in3

"in three"

An integrated interdisciplinary approach to animal-free nanomaterial and chemical safety assessment.

Integrated *in vitro* and *in silico* tools

Paul Jennings
Vrije Universiteit Amsterdam p.jennings@vu.nl

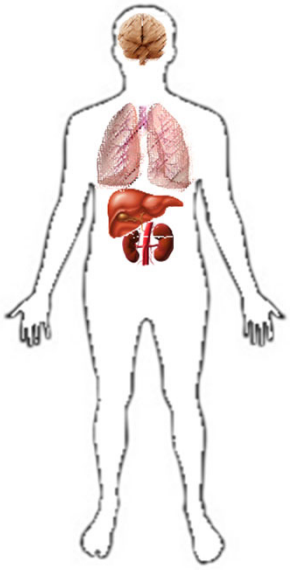
https://www.estiv.org/in3/

Funded by the **Marie Skłodowska-Curie Action** - Innovative Training Network under grant no. 721975.

To drive the synergistic development and utilisation of *in vitro* and *in silico* tools for human chemical and nanomaterial (NM) safety assessment.

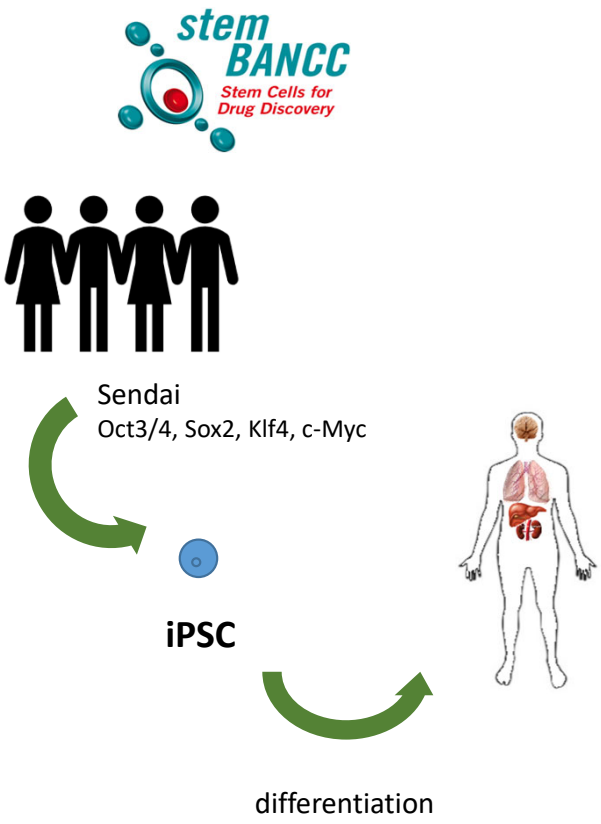
https://www.estiv.org/in3/

Marie Gabrielle Zurich



Differentiation of **human induced Pluripotent Stem Cells (hiPSC)** to toxicologically relevant target tissues. The tissues, from the same genetic backgrounds, will be exposed to selected compounds and the data generated will be used to develop safety assessment approaches by integrating **cheminformatics**, **mechanistic toxicology** and **biokinetics** into computational models.

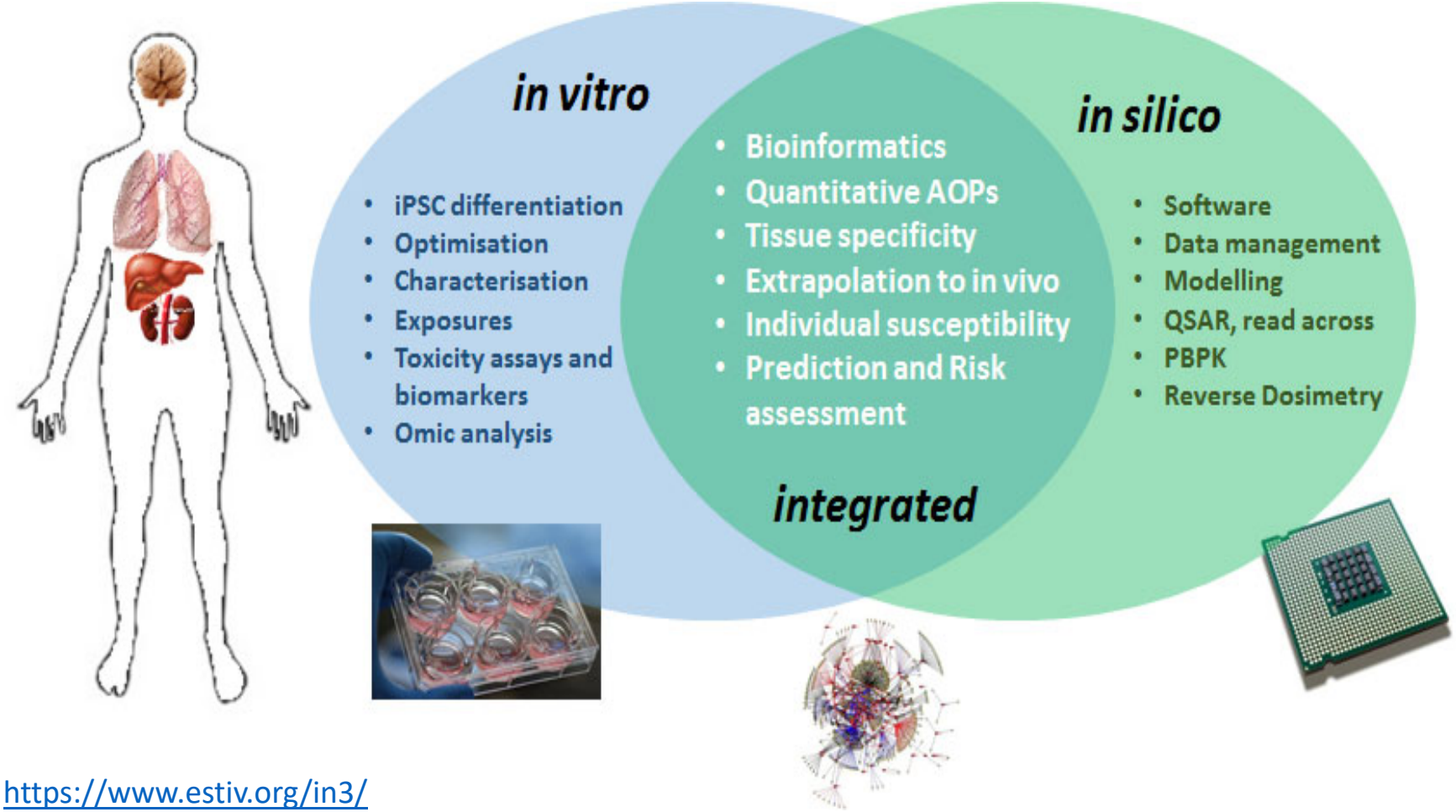
https://www.estiv.org/in3/



Core scientific activities

- Differentiation of well-characterised human iPSC into brain, lung, liver, kidney and vascular cells
- Delineation of tissue specific and donor specific effects of compound exposures (uptake, metabolism, extrusion, and mechanistic toxicity)
- Development and optimisation of quantitative adverse outcome pathways (qAOPs) for each target organ which will be unified in an organism-level model
- Optimisation of QSAR and read-across tools for safety assessment
- Ultimately to create a unified expandable integrated testing strategy for chemical and NM safety assessment

