Instituts thématiques Inserm
Institut national de la santé et de la recherche médicale

Centre Hospitalier Régional Universitaire de Lille

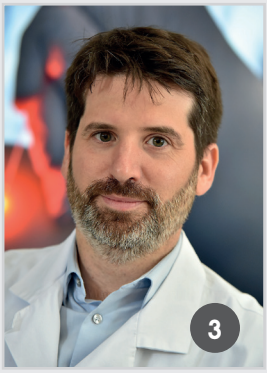
Université de Lille

INNOVATIVE LASER TECHNOLOGY

TO TREAT GLIOBLASTOMAS

Glioblastoma treatment

as seen by the researchers of the ONCO-THAI 1189 project



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- Biophysicist - research director of Inserm
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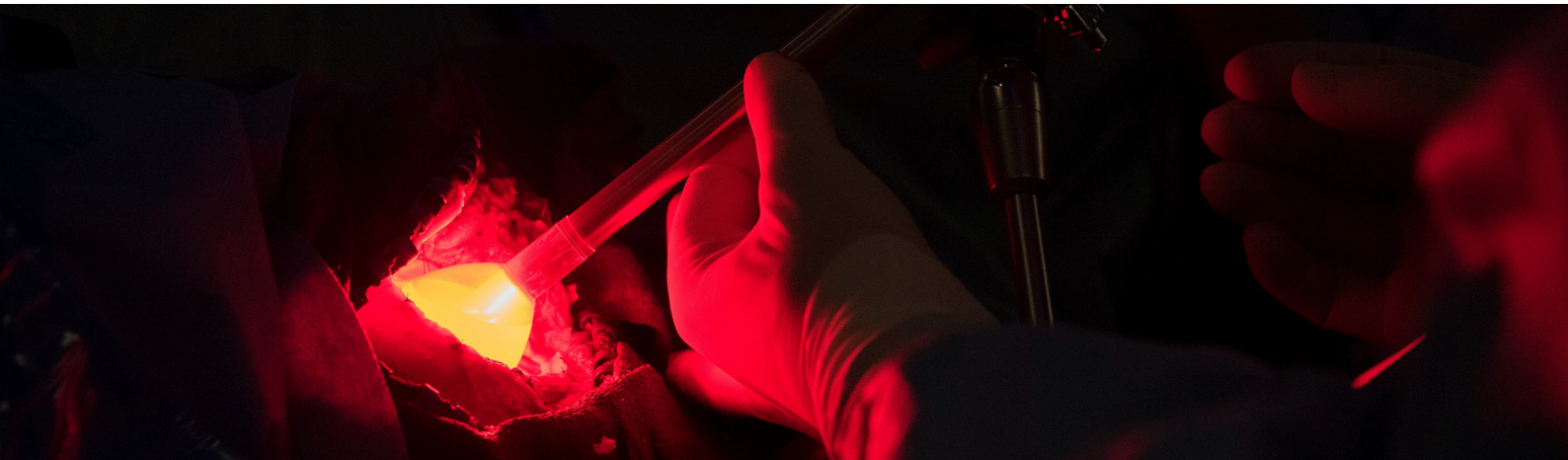
A glioblastoma is a malignant primitive cerebral tumour that appears most frequently in adults with an incidence of 4/100,000 (20,000 cases/year in Europe) and remains the 3rd cause of death due to cancer in young adults (between the ages of 15 and 35). Unfortunately, this is an incurable tumour that has a very low survival rate (median survival is less than 18 months with conventional treatment). Today, the benchmark treatment relies on surgery, cerebral radiotherapy and chemotherapy.

Optimising surgery remains a significant challenge in order to improve survival without progression and overall survival. In fact, even when surgical treatment is satisfactory, the risk of a tumour relapse is very high and the prognosis remains very unfavourable.

In Lille, the ONCO-THAI 1189 project (Inserm, University of Lille, CHU of Lille) is working on the development of new treatment options through photodynamic therapy. This technique consists of exposing tumour cells to a laser light that have been photosensitized by the administration of a pharmacological agent. While the tumour cells are illuminated by a laser, this photosensitizer causes the specific destruction of tumour cells while preserving the healthy tissue.

While being evaluated in the INDYGO study that is promoted by the CHU of Lille and coordinated by professor REYNS in collaboration with professor MORDON and Dr. VERMANDEL, the association of a new intraoperative illuminating laser device with a photosensitizing molecule to treat newly diagnosed glioblastomas is **unique in the world**.



How is a glioblastoma currently treated?

Unfortunately, this is an incurable tumour that has a very low survival rate (median survival is less than 18 months with conventional treatment). Today, the benchmark treatment relies on surgery, cerebral radiotherapy and chemotherapy.

