At the AGM this year Professor Hugues Chabriat and Dr Anne Joutel chose to speak to us about the development of the RHU Project (Hospital-University Research Program).

**Professor Chabriat reminds us of the RHU framework:**

This project is financed by the “Commissariat Général à l’Investissement” (French Investment Board). The award of such funding was the result of very hard competition necessitating six months of intense work. Prof Chabriat and Dr Anne Joutel came out as prize winners for their project which officially started on February 1st 2017.

The first stage consisted in an administrative preparatory work and in involving the teams who participate in this project.

**This project is called “RHU_TRT cSVD”**

TRT stands for treatment and cSVD for “cerebral Small Vessel Diseases”. The aim of this project is to prepare ourselves, starting from targets which must be identified, for future treatments of small vessel diseases (SVD). At the moment we have at our disposal preventative treatments which work upon vascular risk factors, but we have no treatments which operate directly on the mechanisms at the origin of these illnesses located in the very heart of the small vessels walls.

**A reminder concerning the illness of CADASIL**

We are dealing with an illness which displays a huge clinical variability. At the beginning of the illness we can observe attacks of migraine with aura (in 20% – 40% of cases), followed by cerebral vascular accidents (in 68% - 85% of cases) and then, during its evolution, all the other signs: mood changes (depression in 20% of cases), a state of apathy (in 40% of cases), a general slowing down, motor troubles, problems with walking, and cognitive troubles. The huge variability from one patient to another, even within the same family, is a major feature of the illness. Understanding this clinical variability is an important aspect of the research.

CADASIL is an extraordinary model for studying the small vessels illnesses because we have at our disposal a genetic marker, and we can observe all the stages of the illness. What is more, thanks to the participation of the cohort members who are followed by the CERVCO department at Lariboisière Hospital, people can be followed over time, which is also extremely important in trying to understand the mechanisms of the illness. This is much more difficult for all the other more frequent small vessels diseases, which are much more heterogenous with very different evolutions, and for which we do not have a marker as we have in the case of CADASIL.

**The RHU Project: four major objectives.**

1) **To identify the targets for future treatments:**

By discovering new genes which will add to those we know of already, and which will allow us to better understand all the genes involved in the small vessels diseases, i.e. in abnormalities of the vessels walls functioning. The objective is also to determine, thanks to the animal models, the targets where we will be able to intervene with treatments. We need to understand the mechanisms which cause lesions to accumulate in the small vessels walls and in brain tissue and to be able to intervene in the course of the illness. The discovery of new genes can be made thanks to the patients’ families. The choice of targets is made using animal models (mice).
2) To have at our disposal new tools to evaluate the effect of future medicines: the objective is to evaluate the potential treatments on the smallest possible group of people and in the shortest possible time. At the moment, this evaluation requires a period of two to three years. The objective is to use imagery and new tools for clinical evaluation for this purpose.

3) To improve the way of taking care of patients who already have signs of developing deficiencies or actual symptoms: innovations in this domain with new methods of re-education will be possible.

4) To work with a team of sociologists from the Ecole des Mines: the objective of this team is to understand how to continue to work together with complete confidence and with respect for the people concerned (those who are ill and their families) during the duration of the research which aims at reaching a treatment.

This ambitious project includes seven “work packages”: they represent seven “strands” of study to be carried out. The financial provision amounts to eight million euros over five years.

We have a number of different partners, 25 in total, amongst whom are: “Assistance Publique”, the Paris Hospitals (neurology department at Lariboisière, represented by Prof Chabriat, 3 departments of physical medicine and re-education, the genetics and ophthalmology teams and a medical ethics specialist); 4 departments from INSERM; the “Mines ParisTech” (Sociology team); the University Hospital of Montpellier (for a study of the new technologies costs); the University of Picardy (an expert in quantification in neuropsychology and normative data): the Atomic Energy Board; the “Institut Supérieur d’Electronique de Paris”; Telecom ParisTech (for the retina images); 3 private businesses (Genious, ImaginEyes, Medpace). All this is managed by the Paris V delegation of INSERM which centralises all the expenditure and the recruitments which have been made. This follow-up is very complex.

