer Center South Eindhoven. Under her regime the cancer registry and epidemiological research department developed to *the* European leader in this field. In 2014 she switched to Organs-on-Chip (OoC) and established hDMT in 2015, a national OoC Consortium, consisting of the hDMT foundation and 14 partner organizations, including technical universities, medical centers and knowledge institutes. Research is done by the partners and the partners are supported by the foundation. The renowned scientists of the hDMT partners have various backgrounds, and share knowledge, expertise, ideas and facilities to develop human OoC models, that better recapitulate the human body and will reduce animal experiments. The researchers collaborate in specific projects with many companies and other private partners in the hDMT network. Van den Eijnden-van Raaij built a broad international network on OoC in the H2020 ORCHID project, that she co-coordinated with the Leiden University Medical Center, and she is board member (secretary/treasurer) and founding member of the European Organ-on-Chip Society (EUROoCS).

ORCID: 0000-0002-6566-5957

EXPERTISE

organ-on-Chip, stem cells, cancer, growth factors

PRESENTATION:

THE PRESENT AND FUTURE OF ORGAN-ON-CHIP

PRESENTED BY: JANNY VAN DEN EIJNDEN-VAN RAAIJ

Organs-on-Chips (OoCs), also known as tissue chips, and being part of the family of Microphysiological Systems (MPS) have received considerable attention in recent years because of their potential in various scientific fields. An OoC refers to a fit-for-purpose microfluidic device, containing living engineered organ substructures in a controlled microenvironment, that recapitulates one or more aspects of the organ's dynamics, functionality and (patho)physiological response in vivo under real-time monitoring. The development of OoC, bringing technology and biology together, started in universities about 15 years ago, but in the past few years the field has rapidly expanded, thanks to an increasing need for better model systems in pharma and other industry as well as an increasing pressure to reduce animal experiments. The development of OoC requires a wide range of different technologies of varying complexity and the application domains vary from toxicity testing, drug discovery and development (including biokinetics), to personalized medicine. The use of these technologies is also relevant for disease modelling, enabling the study of the mechanisms of specific pathologies such as cancer and neurodegenerative disorders as a basis for new therapies.

OoC is ranked in several foresight exercises among the top emerging technologies (World Economic Forum's Meta-Council on Emerging Technologies, 2016), with the expectation that OoC will lead to:

- More human-relevant approaches in biomedical research;
- Faster, cheaper and more effective pre-clinical evaluation of new drugs;
- Better ways to assess the potential health effects and toxicity of drugs, chemicals, food products and cosmetics;
- Acceleration of drug repurposing;
- Reduction and replacement of animal testing.

Concerted efforts to coordinate standardization, qualification and independent testing of OoC devices are much needed to ensure coherent development of the technology and bring it closer to fulfilling its potential in drug development, disease modelling, and personalized medicine. An OoC roadmap, developed in the EU project ORCHID (Organ-on-Chip In Development), and a dialogue between all stakeholders united in the European Organ-on-Chip Society (EUROoCS), can lead the way forward for adoption, application and a growing demand for OoC.

KARWELAT, DIANA

PhD candidate at Advanced cellular models
Bayer AG, Research & Development, Pharmaceuticals
13342 Berlin, Germany

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EDUCATION

Biologist (Philipps-University Marburg, 2017)

PhD in Biotechnology (TU Berlin, 2021)

BIOGRAPHY

Diana Karwelat is a biologist by training and a soon to be PhD affiliated to the Bayer AG pharmaceuticals at the department of Advanced Cellular since July 2018. During her Master studies in molecular and cellular biology with focus in infectious disease research Diana advanced a three-dimensional human lung co-infection model and obtained her M.Sc. degree 2017 from the Philipps-University Marburg in Germany. Fascinated by the development and prospects of 3D models Diana developed a rat thyroid liver chip during her PhD at Bayer with focus on toxicology aspects to improve human health risk evaluation. Together with a life-science collaboration team Diana was awarded 2020 for scientific progress fostering the 3R´s (replacement, reduction, refinement) idea with the internal Bayer´s 3R´s award dedicated to welfare.

At the Congress of the European Societies of toxicology (EUROTOX) as well as the annual meeting of the society of toxicology (SOT) Diana actively shared her PhD activities and project achievements with the scientific community.

