



Progress report

2 years after



Gérontopôle de Toulouse

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FOREWORD

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In 2007, in view of the public health issues related to life extension, the Ministry of Health created in France and on a trial basis, an expertise and gerontology research organization on international standards. The aim was to organize in a unique framework, all of the medical, pharmacological, epidemiological and sociological research in the field of ageing. The Toulouse CHU - Centre Hospitalier Universitaire (University Hospital Centre), with its long experience in this matter, was chosen to support this project: the G rontop le was created.

After only two years existence, the G rontop le has achieved its assignments committed in 2007 and has proven the usefulness of such a structure dedicated to organizing research in gerontology, and more so towards research on Alzheimer's disease.

The G rontop le sets up research programs and actions with regards to:

- clinical research and trials on promising molecules: the G rontop le coordinates the CeNGEPS - Centre National de Gestion des Essais de Produits de Sant  (National Centre for Management of Trials on Health Products) Alzheimer's disease network. Furthermore, it also coordinates the study on biomarkers research associated to memory disorders.

- policy development, through the Institut du Vieillessement (Ageing Institute), concerning lack of independence and based on an epidemiological research: the G rontop le has conducted the GuidAge (1) and MAPT (2) studies on prevention of Alzheimer's disease and cognitive decline.
- research related to geriatric network support in connection with nursing homes for elderly dependent persons: the G rontop le has created the REHPA (3) research network. It enables to improve care procedures for old people with a better screening of dementia in EHPAD institutes, thus avoiding inappropriate hospital admission.

The Toulouse G rontop le has conducted high variety and quality actions through fundamental research, prevention and modelling of elderly persons'care procedures. It shows the purpose of today's organization dedicated to a still insufficiently explored area: gerontology.

- (1) Phase III trial concerning the efficiency of Ginkgo Biloba on the impact and delay of appearance of an Alzheimer type dementia.
- (2) Multi-domain Alzheimer Preventive Trial
- (3) Research network, identification of specific problems related to old age care in EHPAD

Bruno Vellas

The Toulouse Gérontopôle is a sign of trust. It represents an assignment born by a team committed without fear to the scope of works. Today, the major risk in clinical research is to leave a predefined program unfulfilled. There are many likely reasons for this: numerous demands, heavy work, obstructions and obligations in administrative, psychological, financial, human and scientific terms. Why accept all these difficulties, when bonuses are so remote and uncertain?

Yet the worst thing is to start a project and leave it unattended. What energy, how many working hours, how much financial investment are spent in France and in many other countries, to conceive a research program, to start it up and then to give it up when unavoidable hardships and outside requests come up? It is our duty to get together when difficulties begin, in order to overcome them and allow each actor, whatever his part in the project, to be rightly thanked and rewarded upon its successful outcome.

This is why, under the impulse of the Geriatric Gerontology Centre teams of the Toulouse CHU (University Hospital), of the INSERM U558 unit, of the University Department of Epidemiology, Health Economy and Public Health, as well as of a number of CHU teams, we were able to set up the Gérontopôle action plan, as forecasted. It was owed to the contribution of regional networks (memory consultations, geriatric services, EHPAD, Southern France CMRR Federation), national networks (PHRC, REAL FR, PLASA, CeNGEPS Alzheimer network of the CMRR Federations, REHPA – research network in EPHAD institutions), European networks (EADC – European Alzheimer's Disease Consortium, Ictus, AddNeuroMed, E-ADNI) and international networks (University of New Mexico in USA, IAGG). An important number of

actions are coordinated by the Gérontopôle and are the result of a few decades (two generations) of work, as mentioned by the Professor Joël Ménard in his preface.

The Gérontopôle contributed to an important increase, on behalf of France, in the conception, the methodology and the execution of major therapeutic trials. They aim to modify the progression of Alzheimer's disease assisted by innovative therapeutics: immunotherapy, gamma-secretase and beta-secretase inhibitors (BACE), for example. France's involvement will increase significantly within the next years. With the assistance of our Deans, the Gérontopôle was able to create an Institut du Vieillessement in the heart of the Toulouse-Purpan Medical College. This is where the major GuidAge and MAPT prevention trials are conceived, followed up and organized. They were the first ever undertaken in Europe whilst major trials were carried out in the United States. It is from these major randomised double-blinded trials, conducted over many years and involving an important number of subjects, that significant information will be recorded with regards to the way a simple memory complaint becomes a cognitive decline, and eventually changes into Alzheimer's disease. The associated biobanks will be of considerable help to validate biomarkers.