https://www.estiv.org/in3/



https://www.estiv.org/in3/

Training Content and Structure

Block 1: Learning by Research
- ESRs research project
- Secondments to SMEs and other academic partners

Block 2: in3 virtual laboratory
- Collaboration with other ESRs in tasks
- Virtual Journal Club
- On-line reporting and presentations
- Data sharing
- Scientific paper writing

Block 3: Online learning
- 3Rs – from origins to implementation
- Regulation
- Hazard identification and risk assessment
- Chemical case studies
- Developmental biology and organogenesis
- Scientific writing, poster and oral presentations and grant writing

Block 4: On-site lecture and workshop series
- Adverse Outcome Pathway
- Good cell culture practice and iPSC
- In silico approaches
- Entrepreneurship and intellectual property
- Knowledge management and data integration
- Career development
- University doctoral programs

Block 5: Hands on technical workshops
- iPSC generation, culture and quality control.
- Toxicity assays.
- Methods for gene editing and reporter introduction.
- Nanomaterial manufacturing and characterisation.
- High content imaging.
- Modelling epithelial/endothelial transport.
- Software training course.
- Building AOPs and OECD guidelines

Block 6: Communication and Dissemination
- Interaction and communication with in3 network
- Dissemination to scientific community
- Communication with public

Maxime Culot

“The scientists trained within in3 will acquire a unique multidisciplinary skill set and will be uniquely placed to support these activities in academia and industry within their future careers, giving them a competitive advantage and creating a project legacy”

https://www.estiv.org/in3/

Who are we in in3 ?

Beneficiaries

Vrjie Universiteit Amsterdam, Molecular and Computational Toxicology, Prof. Dr. Paul Jennings. Coordinator.
Evercyte GmbH, Austria. Assoc. Prof. Regina Grillari / Assoc. Prof. Giovanni Grillari
Université d'Artois, France. BBB Laboratory. Assoc. Prof. Maxime Culot
University of Lausanne, Switzerland. Physiology. Marie-Gabrielle Zurich
BIOTALENTUM, Hungary. Prof. Andras Dinnyes
University of Leuven, Leuven, Belgium. KU Leuven Stem Cell Institute, Prof. Catherine Verfaillie
Department of Health – Public Health England, United Kingdom. Toxicology Dept./Centre for Radiation, Chemical and Environmental Hazards/Nanotoxicology Laboratory. Dr. Martin Leonard.
Newcells Biotech, United Kingdom. Prof. Lyle Armstrong
Instituto di Ricerche Farmacologiche Mario Negri, Italy. Environmental Health Sciences/Laboratory of Environmental Chemistry and Toxicology. Prof. Emilio Benfenati
Liverpool John Moores University, United Kingdom. School of Pharmacy and Biomolecular Sciences. Prof. Mark Cronin
National Institute of Chemistry, Ljubljana, Slovenia. Laboratory of Chemometrics. Prof. Marjana Novič
Universiteit Utrecht, The Netherlands. Institute for Risk Assessment Sciences/Toxicology. Ass. Prof. Nynke Kramer
Douglas Connect, Switerland. Dr. Barry Hardy / Dr. Thomas Exner

Partner Organisations

Center for Alternatives to Animal Testing – EUROPE, Universität Konstanz, Germany. Dr. Mardas Daneshian
European Union Reference Laboratory for alternatives to animal testing, Italy. Institute for Health and Consumer Protection, European Commission Joint Research Centre. Dr. Anna Price
European Society of Toxicology in vitro, The Netherlands. Prof. Mathieu Vinken
Nanocomposix Europe, Czech Republic. Karolina Sauerova
L'Oreal, France. Gladys Ouedraogo

Academic and governmental

Companies

Organisations

in3
integrated in vitro & in silico tools


Ivo Djidrovski


Sreya Ghosh


Cormac Murphy


Vidya Chandrasekaran


Susana Proença


Zahra Mazidi


Nicoleta Spinu


Aurore Bourguignon


Leonie Fransen


Liadys Mora Lagares


Sara Wellens


Pranika Singh


Carolina Nunes


Ana Yisel Caballero


Kristijan Vukovic

dedicated, motivated, dynamic,
passionate, hard working,
intelligent, fun, social,
responsible, diverse

In Vitro

In Silico

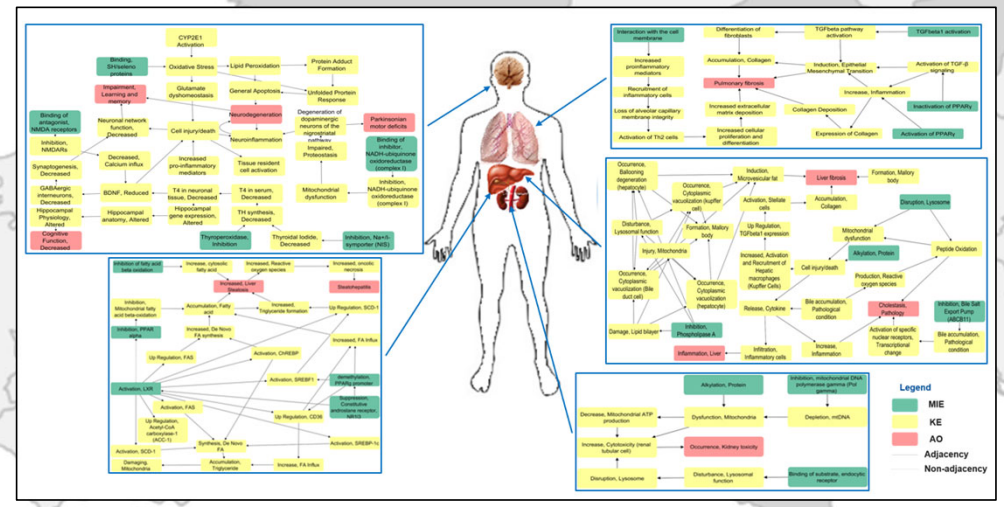
MARIE CURIE ACTIONS

ESR12 – qAOPs

Development and Use of Adverse Outcome Pathway (AOP) Networks Within The in3 Project

ESR Nicoleta Spinu
PI Mark Cronin

AIM: To describe the development and use of AOP networks, focusing on those relevant for in3 project selected organs and suitable for further quantitative modelling.

