CPER CTRL 2015-2020
Centre Transdisciplinaire de Recherche sur la Longévité

Appel à projets 2020 – Phase 4

Cet appel à projets vise à soutenir des projets transdisciplinaires portant sur la longévité dans le cadre du *Centre Transdisciplinaire de Recherche de La Longévité* (CTRL) coordonné par l'Institut Pasteur de Lille (IPL), financé par l'État, la Région Hauts-de-France, la Métropole Européenne de Lille (MEL) et les fonds FEDER dans le contexte du Contrat de Plan Etat Région (CPER) 2016-2020. L'appel est ouvert aux équipes de l'IPL et aux équipes de recherche de la Région selon des modalités indiquées dans les recommandations.

Le but de cet appel à projets est de renforcer la recherche en biologie et santé de la Région Hauts-de-France sur une problématique majeure de santé publique, la prévention des pathologies liées au vieillissement, particulièrement fréquentes dans notre région.

L'appel à projets vise à favoriser les coopérations entre équipes de la Région sur des sujets nouveaux liés à la longévité. Il veut accroître la fluidité et créer une émulation et des synergies nouvelles.

Ces projets seront évalués par le Conseil Scientifique International de l'Institut Pasteur de Lille. L'éligibilité des projets sera examinée par la Direction de l'Institut Pasteur de Lille.

Note importante !

La phase 4 CPER CTRL est la dernière phase programmée sur la période 2015-2020. Les contraintes de calendrier et de budget pour cette dernière phase de programmation ont été intégrées afin de pouvoir financer 4 projets d'un montant de 83 000 € par projet selon les modalités suivantes :

Durée des projets CPER CTRL Phase 4	15 mois
Financement des projets CPER CTRL Phase 4	83 000 € par projet

Précisions : Le budget de 83 000 € permet le recrutement d'un Post Doc sur 15 mois et un budget fonctionnement de 13 000 € (consommables, facturation interne (IPL) sous-traitance). Les frais de mission ne sont pas éligibles.

Recommandations

1. Les prérequis pour l'éligibilité des projets de recherche

- Le projet doit s'inscrire dans le cadre du projet CPER CTRL et de ses *workpackages*, et renforcer la recherche sur la longévité, comprise au sens d'une prolongation de la durée de vie en bonne santé. (cf Annexe 2).
- Le projet ne doit pas être déjà financé ou ne pas être la simple continuation d'une recherche déjà financée sauf dans le cas d'un projet sollicitant la suite d'un projet CPER CTRL Phase 1 ou Phase 2.
- Il convient de bien mettre en exergue dans la demande la dimension novatrice du projet par rapport au travail de recherche déjà accompli.
- L'appel est ouvert à toutes les équipes de recherche (y compris équipes de recherche clinique, sciences du numérique, sciences humaines et sociales, ou autre discipline), dès lors que les projets s'inscrivent dans un contexte de recherche transdisciplinaire sur la longévité du CTRL.
- Tous les projets doivent comporter obligatoirement :
    - soit 2 équipes appartenant à 2 unités de recherche différentes implantées sur le campus de l'IPL, incluant les équipes du pôle de Santé Publique et Environnement de l'IPL.
    - soit une équipe de recherche localisée à l'IPL et une équipe labélisée (EPST ou Universitaire) de recherche de la Région Hauts-de-France. Les équipes cliniques sont éligibles à travers un rattachement à une équipe labélisée.

- Chaque demande doit être déposée par un unique porteur du projet (*CPER CTRL Projet Coordinator- Team 1*), chercheur ou enseignant-chercheur, avec l'accord écrit de son directeur d'unité de recherche et le cas échéant, chef d'équipe. De même, pour l'équipe partenaire co-financée (*CPER CTRL Project Partner – Team 2*), il convient de désigner un co-responsable scientifique (*Principal Investigator*), avec l'accord écrit du directeur de la structure de recherche auquel il est rattaché.

2. Présentation des projets (CPER CTRL 2020 *Application Form*)

- Les premières pages des demandes sont réservées à l'identification du porteur du projet (*CPER CTRL Project Coordinator – Team1)* et de son partenaire (CPER CTRL Project Partner – Team 2) et de leurs équipes.

- Les demandes doivent être rédigées en anglais et ne doivent pas dépasser pour la partie scientifique du projet (section 2) un **maximum 10 pages**, incluant un court état de la question, une description explicite du projet (état de l'art, objectif et rationnel, *workpackages* et délivrables, Gantt chart, bibliographie) sur 15 mois, éventuellement figures et schémas, et une courte bibliographie. Il est demandé d'utiliser la **police Times 12, interligne simple**.

- Les demandes doivent inclure un résumé scientifique de 250 mots et un résumé grand public de 250 mots en anglais et en français expliquant la relation du projet avec la longévité.

- En plus du projet scientifique, il sera joint le CV de chacun des deux *principal investigators* (*CPER CTRL Project Coordinator et CPER CTRL Project Partner*), indiquant les publications scientifiques internationales, les brevets, les titres des contrats de recherche obtenus au cours des 5 dernières années.

- Une annexe financière contenant le budget prévisionnel et sa description ainsi qu'un calendrier (Gantt Chart).

- La signature des *PI* et directeurs d'unité et le cas échéant des chefs d'équipe est obligatoire.

Il est demandé de suivre précisément les recommandations pour garantir l'éligibilité du projet et son évaluation.

