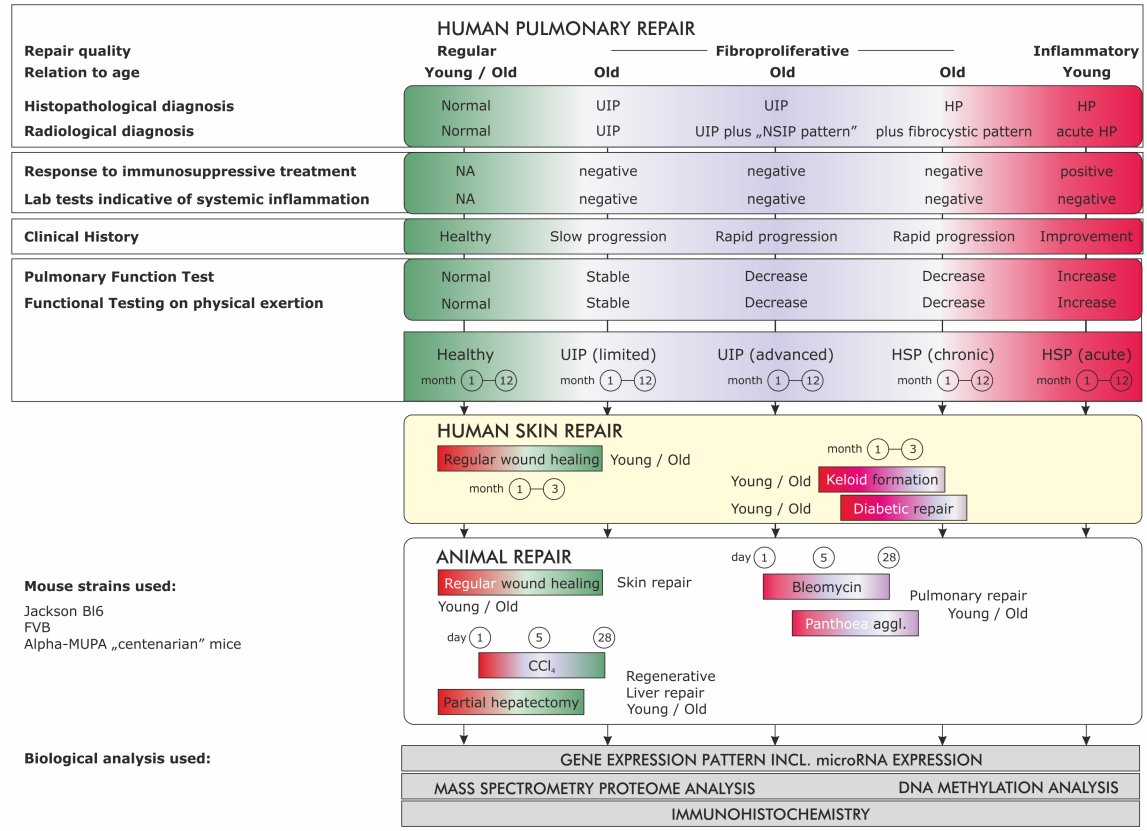
1. Executive Summary

RESOLVE has been outlined to better understand the regulatory networks that control the developmental processes in organ repair and to identify mechanisms, which cause the termination of regular organ development leading to fibroproliferative wound healing or repair. Fibroproliferative repair represents a major pathology in elderly people shifting regular organ development into progressive organ fibrosis with complete loss of organ function.

RESOLVE has been capable of identifying functional checkpoints shifting regular into fibroproliferative repair. Figure 2 illustrates the systematic targeting process used by the RESOLVE consortium.

Figure 2



Sequential biological evaluation was secured via measurements performed at two time points (start of study and 12 months later) in the human disease repair models or at three time points (start of study, after 5 days and after 28 days) in the animal repair models, while all biological measurements were derived from specimens representing actively remodeling organ tissue.

In the human models focusing on pulmonary repair, we have been combining established clinical, functional and pathological assessment with a) a positive or negative response towards immunosuppressive treatment and b) a controlled sequential observational period

(covering at least 12 months in patients with pulmonary fibrosis followed by individual observation until death or transplantation). With this approach, relevance of biological observations for deterioration of organ function and clinical disease progression was effectively assured. In order to further ascertain the significance of the biological findings, patients with limited UIP fibrosis were compared with those having a more advanced disease already at the start of the controlled observational period.

Age-dependence was addressed by means of clinical inclusion criteria as well as by the use of 3 month versus 18–24 month-old mice of different genetic background including those having an extended life span (αMUPA; Fraifeld, VE. et al. (2011) Biogerontology 12:591-597.).

This systematic comparative approach in the setting of age-related fibroproliferative wound healing realized here for the first time yielded important new results not only demonstrating a close connection between gene expression and histopathology but also between disease stage and disease progression according to established clinical features (paper in preparation). Moreover, it allowed for the first time the generation of a novel pathophysiological concept for fibroproliferative diseases of the lung suggesting two main aberrations of repair control.

During RESOLVE's reiterative targeting process, almost all relevant deviations from regular repair were addressed. The process was guided by a combination of validated clinical scoring results and proven functional annotations based on published gene ontology facts. Its results demonstrate for the first time that fibroproliferative wound healing represents a combination of two specific aberrations from regular repair: exaggerated and abnormal embryonic growth combined with persistent loss of cellular differentiation. Even more important, RESOLVE's final data set suggests a close connection between the two leading aberrations and their principal mediators making it possible to devise a novel concept for future research in pulmonary fibrosis aimed at both early detection and functional scoring of fibrosis patients and the development of new treatment options. Fortunately, this includes already suggestions for potential drugs capable of interfering with the pathologic events.

Finally, the studies on mechanisms of epigenetic control conducted within the framework of RESOLVE, particularly those on the regulation of DNA methylation provide evidence for the possibility that these data might serve as a highly valuable diagnostic instrument capable of discerning patients with progressive pulmonary fibrosis from those with other forms of lung fibrosis.

2. Summary description of the project context and the main objectives

As mentioned above, RESOLVE has been outlined to better understand the regulatory networks that control the developmental processes during organ repair and to identify mechanisms, which cause the termination of regular organ development leading to fibroproliferative wound healing or repair.

What is the background of fibroproliferative repair? Maintaining the borders of the body does not only provide its structural integrity towards a gaseous atmosphere, but is also crucial for preserving the metabolic functions assigned to its compartments. Upholding these boundaries for a long period is the result of an amazing regenerative capacity effectively

answering to the intensity and frequency of assaults on the body's boundaries. Yet, while injuries are likely to cause damage repeatedly throughout life, the body's regenerative capacity will progressively shrink as a function of age (Rattan, SI. (2013) Curr Pharm Des. Epub ahead of print) making sustainment of surface structures one of the most pivotal functions in life.

