Final Report Summary - HARC (Healthy Ageing Research Centre)

Executive Summary:
The general concept of the project was developed in response to the increasing need for addressing the problems of ageing population in the Lodz region, Poland and worldwide. HARC brings together a group of 15 internationally recognized researchers of the Medical University of Lodz (most of them heading the University departments) and was dedicated to further development of research focusing on major areas relevant to active and healthy ageing: novel approaches to improve well-being in the elderly, pathogenesis and prevention of neurodegenerative, respiratory, cardiovascular and kidney diseases of the old age and molecular basis of ageing.

The major goal of the project was to upgrade the research potential of research groups at the Medical University of Lodz investigating various aspects of healthy ageing and constituting already established Healthy Aging Research Centre.

During the timeline of the project a significant progress in upgrading and enhancing the research potential of HARC as the entity, as well as individual research groups constituting HARC have been achieved. HARC research on the elderly, ranged from molecular biology to clinical studies, covered a large spectrum of research hypotheses and were conducted in collaboration with international partners. Although the RegPot project did not provide to HARC any direct funding for development of new research projects it was essential for development of several activities supporting on-going research activity. Twinning with international partners allowed for training of HARC scientists in new research techniques for introduction of new technologies to HARC laboratories. This partnership resulted in development of collaborative projects based on already available funding, and allowed for join applications for research funding. Collaboration with international partners resulted in several original join publications. HARC scientists together with international partners were involved in 18 new applications for international research projects, related to the AHA within the Horizon 2020 EU program and others. Within the duration of the projects new researchers with international experience, representing expertise in specific areas of HARC research were recruited. Assisted by newly recruited technicians they have been directly involved in particular research projects significantly enhancing the group research potential. In the same time research infrastructure of HARC groups was significantly upgraded by purchasing up-to-date research equipment from the project funds. HARC researchers activity was promoted by presenting 41 abstracts with original data and 10 invited lectures at 33 international conferences and by organizing two international conferences on “Translational Research in Healthy Ageing” and eight thematic workshops which brought to Lodz over 150 international speakers and more than 1500 participants. Among the most important and spectacular achievements of the HARC we consider the successful application of the Medical University of Łódź to the important initiative of European Institute of Technology (EIT) dedicated to create a Knowledge and Innovation Communities (KIC) HEALTH. Partnership of the Medical University in the INNOLIFE EIT HEALTH is the major step to enhance an international potential of HARC since it gives the group an access to the strongest consortium dedicated to research on active life and healthy ageing in European Union, with timeline to 2030. It may significantly stimulate and enhance MUL healthy ageing research, helping in maintaining sustainability and improving the competitiveness, thus creating new opportunities for collaboration with business.

In conclusion during the project duration the scientific excellence of HARC consortium and the HARC researchers have been significantly improved and achieved international recognition.

Project Context and Objectives:
Healthy Ageing Research Centre (HARC) brings together a group of 15 internationally recognized researchers of the Medical University of Lodz (most of them heading the University departments) and dedicated to further develop research focusing on major areas relevant to active and healthy ageing. The aim of the project was to jointly enhance the development of the Centre’s scientific excellence and unlock its innovation potential in order for HARC to become a top-level,
Chronic respiratory, kidney and cardiovascular disorders are among the most common comorbidities in the elderly. Asthma and Chronic Obstructive

Research Area 3: Neurodegenerative diseases as misfolded protein disorders

This area covered one major research theme:

Research Theme 1. Influence of muscle power and nutritional status on functional capacities and well-being in the elderly;

Therefore, the final goal of enhanced nutritional state and functional status is the improvement of life and well-being in the elderly population.

Both nutritional status and muscular fitness are predictors of functional capacity in advanced age. Functional status, and, more particularly, capacity to perform basic and instrumental activities of daily living are the most important determinants of quality of life and well-being in the elderly. Comparison of different methods of estimating power of the most important muscle groups and its contribution to preserve function in the elderly would give novel important insights into more preventive and rehabilitative strategies in this population. Taking into account a nutritional status and considering different subgroups of older people (e.g. patients with cardiovascular, respiratory, musculoskeletal disorders, dementia) it would enable better treatment and rehabilitation planning.

The eight teams collaborate on project objectives and activities divided in the four Research Areas:

Research Area 1: Novel approaches to improve well-being in the elderly

Both nutritional status and muscular fitness are predictors of functional capacity in advanced age. Functional status, and, more particularly, capacity to perform basic and instrumental activities of daily living are the most important determinants of quality of life and well-being in the elderly. Comparison of different methods of estimating power of the most important muscle groups and its contribution to preserve function in the elderly would give novel important insights into more preventive and rehabilitative strategies in this population. Taking into account a nutritional status and considering different subgroups of older population (e.g. patients with cardiovascular, respiratory, musculoskeletal disorders, dementia) it would enable better treatment and rehabilitation planning. Therefore, the final goal of enhanced nutritional state and functional status is the improvement of life and well-being in the elderly population.

This area covered two major research themes:

Research Theme 1. Influence of muscle power and nutritional status on functional capacities and well-being in the elderly;

Research Theme 2. Nutritional status and body composition in the demented elderly as predictors of quality of life.

Research Area 2: Neurodegenerative disorders in the elderly

Neurodegenerations are chronic, progressive, debilitating diseases that are increasing in prevalence in Europe. Their treatment is, at the very best, only symptomatic, since no specific curative therapies are available. As a result, they present an increasing burden of utmost social impact in aging European societies. The major focus of this group will be newfound knowledge on the etiology and pathogenesis of neurodegeneration particularly the role of toxic proteins, the formation of pathogenic deposits both inside and outside the cell, and the role of neuroinflammation and neuronal stem cells. Furthermore, there will be searched for novel mutations and polymorphism of putative pathogenetic significance. This research will contribute to an expanded classification of neurodegenerative disorders for both clinicians and diagnostic neuropathologists, allowing the identification and selection of new targets for therapeutic intervention.

