Hirszfeld Institute of Immunology and Experimental Therapy
Polish Academy of Sciences
Rudolfa Weigla 12, 53-114 Wrocław

RESEARCH REPORT 2017

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

Laboratory of Experimental Anticancer Therapy
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Studies on the mechanisms of tumour progression, metastasis, and on the effects of experimental anti-tumour therapy

The role of vitamin D binding protein in the process of tumour metastasis

Vitamin D binding protein (DBP) is a protein belonging to the α2-globulin fraction, which has the ability to bind and transport vitamin D. In addition, DBP together with gelsolin form a system to remove actin from the blood. The goal is to answer the question concerning the role of nagalaze (α-N-acetylgalactosaminidase) - the enzyme influencing, according to literature data, the anti-tumour activity of DBP - in the process of tumour metastasis. It has been shown that 4T1-metastatic mammary gland cancer cells possessed similar expression of nagalaze to 67NR non-metastatic cells *in vitro*. In addition, calcitriol and its analogs PRI-2191 and PRI-2205 increased the expression of this enzyme in both cell lines after 72 hours incubation. In analysing the tumours collected from mice treated with the aforementioned vitamin D3 derivatives, it was found that calcitriol and both analogues in the initial stage of tumour progression (day 21) increased the expression of nagalaze in this tissue, while in the later stage (day 33) we observe a significant reduction in enzyme expression. In summary, it has been shown that calcitriol and both analogues can modulate the expression of the enzyme that modifies DBP. This is important from the point of view of published data on the immunosuppressive effects of nagalaze. The observed increase in its expression in the initial stages of tumour progression may contribute to the intensification of the 4T1 cell metastasis process by calcitriol and its analogues observed in our other studies.

Studies on the potential application of bisphosphonates in anti-cancer treatment

Previous studies have shown that the new bisphosphonates show a special (often selective) antiproliferative activity against J774E and RAW264.7 macrophages, which are a model for *in vitro* osteoclast research. Significant pro-apoptotic activity of 12399C and 12592A compounds against J774E cells was demonstrated. The pro-apoptotic activity of both compounds, measured by the increase in caspase activity, was several times higher than in the case of reference zoledronate and incadronate. A similar effect was observed in the case of RAW264.7 cells. In addition, the culture conditions for RAW264.7 macrophages were established: these cells were efficiently differentiated into osteoclasts. Subsequently, the compounds 12399C and 12592A were shown to significantly inhibit the differentiation of RAW264.7 macrophages into osteoclasts. We found approximately 60% inhibition of macrophage differentiation into polymorphonuclear cells by these compounds, an effect similar to the reference zoledronate.

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 tumour antigens

The aim of the task was to obtain vaccines capable of long-term, high production of pro-inflammatory and regulatory cytokines based on cancer cells and dendritic cells. We

attempt to genetically modify of bone marrow-derived dendritic cells (BM-DCs) by means of 3rd generation lentiviral vectors containing the *il-15* and/or *il-2* genes. The lack of a reporter gene in the vector, however, precluded assessment of transduction efficiency. In addition, the production level of both cytokines by BM-DCs turned out to be low. It was also planned to use transductants to activate chosen mechanisms of anti-cancer responses. In light of previously obtained data, the use of supernatants from cultures of transduced tumour cells and their antigens activated BM-DCs, which when employed in mixed culture with spleen cells caused their activation. An attempt to use transduced BM-DCs for the direct activation of effector immune cells did not provide the expected results. Therefore, it is planned to develop a new construct containing additional genes (including a reporter gene in place of the selective gene) and a gene responsible for IL-15R chain expression. It is also planned to re-use JAWS II cells to obtain stable transductants containing the reporter gene. Implementation of the method of genetic modification with the use of lentiviral vectors as carriers of cytokine genes or their receptors will allow for the strengthening of the production of selected cytokines to the renewal of the tumour microenvironment and/or modulation of the anti-cancer response, respectively.

Laboratory of Tumour Molecular Immunobiology
Head: Professor Leon Strządała, Ph.D.

Molecular mechanism of programmed cell death and proliferation in normal and tumour cells

Synergistic activity of sorafenib and betulinic acid against clonogenic activity of non-small cell lung cancer cells

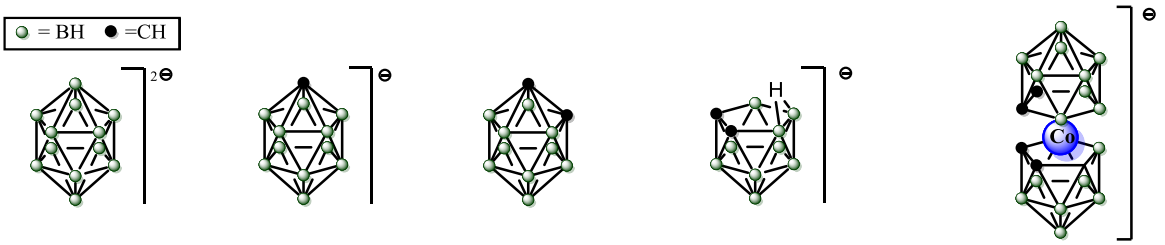
Molecular targeted therapies are now applied in the treatment regimen of human non-small cell lung cancer (NSCLC), as they have been shown to extend progression-free survival and improve overall survival. The highly selective multi-targeted agent sorafenib is an inhibitor of a number of intracellular signalling kinases with anti-proliferative, anti-angiogenic, and pro-apoptotic effects in various types of tumours, including NSCLC. Recent studies have shown that a combination using different drugs to treat tumour patients may increase the efficiency of the anti-tumour response. Betulin displays a broad spectrum of biological and pharmacological properties, including anticancer and chemopreventive activity. The NSCLC cell lines with different KRAS mutations, including A549, H358, A427, and normal human peripheral blood lymphocytes (PBL) cells, were treated with sorafenib and betulinic acid alone and in combination. The combination of sorafenib with betulinic acid had a strong effect on induction of apoptosis of different non-small cell lung cancer cell lines. Significantly, this combination is nontoxic for human PBL. Combination treatment changes the expression of proteins involved in the mitochondrial pathway of apoptosis and induces apoptotic death by caspase activation. Importantly, combination treatment with low concentrations of drugs tremendously reduces the colony-forming ability of A549, H358, and A427 cells as compared to both compounds alone. In conclusion, the present study demonstrates that sorafenib in combination with betulinic acid enhances the inhibitory effect on NSCLC cells. Betulinic acid strengthens the anti-proliferative action of sorafenib, promotes NSCLC cell apoptosis, and allows for the use of lower doses of sorafenib than doses currently used. It should be underlined that combinatorial treatments with low concentrations of sorafenib and betulinic acid have therapeutic potential for NSCLC treatment, as targeting a clonogenic/tumour initiating/stem cell-like subset of cancer cells is thought to be essential for

successful cancer therapy. Moreover, the combination of sorafenib and betulinic acid is effective regardless of KRAS mutations. Hence, it is worthwhile to consider this combination treatment for NSCLC and warrants further evaluation in clinical trials.

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 laboratory we focused on boron clusters as a class of entities suitable for modifications of biomolecules in order to obtain a specific biological effect. We have focused on icosahedral boron clusters, as well as metallacarboranes (Figure 1), their biological activity, and their interaction with the biological environment. Icosahedral boron clusters demonstrate high potential in biological and medicinal applications. They can be used to optimize parameters critical for the biological activity and affinity of therapeutic substances toward biological targets. Boron clusters induce these effects due to their extraordinary properties, including near-spherical geometry; chemical, biological, and thermal stability; low toxicity; high (depending upon structure) hydrophilicity, hydrophobicity, or amphiphilicity; and susceptibility to derivatization. The fact that the electronegativity of boron toward hydrogen is inverted with respect to carbon raises the question of the influence of boron cluster derivative compounds in biological environments. Boron clusters are a new component for the modification of biomolecules and have numerous applications in biomedical chemistry.



