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RESEARCH REPORT 2018

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DEPARTMENT OF EXPERIMENTAL ONCOLOGY
Head: Professor Leon Strządała, Ph.D.

Laboratory of Experimental Anticancer Therapy
Head: Professor Joanna Wietrzyk, Ph.D.

Studies on the mechanisms of tumor progression, metastasis and on the effects of experimental antitumor therapy

Participation of 1.25D3-MARRS in the sensitivity of human colon cancer cells to vitamin D3

Calcitriol (an active metabolite of vitamin D3) may have activity that is not related to the classic vitamin D receptor. Recently, a novel receptor with high affinity to calcitriol, called 1,25D3-MARRS (1,25D3 - membrane associated rapid response to steroids) was identified.This protein belongs to the family of disulfide isomerases (PDI) and is called interchangeably ERp57/PDIA3/GRP58/1,25D3-MARRS. The aim of our research is to analyze the role of this receptor in the sensitivity of colon cancer cells to vitamin D compounds (VDCs): calcitriol and tacalcitol. Neomycin, known as 1,25D3-MARRS inhibitor was used simultaneously with VDCs, and the changes in the cellular location and expression of 1,25D3-MARRS and in the susceptibility to inhibiting the proliferation of human LoVo and HT-29 colon cancer cells were evaluated. LoVo cells are insensitive to inhibition of proliferation by VDCs and the combined use of neomycin has increased their sensitivity. The observed effect was associated with an increase in the amount of mRNA and the 1,25D3-MARRS protein in these cells. On the other hand, in the case of HT-29, originally sensitive to VDCs, a decrease in sensitivity to VDCs was observed after combined use with neomycin. The levels of 1,25D3-MARRS mRNA and protein were also reduced in the combined use of neomycin with VDCs. VDCs caused the accumulation of the receptor in the endoplasmic reticulum around the cell nucleus. The addition of neomycin intensified this process, especially in HT-29 cells.

Research on the use of bisphosphonates in anticancer therapy

Previous studies have shown that the new bisphosphonates show a special (often selective) antiproliferative activity against J774E and RAW264.7 macrophages. Subsequently, compounds 12399C and 12592A were shown to significantly inhibit the differentiation of RAW264.7 macrophages to osteoclasts. Moreover, it has been shown that the combined use of compound 12399C and doxorubicin or 5-fluorouracil, especially if the cells are pretreated with a cytostatic and then treated with a bisphosphonate, gives a synergistic effect. A similar effect was observed for bisphosphonate 12592A combined with 5-fluorouracil. In turn, the combined use of compound 12592A and doxorubicin produced an antagonistic effect. The obtained results indicate a different mechanism of action of the two studied aminomethylidene bisphosphonates, despite being in the same group of N-bisphosphonates.

Optimization of transduction conditions and characteristics of mouse myeloid dendritic cells (BM-DC) and JAWS II genetically modified for the production of IL-2 and/or IL-15 and stimulated with tumor antigens

The aim of the task was to obtain cell vaccines based on genetically modified dendritic cells for the production of proinflammatory and regulatory cytokines. In the reported period,

the focus was on determining the variant of dendritic cell modification with overexpression of interleukin 15 (BM-DC/IL-15) or the IL-15 complex with its receptor (BM-DC/IL-15R). The degree of efficiency of gene insertion was assessed in relation to IL-2 production by BM-DC/IL-2 transductants. Transduction was carried out using III generation lentiviral vectors containing the IL-15, IL-15/IL-15R and IL-2 gene sequence. The use of a functional test allowed us to estimate the effect of transduction on the ability of BM-DC to stimulate non-sensitized splenocytes to produce proinflammatory cytokines. The primary activation of spleen cells in mixed cell culture was associated with slight changes in their surface phenotype (a slight increase in the percentage of CD4+ T cells and a comparable decrease in the percentage of CD8+ T cells in the presence of BM-DC/IL-2+ and BM-DC/IL-15R+). The use of BM-DC/IL-15R+ resulted in a significant stimulation of splenocytes for the production of IFN-γ, and BM-DC/IL-2+ - for the production of IL-2. The calculated IFN-γ/IL-10 ratio indicated that only DC/IL-15R+ cells are capable of targeting Th1-type responses.

Laboratory of Tumor Molecular Immunobiology
Head: Professor Wojciech Kałas, Ph.D.

Currently, 5-fluorouracil, irinotecan (also known as CPT-11) and oxaliplatin constitute the backbone of chemotherapy for CRC. Because the currently approved therapies fail in a substantial number of CRC patients, new efficient drug combinations are constantly being sought. Emerging data indicate that 5-azanucleosides are able to sensitize cancer cells to the standard chemotherapeutic agents and contribute to overcoming intrinsic or acquired chemoresistance.

Previously, we have demonstrated that pretreatment with DNA demethylating agents, 5-aza-2'-deoxycytidine or 5-azacytidine, sensitizes CRC cells to topoisomerase inhibitors (irinotecan, etoposide, doxorubicin, mitoxantrone), reducing cell viability and clonogenicity and increasing apoptosis more effectively than individual compounds at the same or even higher concentrations. The 5-azanucleosides exerted long-lasting effects on phosphoinositide 3-kinase (PI3-kinase)/Akt signaling pathway.

In the current studies, we focused on the nature of long-term actions of 5-azanucleosides on colon cancer cell lines resulting in its sensitization. We found that the treatment with deoxycytidine, but 5-azacytidine leads to long-term inhibition of proliferation. The effect can be observed even 12 days after a single treatment of DLD-1, HT-29, RKO cell lines with a single dose of deoxycytidine. This was reflected in the distribution of cells in the cell cycle phases, and a significant decrease of cells in S phase was observed. Interestingly, deoxycytidine does not affect the growth of such FHs74Int intestine normal cells. Additionally, the proliferation inhibition was accompanied by profound changes in morphology. Cells treated with azadeoxycytidine were bigger, had a bigger nucleus and had a number of vacuoles. Again, the 5-azacytidine does not have such an effect on cellular morphology.

In order to resolve the molecular background of the proliferation inhibition, the expression of six cell cycle regulators were studied: the CDKN1A gene, coding p21, inhibitor of CDK1 and CDK2 kinases, CDKN2A gene, coding p16, inhibitor of CDK4 and CDK6 kinases, CCND1 gene, coding cyclin D1, the CDK4 and CDK6 kinases activator, MDM2 gene, coding Mdm2, p53 inhibitor, MYC gene coding Myc, cell cycle related transcription factor, and GLB1 gene coding beta-galactosisdase, which is the marker of cellular senescence. This last gene was selected, as an increase of cell body and vacuolisation often accompany the cellular senescence. We found that the expression of GLB1 gene was not affected by 5-azacytidine or azadeoxycytidine.

On the other hand, the increase in the expression of CDKN1A (p21), CDKN2A (p16), negative cell cycle regulators genes were observed. The increase of p21 was confirmed on the protein level with the Western Blotting experiment. Additionally, in some cases the inhibition of MYC gene expression was observed. The changes found are consistent with the observed inhibition of proliferation. It is still an open question whether the observed phenomena have an epigenetic nature or are the result of the cell being poisoned with azadeoxycytidine.

Laboratory of Biomedical Chemistry
Head: Professor Janusz Boratyński, Ph.D., Eng.

The use of icosahedral boron clusters as modifying entities for biologically active molecules

In our studies, we have attached anionic boron clusters (dodecaborate [B12H12]2− and metallacarborane cobalt bis(1,2-dicarbollide) [COSAN]−) to therapeutic peptide thymosin β4 (Tβ4) through an ether linker. After trypsin digestion and MS/MS analysis of the conjugates, we observed that boron clusters were attached to carboxylic groups of the peptide via ester bond. Those ester bonds are prone to hydrolysis and have various stabilities depending on modified amino acid residue. The conjugates with modified Glu residues were more stable with half-lives of 372 to 1329 h and the conjugates with modified Asp residues were less stable with half-lives of 3 to 24 h. We determined the affinity of the conjugates to human serum albumin (HSA) using measurements of quenching of HSA fluorescence and surface plasmon resonance (SPR) technique. As opposed to unmodified Tβ4 and Tβ4-[B12H12]2− conjugates, Tβ4-[COSAN]− conjugates have high affinity to HSA, similar to low molecular weight compounds like warfarin and ibuprofen. Furthermore, Tβ4-[COSAN]− conjugates showed no toxicity and superior activity in comparison to unmodified Tβ4 in *in vitro* studies.

