VU VRIJE UNIVERSITEIT AMSTERDAM

Endocrine Disruption

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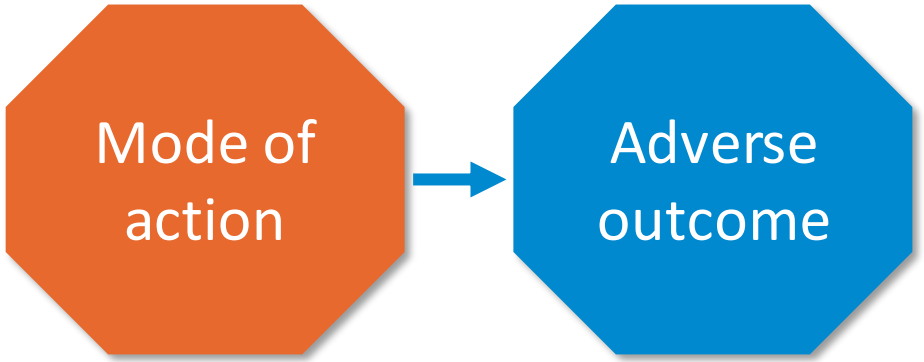
Endocrine disruption (ED)

- Guidance for identification of endocrine disruptors

  EU 2017/2100 and EU 2018/605

- ED criteria



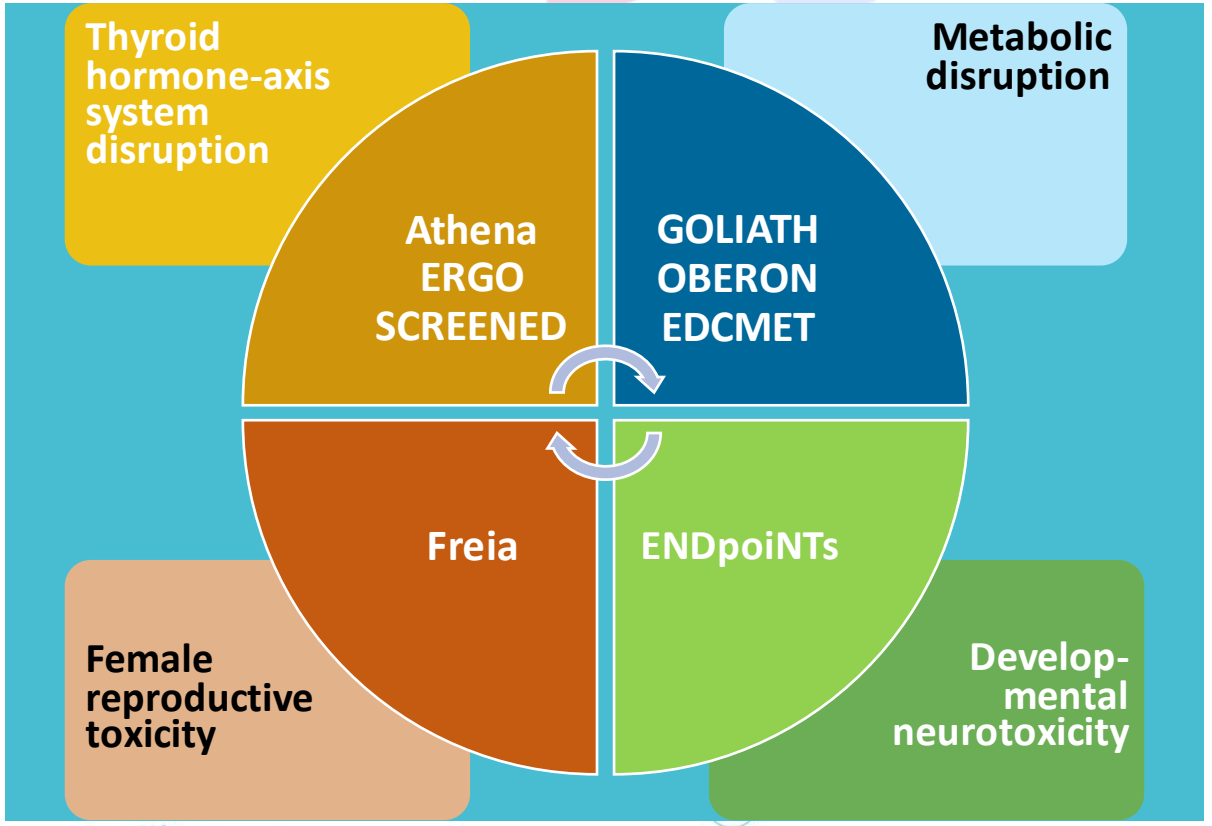
EU 2017/2100, OJ L 301, 17.11.2017

- Weight of evidence approach
- Identification of EDs remains challenging

EURION

European Cluster to Improve Identification of Endocrine Disruptors

