Relazione annuale dell'attività di ricerca dei dottorandi

XXXI CICLO:

Squillace Silvia:

Prokineticins are a new family of chemokines involved in multiple physiological processes including angiogenesis, neurogenesis, circadian rhythms and immune response. Prokineticins have a central role also in pain perception and in modulation of the inflammatory response. In mammals, the family consists of two ligands, Prokineticin 1 (PK1) and 2 (PK2), and two G-protein coupled receptors, PKR1 and PKR2.

Is a well-known fact that same pathologies could have different occurrence in men and women. Among diseases associated with chronic pain, some have a strong prevalence in women while others appear to be exclusive of women. It has been demonstrated that, in mice, inflammatory response and functional recovery following chronic constriction injury (CCI) are profoundly different between males and females [Vacca et al., (2014) Pain 155:388-402]. We have recently demonstrated that peripheral nerve injury causes a dramatic increase of PK2 in DRG neurons and activated astrocytes in the spinal cord, associated with the development of neuropathic pain [Maftei et al., (2014) Br. J. Pharmacol. 171:4850-65].

The aim of the study was to investigate, in a murine model, the involvement of prokineticin system in sex related differences following peripheral nerve injury. Male and female mice KO for PKR1 were used. After CCI, the temporal trend of mechanical nociceptive threshold (Ahestesiometer test), tactile allodynia (Von Frey test) thermal threshold (Plantar test) and weight balance (Incapacitance test) were analysed.

Part of this year of research was dedicated also to the investigation of a possible correlation between Granulocyte-colony stimulating factor (G-CSF)-induced pain and PK2 expression. G-CSF is a current therapy to increase neutrophil counts in peripheral blood of patients that underwent chemotherapy or radiotherapy for cancer treatment. The G-CSF therapy is well tolerated, but some side effects such as abdominal pain, bone pain and muscle-skeletal pain, limit its applicability. It has been established that G-CSF is the major inducer of PK2 expression in bone marrow mononuclear cells (BMMC) and in circulating and tissue-infiltrating granulocytes [Shojaei et al., (2007). Nature, 450:825-31; Qu et al., (2012), J Biol Chem, 287(23):19574-84]. We have already demonstrated that the up-regulation of PK2 in granulocytes infiltrating inflamed tissues is a major determinant in triggering and maintaining inflammatory pain [Giannini et al., (2009). PNAS, 106:14646-51]. Considering these data, the aim of our research was to verify
whether G-CSF-induced pain was related to an increase of PK2 expression and its release and if G-CSF-induced pain could be reduced blocking the prokineticin receptors.

Mice, pre-treated with saline or with the PKR1 preferring antagonist, PC1, were divided in two groups: the first group received a acute administration of G-CSF (10 µg, s.c.) and PC1 (150 µg/kg s.c.), while the second group received repeated administration of G-CSF (10 µg, s.c. once a day) and PC1 (150 µg/kg, s.c, twice a day) for 6 days. Von Frey test and Plantar test were used to evaluated G-CSF-induced tactile allodynia and thermal hyperalgesia respectively. mRNA levels of PK2 in circulating leucocytes, bone marrow, sciatic nerve, dorsal root ganglia and spinal cord were evaluated through Real Time PCR analysis.

Abete Lorena:

Hepatocellular carcinoma (HCC) is the fifth most frequent malignant tumors, and the third leading cause of cancer-related mortality in the world [1]. Early stages of HCC are frequently asymptomatic; so many patients are diagnosed at intermediate or advanced

