Early genotoxicity screening of pharmaceutical candidates: Adaptive approaches and strategies to screening

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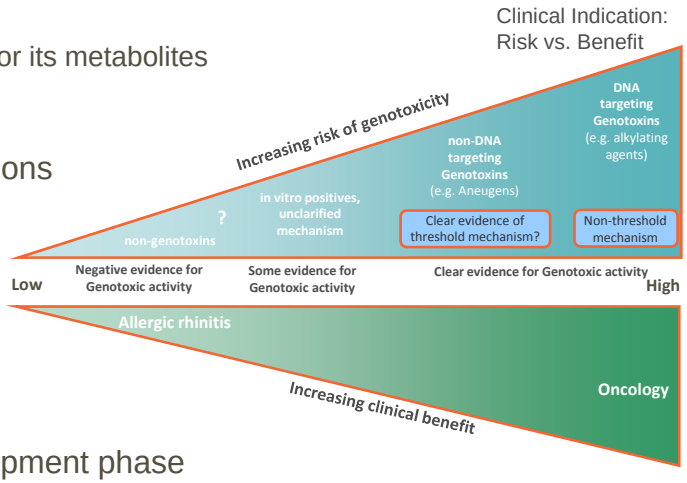
Genotoxicity

- Genotoxicity is the study of the ability of chemicals to cause heritable or somatic genetic defects in humans
- Genotoxicity can be
  - DNA damage, mutagenicity, clastogenicity, aneugenicity induced by a chemical or its metabolites
- **Why conduct Genotoxicity Testing?**
  - Evidence of genotoxicity/mutagenicity is pivotal no-go for many indications
  - Parent genotoxicity testing essential in drug development
  - Regulatory requirements (ICH S2 (R1)) drive the Genotoxicity Screening Strategy
  - **Regulatory** requirement prior to FTIH trials
- Discharges risk of **genotoxic carcinogenesis early** in pre-clinical development phase
- The **earlier** the genotoxicity flag, the **better**:
  - **De-risks** a compound's development

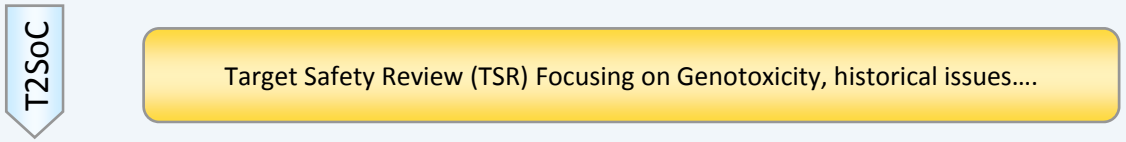


Genetic Toxicology and Photosafety (GTP)

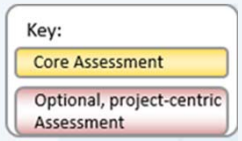
Genetic Toxicology Discovery Support (DS) team

- A core team which focuses on proactive engagement with drug discovery partners to address shift in early screening, providing tailored project support and problem solving
- Core team of individuals aligned to specific Therapy Discovery/Research groups to enhance customer focus and provide a clear line of sight to the screening group
- Toolkit of assays that can be applied from lead discovery to pre-candidate profiling and beyond
- Promote positive attrition/additional testing when a genotoxic liability is identified and bespoke programs can be tailored for specific project needs

Core Genotoxicity Screening Cascade



- TSRs:
  - Identify potential safety hazards and recommend strategies for evaluating these in preclinical studies
  - Are a key tool for programme teams and assists in the smart and timely progression of quality targets and compounds
  - Assess the target and function, associated toxicities, off-target profiling also (e.g. Proteomics, Kinase pathways), considers previous experience, published data and provides recommendations



Core Genotoxicity Screening Cascade

T2SoC

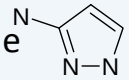
SoC2CS

Target Safety Review (TSR) Focusing on Genotoxicity, historical issues….

in silico SAR (DEREK fW, Leadscope, eHOMO) by Computational Tox

Potential liability identified

project-centric Ames screening for SAR

- SAR - work in collaboration with Computational Tox and the project team to identify genotoxic liabilities of individual compounds, chemical series or specific targets assessed early in Discovery
- Add value - can terminate development, promote additional early testing or provide confidence for continued development.
- Targeted early testing based on structure/class e.g.
  - Aromatic amine (pyrazole amine 

) like substructures are tested in the Ames test initially in strains TA98/TA100 +S9
  - HDAC, MEK classes are known to generate positive invivo Genotox endpoints

Key:
Core Assessment
Optional, project-centric Assessment

Core Genotoxicity Screening Cascade

T2SoC

SoC2CS

Target Safety Review (TSR) Focusing on Genotoxicity, historical issues….

