

**PROGETTO DI RICERCA**

Dott. Francesco Alfano

**Titolo**

Clinical, instrumental and laboratory assessment of the atherosclerotic burden in women with emerging gender-related risk factors for atherosclerotic cardiovascular disease.

**Abstract**

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death in women (1). In the last decades, women have been underrepresented in cardiovascular clinical trials, or excluded from them: this has reduced the ability to measure the safety and efficacy of therapies for women, the potential for identifying sex-specific differences in important outcomes and the development of sex-specific strategies for the prevention and management of cardiovascular disease (2). For this reason, ASCVD in women remains globally understudied, under-recognized, underdiagnosed, and undertreated. Distinct strategies are urgently needed to tackle inequities in the diagnosis, treatment and prevention of heart disease in women in order both to advance innovative solutions for early detection and to understand the underlying biological mechanisms that contribute to sex-specific differences in outcomes (3). In this setting, there is emerging evidence that novel sex-related risk factors may play a fundamental role in the progression of atherosclerosis leading to ASCVD. The aim of this research project, in this context, is to understand the possible role of circulating biomarkers of inflammation, haemostasis, extracellular matrix remodeling and atherosclerosis in the prediction of presence and progression of atherosclerotic burden in women with emerging sex-related risk factors for ASCVD.

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**PROGETTO DI RICERCA**

Dott. Giuseppe Bifulco

**Titolo**

NUTRition and Artificial Intelligence for MUSculoSkeletal health (NUTRAIMUSK)

**Abstract**

Nutritional status is a critical aspect of overall well-being and health and can significantly influence the prognosis of hospitalized patients, especially those undergoing surgical procedures. Maintaining a healthy diet throughout life is a powerful tool for the primary prevention of many chronic degenerative non-communicable diseases. In particular, an adequate protein, calcium and minerals food intake, along with the maintenance of optimal vitamin D status, play a key role for preservation of musculoskeletal health. Identifying nutritional indices that can predict the clinical outcome of patients is critical for improving care management. The integration of artificial intelligence (AI) models into clinical management represents an advanced frontier in medicine. This research project aims to develop an innovative and practical AI model to predict the outcome of hospitalized patients using nutritional status indices. Through a systematic approach that includes data collection and preprocessing, model development and validation, and clinical implementation, the project aims to significantly improve the quality of care and patient outcomes. Collaboration between nutrition experts, clinicians, biomedical engineers and data scientists (collaboration with Scuola Superiore Sant'Anna, Pisa) will be fundamental to the success of this project.

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**PROGETTO DI RICERCA**

Dott. Marco Del Carria

**Titolo**

Deciphering the Clinical and Immunological Landscape of Antisynthetase Syndrome-Associated Interstitial

Lung Disease

**Abstract**

Antisynthetase syndrome (ASS) is an autoimmune rare disease characterized by typical clinical features (Interstitial Lung Disease-ILD, myositis, arthritis, fever, mechanic's hand, Raynaud's phenomenon) along with the presence of one of the eight anti-aminoacyl-tRNA synthetase antibodies. Pathogenesis is largely unknown. This project aims to investigate the clinical and immunological landscape of ASS-ILD in newly diagnosed and previously diagnosed patients. Peripheral blood and bronchoalveolar lavage fluid samples will be analyzed using flow cytometry and single-cell multi-omics to identify phenotypic and functional features of immune cells, uncovering unique immune signatures of ASS-ILD. This analysis will advance our understanding of ASS-ILD biomarkers and pathogenesis, unraveling new targets for more effective treatment.

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**PROGETTO DI RICERCA**

Dott.ssa Cecilia Maria Esposito

**Titolo**

Lived experience of Body and Identity in subjects affected by Fibromyalgia

**Abstract**

Fibromyalgia is an emerging and prevalent clinical condition that significantly impacts quality of life. Despite the different etiopathological hypotheses, there is agreement in considering it a pathology bordering between the psychic and the somatic. However, to our knowledge, no research has yet considered the experiential dimension of these patients, their lived experience of the body, identity and diagnosis. Our research hypothesis, along the lines of clinical phenomenology, is that subjects affected by fibromyalgia are suffering of Optical-Coenaesthetic Disproportion, relying on external models rather than their perception from within to feel their body and define their identity. The aim of this project is to analyze a sample of 40 subjects affected by fibromyalgia and evaluate them from a psychometric and experiential point of view, to understand how they experience the body, identity and diagnosis, as well as which factors (i.e. gender, duration of illness, psychopathology) influence it.