The ability to maintain these structures relies on a coordinated sequence of metabolic processes aimed at the re-establishment of epithelial and endothelial barriers, supported and guided by a mesenchymal matrix ensuring spatial orientation of growth during repair. When effectively orchestrated, this process will re-enact both, organ development and differentiation, a metabolic sequence called "primary" repair. In younger adults, damage to organs is usually answered by primary repair. But even in young individuals, permanent or repeated damage capable of preventing permanent closure of epithelial and/or endothelial boundaries will cause formation of scar tissue that is almost entirely composed of matrix components produced by fibroblasts and myofibroblasts, a process named "secondary" repair. In spite of the resulting loss of organ function, secondary repair serves as a rescue program maintaining surface integrity and structural orientation once regular organ reorganization has failed.

Failing or chronic wound healing in aged individuals, however, is very different as it represents the lost capacity to orchestrate a controlled reactivation of both primary and secondary wound healing leading to a progressive aberration ("shift") of the organ's repair efforts (Figure 1). It is typically characterized by a combination of chronic inflammation and progressive scar formation, a process named fibroproliferative repair. Due to the extensive and progressive replacement of functional organ tissue connected to it, fibroproliferative repair will not only threaten the function of the organ involved, but endanger the function of the whole organism causing substantial morbidity and mortality.

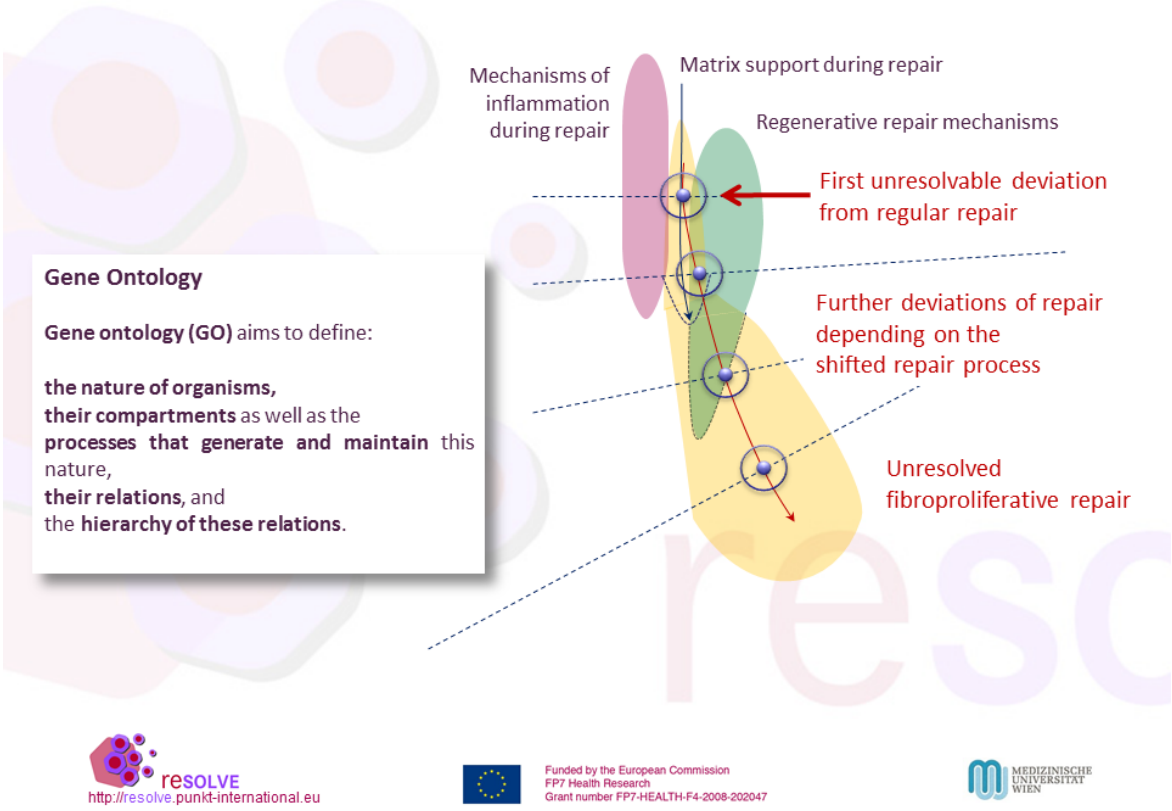


Figure 1: Failing or chronic wound healing in aged individuals, however, is very different as it represents Lost capacity to orchestrate a controlled reactivation of both primary and secondary wound healing leading to a progressive aberration ("shift") of the organ's repair efforts.

The overall aim of RESOLVE was to overcome the intricacy of a composite pathology and to identify functional checkpoints capable of shifting regular repair into fibroproliferative repair, and thus create suitable treatment strategies to achieve healthy ageing and a significant positive impact on life quality of elderly people.

In order to achieve this challenging major goal the following project objectives were defined:

Objective 1: Relevant molecular targets in animal and human disease model systems which act as functional checkpoints for the specific aberrations of fibroproliferative repair need to be identified and separated from those specific for regular repair. This approach needs to be functional (quality of repair and relevant mechanisms of repair), disease-oriented (human diseases related to predominantly fibroproliferative pulmonary repair, in particular to Idiopathic Pulmonary Fibrosis (IPF) or to largely inflammatory repair conditions), and should allow for the assessment of age-dependent and genetic mechanisms.

Objective 2: Highly valuable test systems for future treatment options of fibroproliferative repair need to be generated.

Objective 3: Development of a first diagnostic tool for fibroproliferative wound healing based on the validation of identified relevant molecular targets specific for aberrant fibroproliferative repair.

Objective 4: Identification of biological or (possibly) chemical compounds capable of interfering with targets central to fibroproliferative repair (IFS) in cellular or animal model systems for the development of pharmacological treatments.

The RESOLVE consortium followed the strategy (i) to reduce the abundance of potential targets for fibroproliferative wound healing, (ii) to address the functional relevance of known pathways and mediators involved in fibroproliferative repair, (iii) to detect as yet unidentified molecular targets for this condition, and (iv) to unravel their functional relation to fibroproliferative wound healing by a systematic comparison of clinically relevant model systems.

This was achieved by an integrated acquisition and comparison of experimental and clinical data from regular, inflammatory and fibroproliferative wound healing, which represented a systematic state-of-the-art systems biology approach (Figure 3), and by highly effective mathematical modeling. This translational research approach was important allowing insights into the complex reality of human diseases related to the fibroproliferative aberration of repair.

