APPEL A PROJETS IHU 3 / CALL FOR PROPOSALS IHU3 2022

re-Connect

DOCUMENT SCIENTIFIQUE / SCIENTIFIC SUBMISSION FORM

Acronym (10 charact. max.)	**re-Connect**	
Titre du projet	Institut Audition et Cognition	
Project title	Institute for Hearing and Auditory Cognition	
Key words	Hearing loss, acoustic trauma, noise exposure, prevention, inner ear gene therapy, optogenetic auditory implants, biomarkers, patient cohorts, evidenced-based audiophonological medicine, digital medicine; robotic surgery, auditory neuroengineering, neuro-otology, speech brain computer interface, presbyacusis, tinnitus, hyperacusis, auditory neuropathy spectrum disorders, autism spectrum disorders, dyslexia, vestibular disorders.	
Project leader	**Title, Name, Firstname:** Prof. Giraud-Mamessier, Anne-Lise	
	e-mail address	***Phone number***
	anne-lise.giraud-mamessier@pasteur.fr	+33(0)603080336
Coordinating entity *Name, location*	Institut de l'Audition – Institut Pasteur 63, rue de Charenton, 75012, Paris	
IHU Founders	Institut Pasteur (IP)	
	Fondation Pour l'Audition (FPA)	
	Assistance Publique - Hôpitaux de Paris (APHP)	
	Institut national pour la recherche médicale (Inserm)	
	Université Paris-Cité (UPC)	
Length of the project **120 Months**	**Total requested funding** **50M€**	**Total budget** **333M€**

Partner teams

Name of the partner team / lab	PIs involved
Institut Pasteur - Institut de l'Audition - UMR Inserm UA06 (10 research teams)	P. Avan, H. Thai Van, C. Petit, S. Safieddine, Y. Nguyen, E. Ferrary, N. Michalski, B. Gourevitch (CNRS), R. Etournay, B. Bathellier (CNRS), L. Arnal, J. Barral (CNRS), El Amraoui, A., D. Lazard, S. Bouton (CNRS), S. Delmagani, M. Vinurel, AL. Giraud
Institut Pasteur – Dpt Neuroscience[1]-Dpt Comput. Biology[2]	JB. Masson[1], U. Maskos[1], H. Aschard[2]
Institut Pasteur – DARRI[1] ; - Ethics Unit[2]	I. Buckle[1], N Torno[1], J-C Dupont[1,2]
Fondation pour l'Audition	MJ. Duran, D. Le Squer, L. Francelet, A. Porte
GHU APHP Nord - Lariboisière Hospital Université Paris-Cité[1] Inserm U1144[2,] 3U1141[3], U1148[5], U1153[6], ICM[7]	C. Hautefort[1], P. Herman (ENT) [1,3], E. Mandonnet[1,7] (NeuroSurg), C. Paquet[1,2], J. Dumurgier[1,6,] M. Mazighi[1,5] C. Roos[1] (Neurology), M.Lilamand [1,2](Geriatry) M. Eliezer[1] (Neuroradiology), L. Drouet[1] (Hematology), K. Champion[1] (Int. Medicine), D. Sène[1,] (Int. Medicine), E. Houdart (Neuroradiology)
GHU APHP Centre Université de Paris Cité Necker Hospital- CREA	F. Denoyelle (ENT), N. Loundon (ENT), I. Rouillon (ENT), F. Simon (ENT)
GHU APHP Sorbonne Université Pitié Salpêtrière Hospital- CREA	Y. Nguyen (ENT), G. Lahlou (ENT), S. Borel, P. Gatignol (Speech Therapy)
GHU APHP Centre Université de Paris Cité – Rothschild Hospital[1], Hôpital Hôtel-Dieu[2]	E. Mamelle[1], C. Lemogne[2], D. Lévy[1], D. Ayache[1]
GHU APHP Centre Université de Paris-Cité - HEGP; AMU, CNRS UMR 7291	A. Londero
APHP - DRCI	A. Gysemberg
CEFON – ORL Falguière	C. Hautefort, M. Toupet
IP IdA - Inserm UA06 & Eye & Ear Massachusetts Institute	S. Maison (Phd-MD Audiology)

AMU CNRS UMR 7291 - Cognitive Neuroscience Laboratory	A. Norena, MJ. Fraysse
IRBA – Defense agency research institute	G. Andéol
Lyon Neuroscience Research Center, U Lyon I	E. Macaluso
Syndicat Des Audioprothésistes	B. Jantzem, S. Gallego
AudioCampus Montpellier - Inserm U1298	JL. Puel
Institut de la Vision – IHU ForeSight Inserm U968	D. Dalkara, M. Chalk
Institut du Cerveau – IHU ICM	L. Cohen, S. Samson, V. Navarro, K. Lehongre, N. Renier
IRCAM – CNRS – SU (UMR9912)	I. Viaud-Delmon, L. Hobeika, O. Warufsel
CEA[1] – Inserm U992[2] – Inria[3] – CNRS UMR9197[4]	V. van Wassenhove[1,2], JF. Deleuze[1] B. Thirion[3], A. Gramfort[3], J-M. Edeline[4]
Goethe University, Frankfurt, Germany	C. Kell
Université Paris Cité	I. Altarelli
Université de Nancy	C. Cerisara, M. Amblard, R. Serizel
Université Paris-Saclay – Centre Hospitalier de Versailles	M. Speranza
Co-developing industrial partners	
MyBrainTech GeodAIsics, Sensorion, Electronique Du Mazet, Perha Pharma, Cochlear, Collin, CorTec, SBT Human Matters, Fujirebio, Audika, Starkey, Avatar, Biogen, Iologo, Iqvia, Cilcare, Wise SRI, Amplifon.	**MyBrainTech,** Y. Attal (CEO); **GeodAIsics,** A. Attyé (CEO); **Sensorion,** N. Ouzren (CEO); **Electronique du Mazet**, S. Ailleret (President); **Perha Pharma,** L Mejers (President); **Cochlear,** F. Hayes (CEO France)**; Collin**, N Prevost (CEO); **CorTec** J. Rickert (CEO); **SBT Human Matters,** F Tarpin-Bernard (managing Director); **Fujirebio,** C de Wilde (President); **Audika,** T Lassere (Directeur sante); **Starkey,** F Vigneron (managing Director); **Avatar,** JB. Masson (CSO); **Biogen,** M Vasiliouv (Managing Director); **Iologo,** L Julien (President); **Iqvia,** J-M Aubert, (Président); **Cilcare,** S Pucheu (CSO); **Wise SRI**, L Ravagnan (CEO); **Amplifon,** J. Buisson-Savin

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Project Summary

Auditory disorders are a major burden that affects 20% of the global population and will impact 2.5 billion people by 2050[1]. Industrialized western countries such as France need to adapt to an ever-growing prevalence of progressive hearing loss due to increased life expectancy[2], noise exposure[3], and to the fact that people have children later in life, leading to more genetically determined neurodevelopmental hearing and speech disorders[4]. Both acute and chronic conditions, which current care systems in France and elsewhere fail to adequately detect and address, require innovative and targeted, and eventually life-long treatments. Patients with hearing loss wait on average 10 yrs before seeking help[5], and therapeutic innovation has stagnated for 20 yrs, cochlear implants and amplifying hearing aids still being state-of-the-art. This stagnation has dwindled the attractiveness of the related (para)medical specialties with a shortage of professionals at all levels of the clinical pathway[6]. Regarding central auditory disorders (e.g. tinnitus), the situation is probably even worse as there is no evidence-based treatment, leaving professionals groping for adequate interventions[7]. **Re-Connect addresses these unmet medical, societal and education needs by rapidly diversifying the clinical arsenal via novel therapies and clinical pathways for auditory disorders, combined with actions on prevention and education.** The distinctiveness of re-Connect, that will drive international visibility, lies in its broad scope addressing in a coordinated effort both peripheral and central auditory disorders, and disorders for which the auditory system can be leveraged for treatment. Concretely, re-Connect is based on several flagship projects on which it will take a leadership position, including genetic and cellular therapy of the ear, sono/opto-genetics for ultra-fine resolution cochlear and cortical implants, targeted sonotherapy in dementia, and neurostimulation and brain computer interfaces for auditory communication disorders. **Re-Connect gathers over 200 leading auditory neuroscientists, neurologists, neurosurgeons, ENT specialists, geriatrists, internists, hematologists, hearing aid professionals and speech therapists and actors of the associative and industry sectors, under the double mission of moving from compensatory to curative therapy in the domain of sensorineural hearing loss, and from empirical to evidence-based medicine in that of central auditory disorders.** These goals are articulated around 5 integrated scientific & clinical workpackages (WPs) targeting cardinal clinical challenges, 6 transverse supporting WPs, 7 technical platforms (3 existing), a center for innovation in human audiology (CeRIAH), and a Liaison Office dedicated to innovation/tech transfer strategy. Transdisciplinarity is at the core of each WP gathering researchers, physicians and private companies, and will benefit from a new strategic siting at Lariboisière Hospital (APHP), at the heart of a reinvented clinical and research campus (see Scientific Appendix 7.8). **Re-Connect's timeliness rests on basic discoveries from the last 2 decades, including the identification of many deafness-associated genes, selective neural circuits activation via gene transfer, and the characterization of neural auditory computations enabling targeted neural rewiring interventions.** Re-Connect seizes the opportunity of this third IHU call to engage in a forceful translation of these discoveries into operable clinical applications, via strong and diversified industrial partnerships (hearing aids, implants, sound industry, neurostimulation, pharma, digital health, robotics). According to the WHO[8], investing in an integrated strategy for auditory care should be associated with a gain of up to $37 for each dollar invested. Given these high stakes, and the urgency to transform the therapeutic portfolio, re-Connect is bound to have a major economic, clinical and societal impact. Its efficient scientific and operational organization enabled by the strong support of its founding members (IP, FPA, APHP, Inserm and University Paris Cité), will make re-Connect a leading European center playing a major role in carving the European health policies and attracting the best scientists and clinicians worldwide.

1 NATIONAL AND INTERNATIONAL CONTEXT

Hearing disorders are for a large part still poorly understood, and their clinical treatment is uneven at best. Forty-four million people in Europe suffer from some form of hearing impairment requiring treatment[9]. In France, 1/4 individuals have some degree of deafness[10], resulting in a total economic impact of €38bn annually for the state in diagnosis and treatment[11]. In only partial overlap with deafness, 1/5 persons have balance disorder or tinnitus[9].

It is essential and urgent to deploy innovative transdisciplinary and translational approaches along new and coordinated local and national clinical paths to address these clinical issues. Research has reached the tipping point of applicability while the broader use of conventional approaches like hearing aids is not fully living up to their promise. Though cochlear implants have proved tremendously successful in helping patients[12,13], that success in compensating hearing loss has come with about 20 years of relative stagnation in therapeutic innovation. It is now important to broaden the scope of innovation towards a curative auditory medicine, with the expected side-effect of making careers in the speech and hearing clinical field more attractive and addressing the current shortage of speech and hearing professionals[6].

