Immunotoxicity from a regulatory perspective – challenges and opportunities

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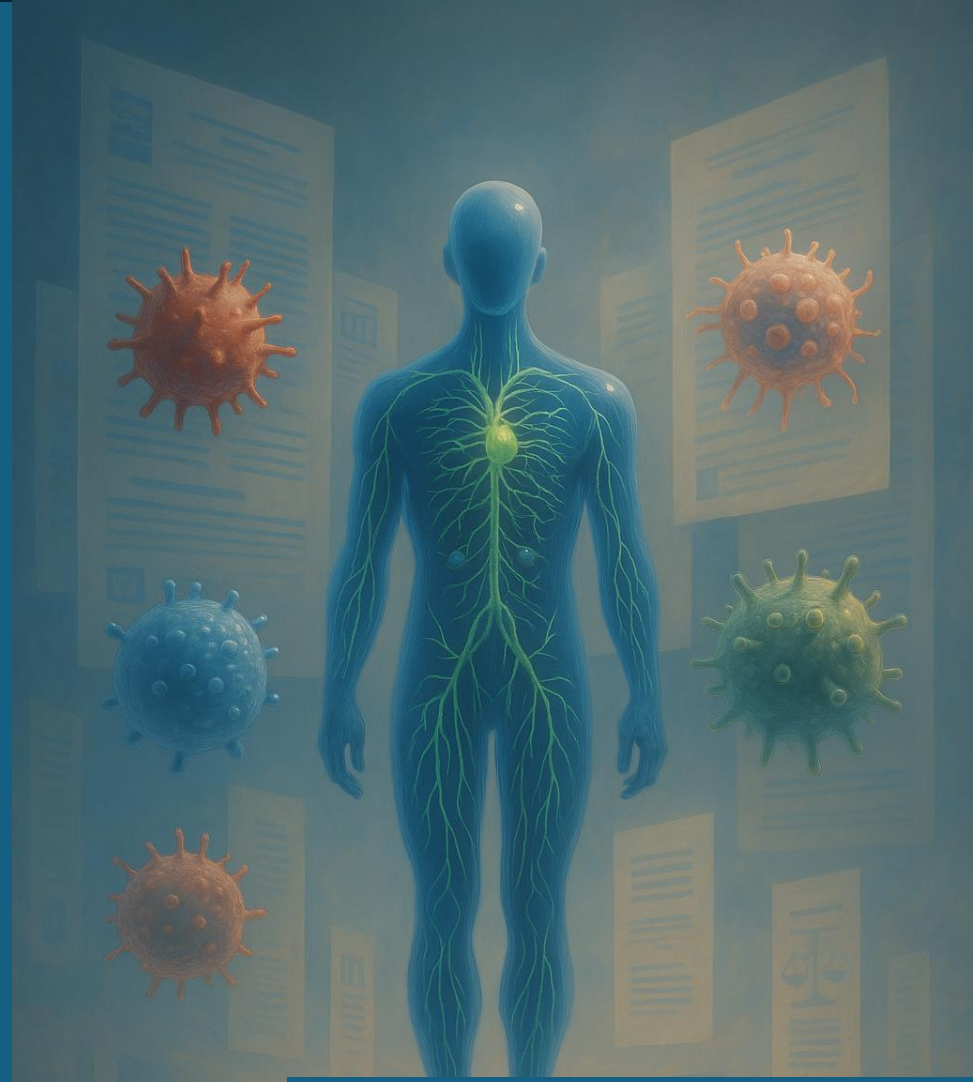
ECETOC Workshop Immunotoxicity assessment:
Addressing Challenges and Advancing Methodologies

