Transcriptomics Acute Model: A concept for general profiling of acute tissue specific chemical responses

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Concept

The Transcriptomics Acute Model (TAM) is a systematic approach to identify acute tissue-specific responses to chemicals using transcriptomics, without needing prior information about the chemicals. It involves:

1. Selecting a robust *in vitro* human cell model that represents the target tissue, such as PHH 3D spheroids.
2. Establishing a baseline transcriptome from the model using RNA-sequencing of 30 samples, to understand its normal expression levels.
3. Exposing the model to 150 chemicals at concentrations relevant to human exposure and monitoring changes in transcriptome profiles over 24 hours.
4. Formatting the resulting data according to the OECD Transcriptomics Reporting Framework and analyzing it using the R-ODAF.
5. Classifying the chemicals by an algorithm that scores the changes in their transcriptomes against the baseline, focusing on differentially expressed genes and key genes related to known Adverse Outcome Pathways (AOP).

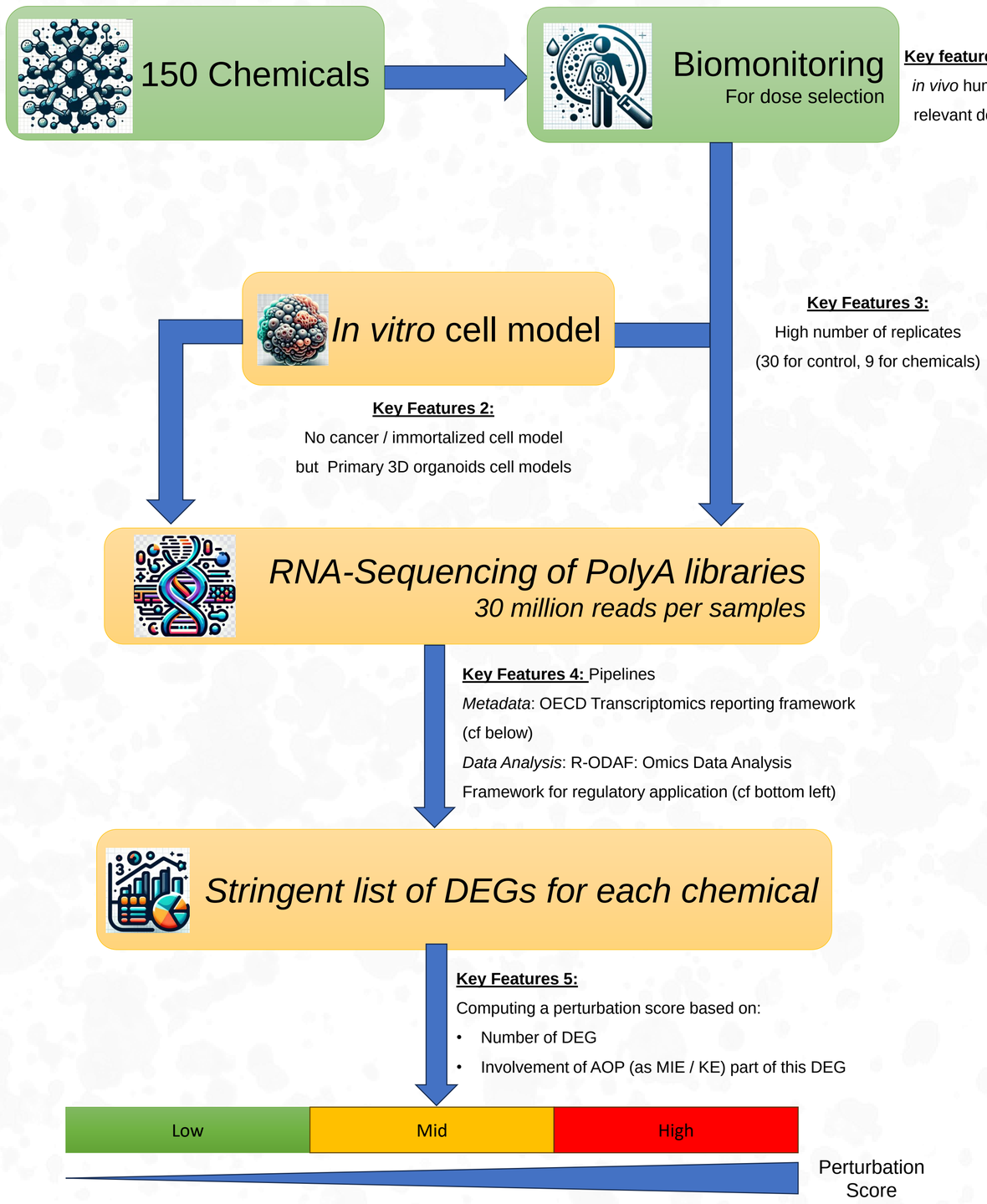
This proof of concept aims to provide a data-driven, unbiased method to classify chemicals based on their transcriptomic impact on a specific tissue type.

