Project Title:

Development of an innovative platform consisting of lipid-polymer hybrid nanoparticles and microneedles for targeted brain delivery of novel GABAkines favored by reverse transport
Acronim: MiNe2Brain
Project number and Fund: 17811, Science Fund of the Republic of Serbia
Budget: 199,164.12 EUR
Project PI: Prof. dr Snežana Savić (University of Belgrade-Faculty of Pharmacy (FPUB))

Project duration: 24 months
Team members:
Prof. dr Miroslav Savić, Prof. dr Bojan Marković, Assoc. prof. dr Biljana Bufan, Assoc. prof. dr Ivana Pantelić, Doc. dr Tanja Ilić, Assist. dr sc. Jelena Đoković (University of Belgrade-Faculty of Pharmacy (MFUB))
Assist. dr sc. Đorđe Đorović (University of Belgrade-Faculty of Medicine)
Senior Lecturer in Pharmaceutics dr Sonja Vučen, Professor of Pharmaceutics dr Abina Crean, Young researcher, PhD student Laura Koenitz (University College Cork-School of Pharmacy (UCC))

Abstract
Recent exciting discoveries suggest that optimizing the exposure of nervous tissue to drugs used in psychiatry and neurology, which is impeded by the blood-brain barrier, can be achieved by promoting reverse transport through the lymphatic vessels. We propose a new, beyond-state-of-the-art concept for the targeted uptake of drugs into the cervical lymph nodes using dissolvable microneedle array patches (MAPs) in addition to a subcutaneous (s.c.) injection in the ventral neck region. GL-II-73 and DS-II-73, the selected patent-protected drug candidates that modulate GABAA receptors (GABAkines), will be incorporated by methods involving microfluidic technology into lipid-polymer hybrid nanoparticles (LPHNPs) tailored to favor uptake by lymphatics. The hyaluronidase-powered dissolving MAPs containing LPHNPs will be optimized in composition, geometry and dimensions, and assessed in vitro (porcine ear skin) and ex vivo (histologic and immunohistochemical analysis of neck skin, superficial and

deep cervical lymph nodes and brain dura matter). In vivo evaluation in rats of the pharmacokinetics (PK) and biodistribution of two GABAkines following administration of MAPs (intradermally) and LPHNPs (s.c.) will gain insight into the distribution pathway and relative tissue exposure at on-target and off-target sites. The rat model of prolonged dual stress will be used as a proof-of-concept to investigate whether the obtained disposition profiles of MAPs and LPHNPs can be translated into effects in the behavioral domains of pleasure/anhedonia, anxiety and/or cognition. Knowledge transfer for the application of dissolving microneedle manufacturing technology from the University College Cork (UCC) to University of Belgrade-Faculty of Pharmacy (FPUB) will substantially increase the technological readiness of FPUB. All other experiments will be conducted at FPUB, with the University of Belgrade-Faculty of Medicine contributing to research in the field of dissection and isolation. It is expected that the developed GABAkine MAPs will be both technologically robust and biologically relevant, especially in terms of the neuroPK and behavioral results obtained, which will make them patentable. Besides the valuable experience in microneedle patenting that UCC has, the partnership with UCC will help to increase FPUB's performance in attracting international investors, which is an irreplaceable step in the development of pharmaceutical products that require costly regulatory studies.