July 9, 2025



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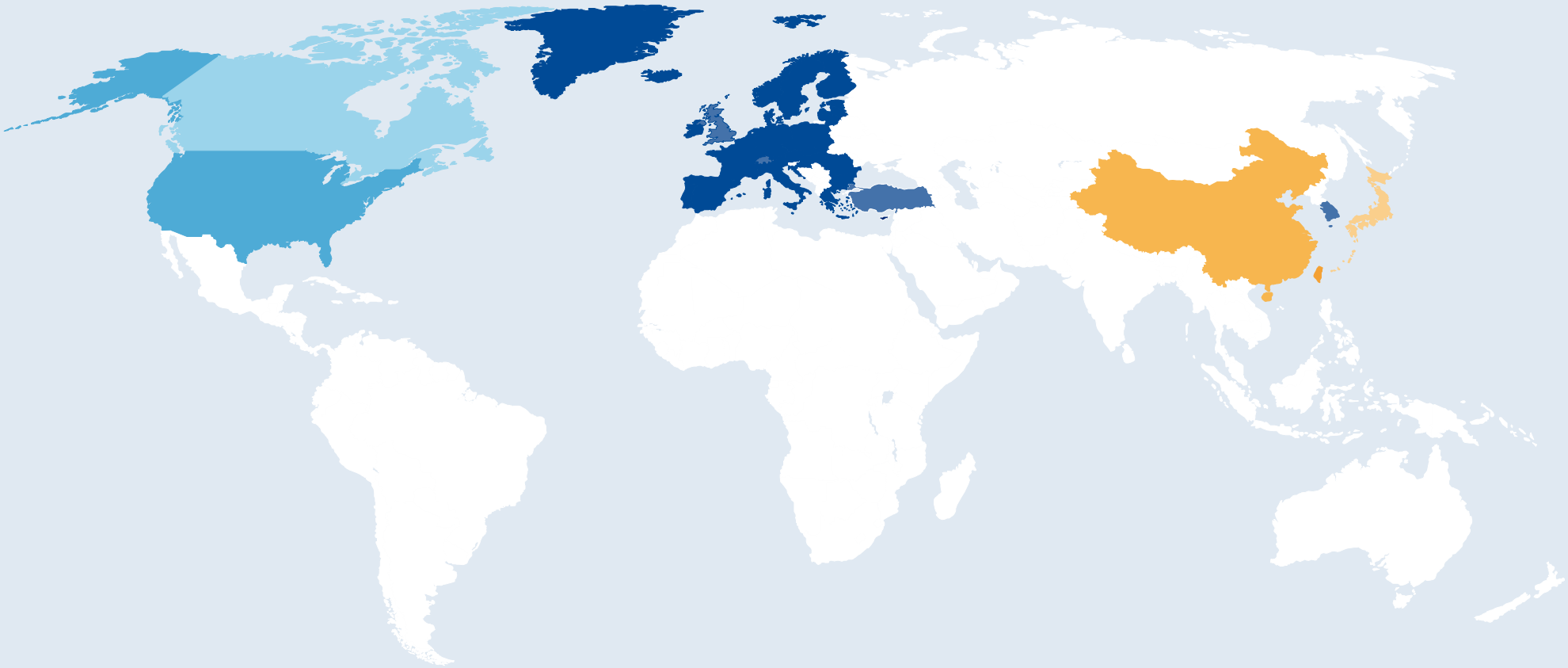
Agenda

1. Global regulatory landscape
2. Immunotoxicity
3. Available OECD guidelines for immunotoxicity
4. Challenges
5. Opportunities

Global regulatory landscape



Selection of chemical regulations in force

- REACH (EU)
- REACH-like Regulations (e.g. UK, K-REACH)
- CEPA (Canada)
- TSCA (USA)
- CSCL (Japan)
- TCCSCA (Taiwan)
- China REACH

Global regulatory landscape

Chemicals

- Wide range of chemical substances

Pharmaceutical products

- Active ingredients
- Excipients / formulation aids

Drinking water

- Materials in contact with drinking water

Agrochemicals

- Active ingredients

Food / Feed / Food contact

- Food additives
- Feed additives
- Materials with food contact

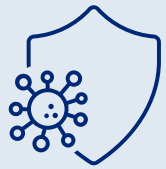
Pictures were in part generated using AI

