Ministero della Salute – Direzione Generale della Ricerca e dell'Innovazione in Sanità

Rendiconto 5 per mille ANNO 2022
Contributo percepito € 1.746.367,12 in data 19/09/2023

Ente della Ricerca Sanitaria
Denominazione Ente: IRCCS Istituto Clinico Humanitas
Codice fiscale: 10125410158
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Dati del rappresentante legale: Luciano Ravera

RESPONSABILE SCIENTIFICO	TITOLO PROGETTO	FINANZIAMENTO ASSEGNATO
DI SIMONE NICOLETTA	HAEMA STUDY (Hemodynamic Maternal Assessment): pilot study on the hemodynamic maternal assessment using a non-invasive monitoring system USCOM	93.657,12
BARTOLETTI MICHELE	Implementazione di una piattaforma per Trial Clinici Randomizzati Adattativi per valutare l'impatto dei test rapidi di sensibilità antimicrobica fenotipica sulla Stewardship Antibiotica e sull'outcome dei pazienti con batteriemia	309.350,00
ARMUZZI ALESSANDRO	Integrated Study of the Gut-Brain Axis in Inflammatory Bowel Disease: Unraveling Psychiatric Comorbidities and Predictive Biomarkers in Anti-TNF-α Therapy	300.000,00
BRUNETTA ENRICO	The long Pentraxin PTX3 in myocarditis: biomarker versus cardioprotective molecule	49.450,00
FOPPA CATERINA	Postoperative and long-term outcomes of Transanal Transection and Single-stapled anastomosis (TTSS) in rectal cancer patients: A multicentric international IDEAL Stage 2b prospective parallel cohort study	103.500,00
GATTI ROBERTO	Avoiding functional decay of frail inpatients through action observation plus motor imagery training followed by early sleep	86.250,00
GRECO MASSIMILIANO	ARTificial Intelligence for antiBIOTIC therapy optimization in Septic patients (ARTIBIOTICS Study)	225.400,00
POLITI LETTERIO	Functional plasticity in pain-related circuits upon brain radiosurgery in patients with refractory chronic pain	300.000,00
LORUSSO DOMENICA	Cerv-NeoImmune: Pioneering the Future of Neoadjuvant Immunotherapy in Cervical Cancer through Translational Research	175.260,00
TORZILLI GUIDO	Advancing Personalized Healthcare: Enhancing Value with Patient-Specific 3D-Printed Models	103.500,00

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Titolo del progetto: HAEMA STUDY (Hemodynamic Maternal Assessment): pilot study on the hemodynamic maternal assessment using a non-invasive monitoring system USCOM

Data di inizio progetto: 01/12/2023	**Data di fine progetto**: 30/11/2026
Fondi 5 per mille assegnati al progetto: **€ 93.657,12**	**Di cui:** **Quota da sostenere entro l'anno di rendicontazione: € 0,00** **Quota accantonata, da sostenere, per progetti pluriennali (durata massima tre anni): € 93.657,12**

VOCI DI SPESA	Quota da sostenere entro l'anno di rendicontazione	Quota accantonata, da sostenere, per progetti pluriennali (durata massima tre anni)
Personale di ricerca (borsista, a contratto e di ruolo in quota parte)	0,00	33.330,03
Apparecchiature (ammortamento, canone di locazione/leasing)	0,00	41.278,52
Materiale d'uso destinato alla ricerca (per laboratori di ricerca, acquisto farmaci ecc.)	0,00	0,00
Spese di organizzazione (manifestazioni e convegni, viaggi e missioni ecc.)	0,00	0,00
Elaborazione dati	0,00	0,00
Spese amministrative	0,00	14.048,57
Altro (patient insurance)	0,00	5.000,00
TOTALE	**0,00**	**93.657,12**

Data, 26/07/2024

Il Responsabile del Progetto

Il Legale Rappresentante

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Il Legale Rappresentante

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Dati del rappresentante legale: Luciano Ravera

Titolo del progetto: HAEMA STUDY (Hemodynamic Maternal Assessment): pilot study on the hemodynamic maternal assessment using a non-invasive monitoring system USCOM

Background: the "Ultrasonic Cardiac Output Monitor" (USCOM), is a non-invasive medical device used to assess cardiac function by measuring blood flow in the heart. While not typically the primary tool for managing complicated pregnancies, it can be valuable in specific situations where close monitoring of maternal and foetal health is crucial. USCOM measures cardiovascular haemodynamic using continuous wave Doppler technology to measure blood flow through the heart valves, providing an assessment of both right and left heart functions.
USCOM can be utilized in high-risk pregnancies in different ways: 1) Assessment of Maternal Haemodynamic in conditions such as preeclampsia, gestational hypertension, or maternal cardiac disease. USCOM can measure cardiac output, stroke volume, and other cardiac parameters non-invasively. 2) Monitoring Foetal Well-being: when maternal cardiac function impacts foetal health, USCOM can provide indirect insights into the foetus's condition. Monitoring maternal cardiac output can help detect potential foetal distress. 3) Fluid Management: Managing fluid balance is critical in complicated pregnancies, such as avoiding over hydration or dehydration. USCOM provides real-time data on cardiac function, guiding fluid therapy decisions to maintain optimal maternal volume status. 4) Risk Assessment: For pregnancies with complex medical histories or comorbidities USCOM can be part of a comprehensive risk assessment. It helps identify maternal cardiac issues that might affect pregnancy outcomes, aiding healthcare providers in making informed decisions about pregnancy management and delivery planning. 5) Therapeutic Monitoring: For pregnant women with pre-existing cardiac conditions or those developing complications, USCOM monitors the effectiveness of

therapeutic interventions. Clinicians can adjust medications or treatments based on ongoing cardiac function assessments.

Objectives: The aim of this research is the comparison of the hemodynamic profile in pathological patients versus a control group. Among pathological patients (pregnant patients with pre-existing cardiovascular disease, obese patients, patients with advanced maternal age, patients with a history of previous intrauterine foetal death, patients with autoimmune diseases, etc…), we decided to start the analysis of the hemodynamic profile of patients undergoing medically assisted fertilization treatments (ART). Recent meta-analyses have established a link between ART and an increased risk of preeclampsia, though the underlying mechanisms remain unclear. It is still uncertain whether the differences in pregnancy outcomes, including hypertensive disorders of pregnancy (HDP), are due to maternal factors, the ART procedures themselves, or a combination of both. ART pregnancies, compared to spontaneous conceptions, exhibit higher odds of HDP and preeclampsia, regardless of whether they are singleton or multiple pregnancies. Specifically, pregnancies resulting from oocyte donation show the highest odds of HDP and preeclampsia. In this scenario, the study of the hemodynamic profile of patients who underwent ART appears a valid tool both in evaluation of the risk of developing HDP, in early detection of HDP and in eventual personalized treatment.