This area covered one major research theme:

Research Theme 3. Neurodegenerative diseases as misfolded protein disorders

Research Area 3: Pathogenesis and prevention of respiratory, kidney and cardiovascular diseases of the old age

Chronic respiratory, kidney and cardiovascular disorders are among the most common comorbidities in the elderly. Asthma and Chronic Obstructive
Pulmonary Disease (COPD) are progressive inflammatory diseases of the airways, and their course may be complicated by various co-morbidities (i.e. ischaemic heart disease, heart insufficiency, diabetes, osteoporosis, lung cancer, depression and cognitive disorders). Current tools used for prevention of exacerbations and for routine monitoring of these diseases focus mainly on the parameters describing functional status of the respiratory system, and do not cover other aspects of these complex diseases. Therefore, there is a need for new approaches including continuous monitoring of patients’ well-being and airway function and further assessment of immunological status (including increased susceptibility to infections). Furthermore, COPD, coronary artery disease and chronic heart failure occur commonly and are associated with similar systemic inflammatory reactions. One of important factors leading to development of cardiovascular disease, particularly in elderly patients, is a nondiagnosed and untreated renal disease. Early detection and elimination of risk factors for development chronic kidney disease may allow for prevention of development of cardiovascular diseases.

This area covered three major research themes:


Research theme 5. Molecular and immunological determinants of increased susceptibility to respiratory infections in elderly patients with chronic respiratory diseases.

Research theme 6. Hampering the progression of chronic kidney disease and subclinical organ damage as a prevention of cardiovascular complications in elderly people with and without hypertension.

Research Area 4: Molecular basis of ageing

Several molecular mechanism are involved in cell senescence. This groups will focus on two selected issues: 1) different aspects of molecular mechanisms regulating adhesion and migration of endothelial cells during angiogenesis induced by different agent and 2) oxidativewtress-induced DNA damage and dysfunctional telomerases in the pathogenesis of atherosclerosis. The teams are particularly interested in the role of integrin receptors and plasminogen activator inhibitor type 1 (PAI-1) in cancer cells, searching for mechanisms increasing their invasiveness. The second area of molecular research will focus on DNA interactions with other biomolecules, elaboration of molecular mechanisms of oxidative stress, causing atherosclerosis, an intrinsically agerelated disease. Premature atherosclerosis is a feature of several human diseases that are known to be defective in DNA repair pathways and characterized by predisposition to early onset of age-related diseases. Department of Structural Biology for many years conducted research on the molecular aspects of gestational diabetes mellitus (GDM), which is an excellent research model of type 2 diabetes primarily affects older people. Lipidomics is a relatively new branch of science whose objective is to characterize lipid occurring in living organisms, their interactions and biological functions. These data are then integrated with the knowledge of their protein targets and the corresponding genes.

This area covered two major research themes:

Research theme 7. Modulation of vascular endothelial cell senescence in ageing - integrins in endothelial cell senescence


In order to integrate research across the whole consortium a project on comorbidity was developed and financed by MUL.

Project Results:

HARC project allowed for enhanced integration of research consortium and extended collaboration with international partners resulting in achieving significant progress in research. The following are the main scientific achievements of the partners involved in HARC.

RESEARCH AREA 1: NOVEL APPROACHES TO IMPROVE WELL-BEING IN THE ELDERLY

Research Theme: 1. Influence of muscle power and nutritional status on functional capacities and well-being in the elderly

Theme leader: Prof. Tomasz Kostka

Overall aims: Research of the theme focused on nutritional status and muscular fitness as predictors of functional capacity in advanced age. Functional status and ability to perform activities of daily living are the most important determinants of quality of life in the elderly. Several cohorts of older subjects were recruited These cohorts were characterized clinically and with respect of nutritional status and muscular fitness.

Major achievements:

1) In disabled patients with multiple comorbidities undergoing conventional rehabilitation, quadriceps muscle power and optimal shortening velocity (υopt) are more important predictors of baseline functional status than muscle strength. Quadriceps muscle strength and power as well as optimal shortening velocity (υopt) were assessed pre- and post-rehabilitation. With rehabilitation, patients improved the values of strength, power and the results of all functional tests. Both baseline and post-rehabilitation functional status was more strongly related to power and υopt than to strength. However, functional gains obtained with rehabilitation were not related to changes in power or υopt, and only very modestly related to changes in strength.

2) Both assessed Nutritional Assessment Short-Forms (MNA-SFs) can be recommended as screening tools in assessing the nutritional state of the community-dwelling and institutionalised elderly in Poland. We assessed the usefulness in different populations of elderly people in Poland of both modified versions of Mini Nutritional Assessment Short-Forms (MNA-SFs) with a three-category scoring classification: one using BMI (MNA-SF-BMI) and another using calf circumference (MNA-SF-CC). Both MNA-SFs can be recommended as screening tools in assessing the nutritional state of the community-dwelling and institutionalised elderly in Poland. The full version of the MNA confirmed the results of MNA-SFs in this group. The “classic” MNA-SF using BMI was found to perform better than the MNA-SF-CC. The MNA-SF-CC should be used only when measuring BMI is not possible. While using MNA-SF-CC in nursing homes, a higher MNA-SF-CC cut-point of eleven should be rather used in this population to screen for “at risk/malnutrition”.

3) Overweight/obesity measures are different predictors of health-related quality of life (HRQL) in community-dwelling and in institutionalised elderly. We estimated the potential association of three distinct nutritional status measures (body mass index – BMI, calf circumference (CC) and the Mini Nutritional Assessment - MNA) with health-related quality of life (HRQL) assessed with Euroqol 5D questionnaire in different populations of elderly people in Poland. BMI and CC as overweight/obesity measures were independent predictors of lower HRQL in urban and rural community-dwelling seniors and higher HRQL in institutionalised elderly. Poor nutritional state as measured with MNA was a similar determinant of well-being in all three environments. This different relationship of popular overweight/obesity measures to HRQL should be taken into account while designing care for older people.

4) More than 90% of the Polish older population does not cover the demand for calcium, potassium, vitamin D, folic acid and α-linolenic acid. It was slightly better in case of the level of intake of polyunsaturated fatty acids, sodium, magnesium, fiber, potassium, vitamin D, folic acid and α-linolenic acid.
water and vitamin C. The appropriate level of their intake was found in 15-40% of subjects. The most important deviations in underlying disorders were found for the intake of sodium, polyunsaturated fatty acids, particularly DHA, vitamin C, iron, fiber, lauric acid, and sucrose.  

