sanofi

Genedata
solutions in silico

> ***Working with Genedata Expressionist provides us with fast, flexible, and reliable options to discover potential biotherapeutic liabilities and thoroughly analyze next-generation antibodies at Sanofi.***
>
> Soraya Hölper, Ph.D., Laboratory Head Mass Spectrometry at Sanofi, Frankfurt am Main, Germany

AUTHORS
Soraya Hölper, Ph.D. &
Jennifer Jung, Ph.D.
Sanofi-Aventis GmbH,
Frankfurt am Main,
Germany

INDUSTRY
Healthcare/
Biopharmaceuticals

CUSTOMER SINCE
2006

ABOUT SANOFI
Sanofi is a global biopharmaceutical company focused on human health.

GENEDATA SOLUTION
EXPRESSIONIST

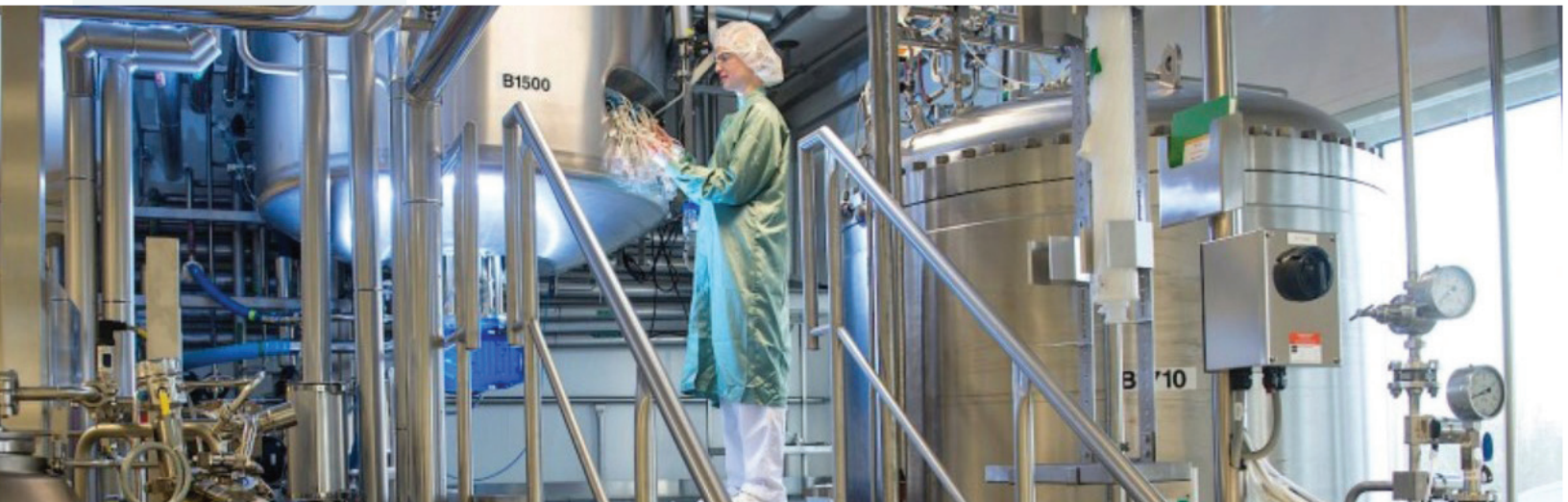
Assessing Developability of Novel Biotherapeutics Through Mass Spectrometry

Background

Numerous characteristics—such as potency and efficacy, consistent manufacturability, physical and chemical stability, and safety—must be considered when developing biotherapeutics. For biopharma companies, identifying and understanding the risk factors inherent to drug candidate development is crucial to implementing effective and timely mitigation strategies.

Novel biotherapeutic constructs are becoming more prevalent in discovery and development pipelines and their complexity results in an increasing need for faster and better characterization tools to identify the key parameters that influence a candidate's potency and physicochemical properties.

To better identify the most promising drug candidates in our pipeline, we worked with Genedata to develop an MS-based analytical approach for quickly and confidently pinpointing potential chemical liabilities and efficiently guiding development of next-generation biotherapeutics at Sanofi.



Main Challenges

Extracting maximum molecular information from complex data sets

Although we mainly focus on multispecifics, our lab works on a variety of constructs and we are also developing fusion proteins and other scaffolds. The large, information-rich MS data sets obtained from in-depth analysis of these complex molecules require sophisticated processing platforms and time-consuming expert evaluation to extract the maximum amount of information.

