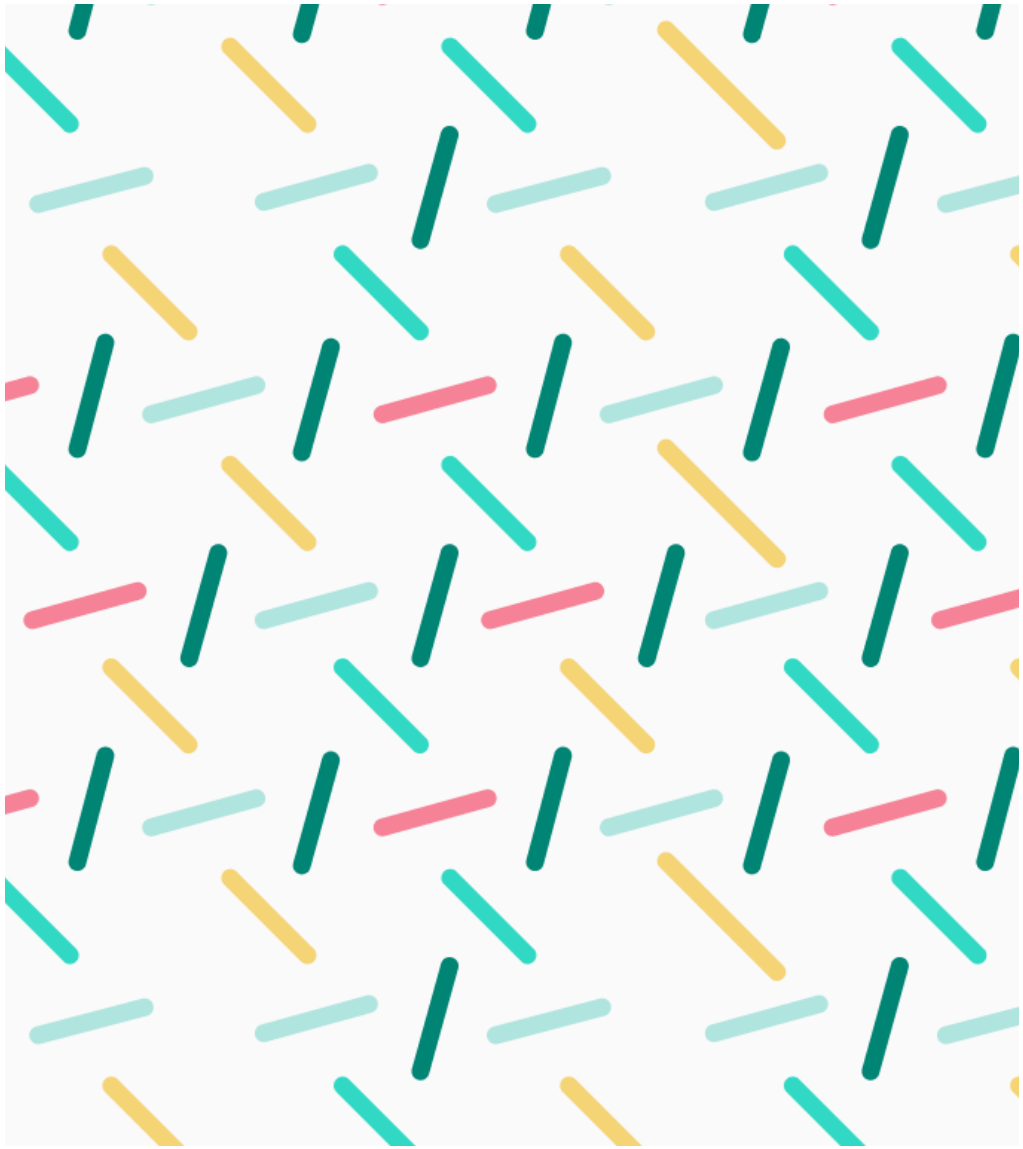
New methods for determining immunosuppressive properties of substances

Ljubljana, October 22th 2026

8th Congress of the Slovenian Society of Toxicology

Nous ne pouvons pas afficher l'image.

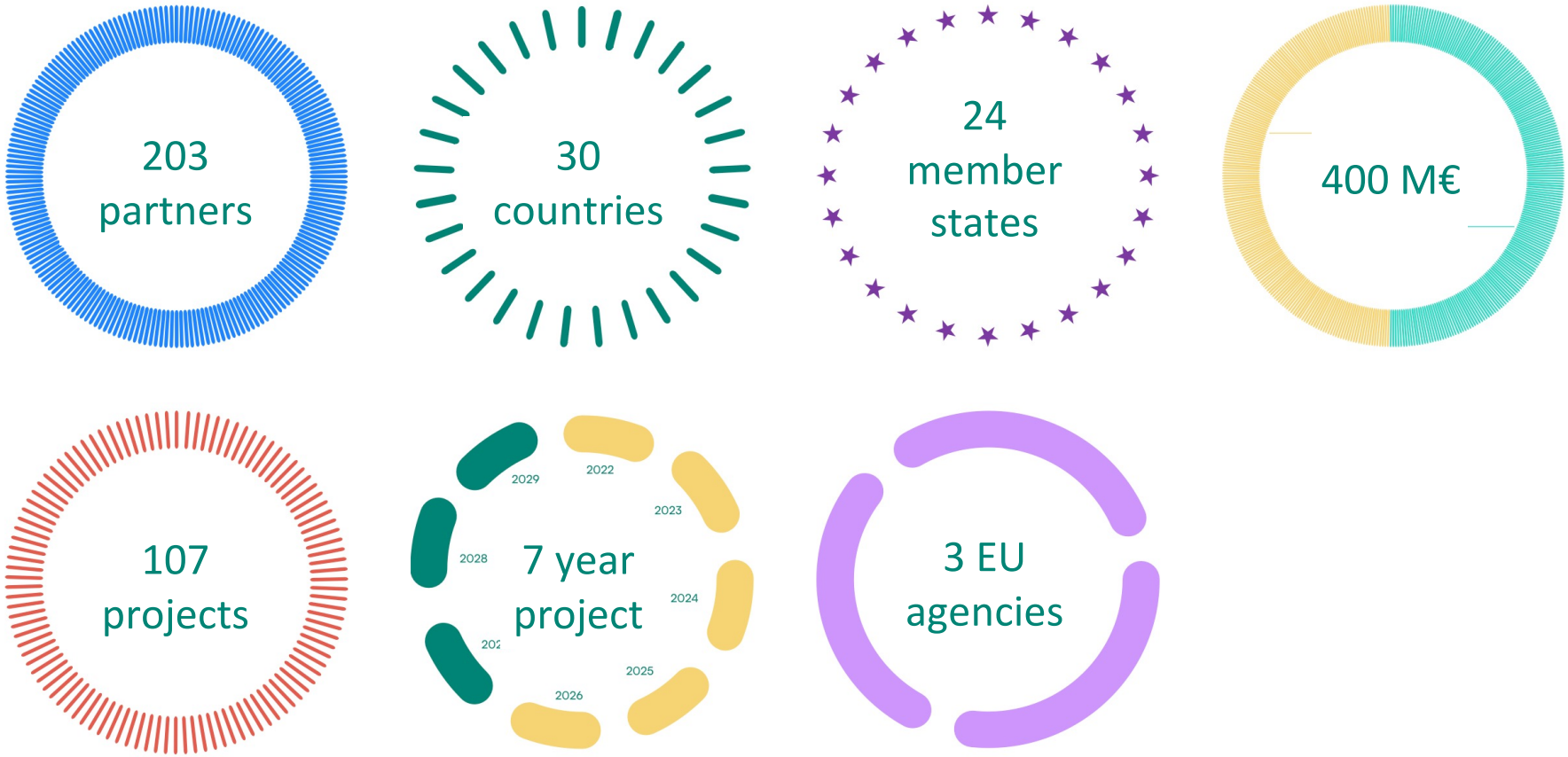
PARC



Conflict of interest

None

PARC overview



PARC

NGRA: Next Generation Risk Assessment

Approach of risk assessment exposure-led and hypothesis-driven which integrate *in silico*, *in chemico* and *in vitro* methods.
It constitutes the global objective of the assessment, whereas the NAMs (New Approach Methodologies) are the tools used to reach it.

