## Background information on the ZF-HEALTH project

The project is coordinated by the Karlsruhe Institute of Technology (KIT), Germany. Dr. Robert Geisler is the project's Scientific Coordinator and Dr. Jana Maier is the Project Manager. Due to the importance of this project, the Scientific Coordinator is assisted by two Co-coordinators: Prof. Uwe Straehle, director of the Institute of Toxicology and Genetics at KIT and Dr. Laure Bally-Cuif of Centre National de la Recherche Scientifique, France. The project officially began on July, 1st 2010 and will end on December, 31st 2015.The project's website is www.zf-health.org.

**Institutions participating in the ZF-HEALTH Integrated Project:**

Karlsruher Institut fuer Technologie, Germany (KIT-G)
Albert-Ludwigs-Universität Freiburg, Germany (ALU-FR)
Centre National de la Recherche Scientifique, Paris, France (CNRS)
Genome Research Ltd, London, UK (GRL)
Koninklijke Nederlandse Akademie van Wetenschappen - KNAW, Amsterdam, The Netherlands (KNAW)
Institut National de la Santé et de la Recherche Médicale, Paris, France (INSERM)
King's College, London, UK (KCL)
Universiteit Leiden, The Netherlands (UL)
Max-Planck-Gesellschaft zur Förderung der Wissenschaften e.V., München, Germany (MPG)
Technische Universitaet Dresden, Germany (TUD)
The University of Sheffield, UK (USFD)
Universita' degli Studi di Padova, Italy (UNIPD)
Universitaet zu Koeln, Germany (UCO)
Universitaet Zuerich, Switzerland (UZH)
University College London, UK (UCL)
Uni Research AS, Bergen, Norway (URA)
The University of Birmingham, UK (BHAM)
The University of Sydney, Australia (USYD)
ZF BioLabs SL, Tres Cantos, Spain (ZFB)

For a full list of participating groups, please see the ZF-HEALTH project's website: www.zf-health.org.

## Contact information

For further information on the project`s scientific goals, planned activities and job opportunities please see the project website (www.zf-health.org) or contact:

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## Job opportunities

The participating institutes will continuously provide job opportunities and training for technicians, PhD students and postdocs. To find out about current openings, please see the project web site (www.zf-health.org) or contact the heads of the labs you are interested in directly (contact details are listed on the project`s web site).

**Photo credits:** Page 1: MPI for Developmental Biology; Page 2: Karlsruhe Institute for Technology (1), MPI for Developmental Biology (2), University College London (3); Page 3: Karlsruhe Institute for Technology (1,2); Page 4: MPI for Developmental Biology

SEVENTH FRAMEWORK PROGRAMME

# ZF-HEALTH

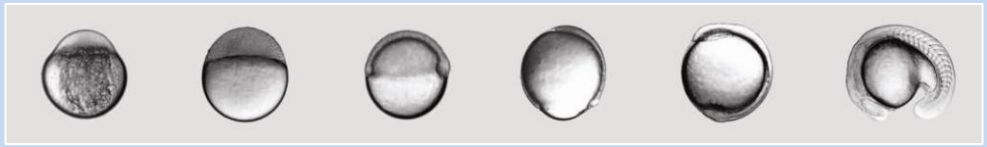
Zebrafish Regulomics for Human Health

## Overview

"ZF-HEALTH - Zebrafish Regulomics for Human Health" is a Large-scale Integrating Project funded by the European Commission as part of its Seventh Framework Programme (EC Grant Agreement HEALTH-F4-2010-242048). The aim of this project is to exploit the advantages of the zebrafish as a model organism for vertebrate development and human disease. Research groups at 19 different institutions in Australia, France, Germany, Italy, the Netherlands, Norway, Spain, Switzerland, and the United Kingdom are working together to achieve this aim. The project, which will run over a period of five and a half years, is funded with € 11,380,000.- from the European Commission.

## Scientific goals of the project

In recent years, the zebrafish has emerged as a new vertebrate model organism for biomedical research which offers a unique combination of traits: a short generation time, small size and efficient breeding procedures make it the best choice among vertebrates for forward genetic screening and small-molecule screens, including toxicology, while the transparent embryo and larva offers unique opportunities for imaging of cell movement and gene expression in a developing organism.