Humanitas ICH Ethical Committee approved the project in November 2023. We started the enrolment in February 2024 and we performed the first USCOM measurement in April 2024. Nowadays, we have evaluated 18 women at first trimester: 5 women with spontaneous pregnancy (controls) and 13 women who underwent ART treatments (2 with heterologous eggs donation).

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Dati del rappresentante legale: Luciano Ravera

Titolo del progetto: Implementazione di una piattaforma per Trial Clinici Randomizzati Adattativi per valutare l'impatto dei test rapidi di sensibilità antimicrobica fenotipica sulla Stewardship Antibiotica e sull'outcome dei pazienti con batteriemia

Data di inizio progetto: 01/10/2024	**Data di fine progetto**: 30/09/2027
Fondi 5 per mille assegnati al progetto: **€ 309.350,00**	**Di cui:** **Quota da sostenere entro l'anno di rendicontazione: € 0,00** **Quota accantonata, da sostenere, per progetti pluriennali (durata massima tre anni): € 309.350,00**

VOCI DI SPESA	Quota da sostenere entro l'anno di rendicontazione	Quota accantonata, da sostenere, per progetti pluriennali (durata massima tre anni)
Personale di ricerca (borsista, a contratto e di ruolo in quota parte)	0,00	242.947,50
Apparecchiature (ammortamento, canone di locazione/leasing)	0,00	0,00
Materiale d'uso destinato alla ricerca (per laboratori di ricerca, acquisto farmaci ecc.)	0,00	0,00
Spese di organizzazione (manifestazioni e convegni, viaggi e missioni ecc.)	0,00	0,00
Elaborazione dati	0,00	0,00
Spese amministrative	0,00	46.402,50
Altro (CRO service)	0,00	20.000,00
TOTALE	**0,00**	**309.350,00**

Data, 26/07/2024

Il Responsabile del Progetto

Il Legale Rappresentante

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Il Legale Rappresentante

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Titolo del progetto: Implementazione di una piattaforma per Trial Clinici Randomizzati Adattativi per valutare l'impatto dei test rapidi di sensibilità antimicrobica fenotipica sulla Stewardship Antibiotica e sull'outcome dei pazienti con batteriemia

Le infezioni del torrente circolatorio da batteri (BBSI) sono una problematica seria di sanità pubblica, vista la loro elevata frequenza ed elevata mortalità. Inoltre, causano un incremento notevole dei costi sanitari e delle durate di ospedalizzazione, ma soprattutto, data l'urgenza di intervenire tempestivamente, comportano un utilizzo spesso inappropriato di antibiotici ad ampio spettro nelle prime fasi terapeutiche (terapia empirica) nell'attesa che i risultati microbiologici permettano di mirare la prescrizione antibiotica: ciò alimenta il circolo vizioso che favorisce l'insorgenza stessa delle BBSI.
Dunque, è necessario ridurre le prescrizioni inappropriate di terapia antibiotica: ciò al fine di migliorare tanto la sopravvivenza dei pazienti con BBSI che l'appropriatezza prescrittiva e la sostenibilità economica sanitaria di queste infezioni (stewardship antibiotica). Non stupisce quindi che un importante filone di ricerca delle aziende che operano in campo medico consista nella produzione di test di diagnostica microbiologica rapida capaci di fornire sempre più precocemente (nell'arco di ore) informazioni sulla specie batterica e la sensibilità antibiotica del patogeno responsabile della batteriemia. Mentre le aziende produttrici spesso si fermano alla dimostrazione dell'accuratezza e rapidità diagnostica dei test microbiologici rapidi, c'è necessità di dimostrare la loro efficacia (e costo-efficacia) su outcome clinici ed il loro impatto su indicatori di appropriatezza quando addottati nella pratica clinica.
In questo contesto, il progetto si propone di costruire una piattaforma per Trial Clinici Randomizzati Adattativi (ACT) per valutare l'impatto dei test rapidi di sensibilità

antimicrobica fenotipica o genotipica sulla stewardship antibiotica e sull'outcome dei pazienti con batteriemia.
Il trial mira a dimostrare che una terapia antibiotica precoce, basata su test di microbiologia rapida, migliori gli outcome di stewardship antibiotica, quando confrontato con lo standard of care corrente. Secondariamente, il trial mira a confrontare fra loro i diversi test microbiologici disponibili, per evidenziare al meglio le loro caratteristiche e deciderne il miglior posizionamento nella pratica clinica. I risultati del trial costituiranno la necessaria base per la progettazione di percorsi integrati diagnostico-terapeutici in grado di garantire la massima qualità di assistenza, che necessariamente dovrà muoversi verso soluzioni sostenibili su h24 e 7/7.
Lo studio prevede la realizzazione di un platform trial ("trial piattaforma") basato su un design adattativo (adaptive clinical trial - ACT) che consente modifiche pianificate in modo prospettico su uno o più aspetti del progetto (ad esempio l'aggiunta o l'eliminazione di un intervento), sulla base dell'analisi dei dati raccolti mentre lo studio è in corso. Questa modalità si adatta bene alla nostra proposta di ricerca perché agevola una valutazione efficiente di multipli interventi clinici in scenari dove ci sono diversi interventi candidati ad essere efficaci e possibilmente altri nuovi emergenti mentre il trial è in corso. Questo è il caso dei test rapidi di diagnostica microbiologica.
Nel caso specifico, la piattaforma di ACT prodotta per questo studio permetterà di aggiungere o rimuovere bracci di studio (corrispondenti a metodiche di microbiologia rapida) al momento della loro introduzione in pratica clinica ovvero al raggiungimento o non-raggiungimento degli outcome prefissati nelle analisi ad interim.
Nello specifico, l'obiettivo primario sarà dimostrare una superiorità in termini di tempo (analisi "time to") alla terapia antibiotica ottimale fra pazienti trattati con ciascun test di microbiologia rapida rispetto ai pazienti trattati con diagnostica standard. In particolare, la "terapia antibiotica ottimale" sono definiti dall'outcome composto da (presenza di entrambi): i) agente antimicrobico attivo in vitro contro il microrganismo documentato con microbiologia convenzionale su emocoltura; o ii) un agente antimicrobico proporzionato per il patogeno identificato, e non eccessivamente ampio spettro.