The Gérontopôle has executed its assignments: be of service to the geriatric field and develop clinical research in Alzheimer care units and in institutes for elderly dependent people from the PHRC PLASA networks (bringing together 20 University Hospitals and 30 General Hospitals). This work has also been applied to the REHPA network and enabled to unite 240 institutes eager to conduct research programs in EHPAD. Indeed, whereas these

places shelter the most frail and dependent elderly persons, clinical research has been lacking in them. The PHRC, REAL FR and PLASA contributed to the definition of indicators for the Presidential Plan on Alzheimer's disease by a better long-term knowledge of this disease. Thirty international publications were based on these works.

The ONRA - Observatoire National de la Recherche sur la maladie d'Alzheimer (National Commission for Research on Alzheimer's disease), entrusted to the G rontop le, updates these indicators and lists the Alzheimer's disease research teams in France, their scientific works and allows an access for all teams to the related therapeutic trials. Under the impulse of our General Manager, an important cultural program is being undergone and will accompany the G rontop le action plan in all its aspects. Today the existence of the G rontop le is due to high expertise and continuous efforts of all involved teams, to their important works and to their passion in the struggle against Alzheimer's disease. It also exists owing to the constant confidence of our different national and regional authorities: French Ministry of Health, General Management of ARH – Agences R gionales de l'Hospitalisation (Regional Agencies for Hospitalization) and of the CHU – Centre Hospitalier Universitaire (University Hospital) and the Deans of the two Toulouse Medical Colleges.

SYNTHESIS

Since a number of years, the CHU – Centre Hospitalier Universitaire (University Hospital Centre) – of Toulouse is engaged in a global approach concerning the care of elderly people. The geriatric centre has been organized together with those involved in internal and external geriatric care throughout the southwest region of France. This interrelated expertise stimulates communication and research at a regional, national and international level. The creation of the Toulouse Gérontopôle, by Professor Bruno Vellas, is therefore a logical and legitimate continuation.

The demographic aging trends will continue in the future and it becomes necessary to develop research in geriatrics and gerontology. Health, social, political and economical issues are the main challenge in this field.

Amongst them, Alzheimer's disease and its associated disorders are a priority. Their prevalence is increasing with 860 000 persons suffering from these disorders and 225 000 new cases observed each year. The impact on family and community is important: it accounts for 70 % of the admission in special care facilities and 72 % of the applications for the "Allocation Personnalisée à l'Autonomie" (a Public Fund for Personal Autonomy). Its annual cost is estimated at 9.9 billion €, 55% of which is directly born by families.

Research programs must be based on a multidisciplinary approach involving different specialties: fundamental, clinical, epidemiological, human and social sciences. Furthermore, they should be conducted together with European and international actions already undertaken in this area.

This is why, reflecting the actual needs of the elderly, the Toulouse Gérontopôle was

created on February 5th, 2007, in response to an engagement of French ministers Xavier Bertrand and Philippe Bas. Its assignment is structured around three types of actions:

- access to diagnosis, to innovative therapy and to clinical research for *elderly and frail persons* often excluded from these programs,
- implementation of the **Institut du Vieillessement** (Ageing Institute) to develop and validate health enhancement and prevention programs for *healthy elderly persons*,
- dedication towards the geriatric network in order to develop clinical research for *elderly dependent persons*.

The aim of the Gérontopôle is to create a dynamic organization between the clinical activities of the Toulouse CHU Geriatrics Gerontology centre and the research works of the Ageing team of the INSERM - Institut National de la Santé et de la Recherche Médicale (National Health and Medical Research Institute) U558 unit. This enables to foster multidisciplinary research associated to quality care. It is born by the Toulouse CHU Geriatrics Gerontology centre (Professor Bruno Vellas), in joint collaboration with the Inserm U558 unit "Risk, chronic diseases, handicap"

(Doctor H el ene Grandjean), and gets methodological support from the Epidemiological and Public Health Department of the Toulouse CHU (Professor Alain Grand) at different research levels.

