The project goal: Positron Emission Tomography (PET) is a molecular imaging modality widely applied in clinical routine. However, conventional PET imaging is only able to capture physiological information by measuring the concentration of the applied radiopharmaceutical tracers by detecting the two-photon *positron annihilations*. On the other hand, the mechanism of positron annihilation carries information about the tissue microenvironment and the underlying physiological processes. However, this additional opportunity of physiological measurements by capturing the ***multi-photon*** annihilations and positronium (positron-electron bound state) lifetime, has not been explored and applied due to limited photon detection and sensitivity of conventional PET scanners. Recent advancements in PET detectors have led to the introduction of long axial field-of-view (LAFOV) PET with high photon detection sensitivity in clinics. In Europe, the first LAFOV PET (Siemens Biograph Vision Quadra) with the length of 106 cm was installed in University of Bern. In the framework of this project, it will be upgraded for the possibility of ***multi-photon*** detection thus enabling positronium lifetime imaging. The first ***positronium images*** of human brain were recently demonstrated by the Krakow group using the first multi-photon J-PET demonstrator. In this project for the first time, this Polish-Swiss collaboration aims to realize positronium lifetime imaging on the clinically certified LAFOV PET in University of Bern.

The second main challenge for ***positronium*** lifetime imaging is the high complexity and low count statistics of triple coincidences. In this case, the reconstruction and quantification become more challenging and conventional methods are less efficient. ***Artificial intelligence*** (***AI***) will be employed to enhance the efficiency and accuracy of imaging. In particular, physics-guided deep learning will be developed to incorporate the physics domain knowledge of positronium in deep neural network. It will enhance the robustness and trustworthiness of the developed ***AI*** methods. The complementary expertise of Krakow (physics and biology) and Bern (***AI***) provides another unique opportunity to enhance potential for the breakthrough research.

On top of methodological development, this project aims to systematically characterize the underlying physiology of positronium lifetime imaging by investigations of positronium properties in cancer cell cultures in different degrees of malignancy. Co-registered histopathology will also be obtained on both patients and rodents to investigate the influence of physiological factors on positronium lifetime imaging.

Reasons for attempting a proposed research topic: (1) Despite the known principles describing ***positronium*** lifetime in materials, its implementation in clinics needs significant methodological developments and optimization of reconstruction methods, thus the proposed developments may bring several methodological breakthroughs. (2) The implementation of ***positronium*** lifetime imaging may significantly increase the throughput of PET imaging by bringing additional physiological information. This may bring new opportunities to improve disease diagnosis and prognosis for patients and eventually may bring benefits to patients. (3) Despite the application in clinical routine, PET is an expensive medical imaging modality with patient radiation burden. The improved throughput of PET imaging with the gain of additional physiological information brings increased value of economic and radiation burden. (4) LAFOV PET is an emerging PET instrument. The success of this project will achieve the first clinical ***positronium*** lifetime imaging of ***prostate cancer***, which will bring a "killing" application for the novel scanner. (5) The joint Polish-Swiss research program provides a unique opportunity for synergetic integration of complementary expertise of the two collaboration groups to achieve paradigm-shift interdisciplinary research.

Description of research: This project will focus on the case of ^{68}Ga-PSMA PET imaging for ***prostate cancer***, which has been well established in clinical routine, for the methodological developments and proof of concept of ***positronium*** imaging with clinical PET. The acquisition, reconstruction and signal correction of multi-photon imaging on the above-mentioned LAFOV PET scanners will be optimized based on Monte-Carlo simulation and phantom measurements. Two physics-guided deep learning methods, including domain transfer and physics-integrated deep neural networks will be developed. The deep learning methods will be trained on Monte-Carlo simulations, and patient measurements. The validation of the developed methods on two different LAFOV PET scanners enhance further potential of generalization of the developed methods.

The studies of ***positronium*** in cultured cells and cell organoids as well as ***positronium*** imaging of animals and patients, combined with the histopathological assessment will enable for diagnostic interpretation of the ***positronium*** images.

Expected results: (1) A protocol for the acquisition of ***multi-photon*** imaging on the LAFOV PET scanners will be established. (2) ***Multi-photon*** imaging methods, including positronium imaging, will be developed (3) A robust and trustworthy physics-guided deep learning approach (***AI***) will be developed for effective reconstruction and quantification for positronium imaging. (4) The first clinical ***positronium imaging*** of ***prostate cancer*** will be achieved. (5) An in-depth knowledge of the underlying pathophysiology of *in-vivo* ***positronium*** imaging will be achieved.