GCB 2012 Satellite Workshop

Systems Biology of Ageing

September 19, 2012

Abbe Centre, Beutenberg Campus, Hans-Knöll-Str. 1, D-07745 Jena / Germany

Jointly organised by the
Jena Centre for Systems Biology of Ageing – JenAge
and the
Jena Centre for Bioinformatics – JCB

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Programme

08:30	Registration
10:00 – 10:45	*Thomas Kirkwood (Newcastle upon Tyne)* **The dynamics of mitochondrial DNA mutations and ageing** **[cancelled]** *Karl Lenhard Rudolph (Ulm, Jena)* **Systems Biology - what do we need it for in ageing research?**
10:45 – 11:15	*Ingmar Glauche, Lars Thielecke, Sebastian Gerdes, Ingo Roeder (Dresden)* **Cellular ageing leads to functional heterogeneity of hematopoietic stem cells: concepts and applications**
11:15 – 11:45	*Markus Maucher, Hans A. Kestler (Ulm)* **The harmonics of Boolean networks**
11:45 – 12:15	*Thimo Rohlf, Jens Przybilla, Jörg Galle (Leipzig)* **A theoretical approach to the epigenetics of adult stem cell ageing**
12:15 – 13:30	Lunch Break
13:30 – 15:00	Poster Session
15:00 – 15:30	Coffee Break
15:30 – 16:00	*Oliver Philipp, Jörg Servos, Nadine Schöne, Heinz D. Osiewacz, Ina Koch (Frankfurt/M.)* **Co-expressed genes of the energy metabolism during ageing of *Podospora anserina***
16:00 – 16:30	*Sascha Schäuble, Karolin Klement, Shiva Marthandan, Sandra Münch, Ines Heiland, Stefan Schuster, Peter Hemmerich, Stephan Diekmann (Jena)* **Quantitative model of cell cycle arrest and cellular senescence in primary human fibroblasts**
16:30 – 17:00	*Uwe Menzel and the JenAge Consortium (Jena)* **Cross-species analysis of age-related transcriptome data**
17:00 – 17:30	*Christoph Englert and the JenAge Consortium (Jena)* **A multi-species and systems biology approach to ageing**
19:00	Welcome reception for participants registered with the GCB 2012 in the atrium of the university main building (Fürstengraben 1, D-07743 Jena)

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Poster Session

(13:30 - 15:00, Foyer of the Abbe Centre)

M. Buck, W. Bechtel, M. Klose, F. Grahammer, T. Huber, M. Börries, H. Busch
Transcriptome and methylome analysis of aged mouse glomeruli

A. Dix, S. Priebe, R. Guthke, M. Baumgart, A. Cellerino
MicroRNA-Seq data analysis for age-related comparison of mouse and short-lived fish *Nothobranchius furzeri*

A. Gross, J. Wang, L. Rudolph, H. A. Kestler
Modeling cross-differentiation across subpopulations of hematopoietic stem cells in response to irradiation

N. Hartmann, C. Englert
The role of mitochondria during aging in the short-lived killifish *Nothobranchius furzeri*

R. Hühne, T. Thalheim, J. Sühnel
Towards data integration in ageing research – The JenAge ageing factor database AgeFactDB

H. A. Kestler, J. M. Kraus
Subscan - a cluster algorithm for identifying statistically dense subspaces

M. Moeller, G. Fuellen
Machine learning on physiological parameters to perform mouse strain characterization

W. Schmidt-Heck, U. Menzel, R. Guthke
Involvement of mTor-pathway in ageing during cultivation of primary mouse hepatocytes

B. Seliger, C. Englert
Addressing the age dependence of kidney regeneration in the short-lived killifish *Nothobranchius furzeri*

T. Thalheim, R. Hühne, J. Sühnel
The JenAge Information Centre – an information hub for systems biology and ageing research

J. Wollbold, O. Wolkenhauer
Concept hierarchies, rule bases and the free radical theory of ageing

J. Wollbold, S. Müller, R. Jaster, K. Rateitschak
A rare ROS regulation triggers apoptosis versus necrosis in acute pancreatitis

K. Zarse. S. Schmeisser, M. Groh, S. Priebe, G. Beuster, D. Kuhlow, G. Guthke, M. Platzer, C. R. Kahn, M. Ristow
Impaired insulin-/IGF-1 signaling extends life span by promoting mitochondrial L-proline catabolism to induce a transient ROS signal

Abstracts of Talks

Listed in alphabetical order by family name of first author,
except for invited talk;
the speaker's name is indicated in capital letters.

Invited Talk

The dynamics of mitochondrial DNA mutations and ageing [cancelled]

THOMAS KIRKWOOD

Institute for Ageing and Health, Newcastle University, Campus for Ageing and Vitality, Newcastle upon Tyne, NE4 5PL, UK

Unfortunately, Tom Kirkwood is not able to come due to the death of a close relative. Thankfully, Karl Lenhard Rudolph has stepped in with the talk

Systems Biology - what do we need it for in aging research?

KARL LENHARD RUDOLPH [1,2]

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Contributed Talk

A multi-species and systems biology approach to ageing

CHRISTOPH ENGLERT[1] and the JenAge consortium[2]

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[2] Jena Centre for Systems Biology of Ageing – JenAge; Participating Institutions and Labs: Leibniz Institute for Age Research – Fritz Lipmann Institute (FLI): Alessandro Cellerino, Christoph Englert, Stefan Diekmann/Peter Hemmerich, Matthias Platzer, Jürgen Sühnel; Leibniz Institute for Natural Product Research and Infection Biology – Hans Knöll Institute (HKI): Reinhard Guthke; Friedrich Schiller University Jena: Udo Hahn, Christoph Kaleta, Michael Ristow, Stefan Schuster; Jena University Hospital: Otto Witte

The goal of the JenAge initiative is to identify conserved transcriptional networks that mediate healthy ageing and to investigate their role in preserving functional integrity in old age. Previous work on model organisms has demonstrated that mild stress can increase lifespan and delay ageing. We are therefore particularly interested in pathways and networks that are activated by mild perturbations including physical exercise. As model systems we use *C. elegans*, two fish species, namely the zebrafish as well as a short-lived killifish, *Nothobranchius furzeri*, the mouse, human fibroblasts as well as in some instances humans. We are employing an iterative process whereby experimental data are communicated to the analysis and modeling groups to generate testable hypotheses, which will in turn be validated by genetic and other manipulations in model organisms.