5) Bioelectrical impedance analysis (BIVA) may be used as an auxiliary method in diagnosing of sarcopenia among hospitalized older women. The European Working Group of Sarcopenia in Older People (EWGSOP) algorithm using two different muscle mass criteria was applied and among misclassified subjects we used BIVA parameters to verify the prevalence of sarcopenia. The prevalence of sarcopenia ranged between 60.7% and 79.8% according to the two suggested different muscle mass cutpoints. Seventeen subjects mismatched according to used muscle mass cutpoints were further analyzed individually on the basis of their mean BIVA parameters. The location of the confidence ellipse of misclassified women overlapped with the women group diagnosed as “nonsarcopenic”, while sarcopenic group was statistically different.  

6) Quadriceps muscle power (Pmax) and optimal shortening velocity (υopt) are more important correlates of functional abilities (FA) of older adults than handgrip strength. We assessed the relative role of handgrip strength (HGS), quadriceps muscle power (Pmax) and optimal shortening velocity (υopt) in maintaining functional abilities (FA) in older adults living in a long-term care home over a one-year follow-up. The 1-year period of physical inactivity among older institutionalized adults was found to have a negative effect on their FA, Pmax and υopt. The study demonstrated that Pmax and υopt are more important correlates of FA of older adults than HGS, both at baseline and at follow-up. Despite this, 1-year natural fluctuations of FA, Pmax and υopt were not significant enough to influence FA in inactive, institutionalized older adults.

Major publications:

Research Theme 2. Nutritional status and body composition in the demented elderly as predictors of quality of life.

The main area of interest for the Partner are relationships between dietary patterns, nutritional status and body composition in the elders as predictors of quality of life. The second area of interest is evaluation of nutritional status, body composition and diet as the risk factors of cognitive decline. For those purposes the Nutrition and Dementia Project was launched. The aim of this prospective, observational study is to determine the influence of dietary patterns, nutritional status and body composition (with an evaluation of visceral fat) in Polish elderly subjects with mild cognitive impairment, mild dementia and healthy controls on cognitive functions and the risk of cognitive impairment. Project was conducted in the Department of Old Age Psychiatry and Psychotic Disorders of MUL and Department of Medical Psychology of MUL.

Over 240 European Caucasian subjects (control subjects, and mild cognitive impairment subjects) were included into the observational study so far. Recruitment of demented cases is ongoing. For all of the cases biological samples were collected and were transferred to HARC BioBank. On April 2016 we started follow-up visits for cases recruited 2 years ago.

Preliminary results of the study were presented and are prepared for presentation during congresses. Data from baseline visits are under analysis and prepared for publications.

We started international research cooperation with Prof. Patrizia Mecocci, Dr Carmelinda Ruggiero (Department of Medicine, Institute of Gerontology and Geriatrics, University of Perugia, Italy), Prof. Manfred Müller, Dr Corinna Geisler (Institute of Human Nutrition, Kiel University (CAU), Germany), Prof. Magda Tsolaki (Department of Neurology at the Aristotle University of Thessaloniki, Greece).

Major publications:

RESEARCH AREA 2: NEURODEGENERATIVE DISORDERS IN THE ELDERLY

Research Theme: 3. Neurodegenerative diseases as misfolded protein disorders

Theme leader: Prof. Pawel Liberski, Assoc. Prof. Beata Sikorska

Main goals: Our studies were based on neuropathology and molecular pathology of neurodegenerative diseases. The main target of this study was evaluation of co-localization of different misfolded proteins with PrP as protein “capture”. In this project we analysed co-morbidity of prion diseases and other neurodegenerations searching for various misfolded proteins in the human brain. The colocalization of misfolded proteins was studied in human brains by laser confocal microscopy. Our main aims were:  

- Studies of co-morbidity of prion diseases and neurodegenerative disorders  
- Study of co-localizations of PrP and various proteins (tau, amyloid-beta, alpha-synuclein, TDP42, p62 and others)
Major achievements:

1. To evaluate the utility of telemonitoring in the assessment of the upcoming COPD exacerbations in the elderly
2. To look for and to define the influence of underrecognized comorbidities of COPD and to evaluate their influence on the disease course

Major publications:


RESEARCH AREA 3 PATHOGENESIS AND PREVENTION OF RESPIRATORY, KIDNEY AND CARDIOVASCULAR DISEASES OF THE OLD AGE

Theme leader: Prof. Pawel Gorski

Main goals:
1. To evaluate the utility of telemonitoring in the assessment of the upcoming COPD exacerbations in the elderly
2. To look for and to define the influence of underrecognized comorbidities of COPD and to evaluate their influence on the disease course

Major achievements:

1. Elaboration of the protocol for the monitoring of COPD patients. We collected data form 20 COPD patients (50 episodes of exacerbations, minimal monitoring period – 6 months). Preliminary results show, that vital signs and respiratory function are not predictors of upcoming COPD exacerbation. Only aggravation of symptoms and loss of compliance seem to be reliable predictors.
2. The best possible management of COPD exacerbations was a subject of an extended metaanalysis, in which we point out to some new aspects of non-invasive ventilation.
3. The study on skin abnormalities in COPD patients as an underrecognized systemic manifestation of the disease is completed. The study was performed in cooperation with Department of Immunology (Psychoimmunology Unit).
4. We are in the process of collecting the COPD cohort above 65 years of age for the study on COPD comorbidities and disease phenotypes.

Major publications

Published:

Accepted:

In preparation:
2. Role of mitochondria and oxidative-antioxidative imbalance in pathobiology of chronic obstructive pulmonary disease
4. Platelet Distribution Width as a prognostic factor in chronic obstructive pulmonary disease

Research theme 5. Molecular and immunological determinants of increased susceptibility to respiratory infections in elderly patients with chronic respiratory diseases.
Theme leader: Prof. Marek L. Kowalski

Overall aims: Research of the theme focused on pathogenies of respiratory infections in the elderly patients and addressed immunological, and genetic determinants of increased susceptibility to infections. Large cohorts including both elderly and non-elderly subjects (from general population and patients with bronchial asthma) were recruited. These cohorts were characterized clinically (including comorbidities) and with respect of immunological status.