As a result, we have obtained analogs of Tβ4 with improved biological activity and ability to bind HSA, which can be used to prolong the half-life of Tβ4. Those results showed the potential of boron clusters to modify therapeutic peptides.

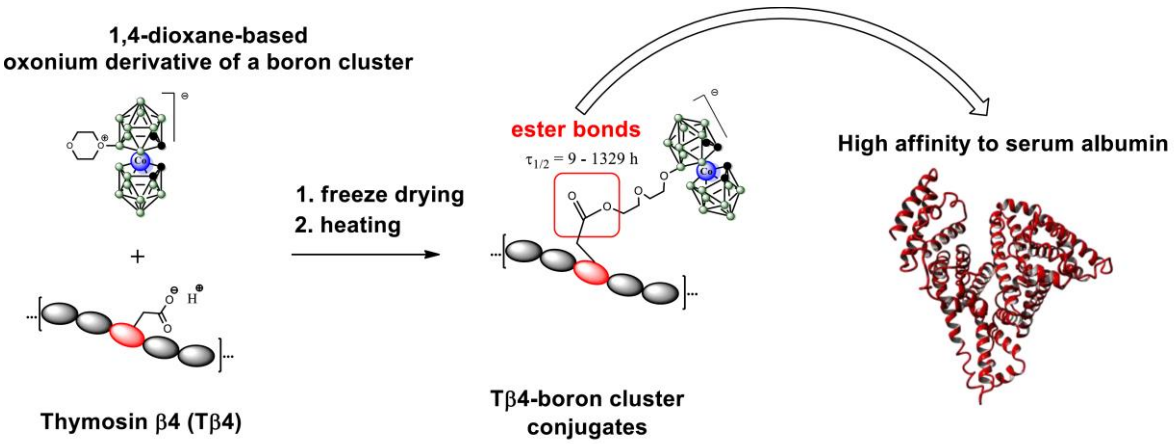
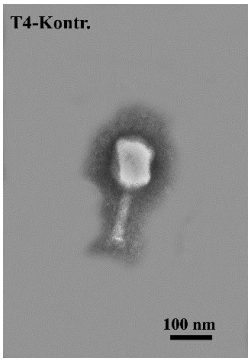


Figure 1. Synthesis of Thymosin β4 - boron cluster conjugates



Bacteriophages

Biological preparations, such as bacteriophages, are beginning to play an increasingly important role in human and animal therapy. They have the potential to be used in the treatment of bacterial infections as a diagnostic

tool, in food processing technology or for the reduction of biofilms in the food and pharmaceutical industries. Adequate stabilization not only ensures the preservation of antimicrobial activity at a constant level, but also affects the reproducibility of the obtained preparations. Despite the attempts to create new formulations, there is a serious problem with maintaining the lytic activity of bacterial viruses during long storage. Bacteriophages stored in the bacterial lysate maintain their biological activity relatively well; however, due to the presence of bacterial components, these preparations do not meet the standards set for medicine. In our laboratory we work on developing the conditions necessary for stabilizing and encapsulating purified preparations of lytic bacteriophages. The proposed research is in line with the global trend of searching for nanoparticles with antibacterial activity.

DEPARTMENT OF CLINICAL IMMUNOLOGY

Laboratory of Clinical Immunogenetics and Pharmacogenetics
Head: Professor Katarzyna Bogunia-Kubik, Ph.D.

Polymorphism and expression of genes encoding proteins associated with thalidomide metabolism in patients with multiple myeloma

Multiple myeloma (MM) is a haematologic malignancy characterized by the presence of atypical plasma cells. Basigin (BSG, CD147) controls lactate export through the monocarboxylic acid transporter 1 (MCT1, SLC16A1) and supports MM survival and proliferation. Additionally, BSG is implicated in the response to treatment with immunomodulatory drugs (thalidomide and its derivatives). In 2018 we investigated the role of single nucleotide polymorphisms (SNPs) in the genes coding for BSG and SLC16A1 in MM. Following an in silico analysis, eight SNPs (four in BSG and four in SLC16A1) predicted to have a functional effect were selected and analysed in 135 MM patients and 135 healthy individuals.

Alleles rs4919859 C, rs8637 G, and haplotype CG were associated with worse progression-free survival ($p=0.006$, $p=0.017$, $p=0.002$, respectively), while rs7556664A, rs7169 T and rs1049434 A (all in LD, $r2>0.98$) were associated with better overall survival ($p=0.021$). Similar relationships were observed in thalidomide-treated patients. Moreover, rs4919859 C, rs8637G, rs8259 A and the CG haplotype were more common in patients in stages II-III of the International Staging System ($p<0.05$), while rs8259 A correlated with higher levels of beta-2-microglobulin and creatinine ($p<0.05$).

Taken together, our results show that BSG and SLC16A1 variants affect survival and may play an important role in MM.

Evaluation of polymorphisms of selected genes in non-small cell lung cancer and their relationship with the course of the disease

Lung cancer is the leading cause of cancer deaths, both in Poland and all over the world. Non-small cell lung cancer (NSCLC) represents the vast majority of lung cancer cases. Although cigarette smoking is the prevalent risk factor for lung cancer, genetic factors are presumed to account in part for this interindividual variation in lung cancer susceptibility. Nevertheless, results have been conflicting. There is no data available regarding the Polish population.

We, therefore, performed a case-control study to investigate the association of 7 selected SNPs, three in excision repair cross-complimentary group 1 (ERCC1 rs11615, rs3212986,

rs2298881), two in nuclear factor κB (NFκB2 rs7897947, rs12769316), one in bone morphogenetic protein 4 (BMP4 rs1957860), complement receptor 1 (CR1 rs7525160) and ins/del polymorphism within the gene coding for family hypoxia inducible factor 2 (EGLN2 rs10680577) in NSCLC patients and healthy individuals of Polish origin. The LightSNiP assays were used for genotyping of 84 patients for rs11615, rs3212986, rs1957860, rs7525160, 146 patients for rs7897947, rs12769316, rs10680577, rs2298881 and 234 healthy individuals for all 8 SNPs. In addition, the levels of 10 cytokines were analysed using Luminex technology.

Two ERCC1 genotypes were found to be associated with predisposition to NSCLC independently of the patients' sex: the rs11615 TT genotype (p=0.021) and the rs3212986 GG homozygosity (p=0.021). In addition, NFκB2 rs12769316 GG homozygosity (p=0.035) increased the risk of NSCLC in males. There is no linkage disequilibrium between these loci. No significant differences were found for the extant five polymorphisms. Based on the ROC analysis, IL-12 serum level appeared to have the most significant predictive value for NSCLC development.

The results indicate that the ERCC1 polymorphisms may affect NSCLC risk and NFκB2 can be markers of the disease in male population while IL-12 serum level seems to have higher predictive value.

Laboratory of Immunogenetics and Tissue Immunology
Head: Professor Piotr Kuśnierczyk, Ph.D.