« In the face of the fast progression of a glioblastoma, an aggressive therapeutic strategy is recommended by the European experts who have established a standard of care. This standard includes surgery, if possible, and concomitant and adjuvant radiotherapy and chemotherapy in order to slow down the relapse that remains inevitable. »

This cancer forms the highest grade of primitive cerebral tumours called gliomas, which are generally classified according to four grades. The current progress of molecular biology makes it possible to make an overclassification of glioblastomas depending on the molecular profile of the tumour. This new classification allows us to better grasp this disease and thus personalise the treatment of the patient.

What are the risks of disabilities and relapse?

« A temporary or permanent neurological deficit remains the main risk of surgery or radiotherapy depending on the location of the tumour. »

Neurological deficits may occur depending on the location of the tumour which, for example, can include hemiplegia when the motor cortex is affected, impaired vision or speech.

The development of a technique that allows us to minimise the surgical risk by associating surgery with an additional intraoperative therapeutic procedure is a considerable challenge in treating glioblastomas. Last January, the CHU of Lille had officially launched the INDYGO study.

What is the purpose of the study?

Even in the case of complete surgery checked by an MRI, the health neighbouring tissue remains invaded by the scattered and invisible tumour cells during surgery. These cells form the headquarters of the relapse. The idea that drives our approach is to selectively treat these residual cells by saving the healthy cerebral tissue.

« The principle is based on combining a photosensitizing pharmacological agent with illumination by means of a laser. »

A few hours upon administration of the molecule, the photosensitizer is integrated specifically within the tumour cells. The illumination using a laser light during surgery causes a photochemical reaction that is responsible for destroying these tumour cells while saving the healthy cells for which there is no accumulation of the photosensitizer.

« A new medical device has been conceived and developed by the researchers of the ONCO-THAI 1189 project to shine the right dose of the laser light within the surgical cavity. »

This device is suitable to adjust to the surgical cavity to illuminate the walls homogeneously and thus treat the residual cells that escape during surgery. The device consists of a refillable balloon, a guide to simultaneously secure the device and let the laser light channel directly into the brain thanks to fibre optics and a dedicated medical laser.

The INDYGO-protocol aims at evaluating the photodynamic therapy to treat newly diagnosed glioblastomas. This is a technique that has never been proposed before. Ten patients will be included in this study to verify the feasibility and safety of the method as a primary objective. Secondly and prior to the start of a study at a grander scale, the study must allow us to observe the first effects on the survival without progression and overall survival of patients, as well as their quality of life.

The patients who are included in the study will simultaneously benefit from conventional treatment in order to observe the possible synergies with our therapeutic solution. In addition to the methodological innovation, the application of this therapy to this population of patients is another original aspect of the project because this is **the first study of photodynamic therapy that is conducted during surgery and as a supplement to the standard of care**.

What are the next steps of this research?

« After the INDYGO-study, the plan is to conduct a study at a European scale to demonstrate the benefit of the treatment and the hope to integrate it in the current treatment options. »

The **ONCO-THAI** research team coordinates a network of scientific partners, **SYNAPS** (www.synaps-pro- ject. eu) who aim to deploy this research at a European level. This network links research teams, industrials and expert and alerted clinicians to treat this disease.

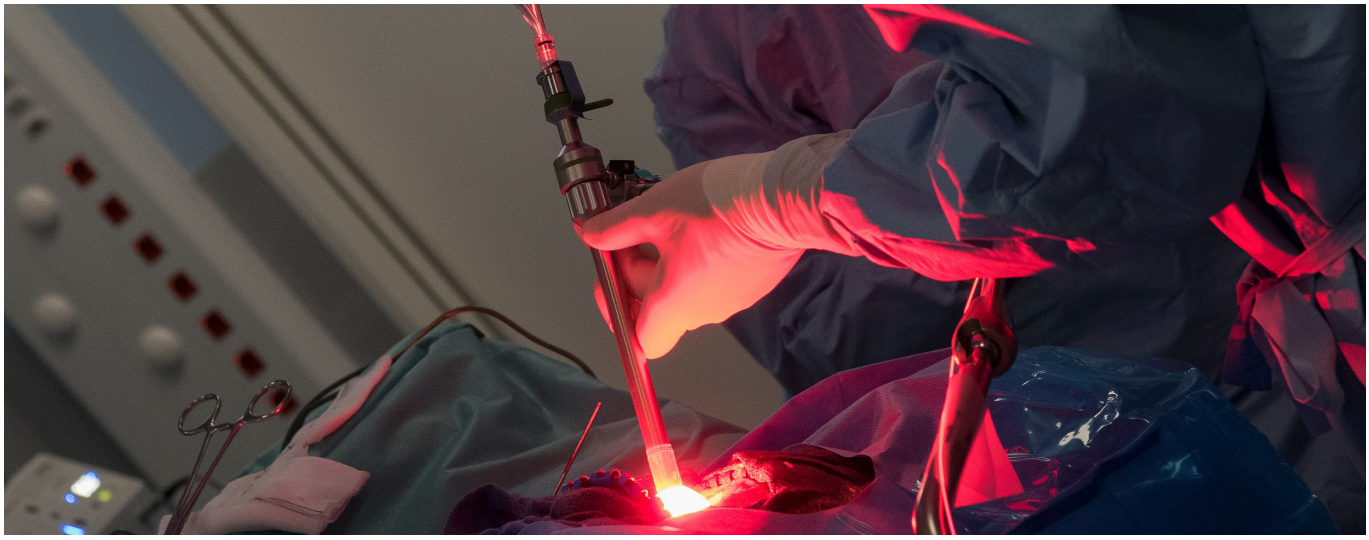
What have been the resources of Lille in developing this innovative technique?

