Synthesis and application of new mixed-mode materials to study the metabolism of drugs used in Poland for the treatment of spinal muscular atrophy

Spinal muscular atrophy (SMA) is a rare genetic disease that is diagnosed in about 100 people a year in Poland. The disease causes atrophy of motor muscles, but also lung or esophageal muscles. As a result, a child suffering from SMA gradually stops moving, grasping, breathing, or swallowing independently. Until the end of 2015, it was a fatal disease. In 2016, the first drug used to treat SMA, Spinraza, was developed. In 2019, another drug, Zolgensma, was developed and began to be used for gene therapy. It is currently the most expensive drug in the world. The oral drug Evrysdi is also currently in use. In Poland, treatment with each of these drugs is covered by reimbursement. Thus, over the past eight years, there has been a breakthrough in the treatment of SMA, which gives great hope to patients and their families.

Nevertheless, to date, no study has linked the type of drug used in SMA therapy to the products of its metabolism in the body (metabolites), their concentration, the type of SMA, or the effectiveness of the therapy. The answers to these questions are very important because these drugs have been used in SMA therapy for a relatively short time. Therefore, it is important to develop appropriate methods to analyze the active substances of Spinraza, Zolgensma and Evrysdi in the plasma and cerebrospinal fluid of patients. Previously used methods in the analysis of similar substances have disadvantages, such as low sensitivity and specificity, long time, and limited separation of metabolites. For these reasons, it is expedient to search for new methods based on new materials synthesized specifically for SMA drug analysis.

For these reasons, the project aims to develop new, sensitive, and specific methods for analyzing the active substances of drugs used in Poland for the treatment of SMA and their metabolites. The research will develop a method to isolate these substances from serum and cerebrospinal fluid using new materials that will allow high recovery and purification. In subsequent stages, an improved method will be developed for the separation and determination of the active substances Spinraza, Zolgensma and Evrysdi and their metabolites. A new generation of analytical techniques and apparatus will be used that will allow their separation and detection in very small quantities. These will include separation techniques (liquid chromatography), mass spectrometry, and new selective adsorbents (designed and synthesized for the project). The use of new materials with mixed hydrophobic-hydrophilic properties is an innovative approach to the problem, allowing to increase in the specificity and sensitivity of the determination of active substances of drugs used in SMA therapy, as well as reducing the time and allowing simplification of measurements. All developed methods will be used to test samples of healthy and SMA patients.

The most important feature of the project is to make significant advances in methods for analyzing drugs used to treat SMA in patients' serum and cerebrospinal fluid. Accurate and more reliable analysis of the active substances of the drugs Spinraza, Zolgensma and Evrysdi can increase the applicability of chromatographic and mass spectrometric techniques for diagnosis, and thus will have an impact on human health. Most importantly for physicians and bioanalytical chemists, the use of these methods in correlation with patients' clinical conditions may provide answers to the question of biomarkers of SMA treatment efficacy. The research performed during the project is novel and of great importance for the treatment of SMA.