Immunogenetics of human diseases

We are presently carrying out 3 projects funded by the National Centre of Science, one from our Institute, and 3 projects (KNOW) were completed in 2018. The most important results are as follows:

a) Associations of single nucleotide polymorphisms (SNPs) in ERAP1 and ERAP2 genes with susceptibility to ankylosing spondylitis (AS) in Polish patients (grant from the Hirszfeld Institute of Immunology and Experimental Therapy)

The aim of this work was to examine whether *ERAP1* (rs2287987, rs30187, rs27044) and *ERAP2* (rs2248374) SNPs and their haplotypes may have a predictive value for estimating the risk of AS. All tested *ERAP1* SNPs were associated with AS risk. The strongest association with AS was observed for rs30187. The minor T allele and homozygous TT genotype of this SNP significantly increased disease risk (OR = 1.56, 95%CI = 1.22 - 1.99, p = 0.0004 and OR = 2.52, 95%CI = 1.50 - 4.25, p = 0.001, respectively). In the case of rs2287987, minor C allele exerted a protective effect (OR = 0.64, 95%CI = 0.46 - 0.88, p = 0.008). In contrast to *ERAP1*, we observed no effect of rs2248374 in *ERAP2* on the disease. We also carried out *ERAP1-ERAP2* haplotype analysis to demonstrate a possible association of both genes with AS. Results showed that the haplotype H4, containing *ERAP1* SNPs associated with high enzymatic activity, together with the presence of ERAP2 expression, increased the risk of AS (OR = 1.97, 95% CI = 1.21 - 3.21, pcorr = 0.048). By contrast, the haplotype H5 coding for low activity of ERAP1 and the lack of ERAP2 expression was strongly protective (OR = 0.41, 95% CI = 0.23-0.72, pcorr = 0.008). Results were accepted for publication in *Human Immunology*.

b) Association of ERAP1 SNP Ile276Met is associated with atopic dermatitis and its effect on the generation of an HLA-C associated antigenic epitope in vitro (grant from KNOW)

We found that an association of *HLA-C*05:01* allele with AD. KIR-HLA-C interactions are affected by peptides presented by HLA-C. The generation of these peptides is strongly influenced by endoplasmic reticulum aminopeptidases 1 and 2 (ERAP1 and ERAP2). Expression and activity of ERAP molecules depend on the polymorphisms of their genes. Only one SNP in the *ERAP1* gene, rs26618T>C, causing the amino acid change Ile276Met, was associated with AD. We collaborated with the National Centre for Scientific Research Demokritos, Agia Paraskevi, Athens, Greece, who produced recombinant variants differing only at position 276 (Ile or Met) and tested their aminopeptidase activity against a N-terminally extended precursor LIVDRPVTLV of the HLA-C*05:01 epitope IVDRPVTLV. Both ERAP1 variants were able to efficiently generate the epitope, but the common 276Ile allotype was able to do this about 50% faster. Furthermore, both variants were quite inefficient in the further degradation of the mature epitope. Finally, we found that the effect of 276Met on susceptibility to AD was seen only in *KIR2DS1*-negative individuals, not protected by this KIR. The manuscript describing these results has been accepted for publication in the *Journal of the European Academy of Dermatology and Venereology*.

c) The role of ERAP, KIR and HLA-C gene interactions in susceptibility to recurrent spontaneous abortion (this topic is a continuation of the grant finished earlier)

HLA-C is the only polymorphic HLA-I molecule present on the trophoblast. In this study we investigated the role of *ERAP1* and *ERAP2* polymorphisms in the context of KIR and HLA-C genes in women suffering from recurrent spontaneous abortion (RSA) in the Polish population. We tested 285 women who experienced recurrent spontaneous abortion (RSA) and 319 fertile women. We observed a significant association of *ERAP1* rs30187TT genotype with RSA (p=0.02, OR=1.89); however, the most striking association was found in a comparison of patients and controls with *ERAP1* rs30187TT and *KIR* Bx genotypes (p=0.006, OR=2.40). Moreover, this effect was even stronger in *HLA-C2*-positive patients (p=0.0031, OR=3.46). Other weaker associations of the remaining tested ERAP single nucleotide polymorphisms with RSA were also presented. In conclusion, *ERAP1* rs30187TT genotype itself increased the susceptibility to RSA, but this effect was much stronger in patients positive for *HLA-C2* and *KIR Bx* genotypes. Results were accepted for publication in *Human Immunology*.

Laboratory of Clinical Immunology
Head: Professor Andrzej Lange, M.D., FRCP

Study on lymphocyte populations of hematologic patients 4 months after alloHSCT, i.e. at the time of regenerated haematopoiesis and not being on immunosuppression. The study was based on 18 patients who underwent transplants in our institution last year. The aim of this study was to find symptoms within the immune system which are predictive of a poor outcome

We found that already 10 days after alloHSCT, when the hematologic recovery starts to be clinically relevant, the patients who died due to post-transplant complications had higher proportions of lymphocyte harbouring DR epitope. This finding was even more more

significant as a prognostic factor if the same was seen one month after transplant, DR positivity of T cells show on their activation. Therefore, alloresponsiveness post-transplant may play a devastating role, making the patients more vulnerable to the infections agent impact.

The other study performed (STAWREG: RPDS.01.02.01-02-0177/17) resulted in the following observation.

Background: We showed (Blood 2005, 106:4319) that mesenchymal stem cells (MSC) retain the recipient phenotype after HSCT in spite of the presence of full haematological chimera. This and other observations led to the conclusion that in the marrow there are several zones with hematopoietic stem/progenitor cells and mesenchymal stem cells (MSC) at different stages of differentiation that are kept in a dormant state. MSC are recognized as master cells that have a broad potential to differentiate into different tissues. The presence of more differentiated MSC in the quiescent stage in the marrow has not been unequivocally confirmed.

Patients: To address this issue we evaluated the efficacy of marrow cells having MSC markers to improve the vascularization of limbs with ischaemia in 28 patients (4F/24M, age median: 51 range 33-64 years old) or to improve the function of worn-out hips and knees (14 procedures in 13 patients, 9F/4M, age median: 58, range 45-71 years old). These two groups of patients received marrow-derived mononuclear cells injected either into the ischemic leg calf muscles or intra-articular into the hip or knee. Ischemic leg patients received autologous leukophoretic product freshly taken from the marrow cavity. Cells were injected into the calf muscles in about 0.7 mL small portions. Patients with worn-out hips received marrow cells into their joints, which were harvested after 50 ml of the marrow was prepared in the Auto Stem Cell Kit (Pharmed) according to the manufacturer's instructions.

Results: Patients who exhibited improvement in joint function had a higher contribution of CD90+ and CD73+ cells to the CD45-CD34- marrow cell population in cells harvested after preparation in the Auto Stem Cell Kit than patients who suffered from a recurrence of symptoms reported 6 months after the procedure (5.470±2.045% vs 1.607±0.128%, p=0.012 for CD90+ in CD45-CD34- population; 13.154±12.550% vs 0.150±0.015, p=0.020 for CD73 in CD45-CD34- cell population).

In contrast, patients with critical limb ischemia who showed remission before 12 months after intervention received less CD73+ than those whose condition deteriorated (0.061±0.011% vs 0.112±0.015%, p=0.022).

Conclusions: Intra-articular injection of CD73+ and CD90+ cells of marrow origin improves joint function, but does not play a positive role in the revascularization process of ischemic legs.

LABORATORY OF BACTERIOPHAGES
Head: Professor Andrzej Górski, Ph.D.

Phage re-purposing

Already in the 1980s we formulated a hypothesis according to which endogenous phages (those present in our bodies, primarily in gastrointestinal tract) may exert not only anti-bacterial but also immunomodulatory properties downregulating aberrant immune responses and inflammation and thereby contributing to immune homeostasis. Our studies carried out in the ensuing years as well as those from other centers have fully supported those assumptions. What is more, most recent data from our group and the Stanford group suggest that phages

may also interfere with some viral and fungal infections (phage treatment of non-bacterial infections). In a series of publications of the past two years we have envisaged that those interactions of phages with the immune system may be therapeutically useful in a variety of disorders where aberrant immune response and pathological inflammation play an important role. Those include: allergy, autoimmune liver diseases, inflammatory intestinal disorders, sepsis, Epstein-Virus – mediated pathologies and prostatitis. We believe that this "phage-repurposing" may offer novel forms of treatment in pathologies where current therapy does not allow for adequate control of disease.