En résumé, chaque demande de soutien financier (*Application Form*) est constituée d'un fichier word contenant:

- **Information générale** : identification des demandeurs et de leurs équipes
- Le **CV de chaque *PI*** avec leurs publications internationales, brevets et contrats de recherche des cinq dernières années.
- **Le projet scientifique** rédigé en anglais de 10 pages maximum
- **L'annexe financière** indiquant la planification du budget prévisionnel
- **L'engagement signé** des *PI*, des directeurs d'unité, et le cas échéant des chefs d'équipe

Tout dossier incomplet ou ne remplissant pas les conditions indiquées ci-dessus ne sera pas considéré.
Les dossiers doivent être déposés le 25 novembre 2019 12h au plus tard pour la version papier et la version électronique.
Aucun dossier ne sera accepté après cette date.
Les dossiers papier seront déposés au Bureau Administration de la Recherche Bâtiment Calmette (6e étage).

3. Évaluation des projets de recherche

Les projets seront évalués par le *Conseil Scientifique International* (CSI) lors d'une audition le 10 décembre 2019. Le SAB proposera une liste de projets pour financement soumise au Comité de Pilotage CPER CTRL et aux institutions (Etat, Région et MEL) pour financement selon les procédures institutionnelles respectives.

ANNEXE 1
CPER CTRL 2020 – Phase 4
EVALUATION FORM

Criteria	Score				
Originality and novelty of the project	5	4	3	2	1
Scientific quality of the applicants	5	4	3	2	1
Clarity of writing and project description (WP and deliverables)	5	4	3	2	1
Adequation between methodology and deliverables	5	4	3	2	1
Adequation between financial means and realization of the objectives	5	4	3	2	1
Impact : 1) On the study of the mechanisms of healthy aging and ageing or, 2) On the management of factors jeopardizing healthy ageing, or 3) Validation of a novel methodology or technology,	5	4	3	2	1

TOTAL: /30

Results:
>27 : A+, excellent, priority
>24 : A, very good
>21 : B, good
<18 : insufficient

Short Comments of the expert:

Please comment on :

- expectable progress beyond state of the art
- innovation in the field of healthy ageing, or on the new methodology enabling research on healthy aging.
- technical skills and complementarity of the teams

General Comments

Strengths of the project

Weaknesses of the project

Recommendations and advices

Annexe 2
CPER CTRL 2015-2020

Centre Transdisciplinaire de Recherche sur la Longévité

Appel à projets 2020

Rappel des Workpackages

Axis 1. Epidemiology and genetics of longevity

- **WP1. From epidemiology to the determinants of longevity**
- **WP2. Molecular and cellular analysis of determinants of longevity**
- **WP3. From determinants to preventative and therapeutic targets**
- **WP4. From therapeutic targets to drug candidates**
- **WP5. From targets to clinical and prevention trials**
- **WP6. From trials to Public Health**

WP1. From epidemiology to the determinants of longevity

The CTRL teams will characterise the environmental and genetic components making up the basis of longevity in human populations. More particularly, they will research the risk factors and the protection factors of age-related chronic diseases (Cardio- and cerebro-vascular diseases, neurodegenerative diseases), and those of the various pathological states associated to these affections (diabetes, obesity, heart failure, alteration of the cognitive functions, inflammation).

The CTRL teams will use classic epidemiological approaches consisting in conducting wide-ranging population or analytical studies, as well as epidemiological approaches specialised in environment and genetics. These approaches will rely on the skills of the research teams, and on the high throughput platforms collaborating with CTRL. Their missions will be specifically to target, both in the

vascular and degenerative risk, the original environmental factors such as the "metabiota" (Mouth and gut flora) and the constitutional factors by decoding particularly the missing heritability, and delivering a detailed mapping of susceptibility genes to identify the functional variants. All these works will feed the next WP with new pathophysiologic hypotheses opening the way to the discovery of new mechanisms and preventative or therapeutic measures used for their control.

The works of UMR1167 focused on improving their knowledge on cardio- and cerebro-vascular and neuro-degenerative diseases, and on the study of nutritional, metabolic and genetic determinants, rely on an infrastructure of research in descriptive and analytical epidemiology, as well as on biological functional analyses. UMR1167 has made major progress in the characterisation of the genetic susceptibility of Alzheimer's disease (AD) and cognitive impairment thanks to Genome-wide association studies (GWAS) developed in the Unit through national and international collaboration. These approaches based on GWAS will be completed by a very high-throughput sequencing strategy that is better adapted to the characterization of the missing heritability. This work has already helped identify 20 targets and opens potential new pathophysiological pathways that must be explored further from a biological and epidemiological angle. These works are in line with the dynamics started by the DISTALZ LABEX.

This WP also relies on the contribution of EquipEx LIGAN-MP, the only one entirely dedicated to the sequencing of the human genome for medical use. The teams of LIGAN-MP have already developed quick and low-cost gene screening protocols for metabolic diseases which have revolutionised the etiological diagnosis of these affections. At a time where the French hospitals are equipping themselves with new generation genome sequencing (NGS) equipment, E.G.I.D. & LIGAN MP's genomics, bio-informatics and statistics platforms gathered in E.G.I.D.+ will be devoted to helping our region take up, in a leading position, the challenges of genomic diagnosis and personalised medicine.

