

CLINICAL RESEARCH

The rise and rise of clinical research

Clinical research is the last, highly delicate, stage in medical research and studies the effects of new therapeutics on humans. Research in the Toulouse region is well organized in this domain.

Clinical research is an important part of hospital-university life. At Toulouse, there are four units that bring together fundamental research, the medical profession and industrial partners.

~~The CHU (Centre Hospitalier-Universitaire)~~ **Clinical Research Regional Delegation and Innovation (DRCI)** of Toulouse supports and accompanies investigators at all stages of clinical research. Made up of representatives from different clinical poles at the CHU, faculties, university and research organisms, it helps forge relations between the Toulouse CHU with different partners. Over the last few years, its scientific advisory role has allowed it to become involved in research project propositions and obtain funding from 12 inter-regional ~~PHRC~~ and 20 national ~~PHRC~~ (1).

Today, more than 1000 projects from research institutions or industry are in progress at the Toulouse CHU, which promotes more than 130 of these. To fully play its role, the DRCI supports a certain number of strategic axes thanks to a specific research budget ~~from MERRIS~~ (2), a local invitation to tender that funds ten or so new projects very year and which supports structured projects like biotherapy, and those in collaboration with other partners, such as CNES and European organizations.

These activities rank the Toulouse CHU 6th in France according to SIGAPS (Système d'Interrogation, de Gestion et d'Analyse des Publications Scientifiques). Research with innovation is also a strong axe in this organization, with project propositions unique to the CHU concerning diagnostics and treatment and national STIC (Soutien aux Technologies Innovantes et Coûteuses) project propositions.

The Centre d'Investigation Clinique (CIC) of Toulouse, ~~created in 1994~~, created in 1994, provides a practical professional structure (buildings and staff) that is regimented (there are good clinical practices in place that follow public health laws). The centre, located at the Purpan hospital, relies on collaborations with research teams from INSERM, CNRS and Paul Sabatier University (UPS), which allows it to develop projects that will have medical applications and provide clinical departments with the infrastructures needed to follow "heavy" clinical research protocols in direct collaboration with the DRCI and the Clinical Pharmacology Department/CHU Clinical Research Support Centre. An integrated module in biotherapy was also put in place at the Ranguel hospital site as well as a functional paediatric unit at the Children's Hospital.

The CIC manages several projects in national clinical research and participates in several European programmes. It welcomes PhD students and post-doctorates, and educates numerous interns in the field of clinical research. The CIC is also one of the main actors in French biomedical research, in direct collaboration with the DRCI and INSERM.

The Institute for Medicine and Spatial Physiology (MEDES)

aims to develop space medicine and related health applications. The Toulouse CHU and the CNES are the main members of this GIE, which belongs to UPS and other French Universities. It is a centre for biomedical experiments, situated at the heart of the Ranguel hospital. It boasts infrastructures, sophisticated equipment, qualified staff and access to the biomedical platform at the hospital. Housing between four and 20 beds depending on its needs, the Spatial Clinic allows for studies in perfectly controlled conditions with regards to acoustics, temperature and light. Here, simulation



>>> Hélène HANAIRE, president of the Délégation Régionale à la recherche clinique et à l'innovation ; Olivier RASCOL, coordinator of the Centre d'Investigation Clinique, medical director at the Clinique Spatiale ; Christophe CAZAUX, vice-president of UPS and vice-president of the Oncopôle de Toulouse Association.

experiments are performed that mimic conditions in a spacecraft to better understand the physiological side-effects for astronauts who spend prolonged periods of time in space.

