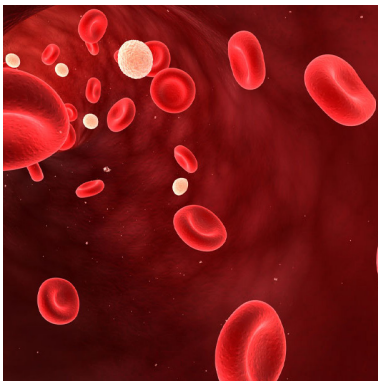
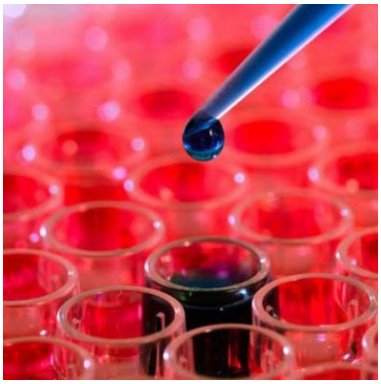
Poster Presentation

Hematology 2018

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Coagulation profile in Myeloproliferative Neoplasms

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Myeloproliferative diseases are a heterogenous group of disorders characterized by cellular proliferation of one or more hematologic cell lines in the peripheral blood. The clinical course of myeloproliferative neoplasms (MPN) being frequently complicated by thrombotic events. The main objective is to evaluate the coagulation profile in patients with Myeloproliferative Neoplasms. The methods included a total of 55 patients of myeloproliferative neoplasms (Chronic Myeloid leukemia, Polycythemia Vera, Essential thrombocytosis and Primary Myelofibrosis) were studied over 1-year period. Coagulation profile was recorded. D-dimer was measured by Latex kit 60X, Prothrombin time, and Activated partial thromboplastin time with KC4 Amelung coagulometer, which resulted 55 cases of myeloproliferative neoplasms Prothrombin time was elevated in 43.64%(n=24) cases, activated partial thromboplastin in 32.73%(n=18) and 20%(n=11) in D-Dimer and concluded the coagulation profile is found to be elevated in patients with Myeloproliferative Neoplasms which is comparable with other international studies.

Speaker Biography

Sadia Taj did her graduation in 2003 and did her FCPS residency from Shaikh Zayed Medical Complex Lahore from Jan 2012- April 2016.After passing her FCPS exam she started working as senior Demonstrator in Pathology department of FMH College of Medicine and Dentistry Lahore and Currently promoted as Assistant Professor Haematology.

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Notes:

E-Poster

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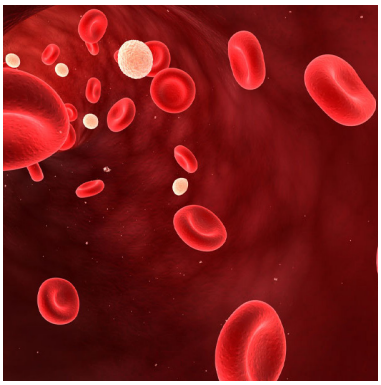


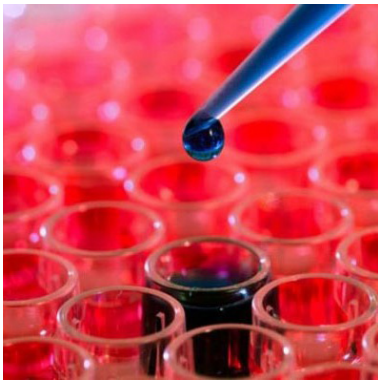


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Imbalanced proportions of phospatidylinositol and phosphatidylcholine in plasma membranes of hematopoietic cells in patients with paroxysmal nocturnal hemoglobinuria