$[B_{12}H_{12}]^{2-}$ $[CB_{11}H_{12}]^{-}$ $C_2B_{10}H_{12}$ $[C_2B_9H_{12}]^{-}$ $[Co(C_2B_9H_{11})_2]^{-}$

Figure 1. Structures of selected boron clusters compounds

Our latest studies prove that metallacarboranes and their derivatives interact strongly with serum albumin and bind specifically to the hydrophobic cavity of albumin. The interaction of boron clusters with albumin has been examined by fluorescence quenching, circular dichroism, dynamic and static light scattering measurements, and MALDI-TOF mass spectrometry. Our results have shown that among the tested clusters metallacarboranes have the strongest interaction with albumin. This finding creates the new possibility of the synthesis of new biologically active hybrid conjugates with beneficial pharmacokinetic properties.

Bacteriophages

Our laboratory is studying the physicochemistry of bacteriophages. We look at bacteriophages as nanoparticles with both therapeutic and biotechnological potential. In our laboratory we have developed a procedure for lipopolysaccharide removal from bacteriophage preparations obtained from Gram-negative bacteria. The method involves extraction with the

use of octanol or butanol interchangeably. During extraction, 99% of the endotoxin is removed, while most of the phage lytic activity is maintained. Our research in the bacteriophage field is currently focused on the development of stabilization conditions for purified preparations and studies on the virus behaviour in different environments. Research topics implemented in our laboratory are part of the global trend of searching for smart nanocarriers used for targeted therapy.

DEPARTMENT OF CLINICAL IMMUNOLOGY

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

Influence of *MICA* and *NKG2D* genetic variants in response to anti-TNF agents and changes of cytokine serum levels during treatment

Rheumatoid arthritis (RA) is an autoimmune disease characterized by the inflammation of joint synovial tissue, resulting in the progression of cartilage and bone tissue damage, ultimately leading to disability. Major histocompatibility complex (MHC) class I chain-related A (MICA) proteins are stress-induced molecules involved in the transmission of activating signals through the NKG2D receptor. The MICA proteins are aberrantly expressed in synovial tissue in patients with RA. NKG2D acts as a powerful activating and co-stimulatory receptor on immune effector cells including NK and T cells. Disruptions within the NKG2D signalling pathway may trigger an exacerbated immune response and promote autoimmune reactions. Therefore, we aimed to assess the role of the MICA and NKG2D polymorphism in RA, as well as the changes in MICA. We selected pro-inflammatory cytokine serum levels prior to, and 3 and 6 months after, anti-TNF treatment.

Serum levels were examined using Human Luminex Assay (MICA) from R&D Systems Inc., and monoplex (IL-17F) and 7xplex ProcartaPlex Multiplex (IL-17A, IL-1beta, IL-6, IL-22, IL-23, sRANKL, TNF-alpha) Immunoassays from Invitrogen Inc., on the Luminex 200 system. Genotyping was performed employing either Taqman (Applied Biosystems) or LightSNiP (TIB-MolBiol) assays. Clinical response was evaluated according to the European League Against Rheumatism (EULAR) criteria at 12 and 24 weeks after initiation of anti-TNF treatment.

Patients before therapy presented with significantly higher serum levels of IL-6 ($p < 0.001$), IL-1beta ($p = 0.002$) and TNF-alpha ($p < 0.001$), as compared to healthy controls. The presence of the *IL6* rs1800795 CC homozygous genotype was associated with the highest IL-6 concentrations before treatment ($p = 0.026$). This homozygosity was also more frequently detected in patients with more active disease ($DAS28 \geq 3$) ($p = 0.048$). *IL1B* genotypes were found not to be significantly associated with serum levels of this cytokine. Patients with RA possessing the *IL1B* rs16944 C allele are characterized with lower CRP levels after 3 months of anti-TNF therapy ($p = 0.035$). As for *TNFA* polymorphisms (rs1800629, rs1799724, rs361525) under study, a significant relationship was identified between *TNFA* rs1799724 CC homozygosity and the presence of the rheumatoid factor ($p = 0.033$).

MICA serum levels rose during anti-TNF therapy ($p = 0.021$) and significantly higher MICA concentrations were observed in patients possessing the rs1051792 GG genotype ($p < 0.001$). Moreover, the GG homozygous genotype was also more frequent among patients characterized with worse clinical response after 12 weeks ($p = 0.010$). In addition, patients

carrying the heterozygous genotype achieved significantly better EULAR responses to anti-TNF agents than patients having homozygous genotypes (p = 0.003).

Among *NKG2D* rs2255336, rs1049174, and rs1154831 polymorphisms, both *NKG2D* rs225336 and rs1049174 were significantly associated with efficacy of the treatment with TNF inhibitors. Inefficient therapy was more frequently observed in patients with rs2255336 GG (p = 0.003) or rs1049174 CC genotype (p = 0.004). The presence of the rs2255336 G or the rs1049174 C allele correlated with a worse EULAR response (p = 0.002 and p = 0.031, respectively). Moreover, patients carrying the rs2255336 or rs1049174 heterozygous genotype achieved better EULAR responses than patients with homozygous genotypes (p = 0.010 and p = 0.002, respectively).

In conclusion, our results imply that *MICA* and *NKG2D* polymorphisms might act as genetic predictors of response to therapy with TNF inhibitors. Additionally, IL-6, IL-1beta and TNF-alfa levels might be associated with predisposition to RA. Moreover, *MICA* polymorphism correlates with its expression, which changes during therapy with TNF inhibitors in patients with RA.

The study was supported by the National Science Centre 2016/21/B/NZ5/01901 project.

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

Immunogenetics of human diseases

We are presently carrying out two projects granted by the National Centre of Science (NCS), and two projects granted by the National Scientific Leading Centre (Krajowy Naukowy Ośrodek Wiodący, KNOW). NCS grants deal with: (i) the role of genetic polymorphisms in recurrent spontaneous abortion and failure of *in vitro* fertilization procedure and (ii) with associations of genes encoding antigen presentation machinery components with non-small cell lung cancer. KNOW grants are focused on the association of *HLA-C* alleles with atopic dermatitis and on the role of *ALCAM* and *CD6* gene polymorphisms in multiple sclerosis and non-small cell lung cancer. These projects are in progress. The main results, which have already been published, are as follows:

a) The role of methylenetetrahydrofolate reductase in human reproduction failures

One of the key enzymes that could contribute to reproductive failure in humans is methylenetetrahydrofolate reductase (MTHFR). It catalyses formation of 5-methyltetrahydrofolate, which is involved in the methylation of homocysteine (Hcy) to methionine. The aim of this study was to evaluate the *MTHFR* c.c.677 C>T and c.c.1298 A>C polymorphisms' association with recurrent spontaneous abortion (RSA) and recurrent *in vitro* fertilization failure (RIF). We observed a protective effect of the female 1298 AC genotype and the C allele against RSA. Moreover, 1298 AA/677 CT women were more frequent in RSA and RIF groups in comparison to fertile women, although this difference was significant only in the case of RSA. Moreover, the association between elevated homocysteine (Hcy) level in plasma of RSA and RIF women and MTHFR polymorphisms was investigated but did not reveal significant differences. In conclusion, for clinical practice, it is better to check the homocysteine level in plasma, and if the Hcy level is increased, to recommend patients to take folic acid supplements rather than undergo screening of MTHFR for 1298 A>C and 677 C>T polymorphisms.