The Clinical Research Unit at the Cancer Institute University

Toulouse's experience in cancerology has led to a coordination in clinical research following the creation of a competitive pole, Cancer-Bio-Health, the Canceropole Grand Sud-Ouest, and the Thematic Research and Care Network (RTRS) in Cancerology, with the creation of the Innabiosanté foundation. Finally, the merger of two university hospital units with the creation of the Cancer Institute University (IUC) on the Toulouse-Langlade Oncopole site, will lead to a new type of hospital structure, born from the merger between the Cladius Régaud Institute and Toulouse CHU. This structure will be exclusively dedicated to cancer. The organization of the future IUC will allow to promote clinical research in cancerology and lead to the creation of a delegation for cancer clinical research in the Midi-Pyrénées with the appropriate infrastructure. It will bring the existing clinical research unit, which boasts the INCa label for early stage phase I clinical trials, up to date. This URC will allow scientists to perform hundreds of trials a year, or 25% of phase I trials. It will also open the way to partnerships with regional establishments to better develop trials and allow to create a biological resources "cancer" centre to work closely with the brand new Toulouse Cancerology Research Centre (CRCT).

The development of clinical research in the future is highly important for society, crucial for scientific progress and an essential step in economical development.

This dossier illustrates how Toulouse has the skills to play a major international role in this field.



1 - Financement Hospitalier dédié à la recherche clinique
 2 - Budget dédié aux Maladies Graves, aux soins de recours et de Recherches des Hôpitaux

à traduire

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CHU: Centre Hospitalo-universitaire/
University Hospital

DRCI: Délégation Régionale à la Recherche Clinique
et à l'Innovation/Clinical Research Regional
Delegation and Innovation

CIC: Centre d'investigation Clinique/
Centre for Clinical Investigation

I2MC: Institut des Maladies Métaboliques et
Cardiovasculaires/Institute of Metabolic and
cardiovascular diseases.

LST: Laboratoire du Stress Traumatique/
Laboratory of Traumatic Stress.

Early detection of Parkinson's disease



>>> Umberto SABATINI, head of medical imaging/diagnostic department of the Santa Lucia foundation in Rome and Patrice PÉRAN, Inserm researcher at the Neuroimagerie Fonctionnelle et Clinique team at the Imagerie Cérébrale et Handicaps Neurologiques lab (UPS/Inserm lab).

Parkinson's disease is the second most frequent neurodegenerative disease after Alzheimer's and its diagnosis often depends on late-appearing symptoms. A team of researchers from Toulouse has discovered a cerebral signature of the disease using a simple MRI scan, something that opens the way to early detection of the disease and better patient care and follow-up.

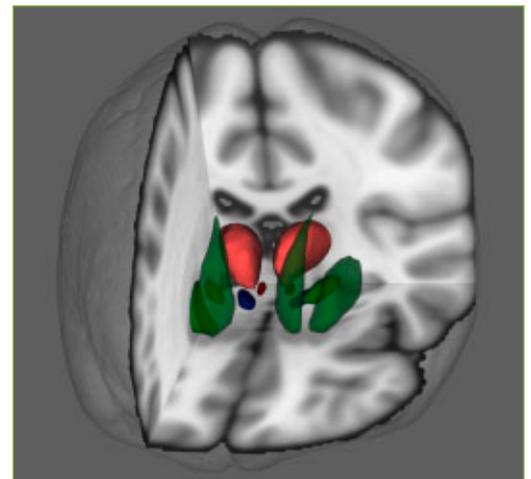
At present, the only way to diagnose Parkinson's consists of studying the symptoms of the patient – notably, those caused by neurodegenerative processes. The disease affects a small structure that lies deep in the brain, the substantia nigra (black substance), composed of neurons that produce dopamine, a neurotransmitter essential for neuromotor function.

A French-Italian team has now set up a clinical research structure, the Centre d'investigation clinique at the Purpan Hospital (CIC, managed by Olivier Rascol), the Cerebral Imaging Laboratory and Neurological Handicaps (Inserm/UPS lab, managed by Pierre Celsis) and the Department of Radiology at the IRCCS Santa Lucia, managed by Umberto Sabatini in Rome. Studies were performed on 30 patients suffering from Parkinson's and 22 control patients to investigate whether MRI (magnetic resonance imaging) is capable of distinguishing between the brains of healthy subjects and those affected by the disease.

More than 95% sure

Three types of measurements were performed on the entire brain of subjects. The measurements focused on the anatomic integrity of regions in different parts of the brain, microstructural orientation and the amount of iron present in these microstructures. The results show that combining these indices allows to diagnose Parkinson's disease with more than 95% certainty, something that classic MRI examination failed to do until now. The studies have allowed the researchers to identify a "cerebral signature" of the disease.

