FET Initiative in Sensory Restoration

1. About the proposers:

This initiative is proposed by a core group of partners representing a broad community of research institutes and scientists in Europe, closely linked with European society and industry. To date, the group consists of twelve core partners, but a large number of research institutes and companies have already expressed their eagerness to join. The core group already includes a number of the best specialists in the field of sensory restoration (see CVs in Appendix):

- Prof. José-Alain Sahel (http://cyscience.aviesan.fr/cv/855/jose-alain-sahel).
- Prof. Robin Ali (https://www.ucl.ac.uk/ioo/genetics/gene-and-cell-therapy/people/staff-iris-profiles/robin-ali)
- Prof. Robert MacLaren (http://www.ndcn.ox.ac.uk/team/robert-maclaren)
- Prof. Serge Picaud (http://www.institut-vision.org/en/retinal-information-processing.html)
- Prof. Botond Roska (http://www.fmi.ch/research/groupleader/?group=112).
- Prof. Christine Petit (https://research.pasteur.fr/fr/team/genetics-physiology-of-hearing/).
- Dr. Ingeborg Hochmair-Desoyer (http://www.medel.com/uk/about-med-el/)
- Prof. Tobias Moser (http://www.auditory-neuroscience.uni-goettingen.de/).
- Prof. Andrej Kral (http://www.neuroprostheses.com/AK/Main.html)
- Prof. Andrew King (http://www.dpag.ox.ac.uk/team/andrew-king).

There is an increased need not only to gather the best experts and companies in the field to address largely unmet needs, but also to both integrate and widely broaden the scope of this research community by opening the door to other scientific and technological fields as well as the social sciences and arts. That is why we are calling for the launch of a €1 billion Flagship Initiative in Sensory Restoration within the H2020 EU Research and Innovation framework programme.

