Genedata
solutions in-silico

Screener® Sarileo

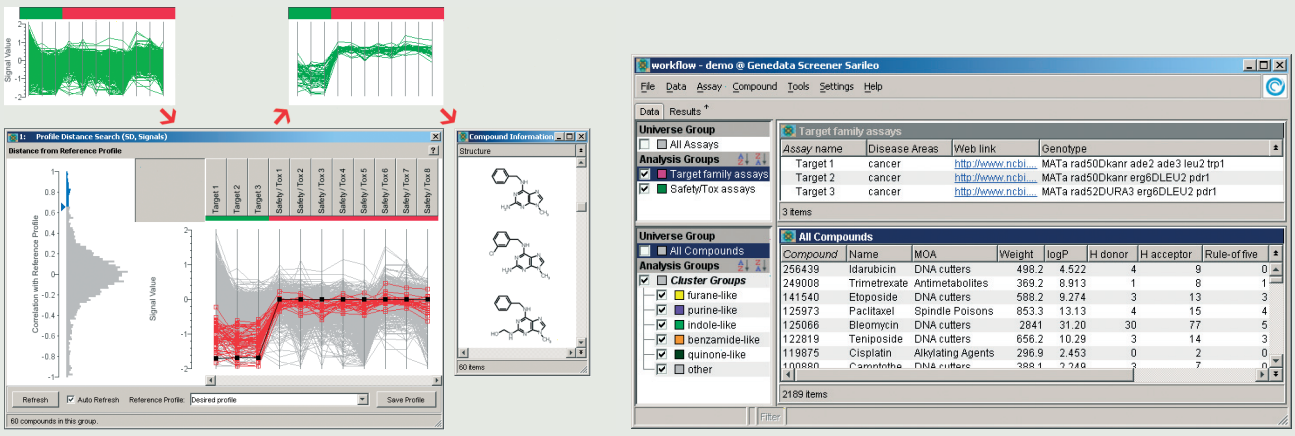
Overview

The wealth of experimental data produced by today's advanced screening technologies, such as high-content screening, holds great potential for drug discovery. The challenge lies in finding efficient ways to turn this complex data into knowledge on compounds, assays and targets and ultimately accelerate the drug discovery cycle.

Sarileo is a scientifically validated analysis platform to leverage this potential. It facilitates data interpretation in the entire lead discovery process, from comprehensive hit list generation to developing sophisticated structure-bioactivity hypotheses in a seamless in-silico workflow.

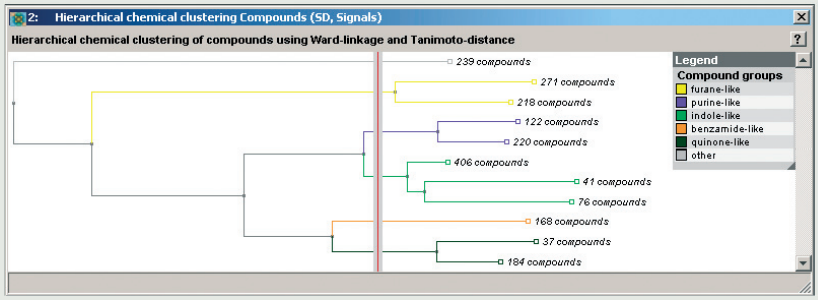
Benefits →	Key Features →
Reduce cost and time of drug discovery	Comprehensive and highly accessible analysis platform supports standardized workflows
	Intuitive analysis environment tailor-made for screening improves efficiency
	Profile-based hit selection discriminates lead compounds from those producing side-effects
Enhance scientific decision making	Highly integrated functionality aids communication within the lead discovery team
	Integrated structural, physico-chemical and ADME/Tox information places results in context
	Transparent result sharing and audit trail facilitate best practice

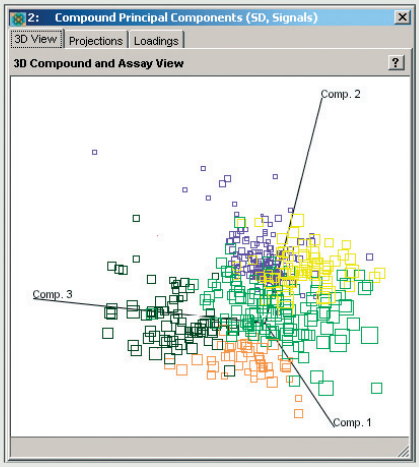
Powerful and Intuitive Analysis Environment for Interpreting Screening Results



Users of Sarileo are placed at the center of a platform for lead identification that supports sophisticated data analysis, data storage, results sharing and publishing. Intuitive interfaces let you get started right away and progress efficiently along the analysis pipeline. For example the Profile Distance Search tool (above left) finds compounds with a desired bioactivity profile across multiple assays; the desired bioprint. In the search for an anticancer drug, use it to identify compounds with strong inhibition in, eg. kinase assays but little activity on assays designed to explore drug side effects. Frequent hitters on the safety and side effects assays (top right) are easily eliminated by their poor correlation with the desired bioprint, making it possible to extract a small hit list from a library of more than a million compounds. Chemical structures of hit compounds can be visualized directly, revealing that some share a common motif. Quantitative chemical information about each compound can be used to refine the hit list further, eg. selecting compounds conforming to Lipinski's rule of five.