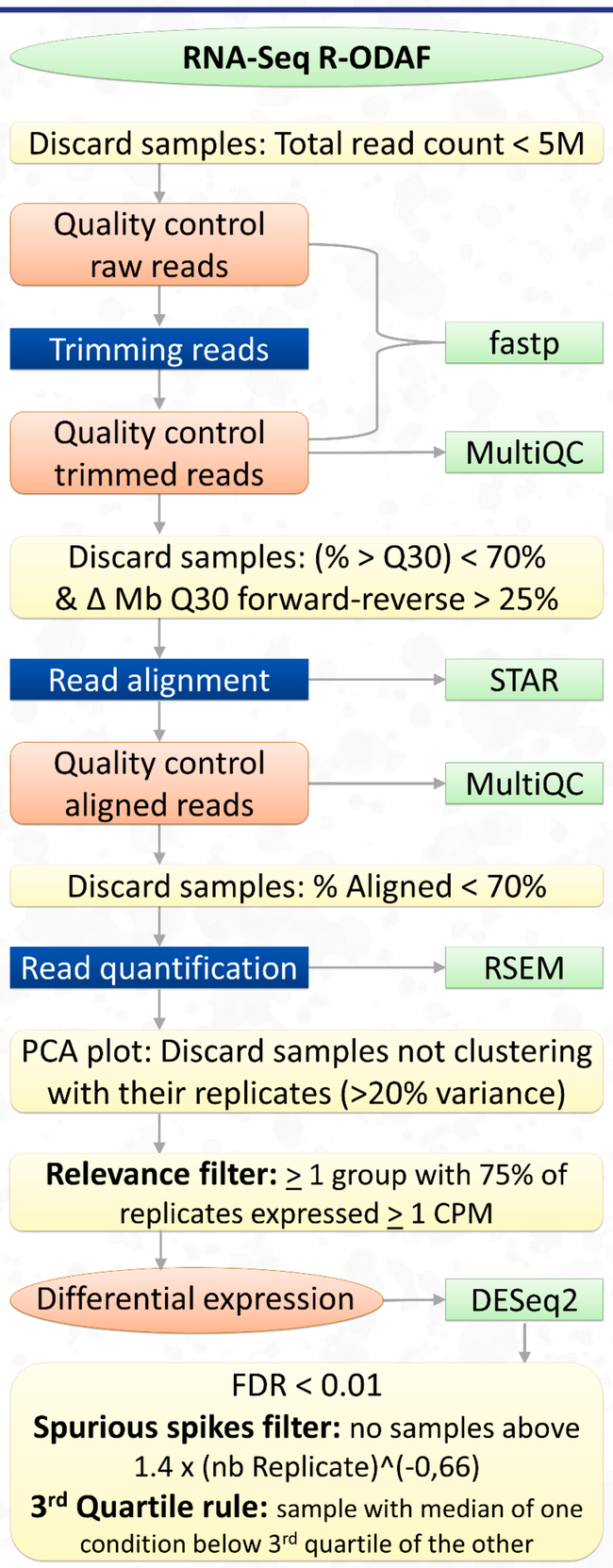
Improving on Omics-Based Initiatives

The proposed solution is aligned with established consortium frameworks, primarily those based in the EU and the US, which utilize *in vitro* systems exposed to chemicals. These systems are evaluated using transcriptomic technologies, exemplified by initiatives such as ToxCast, Tox21, and EutoxRisk. Despite their advancements, these initiatives have significant limitations that TAM seeks to address:

- **Omics Technology**: Existing omics-based consortia utilize cost-effective transcriptomic technologies that rely on hybridization techniques, which are often limited to a subset of genes (e.g., TempO-Seq S1500+, L1000). TAM proposes the adoption of whole-genome RNA-Sequencing methods that cover the entire genome and are unaffected by cross-hybridization issues.
- **Statistical Power**: Prior consortia have generated datasets with a limited number of replicates, typically only technical triplicates. This approach results in an excessively high level of noise, leading to non-reproducible results. TAM suggests producing 30 replicates for control samples (3 biological replicates with 10 technical replicates each) to establish a robust baseline characterization. Each chemical will then be evaluated using 9 replicates (3 sets of biological or technical triplicates).
- **Appropriate Cell Model**: Omics-based consortia often employ cancerous or immortalized cell models. TAM recommends the use of primary human cells as a more accurate representation of biological responses to chemical exposure.
- **Data Pipeline**: TAM proposes using a reference framework that encompasses both metadata capture and data analysis, providing a list of differentially expressed genes for each chemical examined.

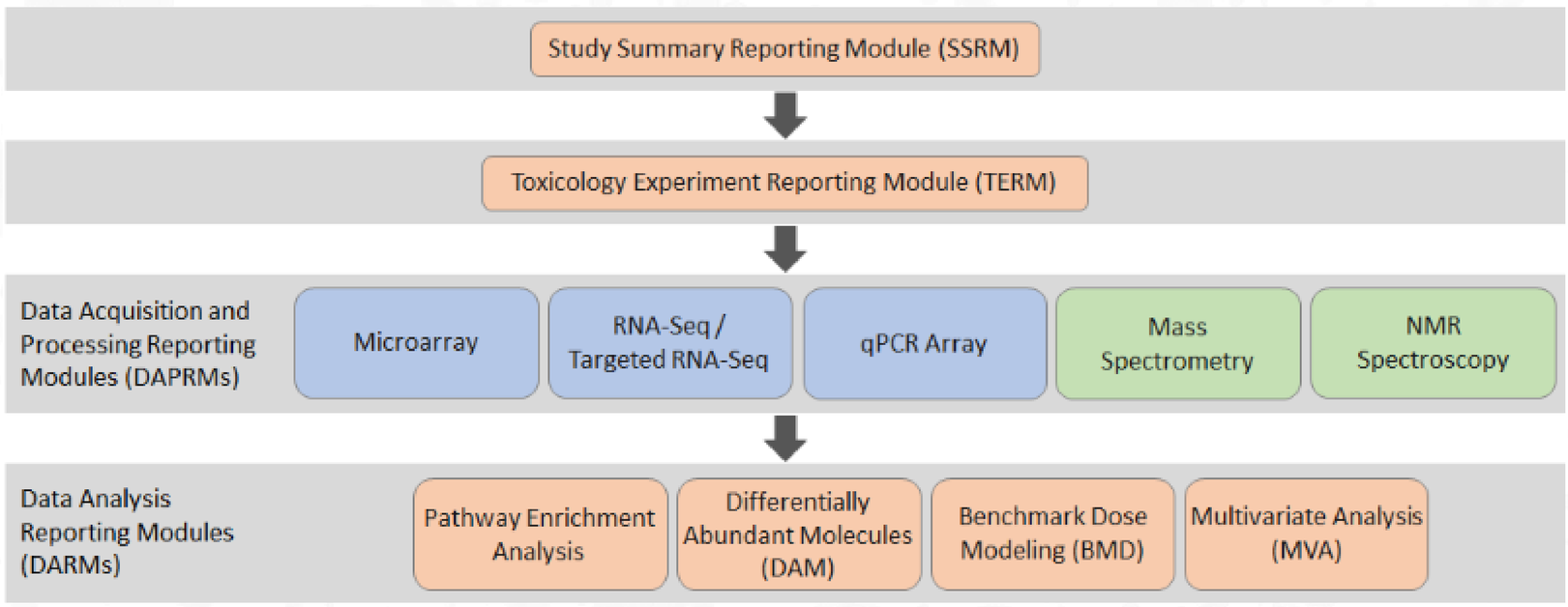
METHODOLOGY STEATOSIS CASE STUDY





OECD (transcript)OMICS REPORTING FRAMEWORK (TRF)

The OECD omics reporting framework provide a set of specialized modules allowing any transcriptomics or metabolomics experiments to be described in view of regulatory assessment.



References

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