

1. Dott.ssa Anna Barbiero

Titolo Progetto di Ricerca

“One-Health” approach for the analysis and surveillance of phlebotomine-borne infectious agents in Tuscany Region, Italy

SUMMARY

Emerging and re-emerging infectious vector-borne diseases represent a global threat that goes beyond the health sphere; not only previously geographically localized infections are spreading globally, but also vector-borne diseases that have for long time been endemic in our country, are now facing relevant changings in their distribution. Cases of human leishmaniasis and Toscana virus (TOSV) infection, both caused by sandflies of the genus *Phlebotomus* (phlebo-borne diseases), have been rapidly increasing in the past years in Tuscany Region and the epidemiological characteristics of these pathologies are changing alarmingly. In order to obtain a deep comprehension of how phlebo-borne diseases are evolving and therefore elaborate efficient foresight strategies for their management and control, innovative and integrated surveillance systems and advanced skills in monitoring their spreading are strongly needed. We propose a research project aimed at analyzing the dynamics of emerging and re-emerging phlebo-borne diseases in Tuscany Region, Italy, through an interdisciplinary and innovative surveillance approach, in a “One-Health” perspective.

2. Dott. Edoardo Biancalana

Titolo Progetto di Ricerca

Study of Epigenetic MArkers for Anti-TNF TherapeutiC Response in Liquid Biopsy sample of Patients with BEhçeT Syndrome (MACBETH study)

SUMMARY

Behçet’s syndrome (BS) is a rare systemic vasculitis that can involve the skin, mucosa, joints, vessels, eyes, nervous and gastrointestinal systems, so that is referred to as a syndrome rather

than as a unique and distinct disease. These manifestations may present alone or co-exist in the same patient in specific clusters which require different treatment strategies. The therapeutic approach includes systemic corticosteroids, colchicine and traditional or biological immunosuppressive agents. Among biologics, anti TNF- α molecules play a central role. Limited response to anti TNF treatments varies among different disease phenotypes. Since early treatment is crucial to reduce relapsing risk and prevent permanent impairments, it would be helpful to preventively identify patients that can benefit from anti TNF- α treatments.

An observational, monocentric, cross-sectional, pharmaco(epi)genetic study will be conducted on liquid biopsy samples of 50 BS patients treated with anti TNF- α drugs (25 responders and 25 non-responders) with the aim to identify genetic and/or epigenetic biomarkers of clinical response to anti TNF- α agents. The study will provide innovative, easily accessible biomarkers to guide clinicians in the best patient-tailored therapeutic choice for this rare and complex condition.

3. Dott.ssa Sara Ceccatelli

Titolo Progetto di Ricerca

Psychosomatic assessment and intervebtion in fibromyalgia

Abstract

Fibromyalgia is a widespread musculoskeletal pain syndrome. It is characterized by physical manifestations which are also the expression of a psychological distress as well as specific illness attitudes and behaviors. Indeed, it is considered a psychosomatic disorder. In this framework, we hypothesize the clinical utility of a psychosomatic assessment guided by rheumatologists and clinical psychologists (Study 1) and the utility of an integrated multidisciplinary psychosomatic intervention based on cognitive restructuring/psychoeducation followed by museum therapy (Study 2). For Study 1 a cross-sectional observation study will be implemented, for Study 2 a randomized controlled trial will be applied.

4. Dott.ssa Laura fortuna

Titolo Progetto di Ricerca

Surgery for gastric and colorectal cancer in elderly patients: assessment of the impact of the robotic approach in association qith a prehabilitation program

Gastric and colorectal tumors represent two of the leading causes of cancer-related death worldwide. Aging plays a major role in the development of these two tumors and their incidence has gradually increased in patients aged 65 and older, over the past decade [1]. Consequently, the increase of the elderly population makes these two cancers a major socio-health problem.

Surgery remains the mainstay of radical treatment for gastric and colorectal cancer. It is well known that surgery is a major stressor and subsequently is associated with significant postoperative morbidity [2]. Opposed to nonelderly patients, elderly patients usually suffer comorbidities and have poor functional capacities that may not allow them to endure severe surgical trauma. Complications strongly impact the postoperative and long-term outcomes of older patients as well as their quality of life. Furthermore, complications impact healthcare systems due to prolonged length of stay, higher readmission rates, and increased costs.