In a preliminary experiment we have performed a comparison of ageing-associated gene expression changes in *C. elegans*, mouse and zebrafish. For further validation we have selected 22 candidate genes that were either up- (10) or downregulated (12) with age and have used RNAi-mediated knockdown in *C. elegans*. Within the first group knockdown of 4 genes extended lifespan while knockdown of one gene reduced lifespan. Inactivation of the other 5 genes did not affect lifespan. Within the latter group, namely those that were down-regulated with age, knockdown of 8 genes extended lifespan, while interference with two genes each did either not affect lifespan or reduced it. As a preliminary conclusion one can state that knockdown of 15 out of 22 candidate genes indeed leads to alterations of lifespan in *C. elegans*, thus underscoring the suitability of our approach. Interestingly, some gene expression changes can be regarded as an *adaptive response* to ageing.

We have meanwhile extended our analysis to all five species and are currently including data from mild stress experiments. We have also started to generate first models based on JenAge data. Our analysis suggests, although ageing is to a large extent organ-specific, the existence of common ageing-associated networks including those regulating specific aspects of metabolism or biology of the extracellular matrix.

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Contributed Talk

Cellular aging leads to functional heterogeneity of hematopoietic stem cells: concepts and applications

INGMAR GLAUCHE, Lars Thielecke, Sebastian Gerdes, Ingo Roeder

Institute for Medical Informatics and Biometry (IMB), Faculty of Medicine Carl Gustav Carus, Dresden University of Technology, Blasewitzer Str. 86, D-01307 Dresden, Germany

Hematopoietic stem cells (HSCs) are the source for the life-long supply of functional cells in peripheral blood while they simultaneously maintain their own reserve pool. However, there is accumulating evidence that HSCs are themselves subject to quantitative and qualitative exhaustion. Although several processes linked to mitotic activity can potentially account for the observed aging phenomena (e.g., DNA damage, telomere shortening, epigenetic modification), a precise understanding of HSC exhaustion is still missing. It is particularly unclear how individual aging processes on the single-cell level translate on the phenotypic level of the overall tissue and whether there is a functional implication of an age-structured HSC population.

We address these issues by applying a novel mathematical model of HSC organization in which division-specific, cumulative alterations of stem cell quality determine the phenotypic and functional appearance of the overall cell population. Adapting the model to a number of basic experimental findings, we quantify the level of additional heterogeneity that is introduced by a population of individually aging cells. Based on this model, we are able to conclude that division-dependent processes of cellular aging explain a wide range of phenomena on HSC exhaustion and that HSC aging needs to be considered as a highly heterogeneous process.

We apply our model of aging hematopoiesis in the context of aplastic anemia and premature aging occurring due to a deficiency of the thrombopoietin receptor MPL. Based on this model we are able to explain premature bone marrow failure as the result of an increased proliferative stress, which is triggered by the impaired ability of MPL deficient HSCs to bind to regenerative HSCs niches.

Contributed Talk

The harmonics of Boolean networks

MARKUS MAUCHER, Hans A. Kestler
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Boolean network models are a means to describe and analyze the dynamic behavior of gene regulatory networks. In this kind of model, the state of each gene is described by a Boolean variable that can only take the two values TRUE ("active") and FALSE ("inactive"), and the dynamics of the network are described by Boolean functions. In line with Occam's razor, this type of model has a very small parameter set and is thus especially suited to model large genetic networks [1].

The Walsh transform and a modified Pearson correlation [2,3] can be used for the reverse engineering of Boolean networks from time series data. Both methods use the fact that in gene regulatory networks, a specific transcription factor often will consistently either activate or inhibit a specific target gene. In this scenario, the observed regulatory behavior can be modeled by the use of monotone functions.

In contrast to the correlation coefficient, the Walsh transform is also able to represent higher-order correlations. The correlation of several combined input variables with one output variable gives additional information about the dependency between these variables, but is also more sensitive to noise. In addition, the computational complexity increases exponentially with the order. We investigate under which conditions (noise, number of samples, function classes) higher-order correlations can contribute to an improvement of the reconstruction process. We present the advantages, as well as the limitations, of higher-order correlations for the inference of Boolean networks.

[1] Bornholdt S.
Systems biology: Less is more in modeling large genetic networks.
Science. **2005**; 310(5747):449-51.

[2] Maucher M, Kracher B, Kühl M, Kestler HA. (2011)
Inferring Boolean network structure via correlation.
Bioinformatics. **2011**; 27(11):1529-36.

[3] Mossel E, O'Donnell R, Servedio R.
Learning juntas.
In *STOC '03*: Proceedings of the thirty-fifth annual ACM symposium on Theory of Computing, pages 206-212, **2003**.