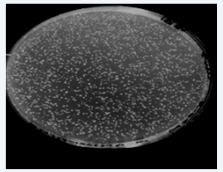
in silico SAR (DEREK fW, Leadscope, eHOMO) by Computational Tox

Pivotal Mini Ames Screen (bacterial mutagenicity)

liability identified

Potential liability identified

project-centric Ames screening for SAR



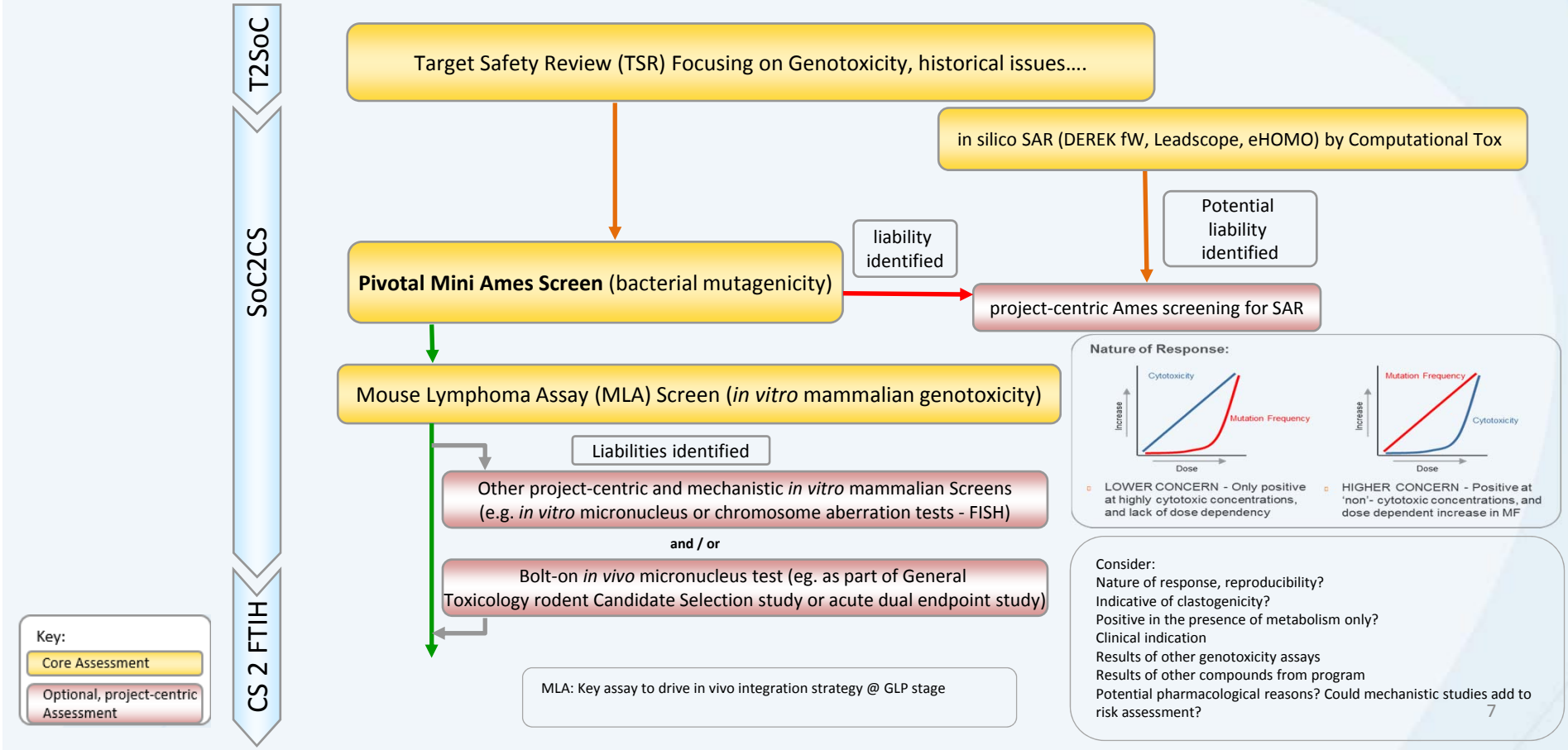
- Bacterial mutagenicity test +/- S9-mix (i.e. the Ames test)
- The 'Gold Standard' assay
- Highly correlated with the outcome of rodent bioassays
- A regulatory required assay prior to FTIH (ICH S2 R1). A cut-down version of the assay is used to assess for mutagenicity prior to candidate selection
- For new chemical classes/series certain strains are initially selected (e.g. TA98 and TA100 +/-S9) and other strains backfilled based on negative results
- Positive results usually triggers screening of further exemplars to understand liabilities
- Positive finding is often a No-Go decision point