WP2. Molecular and cellular analysis of determinants of longevity

To better understand the causes of chronic human diseases associated to ageing, and to facilitate a better "personalised" care management of patients, the molecular mechanisms must be elucidated. The use of functional *'omics'* technology and systems biology will help create various "personalised" models of age related diseases. This will require the use of animal models, an area in which the expertise of the CTRL teams will be even more developed, especially in the creation and analysis of genetically modified rodent models. This will be complemented by the implementation of complementary models that will make it possible to conduct quicker and more cost-effective, high-throughput analysis: nematode invertebrates (*C. elegans*) and vinegar flies on the one hand, zebrafish on the other hand. CTRL will develop somatic cell bio-banks from various cohorts of patients. These cells will be dedifferentiated into pluripotent stem cells (iPSC), and then redifferentiated to the cellular types affected to the pathologies of interest to obtain "personalised" functional models for *in vitro* studies. These models will be combined to the development of DNA bio-banks (WP1), plasma libraries, tissues and cells, and will allow for genomic, transcriptomic, proteomic, phenomic, microbiomic and clinical analyses. These integrative databanks will help identify the molecular and cellular determinants of longevity.

In the wake of its epidemiological works, UMR1167 has developed the functional analysis of the gene polymorphisms involved in the risk of metabolic diseases (nutrition, obesity,...), with the help of cellular and molecular tools. Additionally, this unit has focused on the discovery of the new molecule determinants for cardiovascular diseases through differential "omics" approaches in targeted clinical studies (REVE 1, REVE 2, PTHF, INCA) and in cohorts developed in collaboration (ICFEP, STANISLAS & HOMAGE).

The estimated prevalence of chronic heart failure (CHF) in adults is between 1 and 2%. Moreover, abnormal Left Ventricular Remodelling (LVR) has been observed in 30% of cases of myocardial infraction (MI) after one year, whatever the type of treatment. Despite significant therapeutic progress, the mortality rate in CHF remains high especially for the most serious forms. This research work will therefore concentrate on CHF of ischaemic and non-ischaemic origin and post-MI LVR. The discovery of prognostic bio-markers for these deleterious evolutions could help prevent and improve the care management of these patients. The objectives consist in:

1. Validate the targets identified in proteomics and transcriptomics (RNA & miRNA) for diagnostic and prognostic purposes in the targeted clinical trials and in population.
2. Identify new circulating biomarkers associated to premature cardiac mortality in patients with CHF through proteomic and transcriptomic (miRNA), in order to establish a predictive score for patient stratification.
3. Screen a new class of regulatory RNAs (long non-coding RNAs (lncRNA)) in patients with a post-MI LVR.
4. Understand the underlying pathophysiological mechanisms of these targets (Proteins, post-translational modifications, miRNA) in these diseases.
   Following on from works developed by UMR 744 on neurodegenerative diseases the two dozens of identified targets have been investigated in further details from a molecular and cellular angle. Various approaches have been used: screening of transgenic vinegar flies models, impact in mouse models, molecular and cellular analyses. The objectives consist in developing cellular and molecular studies of the genes identified in order to improve our knowledge on the underlying pathophysiological mechanisms. The DISTALZ LabEx will help, there again, complete this project and expand the works by exploring current and new pathophysiological hypotheses on AD (including the amyloid pathway and pathways related to Tau).

The EGID LabEx and UMR 1011 will aim at modelling the chronic human diseases of metabolic origin with an inflammatory component ("Meta-inflammatory diseases") in order to understand, explain and better manage, or even cure, diseases that remain chronic for the moment. EGID's expertise in particularly in diabetes and its cardiovascular complications and will extend to liver chronic pathologies. UMR 1011 and EGID will take part in the development and operation of innovative animal modelling platforms (*C.elegans*, *Danio rerio,...*) will continue to establish ground-breaking structures for the introduction of genetic modifications to rodents (Talen, CRISP) and for the phenotypic analysis of these models from the metabolic, immunological and inflammatory angles (transcriptomics, proteomics, biochemistry, histology, cytometry, metabolic and inflammatory tests, *in vitro* & *in vivo functional tests,* circadian rhythms). A specific focus will be put on the development of EGID's skills on microbiome analysis. In addition, certain EGID teams have already been involved in the generation of dÏPSC bio banks from cohorts of obese and/or diabetes patients. The analysis, as part of case/control (sick/healthy) clinical studies of patients suffering from obesity, diabetes, hepatic

steatosis and fibrosis, of the regulatory networks leading to the meta-inflammation will corroborate these models. All the data obtained will make-up a databank which will be used for a differential integrated analysis of the pathological biological system against the "healthy" system. The role of nuclear receptors, both as prevention and therapeutic targets, will be more specifically analysed.

In this WP, CIIL will develop an integrative scientific approach, taking into account the diversity of aggressors, i. e. the viral, bacterial and parasitic pathogens and the response of the host in the context of its environment, including translational activities and field studies, including in developing countries. The molecular and cellular mechanisms of pathogenesis will be investigated using the existing infrastructures, such as the high security laboratories (L3/A3), the animal technology unit, the insectarium, imaging platforms, including the Imaginex BioMed EquipEx, proteomics, including LabEx ParaFrap, and genomics platforms. The second aspect concerns the reaction of the host to infections, including the immune and inflammatory responses. The signalling pathways of innate immunity will be analysed, as well as their respective roles in immunological control and inflammation. Finally, the deciphering of the dialogue between the microbiome and its host could also provide new keys in the understanding of chronic inflammatory diseases and will be dealt with by several teams. Particularly, the impact of dysbiosis on the alteration of the innate immune system of the respiratory and intestinal mucosa, as well as infectious susceptibility will be assessed.