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Contributed Talk

Cross-species analysis of age-related transcriptome data

UWE MENZEL[1] and the JenAge consortium[2]

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[2] JenAge: Jena Centre for Systems Biology of Ageing; Participating Institutions and Labs: Leibniz Institute for Age Research – Fritz Lipmann Institute (FLI): Alessandro Cellerino, Christoph Englert, Stefan Diekmann/Peter Hemmerich, Matthias Platzer, Jürgen Sühnel; Leibniz Institute for Natural Product Research and Infection Biology – Hans Knöll Institute (HKI): Reinhard Guthke; Friedrich Schiller University Jena: Udo Hahn, Christoph Kaleta, Michael Ristow, Stefan Schuster; Jena University Hospital: Otto Witte

We analyze the complete transcriptomes of four species (*Caenorhabditis elegans, Nothobranchius furzeri, Danio rerio, Mus musculus*) at different age levels in order to facilitate understanding of the molecular mechanisms behind the process of ageing. RNA-Seq data obtained from the Illumina HiSeq 2000 sequencing machine were mapped to the corresponding reference genomes in order to determine the expression levels of the complete gene sets of these organisms. Genes that are significantly differentially expressed between age levels were determined using state-of-the-art statistical tools for count data. Different filtering methods were developed in order to dispose genes with low expression levels, high variance between replicates, or irregular temporal behavior. Principal component analysis and clustering methods were used to characterize the samples with respect to age levels, species membership, and temporal shape. We identify signaling pathways and gene ontologies that are over-represented amongst the sets of genes which are significantly up- or down-regulated with age, and amongst genes that belong to particular clusters. In addition, lists of age-relevant genes for further biological investigation were established by utilizing a machine learning approach. Gene-networks based on correlation between genes over age were constructed in order to describe the influence on co-expression of perturbations by drugs known to affect life span. Throughout the analysis, we use a Monte-Carlo approach to include replicates of the measurements at the corresponding age levels. As a byproduct, a novel software tool was developed that allows the user to access orthology relationships across multiple species in an easy, fast, and flexible manner.

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Contributed Talk

Co-expressed genes of the energy metabolism during aging of *Podospora anserina*

OLIVER PHILIPP[1,2], Jörg Servos[2], Nadine Schöne[1], Heinz D. Osiewacz[2], Ina Koch[1]

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[2] Johann Wolfgang Goethe University, Faculty for Biosciences & Cluster of Excellence 'Macromolecular Complexes' Frankfurt, Institute of Molecular Biosciences, Max-von-Laue-Str. 9, D-60438 Frankfurt am Main, Germany

Aging of biological systems is a complex process controlled by the genetic constitution of the individual. It is strongly influenced by changes in gene expression resulting from stochastic processes or induced by environmental factors and conditions. To monitor the age-related changes in transcript profiles we performed a genome-wide transcriptome analysis of the fungal aging model *Podospora anserina*. Out of the 10,635 transcripts deduced from the genome sequence of *P. anserina* about 10,200 (coverage of 95%) were identified in a SuperSAGE analysis. We validated the obtained large data set by different statistical methods and analyzed it using clustering techniques. Here, we report the bioinformatics analysis of the differential transcriptomes with special emphasis on transcripts of the energy metabolism which is known to play a key role in aging. Furthermore, for analysis of the transcriptional data, we introduce a new statistical method, based on co-expression networks, which identifies groups of genes with high degree of co-expression and/or co-regulation. More precisely, the basic idea of our method is to reveal whether groups of genes associated with similar processes or complexes as denoted in databases, e.g., the KEGG database, show more co-expression than expected by chance.

We demonstrate that many genes, coding for proteins associated with the mitochondria, are continuously down-regulated during the course of aging. Exceptions to these tendencies are genes coding for proteins that are directly involved in the energy metabolism (e.g. respiratory chain and the citric acid cycle). Although these genes are characterized by irregular patterns, they exhibit a significant degree of co-expression. This emphasizes the importance of a well-controlled expression of genes involved in energy transduction during the lifespan of *P. anserina*.

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Contributed Talk

A theoretical approach to the epigenetics of adult stem cell ageing

THIMO ROHLF[1,2], Jens Przybilla[1], Jörg Galle[1]

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[2] Max Planck Institute for Mathematics in the Sciences, Inselstr. 22, D-04103 Leipzig, Germany

Epigenetic control of gene expression by chromatin re-modeling is critical for adult stem cell function. During ageing a decline in stem cell function is observed that is accompanied by currently unexplained changes of the chromatin structure. Here, we show that these epigenetic changes may originate in the limited cellular capability to inherit epigenetic information. We suggest that spontaneous loss of histone modifications due to fluctuations on short time scales gives rise to long term gene silencing by DNA methylation. This silencing is assumed to impair stem cell function and thus, contributes to ageing. As potential sources of these fluctuations we discuss stochastic modification dynamics and reduction of modification levels due to incorporation of de novo synthesized histones during transcription, DNA repair and cell replication. Specifically, our mathematical model shows that the (experimentally established) coupling between H3K4me3 modifications and DNA methyltransferase DNMT3a, in combination with cooperative, bistable histone modification dynamics, can lead to DNA hypermethylation at specific genomic loci. Feed-back effects from thus silenced genes on DNMT1 expression could explain age-related hypomethylation observed in other genomic regions. We show that this hypomethylation can be further accelerated through experimentally observed feed-back between H3K9me3 marks and DNMT1 recruitment.

Finally, we discuss implications of our model for both stem cell theory and ageing. We argue that noise in histone modification dynamics may contribute to cell differentiation and tissue heterogeneity, and thus be an important aspect of stem cell plasticity. Hence, our ageing model can be interpreted as manifestation of a conflict between stem cell plasticity required in tissue regeneration and permanent silencing of potentially deleterious genomic sequences by DNA methylation.

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Contributed Talk

Quantitative model of cell cycle arrest and cellular senescence in primary human fibroblasts

SASCHA SCHÄUBLE[1,2,6], Karolin Klement[3,4], Shiva Marthandan[3,6], Sandra Münch[3,5], Ines Heiland[2,6], Stefan Schuster[2,6], Peter Hemmerich[3,6], Stephan Diekmann[3,6]

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[2] Department of Bioinformatics, Friedrich Schiller University, Ernst-Abbe-Platz 2, D-07743 Jena, Germany

[3] Leibniz Institute for Age Research – Fritz Lipmann Institute, Beutenbergstr. 11, D-07745 Jena, Germany

[4] Current address: Department of Biochemistry & Molecular Biology, Faculty of Medicine, University of Calgary, 3330 Hospital Drive NW, T2N 4N1, Calgary, AB, Canada

[5] Current address: Medical Research Institute, Ninewells Hospital & Medical School, Dundee, DD1 9SY, Scotland UK