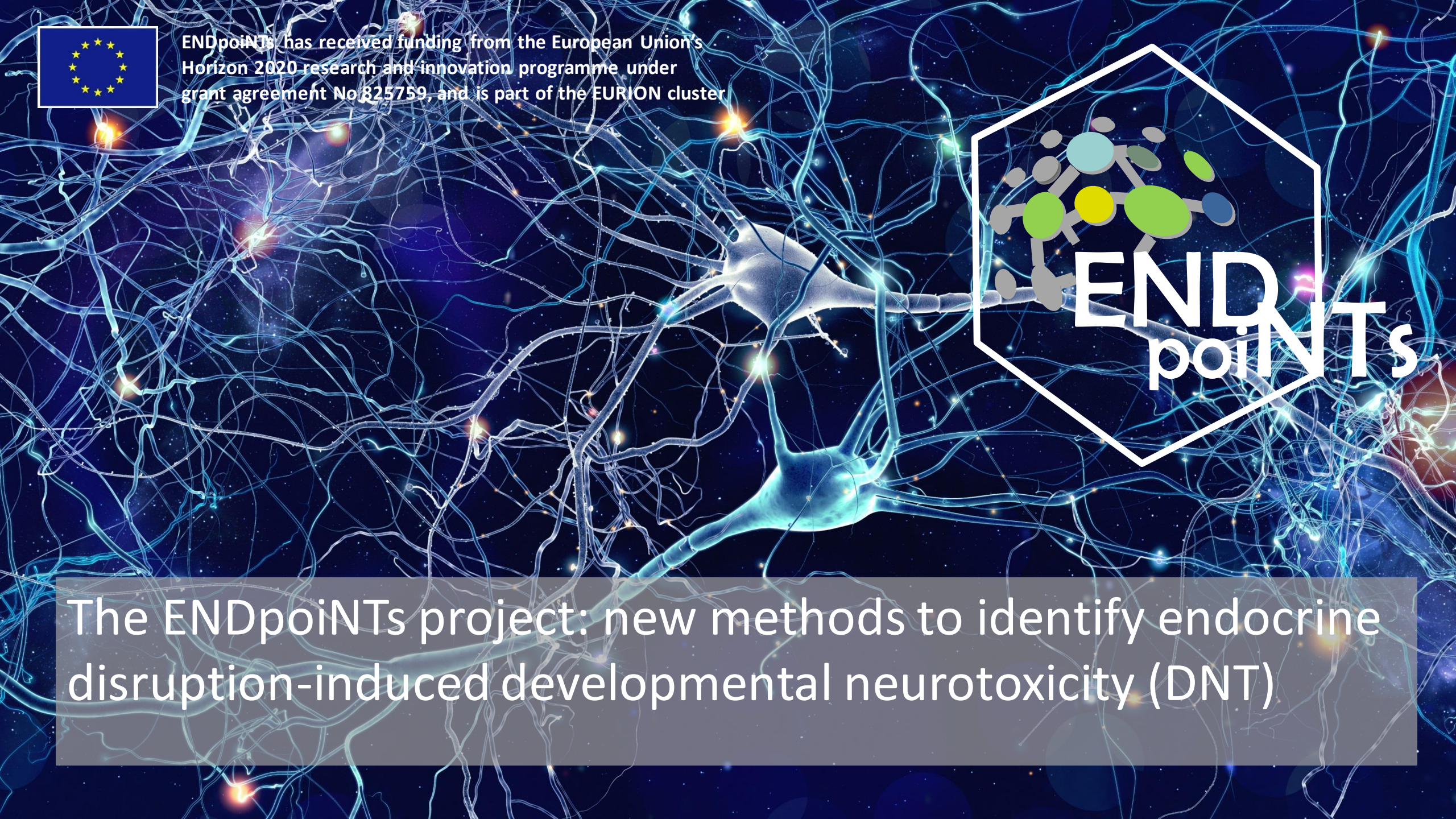
New testing and screening methods to identify endocrine disrupting chemicals



These projects have received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 825161 (ATHENA), No. 825762 (EDCMET), No. 825759 (ENDpoiNTs), No. 825753 (ERGO), No. 825100 (FREIA), No. 825489 (GOLIATH), No. 825745 (SCREENED), No. 825712 (OBERON). This output reflects only the author's view and the European Union cannot be held responsible for any use that may be made of the information contained therein.