Enhanced Recovery After Surgery (ERAS) programmes have been demonstrated to reduce morbidity rates and hospital length of stay even in elderly patients, the majority of the scheduled interventions focus on the intra- and postoperative factors. The preoperative period, though limited to 4-6 weeks can be optimally used to introduce prehabilitation that includes various professional figures (anesthesiologists, surgeons, dieticians, physiotherapists, geriatricians, sports doctors and psychologists) who can prepare the patient by optimizing and increasing his functional capabilities before the surgery [3,4]. The ultimate goal is to reduce the incidence of surgical complications, the time of hospitalization and post-operative rehabilitation in older and frail patients who need major surgery [5,6].

Frail older people are less able to tolerate the stress of medical illness, hospitalization, and immobility; consequently, surgery may be a substantial problem in this population. Minimally invasive surgery (MIS) has been shown to be better tolerated than open surgery, in selected elderly populations. In fact, MIS is often associated with less postoperative pain, faster mobilization, better respiratory function recovery, reduced morbidity, faster recovery, and no difference in oncologic outcomes as compared to open surgery [7,8]. Recently, robot-assisted surgery has been introduced to overcome many laparoscopic drawbacks and limitations, thus allowing more patients to benefit MIS. However, some concerns are recognized in the use of robotic in the elderly population, especially when considering a longer operative time as reported by several studies; furthermore, some procedures require prolonged and steep Trendelenburg position (e.g., rectal surgery), with possible consequences about pulmonary and cardiovascular implications [9,10].

5. Dott. Antonio Andrea Grosso

Titolo Progetto di Ricerca

International REgistry of COnservative or Radical treatment of localized kiDney tumors (i-RECORD)

Abstract

Partial Nephrectomy (PN) is the gold standard treatment for localized renal masses and should be the preferred surgical approach for cT1 Renal Cell Carcinoma (<7 cm in diameter) [1]. At the same time, contemporary clinical series have suggested that alternative management strategies [Ablation Techniques (AT), Watchful Waiting (WW), Active Surveillance (AS)] for clinically localized renal masses may be considered [2]. However, on the basis of current evidences, many questions are still unanswered and several issues remain to be resolved [3].

In the last decade, three national and international multicentric studies have deeply investigated the role of conservative vs radical surgery for localized renal tumors. All these multicentre studies have been conducted under the coordination of our department.

The Italian Registry of Conservative Renal Surgery (RECORd 1 Project), is a multicentric, observational, prospective project involving 19 Italian centers. The aim of this project was to offer a comprehensive view of the national trend of utilization of conservative kidney

surgery and to offer a “real-life” description of the clinical, perioperative, pathological as well as oncological and functional results in patients treated with Nephron-Sparing Surgery (NSS) for renal tumors in Italy from 2009 to 2012 to provide evidence on a significant gap of knowledge [4-11].

The excellent results of this study have prompted the scientific committee to promote a new study on renal surgery (including radical and ablative therapies) for renal tumors: the RECORd2 project prospectively included over 4300 patients undergone surgery from 2013 to 2016 in 34 Italian centers. Follow-up of these patients is ongoing as well as statistical analyses [12–15].

The international study Surface-Intermediate-Base (SIB) Margin score has involved 16 international high-volume Centres. In total, in this study more than 600 patients who underwent NSS between 2014 and 2015 have been included. This study has extensively analyzed the impact of resection techniques (RT) on perioperative and functional outcomes [16,17].

On the basis of current evidences, many questions are still left unanswered and several unmet needs should be filled.

6. Dott.ssa Ingrid Patricia Lamminpaa

Titolo Progetto di Ricerca

Caratterizzazione del profilo neuro-immuno-biomico in pazienti affetti da SLA

Abstract

La Sclerosi Laterale Amiotrofica (SLA) è una malattia caratterizzata da una infiammazione cronica e una progressiva degenerazione dei motoneuroni che porta alla morte del paziente entro 3-5 anni dall'insorgenza della malattia. Studi recenti hanno mostrato come il microbiota intestinale possa aver un ruolo, principalmente attraverso la modulazione della risposta immunitaria, nella patogenesi delle malattie neurodegenerative, inclusa la SLA. L'obiettivo di questo studio è quello di caratterizzare i pazienti affetti da SLA da un punto di vista neuro-immuno-biomico esaminando le relazioni tra lo stato immunologico e clinico dell'ospite, la composizione del microbiota e i metaboliti da esso prodotti. L'intento è quello di definire l'influenza del microbiota sulla progressione e fenotipo di malattia, per meglio profilare i pazienti e facilitare interventi clinici personalizzati.