b) Genetics of endometriosis

Another female reproductive morbidity is endometriosis, which is a disease where endometriotic tissue occurs outside the uterus. Its pathogenesis is still unknown. The most widespread hypothesis claims that ectopic endometrium appears as a result of retrograde menstruation and its insufficient elimination by immunocytes. Some reports have shown expression of non-classical HLA-G molecules on ectopic endometrium. HLA-G is recognized by KIR2DL4, LILRB1, and LILRB2 receptors on natural killer (NK) and other cells. These receptors are polymorphic, which may affect their activity. In this study we investigated whether *HLA-G*, *KIR2DL4*, *LILRB1*, and *LILRB2* polymorphisms may influence susceptibility to endometriosis and disease progression. The *HLA-G* rs1632947:GG genotype was associated with protection against the disease and its severe stages. *HLA-G* rs1233334:CT protected against progression. *LILRB1* rs41308748:AA and *LILRB2* rs383369:AG were predisposed to the disease and its progression. No effect of *KIR2DL4* polymorphism was observed. These results support the role of polymorphisms of the HLA-G molecule and its receptors LILRB1 and LILRB2 in susceptibility to endometriosis and its progression.

c) Genetics of multiple sclerosis

Genome-wide association studies (GWAS) have identified hundreds of new potential genetic risk loci associated with numerous complex diseases, including multiple sclerosis (MS). Genes that have been discovered by GWAS are now the focus of numerous ongoing studies. The goal of this study was to confirm and understand the potential role of one of such genes – the transmembrane protein 39A gene (*TMEM39A*) – in multiple sclerosis. We showed the difference in *TMEM39A* messenger RNA (mRNA) expression between patients with MS and controls ($T^2_{2;74}$ = 5.429; p = 0.0063). In our study, the lower mRNA expression of the *TMEM39A* gene in patients did not correlate with a higher methylation level of the *TMEM39A* promoter. Moreover, neither a decreased level of *TMEM39A* mRNA nor a risk and progression of multiple sclerosis was associated with two single nucleotide polymorphisms of the *TMEM39A* gene. Our investigation is the first to indicate that TMEM39A mRNA expression may be associated with the development and/or course of multiple sclerosis.

d) Microchimerism in psoriasis

Microchimerism is defined as the stable presence of low numbers of cells derived from a different individual due to cell transfer between twins or between mother and fetus during pregnancy. It has been proposed that microchimerism contributes to several human diseases. Fetal cells in the organism of the mother (FMc) have been postulated to play a role in autoimmune diseases. Psoriasis is a disease that has an autoimmune component, but no study on microchimerism in this disease has been reported. Here, we looked for the presence of male cells in mononuclear cell subpopulations from peripheral blood and in skin samples of women with psoriasis as well as of healthy women who had delivered a son. We detected FMc in similar proportions in blood of patients and controls in CD4+, CD8+, and CD34+ cells, whereas in CD34- cells FMc were present in higher fraction of controls, and similar but non-significant difference was observed in CD19+ cells. No microchimeric cells were, however, detected in patients' skin samples, either from affected and non-affected skin or in skin tissue from healthy control individuals. Therefore, although FMc were detected in some women, our result does not prove the involvement of microchimerism in the aetiology of psoriasis.

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

CD8+PD-1+ lymphocytes preferentially reside in marrow as compared to blood, and may witness anti-leukemic activity of the immune system

In our group of patients with HSCT, 45% post-transplant loses were due to relapse. Immunologic surveillance of leukaemia is employed for prevention and may be active in treatment relapsing patients. The issue of exhausted tumour infiltrating lymphocytes has gained a great deal of interest fuelled by scientific data on restoring the function of T cells by blocking CTLA4 and PD-1 receptors on their membrane.

In fighting leukaemia relapse, two approaches were employed at our institution:

(i) donor lymphocytes injection directly into the bone leukemic infiltrates or into the marrow cavity (lower risk of graft-versus-host disease (GvHD), better and more efficient contact between lymphocytes and leukemic blasts)

(ii) the use of a multikinase inhibitor blocking the FLT3 ITD mutation and independently boosting the immune function of the patients (Lange A., PLoS One. 2018 Jan 5;13(1):e0190525).

The clinical effect was monitored and highlighted by thorough observation of the immune environment in the marrow. Altogether, 24 intra-bone donor lymphocyte infusions (IB-DLI) were delivered to eight patients; in three cases sorafenib was used. Overall, a positive effect of IB-DLI was seen; however, temporal IB-DLI led to a decrease in the blast count and to restoration of haematopoiesis.

Three to five IB-DLIs were performed starting from 10E6 and ending with a dose of 10E8 of CD3+ cells/kg body weight. Donor lymphocytes were obtained from unstimulated or stimulated leukopoietic product used for transplantation (Hasskarl J., Bone Marrow Transplant. 2012, 47(2):277-82). The cells were injected directly to the bone marrow cavity via the posterior iliac crest.

Sorafenib was used in three patients with AML (FLT3 ITD-positive, NPM1-positive) who relapsed at 56 (53-year-old male), 256 (50-year-old female), and 30 (50-year-old female) days post-transplant.

Results:

1. GvHD symptoms were not aggravated by IB-DLI in any of the patients in the study.
2. In IB-DLI receiving patients as well in those on sorafenib, the proportions of CD8+ cells and CD8+PD-1+ lymphocytes were higher in the marrow compared to the blood (7.294±0.957% vs 11.18±1.28%, $p < 0.001$).
3. An increase of CD8+PD-1+ lymphocytes in the marrow was associated with a well-documented retreat of blasts from the marrow. In addition, the morphology of lymphocytes depicted their activation; in the marrow biopsies, blast-lymphocyte conjugates could be spotted.
4. Similarly, in sorafenib-receiving patients marrow CD8+ lymphocytes co-expressed PD-1 in higher proportions than those in the blood (163±32 x103 cells/µl vs 38±8 x103 cells/µl, $p < 0.001$). All patients on sorafenib developed skin lesions of alloreactive character.

In spite of the high proportion of CD8+CDPD-1+ lymphocytes in the marrow and their apparent prevalent contribution to the marrow lymphocytes, an anti-leukemic effect of both implemented procedures was documented.

Therefore, PD-1 positivity of CD8+ cells is not necessarily associated with the poor function of T cells, and may represent the presence of an active immune response in the marrow environment to the leukemic blasts.

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

Phage inactivation by sera of patients receiving phage therapy

Two groups of patients were identified with high antiphage activity of sera (AAS) (n = 32) and with low AAS (n = 25). Low AAS was observed in 10 patients with genitourinary tract infection using intrarectal phages. The most common disorders of patients with high AAS were bone infections (71.9%) and upper respiratory tract infections (15.6%).

The biology of *Klebsiella* phages from IIET phage collection

The aim of the study was to investigate the biology of 20 *Klebsiella* phages from IIET phage collection. The phages showed stability at 4°C after one year and were stable at pH 5, 6, and 8. Phages were classified (TEM) as *Caudovirales* and three families – *Myoviridae* (11 phages, including 10 phages as A2 morphotype and one as A1 morphotype); *Siphoviridae* (three phages as B1 morphotype); and *Podoviridae* (15 phages as C1 morphotype).

Real-time qPCR as a method for detection of antibody-neutralized phage particles

The most common method for phage quantitation is the plaque assay, which relies on phage ability to infect bacteria. However, non-infective phage particles may preserve other biological properties, including interactions with the immune system of animals and humans.

We have demonstrated that real-time quantitative polymerase chain reaction (qPCR) is a potent method for phage detection in both animal and human blood and tissues. This detection method is an alternative to the common plaque assay. Moreover, qPCR was also able to detect neutralized phage particles that were not detected by the standard plaque assay, thus demonstrating a substantial time lapse between 'microbiological disappearance' and true clearance of phage particles from the circulation. We propose that phage pharmacokinetic and pharmacodynamic studies should not merely rely on detection of antibacterial activity of a phage. In fact, real-time qPCR can be an important alternative for phage detection.