Major achievements:

1. Frequent infections among elderly are associated with certain comorbidities and medications used.

   At least one infection of respiratory system during last year were reported by 71% of elderly subjects (mean number of infections 3.2). Herpes simplex infection was reported by 40% of subjects (mean number 0.9) and 32% study participants had urinary tract infections (mean number 0.74). At least one course of antibiotics during past year were reported by 37% of elderly, and 2% of study subjects were hospitalized due to infection. The risk factors for frequent respiratory infections were: inflammatory arthritides and polytherapy. Frequent urinary tract infections was associated with diabetes and anti-diabetic treatment.

   Comorbid conditions among these patients were highly prevalent with average 2.76 per patient. As many as 84% of the study subjects suffered from two or more chronic diseases and almost one-third of patients reported five or more comorbid conditions. The average number of all medications used by one study subjects was 5.3 ± 3.69 (range: 0-16) and almost one third (33.1%) of study subjects used a five or more prescription drugs.

2. IFN-λ4-generating ΔG allele protects from atopy older women, but not women below 50 yr of age.

   We have demonstrated that recently described the ΔG allele of interferon lambda gene polymorphism has protective effect against atopy in the older women (aged >50 yr) with OR= 0.379 (95% CI= 0.198-0.724) which is absent in the younger age women's sub-group(<50 yr). Older women with at least one copy of the IFN-λ4-generating ΔG allele were more likely to show a positive reversibility test (OR= 2.58) and also less likely to be treated with iCS (OR= 0.35) and oCS (OR= 0.16) therapy, suggesting that they had less severe asthma compared to the women who had two copies of TT alleles.

3. Induced sputum in elderly and non-elderly patients with stable asthma demonstrate similar pattern and detection rates of respiratory viruses and bacteria.

   Several viruses and bacteria strains were detected in the sputum, and the profile of pathogens detected was similar in elderly and non-elderly subjects. Two or more viruses were present in sputum samples of 13/29 (44.8%) study subjects. The bacterial – viral co-infections were detected in 21/29 (72.4%) asthmatics. Inflammatory cell counts were different in the elderly as compared to non-elderly asthma groups. Elderly patients displayed significantly higher eosinophilia and lower macrophage and lymphocyte counts in the induced sputum than younger. In elderly asthmatics RSV infection was associated with lower ventilator levels (FEV1 % pred and FVC% pred).

4. Differential mechanisms of inflammatory cell recruitment during viral-induced asthma exacerbations in elderly as compared to non-elderly asthmatics.

   We documented that during asthma exacerbation, as compared to recovery, a significant increase in the TLR-4 expression on eosinophil progenitors in the in elderly patients (p=0.032) and on basophil progenitors in non-elderly patients (p=0.03) occurred. The expression of TLR-4 on basophil progenitors during asthma exacerbation was lower in the elderly patients as compared to non-elderly asthmatics (p=0.04).

5. Cytomegalovirus DNA is prevalent in the whole blood of the elderly asthmatics and is associated with the risk of bronchial asthma.

   CMV seropositivity in elderly population is considered to be a part of immune risk phenotype and may be associated with increased morbidity and mortality.

   We presented that with RT-PCR assay that low levels of CMV DNA is present in 42.1% of asthma patients and in 12.6%, of control subjects (p<0.001). The test positivity was higher in elderly asthmatics than in younger patients (52.9% vs. 29.7%, p=0.003) and higher in elderly control subjects than in younger controls (22.2% vs. 1.8%, p<0.001). Presence of CMV DNA was associated with an increased risk of asthma: OR=5.1 [(95% CI: 2.7-9.4 p<0.001]) for the whole population tested and OR=23.3 [(95% CI:3.178.9);p<0.001] for non-elderly subjects. In conclusion CMV replication at low level is highly prevalent in asthmatics and is associated with risk of asthma.

Major publications:


1. Marek L. Kowalski, Aleksandra Wardzynska, Mirosława Studzinska, Małgorzata Pawelczyk, Zbigniew Jan Lesnikowski, Edyta Paradowska, The high prevalence of cytomegalovirus DNA in the blood of asthma patients: its association with age and the risk of asthma. J Allergy and Clinical Immunology

2. Sreedhar Chinnaswamy, Aleksandra Wardzynska, Małgorzata Pawelczyk, Joanna Makowska, Marek L. Kowalski. A functional IFN-λ4-generating DNA polymorphism protects older women from aeroallergen sensitization and associates with clinical features of asthma, Clinical and Experimental Immunology

Research Theme: 6. Hampering the progression of chronic kidney disease and subclinical organ damage as a prevention of cardiovascular complications in elderly people with and without hypertension.

Theme leader: Prof. Jacek Rysz, Prof. Maciej Banach

Overall aims: Research of the theme focused on association with atherosclerosis progression, inflammation and cell proliferation at patients with cardiovascular disease, hypertension and chronic kidney disease and by analyzed indices (biochemical, genetic and ultrasound) searched for mutual correlations. Large cohorts including both elderly and non-elderly subjects were examined.

Major achievements:

a) Collection over 300 of serum samples which has been used in the study of markers of atherosclerosis in chronic kidney disease patients with and without acute coronary syndromes and cardiovascular risk factors in these patients.

b) Study about markers of increased risk of CAD in CKD patients indicated that matrix metalloproteinases and bone matrix proteins may be involved in the pathogenesis of CAD in CKD patients. Hyperphosphataemia-associated development of vascular calcification and arterial stiffness in CKD patients and Ang II-
induced hypertension may play key role in this process.

c) Study about indices of LV diastolic dysfunction in CKD patients indicated that early identification of factors involved is necessary to prevent devastating process. Many indexes of contractility are used and each of them has imperfections. It seems that TVI, E, E/A and E/Em are good instruments for the early detection of left ventricular hypertrophy and diastolic dysfunction.

d) Study about the relationship between selected risk factors for cardiovascular diseases (age, sex, dyslipidemia, hypertension, etc.), intima-media thickness and coronary artery calcium score in patients with chronic kidney disease stages 2, 3 and 4 indicated that age and the presence of hypertension are associated with the growth of IMT in patients with CKD, while age and exposure to tobacco smoke were associated with the increase in CACS in these patients. There was a relationship between thickening of the IMT and the increase in calcification index in patients with CKD.