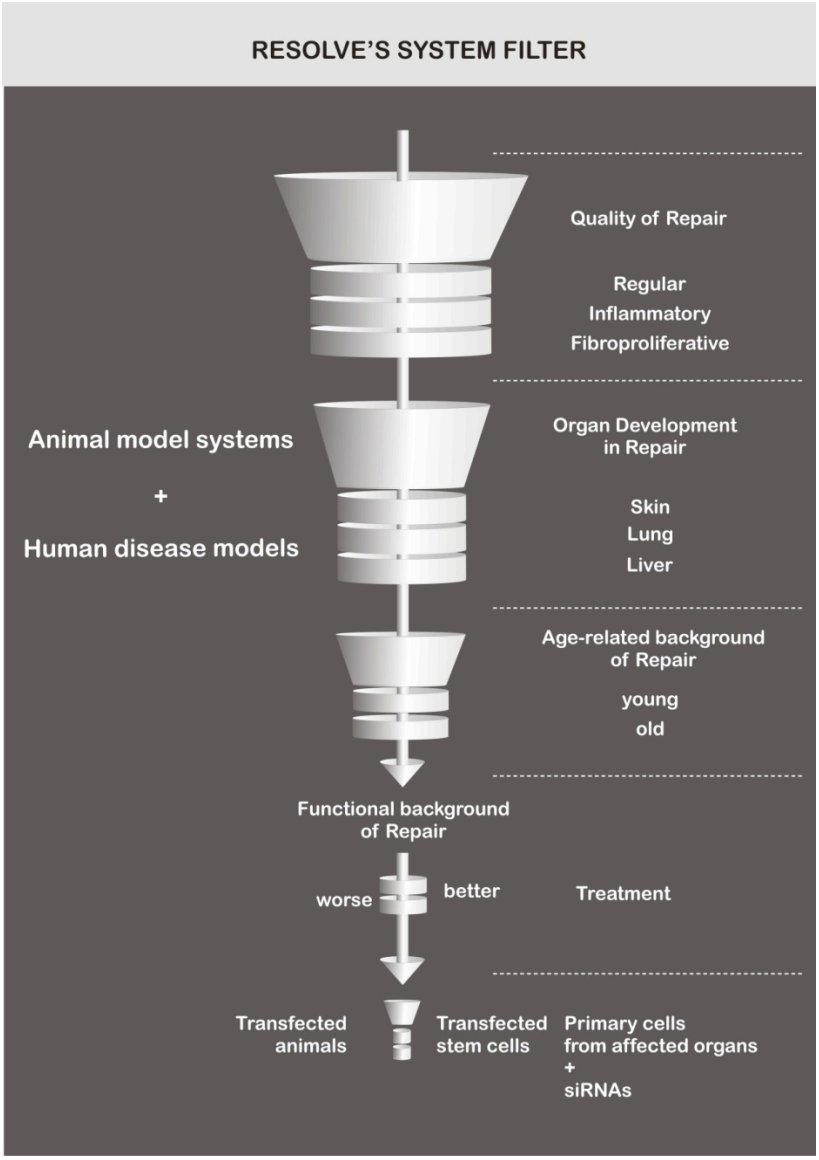


Figure 4.

3. Description of the main S & T results/foregrounds

During a time of five-and-a-half years the RESOLVE consortium composed of 13 academic, clinical and industrial partners cooperated well in order to raise the bar described in the four objectives above.

What are the achievements of these five-and-a-half years funded by the FP7-HEALTH project RESOLVE?

Identification of relevant molecular targets as functional checkpoints specific for aberrant fibroproliferative repair: In order to achieve this objective data analysis by high throughput techniques has been performed using data generated from animal and human samples. Data were generated from regular and inflammatory repair conditions in the skin, the lung and the liver at different ages.

Genotyping and data analysis in idiopathic interstitial pneumonia (IIP) samples revealed a significant association with three targets that are now being replicated in an independent IIP cohort.

In systems biology analysis, human primary fibroblasts from idiopathic pulmonary fibrosis (IPF) and control patients by whole genome mRNA profiling was carried out and identified a substantial increase of functions related to epithelial development and a significant down-regulation of those guiding cardiovascular and circulatory system development. qPCR-validated mRNA markers, qPCR-validated DNA methylation markers and qPCR-validated microRNA markers could be provided. Differentially expressed proteins in human lung tissue proteome (diseased vs. non diseased groups) have been generated and 20 differentially expressed marker proteins of 160 clinical blood samples have been validated. According to recently proposed pathogenic models for Chronic Obstructive Pulmonary Disease (COPD) and IPF, premature cellular senescence likely affects distinct progenitors cells (mesenchymal stem cells in COPD, alveolar epithelial precursors in IPF), leading to stem cell exhaustion. Revealing the characteristic (phenotypic) features of IPF-derived fibroblast, including a higher resistance to oxidative stress and stress-induced cellular senescence, accelerated replicative cellular senescence, accumulation of myofibroblast-like cells in senescent cultures, and morphological changes (enlarged cell size, aberrant expression of actin and its weak association with cell membrane) have been observed.

In order to show the effect of IFS on the new targets for fibroproliferative repair, two targets could be validated with regard to their impact in fibroproliferation, cell migration and epithelial-mesenchymal transition (EMT). These targets are considered to have crucial functions in hepatocellular EMT and liver metastasis. In addition, two targets were validated with regard to their impact in cell invasion, transendothelial migration and metastasis. These targets are thought to have crucial functions in hepatocellular carcinoma progression and liver metastasis.

A workflow for the analysis of RNA-seq data, specifically for the analysis of miRNAs expression and for the discovery of new miRNAs, has been developed. In addition, a tool for the interactive analysis of gene expression data from the Austrian partner AIT (ReGEAE) has been generated.

Mechano-biological modeling of lung stress, modeling and simulation of Darwinian mutations at a cellular scale and selection (related to ageing) in the immune competition and updating

of a new system biology approach have been developed and tested.

Identification of biological or (possibly) chemical compounds effectively interfering in both the transgenic and the animal models for the development of pharmacological treatments: Data Mining of the results of the project permitted the search for profibrotic targets showing age-related differences in response to damage, to study the association between the rate of wound healing (WH) and to better characterize the longevity/aging phenotype. In addition, the molecular links between cellular senescence (CS) and major human age-related diseases (ARDs) and the gene signatures that are similar to the RESOLVE idiopathic pulmonary fibrosis (IPF) transcriptome data have been identified.

Moreover, a list of 300 potential interfering chemical substances (IFS) has been compiled that could target the top up-regulated genes in the IPF profile, thus providing a valuable basis for selecting the potential IFS that could counteract the imbalanced fibroproliferative responses in the human hepatocellular model. Biological IFS have then been selected and characterised. Interestingly, four targets in which siRNA treatment led to reduced cellular activity are connected by biological pathways.

A search for drugs/chemicals (IFS) interacting with the selected key target genes for progressive pulmonary fibrosis has been performed and the pharmacological compounds interacting with the candidate genes from the prototype of “diagnostic chip” for pulmonary fibrosis (IPF) have been selected. Interestingly, many of the drugs are currently being used in clinical trials in phase II-IV for treatment of age-related pathologies.

