Research led by an international academic team reveals a novel pathogenic mechanism for ALS that can be therapeutically targeted by masitinib

Results published in the Journal of Clinical Investigation Insight further strengthen the body of evidence for masitinib’s mode of action in ALS

AB Science SA (NYSE Euronext – FR0010557264 – AB), a pharmaceutical company specialized in the research, development and marketing of protein kinase inhibitors (PKIs), announces the publication by an international team of researchers of a previously unknown mechanism linked to the progression of Amyotrophic Lateral Sclerosis (ALS) and that further reinforces the rationale why masitinib might be protective in ALS.

The publication, led by researchers from the Institut Pasteur de Montevideo, the University of Alabama at Birmingham (UAB), the Oregon State University (OSU) and the IMAGINE Institute of Paris, is entitled, ‘Mast cells and neutrophils mediate peripheral motor pathway degeneration in ALS’. This article and its accompanying Online Supplementary Material are freely accessible online from the peer-reviewed scientific journal JCI-Insight https://insight.jci.org/articles/view/123249.

The press release from the Authors who took part to this research is accessible online at the following address: http://pasteur.uy/en/last-news/ip-montevideo-research-discovers-immune-cells-that-attack-the-motor-system-in-the-als.

This research shows for the first time that significant infiltration of mast cells and neutrophils is found in autopsied muscle from ALS patients, indicating that these cells represent an important pathogenic mechanism for human ALS pathology. These findings in ALS patients were also shown to be in accordance with analyses from the muscles and sciatic nerves of a relevant ALS model (post-paralytic SOD1G93A rat). Moreover, it was demonstrated that masitinib can significantly downregulate mast cell and neutrophil accumulation in this model, decreasing the rate of disease progress and deterioration of motor function.

This article provides a detailed description and interpretation of these findings, which have been validated by the rigorous peer-review process necessary for acceptance. Results from this research will also be presented at the International Symposium on ALS/MND (Glasgow, UK) in December.

Together with previously published evidence in prominent peer-reviewed journals2,3, which showed that masitinib effectively co-targets independent pathological mechanisms in different cell types of the brain and spinal cord (namely, deleterious microglia and mast cells), these data further strengthen the compelling body of evidence for masitinib’s mode of action in ALS and importantly provide a link between SOD1 model-derived evidence and human ALS pathology.

Professor Olivier Hermine, Chairman of AB Science Scientific Committee, member of the French Académie des Sciences and co-author of this publication, commented: “It is noteworthy that these new preclinical data provide a link between SOD1 model-derived evidence and human ALS pathology, with corresponding data being derived from both autopsied ALS patient muscle samples and the post-paralysis ALS SOD1G93A rat model. This infers that the cell targets identified in previous masitinib preclinical studies are also implicated in human pathology of ALS. Overall, masitinib’s mechanism of action in ALS can now be considered very well-demonstrated and its potential as an effective treatment of ALS is clearer than ever.”
Key findings from the new Journal of Clinical Investigation Insight article:

- It has been demonstrated that mast cells infiltrate and degranulate into skeletal muscle of ALS patients to a significantly greater degree than is seen in control samples.
- Neutrophils infiltrate into the degenerating skeletal muscle of ALS patients and interact with mast cells and neuromuscular junctions.
- These findings in ALS patients are in accordance with analyses in muscle from SOD1\(^{G93A}\) rats, where paralysis progression is known to correlate with degranulating mast cells.
  - Neutrophil infiltration and neutrophil extracellular traps (NET) formation was observed in the extensor digitorum longus (EDL) muscle of SOD1\(^{G93A}\) rats during paralysis progression.
  - Massive mast cell and neutrophils infiltration was observed in sciatic nerve and ventral roots of SOD1\(^{G93A}\) rats during paralysis progression.
- Masitinib, administered after paralysis onset, significantly reduced mast cell and neutrophil accumulation and motor pathway degeneration.
- Preclinical data derived from human ALS patients supports relevance of past animal data to human pathology.