Preliminary studies on the efficacy of ovocystatin in the treatment of rheumatoid arthritis in the collagen-induced arthritis model

The aim of this study was to conduct a preliminary assessment of the influence of ovocystatin-albumin bioconjugate (OAB) on the course of collagen-induced arthritis in mice (CIA) – a model of rheumatoid arthritis in humans. Chicken cystatin (ovocystatin) was synthetized at the Department of Pharmaceutical Biochemistry, Faculty of Pharmacy at the Wroclaw Medical University. Cystatins may inhibit cathepsins that contribute to tissue damage in joints and are responsible for the invasive phenotype of activated synoviocytes. In our study we have applied OAB intraperitoneally twice a week in a therapeutic mode (the treatment was started one week after a booster dose of collagen and lasted for three weeks). We were not able to confirm any significant anti-rheumatic activity of OAB (resulting in reduction of clinical symptoms of CIA) at the applied dose of 5 mg/kg of b.w., although it was observed for methotrexate (35 mg/kg of b.w.) used at the same mode as a comparator. We suppose this may be caused by too low doses of OAB or the use of too short linkers between albumin and ovocystatin, which could sterically block ovocystatin interaction with enzymes.

Retrospective analysis of long-term results of the application of phage preparations in patients with chronic bacterial infections

In February 2018 we performed a phone interview with patients (n = 33) with chronic bacterial infections (approximately 70% *S. aureus*) receiving experimental phage therapy (PT) at the Phage Therapy Unit of Hirszfeld Institute. Information was collected from 33 participants who completed PT from 15 months to 7 years ago. All patients used phage preparations topically; in two cases, by oral route as well. Cumulative treatment time was from 3 to 168 days (median: 51 days). A good response to treatment – assessed according to the scale described by Międzybrodzki et al. (Adv Virus Res. 2012; 83: 73-121) – was observed in 36% of patients immediately after completing the PT (eradication or healing in 12%). Over the next twelve months, 24% of respondents still reported good results of PT (eradication or healing in 18%). Interestingly, 64% of patients assessed the PT result as good at the time of interview (52% reported eradication or healing). Although the majority (79%) of respondents also applied another treatment after the PT, 12 patients (36%) linked their current good clinical state to the PT. None of the 33 interviewed persons reported adverse reactions. Two-thirds of patients confirmed that PT had met their expectations. These results confirm the safety and maintenance of good response to PT for a prolonged time after its completion, which suggests that the beneficial results of PT may be long lasting.

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

Biology of cells involved in regenerative and neoplastic processes

In 2017, a research group of the laboratory completed studies on the biology of human endothelial precursor cells (HEPCCB.1 and HEPC-CB.2 cell lines). The results confirmed their proangiogenic potential of the cells by tube formation and growth factors production active in angiogenesis.

Working on the biological properties of mesenchymal/progenitor stem cells of bone marrow (BM-MSC) and adipose tissue (AT-MSC) origin in the context of regenerative processes, immortalized BMMSC-SVT.1 and ATMSC-SVT cell lines were created by using hTERT and pSV402 plasmids. Both cell lines express basic antigens specific for MSC including CD73, CD90, and CD105. Both cell lines are negative for hematopoietic and the mature endothelial markers CD45, CD34, and CD31. Similarities and differences between these cell lines were analysed using Microarray Protein Membrane (Custom C-Series Human Cytokine Antibody Array, RayBiotech Inc.). Among 120 analysed cytokines and growth factors, 90 factors were produced by both cell lines. Whereas IL-7 was exclusively produced by ATMSC-SVT, BMMSC-SVT.1 produced 9 different growth factors including GDNF and SCF. Moreover, the cell line of BM-origin was characterized by a higher level of stemness-related marker SSEA-4. In contrast, CD140a and CD140b antigens, which regulate embryonic development, cell proliferation, survival and chemotaxis, were more frequently seen on the ATMSC-SVT cell line.

We searched for alternative sources of MSC, both for experimental studies and as a potential candidate for tissue regeneration (except BM-MSC and AT-MSC). Thus, phenotype and differentiation potential of primary MSC isolated from human skeletal muscle and skin were analysed. Adherent cells isolated from all examined tissues expressed phenotype characteristic for naïve MSC CD73, CD90, and CD105. The heterogenic nature of MSC isolated from different tissues was confirmed as a co-expression of CD73/CD146,

CD90/CD146, and CD105/CD146 in the proportion of adherent cells. A fraction of cells expressing CD146 strongly co-expressed PDGFR-α (CD140a). Cells isolated from all examined tissues were capable of differentiating into chondrocytes, osteoblasts, and adipocytes. However, MSC isolated from skeletal muscle were not able to form adipocytes. Our observations confirmed that MSC isolated from BM, skin, and adipose tissue biologically represent multipotent cells capable of differentiating into different type of tissue, whereas progenitor cells isolated from skeletal muscle have tissue-specific character.

Working on tumour cell biology, we developed a method of isolating tumour-specific suppressor cells of myeloid-origin (MDSCs) as well as the phenotypic and functional characteristics of the obtained cells. During the culture of murine BM-origin myeloid cells in the presence of GM-CSF and supernatant from tumour cells of the MC38 (colon cancer), LLC (lung cancer), and TRAMP-C1 (prostate cancer) cell lines, under hypoxia conditions, we obtained cells with characteristics similar to MDSC cells present in cancerous tumours.
For a detailed characterization of MDSCs cultured *in vitro*, a multiparameter flow cytometric protocol was developed, allowing for simultaneous analysis of two subpopulations of MDSC, monocytic and granulocytic cells, as well as assessment of the degree of differentiation and activation of these cells. *In vitro* cultured MDSCs showed phenotype specific for immature myeloid-derived cells. There was no expression of costimulatory molecules and MHC II antigens characteristic of mature myeloid cells. In addition, *in vitro* cultured MDSC were characterized by an increased ability to produce IL-10, one of the markers demonstrating the suppressor activity of these cells.

This method allows for preparation of a large number of MDSC with characteristics similar to MDSC cells infiltrating a tumour, which can be used in studies determining the effect of new therapeutics for modulation of suppressive activity of tumour microenvironment.

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

Digit ratio (2D:4D) and hand grip strength on an aggressive stimulus in Polish male and female students

The ratio of the second digit to the fourth digit (2D:4D) lengths is a proxy indicator of intrauterine hormonal exposure to a fetus. A lower 2D:4D in an individual indicates a higher exposure to testosterone during prenatal growth, relative to another individual who has lower testosterone and higher oestrogen exposure. Challenging conditions and male-to-male competition, including intense exercise and watching aggressive videos, can result in short-term increases in testosterone, aggression, and strength. Based on the results on relationships of 2D:4D with aggression and sports performance, it was suggested that 2D:4D was not associated with T level in resting condition, but with the magnitude of T spikes in response to challenge situations. Handgrip strength (HGS) is a simple measure that predicts muscular strength and lean muscle mass, infirmity, morbidity, and mortality. Thus, the present study was conducted to test whether an aggressive video show could change HGS in men and women and if 2D:4D has any moderating effect on the magnitude of this change.

A cross-sectional experimental study included 74 male and 76 female students, from General Tadeusz Kosciuszko Military Academy of Land Forces, Wroclaw. Participants were examined on two occasions with a seven-day gap in the same day of the week. On the first occasion, participants were shown a blank screen. On the second occasion, a seven-minute video film of MMA (Mixed Martial Arts) fight was shown as an aggressive stimulus. On each

occasion all participants underwent measurements of HGS, of both hands, 15 minutes after the show, using a standard isometric dynamometer. Digit length, height, and weight were also measured in all participants. Effect of the sex and 2D:4D on differences in HGS between two measurements (DHGS), allowing for body size (height and BMI) and age, were analysed by Generalised Linear Model (GLM) with logit link function.