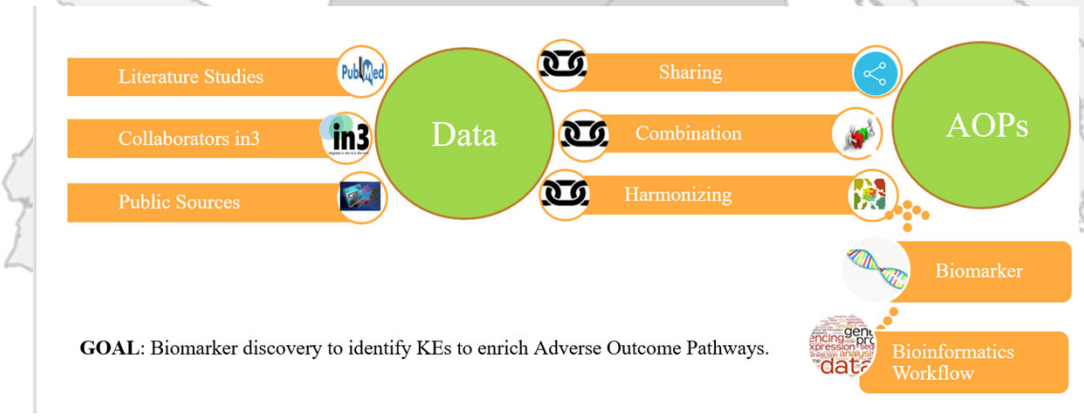


MSCA-ITN-2016 grant no. 721975

ESR15- Data management and bioinformatics

Towards bioinformatics workflow for prediction of chronic kidney disease based on iPS cell data