@EurionCluster www.eurion-cluster.eu

ENDpoiNTs has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 825759, and is part of the EURION cluster



The ENDpoiNTs project: new methods to identify endocrine disruption-induced developmental neurotoxicity (DNT)

Basis for new methods

Chemical exposure

DNT-relevant molecular key events

DNT-relevant cellular key events

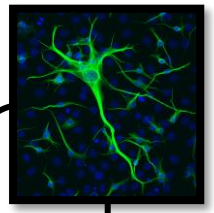
DNT outcomes

In silico

QSARs

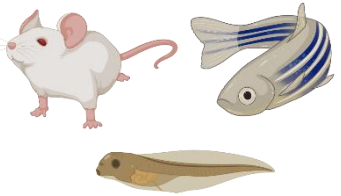
In vitro

***in vitro* assays**



Hormonal involvement on DNT key events

In vivo



Omics integration (Metabolomics, Transcriptomics, Epigenomics)

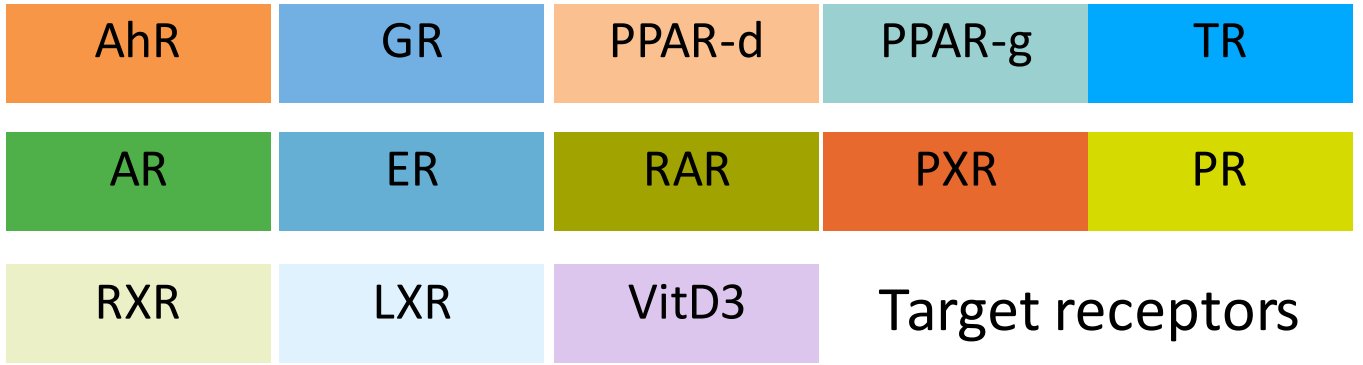
Effects on cognition and behaviour

zebrafish/tadpole assays

OMICs endpoints /biomarkers

In silico predictive models (QSARs)

- *in silico* classification models for **first tier screening** and **molecular initiating events** (MIE) identification
- Models: **21 MIEs involving 13 receptors** associated with endocrine-induced neurodevelopmental effects