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Paroxysmal nocturnal hemoglobinuria (PNH) is caused by somatic mutation in phosphatidylinositol glycan complementation group A (PIG-A) gene in single hematopoietic stem/progenitor cell (HSC). Pathomechanism of clonal domination of mutated HSCs over normal HSCs is not fully clear including autoimmune, pro-survival and/or anti-apoptotic background, among else. Phosphatidylinositol (PI) is important anti-apoptotic second messenger in cells and its conversion to glycosylated PI (GPI) is arrested in PIG-A mutated PNH cells. PI content in cells is fine regulated by highly specific enzyme, the phosphatidylinositol transfer protein that is able to deliver PI to plasma membranes at the expense of equimolar quantity of phosphatidylcholine (PC). In this study we assessed contents of PI and PC phospholipids in nucleated hematopoietic cells in patients with PNH (N=22) and healthy controls (N=6). Phospholipid fractions were isolated from plasma membranes using modified Folch-based lipid extraction protocol and evaluated using high performance liquid chromatography (HPLC) with charged aerosol detection (CAD). Phospholipid contents were expressed as nmoles/10^6 cells to show molecular proportions of PI and PC in cellular membranes. We found significantly higher PI/PC molar ratio in PNH patients than in controls both in polymorphonulear (PMN) (Mean±SE: 16.3±2.6 vs. 8.0±2.0 %mol/mol, p=0.020) and mononuclear cell (MNC) fractions (20.5±3.8 vs. 9.6±2.7 %mol/mol, p=0.024). This PI/PC imbalance was caused mainly by the fall of absolute content of PC in cellular membranes in PNH patients. FLAER(-) cell proportion in PNH patients correlated with PC content in PMN cells (R=0.53, p=0.020). In PNH patients we found highly significant correlation of platelet cell (PLT) counts with PC content in MNC subset (R=0.55, p<0.01). Both white blood cell (WBC) and PLT counts in patients show trend toward lower values with increasing PI/PC molar ratios (R>0.39, p<0.09). The results suggest that i) in PNH patients the proportions of PI to PC molecules in plasma membranes of hematopoietic cells are imbalanced. Higher relative proportions of PI may potentially increase anti-apoptotic capacity of certain PI-dependent enzymes in hematopoietic cells. ii) The results suggest a protective role of PC in platelet aggregation and turnover. In PNH patients PC deficiency in circulating blood cells may be associated with increased risk of thrombosis.

Speaker Biography

Jacek Nowak has completed his PhD from Military Medical Academy, Łodz, Poland and habilitation degree from Institute of Hematology and Transfusion Medicine, Warsaw, Poland. He is the tenure professor and head of Department of Immunogenetics at the Institute of Hematology and Transfusion Medicine. He has over 80 publications that have been cited over 470 times, and his publication H-index is 11 and has been serving as an editor at 2 books and has over 20 published chapters.

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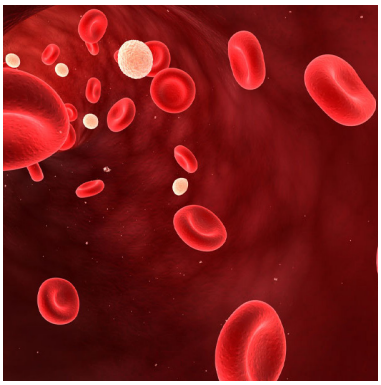


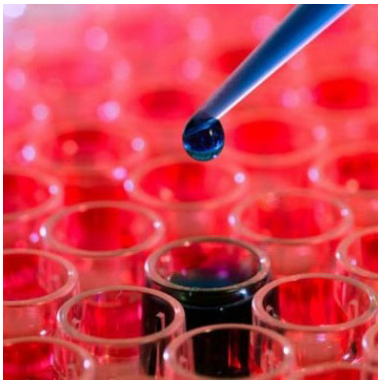


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Manifestation of Antiphospholipid Syndrome among Saudi patients; Examining the applicability of Sapporo

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Antiphospholipid syndrome (APS) is a systematic autoimmune disease featured with vascular thrombosis and pregnancy morbidity, which is likely to be under-diagnosed in the clinical practice. The Sapporo classification criteria of APS was revised in 2006 and are used as the main diagnosis guideline, which validity as standard measurements is still in debate. Few studies had been tackled the clinical and laboratory manifestations of APS among Saudi Arabic population. A total of 72 (90%) females and 8 (10%) males were included, female-to-male ratio was 9:1. The mean (±SD) age at diagnosis was 28.1 (± 8.7) years (range 11-63 years). 22 patients (27.5%) fulfilled the revised Sapporo criteria (definitive APS). There was no significant difference in the clinical manifestations or treatment between the two group (p>0.2). However, we found definitive APS cases had significantly higher percentage of serological manifestation presence than possible APS cases. Although not reaching statistical significance, definitive APS cases had higher odds of experiencing vascular thrombosis (OR=1.61, 95%CI 0.55, 4.71; P=0.39) and DVT/PE (OR=1.53, 95%CI 0.55, 4.31; P=0.42), and lower odds of experiencing recurrent DVT/PE (OR=0.67, 95%CI 0.12, 3.81; P=0.65) and pregnancy morbidity (OR=0.63, 95%CI 0.21, 1.92; P=0.42) than the possible APS cases.