[6] Jena Centre for Systems Biology of Ageing – JenAge

In 1961 Hayflick and Moorhead found that in tissue culture primary human fibroblasts undergo a limited number of cell divisions before entering a non-replicative "senescent" state. While at early population doublings (PD) fibroblasts are proliferation-competent, an increasing number of cells become cell cycle arrested and finally senescent during further cell passaging. This transition from proliferating to senescent cells is driven by a number of endogenous and exogenous stress factors. We have developed a new quantitative model of the stepwise transition from proliferating human fibroblasts (P) via reversibly cell cycle arrested (C) to irreversibly arrested senescent cells (S). In this model, we formulated a stress response function F that aggregates and processes various forms of stress and promotes the transition from P to C and to S cells. Applying senescence marker quantification at the single-cell level to our model, allowed us to discriminate between the cellular states P, C, and S as well as to identify the transition rates between the P, C and S states for different human fibroblast cell types. Unexpectedly, our model-derived quantification revealed significant differences in the stress response of different fibroblast cell lines. By evaluating marker specificity, we found that SA-β-Gal is a good quantitative marker for cellular senescence in WI-38 and BJ cells, however much less so in MRC-5 cells. The differentiation between three cellular states P, C and S and the explicit separation of stress induction from the cellular stress response allows us for the first time to quantitatively assess the response of primary human fibroblasts towards endogenous and exogenous stress during cellular ageing.

Poster Abstracts

Listed in alphabetical order by family name of first author;
the presenter's name is indicated in capital letters.

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POSTER

Transcriptome and methylome analysis of aged mouse glomeruli

M. BUCK[1], W. Bechtel[2], M. Klose[1], F. Grahammer[2], T. Huber[2], M. Börries[1], H. Busch[1]

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Glomeruli constitute the main filtration unit in the kidney. They are partially constituted by podocytes, post-mitotic cells that are highly sensitive to ageing, as any damage causing podocyte death cannot be reversed. This leads to a high correlation between the Glomerular Filtration Rate (GFR) and age, hinting to a major involvement of glomeruli in the process of kidney ageing, and ageing in general.
Here, we present the results of the first combined functional transcriptome and methylome analysis of primary murine glomeruli of different age. For this, glomeruli where extracted from young (8 weeks) and old (21 months) mice using a magnetic-bead perfusion protocol, which then were further processed for mRNA and methylated-DNA microarray hybridization.

Gene set enrichment analysis between young and old glomeruli showed a significant up-regulation of cell-division, DNA-repair and extra-cellular matrix related genes with age. A CpG island chip was used in the search for methylated DNA regions. We used a novel gene-set enrichment method to identify the most likely promoter regions and functional link to gene regulation, which showed that a upstream/ downstream size of 3000bp best matched methylation to gene function.

Direct correlation between methylation sites and regulation of associated genes was found to be weak. However, correlation could be much improved by correlating methylation with interacting genes.

In conclusion, we acquired a first insight into the functional interplay of gene regulation and differential methylation of aging mouse glomeruli, providing important cues for subsequent analysis on the causes of kidney ageing.

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Poster

MicroRNA-Seq data analysis for age-related comparison of mouse and short-lived fish *Nothobranchius furzeri*

A. DIX[1,3], S. Priebe[1,3], R. Guthke[1,3], M. Baumgart[2,3], A. Cellerino[2,3]

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Although many biological principles of the aging process remain to be elucidated, it is known that aging is an accumulation of changes and damage over time [Lombard *et al.,* 2005; Bowen and Atwood, 2004]. This damage results in or is partially caused by changes of gene expression and gene regulation. Since microRNAs (miRNAs) regulate about 30% of all animal genes, they are making a meaningful contribution to gene regulation [Bushati and Cohen, 2007]. Therefore, the analysis of miRNAs is of high importance for age research.

This work compares the infuence of miRNAs on age-related genes between mouse and the turquoise killifish, *Nothobranchius furzeri*. This fish features an extremely short lifespan for a vertebrate making it a suitable organism for aging research [Baumgart *et al.,* 2012]. Throughout this study, numerous mouse miRNAs were identified as age-related. For many of them, the association to aging could be confirmed by other studies. Hence, there is a high probability that the other miRNAs are relevant for aging, too. In contrast to this, the number of age-related killifish miRNAs is much smaller and none of them could be verified as associated to aging by literature.

Additionally, conserved patterns of expression change were found for several miRNAs. In mouse, some of them are predicted to control the expression of age-related genes. However, an association to aging could not be made for the conserved killifish miRNAs.

Baumgart M, Groth M, Priebe S, Appelt J, Guthke R, Platzer M, Cellerino A.
Age-dependent regulation of tumor-related microRNAs in the brain of the annual fish *Nothobranchius furzeri*.
Mech Ageing Dev. **2012**;133(5):226-33.

Bowen RL, Atwood CS.
Living and dying for sex.
Gerontology. **2004**;50(5):265-290.

Bushati N, Cohen SM.
microRNA functions.
Annu Rev Cell Dev Biol. **2007**;23:175-205.

Lombard DB, Chua KF, Mostoslavsky R, Franco S, Gostissa M, Alt FW.
DNA repair, genome stability, and aging.
Cell. **2005**;120(4):497-512.

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Poster

Modeling cross-differentiation across subpopulations of hematopoietic stem cells in response to irradiation

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Hematopoietic stem cells (HSC) are divided into common lymphoid (lineage of T-, B- and NK-cells) or common myeloid (lineage of macrophages, erythrocytes, dendritic cells and others) progenitors. An external stimulus affecting HSCs in a lineage-dependent manner may possibly lead to cross-differentiation of HSC lineages in order to jointly maintain the function of HSCs. In this study, we investigate the behavior of common myeloid progenitor HSCs and common lymphoid progenitor HSCs after irradiation. Although this ultimately leads to their depletion, the experiments show remarkable differences of cell numbers for both groups.