To implement prevention and innovative therapeutic practices, the medical and paramedical education sector must follow suit. Unlike in the US, the UK or Australia, Audiology is not traditionally part of the French education portfolio as a distinct discipline but is instead embedded into other training paths like medical, hearing care, or speech therapy. Although the diversity of training paths can be seen as a plus, a critical mass of pioneer specialists in each of these curricula is lacking. To strategically seed these curricula with cutting edge therapeutic methods (Scientific Appendix 7.2), effective training and updated methods must be implemented. Broadening the therapeutic portfolio also requires strategic partnerships with industry players (Scientific Appendix 7.5), which traditionally move faster than basic research. Engaging pharmaceutical, hearing technology, med-tech, and digital companies in long-term collaborations is an additional key lever that must be pulled now.

2 DESCRIPTION OF THE IHU PROJECT

2.1 VISION, MISSIONS AND OBJECTIVES OF THE IHU

Re-Connect covers the entire transdisciplinary ecosystem of auditory disorders from the ear to the brain and interconnects all its actors from preclinical, to industrial and clinical applications. **Our vision is to move from compensatory to curative medicine to treat auditory disorders, and to leverage auditory processes to treat neurological disorders.** This vision is articulated around four missions: 1) to leverage fundamental auditory neuroscience research to contribute innovative therapeutic developments, 2) to prevent noise-induced hearing loss and reduce the far too long gap between hearing loss onset and its clinical handling (ten years on average)[14], 3) to bridge gaps in academic and professional education and make related careers attractive again, and 4) to connect traditionally dislocated constituents of the audition landscape (clinical specialties, academic and industrial partners, paramedical, medical and associative activity sectors).

Regarding our first mission, our goal is to evolve beyond sound-amplifying hearing aids for moderate hearing loss, cochlear implants for profound deafness, and ad-hoc therapies for speech-related issues to take the most promising preclinical projects to clinical and industrial stages, by embedding structurally and thematically with the newly opened Institut de l'Audition (IdA, Paris, https://www.institut-audition.fr/en), founded in collaboration with the Institut Pasteur, the Fondation pour l'Audition, and Inserm, and by partnering with specific departments at Lariboisière University

Hospital, where a new building will be dedicated to connecting medical specialties, and clinical with industrial projects, notably via new shared platforms, common space, and by immediately embedding re-Connect in its surrounding (other IHUs, AudioCampus Montpellier…) (see Scientific Appendix 7.1 and support letters in 7.6).

Specifically, re-Connect builds on several flagship projects targeting shorter or longer-term innovative hearing, auditory and brain therapies:

- gene and cell therapy of the inner ear[15,16]
- sono/opto-genetics for ultra-fine resolution cochlear implants[17,18]
- robotics for a safe delivery of therapeutic vectors to the inner ear[19,20]
- optogenetics cortical implants for treating central auditory disorders[21]
- combined sono- and chemotherapy for limiting Alzheimer's disease progression[22]
- speech cortico-computer interfaces and neurostimulation for life-long and so far, intractable communication disorders[23,24].

Goals for our second mission are to rebalance cognitive evolution by accelerating clinical handling of hearing impairment and fighting alongside key players against noise-induced hearing loss.

- organizing national prevention to contain the growing and devastating effects of environmental noise[25] and non-adapted listening practices on hearing health[26],
- supplying research-based facts, key figures, and guidelines to authorities to help accelerate the implementation of adapted legal measures,
- fostering an industrial ecosystem that promotes reasonable and interactive progress across the medical and sound/entertainment fields (see support letters in Scientific Appendix 7.6),
- proposing a reasonable trade-off between individual benefits (expensive cutting-edge therapies) versus global sustainability (low-cost measures for prevention, early detection of hearing loss and limitation of auditory-induced disorders).

The objectives of our third mission are to focus on academic scope, skill gaps, and coordinated curricula. We will expand the scope of the audio/otology academic field, and close the gap in skills and training between specialized Ear Nose Throat (ENT[1]) surgeons (MD and/or PhD) and hearing care professionals (bachelor level) to improve professional care for the large variety of auditory disorders. Third, we will improve coordination between audiology, speech therapy, otology and auditory neuroscience training to eliminate redundancy and discontinuities in the education value proposition. Re-Connect will take an active role to achieve these objectives by:

- setting-up high-level research internships as part of the medical cursus at master's and PhD level to re-diversify the audio/otology medical specialty, and promote basic hearing research,
- providing courses taught by the best professionals ranging from molecular neurobiology of the inner ear and sensory neuroscience to deficits and therapeutic solutions,
- upgrading audiology national training in collaboration with the nine French hearing care schools and the Collège National d'Audioprothèse towards a common basis set of courses within a national master program, and work towards standardized practices at the European level.
- providing continuous knowledge updates via focused courses for healthcare professionals from general practitioners to emergency staff (e.g. emergency procedures for acoustic trauma).

[1] All abbreviations are listed in the Scientific Appendix 7.11

Via these ambitious educational measures, re-Connect will federate task forces (medical, neuroscience, audiology and speech therapy trainees) and enhance interactions between healthcare professionals.
Through these 3 first missions, re-Connect will naturally achieve its fourth one to connect traditionally disconnected players through the wide breadth of its scope from the ear to the brain, and fundamental research to novel medical tools and procedures. To attract the best scientists, clinicians, and most dynamic entrepreneurs, we earmark funding for attractive starting packages, retain flexibility for targeted calls on new promising topics that will emerge during the project lifetime, and provide our industry partners with cutting edge platforms for R&D.

2.2 MEDICAL, SCIENTIFIC AND ECONOMIC ENVIRONMENT

In order to achieve its mission and objectives, re-Connect will gather, leverage and accelerate a powerful set of distinctive and complementary assets brought by its founding members and partners, in particular:

- Re-Connect grounds its action into the clinical practice, thanks to tight and well-organized links with **AP-HP** both within the compact and dynamic Lariboisière Hospital that provides re-Connect with the single largest ENT emergency entry point of the Parisian area, and across sites that traditionally collaborate in the ENT domain, i.e. Necker hospital (APHP, children) and Pitié Salpêtrière hospital (APHP, adults). The coordinated action of the 3 sites is expected to endow re-Connect with the most important active patient file in Europe.
- The **Institut de l'Audition** (IdA) constitutes the preclinical launching pad of the project. This new institute gathers 11 fundamental neuroscience research teams (UMR Pasteur/Inserm AO06) within a 4,500 m^2 facility equipped with phenotyping, imagery, data processing platforms for fundamental auditory neuroscience, and a center for innovative audiology for human research (CeRIAH, additional 500m^2). **The Institut Pasteur, Fondation pour l'Audition and Inserm**, its founding members, are already committed to support IdA for its next 10 years, providing a strong basement for the re-Connect project, and being a risk-limiting factor.
- The Institut Pasteur will be the sheltering structure of re-Connect (Scientific Appendix 7.10), granting it access to its well-established infrastructure, e.g. innovation & valorization (DARRI) and philanthropy departments.
- **Inserm** is the main research quality guarantor of the project, with over 9 Inserm Units involved beyond the UMR Pasteur/Inserm AO06 (Institut de l'Audition) that is at the core of the project.
- Thanks to the University of Paris-Cité, re-Connect has intrinsic links with major education players of the project notably the medical and life science faculties and key master programs (Biomedical Engineering, Integrative Physiology).
- Re-Connect also has a strong human resource contribution from the CNRS, and many other partners (Scientific Appendix 7.7).
- Finally, re-Connect has established strategic partnerships with companies that are key for its success (Scientific Appendix 7.5 & 7.6).

The combination of the assets brought by its broad consortium will enable re-Connect to translate its most mature preclinical projects into concrete and innovative clinical applications, while pursuing longer-term fundamental research goals that will continue to fuel future clinical developments.

2.3 RELEVANCE AND INNOVATIVE FEATURE OF THE IHU PROJECT

Re-Connect considers auditory disorders as the cornerstone of an entire system that ranges from the ear to the brain. Thus, re-Connect will both improve treatments of auditory disorders and leverage cutting edge auditory neuroscience to use auditory processes as an entry point to treat other neurological

and neurodevelopmental disorders. This holistic perspective informs re-Connect's entire mission, setting it apart from comparable initiatives in Europe and beyond.

Re-Connect aims to revisit the therapeutic arsenal from an agnostic perspective, giving equal opportunity to radically different approaches to cure auditory disorders, including genetic, pharmacological, and cutting-edge engineering approaches (Scientific Appendix 7.2). Re-Connect expects to be a leading structure to coordinate clinical auditory research at the national level, and a solid collaborator for our fellow European partners (e.g. the Ear Institute at UCL, UK, the Hörzentrum at Oldenburg University, Germany) to homogenize therapies and practices on a European scale. The foreseen impacts are both a qualitative transformation of the therapeutic means and a quantitative change (by a factor of 5 to 10) in the size of the cohorts for clinical research.

Re-Connect is intended as a fully functional IHU that integrates care, research, and training together into a coherent and transfunctional ecosystem (Scientific Appendix 7.7). To achieve this goal, re-Connect will deploy a set of distinctive and innovative features, including a radically novel cross-disciplinary approach, that will be both immediately operational thanks to the Institut de l'Audition where space can still be mobilized, notably for industrial partnerships, and the Lariboisière Hospital where all required medical specialties are present in a relatively compact space, and willing to explore beyond their traditional borders. Re-Connect will rely on its day hospital where ENT and neurology already share space for clinical research, and the existing neurosurgery and biochemistry platforms, where new tools will be set up. The longer-term landing of re-Connect is embedded within the global site restructuring plan, involving a dedicated building of about 5000 sq.m by 2028 (Scientific Appendix 7.8).

Re-Connect expects to coordinate the largest dedicated pool of patients in Europe, a necessary scale to test and deploy therapies within large cohorts. The Parisian area has over two million people with hearing disabilities, and we have access to about 100,000 patients who are followed-up by our hearing care partners (e.g. Audilab, Audika, Audition Conseil, and others). This ties in with our intrinsic collaborative network with ENT departments at Pitié-Salpêtrière and Necker hospitals, which already host successful clinical audiology research platforms (e.g. CREAs research centres in audiology), private ENT clinics (CEFON), the French defense agency (IRBA), and a broad hearing aid suppliers' network. Importantly, re-Connect will feature the largest entry point for ENT emergencies in the Paris area at Lariboisière hospital (23000/annual), an essential asset to target patients with acute hearing loss and develop treatments adapted to emergency.

Taken together, the pool of patients in need of care and ENT professionals will generate a considerable amount of data that we will shape into a highly actionable digital asset by dedicating one work package (WP) to the acceleration of the transition to new digital methods for clinical trials, diagnosis, monitoring and treatments, together with industrial partners (e.g. MyBrainTech), and the hospital system for law-compliant data management. The digitalization of clinical screening and therapy deployment will also require new partnerships with the digital industry sector to solve legal issues regarding medical data handling. From the patient's side, the use of digital, home-based methods and devices will improve early diagnosis and the follow up of disease evolution and provide the structural basis for the development of new care pathways and treatments (see scientific program below). New neuroengineering therapies (e.g. optogenetic implants) will connect MedTech (e.g. optrodes) and pharma (e.g. viruses) industrial fields. These connections form the different facets of our digital asset.

Re-Connect will implement a reference center in a working-class Parisian neighborhood. The north bank location of re-Connect on the Lariboisière site fills a social and geographical gap, providing access

to a highly innovative care/research campus in northern Paris (Scientific Appendix 7.8, Fig. 4). Re-Connect will immediately improve the quality of the local clinical handling and will develop cultural/education programs with the cityhall towards prevention in school pupils.