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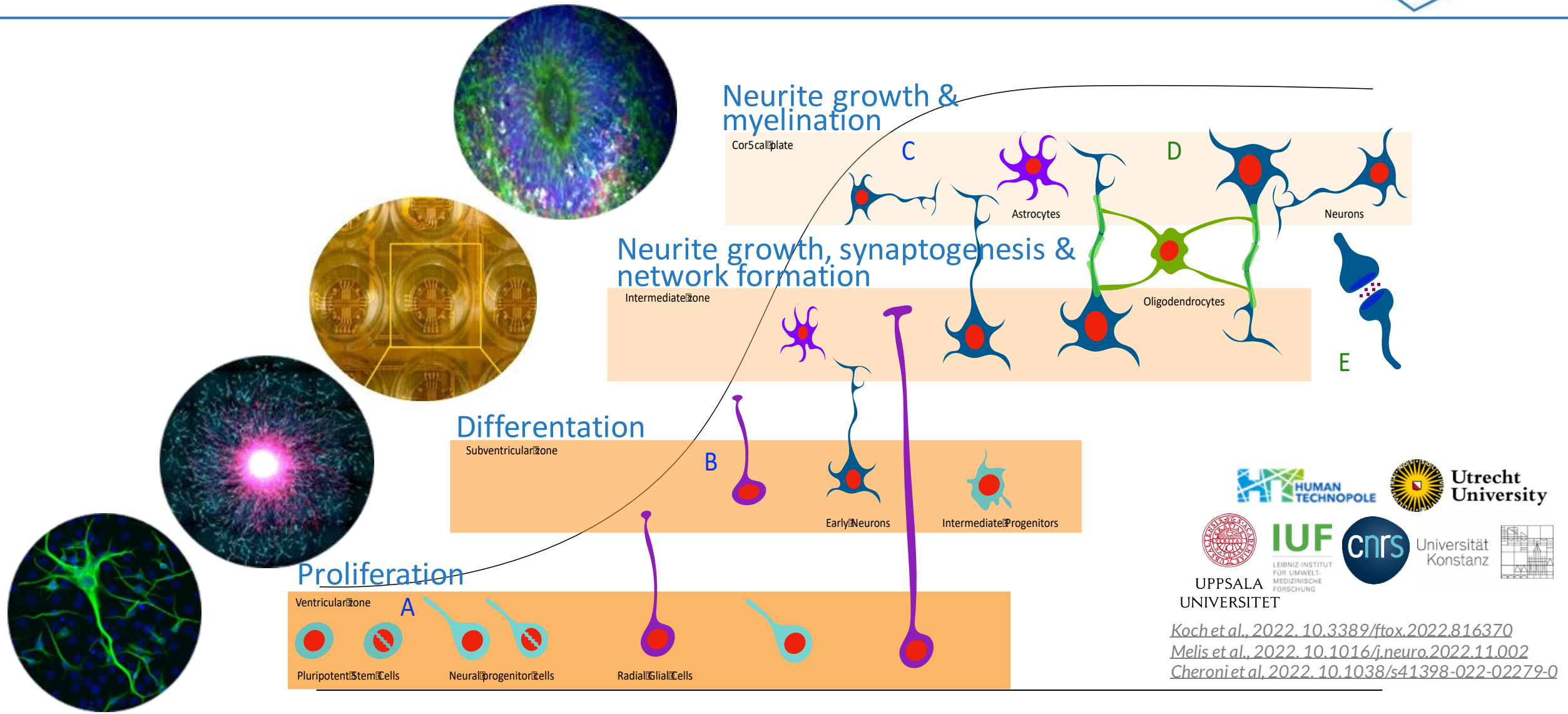
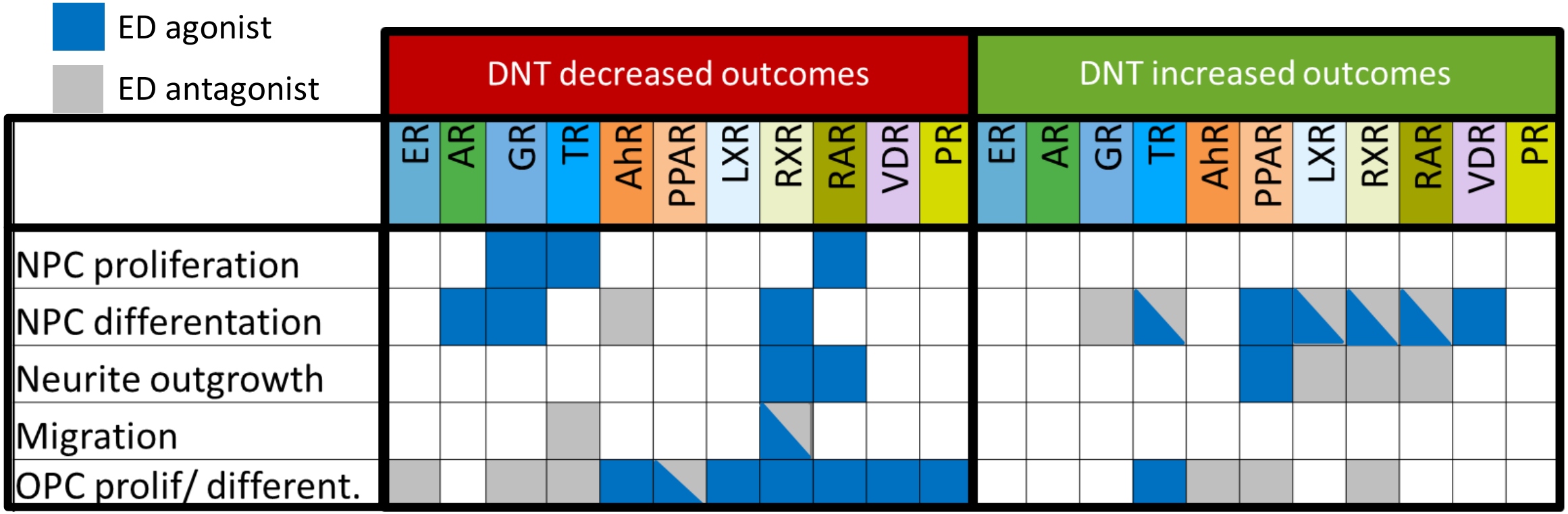
Sapounidou et al., 2023
doi.org/10.1021/acs.chemrestox.2c00267