stages, when therapies are less effective. Currently, the HCC-response to the conventional chemotherapy is poor, and, when
possible, surgical resection seems to be the only effective therapeutic approach.
Doxorubicin represents one of the most commonly drug used in cancer chemotherapy, but at highest tolerable doses it results in severe toxicity (cardiac, hematological, gastrointestinal etc.) [1]. Also cisplatin is active against several types of cancer; however, the use in therapy is limited due to adverse reactions and resistance development [2]. Recently, sorafenib, an orally-available kinase inhibitor, is the only drug approved by FDA to treat HCC, although its beneficial effects (inhibition of tumor progression and enhancement of overall survival) are rather modest [3].
HCC is characterized by the development of multidrug resistance (MDR), in which cancer cells become quickly insensitive to a variety of structurally and mechanistically related and unrelated antitumor drugs [4]. The over-expression of ATP-binding cassette (ABC) transporters seems to be one of the key events involved in MDR, due to their ability to efflux the anticancer drugs from the cell, so hindering the chemotherapy effectiveness. Thereafter, using ABC-transporter inhibitors, which can synergistically act with anticancer drugs, appears a promising approach for restoring the sensitivity of resistant liver cancer cells to chemotherapy. It also represents an interesting strategy for reducing the adverse effects of chemotherapy [5]. Compounds able to increase the anticancer effect of a chemotherapeutic are defined as chemosensitizers. A lot of natural compounds (including flavonoids, carotenoids, and alkaloids) have been found to possess in vitro chemosensitizing properties, particularly by inhibiting the ABC-transporters [6]. Nevertheless, some of them are only weakly effective in vivo or produce severe side effects. In this context, searching for alternative chemosensitizing compounds represents an important goal for overcoming liver cancer.
In the present research project, the natural sesquiterpenes β-caryophyllene (CRY) and β-caryophyllene oxide (CRYO) will be investigated for their potential chemotherapeutic and chemosensitizing properties against liver cancer. These compounds are known to possess interesting protective properties, including analgesic, anti-inflammatory, genoprotective and antiproliferative [7].
Furthermore, preliminary evidences suggest that CRYO modulates some molecular pathways involved in the proliferation of cancer cells [8, 9]. Considering that a poor water-solubility represents the major limit to the application of these sesquiterpenes in therapy, identifying a suitable pharmaceutical form for increasing their bioavailability has been focused as a second major objective of this research.

Cristina Anna Gallelli:
Oleoylethanolamide (OEA) is a gut-derived satiety signal released from enterocytes upon the ingestion of dietary fat. The anorexigenic effect of OEA requires the activation of peroxisome proliferator-activated-receptor-alpha (PPAR-alpha) and is associated with the induction of c-Fos in several brain areas involved in the control of food intake such as the nucleus of the solitary tract (NST), the area postrema (AP) and the hypothalamic paraventricular (PVN), supraoptic (SON) and tuberomammillary (TMN) nuclei. In both PVN and SON, c-Fos mRNA is increased in neurons expressing oxytocin (OXY), whose activation is paralleled by increased OXY neurosecretion and elevated circulating OXY levels, and appears to be regulated by the histaminergic projections from the TMN.
It has been recently demonstrated that OEA stimulates c-Fos expression in specific subnuclei of the NST and strongly activates neurons of the AP. Studies in AP lesioned rats suggest an involvement of this area in the control of food intake and body weight and demonstrated its role in mediating the effects of different peripheral signals. The AP lacks a functional blood-brain barrier (BBB) by virtue of its lack of tight junctions and the

presence of fenestrated capillaries, therefore circulating peptides and other physiological signals have direct access to neurons of the AP. This led us to hypothesize a possible pathway through which the OEA signal can reach the central nervous system (CNS), thus directly activating the AP.
The main aim of this project was to evaluate the way by which OEA can reach the CNS from periphery, in order to better investigate the mechanism of action of this endogenous lipid compound.