WP3. From determinants to preventative and therapeutic targets

In order to better manage patients suffering from age related diseases, prevention and therapeutic care management approaches will be developed on the basis of the knowledge of the cellular and molecular determinants identified in WP1&2. Preclinical models, such as rodents, and also humanised models, more relevant for human pathology, of differentiated iPSC that match the pathophysiology closely, will be created. These models will be used to validate the therapeutic targets (gene, protein, cells), of pharmacological or genetic approaches for both prophylactic and therapeutic purposes as well as for the development of screenings. This step will aim at orienting the knowledge of the mechanisms identified in WP2 to the research of drug candidates (WP4).

The aim of the CTRL teams will be to develop the most relevant genetic, biological,*in vivo* and *in vitro* tests stemming from the results of WP1 and WP2. These various approaches are likely to generate both new bio-markers and experimental screening models. The validation of these bio-markers will be included in the epidemiological and clinical activities connected to WP1. At this stage, development works can be carried out in cooperation with the SMEs present on campus. The screening models will be powerful tools that, combined with high-throughput approaches, will help select the molecules likely to interact with the metabolic pathways governing longevity.

In the cardiovascular field, UMR1167 has developed translational research in close interaction with the cardiologists of the Lille University Hospital, followed by the pathophysiological characterization of these new molecular determinants in various preclinical models. The objectives of these works is to discover and develop new bio-markers of heart failure allowing to predict those subjects who, following an ischaemic heart disease, will evolve towards heart failure. In addition, the experimental works will help study the impact of the molecular targets borne by these bio-markers and facilitate the development of molecule screening tools that could modify these impacts.

Using this strategy, the action mechanisms of the susceptibility genes identified in the pan-genomic studies on Alzheimer disease will be included in specific developments as part of the early diagnosis and therapeutic hypotheses. The objective is to explore the current and new pathophysiology hypotheses of Alzheimer disease, including the metabolic pathways of the amyloid and Tau protein, enhanced by recent genetic discoveries, and then draw from this knowledge new biological hypotheses that can be transferred to the clinical world through bio-markers or potential therapeutic targets. The vinegar flies models developed by this team will be used to develop biological models that allow for high-throughput screening. Thanks to LabEx DISTALZ, genetic and biological tests will be developed, taking into account interactions with other neurodegenerative and cerebrovascular diseases in a logic of personalised medicine. These works will be transferred for their development to the SMEs already involved in this research, particularly Genoscreen. Close links will also be established with other companies on campus (Innobiochips & Lunginov) as well as with other regional companies such as Alzprotect.

The validation of new pharmacological targets will require the prior study of their functions using various models. More specifically, U1011 & EGID will develop preclinical humanised animal models to study the molecular determinants of cardio-metabolic and immuno-inflammatory diseases, as regulatory networks leading to the development of the diseases and on which pharmacological or genetic intervention strategies can be based. At the same time, the pharmacological targets will be validated by the studies of the regulatory networks in case/control (sick/healthy) studies on independent cohorts of patients (from WP2) and in intervention studies in humans (Control of the food intake, exercising, light therapy, bariatric surgery...).

The molecular and cellular studies of the infectious and inflammatory pathogenic mechanisms studies conducted by CIIL should lead to the identification of new therapeutic vaccine targets. The study of the mechanisms of immune regulation, particularly the discovery of new signalling pathways, shall also lead to the identification of immune-stimulators or immune-modulators. The discovery of anti-infective or anti-inflammatory targets will be even more significant that we are currently facing the problem of resistance to antibiotics, antivirals and to antiparasitic drugs. Moreover, treatment with antibiotics or antivirals is often less efficient in the elderly and with a higher risk of adverse reactions, including because of a decline in the liver or kidney functions. Compliance is often a problem, especially for treatments per os and thus often requires a strategy of the DOT type (« *Directly Observed Therapy* »), which is costly and logistically difficult. Vaccination is the most efficient measure to control infectious diseases. However, many studies have shown that vaccines are less immunogenic and therefore less efficient for the elderly, including due to immune-senescence, i. e. the still poorly understood alteration of the innate and adaptive immune systems. New immunisation pathway and new immune-stimulant or immuno-modulating molecules will be identified, on the basis of the discoveries made in WP2. Finally, therapeutic approaches aiming at correcting the dysbiosis by administering probiotic and/or commensal bacteria and fungi will be assessed.

The involvement of UMR 1177 with B. Deprez in this WP3 will be the phenotypic screening of chemical libraries in a strategy of the *'forward chemical genetics'*, type which allows to identify components which restore a normal phenotype in a model of the disease. siRNA screening then helps determine the target or the metabolic pathway on which the component intervenes.