Immunotoxicity

Non-physiological influencing factor

- Pathogens
- Stress
- Hormones
- Chemical substances

Multiple modes of action

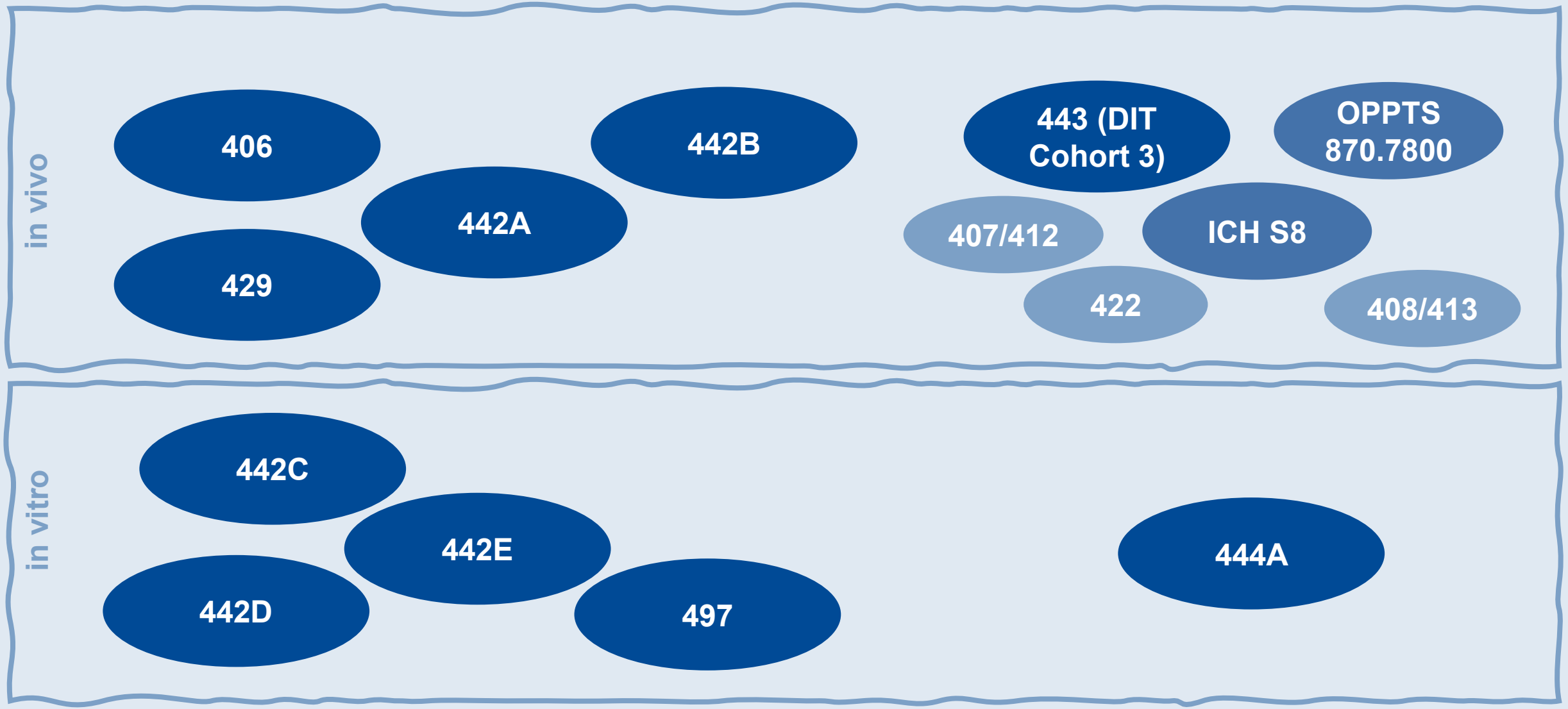


Immune system

Adverse outcome

- Immunosuppression
- Hypersensitivity
- Inappropriate Enhancement
- Autoimmunity