Re-Connect will work hand in hand with the sound industry to boost both the performance and safety of entertainment products (active noise cancellation, safety of radiofrequencies in Bluetooth devices, etc.), while liaising with the public authorities for a fast evolution of regulations as a function of research progress.

Re-Connect will yield new generation of industrial partnerships. With gene and cell therapy, pharmaceutical companies have become strongly involved in prospective trials (Sensorion, Roche, etc.). At present, patents in the auditory domain remain rather scarce. Re-Connect will boost the market by developing radically innovative therapeutic avenues. Notably, the spectrum of collaborations with the pharma sector is due to widely expand within the duration of the project, with the development of mixed academic and industrial labs (e.g. drug (re)engineering in WP2).

Finally, to conduct its ambitious education outreach, re-Connect partners with AudioCampus Montpellier, a structure dedicated to audiology training opening in fall 2022. This timely and strategic partnership will be the logistical basis for jointly deploying key educational assets, namely

- a homogenous audiology cursus with two radiation points in the north and south of France
- standardized clinical explorations of patients to build nation-level clinical cohorts.

3 DETAILED WORK PLAN

To achieve its goal of becoming a national and European leading center for auditory research and innovative therapy, re-Connect is organized around five **mixed scientific and clinical core WPs** covering the broad scope of auditory disorders, 6 transversal WPs that provide technological conceptual support, 3 existing experimental facilities (at IdA), and 4 new ones (at Lariboisière Hospital). In addition, re-Connect includes the existing Centre for Research and Innovation in Human Audiology (CeRIAH-Bench), where innovative tools and protocols are being designed, which will be paired with a CeRIAH-Bedside (at Lariboisière Hospital) where these tools will be clinically validated and disseminated (see Scientific Appendix 7.1). The clinical mission of an IHU is therefore totally embedded in the conceptual structure of re-Connect.

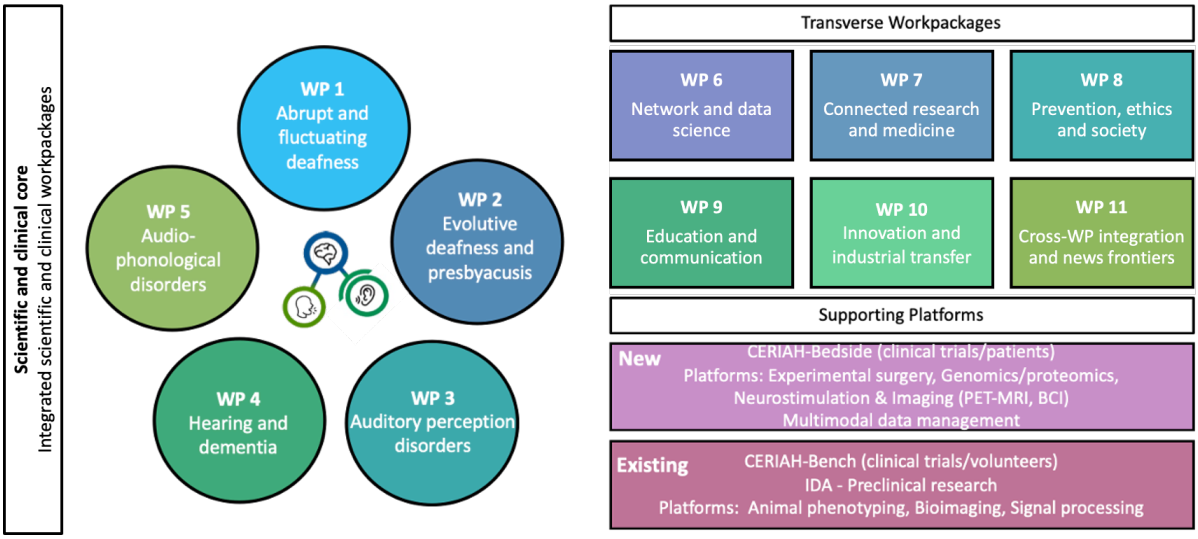

Figure 1: Scientific and support organization of re-Connect. Existing = IdA, New = Lariboisière

3.1 BASIC & TRANSLATIONAL SCIENCE/INTEGRATED SCIENTIFIC & CLINICAL WORKPACKAGES (SEE ALSO SCIENTIFIC APPENDIX 3, PARTNER TEAMS TABLE ON P2)

WP1: Novel treatments and handling of abrupt and fluctuating deafness

WP leaders: *P. Avan* (IP*), C. Hautefort (APHP)*. **Contributors**: *F. Simon, E. Mamelle, I. Rouillon, N. Loundon, A. El Amraoui, S. Delmaghani, A. Attye, D. Levy, D. Ayache, M. Toupet, M. Eliezer, L. Drouet, K. Champion, D. Sène, G. Andéol, F. Denoyelle, F. Herman.* **Industrial partners:** *Audika, Starkey.*

Sudden (e.g. noise trauma) and fluctuating (e.g. Meniere's disease) hearing loss require timely prescription of a proper therapy. WP1's target is the precision medicine of sudden and fluctuating audiovestibular (SFAV) conditions, which form the 3rd cause of deafness after age-related and chronic noise-induced ones (400/100,000/year[27]; 11% over one year for vestibular disorders[28]) with severe long-term consequences. For each of their many different mechanisms, the principles of treatments exist[29] pending a precise immediate diagnosis[30,31] (an unmet medical need for lack of proper logistics), simple biomarkers[32,33] and user-friendly tools[31]. Associating all Paris clinicians who see these patients and the IdA, this WP will build a new paradigm addressing pressing needs.

Task 1: From patient case-studies to a new treatment-oriented strategy (TRL 8). Exemplar phenotypes suggest distinct pathological mechanisms (microvascular, inflammatory, pressure-related, neuropathic or traumatic)[32,34]. Depending on the exact phenotype, targeted treatments must be adjusted with fewer side-effects than reference treatments. Available diagnostic tools, electrophysiology, biology, AI-guided search for malformations (imaging[35]), inflammation[36] or microvascular damage[37] will be reviewed and used in combination with molecular biomarkers of cell lysis, apoptosis, inflammation in use in murine models at IdA. New genetic, molecular and imaging biomarkers will be identified, and clinical trials accordingly launched with re-engineered molecules (anti-inflammatory, modulators of platelet aggregation[32], pressure homeostasis and apoptosis). Guidelines for an organized circuit beyond emergency will emerge, which is expected to unclog emergency units. **Task 2: Exemplar animal models (TRL 3)**. Their goal is to ascertain that the phenotype is caused by a specific physical or biological mechanism due to a gene defect or environmental factor(s). Fine-grained phenotypes will be established in acute acoustically controlled sound trauma; models of hydrops and atelectasis by manipulation of labyrinthine pressure[38]; models of inflammation & microvascular labyrinthine barrier impairment. We expect key pathways to be identified potentially offering us rational opportunities to target these pathways by re-engineered drugs[39] (**Cross-fertilization**: WP2). **Task 3: Toolboxes from emergency units to private practice and home-based use (TRL 2 - 5)**. Failure to collect data between detection and proper referral is due to a lack of medical staff with adequate training and available time. We will build the devices and infrastructure for fine-grained monitoring of transient conditions, after performing a survey of current practices[40]. Next, a paradigm will be tested for data collection with simplified tests (objective and subjective), including data collection at home (Milestone Year 6). This paradigm will be implemented across the IHU network with evaluation of its medico-economic impact. A national database will be built to feed and validate AI models (biology and imaging). We expect the generation of marketable user-friendly diagnostic tablets, usable for patient follow-up and monitoring of clinical trials of specific treatments. **Cross WP fertilization**: input to WP2-5, 8; output from WP6, 7, 9, 11. (details of cross-fertilization between WPs are given in Scientific Appendix 7.3).

WP2: Preventing and curing progressive hearing loss

WP leaders: *C. Petit (IP), Y. Nguyen (APHP).* **Contributors**: *G. Andol, H. Achard, G. Lahlou, C. Pineau, S. Safieddine, R. Etournay, E. Ferrary, J. Barral, D. Dalkara, J-F Deleuze.* **Industrial partners:** *Sensorion, Perha Pharma, Cochlear, Collin.*

WP2 goal is to develop inner ear therapies for preventing and curing hearing loss, based on early diagnosis with improved audiological tests and development of molecular biomarkers. The focus is on the two most frequent forms of hearing loss: age-related hearing loss, especially with early onset forms (EoARHL) and noise-induced hearing loss (NIHL) with 30-34% of the population being at risk[41]. Of note, different hearing loss forms involve common causal deafness genes[42–45]. **Task 1: Functional screening of patients with EoARHL or NIHL to set-up cohorts (TRL4).** Objective: establishment of prospective EoARHL & NIHL patient cohorts to decipher further the genetic architecture of these disorders which have monogenic and polygenic components[45–52], so as to elucidate the underlying pathophysiological mechanisms[53–56] and to develop therapies. *EoARHL* patients (sporadic and family cases): assessed with innovative auditory psychometric tests, cognitive and balance tests; recruited within re-Connect, and at national and European level (25,000 cases). *NIHL* patients assessed as above; recruited among 1) military staff with NIHL (chronic or traumatic noise) indicative of hypervulnerability to sound (500 cases/controls), and with "steel ears" i.e., high resistant to noise (200 cases) and 2) young individuals with unexpectedly severe HL after acute exposure to loud sound (600 cases/controls). Process and feasibility validated in our pilot studies. **Task 2: Genetic architecture and biomarkers of NIHL and EoARHL (TRL4-9)** The objectives are to identify: 1) causal or protective genes for EoARHL (family cases) with used strategies as before[45] plus whole-genome sequencing (WGS)[57]; 2) NIHL and EoARHL predisposing or protective genetic factors, using advanced univariate and multivariate methods applied to genome-wide association studies (GWAS)[58], whole-exome sequencing (WES) and WGS analyses; 3) genetically inferred underlying pathways (with functional validation)[59,60]; 4) candidate blood biomarkers, peptides and proteins (using high-resolution mass spectrometry)[61,62] and RNAs (LncRNA and miRNA) in mice exposed to chronic or traumatic noise; 5) biomarkers validation in patients. See WP1&3 for expected impact of biomarkers. **Task 3: From preclinical POCs to clinical trials (TRL 4-9)**. In the objective of developing gene therapy intervention for deafness after birth, undoubtedly EoARHL are particularly promising[42,47,63–65]. POCs obtained in one mouse model of a congenital deafness form (DFNB9: otoferlin-defect) allow current application with our industrial partner, Sensorion, for clinical trial authorization[66–68]. Our objectives are to: 1) develop an innovative method for generating EoARHL mouse models applicable to numerous genes; 2) improve gene replacement strategy for loss-of-function variants and gene-editing by prime-editing (correcting almost all pathogenic variants); 3) obtain POCs for prevention and curing therapy in several generated models; 4) develop cell therapy for mouse models with loss of cochlear cells; 5) develop viral vectors with various human cochlear cells tropism[69,70]; 6) seek for drugs[71] based on EoARHL and NIHL underlying pathways (see above); 7) engage in large-animal (monkey) preclinical trials; 8) transfer the POCs positive results into clinics, firstly for DFNB9[20]. **Task 4: Robot-based approach to intracochlear therapy delivery (TRL7).** Current access to the inner ear does not offer a controlled delivery of the therapy and can damage inner ear structures[19]. Objectives: 1) to determine routes of administration to preserve inner ear structures, based on 3D images analyzed with WP6; 2) to develop safe methods for perilymph sampling in patients with the RobOtol system[20]. **Task 5: Optogenetic cochlear implantation (TRL2).** Current cochlear implants suffer from low sound fidelity due to the poor spatial resolution of electric stimulation. Light-based stimulation using optogenetic activation of

the auditory periphery with higher spatial resolution can address this major flaw[17]. Objective: to design optical cochlear implants with >50 µLEDs providing flexible insertion and enhanced spatial resolution. Assessment of the benefits of the optical implant in animal models will evaluate: 1) cochlea damages and residual hearing; 2) best targeting strategy for optical activation (sensory hair cells or auditory neurons, viral strategy); and 3) benefits compared to electrical implants. **Cross-WP-fertilization**: input to WP1/3/6/8/10; output from WP2/9.

