

# Toxicology at LEO Pharma

**Klaus A. Rytved, Principal scientist**

Safety and Lab Animal Research  
Research & Early Development  
Global R&D

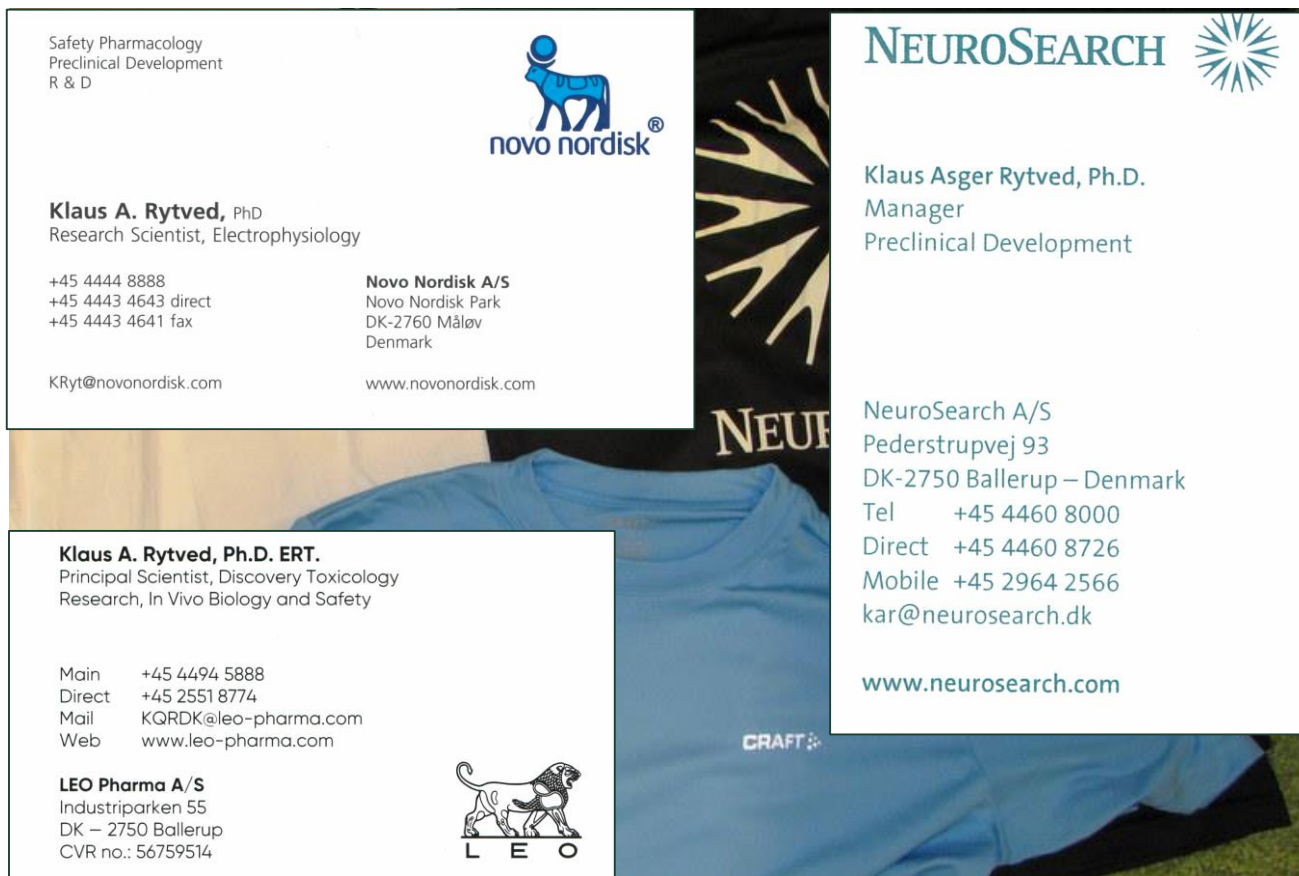
April 25, 2022

Dermatology  
beyond the skin



# Toxicology at LEO Pharma

Mainly small molecule toxicology



**Safety Pharmacology**  
Preclinical Development  
R & D




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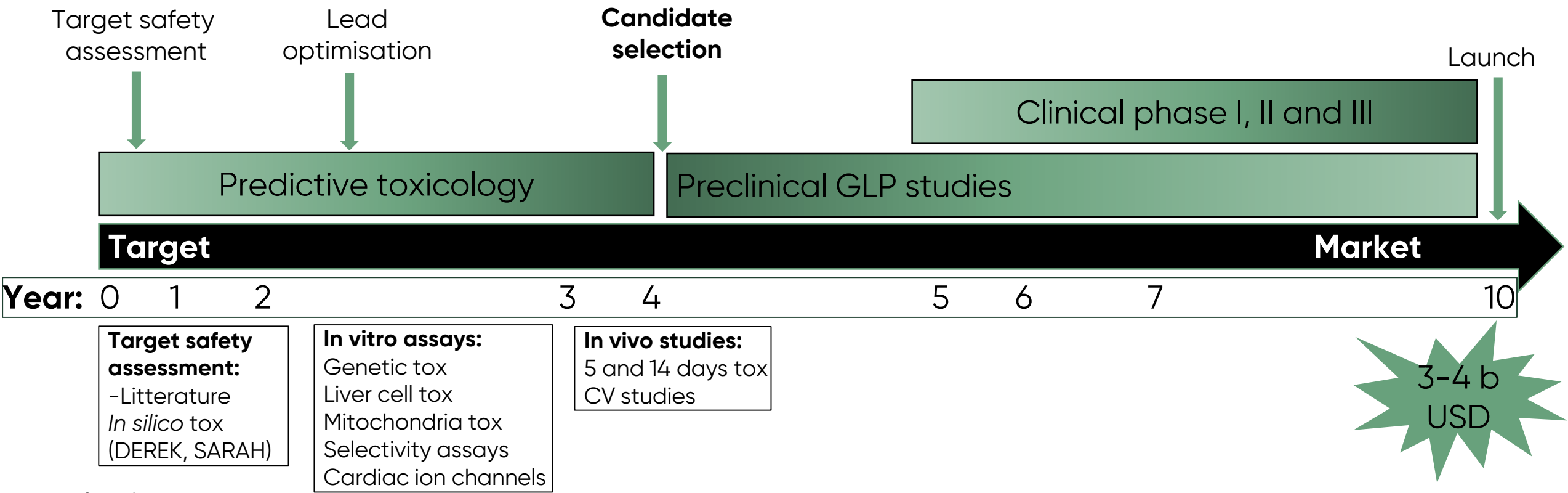


**LEO Pharma A/S**  
Industriparken 55  
DK – 2750 Ballerup  
CVR no.: 56759514

- **A team of 3 predictive toxicologist**
  - Janne Koch, DVM, PhD. Manager
  - Mikael Egebjerg, cand pharm, PhD, ERT.
  - Klaus Rytved, cand scient, Ph.D, ERT
- **Predictive toxicology (non-GLP)**
  - Identify safety risks early “Fail early-fail cheap”
  - Guide of medicinal chemistry by screening and de-selection of molecules.
  - Selects the development candidate



# From target to market



**Target safety assessment:**  
 -Literature  
*In silico* tox  
 (DEREK, SARAH)

**In vitro assays:**  
 Genetic tox  
 Liver cell tox  
 Mitochondria tox  
 Selectivity assays  
 Cardiac ion channels

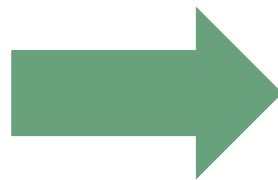
**In vivo studies:**  
 5 and 14 days tox  
 CV studies



# Prediction of safety risks

## Limitations in predictive tox:

- Very limited amounts of test compound.
- But - many different compounds.
- Fast turnaround needed to support MedChem design



Downscaling !