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Dati del rappresentante legale: Luciano Ravera

Titolo del progetto: Integrated Study of the Gut-Brain Axis in Inflammatory Bowel Disease: Unraveling Psychiatric Comorbidities and Predictive Biomarkers in Anti-TNF-α Therapy

Data di inizio progetto: 01/01/2025	**Data di fine progetto**: 31/12/2027
Fondi 5 per mille assegnati al progetto: **€ 300.000,00**	**Di cui:** **Quota da sostenere entro l'anno di rendicontazione: € 0,00** **Quota accantonata, da sostenere, per progetti pluriennali (durata massima tre anni): € 300.000,00**

VOCI DI SPESA	Quota da sostenere entro l'anno di rendicontazione	Quota accantonata, da sostenere, per progetti pluriennali (durata massima tre anni)
Personale di ricerca (borsista, a contratto e di ruolo in quota parte)	0,00	75.000,00
Apparecchiature (ammortamento, canone di locazione/leasing)	0,00	0,00
Materiale d'uso destinato alla ricerca (per laboratori di ricerca, acquisto farmaci ecc.)	0,00	71.000,00
Spese di organizzazione (manifestazioni e convegni, viaggi e missioni ecc.)	0,00	0,00
Elaborazione dati	0,00	0,00
Spese amministrative	0,00	45.000,00
Altro patient insurance, Cerebral MRI, psychiatric evaluation, shotgun sequencing microbiota)	0,00	109.000,00
TOTALE	**0,00**	**300.000,00**

Data, 26/07/2024

Il Responsabile del Progetto

Il Legale Rappresentante

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Titolo del progetto: Integrated Study of the Gut-Brain Axis in Inflammatory Bowel Disease: Unraveling Psychiatric Comorbidities and Predictive Biomarkers in Anti-TNF-α Therapy

Inflammatory Bowel Disease (IBD) is a chronic condition characterized by immune dysregulation and complex aetiology, manifesting primarily in Ulcerative Colitis (UC) and Crohn's Disease (CD). Alongside gastrointestinal symptoms, IBD patients frequently experience psychiatric comorbidities such as anxiety and depression, which exacerbate the disease burden and complicate treatment outcomes.
This research project aims to explore the gut-vascular-brain axis in IBD patients, with a specific focus on the interplay between the gut vascular-barrier (GVB) and the choroid plexus-vascular barrier (PVB) axis. Our goal is to elucidate how these barriers influence psychiatric symptoms, particularly in the context of anti-TNF-α treatment.
Current treatments for IBD include a spectrum of medications, from aminosalicylates and corticosteroids to immunomodulators and biologics, such as anti-TNF-α agents (infliximab, adalimumab, golimumab). These biologics have revolutionized IBD management, achieving endoscopic remission in a significant proportion of patients. However, psychiatric impairments affect up to 40% of IBD patients, a challenging issue often overlooked in clinical care. These psychiatric comorbidities correlate with IBD severity and impact quality of life. The bidirectional relationship between IBD and psychiatric disorders suggests a complex interplay of genetic, environmental, and immune factors, yet the underlying mechanisms are not fully understood.

The PVB, located in the brain's choroid plexus, is a novel component of the gut-brain axis. It regulates the passage of substances between the blood and cerebrospinal fluid (CSF), acting as a barrier during systemic inflammation to protect the brain from potential harm [8]. Our recent findings indicate that the PVB's permeability may alter during intestinal inflammation, and its closure has been linked to anxiety and depressive behaviors, mirroring symptoms seen in IBD patients. Moreover, our studies suggest that gut inflammation can affect brain function and behaviour, potentially through the GVB-PVB axis, and that anti-TNF-α treatments might modulate this effect.

This 3-year prospective study aims to investigate the GVB-PVB axis in IBD patients, focusing on those undergoing anti-TNF-α treatment. Our objectives include the recruitment and evaluation of 80 outpatients (ages 20-45) from the Humanitas IBD Center, diagnosed with active IBD and not undergoing psychiatric treatments at recruitment. We anticipate that approximately 50-60% of UC patients and 40-50% of CD patients will achieve mucosal healing and endoscopic remission, translating to around 40 out of 80 participants responding to anti-TNF-α therapy. The study will assess intestinal mucosal morphology, permeability, immune and microbial profiles, as well as psychiatric evaluations, cerebral MRI, and analysis of neurological markers and inflammatory parameters in the blood. We will integrate these translational research data with clinical outcomes using statistical analysis and machine learning.

This project involves a multidisciplinary collaboration from specialized units in IBD, Psychiatry, Radiology, Mucosal Immunology, Microbiota research, Metabolomics, and Advanced Imaging. Our team from Humanitas leverages a wide array of clinical and translational techniques, ensuring a thorough exploration of the GVB-PVB axis dysregulation and its impact on psychiatric comorbidities. This research aims to advance personalized medicine approaches, enhance therapeutic strategies for IBD patients, and provide insights into the complex interactions between gut and brain health, ultimately improving patient outcomes.

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Dati del rappresentante legale: Luciano Ravera

Titolo del progetto: The long Pentraxin PTX3 in myocarditis: biomarker versus cardioprotective molecule

Data di inizio progetto: 01/01/2025	**Data di fine progetto**: 31/12/2027
Fondi 5 per mille assegnati al progetto: **€ 49.450,00**	**Di cui:** **Quota da sostenere entro l'anno di rendicontazione: € 0,00** **Quota accantonata, da sostenere, per progetti pluriennali (durata massima tre anni): € 49.450,00**

VOCI DI SPESA	Quota da sostenere entro l'anno di rendicontazione	Quota accantonata, da sostenere, per progetti pluriennali (durata massima tre anni)
Personale di ricerca (borsista, a contratto e di ruolo in quota parte)	0,00	0,00
Apparecchiature (ammortamento, canone di locazione/leasing)	0,00	0,00
Materiale d'uso destinato alla ricerca (per laboratori di ricerca, acquisto farmaci ecc.)	0,00	39.032,50
Spese di organizzazione (manifestazioni e convegni, viaggi e missioni ecc.)	0,00	0,00
Elaborazione dati	0,00	3.000,00
Spese amministrative	0,00	7.417,50
Altro (indicare quali)	0,00	0,00
TOTALE	**0,00**	**49.450,00**

Data, 26/07/2024

Il Responsabile del Progetto

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Dati del rappresentante legale: Luciano Ravera

Titolo del progetto: The long Pentraxin PTX3 in myocarditis: biomarker versus cardioprotective molecule