Consolidating data across instruments and labs and standardizing results across methods

In-depth analysis of a drug candidate is performed in collaborative projects that typically use a range of instruments from different vendors. Often, it is necessary to apply a range of MS approaches, such as peptide mapping, intact mass, and released glycan analysis. Consolidating and comparing these data is labor intensive and requires familiarity with multiple software packages. In addition, analyzing such compartmentalized data can lead to biased results.

Obtaining a transparent and complete overview of the data at every stage of processing

For each sample, we initially need to check a basic set of signal characteristics—such as intensity, retention time shifts, and peak shapes—to verify MS data quality. Later, in the characterization phase, experimental data are analyzed very carefully to detect modifications that can potentially affect the function of the biotherapeutic.

To facilitate raw data evaluation and in-depth analysis we require a single platform providing both intuitive visualization across multiple samples and comprehensive and transparent analysis for each sample.

Managing ever-increasing numbers of samples

Several stress tests are performed on each drug candidate to assess its chemical stability. Keeping pace with the resulting number of samples requires a high-throughput platform to prevent data processing, analysis, and reporting becoming bottlenecks in drug development.

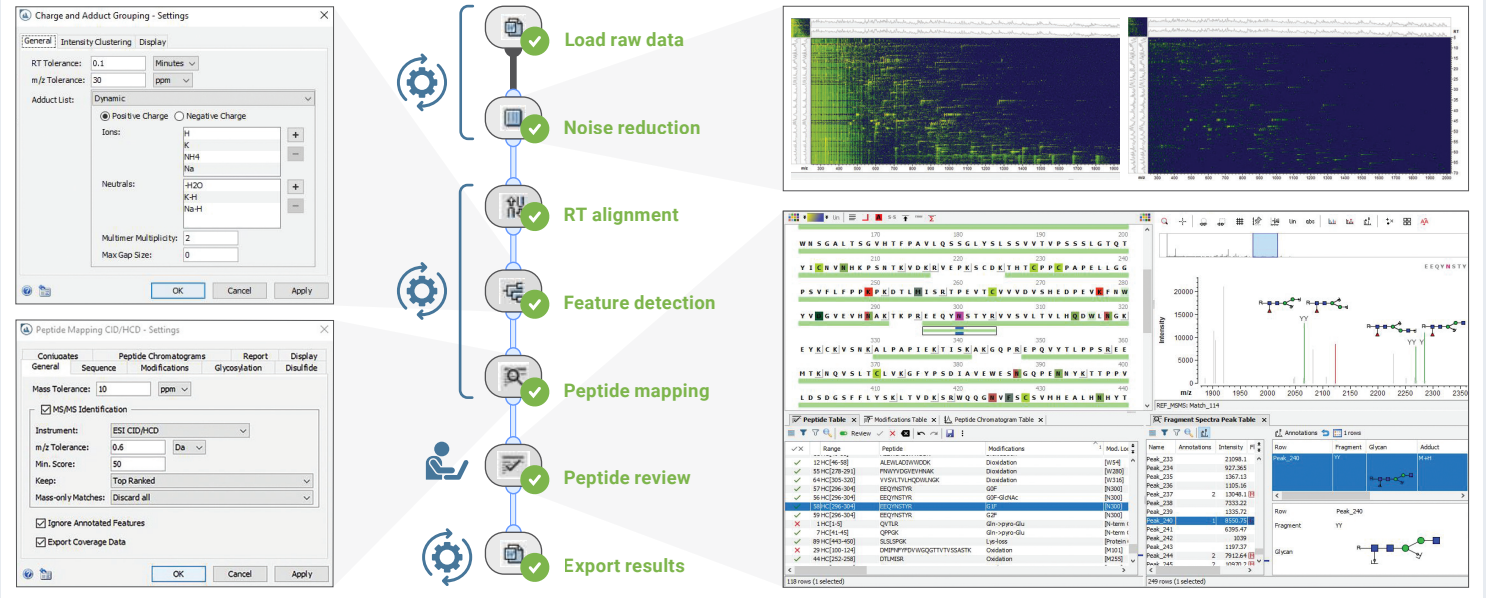
Solution

Highly configurable application-specific data workflows

Due to the variety of structures and modalities of our drug candidates, an in-depth characterization of our drug candidates simply cannot be achieved using a “one-size-fits-all” data processing solution. Using Genedata Expressionist, we can adapt and configure application-ready workflows to create tailored data processing solutions that meet our specific analytical needs (Figure ❶). Once created, we can use, share, and further adapt these workflows to test new ideas and address new approaches and requirements.