Finally, a classifier of 19 mRNA markers enabling perfect distinction of IPF patients from healthy patients using lung biopsies could be provided for the next step, which is intervention with gene expression through IFS. This intervention was successfully achieved by RNA interference, either transiently by siRNAs or stably by the employment of shRNAs. The Austrian partner Wolfgang Mikulits and his team showed the functional implications of Gpnmb and Wisp1 in both, proliferation of EMT-transformed cells and in cell invasion. Furthermore, Axl and Nrp2 could be identified in vitro and in vivo as key players of fibroproliferation that are essentially involved in the regulation of human hepatocellular EMT. Vadim Fraifeld and his team in Israel extended phenotyping of pulmonary fibroblasts derived from IPF patients by comparison with normal human pulmonary fibroblasts. In particular, IPF-derived fibroblasts display high resistance to oxidative stress, rapid accumulation of senescent and myofibroblastoid features as well as low density of actin, suggesting a progressive course of IPF and its link to aging. Paolo Madeddu and his team in Bristol showed that the expression of a specific control gene for spatial-oriented tissue regeneration in cultured primary fibroblasts reflects the situation in diseased patients. This gene exhibits low abundance in fibroblasts from healthy donors while it is increasingly expressed in primary fibroblasts obtained from limited and advanced UIP patients. Finally, Francois Huaux and his group in Louvain evaluated the delivery of siRNAs by cationic microspheres in cell culture for the further efficient treatment of Bleomycin-induced lung fibrosis in mice.

Development of a first diagnostic tool for fibroproliferative wound healing based on the validation of the identified relevant molecular targets specific for aberrant fibroproliferative repair: In order to setup an assay measuring fibroproliferative wound healing, 270 gene expression markers were selected from the data analysis by high throughput techniques, qPCR assays were designed and validated to MIQE guidelines (wet-lab validation). Using this gene expression assay, we were able to predict IPF/UIP in 98% of cases correctly, even when using only data from 9 genes.

As the diagnostic value of gene expression measurements from lung biopsies was limited, additional studies on DNA methylation were performed which yielded suitable results. DNA methylation assays (based on the MSRE principle) covering 220 genomic loci were set up and again validated to MIQE standards. This assay was able to predict IPF/UIP not only from tissue but also from cell-free DNA in serum. In tissue, the prediction of 99% of the cases were correct, and even the DNA methylation measurement from cell free DNA in serum yielded a correct identification of advanced UIP for up to 93% of cases.

Highly valuable test systems for future treatment options of fibroproliferative repair need to be generated: The Hungarian partner BioTalentum has successfully generated a conditional knock-out germline chimera for the second target gene upregulated during intensified mesenchymal repair driven by mechanisms of inflammation. However, further mating is needed to obtain the final mouse model for this gene. Additional conditional-KO-chimeras generated have been under germline testing to find better transmitting candidates. Germline transmission- (GLT-) test-crossings of the chimeras need to be continued until having clear information on their germline transmission potential (based on checking at least 5-10 litters and/or a total of 50-100 pups per chimera).

In parallel, a total of 6 mice have been generated by use of the TALEN-technology, which carry mutations in the targeted third gene that controls membrane functions during vasculogenesis. The majority of the identified mutations resulted in a frameshift and destroyed the gene function. The expression of a truncated, non-functional form of the protein generated a suitable system for the generation of the constitutive knock-out model. The knock-out mice are heterozygous for the mutation and 5-7 weeks old now. If everything goes well, the heterozygous embryo bank can be generated within a month, however, it will take 2 generations (4-5 months) from this point to have the homozygous knock-out mice for cryopreservation.

In addition, several patient specific IPF hiPS lines could be established. The characterization of these lines demonstrated their similarity to ES lines in their morphology and expression pattern of the pluripotency markers. They were also capable to differentiate spontaneously into the three germ layer.

4. Description of the potential impact

Socio-economic, medical and biological impact

The rising incidence of debilitating diseases in the elderly puts health care programmes more and more at risk, and dramatically reduces life quality in a growing number of individuals. In appreciation of the fact that the large group of *degenerative* diseases in aging, such as organ fibrosis, atherosclerosis, cancer, diabetes type II, and neurodegeneration share many important pathologies, they have been collectively named age-related diseases (ARDs). Thus, the ability to maintain health and quality of life in older people directly relies on our understanding of ageing and its influence on pathology. In the past, biomedical research was predominantly aimed at the assessment of disease-oriented mechanisms. Unfortunately, despite considerable investments, the research successes in terms of practical outcomes including treatment opportunities have been low. This may be, in part, a result of the number

and complexity of pathways involved, but it could also mean that the right questions have not been asked, since some of the pathologies may directly be promoted by mechanisms of ageing. Given the high probability that a lifelong preservation of structural and functional integrity of the body's various organs provides the most effective way of preventing illness and to a certain extent also of the ageing process itself, the understanding of wound healing mechanisms in different ages and pathologies related to age could become a key for the successful approach towards combating age-related diseases.

Contribution to knowledge, medical procedures and health policies

RESOLVE's strength originates from the close collaboration between high-level basic researchers and clinical experts who share the knowledge and expertise necessary to undertake such a challenging project. The building of RESOLVE has gathered a consortium of thus far independent researchers, which share the same visions and goals. The various strategies provided by these experts allowed for the first time for a new strategic approach to ageing research: the assessment of age-related changes of repair mechanisms serving as the basis for age-related illnesses. By following this road, RESOLVE's final targeting process - guided by a combination of clinical scoring and proven functional annotations according to gene ontology - demonstrated that the aberrations situated in the core of the newly defined pathophysiological concept represent a metabolically stable yet in the course of disease progressive aberration of repair. It is composed of significantly exaggerated growth mechanisms in the presence of a dramatic and sustained loss of cellular differentiation. Even more importantly, the final data of the RESOLVE project suggest a close association between the two leading metabolic events and their principal mediators making it possible to devise a clear concept for future research aimed at both detection and scoring of fibrosis patients with regard to new therapeutic regimens. This even includes the suggestion of potential drugs for interfering with these pathologic metabolic events.

Finally, the studies on mechanisms of epigenetic control conducted within the framework of RESOLVE, particularly those on the regulation of DNA methylation provide evidence for the possibility that these data might serve as a highly valuable diagnostic instrument capable of discerning patients with progressive pulmonary fibrosis from those with other forms of lung fibrosis.

Thus, it can be anticipated that the results and the options generated by RESOLVE's efforts will in long-term influence future developmental strategies in health care, medical research and pharmacology by generating new means and instruments for diagnosis and therapy of these presently untreatable pathologies. In long-term the consortium expects that RESOLVE's outcomes will have a profound impact on public health strategies as well as European and national policies related to healthy ageing.

Impact on economics and social issues

The project's consortium integrated all competencies relevant to take advantage of intellectual property rights (IPR) protecting and assuring further exploitation of the generated knowledge within RESOLVE. The consortium expects major commercially exploitable outcomes, in particular targeted human gene expression arrays serving as the basis for highly innovative diagnostic tools and for transgenic animals providing future pharmaceutical

models for drug development against fibroproliferative diseases. Equally important, RESOLVE identified compounds capable of interfering with the newly defined targets, by that providing the means to accelerate the efficacy of drug development against age-related diseases.