Safety Studies of Pneumococcal Endolysins Cpl-1 and Pal

Bacteriophage-derived endolysins have gained increasing attention as potent antimicrobial agents and numerous publications document the in vivo efficacy of these enzymes in various rodent models. However, little has been documented about their safety and toxicity profiles. We investigated preclinical safety and toxicity data for two pneumococcal endolysins, Pal and Cpl-1. A microarray and gene profiling was performed on human macrophages and pharyngeal cells exposed to 0.5 μM of each endolysin for six hours and no change in gene expression was noted. Likewise, in mice injected with 15 mg/kg of each endolysin, no physical or behavioral changes were noted; pro-inflammatory cytokine levels remained constant, and there were no significant changes in the fecal microbiome. Endolysin also did not cause complement activation via the classic pathway, the alternative pathway, or the mannose-binding lectin pathway. In cellular response assays, IgG levels in mice exposed to Pal or Cpl-1 gradually increased for the first 30 days post exposure, but IgE levels never rose above baseline, suggesting that hypersensitivity or allergic reaction is unlikely. Collectively, the safety and toxicity profiles of Pal and Cpl-1 support further preclinical studies.

Searching, isolation and characterization of new therapeutic phages specific for *Acinetobacter baumannii*

The aim of the studies was to procure and initially characterize new lytic bacteriophages (with therapeutic potential) specific to clinical isolates of *Acinetobacter baumannii*. These bacteriophages will be included in the collection of the Laboratory of Bacteriophages and will be used to treat chronic bacterial infections among patients.

Searching for new active phages against *Acinetobacter spp* strains

To find active phages against *Acinetobacter spp* strains (n=36), 364 environmental samples available in laboratory of Bacteriophages collection and 18 newly collected water samples were tested. The study used a standard microbiological phage typing method. For samples that gave pre-positive results, a routine test dilution (RTD) was performed and those samples were amplified.

Bacteriophages from newly collected water samples

From newly collected samples, 11 probably lytic bacteriophages were isolated. In the next study, biological properties and the morphology of phages will be characterized, and the sequence of phages genomes will be determined.

Application of newly obtained phages

Acinetobacter strains have become one of the most dangerous pathogens, classified by World Health Organization as critical priority pathogens which pose a dangerous group of opportunistic bacteria for patients with immunological deficiency. The new 11 phages increase the chance of applying experimental phage therapy in patients with chronic infections caused by *A. baumannii.*

LABORATORY OF BIOLOGY OF STEM AND NEOPLASTIC CELLS
Head: Aleksandra Klimczak, Ph.D., D.Sc.

Biological properties of mesenchymal stem/progenitor cells derived from various tissues

Mesenchymal stromal/stem cells (MSCs) constitute a promising tool in regenerative medicine and can be isolated from various human tissues; however, their biological properties are still not fully characterized. MSCs residing in different tissues exhibit many common characteristics, but their biological activity and some markers are different and depend on their tissue of origin. We assessed the maintenance of the basic phenotype of MSCs, their differentiation potential, as well as the mRNA expression profile associated with the pluripotent (Sox2, Oct4), suppressor (p53), and proto-oncogenic (c-Myc) function of the examined MSCs. The stability of multipotency and stemness markers of MSC isolated from different tissues such as: bone marrow (BM-MSC), adipose tissue (AT-MSC), skeletal muscle (SM-MSC) and skin (SK-MSC) were examined in long-term culture up to passage 10.

All studied MSCs showed the basic MSC phenotype CD73, CD90, CD105 stable up to P10; however, their expression decreased with the age of culture, as confirmed by fluorescence intensity. The proangiogenic properties of MSCs were confirmed by CD146 expression, however, long-term culture is unfavorable for maintaining the proangiogenic function of examined MSCs, apart from BM-MSCs. Tissue-origin MSCs, except BM-MSCs, expressed PW1, a marker associated with differentiation capacity and apoptosis. BM-MSCs and AT-MSCs expressed the stemness markers Sox2 and Oct4, corresponding to cells capable of multipotential differentiation, whereas MSCs from skeletal muscles and from the skin revealed a decreased ability to express Sox2 and Oct4 in long-term culture. Genetic stability was confirmed by the stable expression of mRNA for p53 and c-Myc in MSC isolated from bone marrow, adipose tissue and skin. Expression of the mRNA for c-Myc was the highest in AT-MSCs which may be related to their high proliferative potential. The differentiation capacity of BM-MSCs and AT-MSCs into osteo- and chondrogenic lineages was maintained during the follow-up period. In contrast, SK-MSCs and SM-MSCs had a limited capability to differentiate into adipocytes.

The results indicated differences in the biological activity of MSC isolated from various tissues. The studies showed that MSCs with specific biological properties can be used in targeted therapies in which the source of MSCs, cells acquisition, and the duration of the culture will be important for their selection in terms of regenerative potential and genetic stability.

Biology of suppressor myeloid cells of tumor-origin

Working on tumor cell biology, we continued the study on tumor-specific suppressor cells of myeloid-origin (MDSCs) and the modulation of tumor microenvironment influencing anti-tumor activity. We developed a method of isolating myeloid tumor-suppressor cells

(MDSCs) specific for prostate cancer TRAMP-C1. A differentiating culture of mouse myeloid cells was performed in the presence of GM-CSF and various concentrations of supernatant collected from TRAMP-C1 cell culture were carried out under hypoxia or normoxia conditions. The results proved that the process of myeloid cells differentiation towards MDSC was most effective in the presence of 75% of supernatant collected from cancer cells cultured in hypoxia conditions. On the sixth day, the culture consisted of almost 80% of monocytic MDSC cells (M-MDSC) and approximately 10% of granulocytic MDSC cells (PMN-MDSC), and these cells were characterized by low expression of surface antigens, e.g. MHC class II, CD86 and PD-L1. These results proved that we obtained myeloid cells at an early stage of differentiation. Inhibition of IL-10 production by M-MDSCs resulted in increased expression of MHC class II and CD86 markers, which may suggests that elimination of IL-10 increases the ability of these cells to differentiate into mature myeloid cells. In turn, the inhibition of IL-10 in PMN-MDSCs increases the expression of PD-L1, which may increase the suppressor activity of these cells in the context to effector T-lymphocytes.

Studies on phenotypic and functional characteristics of MDSC suggest that the modulation of suppressive activity of tumor microenvironment can be helpful in studying the anti-tumor activity of new immunomodulatory agents.

DEPARTMENT OF ANTHROPOLOGY
Head: Professor Sławomir Kozieł, Ph.D.

Digit ratio (2D:4D) moderates the change in handgrip strength on an aggressive stimulus: a study among Polish young adults

The ratio of the lengths of second finger (2D) to the fourth (4D) is a putative indicator of foetal hormonal exposure. The link between 2D:4D and physical strength or sports performance in not consistent. It was suggested that the association of 2D:4D with physical ability is better demonstrated in the context of challenge and competition, either real or simulated. However, the evidence is currently limited to a few studies. The objective of this study was to assess whether a video depicting aggressive material could increase muscular strength and if 2D:4D moderated such an increase. We compared outcome measures in two experimental conditions. Lengths of second (2D) and fourth (4D) digits and their ratio (2D:4D) for both hands, height and weight, handgrip strength of both hands. Two hundred fifty healthy young adults (76 female) took part in the study. The mean left-, right- and average HGS values increased after the subjects watched the aforementioned video than after watching the control blank screen. The increase was higher in females compared to males. The increase was higher among the individuals with lower 2D:4D, more clearly among females. The 2D:4D correlated negatively with HGS after subjects were exposed to physically challenging conditions and this relationship is more pronounced in females than in males. Thus, there is a link between prenatal androgenisation and enhanced physical power in challenging situations.

Secular trend and social variation in age at menarche among Polish schoolgirls before and after the political transformation

The aim of the study was to describe the biological results of the political and economic transformations that took place in Poland between 1966 and 2012, based on an analysis of age at menarche, and to determine changes across social groups. Data were collected in 1966,

1978, 1988 and 2012 in several districts of Poland. The study included 34,940 schoolgirls. Age at menarche was assessed with the use of *status quo* method. Definition of socio-economic status was based on 4 factors: urbanization level, educational level of parents, and family size. When the political and economic situation in Poland improved, a decrease in age at menarche was observed, whereas in years of crisis it was increased. The same social differentiation in menarcheal age observed before the political transformation continued to be present in 2012. Socio-economic changes were significantly associated with age at menarche. Social inequalities, reflected in menarcheal age, continue to be present in Poland.