The convergence of clinicians, physicians, methodologists, academic and clinical research specialists makes it possible to unit a field of extensive expertise within the same research unit. This transversal expertise has made it possible to identify the need, propose and develop technological solutions, evaluate and validate these in a laboratory to then finally implement these in clinical research. All of this is only possible because of the permanent exchanges between these different fields of expertise, a continuous presence in hospital departments and immersion into the reality of care.

« The excellence of the technical plateau of neurosurgery at the CHU of Lille and the referencing of its team in the treatment of the pathology are also key elements for innovations to emerge »

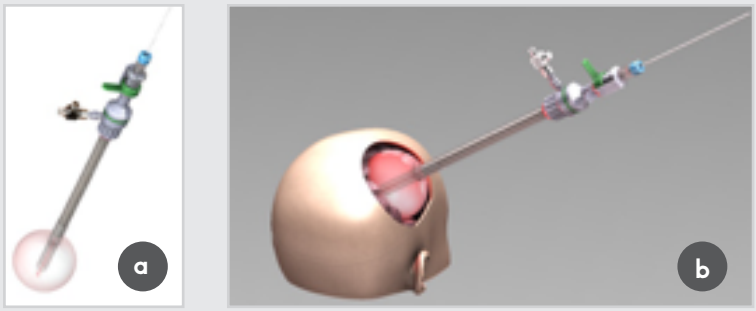
« This academic research work and the work of developing the technique beside is supported by the University of Lille, Inserm and the CHU of Lille through its Clinicians and clinical research coordination teams. »

TECHNICAL FOCUS



Photodynamic therapy (PDT) consists of administering a photosensitizer that accumulates specifically at the level of tumour cells. Once activated by laser illumination at a specific wavelength, it is possible to destroy the tumours while preserving the healthy tissue.

The device that has been created to implement the procedure has been designed such that it can be inserted in the surgical cavity during surgery to achieve an optimal diffusion of the laser light and thus treat the cells away from the cavity wall.



› 3D modeling of the light device (a) and its insertion in patient's brain (b)

Upon administration of the photosensitizer, the surgical procedure that integrates PDT proposed in the INDYGO-study is sequenced in 3 stages:

> Surgery under fluorescence-guided microscope
> Intraoperative MRI
> Installation of the illumination device and PDT-treatment

To our knowledge, not a single trial of PDT 5-ALA during surgery has been conducted to date, to treat newly diagnosed glioblastomas. Such a trial is thus an innovative perspective where 5-ALA is very promising in the literature, both in terms of efficiency and tolerance.

THE UNIT 1189 - ONCO-THAI

ONCO-THAI "Laser treatments assisted by oncology imaging" is a mixed research unit that combines Inserm, the University of Lille and the CHU of Lille, and was created in 2005. Renewed under the label UMR Inserm 1189, the laboratory is located on the campus of the university hospital of Lille. It benefits from a clinical and technical environment that is favourable to implement translational research.

ONCO-THAI develops minimally invasive treatments using a laser light. These treatments fall back on multimodality imaging during the preoperative phase (simulation, planning, etc.), intraoperative phase (surgical imaging) or post-surgery phase (follow-up, therapeutic evaluation, etc.).

The research team that is built by ONCO-THAI is a collection of researchers stemming from different specialisms. Physicians, mathematicians, computer scientists and automation engineers working closely together with the medical teams involved to develop new therapeutic solutions. Thanks to this multidisciplinary configuration, ONCO-THAI is the sponsor of several clinical studies that make it possible to evaluate the different technologies that have been developed in the lab.