The approach has shown that, like for Alzheimer's disease, using an ensemble of biomarkers in MRI is promising for diagnostics and patient follow-up for neurodegenerative diseases. The goal of the research is to have a "brain test" that works using MRI.



>>> 3D image of a human brain showing central grey nuclei and target black substance with degeneration and diagnostic markers for Parkinson's.

For more information: Magnetic resonance imaging markers of Parkinson's disease nigrostriatal signature. Pérán P, Cherubini A, Assogna F, Piras F, Quattrocchi C, Peppe A, Celsis P, Rascol O, Démonet JF, Stefani A, Pierantozzi M, Pontieri FE, Caltagirone C, Spalletta G, Sabatini U. *Brain*. 2010 Nov;133(11):3423-33.

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Stem cells could help treat cardiovascular diseases

A collaboration between clinicians and research teams from various disciplines are testing whether stem cells can be used to repair cardiac function



>>> Professor Jérôme Roncalli (centre) and the Cardiology team of the Toulouse CHU.

For over a decade now, researchers from various disciplines and clinicians specialized in cardiovascular diseases have allowed the Toulouse CHU (~~Centre Hospitalier Universitaire~~) to become a leader in the domain of cardiac cell therapy. The department of cardiology has been involved in several clinical research studies in cellular therapy (for example, the MAGIC and BONAMI projects) and is presently carrying out a phase I/II programme to show how mesenchymal stem cells from bone marrow can be used to fight myocardial ischaemia.

Cardiac biotherapy

As part of the clinical transfer of cardiac biotherapy applications, the MESAMI (MESemchymal cells and Myocardial Ischemia) project is an ambitious one. It is coordinated by Jérôme Roncalli, who is supported by the Toulouse CHU. Phase I of the project is currently under way in collaboration with the Etablissement Français du Sang Pyrénées-Méditerranée (EFS-PM) and the Institut du Thorax de Nantes. Clinical trials are organized and regimented by the Centre d'Investigation Clinique Intégré en Biothérapies (CIC BT).

Bone marrow

Once bone marrow has been removed, in the Haemodynamic Department at the Rangueil

Hospital (by a team led by Anne Huynh of the Haematology Department at Purpan), the cells are isolated and amplified for 18 days at the EFS-PM (by a team team led by Phippe Bourin). They are then injected via intramyocardial trans-endocardial channels thanks to guiding by electromagnetic imaging (NOGA XP). Until now, five patients have been treated and their health seems to be improving. This trial is being carried out as part of the strong partnership developed between the CHU, the EFS-PM, Inserm and Paul Sabatier University.

Thanks to the research carried out with the Institut des Maladies Métaboliques et Cardiovasculaires (I2MC, UPS/Inserm lab), clinical transfer of data obtained on animals on cells transplanted by melatonin (to increase their lifetime), has allowed the researchers involved to obtain PHRC 2010 national funding for phase I of these studies.

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Headline



>>> Reconstruction of the left ventricle in a cartographic form (panel A) with a catheter introduced via the femur in the left ventricle (panel B) thanks to the NOGA XP system (panel C) as part of the MESAMI study.

Patients with Alzheimer's disease: how to improve follow

A recent published trial shows that a comprehensive specific care plan has no additional positive effects on functional decline in patients with mild to moderate Alzheimer's disease.

Alzheimer's disease (AD) is the leading cause of dementia and is characterized by a progressive decline in cognitive function, which typically begins with deterioration in memory. Before death, individuals with this disorder have usually become dependent on caregivers. Providing care for patients with AD is complex and the type of care required depends on the stage of the disease and varies over time. However, to date there are no validated follow-up guidelines for these patients.

Memory Centres

The Toulouse University Gerontological team is part of French Memory Centres network. In many countries, memory clinics with multidisciplinary teams have been established to facilitate the early detection and management of dementia.

