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TRENDS IN OLIGONUCLEOTIDE DRUG DEVELOPMENT - A VIRTUAL PANEL DISCUSSION

WILLIAM FANG
VP, Head of New Modality Oligo & Peptide
WuXi STA, a subsidiary of WuXi AppTec

Natural disasters, the recent pandemic, and transportation issues all combined to create supply chain disruptions across multiple industries. What supply chain challenges has the oligonucleotide industry faced in the past 18 months?

Certain starting materials and production supplies have become more expensive due to high demand and disruptions in the global supply chain. We have invested in optimized processes that require less amount of materials to reduce the dependency, and through our extensive small molecule chemistry platform, developed methods to produce some scarce building blocks, reagents and intermediates to avoid delays.

Most oligonucleotides are produced using the same solid phase synthesis and purification methodologies that have been used for decades. Do you see areas where these methodologies can be improved to reduce cost or minimize environmental impact?

Traditional manufacturing methods for oligo production can be costly and unsustainable when it comes to high-volume commercial products. Currently, we are moving forward on three fronts working with various partners; expanding liquid-phase synthesis, applying a fragment based process, and exploring an enzymatic approach.

Liquid-phase oligo synthesis (LPOS) is a new technology utilizing conventional reactors without additional investments in synthesis and purification equipment. Our strong chemistry experience enabled our teams to develop liquid phase synthesis using small molecule reactors up to 20,000 L.

In addition, LPOS enables the application of convergent synthesis with higher coupling efficiency and simpler impurity profile. Compared with solid-phase oligo synthesis (SPOS), it uses less amide as well as solvent due to fewer purification steps, resulting in lower PMI.

We are collaborating with some big pharma partner to build the LPOS platform including process R&D, analytical and production.

As the number of approved oligonucleotides has increased, CDMOs have responded by expanding manufacturing capacity. Do you feel the market has adequate manufacturing capacity to meet the current and near term demands of oligonucleotide drug developers?

There are still few providers with large and commercial-scale manufacturing capacity for Oligos on the global market with key barriers including large investment, talent, experience, etc.

We saw in our pipeline a large number of early-stage candidates progressing to phase II and III so we anticipated the need for increased late-stage production capability and recently expanded our large-scale oligo manufacturing, to support the solid phase oligo production. We currently have 15+ production lines in various scales from nmol to mol to cover the material request from discovery to commercial. We will add 2 new large scale oligo production plants in 2022 and 2023, respectively.

Are the current analytical tools available for oligonucleotide impurity identification and characterization adequate? Where do you see room for further improvement?

Currently, two approaches are generally used to determine the oligonucleotide impurities: the ion-pairing reversed-phase (IP-RP) chromatography and the anion exchange (AEX) chromatography. For the IP-RP approach it can be directly connected to the high resolution mass (HRMS) spectrometer for the molecular weight determination and tandem MS fragmentation for sequence determination of the unknown impurities. As for the AEX approach, due to the presence of a high concentration of salt in the mobile phase, utilization of HRMS is not an option for the impurity ID or characterization, which may cause extra resources in the analysis of oligonucleotide impurities. Another aspect of the impurity characterization of oligonucleotide impurities, in terms of separation, relies heavily on the separation efficiency of the chromatography method used. Micro-flow methods are still the dominant approaches used in industry but nano-flow methods routinely used in academia, are showing multi-fold increases in separation efficiency. Currently nano-flow is not widely used in industry but we are have dedicated teams determined to incorporate this technology with our customers.

2D HPLC coupled with HRMS is commonly used in academia for research purposes where more attention is on impurity qualification (identification), with limited quantitation. The technique could be a powerful tool for the identification and quantitation of impurities present in oligonucleotide species so adaptation from academia to industry would be a big improvement. In academic setting, thorough analytical methodology, qualification and only limited demonstration of the method reliability would be sufficient. However, the pharmaceutical industry, especially for GMP release, needs to follow ICH guidelines and requires higher standard for the method robustness to qualify and validate the analytical method to ensure reliable and repeatable results for analysis and release. One reason it is not adopted widely by academia is the capability requirement for efficient high-throughput analysis of these complex mixtures. To increase efficiency, our 2D UPLC-HRMS system uses automated instruments and data analysis programing, which would traditionally be performed manually, for the sample pre-treatment: separation, fraction collecting, desalting, 2nd HPLC analysis coupled with HRMS analysis in our case.

WuXi STA has established the capability of 2D UPLC-HRMS for the oligonucleotide impurity analysis that for the 1st dimension the normal AEX would be used for the better separation efficiency between full-length product against n-1, n+1, oxidation, or other types of impurities.

In the 2nd dimension desalting as well as IP-RP chromatography separation that is compatible with quadrupole HRMS for the characterization of impurities in oligonucleotide matrices to achieve maximum accuracy and efficiency. Automated impurity quantitation that is often used in the regular IP-RP approach can be adapted in the 2D UPLC-HRMS analysis as well further decreasing the turnaround time for reporting the results.

Nano-flow chromatography methods can also potentially be a game-changer in the oligonucleotide analysis field due to a multi-fold increase in the separation efficiency. The technique is still yet to be applied in practical application for industry.

What do you feel are the most promising technologies for systemic delivery of oligonucleotides to extrahepatic tissues?

First of all, the majority of oligonucleotide therapeutics (and almost all of the approved nucleic acid drugs) have focused on either local delivery (for example, to the eye or spinal cord) or delivery to the liver. Achieving efficient oligonucleotide delivery, particularly to extrahepatic tissues, remains a major translational limitation.

Nowadays, commonly used strategies employed to improve nucleic acid drug delivery include:

1) Chemical modification to improve 'drug-likeness' (e.g. chemical modification of second-generation gapmer ASOs is sufficient to enable delivery to a wide variety of tissues)

2) Covalent conjugation to cell-targeting or cell-penetrating moieties (e.g. lipids, peptides, aptamers, antibodies, and sugars/GalNAc)

3) The newest approach is nanoparticle formulation (e.g. Lipid Nanoparticles (LNP/Liposome technology). WuXi STA's LNP platform is proving to be a fully scale-able technology able to delivery of oligonucleotides, and other API, in lipid nanoparticles through various assembly structures from R&D to GMP manufacturing.