WP3: Characterizing and treating Auditory Perception Disorders

WP leaders: *A. Norena (Aix-Marseille Université), A. Londero (APHP).* **Contributors**: *B. Bathellier, J. Barral, R. Couderc, JM Edeline, MJ Fraysse, B. Gourévitch, L. Hobeika, E. Houdart, C. Lemogne S. Maison, N. Michalski, C. Roos, S. Samson, Y. Savin, H. Thai-Van, I. Viaud-Delmon, O. Warufsel.* **Industrial partners**: *Cilcare.*

This WP focuses on the mechanisms (Task 1), functional assessment (Task 2), innovative clinical handling (Task 3) of auditory perception disorders (APDs), namely tinnitus, hyperacusis and misophonia. **Task 1A: Neurophysiological mechanisms (TRL 2-7).** Behavioral paradigms will be developed in animals to assess the effects of sensory deprivation on neurotransmission[72], as well as electrophysiological biomarkers of tinnitus and hyperacusis. Modulation of neural correlates of APDs by means of cochlear[73] and/or cortical implant[74] stimulation (optogenetic/WP2) will be tested. Animal models of autism spectrum disorder (ASD) with hyperacusis[75] and of hydrops will also be developed. In humans, APDs are putatively accounted for by a variety of pathophysiological mechanisms. We will investigate homogeneous subgroups of patients, e.g. pulsatile[76] and somatosensory tinnitus[77], and in collaborations with WP1 and 2, patients displaying specific patterns of hearing loss[78] such as hydrops[79], noise trauma[80], sudden hearing loss[81] or genetic hearing loss[82]. A genetic screening for ASD related genes, will be performed in hyperacusis, and vice-versa people diagnosed with ASD and hyperacusis will be investigated within a specific cohort. Besides genetic screening, all subjects will undergo a comprehensive audiological and psychoacoustic assessment along with medical imaging (MRI +/- PET Scan) and electrophysiological recording (see Task 2). **Task 1B: Cognitive background (TRL 1-6).** This task addresses the psychological and cognitive mechanisms associated with APDs. The latter induce various degrees of experienced intrusiveness that may depend both on psychoacoustic patterns (e.g.: tinnitus pitch or tinnitus loudness)[83–86] and on impaired cognition (e.g.: memory, attention)[87] and psychology (lived experience, anxiety, depression)[88]. We will disentangle these intertwined mechanisms by means of cognitive/psychological explorations and functional imaging. In collaboration with WP6, analyses of patients verbatim based on natural language processing (NLP) algorithms will help to achieve this goal[89]. **Task 2: Functional assessment (TRL 3-7).** We will develop new approaches to characterize APDs and their impact on patients' cognition. New psychoacoustic tools probing attentional focus and information masking associated with APDs will be set up and validated on a large cohort of patients (n=500). In parallel we will develop and validate new approaches for exploring the auditory system such as pressure sensor (pulsatile tinnitus, somatosensory tinnitus, middle-ear muscle dysfunction)[90] or Reemerging Auditory Brainstem Responses[91] (with WP1/2), high-threshold cochlear fibers exploration, or Frequency Following Responses using natural sounds assessing hypersynchrony in subjects with loudness hyperacusis. **Task 3: APD innovative management (TRL 3-7)** This task will develop and test innovative therapeutic tools and interventions. With WP1, we will follow the outcome of the APDs after sudden hearing loss and identify key prognosis factors predicting APD onset after hearing loss. The preventive or curative effects of early acoustic (customized acoustic stimulation, hearing aid amplification) or electrical stimulation (cochlear/cortical implants)[92] on APDs will be assessed. The effect of specific interventions (e.g. Botulinum toxin injection, middle ear tenotomy)[93] on

tinnitus and hyperacusis will be thoroughly monitored. Cognitive behavioral therapies for tinnitus, hyperacusis, and misophonia will be enhanced by means of controlled 3D auditory/visual virtual reality environments[94]. Finally, an app will be developed (with WP8) to monitor sound environment and to track symptom evolution. Ultimately, the app is expected to help patients adapt to ever changing challenging auditory environment and scenes. The app will be used by other WPs as an educative tool to avoid sound over-exposure and then prevent hearing loss. **Cross WP fertilization**: input to WP4, 5, 8, 10; output from WP1-2, 6, 9, 8.

WP4: Hearing and dementia: from pathomechanisms to treatments

WP leaders: *C. Paquet (APHP), N. Michalski (IP).* **Contributors**: *J. Dumurgier, M. Mazighi, M. Lilamand, E. Macaluso, L. Arnal, F. Mouton-Liger, U. Maskos, N. Renier.* **Industrial partners**: *Biogen, Fujirebio, Iqvia.*

Hearing and auditory dysfunctions in dementia (HEADD) have been largely overlooked although hearing loss at middle age stands out as the first potentially modifiable risk factor of this condition[95]. The lack of mechanistic knowledge likely represents a missed opportunity for preventing, diagnosing, and treating dementia. WP4 proposes a bench-to-bedside approach to characterizing the role of hearing in dementia focusing on two most frequent forms of dementia (> 80%), Alzheimer's disease (AD) and Vascular dementia (VD)[96,97], benefiting from the large cohorts of Lariboisière Hospital[98,99] and from genetic mouse models for different forms of hearing loss and neurodegenerative diseases[100–104]. **Task 1: A patient cohort to explore HEADD (TRL:0-1)**. We will explore in a cohort of at least 600 patients the link between hearing and dementia (HLD) in well-characterized patients in 4 groups: (i) 150 AD patients and (ii) 150 VD patients at different stages, (iii) 150 age- and sex-matched controls with peripheral hearing loss but no cognitive impairment and (iv) 150 other controls without hearing or cognitive impairment from the geriatry department and patients' relatives. Cohorts (i) and (ii) will be further stratified in patients without peripheral hearing loss, with hearing impairment, with hearing impairment and fitted with hearing aids. **Task 2: The audiological component in HEADD (TRL 1-3).** (i) Our cohort will be monitored every year by the CeRIAH-bedside (described below) for hearing dysfunctions with peripheral and central explorations, and with tests implemented for auditory neuropathies in WP3. (ii) To decipher the underlying mechanisms, we will test the impact of peripheral hearing loss (congenital, progressive, classical, auditory neuropathy) on the evolution of dementia biomarkers in our animal models using *in vivo* electrophysiology and histology[104]. **Task 3: Neuronal mechanisms and pathways in HEADD (TRL 1-7)**. (i) Each participant in the HLD cohort will undergo an in-depth neuropsychological assessment annually to explore cognitive evolution over 5-years. (ii) Blood samples will be collected to assess biomarkers of neurodegeneration including AD[105,106]. (iii) A third of patients in each sub-cohort will undergo a yearly SV2A PET-MRI scan to provide new biomarkers of dementia severity in relation to hearing dysfunctions. (iv) Building on our previous findings we will use salient sounds to restore neuronal excitability in widespread brain circuits[107,108]. The effects of the treatment on central auditory processing in dementia patients will be assessed using electroencephalography (EEG) recordings, functional MRI, and behavioral tests. (v) With WP3 and 7, we will develop connected home-based follow-up and treatment protocols. These tools will provide a continuous measure of the patient sound-environment and allow us to assess auditory associative memory ("what-where-when") under real-world conditions. (vi) Using an innovative model of humanized mice[109] injected with human neurons from healthy or AD patients, we will characterize the spreading and survival of human neurons in auditory regions after mice have undergone different forms of hearing loss. **Task 4: The vascular component in HEADD (TRL 1-3)**. Our preliminary results in mice[110] show that the whole auditory cerebrovasculature may be remodeled because of peripheral

hearing loss. (i) We will determine whether different forms of hearing dysfunction directly increase the dementia risk by affecting the vascular organization of the auditory system using MRI. (ii) To study the role of the cerebrovascular system in the link between hearing loss and dementia, and develop new therapeutic targets, we will fully reconstruct the cerebrovascular system of deafened AD mouse models by using our new pipeline combining brain clearing techniques with light-sheet microscopy[110]. **Task 5: Auditory rehabilitation and interventions (TRL 1-9)**. We will test the benefits of (i) auditory rehabilitation on the prevention/delay of dementia symptoms in the HEADD cohorts by probing the biomarkers developed in tasks 2-4, and (ii) chronic exposure to salient sounds on our dementia biomarkers in a subgroup of AD patients[111,112]. Finally, we will probe the reversibility of cerebrovascular and central neuronal deficits linked to hearing loss using two models: gene therapy intervention in Otoferlin mutant mice[68] and direct electrical chronic stimulation of the mouse cochlea[113]. **Cross WP fertilization**: input to WP3,6, 7, 11, 10; output from WP8, 9, 10.