2. What are the challenges and the vision?

Sensory restoration is coming of age. The possibility of regaining hearing following cochlear implant surgery has opened a new field that will, over the next decade, transform the treatment of blindness and deafness. Current progress in these fields is still limited to treating some frequent conditions such as cataracts, and most patients suffering from degeneration of the sensory cells have little hope of regaining their sight or hearing. In recent years, regenerative medicine (e.g. gene and stem-cell therapies) and prosthetics (e.g. implants, neuromodulation, optogenetics) have entered the phase of early clinical trials and are poised to face this challenge. In order to fulfill such promises, a large-scale, holistic, ambitious strategy must be undertaken, built on these advances utilizing detailed personalized analysis of the status of remaining tissue (especially neural tissue) and the underlying causative mechanisms. Using big data mining for deep-phenotypic and genetic determinants will enable the patient-specific application of the relevant technology. This will require a massive effort in developing imaging technologies, preclinical models, manufacturing infrastructures, databases, big data computing, rehabilitation techniques and education. Sensory restoration and/or substitution will help patients affected by aging, or vascular or genetic conditions such as Usher syndrome (a devastating condition leading to both deafness and blindness) to gain or regain autonomy. Such restoration will depend on the stimulation of cortical plasticity through rehabilitation programmes based on patient-centred outcome assessment and functional imaging. These issues, which have been considered by Western philosophy since Hume, Molyneux and Diderot, will be revisited within unprecedented, real life, paradigms that will lead to a better understanding and utilization of the virtually unlimited capabilities of the human mind. The impact on the European and global economy of fighting these devastating sensory handicaps will pair with a new marriage of science, humanities and art that has only recently been anticipated and will form the basis for renewed industrial, social and cultural patterns for dealing with the loss of our most sophisticated and precious gifts. Furthermore, the project also has implications far beyond restoring senses. We are on the verge of a huge revolution in medicine and science: implants and, more importantly, optogenetics will be used to treat more and more people in the world over the next decade or two. In addition to applications in other fields such as mental health and obesity, initial work in animal models is starting to emerge augmenting abilities and creating new senses (e.g. using implants to give animals infrared vision). Although the challenges to humanity remain enormous, there is also an unlimited potential. We suggest here that sensory restoration is the optimal model for solving the big challenges, scientific, technological and ethical, these most promising technologies pose, and that Europe can be the global leader in optimizing sensory restoration within this global scope. Our integrated effort encompassing scientific and technological expertise in systems and integrative biology, informatics, materials, optoelectronics, robotics, rehabilitation, social sciences and humanities, proposes for the first time ever a holistic strategy for maintaining and restoring sensory perception in patients suffering from deafness.
and/or blindness. The increased need for sensory restoration methodologies stems from the combination of two trends – the first is the projected growth in the prevalence of sensory loss, mainly due to the increasing age of the global population, the second is the disappointing gap between the promises of the new restoration technologies and their current practical outcomes. In hearing loss, no drug, gene or cell-based therapy is yet available for the most common forms of sensorineural hearing impairment. In particular, there is no treatment for Usher syndrome. The current intervention for sensorineural hearing loss is limited to the use of hearing aids: sound amplifiers for moderate to severe hearing impairment, and electric prostheses (cochlear implants) that bypass the cochlea and stimulate the auditory nerve directly to treat severe to profound hearing loss. Over 450,000 people worldwide have these implants. However, the resulting improvement in auditory perception can be very variable, depending on the patient history, and is often limited for various auditory capabilities beyond speech. For vision, recent clinical trials of a retinal prosthesis have demonstrated its feasibility despite poor performance, which was mainly due to the overall low acuity of the restored visual input, the small restored visual field, and the difficulty in learning to process the new visual information. In addition, despite promising results in the 1970s, no cortical implants are undergoing clinical trials yet to restore vision in patients who have lost their optic nerve following glaucoma (the 2nd most common cause of blindness) or diabetic retinopathy. The success of gene therapy, together with the development of cell therapies based on induced pluripotent stem cells (iPSC) and the emerging optogenetic therapy provide great hope for changing this situation. However, a major research effort is needed to turn these promising results into clinical successes to benefit patients.

Here we propose a major effort to bring our understanding of the sensory systems to a new level, emphasizing the design and validation of therapeutic breakthroughs, while giving a major, unprecedented priority to coupling these with rehabilitation, education and social insertion. The game changer will be to gather the latest innovations in optoelectronic engineering, systems biology and cognition, wave physics, material chemistry, and mathematical algorithms and use these to develop medical breakthroughs for the diagnosis and treatment of sensory diseases. Sensory systems will serve as accessible parts of the brain to accelerate the development and validation of cellular gene therapies and prosthetics designed for neuronal tissues and their proper integration into the intact brain.

a. Understanding of sensory systems relevant for therapy.

The translation to humans of therapies developed in small-animal models has been difficult. Although the overall structure of the sensory systems is conserved, cell promoters, immune systems and AAV transfections differ: these differences hinder the translation of new therapies to humans. A great effort is needed to develop and use new iPSC-based models. In addition, one of the key properties of the human visual system is the existence of a “central vision” which is used for the high-resolution vision necessary for face recognition, reading and colour processing. This central pathway originates in a remarkably small structure in the retina, called the fovea, which acts as a very high-resolution camera. The loss of foveal vision results in an almost complete lack of visual functions, although humans can lose function in 90% of the visual periphery without any major consequences for our daily activities. Understanding of the central, foveal pathways is still in its infancy because primates are the only mammals which have a fovea, and much of our retinal knowledge about cell types and circuits comes from model organisms such as mice and zebrafish. Similarly, our understanding of auditory deficits has been limited to investigations in postnatal rodents. Indeed, the cochlea is surrounded by bone, making access difficult.

