6.ΜΗ ΤΕΧΝΙΚΗ ΠΕΡΙΛΗΨΗ

Συμπληρώστε τα ακόλουθα σε απλή γλώσσα και χωρίς αναφορά σε τεχνικές λεπτομέρειες. Η μη τεχνική περίληψη δημοσιεύεται από την αρμόδια αρχή στα πλαίσια της πληροφόρησης της κοινής γνώμης. Για περαιτέρω διευκρινήσεις ακολουθήστε τον σύνδεσμο.

Τίτλος του έργου	Nickel Leaching from Cardiovascular Stents: Development of an In Silico Toxicokinetic Model (NITOXILICO - POST-DOC/0916/0237)
Διάρκεια του έργου	24 months
Λέξεις ευρετηριασμού	Biomaterials Toxicology, In Silico Modeling, Cardiovascular Implants,
Σκοπός του έργου	✓ Βασική έρευνα
	☐ Μεταγραφική ή εφαρμοσμένη έρευνα
	☐ Κανονιστική χρήση (χρήση στο πλαίσιο νομοθετικών απαιτήσεων)
	☐ Προστασία του φυσικού περιβάλλοντος με γνώμονα την υγεία ή την καλή διαβίωση ανθρώπων ή ζώων
	☐ Έρευνα με σκοπό τη διατήρηση ζωικών ειδών
	☐ Εκπαίδευση ή κατάρτιση για την απόκτηση, διατήρηση ή βελτίωση των επαγγελματικών δεξιοτήτων
	☐ Ιατροδικαστικές έρευνες
	☐ Διατήρηση γενετικά τροποποιημένων ζώων που δεν χρησιμοποιούνται σε άλλα πρωτόκολλα
Περιγραφή των στόχων του έργου (π.χ τι είναι επιστημονικά άγνωστο ή ποιές είναι	1) Develop a novel biokinetic murine-based in silico model that will combine a traditional toxicokinetic compartment with a physics-

οι επιστημονικές/κλινικές ανάγκες)	based model to estimate nickel release from an implanted device. The model will link the rate of in vitro nickel leaching from a cardiovascular stent to serum nickel concentrations, to estimate the rate and extent of in vivo release. 2) Evaluate the vessel inflammatory response after stent implantation via an in house developed whole body reflectance imaging system. The effect of stent corrosion will be investigated in order to explore a possible link between the level of nickel ion release, inflammation, and factors thought to initiate in-stent restenosis (ISR).
Ποιά οφέλη αναμένονται από την υλοποίηση του συγκεκριμένου έργου (σε σχέση με τον άνθρωπο, τα ζώα ή το περιβάλλον)	1) Scientific, Technological and Academic Benefits: The proposed work will significantly improve the nonclinical methods used to evaluate corrosion in medical devices. The study will provide cardiovascular device manufacturers with a useful analytical tool to assess corrosion susceptibility and nickel leach and will enable enhancements in material properties, design characteristics and surface processing in order to meet the clinical acceptance criteria and augment the longevity of cardiovascular implants. The suggested in silico toxicokinetic model will provide new avenues for assessing the impact of nickel released from implanted cardiovascular devices by predicting the distribution of nickel in the body based only upon relatively straightforward in vitro experiments. Therefore, the successful completion of the project holds potential to develop alternative approaches that promote the principles of the 3Rs and minimize the use of animals in biomaterial testing. 2) Economic and Social Benefits: The development of the proposed in silico toxicokinetic model and its successful introduction in preclinical testing practices, will enable the consortium to exploit the increased market acceptance of such niche technologies and benefit fully from entry in this rapidly expanding sector. It is anticipated that the current project will lead to the generation of significant intellectual property rights (IPR) related to material properties and design requirements that will open new business opportunities in this huge, competitive marketplace. The collaboration aims to support the development and commercial exploitation of the biokinetic model and to provide opportunities to promote analytical tools for nonclinical testing closer to the market.
Είδος και συνολικός αριθμός ζώων που αναμένεται να χρησιμοποιηθούν στη διάρκεια του έργου	A total of 130 CD1 male mice will be used throughout the study
Στο πλαίσιο υλοποίησης του έργου α. ποιές είναι οι αναμενόμενες δυσμενείς επιπτώσεις στα ζώα, β. ποιό θα είναι το εκτιμώμενο επίπεδο δριμύτητας των διαδικασιών καθώς και γ. ποιά η τύχη των ζώων μετά την υλοποίηση του έργου; *Να αναφερθεί το υψηλότερο εκτιμώμενο επίπεδο δριμύτητας και το ποσοστό των ζώων που αναμένεται να το υποστούν*	(a) A procedural issue that might be encountered is leg paralysis after in situ stenting. This occurs in a small number of mice undergoing the procedure, with a higher incidence (10%) during the initial development of the technique. Another complication that may rarely arise (<5% of cases) is tail tissue necrosis during the injection of MMPSense-680. (b) The severity level of the proposed procedures is: moderate for WP5: Task 5.1, mild for WP6 and non-recovery for WP5: Task 5.2. (c) Mice will be euthanized and tissue samples will be harvested. During non-recovery procedures the animal is placed under