Reminder of key findings from previously published preclinical studies\(^2,3\) and clinical data

- Masitinib treatment significantly prolonged survival in post-paralytic SOD1\(^{G93A}\) rats.
- Disease progression in this animal model of ALS was accompanied by massive infiltration and accumulation of mast cells around degenerating motor axons and neuromuscular junctions. This correlated with paralysis progression, suggesting mast cells may be deleterious for the maintenance of functional neuromuscular junctions.
- Masitinib-induced mast cell reduction significantly reduced the rate of neuromuscular junction denervation, progression of motor deficits, and prevented morphological changes in Schwann cells and capillary networks that are typically observed in advanced paralysis.
- Immunohistochemistry data showed that masitinib treatment modulated microgliosis activity improving microgliosis and motor neuron pathology.
- In the phase 3 clinical setting, masitinib orally administered at 4.5 mg/kg/day as an add-on to riluzole demonstrated benefit in ALS patients with a baseline ALSFRS-R progression rate of <1.1 points/month.
  - Significant (p<0.05) 27% slowing of ALSFRS-R deterioration (primary endpoint)
  - Significant 29% slowing of deterioration in quality-of-life (ALSAQ-40)
  - Significant 22% slowing of deterioration in respiratory function (FVC)
  - Significant 25% delay in disease progression (survival-to-event analysis)
  - Safety was acceptable


About Amyotrophic Lateral Sclerosis
Amyotrophic lateral sclerosis is a rare degenerative disorder that results in progressive wasting and paralysis of voluntary muscles. There are approximately 50,000 people with ALS in the European Union and in the US, with more
than 16,000 new cases diagnosed each year in Europe and in the US. Almost 80% of ALS patients die within 5 years and 90% die within 10 years.

About masitinib
Masitinib is a new orally administered tyrosine kinase inhibitor that targets mast cells and macrophages, important cells for immunity, through inhibiting a limited number of kinases. Based on its unique mechanism of action, masitinib can be developed in a large number of conditions in oncology, in inflammatory diseases, and in certain diseases of the central nervous system. In oncology due to its immunotherapy effect, masitinib can have an effect on survival, alone or in combination with chemotherapy. Through its activity on mast cells and microglia and consequently the inhibition of the activation of the inflammatory process, masitinib can have an effect on the symptoms associated with some inflammatory and central nervous system diseases and the degeneration of these diseases.

About AB Science
Founded in 2001, AB Science is a pharmaceutical company specializing in the research, development and commercialization of protein kinase inhibitors (PKIs), a class of targeted proteins whose action are key in signaling pathways within cells. Our programs target only diseases with high unmet medical needs, often lethal with short term survival or rare or refractory to previous line of treatment.
AB Science has developed a proprietary portfolio of molecules and the Company’s lead compound, masitinib, has already been registered for veterinary medicine and is developed in human medicine in oncology, neurological diseases, and inflammatory diseases. The company is headquartered in Paris, France, and listed on Euronext Paris (ticker: AB).

Further information is available on AB Science’s website: [www.ab-science.com](http://www.ab-science.com).

Forward-looking Statements - AB Science
This press release contains forward-looking statements. These statements are not historical facts. These statements include projections and estimates as well as the assumptions on which they are based, statements based on projects, objectives, intentions and expectations regarding financial results, events, operations, future services, product development and their potential or future performance.

These forward-looking statements can often be identified by the words "expect", "anticipate", "believe", "intend", "estimate" or "plan" as well as other similar terms. While AB Science believes these forward-looking statements are reasonable, investors are cautioned that these forward-looking statements are subject to numerous risks and uncertainties that are difficult to predict and generally beyond the control of AB Science and which may imply that results and actual events significantly differ from those expressed, induced or anticipated in the forward-looking information and statements. These risks and uncertainties include the uncertainties related to product development of the Company which may not be successful or to the marketing authorizations granted by competent authorities or, more generally, any factors that may affect marketing capacity of the products developed by AB Science, as well as those developed or identified in the public documents filed by AB Science with the Autorité des Marchés Financiers (AMF), including those listed in the Chapter 4 "Risk Factors" of AB Science reference document filed with the AMF on November 22, 2016, under the number R. 16-078. AB Science disclaims any obligation or undertaking to update the forward-looking information and statements, subject to the applicable regulations, in particular articles 223-1 et seq. of the AMF General Regulations.

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