We discriminate cell populations by CD150 cell surface markers. $CD150^{hi}$ cells represent the lineage of myeloid progenitors, while $CD150^{lo}$ cells stand for lymphoid progenitors. Their interactions are described in a computational model based on delay-differential equations. Several cellular processes involving these populations are specified. $CD150^{hi}$ HSCs can differentiate into $CD150^{lo}$ HSCs and the latter to further lymphoid progenitor cell lineages. Proliferation and apoptosis happen in all HSCs subpopulations and are based on measurements of further markers.

We translated the specified populations and cellular processes into a model of coupled delay-differential equations. After inferring the corresponding kinetic parameters, we simulate the dynamics of the subpopulations and compare them to the experimental observations. Enabling differentiation from $CD150^{hi}$ to $CD150^{lo}$ and from $CD150^{lo}$ to further lineages yields a significantly lower error between the experimentally observed cell numbers and results from computational model simulations.

The experiments demonstrate that different HSCs populations show distinct responses to external stimuli like irradiation. The results from our computational model indicate that in response to irradiation myeloid progenitor HSCs differentiate into lymphoid progenitor HSCs.

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Poster

The role of mitochondria during aging in the short-lived fish *Nothobranchius furzeri*

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[2] Jena Centre for Systems Biology of Ageing – JenAge

Mitochondria have been suggested to play an important role in aging for decades. One observation is that mitochondrial function declines with age in numerous organisms. In humans, age-related mitochondrial dysfunction has been frequently described to accumulate in patients with sarcopenia, metabolic disorders and neurodegenerative diseases. We use the short-lived killifish *Nothobranchius furzeri* as a model to study the impact of mitochondria on aging. For a vertebrate species, *Nothobranchius furzeri* has an exceptionally short lifespan of four to ten months and shows typical signs of aging. We recently observed that mitochondrial respiration, ATP content and the amount of respiratory chain complexes III and IV are significantly reduced with age in the skeletal muscle of *N. furzeri*. We also found that the expression of the genes *Pgc-1α* (*peroxisome proliferator-activated receptor γ coactivator-1α*) and *Tfam* (*mitochondrial transcription factor A*) as well as the mitochondrial DNA content are significantly decreased with age in several tissues.
We are currently studying how this age-related decline can be prevented or even reversed. One approach that has been shown to increase mitochondrial function is physical exercise. Preliminary results suggest that mitochondrial genes are up-regulated in the skeletal muscle of exercised fish. A study to determine the effect of exercise on survival and lifespan is under way. Another approach to improve mitochondrial function is to over-express mitochondrial genes in adult fish, which requires the possibility to perform transgenesis in *N. furzeri*. Therefore, we developed a microinjection protocol to introduce DNA constructs directly into the 1-cell stage of the embryo. We could show that the injected transgene was integrated into the genome and transmitted to subsequent generations. Altogether, we want to find out whether increased mitochondrial activity can extend the lifespan of *N. furzeri*.

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Poster

Towards data integration in ageing research – The JenAge ageing factor database AgeFactDB

R. HÜHNE[1,2], T. Thalheim[1,2], J. Sühnel[1,2]

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The Jena Centre for Systems Biology of Ageing – JenAge adopts a systems biology approach to ageing research. On the experimental side these approaches generate new data of increasing complexity at an unprecedented pace. On the other hand systems biology modeling requires an effective processing and analysis of these data and most importantly the integration of data from different sources. The JenAge ageing factor database AgeFactDB [1] is aimed at the capturing and integration of ageing-related data. In a first step it combines data from existing databases with age-related information, such as the Lifespan Observations Database [2] and the GenAge Database [3]. Information from further data sources will be included step by step. The next data source will be the GenDR database [4], which offers information on genes associated with dietary restriction. In the future new ageing-related information will be included both by manual and automatic information extraction from the scientific literature.

Information related to the effect of ageing factors on life span and/or ageing phenotype is called an observation and is presented in the database on observation pages. Information reported in one paper can lead to one or more observations. Ageing factors include genes, chemical compounds and other factors such as dietary restriction or overfeeding, heat shock, low temperature and so on. To provide an easy and compact access to the complete information for a particular gene or a specific compound or for one of the other factors the corresponding observations are also summarised on ageing factor pages. Based on a comprehensive homology analysis, AgeFactDB provides, in addition to known ageing-related genes a compilation of genes that are orthologous to these known genes. These orthologs can be considered as candidate ageing-related genes.

AgeFactDB makes an attempt to unify gene symbol names. In addition to the unified name AgeFactDB provides also information on many synonym names.

Currently, AgeFactDB offers information on 1572 ageing-related genes, on 83 chemical compounds with a lifespan effect and on 56 other ageing factors. In addition, 9618 putative genes that are orthologous to known ageing-related genes are included.

[1] AgeFactDB http://agefactdb.jenage.de/
[2] Lifspan Observations Database http://lifespandb.sageweb.org/
[3] GenAge Database http://genomics.senescence.info/genes/
[4] GenDR Database http://genomics.senescence.info/diet/

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Poster

Subscan - a cluster algorithm for identifying statistically dense subspaces

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Cluster analysis is an important technique of initial explorative data mining. It refers to a collection of statistical methods for learning the structure of data by solely exploring pairwise distances or similarities in feature space. Recent approaches in clustering aim at detecting groups of data points that exist in arbitrary, possibly overlapping subspaces. Generally, subspace clusters are neither exclusive nor exhaustive, i.e. subspace clusters can overlap as well as data points are not forced to participate in clusters. In this context subspace clustering supports the search for meaningful clusters by including dimensionality reduction in the clustering process. Subspace clustering can overcome drawbacks from searching groups in high-dimensional data sets, as often observed in clustering biological or medical data. In the context of microarray data this refers to the hypothesis that only a small number of genes is responsible for different tumor subgroups. We generalize the notion of scan statistics to multi-dimensional space and introduce a new formulation of subspace clusters as aggregated structures from dense intervals reported by single axis scans. Our approach objectifies the search for subspace clusters as the reported clusters are of statistical relevance and are not artifacts observed by chance. Like in hierarchical cluster analysis there are two possible strategies to detect relevant subspace clusters. In a top-down approach, the dimension of clusters identified in the full space is reduced until a minimal subspace supporting the cluster assumption is reached. Using a bottom-up strategy allows the agglomeration of clusters from regions of high density across intervals from different dimensions. We present a bottom-up algorithm to grow high-dimensional subspace clusters from one-dimensional statistically dense seed regions. Our experiments demonstrate the applicability of the approach to both low-dimensional as well as next generation sequencing data.

