Artificial siderophores for molecular imaging applications

Modern medicine uses precise and safe tools for recognition of the developing diseases. Among them, molecular imaging has been already recognized as a powerful, non-invasive method used for visualization and quantification of biological processes at the cellular and subcellular levels. Applied for human patients and other living systems, it allows identification of mechanism of infection or tumour growth, as well as monitoring of surgeries or therapies. Multimodal imaging, which harnesses two or more imaging modalities to produce complementary anatomical and molecular information of a living subject, has become a powerful tool in both basic biomedical research and clinical diagnosis. Common is the combination of Positron Emission Tomography (PET) with computed tomography (CT) and magnetic resonance imaging (MRI) techniques. Current developments highlight the potential of combining PET with optical fluorescence imaging (OFI). These developments remain a challenge and the subject of ongoing research. In order to generate the physical phenomena behind particular techniques and to improve the quality of the image, the patient is given the so-called contrast agents, *i.e.* for PET compounds containing radioactive isotopes.

Nature has designed and uses siderophores, produced by bacteria, fungi and plants to bind ferric ions (necessary for the development of almost all living organisms, including microorganisms), thereby providing a competitive advantage in an essentially iron deplete environment. Siderophores have been widely investigated in biomedical research. In recent years our groups have concentrated on developing siderophore based probes for Positron Emission Tomography (PET) imaging of infection using ^{68}Ga-labelled natural siderophores. The excellent coordination properties for Ga-68 has led us to use hydroxamate based natural siderophores for the development of targeted tumour imaging agents and enabled the development of multivalent and targeted bimodal agents combining PET with OFI. Natural siderophores often lack functional groups for modifications, have insufficient coordination properties for certain radiometals, e.g. Zr-89, may have suboptimal *in vivo* properties or limitations for the process of pharmaceutical translation.

In SideroArt we therefore focus on synthetic biomimetic analogues of natural hydroxamate siderophores to reveal their potential as basis for novel non-invasive in vivo imaging agents. Our preliminary investigations showed excellent properties of artificial, ^{68}Ga-labelled ferrioxamine biomimetics for infection imaging, and improved properties for Zr binding. Modification of these candidates allows development of multifunctional chelators for multimodal or multivalent agents. This main objective, i.e. the design and development of novel non-invasive *in vivo* imaging agents, biomimetics for the internalization of ferric-siderophores, and possibly drug delivery systems, will be achieved through an interdisciplinary approach that combines the unique expertise of 4 research groups.

Based on the experience in coordination chemistry E. Gumienna-Kontecka (University of Wroclaw), supported by expertise of E. Wojaczynska in organic synthesis of natural compounds (Wroclaw University of Science& Technology), will focus on the synthesis of cyclic and acyclic analogues of hydroxamate-based siderophores for Ga-68 and Zr-89 radiometal labelling. The radiopharmaceutical know-how of C. Decristoforo (Medical University Innsbruck, MUI) on ^{68}Ga radiolabelling will enable us to directly follow the fate of siderophores biomimetics in vitro. Recognition by siderophore transporters will be performed with support by H. Haas (MUI) in siderophore pathways at the molecular level. In vitro studies on tumor cell lines and microbial cell cultures, followed by biodistribution and PET/CT/MRI/optical imaging studies on relevant animal models of infections and tumours, enabled by the expertise of M. Petrik (Palacky University, Olomouc), will ultimately allow us to validate and prove the proposed concept.