Case Study

An Integrated Solution to Accelerate a Radionuclide Drug Conjugate to IND

Introduction

Radionuclide drug conjugates (RDC) have shown great potential in the fields of early tumor imaging and radioactive nuclide therapy. A RDC molecule consists of a targeting ligand, a linker, a chelator, and a radioisotope. Peptides serve as ligands in RDC, exhibiting high affinity and binding properties to specific receptors on tumor cells. Because of this complex molecular structure, RDC synthesis is a highly intricate process, requiring a broad spectrum of expertise, including small molecule and peptide synthesis, conjugation chemistry, and radioactive compound handling.

In this case study, we demonstrated a project in which the WuXi TIDES peptide team successfully enabled a challenging RDC to IND filing in three months. Leveraging our extensive expertise and capabilities in peptide and small molecule chemistry, robust synthesis and manufacturing solutions were developed.

Background

A client had a peptide-RDC candidate which has very low purity and yield from its current synthesis route. Without an optimized process to produce enough API, the toxicology and pharmacology studies could not be conducted.

Delivery of milligram scale product in one month

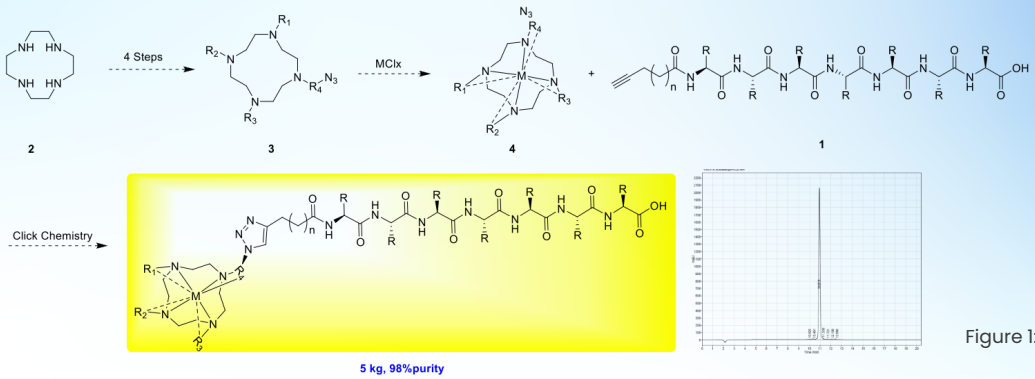

Figure 1: Synthesis route of the RDC

This RDC compound comprised a coordination complex linked to a peptide. To maximize working efficiency, we assigned the process development tasks to two teams in parallel.

The first team, specializing in **solid-phase peptide synthesis** with over a decade of experience, swiftly developed a viable route and synthesized the peptide within a week.

The second team, responsible for **the coordination complex**, faced the challenge of modifying a multifunctional cyclen (Figure 1, compound 2) with regioselectivity issues in the process - The four identical amine groups required different installations. Through these steps, constitutional isomer impurities emerged. The originally proposed process involved additional purifications after each installation, aiming to enhance the intermediate purity but at the expense of the overall yield and atom economy. To overcome these challenges, our team strategically applied a series of orthogonal protections. This approach substantially improved the regioselectivity of the reactions, eliminating the need for multiple rounds of separation and purification.

Both teams proficiently developed the process for the two fragments, and the final compound was assembled after the click chemistry. From this process, we obtained the target RDC compound with a high purity of 98% at gram scale. What set WuXi TIDES apart was our remarkable speed. The entire process R&D took our team only one month, surpassing the client's expectation.

Optimization and scale-up in three months

After the successful toxicology and pharmacology studies, the project steadily progressed forward to the IND filing. The client anticipated the kilogram scale API for upcoming clinical trials. Compared to gram scale synthesis in the earlier phase, which valued mostly speed, the process for manufacturing required additional considerations for cost-efficiency, scalability, and reliability.

In pursuit of more efficient peptide synthesis, the team conducted thorough screenings for each condensation step of the solid phase peptide synthesis route. With each step optimized, the scaled-up process elevated the crude peptide purity to above 85%, suitable for kilogram scale manufacturing.

The chelator synthesis also needed optimization for scale-up. The foremost challenge that the previous process faced was during the azide preparation step (Figure 1, compound 3 to 4). This crucial step was the last reaction before the click chemistry, which had notably low purity and yield. In gram scale, this problem could be overcome by an additional reverse phase chromatography (RPC) purification to enhance the final purity. But in larger scale manufacturing, such additional purification step would incur considerable cost and time. In response, our process chemists started to seek further optimization by systematically screening

various reaction conditions and reagents. Through strategically re-arranging this reaction step to occur before the amine installations and selecting better reaction conditions, we successfully enhanced the final yield by a remarkable six-fold, eliminating the need for the supplementary RPC step. Furthermore, precise pH adjustments during the chelation step resulted in an impressive conversion rate exceeding 90% in merely a ten-minute reaction. With these optimizations in place, the scaled-up process only required a single HPLC purification at the end.

The efficiency of this work was also impressive. The first five-kilogram batch of the API, with the purity exceeding 98%, was delivered to our client in only three months.

Summary

Currently, this RDC has progressed into clinical trials, and the large scale GMP production is ongoing. The WuXi TIDES peptide teams who carried out the discovery synthesis maintained seamless communication with the peptide process development and manufacturing teams, empowering them by the smooth technical and material transfer to GMP manufacturing. In our 'end-to-end' platform, the communication costs in material and technology transfer typically associated with multiple suppliers was minimized, bringing speed and quality to our client.