Gigli Stefano:
Colon Cancer (CC) is one of the most common form of neoplasia worldwide and represents the second tumor for incidence and mortality in Italy. Several studies suggested a close correlation between CC and a state of intestinal chronic inflammation, as putative cause of epithelial cell mutations leading to the carcinogenic development. Indeed, it has been shown that patients affected by inflammatory bowel diseases (IBD), such as Chron's disease (CD) and ulcerative colitis (UC), exhibit an increased incidence of CC resulting in a marked sensitiveness to tumorigenic drift due to their long-standing condition of chronic inflammation. The enteric nervous system (ENS) displays a critical role in the gut homeostasis, motility and fluid secretions. Moreover, among the cellular populations composing ENS, enteric glial cells (EGCs) are involved in the onset and perpetuation of intestinal inflammation condition thus actively participating to CC development. Once activated, EGCs are able to release proinflammatory cytokines and cellular mediators, such as S100B and nitric oxide (NO), which support the intestinal inflammatory state and, on other hand, induce epithelial proliferation and neovascularization. In particular, S100B is a calcium binding protein over-released by EGCs activated and represents an ideal bridge between intestinal chronic inflammation and the carcinogenic drift. Indeed, this protein is capable to inhibit tumor suppressor p53 itself and accumulates at RAGE (receptor for advanced glycation end-products) in micromolar concentrations, activating downstream NF-κB thus promoting the transcription of proinflammatory cytokines and inducible nitric oxide synthase (iNOS) protein. In this context, it becomes clear that compounds able to modulate EGCs activation and, consequently, reducing S100B release, may represent interesting candidates to prevent the outbreak of colon adenocarcinoma. Aim of this project is to evaluate the implication of enteric glia in the intestinal chronic inflammation and, consequently, in the tumorigenic drift through in vitro and ex vivo experimental models, in order to both amplify the current knowledge about the ENS and EGCs involvement in neoplastic onset from intestinal chronic inflammation and to identify new innovative therapeutic targets against CC.

JUSTYNA BARBARA KOCZWARA:
Oleoylethanolamide (OEA) is a lipid messenger synthesized in the upper portion of the gut. It has been demonstrated that, if administered intraperitoneally (i.p.) in animals,OEA leads to a decrease in food intake (increased intermeal interval, increased latency to eat and decreased meal size) and to the activation of brain areas involved in the control of food intake, such as the nucleus of the solitary tract (NST), the area postrema (AP) and the hypothalamic paraventricular (PVN) and supraoptic (SON) nuclei.
However, the mechanism through which OEA-mediated satiety signal reaches the central nervous system (CNS) is poorly understood. It has been hypothesized that OEA may activate afferent fibers of the vagus nerve, that represents one of the most important connections between the gut and the CNS. To investigate the role of the vagus nerve in the mechanism of action of OEA, several experiments have been performed and demonstrated that both after the lesion of afferent fibers by using the neurotoxin capsaicin and the removal of the subdiaphragmatic branches (both afferent and efferent) of the

vagus nerve, OEA's satiety effect is completely abolished. However, since capsaicin is toxic for non-myelinated fibers, it is not selective for vagal afferent fibers; in addition, the total subdiaphragmatic vagotomy causes many side effects due to the removal of vagal efferent fibers (e.g. impairment of gastric emptying), that may compromise feeding behavior.

Saponaro Angelo:
A through preoperative assessment of neuroendocrine, metabolic and emotional status could predict the level of emotional distress either for surgeons and patients. Currently, the potential for stress-induced damage is primarily based on the theoretical (obvious) side effects of stress. In fact, we use the word "stress" to describe the feeling of being overwhelmed by the psychophysical stress-induced challenges of daily life; this feeling may be highly adaptive from an evolutionary point of view because it allows us to cope with similar circumstances in the future. For the sake of brevity and to avoid delving too far into the details of the evolution of the concept of stress that has occurred over the past few centuries, we will refer to the modern and very comprehensive proposal that was put forth by Bruce McEwen to explain the complexity of the stress response. This proposal can be synthesized by the expressions "to be stressed" and "to be stressed out", which distinguish good stress challenges from bad stress challenges. According to McEwen's proposal, the pathophysiology of the stress response can be described by the concept of allostasis, which is the process of achieving stability (or homeostasis) through physiological or behavioral change. Allodynamic processes can be adaptive in the short term (allostasis) and maladaptive in the long term (allostatic load). The identity of the factors that determine the threshold between adaptive and maladaptive responses to stressors remains an open question for researchers in the field of psychopathology; this question highlights the need to search for predictive biomarkers of the risk of developing stress-related diseases. The measures used as subclinical indicators of hypothalamic-pituitary-adrenal (HPA) axis and sympathetic adrenomedullary system (SAM) activity during pathophysiological stress responses require additional and definitive validation.

