Genedata

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> The automated workflow dramatically accelerates data processing, eliminates tedious manual operations, and facilitates review, allowing us to focus on tasks that are key to business success, while reducing the time required to deliver high-quality results from weeks to days.
>
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NOVARTIS

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Industry
Pharmaceuticals

Customer Since
2005

About Novartis
Novartis is a global healthcare company based in Switzerland that provides solutions to address the evolving needs of patients worldwide.

Genedata Solution
EXPRESSIONIST

Automating MS Analysis of Therapeutic Oligonucleotide Biotransformations

Background

Due to their potential to deliver personalized medicine for diseases that are difficult or impossible to address with conventional therapies, oligonucleotide drugs are becoming increasingly important to pharmaceutical companies. The Novartis ADME (absorption, distribution, metabolism, and excretion) laboratory investigates the metabolism of oligonucleotide drugs by analyzing *in vitro* and *in vivo* samples using UPLC combined with high-resolution MS, which enables highly sensitive and accurate identification of analytes. However, the complexity of the analytes and sample matrix and the large volumes of MS data generated make MS-based metabolic profiling challenging, time-consuming, and unfeasible without a dedicated computerized solution.

We worked together with Genedata to develop and implement an automated solution for processing, analyzing, and reporting MS data that enables comprehensive insights into the metabolism of oligonucleotide therapeutics while delivering significant time savings.

Main Challenges

Processing large volumes of complex data

High-resolution MS enables sensitive and accurate molecular-level identification of analytes. However, current MS instruments generate large and complex data sets that can accumulate very quickly, and in many cases, create a bottleneck in MS data processing, analysis, and reporting.

Profiling a large number of analytes

Oligonucleotides are primarily metabolized by hydrolytic cleavage of the phosphate backbone by endo- and exonucleases, resulting in truncated or fragmented oligomers and mononucleotides. While nuclease action is well understood, multiple cleavage reactions lead to large numbers of potential metabolites from a given sequence. Moreover, tag modifications and *in vivo* nucleotide biotransformation reactions—such as deamination—significantly increase analyte heterogeneity. Identification and profiling of this wide range of analytes is required to obtain a comprehensive overview of therapeutic oligonucleotide metabolism and elimination routes, which have an impact on their potential pharmacological activity and toxicity.

Eliminating laborious manual procedures

MS-based analysis of oligonucleotide biotransformations typically requires laborious consolidation of siloed data and time-consuming creation of comprehensive analyte libraries, making large-scale biotransformation studies using conventional software tools error-prone and impracticable. In addition, the large number of potential hits generated occupies valuable expert resources in time-consuming result reviews.