WP4. From therapeutic targets to drug candidates

The starting point for WP4 is a gene which plays a causal role in one of the pathologies studied. The goal of UMR1177 will consist in discovering, in a reasoned manner (thanks to molecular modelling) or using high throughput screening, one or more modulators of the target protein. These modulators are then optimised to be used in more and more complex models of the disease (Cell lines, primary cells, model animal). During this optimisation step, we must not only improve the activity on the models (power and efficacy), but also optimise stability, harmlessness and bio-availability of components. UMR1177 also benefits from a presence on campus of an ADME platform which delivers all this information in parallel to the project leader. A strategic contribution of this platform is the database made up of all the results acquired in all programs, regardless of the therapeutic applications. These pharmacokinetics results are of particular value since they help educate an expert system that is independent from the therapeutic field. As of 1st January 2014, over 400 components have been profiled that way. Since 2006, several drug candidates have been discovered on campus with or without the initial contribution of drug companies. One of them is currently being developed with GSK. In this WP, UMR 1177 will identify the components which modulate the activities of the protein coded in a gene candidate and thus help prove its causal role in the pathology. If the causal role is established, the modulating component is the starting point for a medicinal chemistry program and the development of a drug candidate.

CIIL has also been involved in this approach, especially for the identification of new therapeutic or vaccination targets, as well as their pharmacological validation. The proofs of concept, both of the efficacy of new drug candidates and of vaccine candidates, will be provided through animal models, including primates in cooperation with research centres on primates in France, in Europe and in the United States, thanks to already established preferred partnerships.

Once the drug candidates have been identified, in collaboration with companies, pre-clinical studies can be conducted. Thanks to high-performance clinical teams including in cardiology, diabetology, endocrine surgery and neurology at the Lille University Hospital, works on humans could be initiated under the form of studies and clinical trials. Access to the clinical investigation centre (CIC) at the Lille University Hospital and its networks will guarantee optimum initial development for these drug candidates in our region. Given the results obtained in this way, new start-ups could be launched where appropriate.

In the field of cardio-metabolic pathologies and meta-inflammation, once the therapeutic targets have been identified, drug candidates will be developed via a therapeutic innovation platform, to which EGID will contribute its skills in terms of screening development. High-throughput screening strategies, for example vis-à-vis bile receptors FXR & TGR5, and PPARs, will help, using relevant *in vitro* (differentiated iPSC) and *in vivo* models, select the most efficient molecules. In addition, these innovative medical devices could be developed using human relevant models.

WP5. From targets to clinical and prevention trials

Moving from therapeutic or vaccination targets to clinical trials will require very strong partnerships between CTRL and other CICs in France and abroad, the drug and vaccine industry, as well as very

close interactions with regulatory and Public Health agencies in France and internationally. All resources will be implemented in order to help the most promising drug and vaccine candidates efficiently enter the pipeline of product development and clinical development. We will use the expertise already acquired within the CTRL teams (Several drug/vaccine candidates developed by our teams have already reached phase I to III in clinical trials). We will also use the services of existing services in our partner institutions, as well as their promotion services (Such as SATT, Inserm Transfert etc.). The industrial partners or some of our partner institutions (*e.g.* CHRU, Inserm, CNRS, Universities) will also be able to act as promoters of clinical trials.

LabEx EGID is made up of three labelled units, including UMR1190. This unit, which is hosted by, and fully integrated in, the Lille University hospital's environment, best reflects WP5: A multidisciplinary unit, which gathers clinical researchers and biologists whose objective is the development of therapeutic approaches for diabetes and their clinical application. Even though this unit was initially focused on cellular therapy of type 1 diabetes and more particularly on the isolation and allograft of human islets of Langerhans, its scope has been extended since 2009 to the treatment of type 2 diabetes through metabolic surgery and more recently a second team has been working on β cells biology. For example, treatments preventing the death of insulin producing cells, in the islets before the graft and in diabetes patients, which is today of utmost importance. The improvement in the number of functional pancreatic islets is a therapeutic priority for the prevention and treatment of diabetes, and is one of the main objectives of UMR UMR1190. In the unit, a team has been working on the role of inflammatory signalling in the dysfunction and death of insulin producing cells, as a response of isolation and diabetogenic stress.

E.G.I.D. teams, in addition to UMR 1190, have been progressively welcoming personnel from the clinical world or have developed with them innovating translational collaboration. For E.G.I.D. +, the desire of translation in fundamental research is a state of mind that suffers no compromise. E.G.I.D. + will extend this natural link beyond diabetes. This will go through the financing of research projects and contracts for postdocs, Ph.D. students or engineers, who are indispensable as they extend the reach of clinicians already very busy with other matters. This will be deployed in connection with the Regional Clinical Research House, with personnel dedicated to clinical research within the region's main hospitals.

WP6. From trials to Public Health

All the work accomplished by the teams at CTRL and stemming from the regional collaboration engaged will help define new axes for both medicinal and non-medicinal care management. These trials tries will benefit from the access to the populations of the Centre for prevention and health education of Institut Pasteur de Lille, as well as its vaccination centre. It will therefore be possible to launch prevention clinical trials with adapted structures and significant volumes of population, thus ensuring an immediate benefit of the research work of the CTRL teams for the men and women of our region to help them live a better, longer life.

The various research results produced by UMR1167 will lead to the discovery of new environmental risk factors and mechanisms acting on the pathways related to the individual susceptibility to these diseases. The first results will help, including in terms of cardiovascular risks, prepare protocols for

the optimisation of preventative measures which shall be tested on the platform offered by the Centre for Prevention and Health Education present on the Institut Pasteur de Lille campus. In the field of neurodegenerative risk, the early diagnosis of a disease whose symptoms may appear years later, and for which no treatment is available, raises significant ethical questions which must be anticipated. DISTALZ's partners are recognised references in the field of biomedical ethics and will be in a position to supervise the ethical contents of the various aspects of the research programmes of the genetic selection for the implementation of clinical trials.