Understanding the first-person experience of patients is of fundamental importance as it aims to develop a person-centered treatment and not just a disorder-centered one, with a view to the interdisciplinary integration of psychological and medical fields.

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**PROGETTO DI RICERCA**

Dott.ssa Alessia Frosini

**Titolo**

Activity and resistance mechanisms of new  $\beta$ -lactams and  $\beta$ -lactam/ $\beta$ -lactamase inhibitor combinations against clinical and environmental isolates of carbapenem-resistant *Enterobacterales*

**Abstract**

Carbapenems are last resort  $\beta$ -lactams with a broad-spectrum activity, but the recent worldwide spread of carbapenem-resistant *Enterobacterales* (CRE) represents a limit for their clinical applications. *Enterobacterales* resistance to carbapenems is contributed by several mechanisms, including membrane permeability alteration, resident  $\beta$ -lactamases overexpression, PBP alteration and carbapenemase genes

acquisition (mostly represented by *blaKPC*, *blaOXA-48*, *blaNDM*, *blaVIM* and *blaIMP*).

In 2017, the World Health Organization listed CRE among critical pathogens for which new drugs should be urgently developed due to the lack of effective therapies and high mortality rates of associated infections. CRE spread is usually contributed by intestinal carriage of hospitalized patients, but is rising also in the community, among animals and in the environment, consequently requiring a “One Health” approach to limit their diffusion.

Novel  $\beta$ -lactams and  $\beta$ -lactam/ $\beta$ -lactamase inhibitor combinations (BLICs) have been recently introduced in the clinic practice (cefiderocol, ceftazidime/avibactam, ceftolozane/tazobactam, meropenem/vaborbactam, imipenem/relebactam and aztreonam/avibactam) and several other promising combinations are in development process, but resistant isolates have been already reported confirming the relevance of CRE spreading problem for the global health.

This project aims to characterize genotypically and phenotypically a collection of clinical and environmental CRE strains from acute care and long-term care clinical settings and wastewater treatment plants with the purpose of monitoring CRE spread, assessing the activity of novel  $\beta$ -lactams and BLICs, characterizing potential unknown resistance mechanisms, finding innovative therapeutic strategies and optimizing current surveillance strategies to limit their diffusion in both nosocomial settings and the environment.

The isolates will be plated on CRE selective media, identified by mass spectrometry and screened for the detection of the most common carbapenemase genes. Then, antimicrobial susceptibility testing to cefiderocol and/or novel BLICs and whole genome sequencing will be performed to characterize their resistome, virulome and clonality. Finally, potential novel  $\beta$ -lactamases will be studied with mobilization and cloning experiments and characterized with biochemical methods (involving expression, purification and kinetics experiments).

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## **PROGETTO DI RICERCA**

Dott. Alberto Galeotti

### **Titolo**

Studio longitudinale prospettico di correlazione tra i dati quantitativi delle cartilagini di accrescimento del ginocchio ottenuti tramite RM con Tensore di Diffusione e la velocità di crescita degli arti inferiori in pazienti in accrescimento scheletrico con eterometria degli arti inferiori

### **Abstract**

La crescita scheletrica residua e la velocità di crescita rappresentano due parametri di fondamentale importanza nell'Ortopedia Pediatrica, con implicazioni in molteplici condizioni cliniche, tra le quali la scoliosi e le altre deformità vertebrali, le deviazioni assiali degli arti inferiori, l'eterometria degli arti inferiori. Infatti, per una gestione ottimale di queste condizioni patologiche, l'ortopedico pediatrico deve essere in grado di prendere delle decisioni non solo in base ai dati clinici ottenuti alla valutazione del paziente ma anche prevedendo come questi potranno modificarsi con la crescita.

Questo risulta ad esempio di fondamentale importanza nel caso di eterometria (differenza di lunghezza) degli arti inferiori, una condizione clinica di frequente riscontro.

La previsione del calcolo della velocità di crescita degli arti inferiori e della stima della differenza di lunghezza degli arti inferiori a fine della crescita risulta di fondamentale importanza per scegliere la tipologia di trattamento corretto per il paziente e, in caso di scelta di intervento di epifisiodesi, anche per scegliere il timing corretto. Infatti, al contrario degli interventi di allungamento scheletrico che vengono eseguiti sull'arto più corto a fine della crescita, l'epifisiodesi viene eseguita sull'arto più lungo durante il periodo di accrescimento rallentandone la sua crescita e permettendo all'arto più corto di continuare a crescere e annullare la differenza di lunghezza. In questo caso se l'intervento dovesse essere eseguito troppo precocemente porterebbe a una iper-correzione, mentre in caso fosse eseguito troppo tardi porterebbe a una ipo-correzione.

