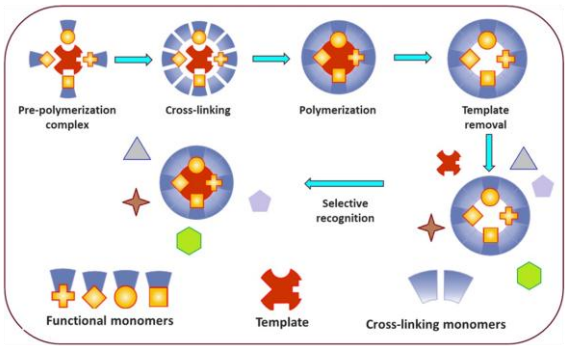
Project scientific goal. Drugs against SARS-CoV-2 are now under intense investigation worldwide as potential therapeutics against other diseases caused by RNA viruses, which use RNA polymerase for replication. These drugs also show activity against Respiratory Syncytial Virus (RSV), pictured left, a major pathogen causing respiratory tract infections in children and infants. RSV infection is currently considered a so-called "compensatory epidemic" arising from COVID-19. Every year, 34 million children under five worldwide suffer from RSV infection, which causes 59,600 in-hospital deaths. Over 95% of children experience RSV infection up to age two, but the current treatment has primarily been symptomatic. If the antiviral therapy is to be effective and safe, it is essential to administer the appropriate drug dose in the first days of infection. That means prompt determining the drug in body fluids becomes crucial for therapeutic drug monitoring and dose adjustment. Therefore, ***the Project's objective*** is to establish the fundamentals, elucidate the mechanism of functioning, and design and prepare molecularly imprinted polymer (MIP) films suitable as chemical sensor recognition units for the chosen antiviral drugs, namely, ***molnupiravir, galidesivir, lufotrelvir***, and ***nirmatrelvir***. Then, we will integrate the MIP films with sensitive transduction units devised within this Project. That will allow the devising of portable chemosensors to selectively and rapidly determine the drug substances directly in patients' body fluids. The devised MIP chemosensors will fulfill the ***unmet medical need*** for their selective bioanalysis by point-of-care testing (POCT). They will also allow the unraveling of pharmacokinetics and optimal dosage regime for ***personalized therapy***. Moreover, these chemosensors can be applied to facilitating ***clinical trials*** by enabling fast determination of the drug substances and their metabolites. Furthermore, the MIP chemosensors can be conveniently integrated with MIP-based drug delivery systems leading to the fabrication of devices used in the emerging field of ***theragnostic***.

Project research methodology. The Project is interdisciplinary. It requires the involvement of specialists from the life, natural, and computational sciences, including pharmacy, bioanalysis, pharmacology, polymer and materials science, as well as analytical and physical chemistry. The modern methodology will ensure the designing of MIP materials capable of selectively binding the chosen drugs, allowing these materials application as recognition units in chemosensors operating in complex biological matrices. The flowchart (pictured right) summarizes the MIP preparation procedure. In this procedure, a pre-polymerization complex is formed in solution between a template molecule and functional monomers bearing suitable functionalities. As the template, either the analyte itself or its close structural analog is used. Next, this complex is polymerized with a cross-linking monomer forming a polymeric network. Subsequent removal of the template molecules leaves in it vacated molecular cavities of the size, functionality, and shape matching those of the template molecules. These cavities are then capable of selective binding of analyte molecules even in the presence of close structural interfering analogs.



We will apply the above procedure to devise chemosensors selective for the chosen antiviral drugs determined in a complex matrix of body fluids. For that, we will design and synthesize a range of carbazole and dithienopyrrole derivatives with suitable functional groups capable of electrochemical polymerization. Extensive, "in silico" modeling will help design monomers capable of effectively binding the analytes, thus forming selective MIPs. The modeling will also study molecular cavity interactions with the molecules of drug substances, their metabolites, and interferences. We will adopt electrochemical, fluorescence, and electrochromic techniques to devise selective and sensitive chemosensors with signal transduction involving the extended-gate field-effect transistors (EG-FETs). Furthermore, we will develop methods for fabricating MIP films with controlled porosity to improve the chemosensors' detectability and response time.

Expected impact of the research. The Project's positive outcome will strongly influence bioanalysis and pharmacokinetics by supporting its dynamic development. Designing and fabricating novel "intelligent" materials such as MIPs for efficient recognition of drugs in natural complex matrices will allow for devising new bioanalytical tools that will enable less time-consuming and more environmental-friendly and cost-effective research on drug pharmacokinetics. Moreover, they will facilitate clinical trials of the new drugs. Our research results will contribute to the faster development of pharmacology due to the possibility of broader conduct of personalized pharmacokinetic studies. Furthermore, it will contribute to developing the emerging field of theragnostic, i.e., the combination of diagnostic and therapy.