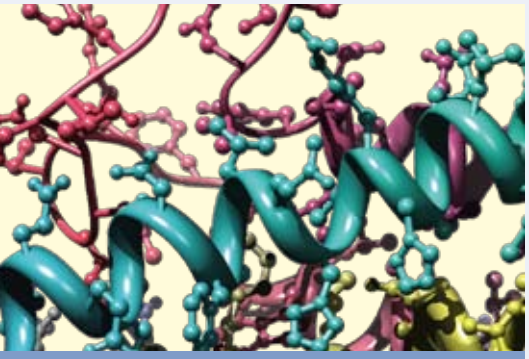
IOP: Cellular protein defence

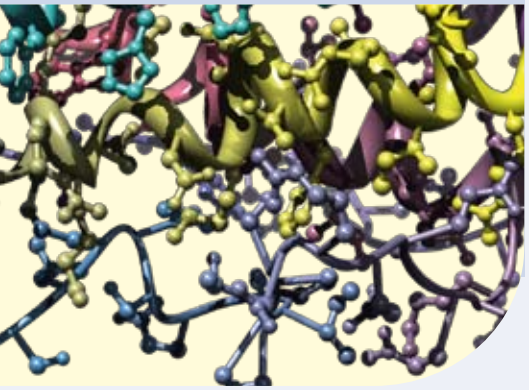
Improving the cellular defence system by enhancing stress response

Stress conditions like heat and exposure to toxins cause eukaryotic cells to upregulate a cellular defence and survival system. This so-called stress response system repairs or disposes of misfolded proteins. During ageing the system starts to fail, increasing the risk of age-related protein folding diseases like Alzheimer's or Huntington's disease, as well as of chronic inflammatory disease. In this IOP project the researchers are looking for ways to boost the repair and defence system, which may prevent or treat these diseases.



IOP Project

- **Title** Helping Health: Boosting the cellular defence system.
- **Participants** Faculty of Chemistry, Utrecht University; Faculty of Veterinary Medicine, Utrecht University; Faculty of Medical Science, Groningen University; Faculty of Science, Radboud University Nijmegen.
- **Business partners** Unilever R&D, Pepscan Presto, Angteq, Galapagos, ModiQuest, DSM, Alfa Biogene International, Solvay.



Under normal, non-stressful conditions members of the heat shock protein (HSP) family are present in all cells in all life forms. They are also referred to as stress proteins and their upregulation is sometimes described more generally as part of the stress response. HSPs act like 'chaperones', making sure that the cell's proteins are in the right shape and in the right place at the right time – just as their stress induced relatives do in the stressed cell.
They help new or distorted proteins fold into shape, which is essential for protein function. They also assist the transport of proteins from one compartment to another inside the cell, and the transfer of irreversibly misfolded proteins to 'garbage disposals' inside the cell. Furthermore, HSPs play a role in triggering the immune system. They help to present pieces of the proteins (peptides) on the cell surface, which helps the immune system to recognize diseased cells. In this way HSPs induce anti-inflammatory immunoregulatory T cell responses, and in experimental models HSPs have proven to prevent or arrest inflammatory damage.
"The integrity of the stress response system is crucial for cell survival," says Lettie Lubsen, professor of Molecular Biology at the Radboud University in Nijmegen. She is leader of one the academic teams participating in the IOP project.
"The system ensures the quality control of cellular proteins with respect to structure as well as synthesis and degradation. Increasing failure of the cellular repair and quality control mechanisms is thought to be involved in many age-related syndromes in which large protein aggregates are found, for instance Alzheimer's and Huntington's disease. But also in chronic inflammatory diseases like rheumatoid arthritis."
Since different factors can induce the stress response, researchers have used them to boost up the defence and repair system. For example, Willem van Eden and his group, also partners in the IOP project, have found that various forms of arthritis in rat and mouse models could be suppressed by HSP immunization or by boosting the heat shock system. The IOP participating group of Harrie Kampinga has shown that triggering the stress system is beneficial in animal models for atrial fibrillation (cardiac arrhythmia). Others have published similar results for a polyglutamine disease (spinal and bulbar muscular atrophy) and for Amyotrophic Lateral Sclerosis (ALS). A clinical trial is running now in the USA in which the efficacy of arimoclomol, a co-inducer of the stress response, is tested in ALS patients.