DEPARTMENT OF MICROBIOLOGY

Laboratory of Molecular Biology of Microorganism (LMBM)
Head: Professor Anna Pawlik, Ph.D.

Replication of bacterial chromosomes
Polyketide synthesis and its regulation in *Streptomyces*

The research activity of LMBM is focused on two scientific issues: i/ replication of bacterial chromosomes, and ii/ polyketide synthesis in *Streptomyces*.

i/ Chromosome replication is an important event of the bacterial cell cycle. The decision to initiate chromosome replication is crucial for the cell cycle progression and depends both on the intracellular as well as on the environmental signals. We are interested in the mechanisms of the initiation and regulation of bacterial chromosome replication, with special emphasis on the key factors engaged in initiation complex (orisome) formation, namely the initiator protein DnaA, the origin of chromosome replication *oriC* and origin binding proteins oriBPs, which coordinate the initiation of the cell cycle. We are especially interested in orisome formation in Epsilonproteobacteria. Many of the known Epsilonproteobacteria are obligate or facultative human and/or animal pathogens, including *Helicobacter pylori* and *Campylobacter jejuni*, which are the leading causes of gastric ulcer/gastric cancer and bacterial foodborne infections worldwide, respectively. The *H. pylori oriC* is bipartite and consists of two DnaA box clusters and a DNA unwinding element (DUE). The DnaA protein is composed of four domains, which have distinct functions in initiation complex assembly. The C-terminal domain IV is responsible for DNA binding via a helix-turn-helix motif. Domain III belongs to the AAA+ class of proteins. Upon interaction with ATP, domain III changes its conformation, enabling DnaA to properly assemble at *oriC* and build up a filament. Domain II links domain III and domain I. The N-terminal domain I of some species mediates interaction between individual DnaA molecules; however, the role of this interaction for initiation complex assembly or for DnaA activity is largely unknown. We have recently focused on a detailed analysis of domains I and III of *H. pylori* DnaA, especially in the context of proper DnaA assembly on bipartite *H. pylori* origin of chromosome replication. Our results revealed the importance of these two domains for DnaA oligomerisation on *oriC* and ATP-dependent regulation of *H. pylori* chromosome replication *in vitro* and *in vivo*, but also indicated common and unique features of *H. pylori* DnaA in the context of bacterial imitator DnaA proteins.

ii/ Polyketides is a large class of bioactive compounds with extremely diverse structures and functions. They are synthesized as secondary metabolites by giant multienzyme complexes – polyketide synthases. Our work is focused on a polyketide synthase Cpk from *S. coelicolor* A3(2), which is responsible for the synthesis of a yellow pigment coelimycin. Expression of *cpk* genes is tightly controlled by regulatory proteins encoded by the genes

within the *cpk* cluster and most probably by several pleiotropic regulators connected with the regulation of secondary metabolites production as well as *Streptomyces* morphological differentiation. We are interested in deciphering the regulatory circuits governing the synthesis of coelimycin as well as in the discovery of its biological activity.

Laboratory of Signaling Proteins
Acting Head: Professor Jakub Siednienko, Ph.D.

Study of the effect of yolkin polypeptide complex on the activation of TLR4 -dependent innate immunity mechanisms on bone marrow derived macrophages BMDM

Innate immunity is the first line of a host's defense mechanism that protects multicellular organisms from infectious disease. The stimulation of innate response is regarded as one of the most important strategies to enhance the body's defense systems, especially in elderly patients, who are more susceptible to bacterial and viral infections and have an increased incidence of autoimmune diseases and malignancy. Macrophages are key innate immune cells of tissue homeostasis with active involvement in primary immune response to the pathogens, tumors, and also neurodegenerative disorders. As professional antigen presenting cells help form the innate and adaptive immune responses producing and releasing a wide spectrum of pro-inflammatory mediators at the early stage of injury or infection.

The results of the conducted research show that polypeptide complex yolkin obtained from hen egg yolk by SEC method can activate BMDM cells to secrete significant amounts of type I Interferons, TNFα and NO. Additionally, sustained activation of ERK 1/2 kinases and upregulation of iNOS expression by yolkin complex was observed. It was also checked if yolkin complex can activate BMDM cells via the TLR4 receptor; however the results obtained were contradictory and did not give an unambiguous answer.

The conducted research allowed us to explain the mechanisms of the protective action of yolkin in the light of research on the use of natural preparations as a therapy supporting the treatment of congenital immunity and viral / bacterial infections.

DEPARTMENT OF TUMOR IMMUNOLOGY
Head: Professor Paweł Kisielow, Ph.D.

Laboratory of Molecular and Cellular Immunology
Head: Professor Małgorzata Cebrat, Ph.D.

Molecular role of NWC protein during spermatogenesis

NWC is an evolutionarily conserved protein which is expressed at the highest level in testis. Our previous research has shown that, although the NWC-knockout male mice are fertile, the abrogation of NWC expression results in a significant functional impairment of the sperm which manifests itself in the decreased ability of the NWC-KO sperm to compete with WT-sperm in the female reproductive tract. The research undertaken this year aimed at finding the molecular processes during spermatogenesis in which NWC protein could be involved.

The starting point of our investigation was establishing (using immunoprecipitation assay) that NWC interacts with IFT-122 protein, which is a part of the complex involved in intracellular microtubular transport. Our recent experiments have confirmed the possibility of

these proteins interacting by demonstrating their simultaneous, high expression (both at the level of transcription and translation) in some cells from the spermatogenesis pathway - the round spermatids from step 1 to the steps 11-12 of their differentiation. This allowed us to narrow down the search to the developmental stage of reproductive cells, in which the NWC may engage in processes mediated by IFT-122. This interaction has been confirmed using bimolecular fluorescence complementation (BIFC assay), which has also allowed us to determine the fragments of both IFT-122 and NWC proteins involved in this interaction. By replacing the highly conserved fragments of NWC protein, which are present both in vertebrates and invertebrates (including protozoa), with alanine stretches, we have shown that these fragments are indispensible for interaction with IFT-122.

Importantly, our results have shown that the time window of IFT-122 and NWC co-expression coincides with the formation and elongation of flagellar axoneme and the formation of the manchette structure. Thus, the interaction between IFT and NWC can occur during axoneme formation, precursors assembly of auxiliary structures, formation of acrosome vesicle and the first stages of manchette action. We have also started to verify the NWC interaction with other candidate partners involved in these processes. We have shown that:

-NWC interacts directly with IFT122 and Rshp9, but does not interact with Rshp6a or Rab8a;

-IFT122 interacts with NWC, Rshp6a, Rab8a, but does not interact with Rshp9;

-Rshp9 interacts with Rshp6a;

-Rab8a interacts with IFT122 and Rshp9, the interaction with Rshp6a has not been tested yet.

The pattern of interaction between NWC, IFT122 and radial spoke head proteins is particularly interesting, because it indicates the possibility that NWC protein is involved in the assembly of Rshp pre-complexes. The pattern of mutual interactions between them may also suggest the likely architecture of potential complexes. Importantly, the interaction between Rshp9 and Rshp6a was first shown in Chlamydomonas and recently confirmed in recombinant proteins of mice. Thus, with the BIFC system used by our team, we were able to correctly detect this interaction, although it was reported as being difficult to demonstrate using tagged proteins. What is important, radial spoke head proteins are not only the structural part that connects the central pair of microtubules with the outer ones but also act as signal transducers controlling protein phosphorylation. Intriguingly, Rshp6a has been found to be more phosphorylated during sperm capacitation and proposed as a mediating protein in such signalling processes. It is also noteworthy that the interaction between human NWC ortholog (c11orf74) and PP1?2 – testis/sperm enriched variant of ser/tre phosphatase PP1 has been demonstrated. However, confirmation of this interaction in mice is still missing. Any disturbances in the assembly, modifications or transportation of Rshp pre-complexes may translate into functional sperm disorders with different intensity and could potentially explain the observed NWC-KO phenotype. In mammals, mutations in radial spoke proteins are linked to primary cilia dyskinesia; therefore, exploring the processes related to the assembly of the Rshp complexes may be very important for understanding the development of ciliopathies and fertility problems.