Key:

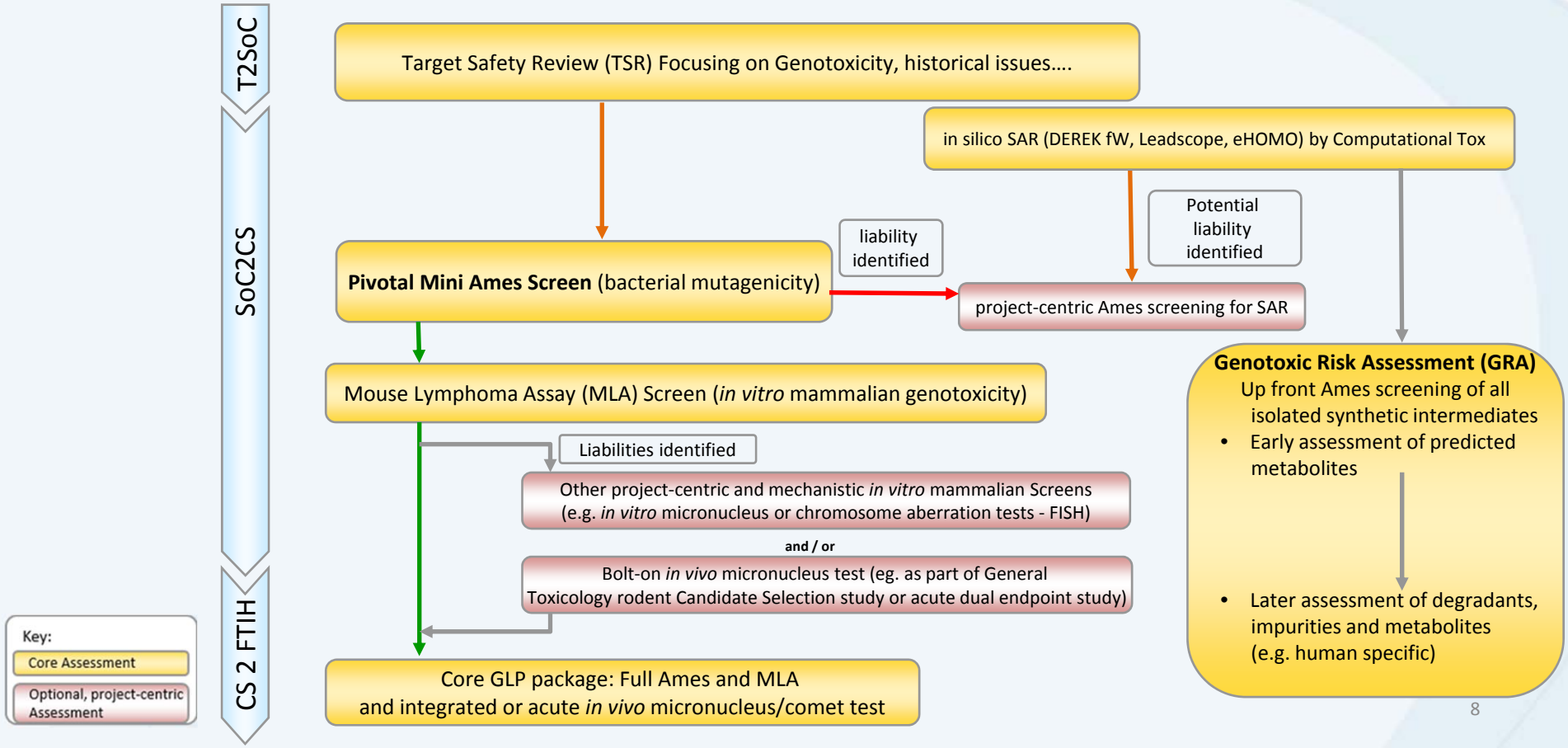
Core Assessment

Optional, project-centric Assessment

Core Genotoxicity Screening Cascade