PLASA study (Specific Care and Assistance Plan for Alzheimer's Disease) is a cluster randomized trial coordinated by the Toulouse team. The main objective was to test the effectiveness of a comprehensive specific care plan in decreasing the rate of functional decline in community dwelling patients with mild to moderate AD compared with usual care in memory clinics.

The specific care plan for AD was developed by a multidisciplinary working group mandated by the French Ministry of Health as part of the French government's first plan of action for AD. 1131 community-dwelling patients were included: 574 from 26 clinics in the intervention group and 557 from 24 clinics in the usual care (control) group. The intervention included a comprehensive standardized twice yearly consultation for patients and their caregivers, with standardized guidelines for the management of problems identified during the assessment.

The results of the primary intention to treat analysis of this trial showed no difference in the rate of functional decline between patients with mild to moderate AD randomized to a specific care plan and

those randomized to usual care after the two years of follow-up. More over, the cost of care as well as the evolution of quality of life are similar between the two groups.

Quality of care

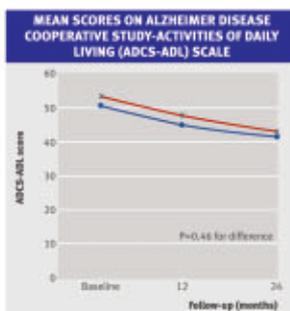
This finding underlines the fact that this kind of regular follow-up and broad intervention in memory clinics does not convey benefit in activities of daily living and may have little public health value. To have a beneficial effect on disease progression it may be that interventions must be targeted towards patients at particular risk of decline or we may need to develop a more effective intervention and ensure that it is correctly implemented in all patients. This study suggests that the contribution of advice to caregivers and general practitioners alone is not sufficient. Future research is needed to determine whether functional decline can be improved by more direct involvement of general practitioners or by using case manager programmes

For more information: Nourhashémi F, Olde Rikkert MG, Burns A, Winblad B, Frisoni GB, Fitten J, Vellas B. Follow-up for Alzheimer patients: European Alzheimer Disease Consortium position paper. *J Nutr Health Aging.* 2010 Feb;14(2):121-30
Nourhashemi F, Andrieu S, Gillette-Guyonnet S, Giraudeau B, Cantet C, Coley N, Vellas B; PLASA Group. Effectiveness of a specific care plan in patients with Alzheimer's disease: cluster randomised trial (PLASA study). *BMJ.* 2010 Jun 3;340:c2466. doi: 10.1136/bmj.c2466

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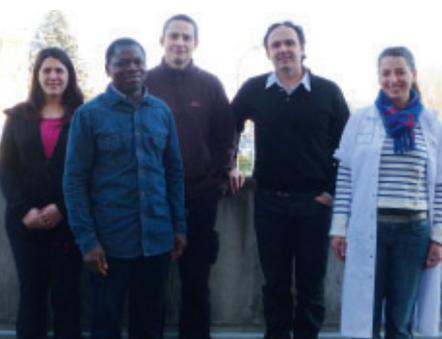


>>> Fati Nourhashémi, physician,
Gérontologie Clinique du CHU
(Centre Hospitalier Universitaire) of Toulouse.



Stress in children following a road accident

Nightmares, insomnia, behavioural problems. After a road accident, children develop symptoms that can be serious. It is now possible to determine which children will suffer the most, so they can be taken care of in a specific way.



>>> Philippe BIRMES, professor at the Toulouse CHU and his team at the Laboratoire du Stress Traumatique, Department of Psychiatry, Purpan Hospital

The Laboratoire du Stress traumatique (LST) at Toulouse studies post-traumatic stress disorder, which can occur after being exposed to a traumatic event such as an accident. The stress manifests itself in the form of flashbacks, hypersensitivity, insomnia and nightmares, among other symptoms, and can lead victims avoiding activities linked to the event. An analysis of the relationship between reactions shown during and immediately after an accident and the development of symptoms in the year that follows the event has been undertaken in collaboration with ~~emergency room and trauma teams at the Toulouse Children's Hospital~~, the adult emergency team, the Epidemiology and Public Health Analysis lab and the Biochemistry of Toulouse CHU lab.