Background

The long Pentraxin 3 (PTX3) is an Acute Phase Response protein belonging to the humoral arm of the innate immune system and to the family of pentraxins, with promising performance as an early biomarker in infectious, inflammatory and cardiovascular diseases. In contrast with the related molecule C reactive protein (CRP), which is mainly produced by the liver in inflammatory conditions in response to IL-6, PTX3 is produced by several cell types in response to different inflammatory molecules and microbial moieties. As a consequence, its expression is rapidly induced at the local level in inflammatory sites and its circulating levels rapidly increase in inflammatory conditions and different pathologies, with a more rapid kinetics compared to CRP. Circulating PTX3 is rapidly increased in patients with different cardiovascular diseases (CVDs) such as acute myocardial infarction (AMI), heart failure and atherosclerosis, reflecting the extent of tissue damage and predicting the risk of short- and long-term mortality. Furthermore, several studies reported that PTX3 plays a cardioprotective role in different murine models of cardiac damage. In the heart, PTX3 is induced in cardiomyocytes and endothelial cells that can release PTX3 after injury. In addition, PTX3 can be rapidly released from ready-made for release, neutrophil granules in patients undergoing AMI. PTX3 is expressed in the cardiac tissues of patients with infectious myocarditis [9]. It is localized within and around histological lesions and predominately produced by macrophages and endothelial

cells. However, to the best of our knowledge, no indications concerning the circulating PTX3 concentration in patients with myocarditis are reported in literature.
Currently, the gold-standard method for the diagnosis of myocarditis is the endomyocardial biopsy (EMB) which allows the clear identification of the underlying etiology of cardiac inflammation. However, because of the complexity of EMB, cardiac magnetic resonance imaging (MRI) is also used, a test can suggest but not diagnose the condition. Despite these diagnostic tools, the risk of under-diagnosing myocarditis is high, given their limited availability in the standard clinical practice. In addition, required multiple EMB samples may be associated with complications such as ventricle perforation. Thus, the identification of myocarditis blood biomarkers potentially benefits the diagnosis of this pathology. So far, different molecules have been evaluated, such as Troponin I, Creatine Phosphokinase and Myoglobin, but no specific biomarkers have been established.

Aim

On these bases, the aim of this study is to evaluate the potential role of PTX3 as early biomarker of heart damage associated with myocarditis. Since PTX3 is not a myocarditis-specific biomarker, but an early marker of heart damage, we hypothesize that PTX3 plasma concentration could reflect the severity of the condition and potentially its clinical evolution, as observed in other CVDs. We also hypothesize that the inflammatory component of myocarditis will be associated with higher PTX3 plasma concentration compared to that observed in CVDs, such as AMI. We thus aim to compare its plasmatic levels with classical biomarkers used in this condition, such as Troponin I, Creatine Phosphokinase and Myoglobin, and informatio retrieved from EMB and MRI, at the diagnosis and in the follow-up of patients. If our hypothesis is valid, PTX3 might be exploited in the future for rapid and low-cost evaluation of myocarditis severity and evolution, to be combined with EMB and MRI. Taking advantage of our ptx3-deficient mice, we also aim to elucidate the role of this protein in the context of a murine model of myocarditis induced by Immune Checkpoint Inhibitors (ICIs) treatment. We hypothesize that the absence of the cardioprotective protein could exacerbate the inflammatory status of the myocardium, increasing the cardiac damage.

Study strategy: This study is divided in 2 lines of activities:
Task 1. PTX3 as biomarker of myocarditis. To evaluate the properties of PTX3 for the identification of myocarditis, we propose a prospective study for the analysis of PTX3 plasma levels in samples from 90 patients, with the aim of developing an innovative diagnostic biomarker. We will evaluate the circulating concentration of PTX3 in n=90 patients admitted at the Emergency Department of Humanitas Research Hospital with diagnosis of myocarditis, confirmed by clinical evaluation, laboratory (Troponin I, Creatine Phosphokinase and Myoglobin) and instrumental tests (ECG, echocardiography, cardiac MRI or EMB). Samples from patients with acute symptoms and clinical onset will be preferentially assessed. PTX3 concentration will be measured in plasma EDTA samples of these patients, collected as close as possible to the diagnosis and then longitudinally. As control, PTX3 will be measured in plasma samples of healthy donors, AMI patients and patients with clinically suspected but not EMB-confirmed myocarditis. PTX3 plasma levels will be associated with myocarditis severity, and prediction of mortality will be assessed. The classical circulating biomarkers of this pathology, such as Troponin I, Creatine Phosphokinase and Myoglobin, and also of systemic inflammation, such as CRP and IL-6, will be analyzed and combined with PTX3. This may lead to the generation of a

circulating myocarditis-associated signature, acting as an early and easy tool for the laboratory analysis of the condition. In specific health care settings, this signature might compensate for the lack of EMB or MRI accessibility. The modulation of PTX3 will be also evaluated longitudinally after treatment, in order to elucidate its potential as marker of response to therapy. Finally, in a sub-group of 15 patients, the expression and localization of PTX3 will be evaluated by immunohistochemistry in EMB samples, in order to assess PTX3 cellular sources in the cardiac tissue.

Task 2. Role of PTX3 in response to ICI-induced myocarditis. To evaluate the molecular role of PTX3 in myocarditis, we will use the model of myocarditis induced by anti-PD-1 therapy, which develops in 100% of treated animals [11]. C57BL/6J (Wt) and Ptx3-/- male and female mice will be injected intraperitoneally (IP) with 200 µg/mouse of anti-PD-1 (Bioxcell) or with Isotype control, twice a week for 2 weeks [11]. The plasma concentration of PTX3 will be evaluated in comparison with Troponin I, CRP and IL6 in order to elucidate the possible profile of PTX3 as early biomarker for myocarditis. Mice will be assessed by echocardiography and cardiac tissue will be processed for the evaluation of immune cells infiltration (B, T cell and monocytes and macrophages) and cardiac inflammation (inflammatory cytokines) in different time points during the anti-PD1 treatment. Cardiac fibrosis, CD3+ positive cells infiltration and the expression/localization of PTX3 will be tested by immunohistochemistry. To evaluate the possible therapeutic role of the protein, rescue experiments will be performed by the co-injection of anti-PD1 and recombinant human PTX3 (1 mg/kg IP; [12]) in Wt and Ptx3-/- mice.

Ministero della Salute – Direzione Generale della Ricerca e dell'Innovazione in Sanità

Rendiconto 5 per mille ANNO 2022
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Ente della Ricerca Sanitaria
Denominazione Ente: IRCCS Istituto Clinico Humanitas
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amministratore.delegato@humanitas.it
Humanitasmirasole@legalmail.it
Dati del rappresentante legale: Luciano Ravera

Titolo del progetto: Postoperative and long-term outcomes of Transanal Transection and Single-stapled anastomosis (TTSS) in rectal cancer patients: A multicentric international IDEAL Stage 2b prospective parallel cohort study

Data di inizio progetto: 01/12/2025	**Data di fine progetto**: 31/12/2027
Fondi 5 per mille assegnati al progetto: **€ 103.500,00**	**Di cui:** **Quota da sostenere entro l'anno di rendicontazione: € 0,00** **Quota accantonata, da sostenere, per progetti pluriennali (durata massima tre anni): € 103.500,00**

VOCI DI SPESA	Quota da sostenere entro l'anno di rendicontazione	Quota accantonata, da sostenere, per progetti pluriennali (durata massima tre anni)
Personale di ricerca (borsista, a contratto e di ruolo in quota parte)	0,00	60.000,00
Apparecchiature (ammortamento, canone di locazione/leasing)	0,00	0,00
Materiale d'uso destinato alla ricerca (per laboratori di ricerca, acquisto farmaci ecc.)	0,00	0,00
Spese di organizzazione (manifestazioni e convegni, viaggi e missioni ecc.)	0,00	12.975,00
Elaborazione dati	0,00	0,00
Spese amministrative	0,00	15.525,00
Altro (CRO service)	0,00	15.000,00
TOTALE	**0,00**	**103.500,00**