WP5: Rewiring disrupted audio-phonological networks

WP leaders: *D. Lazard (IP), E. Mandonnet (APHP).* **Contributors**: *S. Bouton, L. Cohen, AL. Giraud, I. Altarelli, P. Gatignol, M. Vinurel, C. Huron, M. Speranza, S. Borel, K. Lehongre, V. v. Wassenhove, B. Thirion, C. Kell, V. Navarro.* **Industrial partners**: *Iologo, Cortec, Wise SRI.*

The diagnosis of auditory, speech and language disorders is on the rise, leading to a growing demand for treatments in both children and adults, which clinicians and speech therapists are not able to meet. We will deploy **evidence-based therapy for disorders of the audio-phonological loop**, grounded in cutting edge neurophysiological hypotheses, converging on the development (with WP, 3, 4, 6 and 7) of standardized, home-based when applicable, treatments prescriptible by clinicians and therapists. **Task 1: Re-opening neuroplasticity in acquired deafness (TRL 3-8).** During deafness, the brain adapts by staying tuned to speech or rewiring[114] in ways that compromise auditory rehabilitation (cochlear implant)[115]. We will use behavioral markers of maladaptive neural reorganization (reading speed, phonological scores) in subjects with deafness (n=300) [116], and assess using audio-visual speech virtual reality (AVVR) tasks[117] the relative benefit of transcranial direct current stimulation (tDCS) to disrupt maladaptive networks (n=100), tACS (alternating current) to re-engage phonological processing (n=100)[118–120], and drugs (psilocybin, ketamine[121,122]) to reopen plasticity windows (n=100)[123,124]. **Task 2: Reformatting phonemic representations in dyslexia (TRL 5-8).** Among the 7% of schoolers with dyslexia[125], 75% have a phonological deficit[126] that is associated with atypical oscillatory auditory activity[127–129]. Correcting these functional anomalies is possible using brief tACS exposure, and rhythmic sounds[130]. In a large trial involving 400 adults with dyslexia, we will assess chronic tACS treatment comparing low- and high-frequency stimulation, and their combination. Via our network of >300 speech therapists we will also evaluate in children (n=300) the short- (weeks) and long- (years) term benefit of a non-invasive audio-based treatment. We will also restore correct phonemic encoding using M/EEG-Brain Computer Interface (BCI) (n=50). **Task 3: Synchronizing speech reception in autism spectrum disorders (ASD) (TRL 1-3).** In collaboration with WP1 and 3, we propose to improve social interactions in ASD by correcting auditory and speech processing anomalies, targeting anomalies of auditory oscillations[131–133]. In young adults (n=200) we will 1- reinstate auditory theta/low-gamma coupling using tACS, 2- disrupt abnormal beta/gamma nesting (a predictor of poor language development) using tDCS[134], 3- assess the combined effect of the two treatments (+sham). Should clinical benefits be found in 1-5 years old children, we will move to 5-9 years old children (n=200), and additionally evaluate in the latter group the use of AVVR (Task 1). **Task 4: Restoring speech communication using invasive and non-invasive BCI (TRL 3-8).** Decoding speech from cortical

(auditory and motor) neural activity holds the promise to reinstate communication in patients with severe speech production disorders, e.g. locked-in syndrome (LIS)[24,135,136]. We will develop a syllable-based brain computer interface (BCI) based on a large interface of the cortical speech network, first in 3 LIS patients (y3-7), who will benefit from the intervention, and help us improve communication, features[23] and decoding strategies. In parallel, we will continue exploiting intracortical recordings in epileptic patients (n=15/y, y1-5), and develop non-invasive MEG/BCI (y5-10). The large clinical cohorts in the WP will enable us to establish for each treatment a viable range of therapeutic parameters allowing for both standardized and individualized treatments. A key outcome of this WP at ten years will be an informed decision tree about individual benefit against treatment side-effects, as well as the industrial development and marketing of the treatments. This WP works with WP1,2,4 towards a genetic screening of patients in order to relate polygenic scores to neural phenotypes (y 6-10). **Cross WP fertilization**: input to WP1, 3, 4, 10; output from WP1, 3, 4, 6-9.

3.2 SUPPORTING PROGRAM

WP6: Network and data science

WP leaders: *B. Bathellier (IdA), JB. Masson (IP).* ***Contributors:*** *B. Thirion, R. Serizel, A. Attyé, A. Gramfort, M. Amblard, C. Cerisara, C. Dussaux, M. Chalk.* ***Industrial partners***: *Avatar, GeodAIsics.*

This transversal WP will provide state-of-the-art computational solutions to adapt the diagnosis of hearing impairments to their diversity and multifactorial aspects and provide new AI-based technologies for implantation and operation of hearing restoration devices (hearing aids, cochlear implants, prototypes of cortical implants). This will be enabled by a core team of data science specialists, all already involved in medical or neuroscience applications and mastering a large range of tools from deep neural networks to time series analysis and generative models[137–139]. **Task 1: Advanced tools for diagnosis & quantification through image analysis** (TRL 3-8) We will use recent developments in machine vision transformers[140] and generative models to carry out metrology and perform automated diagnostic tasks for both computed tomography scan (CT-scan) and MRI data. Applied to brain and inner ear scans[141], these developments will help detect abnormal morphologies in pathologies ranging from Meniere's disease (WP1, y1-3) to dementia (WP4, y5-7). They will then be converted to a marketable clinical decision support system (CDSS). **Task 2: Image fusion software for middle and inner ear surgical planning** (TRL 5-9) We have previously developed a software providing fused, segmented multimodal 3D images[142] in augmented reality[143] enabling surgeons to prepare for interventions, review in the operating room and interface with robots. This will be applied to cochlear implant surgery (WP2) and transferred as a new product of the startup company Avatar (y1-4). **Task 3: Encoding and decoding algorithms for neural prosthetics and time series analysis** (TRL 2-7) We will provide key algorithms[144] for the AI-based, trainable software interface for artificial speech production by decoding speech intentions from recorded brain waves for WP5 cortical implants. Self-supervised learning[145] for long neural time series and transfer learning will also be applied in this task for EEG/MEG recordings made in WPs 3, 4 & 5 (y1-8). **Task 4: Natural language processing tools for refining auditory perception and mental disorder diagnosis** (TRL 4-8) We will provide Natural Language Processing (NLP) tools to identify and categorize tinnitus (WP3, y2-6) and hearing-related mental disorders[146] (WP4). NLP models will be trained on labeled textual reports of misophonic symptoms from the patient cohorts observed in WP3, to obtain a new clinical decision support system (TRL8) then extended to dementia detection (WP4, y6-10). **Task 5: Advanced signal extraction for hearing aids and cochlear implants** (TRL 4-9) We will apply deep learning-based[147,148] clean speech

extraction tools to adjust hearing aids for specific hearing loss conditions, in particular auditory neuropathies[149–151] (WP2, TRL4-5), using direct algorithm training on patients (y1-5). This technology will be evaluated in clinical tests at CeRIAH and transferred to commercial devices (y5-10). **Task 6: Encoding algorithms for cortical implants** (TRL 3 to 7) Deep autoencoders networks matched to stimulation device size and constraints will be used to optimize sound encoding into cortical stimulation implants[152] for auditory restoration[21] (H2020 FET Open Hearlight, PI: Bathellier). This will contribute to bringing cortical implants to pre-clinical (y2-5) and clinical phases and extend their use to tinnitus[153] (WP3, y5-7). **Task 7: Data management platform** (10 years) To enable secure and standardized data storage for all WPs, accessible to large scale computational analysis, a data management facility will be set up together with the Institut Pasteur data management services. **Cross WP fertilization**: input to WP1-5; output from WP1-5.

WP7: Connected research and medicine (CoReMed)

WP leaders: *L. Arnal (IdA), Y. Attal (MyBrainTech).* ***Contributors:*** *C. Hautefort, M.J. Duran, S. Bouton, P. Avan, C. Paquet, E. Macaluso, A. Norena, E. Mandonnet.* ***Industrial partners***: *Mybraintech, MyMedical Assistant, SBT.*
The goal of WP7 is to facilitate access and integration of connected solutions (apps, devices) to leverage the opportunities of the digital revolution in the re-Connect project. WP7's *CoReMed* platform is a suite of digital solutions aiming at promoting novel experimental research and clinical practices, from observational (gathering data and providing insights) to interventional practices (effectively acting in the treatment process). WP7 facilitates the collection of multimodal data to link patients, disease, and treatment, allowing for time-saving diagnosis and treatment tools while enforcing all necessary safety measures (*i.e.* RGPD) for sensitive data storage and access. **Task 1: Online/App based recruitment platform.** Massive online screening platforms provide a unique opportunity to sample large populations for behavioral assessment. However, there is currently no homogenous solution to collect, assess, and integrate multimodal (behavioral, physiological, medical) data from connected tools. Our goal is to deliver a platform (web/app based) enabling large-scale online recruitment, screening (questionnaires, tests) and curation of patients and participants data (medical –i.e. audiological, neuropsychological– status). **Task 2: Platform for multimodal recordings using connected devices.** Current portable solutions for connected health (devices, apps) are often (re)developed from scratch by startups, without exploiting existing resources, which ends up inefficient and costly. Here, owing to advanced tools provided by our partner MyBrainTech, *Coremed* will provide unique facilities to connect existing –or emerging– devices in order to collect, assess, and integrate massive multimodal (audiological, physiological, neurological) datasets in the field of auditory science. Ensuring interoperability across devices (EEG headphones, smartwatches, apps), *CoReMed* will promote efficient and reliable data streaming. Providing a common data acquisition pipeline ensuring compliance with current medical norms and regulations, *CoReMed* will upscale IHU connected research and medicine projects to accelerate re-Connect's translational research, delivery to patients and access to market. **Task 3: Autonomous experimental practices for digitalized research and medicine.** To facilitate compliance and adherence of participants, patients, and practitioners to digital tools, WP7 will integrate a complete suite of user-friendly interfaces and applications, for an easy and independent use of connected solutions (apps and devices). A dedicated soft-/hardware team will strive to optimize the design at each level (privacy, ecology, costs). From the set-up to online data quality monitoring, analysis and display, this task embeds a series of crucial functional modules to accompany the patients' digital journey on the *CoReMed* platform at four levels: prevention, diagnostic, treatment and follow-up monitoring. **Cross WP fertilization:** input from WP1-5, 9 output to WP1-5, 8, 10.

WP8: Prevention, ethics and society

WP leaders: *MJ. Duran (FPA), P.Avan (IDA), JC. Dupont (IP).* ***Contributors:*** *L. Francelet, A. Porte, C. Hautefort, Y. Nguyen, C. Paquet, A. Norena, A. Londero, H. Thai-Van, AL. Morin.* ***Patient associations:*** *Scientific App. 7.7.*
In the domain of auditory disorders France suffers from a lack of health promotion and prevention[154] , with newborns screened at birth for deafness only since 2015[62,63]. WP8 builds on new tools and services tested & validated by other WPs (*e.g.*, new healthcare path for sudden deafness, therapeutic patient education program for tinnitus and hyperacusis) to design hearing prevention material & activities. Health problems (sleep, balance, ability to concentrate) and annoyance linked to risky noise exposures[155] (transportation increase, amplified music…) are reported by the public but not yet covered by protective regulations[156,157]. To tackle these issues, WP8 aims to explore these new situations, coordinate the required expertise to generate reliable data and establish bases for new state regulations. **Task 1- Scientific and clinical research to promote prevention. *Dissemination of emergency care guidelines for sudden and fluctuating deafness*** *(72 months).* Most patients and professionals miss the 48 hours critical window for the care of sudden and fluctuating deafness[158,159]. Based on the healthcare path designed by WP1, WP8 will work on plea messages towards public authorities to advocate for the approval of the guidelines to improve patient care. Subsequently, WP8 will design prevention messages and disseminate campaigns using different media to inform health professionals (GP, occupational MDs, pharmacists…). The public and professionals will be educated on how to identify emergencies for sudden and fluctuating deafness leveraging new and dedicated social media strategies. ***Presbycusis prevention and lobbying for hearing screening*** (*120 months).* Hearing screening will be promoted at all ages using state-of-the-art tests like in our Höra app in medical settings or at home (cross-fertilization with WP2/WP4) as well as information about hearing loss as a modifiable risk factor for the development of dementia[95,160]. Lobbying actions targeting legislators aiming to include systematic hearing screening in occupational health laws in France and to raise-awareness about the risks of compressed music will be developed. ***Dissemination of the therapeutic patient education program for APDs (tinnitus, hyperacusis) and awareness about misophonia*** (*120 months).* Actions will be undertaken to inform patients, the public and health professionals about the existing and new apps, and the therapeutic patient education program developed by WP3 for tinnitus, hyperacusis and misophonia, including screening and handling recommendations. **Task 2- Assessing new noise risks** *(120 months)*. While exposure to occupational noise is now carefully monitored, voluntary exposure to amplified music[161] and increased levels of environmental noise with unusual spectral characteristics (compressors, transformers, windmills)[157] may have harmful effects currently neither understood nor documented, the goal of task 2. We will initiate interactions within re-Connect to inspire research on novel animal models and specific diagnostic tools (*e.g.*, a yearly workshop with invited speakers outside the hearing field). Importantly we will run epidemiologic studies based on the data collected in all scientific WPs, notably thanks to WP7 tools, that will also help us collect simple measures (*e.g.,* in-ear acoustic level detection, etc.). The ensuing statistics will be leveraged to inform policy makers, physicians, patient's associations and the general public. **Task 3- Fostering evidence-generation and early dialog on ELSI** *(120 months)*. Prevention strategies, medical devices, as well as high impact innovations – all foreseen beneficial innovations in re-Connect – raise methodological challenges to provide evidence on the Ethical, Legal and Social Impacts (ELSI). An ELSI Advisory Committee will be operated within the legal department (health, compliance and ethics) at the Institut Pasteur with two complementary transversal objectives: *i)* to identify opportunities to nest social sciences empirical studies within trials and research promoted by the IHU and *ii)* to stimulate high-level early dialog and dissemination

activities with stakeholders, partners and regulatory bodies on individual and collective impacts expected from the innovative approaches under development. **Cross-fertilization:** output from WP1-7, 9, input to WP9-11. **Cross WP fertilization:** input to WP9-11; output from WP1-7, 9.

