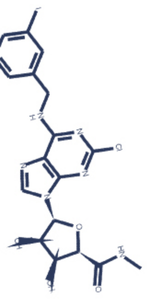
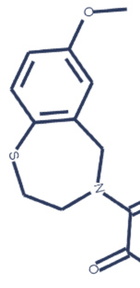
SYSTEMETRIC® Cell Health Screen

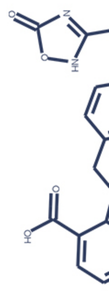
Enabling Discovery teams to predict the impact of SAR on the required Therapeutic Index



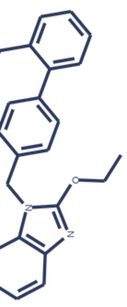


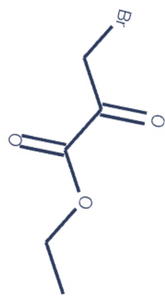
One of the most significant challenges for Drug Discovery teams throughout lead generation and optimization, is trying to determine an early estimate of the potential **Therapeutic Index (TI)** of compounds within a chemical cohort, or across different cohorts. Providing an evolving view of predicted TI is a more realistic tool in decision making around chemistry strategy and stage gate progression, as it balances the molecules potency with safety considerations.

To help integrate prediction of TI into the design space, AsedaSciences® has developed an AI enabled discovery platform integrating standardized, high content, **acute cellular stress** screens with **machine learning (ML)** and cloud computing. This platform provides teams with the ability to assess the impact of different chemistry scaffolds and specific SAR modifications on the TI and determine the potential tradeoffs to safety, dose and efficacy. As a result, AsedaSciences can provide teams with a rolling, visual prediction of the impact of each modification on the decision landscape across time. By independently comparing the TI margin on an ongoing basis for each modification, **rational selection of the right compound profile** can be achieved to meet the design objectives, while balancing off-target promiscuity and pharmacokinetics.



Our **SYSTEMETRIC® Cell Health Screen**, in combination with our ML algorithms, provides this rational selection capability to the earliest possible stages of hit to lead chemistry. This is achieved by measuring 12 different phenotypic descriptors of acute cellular stress (e.g., mitochondrial), across 10 individual concentrations for each compound, with 10 thousand cells sampled per concentration. The resulting data is then transformed into information rich biosignatures, or **biological fingerprints**, which are then automatically compared to a thoroughly curated training set of similar fingerprints from withdrawn and discontinued drugs, know toxins and on-market therapeutics. Based on fingerprint similarity and nearest neighbor associations, an accurate overall risk probability is assigned that appropriately depicts a compound's potential safety risks. This risk probability can either be used on its own to help guide chemistry efforts, or incorporated into a bespoke predictive TI score for each project.





With the AsedaSciences' **3RnD® cloud** platform, new and historical biological fingerprints can then be combined with binding affinity, structural properties and pharmacokinetic parameters, and elegantly visualized to accelerate the selection process. Predictions can be further enhanced by comparing to the expanding library of thousands of historical, annotated compound fingerprints, representing diverse chemical space, targets and indications.

Advantages: improving selection during SAR by understanding the impact of modifications on the TI