Core Genotoxicity Screening Cascade



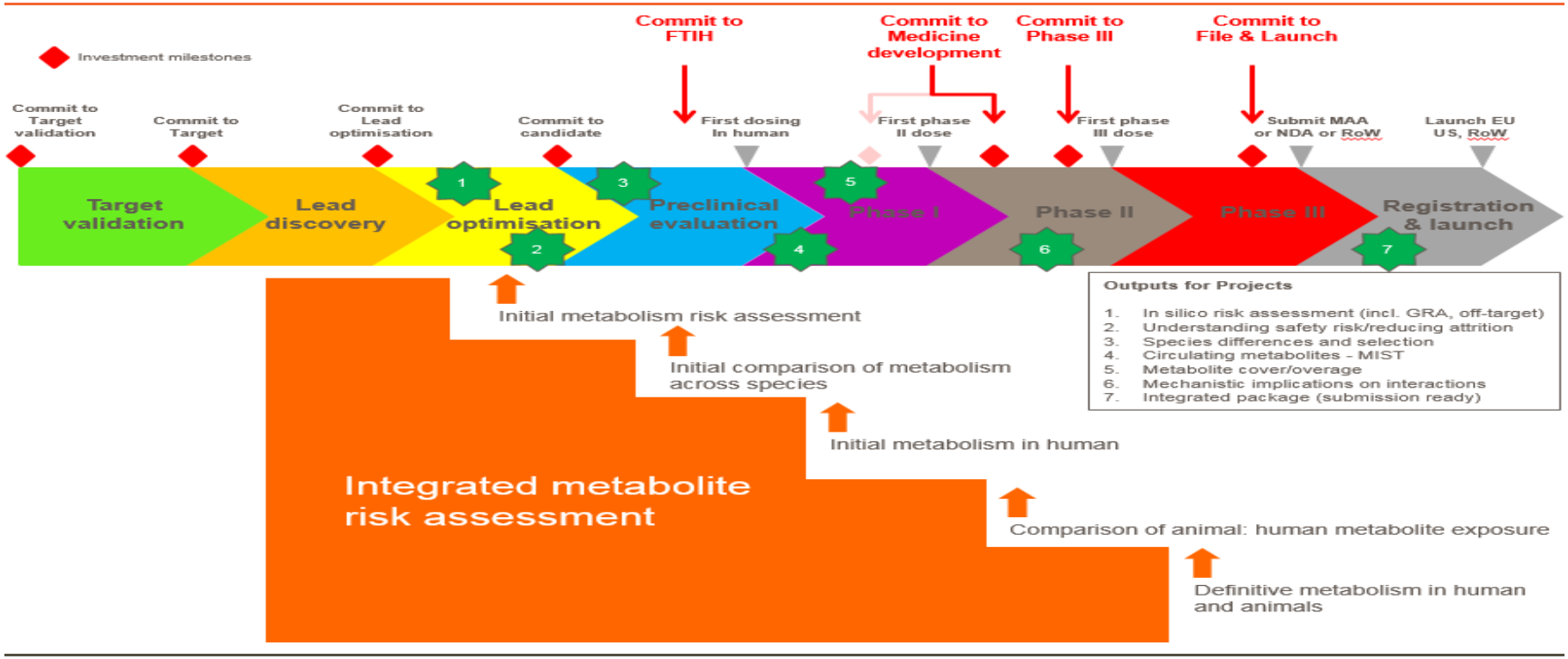
Genetic Tox in the Metabolism Risk Strategy