Data, 26/07/2024

Il Responsabile del Progetto

Il Legale Rappresentante

Si autorizza al trattamento dei dati ai sensi del d.lgs. 196/2003

Il Legale Rappresentante

Ministero della Salute – Direzione Generale della Ricerca e dell'Innovazione in Sanità

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Dati del rappresentante legale: Luciano Ravera

Titolo del progetto: Postoperative and long-term outcomes of Transanal Transection and Single-stapled anastomosis (TTSS) in rectal cancer patients: A multicentric international IDEAL Stage 2b prospective parallel cohort study

Background: In rectal cancer surgery, Transanal Transection and Single Stapled anastomosis (TTSS) has become a valid alternative to standard double-stapled technique, with the main advantages of single-stapled anastomosis- effective in reducing the rate of anastomotic leak-, direct visual control of transection from the anal orifice- which may allow an oncological safe distal margin resection-, and strategy versatility, being applicable to open, laparoscopic, or robotic approaches.
Objectives: The objective of the study is to prospectively and internationally validate previous retrospective single-center results, comparing postoperative, functional, and oncological outcomes of TTSS versus double-stapled technique.
Methods: This is a multicentric, observational, two-parallel cohort, IDEAL Stage 2b study. Patients diagnosed with rectal cancer scheduled for elective open or minimally invasive rectal resection, with or without stoma, will be included and allocated in one of the study cohort according to the intervention performed, TTSS or standard double-stapled Total Mesorectal Excision (TME). The primary endpoint will be the difference in the rate of 90-day anastomotic leak. The secondary endpoints will include the rate difference of 90-day postoperative complications, the median difference of healthcare costs, the median difference of Low Anterior Resection Syndrome (LARS) score six, 12, and 24 months after surgery or stoma closure, and the incidence rate difference of 24-month cancer recurrence. A sample size of 236 patients in each cohort will allow an 80% power to detect a 0.5 decrease of 90-day anastomotic leaks between the study cohorts, allowing for a 5% of lost to follow-up.

Conclusions: This trial aims to compare postoperative, functional, and oncological outcomes of TTSS and double-stapled technique in rectal cancer resection in a multicentric prospective setting. The study, thanks to its pragmatic approach and bias mitigation strategy, will allow for good quality real-world data on the effectiveness of TTSS.
Registration number: NCT06314646 (Study Details | Transanal Transection and Single-stapled Anastomosis (TTSS) in Rectal Cancer Patients | ClinicalTrials.gov)

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Dati del rappresentante legale: Luciano Ravera

Titolo del progetto: Avoiding functional decay of frail inpatients through action observation plus motor imagery training followed by early sleep

Data di inizio progetto: 01/01/2025	**Data di fine progetto**: 31/12/2027
Fondi 5 per mille assegnati al progetto: **€ 86.250,00**	**Di cui:** **Quota da sostenere entro l'anno di rendicontazione: € 0,00** **Quota accantonata, da sostenere, per progetti pluriennali (durata massima tre anni): € 86.250,00**

VOCI DI SPESA	Quota da sostenere entro l'anno di rendicontazione	Quota accantonata, da sostenere, per progetti pluriennali (durata massima tre anni)
Personale di ricerca (borsista, a contratto e di ruolo in quota parte)	0,00	0,00
Apparecchiature (ammortamento, canone di locazione/leasing)	0,00	60.000,00
Materiale d'uso destinato alla ricerca (per laboratori di ricerca, acquisto farmaci ecc.)	0,00	5.000,00
Spese di organizzazione (manifestazioni e convegni, viaggi e missioni ecc.)	0,00	5.000,00
Elaborazione dati	0,00	3.312,50
Spese amministrative	0,00	12.937,50
Altro (indicare quali)	0,00	0,00
TOTALE	**0,00**	**86.250,00**

Data, 26/07/2024

Il Responsabile del Progetto

Il Legale Rappresentante

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Il Legale Rappresentante

Ministero della Salute – Direzione Generale della Ricerca e dell'Innovazione in Sanità

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Dati del rappresentante legale: Luciano Ravera

Titolo del progetto: Avoiding functional decay of frail inpatients through action observation plus motor imagery training followed by early sleep

Background

Major surgical procedures and internal medicine conditions represent leading causes of hospitalization in frail elderly, which often experience motor performance decline and functional decay as a result of bedrest during hospital stay (*Dualeh et al., 2024*). A considerable prevalence of residual disability has been reported in these patients at discharge, suggesting the need to adopt strategies aimed at avoiding or reducing the motor and functional decay during hospital stay (*Gill et al., 2010*). Moreover, an increase in length of hospital stay has been described in these patients, leading to higher likelihood of complications and an increase in National Healthcare System costs (*Surkan et al., 2018*).

The discovery of the Mirror Neuron System (MNS) as brain network involved in motor learning promoted MNS-based approaches such as action observation and motor imagery (AOMI) to enhance motor skills in humans (*Rizzolatti et al., 2021*). These interventions include the careful observation of video-clips representing motor contents followed by the mental rehearsal of the observed tasks (*Rizzolatti et al., 2021*). The rationale for the adoption of these approaches is based on the MNS peculiarity to show a partial overlap in terms of brain activity during observation, imagination and execution of motor acts. These processes have been reported to allow the observer to build a motor memory of observed and imagined tasks, facilitating the acquisition of new motor skills through the building of a motor memory (*Rizzolatti et al., 2021*).

Studies have supported the adoption of AOMI to improve motor and functional performance in patients with disability due by motor impairments, where benefits may also be achieved in the absence of active movement performance (*Ryan et al., 2021*). In

addition, a recent study has demonstrated that the administration of an AOMI-training including the occurrence of early sleep after each session represent an effective strategy to enhance gait and balance abilities in older adults. In fact, electrophysiological investigations have described specific neural activity patterns during the slow-wave sleep phase, which have been directly related to motor learning consolidation (e.g., sleep spindles and k-complexes waves in the sigma electroencephalographic band) (*Peters et al., 2008*).

In this scenario, the main hypothesis of this project is that the administration of AOMI before sleeping might reduce functional decay in frail elderly hospitalized for undergoing major surgical procedures or cares for internal medicine conditions. In particular, the delivery of visual and imaginative stimuli including functional task requiring advanced gait and balance abilities might represent a modality of enriched environment able to boost the effects of conventional physiotherapy in these patients. In addition, this cost-effectiveness intervention might also decrease length of stay, in-hospital complication rate, and result in lower re-admission rate for fall-related injuries after discharge. Finally, an accurate investigation on patients' and stimuli characteristics able to modulate MNS activity might suggest the most suitable visual stimuli to be adopted. In fact, it is reasonable to speculate that some personal features and the environmental conditions in which the observed task occurs might influence the MNS activity during action observation.