Pranika Singh, Thomas Exner



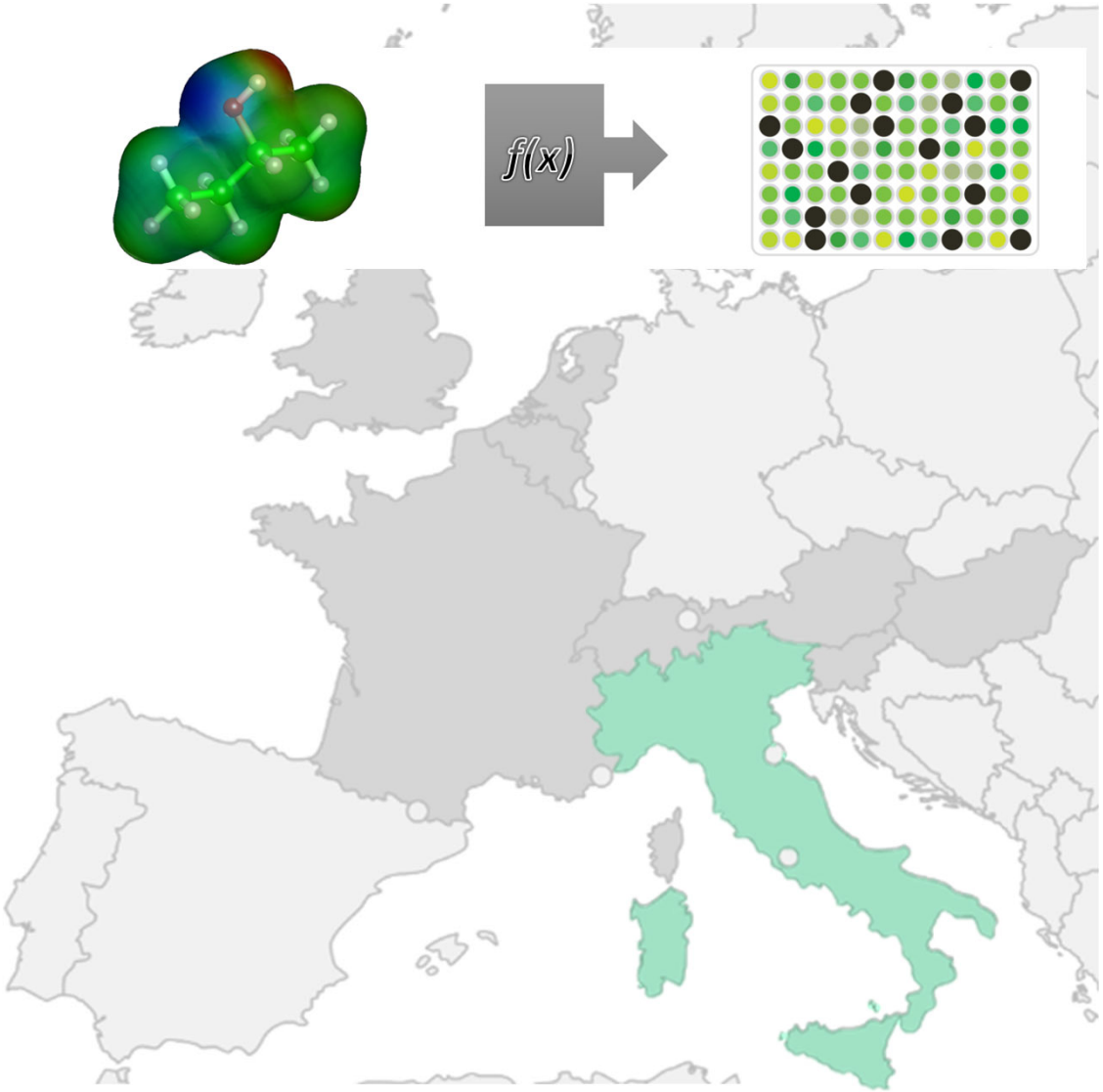
MSCA-ITN-2016 grant no. 721975

University of Basel

douglasconnect working communities

in3 integrated in vitro & in silico tools

ESR10 - QSAR



Introducing *ab initio* QSAR, a versatile tool for regression and classification

Kristijan Vukovic, Emilio Benfenati

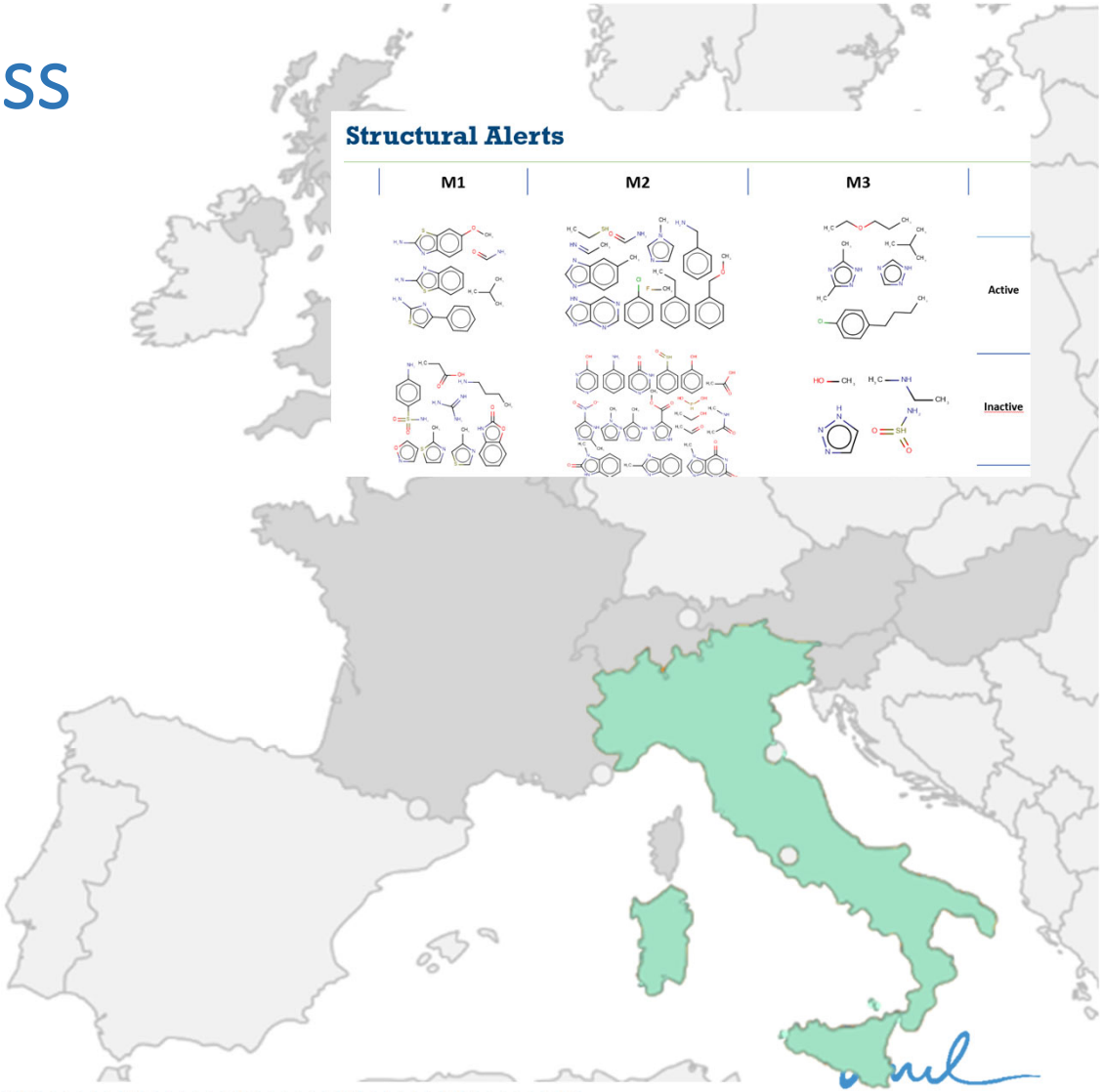
MARIO NEGRI
ISTITUTO DI RICERCHE FARMACOLOGICHE

MSCA-ITN-2016 grant no. 721975

ESR11 – Read Across

Development of *in silico* classification models to predict the toxicity of azoles as aromatase or not aromatase inhibitors

Ana Caballero Alfonso, Emilio Benfenati



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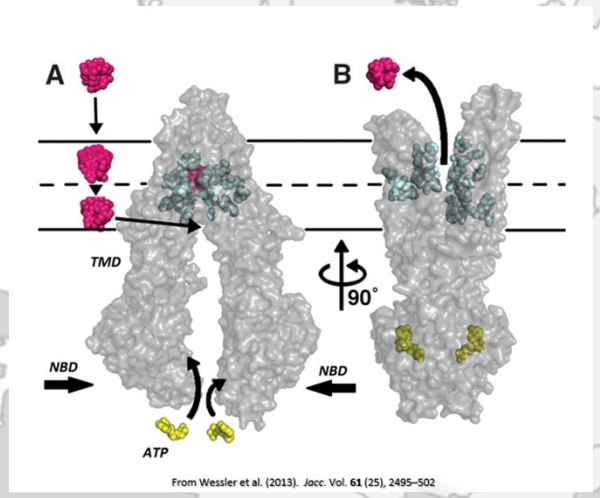
ESR13 : P-glycoprotein

P-glycoprotein modelling: a combined in silico approach towards identification of safer chemicals