# Ames test

"Classic" AMES full plate:  
500-1000 mg

"mini AMES" microplate format

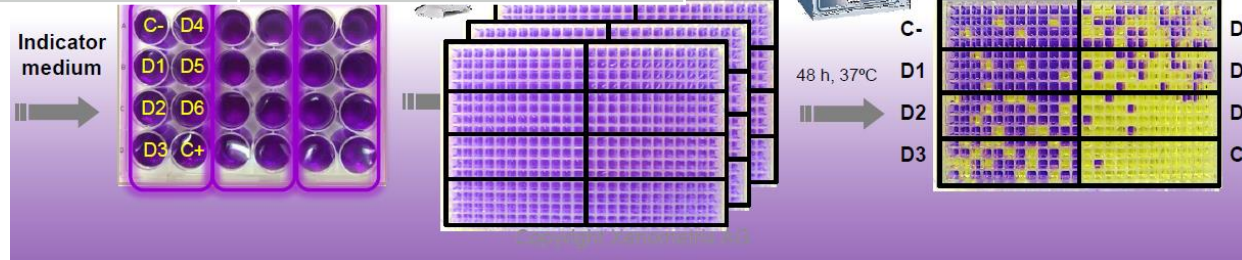
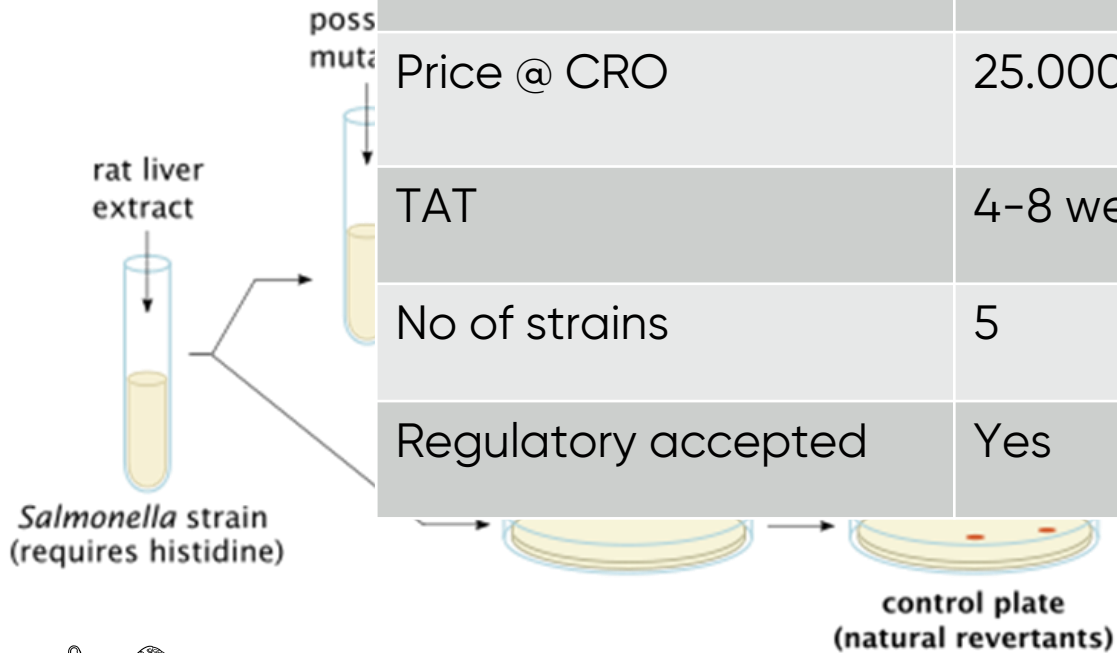
	Regulatory compliant AMES test	Mini AMES MPF (screening)
Compound requirement	500-1000 mg	6 mg/strain
Price @ CRO	25.000 DKK	12- 18.000 DKK
TAT	4-8 weeks	3-4 weeks
No of strains	5	2-3
Regulatory accepted	Yes	No

**Microplate Assay**

**Exposure cultures**  
 replicates 1 replicates 2 replicates 3

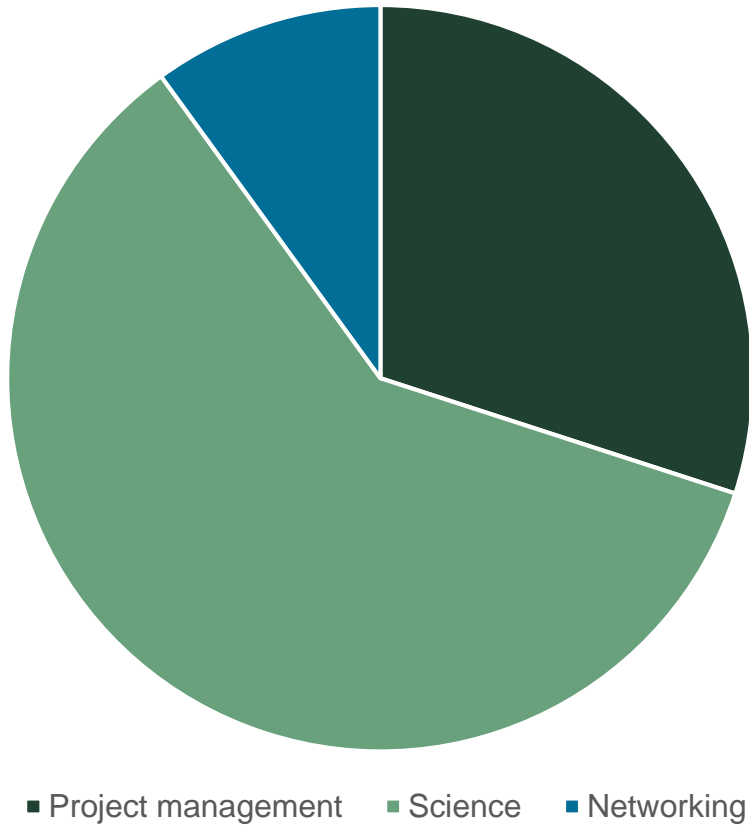
C-	D4	C-	D4	C-	D4
D1	D5	D1	D5	D1	D5
D2	D6	D2	D6	D2	D6
D3	C+	D3	C+	D3	C+

37°C, 90 min, 250 rpm  
(20 min E.coli +S9)



# Summary

Working as a toxicologist in a private pharma company is a diverse task requiring skills as a:



- Scientist
  - Design, monitor, interpret and present tox studies
  - Collaborate with other disciplines: MedChem, DMPK/ ADME, formulation, research informatics
- Project manager:
  - Coordinate activities, booking studies at CROs, logistics and shipping expert.
- Networker:
  - Align with regulatory toxicologist. ICH Guidelines.
  - Keep in touch with CROs, colleagues from other companies, attend conferences etc