The obtained results suggest that NWC could be involved in flagella formation, transportation of constituent elements, preparation of building blocks and/or their biochemical modifications; however, pinpointing the exact mechanism will need further experiments. Any new information concerning IFT and Rshp complexes or other proteins involved in the investigated processes will be beneficial to our understanding of sperm tail formation and, more generally, of the transportation systems involved in the development of motile cilia.

Laboratory of Tumor Immunology
Head: Professor Arkadiusz Miążek, Ph.D.

Focal Adhesion Kinase (FAK) inhibitors potentiate cytotoxic activity of anti MHC II-DR antibodies towards canine lymphoma cell lines

Monoclonal antibody (mAb)-mediated crosslinking of major histocompatibility class II antigens (MHC-II) on B-cell lymphomas induces death and survival signals through the concomitant activation of at least three signaling pathways including MAPK, PI3K/Akt and STING. Reportedly, combination treatment aiming at diminishing pro-survival signaling is expected to enhance the efficiency of anti MHC-II mAbs in the context of lymphoma treatment. Here, using three canine B-cell lines and an anti-dog MHC-II DRα antibody B5, we aimed at identifying signaling nodes influencing the efficiency of MHC-II mediated apoptosis. To this end, we found that homotypic cell adhesion, caspase activation, and STING signaling were all necessary for B5 mediated cell death. In contrast, integrin signaling inhibition with two different focal adhesion kinase (FAK) inhibitors at non-cell toxic doses, potentiated B5 induced cell death. Thus, our data support FAK as a potential new target for a combination canine lymphoma treatment.

DEPARTMENT OF EXPERIMENTAL THERAPY
Head: Professor Michał Zimecki, Ph.D.

Laboratory of Immunobiology
Head: Professor Michał Zimecki, Ph.D.

Effect of recombinant lactoferrins (LF) on activity of natural killer cells

We evaluated the effects of recombinant human lactoferrin (LTF) produced by Chinese hamster ovary cells and a chimera consisting of LF molecule combined with immunoglobulin G Fc fragment (Fc-LTF) on the cytotoxic activity of NK-92 cell line against K562 target cells at a concentration range of 5-60μg/ml. The cytotoxicity of NK-92 cells was measured by lactate dehydrogenase (LDH) test. We also investigated the effects of exogenous IL-2 on this process. We found that both lactoferrins have the ability to stimulate NK cell cytotoxicity. However, the stimulatory efficacy of Fc-LTF construct was higher at all concentrations. A stimulatory effect of IL-2 on cell cytotoxicity was also registered. Next, we plan to investigate the anticipated ability of both lactoferrins to elicit expression of MAP kinases in NK-92 cells and the role of Fc gamma receptor on NK cells in enhancing the cytotoxic action by the chimera.

Effect of yolkin on maturation and activation of immature T and B cells

Yolkin is defined as a set of low molecular weight proteins (35 kDa and less), isolated from egg yolk, of already described procognitive and immunotropic properties. Preliminary studies established its stimulatory action of the humoral immune response and phenotypic changes in T and B lymphocytes. Our working hypothesis assumes that the protein will promote T and B cell maturation and regulate immune functions. In vitro studies demonstrated that yolkin significantly increases the content of CD19+ B cells in bone marrow and spleen. In turn, an increase of single positive T cells in thymus (CD4+ and CD8+) was small. Yolkin stimulated, in addition, the proliferative response of double negative and whole

thymocyte populations to concanavalin A. Yolkin did not induce the expression of signaling proteins associated with apoptosis in Jurkat cells. In contrast, it induced the expression of all MAP kinases (ERK, p-38 and JNK), suggesting that cell differentiation/activation process was triggered. In addition, we showed that yolkin partially prevented the apoptosis of immature WEHI 231 B cells, induced by anti-Ig antibodies, which suggests the promotion of cell differentiation process.

Studies on activity and mechanism of action of MM isoxazole derivatives

Synthesis of a new series of isoxazole derivatives was described and their immunotropic activity was investigated in several in vitro experimental models using human blood lymphocytes and cell lines. The compounds inhibited, to a various degree, phytohemagglutinin A induced proliferation of peripheral blood mononuclear cells. The toxicity of the compounds towards reference A549 cell line was low and dose-dependent. For subsequent studies we selected one compound (5-amino-N'-(2,4-dihydroxyphenyl) methylideno-N,3-dimethylo-1,2-oxazole-4-carbohydrazide). The compound (MM3) inhibited, at low concentrations, the production of tumor necrosis factor alpha induced by lipopolysaccharide in human whole blood culture. In addition, expression of signaling proteins, associated with apoptosis (caspases 3, 7, 8, 9, Fas, Bcl-2, NF-κβ1), as well as expression of IL-2 receptor subunits (α,β,γ), were determined by RT PCR method. In the model of Jurkat cells, MM3 strongly induced expression of mRNA for caspases, Fas and NF-κB, which suggests its proapoptotic action.

Studies on signaling pathways associated with suppression of immunocompetent cells by an isoxazole derivative RM33

Immunologic activities of immunosuppressive RM33 compound (isoxazolo[5,4-e] triazepine) have been previously described in several *in vivo* models in mice and rats. However, the mechanism of action of his isoxazole derivative is still unknown. In 2018 we determined the effects of RM33 on the expression of signaling molecules in bone marrow cells, thymocytes and splenocytes. In thymocytes the increases in signaling proteins were as follows: caspase 3 (9.5 x), caspase 9 (222 x), Bcl2 (18 x), Fas (5.6 x), NF-κB1 (10.7 x), NF-κB2 (14 x). In splenocytes we observed 5.4-fold stimulation of caspase 3, 2-fold of caspase 9, 22-fold of Fas, 8,7-fold of NFκB1 and 25-fold of NF-κB2. In bone marrow cells caspase 3 was stimulated 2 times, caspase 9 23 times, Fas 19 times, NFκB1 4.8 times and NF-κB2 6,6 times. In the case of MAP kinases the increases of signaling molecule expression were found in thymocytes (p38b and p38 subunits and JNK), in splenocytes (subunits p38a and p38d and exceptionally high in p38g - 200 times, and JNK). On the other hand, in the bone marrow cells increases in ERK2 and p38b were found. The obtained results indicate that RM33 induces a process of apoptosis, dependent mainly on Fas and caspase 9 with the contribution of p38 and NF-κB. We conclude that apoptosis is predominantly induced in the spleen and thymus and to a lesser degree in bone marrow cells. The project will be continued and will involve an investigation of signaling pathways in T, B cell and macrophage cell lines.

Laboratory of Immunopathology
Head: Professor Irena Frydecka, M.D., Ph.D.

Association of genetic variation within *XRCC3* gene with cervical cancer

Genes engaged in DNA repair machine are critical elements in anti-tumour tools. The *XRCC3* gene (NM_001100118.1), an important element of DNA repair network, is located on the 14q32.3 chromosome and encodes a member of the RecA/Rad51-related protein family that participates in homologous recombination to maintain chromosome stability and repair DNA damage. Polymorphic variation of DNA repair enzymes, which may alter the function or repair efficiency, may be responsible for carcinogenesis.

The aim of the study was to evaluate selected *XRCC3* genetic variants as a potential disease risk- and disease-modifying factor.

A population-based, case-control association study was conducted. The research comprised 143 patients (pts) with cervical cancer, treated at Department of Oncology and Gynaecological Oncology Clinic, Wroclaw University of Medicine, and 207 healthy cancer-free women at the time of recruitment (control group). All cases of cervical cancer were histologically defined as cervical squamous cell carcinoma (CSCC), of which 23 cases were well differentiated (G1), 89 cases moderately (G2), and 16 poorly differentiated (G3), and in 15 pts grading was not established. Stage of the disease was classified according the FIGO: stage I=23 pts; II=49 pts; III=53 pts; and IV=9 pts. In nine patients there was no stage description.