Available OECD Guidelines



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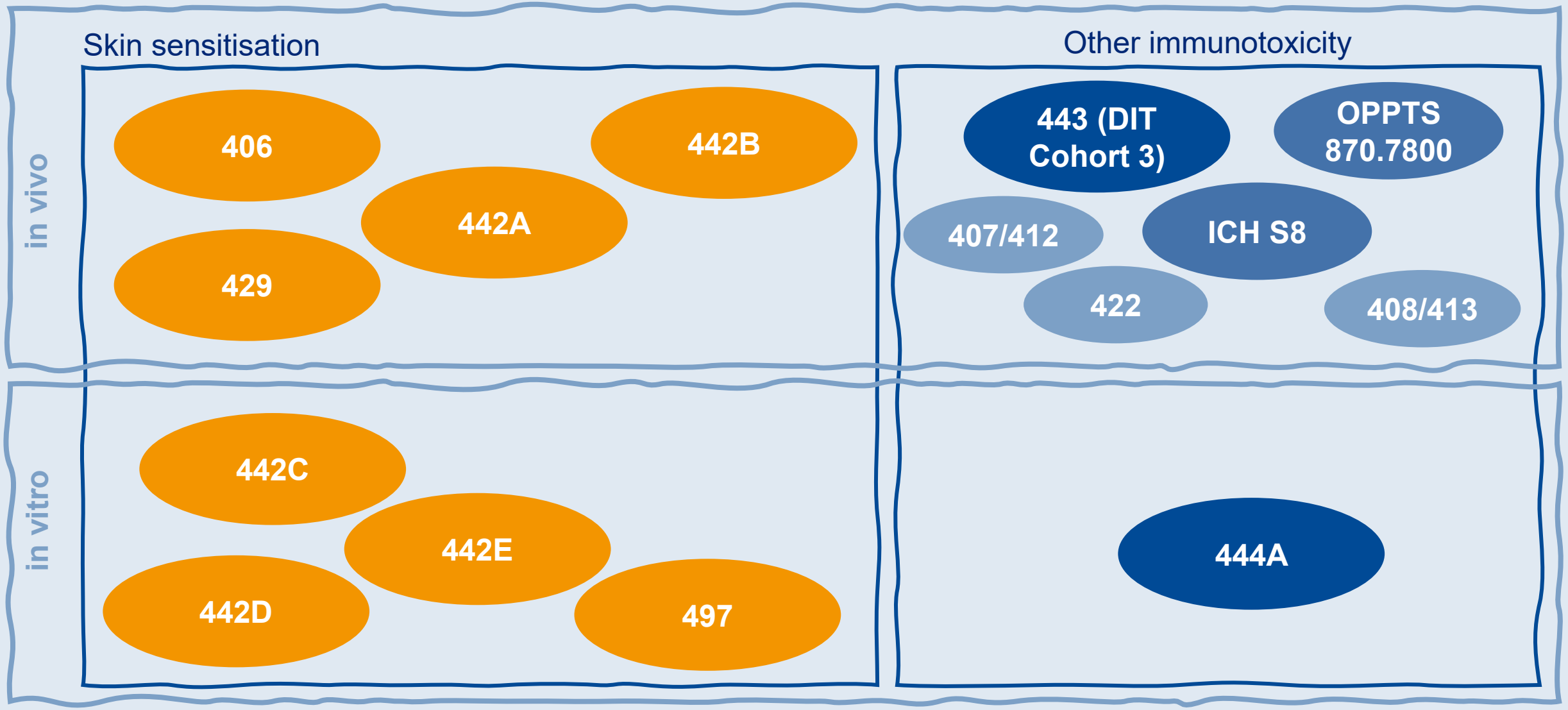
Hypersensitivity