e) Study about the markers of increased risk of atherosclerosis in CKD show high prevalence of ventricular hypertrophy and diastolic dysfunction in CKD patients. Contralateral dysfunction, mitral and aortic valve calcification in HD patients was significantly more frequent than in patients with other CKD stages. Significantly increased levels of MMP-2, MMP-2/TIMP-2 ratio and lower TIMP-1 suggest that these factors may be involved in the pathogenesis of atherosclerosis in CKD patients.

f) Analysis of blood samples of patients with chronic kidney disease and cardiovascular diseases with the use of pyrosequencer. Methylation of the following genes: eNOS, iNOS, Fads2, c-fos, MMP-2, MMP-7, MMP-9, ICAM-1, p53, EC-SOD, 15-LO, estrogen receptor a and b, IFN-γ, PDGF-A and P66Shc associated with atherosclerosis progression, inflammation, shear stress and cell proliferation has been analyzed. Work still in progress, results plan to be published in the near future.

Major publications:

RESEARCH AREA 4 MOLECULAR BASIS OF AGEING

Research Theme:7. Modulation of vascular endothelial cell senescence in ageing - integrins in endothelial cell senescence
Theme leader: Prof. Jolanta Niewiarowska
Main goals: Research of the theme focused on study the molecular mechanisms involved in the regulation of vascular endothelial cell senescence. Additionally researchers concentrate on searching new senescence markers.

Major achievements:
1. Developing and evaluating cellular models for studying endothelial cells senescence on the molecular level.
2. Searching a new endothelial senescence markers.

The main goal of this study was searching a new potential senescence markers. Most EC receptors for extracellular matrix proteins involved in maintenance of endothelial monolayer integrity and proper functions belongs to the integrin superfamily. Thus, integrins and integrin-dependent pathways were studied. Kinase stress-induced premature senescence was evaluated by a common markers of senescence. Morphological cell changes was determined by analyzing differences in cell diameter and expression of vimentin. Additionally, endothelial cell behavior of both senescent and non-senescent cells was studied by using tube formation assay and cell-cell adhesion assay. The obtained results revealed that HMEC-1 cells, despite of some pathways involved in cell senescence dysfunction, are sufficient model to study a cellular senescence processes.

3. Characterization of novel marker of senescence and its contribution in endothelial cells dysfunction.

Our preliminary data suggested that previously selected in screening study kinase is involved in regulation of endothelial cell function during senescent process. To understand its contribution in endothelial cells dysfunction and the role in pathogenesis of endothelium additional study should be performed.

Major publications:
3. Characterization of novel marker of senescence and its contribution in endothelial cells dysfunction.

Overall aims: Research of the theme focused on commencement a cooperation with national and foreign research units and application of the purchased
HARC INTEGRATIVE PROJECT ON COMORBIDITIES IN THE ELDERLY

The HARC project was dedicated to the problem of multimorbidity in the elderly population of Lodz city and the Lodz region. The coexistence of several chronic diseases in elderly patients is a common and increasing problem. Multimorbidity negatively impacts quality of life and overall prognosis, it may also be a cause of treatment failure and may increase economic burden.

Important aspect of the project is to take the advantage from interdisciplinary expertise of HARC research groups and to improve internal collaboration between HARC partners. The aims are in particular:

- To estimate what is the real occurrence of multimorbidity in men and women above 65 years of age;
- To define risk factors and subpopulations at the highest risk of multimorbidity;
- To assess a phenomenon of clustering of chronic diseases;
- To estimate prognostic meaning of multimorbidity in a prospective study;
- To prepare a pre-defined subpopulations of patients with specific index diseases for further evaluation in separate future projects (pulmonology, allergology, cardiovascular diseases, psychiatry).

A set of questionnaires has been prepared dedicated to specific problems of multimorbidity (demographic data, chronic diseases and treatment, dementia and psychiatric disorders, infections, nutrition). Ethics Committee at MUL gave the consent for the study and all participants sign the consent form. In the second stage of the project it is planned to receive blood sample from all participants who gave the consent. The biological samples will be stored at the HARC Biobank for further analysis (biomarkers will be estimated in separate projects realized by participating scientific partners).

The study is ongoing from the Lodz citizens register 6000 potential participants (addresses) have been randomly selected. A group of pollsters is visiting participants at home. It is planned that at least 1500 participants will be completed by the end of march 2017. The study has been funded by MUL.
VIRTUAL LABORATORY (Vir-Lab)

In order to upgrade the research potential of HARC consortium highly innovative equipment of strategic significance to the Centre (not previously available at the MUL) was acquired. The instruments have been purchased within the first six month of the project, the personnel was trained, and the equipment have already extensively used to keep going on and further develop collaborative research between HARC teams and their local and international partners. It is crucial to emphasize the complementarity of the new equipment with the already existing infrastructure within HARC. The HARC laboratories have been also made widely available for researchers who want to develop new projects but do not have the access to the equipment and experienced staff. The Virtual Laboratory was created to allow the coordination of the efforts at the level of the HARC consortium. The newly purchased research equipment (instruments) have been listed in the database of the Vir-Lab and the information is available for all partners of the consortium via Vir-Lab website (available at: https://intranet.umed.pl/witryn/HARC/Strony/default.aspx). In addition, laboratory methods and techniques used currently by all partners are listed and described at the Vir-Lab website. The information on currently available instruments and methods is delivered to every interested person by contact person dedicated to the particular piece of equipment.

BIOBANK

In accordance with the objectives of the Healthy Ageing Research Centre - HARC, a biobank was established at Medical University of Łódź with aim to store, process and distribute biological human material (tissue samples and/or body fluids) and the data associated with these materials. The Biobank was established according to the best international standards, as a tool for optimisation and coordination of access to various biological samples (sera, biological fluids, frozen cells, DNA, and mRNA), collected within HARC. The first samples were stored in September 2014, and since then the number of biological samples stored is steadily increasing. The combined storage capacity allows to keep approximately 160 000 samples. In the end of 2014 the Biobank was approved by authorities of Medical Faculty and MUL as the research unit of the Department of Immunology, Rheumatology and Allergy of MUL, which has been a significant step towards the sustainability of the Biobank beyond the timeline of the EU funding of project. The number of biological samples stored is steadily increasing during the HARC project implementation.