In vitro screening models: cell lines, primary cells, iPSCs, spheres, organoids



Koch et al., 2022. 10.3389/ftox.2022.816370
Melis et al., 2022. 10.1016/j.neuro.2022.11.002
Cheroni et al, 2022. 10.1038/s41398-022-02279-0

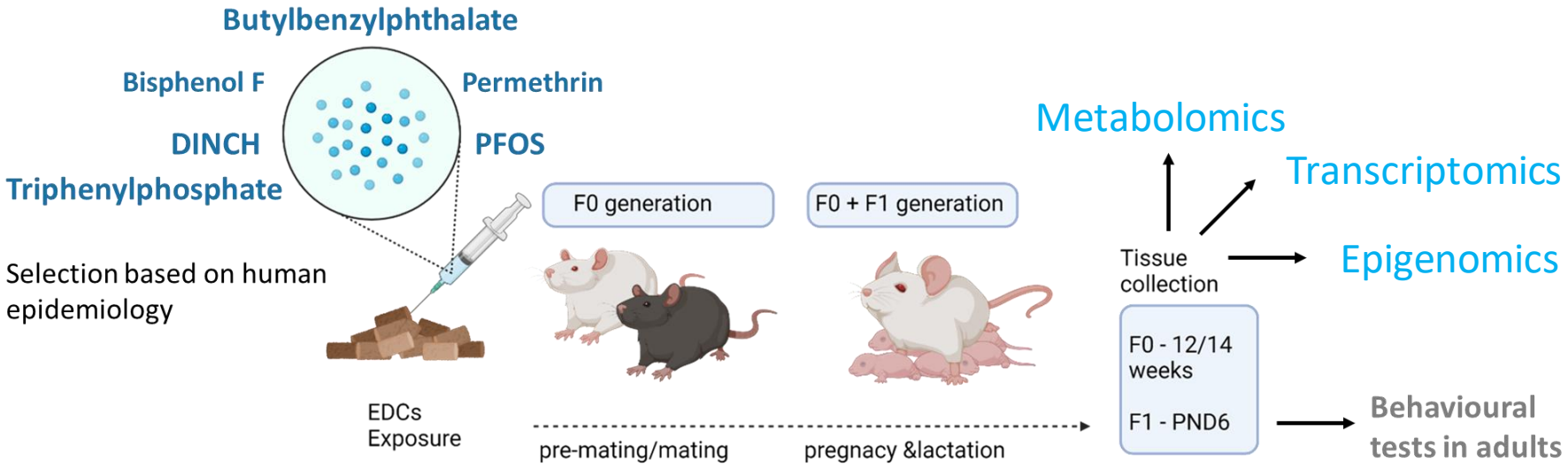
In vitro models: many DNT key events (KE) are regulated by endocrine signalling



NPC: neuronal precursors
OPC: oligodendrocyte precursors

Molecular markers for use in existing TGs

- Molecular markers (omics) with predictive value to identify DNT effects in lower tier TGs (level 4/3)
- To improve existing TG by reducing the length, number of animals, and costs