ACTION N o 1

Access to diagnosis, to innovative therapy and to clinical research for elderly and frail persons

One of the main issues of the struggle against Alzheimer’s disease is the implementation of major therapeutic trials. There are currently no structured research plans to lead these trials, such as those carried out for other pathologies like cancer.

Furthermore, as opposed to eastern European countries, Asia or even Western Europe (Germany, Spain), a decline in research activity in major pharmaceutical laboratories in France has been registered. The G erontop ole set up a certain number of actions to improve therapeutic trials recruitment:

- organizing research on a local and national basis with:

■ **organization of therapy research** within the Toulouse CMRR - Centre M emoire de Ressource et de Recherche (Memory Resource and Research Centre) as well as the memory consultations in the Midi-Pyr en ees region: set up of clinical research consultation, recruitment and coordination of clinical research technicians in different regions, organization of telemedicine sessions, and creation of a newsletter intended for G erontop ole medical teams, regional memory consultations and general practitioners network,

■ **set up and management, on a national basis, of the CeNGEPS - Centre National de Gestion des Essais des Produits de Sant e (National Centre for Management of Trials on Health Products) “Alzheimer” network of the CMRR organization** since July 2008,

■ **national coordination of 10 therapeutic trials** on promising molecules that have a potential disease modifying effects on mechanisms and evolution of Alzheimer’s disease:

2007-2008	Therapeutic trials
Phase II	<ul style="list-style-type: none"> • Alpha secretase modulator, Exonhit (IIa) • Lecozotan, Wyeth (IIb)
Phase III	<ul style="list-style-type: none"> • Alzhemed, Neurochem • Rosiglitazone, GSK • Gamma secretase inhibitor, Lilly
2009	
Phase II	<ul style="list-style-type: none"> • Immunoglobulin, Baxter (IIb) • Histaminic antagonistic H3, Servier (IIa) • Nicotinic agonist, Roche (IIb) • Monoclonal antibody, Lilly (IIb)
Phase III	<ul style="list-style-type: none"> • Dimebon, Mediavation

With all these efforts, we have registered an important increase of the number of subjects recruited in 2008 for therapeutic trials. In Toulouse, 55 patients were included in phase II or III of the therapeutic trials in 2008 (against 30 in 2007), and 41 patients were randomised (against 24 in 2007). On a national level, and due to the CeNGEPS network, the number of patients included in phase II or III of the therapeutic trials raised considerably from 2007 to 2008. It passed from 149 to 225 patients included and from 113 to 176 patients randomised, progressing by about 50%. One must add to these figures, the patients included in industrial promotion trials on biomarkers research and prevention trials jointly conducted with industry (respectively 161 and 184 patients in 2008). The aim is to reach by 2012, 400 to 500 patients included every year in phase I, II or III concerning Alzheimer’s disease. This could be done by intensifying the above mentioned actions and by increasing the number of recruiting centres involved in the CeNGEPS network, at a regional and national level.

The G erontop ole develops proper research on the methodology used on the Alzheimer’s disease therapeutic trials. This includes, in

particular, the coordination of international meetings combining experts from different backgrounds (academic, industrial, agencies) implied in the trials' concept. This enables to engage a methodological analysis on Alzheimer's disease's new trials outline and the criteria of judgment to be taken into account, particularly the position of biomarkers. These works lead to the publication of recommendations in the *Lancet Neurology* in 2007 and 2008.

Through a quantity and quality approach, we coordinate a multidisciplinary research, specifically dedicated to the study of reasons for involvement and support in a therapeutic trial (**ACCEPT study**). The outcome will allow us to understand more easily why patients accept to attend trials and to distinguish those who might reject the offer and finally to find means to brush away the dread of acceptance. Examination of these reasons will permit a better fitting of the concept and management of therapeutic trial plans. This study will then be presented to general practitioners, and to patients suffering from Alzheimer's disease and their families. It will enable a better definition of the limits to participation in clinical and therapy research.