- **Predict First**: front load with predictive work (in silico and in vitro) before in vivo
- **Human First**: use FTIH samples as earliest opportunity to get human in vivo metabolism (at steady state)
- **MIST**: address through exposure comparisons animal:human as part of Phase I
- **File ready**: definitive ADME using radiolabel, to understand routes, rates and body burden

ADMET

MIST = Metabolites in Safety Testing

Genetic Tox in the Metabolism Risk Strategy



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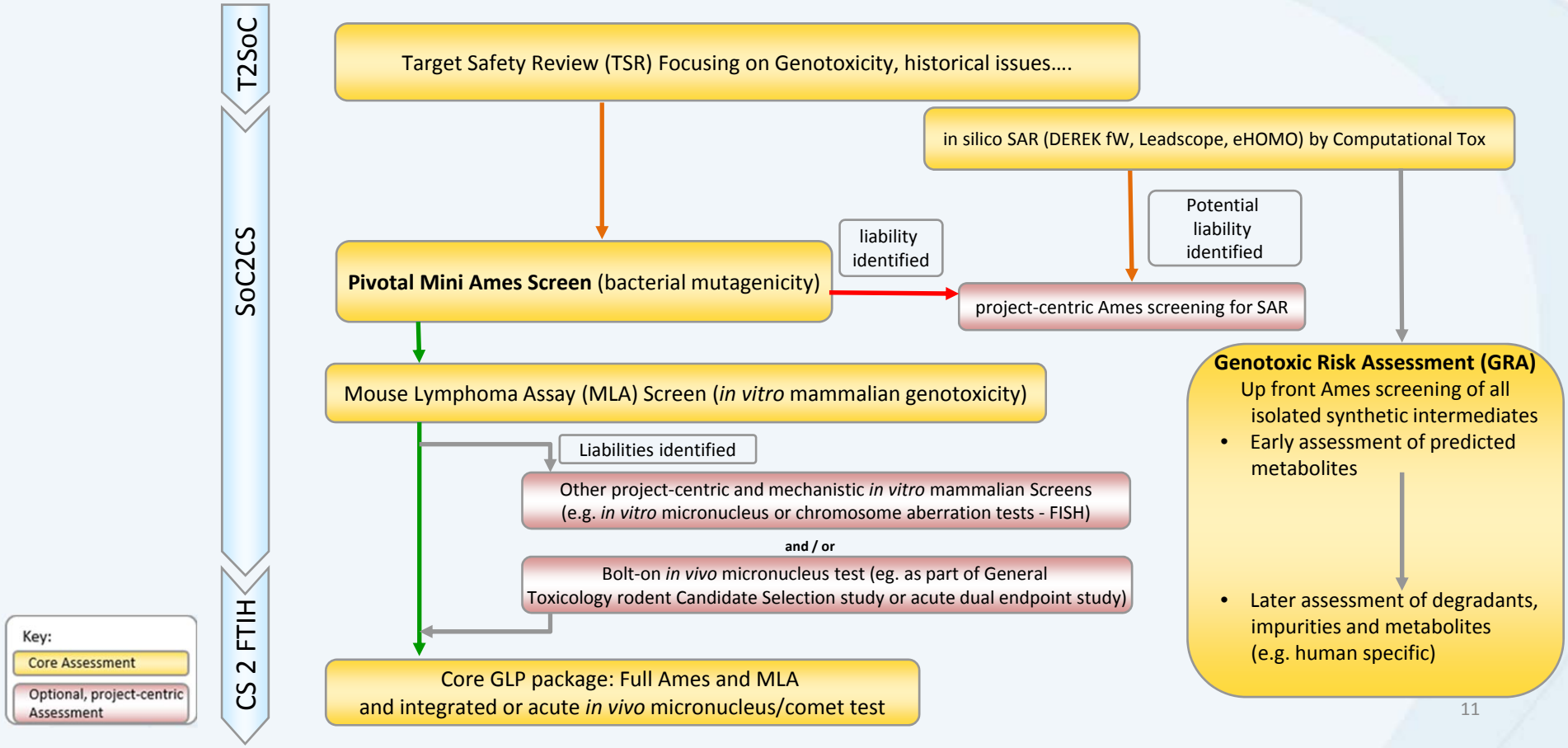

Questions