XXX CICLO:
Fusco Ilaria:
Inflammation is a process that involves the synthesis/release of pro-inflammatory mediators, such as cytokines and chemokines. In periphery, the main cells that are producing these soluble mediators are neutrophils and monocytes/macrophages, whereas in central nervous system (CNS) are microglia and astrocytes.
Nowadays, among the mediators responsible of inflammatory processes we can include a new family of chemokines named Bv8/Prokineticins (Prokineticin 1 and 2 (PK1 and PK2)) whose members activate two G protein-linked receptors named PKR1 and PKR2 distributed in both peripheral and central nervous system. PKR1 is mainly distributed in the peripheral tissues (such as intestinal tract, cardiac cell, endothelial cell and neutrophils), while PKR2 in CNS (such as cortex, hippocampus, striatum, thalamic and hypothalamic, amygdala and suprachiasmatic nucleus); therefore the PKs are involved in numerous biological function as immune response, pain perception, circadian rhythms, angiogenesis and haematopoiesis.
Our group already demonstrated that PK2 plays a role in inflammation and neuroinflammation: PK2 is highly up-regulated in inflamed tissues associated with infiltrated neutrophils and was demonstrated to be a major determinant in triggering inflammatory pain (Giannini et al., 2009). PK2 is also an insult-inducible endangering mediator for cerebral ischemic injury. Indeed, PK2 mRNA expression is up-regulated by

several pathological stressors including hypoxia, reactive oxygen species (Cheng et al., 2012) and excitotoxic glutamate (Landucci et al., 2016).
Recent evidence from our laboratory demonstrated that modulation of Prokineticin system could be a general response to Amyloid beta (Aβ)1-42 injury in primary cortical cultures (CNs) (Severini et al., 2015): indeed, mRNA and protein levels of PK2, PKR1 and PKR2 are significantly increased after Aβ treatment and only the PK2 increase is reduce by PC1 treatment (a non-peptide antagonists of PKRs).
Based on this premise, I principally spent my second year of PhD learning and employing immunofluorescence and western blot assays for the evaluation of Prokineticin system in an animal model of Aβ-induced toxicity.