HARC Biobank has a unique system for the preparation of samples for long term storage and a flexible system for automation of labor intensive and complex pipetting tasks with labs. The tubesorter can quickly transfer tubes between multiple 96 tube racks while maintaining sample identity and advanced tube management system supports sorting of a nearly unlimited number of tubes. The current biobank storage capacity is 160 000 samples.

HARC Biobank has also a unique system to store samples. The use of liquid nitrogen (LN2) freezers for long – term specimen preservation is optimal for storage of some types of biological material (vapor phase LN2 or liquid phase LN2). In HARC Biobank we have LN2 tank which is able to automatically monitor and control the level of liquid nitrogen. The high capacity makes it possible to hold up to 8 000 vials. HARC Biobank has also freezers (-80C) which are equipped with emergency back-up systems that automatically cool their contents in the event of an extended power loss. A computer – based system allows to register each sample entering and exiting the system and to store the information on sample origin and current location. HARC Biobank established procedures to ensure the protection of its donors’ privacy. All information’s are coded, and scientist has no access to the actual identity of the donor. HARC Biobank is also equipped with a system that adequately limits access to appropriate staff and protects against physical intrusion from unauthorized individuals.

HARC Biobank is available to all HARC partners and other MUL researchers. The Biobank was supported by the additional funds from the Ministry of Science and Higher Education for Biobank’s infrastructure with total amount of 350 000 eur. Due to that the complementary equipment was bought to up-grade the already owned assets. The Biobank was also a part of application regarding structural funds for digitalization of MUL resources.

In order to secure sustainability of the HARC beyond the timeline of the EC funding, and in line with the Strategy, several initiatives were developed:

- Projects proposals have been prepared by HARC partners and submitted for financing to Horizon 2020 (SCOPE (received funding), GO-DEPRESSING, ACREDIT, DE-METER, ELDERDIET, MedCheMed, OBODO, Icri-BioM and I2ISquare), 3rd Health Programme (SUNFRAIL (received funding), AFIM, SSMI and Homyal Care) and COST action (CM1201 – received funding); Study on nutrition, metabolic processes, inflammation, and cognition; Call 2015: “Nutrition and Cognitive Function” (NutriCog), the Joint Programming Initiative “A Healthy Diet for A Healthy Life” – 3 applications; OEAD bilateral co-operation with Austria: „Neuropathological hallmarks of misfolded protein cross-reactions in the human brain”, OEAD 2014-2015; Joint Call for Proposals 2016 “Coordination of European funding for infectious diseases research” – 1 application; EIT Health - Innovation by design proposal – BEGIN (Breaking the ground for preventive airway immune monitoring); RISE 2015: - Omix studies for biomarkers and obesity; Polish-Nordic Axis to Increase Fibrosis Research Momentum - MOMENTO II; H2020-TWINS-2015;

HARC researchers developed the collaboration with:

- European Innovation Partnership on Active and Healthy Ageing - 2016 Call for Reference Sites of the European Innovation Partnership on Active and Healthy Ageing - Lodz has been awarded with "Reference Site" status as one of the 74 regional and local organizations. Lodz consortium was rated at two stars in the scale of 1-4 and will be the only center/site in Poland with such rank. The proposal has been prepared in partnership with the Province of Lodz, City of Lodz, Institute of Occupational Medicine in Lodz, University Clinical Hospital No. 1 named N. Barlicki in Lodz and Ericpol Sp. o.o. Coordinator of the initiative was prof. Lucyna Wozniak - Vice-Rector for Research and International Realtions of the Medical University of Lodz.
- MACVIA LR (Reference site of the European Innovation Partnership on Active and Healthy Ageing)
- Polskie Towarzystwo Gerontologiczne
- National Contact Point in Poland
- Regional authorities and organizations

Prof. Lucyna Wozniak has become a member of High Level Group on maximising impact of EU Research and Innovation Programmes. The Group comprises 12 highly qualified, independent members who have been selected from over 350 candidates (public call for expression of interest, with the aim of ensuring high-level professional experience and a good balance in terms of skills, experience, knowledge, geographical diversity, gender and age). The Group will base its work on the results of the interim evaluation of Horizon 2020, the EU’s current research and innovation funding scheme, and other evidence such as the results of the related public consultation. There will be produced a final report with recommendations which will be taken forward by the European Commission in the future development of EU research and innovation funding.

To sum up the HARC project and its outcomes and review the activities in the region for the future the conference on: “Healthy Ageing Research Centre – integration of initiatives emerging from HARC. Active living and healthy aging in Lodz and the region” was held at Medical University of Lodz on November 29th, 2016. The conference aim was also to present a new initiative – Lodz Reference Site which was set up in the framework of the European Innovation Partnership on Active and Healthy Ageing (EIP AHA). During the meeting the discussion was concentrated on the widening activities and scaling up the
recognition of the initiatives of the research representatives/units (dissemination of activities and results) regarding:

- Research conducted jointly with international partners
- Development of cooperation between academia and industry/business
- Development of cooperation between academia and social partners (local authorities, NGOs, lay public).

Further activities should be built up from the EU research programmes (Horizon2020) and other supportive actions – EIT Health and European Innovation Partnership on Active and Healthy ageing (EIP AHA) - on healthy living and active ageing. Researchers at the Medical University of Łódź will develop international cooperation (EIT Health, the European Innovation Partnership on Active and Healthy Ageing) and regional activities in this area in cooperation with both research centers, innovative companies operating in the development of products, technologies and organizational solutions lifting quality of life and well-being of the elderly, as well as the social partners, in order to diagnose the needs of this group of our society.

The activity in international and cross-sectoral environment should allow to mobilise the relevant stakeholders (local, regional and national) to involve, create and scale up the funding opportunities for academic initiatives on active and healthy ageing. Currently the funding opportunities are available as published on November 30th, 2016 in adopted schedule of calls for proposals for funding through a competition in the Regional Operational Programme for the Lodz Region for 2017.