Specific issues relating to the care management of Alzheimer disease will be dealt with, including: 1. Implementation of multidisciplinary steering committees; 2. Organisation of thematic think tanks for concerned researchers and doctors, nurses or carers; 3. The dissemination of information to the wider public on this specific field of research via seminars and day conferences on these themes. Besides, within the context of DISTALZ, works will be devoted to assessing the risk-benefit ratio which could potentially jeopardise the development of the clinical protocol (for example, based on which criteria can we include someone in a research programme when we don't know how the disease is going to evolve? Is there a risk that the treatment could speed up this evolution? The modalities of the access to an early diagnosis and the disclosure of results will be explored. Within this context, a systematic follow-up for the people involved, particularly from a psychological point of view, could be implemented. This will lead to the establishment of guidelines which will allow to conduct clinical trials in the best conditions for patients and their relatives.

Beyond these various specific approaches, UMR 744 will take advantage of the invasion of techniques and knowledge stemming from molecule biology and IT in clinical research to start proposing a type of medicine that is better targeted to the specifics of each patient leading to the emerging of a new medical approach: personalised medicine. By combining the usual clinical and paraclinical data with information stemming from the genome, the proteome or high resolution imaging systems, it is then possible, for doctors, to speed up their diagnosis procedures, improve the efficacy and observance of treatments and promote prevention measures adapted as closely as possible to the risk profile of their patients. The emergence of personalised medicine, beyond the clinical and therapeutic benefits it implies, represents a growing economic field impacting all health sectors, from diagnosis to drugs through information technologies and communications. However, despite the success of personalised medicine in the field of cancer, it is still indispensable to provide concrete proofs that this approach is worthy of interest. The whole medical community must therefore be convinced of the worthiness of these new approaches to ensure their dissemination, especially in the field of chronic diseases with ever increasing costs linked to the ageing populations and that have an impact on longevity. This is what the works of UMR1167 will be focused on within the context of CTRL.

The prevalence of metabolic diseases in the Lille region is 1.5 times higher than in the rest of France, including type 2 diabetes for which prevalence stands at 5,1% in our region. Patients are diagnosed late and often at an advanced stage of the disease, especially at a stage of complications where there are significant consequences particularly in terms of budget. In addition, this sad record could get worse in the future due to the ageing of the population and the extension of the life expectancy.

Our objectives are clear. It is indispensable to test patients at an earlier stage, especially for susceptible populations if we are to reduce the complications of diabetes on the one hand, and

maintain the quality of life of the people affected, on the other hand. To this end, we must pool our knowledge and actions with the regional players of the health sector such as the Lille University Hospital, the so-called diabetes houses, the Regional Council, ARS...

Translational research is a significant axis for EGID, Pr Anne Vambergue and Pr Pierre Fontaine have been working together with EGID on gestational diabetes for which we unfortunately have a prevalence of 12 to 15% in the region, essentially due to risk factors such as overweight, obesity and a family history of diabetes. This is why, thanks to our cohorts and data, we would like to continue optimising the care management of pre-gestational diabetes. The number of type 2 diabetes patients who are pregnant has increased considerably due to an increase in obesity and overweight among younger and younger women. We would like also, and more importantly, to reinforce the *post-partum* metabolic follow-up of these women who have developed gestational diabetes, and consequently prevent type 2 diabetes. Women who have developed gestational diabetes are seven times more likely to develop type 2 diabetes. We can therefore think that the care management during pregnancy, especially from a nutritional point of view, and encouragement to exercise will be instrumental to reducing this risk. These objectives are fully in line with the action programmes on the health paths of people with chronic diseases developed by ARS for 2013 - 2017 "DIABEVI".

CIIL will also be involved at that level. The first product from Institut Pasteur de Lille to have passed clinical trials and to have had a significant impact on public health is BCG, Bacillus Calmette-Guérin, remaining today the only vaccine available against tuberculosis. Since its use in humans (in the 1920s), two other vaccines have been tested in various phases of clinical trials. Other vaccine and drug candidates are in advanced pre-clinical phases and should soon enter phase I. Very close relations with international foundations and above all the drug industry, already formalised through significant licence and cooperation contracts, both in Europe and the United States, guarantee that discoveries quickly move from the laboratory stage to the development of diagnosis tools, vaccines and anti-infective and anti-inflammatory drugs. Another important aspect concerns pro- and pre-biotic food supplements and their immunomodulating actions both at intestinal level and at the level of the respiratory system. One of the significant strengths of this project resides in the translational and clinical research activities in developing countries, via instruments such as the "Espoir pour la Santé" structure in Senegal and the international associated laboratory "*Systems Immunology and Genetics of Infectious Diseases* " (SIGID) in India. These structures will be used to study the risk factors in African and Indian populations and to measure the impact of therapeutic or preventative interventions. In addition, the CTRL project will fully benefit from the participation of Institut Pasteur de Lille in the international network of Instituts Pasteur, which will considerably increase its field of action.