The ZF-HEALTH project builds on technologies and concepts developed in the preceding EU project ZF-MODELS. The ZF-HEALTH project aims to utilise these advances for the high-throughput phenotyping of at least a thousand regulatory genes relevant for human disease, by behavioural characterisation of the mutant fishes, 3D / 4D imaging and expression profiling by high-throughput sequencing. The groups involved in the ZF-HEALTH project further characterise regulatory elements of such genes by a combination of bioinformatics and transgenics. Furthermore by screening for small-molecules capable of rescue mutant phenotypes or disease-relevant processes, the project will identify candidate drugs and provide novel insights into gene function. The increasing knowledge on the regulators and their interactions with regulatory targets will be integrated with knowledge at cellular and organismic level. By capitalising on the virtues of the zebrafish system, this systems biology approach to the regulome will gain unique knowledge complementing ongoing work in mammalian systems, and provide important new stimuli for biomedical research.

**The research effort is divided in five workpackages covering:**

1. Generation and distribution of mutants for potential human disease genes
2. Phenotyping of mutants
3. Characterisation of enhancer elements of human disease genes
4. Gene expression mapping in the brain
5. Small molecule screening

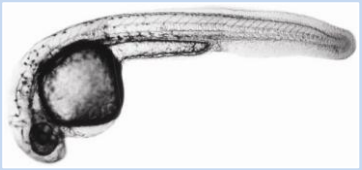
## 1. Generation and distribution of mutants for potential human disease genes

*Zebrafish husbandry at the European Zebrafish Resource Center*

Partners of the ZF-HEALTH project are using recently developed high-throughput mutagenesis screening methods to generate knock-out mutations in zebrafish in at least a thousand regulatory genes that are relevant for human diseases. These knock-out mutants, as well as an additional thousand mutants from the previous ZF-MODELS project, which have not yet been phenotyped in depth, will be deposited at the European Zebrafish Resource Center (EZRC) at the Karlsruhe Institute of Technology, Germany. The resource center will maintain the knock-out mutants and transgenic fish lines produced in this project and distribute them to the researchers inside and outside the Consortium. Besides distribution of the mutants to laboratories performing phenotyping, it will further provide facilities for screening and a database to collect the results. This resource center will be only the second one for the zebrafish worldwide, and the first one to act as a screening center. By providing facilities for performing shelf screens of the mutants, it will be instrumental in mobilising the expertise of European zebrafish researchers for the phenotyping of our knock-out mutants.

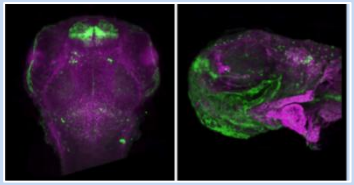
## 2. Phenotyping of mutants

We will conduct phenotyping in a three-tiered approach in order to create a comprehensive and data-rich annotation of the mutants, utilising the specialist expertise of the European zebrafish research community: Initial phenotyping for morphology and behaviour at day 5 will be carried out by the laboratories that generate the mutants. Second-level phenotyping, including behavioural phenotyping and transcript counting, will be carried out for a subset of mutants, as well as morphants or pharmacologically-treated animals. Third-level phenotyping will include shelf screens for additional phenotypes in which all project partners as well as external researchers will be invited to participate, contributing their assays; as well as in-depth analysis of disease-relevant pathways in the home labs of the participants. We will establish a facility for behavioural screening which will allow to screen for the first time on a large scale for phenotypes related to neurological disorders such as locomotion, olfaction and sensory-motor gating, as well as mood, motivational and cognitive behaviours including aggression and exploratory activity, and memory. Genetic abnormalities of the eye and visual processing will be studied both by behavioral and visual means. We will further perform studies providing insight into the genetic pathways underlying tissue regeneration and repair, including regeneration of the brain, and into process related to diabetes, obesity, infectious diseases and cancer.