The validation strategies of RESOLVE's scientific and technological concept ensured the highest level of significance due to internal verification by complementary techniques, e.g. methylation and microRNA analysis, and by additional assessment of serum protein targets derived from RESOLVE's final phase. As this wealth of information will be continuously compared to the growing knowledge in the field, the outcomes of this collaborative endeavour has not only generated new perspectives for future ageing research, but also various test systems necessary to do so. This will have a profound impact on the exploitation of RESOLVES results ranging from patent applications to the generation of negotiable market products.

A good part of the above-mentioned results were only possible due to a well-working cooperation between basic and clinical research partners. The RESOLVE consortium succeeded to improve this cooperation and especially the understanding between basic and clinical researchers and their different pattern of thinking. This was achieved by organizing regular, in some cases weekly, meetings, discussing results and sharing basic and clinical knowledge and thus "teaching" each other in the different pattern of thinking. We still believe this is one of the bottlenecks in science, which needs to be overcome. RESOLVE's consortium published a pile of jointly and individual scientific papers in acknowledge international journals as you can see on the project website http://resolve.punkt-international.eu and this final report submission. Additional publications will follow, which are based on the results generated during the lifetime of RESOLVE. The partners individually transferred their knowledge at international conferences in talks and by posters and in lectures to their colleagues but also by staff exchange between partners in order to learn new techniques. At two international symposia the RESOLVE consortium exchanged and discussed their results and knowledge with internationally acknowledged researchers in the multi- and interdisciplinary field. The focus in Vienna March 2012 was on "Tissue remodeling in Ageing and Diseases" with talks and posters on (i) Regular and fibroproliferative wound healing, (ii) Regenerative medicine, and (iii) Mechanisms of cellular ageing. The focus one year later in Beer Sheva and at Dead Sea was on "Healthy Ageing and Regenerative Medicine" with talks and posters on the question (i) Is ageing a common mechanism of age-related diseases?, (ii) How can the breakthroughs in regenerative medicine help in promoting healthy lifespan?, and (iii) What are other ways to promote a healthy lifespan?. This international symposium was jointly organized together with 8th European Congress of Biogerontology. Both symposia were visited by 80 to 100 researchers from all over the world and were very well appealed by the participants. In order to recognize best presented results by young colleagues, we awarded the best three talks and the best poster at both of the symposia. In addition to these awards and the exchange of young fellows we offered three different soft skill workshops (i) Sharpen your communication, (ii) Reaching your dream job in order to advanced presentation skills on one hand and on the other to give a clear guidance first to find out what one wants, and second to learn how to apply and succeed in job interview. Finally, knowledge about which intellectual property rights (IPR) should be protected how and at what time point was presented to the entire consortium, additionally to the "agreement on the dissemination and use of the intellectual properties of RESOLVE"

effective *after* end of the project RESOLVE. Subject of this agreement is the supplementation of regulations of the Grant Agreement and Consortium Agreement regarding the ownership, protection and defence of IPR, the dissemination of Foreground and the regulation of rights to use IPR after the end of the project RESOLVE.

Public awareness was achieved by press releases, radio and TV interviews of different partners in their countries. Nearly all partners added a description of the RESOLVE project to their websites. Finally the project has also been published 26.03.2013 on the FP7 website cordis on http://cordis.europa.eu/projects/rcn/86774_en.html.

A patent application is planned to be submitted by the Medical University of Vienna and the Università degli Studi di Verona for targets indicating the loss of differentiation capacity followed by further investigations in order to clarify mechanistic details about reduced epithelial trans-differentiation important in long-term to develop therapeutics. Prerequisite continuing this work are available grants. Actions towards grant-acquisition are ongoing. Expected time: 2015 onwards; IPR measure: Joint ownership of the Medical University of Vienna and the Università degli Studi di Verona is ruled in the "Agreement on the dissemination and use of IPR for the RESOLVE project". Potential impact: In the long run development of therapeutics. Quantifying is not possible at the present.

A patent application is planned to be submitted by the Medical University of Vienna for targets indicating the loss of differentiation capacity followed by further investigations in order to clarify mechanistic details about reduced vascular sprouting during the regenerative process together with formation of aberrant vessels important in long-term to develop therapeutics. Prerequisite continuing this work are available grants. Actions towards grant-acquisition are ongoing. Expected time: 2015 onwards; IPR measure: Joint ownership of the Medical University of Vienna and the University of Bristol is ruled in the "Agreement on the dissemination and use of IPR for the RESOLVE project". Potential impact: In the long run development of therapeutics. Quantifying is not possible at the present.

A patent application is planned to be submitted by the Medical University of Vienna for targets indicating the regulation of gene expression followed by further investigations by the Medical University of Vienna, the Austrian Institute for Technology, the Ben Gurion University of the Negev and BioTalentum in order to clarify the mechanistic details important in long-term to develop therapeutics. Prerequisite continuing this work are available grants. Actions towards grant-acquisition are ongoing. Expected time: 2015 onwards; IPR measure: Joint ownership of the Medical University of Vienna, the Austrian Institute for Technology, the Ben Gurion University of the Negev and BioTalentum is ruled in the "Agreement on the dissemination and use of IPR for the RESOLVE project". Potential impact: In the long run development of therapeutics. Quantifying is not possible at the present.

The Medical University of Vienna and the Austrian Institute for Technology will include the comparative methylation analysis in further investigations in order to clarify the mechanistic details and importance in the signaling pathways and to possibly submit a patent application. Prerequisite continuing this work are available grants. Actions towards grant-acquisition are ongoing. Expected time: 2015 onwards; IPR measure: Joint ownership of the Medical University of Vienna and the Austrian Institute for Technology is ruled in the "Agreement on the dissemination and use of IPR for the RESOLVE project". Specific claims and patent content will be subject to negotiations between the Medical University of Vienna, the Austrian

Institute for Technology and University of Bristol. Potential impact: In the long run development of therapeutics. Quantifying is not possible at the present.

BioTalentum will do further mating of the successfully generated conditional knock-out germline chimera for the two of the targeted genes in order to obtain the final mouse models for the concerning target genes. Expected time: 2014 onwards; IPR measure: Joint ownership by the Medical University of Vienna and BioTalentum and profit of sold models to research centres will be distributed 50:50 as stated in the "Agreement on the dissemination and use of IPR for the RESOLVE project". A patent application is planned. Prerequisite continuing this work are available grants. Actions towards grant-acquisition are ongoing. Potential impact: Availability of a test system for future treatment options of fibroproliferative repair. Quantifying is not possible at the present.

A patent application is planned to be submitted by the Austrian Institute for Technology for the assay being used as diagnostic tool measuring fibroproliferative wound healing and a patent application to be submitted by the Medical University of Vienna for targets responsible for fibroproliferative wound healing followed by further validation with a higher amount of patients (several hundreds) and if prediction for measuring fibroproliferative wound healing is reliable and grants are available a patent will be submitted. Actions towards grant-acquisition are ongoing. Expected time: 2015 onwards; IPR measure: Joint ownership of the Medical University of Vienna, the Austrian Institute for Technology and BioTalentum is ruled in the "Agreement on the dissemination and use of IPR for the RESOLVE project". Potential impact: In the long run development of a diagnostic tool and of therapeutics. Quantifying is not possible at the present.