Potential Impact:
The most important and spectacular achievement of the HARC consortium within this first project’s period has been its involvement in successful application of the Medical University of Łódź to the most important European initiative dedicated to active and healthy ageing. MUL, together with two regional partners was selected by the European Institute of Innovation and Technology’s (EIT), into the public-private partnerships Knowledge and Innovation Communities – KIC Innolife. Partnership of the Medical University in the INNOLIFE EIT HEALTH is the major step to enhance an international potential of HARC since it gives us an access to the strongest consortium dedicated to active life and healthy ageing in EU, with timeline to 2030. It will significantly stimulate and enhance Innovation Partnership on Healthy Ageing research with strengthened IPR protection and other activities improving the sustainability and efficiency of social and health care systems, boosting and improving the competitiveness of the markets for innovative products and services, responding to the ageing challenge at both EU and global level, thus creating new opportunities for collaboration with businesses for MUL in general, and for HARC partners in particular. It is also a perfect platform, based on knowledge triangle, excellence of projects and partners to achieve and increase sustainability of research and networking results of HARC within ERA.

Innolife has formed six co-location centres across Europe: in London (UK/Ireland), Stockholm (SCAN), Barcelona (ES), Paris (FR), Heidelberg (GER) and Rotterdam (BENE). All six co-location centres are defined by the EU Innovation Scorecard as high innovation performers and have several collaborative partnerships with reference regions in the European Innovation Partnership on Active and Healthy Ageing. Each co-location centre and the Innostars are characterised by geographical and/or functional proximity, providing the density required for the creation of a stimulating innovation eco-system. They provide a shared physical space, with potential access to laboratories, test beds, offices and seminar rooms to promote close cooperation. This partnership is going to increase pro-innovation approach to research and collaboration with proper intellectual property right protection within HARC and with international partners (participation in Ethical Committee) of NNOLIFE.

SPREADING RESULTS OF RESEARCH CONNECTED TO HARC PROJECT
HARC scientists attended international conferences to present the results of research and acquired up-to-date knowledge in the field. In total HARC scientist attended 33 international conferences, presented 41 abstracts with original data and 10 invited lectures all over the world.

Healthy Ageing Research Centre organized 2 international Conferences on Translational Research in Healthy Ageing.

The first conference was held on April 16-18, 2015. More than 30 internationally recognized scientist have accepted the invitation to speak at the congress and the program of the conference is available at the conference website: http://harccconference2015.umed.pl/ About 300 scientists, physicians and students participated in the conference and nearly 40 lectures were delivered by specialists from 12 European countries and the United States. Conference was divided into 9 scientific sessions. Over 40 original research communications presented at poster sessions addressed various aspects of disorders of old age: neurodegenerative, circulatory and respiratory diseases and the role of nutrition and physical activity in maintaining physical and mental health in the elderly.

The second conference was held on May 11-13, 2016. Almost 30 internationally recognized scientist have accepted the invitation to speak at the congress and the program of the conference is available at the conference website http://harccconference2016.umed.pl/ During the three-day lasting meeting consisted of nine sessions scientists, researchers and participants from 15 countries discussed how to maintain health and fitness for life. The 2nd HARC Conference on Translational Research in Healthy Ageing was an opportunity for scientists and clinicians to undertake discussions on the effective use of research findings in clinical practice in some areas of gerontology. Conference was attended by over 300 participants who had the opportunity to listen to more than 30 lectures from around the world. Almost 60 abstracts were submitted from 18 countries. Event accompanying the Second HARC Conference was satellite session was “INCONet CA Session in EIT Health Innostars ” during which the cooperation between European Union's with the countries of Central Asia was summarized.

HARC WORKSHOPS
During the project eight international workshops were organized. Each workshop was organized by different HARC partner, and focused on specific area of expertise and aimed to provide the opportunity to young HARC in their fields. HARC international partners were invited to report results of their research as well as to discuss current research conducted by the HARC researches on healthy aging. The workshops provided the attending researchers with the wide scientific background for their current and future research work. HARC scientists had opportunity to present the result of their studies on healthy aging during original presentations sessions. Particularly important were personal interactions of young HARC scientists with the top scientists in the field of healthy aging.

Proceedings from the workshop “Nutrition and diet for age-related cognitive decline and dementia” were published in internationally recognized journal European Journal of Clinical Nutrition (IF-2.95).

- I HARC Workshop “Nutrition and diet for age-related cognitive decline and dementia” (March 6-7, 2014) – Chair: Professor Iwona Kłoszewska, Professor Tomasz Sobóń

The aim of the Workshop was to meet world-class experts within the field of dementia and nutritional sciences. Lectures grouped with 4 tracks (early detection of cognitive decline, nutrition and cognitive decline pathogenesis, diet, nutrition and body composition assessment and, finally, nutritional and diet interventions for cognitive decline and other disorders) was of a state-of-the-art type with questions and answers following each session.
Workshops

physical health in old age, healthy eating and diseases in old age.

and between 150 - 250 attended each session. Students of the Academy were also invited to participate in workshops focusing on issues of mental and related to the regional, social and economic issues regarding elderly activity. In total approx. 300 students have been a part of the Healthy Ageing Academy comprehensive activation. During 3 years of Healthy Ageing Academy students had the opportunity to listen to 64 lectures on medical issues, as well topics on elderly issues in medical, social and economic areas to develop the intellectual capacity and improve the quality of life of older people through their

Thanks to this initiative we build up a net of cooperation with regional partners who also promote healthy ageing in the community and cooperate with lay public

have the opportunity to participate in the Healthy Ageing Academy organized by the Research Center for Healthy Aging at the Medical University of Lodz.