3.3 INNOVATIVE TRAINING AND EDUCATION

WP9: Education and communication

***WP leaders**: B. Bathellier, H. Thai-van. **Contributors**: B. Janzem, S. Gallego, P. Avan, F. Simon, JB. Masson, P. Gatignol, E. Ferrary, JL. Puel, CeRIAH-Bench, FPA. **Industrial partners**: Electronique Du Mazet.*

Unlike in most European countries, audiology is not a recognized discipline in France, leaving detection and handling of impairments to ENT practitioners in insufficient numbers and hearing aid professionals undertrained to cross-diagnose the wide range of auditory deficits. We address these challenges through a visible and far-reaching center of competence for continuous training of practitioners, new multidisciplinary courses for students, and targeted upgrades for hearing aid professionals. **Task 1: Continuous training of medical staff and audiologists.** In partnership with University Paris-Cité, Sorbonne University, Université de Lyon and AudioCampus Montpellier, re-Connect will provide a range of continuous training courses modeled on the existing DU Audiology (UPC) to accompany the upcoming inclusion of the hearing professional training into the university curriculum (LMD, y1-4). These will target topics insufficiently covered during hearing aids prescriptions: hearing in noise, auditory neuropathies, central deficits, vestibular impairments, ear biophysics & neuroscience. Based on this, a new Audiology master program (Paris, Lyon) will be created in synergy with the Audiology master at AudioCampus and the College national d'Audioprothèse (y4-10). For continuous training of physicians, online master classes generated by a new dedicated Communication Service at the IHU will diffuse best practices at the international level (Scientific Appendix 7.9), partly financed by a pay-per-view system. For ENT practitioners, a yearly course on 3D analysis of MRI scanner data and surgery planning will accompany the development of new AI-based tools in WP6. **Task 2: Hearing Science training for university students.** To attract and train outstanding students, re-Connect will expand the 1-year-old Institut Pasteur course HeaR (3 weeks), which covers central and peripheral mechanisms and new therapeutic strategies, to local PhD students, practitioners and master students, with targeted stipends. It will be proposed to the Master Biomedical engineering- Bioimaging (UPC), Integrative Biology and Physiology (BIP) (Sorbonne University) and International Dual Master (UCL – ENS – Sorbonne University) in 2023-24. **Task 3: Communication to the general public.** The re-Connect communication service will identify internal scientific breakthroughs and produce high quality multimedia contents (video & podcast) for the public, with supporting social media and press releases. An open-lab space will be created (with the Paris cityhall) in the new IHU building for interaction hosting school classes and direct interventions in schools will be performed. **Task 4: Communication with patient associations** A yearly meeting with patient associations will be organized with the FPA, to exchange on patient needs and therapeutic perspectives. This will be organized in synergy with the actions of the Innovation Management team (e.g. Hackathons) **Task 5: Scientific communication.** Unless critical for intellectual property protection, IHU scientific results will be communicated in international conferences (e.g. ARO meeting). A yearly symposium will be organized at the IHU focusing on a different topic each year. Open access publication will be favored for articles produced by IHU. **Task 6: Broadcast innovations on a national scale** (CeRIAH, y1-10). We will set up a CeRIAH mobile unit whose mission is to send experienced R&D biomedical engineers with dedicated equipment provided by our partner *Electronique Du Mazet* to key audiology centers and research

hospitals throughout France. The unit will inform local staff about re-Connect education programs and train them on site to the latest CeRIAH-Bench technology and practices. A CeRIAH certification will be delivered with an annual updating course to maintain the standards at the highest level. This process includes the diffusion of assessments and treatments to the patients' homes, notably via telemedicine (WP7), and recommendation of patients with specific or rare pathologies to re-Connect for eventual clinical trials. **Cross WP fertilization:** input from WP1,3,5,6,10; output to WP1-6,10.

3.4 INNOVATION MANAGEMENT AND INDUSTRIAL TRANSLATION

WP10: Manage the Innovation

WP leaders: *I. Pelletier-Bressac, I. Buckle.* ***Contributors:*** *A. Gysembergh, N. Torno.*

WP10's mission is to generate revenues and employment and develop the best ecosystem among industry players. It brings innovation to the patients thanks to a well-crafted organization allowing the development of licensed industrial partnerships or start-ups (SUs) in re-Connect labs and clinical units. It will generate resources. These partnerships will boost re-Connect‘s research excellence and deliver solutions to industry's current challenges and needs. Intellectual property (IP) matters will be dealt with via a single highly experienced representative referred to as “Mandataire Unique”, the Institut Pasteur. For clinical projects and associated clinical services, however, the Mandataire Unique will be the clinical trial Founder Sponsor for the IP of clinical trials. Information will be provided to the Innovation Committee by the Liaison officer. The rules for sharing and promoting IP will be managed according to dedicated specific master agreements between the Institut Pasteur and the Founders. WP10 will operate via an Innovation Committee meeting on a bimonthly basis (see Scientific Appendix 7.4). **Task 1: Leveraging the best expertise in Technology Transfer.** Re-Connect will primarily rely on the Innovation instrument of the Institut Pasteur, DARRI, which has a long-standing expertise in supporting the innovation chain, by identifying potential applications, protecting IP, de-risking, promoting, ensuring transfer and post-contractual management, accelerating health product marketing, via industrial partnerships, licenses or SU creation. Support to SUs includes project evaluation, coaching, funding for maturing scientific projects. Incubation will be led by the Founders and their partners (Agoranov, Paris Biotech Santé and Genopole) and SU studios (Argo Bio), PSL Tech Acceleration, Medtech Generator & Accelerator and the AMI Biocluster *Brain&Mind*. Re-Connect is supported by Medicen and Cap Digital, the two relevant thematic industrial clusters (*Pôles de Compétitivité*). Re-Connect SUs will have dedicated space at IdA (years 1-6), and at re-Connect Lariboisière (year 6 on). **Task 2: Liaison Office: a single-entry point**. With a team of 4 people, it will promote collaboration opportunities for re-Connect researchers and industrial partners worldwide. It will offer a proactive and time-efficient interface as a point of entry with researchers and industries, with a reactive team of specialists. It will translate industry needs into scientific and technological requirements, and map re-Connect resources with technological needs. With DARRI, it will coordinate visits, networking, and seminars on site with private companies, will identify with the grant office of the Institut Pasteur the appropriate financial tools for private and public projects, and will establish long-term industrial partnerships, such as Iqvia/APHP, Sensorion, Mybraintech. All agreements will be signed by re-Connect (as a sheltered foundation by the Institut Pasteur, see 4. Governance) except clinical trial agreements who shall be signed by the Sponsor (see Task 3). The Liaison Office will coordinate with DARRI and other Founders for IP issues on a day-to-day basis and will assist the Innovation Committee. The Institut de l’Audition (IdA) already benefits from the label “Carnot Voir et Entendre”, which is attributed to research institutes that notoriously work in close partnership with industrials. **Task 3:**

Academic Sponsor Trials. Thanks to the broad clinical network of its founders, notably that of the APHP recognized by the Carnot label in 2019, re-Connect will mobilize an important active patients' file. In the context of clinical trials, the Liaison Office will support coordination with the Founder sponsor regarding non-interventional and interventional academic sponsored trials and will be the contact point for the CeRIAH, the IdA (Institut Pasteur) AP-HP and INSERM. The Founder sponsor is the sole signatory of the Clinical research agreement. **Task 4: Living Lab.** A Living Lab will carry out multifaceted and demanding open innovation approaches and design thinking, fruitfully combining science, industrial competitiveness, social innovation and participatory research. The formalization of the offer and the typology of the Living Lab will be adapted to the hearing field in connection with the CeRIAH. Hackathons will be organized and open to researchers outside re-Connect. **Cross WP fertilization:** output to WP1-8

WP11: Cross-WP interfaces and new frontiers

WP leaders: *AD. Lodeho, D. Oficjalska, C. Quinsac.* ***Contributors:*** *A. Boggaerts, C. Baillergeau, D. Le Squer.*
The goal of WP11 is to maintain the level of excellence and novelty in research throughout the first 10 years of the IHU lifetime and identify novel avenues, by promoting cross WP interactions and enabling flexibility for new team creation. Three major actions will be undertaken. **Task 1: Step outside re-Connect** (CeRIAH-Bench + Communication team, y1-10). The goal of this task is to develop and structure re-Connect's local, national and international network. The latter will be entertained via encouragements for multi-partner/country grant applications. We will encourage national collaborations via our own project grant program, and via an annual 2-day workshop on topics connected to but outside the immediate scope of re-Connect (e.g., new frontiers in AI and prosthetics, human genetics, etc). An annual open day event will present re-Connect's latest innovations to patient's associations and the public. Together with patient-oriented Hackathons, this will be essential to design novel approaches that closely meet the patients' needs. **Task 2: Cross-WP interactions** (Communication team + all principal investigators (PIs) + platforms, y1-10). Work in progress and scientific challenges will be presented by the PIs, students and platform managers, at a biannual project report meeting. These regular interactions will generate cross-WP ideas and new collaborative teams, who can then apply to re-Connect project calls. **Task 3: Manage the unexpected** (Steering committee, y1-10). To stay tuned to new ideas, potential technological or knowledge breakthroughs, possible social shifts, or unexpected new clinical situations (e.g. Impact of COVID-19 on the auditory system[162]), an internal grant scheme will be set up. Every six months, a call for proposals will be opened and a project management committee will decide to fund projects including at least 2 IHU teams. This grant scheme will enable fast pilot studies to get preliminary results and apply to national and European health programs or set up new industrial contracts. Budget will also be earmarked for the creation of two new research groups (starting budget). **Task 4: Fundraising**. Re-Connect's ambition is only viable with a sustainable and efficient fundraising strategy. WP10 will organize a coherent fundraising activity, e.g. nationwide sensitization and fund-raising campaigns together with famous ambassadors from the music world, with an annual expected income about €2M. A team will be dedicated to work closely with our founding members, FPA and the fund raising department of the Institut Pasteur. **Cross WP fertilization:** input/output to/from WP1-10.