Marcelli Serena:
Alzheimer's disease (AD) is a severe progressive neurodegenerative condition, recognized as the most common cause of chronic dementia among the ageing population. It is typically characterized by loss of synaptic connections, leading to a gradual but irreversible decline of cognitive and behavioural functions.
Intracellular neurofibrillary tangles composed of hyperphosphorylated tau proteins and extracellular senile plaques of aggregated Aβ peptides are AD histopathological hallmarks, mostly found in fronto-temporal lobes, entorhinal cortex, amygdala and hippocampus of affected AD patients (Holtzman et al. 2011; Serrano-Pozo et al. 2011).
Recent studies claimed "synaptopathy" as a putative culprit at the basis of AD. Accordingly, synaptic dysfunction seems to be one of the first neuronal defects at the onset of AD, associated with a compromised neurotransmission that leads to synaptic loss and progressive neuronal death. In addition, the dysregulation of Ca2+ homeostasis has also been associated with neuritic dystrophy and dendritic spine loss in response to Aβ insult. Consequently, Ca2+ leakage from ER and the subsequent excitotoxic events might be potentially responsible for the presynaptic dysfunction occurring at the very early stages of AD synaptopathy (Sheng et al. 2012).
On the other hand, the fine regulation of post-translational modifications (PTMs) appears increasingly critical in the functional physiology of the nervous system, given their contribution to synaptic communication, homeostatic modulation and general brain functioning. So far, most of the AD key players are known to be modified by PTMs during the disease progression, apparently contributing to their physiological alteration.
In the frame of this emerging field of scientific research, the focus of our project is to investigate how and to what extent the homeostatic dysfunction of PTMs might contribute to the arising of pathological conditions, with particular concern to the cognitive alteration and synaptic neurodegeneration observed in AD.
Among the PTMs, SUMOylation is currently the most reported in literature as potentially involved in the etiopathogenesis of AD, interestingly endowed with a newfound role at synaptic level during AD onset and progression (Sarge et al. 2011; Lee et al. 2013).
Consequently, SUMO modification of fundamental AD proteins like AβPP, tau, BACE1 and GSK3β is nowadays largely studied (Martins et al. 2016). Increased levels of global SUMOylation were detected in APP overexpressing mice (Yang et al. 2012) as well as in Tg2576 animals at 3 (onset of the pathology) and 6 (early stage) months of age with respect to age-matched controls (Nisticò et al. 2014).
Under a clinical prospective, moreover, post-mortem brain specimens from AD patients reported altered levels of SUMOylation and SUMO-related proteins expression, especially in the hippocampus.
We preliminarily found that presynaptic protein SUMOylation was able to modulate synaptosomal glutamate release and calcium influx, thereby intervening in synaptic functionality (Feligioni et al., 2009). We consequently hypothesize that an eventual

unbalance in SUMO/deSUMOylation processes could alter specific intracellular signalling pathways and basal synaptic transmission, possibly promoting AD pathogenesis. In this scenario, we have targeted the modulation of neuronal protein SUMOylation by manufacturing two peptide-like tools that laid the foundation for a novel potential clinical avenue in AD therapy.

Reggi Raffaella:
Based on the role of oxidative stress and dietary habits in the onset of many diseases, many supplements have been marketed. Those containing catechins and flavonoids are very interesting in relation to their potential effect on uricemia and in relation to interaction with prebiotic and probiotic substances.
Wheat germ has a high contents of proteins proteins, lipids, sugars and minerals, as well as tocopherols (vitamin E), B-group vitamins, carotenoids, flavonoids, phytosterols and policosanols (Fardet, A. 2010. New hypotheses for the health-protective mechanisms of whole-grain cereals: What is beyond fibre? Nutrition Research Reviews 23:65–134).
The aim of this study is to evaluate the antioxidant capacity of different fractions extracted from wheat germs by using different polarity solvents, in relation to antioxidant markers.
0.5 mm grained wheat germs and after SC-CO2 were used for the extraction by PLE. The efficiency of the extraction procedures was assessed, applying a systematic evaluation of antioxidant potential by measuring extract properties using several assays.
The supercritical carbon dioxide extraction/fractionation was used for the isolation of lipophilic fraction from the grained wheat germ and then using of multistep pressurized liquid extraction/fractionation for the isolation of higher polarity fractions (Acetone, methanol and water).
In order to do the evaluation of antioxidant presence, we want to study in vitro the antioxidant activity, radical scavenging capacity , using PLIR Method.
This pilot study will be useful for designing studies in acute and / or chronic greater sampling , which also take into account inflammation and immunological markers. The results of this pilot study will be also useful for designing in vitro studies to evaluate the mechanisms of action .