The left 2D:4D in males and the right 2D:4D in females had a significant independent impact on the right hand DHGS. In males, 2D:4D had no significant impact on the left hand DHGS. But in females, the left 2D:4D had a significant impact on the left hand DHGS. Both right and left hand 2D:4D had highly significant impact on the average DHGS only in females. Also, in the average DHGS the interaction between 2D:4D for both hands with sex showed a significant effect. The results are discussed in the context of sex differences in a challenge and aggression.

The influence of the presence of a tattoo in men on the assessment of their attractiveness and health

Very few studies published in up-to-date literature have examined and demonstrated a positive association between tattooing and the assessment of male attractiveness, health, or dominance. The existence of such an association is postulated and explained by the higher biological quality of men who wear tattoos, manifesting in the more efficient functioning of the immune system. The aim of the current study was to further explore this relationship by demonstrating how adding a tattoo to the photographs of men changes their perception and assessment of such characteristics as attractiveness, dominance, health, masculinity, and potential as a partner and parent. The study also examined whether the assessment of male images varied depending on the phase of the menstrual cycle of female evaluators.

Nine shirtless men without tattoos were photographed from the waist up. These pictures were digitally modified by adding a black arm tattoo with an abstract, neutral design and presented to 2584 men and women. Pictures with and without tattoo were rated in several categories such as health, attractiveness, aggressiveness, dominance, masculinity, and potential to be a good partner and parent.

Statistical analysis revealed that women rated tattooed versions of the pictures as healthier, but not more or less attractive than the originals. Inversely, men rated tattooed versions of pictures as more attractive, but not more or less healthy than the originals. Both men and women rated pictures of men with a tattoo as more masculine, dominant, and aggressive. Women but not men assessed tattooed men as worse potential partners and parents than non-tattooed men. Furthermore, based on the analysis of effect size, it was demonstrated that adding a tattoo to a photo had higher impact on men's than on women's ratings and that the phase of the menstrual cycle of female evaluators had no effect on women's ratings.

These results confirm that adding tattoos changes others' perception of men. They demonstrate that tattoos not only influence female preference, but they may be even more important in male-male competition. They also suggest a lack of changes in women's preferences toward certain male characteristics depending on the phase of the menstrual cycle postulated in other studies.

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: 1) replication of bacterial chromosomes, and 2) polyketide synthesis in *Streptomyces*.

1/ 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 intracellular as well as on environmental signals. We are interested in mechanisms of the initiation and regulation of bacterial chromosome replication, with special emphasis on the characterization of key factors engaged in initiation complex (orisome) formation, namely the initiator protein DnaA, the origin of chromosome replication *oriC,* and the origin of binding proteins oriBPs, which coordinate the initiation with 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). We identified two topology- and ATP-dependent binding sites that may play important roles in DnaA assembly. Moreover, we observed that *H. pylori* has adopted a strategy similar to that of other known bacteria for DnaA box affinity regulation. The analysis of mutations introduced within the DUE indicates the importance of the DNA sequence and location of each submodule to *in vitro* DnaA binding and DUE opening. Our results show that interplay occurs between DnaA molecules bound to ssDNA and dsDNA. They thus contribute to the ongoing discussion of models of DnaA assembly on *oriC* and the initial steps of DNA melting. We performed the first systematic analysis of chromosome replication initiation in *C. jejuni*. Interestingly, unlike other *Epsilonproteobacterial oriC*s, the *C. jejuni oriC* is monopartite. The cluster of five DnaA boxes and the DUE were found in the *dnaA-dnaN* intergenic region. Binding of DnaA to this cluster of DnaA-boxes enabled unwinding of the DUE *in vitro*. However, it was not sufficient to sustain replication of minichromosomes, unless the cluster was extended by additional DnaA boxes located in the 3' end of *dnaA*. This suggests that *C. jejuni oriC* is the first bacterial origin extending into a coding region. *In vitro* DUE unwinding by DnaA was inhibited by Cj1509, an orphan response regulator. We expect that these studies will provide a basis for future research examining the structure and dynamics of the *C. jejuni* chromosome, which will be crucial for understanding the pathogens' life cycle and virulence.

2/ 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 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.

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

Studies of proteins regulating the autophagy process in Toll-like receptors signalling

Autophagy, due to its participation in the innate immune response and many immune processes, plays an important role in the neutralization of pathogens by the organism. This process is used by many types of immune cells, e.g. dendritic cells, monocytes, macrophages, and B lymphocytes. A parallel significant role of the autophagy and Toll-like receptors was observed in bacterial and viral infections. In addition, autophagosomes have been shown to be involved in the presentation of viral nucleic acids to the TLRs 7 and 9. Other obtained data indicate that LPS induces TLR4-dependent autophagy in macrophages. Although the phenomenon of autophagy is relatively well described, its function in the aspect of host immune processes requires a better understanding.

The results of the conducted research show that the Mal adapter protein interacts directly with the ATG16L protein, a component of a large protein complex necessary to create autophagosome. Experiments using the autophagy inhibitor 3-Methyladenine (3-MA - PI3 inhibitor) confirmed that this process is essential for activating the Herpes Simplex Virus 1-induced TLR9 signalling cascade. As a result of TLR9 stimulation with ligands and viral particles in the presence of 3-MA, a decreased level of cytokine mRNA was observed: IFNβ, TNF, and CCL5. A similar situation occurred in cells with the knockout gene for the Mal protein, which suggests that the interaction of the Mal protein with ATG16L is required for optimal receptor activity.

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

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

Our work is aimed at explaining at which stage of hematopoiesis and in which developmental lines the expression of VDR is activated and how the hormonal form of vitamin D regulates the differentiation of progenitor cells.

In the course of the work, transcription variants of the VDR gene found in blood cells have been identified. Using the 5'RACE PCR method, information was obtained on the VDR gene transcription start site in cells isolated from the bone marrow. The VDR gene expression profile at various stages of hematopoiesis was analysed. The expression of the VDR gene was tested before and after stimulation with vitamin D, ATRA or vitamin D, and ATRA using the Real-Time PCR method. Information on VDR, Cyp24a1, and Cyp26a1 gene expression was obtained in such cell populations as hematopoietic stem cells (HSC), common lymphoid progenitors (CLPs), common myeloid progenitors (CMPs), granulocyte progenitors (GMPs), as well as megakaryocyte-erythrocyte progenitors (MEP) progenitors. The level of methylation of the VDR gene promoter in lymphocytes and granulocytes isolated from the bone marrow were determined.

Our results have confirmed the presence of only one transcriptional variant of the VDR gene in mice.

During the experiments aimed at determining the VDR gene expression at various stages of hematopoiesis, we have shown that this gene is active in all studied populations except for common lymphoid progenitors (CLP). Autoregulation of the VDR gene promoter in hematopoietic stem and progenitor cells has been demonstrated. The lack of methylation of the VDR gene promoter was found in all of the cell populations studied.

