1. PHD PROJECT DESCRIPTION (4000 characters max., including the aims and work plan, all in English)

Project title: Surface modification of cardiac stents using new coordination compounds and hybrid materials with potential antithrombogenic properties

1.1. Project goals: The scientific goal of the proposed project is to gain the comprehensive knowledge about the relationship between the structure and the morphology of surface-modified metallic or composite cardiac stents, and their mechanical properties, wettability, corrosion susceptibility as well as biocompatibility and biological activity. The surface of stents, made mainly of nitinol (titanium-nickel alloy with shape memory) or Co-Cr alloy is planned to be functionalized by coordination compounds or hybrid inorganic-organic compouds of antithrombogenic and anti-inflammatory properties. The knowledge acquired in the field of basic research on surface chemistry, the way of coordination compounds bonding with the stents' surface and new coordination compounds possesing ligand of antithrombogenic properties, can broaden the current knowledge about functional biomaterials and in the future it can serve as the foundation for application research aimed at using surface-modified metallic biomaterials to create innovative cardiac stents. However, for this to be possible, it is necessary to acquire a fundamental basic knowledge about the relationship between coating's chemistry and their biological properties.

1.2. **Outline:** Percutaneous coronary intervention (PCI) technology has advanced significantly since the first balloon angioplasty by Gruentzig in 1977 [1]. Initial efforts with balloon angioplasty were fraught with exceedingly high rates of restenosis, dissection, and abrupt vessel closure. These initial issues led to the development of the bare-metal stent (BMS) to scaffold vessels, leading to increased acute coronary artery luminal gain and maintenance of luminal integrity. Significant improvement in acute clinical outcomes was noted following the use of BMS, with a 20% to 30% decrease in clinical and angiographic restenosis [2] However, vessel response to stent-mediated vascular injury leads to a significant amount of neointimal hyperplasia, vascular smooth muscle cell migration, and proliferation. This, in turn, leads to negative re-modeling, restenosis, and late luminal loss, portending a high risk of need for reintervention. The drug-eluting stent (DES) was developed to minimize the risk of in-stent restenosis. First-generation DESs have consistently been shown to decrease the risk of restenosis and need for reintervention compared with the BMS [3] Despite proven clinical efficacy in the treatment of coro- nary disease, reports of adverse clinical outcomes, mostly related to stent thrombosis (ST) and late restenosis, raised concerns regarding DES safety and limitation of these devices. Since the initial experience with first-generation DES, significant improvements have occurred with current DES platform technology, leading to increased safety and efficacy [4–6]. Nowadays DES platforms consist of 3 main components: (a) a stent metallic platform or scaffold, made from 316L stainless steel, nitinol and cobalt-chromium alloy, which are corrosion-resistant systems (b) a stent polymer coating that allows for controlled drug release, and (c) a released antiproliferative drug. Within the proposed project it is planned to make studies on the synthesis of new group of antithrombogenic agents (coordination complexes, with ligands possessing already antithrombogenic properties or hybrid inorganic-organic materials), to estimate their biological activity (antiplatelet, antithrombogenic) and to optimize their bonding with the surface of metallic stents. The most desirable would be to obtain a two-component system without the need for a polymer - this would simplify the system and make it more biocompatible, assuming of course the biocompatibility of the antithrombogenic individual.

1.3. Work plan: The works planned for a period of four years are divided into seven research tasks: 1. Synthesis of coordination compounds of desired antithrombogenic properties and their structural characteristic with the use of diffraction methods and spectroscopic studies; 2. Estimation of hemocompatibility and antiplatalet properties; 3. Functionalization of the metallic stents' surface by new synthesized coordination compounds or by inorganic-organic hybrid materials obtained with the use of coordination compounds; 4. Analysis of physico-chemical properties, wettability and free surface energy of surface-modified stents; 5. Estimation of the coatings stability in

environments of body fluids, including blood 6. Analysis of mechanical properties of surface-modified stents; 7. Analysis of the obtained biomaterials (metallic stent with „coating") in terms of their biocompatibility and biological activity (anti-inflammatory, antimicrobial and antithrombogenic one)

1.4. Literature:

1.Sigwart U, Puel J, Mirkovitch V, et al. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. N Engl J Med 1987; 316:701–6.
2. Serruys PW, de Jaegere P, Kiemeneij F, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. N Engl J Med 1994;331:489–95.
3. Stefanini GG, Holmes DR Jr. Drug-eluting coronary-artery stents. N Engl J Med 2013;368: 254–65.
4. Cassese S, Piccolo R, Galasso G, et al. Twelve- month clinical outcomes of everolimus-eluting stent as compared to paclitaxel- and sirolimus- eluting stent in patients undergoing percutaneous coronary interventions. A meta-analysis of randomized clinical trials. Int J Cardiol 2011;150:84–9.
5. Raber L, Magro M, Stefanini GG, et al. Very late coronary stent thrombosis of a newer-generation everolimus-eluting stent compared with early- generation drug-eluting stents: a prospective cohort study. Circulation 2012;125:1110–21.
6. Garg S, Bourantas C, Serruys PW. New concepts in the design of drug-eluting coronary stents. Nat Rev Cardiol 2013;10:248–60.

1.5. Required initial knowledge and skills of the PhD candidate: Knowledge of basic methods of synthesis of coordination compounds (also with the use of Schlenk line, under inert gas) and analytical methods for conducting structural characteristics of new compounds; structural and morphological characteristics of new materials. Willingness to increase the competence in the field of biomaterial chemistry. Very good command of English in writing and speaking, due to planned extensive scientific cooperation. Ability to work in a team. Possibility of being involved in an internship and several shorter study visits.

1.6. Expected development of the PhD candidate's knowledge and skills: The PhD student will acquire interdisciplinary knowledge in the field of modern biomaterials, material engineering, methods of instrumental analysis to characterize the structure, morphology, mechanical properties and basic knowledge in the field of in-vitro and in-vivo biological research. In addition, the doctoral student will gain experience in preparing conference presentations and publications.