Objectives

The current project includes 2 work-packages (WPs). The WP1 procedures will be addressed to investigate the effects of AOMI followed by early sleep on motor and functional abilities, length of stay, complication, re-admission rates, and neurophysiological correlates of frail elderly hospitalized for major surgery procedures and internal medicine conditions. The WP2 procedures will be addressed at exploring the modulation of the MNS activity during the observation of a motor task performed in different environmental conditions.

Ministero della Salute – Direzione Generale della Ricerca e dell'Innovazione in Sanità

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Dati del rappresentante legale: Luciano Ravera

Titolo del progetto: ARTificial Intelligence for antiBIOTIC therapy optimization in Septic patients (ARTIBIOTICS Study)

Data di inizio progetto: 01/01/2025	**Data di fine progetto**: 31/12/2027
Fondi 5 per mille assegnati al progetto: **€ 225.400,00**	**Di cui:** **Quota da sostenere entro l'anno di rendicontazione: € 0,00** **Quota accantonata, da sostenere, per progetti pluriennali (durata massima tre anni): € 225.400,00**

VOCI DI SPESA	Quota da sostenere entro l'anno di rendicontazione	Quota accantonata, da sostenere, per progetti pluriennali (durata massima tre anni)
Personale di ricerca (borsista, a contratto e di ruolo in quota parte)	0,00	174.590,00
Apparecchiature (ammortamento, canone di locazione/leasing)	0,00	0,00
Materiale d'uso destinato alla ricerca (per laboratori di ricerca, acquisto farmaci ecc.)	0,00	0,00
Spese di organizzazione (manifestazioni e convegni, viaggi e missioni ecc.)	0,00	2.000,00
Elaborazione dati	0,00	5.000,00
Spese amministrative	0,00	33.810,00
Altro (insurance patient)	0,00	10.000,00
TOTALE	**0,00**	**225.400,00**

Data, 26/07/2024

Il Responsabile del Progetto

Il Legale Rappresentante

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Il Legale Rappresentante

Ministero della Salute – Direzione Generale della Ricerca e dell'Innovazione in Sanità

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Dati del rappresentante legale: Luciano Ravera

Titolo del progetto: ARTificial Intelligence for antiBIOTIC therapy optimization in Septic patients (ARTIBIOTICS Study)

Background:
Sepsis and septic shock are severe diseases with a significant impact on morbidity and mortality in hospitals. The incidence of sepsis and septic shock has been increasing in recent years, due to the ageing and frailty of hospitalized population.
Antibiotic therapy plays a crucial role in sepsis treatment, but has also a major impact on costs and on epidemiology of bacterial resistance at hospital and regional level. While delay of necessary antibiotic treatment is associated with increased morbidity and mortality in septic patients, prolonged antibiotic therapy can lead to adverse effects and increased microbial resistance, which negatively impact costs, patient outcomes, and strains hospital systems.
Despite extensive medical literature on antibiotic discontinuation, clinicians often face challenges in promptly applying antibiotic discontinuation criteria recommended by guidelines.
Artificial intelligence (AI) techniques are increasingly being recognized as valuable, versatile tools for assisting clinicians in decision making by synthesizing complex clinical data in a timely manner. Due to its capability to analyze multidimensional data, AI can be effectively employed to predict the optimal timing for discontinuation of antibiotic therapy.
Aim of this study is to assess whether a clinical decision support system based on an artificial intelligence model is able to optimize antibiotic duration and reduce detrimental effect of unnecessary prolonged antibiotic therapy.

Objects:
The study will be conducted in two phases, with two distinct objects

Phase 1: This is a retrospective Electronic Health Record (EHR) study, using deidentified data collected from surgical and medical patients admitted to Humanitas Research hospital from 2018 to 2024. We will include patients over 18 years, who underwent antibiotic therapy during their hospital stay.

Object of phase 1 is to develop a prediction algorithm based on time series analysis of clinical health record data, which includes the site of infection, comorbidities, microbiological data, laboratory data, baseline and admission clinical data, and vital parameters. Data will be extracted using SQL and processed and analyzed using Python, employing well known frameworks such us Pandas, Numpy and Tensorflow. Model will be developed on the training cohort and will be validated internally on the validation cohort, and also externally on other published patient population cohort, such as MIMIC-IV data.

Phase 2- prospective stepped wedge RCT: in phase 2 we will implement the AI algorithm developed in phase 1, to conduct a stepped-wedge cluster randomized trial across wards at IRCCS-Humanitas Research Hospital.

Object of phase 2 will be to determine whether an AI model can reduce the length of antibiotic therapy, when implemented as a Clinical Decision Support System (CDSS) designed to alert physicians as soon as the condition for best timing for discontinuation of antibiotic therapy are met. Quasi real-time data extraction from hospital EHR data will provide updated information every day to the hospital data warehouse. Patients started on antibiotic therapy will be automatically identified for inclusion in the study in the wards already randomized to intervention.

The primary endpoint will be: Antibiotic-free days at 28 day.

Secondary endpoints will be median duration of antibiotic therapy, ICU admission, mortality, and costs, and safety of the AI algorithm implementation.

For study feasibility and safety, we will implement the CDSS using the hospital email addresses of as an internal alert system. When a patient is identified as a possibile candidate for discontinuation of antibiotic therapy, the caring physician and study team will be alerted. The caring physician will have the possibility to discontinue or discuss the antibiotics therapy with the study team, granting the safety of the procedure through human reevaluation of the intervention proposed by CDSS.

Ministero della Salute – Direzione Generale della Ricerca e dell'Innovazione in Sanità

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Dati del rappresentante legale: Luciano Ravera

Titolo del progetto: Functional plasticity in pain-related circuits upon brain radiosurgery in patients with refractory chronic pain

Data di inizio progetto: 01/01/2025	**Data di fine progetto**: 31/12/2027
Fondi 5 per mille assegnati al progetto: **€ 300.000,00**	**Di cui:** **Quota da sostenere entro l'anno di rendicontazione: € 0,00** **Quota accantonata, da sostenere, per progetti pluriennali (durata massima tre anni): € 300.000,00**

VOCI DI SPESA	Quota da sostenere entro l'anno di rendicontazione	Quota accantonata, da sostenere, per progetti pluriennali (durata massima tre anni)
Personale di ricerca (borsista, a contratto e di ruolo in quota parte)	0,00	120.000,00
Apparecchiature (ammortamento, canone di locazione/leasing)	0,00	70.000,00
Materiale d'uso destinato alla ricerca (per laboratori di ricerca, acquisto farmaci ecc.)	0,00	0,00
Spese di organizzazione (manifestazioni e convegni, viaggi e missioni ecc.)	0,00	10.000,00
Elaborazione dati	0,00	10.000,00
Spese amministrative	0,00	45.000,00
Altro (RMN, valutazione psichiatrica, assicurazione)	0,00	45.000,00
TOTALE	**0,00**	**300.000,00**