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

Phenotypic and molecular characterization of *Spna2* dominant mutant mice: a new model of human cerebellar ataxias

Research project objectives/Research hypothesis

The project aims at characterizing the phenotype of a new mouse strain carrying a spontaneous point mutation of the *Spna2* gene (Spna2mut) encoding the alpha II chain of the non-erythrocytic spectrin. Unlike genetically engineered *Spna2* knockout mice, whose heterozygotes reveal no phenotype, and mutant homozygotes die at early embryonic stage, Spna2mut mice have a dominant-negative point mutation that is revealed in the heterozygous mice during the postnatal life in the form of gait disorders, ataxia, aggression, and splenic hypoplasia. Mutant homozygotes suffer from perinatal mortality with features of brain underdevelopment and multiple intracranial haemorrhages. Preliminary analysis shows that the expression of the alpha II chain of spectrin in heterozygotes of Spna2mut mice is normal. Therefore, the hypothesis assumes that the observed phenotype is due to the lack of necessary but not yet known interactions of the alpha II chain with other cytoskeletal proteins or interactions leading to transmission of signals critical for the development, proliferation, and differentiation of neurons and splenocytes.

Research project methodology

Mice in different age groups will be tested for motor coordination, muscle tone and strength, and aggressive behaviour. Immunohistochemistry, electron transmission microscopy, confocal microscopy, and flow cytometry will be used to characterize changes in the cerebellum, peripheral nerves, and primary and secondary lymphoid organs using a panel of specific antibodies to molecules expressed by neurons and innate/adaptive immune system cells. In addition, primary neuronal and fetal fibroblast cultures will be used to study protein-protein interactions, subcellular localization of spectrins, and functional studies on neurite outgrowth following stimulation with mimetic peptides against the NCAM molecule. Functional tests of the immune system including serum nitric oxide measurements after bacterial lipopolysaccharide challenge, adoptive transfer of labelled T lymphocytes to lymphopenic mice, and determination of effectiveness of immune response to defined antigens by ELISPOT and *in vitro* proliferation assays. To investigate novel interactions in the mutated region of the alpha spectrin chain, yeast two-hybrid system will be used as well as a recombinant bacterial fusion proteins will be produced for use in pull-down assay assisted by mass spectrometry-based protein identification.

Expected impact of the research project on the development of science

All previously produced complex research models lacking the expression of the alpha chain of non-erythrocytic spectrin in *Caenorhabditis elegans*, *Drosophila melanogaster*, *Danio rerio*, and *Mus musculus* showed mortality at early stages of larval or fetal development. In turn, the mouse carrying an in-frame deletion in a region of alpha II spectrin sensitive to proteolysis by calpain and caspase (ccc region) in the middle part of the molecule

did not show any abnormality. For this reason, Spna2mut mice that carry a mutation that retains a reading frame and changes only one amino acid residue in the central, highly evolutionary conserved region are unique. The position of the mutation highlights a domain that is novel and critical to maintaining the biological activity of the protein. Examining the mechanisms that govern the functioning of this domain may contribute to a better understanding of the functioning of the nervous and immune systems, which are fully developed only during postnatal life and also dramatically differ in their ability to proliferate and self-renew.

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

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

Protective effect of lactoferrin on apoptosis of WEHI 231 cells, induced by anti-Ig antibodies

We showed that antibodies directed against mouse immunoglobulins inhibited growth of WEHI 231, an immature B cell line, in a dose-dependent manner. Lactoferrin (LF) alone had no effect on cell viability. The cells exposed to LF prior to treatment with anti-Ig antibodies were protected to a significant degree against cell death. Determination of signalling molecule expression revealed a total block of caspase 3 and NF-κB1 expression in cells not treated with the antibodies, as well as a deep suppression of caspase 3, block of Fas, and a fourfold increase of NF-κB1 in cells preincubated with LF prior to exposure to the antibodies. In addition, differential changes in expression of interleukin 2 receptor (IL-2R) subunits upon 24h culture with LF were determined (loss of IL-2R function), indicating an induction of a cell differentiation process. In summary, the effect of LF on differentiation of WEHI 231 cells was found, correlated with increased resistance of these cells to anti-Ig induced apoptosis.

Studies on immunosuppressive activities of isoxazole derivatives in *in vitro* immunological models

Investigation of a new series of isoxazole derivatives was conducted. PUB1 and PUB6 compounds inhibited phytohemagglutinin A-induced proliferation of human peripheral blood mononuclear cells at a concentration of 100 and 10 μg/ml. Lipopolysaccharide (LPS)-induced tumour necrosis factor alpha (TNF α) production in human whole blood culture was inhibited by PUB6 but not by PUB1. In the human model of two-way mixed lymphocyte reaction, PUB1 was inhibitory at 50 μg/ml. Expression of signalling molecules in Jurkat cells revealed that in the case of PUB1, its suppressive activity *in vitro* was not associated with changes in caspase activity but rather with strong increases in expression of Fas and p53.

Evaluation of therapeutic utility of selected azaphenothiazines in mouse models

The therapeutic efficacy of azaphenothiazine derivatives, compound **5** (6-chloroethylureidoethyldiquino[3,2-b;2',3'-e][1,4]thiazine), and compound **4** (6-acetylaminobutyl-9-chloroquino[3,2-b]benzo[1,4]thiazine) was evaluated in several mouse models. The compounds, contained in ointment, were applied topically 24 hours after

elicitation of contact sensitivity to oxazolone in BALB/c mice. Protopic® served as a reference drug. The studied azaphenothiazines showed a high efficacy in diminishing antigen-specific inflammatory response of the skin (auricles), as determined by histological analysis and evaluation of systemic effects of the compounds on immune parameters. The compounds, applied topically, were also tested for their therapeutic potential in experimentally induced psoriasis in BALB/c mice. Clobederm® (a steroid) was used as a reference drug. The compounds also proved to be effective in this model by reducing inflammatory changes in the epidermis and skin. The compounds were devoid of side effects, in contrast to Clobederm®, which drastically distorted the blood cell composition and reduced the numbers of lymphocytes in blood and lymphoid organs. Compounds **4** and **5**, administered with a stomach tube, were also applied in dextran sulfate-induced colitis in C57Bl/6 mice, with 5-aminosalicylic acid (5-ASA) as a reference drug. The compound **4** also exhibited therapeutic properties in this model as assessed by a histological examination and by general condition and behaviour of mice. In turn, in the model of allogeneic skin transplantation between BALB/c and C57Bl/6 mice, compound **5** prolonged skin graft survival by 18.5%. In the studies, aimed at elucidation of the mechanism of action of the compounds, we showed that compound **5**, but not compound **4**, demonstrated proapoptotic action in tumour cell lines. The compound also inhibited the production of chemokines IL-8 and CXCL10 by an epidermal human KERTr cell line. On the other hand, both compounds strongly inhibited production of LPS-induced TNF α production in human whole blood cultures. In summary, these studies revealed for the first time the potential therapeutic utility of azaphenothiazines.

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, 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), and rs861537 (c.562-1162G>A) 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, and C___2983919_10, respectively).

All studied *XRCC3*tagSNPs genotypes in the controls as well as in CSCC patients were distributed with consistency with those expected from the Hardy-Weinberg Equilibrium model.

Univariate analysis showed that rs3212079 and rs3212102 SNPs were associated with CSCC. The genotype distribution at site rs3212079 varied significantly between CSCC patients and healthy cancer-free women ($p_{after\ Bonferroni\ correction} = 0.0006$). Moreover, one copy of [G] is enough to modify the risk when the dominant model was applied ([GG]*vs.*[AA]+[GA], p=0.0002). Similarly, different genotype distribution between the analysed groups was seen in case of tagSNP rs3212102.

Global haplotype distribution of all studied *XRCC3*tagSNPs differed statistically between CSCC patients and healthy cancer-free women ($\chi^2_{Global,df=5}$=17.95, $p_{Global,\ Bonferroni\ correction} = 0.003$), and haplotype rs3212079[A]/rs3212102[C]/rs861534[T]/rs861537[T] 6.27-fold increased risk of CSCC development ($p = 0.0006$).

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.

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 predictor factors.