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The Anti-Cancer Potential of Polyphenols in the Treatment of Leukemia

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Leukaemia is a complex disease affecting all blood cell lineages. It affects millions of people worldwide each year and mortality rates are high, despite considerable improvements in treatment. Thus, new therapies for leukemia are urgently needed to improve leukemia patients' health and survival. Since polyphenols exert pro-apoptotic effects in solid tumours, our study investigated the effects of polyphenols in Hematological malignancies. Methods: The effects of eight polyphenols (quercetin, chrysin, apigenin, emodin, aloe-emodin, rhein, cis-stilbene, and trans-stilbene) was studied on cellular proliferation, the induction of apoptosis and cell cycle progression in four lymphoid (JURKAT, MOLT-3, CCRF-CEM and U937) and four myeloid (HL-60, THP-1, K562 and KG-1a) leukaemia cells lines, together with normal haematopoietic control cells (CD34+ HSC and CD133+ HSC) from cord blood. Further to this, an investigation was made of the effects of the most promising polyphenols used in combination with five standard chemotherapeutic agents (etoposide, doxorubicin, methotrexate, 6mercaptopurine, and 5-fluorouracil). For this polyphenol and chemotherapy combination work, four leukemia cells lines were used: the two most sensitive (JURKAT and CCRFM-CEM) and two most resistant (KG1a and THP-1) to polyphenol treatment. Subsequently, an investigation was undertaken to identify potential mechanisms of action of these polyphenols when used alone and in combination with chemotherapeutics. The extrinsic and intrinsic apoptotic pathways were investigated together with effects on glutathione levels and DNA damage. Results: Emodin, quercetin, and cis-stilbene were the most effective polyphenols at decreasing cell viability and inducing apoptosis. Lymphoid cell lines were normally more sensitive to polyphenol treatment compared to myeloid cell lines; however, those myeloid (KG-1a and K562) cell lines which were most polyphenol resistant; were however affected by emodin and quercetin at micromolar treatment doses. Non-tumour cells were less sensitive to all polyphenols compared to the leukemia cells. Mechanistically, most polyphenols alone depleted glutathione (GSH) levels associated with a direct activation in caspase 8 and caspase 9 in leukemia cell lines at 24 h. Polyphenols also had differential capacities to induce DNA damage in the leukemia cell lines. Polyphenols acted synergistically in lymphoid cell lines and differently in myeloid cell lines producing either synergistic, additive, competitive antagonistic or antagonistic effects; when they were combined with topoisomerase inhibitor agents (etoposide and doxorubicin). In contrast, they worked antagonistically with anti-metabolites agents (methotrexate and 6-mercaptopurine) in both lymphoid and myeloid leukaemia cell lines. Mechanistically the synergistic induction of apoptosis observed following the combination of polyphenols with chemotherapeutic agents was caused by the direct activation of intrinsic or/ and extrinsic apoptotic pathway through the up-regulation of caspase 8 or caspase 9 within the lymphoid and myeloid leukaemia cell line. Furthermore, it has been shown the synergistic effects observed when polyphenols and chemotherapy agents were combined was correlated with down regulation of GSH levels and an induction of DNA damage which drove apoptosis. Alternatively, where there was an antagonist effect, there was an upregulation of GSH levels, a reduction in DNA damage and the level of apoptosis. Conclusions: These findings demonstrate that polyphenols induce apoptosis and arrest cell cycle in leukemia cell lines which could translate to anti-cancer activities in leukemia, although the effects were dependant on polyphenol type and origin of the cell line investigated. Importantly, the differential sensitivity of emodin, quercetin, and cis-stilbene between leukemia and normal cells suggests that polyphenols are potential therapeutic agents for leukemia. Furthermore, this study concluded that the efficacy of standard chemotherapeutic agents was differentially modulated by polyphenols, producing either synergistic, additive or competitive antagonistic/antagonistic effects, which was dependent on the type of polyphenol, chemotherapy agent and cell line. Interestingly the study showed that synergistic or antagonistic effects observed following the combination treatments were strongly dependent on the modulation of glutathione levels in association with the formation of γ-H2AX nuclear foci and DNA damage in leukemia cell lines.