7. Dott.ssa Francesca Matani

Titolo Progetto di Ricerca

Studio multiomico dei meccanismi patogenetici nell'immunodeficienza comune variabile

ABSTRACT

L'IDCV (Immunodeficienza Comune Variabile) è la più comune immunodeficienza primaria sintomatica nell'adulto. Si tratta di una patologia caratterizzata da una grande eterogeneità dal punto di vista clinico, immunologico e genetico. Nonostante ciò, l'avvento delle tecniche NGS ha permesso di individuare numerose mutazioni che ne sono alla base, fornendo una possibile spiegazione per la patogenesi di questa malattia. Lo scopo di questo studio sarà quello di ricercare le varianti genetiche alla base dell'IDCV, mediante l'utilizzo del sistema di sequenziamento WES (Whole Exome Sequencing). Laddove verranno identificate varianti non note, oltre ad una preliminare caratterizzazione fenotipica delle PBMNCs (Peripheral blood mononuclear cells) mediante analisi citofluorimetrica, seguirà una caratterizzazione funzionale delle stesse, al fine di chiarire l'effetto che le alterazioni geniche hanno sulla funzionalità del comparto cellulare immunitario. Infine, con lo scopo di valutare l'impatto delle mutazioni sul trascrittoma delle singole cellule, verrà sfruttata la tecnica del single cell RNA sequencing (scRNAseq). Quest'ultima, nella sua versione bulk, si rivelerà anche un importante strumento per indagare la presenza di eventuali alterazioni relative ai meccanismi di splicing. Tutto questo sarà essenziale al fine di raccogliere informazioni utili per quanto riguarda la diagnosi e la messa a punto di terapie specifiche e personalizzate.

8. Dott. Francesco Pegoraro

Titolo Progetto di Ricerca

Exploring the genetic landscape of histiocytoses by integrating GWAS and -omic data

Abstract

Langerhans Cell Histiocytosis (LCH) and Erdheim-Chester disease (ECD) are the main forms of histiocytosis, caused by proliferation and infiltration of histiocytes that leads to irreversible damage to several organs. LCH is typical of the pediatric age, while ECD affects older adults more frequently, but the two diseases often show clinical and pathology overlap and share pathogenic pathways. Moreover, the pathomechanisms of histiocytic infiltration and organ damage are poorly studied, and knowledge on the genetic predisposition to these entities is limited.

A genome-wide association study (GWAS) performed in a small cohort of patients with LCH identified a risk locus in SMAD6, a gene involved in bone morphogenesis. Conversely, to investigate the genetic predisposition to ECD, we performed a GWAS on ECD and identified a genetic risk locus related to myeloid cell proliferation and myeloid neoplasms.

The present research project aims to integrate and expand the already available GWAS data on ECD with the results of a GWAS on patients with LCH, in order to obtain a wider picture of the genetic predisposition to the main forms of histiocytosis through a meta-analysis of the two GWAS. Moreover, epigenomic and transcriptomic data from whole blood of patients with LCH and ECD and from healthy controls will be analyzed to interpret the biological meaning of GWAS findings and to investigate the molecular network involved in the pathogenesis of the two diseases. Then, we will focus on the methylome and transcriptome in monocytes, in order to study the molecular pathways involved in histiocytosis pathogenesis in the cellular line thought to be pivotal in these diseases. Finally, we will perform an integrative analysis of -omic (genomic, epigenomic, and transcriptomic) data to identify LCH/ECD-associated variants influencing gene expression and DNA methylation levels. The results of this study may help clarify the genetic predisposition to histiocytosis and provide insights on how histiocytes infiltrate and damage target organs, and possibly, help discover molecules targetable by specific treatments.