Thus, some of the fundamental knowledge required to advance the progress of sensory restoration and implement its remarkable rehabilitative potential is still missing. We need to be able to describe the gene expression patterns and connectivity of cell types, we need to understand how human visual and auditory circuits mediate function, and we need to know how human cell types and circuits develop. In parallel, direct access to patients affected by severe diseases will continue to drive the identification of novel mechanisms and pathways in humans.

The main scientific objectives are the following: (i) Neuroprotection is a key therapeutic strategy for preventing the development of deafness and blindness. In many genetic diseases, specific cell types have been found to be selectively vulnerable to the oxidative stress generated by light, noise or drugs. We need to understand the cell-type-specific biological pathways that make cells selectively vulnerable, and develop genetic, small molecule or bio-similar based approaches to prevent degeneration. We also have to understand how mutations in cell-type-specific genes lead to this greater stress sensitivity. Studies on iPSC-based cells and organoids, together with post mortem tissues, will lead to the identification of more relevant neuroprotective agents. (ii) Gene replacement therapy was recently validated in ophthalmology in genetic diseases. To address the great genetic heterogeneity of patients affected by sensory diseases, there needs to be a massive effort to develop single-cell-based gene expression atlases (viral vectors, promoters, subcellular targeting sequences). New approaches should be developed for safe in vivo gene editing using CRISPR and other technologies. The resulting vectors have to be tested in patient-derived or engineered iPSC-based cells and tissues, making the approach predictive and personalized. (iii) Electric implants in severely/profoundly deaf patients have revolutionized their management and have shown promising results in restoring some sensory function in blind human patients. Major breakthroughs are needed to develop high-density arrays with new innovative materials (e.g. diamond, graphene) and encoders of sensory information with greater resolution in the retina and at the level of the central nervous system. The improvement of cochlear implants to enable clear speech to be understood in noisy conditions, and enable better appreciation of music, including the development of implants based on optical stimulation is a high-priority goal; the development of vestibular implants
will provide the first ever treatment of balance-related disorders. There needs to be a specific emphasis on developing central visual and auditory implants for patients who have lost their optic or auditory nerves. (iv) Sensory substitution devices and biomimetic encoders (intelligent goggles or auditory systems) should record sensory information and replay it in a format understandable by the cochlea, the retina, the vestibulum, or the central pathways. For patients with impaired sensory function, these neuromorphic orthoses have to target the residual functioning cochlea or retina. These new and adaptable stimulus encoders should be specific to the targeted cell type in the circuit. (v) Cell therapy is a major emerging field in medicine. For sensory diseases, we need to characterize donor cells from iPSC-based human cells, and understand the potential for these cells to integrate into human tissue at different developmental stages. In particular, we need to consider the regrowth of axons and the establishment of connections to the auditory brainstem and auditory and visual subcortical nuclei, study the efficacy and safety of these cell therapy approaches and find safe ways to edit patient-derived cells and perform therapy with these personalized repaired cells.(vi) Optogenetic therapy is emerging as a possibility for cell-type-targeted, high-resolution sensory restoration using microbial opsins to allow optical control of neurons. As in gene therapy, this strategy requires validated viral vector libraries. For this therapy, ultrathin optical devices have to be developed to focus light onto the targeted sensory circuit according to the biomimetic sensory encoder. (vii) Methods for stimulating brain plasticity will be developed and combined, including electrical deep central stimulation, targeted pharmacological treatments modulating plasticity, the transplantation of neuronal cells derived from embryonic stem cells (ESCs) or iPSCs and advanced training techniques. Targeting these methods to the relevant group of patients will depend on developing high-resolution morphofunctional diagnostic technologies from the sensory organ to the cortex using photonic, ultrafast ultrasound, holography and high-resolution magnetic resonance imaging (MRI), concentrating on studying post-lesion and post-therapy plasticity. Moreover, it is not enough to offer the patients the missing sensory information: they must learn to process and use it, requiring both behavioural and neuroimaging tracking systems to diagnose the user’s status and difficulties, and the development of practical rehabilitation therapies. Of note, one of the hallmarks of the outcomes of the use of hearing aids and cochlear implants is the enormous variability in the effects reported in auditory functioning. A lot of evidence indicates the role of central brain adaptation defects in this inter-individual variability in outcomes of prosthetic therapy. This highlights the exploration of central brain adaptations in hearing-impaired individuals, currently ignored, as a major step to better designed strategies of auditory rehabilitation, with the improvement in our understanding of auditory brain plasticity (in both humans and animal models) as a corollary. The integration of rehabilitation programs into surgical management will also condition the success of visual prostheses.