Data, 26/07/2024

Il Responsabile del Progetto

Il Legale Rappresentante

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Il Legale Rappresentante

Ministero della Salute – Direzione Generale della Ricerca e dell'Innovazione in Sanità

Rendiconto 5 per mille ANNO 2022
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Dati del rappresentante legale: Luciano Ravera

Titolo del progetto: Functional plasticity in pain-related circuits upon brain radiosurgery in patients with refractory chronic pain

Chronic pain is a common, complex and distressing problem that has a significant socio-economical impact and is associated with multiple physical, psychological and social factors. In certain conditions, chronic pain results in drug abuse, such as opioids, and suicidal ideation. Neuropathic pain, defined by the International Association for the Study of Pain as "pain initiated or caused by a primary lesion of dysfunction of the nervoussystem," is a disabling and chronic pain with limited effective treatments. Surveys of primary care patients estimate the incidence of neuropathic pain to approximately 10%. This type of pain is difficult to treat despite multimodal therapies with ~50% patients achieving only partial relief. A proportion of patients presenting with intractable and refractory neuropathic pain resort to surgical interventions aimed at disrupting the aberrant transmission of pain signaling centrally.
Among the ablative targets studied, the posterior aspect of the central lateral nucleus of the thalamus, previously referred to as the "medial thalamic center" (CLp), stands out for its promising safety profile. Radio-frequency central lateral thalamotomy (CLT) has demonstrated sustained clinical alleviation of NP severity, especially when conducted bilaterally, particularly effective for intermittent or allodynic pain, and potentially more beneficial for peripheral origins (Jeanmond et al. 1994). CLT is hypothesized to disrupt thalamocortical dysrhythmia, thus ameliorating the cognitive and affective dimensions of pain (Jeanmond et al. 2001).
Despite presenting a promising solution for refractory drug restistant pain, its mechanism of action, as well as it short and long term effects on brain functional connectome and brain function remain unknown. Moreover, while no major side effects have been reported for this intervention, a finer behavioral investigation of the possible neuropsychitric effects

of this procedure have never been investigated. Lastly, CLp thalamothomy has beneficial effects only in a fraction of treated patients (around 50%), but the determinants of this variability remain unclear. In light of this, an integrated patients stratification based on targeted neurological, psychiatric and brain connectivity data may help refine patients selection as well as shed a new light on its mechanism of action.
The overarching goal of the project is to investigate the effects of radiosurgical treatments for chronic pain on pain processing circuits, and subsequently infer on the pathophysiology of chronic pain and on how the GK treatment induces its therapeutic effects. Further, this project will provide useful non-invasive markers MRI-derived structural and functional connectivity for identifying patients that could benefit from a GK thalamothomy intervention, given the absence, to date, of scientifically validated criteria. In particular, we aim to: - Study the activity and the connectivity of thalamic circuits and other brain networks involved in chronic pain through the integration of advanced MRI techniques with clinical, neurological and neuropsychological assessment; - Assess the modification in the chronically activated brain pain circuits induced by the GK treatment. - Identify predictors of response to treatment by investigating the functional changes induced by chronic pain in circuits involved in pain processing; - Through DTI and a specific fMRI paradigm to evaluate whether, similarly to what we observed in mouse models, the midline thalamus serves as a hub structure for the emotional regulation in relation to traumas, a key factor in the development of nociplastic pain.

Ministero della Salute – Direzione Generale della Ricerca e dell'Innovazione in Sanità

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Dati del rappresentante legale: Luciano Ravera

Titolo del progetto: Cerv-NeoImmune: Pioneering the Future of Neoadjuvant Immunotherapy in Cervical Cancer through Translational Research

Data di inizio progetto: 01/01/2025	**Data di fine progetto**: 31/12/2027
Fondi 5 per mille assegnati al progetto: **€ 175.260,00**	**Di cui:** **Quota da sostenere entro l'anno di rendicontazione: € 0,00** **Quota accantonata, da sostenere, per progetti pluriennali (durata massima tre anni): € 175.260,00**

VOCI DI SPESA	Quota da sostenere entro l'anno di rendicontazione	Quota accantonata, da sostenere, per progetti pluriennali (durata massima tre anni)
Personale di ricerca (borsista, a contratto e di ruolo in quota parte)	0,00	0,00
Apparecchiature (ammortamento, canone di locazione/leasing)	0,00	0,00
Materiale d'uso destinato alla ricerca (per laboratori di ricerca, acquisto farmaci ecc.)	0,00	88.971,00
Spese di organizzazione (manifestazioni e convegni, viaggi e missioni ecc.)	0,00	10.000,00
Elaborazione dati	0,00	10.000,00
Spese amministrative	0,00	26.289,00
Altro (Shotgun metagenomic sequencing; Samples shipment from MITO CERV3 centers)	0,00	40.000,00
TOTALE	**0,00**	**175.260,00**

Data, 26/07/2024

Il Responsabile del Progetto

Il Legale Rappresentante

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Il Legale Rappresentante

Ministero della Salute – Direzione Generale della Ricerca e dell'Innovazione in Sanità

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Titolo del progetto: Cerv-NeoImmune: Pioneering the Future of Neoadjuvant Immunotherapy in Cervical Cancer through Translational Research

BACKGROUND

Cervical cancer (CC) is the fourth most frequently diagnosed cancer and the fourth leading cause of cancer death in women worldwide. The majority of early-stage tumors (FIGO stage IA or IB1) are treated with surgery, while those presenting with locally advanced disease (LACC) are mostly given concurrent chemoradiation (CT-RT). Of note, in patients (pts) with LACC eligible for concurrent CT-RT, the addition of immunotherapy with pembrolizumab recently demonstrated a significant improvement in clinical outcomes. Neoadjuvant chemotherapy (NACT) followed by surgery in the primary treatment of CC may be a valuable option to reserve RT at the time of recurrence and to spare non-negligible toxicities to pts. Unfortunately, 20% of pts may not experience a tumor response after NACT, and roughly 30% of pts receiving NACT are submitted to post-operative RT or CT-RT because of the presence of high-risk factors at the surgical pathologic report. The collaborative MITO group designed and conducted the MITO CERV 3, a multicenter, phase II, non-comparative trial to evaluate the role of the anti-PD1 monoclonal antibody pembrolizumab in combination with chemotherapy in the upfront treatment of LACC FIGO stage IB2-IIB. The trial was designed using a Simon 2-stage Minimax design, taking into account a type I and II error of 0.05 and 0.10, respectively, and to demonstrate an improvement of 2-year PFS from 60% (historical controls) to 80% with the experimental treatment, and a total of 45 pts were enrolled. Pts are treated with 3 cycles of neoadjuvant carboplatin AUC5 and paclitaxel 175 mg/mq plus pembrolizumab 200 mg flat dose every 3 weeks. After 3 cycles, pts with non-progressing disease undergo radical surgery. After surgery, pts presenting post-surgical high-risk factors receive 3 additional cycles of chemoimmunotherapy followed by maintenance with pembrolizumab 200 mg every 3

weeks for up to 35 cycles. The primary endpoint is the 2-year PFS. Key secondary endpoints are OS, radiological response rate, optimal pathologic response, toxicity and quality of life. Treatment is ongoing and biological samples, including formalin-fixed, paraffin-embedded (FFPE) tumor tissue, and serum, stool, and vaginal swab samples were/will be collected as per protocol throughout the study for translational analyses.

