lines to NKG2D-dependent cell killing exerted by natural killer and γδ T cells; 6) they can also reduce in vitro the metabolism and growth of RS cells. Inhibition of cleavage of other ADAM10 substrates, such CD30, a target for antibody-based anti-lymphoma therapy, might also be useful in HL. Thus, we think that selective ADAM10 inhibitors may be proposed as part of anti-lymphoma therapeutic schemes and contribute to the enhancement of anti-tumor immune response.

P9.07

Effect of novel polyphenol compound from yeast-like fungi Nadsoniella nigra sp. X1 (Antarctica) Melanin on serum cytokine profile in patients with advanced urological cancer in the adjuvant setting

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Background: Cancerogenesis occurs against deterioration of immunosurveillance and growing immunodeficiency. This requires addition of adjuvant treatment correcting immune status in patients. It was postulated that polyphenol substances yield positive effects on cancer pathogenesis exerting anti-proliferative, DNA-damaging, anti-angiogenic, anti-metastatic and other functions.
Purpose: To assess prospectively the immunomodulating effect of novel polyphenol substance Melanin on cytokine profile in patients with advanced urological cancer in the adjuvant setting.
Methods: Fifteen random patients with advanced urological cancer (kidney, bladder, prostate) scheduled for cancer treatment (surgery, chemotherapy) were administered Melanin from yeast-like fungi *Nadsoniella nigra* sp. X1 (Antarctica), one capsule (10 mg) twice daily for 30 days after initiation of treatment. Controls were twenty random uro-oncological patients of identical clinical stages subjected for the same treatment protocol, receiving placebo, and ten healthy individuals. We drew plasma samples in all groups at the beginning of the study and after 1 month of treatment. We analyzed serum cytokines (IL-1β, IL-12, IFN-γ, TNF-α, IL-4 and IL-10) by ELISA.
Results: Administration of Melanin in study group caused statistically significant changes in cytokine profile. The pro-inflammatory IL-1β dropped by 24 %, IFN-γ rose by 50 %, and IL-12 stayed unchanged. All anti-inflammatory cytokines showed increase: TNF-α rose by 184 %, IL-4 rose by 44 %, and IL-10 rose by 85 %.
Conclusions: Application of novel polyphenol substance Melanin 10 mg as cancer treatment adjuvant in patients with advanced urological cancer exerts evident immunomodulating effect, affecting the level of cytokines in peripheral blood. Considering state of decreased immunosurveillance, studied polyphenol substance may be considered a beneficial immune-rehabilitative compound deserving further study of its biochemical and clinical effects.

P9.08

Oxaliplatin neuropathic pain: involvement of the P2X7 receptor and recruitment of pannexin1

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Development of neuropathic syndrome limits anticancer therapy with oxaliplatin. Increasing evidence indicates that complex mechanisms and maladaptive plasticity of the central nervous system, including central sensitization, are involved in the pathophysiology of chemotherapy-induced neuropathies. The insufficient information on the pathophysiology and molecular basis of the chemotherapy-induced peripheral *neuropathy* is an important limit to the development of new effective treatments.

In a rat model of oxaliplatin-induced neuropathy, we found that activation of presynaptic P2X7 receptors for ATP evoked an increased glutamate release from cerebrocortical nerve terminals. The release was abolished by the P2X7 antagonists Brilliant-Blue-G and A-438079, and reduced by carbenoxolone and the Pannexin1 selective inhibitors erioglaucine and ^{10}Panx, suggesting the recruitment of the accessory protein Pannexin1. Aimed to evaluate the significance of P2X7-Pannexin1 system activation in pain induced by oxaliplatin, pharmacological modulators were intrathecally infused in oxaliplatin-treated animals. Brilliant-Blue-G, erioglaucine and ^{10}Panx reverted oxaliplatin-induced pain. Finally, the influence of the P2X7-Pannexin1 system blockade on oxaliplatin anticancer activity was evaluated on the human colon cancer cell line HT-29. Prevention of HT-29 apoptosis and mortality was dependent on concentration of P2X7R antagonists. On the contrary, the inhibition of Pannexin1 did not alter oxaliplatin lethality in tumor cells.

In summary, glutamate release dependent on P2X7 receptor is increased in cerebrocortical nerve terminals from oxaliplatin-treated rats; the increase is mediated by functional recruitment of the accessory protein Pannexin1; P2X7 antagonists and Pannexin1 inhibitors revert oxaliplatin-induced neuropathic pain; Pannexin1 inhibitors did not alter the oxaliplatin-induced mortality of cancer cells HT-29. In conclusion, our results highlight the relevance of P2X7-Panx1 complex in the maladaptive response of central nervous system to oxaliplatin neurotoxicity. P2X7 receptor- Pannexin1 participates in alteration of neuronal functions leading to central sensitization and pain chronicization. The selective inhibition of Pannexin1 channel is suggested as new pharmacological target for oxaliplatin-induced neuropathic pain relief.