3.5 PARTNERSHIP AND NETWORK STRATEGY (SEE ECOSYSTEM IN SCIENTIFIC APPENDIX 7.7)

Re-Connect hosts an important structure, the CeRIAH-Bench, whose mission is to devise novel audiological exploration methods and to ensure their application, at the national level via a network of

clinical partners, and abroad in order to assemble nationwide and eventually European clinical cohorts (see also WP10&11). Re-Connect is intrinsically built from existing collaborations with its surrounding clinical environment, notably the teams involved in the two CREAs present at Necker and Pitié-Salpêtrière Hospitals. Re-Connect will extend and further structure this network via its implantation at Lariboisière Hospital, where it will gain access to the network of our key clinical members, such as the national memory centers network (centres-mémoire). Re-Connect is also naturally connected to the nearby existing IHU network, via scientific collaborations and research facility mutualization (ICM, IdV), and an organized clinical pathway for patients with genetic hearing disorders (Imagine, Centre de Référence des Surdités Génétiques). In particular, the initial phase of the project will be deployed via collaborations with the ICM platforms CENIR-MRI, CENIR-MEG, iVECTOR and iGenSeq platforms, which do not only provide resources to the ICM but cross-fertilization via a window on novel challenges (e.g. speech BCI in WP5). This structural collaboration will be particularly valuable in the first phase of the proposed IHU project, before re-Connect gets its new building at Lariboisière Hospital. During its lifetime, re-Connect will co-develop with ICM an OPM-MEG (Magnetoencephalography based on optically pumped magnetometers) research infrastructure, helping our partner reach a critical mass of potential users, and sharing manpower resources. Regarding education, we team up with the AudioCampus Montpellier to work toward a coherent cutting-edge national audiology education program. The benefit is immediately mutual and expected to spread to all our national partners. The collaboration will continue when Audio-Campus will launch its second phase centered on clinical cohorts. This will enable both parties to jointly apply to large-scale European research and health programs. While national collaborations will be encouraged within our own grant program, re-Connect will also apply to major European programs, in collaboration with international partners (e.g. UCL Ear Institute, Hannover medical school, Oldenburg Hörzentrum), and will deploy collaborations with equivalent structures oversees, such as the Eye and Ear Massachusetts Institute (Scientific Appendix 7.9). Last, re-Connect adopts a patient-centered approach implying gathering all partners concerned with each clinical entity (Figure 2). This requires tight collaborations with patients' associations and federations of related professionals (hearing aid professionals, speech therapists, educators, industrials, health insurance partners, policy makers etc., Figure 3). If successful in uniting the various activity sectors around clinical entities, re-Connect will naturally become the single most visible interface between the research and medical worlds and the lay public for all Auditory-related issues in France.

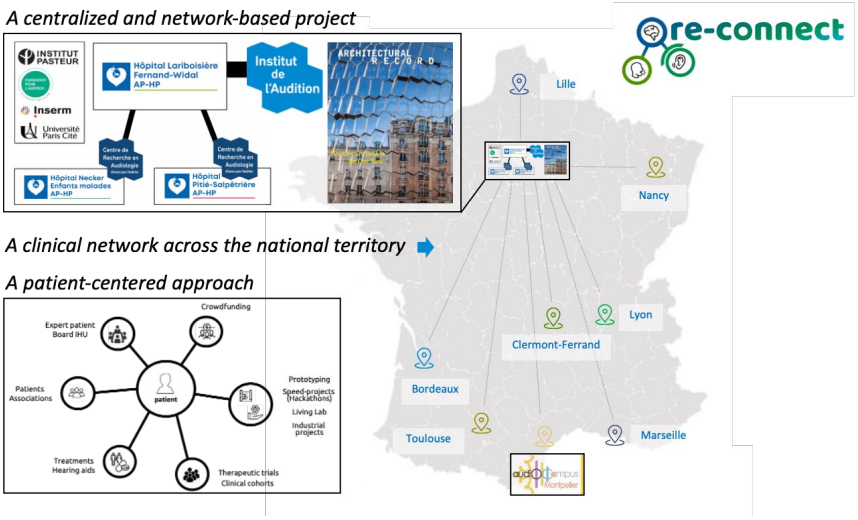

Figure 2. Re-Connect's local structure, national network, and patient-centered concept.

4 SCIENTIFIC GOVERNANCE AND PROJECT MANAGEMENT

4.1 RELEVANT EXPERIENCE OF THE PROJECT LEADER

The re-Connect project is led by Anne-Lise Giraud (ALG), Professor at the Institut Pasteur, head of the Institut de l'Audition (IdA) and the corresponding Inserm/Pasteur UMR AO06. ALG was trained as an auditory neuroscientist within an ENT clinical/research entity (CNRS/Edouard Herriot University Hospital, Lyon-France). After two post-docs, at UCL (UK) 1997-99 and at Frankfurt Goethe University (Germany) 1999-01, where she pursued her work on the neurophysiological predictive factors of cochlear implant success and diversified to other disorders of the audio phonological loop, she became a junior group leader (BMBF) at the Brain Imaging Center Frankfurt (Germany). In 2004, she joined the CNRS as research director and headed an Inserm/ENS research team on auditory cognition (2007-12). In 2012, she was appointed full professor at the University of Geneva where she led for 10 years the research unit 'Auditory, Speech and Language Neuroscience'. Her research employs all tools applicable to the study of auditory processes in humans (PET, fMRI, EEG/MEG, ECoG, SEEG, tA/DCS, computational modeling). In 2019, she became co-director of the Swiss National Center of Competence in Research (NCCR) EvolvingLanguage, after an all-disciplines competitive call (rank 2/54 proposals). The structure is endowed with a budget of CHF 40M for 4 years renewable twice and gathers 50 PIs and over 200 collaborators. Through this demanding multicentric project ALG has experience with maintaining scientific and operational cohesion in a large group of people. At the beginning of 2022, ALG moved back to Paris, to take over the head of the IdA, successfully launched by her predecessor Pr. Christine Petit. As head of the IdA, ALG is ideally positioned and qualified to lead the re-Connect project that intends to coordinate research and clinical activities across a large scope of disciplines. Reflecting a collaborative and multidisciplinary vision for re-Connect, she will be assisted in the IHU leadership team by two deputy directors, Prs. Claire Paquet (Neurologist) and Emmanuel Mandonnet (Neurosurgeon) at Lariboisière Hospital, and two clinical directors, Pr. Yann Nguyen (ENT surgeon) at Pitié-Salpêtrière Hospital and Dr. Charlotte Hautefort (Otologist) at Lariboisière Hospital.

4.2 IHU GOVERNANCE AND OPERATIONAL ORGANIZATION

4.2.1. General organization and governance model (see also Governance Appendix)

Re-Connect is conceived as a **"sheltered foundation" under the aegis of the Institut Pasteur** (a French non-profit foundation with charitable status), in accordance with law n° 87.571 of 23 July 1987 and the Institut Pasteur Internal Rules. The purposes of the re-Connect Foundation are to define and lead a common strategy in research, health care, innovation and teaching activities in the domain of Hearing and Auditory Cognition, between the founding members within the limit of their corporate purpose. Multiannual agreements or a consortium agreement will be signed between the Institut Pasteur and founding members to define the resources made available to perform the re-Connect activities (funding, research funds, existing staff, new recruitments…) and the founding members obligations (research, health care, teaching, IP, provision of premises…). An **initial endowment** is established between founding members. Grants and other financial resources are received by the Institut Pasteur and retransferred to each founding member to fulfill its commitments. Management fees (<10%) will be charged by the Institut Pasteur. Re-Connect will set up Functioning and Operating Rules in accordance with the Institut Pasteur Internal Rules, as described hereafter.

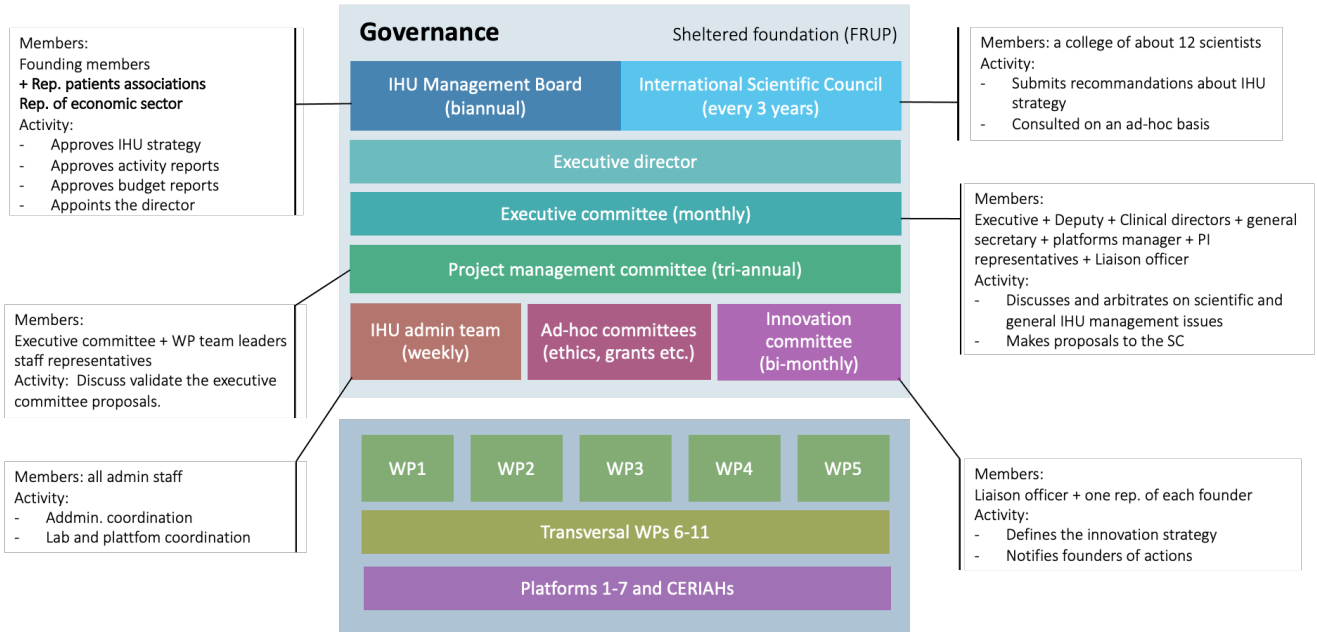

Figure 3. General overview of the IHU re-Connect organization, an Institut Pasteur sheltered foundation