9. Dott.ssa Margherita Perlato

Titolo Progetto di Ricerca

Hypersensitivity reactions to chemotherapy: definition of novel endophenotypes for a precision-medicine approach in drug allergy

Abstract

Immediate hypersensitivity reactions (HSRs) can complicate the infusion of chemotherapy and biological agents. This may lead to discontinuation of the needed first-line therapy in critically ill patients, with a negative impact on their life expectancy. Current understanding of the immunological mechanisms underlying HSRs is limited and insufficient for the optimal management of these patients. This study aims to define the pathophysiological mechanisms of HSRs and to implement specific drug desensitisation (DD) strategies accordingly. The study of the mediators and effector cells involved will help to identify different endotypes of reactions, that will be correlated to their clinical phenotype. The comparison between the endo-phenotype of HSRs with the outcome of DD protocols will allow the identification of biomarkers able to predict the success of DDs. This data will enable the use of tailored DD protocols to increase the safety, feasibility and success rate of DD procedures. Overall, this will expand on the knowledge required for a novel precision-medicine approach in drug allergy.

10. Dott. Roberto Scanferla

Titolo Progetto di Ricerca

Characterization of the tumor microbiome in soft tissue sarcomas: relationship between changes in the bacterial population of the tumor and patient's outcome

Introduction

Soft-tissue sarcomas (STS) are rare malignant tumors and represent less than 1% of human malignancy; they include a heterogeneous group of more than 70 different histopathologic entities with a common mesenchymal origin [1, 2]. Deep, large and high-grade STS have a higher risk of local recurrence and distant metastasis, despite the improvements in knowledge about surgical margins and radiation-therapy protocols, with an overall survival of 50% at five years after surgery [3, 4].

Chemotherapy protocols based on administration of Doxorubicin and Ifosfamide poorly improved disease-free survival and overall survival in patients with non-metastatic STS surgically treated [4].

Commensal bacteria and other microorganisms that reside in the human body are associated with the development and treatment of tumors. Recently, tumor microbiome (TM) has been identified in a variety of cancers (pancreatic, lung, and breast cancers) [5,6] TM has different compositions in different tumors and has different effects on tumors and exerts a role in the formation of the tumor microenvironment, regulation of local immunity, and modification of tumor cell biology, and directly affects the efficacy of drug treatment for tumors [5,6,7].

Preclinical and clinical evidence have identified a relationship between the presence of precise species of commensals and the response to immunotherapy, in particular of positive and negative regulatory bacteria [7,8]. The mechanism of interaction and influence on the host immune system occurs not only through direct recognition of microbial antigens, but also indirectly through the release by bacteria of metabolites (e.g. short-chain fatty acids) into the blood. As many as 5-10% of plasma metabolites, in fact, are of microbiological origin [9] None reported

data about bacterial population in musculoskeletal tumors such as STS. The study and typing of the bacterial population of these tumors could give more information about their influence in tumor progression and in resistance to chemotherapy and immunotherapy. For example, in colon-rectal cancer and in gut flora have been identified bacteria that express cytidine deaminase with the ability of metabolize gemcitabine, mediating chemotherapy resistance of the tumor [10,11]. Nowadays, none analyzed the microbiome and the bacterial population of STS and their relationship with response to treatment and prognosis in patients with these musculoskeletal tumors. In particular, STS could have a type-specific microbiome that influences patient survival and oncologic outcome.

The aim of this retro-prospective observational study is to understand the relationship between changes in the TM and outcome, in order to identify new prognostic and biomarkers in patients with STS.

The primary objective of the retrospective study will be to describe the taxonomic variations of the TM and correlations with clinical features and outcome. The secondary objective will be the longitudinal evaluation of the presence of related plasma metabolites and the correlation with outcome.

11. Dott. Simone Sforza

Titolo Progetto di Ricerca

Prospective Observational Study on Functional Outcomes, Recurrence, Overall Survival, and Cardiovascular Accidents in Patients Treated with Robot-Assisted Partial Nephrectomy: A Monocentric Analysis

Introduction

Robot-assisted partial nephrectomy (RAPN) has emerged as a minimally invasive surgical technique for the treatment of renal tumors [1–3]. RAPN offers several advantages over traditional open or laparoscopic approaches, including improved visualization, enhanced dexterity, and reduced morbidity [4–6]. While there is a growing body of literature on the perioperative outcomes of RAPN, there is a need to investigate its long-term functional outcomes, recurrence rates, overall survival, and potential cardiovascular complications [7].