One activity of the Healthy Ageing Research Centre is Healthy Ageing Academy addressed to older citizens of Lodz region. Since the second half of 2013 they

The workshop was devoted to selected problems of cardiovascular (CV) and respiratory diseases in the elderly. The special emphasis was put on common pathogenetic pathways between heart and lung pathologies, with special regard to systemic inflammation.

http://harc.umed.pl/events,harc_iii_workshop_age-related_cardiovascular_and_respiratory_diseases,13

• V HARC Workshop “Disregulation of cell-matrix interactions in age-related diseases” (November 5-6, 2015) – Chair: Professor Jolanta Niewiarowska

The special emphasis was put on molecular aspects of cell-matrix interactions of endothelial cells in ageing, but also targets for vasculature in cancer and age related diseases, and molecular therapy in ageing.

http://harc.umed.pl/events,5th_healthy_ageing_research_centre_harc_workshop_disregulation_of_cell-matrix_interactions_in_age-related_diseases,21

• VI HARC Workshop “Innovation and intellectual property protection management” (November 18-19, 2015) – Chair: Professor Lucyna Woźniak

The event was to explore issues related to the management of innovation and entrepreneurship academic. The aim of the workshop was to introduce the subject of management and implementation of innovations in medicine and medical sciences. An important element of this process is the knowledge and experience in intellectual property management, which is crucial for the success of the business implementation of scientific projects.

http://harc.umed.pl/events,innovation_and_intellectual_property_protection_management_workshop,23

• VII HARC Workshop “Molecular Pathology of the Nervous System” (February 25-26, 2016) – Chair: Professor Paweł Liberski

The main aim of this workshop was to present the to the Polish and European audience the modern views on the molecular pathogenesis of the neurodegenerative diseases of the nervous system.


• VIII HARC Workshop “Nucleic Acids in Medicine: perspectives for new diagnostic and therapeutic tools” (March 10—11, 2016) - Chair: Professor Lucyna Woźniak

The workshop was primarily aimed to build a synergistic relationship between chemists, molecular biologists and medical doctors in the field of synthesis of modified nucleic acids and their application in biological and medical sciences.

http://harc.umed.pl/events,8th_harc_workshop_nucleic_acids_in_medicine_perspectives_for_new_diagnostic_and_therapeutic_tools,27

CONFERENCES FOR PROFESSIONALS

The 1st HARC Conference “Geriatrics in practice of primary care physicians” covered issues of the health problems of old age. During the conference the problems of rehabilitation and prevention of fractures the elderly and sarcopenia, the distinct treatment of allergic diseases and respiratory diseases in seniors were discussed. Participants of the conference were could also deepened their knowledge in depressive disorders, sleep disorders and cardiac problems, renal and diabetes. The conference ended with a lecture on polypharmacy and principles to reduce the doses of drugs taken by elderly patients. In the Conference took part over 120 participants.

During the 2nd HARC Conference “Geriatrics in practice of primary care physicians” the problems of rehabilitation and prevention of fractures the elderly, the distinct treatment of allergic diseases and respiratory diseases in seniors were discussed. Participants of the conference were also interested in depressive disorders, sleep disorders and cardiac problems, renal and diabetes. The conference was attended by over 100 primary care physicians, nurses and physiotherapists who meet geriatric issues every day

ACTIVITIES FOR THE LODZ REGION

Healthy Ageing Academy

One activity of the Healthy Ageing Research Centre is Healthy Ageing Academy addressed to older citizens of Lodz region. Since the second half of 2013 they have the opportunity to participate in the Healthy Ageing Academy organized by the Research Center for Healthy Ageing at the Medical University of Lodz. Thanks to this initiative we build up a net of cooperation with regional partners who also promote healthy ageing in the community and cooperate with lay public on elderly issues in medical, social and economic areas to develop the intellectual capacity and improve the quality of life of older people through their comprehensive activation. During 3 years of Healthy Ageing Academy students had the opportunity to listen to 64 lectures on medical issues, as well topics related to the regional, social and economic issues regarding elderly activity. In total approx. 300 students have been a part of the Healthy Ageing Academy and between 150 - 250 attended each session. Students of the Academy were also invited to participate in workshops focusing on issues of mental and physical health in old age, healthy eating and diseases in old age.
Due to the great interest in the HARC workshops related to seniors’ health, a series of workshops was organized beyond the Healthy Ageing Academy in cooperation with the City Council of Lodz. Educational package was prepared with practical information on maintaining optimal health by seniors. Workshops were prepared and conducted by physicians at the Medical University and their topics included contemporary recommendations for health care for the elderly. The workshops were held at Active Senior Centers located in several districts of the City of Lodz.

In May 2014 and 2015 Healthy Ageing Research Centre took part in „Senioralia” – special event for the elderly people organized by the City Council of Łódź. During the Senioralia, HARC organized workshops for seniors, where participants could develop their knowledge on maintaining physical and mental activity, healthy nutrition, and on diseases of the old age. Healthy Ageing Research Centre regularly collaborates with the City Council of Seniors participating in their meetings and activities. Healthy Ageing Research Centre has organized 44 workshops so far with 900 participants. Attached documents: Furthermore, project logo, diagrams or photographs illustrating and promoting the work of the project (including videos, etc...) as well as the list of all beneficiaries with the corresponding contact names can be submitted, provided the consortium ensures that all necessary authorisations have been obtained and that the publication of the information by the Commission does not infringe any rights of third parties (e.g. commercial interests, including intellectual property, or privacy and the integrity of the individuals, in particular in accordance with Community legislation regarding the protection of personal data).

TV programmes
Assuming that significant proportion of elderly have no access to internet and have mobility problems we prepared the series of TV dissemination programs (broadcasted in the regional TV) on active and healthy ageing.

FUTURE
In the nearest future Centre is supposed to continue its activity within the structure of Medical University of Lodz. We are going to create and develop new research activities developed based on national and European funds. What is more the Virtual Laboratory established during the project lifetime will be further developed and integrated with the Medical University of Lodz CoreLab network. Also our Biobank will be developed and incorporated into the network of European Union depositories available for European Union researchers.

The main aim of HARC is to coordinate and conduct activities in the field of scientific research, medical effects, organizational and social benefits from the increase in life expectancy of citizens.

In the nearest future the mission of HARC will be continued beyond the EC funding with major goals as follows:
- coordinate of research and innovation programs
- implement prevention and treatment programs
- promote health and prevention
- train and educate medical personnel
- coordinate of activities resulting from the task in collaboration with other academic institutions, research institutes and regional authorities
- develop international scientific cooperation through the creation of and participation in research consortia and carrying out research projects together with foreign partners.

List of Websites:
www.harc.umed.pl

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