I metodi di previsione di crescita attualmente in uso sono svariati: Green and Anderson Growth Remaining Model, Moseley Straight-Line Graph Method, Menelaus /White—Arithmetic Model, DiMeglio Method, Paley Multiplier Method.

Essenzialmente, la maggior parte dei metodi si basano fortemente sul lavoro iniziale di Green e Anderson, che ha raccolto e catalogato i dati di una ampia popolazione di riferimento, e ciascuno tenta di utilizzare questi dati in modi diversi (matematicamente e/o graficamente). Si parte dunque da una raccolta di dati di popolazione generale da cui si ricava informazioni per il singolo paziente. Questi dati però risalgono ormai alla prima metà del secolo scorso e derivano da una popolazione sana di un'unica etnia. Per questo motivo i metodi sopra elencati, nonostante ancora universalmente accettati ed applicati, sono stati messi in discussione e numerosi lavori dimostrano come il loro utilizzo possa portare ad errori di previsione. Per poter approcciare al meglio questa condizione sarebbe dunque necessario un metodo individualizzato sul singolo paziente che, sulla base dell'attività biologica delle cartilagini di accrescimento, possa predire la velocità di crescita e la crescita residua degli arti inferiori del paziente.

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## **PROGETTO DI RICERCA**

Dott. Luca Lambertini

### **Titolo**

International Curriculum for Single Port Robot Assisted surgery. Development, validation and clinical assessment of a multicentre standardized simulation program to minimize the learning curve burden on patient outcomes after new minimally invasive approaches.

### **Abstract**

Surgeons learning phase can increase the patients risk to achieve inferior outcomes relatively to those treated when adequate experience is accumulated, also in case of robot assisted procedures<sup>1</sup>. In this light, the development of validated trainings for the Multi Port (MP) robotic platforms has shown to significantly improve patient surgical outcomes in this setting<sup>2</sup>. The daVinci Single-Port<sup>1</sup> (SP) platform (Intuitive Surgical, Sunnyvale, CA) represents the latest innovation in the field of surgical technology, allowing to perform also complex surgeries extraperitoneally, with a supine patient positioning and through a single skin incision. These factors further minimized the impact of robot assisted surgery on the USA patients health care pathways allowing to successfully perform several major urological procedures in an outpatient setting. Notwithstanding its recent approval and introduction in Europe for several disciplines, the development of a standardized and validated training program still represents an unmet need.

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## **PROGETTO DI RICERCA**

Dott.ssa Rossella Nicoletti

### **Titolo**

Development of an Artificial-Intelligence based risk stratification model for non metastatic Prostate Cancer patients to predict oncological outcomes using Big data within the OPTIMA oncology project – *Optimal treatment for patients with solid tumours in Europe through Artificial Intelligence*

### **Abstract**

Prostate cancer (PCa) is the second most diagnosed cancer in men, with non-metastatic disease accounting for more than 70% of the new diagnosis. The current European Association of Urology (EAU) guidelines suggest stratifying patients with non-metastatic PCa (Localized and Locally advanced) disease into risk group using D'Amico's classification system for PCa as a guide for treatment plan.

Recent evidences suggested that overall mortality of the available treatments choices for non-metastatic PCa, namely Active Surveillance (AS), Radiotherapy (RT) and Radical Prostatectomy (RP), were low. However, when compared to AS, RP and RT reduced disease progression, highlighting the need for new stratification tool for patients with non-metastatic PCa, aiming to find a trade-off between encountering higher risk of disease progression with AS versus experience the treatment's related adverse effects of RP and RT.

The OPTIMA Oncology is a multistakeholder consortium working in research programs seeking to use artificial

intelligence (AI) to improve care for patients with cancer, establishing the roots in the PIONEER project (the European Network of Excellence for Big Data in Prostate Cancer) on big data analysis.

We aim to clinically characterize patients with non-metastatic PCa, externally validate the D'Amico Risk groups and to optimize the EAU Guideline risk stratification to better predict oncological outcomes, in men with localized and locally advanced PCa, using artificial intelligence and real world data in an international federated network across multiple data sources within the OPTIMA Oncology Project.