EXPERTISE

in vitro toxicology, 3D cell culture models, liver, lung, thyroid, organ-on-a chip

STEGER-HARTMANN, THOMAS

Heads the department of Investigational Toxicology (VP) at Bayer AG, Pharmaceuticals, Germany

Thomas overviews more than thirty scientists and technicians at the two experimental testing sites Berlin and Wuppertal. He is responsible for both early and mechanistic safety assessment of drug candidates and pharmaceuticals as well as environmental risk assessments. Thomas has more than 25 years of experience in the field of preclinical and eco-toxicological assessment of pharmaceuticals and early drug development, particularly in the field of contrast agents, hormonal compounds and oncology indications. Thomas is member of Bayer's Animal Welfare Committee.

Thomas' main research interests lie in mechanistic prediction and elucidation of unwanted drug effects. He has evaluated and established numerous techniques, assays, and safety biomarkers in his function, particularly in the field of *in silico* tools and *in vitro* models. His special interests are the advancement of *in silico* safety assessment (predictive tools, databases and read-across) as well as Organs-on-a-chip.

Thomas is involved in several international research collaborations in the field of non-animal safety assessment. He was deputy leader of the concluded European Innovative Medicines Initiative (IMI) project “eTox”, a European public-private partnership for gathering *in vivo* drug toxicity data for the development of improved *in silico* prediction tools. Thomas acts in the same role in the follow-up IMI2 project "eTRANSAFE" (TRANslational SAFEty Assessment through Integrative Knowledge Management), which focusses on the translational aspects of preclinical safety prediction for human safety.

Thomas was appointed to serve as member in Scientific Advisory Boards of several international consortia. Currently, he serves as Chair of the SAB of the Horizon2020 flagship projects "EUToxRisk" and “RiskHunt3R”.

Thomas is a trained biologist with a major in Plant Physiology. He acquired a diploma at the University of Freiburg i.Br., a M.Sc. degree from the University of Michigan and a PhD from the University of Freiburg i.Br., Germany. He is a Eurotox registered toxicologist.

PRESENTATION:

PRESENTED BY: DIANA KARWELAT

A THYROID-LIVER CHIP TO INVESTIGATE MECHANISMS OF THYROID TOXICITY IN HUMANS AND RATS ON ORGAN-FUNCTION LEVEL

Background: Endocrine disrupting chemicals (EDC´s), are by definition substances that interact with the endocrine system, with the consequence of adverse health effects in an intact organism. Due the importance of thyroid hormones during many physiological processes, concerns about chemical induced adverse effects on animal and human health caused by funcitonal thyroid impairment have increased. Perturbation of thyoird homeostasis may result from direct effects on thyroid gland function or be mediated e.g. by inducing liver biotransformation, referred to as direct and indirect thyroid toxicity, respectively. The assessment of the human relevance of thyroid toxicities, observed in animal assays remain challenging, by reasons of species-specific differences in thyroid biology and perturbation susceptibilities. Thus, it is known that the rat, a widely used model organism in toxicology, is particularly sensitive to chemical-induced thyroid change. Consequently, this leads to uncertainty in human safety risk assessments, particularly when a direct comparison of rat and human in vivo is not amenable, e.g. agrochemicals.

Aim: We envisaged two *in vitro* systems, for rat and human, that recapitulate organ-cross talk of the two target organs, liver and thyroid. Therefore, we developed and combined a thyroid and a liver organ model to allow simultaneous investigation of direct as well as indirect (liver-mediated) perturbations of the thyroid homeostasis on organ- function level. Ideally these liver-thyroid chips would allow a comparative and direct evaluation of potential species-specific responses of the thyroid homeostasis following compound treatment.

Methods: A three-dimensional rat thyroid and liver *in vitro* model was developed using thyroid follicles isolated from rat thyroid explants and liver spheroids consisted of primary rat hepatocytes and corresponding primary non-parenchymal liver cells, respectively. Likewise, the human thyroid model was developed using thyroid follicle isolates from human surgery explants. For the liver model, spheroids were formed from mixture of HepaRG hepatocytes and human stellate cells. Organ crosstalk was accomplished by using a microphysiological systems (MPS), which represent a promising approach to reproduce physiological and toxicological interactions of target organs which previously required animal studies or clinical trials.

