The goal of the "Regenerative Mechanisms for Health" Agenda, referred to as ReMedy, **is to understand and to harness stress-evoked adaptability of cells at the molecular and biochemical level, in order to combat human diseases and pathologies**. The life and health of living organisms relies on molecular processes and biochemical reaction networks at the level of a single cell. Cells have intrinsic programs to respond and adapt to stress. These programs, called cellular stress responses, are triggered by various stimuli, including stress, and remodel molecular and biochemical pathways underlying cell behavior and physiology. The stress response pathways lead to restoration of homeostasis at the molecular and cellular level, and consequently of the organismal health (Figure 1). Interestingly, through these processes, cells frequently gain an increased stress resistance and vitality. Intrinsic stress defense mechanisms are exciting targets to increase cellular fitness and decrease vulnerability to degenerative pathologies. Inhibiting cellular stress response pathways is a strategy against cancer cells that misuse cellular stress defense systems to increase their survival

ReMedy aims to i) understand mechanisms of stress response, ii) discover short- and long-term consequences of responses and their crosstalk in physiology and iii) apply the gained knowledge about stress responses for the development of new medical treatments. The ReMedy Unit intends to make breakthrough discoveries that will open new lines of research and new strategies to maintain and restore health. To realize its vision, ReMedy will be committed to research excellence through recruitment of outstanding individuals and nurturing their creativity through the creation of a stimulating environment of high scientific and organizational standards, focused on collaboration and productivity.

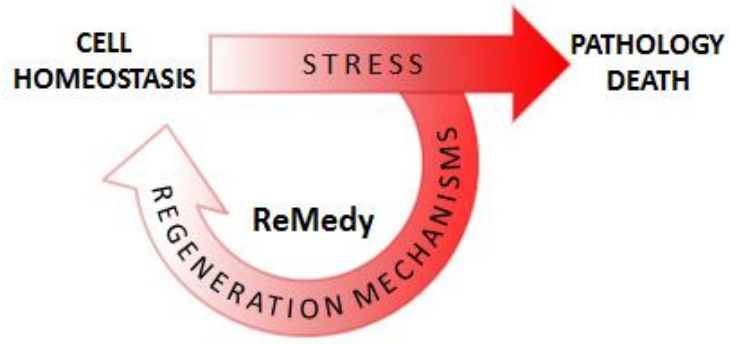

FIGURE 1.

<u>Outline of the scientific and/or economic and social challenge</u>

The scientific challenge undertaken by ReMedy is to comprehensively understand and predict cellular adaptability to stress.

Genetic information is passed through generations and is expressed at several steps, including transcription, translation and further levels of processing, resulting in the formation of fully mature proteins, the main function executors in living cells. All cells of our body carry the same genetic information; however, its expression gives rise to a surprising variety of cell types, as different as bone cells and neurons. This cellular plasticity, defined as an ability of one genome to produce a variety of forms and functions of cells, is commonly appreciated.

A more subtle and less recognized aspect of plasticity is the cell's ability to adapt to stress and homeostasis disturbances. These disturbances stem from diseases, either genetically inherited, caused by the environment or by time passing during organismal ageing, and may result in pathology and eventually – death. However, if not lethal, they impose stress and imbalance affecting cellular homeostasis. The presence of inherently build-in programs that minimize the effects of cellular stresses in order to restore

cellular homeostasis is the universal cell feature of uni- and multicellular organisms. Stress-response programs operate at all levels of gene expression and regulation of functional proteome defined as the entire complement of proteins present in the cell. Our understanding of mechanisms that govern cellular plasticity and adaptability in response to stress is a prerequisite to better unravel and cure human pathologies.

The unfolded protein response (UPR) was discovered more than 20 years ago by Peter Walter, Kazutoshi Mori and others, and represents an example of a conserved pathway that reprograms cells in response to stress of the endoplasmic reticulum, a cellular compartment that hosts and matures proteins destined to various locations of the cellular membrane system. The UPR leads to cellular rewiring at various levels of gene expression and proteome content regulation and has vast implications for pathology. Recently, new pathways have been discovered that are triggered in response to dysfunctional mitochondria and lead to changes at different levels of gene expression, protein biogenesis and degradation (Wrobel et al., 2015 - see the list of scientific achievements of A. Chacinska). These findings lead to realization that **molecular rewiring and biochemical adaptability of cells are still understood only fragmentarily.**

The social/economical challenge undertaken by ReMedy is to deliver strategies targeting cellular adaptability as the means to improve health.

The rationale that stress- and pathology-caused cellular adaptability is beneficial for cells as it increases their fitness has important implications for planning new strategies for medical treatments. It implies that activating stress-response programs, in the absence of stress conditions, will promote cellular health and inhibiting these programs will lead to reduction of cells vitality.

We envision two large areas that constitute the biggest medical and social challenges in highly developed societies, in which discoveries and inventions of ReMedy can be applied. The first field comprises incurable **neurodegenerative and age-related pathologies**. They constitute medically separate conditions; however they share common features, such as the protein homeostasis collapse and mitochondria impairment. The knowledge gained in ReMedy will allow to activate intrinsic molecular and biochemical regenerative pathways in cells that will prevent and/or reverse age-related neurodegeneration. The second area involves **cancer**, which is a growing health problem, and for which many medical treatments have only a limited success. In the course of cancerogenesis, changes in cell proliferation are accompanied by suppressing safety inhibitory mechanisms and activating, still not fully known, long-lasting stress resistance pathways. This results in enormous vitality of cancer cells, which is devastating and frequently lethal for organisms. The knowledge gained through ReMedy research will deliver treatment strategies to disable or shut down adaptive pathways that provide unwanted benefit to cancer. ReMedy will offer innovative strategies for preventing and combating diseases, such as neurodegeneration or cancer, for which, despite strong efforts over last decades, treatments do not exist or are insufficient.