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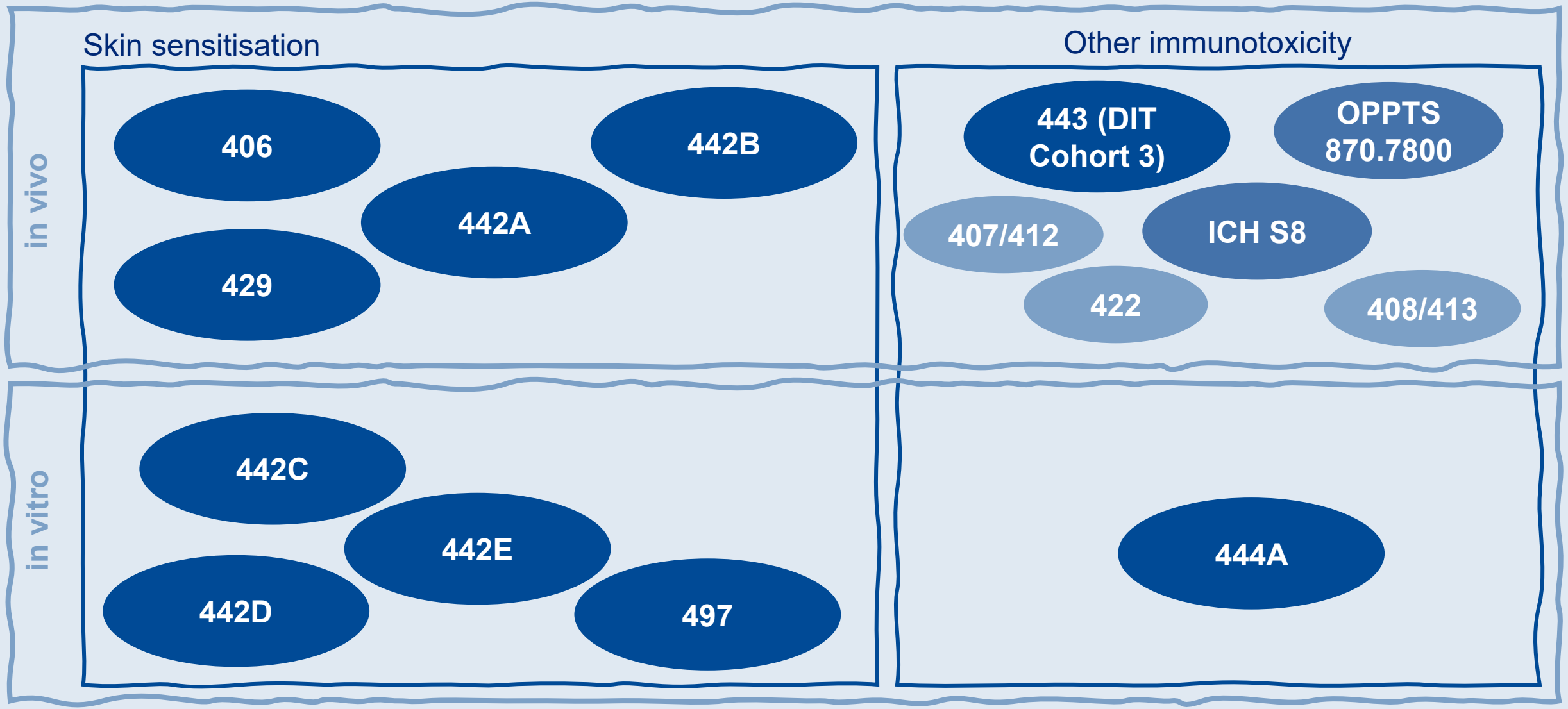
Respiratory sensitisation



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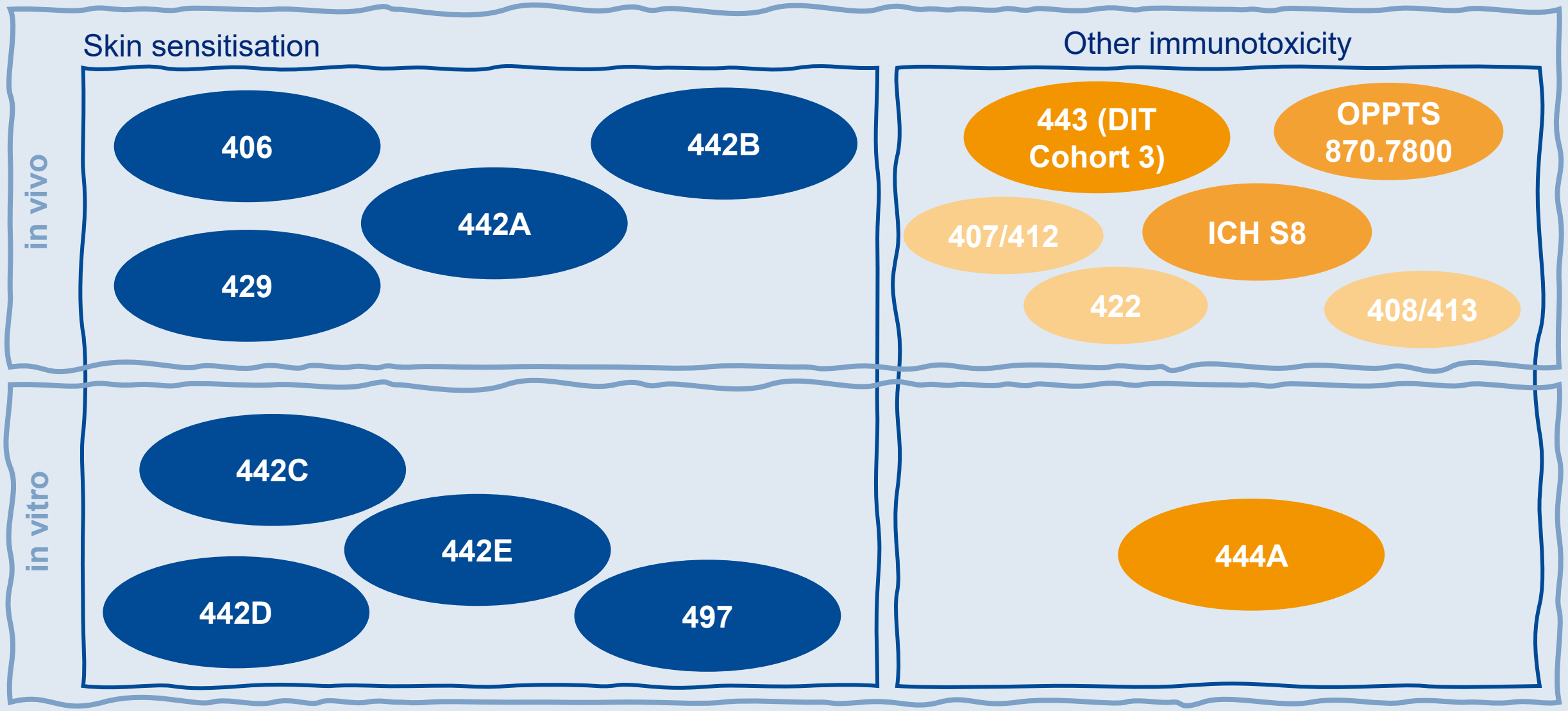
Immunosuppression