A single, scalable enterprise software platform for all MS-based biopharma analyses

As a high-performance vendor-independent platform, we can use Genedata Expressionist to process the large volumes of multidimensional data generated by all our MS instruments



❶ *Genedata Expressionist workflows provide complete control and a transparent overview at every stage of data processing.*

and experimental approaches. If peptide mapping alone is not sufficient to characterize a candidate biotherapeutic, we can use Genedata Expressionist for intact mass- or released-glycan analysis to further deepen our understanding of the molecule.

Transparent data processing and precise analytical tools

We use a variety of Genedata Expressionist visualizers to perform a preliminary data quality evaluation. Intuitive displays enable us to quickly determine noise reduction thresholds, confirm the completeness of consecutive charge-state series, and identify complementary peaks in the TICs of experiments using different fragmentation modes (Figure ❷).

During in-depth analysis, sequential, stepwise processing allows interrogation and iterative analysis of data at any stage of the workflow. Dedicated review functionalities, such as the Peptide Mapping Review feature, enable us to pause at critical points in the workflow to confirm data quality or validate initial results that can then be subjected to further analysis. Interpretation of results is aided by customizable reports that provide at-a-glance interpretation of statistical analyses and trends across data sets.

Any degree of automation for MS data analysis

The workflow approach of Genedata Expressionist enables us to optimize and fully automate routine data processing in our peptide mapping workflow. In this workflow, an initial preprocessing section includes activities that perform noise reduction, thresholding, and smoothing.

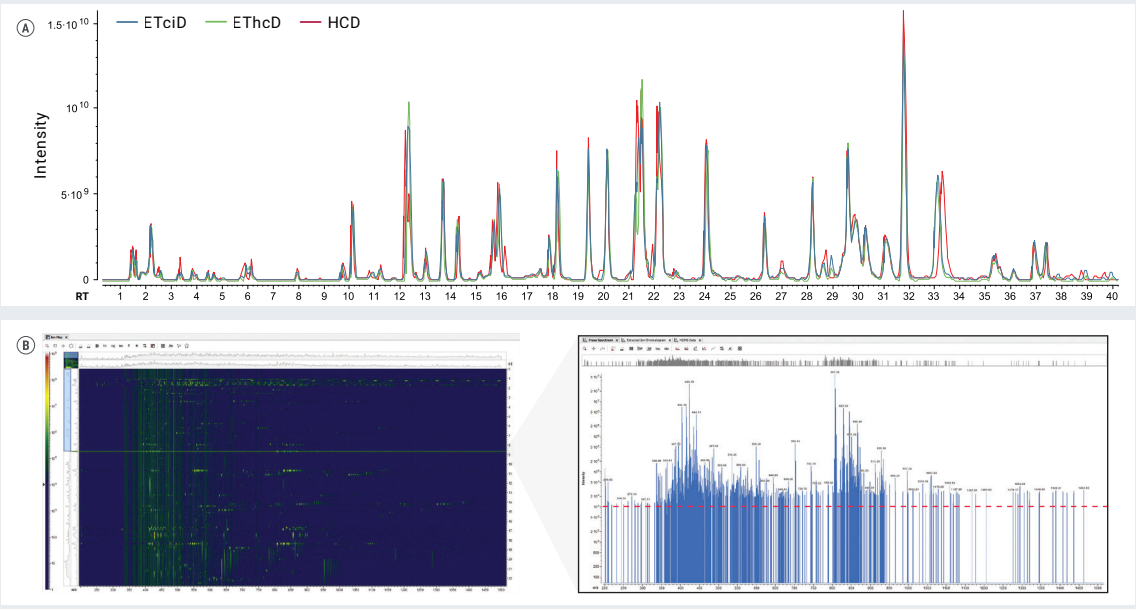
A second section consolidates MS/ MS data and performs grouping and annotation. Once optimized, both these sections can be run automatically for most samples. A third section, which contains peptide mapping and review activities, is where we perform expert analysis of the samples. Finally, the curated results are summarized in an automatically generated custom report. This flexible approach to automation results in a dramatic increase in throughput, while enabling our scientists to focus and bring their expertise to bear on the crucial steps of the analysis.