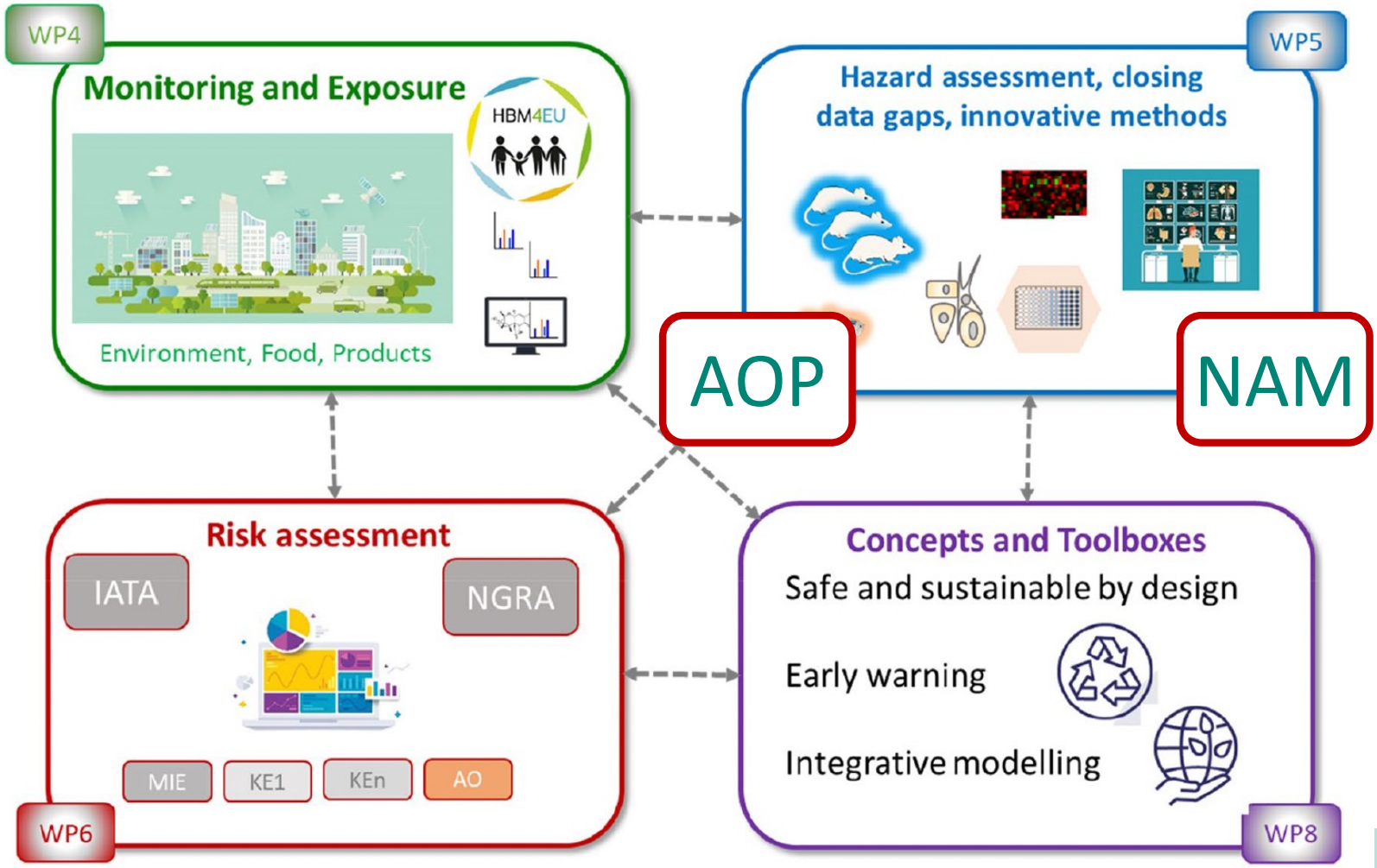
	Classical approach	NGRA
Principles	Hazard identification Human extrapolation with safety factor	Exposure assessment Identification of molecular/cellular effect Adverse effect prediction
Results	Classification of the hazard Toxicological reference values	Risk assessment regarding the exposure scenario