A patent application is planned to be submitted by the Austrian Institute for Technology for the assay being used as diagnostic tool measuring fibroproliferative wound healing and a patent application to be submitted by the Medical University of Vienna for targets responsible for fibroproliferative wound healing followed by further validation with a higher amount of patients (several hundreds) and if prediction for measuring fibroproliferative wound healing is reliable and grants are available a patent will be submitted. Actions towards grant-acquisition are ongoing. Expected time: 2015 onwards; IPR measure: Joint ownership of the Medical University of Vienna and the Austrian Institute for Technology is ruled in the "Agreement on the dissemination and use of IPR for the RESOLVE project". Potential impact: In the long run development of a diagnostic tool and of therapeutics. Quantifying is not possible at the present.

The Medical University of Vienna and the Austrian Institute for Technology will include the comparative analysis of quantitative proteomics data of wound healing in human lung tissue in further investigation in order to clarify the mechanistic details and importance in the signaling pathways and to possibly submit a patent application. Prerequisite continuing this work are available grants. Actions towards grant-acquisition are ongoing. Expected time: 2015 onwards; IPR measure: Joint ownership of the Medical University of Vienna and the Austrian Institute for Technology is ruled in the "Agreement on the dissemination and use of IPR for the RESOLVE project". Potential impact: In the long run development of therapeutics. Quantifying is not possible at the present.

A patent application is planned to be submitted by the Austrian Institute for Technology for the diagnostic test followed by further validation with a higher amount of patients (several hundreds) and if prediction for measuring fibroproliferative diseases is reliable and grants are available a patent will be submitted. Actions towards grant-acquisition are ongoing. Expected

time: 2015 onwards; IPR measure: Joint ownership of the Medical University of Vienna and the Austrian Institute for Technology is ruled in the "Agreement on the dissemination and use of IPR for the RESOLVE project". Potential impact: In the long run development of a diagnostic tool. Quantifying is not possible at the present.

The Christian-Albrechts-Universität zu Kiel and the Ben Gurion University of the Negev will further investigate the genotyping results of human candidate genes in order to clarify the mechanistics regarding their influence on wound healing and repair in aged humans. A patent application is planned to be submitted by the Christian-Albrechts-Universität zu Kiel and the Ben Gurion University of the Negev for the identified targets. Prerequisite continuing this work are available grants. Actions towards grant-acquisition are ongoing. Expected time: 2015 onwards; IPR measure: Joint ownership of the Christian-Albrechts-Universität zu Kiel and the Ben Gurion University of the Negev is ruled in the "Agreement on the dissemination and use of IPR for the RESOLVE project". Potential impact: In the long run development of therapeutics. Quantifying is not possible at the present.

The Christian-Albrechts-Universität zu Kiel will further investigate the genotyping results of human candidate genes in order to clarify the mechanistics regarding their influence on wound healing and repair in aged humans. A patent application is planned to be submitted by the Christian-Albrechts-Universität zu Kiel for the identified targets. Prerequisite continuing this work are available grants. Actions towards grant-acquisition are ongoing. Expected time: 2015 onwards; IPR measure: Ownership of the Christian-Albrechts-Universität zu Kiel is ruled in the "Agreement on the dissemination and use of IPR for the RESOLVE project". Potential impact: In the long run development of therapeutics. Quantifying is not possible at the present.

The inhalation system has been exploited by the Instytut Medycyny Wsi im Witolda so far. A commercial offer has been prepared and research centres were contacted. IPR measure: Ownership of the Instytut Medycyny Wsi im Witolda is ruled in the "Agreement on the dissemination and use of IPR for the RESOLVE project". Impact: The system provides an excellent tool for research centers to generate data under standardised conditions.

A patent application is planned to be submitted by the Ben Gurion University of the Negev for the approach predicting profibrotic targets in order to clarify age-related mechanistic details important in long-term to develop therapeutics. Prerequisite continuing this work are available grants. Actions towards grant-acquisition are ongoing. Expected time: 2015 onwards; IPR measure: Ownership of the Ben Gurion University of the Negev is ruled in the "Agreement on the dissemination and use of IPR for the RESOLVE project". Potential impact: In the long run contribution to therapeutics. Quantifying is not possible at the present.

This online application will be further used as data mining tool in case the planned work of RESOLVE can be continued due to available grants. The tool is able to perform statistical tests in order to gain insights into the statistical significance of results obtained from data mining. More specifically, the co-occurrence discovery algorithm performs the well-known hypergeometric distribution test on found annotations. The text mining algorithm implements calculation of a co-phenetic correlation coefficient in order to assess the quality of factorization(s). Expected time: 2015 onwards; IPR measure: Joint ownership of Integromics and Agencia Estatal Consejo Superior De Investigactiones Cientificas is ruled in the "Agreement on the dissemination and use of IPR for the RESOLVE project". The need of a patent application will be discussed in due time. Potential impact: Being used at research centres. Quantifying is not possible at the present.

A patent application is planned to be submitted by the Medical University of Vienna for the identified targets for wound healing in scarred skin, hyperthrophic scars and for human diabetic wound healing followed by further investigations in order to clarify mechanistic details about wound healing in skin important in long-term to develop therapeutics. Prerequisite continuing this work are available grants. Actions towards grant-acquisition are ongoing. Expected time: 2015 onwards; IPR measure: Joint ownership of the Medical University of Vienna and the BioTalentum is ruled in the "Agreement on the dissemination and use of IPR for the RESOLVE project". Potential impact: In the long run development of therapeutics. Quantifying is not possible at the present.

A patent application is planned to be submitted by the Medical University of Vienna for the identified targets for wound healing in skin of human keloids followed by further investigations in order to clarify mechanistic details about wound healing of keloid skin important in long-term to develop therapeutics. Prerequisite continuing this work are available grants. Actions towards grant-acquisition are ongoing. Expected time: 2015 onwards; IPR measure: Joint ownership of the Medical University of Vienna and the BioTalentum is ruled in the "Agreement on the dissemination and use of IPR for the RESOLVE project". Potential impact: In the long run development of therapeutics. Quantifying is not possible at the present.

A patent application is planned to be submitted by the Medical University of Vienna for the identified targets for wound healing in skin of mice followed by further investigations in order to clarify mechanistic details important in long-term to develop therapeutics. Prerequisite continuing this work are available grants. Actions towards grant-acquisition are ongoing. Expected time: 2015 onwards; IPR measure: Joint ownership of the Medical University of Vienna and the BioTalentum is ruled in the "Agreement on the dissemination and use of IPR for the RESOLVE project". Potential impact: Use of data in human studies (see above) and in the long run contribution to therapeutics. Quantifying is not possible at the present.

5. public website address as well as relevant contact details.

http://resolve.punkt-international.eu/

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Gene Ontology

Gene ontology (GO) aims to define:

the nature of organisms,
their compartments as well as the
processes that generate and maintain this nature,
their relations, and
the **hierarchy of these relations**.