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miRNAs Modulate Chemotherapeutic Sensitivity in a model of Acute Myeloid Leukemia

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A substantial number of chemo-refractory Hematological malignancies involve CNS localization, causing impairments in cognitive function as well as enhanced co-morbidities associated with tumour infiltration into the brain parenchyma. Identifying therapeutic strategies that reduces CNS infiltration would greatly improve leukemic patient outcomes, as those with Hematological malignance absent of CNS localization are responsive to various chemotherapeutic agents such as rituximab. Noncoding RNAs play an important role in regulating the cellular pathways that modulate responses to chemotherapeutic agents. Therefore, we performed a microRNA (miRNA) gain-of function screen to identify miRNA(s) that function as drivers of chemotherapeutic resistance. Using HL-60 cells, a drug-sensitive acute myeloid leukemia (AML) cell line, we identified certain miRNAs from a pool of >400 of miRNAs as robust drivers of resistance to the chemotherapeutic agents cytarabine (Ara-c) and daunorubicin (DNR). Forced expression of these miRNAs in HL-60 cells decreased DNR- and Ara-c-induced cell death. Furthermore, HL-60 cells expressing high levels of these miRNAs proliferated at slower rates than those without the miRNA. Out of the miRNAs tested, miRNAs that drive chemotherapeutic resistant also induced a quiescence-like phenotype, as determined by CFSE staining experiments, by assessing direct miRNA targets such as CCDN2, the modulation of which results in an increased frequency of cells in G1. This in vitro data is supported by the finding that high levels of these miRNAs in AML clinical samples correlated with poorer overall survival (OS). Therefore, we argue that miRNAs can functions as a diagnostic marker in AML patients, and specifically as a predictor of chemotherapeutic response. These findings are the basis for ongoing studies elucidating the role of miRNAs within Hematological malignancies involving CNS localization.

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Hemotopoietic toxicity and blood diseases induced by benzene exposure

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Benzene is a representative compound of volatile organic compounds (VOCs). As an organic solvent, benzene has been widely used in various areas such as rubber, plastic, and petroleum industries. Contamination of benzene may not only occur in occupational settings but also in general environment since it is a component in petrol, paints and cigarette smoke. People are exposed to benzene mainly through inhalation but digestion and dermal contact may also lead to benzene exposure. Notably, benzene is an established environmental leukemogen that can causes haematological malignancies and has been classified as Group 1 carcinogen by IARC. Although the toxicity and health effect of benzene have been extensively studied and documented, the exact mechanisms of these effects remain to be fully addressed. This talk will discuss recent progress and gaps in the benzene metabolism as well as the genetic and epigenetic effects of its metabolites leading to benzene-induced hemotopoietic toxicity and blood disorders, particularly acute myeloid leukaemia.

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Intracellular oxidative stress contributes to the oncogenic potential of mutant FLT3 in acute myeloid leukaemia patients, and is a synergistic treatment target

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Leukaemic transformation of haematopoietic progenitors is a multistage process characterised by the overproduction of reactive oxygen species (ROS). AML patients diagnosed with recurring mutations to the FMS-like tyrosine kinase-3 (FLT3) commonly relapse after they achieve initial remission, succumb to a treatment resistant AML. FLT3-ITD (Internal Tandem Duplication) mutations are the most common genomic driver lesion, and are associated with the overproduction of ROS. Overproduction of ROS is induced by the activation of alternative metabolic pathways causing increased genomic instability through the oxidation of DNA bases, influencing clonal evolution. Importantly, ROS oxidises and inactivates key proteins indispensable for the regulation of growth and survival signalling pathways. To determine the cooperative mechanisms underpinning leukaemogenic growth and survival signalling, bone marrow trephine biopsies from AML patients at diagnosis were subjected high-resolution quantitative proteomic, phosphoproteomic and REDOX sequencing. Patients expressing FLT3-ITD mutations showed significantly increased expression of proteins directly responsible for the production of ROS. Oxidation and inactivation of tumour suppressor proteins particularly, protein tyrosine phosphatases (PTPs) directly downstream of FLT3, and directly upstream of STAT5 were seen compared to AML patients expressing wild-type FLT3. Proteins important in maintaining cellular homeostasis, such as antioxidants were differentially dysregulated between patient subtypes supporting the notion of REDOX dysfunction in FLT3-ITD+ AML patients. Reducing intracellular oxidative stress levels using novel clinically relevant compounds, reactivated intrinsic cellular defence systems, inducing selectively synergistic cell death when combined with FLT3-ITD inhibitors currently in clinical trials. Importantly, analysis of AML cells grown under conditions mimicking the bone marrow microenvironment, enhanced the anti-leukaemic efficacy of our novel therapies by reducing oxidative stress, decreased oncogene addition, highlighted the divergent metabolic requirements of AML blast cells in the bone marrow compared to the circulation. These studies suggest a mechanism of cooperation between oncogenic kinases, metabolism and oxidative stress to reveal a novel treatment paradigm currently under preclinical evaluation.