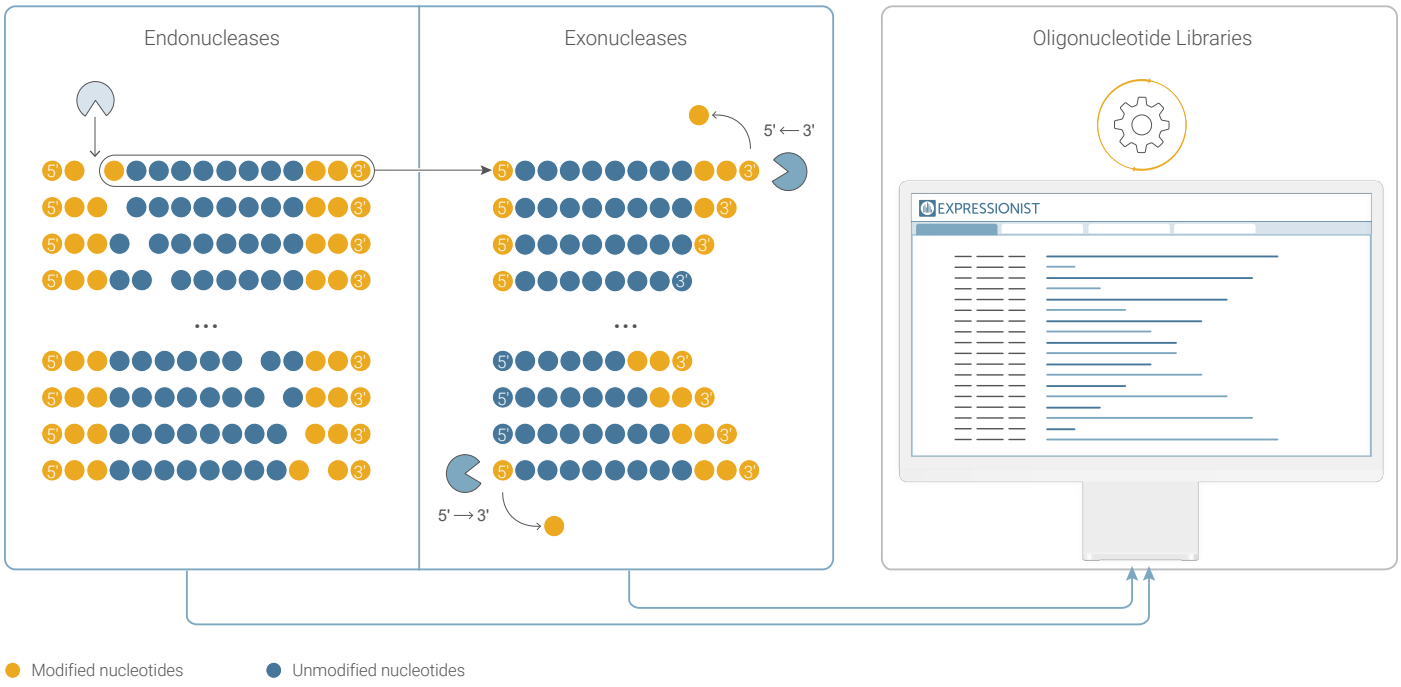

Figure 1. Automatically generated MS search libraries based on the full parent drug structure including the tag modification, the oligonucleotide sequence (containing the sense and antisense strand in case of siRNA sequences), nuclease action, and predefined metabolic reactions enable generation of comprehensive metabolic profiles.

Solution

Flexible and configurable high-performance data processing workflows

Specifically designed as a high-performance, server-based platform, Genedata Expressionist can quickly and efficiently load and process large volumes of MS data. The software's workflow-based approach enables us to break down data processing into a series of discrete steps, each of which can be ordered to address specific analytical strategies and configured to optimize processing to the sample or data set at hand.

Auto-generated, sample-specific metabolite libraries

Dedicated metabolite libraries are automatically generated within the Genedata Expressionist workflow during data processing and used to identify corresponding signals by accurate mass matching. These libraries contain a complete list of potential metabolites based on the full parent drug structure, the oligonucleotide sequence, and predefined metabolic reactions—such as sequence clipping reactions, tag metabolism, and other specific biotransformations—enabling us to generate a comprehensive knowledgebase that grows through a dynamic process of accumulation, organization, and refinement of data (Figure 1).

An automated data processing solution that accelerates expert review

The software solution is designed to simplify and accelerate the analytical process, from raw MS data to final report. With a single click, the workflow loads, processes, and analyzes MS data, minimizing manual operations and human errors. A stepwise search approach that excludes previously identified signals minimizes false-positive identifications, while a rule-based filtering of hits reduces the number of results that require expert review (Figure 2). In a final automated step, customizable reports containing chromatograms, spectra, summary tables, and kinetics curves of drug candidates and their metabolites are shared with key stakeholders and exported in a format ready for direct submission to regulatory authorities.