*Zebrafish larva 24 hours after fertilisation. Internal organs such as the brain, the heart, the inner ear and the muscles of the trunk can be seen.*

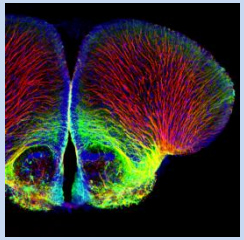
## 3. Characterisation of enhancer elements of human disease genes



*Staining of a transgenic zebrafish embryo to reveal the activity of a human disease gene*

We aim to perform a systematic characterisation of enhancer elements of potential disease genes. This characterisation builds on the concept of genomic regulatory blocks which contain highly conserved non-coding elements acting as long-range enhancers of developmental genes. It will allow us to test the complete set of regulatory elements of any given, disease relevant gene and to elucidate where and when human sequence variants predispose towards disease. This information, mapped to the human genome assembly, will help substantially in understanding human genetic variability and disease association as regulatory mutations affect these enhancers. The identification of such mutations will provide a unique new view of the large-scale organization of vertebrate genomes and eventually open the door to an individualized medicine.

## 4. Gene expression mapping in the brain

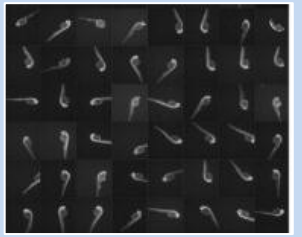


*Fluorescent analysis of the zebrafish brain*

To understand the function of genes that give behavioural phenotypes when mutated, a detailed description of neuroanatomical gene expression domains as well as of the circuitry of the zebrafish brain is a prerequisite. The overall objective of this work package is to establish a framework to link high resolution 3D gene expression pattern to neuroanatomical structures. It will further resolve the connectivity of circuits in the developing brain with an emphasis on circuits that are likely to be central to many of the behaviours that will be analysed in genetic and small molecule screens. In addition to presentation of data in publications, neuroanatomical information will be made available online. There is a growing appreciation that the results of such testing in the zebrafish are directly applicable to mammalian brains, and hence to clinicians.

## 5. Small molecule screening

A major advantage of the zebrafish for drug screening is the possibility to test compounds at a medium to high throughput, as in a cell-based assay, but in the context of a whole organism, allowing to detect bystander effects that are not visible with in vitro assays. Thus zebrafish screens allow us to test for drug efficacy and toxicity in a single step. We expect to identify a group of genes or disease-relevant processes as druggable targets based on their phenotypic analysis. Mutants of these genes or transgenic reporter lines for these processes will be subjected to small molecule screening to gain deeper insights into their regulation and function and to identify drug candidates. To achieve this, we will conduct technology development in the field of small-molecule screening, in particular with regard to high-throughput embryo handling and robotic microscopy. Existing robotic platforms will be refined and improved to handle the needs of large-scale screens, encompassing thousands of compounds. Compounds that give validated hits will be used as research tools for the analysis of regulatory pathways in development and disease. If suitable they will also be licensed to pharmaceutical companies as a starting point for drug development.



*Multi-well plate with laterally orientated zebrafish embryos for high content screening microscopy*

## Outreach

The ZF-HEALTH project intends to share the knowledge generated during the project with the wider scientific community and the general public as a whole. This is done, for example, by sharing its large-scale resources with scientists outside the consortium and by providing an integrative element for all of European zebrafish research (please see www.zf-health.org for details on the projects and resources open to interested parties).

In addition to reaching out to groups involved in basic research, the ZF-HEALTH consortium interacts with clinical researchers and the pharmaceutical industry seeking to address human diseases. This is achieved by, for example, inviting stakeholders from these communities to participate in events (e.g. meetings, symposia, workshops) organised by the ZF-HEALTH consortium. Also, visits and placements of staff from these communities to labs of the ZF-HEALTH consortium are strongly encouraged.

The ZF-HEALTH consortium is strongly committed to furthering the understanding and acceptance of science by the general public. A particular focus of the initiatives aimed at the general public is to get young people interested in taking up a career in science. To help those already training to be scientists, the ZF-HEALTH consortium is establishing training and exchange programmes for students, young researchers as well as junior technical staff.