The selected *XRCC3*tagSNPs: rs3212079 (c.407-801C>T), rs3212102 (c.562-1081G>T), rs861534 (c.561+809G>T), rs861537 (c.562-1162G>A), rs709399 (c.562-1632C>T), rs12432907 (c.561+1132G>A), and rs1799796 (c.562-14A>G) were genotyped with the Allelic discrimination (AD) technique with use of the appropriate TaqMan®SNP Genotyping Assays (C__44801819_10, C__27457316_10, C___2983915_20, C___2983919_10, C___2983918_10, C___2983916_20, and C___2983922_20, respectively). The rs861539 (Thr241Met) SNP was genotyped with use of PCR-RFLP method with using the specific restriction enzymes *Nla*III.

An univariate analysis showed that only 2 from 8 studied *XRCC3*tagSNPs: rs3212079 and rs3212102 were associated with CSCC. One copy of *XRCC3*rs3212079[A] as well as *XRCC3*rs3212102[C] is enough to modify the risk of CSCC (p=0.0002 and p=0.04). Next, a combined association analysis of pointed disease-related markers rs3212079([AA]+[GA]) and rs3212102[CC] revealed an interaction between those two factors since both were crosswise deviated in patients positive to each other (p=9.42x10^{-6}, OR=5.20, and $p_{Yate's\ correction}$=0.007, OR=11.28). Furthermore, a combined action of those factors existed when compared relative to their absence (p=2.39x10^{-5}, OR=8.20).

Haplotypes (in order: rs3212079/rs3212102/rs861534/rs861537/rs861539/rs709399/rs12432907 /rs1799796): ACTTCACC and GCCTTGCT 15.14- and 6.07-fold increased risk of CSCC (p=0.0003, and p=0.003), whereas haplotypes GCCTCACT and GTCTTACT strongly protected against CSCC (p=0.04, OR=0.34, and p=0.03, OR=0.35).

Neither univariate analysis nor haplotype analysis of selected *XRCC3*tagSNPs linked any of those polymorphisms with the response to treatment. Kaplan-Meier analysis and the log-rank test showed no influence of studied *XRCC3* polymorphisms on the progression-free survival.

Additionally, a meta-analysis showed that *XRCC3*rs861539 (Thr241Met) SNP was neither CC nor CSCC risk factor under dominant model as well as on allele level (p=0.36, p=0.59 and p=0.40, p=0.57).

In conclusion, our population-based case-control association study may indicate that *XRCC3*tagSNPs are a CSCC risk factor, but not a prognostic as well as a predictor factor in CSCC patients.

Laboratory of Reproductive Immunology
Head: Professor Anna Chełmońska-Soyta, Ph.D, V.D.

Immunological mechanisms associated with reproductive processes in health and disease

Title: IL-24 expression in Treg lymphocytes in women with endometriosis

The aim of the planned studies was to determine the level of IL-24 expression in regulatory T lymphocytes in peripheral blood in healthy women compared to women with endometriosis.

Methods: The study used peripheral blood from 28 women diagnosed with laparoscopy and 28 healthy women as the control group. In order to determine the production of interleukin 24 in regulatory T cells, the blood was stimulated with phorbol 12-myristate 13-acetate (PMA), Brefeldin A and Monensin. Blood lymphocytes were surface-stained with anti-human CD4 antibodies, CD25 and CD127 antigens and intracellular staining was carried out with anti-human interleukin 24 antibodies and the Foxp3 transcription factor. Samples were analyzed with a Fortress LSR flow cytometer.

Results and conclusion: The performed tests for the first time showed the ability of human regulatory T cells with the CD4 + CD127-CD25 + FoxP3 + phenotype for the production of IL-24 and varied levels in patients and healthy people. The research is ongoing.

Expression of TLR2,4,9, MHC class II and costimulatory molecules in splenic B lymphocytes (CD19 +) in the normal model (CBA / 2JxBALB / c) and abortion-prone pregnancy (CBA / 2JxDBA / 2J)

The aim of the study was to determine the expression of TLRs and co-stimulatory molecules in B-cells in the mouse abortion-prone model as a component of the process of regulating the level of immune tolerance in pregnancy.

Methods: The expression of co-stimulatory molecules: CD80, CD86, CD40 and MHC class II, as well as toll like receptors: TLR9, TLR4, TLR2 on splenic B lymphocytes (CD19 +) was determined in both groups of pregnant mice on the day 3 (preimplantation) and on day 14 (period of stabilized mother-fetal contact) of pregnancy using flow cytometry.

Results: The obtained data allow us to state that on day 14, during normal and abortion-prone pregnancy, there was an overall reduction in the number of CD19 + lymphocytes in the spleen compared to the 3rd day of pregnancy. On day 3 of pregnancy, there was also a decrease in TLR4 expression and an increase in TLR9 expression on B lymphocytes in females in normal pregnancy. In addition, lower expression of CD86 is observed as well as higher expression of CD40 on test lymphocytes in pregnant females. There were no differences in protein expression for MHC II and TLR2 between the examined groups. All the differences in protein expression described above were observed only at the 3rd day of pregnancy.

Conclusions: The differential expression of TLRs and costimulatory molecules in maternal splenic B cells in normal and abortion prone pregnancy indicates their presumptive contribution to the development of fetal tolerance.

DEPARTMENT OF IMMUNOLOGY OF INFECTIOUS DISEASES
Head: Professor Andrzej Gamian, Ph.D.

Laboratory of Medical Microbiology
Head: Professor Andrzej Gamian, Ph.D.

Studies on the pathogenesis of some diseases of bacterial etiology and a role of phages and bacterial surface glycoconjugates and protein antigens in immune response, as well as studies on probiotics proteins and glycoconjugates, structure and role in immunity

The main area of studies in our laboratory is focused on mechanisms of pathogenicity of diseases with bacterial etiology, the role of bacterial glycoconjugates and proteins in the immune processes, the structure and functions of bacterial exopolysaccharides, including these from probiotics. The structural studies of bacterial antigens revealed that surface polysaccharide of actinomycetal representative *Tsukamurella pulmonis* is arabinomannan with a structure similar to antigens from *Mycobacterium tuberculosis*. Monoclonal antibodies against this polysaccharide allowed us to identify *T. pulmonis* in granules located intracellularly when immunohistochemically stained. Ultrastructural studies proved the presence of *T. pulmonis* cells in these granulations. These results indicate the possibility for application of these monoclonal antibodies in diagnostics. Concerning the studies on bacteriophage adhesins, the experiments with atomic force microscopy allowed us to determine interaction forces of adhesin from T4 phage specific to *E. coli* B LPS, in relation to not interacting nonspecific lipopolysaccharides. Phage protein gp37 was used to functionalize the surface with Ti, Au and Ru in order to bind *E. coli* cells, which showed that the best biosensor in terms of specificity and yield were surfaces functionalized with titanium to bind proteins recognizing bacteria. Identification of bacteria with MALDI mass spectrometry was performed on a group of *Yersinia enterocolytica* strains isolated from humans, pigs and animals from the zoological garden, as well as on *Staphylococcus haemolyticus* from the milk of cows with inflammatory disease, and also on *Campylobacter* strains derived from poultry. These studies are important from the epidemiological point of view. Studies focused on determining the biological activities of probiotic strains of *Lactobacillus* have led to the identification of polysaccharides with immunomodulating properties or lowering the hypersensitivity. Several polysaccharides have been tested in *in vivo* experiments in mice models of the allergy to check their therapeutic properties. Results indicate a distinct therapeutic potential of *Lactobacillus* polysaccharides toward allergy treatment. These studies are pioneering in the world towards an understanding of the role of probiotics polysaccharides in immune system activation. Immunochemical studies are crucial for understanding biological functions and interactions of bacteria with the host and bacteria with other microorganisms.

Laboratory of Virology
Head: Professor Egbert Piasecki, Ph.D.

Oncolytic vesicular stomatitis virus (VSV) can be delivered intravenously to target primary and metastatic lesions, but the interaction between human peripheral blood leukocytes (PBLs) and VSV remains poorly understood. Our study aimed to assess the overall immunological consequences of ex vivo infection of PBLs with VSV. Phenotypic analysis of lymphocyte subsets and apoptosis were evaluated with flow cytometry. Caspase 3/7 activity was detected by luminescence assay. Virus release was evaluated in a murine cell line (L929).