b. Structuring clinical care at the European level.

In order to tackle sensory impairment, developing a large venture on a European scale should enable the following clinical issues to be immediately addressed:
- The implementation of systematic, evaluated approaches to the diagnosis of sensory deficits (European registries of volunteers with sensory impairment, normal senses or super acute senses); the establishment of a system of alerts concerning emerging risks, including attempts at better identifying cases of ‘hidden’ sensory losses (e.g. among risk populations, patients with past exposures to intense sound/light).
- The implementation of screening tests for children or elderly individuals.
- Systematic evaluation of balance problems in individuals with hearing and/or visual impairment.
- Development of European platforms for high-throughput gene mutation and identification of polymorphisms in monogenic and aging sensory loss: this will feed databases, enabling big data analysis of genotype/phenotype correlations to build the basis for personalized patient management.
- Definition of standardized clinical protocols for European harmonization of clinical practices.
- Standardized tests evaluating comparative longitudinal success of sensory restoration attempts.

c. Integration of sensory inter-modality in therapy.

A key task of human perception is integrating the senses to give a unified understanding of the world. When a sensory channel is blocked, the neural regions devoted to its processing are cross-modally recruited for other tasks (such as recruitment of the visual cortex for language in congenital blindness) and sensory processing. Using sensory substitution devices, it has been shown that the ‘visual’ cortex can be recruited for visual computational tasks in both blind and sighted individuals through their other senses, even during adulthood. These observations have revolutionized the basic idea of the sensory brain itself, suggesting it is organized as a task machine rather than as a sensory machine. We need to address both levels of this brain plasticity occurring upon loss and restoration of senses. We will assess how multi-sensory combinations can best supra-additively boost the restored sense by offering an online interpretation of the new information via parallel senses. Using the most sophisticated imaging and behavioural tests, together with multisensory training, will further improve patient performance. These investigations will lead to new insights into the principles behind brain reorganization, including in the healthy brain, and to a significantly deeper understanding of human perception in general. Our program will also build upon the power of active sensing, the advantages of gamifying the training process, and the potential of virtual environments as training platforms both on the restoration device and on learning the principles of the new modality. We need: (i)
to develop multimodal sensory substitution devices conveying visual or auditory information through other senses; (iii) to explore potential brain plasticity in the different sensory systems; and (iii) to assess and compare the efficacy of multimodal training protocols.

This multisensory approach boosts the above-mentioned methods on several levels. First, combining several approaches is expected to work better than researching each alone. We need to define the benefits and constraints provided by this multisensory processing, and the cross-modal correspondences using invasive (implants or gene therapy) and non-invasive approaches (sensory substitution devices). Second, the basic science behind sensory restoration has to be explored to understand the brain reorganization following both sensory loss and restoration. Finally, we need to explore how users learn to process new sensory information in order to create standardized training and tracking procedures for all approaches.

d. The social aspect of sensory loss and restoration.

We are about to start observing and using brain reorganization following both sensory loss and sensory restoration, which is of major relevance for regaining autonomy but will also impact how the society and its constituents build a shared perception of the world. In our era of information and communication technologies, such a project will have a huge societal impact with the restoration of sensory inputs involving social sciences in the assessment of the impact of sensory impairment on daily life, education, employment, and depression will form the basis for preparing society to include affected citizens fully and facilitate the return to “normal life” of individuals who will benefit from sensory restoration. A large body of knowledge has emerged from the centuries of insights provided by writers and artists on the meaning, symbolism, and perception of the world, as well as the relationship between fellow human beings experienced through normal and impaired senses. A continuous, unprecedented dialog with art and humanities will provide an opening into an existential, phenomenological perspective on normal and restored perception.

