"Dr. Joutel talks about future medical trials. This hope of reaching a cure one day (and everyone is anxious for it) is what supports us. We have difficulties in imagining different stages to obtain the approval for a drug (or treatment). We hear about evaluation phases 1, 2, 3, etc. Could you tell us where we are today and what steps have already been accomplished? What steps are left to go? What are their potential durations? Can we have an idea of the process costs and how we can hope enough funding will be found?

A: (Dr. Joutel and Pr. Chabriat) The initial step, prior to phase 1, in evaluating an hypothesis of treatment strategy is to evaluate the potential drug on animals. This process includes verifying its effectiveness, defining mechanisms of action of the treatment, determining biomarkers as proof-of-concept and tools permitting to measure and monitor the effect of the tested drug. It is also necessary to evaluate the toxicity of the treatment, generally in two different animal species. For these toxicity tests, the drug must be produced in sufficiently large quantities under very controlled conditions. Such a stage would last about five years. If we would manage to pass this animal stage with antibodies testing, the clinical phase could be faster compared to other drugs because there are already a lot of data on this component. In humans, phase 1 lasts about a year and a half. We first study reactions in healthy subjects.

Phase 2’s goal is to assess dosage of the drug as well as potential tolerance and toxicity. The group of people participating in the test receives different dosages in order to identify which one is the most effective with no side effects.

Phase 3 is used to test effectiveness based on clinical criteria or markers of effect assessment e.g. MRI. These last two steps require a few years, in general, based on number of participants. For a test to have high probability of success, we must be able to prove it: we must take precautions to properly select the composition of the treatment sample, select participants at an age and stage of disease corresponding well to the target mechanism of the treatment, have identified and validated markers so that the effect can be validated and measured.

It is better not to rush in order to make sure that the strategy is good in humans. In the case of the NOTCH3 antibodies strategy currently under CADASIL evaluation, it is very important to validate its effectiveness in several mouse models, and to try developing evaluation methods.
transposable to humans, in order to minimize the risk of failure.

It is also important to understand the mechanism of action of the treatment and to have established a method to measure its impact. It will cost several million euros to arrive at a treatment. The support of an association is critical to collect donations and grants. Projects on therapeutic tools to prevent or delay effects of CADASIL disease are complemented by other research work on finding ways to care for and improve conditions of patients who are already experiencing problems related to the disease. A Chinese post-doctorate researcher has just joined Pr. Chabriat’s team in a program of cooperation between the Chinese and French Academies of Sciences, as well as thanks to a grant from ARNEVA (Association for Neuro-Vascular Research at Lariboisière Hospital). He will lead a study on blood pressure of arteries.

We will study its role in the disease and the occurrence of new small infarcts, using MRI. It might be possible to intervene early enough if we could evaluate pressure variation indexes that are associated with the occurrence of strokes. It is also important to help patients recover from a succession of strokes and improve rehab of functional state (General Assembly, France 2016)