The development of new strategies to treat neurodegenerative diseases is currently among the most challenging and expensive tasks for pharma. Only a minor number (3-5%) of brain-directed candidate drugs is reaching the market since most of them are incapable of efficiently crossing the blood-brain barrier (BBB). Various types of nanoparticles (NPs) are considered as versatile drug delivery systems to the brain. *In silico* (computational) methods have been used for supporting *in vitro* and *in vivo* (experimental) studies at the preclinical stage of designing NP-based drug delivery systems. However, classic (physics-based) *in silico* methods are often limited by extensive computational resources and time needed.

The "Fourth Industrial Revolution" brought novel digital solutions for drug discovery based on artificial intelligence (AI) and machine learning (ML). Unfortunately, the application of AI/ML to nanomedicine is still uncommon. There were no attempts to develop ML-based predictive models for designing NP-based drug delivery systems to the best of our knowledge. It raises an important question: *Can machine learning be used for overcoming the limitations of the classic physics-based in silico methods?*

In this project, we hypothesize that the integration of MM with ML methods would significantly increase the potential of *in silico* methods to be used for designing NPs-based drug delivery to the brain (i.e., more structure modifications would be considered, and a more comprehensive description of NPs would be possible at the same time).

The project's overall concept is to select five endpoints (properties of nanocarriers) of high relevance for safe and efficient systemic drug delivery to the brain. We will focus on receptor-mediated transcytosis as the most promising active mechanism of passing the BBB. For each endpoint, we aim to develop in silico models that integrate classic MM with ML methodology for proving the-concept. The selected endpoints are (i) interactions with immunoglobulins (Task 1), interactions with specific protein ligands (Task 2), zeta potential (Task 3), cytotoxicity to endothelial/neuronal cells (Task 4), the ability of oxidative stress generation (Task 5). We will study NPs varying in three elements: (i) core, (ii) surfactant ligands, and (iii) targeting ligands. The candidate NPs will be designed to deliver known drugs for stroke, Alzheimer's Disease, and Parkinson's Disease treatment. The number of possible combinations of NPs' structural features (> 10000) is out of the performance of classic physics-based methods. The integration with ML methods will increase the efficiency of *in silico* techniques by modelling the whole, extensive library in a reasonable time. Besides, we will quantify the influence of the structural features of NPs on the modelled endpoints.

The proposed methodology is based on six original concepts confirmed by preliminary studies. This includes (i) involving ML methods into searching the stable structures in MM; (ii) developing numerical combinations of descriptors for individual components of the nanostructure and descriptors related to interactions between these components; (iii) expressing NPs activity in ML models as a function of their interactions with microenvironment; (iv) partial development of ML models based on data derived from MM simulations; and (v) developing the models concerning the known Adverse Outcome Pathways (AOPs).

The project is based on the synergy of partners. The Polish partner has experience in developing AI/ML models for studying relationships between the structural features of NPs and their properties. The Chinese partner has a large MM experience for exploring the chemical interactions at the nano-bio interfaces and designing NPs for nanomedicine.

The confirmation of the central project hypothesis will open new horizons for the digitalization of designing NP-based BBB drug delivery. Since the project is focused on new research methods on nanomaterials properties and the main expected progress will be related to the relationships between the structure, microenvironment, and properties of NPs, it has a significant impact on materials science.