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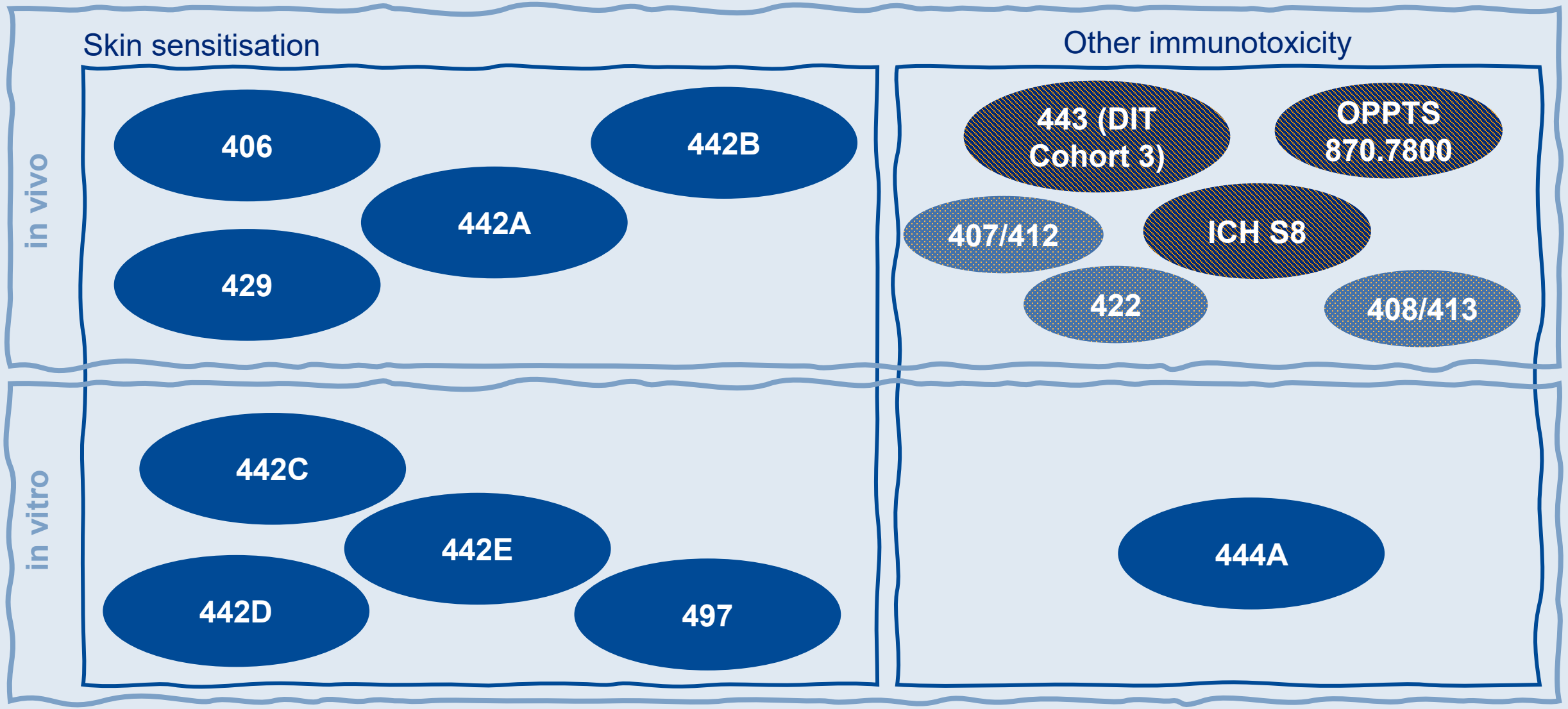
Immunostimulation