	general anaesthetic before the start of the procedure and is humanely killed without ever regaining consciousness
Οι αρχές των 3R	
Αντικατάσταση (Replacement) Γιατί είναι απαραίτητη η χρησιμοποίηση ζώων και όχι κάποια άλλη εναλλακτική μέθοδος πειραματισμού που δεν χρησιμοποιεί ζώα;	Even though metal implants experience different levels of wear and corrosion due to the mechanical and biochemical environment at the implantation site, there is currently no recognized standard test method for metal ion release from medical implants. While nickel release from these devices is typically characterized through in vitro immersion tests, it is unclear if the rate at which nickel is released from a device during in vitro testing is representative of the release rate following implantation in the body. To address this uncertainty and in an attempt to better understand current test practices and improve nonclinical testing, this study aims to develop a novel biokinetic murine-based in silico model to determine concentrations of released nickel ions from cardiovascular stents into the human body over time. The model will link the rate of in vitro nickel leaching from a cardiovascular stent to serum nickel concentrations, to estimate the rate and extent of in vivo release. The suggested in silico toxicokinetic model will provide new avenues for assessing the impact of nickel released from implanted cardiovascular devices by predicting the distribution of nickel in the body based only upon relatively straightforward in vitro experiments. Therefore, the successful completion of the project holds potential to develop alternative approaches that promote the principles of the 3Rs (Replacement, Reduction, Refinement) and minimize the use of animals in biomaterial testing.
Μείωση (Reduction) Τι μέτρα θα εφαρμοστούν ώστε να χρησιμοποιηθεί ο μικρότερος αριθμός ζώων χωρίς να επηρεαστούν τα ερευνητικά αποτελέσματα;	A total of 130 animals will be used throughout the implementation of the proposed study. To reduce the use of animals to a minimum, experiments have been carefully planned (considering the information that should and/or can be extracted by using fewer animals) and procedures will be performed by well-trained personnel. Also, the minimum required number of animals will be used for each experiment. Furthermore, statistical analysis will be taken into account in designing the experiments in order to obtain information and extract conclusions without the need to perform animal experiments, where possible. Finally, the project will apply novel imaging tools and methods that allow for in vivo investigations of complex biological processes of the host vascular wall response. The ability to track cellular changes within the same animal over time enables the dynamic monitoring of the response at different time points and thus avoiding the need to collect blood samples or sacrifice multiple animals.
Βελτίωση (Refinement) Λαμβάνοντας υπόψη τους στόχους του έργου εξηγήστε την επιλογή σας ως προς την επιλογή σας ως προς το είδος, το/τα πρότυπο(-α) και τη/τις μέθοδο(-ους). Εξηγήστε για ποιο λόγο είναι τα πλέον ενδεδειγμένα για τον προβλεπόμενο σκοπό. Τι μέτρα θα εφαρμοστούν ώστε τα ζώα να υποβληθούν στη μικρότερη δυνατή	Specific pathogen-free male CD1 mice, weighing 35±5 g (12-16 weeks old), will be used for all experiments. The CD1 species was chosen (based on previous experience; see Kapnisis et al. 2016) as the most appropriate for both the stent deployment and the in vivo imaging studies. The use of specific pathogen-free mice ensured that specified diseases did not interfere with the monitoring of the inflammatory response in our experiments. The CD1 (albino) strain was specifically chosen for its relatively large body size and its reduced tissue autofluorescence. Male mice were used to avoid errors due to sex idiosyncrasy owing to the positive effect of estrogen on inflammation-

ταλαιπωρία;	related diseases [40]. To refine the way experiments are carried out, and to make sure that animals suffer as little as possible, all experimental procedures will be performed based on the European Directive 2010/63/EE and Cyprus Legislation for the protection and welfare of animals, Laws 1994-2013. Animals will be maintained in cages with free access to water and food and will be kept under a 12h light/dark cycle in a temperature-controlled environment (22°C, 45% humidity). Mice will be kept in an individually ventilated cage (IVC) system at the licensed animal facility at Cyprus University of Technology and will be periodically screened for health status. In addition, to minimize pain and suffering as well as to improve animal welfare, in cases where their health is compromised (as part of an experiment), they will be closely monitored. To reduce the pain during in vivo procedures, animals will be pre-treated for 48 h with aspirin (75 mg in 250 mL drinking water) and general anesthesia will be induced with isoflurane (3% for induction and 1.0-1.5% for maintenance of general anesthesia). The exposed femoral artery and vein will be bathed in a solution of 1% lidocaine hydrochloride. All the procedures will be performed in the animals' environment (mouse facility) by the well-trained personnel undertaking the study and experiments shall be terminated if animals suffer in accordance with published protocols, data in bibliography and regulations.