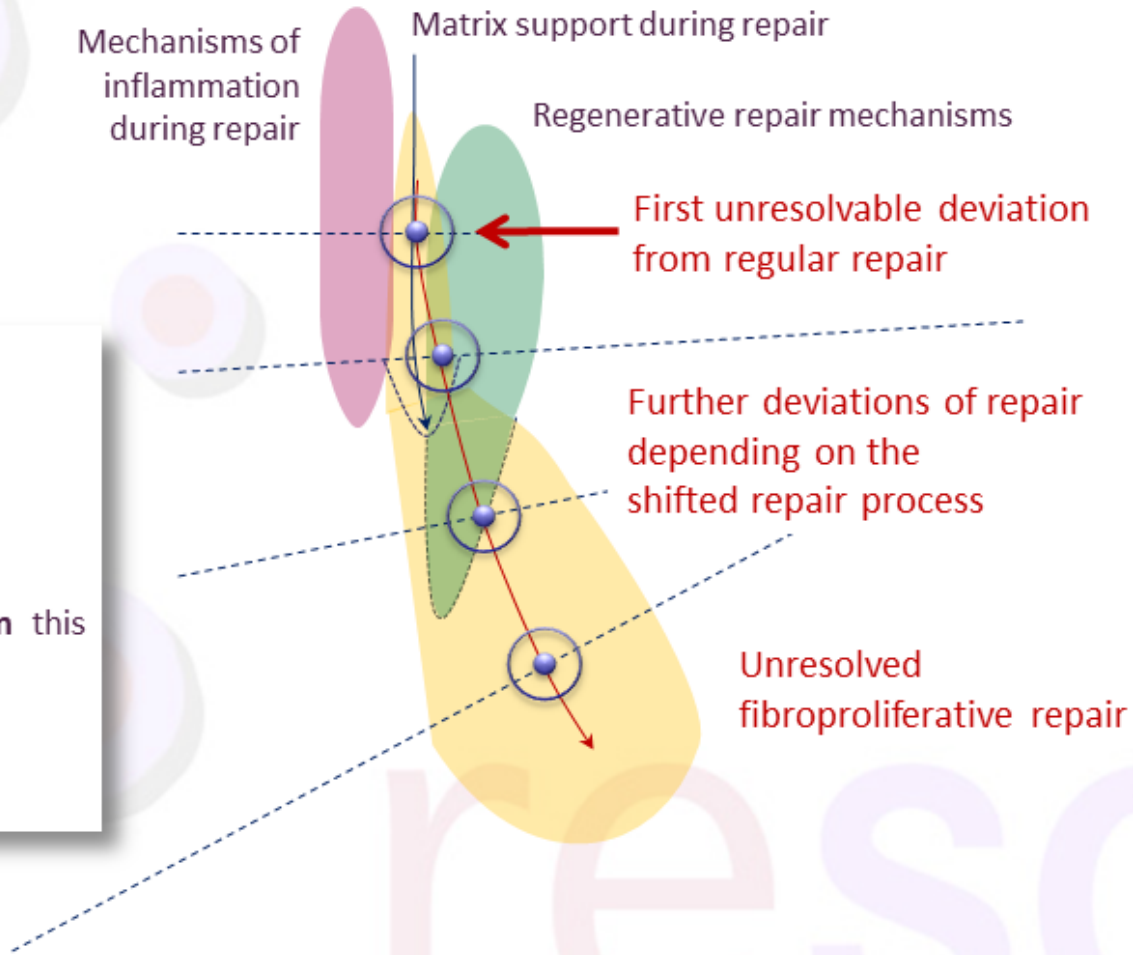

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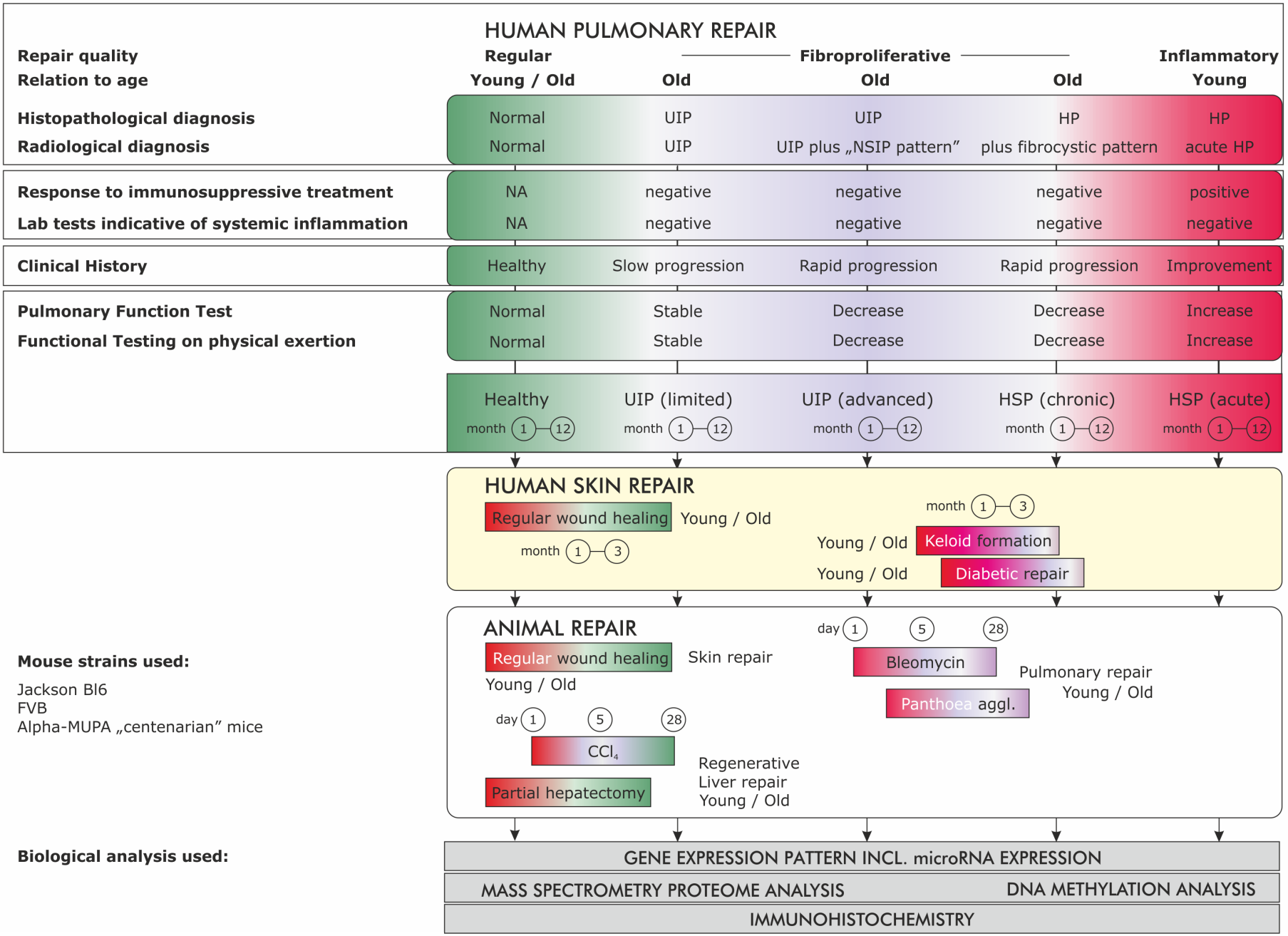
Figure 2