Gene expression and cytokine/chemokine secretion were assessed by real-time PCR and multiplex assay, respectively. Ex vivo infection of PBLs with VSV elicited upregulated expression of RIG-I, MDA-5, tetherin, IFITM3, and MxA. VSV infection triggered rapid differentiation of blood monocytes into immature dendritic cells as well as their apoptosis, which depended on caspase 3/7 activation. Monocyte differentiation required infectious VSV, but loss of CD14+ cells was also associated with the presence of a cytokine/chemokine milieu produced in response to VSV infection. In conclusion, systemic delivery is a major goal in the field of oncolytic viruses. Our results shed further light on immune mechanisms in response to VSV infection and the underlying VSV-PBL interactions, bringing hope for improved cancer immunotherapies, particularly those based on intravenous delivery of oncolytic VSV. The results were published in *Journal of Innate Immunity, 2018; 10: 131-144*.

DEPARTMENT OF IMMUNOCHEMISTRY
Head: Professor Czesław Ługowski, Ph.D.

Laboratory of Glicoconjugates
Head: Professor Marcin Czerwiński, Ph.D.

Role of ceramide galactosyltransferase (UGT8) and galactosylceramide (GalCer) in drug resistance of breast cancer cells

It was previously shown that GalCer increases resistance of tumor cells to stress induced apoptosis and its expression is elevated in multidrug resistant cells. To further reveal the role of UGT8 and GalCer in breast cancer progression, tumorigenicity and response for doxorubicin, the treatment of control 4T1 cells (4T1.PURO) and 4T1 cells (4T1.PURO/UGT8) with overexpressed UGT8 and GalCer was studied *in vivo* in BALB/c mice. The cells were transplanted orthotopically into the mice. Four weeks after cancer cell transplantation, statistically important decreases in volumes were observed in the case of 4T1.PURO tumors in comparison to tumors formed by 4T1.PURO/UGT8 cells after doxorubicin treatment. This study demonstrates that increased synthesis of galactosyloceramide increases resistance cancer cells to anticancer drugs such as doxorubicin.

Antigens of human blood group system P1PK in birds

It was shown before that some birds express antigens belonging to human P1PK blood group system. We showed that there are differences in the expression level between birds belonging to *Neoaves*. Purified glycosphingolipids obtained from red blood cells contained GlcCer, LacCer and Gb3Cer and were bound by Shiga toxin subunit Stx1B. In addition to the *Columba livia* gene encoding Gb3/CD77 synthase (*A4GALT*), a homologous gene from the same species was cloned and sequenced. It contains 55 amino acid differences in comparison to *A4GALT* described previously. We hypothesize that enzymes encoded by these genes differ in specificity, so the genes will be cloned, expressed in 2102Ep cells and analyzed by flow cytometry.

Glycosylation *Ex vivo* as a method to obtain cells of rare phenotype

Ex vivo glycosylation is a method by which new glycoconjugates on the surface of the cells can be synthesized using recombinant glycosyltransferases. Using insect cell-expressed Gb3/CD77 synthase and rare p red blood cells, we obtained red blood cells with P_1 phenotype, which contained P1 and P^k antigens. These data show that recombinant glycosyltransferases

may serve as a valuable tool to change the blood group of erythrocytes and synthesize glycoproteins and glycolipids on the cell surface.

Laboratory of Microbial Immunochemistry and Vaccines
Head: Professor Jolanta Łukasiewicz, Ph.D.

Biochemical characteristics of macromolecules involved in immunological processes. Immunochemical studies of bacterial endotoxins

A variety of Gram-negative species, such as *Klebsiella pneumoniae, Escherichia coli, Hafnia alvei, Proteus penneri*, and *P. mirabilis*, represent opportunistic human pathogens associated with extraintestinal and nosocomial infections in humans and animals. Moreover, *K. pneumoniae*, particularly ESBL- and KPC-strains, has been singled out in 2017 as *"priority 1. critical pathogen"* for health care by the WHO, CDC, and the UK Department of Health. Major virulence factors and surface antigens of these species are: lipopolysaccharide (LPS, endotoxin, O antigen), capsules (antigen K, i.e. capsular polysaccharide - CPS and exopolysaccharide - EPS), and fimbriae. LPS is built up of lipid A, core oligosaccharide (OS), and O-specific polysaccharide (O-PS). LPS and CPS determine O serotype or K serotype, respectively. Precisely, O serotype is defined by O-PS region built up of carbohydrate repeating units.

Some K antigens and O antigens seem to be promising targets for antibody-based therapy (active and passive immunisation) against infections as an alternative to antibiotics. For more variable LPS within the O-PS region, as for *E. coli* LPS, core OS was suggested as a conservative region and a promising target for therapeutic antibodies. To make such immunotherapy effective, complete knowledge about LPS, O/K antigens' structure and their distribution among clinical isolates (seroepidemiology) is required.

At first we continued our studies on diversity of *K. pneumoniae* O antigens and their use as immunogens for the generation of cross-protective human and humanised monoclonal antibodies (mAb) as a therapeutic and diagnostic tool against *Klebsiella* infections. In collaboration with Max Planck Institute for Infection Biology (Berlin), Cancer Research Center (Heidelberg), and Arsanis GmbH (Vienna), we generated and described a panel of affinity-matured human mAb from peripheral blood immunoglobulin M–positive (IgM+) and IgA+ memory B cells and clonally related intestinal plasmablasts, directed against *K. pneumoniae* O1, O2, and LPS (Rollenske T. et al. *Nature Immunol* 2018). The mAb showed distinct patterns of *in vivo* cross-specificity and protection against different clinically relevant *K. pneumoniae* serotypes (including O3, O3a, O3b cross-reactivity). Moreover, cross-specificity was not limited to *K. pneumoniae*, and 40% of mAb revealed cross-reactivity with non-*K. pneumoniae* antigens, such as *P. luteola* LPS, *S. cerevisiae* bacteria, and gp140 HIV protein. Effective candidates have been chosen for further development of mAb-based therapy against *Klebsiella* infections.

Further, we have identified the new type of the core OS in *P. penneri* 40A and 41 LPS. The new type of structure is typical for *P. penneri* core regions in its inner part and represents glycoform III containing Kdo and Ara4N residues, rich heptose region (5 residues), Glc*p*, and Gal*p*A. Identification of new chemotype was a result of outer core trisaccharide structure built up of (β-D-Gal*p*-(1→4)-α-D-Glc*p*NAc-(1→4)-α-D-Gal*p*N6OAc), and particularly terminal β-D-Gal*p* determining serospecificity of this core type. The new core OS serotype has extended the core OS serotypes scheme for *Proteus* spp. and confirmed the huge structural heterogeneity of *P. penneri* LPSs, a unique phenomenon among other *Enterobacteriaceae*. The study supported the conclusion that the identification of the most common outer part of

the core OS is necessary to develop core OS-based vaccine against *Proteus* infections (Palusiak A. Int J Mol Sci. 2018). Additionally, the impact of planktonic and biofilm lifestyles of the clinical isolate *P. mirabilis* 9B-m on its LPS structure has been evaluated. By structural analyses of LPS we demonstrated that the structure of P. mirabilis 9B-m O-PS did not depend on the form of cell growth; however, the length of the O-PS was reduced when bacteria grew in biofilm. Additionally, some minor changes have been observed in core OS region – PEtn and AraN substitution (Zabłotni A. Med Microbiol Immunol. 2018). No lipid A modifications were observed. Future studies will show the significance of these changes on the pathogenicity of this species.

To conclude, we have demonstrated that a variety of Gram-negative LPS react strongly with human and murine mannose-binding lectins (MBL). *Hafnia alvei* LPS was used as a model pathogen to investigate the biological consequences of these interactions. MBL-binding motifs of LPS are accessible to MBL on the surface of bacterial cells and LPS aggregates. The LPS core OS–MBL interactions led to complement activation and also induced an anaphylactoid shock in mice. Our results contribute to a better understanding of MBL–LPS interaction and may support development of therapeutic strategies against sepsis based on complement inhibition (Man-Kupisinska A. et al. Front Immunol. 2018).

Publications – 2018

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