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Poster

Machine learning on physiological parameters to perform mouse strain characterization

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Mice are among the most widely used animals for research studies. Being genetically well defined, characterized and having a manageable life expectancy, they are well useful for longevity experiments.

Our aim has been to find the best physiological parameters to allow the successful allocation of a sample mouse to the correct strain. Therefore we used RandomForest™ as a machine learning approach and variable importance as the feature selection algorithm.

The Mouse Phenome Database by the Jackson laboratory provided us with valuable longevity-related data records for different experiments including several blood analyses of an average of 30 inbred strains of mice. This time dependent data (6 months, 12M, 18M/20M, 24M) allowed us to check how the predictive quality of the implied model is changing with the increasing age of the mice.

It can be concluded that a complete blood count provides very good data to differentiate between laboratory mouse strains with an accuracy of over 80%. The best results have been achieved using the more detailed peripheral blood leucocyte profiles with accuracies over 90%, supporting the strain specificity of the immune system.

The accuracy of prediction is age dependent. The younger the mouse, the better are the results. This might be explained by the increasing variance of the measured values for older mice.

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Poster

Involvement of mTOR-pathway in aging during cultivation of primary mouse hepatocytes

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Liver is the main organ of intermediary metabolism. Lipids, amino acids and sugars are metabolized by hepatocytes according to the need of the body. Isolated hepatocytes can be used to study these topics of liver metabolism in vitro. Therefore, there is a need to understand signal transduction and metabolic pathways of hepatocytes. On the other hand, it is necessary to characterize the influence of the in vitro culture conditions on signal transduction and metabolism of hepatocytes.

Data of cultivated hepatocytes (Zellmer *et al.)* was used to investigate the cellular response to cultural adaptation. To monitor changes at the transcription level, Affymetrix GeneChip MOE 430 2.0 oligonucleotide arrays were used for hybridisation. Six samples were taken within a period ranging from 3 to 48 hours after isolation. The mRNA of freshly harvested cells (3h = immediately after attachment) was used as control. The data were pre-processed using Bioconductor Software. 3362 probesets were found to be differentially expressed by a fold change greater three in one or more samples after isolation. Scaled expression profiles of the differentially expressed genes were clustered using Fuzzy c-means algorithm into eight groups.

The result of transcriptome data analysis was mapped to the signalling pathways linking mTORC1 and mTORC2 to ageing via protein synthesis and autophagy (Hands *et al.*). The activated sub-networks were described by a system of linear differential equations. The simulation of the obtained network shows an activation of the mTor pathway by nutrients activated signals (PI3K/Akt, Erk12/Rsk and p38/Mk2 signalling). The direct activation of „mTor complex 1“ through Nrf2 signalling was observed.

Zellmer *et al*.
Transcription factors ETF, E2F, and SP-1 are involved in cytokine-independent proliferation of murine hepatocytes.
Hepatology **2010**;52(6):2127-36.

Hands SL, Proud CG, Wyttenbach A.
mTOR's role in ageing: protein synthesis or autophagy?
Aging (Albany). **2009**;1(7):586-97.

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Poster

Addressing the age dependence of kidney regeneration in the short-lived killifish *Nothobranchius furzeri*

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Ageing is an irreversible process. Over time, age-related diseases occur, affecting different organs in the body. It is known that during ageing kidney functionality declines and results in a number of diseases. While fish and reptile nephrogenesis and renal regeneration persist throughout life, mammals can only partly repair the damaged functional units (nephrons) in the kidney.

Our focus is on kidney regeneration of the short-lived vertebrate *Nothobranchius furzeri*. This fish is found in ponds in the south of Africa, which desiccate during the dry season. As an adaption to this environment these fish have an extremly short lifespan with a maximum of 12 months. This makes it an ideal model organism to study the differences in kidney regeneration in both young and old organisms. To address a potential age-dependence as well as the underlying mechanisms, the kidney of young (16 week-old) and aged (42 week-old) *N. furzeri* was damaged with a sufficient dose of the nephrotoxin gentamicin. Damage and renal regeneration could be observed. Kidneys of fish were prepared at different time points post injection. FITC-conjugated dextran is taken up only by the proximal part of intact nephrons and fails to be filtered after an injury occurred. This dye was injected 24 h prior to preparation to compare the dynamics of filtration in young and old animals. At 2 days post injection (dpi) no dextran was filtered in the kidney, neither in young nor in old animals. Young fish started to recover at 4 dpi whereas recovery was delayed in old fish. At 6 dpi dextran uptake was found in all young fish, however, not all old fish recovered even after 8 dpi. One kidney from each fish was used to isolate total RNA and qRT-PCR was performed. The other kidney was embedded in paraffin and cut for histological analysis. At 2 dpi sloughed cells and protein aggregates were visible in the lumen of some nephrons in both age groups. They disappeared at 4 dpi. A TUNEL-assay showed apoptotic areas in the kidney at 2 dpi, returning to normal levels at 8 dpi in both age groups. Analysis by qRT-PCR showed an upregulation of developmentally relevant genes such as *wt1a*, *wt1b*, *lhx1* and *wnt9b*. In young fish, gene expression returned at 8 dpi, while in old fish it remained high, except for *lhx1*, which was not upregulated in aged fish at all. Immunofluorescence analysis of proliferation marker, PCNA, revealed a peak expression in young fish and a sustained high level in old fish. Taken together, these data indicate that the regeneration process is delayed in old fish.