3. Why is it good for Europe?

Our initiative is unprecedented as it aims not simply to slow the advent of sensory impairment, but to restore sight and hearing in patients affected by previously untreatable blindness and deafness. Hearing has become the major sense underlying ‘inter-individual communication’ through the development of language and music, and deafness is thus a major handicap for social communication. Early-onset forms impede spontaneous language acquisition and limit academic achievements. Late-onset forms frequently lead to social isolation with a negative impact on mood and cognitive functions. For example, cognitive conditions deteriorate, on average, 10 years faster in a person with untreated hearing loss. In Europe, one in every 700 neonates presents severe or profound hearing impairment. A similar proportion of young adults develop severe hearing impairment. Mild to moderate hearing impairment is under-diagnosed in youths, as demonstrated by the subsequent diagnosis of hearing impairment in about one third of all children initially considered dyslexic. Presbycusis, an age-related neurosensory hearing impairment, affects about one in three individuals over the age of 50. The frequency of presbycusis has increased with growing life expectancy and, according to the WHO, it will be the 7th most frequent non-lethal disabling condition worldwide by 2030. Overexposure to noise is creating a global threat to hearing and is acknowledged to be the major factor that triggers presbycusis. Noise-induced hearing loss is becoming increasingly frequent in our overpopulated cities, which are becoming ever noisier. By 2050, 85% of the world’s population will be living in cities and, according to the WHO, one billion people will be at risk of hearing loss due to over-exposure to noise. On the visual side, according to the WHO, over 285 million people in the world are visually impaired, of whom 39 million are blind and 246 million have moderate to severe visual impairment. It is predicted that, without extra interventions, these numbers will rise to 75 million blind by the year 2020. In Europe alone, an estimated 30 million individuals are blind or visually impaired. This higher figure takes into account the prevalence of sight-loss amongst an increasing population of elderly people in Europe, which is extremely difficult to accurately quantify. These numbers are certainly underestimated because many people suffer from varying degrees of sight or hearing loss but either ignore it or, for personal reasons, do not declare their condition. The conservative estimate of personal productivity losses associated with blindness, which is growing in prevalence, estimates the economic productivity cost to be several billion US$ per year. Thus, developing efficient rehabilitative methods and devices for these growing populations is clearly a hugely important. The European population has important unmet medical needs in sensory diseases, representing a significant economic burden to society. These needs are expected to increase in our ageing society and need to be addressed at a European level. The potential market of such a Flagship Initiative for European industry is thus tremendous. In the field of vision, even just surgical devices and a few pharmacological strategies have greatly improved patients’ lives and generated major economic rewards for European companies. The field of prosthetics and regenerative medicine is emerging, with a few large companies and a network of start-up companies in Europe, Japan and the US. Even now, in Europe barely 30% of hearing-impaired subjects who could benefit from hearing aids are equipped, regardless of the local reimbursement mechanism. However, several European industrial groups lead the hearing-aid market worldwide (Phonak, Oticon) and three of the four brands of cochlear implants are European (MED-EL, Sonova-Advanced Bionics and Oticon-Neurelec). The market in diagnostic equipment, with several major companies in Europe (e.g. GN Otometrics,
Interacoustics), will benefit from the development of new diagnostic tools. In the field of gene therapy, the retina and the cochlea appear to be good organ models. Therefore, audition and vision are likely to become the forefront of gene therapy development in the coming years. Already several European start-ups have emerged and started clinical trials (NightStarX, GenSight Biologics, OxfordBiomedica). These start-ups can rely on major platforms for the production of viral vectors at GMP clinical grades (OxfordBiomedica, Genethon).