Tittone Francesca:
The second year of my PhD program was focused on the new disease-modifying drugs developed for treating Cystic fibrosis (CF).
CFTR modulators are designed to treat the underlying cause of cystic fibrosis by targeting the CFTR protein defect. Small pharmacologic agents that target defects in CFTR gating, processing, and synthesis have undergone rigorous preclinical evaluation over the past decade and include CFTR potentiators, correctors, and translational read-through agents, respectively.
CFTR read-through agents promote the ribosomal “read-through” of premature termination codons (PTCs) in CFTR mRNA. The first read-through agents examined in CF were aminoglycoside antibiotics, which are commonly used in cystic fibrosis to treat Gram negative bacteria infections, such as Pseudomonas aeruginosa. Aminoglycoside antibiotics such as gentamicin are capable of inhibiting ribosomal “proofreading” by binding to the decoding site of rRNA. This reduces the fidelity of the codon-anticodon pairing and permits the erroneous addition of an amino acid to the polypeptide chain at the site of the PTC, allowing translation to continue to the end of the gene. Unfortunately, high systemic levels of gentamicin, which can cause serious renal toxicity and ototoxicity, are needed to induce translational read-through. Consequenlty, high throughput screening was performed in order to identify more potent, orally bioavailable, non-toxic alternatives to aminoglycosides that are capable of selective read-through of PTCs in cystic fibrosis and

other genetic disorders characterized by nonsense mutations (such as Duchenne muscular dystrophy and Hurler's disease). Ataluren (formerly PTC124) was identified as a lead candidate after medicinal chemistry optimization. The compound has no structural similarity to aminoglycosides or other clinically developed drugs. PTC124 promoted dystrophin production in primary muscle cells from humans with Duchenne muscular dystrophy and a mouse model expressing dystrophin nonsense alleles. Subsequent in vivo experiments found that PTC124 could suppress the G542X nonsense mutation in a cystic fibrosis mouse model expressing the human CFTR-G542X transgene, restoring CFTR expression and function. Currently, a phase III clinical trial of Ataluren in cystic fibrosis patients with nonsense mutations is ongoing.

Bove Maria:
In the past decade, we have been facing a dramatic increase in the prevalence of depression. This made mandatory the research of risk factors for the development of depressive symptoms; between them, dietary and genetic factors play a key role. Indeed, diet composition seems to be strongly correlated with depressive symptoms, both positively and negatively. In this regard, the first aim of this project has been to investigate the neurochemical and behavioural effects of n-3 and n-6 polyunsaturated fatty acids (PUFA) enriched diets in adult rats, fed lifelong with the same diet. Results showed that an improper n-6 PUFA diet consumption can be detrimental, increasing depressive-like behaviour and altering neurochemical parameters involved in the development of depressive disorders, while n-3 PUFA enriched diet seems to be protective towards stress and depressive-like symptoms.
Moreover, emerging evidence suggests a potential role of soluble Beta amyloid 1-42 (Aβ1-42) peptide in the development of depression. To systematically investigate this possibility, adult rats, fed with the diets described above, received an Aβ1-42 intracerebroventricular (icv) injection in order to evoke a depressive-like state. Results confirmed the negative role of n-6 PUFA overconsumption and the beneficial effects of n-3 PUFA use.
On the other hand, genetic determinants must be taken into account to deeply understand the pathogenesis of depressive symptoms. For this purpose, a new behavioural paradigm to study the social withdrawal with relevance to depressive disorders will be implemented and validated. In particular, genetic mouse models for human candidate genes associated with neuropsychiatric disorders will be studied at the level of social group behavioural dynamics.

Cavaliere Arturo:
Background: Le patologie dermatologiche autoimmuni sono caratterizzate da una condizione di stress ossidativo talvolta associata ad una ridotta resistenza alle infezioni. Il Peroxidation of Leukocytes Index Ratio (PLIR) è un test che misura il rapporto tra la resistenza dei leucociti ad uno stress ossidativo esogeno e la loro capacità funzionale di burst ossidativo in seguito ad attivazione. Per questi motivi risulta interessante analizzare il PLIR in pazienti con psoriasi ed in particolare in quelli in trattamento con immunosoppressori substrati delle MDR (come gli inibitori della calcineurina) e farmaci biologici (anti-TNF-).
Obiettivo: Gli obiettivi principali dello studio sono il confronto sano-patologico e la valutazione della correlazione tra PLIR e markers diagnostici e di prognosi. Obiettivi secondari sono il confronto PLIR pre e post trattamento farmacologico e tra trattamenti alternativi, il confronto PLIR con la valutazione del burst ossidativo mediante diidrorodamina 123 (DHR123) e la correlazione tra PLIR e markers di sindrome metabolica.