Explore Correlation between Chemical Structure and Bioactivity

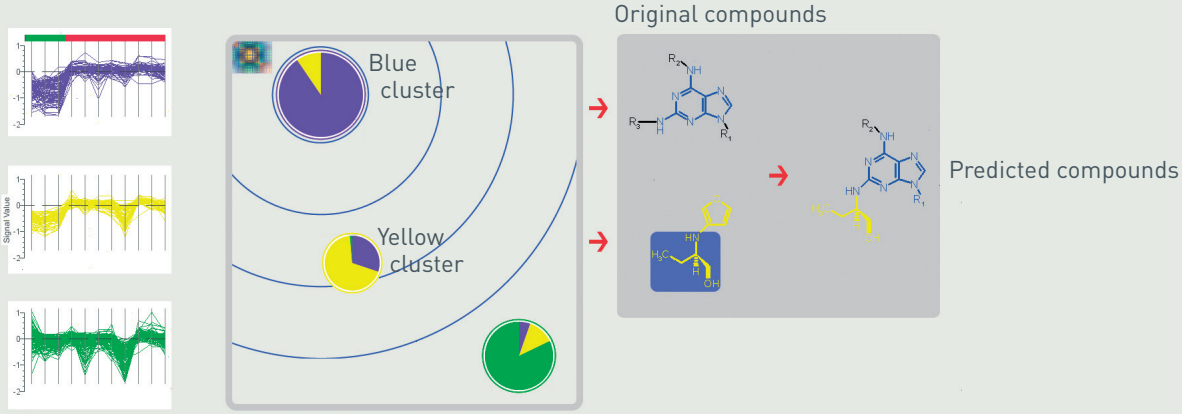




Sarileo boasts a unique integration of powerful database functionality with advanced statistical and visualization tools. The example above demonstrates the use of Principal Component Analysis (PCA) to explore the correlation between chemical structure and the measured bioprint. Following chemical expansion of the hit list, compounds are grouped into 5 classes according to their chemical similarity, as measured by a Tanimoto metric on structural fingerprints (left). The PCA is performed on the bioactivity values. In the 3D plot of principal components, compounds belonging to the same chemical class are plotted in the same color. Each chemical class is confined to a specific region, giving the appearance of discrete clusters (right).

The tight correlation between chemical structure class and bioactivity means that a compound's bioprint can be predicted from its chemical structure, and vice versa. This facilitates further refinement of the hit list. For example, compounds may have satisfactory chemical properties but produce the optimal bioprint only weakly. The analysis makes it possible to predict that these compounds could be added to the hit list and enhanced through chemical modification. Other cheminformatic approaches can be used to further explore structure-bioactivity relationships including similarity search and chemical homogeneity profiling. ADME / Tox information is incorporated into the environment as part of a rich database of annotation.

Guide Chemical Optimization using in-silico Approaches



In-silico methods can be used to guide the search for an optimized pharmacophore, gaining maximal value from data already obtained. Consider the following in-silico workflow. The Cross-Validation algorithm positions chemical clusters, displayed as pie plots (above), in a bioactivity map. The map represents the overall biological behavior found in the screening data. The blue cluster yields the most satisfactory bioprint overall, as can be seen in the adjacent blue profiles. The chemical structure characteristic of this cluster may provide a useful chemical foundation for lead compounds, eg. a particular ring system. But the map also identifies a second cluster, the yellow one, with some compounds displaying the optimal bioprint. This fact is indicated by the blue segment in the yellow pie plot. The yellow cluster belongs to a different chemical class and is positioned in a different part of the bioactivity map. However, the analysis predicts that chemical properties of compounds in the blue segment, eg. a side chain, could be added to the ring system identified from the blue cluster to yield compounds with a better bioprint than any in the original compound library. Thus, the combination of powerful algorithms with chemical structure information can guide chemical optimization. Sophisticated analyses like these can be performed easily in Sarileo. An in-depth understanding of results is gained quickly and routinely, saving time and improving the quality of scientific decision making.

Sarileo is a module of the Screener® system. Together with the Condoseo module for dose-response analysis, and the high-throughput quality control environment AssayAnalyzer, Screener covers the complete screening analysis cycle - from validating primary data to finding high potential leads. Genedata has a proven track record integrating the Screener system with existing corporate IT infrastructure to deliver a seamless scientific computing platform.

For further information contact us under screener@genedata.com or visit our website at www.genedata.com