12. Dott.ssa Alessandra Sorano

Titolo Progetto di Ricerca

Preclinical and clinical assessment of effectiveness and safety of a newly patented inhalatory lidocaine formulation in patients with difficult-to-treat chronic cough

Abstract

Chronic cough is a common reason for seeking medical attention (up to 40% of the population). Upper respiratory infections are one of the most frequent causes, along with unexplained/refractory chronic cough, asthma, COPD, idiopathic pulmonary fibrosis, and lung cancer. Cough can be unresponsive to therapy, leading to impaired quality of life and high costs. Local anaesthetics have antitussive effects, presumably blocking NaV⁺ channels in nerves. Recently, a novel patented lidocaine-sodium hyaluronate powder formulation, delivered by a portable inhaler, shows promise. The formulation provides a slow release of the active component lidocaine and minimises the oropharyngeal drug deposition, the excess penetration into the lungs and systemic absorption. This project aims to study its effectiveness and safety through preclinical and clinical trials. Preclinical studies will follow regulatory guidelines, testing tolerability in rodents and assessing toxicity. Clinical studies will be randomized, double-blind, placebocontrolled, evaluating lidocaine's antitussive effect in terms of reducing cough frequency and improving cough-related quality of life variables in patients with intractable chronic cough and secondly testing its safety. The collected data will advance the technology readiness of the drug and bridge the gap between research and clinical development, making it more attractive to potential investors.

13. **Dott.ssa Nevena Todorović**

Titolo Progetto di Ricerca

Insights on the Microbiota-Immunity Axis through AI: the Impact of Microbiota on Liver Cancer and the Immune System

Abstract

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and one of the leading causes of cancer-related deaths worldwide. HCC is surely a global health problem, owing to the widespread influence of its etiological factors and due to the poor prognosis. The HCC pathophysiology is a complex and multistep process. Among the pivotal mechanisms of carcinogenesis are gene mutations, dysregulation of diverse signaling pathways, epigenetic alterations, hepatitis B virus-induced hepatocarcinogenesis, chronic inflammation, impact of tumor microenvironment, oxidative stress. The immune cells play a critical role in both onset and development of chronic liver diseases. Considering the substantial HCC percentage arising from chronic inflammation, which involves cell death, regeneration, and consequent liver fibrosis or cirrhosis, investigating and understanding immune system disorders and the microenvironment in general are crucial. On the other hand, liver is an organ highly conducive to metastasis. While the exact prevalence of metastatic liver disease remains uncertain, between 30-70% of cancer patients develop hepatic metastases, suggesting the formation of secondary liver tumors. The microbiota relevance is widely acknowledged across various disorders and different studies suggested that changes in the composition of gut microbiota can potentially foster the HCC onset and progression

14. **Dott. Lorenzo Viola**

Titolo Progetto di Ricerca

The development of eye tracking technology in urological surgery

Summary

In the last years, interest in novel technologies and techniques is rapidly increasing in the urological field, The diffusion of robotic surgery and related available technologies have led the surgical performance into the future, while training programs have not been developed at the same time in fact the majority of surgical

curricula currently follow traditional and subjective methods that do not incorporate novel technologies.

Eye tracking represents a promising area of research in various industries, but only few studies in literature proposed it as a potential tool in surgical practice and training.

The object of this project is to introduce and integrate the use of eye-tracking devices into the routine urological practice such as adjuvant means for surgical team; therefore, this project aims to evaluate the role of eye tracking technology as an assessment tool of surgical skills acquisition in surgical education so as to develop structured simulated programs of surgical training; however there are many other potential applications of eye tracking features undennvestigated including the evaluation of vigilance, fatigue and team cognition.

The integration of these technologies could fill the current unmet needs in order that improvements to training standard and understanding performance data have good potential to significantly lower complications in patients

15. Dott. Emanuele Vivarelli

Titolo Progetto di Ricerca

Asthma in Primary Immunodeficiency: clinical features, endotypes and Immunoglobulin replacement therapy efficacy in a real-life setting

Summary

Primary antibody deficiencies (PAD) are an important comorbidity in asthma. The role of PAD in shaping asthma endotype and prognosis and the effect of immunoglobulin replacement therapy (IRT - PAD standard of care) on asthma outcomes are largely unknown. The aim of this study is to investigate clinical features, asthma endotype and efficacy of IRT on exacerbations, hospitalizations and cumulative steroid dose in a cohort of patients affected by PAD and asthma.