HUMAN PULMONARY REPAIR
Repair quality
Regular
Fibroproliferative
Inflammatory
Relation to age
Young / Old
Old
Old
Old
Young
Histopathological diagnosis
Normal
UIP
UIP
HP
HP
Radiological diagnosis
Normal
UIP
UIP plus „NSIP pattern"
plus fibrocystic pattern
acute HP
Response to immunosuppressive treatment
NA
negative
negative
negative
positive
Lab tests indicative of systemic inflammation
NA
negative
negative
negative
negative
Clinical History
Healthy
Slow progression
Rapid progression
Rapid progression
Improvement
Pulmonary Function Test
Normal
Stable
Decrease
Decrease
Increase
Functional Testing on physical exertion
Normal
Stable
Decrease
Decrease
Increase
Healthy
month 1 12
UIP (limited)
month 1 12
UIP (advanced)
month 1 12
HSP (chronic)
month 1 12
HSP (acute)
month 1 12
HUMAN SKIN REPAIR
Regular wound healing
Young / Old
month 1 3
month 1 3
Young / Old
Keloid formation
Young / Old
Diabetic repair
ANIMAL REPAIR
Regular wound healing
Skin repair
Young / Old
day 1 5 28
Bleomycin
Pulmonary repair
Young / Old
Panthoea aggl.
day 1 5 28
CCl4
Regenerative
Liver repair
Young / Old
Partial hepatectomy
Mouse strains used:
Jackson Bl6
FVB
Alpha-MUPA „centenarian" mice
Biological analysis used:
GENE EXPRESSION PATTERN INCL. microRNA EXPRESSION
MASS SPECTROMETRY PROTEOME ANALYSIS
DNA METHYLATION ANALYSIS
IMMUNOHISTOCHEMISTRY

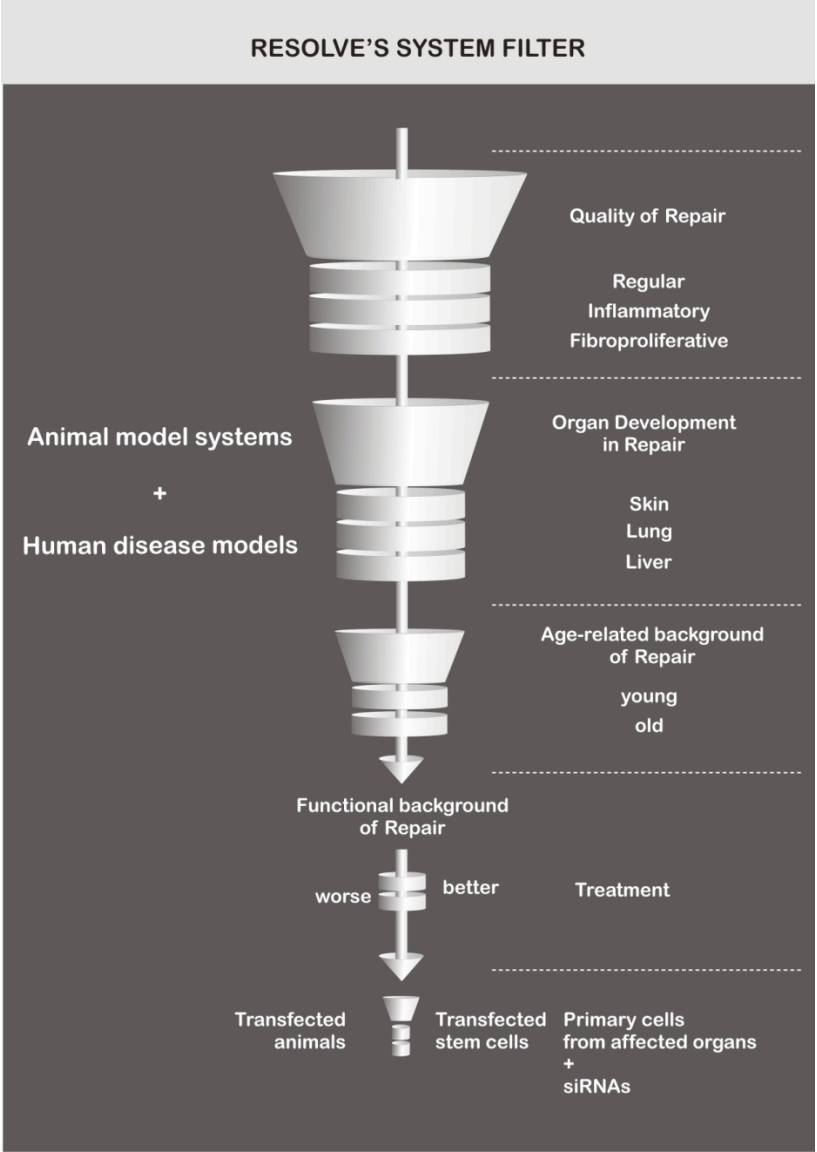
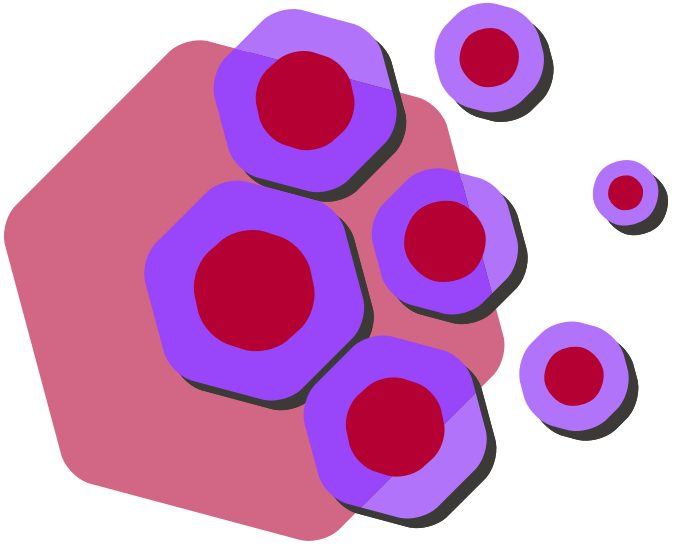

RESOLVE'S SYSTEM FILTER
Quality of Repair
Regular
Inflammatory
Fibroproliferative
Animal model systems
+
Human disease models
Organ Development in Repair
Skin
Lung
Liver
Age-related background of Repair
young
old
Functional background of Repair
worse
better
Treatment
Transfected animals
Transfected stem cells
Primary cells from affected organs
+
siRNAs

Figure 4.



resolve