Benefits

Deeper insights that enable faster delivery of best-in-class molecules

The flexibility provided by Genedata Expressionist is crucial when analyzing novel or highly complex biotherapeutics for which no “off-the-shelf” solution is suitable. By precisely defining data processing criteria, highly specific analytical questions can be answered, thereby providing deeper insights into drug candidates. Flexible processing also increases productivity.

For example, our peptide mapping workflow is configured to search for a defined set of adduct species arising from the same peptide and to disregard spurious signals. Performing this fully automatic step significantly reduces the number of false-positive peptide identifications; saving time and enabling our scientists to concentrate on characterizing genuine identifications.



❷ *Evaluating MS data sets.*
Ⓐ *Comparing TICs from different fragmentation strategies; ETciD: Electron-transfer/collision-induced dissociation; EThcD: Electron-transfer/higher-energy collisional dissociation; HCD: Higher-energy collisional dissociation.*

Ⓑ *Taking a cross section through the ion map (which gives an overview of all mass spectra obtained at each retention time point and displays signal intensity as a color gradient) enables easy determination of suitable signal-noise threshold.*

Standardization, reproducibility, and reduced costs

Because it is a vendor-independent platform, we can use Genedata Expressionist to process data from all our MS instruments and experiments. Using a single software standardizes our data analyses, increases reproducibility, and provides us with meaningful, unbiased comparison of data and results across projects, samples, and labs. Previously obtained results can be effortlessly reanalyzed and reappraised by reprocessing the raw data using updated workflows. In addition, using a common platform for all our MS-based analyses eliminates costs for training in and maintenance of multiple software packages.

High-quality and high-confidence results enabling better decision-making

The Genedata Expressionist workflow approach enables us to thoroughly investigate and understand the complex relationships between biotherapeutic function and structure. The precise level of control available in our workflows enables us to leverage our expertise when confronted with new challenges. In addition, the inherent transparency and standardization of data processing delivers unbiased results that enable better decision-making when informing and guiding optimal product development. Individual features of interest can be investigated on multiple levels. Information from ion maps, feature chromatogram traces, and MS/MS fragment spectra peaks can be combined to identify and quantify individual peptides with high precision. The ability of Genedata Expressionist to simultaneously display and compare multiple data sets further speeds up and facilitates in-depth characterization. The comprehensive overview and transparency of the workflow approach enables thorough assessment of the data after every processing step. This enables potential issues to be traced more easily and enables timely implementation of mitigation strategies to avoid them.

Quick answers enabling earlier interventions

The results of our in-depth characterization studies are used to induce and guide molecular engineering cycles with the goal of stabilizing a biotherapeutic's structure. Automating the routine stages of MS data processing accelerates candidate assessment by enabling us to concentrate our time and efforts on in-depth characterization. The ability to design and automatically deliver customized reports containing as little or as much information as required to different stakeholders facilitates information transfer and eliminates laborious and time-consuming manual creation and distribution of reports. Early identification of degradation-prone drug candidates greatly benefits the success of projects by enabling us to increase stability by reengineering problematic molecules rather than adjusting manufacturing or formulation processes. This optimization of the inherent chemical stability of a biotherapeutic should not only facilitate its production using proven processes, but also improve its shelf-life and serum stability.

Summary

Genedata Expressionist provides us with high-quality, high-confidence results using a transparent MS data processing workflow, enabling us to obtain a comprehensive, in-depth characterization of biotherapeutic candidate molecules. A high degree of automation with control at every stage of processing enables us to save precious time and scale our resources while addressing highly complex analyses. We can use the information gained in these studies to complement functional analyses and guide molecular biological engineering of more efficacious biotherapeutic candidates. Gaining such a comprehensive molecular understanding of candidates during developability studies leads to much lower attrition rates in later stages, less-problematic processes, and ultimately, a faster time in clinic with best-in-class molecules.

"I really enjoy performing data analysis with Genedata Expressionist, because I know that if the automated workflow needs fine-tuning for a specific therapeutic protein, its flexibility will enable me to easily make the required changes and quickly obtain the results I need.

Jennifer Jung, Ph.D., Laboratory Head Mass Spectrometry at Sanofi, Frankfurt am Main, Germany

GENEDATA SOLUTION

EXPRESSIONIST