NAM

AOP

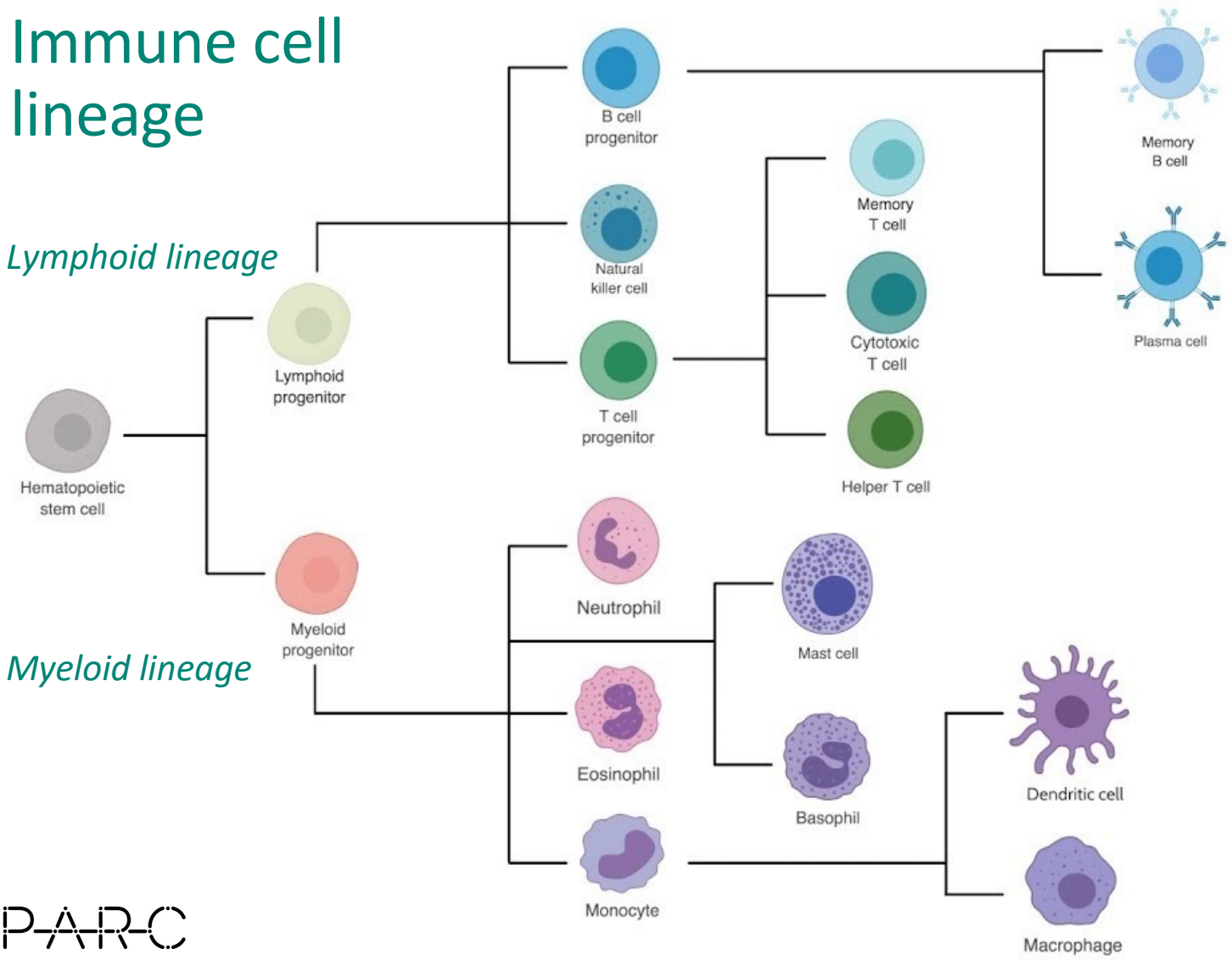
Marx-Stoelting et al, 2023

PARC stucture



Marx-Stoelting et al, 2023

Immune cell lineage

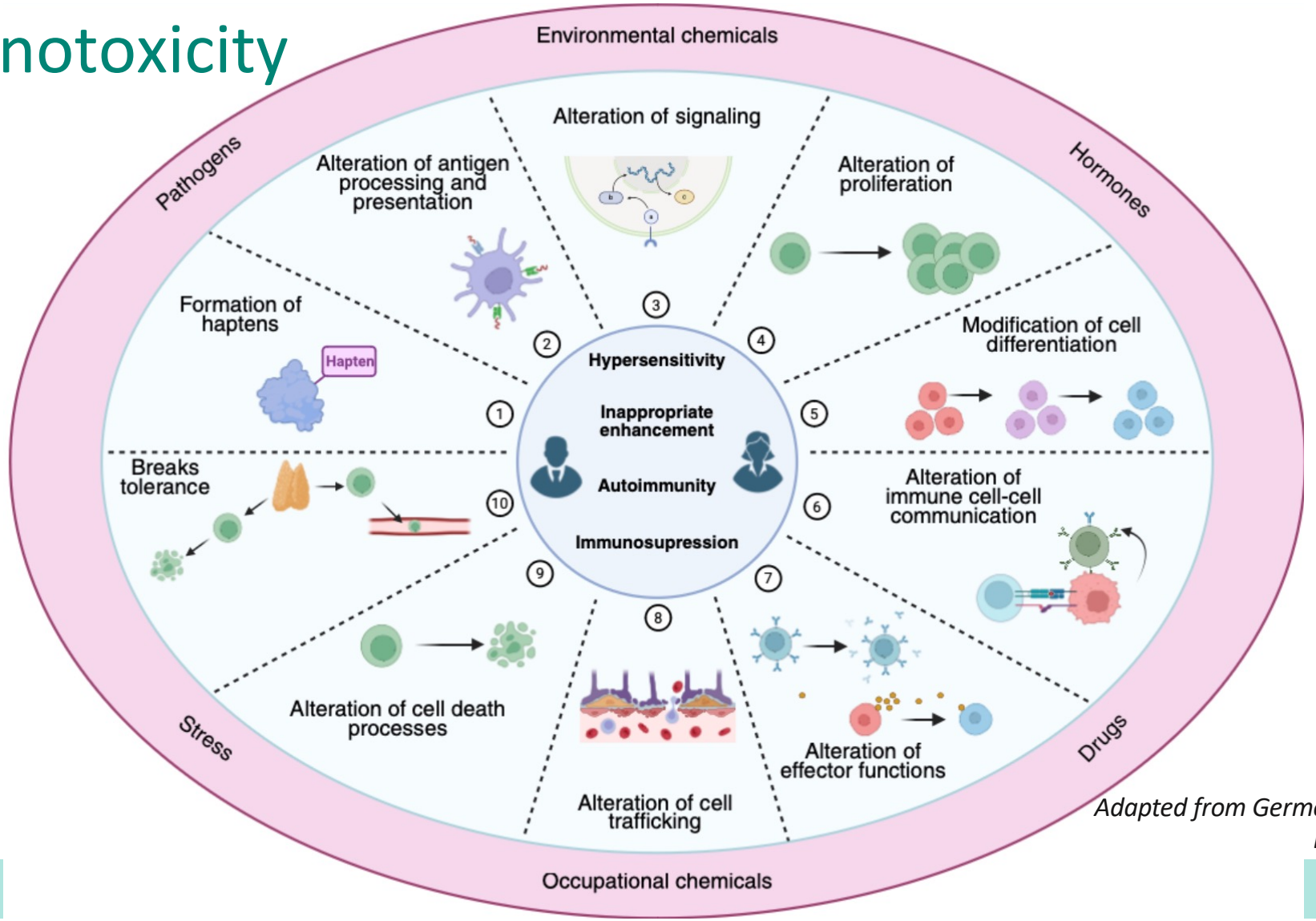


Impact on:

- Stem cells
- Differentiation
- Maturation
- Activity

PARC

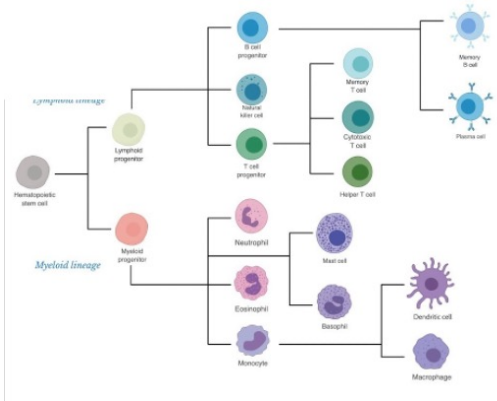
Immunotoxicity



Adapted from Germolec et al., EHP 2022

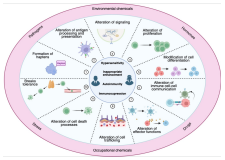
Immunotoxicology

Immune cell lineage



Key characteristics of immunotoxic agents

- KC1: Covalently binds to proteins to form novel antigens
- KC2: Affects antigen processing and presentation
- KC3: Alters signaling
- KC4: Alters proliferation
- KC5: Modifies cellular differentiation
- KC6: Alters immune cell-cell communication
- KC7: Alters effector functions
- KC8: Alters cell trafficking
- KC9: Alters cell death processes
- KC10: Breaks tolerance



Hazard

- Hypersensitivity
- Increase infections
  Decrease vaccine response
  Increase inflammation
  Increase autoimmunity and immune-related adverse effects
  Increase cytokine release syndrome
  Increase cytopenias
  Increase cancer
  Increase adverse pregnancy outcome
- Increase Inflammation
  Increase Autoimmunity
  Increase Abortions

Gap and Regulatory relevance

Several regulations or reports highlight the importance of phasing out animal testing in immunotoxicity research, report the lack of *in vitro* methods measuring immune endpoints, and point to areas where further exploration of alternative methods is needed.