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## **PROGETTO DI RICERCA**

Dott.ssa Elisa Berni

### **Titolo**

A possible association linking frailty and biological and clinical characteristics of older patients with atrial fibrillation. A key to an age-oriented approach

### **Abstract**

Atrial fibrillation (AF) is the most common arrhythmia in older people and has emerged as a growing and significant concern in public health due to the expanding of elderly population; it is strictly associated to frailty, a multi-factorial syndrome related to ageing that impairs the health condition of AF patients and their treatment. To date, the scientific research has not yet been able to identify the main triggers that lead to AF, although inflammaging has presumably an important role in its pathogenesis. Recently, a correlation between AF and NAFLD (Non-Alcoholic Fatty Liver Disease) has been underlined; these pathologies share many risk factors, and their appearance is often concomitant. The proposal of this project is to deepen the relation between AF and NAFLD in the context of ageing. Both a clinical study on different aged group of AF patients and a cellular and molecular biology study will be performed; in particular, targeted metabolomic studies using liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) will be assessed on patients' plasma, looking for different metabolites related to inflammation, fibrosis, tissue and cellular damages. Moreover, interactions between hepatocyte cell lines and cardiac or cardiac-like cells will be examined, and different molecules and pathways will be investigated. Furthermore, we planned to explore in the biological and clinical grounds the effects of a rhythm-control strategy of AF versus the rate-control one to hinder frailty development or to reverse the condition in older patients with the arrhythmia.

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## **PROGETTO DI RICERCA**

Dott.ssa Maria Canfora

### **Titolo**

Oxidative Stress biomarkers and thrombotic involvement in patients with Antiphospholipid Syndrome and asymptomatic carriers: the SISTOS study

### **Abstract**

Thrombotic antiphospholipid syndrome (APS) is an autoimmune condition characterized by both venous and arterial events associated with a hypercoagulable state due to the persistent presence of circulating antiphospholipid antibodies (aPLs). APS is a paradigmatic thromboinflammatory disease, coupling inflammation and thrombosis, which contributes to the pathophysiology of cardiovascular (CV) disease. Oxidative modifications are implicated in the formation of aPLs, which in turn may favour the oxidative imbalance in APS patients that may contribute to the progression of the atherosclerotic process and to the onset of thrombotic complications. The aPLs positivity in asymptomatic carriers without clinical manifestations seems to predispose to thrombotic events and subclinical atherosclerosis development.

To date, no study has investigated oxidative stress in patients with thrombotic APS and in aPLs carriers. On these bases, an observational, monocentric, prospective cohort study will be conducted on APS patients and aPLs carriers to assess: 1- the role of oxidative stress in the pathophysiology of thrombosis and 2- the

relationships between biomarkers of oxidative stress and early signs of thrombotic risk, evaluated by carotid artery intima-media thickness (IMI) and femoral vein wall thickness (VWT) by ultrasound (US). This project will shed light on the pathogenic mechanisms of inflammation-induced thrombosis in APS patients.

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## **PROGETTO DI RICERCA**

Dott. Roberto Falso

### **Titolo**

Protocollo "zero-contrasto" nel trattamento endovascolare della patologia aortica complessa

### **Abstract**

The use of iodinated contrast medium (ICM) in patients undergoing endovascular repair of abdominal aortic aneurysm may be associated with a deterioration of renal function (contrast-induced nephropathy, CIN), especially in those patients with a pre-existing renal impairment.

ICM can potentially damage renal function not only intraoperatively, in fact its use is still the gold standard both in the preoperative evaluation of the aneurysmatic disease and during follow-up to perform computed tomography angiography scan (CTA-scan), according to international guidelines.

Nowadays, the development of nonnephrotoxic mediums of contrast, such as carbon dioxide (CO<sub>2</sub>), allows to perform endovascular procedures paying more attention to this kind of issues. Immediately after the procedure and during follow-up, patients that underwent endovascular aortic repair (EVAR) without iodinated contrast medium showed values of serum creatinine and eGFR comparable to the preoperative ones.