Existing international research initiatives linked to this proposal

Some international initiatives are linked to this proposal, like the EU and American Brain Initiative that aims to revolutionize our understanding of the human brain. By accelerating the development and application of innovative technologies, researchers are expecting to produce a revolutionary new dynamic picture of the brain that, for the first time, shows how individual cells and complex neural circuits interact in both time and space. In our project, we similarly want to produce innovative technologies, but also understand function in the sensory systems: our ultimate goal is the development and industrialization of the most novel therapies to keep or even restore sight and hearingfor millions of people, thanks to new therapies and devices which could be onthe market at an affordable price for countries and individuals.

4. What would it take to do it?

The principle of sensory restoration has been validated by hearing and retinal implants. Gene therapy in ophthalmology has also been validated recently in clinical trials. Although these therapeutic approaches have demonstrated some degree of efficacy and safety, the resulting performances of patients leave room for great improvements. Optogenetic therapy has already been validated at the preclinical stages for the cochlea and retina but, in addition to the clinical trials, further studies are also required at higher levels to generalize its application. Such developments can only be achieved with biomimetic models of sensory information processing. Furthermore, new diagnostic tools will greatly facilitate the precise phenotypic characterization of complex aging diseases, allowing the monitoring of disease progression over months to validate therapies. All these developments are expected to reach clinical validation within the next decade, leading to a complete change in our clinical care of sensory diseases.

a. Position of Europe to address the challenge and exploit the results. Europe is well positioned in the field of sensory restoration because the industry leaders in auditory implants are European companies: two emerging start-ups in retinal implants are also European. The concept of optogenetic therapy was invented by the group of Dr. Ernst Bamberg, and its applications in sensory restoration have mostly been developed by European researchers. This novel therapeutic strategy is likely to occur in the sensory system because of its accessibility and confinement. In particular, the retina offers a natural window particularly well adapted to the optical stimulation required for optogenetic therapy. For gene therapy in general, platforms for GMP viral vector productions are already available in Europe in response to the expected explosion of clinical trials. The challenge for gene therapy will be to address the great genetic heterogeneity in hereditary diseases to bring therapies to the greatest number of patients. In the development of diagnostic tools, Europe has leaders in ultrafast ultrasound imaging, adaptive optics, and optoelectronics, with existing collaborations within all these communities. Finally, neuromorphic sensory systems were first generated in Switzerland and have now diffused to other European countries. The challenge for this field of research is not only to demonstrate its importance for visual and auditory restoration but also to implement the new biomimetics asynchronous sensors in other scientific areas such as robotics, the automobile industry, and areas of information, security and communication technologies.

b. Existing national or European research initiatives linked to this proposal. Some national and European research initiatives like the Human Brain Project (HBP) Flagship and the Graphene Flagship are linked to this proposal. However, this project has a specific emphasis on therapies and on sensory systems which are under-represented in the HBP, which does not contain the proposed cutting edge medical applications in sensory restoration. The Flagship Graphene is generally aimed at defining health applications which could benefit from the development of this very innovative material. However, these health applications are limited to the introduction of graphene as an electrode material for brain machine interfaces including retinal prostheses. The proposal is also linked to the EIT HEALTH but it focuses on very specific health handicaps requiring a massive and sustained effort to bring therapies to patients. This proposal is also linked to several ERC grants (e.g. OptoHear, Optoneuro) including the ERC Synergy grant HELMHOLTZ that aims to develop prototypes for new non-invasive imaging technologies for ophthalmology. These initiatives have given rise to an explosion of research and technology and the resulting huge body of knowledge about the visual and hearing systems is extremely large.

This Flagship proposal is positioning itself at a new level. Simply stated, we could achieve no less than moving from a society barely coping with disabilities to an inclusive and innovative European culture.