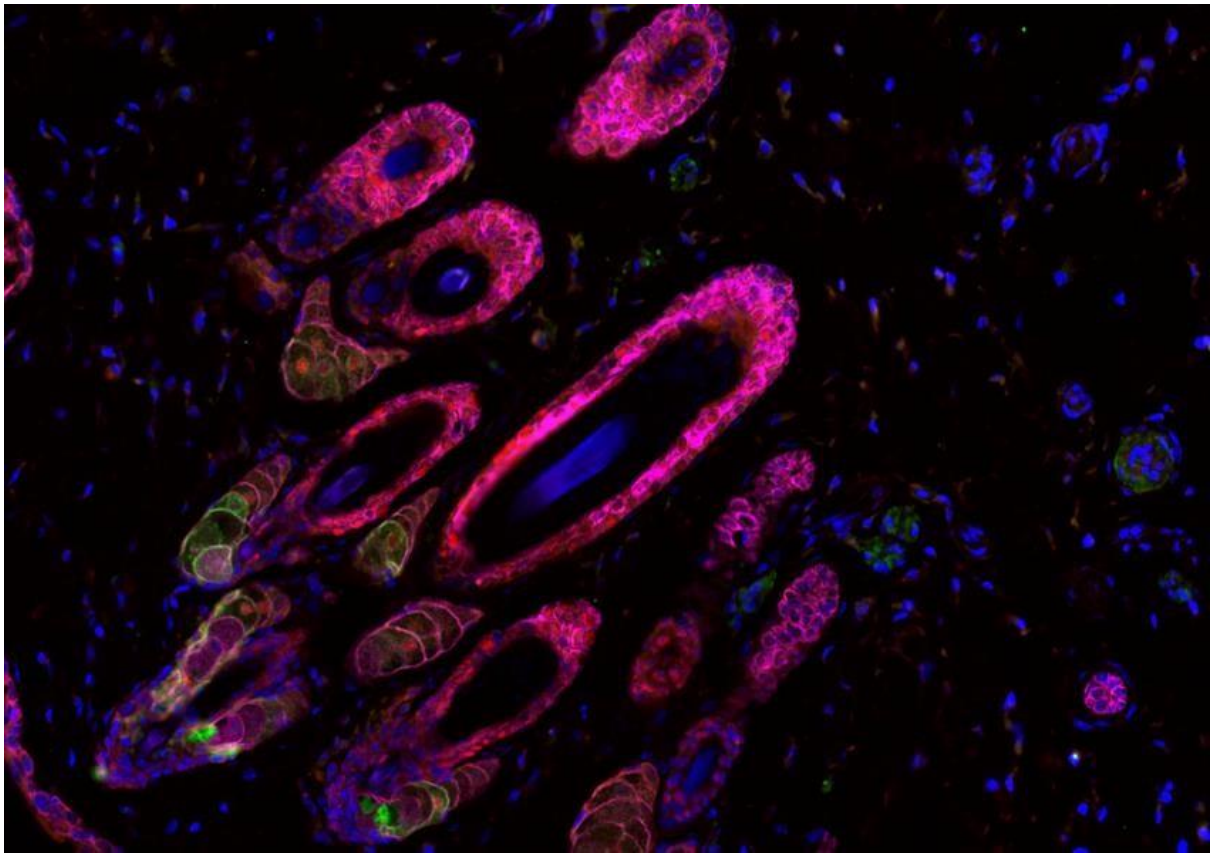
Paris, January 25, 2022

Press information

Improvement in the Health of Two Infants with Severe Disharmonious Overgrowth Syndromes



Co-labeling of mouse skin expressing a *PIK3CA* gene mutation. ©Marina Firpion/Guillaume Canaud – Inserm unit 1151

Disharmonious overgrowth syndromes are rare genetic diseases associated with a *PIK3CA* gene mutation. Since 2016, a team of researchers from Inserm, Paris Public Hospitals Group (AP-HP), Université de Paris, the Disharmonious Overgrowth and Vascular Abnormalities Unit of Institut Necker-Enfants Malades and the clinical departments of Hospices Civils of Lyon has demonstrated the therapeutic efficacy of alpelisib, a molecule used to fight certain cancers, in treating a group of children and adults with severe forms of these diseases. In a new publication, the team reports clinical, biological, and imaging improvements in two infants with severe forms of disharmonious overgrowth syndromes treated with alpelisib. These are the first data obtained on the use of this molecule in severe neonatal forms of the disease. The results of this one-year follow-up have been published in *Journal of Experimental Medicine (JEM)*.