Axis 2. Senescence, immunity and infection

WP 1. Pulmonary tuberculosis: dormancy, TB drug resistance, vaccination
WP 2. Bacterial and viral respiratory infections
WP 3. Chronic inflammation and environment
WP 4. Microbiota and longevity

WP 5. Infection and cancer

The sensitivity of the elderly people to infections

Ageing leads to the senescence of the immune system, which explains a higher sensitivity to infections and a reduction in the efficacy of vaccines, antibiotics and antivirals in the senior population. This is added to frequent co-morbidity (Liver, kidney, gastrointestinal…) and disruptions to the intestinal microbiota. This explains that infectious diseases (Whether respiratory, enteric, urinary…) are one of the major causes of mortality of the elderly in developed countries accounting for a third of the deaths of over 65 year-olds.
We have also observed an increase with age in chronic inflammatory intestinal and respiratory pathologies, which contributes to an increase in the incidence of infections among the elderly. We can mention chronic obstructive pulmonary diseases (COPD), which provide a fertile ground for respiratory infections by exacerbating these pathologies. Additionally, we must underline the frequency of clinically silent inflammations observed in this age bracket: chronic infections (CMV, type C hepatitis, herpes, *Helicobacter*), combined to an increase in the risk of atherosclerosis, diabetes, dementia, cancers, obstructive pulmonary diseases and auto-immune diseases.
If longevity represents a major challenge in developed countries, especially due to human and social economic consequences, it also concerns developing countries. Even if some progress has been made, including in Africa, thanks to hygiene, vaccination and antibiotics, the average life expectancy remains well below that of Western countries (52 *vs* 79): AIDS, malaria, schistosomiasis and tuberculosis strongly contribute to this difference between rich and poor countries.
In order to better understand the link between longevity and infections, CIIL has developed an integrative approach, combining fundamental and translational research, that takes into account the diversity of pathogen agents, of the host and its environment. Some research has also been developed by certain teams of CIIL, including in developing countries, as part of an International Associated Laboratory (so-called LIA) with several research centres in India (*Systems Immunology and Genetics of Infectious Diseases*, SIGID, S. Pied) and with the "Espoir pour la Santé" platform in Senegal (G. Riveau). Several teams from CIIL have also developed cooperative projects with the Lille University Hospital and other French University hospitals.
The immunity and infection centre (CIIL) is at the interface of the CTRL's various axes namely Environment, "Drug Discovery" (with the development of new drugs and vaccines), Cancer (at least one third of cancer cases may be due to an infectious cause) and the DISTALZ (infection/neurodegenerescence link) EGID (increased risk of infection among the elderly suffering from metabolic disorders and/or diabetes) Labex.

Strategy: understand and prevent the consequences of immuno-senescence

Thanks to animal models and clinical studies, we will try and better understand the mechanisms that could explain the decline of the immune response in the elderly. Jointly, we will study the consequences of chronic lung (Asthma, chronic obstructive pulmonary disease, COPD) and intestine (Inflammatory intestinal diseases) inflammation, that promote infections. A number of infectious models will be studied.

WP 1. Pulmonary tuberculosis: dormancy, TB drug resistance, vaccination

Tuberculosis is a significant problem in many countries, including Western countries: one third of the world population carries dormant lives bacilli in the lungs, that can be reactivated in certain circumstances, in the elderly when they suffer from diabetes, malnutrition, immune-depression or chronic renal failure. Countering the reactivation of the bacillus in the elderly could be done via an antibiotherapy targeted against latent forms of the bacillus and/or a booster vaccine strategy. Moreover, the efficacy of the BCG vaccine to prevent the pulmonary forms of tuberculosis quickly decreases with age. C. Locht's team has developed a new vaccine strategy based on the HBHA antigen. These very promises studies on young animals will be extended to older mice models, before they may be applied to humans. The resistance of the TB bacilli to antibiotics will also be a major issue in the decades to come. P. Brodin's team has focused on trying to discover new TB drugs, especially targeted to transcription regulators, which should lead to new drugs being available. This team has also studied the cellular factor of the host involved in the control of the pathogenesis when infected by *M. tuberculosis*. This team has identified players of the innate immunity diverted by the bacteria which could become targets for the development of new "personalised" therapies taking into account the genetic susceptibility of the patients.

WP 2. Bacterial and viral respiratory infections

Some elderly people are more sensitive to bacterial (pneumococcus) and viral (flu, coronavirus…) infections. To study this phenomenon, F. Trottein's team has developed experimental models of colonisation and infection from pneumococcus (*Streptococcus pneumonie*), a very common bacteria responsible for pneumonia, particularly among the elderly. It has studied the early mechanisms of colonisation and invasion of these bacteria, and the effect of immunomodulators, potentially associated with antibiotics, to prevent this invasion. The mechanisms of post-influenza bacterial superinfection have also been studied in animal models.

The team led by Jean Dubuisson has been working on coronaviruses (CoV) and the origin of mild infections in humans (15% of cases of cold). Among the elderly, these viruses cause serious lung infections (10% of viral respiratory diseases). Recently, we have seen appear the SARS-CoV & MERS-CoV viruses, which are highly pathogenic coronaviruses that may cause lethal infections. MERS-CoV seems particularly pathogenic among older people or patients treated with immunosuppressants. The team has been studying the infectious cycle of these viruses to develop new therapeutic approaches, particularly on the proteins involved in the virus replication. *In vitro* and *in vivo* models, connected to the longevity project, will be developed. At the same time, molecular epidemiological research will be conducted in humans.