Liadys Mora Lagares, Marjana Novič, Nikola Minovski



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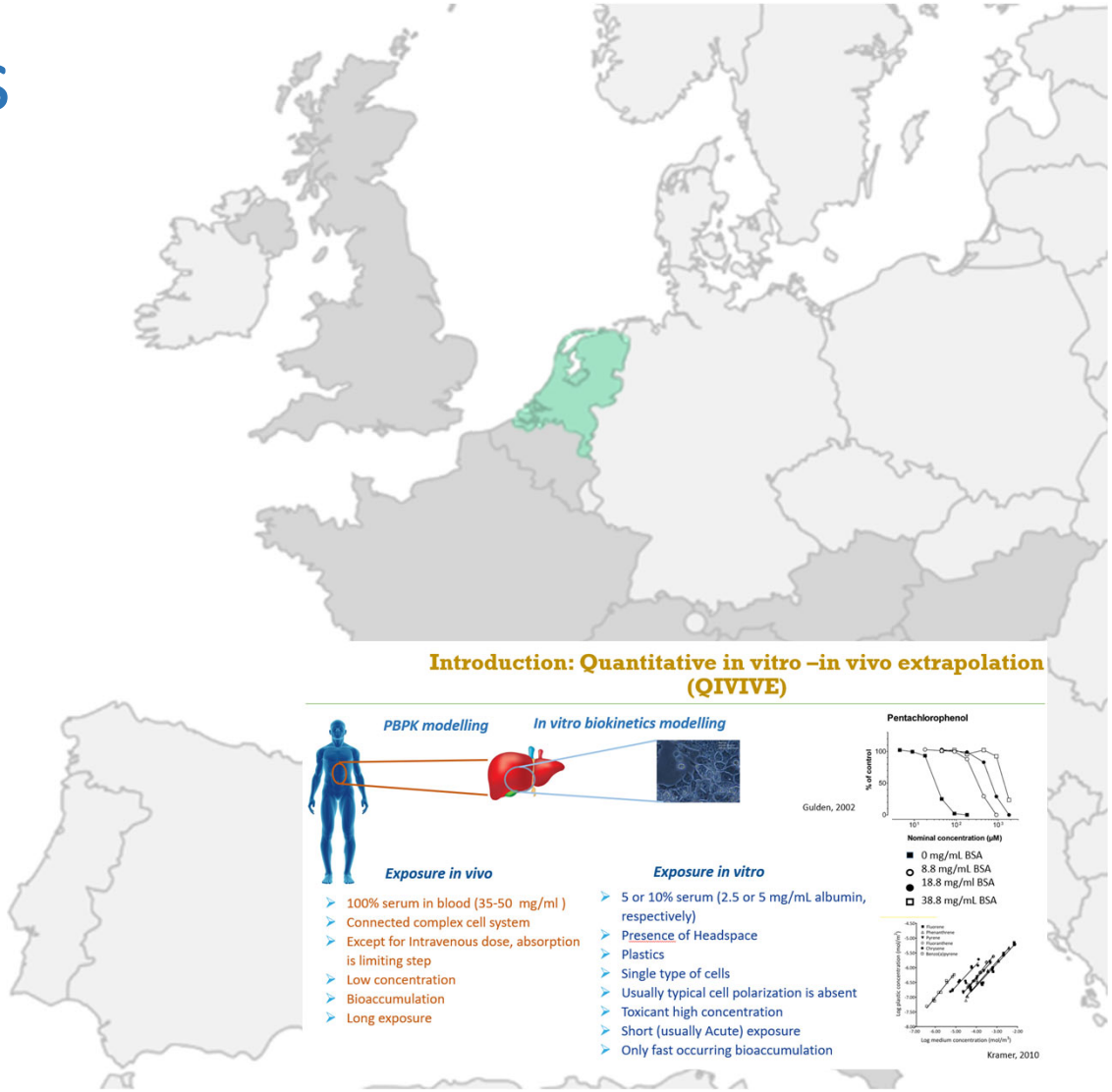
KEMIJSKI INŠTITUT

ESR14 - Biokinetics

Evaluation of models to estimate the distribution kinetics of test chemicals *in vitro*

Susana Proença, Nynke Kramer



MSCA-ITN-2016
grant no. 721975

Universiteit Utrecht

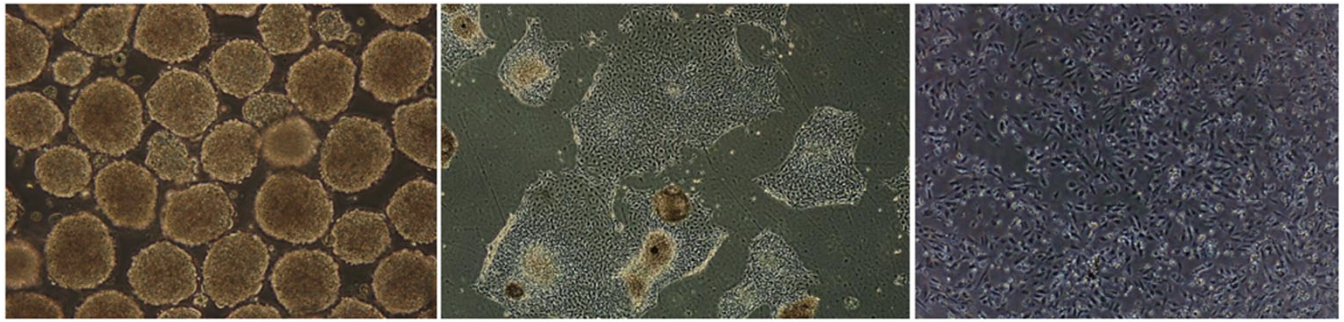
ESR3 – Endothelial cells

IPSCs DIFFERENTIATION TO ENDOTHELIAL CELLS AS MODL SYSTEM FOR *IN VITRO* TOXICOLOGY

Zahra Mazidi, Johannes Grillari, Regina Grillari, Mathias Wieser



iPS cell aggregates | Endothelial colony forming cells | Mature endothelial cells

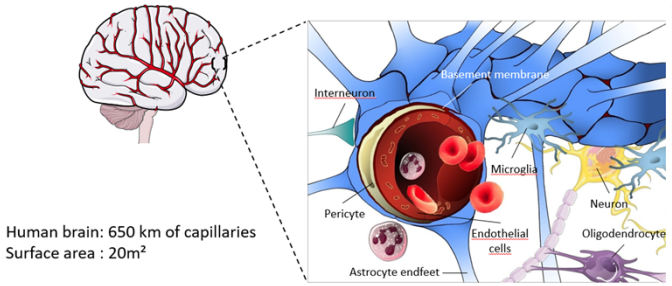


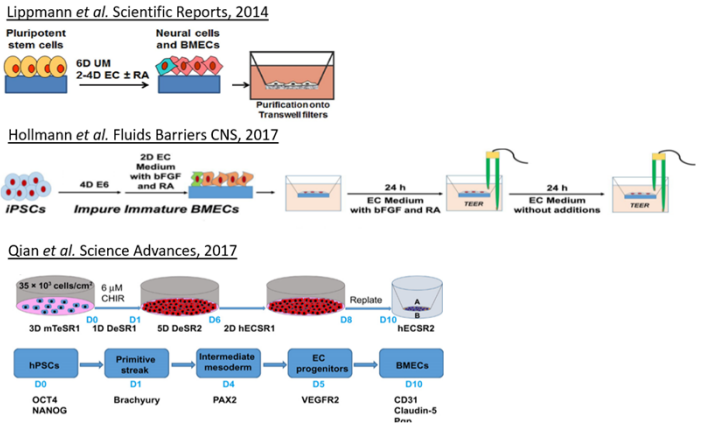
MSCA-ITN-2016 grant no. 721975

ESR4 – Blood Brain Barrier

Protocol comparison for deriving BBB-models from iPSCs for use in toxicological assessment of chemicals