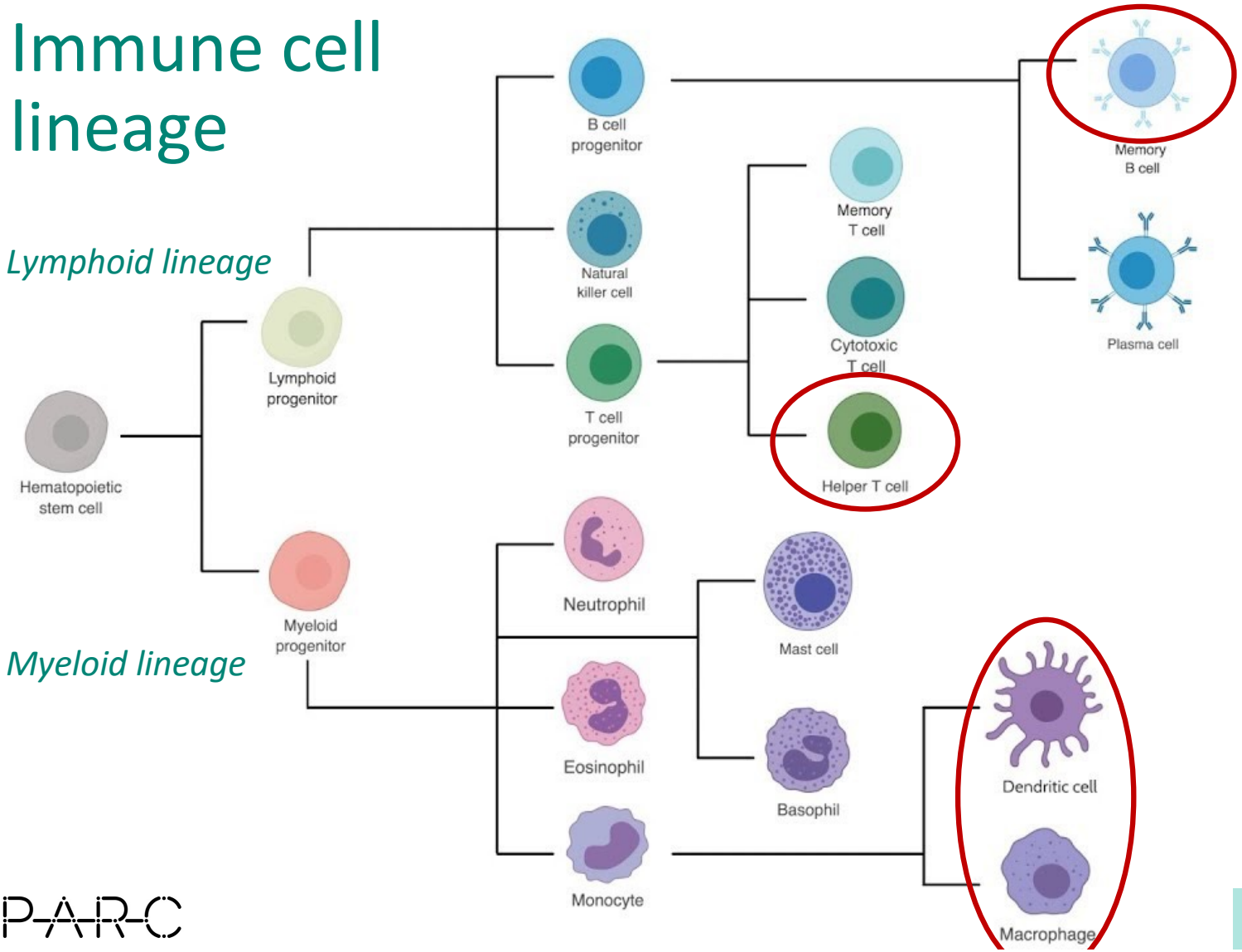


DRP on immunotoxicity

Plant protection products and biocides EU regulation
Cosmetic products
➡ Skin sensitization

Food contact materials and Food contaminants
➡ Allergenicity

Immune cell lineage



OECD TG443 (TDAR)



+TGs 407, 408, 421/422 without functional assays

June 2025 : OECD TG444A (IL-2) (T cell)

PARC

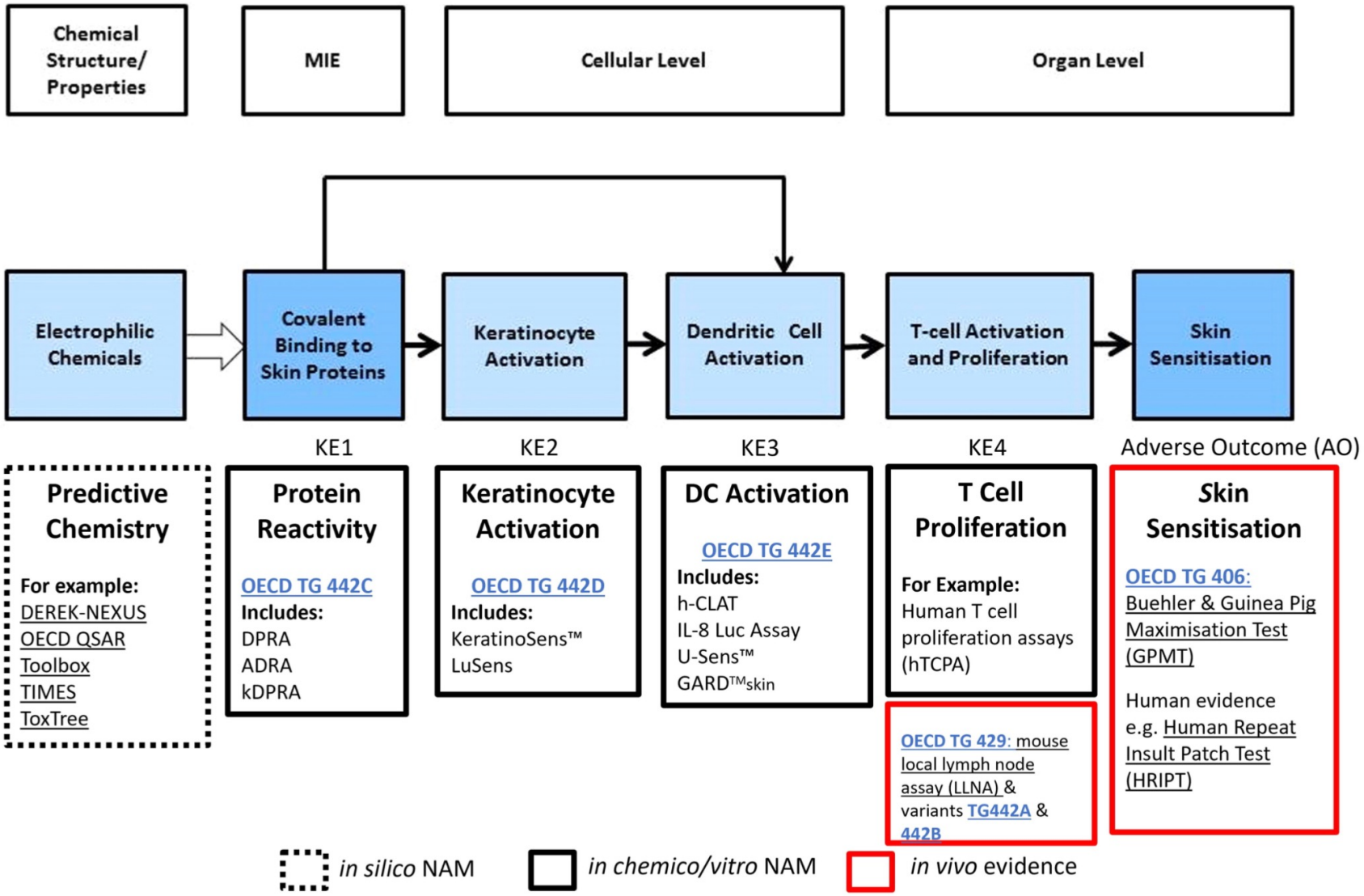
AOP



Few AOP related to immunotoxicity. However, they are already sufficient to develop tests related to specific KE. The PARC project also worked to enhance the number of AOPs with immunotoxic endpoints (ex: addition in AOP39-respiratory sensitizer; development of AOP573-Immunosuppression and Cancer).