CONTINUED:

PRESENTED BY: DIANA KARWELAT

A THYROID-LIVER CHIP TO INVESTIGATE MECHANISMS OF THYROID TOXICITY IN HUMANS AND RATS ON ORGAN-FUNCTION LEVEL

Results: The developed organ models maintained their tissue-specific phenotypes for at least 14 days. More precisely, thyroid follicles maintained follicular organization and secreted thyroid hormones in a TSH-dependent manner. Likewise, liver spheroids retain hepatocellular characteristic including stable albumin release, the presence of bile canalicular networks as well as and the metabolic capacity to form T4-glucuronide or T4-sulfate. (thyroid hormone elimination).

Chemicals known to directly perturbate thyroid hormone formation, decreased *de novo* synthesized thyroid hormones in both species. Treatment with known inducers of liver biotransformation enhanced T4 glucuronidation in rats as reported from *in vivo* studies.

Conclusion: We established a model of the hepatic-thyroid axis on organ-functional level as single *in vitro* assay for two species (human and rat). These models demonstrated proficiency to detect direct and indirect mechanisms of thyroid perturbation and represent a major and promising step towards an improved assessment of potential species similarities/differences of certain toxicity findings observed in rats with significant contributions to the 3R principles.

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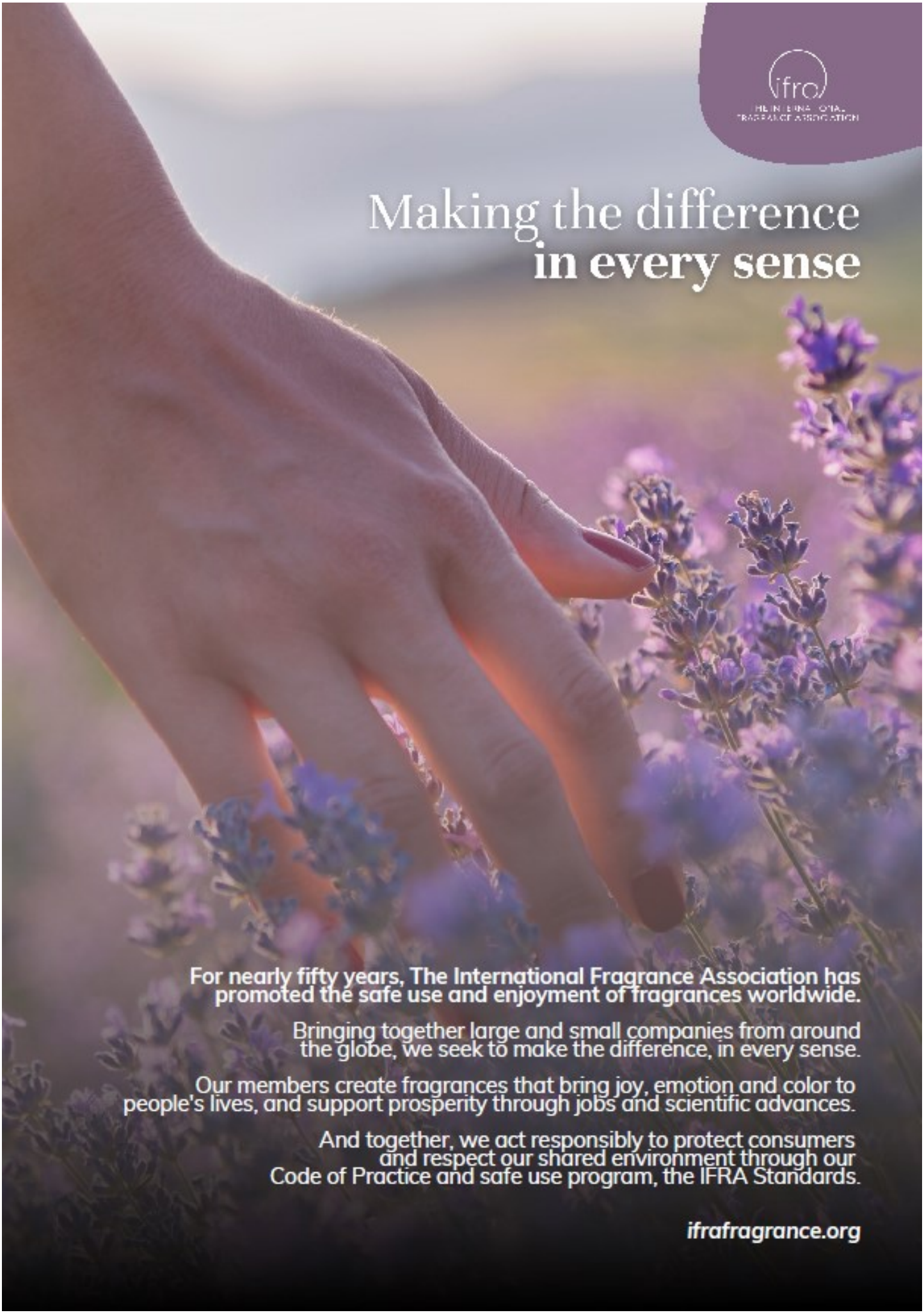
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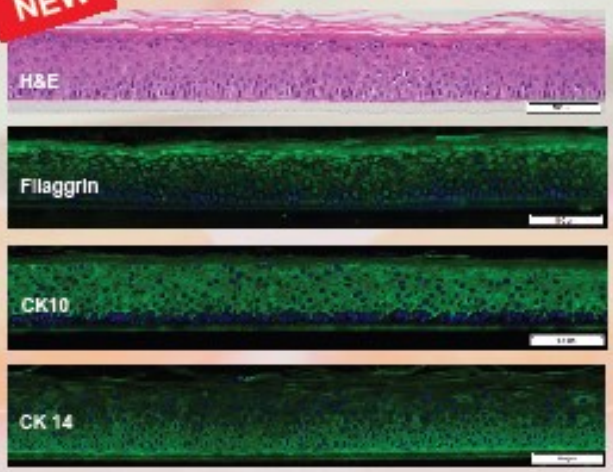