Sara Wellens, Maxime Culot





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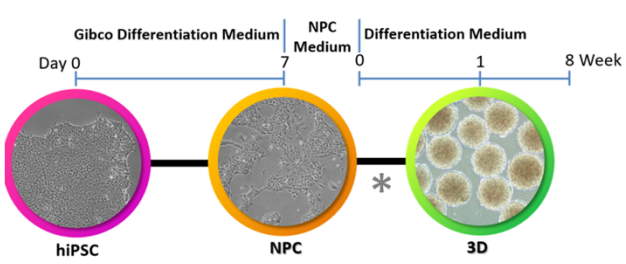
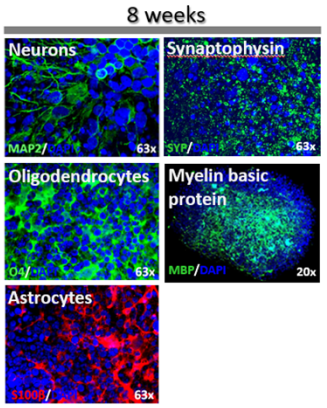
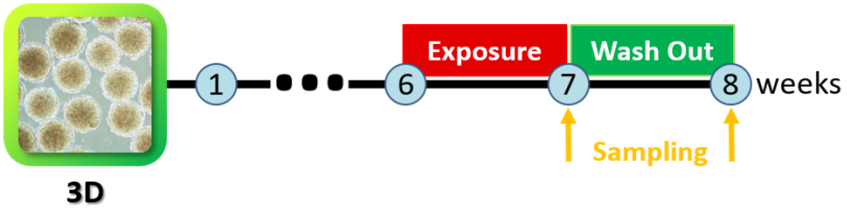
ESR5 - Brain

iPSC-DERIVED HUMAN 3D BRAIN MODEL FOR NEUROTOXICITY TESTING

Carolina Nunes, David Pamies , Marie-Gabrielle Zurich





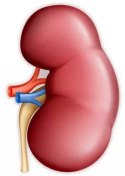


UNIL | Université de Lausanne

MSCA-ITN-2016 grant no. 721975

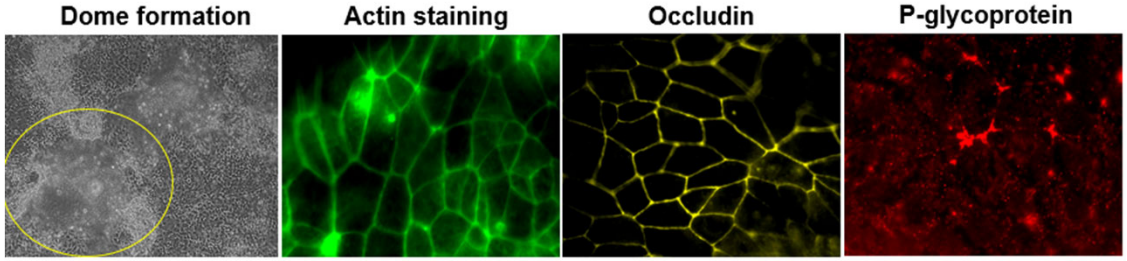
in3 ESR1 - Kidney

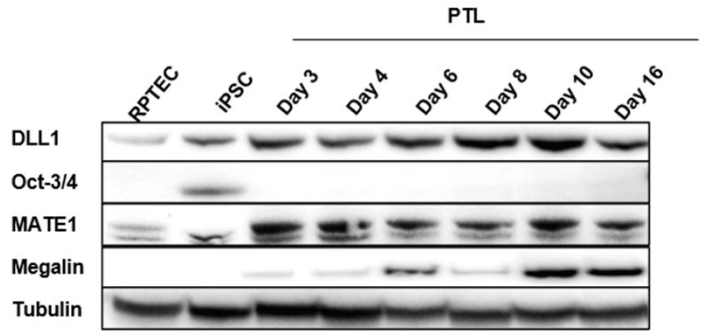
integrated in vitro & in silico tools



Evaluation of iPSC derived renal proximal tubular epithelial cells for toxicity assessment

Vidya Chandrasekaran, Prof. Dr. Paul Jennings





VU VRIJE UNIVERSITEIT AMSTERDAM

Division of Molecular and Computational Toxicology

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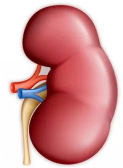
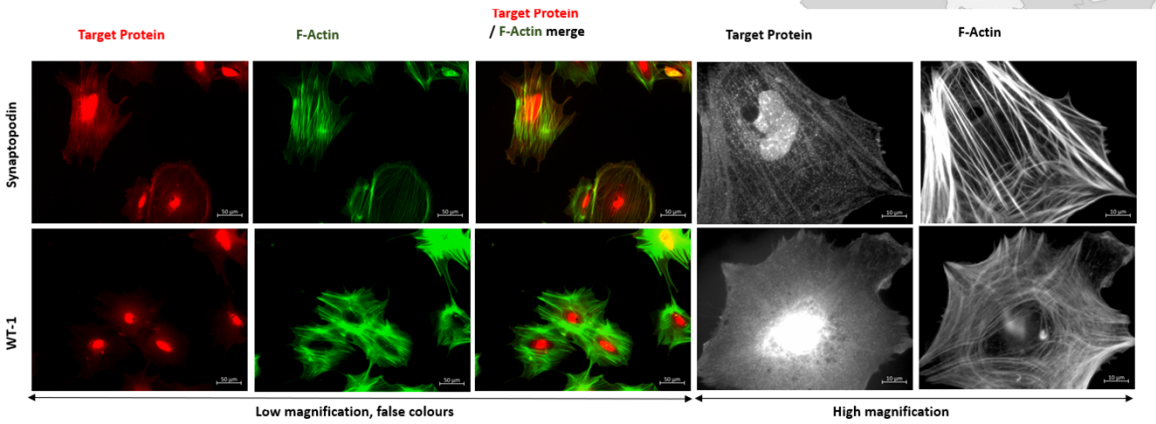
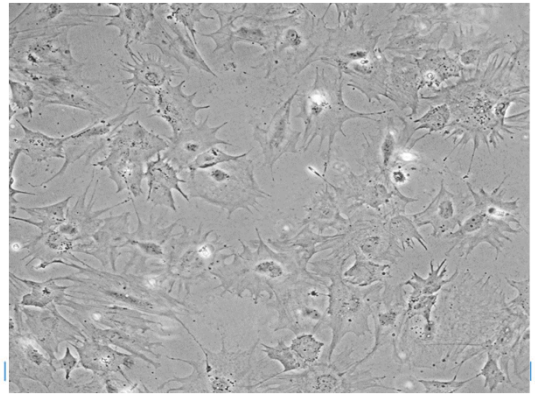
ESR2 - Kidney