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PICCs & Central Line Associated Blood Stream Infections in Aneurin Bevan Health Board

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Peripherally inserted central catheters (PICCs) are specialised venous catheters made of strong, flexible, radio-opaque material such as polyurethane or silicone. They terminate in the distal superior vena cava and provide reliable venous access for the delivery of a broad range of intravenous agents; they also allow blood to be safely drawn for laboratory testing. The popularity of PICCs has grown in contemporary medical practice for numerous reasons such as relative cost-effectiveness, perceived safety and ease of insertion. They have taken over from traditional central venous catheters (CVCs) which are inserted by directly puncturing one of the great veins at the upper thoracic aperture. Central line-associated blood stream infection (CLABSI) is one of the major potential complications among all CVCs, particularly among critically ill or immunocompromised patients. This quality improvement project aims to review CLABSI rates in PICC lines inserted in The Royal Gwent Hospital & implement interventions to reduce the rate of infection. A retrospective data collection was carried out identifying all patients who had received a PICC line in the year running January to January 2016-2017. This period was chosen because it was the first year in which more than 50 PICCs were inserted by the Radiologists and it was felt that a sample size of less than 50 could provide inadequate or biased data. 54 patients from the Radiology database and 54 patients from the Haematology database were randomly selected and comprehensive data was extracted from CWS, RADEX and patient notes. Interventions were then implemented including updating guidelines for PICC care on the intranet, producing a proforma for use in patient's notes and organising teaching at Foundation Doctor weekly sessions as well as on the wards. Data was then collected again to assess the effect of the interventions and run-charts were produced to demonstrate significance. Results Four lines in the initial data collection fulfilled the criteria for CLABSI. Three of these infections were for PICC lines from the Haematology arm and one was from a PICC line from the Radiology arm. Since PICCs are present for a varying duration in different patients, expressing the risk of CLABSI per 1,000 line days rather than per 100 PICCs allows for a more meaningful estimation of risk. The overall rate of infection was 0.92 infections per 1,000 line days with a rate of 1.05 infections per 1,000 line days in the Haematology arm and 0.67 infections per 1,000 line days in the Radiology arm. The subsequent data collection demonstrated an overall rate of infection of 0.76 infections per 1,000 line days with a rate of 0.94 infections per 1,000 line days in the Haematology arm and 0.45 infections per 1,000 line days in the Radiology arm. Discussion In both The Radiology Suite and Medical Day Case Unit, the rate of proven CLABSI is <1.2 per 1,000 line days which is far superior to the average quoted in the literature of 2.1 per 1,000 line days (3) in hospitalised patients. However, as the data was gathered it became apparent that there were multiple PICC lines which were removed for suspicion of infection in which the line was not sent for culture. Therefore, the apparently favourable rates of line infection at RGH may merely be an anomaly due to poor practice with regards to microbiological protocol. All lines which are removed for suspicion of CLABSI must be sent to microbiology for line-tip culture, along with a simultaneous blood culture ideally taken prior to line removal. It is prudent to note that if there is no demonstrable advantages in terms of outcomes when placing PICC lines in Interventional Radiology Suites then the procedure could simply be completed at the bedside by specially trained nurses. However, the data collected through this project showed that there were significantly fewer infections per 1,000 lines days when PICC lines were placed in The Radiology Suite. While this may justify the extra cost involved, it may simply reflect the different subgroups of the population admitted into the two different services. The majority of patients undergoing PICC line insertion in Medical Day Case Unit require long-term chemotherapy and are therefore more susceptible to CLABSI. In addition, patients who are frailer, hospitalised, more elderly or suffering from concurrent infections are more likely to contract CLABSI. The overall average time until infection was 57 days with the longest time until infection being 134 days and the shortest being 11 days. An early infection (within two weeks) would suggest that it was procedure-related.