WP 3. Chronic inflammation and environment

We know that chronic inflammation phenomena increase with age and increase flareups of infectious origin. A significant research component will then concern the regulation and restoration mechanisms of the immune competence of older patients developing chronic inflammation (Asthma, COPD, chronic inflammatory bowel diseases [IBD], obesity). The CIIL teams have developed chronic pulmonary inflammation models (asthma/A. Tsicopoulos,

BPCO/F. Trottein/P.Gosset), IBD (M. Chamaillard, B. Pot) and obesity (I. Wolowczuk/F. Trottein in connection with U1011/B. Staels) models which could be used as part of this research axis. The impact of age on vaccine efficacy in inflammatory situations (COPD/pneumococcus, obesity/flu, IBD) has been the object of recent investigations.
The signalling pathways of innate immunity are analysed during chronic inflammation phenomena, as well as the respective roles in the control of the immune and inflammatory response. This approach may lead to the identification of new pathways for the stimulation of the immune system and potentially new immuno-stimulators.
Within this context, a specific emphasis is will be put on the study of comorbidity (obesity) and environmental (cigarette smoke, xenobiotic factors [heavy metals, chemicals pollutants, drug metabolites...]) factors which could influence the innate and adaptive immune response. Among these factors, the diet (often too rich in our industrial societies) and the intestinal microbiota play an essential role. An experimental approach has been developed in order to study the impact of obesity on the susceptibility to infections (flu) and to the development of the pulmonary inflammation (COPD).
A systems biology approach could help integrate the many parameters (Genomics, epigenetics, transcriptomics, proteomics, metabolomics) in order to identify new research pathways and innovative therapeutic targets. The impact of the individual exposome and the accumulation of xenobiotics in the organism has been clearly associated to infectious, inflammatory and metabolic pathologies and to cancers (genotoxicology/ F. Nesslany), as well as age-related neurological deficits. These (Eco)-toxicological aspects which have already been developed at CIIL (B. Foligné, A. Tsicopoulos), at CHRU (U995/P. Desreumaux) and on the Calmette site (EA4483/Lo Guidice/Allorge) must be dealt with in an integrated manner (UMR 8161/Y. De Launoy, UMR1167/P. Amouyel). The anti-inflammatory properties of certain microbial agents and their assessment as therapeutic or preventative tools will also be explored (B. Pot, C. Locht, A. Tsicopoulos, P. Gosset).

WP 4. Microbiota and longevity

Immuno-senescence is associated to a modification in the composition of the intestinal microbiota (*dysbiosis*), in turn influenced by the chronicity of the inflammatory (*e.g.* gastrointestinal) pathologies, the repetition of urinary and enteric infections, metabolic disorders and obesity. A better understanding of the complexity of the intestinal communities and how they vary with age, as well as their potential to improve well-being, is essential. Within CIIL; several team are envisaging the manipulation of the microbiota (nutrition, faecal microbiota transplantation, pro/pre/syn-biotics) as a prophylactic/therapeutic option to prevent/treat immune-senescence and age-related gastro-intestinal and pulmonary diseases. To this end, access to patients' biological banks (Blood, faeces, tissue/organs), as well as the development of new, relevant experimental models and the provision of powerful genomics tools is necessary. Fédération Hospitalo-Universitaire (FHU) (M. Chamaillard et L. Poulin) has the ambition of identifying the cellular and molecular mechanisms through which the microbiota modulates the age-related pathologies while developing nutritional approaches aiming at restoring the mutualistic relationships with our microbiota.
B. Pot's team has had a long experience in the use of probiotic strains with specific metabolic properties, capable of modulating the immune response or interfering with the development of pathogenic germs such as *C. difficile*. More recently, B. Pot & M. Chamaillard's teams have initiated a project aiming at selecting probiotic strains based on their anti-inflammatory and anti-infective activities. (*E. coli* enteropathogens). The use of the strains could restore the defective anti-microbial immunity in patients suffering from IBD (Crohn disease) and

rebalance the disturbed microbiota. Such an approach could also be developed in models of obesity and exposure to cigarette smoke.
F. Trottein's team, in connection with B. Foligné, has also been attempting to identify bacterial strains stemming from fermented food and capable of durably and specifically modulating the immune system. The role of the intestinal microbiota in the management of inhaled and ingested pollutants is demonstrated. (B. Foligné). On the other hand, the microbial ecosystem can selectively limit the penetration of these xenobiotics. It is possible to act through the diet by specifically modulating the transient microbiota to limit the penetration, accumulation and effects of these xenobiotics. The study of the microbiota and the bowel-lung axis is essential, for it will make it possible to design a new organisational scheme promoting the collaboration of CIIL teams with clinical teams from the University hospital, in order to create a single hub in the Lille region.

WP 5. Infection and cancer

Many parasitic chronic infections are described as contributing to the onset of cancer. More particularly, genital and digestive cancers have a very significant prevalence among adults living in countries where schistosomiasis (J. Khalife/R. Pierce) or *Cryptosporidium* infections are endemic.(E. Viscogliosi). Accordingly, the infectious causes of cancer will have a significant impact on life expectancy in developing countries. Chemotherapy and vaccination against schistosomiasis (J. Khalife/R.Pierce/G Riveau) could therefore reduce the frequency of certain types of cancer. At the same time, multiple organic disorder connected to parasitoses are often associated to thymic autoimmunity and immune-senescence. These phenomena could contribute to ageing and will be studied on cohorts of patients in India (team led by Sylviane Pied).