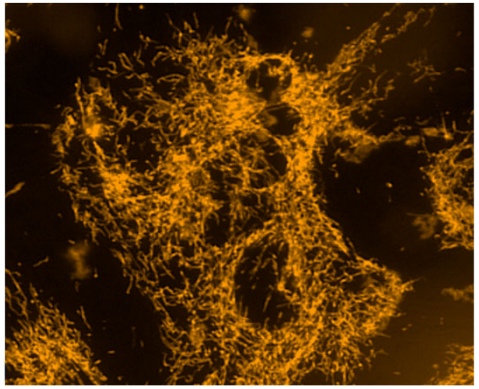


The development and optimisation of iPSC-derived podocytes and their integration into a glomerular model for toxicity testing

Cormac Murphy, Anja Wilmes , Paul Jennings







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Division of Molecular and Computational Toxicology

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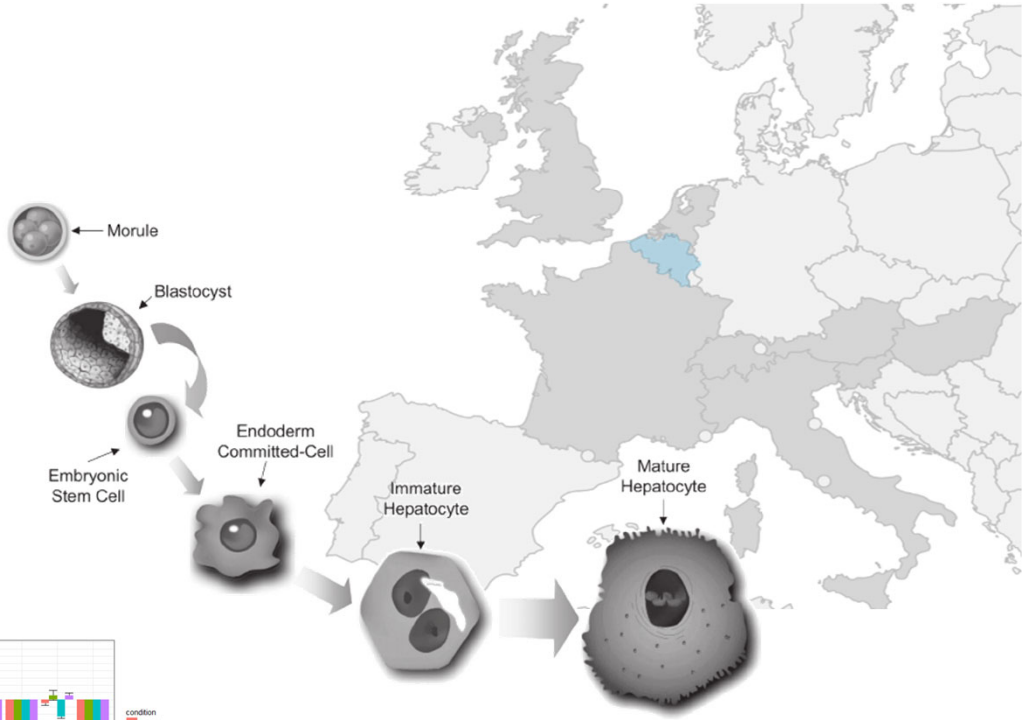
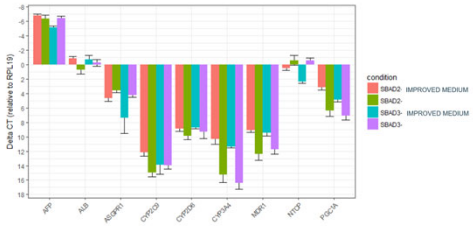
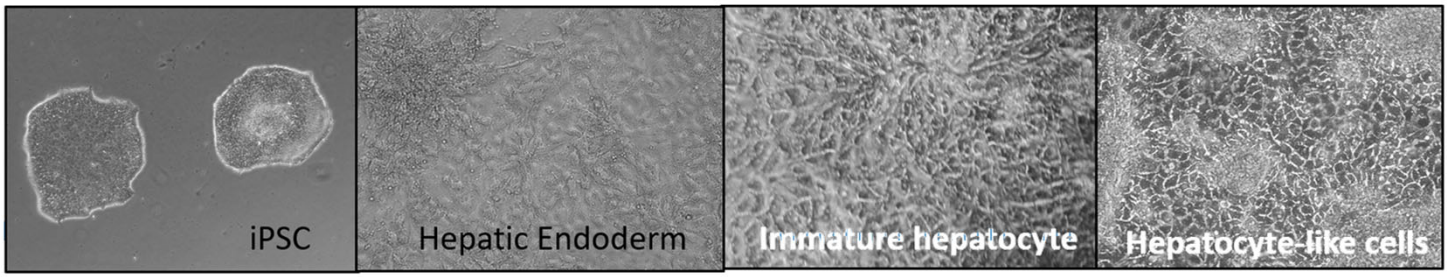
ESR7- Liver

Differentiation of hepatocyte-like cells from induced pluripotent stem cells (iPSCs) and application to hepatotoxicity testing

Sreya Ghosh, Prof. Dr. Catherine M. Verfaillie



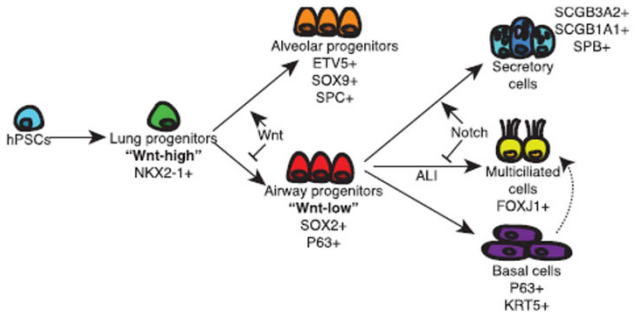




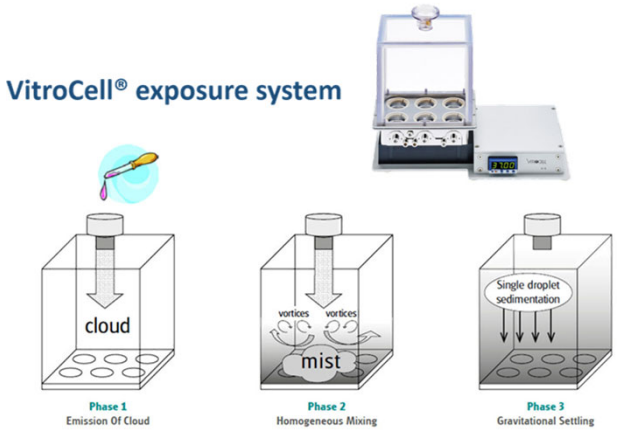
ESR8 - Small airways

DEVELOPMENT OF iPSC-DERIVED SMALL AIRWAY MODELS AND APPLICATION TO TOXICITY TESTING

Leonie Fransen, Dr. Martin Leonard



McCauley, K. B., Hawkins, F., Serra, M., Thomas, D. C., Jacob, A., & Kotton, D. N. (2017).