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

Immunological mechanisms associated with reproductive processes in health and disease

TLR receptors and costimulatory molecules gene expression of spleen B (CD19+) lymphocytes in abortion-prone female mice

The presence of an embryo and a fetus influence peripheral immunity in pregnant females.

It may be assumed that a mother's peripheral response of the immune system, similar to a local immune reaction for the presence of the conceptus, leads to establish maternal tolerance towards an antigenically foreign fetus. Both the induction mechanisms and the effects of paternal antigens stimulation on the development of specific tolerance are not well recognized. Our previous experiments have shown that during early pregnancy, costimulatory phenotype of spleen antigen presenting cells is modulated by the presence of pre-implantation embryo (Slawek et al., 2013). On the other hand, the costimulatory effect of antigen presenting cells on lymphocyte activation and differentiation into tolerogenic phenotype is regulated by antigen recognition with an involvement of TLR receptors.

The aim of this study was to investigate the level of toll-like receptors (TLR) 2,4 and 9, costimulatory molecules (CD80, CD86, and CD40), and MHCII gene expression in spleen CD19+ B lymphocytes at third day of pregnancy of abortion-prone female mice (♀CBA/Jx♂DBA/2J) in comparison with control pregnant mice (♀CBA/Jx♂BALB/c). We have shown a statistically significant increase of gene expression of TLR9 receptor compared to females in normal pregnancy (♀CBA/Jx♂BALB/c) in the pre-implantation period of pregnancy. We also observed, on the same cell population, augmentation in the expression of MHC II and CD86 genes. This suggests that splenic B cells are able to activate naive T cells via this molecule. Because the TLR9 receptor is able to recognize not only pathogen associated molecular patterns but also own antigens, we suppose that B lymphocytes ($CD19^+$) are capable of recognizing male antigens via TLR receptors (TLR9). In our study, the TLR9

receptor activation signal was not derived from pathogens, because all mice were kept under the same SPF (specific pathogen-free) conditions. Moreover the examined composition (3-OH fatty acid analysis using gas chromatography tandem mass spectrometry) and the intestinal microbial metabolic profile (short chain fatty acid analysis), which may provoke PAMPs recognition, did not change in either group in 3dpc. Also, expression of the TLR4 receptor gene (recognizes bacterial LPS) and the TLR2 receptor in the studied cell population was not altered in DBA/2J-mated and BALB/c-mated females.

In conclusion, we hypothesized that in pre-implantation pregnancy of abortion-prone female mice, the increased expression and presumably activation of TLR9 receptor lead to development of activating instead of tolerogenic costimulatory phenotype of splenic B cells.

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 role of phages and bacterial surface glycoconjugates and protein antigens in immune response, as well as studies of probiotic proteins and glycoconjugates, structure, and role in immunity

Our laboratory focuses on studies that concern mechanisms of pathogenicity of diseases with bacterial etiology, the role of bacterial glycoconjugates and proteins in the immune processes, and the structure and functions of bacterial exopolysaccharides, including these from probiotics. Studies of the OmpC protein recognized by umbilical cord serum have revealed that cyclic hexapeptide mimicking epitope on OmpC protein, when coupled with carrier protein, is a useful diagnostic tool for determining specific humoral immune deficiencies in children. Studies on dual-function tubular proteins of bacteriophages have revealed that tail proteins of these bacteriophages possess structural and enzymatic functions. Studies of antibacterial and other biological functions continue, as well as studies of mechanisms of enzymatic activity of such phage proteins. Regarding the studies of advanced glycation end-products (AGE), a mouse monoclonal antibody of IgE class was purified with affinity column on protein L. AGE were determined to be a marker of tissue damage due to exposure to dioxins. We have shown serious developmental distortions and increased AGE level in chicken embryos, while the use of vitamin E, acetylsalicylic acid or combination of both factors inhibited the formation of AGE in embryos and caused reductions of the level of distortion caused by dioxins. Determination of the level of this antigen in different clinical cases allows for the understanding of the biology of these advanced glycation end-products and their significance in pathology. It also provides new information related to mechanisms of disease. Other studies have indicated that exopolysaccharides of probiotics express the potential to modulate the immune system. Our results about structure and function of probiotic polysaccharides from *Lactobacillus* are pioneering studies in the world towards the understanding the role in immune system activation. We have shown that polysaccharide from *Lactobacillus* is able to modulate immune response of other antigens. Results of anti-allergic properties of polysaccharide from one *Lactobacillus* strain have practical significance for potential therapeutics. Immunochemical studies are crucial for understanding biological functions and interactions of bacteria with host and bacteria with other microorganisms.

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

Contemporary neurobiology, periodontal medicine, and immunology are now focusing on the relationship between chronic periodontitis and systemic diseases, including Alzheimer's disease (AD). A causative relationship between dementia and periodontitis, however, has yet to be confirmed. The aim of the study was to determine whether periodontal health status and cognitive abilities are correlated with the relative changes in systemic measures of pro- and anti-inflammatory cytokines as a reflection of systemic inflammation. We hypothesized that poor periodontal health may be associated with cognitive impairment and dementia via the exacerbation of systemic inflammation. Based on the periodontal and psychiatric examinations and the cytokine levels produced by unstimulated and LPS-stimulated PBL isolated from 128 research participants, we have examined whether the coexistence of these two clinically described conditions may influence systemic inflammation. Mini-Mental State Examination (MMSE) and Bleeding on Probing (BoP) test results were combined into the one mathematical function U, which determines the severity of specific condition, called Cognitive and periodontal impairment state. Similarly, the levels of cytokines were combined into the one mathematical function V, whose value determines the level of inflammatory state. The correlation between U and V was determined. These results confirm that the presence of cognitive decline and the additional source of pro-inflammatory mediators, such as periodontal health problems, aggravate systemic inflammation. It is most likely that the comorbidity of these two disorders may deepen cognitive impairment, and neurodegenerative lesions and advance to dementia and AD. The results were published in *Current Alzheimer Research, 2017; 14: 978-990*.

Betulin derivatives containing a 1,2,3-triazole ring possess a wide spectrum of biological activities, including antiviral, anticancer, and antibacterial activity. A series of novel triazoles was prepared by the 1,3-dipolar cycloaddition reaction between the alkyne derivatives of betulin and organic azides. The chemical structures of the obtained compounds were defined by 1H and 13C NMR, IR, and high-resolution mass spectrometry (HR-MS) analysis. The target triazoles were screened for their antiviral activity against DNA and RNA viruses. The cytotoxic activity of the obtained compounds 5a–k and 6a–h was determined using five human cancer cell lines (T47D, MCF-7, SNB-19, Colo-829, and C-32) by a WST-1 assay. The bistriazole 6b displayed a promising IC50 value (0.05 μM) against the human ductal carcinoma T47D (500-fold higher potency than cisplatin). The microdilution method was applied to evaluate the antimicrobial activity of all of the compounds. The triazole 5e containing a 30-deoxythymidine-50-yl moiety exhibited antibacterial activity against two gram-negative bacteria, *Klebsiella pneumoniae* and *Escherichia coli* (minimal inhibitory concentration (MIC) range of 0.95–1.95 μM). The results were published in *Molecules, 2017; 22: 1876*.

The reaction of bis[(2-chlorocarbonyl)phenyl] diselenide with various mono- and bisnucleophiles such as aminophenols, phenols, and amines have been studied as a convenient general route to a series of new antimicrobial and antiviral diphenyl diselenides. The majority of compounds demonstrated high levels of activity against human herpes virus type 1 (HHV-1) and moderate activity against encephalomyocarditis virus (EMCV). They were generally inactive against vesicular stomatitis virus (VSV). The results were published in *Molecules, 2017; 22: 974*.

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

Laboratory of General Immunochemistry
Head: Professor Maria Janusz, Ph.D.