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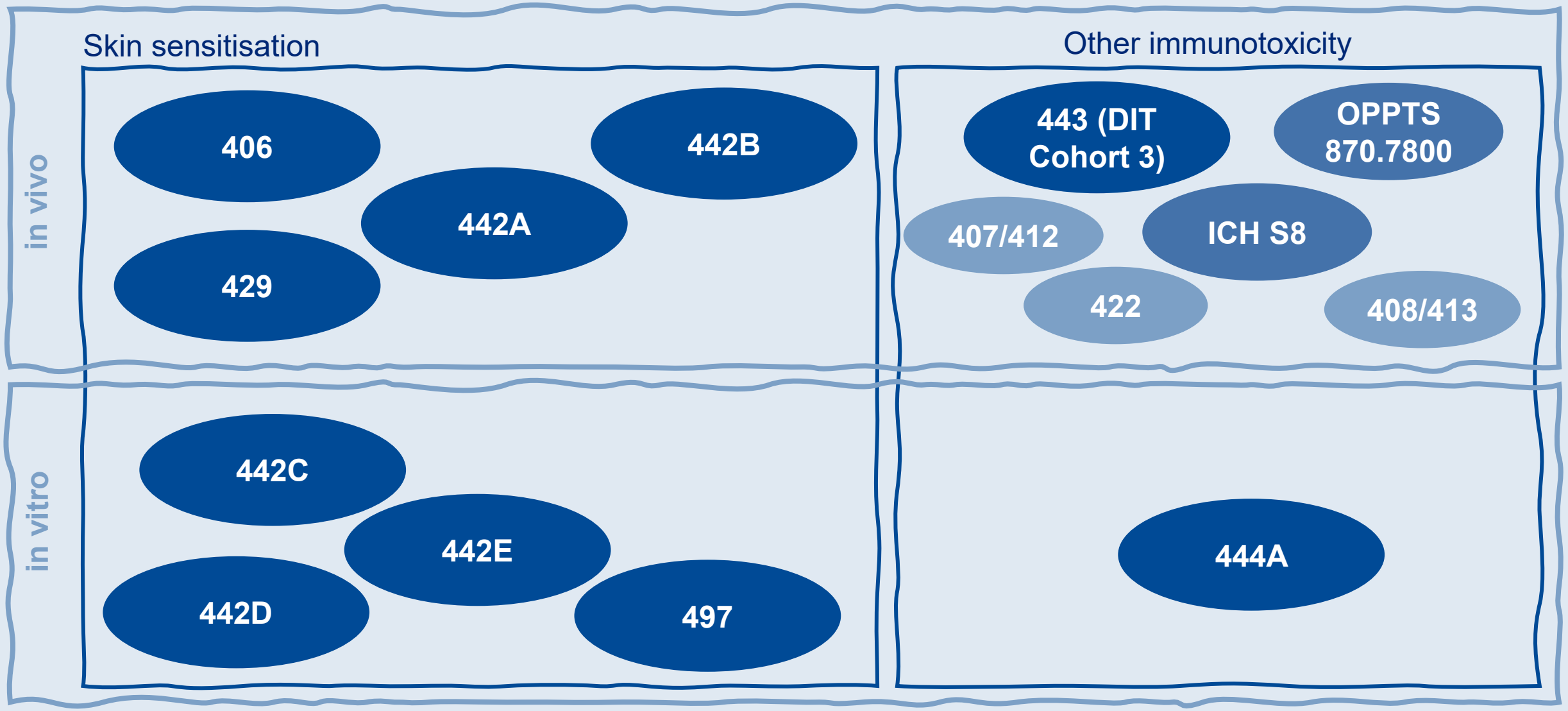
Autoimmunity