Another focus will be on the identification and characterization of renal vesicles during the regeneration process. Diep and colleagues reported that these structures are formed during growth and after an injury (Diep *et al.,* Nature, 2011). The detection and quantification of renal vesicles in young and old fish during the regeneration process could give yet another hint regarding differences in aging. However, detection and quantification of these structures is challenging, since they have not been characterized yet.

As a future perspective we want to perform transplantation experiments, e.g. transplantation of nephrons from ubiquitously GFP-expressing transgenic young/old fish (*actin::GFP*) to young/old recipients to study nephron regeneration.

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Poster

The JenAge Information Centre – an information hub for systems biology and ageing research

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The JenAge Information Centre (info-centre.jenage.de**)** is a web resource with ageing-related and systems biology information that is intended to assist researchers in these fields. Currently it provides the following information:

- Journals,
- Books,
- Papers (compilation of important historical and current papers and of most highly cited papers),
- Compilation of ageing-related databases,
- List of ageing-related centres, institutes and interest groups,
- Meetings calendars (ageing-related and systems biology) and
- Science news.

The Information Centre's content is not community-driven but contributions and suggestions from the scientific community are welcome.

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Poster

A rare ROS regulation triggers apoptosis versus necrosis in acute pancreatitis

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The classical free radical theory of ageing (FRTA) states that organisms age because cells accumulate damage by free radicals (or more generally reactive oxygen species, ROS) and undergo senescence, apoptosis or necrosis. During the last years, however, the FRTA has been challenged, and more attention is given to physiological conditions where ROS have an important role for signalling processes, e.g. in the immune system. Recent findings [1] suggest that - in contrast to other tissues - in inflamed pancreatic acinar cells pro-apoptotic effects of ROS dominate their effect and the effect of Ca2+ on mitochondrial permeability transition pore (MPTP) opening, which in excess leads to necrosis and spreading of inflammation. It was hypothesized that this is caused by the absence of mitochondrial swelling, loss of antioxidants and consequent ROS burst after MPTP opening, in spite of the related breakdown of mitochondrial membrane potential. [2]

In order to test these explanations, we defined an interaction network in multi-valued logic with - at present - the following variables: bile acid (stimulus), Ca2+, NADH, membrane potential, ATP, ROS, antioxidants, MPTP, necrosis (trypsin activation) and apoptosis (cytochrome c release and caspase activation). We adapted the logical functions to the data provided by [1]; alternative explanations will be decided by our own supplementary data. Relevant factors for Ca2+ oscillations like ATP, plasma membrane channels and intracellular store depletion were and will be tested.

Simulations, computations of logical steady states, attractors and temporal rules aim at revealing critical interactions influencing the subtle balance between apoptosis and necrosis and at predicting effects of different rates of ROS production (caused, e.g., by age related defects in the complexes of the respiratory chain). If increased antioxidant levels result in enhanced necrosis, this explains reported failures of antioxidant therapy. Overall, the investigation of beneficial ROS signaling can contribute to a more differentiated knowledge of its deregulation and of real ROS influences on ageing.

[1] D M Booth *et al.*
Reactive oxygen species induced by bile acid induce apoptosis and protect against necrosis in pancreatic acinar cells.
Gastroenterology. **2011**;140(7):2116-25.

[2] I Odinokova et al.:
Mechanisms regulating cytochrome c release in pancreatic mitochondria.
Gut. **2009**;58(23):431-42.

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Poster

Concept hierarchies, rule bases and the free radical theory of ageing

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The *Free Radical Theory of Ageing (FRTA)* states that organisms age because cells accumulate oxidative damage over time. Even if still alive, this theory is being challenged: Free radicals and, more generally, levels of *reactive oxygen species (ROS)* can be enhanced in long-living animals, new and important signaling effects of ROS are discovered and - of course - ROS are only one component within the complex regulation of ageing processes.

A major challenge in assessing the FRTA is to decide upon relevant players and their interactions, to discover logical inconsistencies and, given a knowledge base, to formulate testable hypotheses.

In the present work, we propose a formal conceptual framework to gather relevant biological evidence in the form of logical if-then-rules from the literature as well as from data. Specifically, we bring together two methods being new in systems biology: First, the construction of a knowledge base of *Ripple Down Rules (RDR)* can trace a scientific process of hypotheses and new discoveries, of rules and exceptions. Second, the resulting knowledge base is completed systematically by the attribute exploration algorithm of *Formal Concept Analysis (FCA)*. The RDR are translated into a data table of transitions young - old with observations as attributes. Then the algorithm helps to find all implications between the attributes: A minimal number of implicational rules is approved by experts, supported by literature and data analysis tools, or counterexamples are given. The resulting *stem base* represents the current knowledge of the experts, and all implicitly accepted rules can be derived logically from it.

Data were generated within the *ROSAge* consortium, where mouse strains with mutations in the protein complexes of the mitochondrial respiratory chain (the main origin of ROS) are under investigation. Stimuli comprise superoxide, hydrogen peroxide, triggers of cell proliferation, cancer, secretion or neural activity, as well as specific diets. As outcome, markers of cell senescence, cancer or cell viability are measured, furthermore glucose, ATP or ROS.

We focus upon the question which changes in ROS generation can influence the ageing process.

Hence, together with a visualisation of the transitions, attributes and rules by *concept hierarchies*, the project aims at clarifying scientific ideas, discovering hidden knowledge, provoking deeper literature quests and even at motivating new experiments.

