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ImmuPharma

NATIONAL PRESS RELEASE I PARIS I 15 DECEMBER 2015

Treatment of lupus: Lupuzor™ enters phase III

Lupuzor™ may become the first specific and non-immunosuppressant therapy for lupus, a disabling autoimmune disease that is currently incurable. Discovered by Sylviane Muller's team in the CNRS Immunopathologie et Chimie Thérapeutique laboratory, in Strasbourg, this peptide is the subject of a CNRS patent (granted in 2009) and has already successfully completed phases I and II of its regulatory clinical trials, supervised by ImmuPharma-France. An international phase III pivotal trial[1], also managed by this company, will begin in a few days' time in the US when the first patient starts the treatment, before the trial is extended to Europe. Phase III is the last stage in the testing of a candidate drug, before it can be given market approval. The launch of phase III was the subject of a meeting involving around a hundred physicians on December 11-12, in Paris.

Lupus[2] is a chronic autoimmune disease that affects more than five million people worldwide (around 30,000 in France), 90% of whom are women. It is characterized by the production of autoantibodies that attack different organs (skin, joints, vascular system, brain, kidneys) and cause inflammation, hence the broad range of possible symptoms: skin lesions, joint pain, thromboses, psychotic episodes, etc. To alleviate this disease with many causes, only palliative treatments are available at present, most of which are non-specific: corticosteroids and immunosuppressants, but they also weaken the immune system. Although they can stop autoimmune attacks, they also render patients highly susceptible to multiple infections. It was therefore urgent to develop a more targeted therapy.

The team led by Sylviane Muller, who received the 2015 CNRS Medal of Innovation[3], developed a family of peptides (protein fragments) that can specifically correct dysfunction of the immune system[4]. One of these peptides, called P140[5], proved capable of delaying the development of lupus in affected mice, while preserving their immune systems' ability to fight infective agents. Since then, phase I and II clinical trials have been carried out[6] by the company ImmuPharma-France, which holds an exclusive license for the patents that protect this family of peptides, all owned by the CNRS or filed as joint property. During phase II trials, the disease regressed in 62% of patients after 3 months of treatment: this is the best result ever to have been achieved for this pathology.

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[1] *If it is successful, a pivotal phase III trial can lead directly to market approval. This is a special procedure that is granted for diseases where no specific therapies are available.*

[2] *In this case, systemic lupus erythematosus, also called systemic lupus. This is by far the most common type of lupus.*

[3] *To find out more. Sylviane Muller is also co-founder of the company ImmuPharma.*

[4] *More specifically, Lupuzor™ prevents autoreactive T lymphocytes from recognizing self-antigens. Because they are not stimulated, they can no longer activate the B-lymphocytes, which secrete the autoantibodies directed against the patient's organs.*

[5] *The P140 peptide corresponds to the 131-151 sequence of nuclear ribonucleoprotein U1-70K, whose residue 140 is a phosphoserine.*

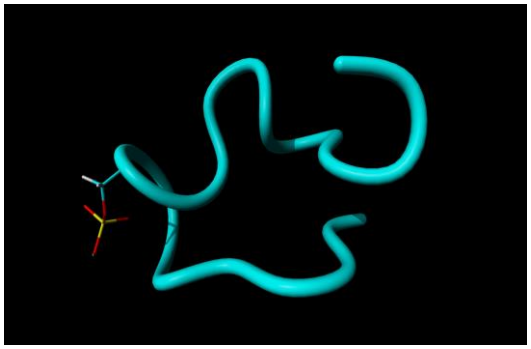
[6] *Read our previous press releases: Hope for the treatment of systemic lupus erythematosus (26 November 2008) and Lupus: peptide P140/Lupuzor™ effectiveness confirmed (21 January 2013).*

Following these successes, ImmuPharma-France launched its pivotal phase III trial. In the same way as during the phase IIb trials, the candidate drug will be administered under double-blind conditions once a month by the subcutaneous route, at a rate of 200 µg per injection, but the duration of treatment will be extended to a year, as opposed to 3 months previously. Two hundred patients will be included in this trial, spread across 45 centers (10 in the US and 35 in Europe[7]). The first patients will be recruited in the US by the end of 2015. In Europe, the trial should be starting in mid-January in the first centers, which include those in France. Recruitment should be completed by mid-2016 and the final results are anticipated at the end of 2017.

The first Investigators' Meeting for the phase III trial took place on December 11 and 12 in Paris, and involved around a hundred American and European physicians.

Once this final phase of clinical trials is completed, and provided the results confirm those of phase IIb, Lupuzor™ could be put on the market and subsequently play a central role in the treatment of patients with lupus.

According to preclinical findings, Lupuzor™ may also be effective in other chronic autoimmune pathologies, such as Sjögren's syndrome (dry eye syndrome) or Crohn's disease (an autoimmune disease that causes chronic intestinal inflammation). Fundamental studies on these promising leads are now underway in Sylviane Muller's laboratory.



Modeling of the 3D structure of the P140 peptide. *The P140 peptide corresponds to the 131-151 sequence of the nuclear ribonucleoprotein U1-70K, whose residue 140 is a phosphoserine (visible on the left).*

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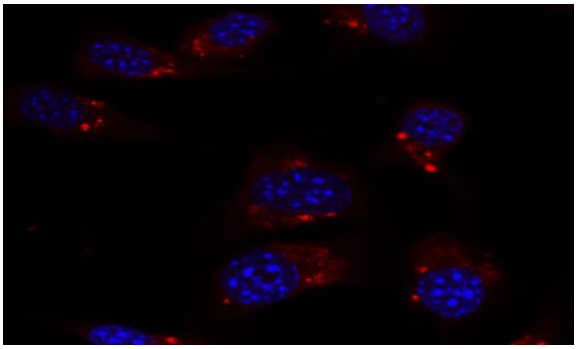

The P140 peptide acts by regulating excess autophagy of the immune cells in lupus. *It thus corrects the production of auto-antigens, and consequently, downstream of the cascade of events, the production of autoantibodies.*

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[7] *The European centers are spread across six countries: Germany, France, Hungary, Italy, Poland and the Czech Republic. The French centers are located in Bordeaux, Marseille, Paris and Strasbourg.*

For further information:
- Article in *CNRS News* : A new hope for lupus treatment
- Previous press releases:
  - Hope for the treatment of systemic lupus erythematosus (26 November 2008)
  - Lupus: peptide P140/Lupuzor™ effectiveness confirmed *(*21 January 2013)

Clinical studies are structured in several phases:

Phase I is a clinical study of toxicity in healthy volunteers.
Phase IIa involves a clinical trial in patients who are aware of the fact they are receiving the active substance (cohort of around 20 people).
The next phase (phase IIb) involves a similar comparative trial but with more patients and the introduction of a placebo arm. It is **multicenter** (the patients are recruited in several hospital centers so as to prevent any bias in the clinical trial), **randomized** (the choice of patients who will receive the active substance or the placebo is made at random and anonymously) and **"double-blind"** (patients do not know whether they are receiving the active substance or the placebo, and the person injecting the product does not know either what is being injected, so that they are not influenced).
Phase III constitutes the final, decisive and decision-making phase. A multicenter trial is carried out in an even greater number of patients under "double-blind" conditions. If upon completion the positive results are confirmed, and with the agreement of the competent authorities in each country, a drug can then be put on the market.

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