Critical nodes

Lubsen: "With increasing age the transcription factors that regulate the expression of HSPs become inactive and the system can no longer be upregulated this way. Furthermore, the only known way to upregulate the stress system is to cause cellular stress, which ultimately may be deleterious. Our aim is to find ways to boost the defence and repair system without the deleterious effects. However, to do that we need to know more about the system, its critical nodes and rate limiting steps."
So far some 60 heat shock proteins have been found. For most of these the precise function is not known. Only a few have been described more extensively in the scientific literature.
"We want to know which proteins are crucial elements in the prevention of age-related diseases. Possibly we can upregulate one or more of these proteins, to prevent or treat these diseases. The challenge in upregulation is to bypass the stress activated transcription

factors. In addition, by measuring the level of crucial proteins we may have a read-out system for checking the cell's health. This way one could check if (older) patients are healthy enough to undergo certain treatments."
Since the stress system is active in different compartments of the cell and also plays a systemic role in the immune system, all these different aspects need to be studied in order to be able to manipulate the system. The research required a multidisciplinary approach and therefore four different academic groups collaborated in this IOP-project and its follow-up. The research group of Professor Willem van Eden specifically focuses on the role of HSPs in the immune system; Professor Ineke Braakman's group studies the role of HSPs in the endoplasmatic reticulum (the cellular protein factory); and the teams of Professor Harrie Kampinga and Professor Lettie Lubsen focus on cytoplasmic proteins.

Harvest

"In the first IOP project we discovered some essential proteins, which we want to study in more detail in our second IOP project," says Professor Lettie Lubsen. The essential proteins were discovered by using cell-based model systems for protein folding diseases in which the action of single HSP proteins can be studied. For *in vivo* studies Drosophila models for protein folding disease and longevity are used as well. Mouse models were used to discover crucial proteins for induction of the immune system. "Fortunately, a new project has been funded, so hopefully we will now be able to reap the harvest from the investments we have made in the first project."
Lubsen is very satisfied with the way the academic groups collaborated. "There are very open discussions. Next to the regular meetings there was a lot of e-mail contact between the groups, especially between the PhD students, and also a lot of research material was exchanged."
"In the beginning there was not such an active role for the participating companies, but this was also due to the very fundamental character of the research at that early stage. However, the fundamental stage of finding essential HSPs is crucial for the success of the whole project."
"In the second project we want to develop bioactive compounds that affect the expression of the essential proteins (targets) circumventing the route of stress-related induction of the transcription factors.
At this stage the participating companies can contribute by delivering all kinds of compounds that we can test for effectiveness. Eventually they might be used in human medicine or as food components. Initially, tissue culture cells will be used to test the usefulness of such compounds and later on we will use mouse models for human diseases."

Diagnostic test

"Since some interesting HSP proteins have now been discovered, we hope to explore whether we can use them as targets in antibody-assays," says Dr. Jos Raats, Managing Director of ModiQuest. ModiQuest develops diagnostics and therapeutics for the human market.
"We specifically focus on the development of antibodies for use in diagnostic tests to detect markers for certain diseases. As a company, we are of course interested in new markers with predictive and commercial value and therefore this project is interesting to us. We contribute to this project by delivering knowledge and reagents. The ultimate goal is to develop a diagnostic test that is indicative for the stress level and stress resistance of cells."

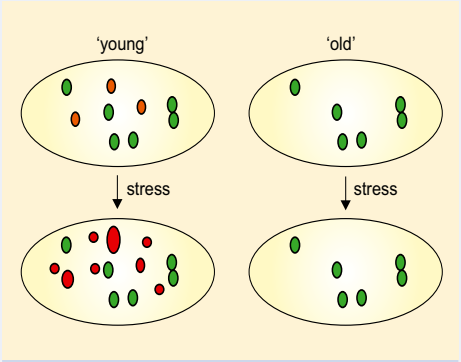


Figure 2 *Heat shock protein pattern in 'young' and 'old' cells before and after stress. Cells contain a lot of chaperone proteins (green) and young cells under non-stress condition also contain stress-regulated chaperones (orange). Under stress conditions, more chaperones are made (red). 'Old' cells lack the stress-regulated chaperones under non-stress conditions and also cannot increase chaperone synthesis when stressed; they only contain the non-stress regulated chaperones (green).*
Source: Inauguration Professor Lettie Lubsen (2008)

IOP Genomics Report

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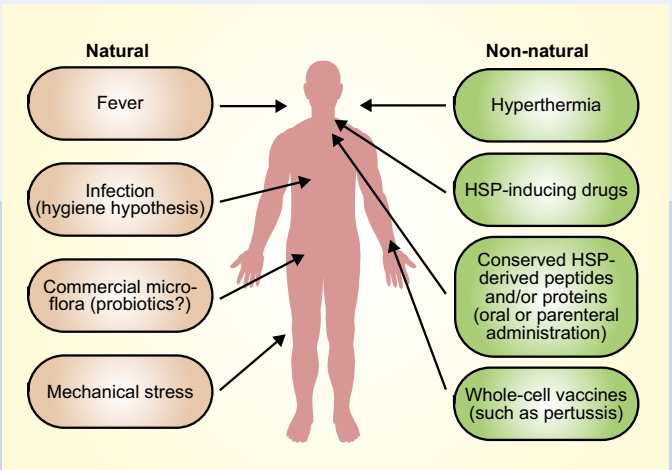

Figure 1
Natural and non-natural factors which can induce the stress response system.
Source: Nature Reviews Immunology (2005)