According to this evidence, we recently evaluate the efficacy and safety of a zero-contrast protocol in patients with an infrarenal abdominal aortic aneurysm (AAA) that were candidates to EVAR. This protocol consisted in preoperative plain-CT and duplex ultrasound (DUS) evaluation, followed by a CO<sub>2</sub>-EVAR procedure and then with a follow-up program consisting in plain-CT at one month and DUS evaluation with or without nonnephrotoxic medium of contrast (contrast enhanced ultrasound, CEUS), performed at 3, 6 and 12 months. In patients with more extended aneurysmatic disease, such as juxta/pararenal aneurysms or thoraco-abdominal aneurysms (TAAA), the damage for renal function could be even worse, given the greater complexity of the procedure and the need to use greater quantity of ICM.

The aim of this study is to evaluate the feasibility, the safety and the efficacy of a zero-contrast protocol for patients with initial renal impairment (CDK 3a-3b) that underwent to complex endovascular aortic repair, starting from preoperative assessment to follow-up

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## **PROGETTO DI RICERCA**

Dott.ssa Nunzia Porro

### **Titolo**

Oncostatin M as a pro-inflammatory cytokine modulating intrahepatic cholangiocarcinoma progression and tumor-stroma interaction

### **Abstract**

Intrahepatic cholangiocarcinoma (ICCA) is the second most frequent primary liver cancer, and its incidence is increasing worldwide. It is associated with a high mortality rate due to its silent presentation and thus, with a late diagnosis, highly aggressiveness and resistance to treatment. Increasing evidence highlights that oncostatin M (OSM) acts as a pro-tumorigenic cytokine, specifically regulating the tumor microenvironment (TME) and orchestrating the crosstalk between cancer and stromal cells. CCA TME is characterized by an abundant desmoplastic stroma in which each component (cancer-associated fibroblasts (CAFs), tumor-associated macrophages (TAMs) and immune cells, support and promote tumor progression.

This project aims at elucidating a novel aspect of the stroma-tumour interaction in CCA, analysing in vitro and in vivo the biological effects of OSM in iCCA cells, including tumour progression, cell proliferation, and motility, and epithelial mesenchymal transition (EMT). The role of OSM in the crosstalk between iCCA cells, macrophages, and human, hepatic stellate cells (HSCs, main source of CAFs) will be also evaluated, by employing 2D systems and 3D scaffolds. These results will be translated in an orthotopic mouse model injected with iCCA cells silenced for OSMR and in myeloid cell-specific LysCre OSMR-KO mice. In addition, the project will be pursued by analysing the prognostic value of OSM expression and OSM-related genes and mediators in iCCA plasma/serum samples and liver specimens, outlining their significance in relation to clinical parameters.

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**PROGETTO DI RICERCA**

Dott. Roberto Presta

**Titolo**

Polypharmacy and Inappropriate Prescriptions: Clinical Implications for Frail Elderly Nursing Home Residents

**Abstract**

The growing elderly population has led to a rise in the number of admissions to nursing homes. However, clinical research remains sparse in this setting, mainly due to high organizational fragmentation. Among the concerning issues of institutionalized older patients, the high prevalence of polypharmacy and inappropriate drug prescriptions has significant implications for both patients and the healthcare system. This project aims to retrieve data from routine practice to estimate the prevalence and clinical implications of polypharmacy and potentially inappropriate prescriptions in older persons living in a sample of northwestern Italian nursing homes.

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**PROGETTO DI RICERCA**

Dott.ssa Ilaria Rapi

**Titolo**

Exposure Mapping and Risk Mitigation using exposome approach: Enhancing Worker Safety through Advanced Monitoring of new Airborne Hazardous Substances

**Abstract**

Evaluating human exposure to Airborne Hazardous Substances (AHSs) in the workplace is crucial to understanding the causes of many occupational diseases. Emerging technologies, such as 3D printers, can emit certain types of AHSs, namely nanoparticles and Volatile Organic Compounds (VOCs), that pose health risks, including carcinogenic effects. Furthermore, in recent years, the European Commission has regulated substances such as diisocyanates, utilised in various industrial sectors, due to their potential to sensitise the respiratory system and skin. Exposome, using wearable and portable devices, is a promising approach for the continuous monitoring of AHSs and integrates perfectly into the One Health principle, which connects human and ecosystem health. The devices collect detailed data without interfering with work activities, enhancing the understanding of multiple exposures and their cumulative impact. This research uses advanced devices to monitor AHSs, analyse the resulting data, and develop an adaptive response algorithm to implement prevention actions in response to the AHSs encountered. Expected outcomes from this work include exposure mapping, effective control measures, and increased worker safety.