Disharmonious overgrowth syndromes are rare genetic diseases characterized by an increase in both the size and number of cells in the body. They manifest by an asymmetry that can affect any body part or tissue (fat, vessels, muscles, bones, etc.), including the brain. In 95% of cases, the disease is linked to a mutation, occurring during embryonic development, of the *PIK3CA* gene that regulates cell growth and proliferation.

When *PIK3CA* is overactivated, the parts of the body affected by the mutation grow excessively, leading to physical deformities that are more or less debilitating depending on the number of tissues affected. While some symptoms can be alleviated by surgery and other supportive care, there is currently no approved drug treatment for the disease.

In previous research, the drug alpelisib, a PIK3CA inhibitor recently approved for the treatment of certain forms of breast cancer[1], had shown promising results – first in animal models of overgrowth syndrome, and then in a small number of adults and children. The drug is currently undergoing a series of larger-scale clinical trials, but until now there had been no data on its efficacy in infants.

In this new study, a team of researchers from Inserm, Paris Public Hospitals Group (AP-HP) and Université de Paris, coordinated by Professor Guillaume Canaud, reports encouraging results with alpelisib administered for one year to two infants – one girl and one boy aged 8 months and 9 months, respectively, at the start of treatment – presenting with a variety of severe symptoms caused by *PIK3CA* gene mutations. These symptoms included extreme blood vessel malformations, anemia, excessive asymmetric growth of the limbs and fingers and, in the boy, excessive growth of one of the brain hemispheres (hemimegaloencephaly) associated with epileptic seizures[2]. Before the start of treatment, the girl's condition was life-threatening and the boy had a serious neurological prognosis, which did not respond to conventional epilepsy drugs.

Good tolerability

In both infants, daily oral doses of 25 mg alpelisib led to rapid and significant clinical improvement in the symptoms. Twelve months of treatment stopped the boy's epileptic spasms and reduced the girl's number of vascular malformations. The considerable decrease in the volume of her right leg has enabled her to remain upright and walk, with assistance. The anemia resolved in both children following initiation of the treatment.

The infants' length and weight that initially were outside the norm for their age corrected themselves following the introduction of alpelisib. It is important to note that they had no side effects related to the treatment. Further analyses revealed that with a dose of 25 mg per day, their blood levels of alpelisib were much lower than those safely tolerated by adults[3].

"The results of the alpelisib treatment in these two infants are encouraging because they show an improvement across all parameters, whether clinical, biological, or radiological. The high level of efficacy observed may be because alpelisib was started early. The patients had no history of surgery, which is relevant because we know that the remodeling caused by it can affect how well alpelisib is absorbed by the tissues. Furthermore, it is very likely that the plasticity of the tissues at this age enables the treatment to work better, explains Professor Canaud, coordinator of the study*. These results should however be interpreted with caution and be confirmed over time and with further monitoring*," he says.

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[1] The *PIK3CA* gene is frequently mutated in a certain number of cancers. This mutation is believed to occur in approximately 40% of breast cancers.

[2] The boy had West syndrome, also known as infantile spasms, a rare form of epilepsy in infants.

[3] When treating cancer, the daily dose of alpelisib administered to an adult (between 300 and 350 mg) is approximately 15 times higher.

This use of alpelisib in overgrowth syndromes continues to be the subject of clinical trials in a population of consisting not just of adults but also of children from 6 years of age. These encouraging results make it possible to envisage extending the drug's approval to include the clinical treatment of severe neonatal forms.

The treatment of these infants with alpelisib is provided as part of a compassionate use program, in which the French medicines agency (ANSM) issues exceptional approval to treat patients suffering from diseases with a severe prognosis and with no appropriate treatment available, in a given therapeutic indication.

Sources

Treatment of two infants with PIK3CA-related overgrowth spectrum by alpelisib

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Journal of Experimental Medicine, 26 January

2022 DOI : 10.1084/jem.20212148

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