Public Health England

in3 integrated in vitro & in silico tools | ESR9 - Lung

Development of iPSC derived Conducting Airways and application to toxicity testing

Ivo Djidrovski, Mike Nicholds, Lyle Armstrong



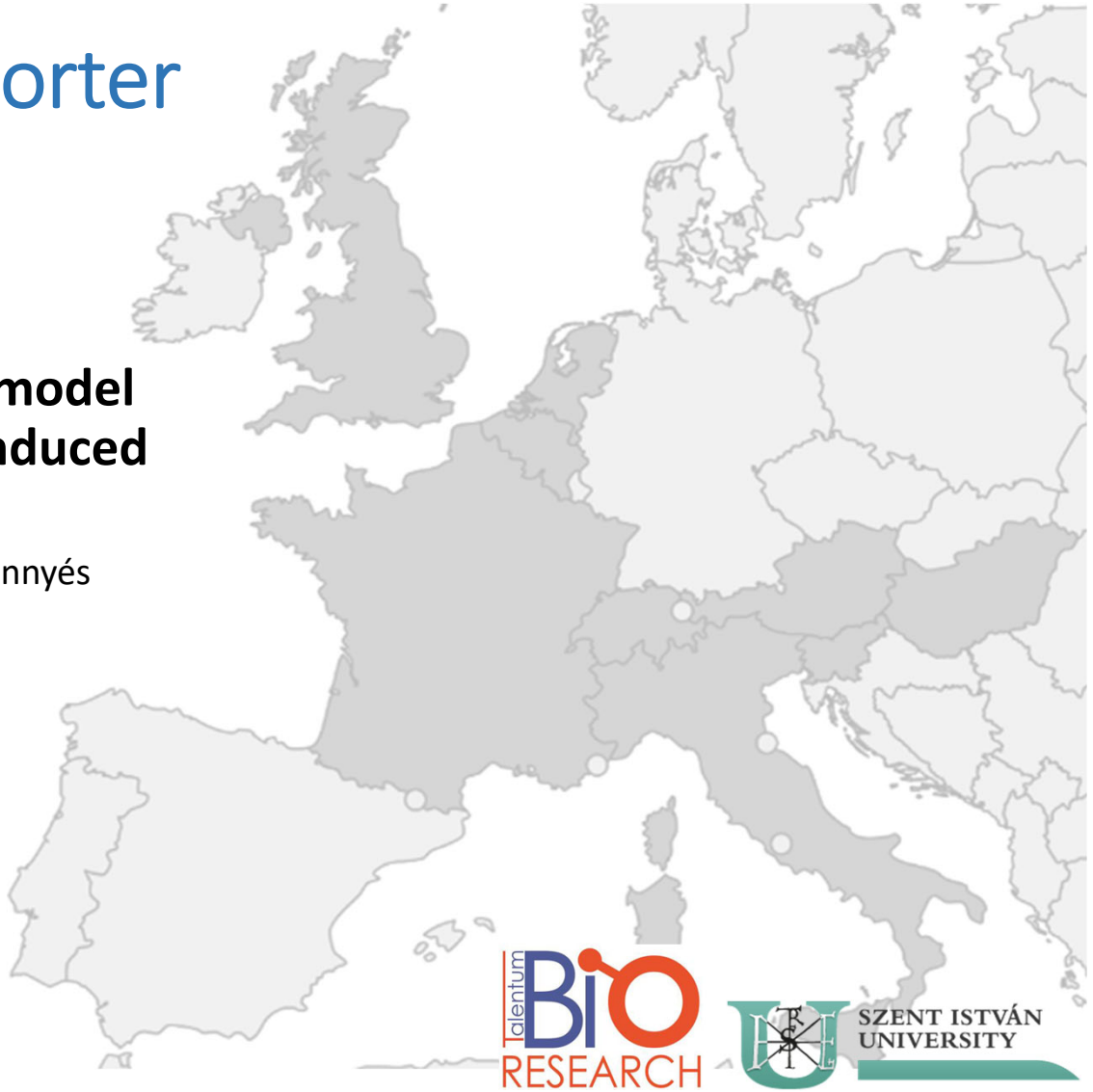
Newcastle University

Newcells BIOTECH

ESR6 – Toxicity reporter

Development of a cellular toxicology model using genetically engineered human induced pluripotent stem cells.

Aurore Bourguignon, Julianna Kobolák, András Dinnyés



MSCA-ITN-2016 grant no. 721975

Integrated Approaches to Testing and Assessment

Sendai
Oct3/4, Sox2, Klf4, c-Myc

* Reporters

iPSC

differentiation

Gene editing

- P - glycoprotein
- MATE-1
- BSEP

AOP

Lung

AOP

Vasculature

biokinetics

modelling

transcriptomics

bioinformatics

AOP

Liver

Kidney

AOP

Blood brain barrier

AOP

Brain

AOP

Read Across and QSAR

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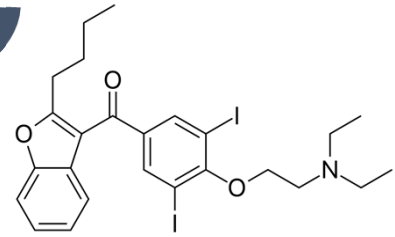
integrated in vitro & in silico tools

Toxicity testing



in3

integrated in vitro & in silico tools

An integrated interdisciplinary approach to animal-free nanomaterial and chemical safety assessment.

EUTOXRISK

MARIE CURIE ACTIONS

Dr. Ellen Langemeijer
e.v.langemeijer@vu.nl
estiv.org/in3

Funded by the **Marie Skłodowska-Curie Action** - Innovative Training Network under grant no. 721975.