OBJECTIVES

Objective 1 To investigate by spatial transcriptomic the tumoral and immunological content by that could be associated with experimental neoadjuvant immunochemotherapy sensitivity/resistance in LACC. Spatially resolved transcriptomic analysis will be conducted on pre and post neoadjuvant treatment FFPE samples using multiplex Digital Spatial Profiling (DSP) with the "GeoMx DSP" technology (NanoString).

Objective 2 To investigate the dynamics of cytokines, chemokines, and inflammatory factors in the serum of pts with LACC undergoing experimental neoadjuvant immunochemotherapy and assess their association with clinical outcomes. We will exploit the Olink platform enabling high-throughput analysis of a comprehensive panel targeting a wide array of cytokines, chemokines, and inflammatory markers. Serum samples were/will be collected from patients per protocol at different timepoints.

Objective 3 To study the influence of gut and vaginal microbiota on the clinical outcomes of pts with LACC treated with neoadjuvant chemoimmunotherapy.

Fecal and vaginal samples were/will be collected as per protocol at different timepoints. Microbiota analysis will be conducted by shotgun metagenomic sequencing.

Objective 4 To investigate serum metabolite dynamics during experimental neoadjuvant chemoimmunotherapy in pts with LACC treated within the MITO CERV 3 trial and assess their association with clinical outcomes. To identify metabolites (in particular, microbiome-related metabolites) an untargeted metabolomics analysis will be performed. Serum samples were/will be collected, as per protocol at different timepoints.

Ministero della Salute – Direzione Generale della Ricerca e dell'Innovazione in Sanità

Rendiconto 5 per mille ANNO 2022
Contributo percepito € 1.746.367,12 in data 19/09/2023

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Titolo del progetto: Advancing Personalized Healthcare: Enhancing Value with Patient-Specific 3D-Printed Models

Data di inizio progetto: 01/01/2025	**Data di fine progetto**: 31/12/2027
Fondi 5 per mille assegnati al progetto: **€ 103.500,00**	**Di cui:** **Quota da sostenere entro l'anno di rendicontazione: € 0,00** **Quota accantonata, da sostenere, per progetti pluriennali (durata massima tre anni): € 103.500,00**

VOCI DI SPESA	Quota da sostenere entro l'anno di rendicontazione	Quota accantonata, da sostenere, per progetti pluriennali (durata massima tre anni)
Personale di ricerca (borsista, a contratto e di ruolo in quota parte)	0,00	0,00
Apparecchiature (ammortamento, canone di locazione/leasing)	0,00	0,00
Materiale d'uso destinato alla ricerca (per laboratori di ricerca, acquisto farmaci ecc.)	0,00	67.975,00
Spese di organizzazione (manifestazioni e convegni, viaggi e missioni ecc.)	0,00	5.000,00
Elaborazione dati	0,00	10.000,00
Spese amministrative	0,00	15.525,00
Altro (patient insurance)	0,00	5.000,00
TOTALE	**0,00**	**103.500,00**

Data, 26/07/2024

Il Responsabile del Progetto

Il Legale Rappresentante

Si autorizza al trattamento dei dati ai sensi del d.lgs. 196/2003

Il Legale Rappresentante

Ministero della Salute – Direzione Generale della Ricerca e dell'Innovazione in Sanità

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Titolo del progetto: Advancing Personalized Healthcare: Enhancing Value with Patient-Specific 3D-Printed Models

Background

In recent years, 3D printing has garnered increasing interest in the medical field, demonstrating promising applications in the planning and execution of complex oncological surgical procedures. This study focuses on two main uses of 3D printing: the creation of patient-specific anatomical models and the production of hepatic resection-guides based on 3D liver reconstruction.

Patient-specific anatomical models are detailed physical reproductions of a patient's internal structures, obtained through medical imaging and subsequent 3D printing techniques. These models are particularly useful for preoperative planning in fields such as cardiac surgery, urological surgery, thoracic surgery, hepatobiliary-pancreatic surgery and colorectal surgery. The ability to visualize and manipulate a three-dimensional model of a patient's pathology allows surgeons to plan operations with higher precision, anticipate and mitigate complications, and improve communication with the surgical team and the patients themselves.

Similarly, patient-specific hepatic resection-guides represent another important use of 3D printing in complex oncological surgery. These guides are designed based on detailed radiological images (i.e. CTMRI Scan) of the liver affected by primary and secondary disease and are used to intraoperatively guide the surgeon to define the planned resection areas in very complex tumour burden. 3D segmentation of the liver allows the accurate identification of tumour location (specially in multiple cluster of lesions) and critical

vascular structures, reducing the risk of unintentional damage and improving the accuracy and safety of the procedure.

Objectives

The main objective of this study is to evaluate the impact of 3D printing on the quality of complex oncological surgical procedures, with particular focus on advancing personalized healthcare through:

1. **Surgical Precision**: Analysing how anatomical models and resection guides impact on the precision of surgeries, reducing intraoperative errors and improving the safety.
2. **Operating Times**: Assessing whether the use of 3D printing can reduce operation times through better preoperative planning and more efficient execution of procedures.
3. **Clinical Outcomes**: Monitoring postoperative clinical outcomes, including complication rates, recovery times, and long-term patient results.
4. **Cost-Effectiveness**: Considering the cost-benefit ratio of 3D printing in surgical settings, comparing the additional costs of the technology with potential savings from less post-operative complications.
5. **Learning Curves**: First, evaluating the impact of 3D printing on the learning curves of surgical teams, particularly in complex oncological surgeries; Second, providing a clearer understanding of patient-specific anatomy and procedural steps, thus potentially shortening the time required for surgical proficiency.

Through the analysis of specific clinical cases and the collection of quantitative and qualitative data, this study aims to provide an in-depth view of the effectiveness and added value of 3D printing in complex oncological surgery, contributing to the advancement of personalized healthcare. By tailoring surgical planning and execution to the unique anatomical features of each patient, 3D printing stands to significantly enhance the precision, safety, and overall outcomes of oncological operations. This allows the potential establishment of best practices for the adoption of this innovative technology in everyday clinical practice.