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FBXO11 is a frequently mutated oncosuppressor in Burkitt Lymphoma

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Introduction: FBXO11 is a ubiquitin ligase involved in the degradation of BCL6, a key oncogene in lymphoma pathogenesis. We previously described inactivating mutations of the FBXO11 gene in Diffuse Large B Cell Lymphoma (DLBCL) (Duan et al, Nature 2012). Thus, FBXO11 acts as an oncosuppressor in DLBCL by promoting the accumulation of BCL6. In the present work we searched for FBXO11 mutations in BCL6-positive lymphomas and we investigated its role in lymphoma development in vivo.

Methods: We sequenced the FBXO11 coding sequence in 100 cases of Follicular Lymphoma (FL), 36 cases of Burkitt Lymphoma (BL), 8 BL cell lines and 8 Anaplastic Large cell lymphoma cell lines, all BCL6-positive lymphomas, and 50 cases of Marginal Zone B Cell Lymphoma (MZL), with variable expression of BCL6. We functionally validated the FBXO11 mutations by testing their ability to induce BCL6 degradation. We then applied the CRISPR/Cas9 system to disrupt the endogenous FBXO11 gene in BL cells and evaluated its effect on BCL6 stability. We tested the sensitivity of FBXO11 knock-out (KO) BL cells to a BCL6 inhibitor (FX1) alone or in combination with chemotherapy (doxorubicin). To dissect the in vivo role of FBXO11 in lymphomagenesis we generated conditional FBXO11 KO mice (CD19/Cre-FBXO11fl/fl) and we crossed them with Eμ-myc transgenic mice to investigate whether FBXO11 inactivation cooperates with c-myc in lymphomagenesis.

Results: We identified FBXO11 mutations in BL cases and cell lines (10/44, 22.7%), one case of FL (1/100) and one case of MZL (1/50). Recurrent FBXO11 mutations in BL were further identified in publicly available sequencing databases of 66 BL cases (13/66, 19.7%) (Love et al Nat Genet 2012, Grobner et al Nature 2018). BL mutations found in our series were mostly missense and splice-site mutations located in the functional domains and all of them impaired FBXO11 ability to induce BCL6 degradation. CRISPR/Cas9 mediated KO of FBXO11 in BL cells resulted in an almost complete stabilization of BCL6, thus suggesting that FBXO11 is the main ubiquitin ligase that controls BCL6 stability in BL. FBXO11-KO BL cells showed increased resistance to standard chemotherapy as well as increased sensitivity to BCL6 inhibition compared to the FBXO11 WT BL cells. The simultaneous combination of FX1 with doxorubicin restored the sensitivity of FBXO11-KO BL cells to standard chemotherapy. Finally, we observed an acceleration of lymphoma development in the CD19/Cre-FBXO11fl/fl mice crossed with Eμ-myc transgenic mice. The lymphomas showed histologic features of high-grade disease with a more mature B-cell phenotype, stabilization of BCL6 and reduced apoptotic fraction compared to Eμ-myc only tumors.

Conclusion: Our results demonstrate that FBXO11 is frequently mutated in BL with a mutation frequency of about 20% of cases. Thus, FBXO11 is one of the top five most frequently mutated genes in BL. Biological experiments in vitro and in vivo show that FBXO11 deletion cooperates with c-myc in accelerating lymphomagenesis. Remarkably, FBXO11 deletion in the context of c-myc overexpression generates more mature lymphomas that closely resemble human BL, providing a novel tool for potential preclinical testing of therapies with BCL6 inhibitors. Indeed, the combination of BCL6-targeted therapy restored the sensitivity of FBXO11-KO BL cells to standard chemotherapy suggesting potential combinational strategies for the treatment of BL patients

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Chronic liver disease and hemostatic disturbances