Neuroprotective properties of the naturally derived polypeptide complexes

1. Study the effect of yolkin polypeptide complex on p38 kinase activation under oxidative stress on the PC12 Tet On cell line model

2. Study the effect of yolkin polypeptide complex on regulation of the inflammatory response. Effect of nitric oxide secretion and iNOS activity on murine bone marrow-derived macrophages BMDM

Egg yolk proteins are considered a rich source of nutrients. Among these proteins, yolkin plays an important role. Yolkin is a polypeptide complex with properties similar to colostrum-derived proline-rich polypeptide complex PRP/Colostrinin. Yolkin demonstrates immunoregulatory activity, and its polypeptides were found to be strong inducers of cytokines secretion. Yolkin also may mitigate the behavioural symptoms of aging, and support cognitive learning and memory in rats. The neuroprotective effect of yolkin is connected with its positive effect on cell viability and BDNF production/secretion.

The deposits of pathological forms of proteins accumulating in the brain induce an inflammatory reaction. This reaction is accompanied by the secretion of large amounts of pro-inflammatory cytokines and reactive oxygen and nitrogen radicals. The consequence of oxidative stress induced by β-amyloid protein is, among others, activation of signalling pathway dependent on p38 kinase controlling the process of apoptosis of nerve cells. To consider the mechanism of neuroprotective yolkin action in neurodegenerative processes, its effect on p38 protein kinase activity was examined. As a model, rat pheochromocytoma cell line PC12 Tet On was used. It has been shown that both yolkin alone and yolkin applied to the cells simultaneously with hydrogen peroxide had no effect on p38 kinase activity.

The stimulation of innate response is regarded as one of the important strategies to enhance the body's defence systems, especially in the elderly and cancer patients. Activated macrophages produce a wide spectrum of proinflammatory factors. Among them nitric oxide (NO) is one of the most important due to its biological function, e.g. immune regulation, cell differentiation, apoptosis or defence against tumour cells or microorganisms. To consider the potential immunomodulatory activity of yolkin, its effect on iNOS activation and NO production was checked. As a model, bone marrow mouse macrophages BMDM were used. BMDM were stimulated *in vitro* with crude yolk fraction (containing both IgY and yolkin), IgY, and yolkin samples (yolkin after Sec and two yolkin fractions obtained by HPLC: $M_w \geq$ 25 kDa and $M_w \leq$ 35 kDa). It was found that yolkin and its fractions stimulated BMDM cells to release significant amounts of NO. No stimulatory effect was observed to crude yolk fraction and IgY. It has been also shown that this process is dependent on iNOS induction.

The results obtained shown that yolkin polypeptide complex might be used as a potential immunostimulator.

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

Expression and characterization of *Plasmodium falciparum* EBA-181 merozoite ligand

Erythrocyte binding-antigens (EBA) play a crucial role in the attachment of merozoites to human erythrocytes by binding to specific receptors on their surface. Four functional *P. falciparum* EBA proteins were identified: the erythrocyte binding ligand EBL-1 that binds glycophorin B; the erythrocyte binding antigens EBA-140 and EBA-175 that target the glycophorin C and A, respectively; and EBA-181, which is the subject of our study due to the fact that its receptor remains unknown.

Based on our experience, we attempted to obtain the *P. falciparum* EBA-181 ligand, using the baculovirus expression system. The recombinant baculovirus coding for *P. falciparum* EBA-181 binding region (Region II) was ordered from Genescript. The EBA-181 Region II sequence from 3D7 parasite strain with known polymorphism in nonconserved region (RVNKN) was chosen based on literature review. Two tags were added to this sequence on C-terminus: his-tag and c-myc. Expression was performed in insect cells, line High Five™ from *Trichoplusia ni*, which are available in our laboratory. Optimal conditions, such as time of expression (48 hours) and the most suitable multiplicity of infection (MOI 5), were used. The presence of the recombinant protein in culture supernatant was confirmed by Western blotting using anti-myc and anti-his monoclonal antibodies. Large-scale expression (400 ml) was performed to obtain sufficient quantities of recombinant protein for further studies. One-step purification from cell culture medium was performed using NiNTA affinity chromatography.

Binding of partially purified recombinant Region II of EBA-181 ligand to native human erythrocytes as well as erythrocytes treated with enzymes was estimated using the FACS technique. We confirmed that recombinant protein was functional and specific. Because the purity of obtained recombinant Region II based on SDS-PAGE assay was not satisfactory, we decided to improve the new expression system using HEK 293E mammalian cells in order to enhance yield and purity of recombinant EBA-181 Region II for further studies.

Laboratory of Microbial Immunochemistry and Vaccines
Head: Professor Czesław Ługowski, Ph.D.

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

Plesiomonas shigelloides, Citrobacter, and *Edwarsiella tarda* represent opportunistic human and animal pathogens associated with gastroenteritis and extraintestinal infections in humans. Moreover, *P. shigelloides* and *E. tarda* are frequent pathogens of farmed fish. In contrast to other Gram-negative bacteria, these species are still poorly characterized when taking into account the relationship between the activity and structure of lipopolysaccharide (LPS, endotoxin), the main virulence factor of Gram-negative bacteria. Moreover, all the aforementioned species microorganisms that require better characterization of genetic background of LPS biosynthesis.

In 2017, we focused on two important aspects of *P. shigelloides* LPS. The report on the influence of lipid A structure on LPS *in vitro* activity was provided for the first time for this species (Kaszowska et al. Front. Immunol. 2017). Four native preparations differing in lipid A composition were selected as a result of structural screening among 85 strains

representing different O-serotypes. They were analysed for their ability to induce proinflammatory cytokines (TNF-α, IL-1β, and IL-6) *in vitro* by in human and murine macrophages. We showed that *P. shieglleoides* lipids A represent highly immunostimulatory structures despite the presence of shorter acyl chains and unsaturated acyl residue (16:1). Secondly, we continued structural analyses into the diversity of *P. shigelloides* O-antigens, identifying a strain CNCTC 78/89 of O12 serotype characterized by modified D-galactan-I of *Klebsiella pneumoniae* O2. The modification, which was attributed to nonstoichiometric O-acetylation (~32%), did not influence cross-reactivity of O12-specific sera with *K. pneumoniae* O2 LPS. High-resolution magic angle spinning nuclear magnetic resonance spectroscopy (HR-MAS NMR) was used as an analytical tool to speed up comparative analysis of relevant strains of *P. shigelloides* and *K. pneumoniae* (samples of bacteria and LPS).

Regarding *Citrobacter* LPS, we provided new data supporting the reclassification of selected strains in terms of appropriate O-serotype assignment within O6, O2, O3, and O8 serotypes (Katzenellenbogen et al. BMC Microbiol. 2017).

Finally, the LPS core oligosaccharide structure and genomics of *E. tarda* strain EIB 202 were studied for the first time, including the complete biosynthesis gene assignment and functions (Kaszowska et al. Int J Mol Sci. 2017).

Publications – 2017

Articles published in the journals from Thomson Reuters Master List:

1. Al-Wrafy F., Brzozowska E., Górska S., Gamian A.: Pathogenic factors of *Pseudomonas aeruginosa* - the role of biofilm in pathogenicity and as a target for phage therapy. Post Hig Med Dosw. 2017;71(0):78-91 **IF 0.690 (15 pkt MNiSW)**
2. Antoszczak M., Maj E., Borgström B., Oredsson S., Huczyński A., Wietrzyk J., Strand D.: Bivalent polyether ionophores: Synthesis and biological evaluation of C2-symmetric salinomycin dimers. Tetrahedron Letters. 2017;24:2396-2399 **IF 2.193 (25 pkt MNiSW)**
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