Within the framework of Step 41 of the Presidential Plan on Alzheimer's disease, we were assigned to put information on **the ONRA - Observatoire National de la Recherche sur la maladie d'Alzheimer** (National Commission for Research on Alzheimer's disease) website related to all of the research currently conducted in France, including therapeutic trials undergone in the country. With this action patients and their families have access to therapy innovation and clinical research. This work should ease information circulation and inclusion in research protocols for patients.

- **Involvement in a number of trials:**

■ **the carrying out of 4 studies concerning biomarkers** for Alzheimer's disease:

- European study AddNeuroMed: "Research of biological markers associated to memory disorders".
- E-ADNI study: "European Alzheimer's Disease Neuroimaging Initiative"

- EHT AD/002 study: "Blood diagnostic test of Alzheimer's disease", Exonhit
- ROSAS Study: "Search of proteic biomarkers in Alzheimer's disease", Servier

At the same time as therapeutic trials are being conducted for Alzheimer's disease, the G rontop le recently develops research programs on **sarcopenia** (age-related loss of muscle mass) and **frailty** with in particular, identification of frailty biomarkers (05.04.NRC study "Identification of frailty biomarkers in elderly persons", Nestl ), and involvement in a Phase IIa trial on treatment of sarcopenia (MK0773-005 study "Phase IIa clinical study, at random against placebo, assessing the efficiency and acceptance of MK-0773 from sarcopenia suffering patients", MSD).

ACTION N  2

Implementation of the Institut du Vieillissement which will contribute to develop and validate programs for health enhancement and prevention for elderly persons in good health

The G rontop le created the Institut du Vieillissement in the Toulouse city centre, giving a better access to elderly persons unconcerned by hospital care:

- the Toulouse Purpan Medical College (situated All es Jules Guesde) is running since summer 2008 (official opening on November 6th, 2008). It is dedicated to promoting health and training. A second period of works is planned in 2009.
- the La Grave centre, will open in April 2009. It will be dedicated to clinical research, carrying out prevention trials, Step III trials, and follow up of groups established by the Fondation de la Coop ration Scientifique Alzheimer (the Alzheimer Scientific Cooperation Foundation).

- Two major prevention trials are currently managed by the G rontop le:

- the **GuidAge study** recruited 2800 elderly people declaring memory disorder. These persons are divided at random into two groups and are given either Ginkgo Biloba, either a

placebo, during 5 years. This study is the first major trial on prevention of Alzheimer's disease in Europe and it will bring important information with regards to the way initial complaint becomes Alzheimer's disease. Furthermore, biological samples will be collected during the survey. This will permit to identify biomarkers that will be useful in prognosis and diagnosis of the disease. The last participant involved in the survey will undergo his 5-year end-of study consultation in October 2009. The results of this study will be available beginning 2010.

– the Gérontopôle, operating with major American teams, validates a multi-domain intervention program associating nutrition, cognitive stimulation, physical exercise, detection of sensory disorders and support of cardiovascular diseases. This intervention is tested as part of the **MAPT (Multi-domain Alzheimer Preventive Trial) study**, fostered by the Toulouse CHU. This study's aim is to assess the impact of omega-3 fatty acid and of the multi-domain intervention program on the cognitive decline on 1.200 frail elderly subjects during a 3-year period. Recruitment is currently underway in Toulouse, Bordeaux, Limoges and Montpellier. Three hundred and six old people were recruited by 10th March 2009. On average, 45 contributors are included every month since the opening of the 4 centres (October 2008).

■ **Actions related to health promotion** are organized in a joint effort with the Senior Citizen's University of Social Sciences of Toulouse, Pension Funds and Toulouse town council. They offer the possibility for elderly people to receive training concerning prevention for age-related pathologies.

■ The Institut du Vieillessement is a place for discussion and professional training. Furthermore, it hosts the IAGG (International Association of Gerontology and Geriatrics) headquarters from 2009 to 2013.

ACTION N° 3

The Gérontopôle is dedicated to service for the geriatric network in order to develop clinical research for elderly and dependent persons.