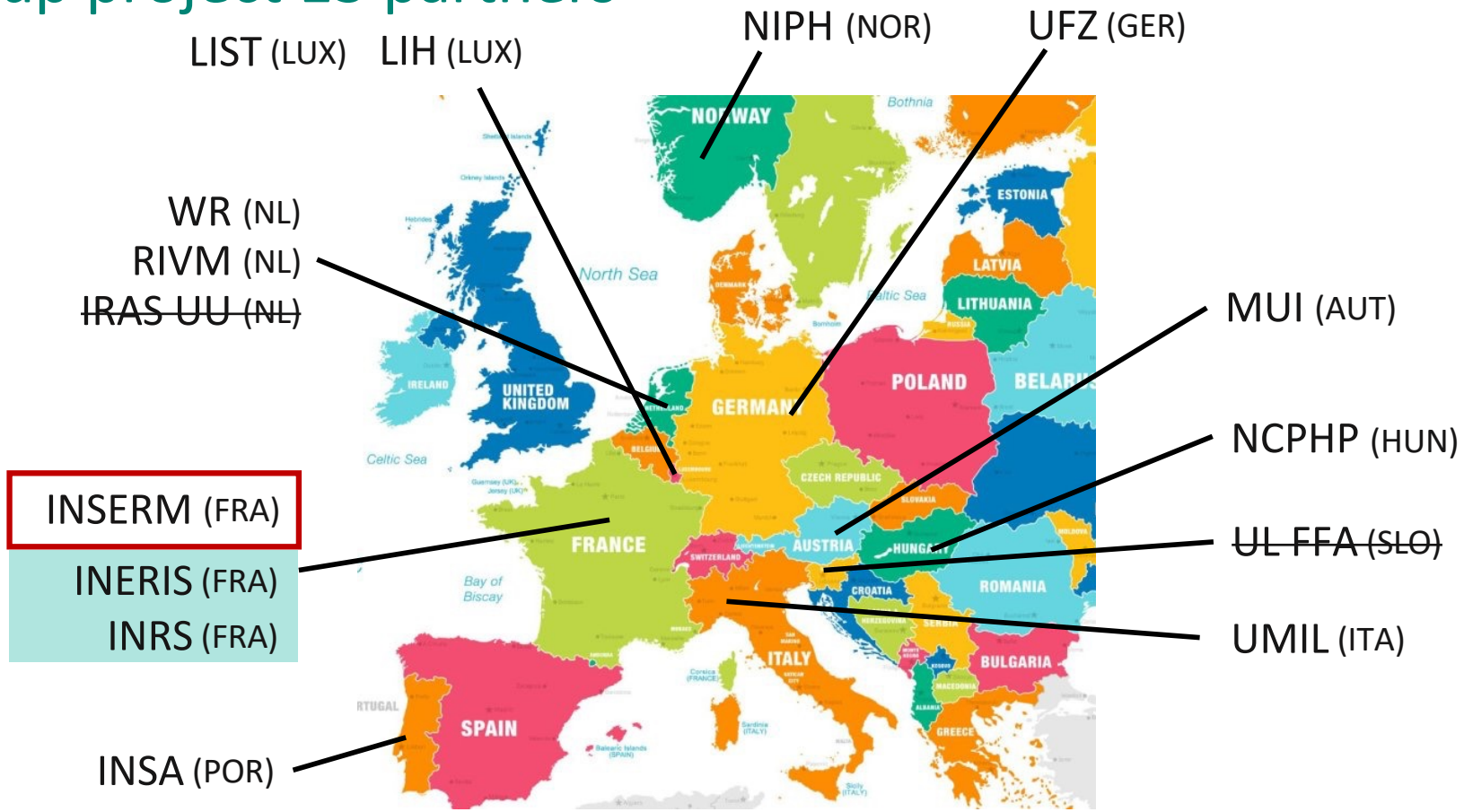
At the beginning of the project, four AOPs were related to immunosuppression (AOPs 315, 154, 277, and 14), primarily focusing on adaptive immune responses. However, none address innate immune mechanisms, direct effects on B-cell populations, or cell-mediated immunity.

AOP 40



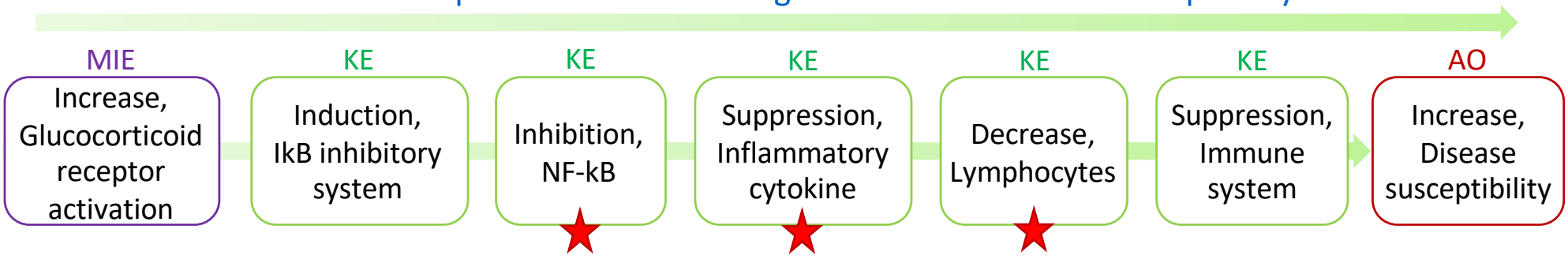
Aleksik et al. 2024

First project : 13 parters
Follow-up project 13 partners



Link with existing (or ongoing) AOPs

AOP 14 Glucocorticoid Receptor Activation Leading to Increased Disease Susceptibility





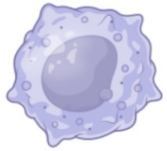
NK cells (LIH)



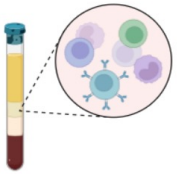
T cells (UL-FFA)



B cells (WR)



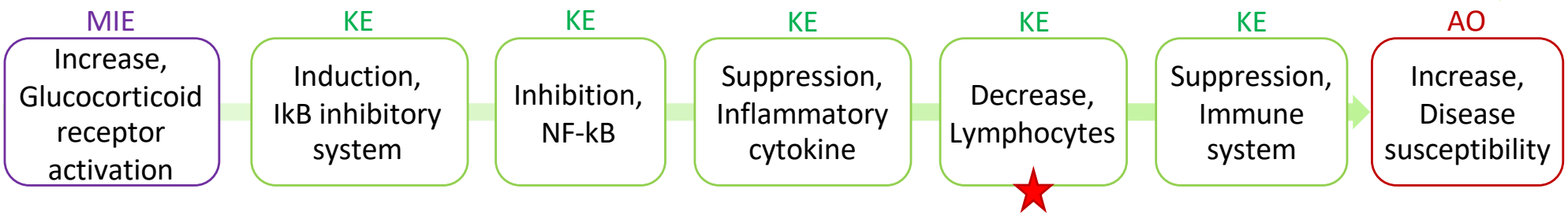
Macrophages (INSA, UFZ)

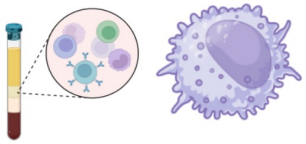


PBMCs (UFZ, MUI, WR, LIH, UMIL)

Link with existing (or ongoing) AOPs

AOP 14 Glucocorticoid Receptor Activation Leading to Increased Disease Susceptibility





PBMC => NK cells
HSC => NK cells

Screening assays for Natural killer cells immunotoxicity
- apply to a context of early exposure

Cytotoxicty => Score ICAI

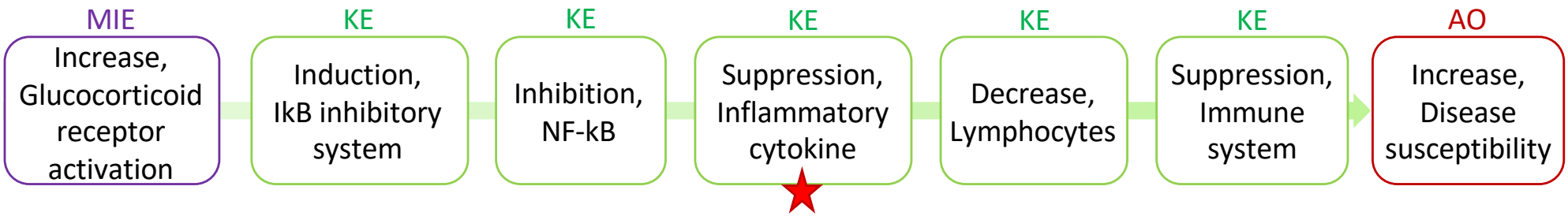
Cell surface marker expression
– differentiation capacity