4.2.2. Functioning of governance bodies and ad hoc committees

Re-Connect's governance has been devised to confer the IHU a maximal efficiency and coherence between its actions and the strategic goals of its founding members. The **Management Board** brings together all founding members and qualified personalities who can provide an external and strategic perspective on the IHU missions. The IHU Executive Director implements the guidelines of the Management Board and reports on the IHU actions. The Management Board elects a President. It adopts the re-Connect Functioning and Operating Rules in compliance with the Institut Pasteur Internal Rules. The first IHU **Executive Director** is Anne-Lise Mamessier Giraud, re-Connect's coordinator. The procedures for the appointment of her successor are defined by the IHU founding members in the re-Connect Functioning and Operating Rules and outlined in the dedicated Governance Appendix. The Executive Director leads the development of the IHU and its strategy implementation as decided by the Management Board. The Executive Director has the power of attorney for signature within a perimeter to be defined. To ensure the proper functioning of the IHU re-Connect, the Executive Director will preside *adhoc* committees, e.g. grant Allocation committee. An **International Scientific Council** of 12 to 15 members is proposed by the Steering Committee for the quality of their scientific expertise and their strategic vision. It is approved by the Executive Director and validated by the founding members. It has an advisory role and enables the re-Connect Foundation to guide its scientific, clinical, industrial and teaching strategy. The **Executive Committee** is composed of the IHU Executive Director, two deputy directors and two clinical directors, the IdA deputy director, the IHU general secretary, two representatives of the IHU PIs, the platforms manager, and the Liaison Officer. Among the director and deputies, one is the IdA director. The role of the Executive Committee is to deal with organizational, scientific and/or general management issues of the Institute, and to advise the IHU steering committee. The **Steering Committee** is composed of the Executive Committee and is extended to the WP Team Leaders, one research staff representative, one students' representative, and one technical staff representative. Its role is to discuss and validate the executive committee's proposals about e.g., scientific objectives, priorities, new teams, recurring budget planning, purchase of shared equipment,

etc. The IHU also has an **Innovation Committee,** i.e. an advisory body that includes a representative of each Founding Member competent in IP matters in order to discuss IP and technology transfer strategy (see Scientific Appendix 7.4). Whenever necessary, the re-Connect foundation may call upon the expertise of the hosting foundation and existing committees for ethics and compliance matters such as scientific integrity, research ethics issues, professional deontology, human resources. It may also call upon the expertise of the other founding members.

4.2.3. Performance management/monitoring

Several mechanisms to manage performance will be established to identify early or even anticipate and actively address potential deviations from the re-Connect ambition and plan:

- The international scientific council (ISC) formally reviews scientific progress every two years, and provide feedback/guidance to the re-connect Executive Committee and Management board
- The Executive committee tracks progress by WP on an ongoing basis, and reports progress twice a year to the Management board monitoring key performance indicators across several dimensions incl. resources deployed (Full Time equivalents, costs per WP/task), resources generated by WP and revenue source (grants, industrial partnerships, fund-raising, spin-offs, etc.), and milestone achievements, e.g. # patients treated or enrolled in trials, # professionals trained.
- Re-Connect will also be subject to regular external evaluation, notably via those of its constituting UMRs (HCERES and Pasteur Scientific Council).
- The Innovation Committee reports about innovation progresses (# projects of high potential, IP, strategic partnerships, commercialization strategies and creation of start-ups).

5 BUSINESS PLAN

Re-Connect's goal is to deploy an ambitious scientific project bringing breakthrough innovation in the coming years, generating major impact on patients, the research community, and the French innovation ecosystem in the field. This project will deploy a total financial envelope of €156M over the first 5 years and €333M in total over 10 years (see Scientific Appendix 7.12). To allow the funding of this ambition, re-Connect will leverage multiple revenue engines and develop self-generated resources representing €121M (45% of 2033 expected revenues). The requested ANR-IHU support (€50M) will be critical to fuel the ambition and secure ambitious scientific projects and will be matched by €283M from other funding sources, ensuring an almost 7X leverage ratio on the ANR funding support.

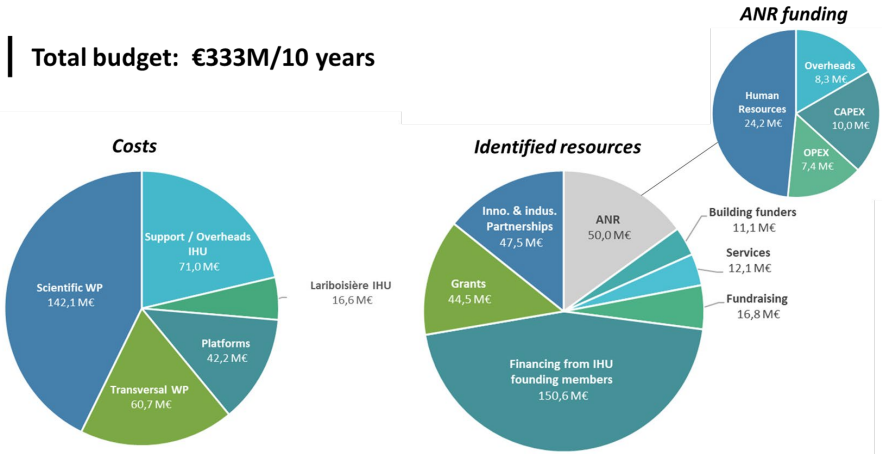

Figure 4. Total budget and general overview of the IHU re-Connect costs, resources and ANR funding use.

5.1 DESCRIPTION OF THE EXPENSES

Resources required to implement the proposed project are outlined in the exhibit below. These will represent a significant acceleration of the baseline currently existing within founding institutions, which it seeks to leverage, strengthen and significantly expand to new horizons. The institute's overall expenses would represent €30M deployed right from Year 1 and should increase to reach €34-35M in 2032/33 (expected compound annual growth rate (CAGR) of 2%) (Scientific Appendix 7.12). Remarkably, ~74% of the total expenses will be devoted to the WPs forming the core of the scientific, care and education projects. From 2024 to 2033, re-Connect will dedicate a total of €203M to the research/care continuum and to education and another €42M to the development of platforms. In addition, while the development the new re-Connect building embedded within the new Lariboisière University Hospital will be a key element to further integrate teams (on a total of ~5000 m^2 of which 2500 m^2 of labs and platforms and 500 m^2 dedicated to SUs) the running costs of this development (€0,8M per annum from 2027 onwards) are meant to divert a minimal amount of costs away from the core of the project.

5.2 DESCRIPTION OF THE RESOURCES

Re-Connect will mobilize a range of funding sources (Scientific Appendix 7.12). First, this financing plan relies on confirmed engagement of resources by founding members, which represent an annual amount of €15-16M. In addition, re-Connect will actively seek to develop self-generated resources representing €121M over the 10-year period, and which are expected to amount to ca. €8M annually in year 1 (based on already signed partnerships, current grants, etc.) and to grow to an annual €15M by 2033. Industrial partnerships will bring the most value with an average expected growth of 9% per year and should increase from approximately €3M in 2024 to €6M in 2033. This will be achieved by signature of master agreements with specific biotechs, service agreements with CeRIAH and platforms, collaboration agreements with biotech, digital and medtech companies, and license agreement to existing companies or SUs based of the patents to be filed. A significant part will also arise from patentable digital applications, and valorization of patient cohorts. Over the period, project grants will also be an important source of income: €45M. We will obtain funding from ERC, ANR (PRC, PHRC, ExcellencES…), DIM, FRM, Fyssen Foundation, international governmental funding (NIH, UK Foundation…) and national founds (Swiss, Luxembourg, German…). In addition, re-Connect will develop fundraising (expected to reach an annual €3M in 2033), through regular fundraising campaigns (incl. on the new Lariboisière site as of 2028) and in coordination with the Institut Pasteur and FPA fundraising strategy.

Finally, the buildup of our platforms will allow to generate service fees from third-party usage of these, as of 2027/28. These would notably include revenues generated by the Neuroimaging facility.

We believe our revenue projection to be realistic for the next ten years since it is based on past successes, a robust pipeline, and conservative hypotheses:

- Successful track record. We capitalize on our past performance to develop self-generated resources. An example is Sensorion with a 5 yrs master agreement of several €M.
- Conservative hypotheses. Each hypothesis used in the business plan has been detailed and assessed to retain conservative projection ensuring the robustness of our estimation.

Importantly, this funding strategy will allow us to gradually reduce the dependency of the project on the ANR funding towards the end of the 10-years, in order to near a self-supporting project by then, and to be able to index any future new/incremental funding on new projects.

5.3 DEPLOYMENT OF THE REQUESTED ANR FUNDING

The overall strategy is to devote most of the ANR funding to scientific and clinical WPs via HR and technological platforms (>80%) and reduce the dependency of the planned activity on ANR funding towards the end of the first project cycle. For details, see *Figure 4*.

6 MEDICAL IMPACT AND INSTITUTIONAL TRANSFORMATIVE EFFECT OF THE IHU

Re-Connect's chief mission is to rapidly renew and expand the therapeutic arsenal in the domain of hearing and auditory disorders. This ambitious goal will enable a radical improvement of clinical pathways for patients according to a new stratification of disorders and corresponding therapies, as informed by the discovery of new biomarkers and the progressive availability of new therapeutic tools. Our siting at Hôpital Lariboisière will allow re-Connect to work as a sizable test-case for new patient care paths, with direct and rapid benefit locally for the patients. Re-Connect will also be one of the very first centers worldwide to conduct clinical trials for deafness gene therapy. Re-Connect will lay the foundations for therapies of the future leveraging novel bioengineering technologies (e.g. optogenetic, virus-based drug delivery, brain implants, etc.) and continued fundamental research allowing for serendipitous discoveries with a clear path to the clinic.

Transformative effects are expected on the medical, public health, economic, and education fronts. On the medical side re-Connect will move from compensatory to curative medicine for hearing disorders and establish evidence-based medicine for auditory perception and audio-phonological disorders. According to the WHO, investing in an integrated strategy for auditory care will considerably impact DALYs and productivity[8]. While re-Connect fully aligns one the WHO recommendations, providing exact figures about the medico-economic impact is nearly impossible as many auditory disorders do not have yet state-of-the-art therapy and their cumulated social impact is unknown (presbyacusis, tinnitus, dementia, mutism/aphasia, dyslexia). Yet, at least half of the people with auditory disorders remain untreated due to a lack of awareness of the impact of leaving their condition unaddressed (dementia, irreversible sensorineural loss) and to a sheer lack of curative therapies. **One of re-Connect's major goals is to reach out to the public, inform public health policies, educate physicians and hearing aid specialists to make finer-grained diagnoses and refer to appropriate therapies, run large clinical trials, while gathering during the project's lifetime epidemiological and medico-economic data to precisely document re-Connect's impact.**

On the economic and industrial side, re-Connect will enable new industrial developments by attracting actors not traditionally involved with auditory disorders, e.g. for new drug synthesis or re-engineering. To achieve this, our project will set-up mixed academic and industrial labs for a fast translation of fundamental findings into clinical applications, and work in close industrial partnerships (Sensorion, CilCare, PerhaPharma, Geodaisics, MyBrainTech, Iologo, Colin, Electronique du Mazet Electronics, Roche, Biogen), offering partners dedicated spaces within the IHU. Re-Connect's critical mass and tight links with its funding members will also set up fast tracks for clinical trials and IP issues that will make it a world leader in auditory innovation and restore France's competitiveness with respect to other countries such as the US. Finally, in alignment with the goals of the French Plan Santé 2030, and with the strategic plans of each of its founding members, re-Connect will be an important testbed to fundamentally accelerate the conjunction of public and private actions for the benefit of patients with auditory disorders and, by teaming up with Fondation pour l'Audition, enable a new form of public/private partnerships, which are quite common and successful abroad (e.g. US, UK, Israël), and which will also support the financial sustainability of the re-Connect IHU.