The actions are developed around three majors issues: assessment of the care given to the elderly persons suffering from Alzheimer's disease and identification of the specific problems concerning care of old people living in EHPAD - Etablissements d'Hébergement pour Personnes Agées Dépendantes (Institutes for Elderly Dependent Persons). The last issue is related to assessment of geriatric network. This is done through evaluation of the geriatric mobile teams' performances and of the first mobile team concerned by severe dementia, set up by the Gérontopôle on the 1st January 2008.

■ More than 600.000 elderly subjects live in nursing homes and report many pathologies. However, research is almost completely lacking in these organizations. The Gérontopôle has set up a network called **REHPA - Recherche en Etablissement d'Hébergement pour Personnes Agées** (Research in Institute for Elderly Persons). Its aim is to identify clinical problems that could benefit from added research. The network currently involves 240 homes in France, of which 178 are situated in the Midi-Pyrénées region. The primary data available from the REHPA survey reveals that 50% of Alzheimer's disease cases were not detected in EHPAD. One of the outlooks of the network is to assess whether there is an advantage in an automatic tracking of dementia inside nursing homes, through pluri-disciplinary consultation meetings related to the hospital admission rate of elderly people living in EHPAD.

■ The first Alzheimer's disease intensive care unit was created in Toulouse in 1996, with three major assignments: diagnosis of difficult cases, management of acute complications and treatment of acute associated diseases. The unit receives an increasing number of patients reporting severe behaviour disorders, such as aggressiveness. At this point, a new hospital admission is then often observed. For this reason, the Gérontopôle set up the first **mobile team concerned by severe dementia**. Made up

of a practitioner and a nurse, this team managed 184 subjects (41,3%) out of the 445 patients admitted in the Alzheimer's disease intensive care unit from January to November 2008. Assessment of the mobile team's performances is being undergone. Other similar actions will be prepared in 2009: such as a cognitive-behaviour unit scheduled for opening during the first half-year according to the French presidential program on Alzheimer's disease.

■ The Gérontopôle continues research programs concerning patient care for those affected by Alzheimer's disease subject of 42 international publications and that allows us to provide indicators concerning the development of the disease for the Presidential Plan:

- PHRC 1998: "Care network for Alzheimer patients and predicted factors for admission in related facilities. Multi-centric survey network" and PHRC 2001 "Multi-centric survey concerning the reel impact of cholinesterase inhibitors in Alzheimer's disease": 686 patients followed up during 4 years
- PHRC 2003: "End of life and Alzheimer's disease. ALFINE study": 100 patients followed up during 2 years
- European project: "ICTUS study: The impact of treatment with acetyl-cholinesterase inhibitors on Europeans with Alzheimer's disease": 1385 patients followed up during 2 years
- PHRC 2002 and 2006: "PLASA study: Alzheimer's disease care and specific assistance program": intervention study assessing standard care, 1121 patients followed up during 4 years

■ Within the framework of the Presidential Plan, the Gérontopôle has also written two documents for the DGAS - Direction Générale de l'Action Sociale (National Social Services Department): [a reference book on Alzheimer's disease care units in EHPAD](#) and a journal on [respite facilities](#).

SCIENTIFIC WORKS (2007-2008)

The global actions of the Gérontopôle lead to the publication of 61 articles in international journals registered on Medline in 2007 and 2008 (compared to 35 in 2005 and 2006).

Five major publications:

- Vellas B, Black R, Thal L, Fox NC, Daniels M, McLennan G, Tompkins C, Leibman C, Pomfret M, Grundman M; for the AN1792 (QS-21)-251 Study Team. Long-Term Follow-Up of Patients Immunized with AN1792: Reduced Functional Decline in Antibody Responders. *Current Alzheimer Research*, 2009 (in press)
- Vellas B, Andrieu S, Sampaio C, Coley N, Wilcock G; European Task Force Group. Endpoints for trials in Alzheimer's disease: a European task force consensus. *Lancet Neurol*. 2008 May; 7(5):436-50
- Andrieu S, Ousset PJ, Coley N, Ouzid M, Mathiex-Fortunet H, Vellas B; GuidAge study GROUP : GuidAge Study: A 5-Year Double Blind, Randomised Trial of EGb 761 for the Prevention of Alzheimer's Disease in Elderly Subjects with Memory Complaints. I. Rationale, Design and Baseline Data. *Curr Alzheimer Res*. 2008 Aug;5(4):406-15.
- Coley N, Andrieu S, Gardette V, Gillette-Guyonnet S, Sanz C, Vellas B, Grand A. Dementia Prevention: Methodological Explanations for Inconsistent Results. *Epidemiol Rev*. 2008 Sep 8.
- Vellas B, Andrieu S, Sampaio C, Wilcock G; European Task Force group. Disease-modifying trials in Alzheimer's disease: a European task force consensus. *Lancet Neurol*. 2007 Jan; 6(1):56-62. Review

Complementary financial support	Amount granted
- Funds from PHRC 2008 – Programme hospitalier de recherche clinique (National Hospital Program for Clinical Research): “Prevention of cognitive decline: impact of a multi-domain stimulation and an omega-3 fatty acid complement. MAPT study”	294 000 €
- Funds from ARH – Agence Régionale d’Hospitalisation (Regional Agency for Hospitalization): ARC - Attaché de Recherche Clinique (Clinical Research Assistant) jobs	120 000 €
- Funds from DGAS - Direction Générale de la Santé (National Health Department): . ONRA – Observatoire National de la Recherche sur la maladie d’Alzheimer (National Commission for Research on Alzheimer’s disease) . Develop a communication tool for circulation of the Care and Aide Program for Alzheimer patients: creation of a follow-up record for general practitioners”	145 000 € 40 000 €
- Funds from DGAS - Direction Générale de l’Action Sociale (National Social Services Department): “Drafting of references on Alzheimer’s disease care units in EHPAD and respite facilities”	60 000 €
- Funds from INPES – Institut National de Prévention et d’Education pour la Santé (National Institute for Health Prevention and Education) tender from IReSP - Institut de Recherche en Santé Publique (Public Health Research Institute): ACCEPT study	100 000 €
- Funds from CeNGEPS - Centre National de Gestion des Essais des Produits de Santé (National Centre for Management of Trials on Health Products)	263 000 €
- Funds from industrial partnerships: . Pierre Fabre laboratory (MAPT study) . Exonhit laboratory (MAPT study) . Nestlé laboratory (biomarkers on frailty) . Servier laboratory (biomarkers on Alzheimer’s disease)	2 100 000 € 220 000 € 91 540 € 520 430 €
- Funds from European Commission: . AddNeuroMed study . Ictus study . E-ADNI study	29 516 € 90 035 € 14 997 €
- Funds from ANR- Agence Nationale de la Recherche (French National Research Agency): MIRAS study (ANR-o8-ECS-009-06)	59 696 €

FUNDS RECEIVED (2007-2008)

The means granted to the Gérotopôle amount at 345.000 € in 2007 and 2008. This includes the 150.000 € granted by the DHOS - Direction de l’Hospitalisation et de l’Organisation des Soins (Hospitalization and care planning Department) and the 195.000 € granted by the ARH - Agence Régionale d’Hospitalisation (Regional Agency for Hospitalization). Complementary resources have been obtained for the set up of the Gérotopôle’s action program.

Call up for grants in 2009:

- reply to the PHRC 2009 tender (application for: 586.000 €)
- reply to the joint Aquitaine/Midi-Pyrénées inter-regional tender (application for: 927.720 €)
- reply to the CeNGEPS 2009 tender (application for: 380.000 €)
- reply to the ANR 2009 tender (application for: 312.416 €)

Conclusion

During the last two years, the Gérotopôle set up committed assignments in major, fast-growing fields. It is now become an outstanding organization dedicated to care, health development and clinical research. We are able to conceive original research programs. Reinforcement of clinical research means to increase quantity and inclusion rate in new drug and prevention trials is another of our tasks. We also organize regional, national and European research networks and develop partnership with international research teams. The build-up of research activities has led to an increase of scientific works.

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