P9.09

Regulation of p53-dependent genes expression in multiple sclerosis: the effect of MDM2 inhibitor Nutlin-3a

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Transcription factor p53 is a well-known oncosuppressor protein with thoroughly explored role in cancer. However, recent

advances suggest that both p53 and its negative regulator MDM2 might be involved in autoimmune processes. Inhibition of MDM2 (i.e. by small molecule Nutlin-3a) and associated activation of p53 are considered as a promising therapeutic approach for treatment of autoimmune diseases, i.e. multiple sclerosis.

In the current study we compared Nutlin-3a-induced expression of p53-dependent genes (*p21*, *mdm2* and *PUMA*) in peripheral blood mononuclear cells (PBMCs) from patient diagnosed with multiple sclerosis (MS) and a healthy volunteer. The results indicate that gradual increase of Nutlin-3a concentration (5uM, 10uM, 20uM, 40uM) leads to higher expression levels of *p21*, *mdm2* and *PUMA* genes in MS samples compared to healthy control. These preliminary data suggest that the transcription functions of p53 protein might be enhanced in patients with MS. Data obtained by TaqMan real-time PCR technique using CFX96 Touch Detection System (Bio-Rad). The study was funded by RFBR research grant 16-34-60213 mol_a_dk.

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P9.10
Autoimmune component of essential hypertension and prostate cancer: tyrosyl-trna synthetase and their fragments are novel subpositional antigens

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There are growing evidences that etiology and pathogenesis of essential hypertension and prostate cancer include autoimmune component. However, autoantigens involved in these processes are still largely unknown. Separated fragments of tyrosyl-tRNA synthetase (TyrRS) miniTyrRS and C-terminal domain (CTD) provide non-canonical functions such as immune cell signaling and can potentially serve as autoantigen.

The aim of the study was to investigate antibodies to full-length TyrRS and its domains in sera of patients with essential hypertension and prostate cancer.

Patients with essential hypertension and prostate cancer, as well as healthy subjects were recruited to participate in the study. The recombinant proteins generated by *Escherichia coli* were purified by chromatography on Ni-NTA-agarose. Specific autoantibodies (aAbs) were measured by ELISA and confirmed in an immunoblotting assay. From 6% to 12% of subjects with elevated levels of aAbs against the full-length enzyme were detected in all the cohorts studied. 52 % of patients with essential hypertension were identified as immunoreactive against miniTyrRS and 50 % - against CTD ($P << 0{\cdot}01$). In 41·8 % of individuals with prostate cancer the levels of anti-CTD aAbs were elevated, meanwhile, only 22,4% of these oncology patients were immunoreactive for miniTyrRS ($P << 0{\cdot}01$).

We propose that autoantibodies to Tyrosyl-tRNA synthetase and their fragments provide one of the triggers for autosensibilization in essential hypertension and prostate cancer which may well extend to other autoimmune disease in humans.

P9.11
Cytokine balance as criterion for colorectal cancer immunomodulation

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Background: Mucosa-associated lymphoid tissue is the largest reserve of immune cells along the gastro-intestinal system to front microorganisms that are confined in gut lumen by a thin epithelial barrier. In colorectal cancer (CRC) mucosa equilibrium is subverted becoming antigen-permeable, switching-on a strong inflammatory response that can inhibit the anti-tumor T-cells response. COX-2, the key enzyme of PGE2 synthesis, and IL8 are highly expressed in CRC and linked to bad prognosis. Both factors can recruit immunosuppressive cells and recent studies showed a correlation between COX-2 and IL8 mRNA in CRC samples, though their relation has neither been investigated at protein level, nor used for defining CRC clusters.

Methods: COX-2 and IL8 modulation by IL1b, IL17 and IL22 were tested *in vitro* both on CRC cell lines and on primary CRC-associated fibroblasts (CAF) to identify different responses of cancer and stromal cells. COX-2, IL8 and IL1b were also measured in 100 human CRC specimens by quantitative western blot and ELISA. Their expression was related to each other and to clinicopathologic parameters to define clusters of tumors with a different immune-modulatory microenvironment.

Results: We found that IL1b strongly induces a synchronous expression of COX-2 and IL8 in CAF, while its activity in cancer cells is lower and cell line-specific. We also observed that IL22 is active only on cancer cells, triggering STAT-3 and down-regulating COX-2.

Protein analysis of CRC samples identified two subsets of tumors: one where COX-2 and IL8 are modulated in tandem and associated with IL1b levels, the other with dominant COX-2 or IL8 alone, showing a more aggressive phenotype (prevalence of stage IV/worse prognosis).

Conclusions: The evaluation of COX-2/IL8 balance in primary tumors represents a new criterion for CRC patients clustering after surgery, providing a rationale for the experimentation of immune-modulatory targeted therapies according to a defined cytokine balance.

P9.12
Combined immunotherapy with anti-PDL-1/PD-1 and anti-CD4 antibodies cures syngeneic disseminated neuroblastoma

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Purpose: Anti-PD-1 or anti-PD-L1 blocking monoclonal antibodies (mAbs) have shown potent anti-tumor effects in mouse tumors and adult cancer patients. Clinical studies have recently been started in pediatric cancers, including high-risk or relapsing neuroblastoma (NB).