In summary, **ReMedy discoveries will have potential to provide a rationale and strategies for novel therapies and interventions to preserve health and cure disease**. These strategies will be protected by patent applications and patents and will be managed by the intellectual property office.

Original approach to solving the challenge

ReMedy will merge diverse approaches and expertise of ReMedy scientists working on various cellular models and model organisms to provide "pan-cellular" answers.

Scientific interests of ReMedy cover a variety of stress-triggered processes of cellular adaptability that rely on gene expression and functional execution. Plasticity and adaptability of cells involve cellular processes such as: chromatin function, transcription, RNA biogenesis and turnover, protein synthesis, protein targeting and degradation, metabolism and organellar dynamics and cross-talk, all governed and orchestrated by a network of signaling events. To perform high level research that will lead to significant discoveries, ReMedy will combine diverse interests, various methodologies and different model organisms (Figure 2). **Group Leaders, who will be recruited based on excellence criteria, will be free to choose their own scientific interests within the scope of ReMedy Agenda**. The interests and approaches of individual Group Leaders will contribute to, and be unified by, the main goal to identify and utilize intrinsic cellular stress mechanisms that control organismal homeostasis in pathology by activation of regenerative pathways.

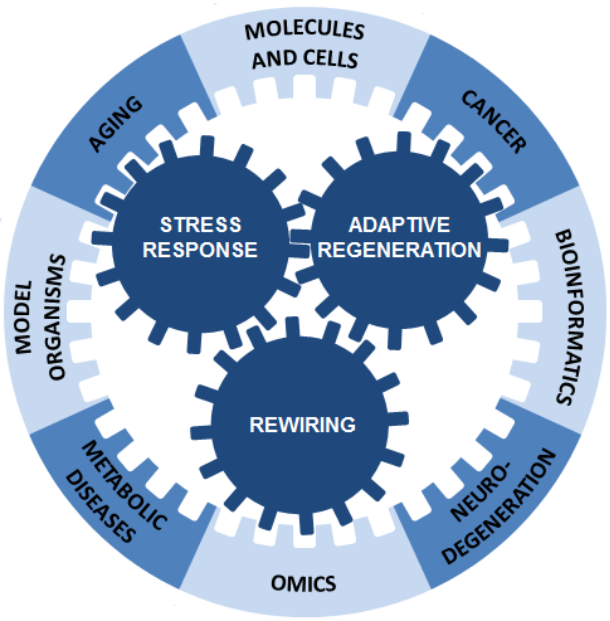

FIGURE 2. A diagram representing scientific interests and approaches of ReMedy.

The conceptual basis of the ReMedy Agenda is built on the following proposals:

a. stress-induced molecular and biochemical plasticity is a general paradigm of cells and involves a crosstalk of various processes at different levels,

b. the framework of cellular plasticity and stress rewiring is evolutionarily conserved, allowing for the use of various model organisms,

c. cellular stress management involves two main classes of adaptations, fast processes (such as signaling through protein modification and degradation) to minimize stress and long-lasting adaptations leading to rewiring of expression programs and cellular function,

d. triggering and switching off stress-induced adaptation mechanisms can be utilized to manipulate cellular and organismal fitness.

This conceptual basis of the ReMedy Agenda also constitutes a framework for intensive crosstalk between research fields and collaboration between scientists that will have an enormous added value. **Collaboration is envisaged as the key factor that will unify the efforts of various groups to bring the knowledge to a higher level of understanding of cellular stress pathways networks and cross-talk**. Through collaborations, scientists of ReMedy will have access to diverse expertise, approaches and model organisms ranging from unicellular model yeast, cultured mammalian cells and model organisms (nematodes, fly, mouse). This will facilitate the ReMedy's goal to obtain a holistic and systemic view on stress consequences in the cell. Furthermore, collaborative activities will be directed towards a thoughtful and knowledge-based rationale to

regenerate cells in a way that predicts not only the consequences concerning one process but the entire cell. This will result in important discoveries and in turn will also foster patenting and commercialization activities.

Thus, the approach used by ReMedy differs from, and is advantageous over, a classic way of doing research, where individual scientists lead individual projects focused on individual questions that concern one of the fields of biochemistry, molecular or cellular biology, working on their favorite selected model organisms. The ReMedy Unit will also differ significantly from consortia programs, formed by a group of scientists, in which questions and projects are predefined and assigned *a priori*. ReMedy will recruit new, highly motivated individuals and provide them with excellent conditions for the development of their own research in line with ReMedy goals. We anticipate that this approach will strengthen ReMedy in the coming years, ensuring its dynamic growth and long-term prospects, exceeding the initial Agenda funding period.

In terms of scientific interests, **the ReMedy groups should ideally represent each of two broad areas of research, expression regulation or proteome regulation**. To fully develop the holistic nature of the ReMedy goal, **special attention will be given to systems biology approaches**, including bioinformatics and “omics” (i.e. transcriptomics, metabolomics and proteomics). Examples of research questions that would align with the main goal of the Remedy Agenda include the following: how disease-related changes in the proteome affect gene expression? how gene expression rewiring influences organellar function? what is the contribution of protein homeostasis to aging? how metabolism affects chromatin remodeling during stress? can cells modify the programs of gene expression to reduce or postpone protein homeostasis collapse? can these programs prolong healthy life-span? how metabolic rewiring of cancer cells crosstalks to stress response programs? how gene expression contributes to neurodegeneration? can stress response pathway be activated chemically without the source of stress to increase cellular and organismal fitness?