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GREEN TOX
Group for Reproductive, Endocrine and Environmental Toxicology

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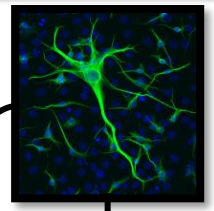
Cognition AOPs – RAR pathway

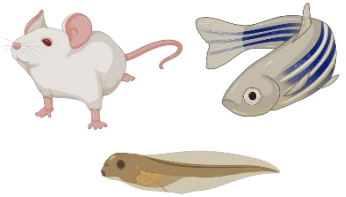
RAR* agonism → Gene expression altered → NPC** proliferation altered → Hippocampal physiology altered → Impairment learning and memory

In silico

In vitro

In vivo





Hormonal involvement on DNT key events

Omics integration (Metabolomics, Transcriptomics, Epigenomics)

Effects on cognition and behaviour

OMICs endpoints /biomarkers

**RAR: retinoic acid receptor* ***NPC: neural precursor cells*

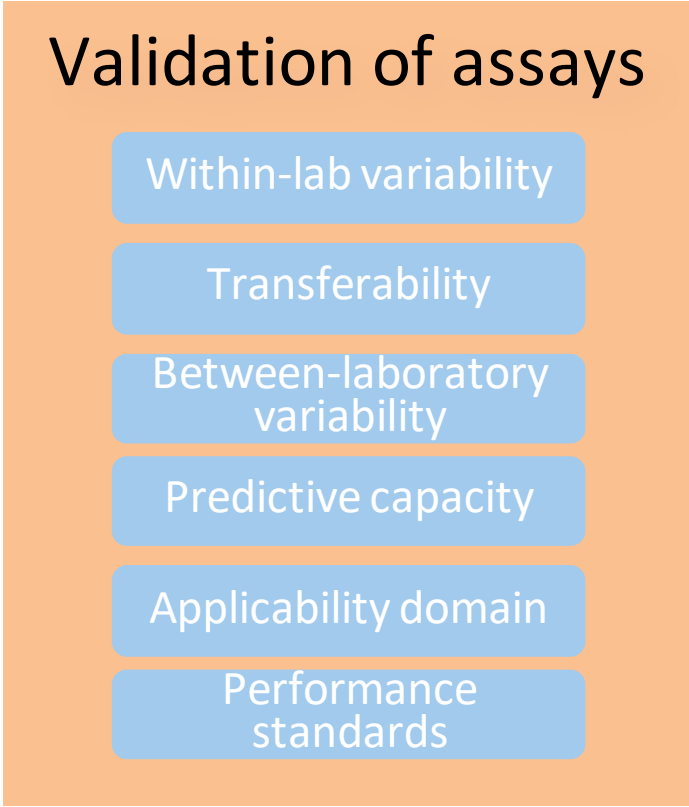
Readiness of ED NAMs

- ✓ **Battery of NAMs** and **new knowledge** on ED systems provided by **EURION projects**
  - *In silico*, *in vitro,* non-mammalian, biomarkers (molecular readouts) for adverse outcomes
- ✓ NAMs and ED criteria
  - Complicated to link endocrine mode of action to an adverse outcome in an **intact organism**
  - NAMs should be part of an AOP

VU

Short and medium term needs

1. **Pre-validation time consuming**
2. **Transferability** often high-end knowledge, lab and equipment needed
3. **Financial resources** are lacking to perform pre-validation



Medium-long term needs

1. Time consuming from NAM development to OECD guideline
2. Regulatory need: interpretation of “omics” readouts
3. Fill scientific knowledge gaps in understanding EDC effects to support more effective and evidence-based regulation of chemicals at the EU level
   - Interaction between ED systems
   - Sensitive windows of susceptibility
   - Mixtures of EDCs

Policy changes to move NAM

1. How to speed up the process from NAM development to OECD guideline?
2. Initiate more platforms for pre-validation of NAMs
   - such as PEPPER (platform for the pre-validation of testing methods on endocrine disruptors)
3. Increased use of data from non-TG studies

Thank you!

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www: https://endpoints.eu/

Twitter: @ENDpoiNTs_EU

YouTube: https://www.youtube.com/channel/UC-7hPA8eVthZ4ZgICeDj0nw

https://eurion-cluster.eu/