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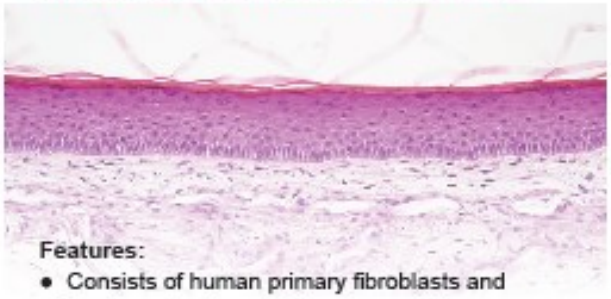

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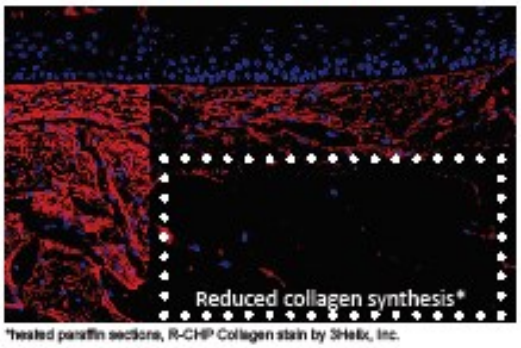

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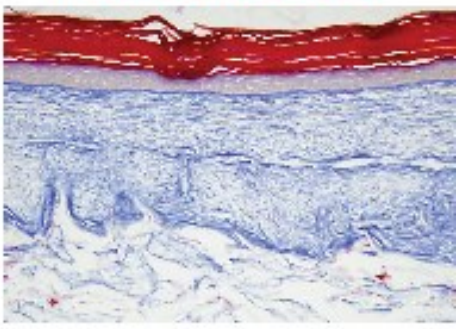

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Heel wat mensen en bedrijven hebben hun financiële schouders al onder het unieke Villa Samson gezet. Maar... **extra middelen én helpende handen zijn nog altijd welkom**! Nu Villa Samson er staat, is het tijd om de eigenlijke werking op de rails te zetten en ook dat kost geld. Steun Villa Samson, financieel en/of logistiek... en maak zo mee het verschil voor duizenden zieken. Want: de wereld een beetje beter maken, dat doe je zélf.

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