LIH : Jonathan Turner

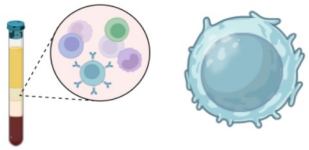
Unpublished

Link with existing (or ongoing) AOPs

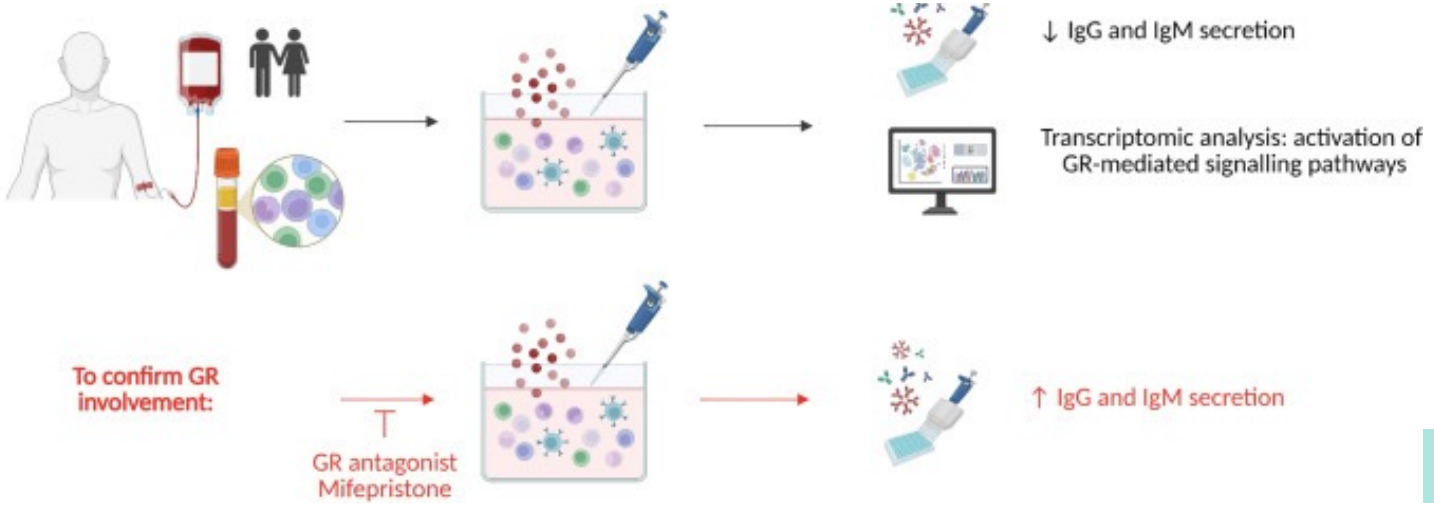
AOP 14 Glucocorticoid Receptor Activation Leading to Increased Disease Susceptibility



Screening of immunotoxic effects in B cell-stimulated PBMCs



PBMCs => B cells



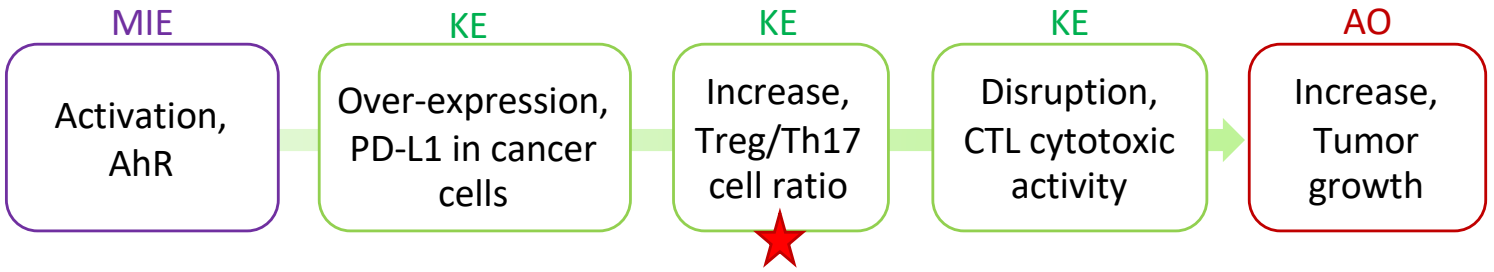
WR: Aafke Janssen

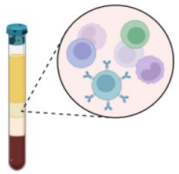
Iulini et al.2024

PARC

Link with existing (or ongoing) AOPs

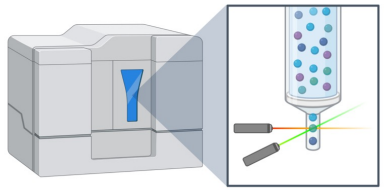
AOP 578 AhR activation leading to cancer progression via immunosuppression

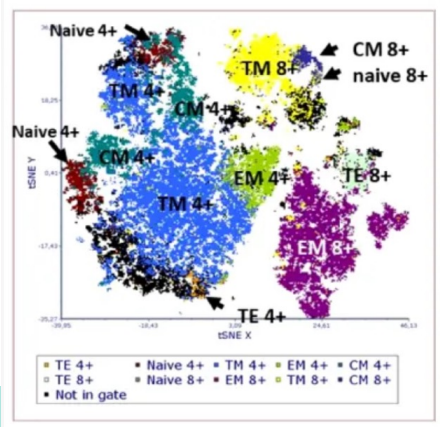


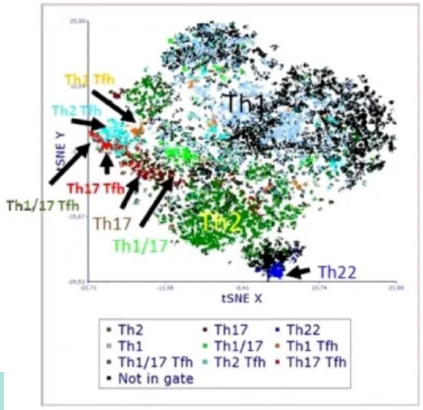


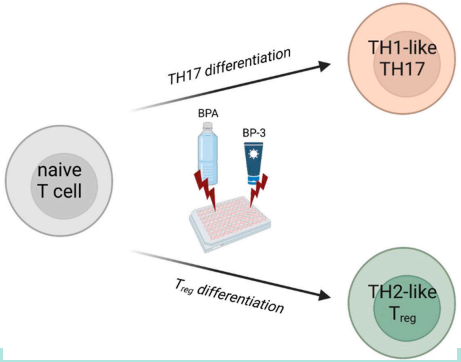
PBMCs

25-multiparameter flow cytometry immunoassay for characterization of immune cell population