Reduce Timelines

Improved Productivity

Patient Safety

Supports 3Rs

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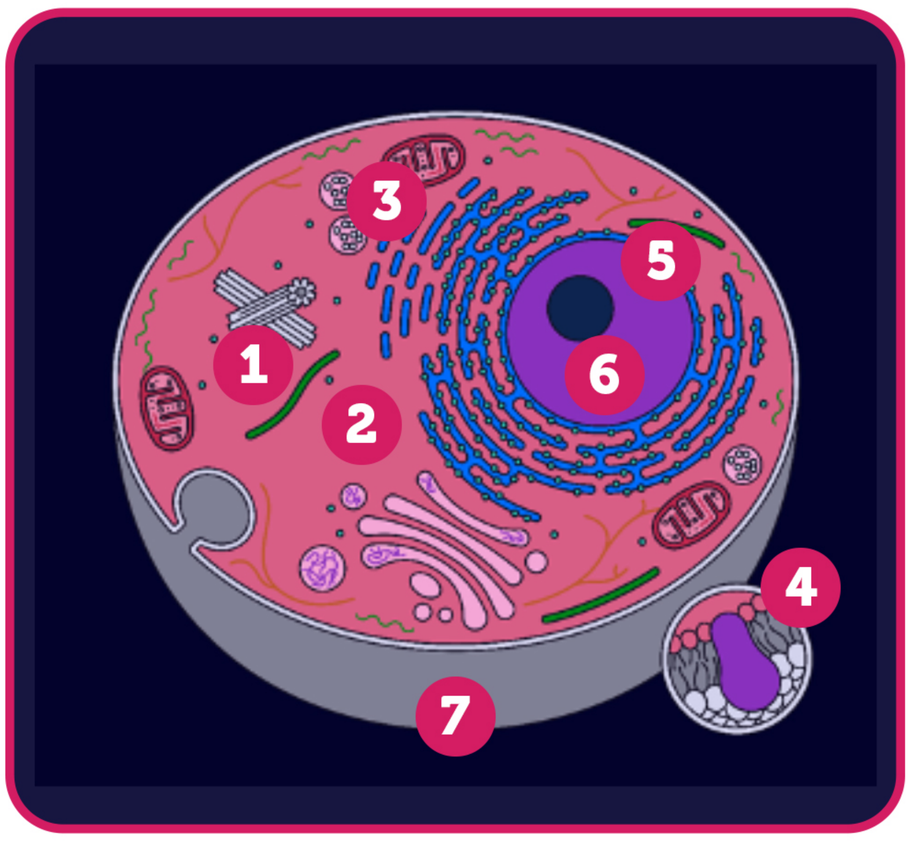
Parameters Measured:
The SYSTEMETRIC Cell Health screen is a multiparametric, Flow Cytometry based screen for the assessment of acute cellular stress caused by a compound.

Parameters Measured*:

1. Reactive Oxygen Species
2. Glutathione
3. Mitochondrial Membrane Potential
4. Cytoplasmic Membrane Integrity
5. Nuclear Membrane Integrity
6. Cell Cycle
7. Morphology (size, internal complexity)



*Multiple phenotypic descriptors measured in some parameters

The use of multiple mechanistic endpoints, when combined with our proprietary ML algorithms, provides far greater information diversity and dynamic range to the generated fingerprints, with demonstrated fidelity down to a single side chain modification on a compound. This combination of diversity and fidelity can help Discovery teams directly compare the impact of SAR on the TI throughout lead optimization, enabling rational selection of the right compounds.

SYSTEMETRIC Cell Health Screen Features:

Measurement Type:	Acute Cellular Stress, or Acute Toxicity exclusively for parent molecule
Cell Type Used:	HL60
Parameters Measured* (12): (*multiple parameters within some features)	Morphology, Reactive Oxygen Species, Glutathione, Mitochondrial Membrane Potential, Cytoplasmic Membrane Integrity, Nuclear Membrane Integrity, Cell Cycle
Measurement Output:	Cell Health Index - Risk Probability
Measurement Scale:	Color coded scale from “0” to “1” with increasing probability of potential safety risk
Analysis Method:	Automated Flow Cytometry, automated algorithms and Machine Learning
Concentration Range Tested:	10 concentrations, 100 µM down to 5 nM
Incubation Period:	4 hours – designed to detect acute toxins with high specificity
Amount of Compound Required:	20 µL of 10 mM stock in DMSO
Shipping and Logistics Process:	Instructions provided on request
Ordering Information:	SYST-1

Reference:
Bieberich et al (2021). Acute cell stress screen with supervised machine learning predicts cytotoxicity of excipients. Journal of Pharmacological and Toxicological Methods. Sep-Oct 2021;111:107088
https://doi.org/10.1016/j.vascn.2021.107088