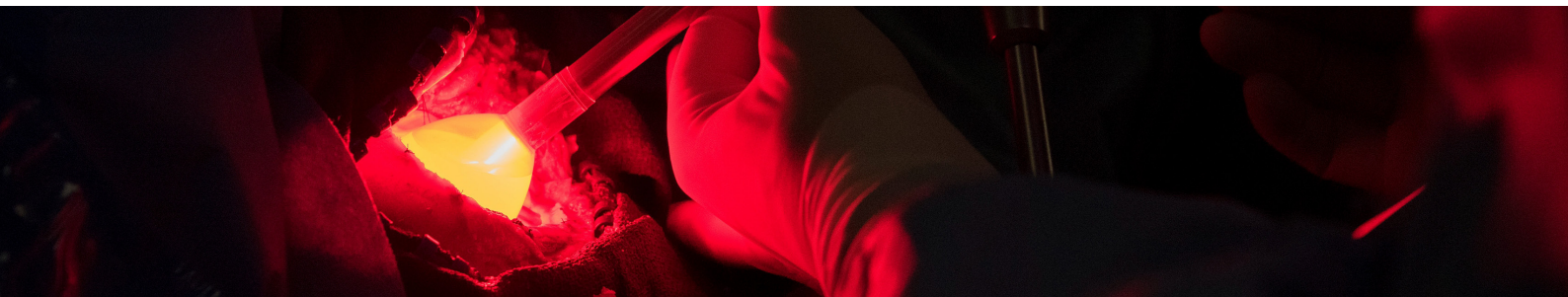
ONCO-THAI is endeavouring to manage all the processes to conduct applied and applicable research.
Its expertise goes from the development of concept proof to applications in clinics and thus involves a know-how of the original design of medical devices, the development of software to assist in treatment or the implementation and achievement of preclinical and clinical evaluations.

Today, ONCO-THAI is involved in several clinical studies resulting from its research work in urology, gynaecology, neurosurgery, dermatology or thoracic surgery and is an essential factor in several national and international partnering research projects.

http://www.onco-thai.fr

As for laser treatments for neurosurgery, ONCO-THAI coordinates a European network called SYNAPS: Synergizing Photodynamic Therapies for Neurosurgery. This network is based on a partnership between neurosurgical departments, research teams and manufacturers of health technologies. The purpose of SYNAPS is to succeed in a multi-centre and randomised clinical trial throughout Europe.

http://www.synaps-project.eu



About the CHU of Lille

The CHU of Lille appears among the largest university hospital institutions of France, forming a community of more than 16,000 professionals, the multidisciplinary expertise of which in the field of care, research and innovation is recognised on an international level. In 2016, the facility was the sponsor of more than 360 active clinical trials that included 8000 patients.

The CHU of Lille is committed to cancer research. It is a health facility that is recognised for its expertise at an early stage in the field of cancerology in adults and children with the CLIP2 Lille, for its translational research with SIRIC ONCOLille and for its capacity to innovate, for example, the creation of reference tools in public health, such as the Clinical-Biological Base FREGAT, which is dedicated to collecting clinical data of patients who have oeso-gastric cancer throughout the French territory.

www.chru-lille.fr

About the University of Lille

The ambition of the University of Lille is to be one of the largest French research universities. In partnership with large schools, national research bodies, the University Hospital Centre of Lille and the Pasteur Institute of Lille, it is developing high-level research and technological and service innovations through scientific projects, pointed technological means and partnerships with socio-economic actors (corporations, foundations, associations, communities). The University of Lille develops its projects within an international research framework especially with north-western Europe and with several partners across in the whole world.

Projects in collaboration with the CHU of Lille

In the health sector and particularly in the cancer research, a strong synergy at the university hospital site is translated by the recognition of the integrated research site on cancer, Siric OncoLille, one of 8 sites certified in France.

Panorama of the research

65 research units
3300 teacher-researchers
Member of the I-SITE University Lille Northern Europe
For more information: www.univ-lille.fr

About Inserm

Created in 1964, the national institute of health and medical research is a public institute of a scientific and technological nature that has been placed under the authority of the ministry of health and the ministry of research. Inserm, which is the only French public research entity completely dedicated to human health, has been entrusted in 2008 with the responsibility of ensuring the strategic, scientific and operational coordination of biomedical research. It not only merits this central coordinating role because of the scientific quality of its teams but also because of its capacity to ensure translation research from the lab to the bedside.

Established in Lille, the Regional Delegation of Inserm Northwest units 34 training research facilities spread out across the regions of Hauts-de-France and Normandy: 2 research centres, 25 research units, 1 team supported by the Region and by Inserm (ERI), 2 clinical investigation centres (CIC) and 2 federal research structures (SFR). The Regional Northwest Delegation has 81 Inserm researchers, 113 engineers, technicians, administrative workers of Inserm and 148 contractual agents. Eight Inserm teams of which UMR 1189 are involved in

www.inserm.fr

www.nord-ouest.inserm.fr

OncoThAI

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