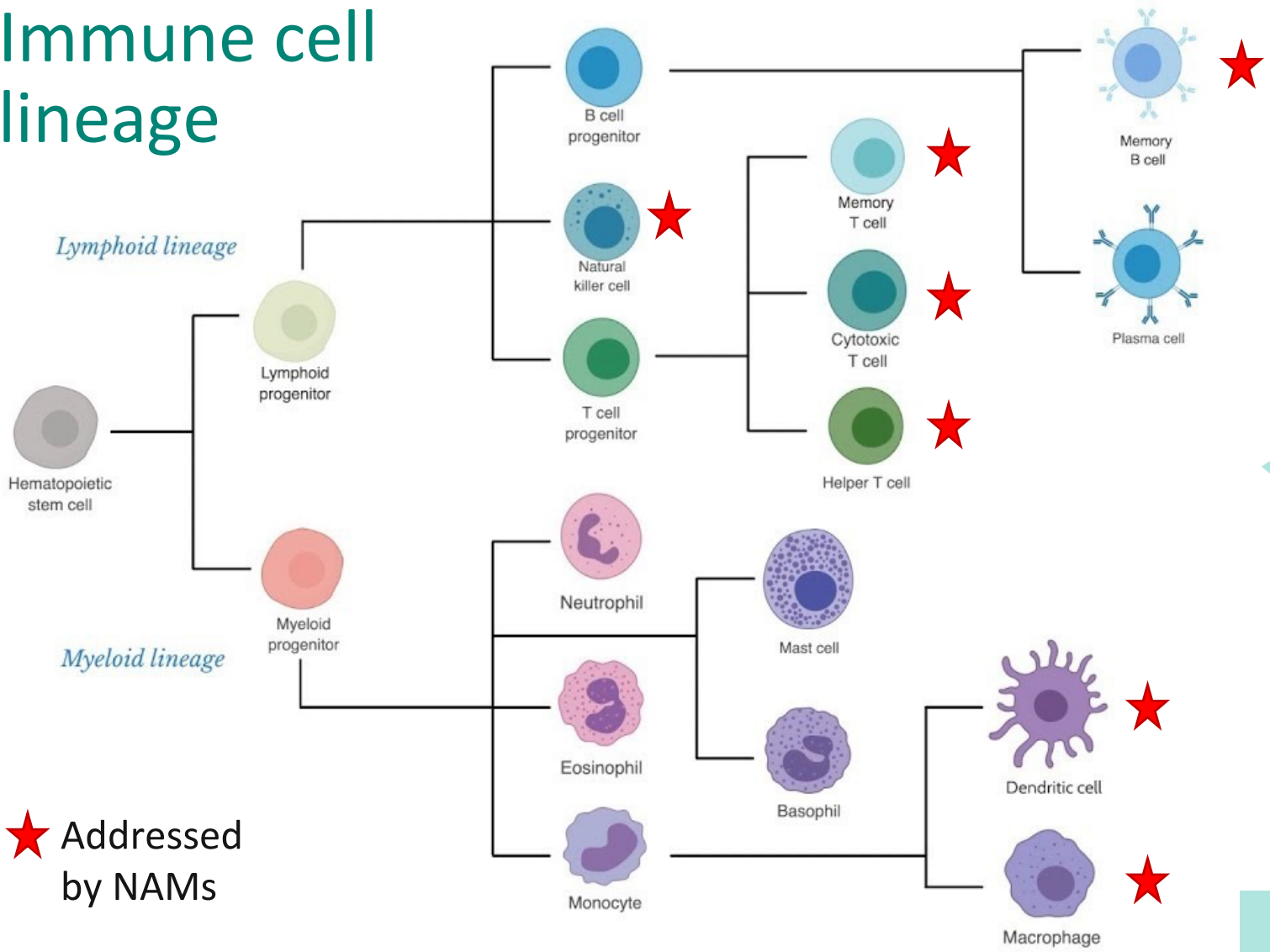


UFZ: Ana Zenclussen

Pierzchalski et al, 2024

Fisher et al, 2024

Immune cell lineage



★ Addressed by NAMs

Impact on:

DIT

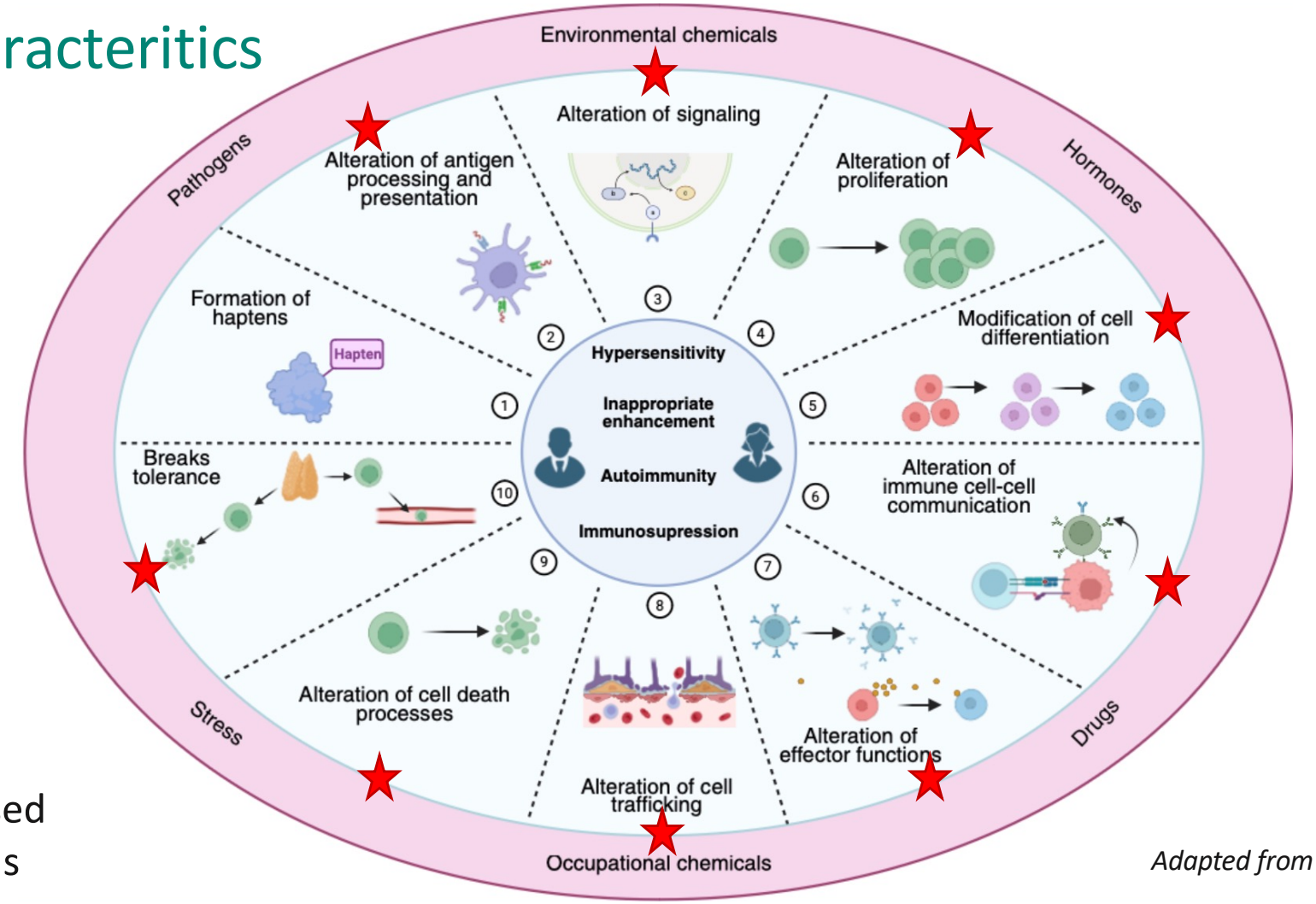
Stem cells

Differentiation

Maturation

Activity

Key characteritics



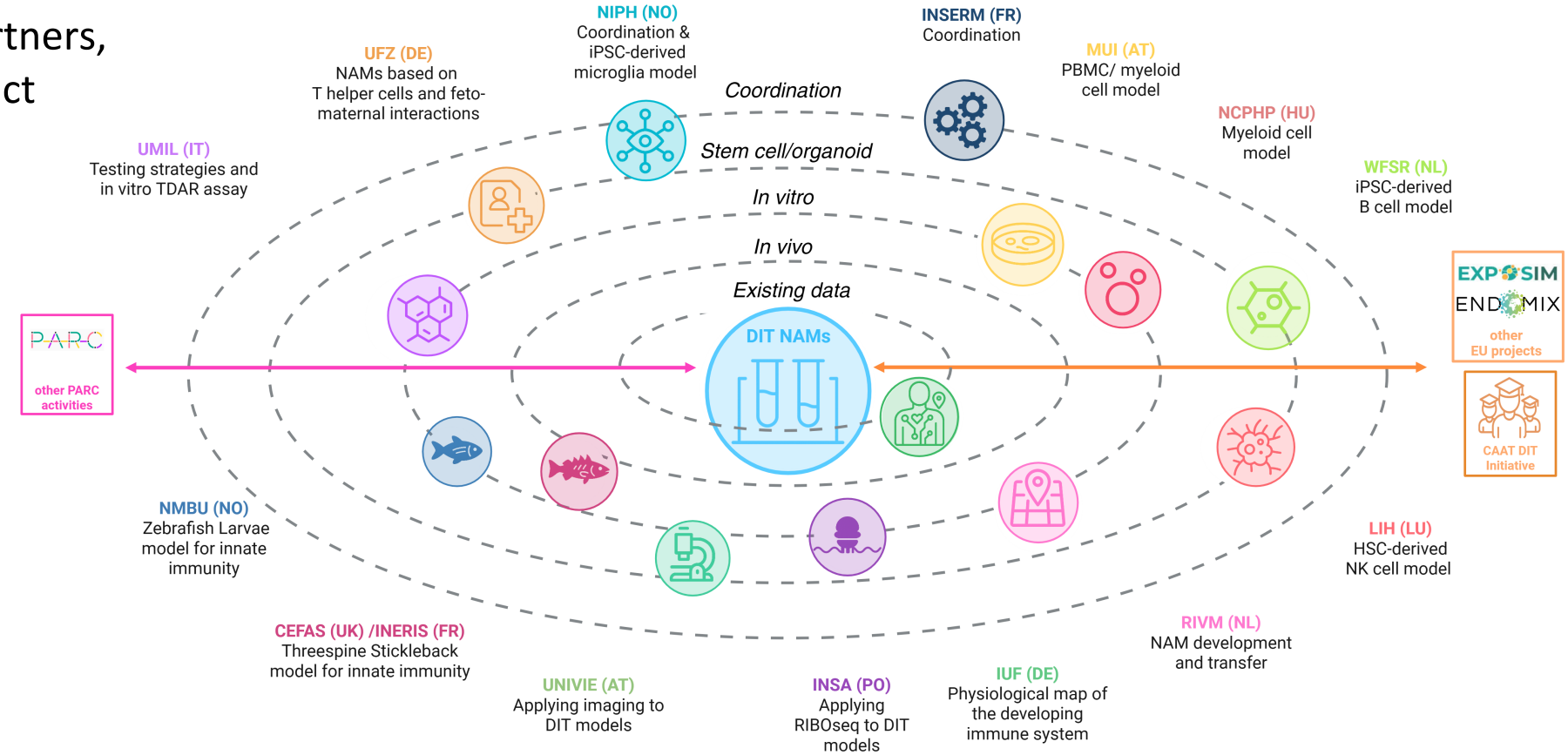
★ Addressed by NAMs

Adapted from Germolec et al., EHP 2022

Developmental immunotoxicology

The KARC document (first 2023, revised annually) stated the need for the assessment method in developmental immunotoxicology

PARC partners,
DIT project



PARC



PARCopedia

Knowledge management and social media platform for the international community of chemical risk assessment professionals created by PARC

It gather scientists and experts from many different disciplines and contexts regarding the risk assessment: method developers, experts in modelling, risk assessors and managers, legislators, policymakers, and specialised media to spark dialogues between them.

Yesterday : 1543 members

Nous

Immunotoxicology Training School

23 – 25th November 2026 (Paris, France)

23.11.2026

Afternoon : **Session 1. Immunotoxicology Mechanisms**
Speakers confirmed: Emanuela Corsini, Philipp Esser, Marc Vocanson, Saadia Kerdine-Römer, Bernard Maillère

24.11.2026

Morning: **Session 2. Regulatory in Immunotoxicology**
Speakers to be confirmed:

Afternoon: **Session 3. NAMs in Immunotoxicology**
Speakers confirmed: Etienne Blanc, Martina Iulini, Ana Zenclussen, Rita Hargitai (and more to be confirmed)

25.11.2026

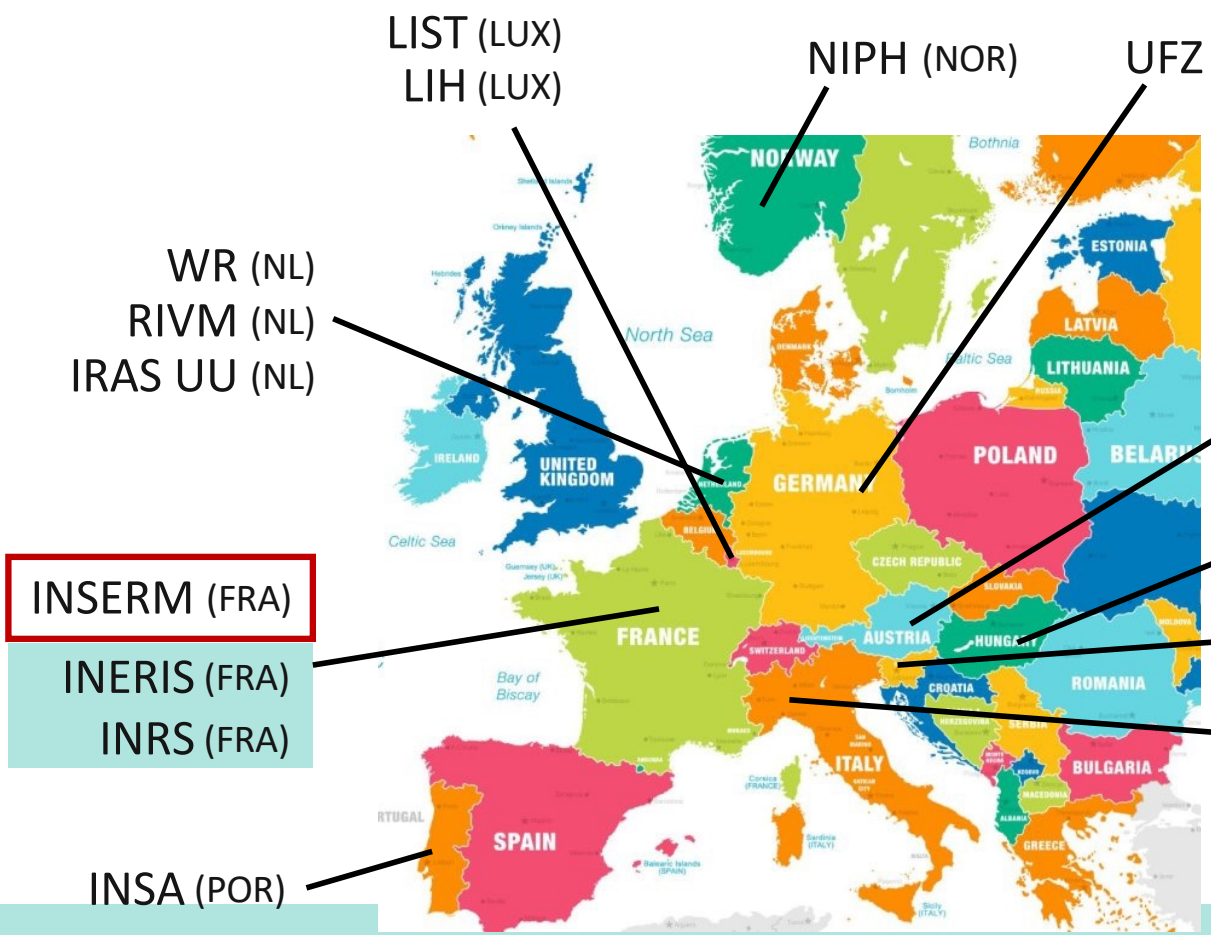
Morning: **Session 4. Oral Presentation by PhD student or post doc**

Website : eu-parc.eu

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Acknowlegment



Université de Rennes

Université Paris Cité

Inserm

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