The parameters studies were psychological with psychometry tests, but also biological with saliva tests to measure cortisol levels, a stress hormone. This was done to evaluate a relation between post-traumatic stress and a biological response to acute stress. The study involved 160 children that had been admitted to emergency. Among these, around a 100 were followed over a period of one year with the psychometric and saliva tests - one week, five weeks and one year after the accident. Cortisol results from these studies are currently being analysed.

Emotional distress

The clinical part of the study has already allowed to confirm the immediate emotional distress (after one week) that children involved in accidents experience - this usually manifests itself as acute fear - and cognitive dissociation (a feeling of unreality). Preliminary conclusions of the study: the degree of distress and dissociative feelings experienced in the early days after an accident could be predictors of more persistent, long-term post-traumatic symptoms. The result of this work, which was a

collaboration between several departments at the CHU, should allow early identification of children that might be vulnerable to long-term suffering after a trauma and those likely to develop post-traumatic stress disorder.

For more information: Bui, E., et al. (2010). Validation of the Peritraumatic Dissociative Experiences Questionnaire and Peritraumatic Distress Inventory in school-aged victims of road traffic accidents. *European Psychiatry*, .eurpsy.2010.09.007
Bui, E., et al.. (2010). Peritraumatic Reactions and Posttraumatic Stress Symptoms in School-Aged Children Victims of Road Traffic Accident. *General Hospital Psychiatry*, 32, 330-333
Allenou, C. et al. (2010) Symptoms of Traumatic Stress in Mothers of Children Victims of a Motor Vehicle Accident. *Depression and Anxiety*, 27, 652-657

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headline

Learning trials in oncology: the best way to cure?

Our clinical trials unit “Personalized Medicine in Oncology” at the Institut Claudius Regaud performs around 100 clinical trials at any one time. Every year, between 400 and 600 new patients devote some of their time and participate in these trials. During that time our team takes charge of them.



>>> Jean-Pierre DELORD,
physician (PU-PH) at
the Institut Claudius Regaud.

Secondary effects

Many of the patients participate in “phase I studies”, also called “first-in-human” trials. The main objective of these trials is to determine if a drug can be used in humans (as it has only been previously tested in pre-clinical models) and also to determine the best dose.

As an example, our team has been taking part for more than two years now in first-in-human trials to determine the best way to use MEK- $\frac{1}{2}$ kinase inhibitors. Such proteins are involved in the transduction of proliferating cellular signals. In pre-clinical models, blocking this pathway has proven efficacy against some type of cancer cells.

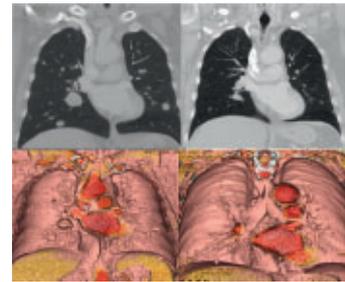
Efficacy

One of the first patients to take part in this trial was suffering from a metastatic melanoma. At that time, some preliminary reports showed that melanoma progression could be related to MAP kinase pathway mutations, including “BRAF” mutations. Nevertheless their biological role in oncogenesis was not fully elucidated. We have been the first (rapidly followed by other colleagues in the world) to show the efficacy of these compounds and indeed reinforce the rationale for using them. Improvement was seen using radio images of the patient’s lungs – some metastases had disappeared and others had regressed.

Since that first exciting period of evaluation, additional questions have come up: how can we predict mutations; is there a specific molecular mechanism of resistance; is there any pharmacodynamic-driven escape process; is a combination strategy of drugs possible? Clinical trials are ongoing in order to address these questions.

Approval as a full drug?

The results from early trials have already been



>>> Regression of metastatic pulmonary nodules can be seen in thorax images after 15 days of treatment (right) compared to initial pre-therapeutic assessment (left)

presented all over the world. In our region, the medical oncologist organization is ready to screen and enrol patients in the late stage of clinical trials.

In our team, we are really happy to see patients that have been receiving treatment for more than two years and who are very well indeed. This is certainly for us the best encouragement we could receive.

We also hope that Toulouse’s translational research will be more and more successful. The clinical research unit is ready to help.

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