Metodologia: Lo studio osservazionale verrà condotto su campioni di sangue prelevati (previo consenso informato) da soggetti che effettueranno prelievi presso l'IDI-IRCCS alla diagnosi di psoriasi. Soggetti di controllo saranno reclutati preso l'Università La Sapienza di Roma. I risultati del PLIR saranno confrontati con quelli del metodo che usa il probe DHR123 e saranno messi in relazione a parametri clinici ed indici di attività della malattia.
Campione: In questo studio pilota verranno inclusi 10 soggetti per ogni gruppo di trattamento (10 in terapia con ciclosporina e 10 in terapia con anti-TNF-) al fine di calcolare il "sample size" del nuovo marker di stato redox per studi successivi. Saranno usati come controllo 20 soggetti di età, sesso, indice di massa corporeo, abitudine al fumo e markers metabolici paragonabili ai pazienti affetti da psoriasi.
Risultati attesi: Tutti i leucociti (linfociti, monociti e granulociti) dei pazienti con psoriasi dovrebbero essere più sensibili ad uno stress ossidativo esogeno rispetto a quelli dei soggetti sani. Il burst ossidativo potrebbe essere diverso sia rispetto ai soggetti sani, sia in base al tipo di trattamento. Sarà particolarmente interessante analizzare il PLIR in relazione ai markers di sindrome metabolica ed all'abitudine al fumo. Nei soggetti pre e post-trattamento con ciclosporina ci aspettiamo risultati più attendibili e coerenti con i dati clinici con il PLIR rispetto alla valutazione del burst con DHR123.

Guaglianone Giuseppe:
Obiettivo primario: L'obiettivo dello studio è valutare la strategia del trattamento in termini di sopravvivenza globale (OS: overall survival) a 24 mesi.
Obiettivi secondari: − Sopravvivenza libera da malattia (DFS: Disease Free Survival); − Sopravvivenza libera da eventi (EFS: Event Free Survival); − Incidenza Cumulata di Recidiva (CIR: Cumulative Incidence of Relapse); − Tasso di risposta dopo la terapia d'induzione; − Safety: eventi avversi (AE) ed eventi avversi gravi (SAE); − OS, EFS, DFS e CIR nei differenti gruppi di rischio; − OS, EFS, DFS e CIR secondo il livello di Malattia Minima Residua (MMR); − Percentuale di risposta, OS, EFS, DFS e CIR secondo le caratteristiche di base: età, performance status, globuli bianchi, morfologia, citogenetiche e molecolare; − Valutazione della qualità di vita.

Ulivieri Martina:
Along the kynurneine pathway (KP), an enzymatic route involved in the metabolism of L-tryptophan, some metabolites are endowed with immune activity and are also capable of interacting with different kind of glutamate receptors. In particular, two kynurenines, the kynurenic acid and the quinolinic acid interact with ionotropic glutamate receptors, behaving respectively as an antagonist and agonist of the NMDA receptors. Among kynurenines, the metabolites of the KP, cinnabarinic acid was shown to activate metabotropic glutamate receptor type 4 (mGluR4) and, by this activation, to downregulate the response of the Immune System (IS). Both metabotropic andin in ionotropic glutamate receptors are crucial in the regulation of central nervous system (CNS) but recently they also emerged as players of the immune system. Glutamate receptors are present in the immunological synapse, and, in different ways, take part to the control of the immune responses. The relationship between the CNS and the IS is an established finding.
Drugs counteracting immune responses have been associated to depression or mood disorders. In this second part of my PhD I have focused my efforts to the physiological function of cinnabarinic acid in mood disorders, with a particular regard to schizophrenia and anxiety disorders. Moreover, I will perform experiments to clarify the role of xanthurenic acid in autoimmune disorders.