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The liver is the primary site of synthesis of most of the clotting factors and the proteins involved in the fibrinolytic system. These include all the vitamin K-dependent coagulation proteins (factors II, VII, IX, X, ATIII, protein C, protein S and protein Z), as well as factor V, XIII, fibrinogen, antithrombin, and plasminogen. Decreased plasma concentrations for all proteins except for factor VIII are observed in patients with hepatic failure. Besides low levels of clotting factors due to impaired synthesis capacity, also dysfunctional proteins are found in patients with liver failure. Additionally, liver plays a vital role in the regulation of anticoagulation. Removal and clearance of activated clotting and fibrinolytic factors, especially tissue plasminogen activator (tPA), is mediated through the hepatic reticuloendothelial system. Multiple alterations in platelet number and function can be found in patients with liver disease. A mild to moderately reduced platelet count is frequently present in patients with acute or chronic liver failure. The net outcome of these alterations in the hemostatic system is a bleeding diathesis, although thrombosis of the portal vein is also frequently seen in patients with cirrhosis. As liver disease has multiple effects on the hemostatic system, it is difficult to determine which factors contribute most to the bleeding diathesis. No single coagulation test is predictive of hemorrhage or thrombosis in patients with chronic liver disease. A prolonged PT or international normalized ratio (INR) is a key indicator of hepatic dysfunction and commonly used as a trigger for liver transplantation. Thrombophilia tests: levels of the naturally occurring anticoagulants (ATIII, protein C, protein S) may all be reduced as a consequence of liver disease. In conclusion: Because of the hemostatic problem of liver disease is multifactorial, the follow up and management of chronic liver disease may ameliorate the bad prognosis.

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Diffuse Large B Cell Lymphoma and Clinical Intervention

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Diffuse large B-cell lymphoma: It is the most common type of non-Hodgkin lymphoma among adults. Diffuse large B-cell lymphoma occurs primarily in older individuals, with a median age of diagnosis at approximately 65-70 years of age, though it can also occur in children and young adults in rare cases. Diffuse large B-cell lymphoma is an aggressive tumor, sometimes associated with fever, weight loss, and night sweats. The cause of diffuse large B-cell lymphoma is not well understood. Typically, diffuse large B-cell lymphoma arises from normal B cells, but it can also represent a malignant transformation of other types of lymphoma or leukemia. However, the usual treatment of these is chemotherapy, often in combination with an antibody targeted at the tumor cells. However, survival rate of patients varies. The details of the clinical data will be presented.

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In vitro culture of BM cells and CytB polymorphisms can predict the *In-vivo* Hematological response induced by deferasirox

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Background: Many studies showed that iron chelation therapy (ICT) can induce hematological improvement and transfusion independence in a significant percentage of MDS patients. At now we do not have clinical or biological parameters to identify the patients with high probablility of hematological response. The aim of the study was to set up an in vitro assay able to predict in vivo hematological improvement to deferasirox treatment and to identify additional markers of response.

Methods: 22 MDS patients from 9 Italian centres were enrolled in the study. Five were RA, 4 RARS, 8 RCMD, 4 RAEB I , 1 CMML. In 6 of them ICT induced RBC transfusion independence during the first 6 months of therapy, one experienced hematological improvement but he stopped therapy after few months for progression. BM samples were collected from 22 patients before deferasirox treatment and during follow up. BM cells were incubated with deferasirox 50 micromolar for 12 hrs and tested for colony formation in semisolid culture. In addition, different mitochondrial genes were sequenced, including COX1, COX2 and CytB in all the patients enrolled.

Results: In 8 out of 22 patients (3 RA, 2 RARS, 2 RCMD, 1 CMML) the in *vitro* incubation with deferasirox resulted in a significant increase of colonies (BFU-E, CFU-GM and CFUGEMM). (mean value of BFU-E: 9±4 before incubation and 19±11 after incubation). Interestingly, 6 of these 8 patients who showed an "*In vitro*" response experienced transfusion independence after *In vivo* treatment with deferasirox, one showed hematological improvement according to Cheeson's criteria but he died for progression few months after starting therapy and one could not be evaluated because of intolerance to treatment. By contrast patients who did not respond in vitro to deferasirox did not significantly reduce the transfusion requirement. In parallel we analysed mtDNA in BM MNC cells and we found a strict association between two polymorphisms of CytB (14766 and 15326) and the hematological response to deferasirox therapy.

Conclusion: The hematological improvement during deferasirox therapy in MDS patients can be predicted by colony assay after in vitro incubation with deferasirox. In addition, mitochondrial gene polymorphisms can be associated with hematological response. Finally, although not conclusive, the fact that 12 hours of deferasirox incubation can increase the number of BFU-E suggests that deferasirox is probably able to overcome the defect of erytroid progenitors thus pushing the MDS clone towards terminal differentiation rather than to reduce the number of MDS cells thus favoring the normal cells.

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