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Poster

Impaired insulin-/IGF1-signaling extends life span by promoting mitochondrial L-proline catabolism to induce a transient ROS-signal

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[6] Section on Integrative Physiology and Metabolism, Research Division, Joslin Diabetes Center, Harvard Medical School, Boston, Massachusetts, US

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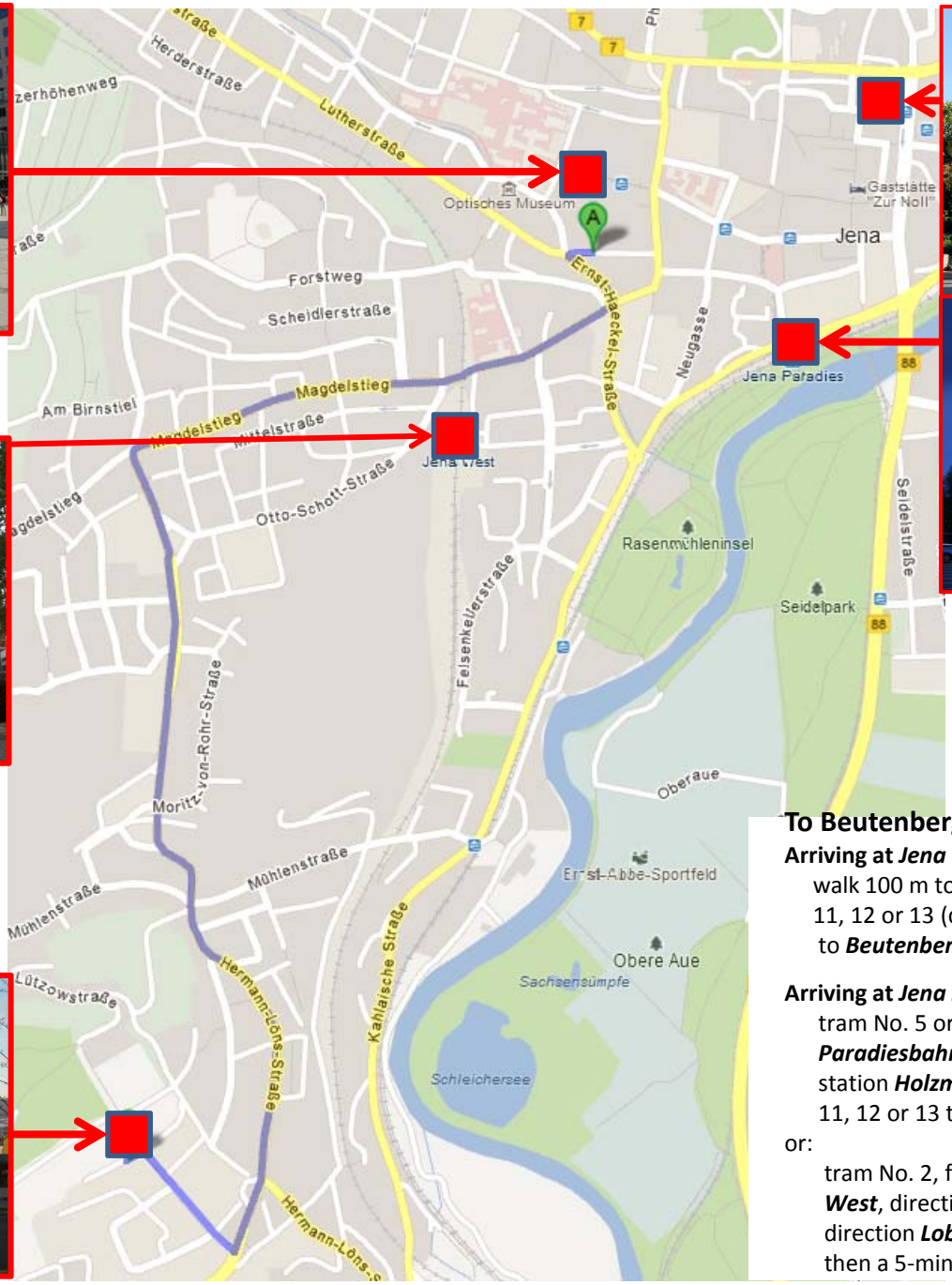
Impaired insulin and IGF-1 signaling (iIIS) in *C. elegans daf-2* mutants extends life span more than 2-fold. Constitutively, iIIS increases mitochondrial activity and reduces reactive oxygen species (ROS) levels. By contrast, acute impairment of *daf-2* in adult *C. elegans* reduces glucose uptake and transiently increases ROS. Consistent with the concept of mitohormesis, this ROS signal causes an adaptive response by inducing ROS defense enzymes (SOD, catalase), culminating in ultimately reduced ROS levels despite increased mitochondrial activity. Inhibition of this ROS signal by antioxidants reduces iIIS-mediated longevity by up to 60%. Induction of the ROS signal requires AAK-2 (AMPK), while PMK-1 (p38) and SKN-1 (NRF-2) are needed for the retrograde response. Lastly, transcriptome analyses identified mitochondrial L-proline catabolism to be uniformly upregulated in all three models of iIIS studied, and impairment of L-proline catabolism in nematodes impairs the life span extending capacity of iIIS while L-proline supplementation extends *C.elegans* life span. Taken together, iIIS promotes L-proline metabolism to generate a ROS signal for the adaptive induction of endogenous stress defense to extend life span.

Ernst-Abbe-Platz Campus
Ernst-Abbe-Platz, 07743 Jena
Conference Venue

Jena-West Train Station

Abbe Centre, Beutenberg Campus
Hans-Knöll-Str. 1, 07745 Jena
Workshop Systems Biology of Ageing
GCB Registration on Wednesday



University Main Building, Fürstengraben 1,
07743 Jena, **GCB Welcome Reception**

Jena-Paradies Train Station

Conference Locations and Train Stations

To Beutenberg Campus:

Arriving at *Jena Westbahnhof* (Jena-West Train Station)
walk 100 m to ***Magdelstieg*** and take buses No. 10, 11, 12 or 13 (direction ***Burgau/Göschwitz***) to ***Beutenberg Campus***

Arriving at *Jena Paradies* (Jena-Paradies Train Station)
tram No. 5 or 35, from tram station ***Paradiesbahnhof*** direction ***Ernst-Abbe-Platz*** to the station ***Holzmarkt*** (1 Stop) - change to buses No. 10, 11, 12 or 13 to ***Beutenberg Campus***

or:

tram No. 2, from tram station ***Paradiesbahnhof West***, direction ***Winzerla***, or tram No. 3 or 34, direction ***Lobeda-Ost***, to the station ***Ringwiese*** - then a 5-minute-walk uphill ***Hermann-Löns-Straße***