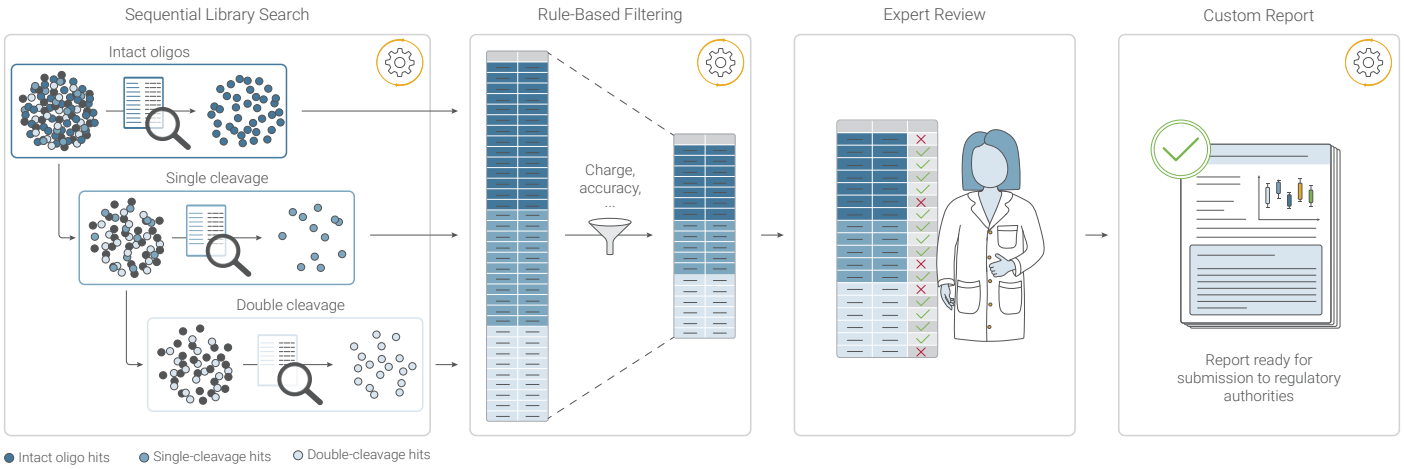

Figure 2. Signals are processed using sequential MS searches with separate libraries and rule-based filters to dramatically reduce the number of results requiring expert review.

Benefits

Improved productivity

Automating data analysis with a workflow that is designed and optimized to meet our specific requirements dramatically accelerates our analytical processes, enabling us to deliver high-quality results within 1–2 days rather than weeks. The Genedata Expressionist platform provides us with the scalability that allows our group to keep pace with the increasing demands for MS-based analyses, and the flexibility to develop analytical strategies in line with evolving industry needs and emerging therapeutic modalities.

Deeper insights for high-quality drug candidates

The combination of extensive MS search libraries and intuitive data visualizations provides a comprehensive overview of oligonucleotide biotransformations, allowing us to better understand the metabolism of drug candidates and helping us to deliver expert insights to the project team during the optimization and development phases. These insights are key to supporting risk mitigation (immunogenicity assessment), safety, and toxicology studies, which are critical in bringing novel medicines such as oligonucleotide-based therapeutics to patients and are also required for submission to regulatory authorities.

Reduced risk and data-driven decision-making

Automating the MS data workflow minimizes human error and removes the burden of performing laborious manual data operations from our analysts. In addition, embedding domain knowledge into the configurable workflows greatly reduces the number of results requiring review, delivering significant time savings, and allowing our experts to focus on other high-value tasks. This combination of automated data processing and built-in business logic facilitates unbiased decision-making and enables us to scale our analytical operations using existing resources.

Summary

The complexity and the amount of data make a dedicated computerized solution a prerequisite for efficient and comprehensive MS-based metabolic profiling of oligonucleotide-based therapeutics.

Working in close collaboration with Genedata, we rapidly developed and implemented a software solution based on a flexible data processing workflow, auto-generated metabolite libraries, and a software-assisted result review that simplified and accelerated the analysis of oligonucleotide biotransformations.

The implemented solution:

- dramatically reduces the time required for biotransformation analysis
- unburdens our experts by eliminating tedious manual operations
- delivers high-quality results that provide deeper insights

enabling us to streamline the entire analytical process, from loading raw MS data to generating a final report ready for submission to regulatory authorities.

Genedata EXPRESSIONIST

Genedata Expressionist® is part of the Genedata portfolio of advanced software solutions, which digitalize and automate data-rich and complex biopharma R&D processes. From early discovery all the way to the clinic, Genedata solutions maximize the ROI in R&D expenditure.