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Regulatory triggers for immunotoxicity testing

- Triggers for functional immunotoxicity testing:

		Regulatory framework		
		EU REACH	ICH S8	40 CFR Part 158
Trigger	Hematology	x	x	x
	Clinical chemistry	x	(x)	(x)
	(Immune) Organs: weights and/or histopathology	x	x	x
	Hormonal changes	x		
	Related substances	x		x
	(Respiratory) Sensitisation	(x)		
	Other information	x	x	

Based on: ECHA Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.7a: Endpoint specific guidance (2017, DOI: 10.2823/337352)
ICH Topic S 8 Immunotoxicity Studies for Human Pharmaceuticals, CHMP/167235/2004 (2006)
US EPA 40 CFR Part 158 Toxicology Data requirements (Link: US EPA - Part 158 Toxicology Data Requirements)

Immunotoxicity – Regulatory consequences

- Assessment of available data:
  - No concern → no further actions required
  - Some concern, but clarification required → additional data needed/requested
  - Evidence is conclusive and sufficient to conclude as immunotoxic (i.e., biologically relevant functional changes, not secondary to systemic toxicity, relevant to humans) → hazard classification and risk assessment

(Developmental) Immunotoxicity – Regulatory consequences

- Hazard classification:
  - Immunotoxicity – covered in GHS under Specific Target Organ Toxicity (STOT (Immune System))
  - Developmental Immunotoxicity – covered in GHS under Developmental Toxicity

- Developmental Toxicity may lead to identification as Substance of Very High Concern (SVHC)
  - Inclusion in candidate list with immediate obligations for suppliers
  - Restriction/authorization
  - Immediate consequences for use

Challenges in immunotoxicity assessment (regulatory perspective)

- Triggers for further testing based on data available from subacute and/or subchronic studies
- Triggers for further testing unspecific, adversity often unclear
- Tiered approach system to immunotoxicity is lacking
- Only OECD Guideline testing method available to assess functional immunotoxicity in vivo is OECD 443 (Cohort 3)
- Distinguish immunotoxicity from developmental immunotoxicity – specific challenge regarding OECD 443

Challenges in immunotoxicity assessment (regulatory perspective)

- Data interpretation and understanding of adversity in immunotoxicity may differ between regulations and regions
- Differences in approaches to testing or testing protocols
- challenge for OSOA (one substance – one assessment) principle
- Example: Bisphenol A and EFSA‘s derivation of TDI
  - Use of apical vs. intermediate effects for assessment
  - Adversity in immunotoxicity
  - Diverging assessments between EFSA, EMA and BfR

Based on: EFSA CEP Panel, Re-evaluation of the risks to public health related to thepresence of bisphenol A (BPA) in foodstuffs (2023), doi: 10.2903/j.efsa.2023.6857
Report on diverging views between EFSA and BfR on EFSA updated bisphenol A assessment (Link)
Report on divergent opinion between EFSA and EMA on bisphenol-A_final adopted, EMA/150385/2023

Opportunities in immunotoxicity assessment (regulatory perspective)

- Harmonized approaches to (tiered) immunotoxicity testing needed
- Development of NAMs to support immunotoxicity assessment
  - Targeted approaches to different aspects of immunotoxicity
  - Validated and reproducible methods with regulatory acceptance
  - Understanding of applicability domains, biological relevance and human relevance
- Assessment strategies for immunotoxicity including
  - Existing data
  - NAMs
  - Focus on biological relevance of functional changes
  - Assessment of human relevance

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