Due to the involvement of so many partners, the project should result in a breakthrough in this field of research, with innovations. The management of such a large number of partners is one of its difficulties. The team is “in the limelight” because a big budget has been allocated, and results are expected. Annual evaluations have been set up and the first report must be handed in soon. The regulatory and ethical aspects must be followed scrupulously. We have a consortium agreement which has taken several months of work: it was necessary for everyone to agree on who should benefit in terms of subsequent revenue and potential discoveries; “Inserm Transfert”, the private branch of INSERM, has prepared this agreement. We also have to manage the administrative aspects.

Our assets: we are surrounded by very motivated collaborators who are all working in complementary areas. The interaction between these different partners is a crucial aspect of the project: the different teams will share their knowledge which will enrich their skills.

We have pre-clinical teams (from animal to man) and their work with Dr Anne Joutel is to link the research together in order to gradually allow its application to pass from animal to man.

Another considerable asset is the fact of having a cohort of patients; this link does not exist as strongly anywhere else in the world.

We also benefit from the expertise of INSERM for its administrative and legal support.

There are two of us coordinating the RHU project, Dr Anne Joutel and myself, because there are both pre-clinical and clinical aspects. We are present at meetings in both areas in order to exchange ideas and make links between them. The project manager is Nathalie Gastellier. Our role is to be the driving force behind the RHU and to follow the project as it runs its course.
We also have a “scientific advisory board” which is made up of foreign specialists who will soon meet together. Amongst them are: José Ferro, from Lisbon, Portugal, a Professor of Neurology who has been working for a long time with Marie-Germaine Bousser; Miikka Vikkula who is Professor of Genetics in Louvain, Belgium; Reinhold Schmidt, Professor of Neurology at Graz, Austria, who has a good knowledge of diseases of the small vessels; Edith Hamel, Professor of Neurosciences at Montreal in Canada, who is knowledgeable about animal models as well as the physiology and physiopathology of cerebro-vascular diseases. We have to be accountable to them and they will tell us if there are things to review in the course of our work.

We also have a strategic committee, a steering committee, committees to give us access to data, and a general assembly; all of which generates a considerable work load.

In the near future, we will have a website for the RHU which will coordinate all the researchers’ activities, with a space reserved for the RHU partners, and a public section with a specific logo to which you will have access. And if you like, we will create a link between the CADASIL France website and that of the RHU, because you are so completely involved in this study.

We have already had a “kick-off meeting” for launching the project with the 25 teams; there were about 60 of us, who presented the overall project. We also have regular meetings with groups of teams who are focusing their work around different areas.

**Dr Anne Joutel presents the pre-clinical work**

In terms of pre-clinical work, things are progressing in quite an important way at the current time: there is this huge RHU network and there are around it other international networks with two Leducq transatlantic ones and at the European level a H2O2O network. These networks do not work in separate silos because there is a lot of overlap amongst the researchers. Dr Joutel herself is part of these three networks. Globally, in terms of pre-clinical studies there are more and more huge teams at an international level who are starting work on CADASIL. It is on the one hand a very good thing. But on the other hand it puts a huge amount of pressure on us for keeping our international status, getting contracts and being able to find the finance to keep the teams functioning. Amongst other things we have to pay the salaries of the researchers (all the post-doctoral researchers in the laboratory are financed by outside contracts; there is no more funding for such contracts from either the University or INSERM). It is the same rule for everybody. On the one hand, it is important to be able to work with other teams in order to maximize what we have learnt. But on the other hand there is also some competition between teams in order to find funding.

About two or three years ago we progressed to a superior level in world research in networks terms. Recently for example the British Government has freed up an enormous amount of money for research into dementias and diseases of the small vessels. As a consequence, teams in England are beginning to be built. They unite clinicians and researchers who are working on animal models, in the context of research on the small vessels diseases. Dr Joutel was invited to join this network. This is important, because it allows us to collaborate and to explore this illness in a way we would not be able to at our level alone. There are some investigations which have been completed abroad on mice which have received CADASIL characteristics. We might perhaps have done these by ourselves, but we did not have the know-how. In summary, all this can only help our knowledge of the disease.

**Professor Chabriat’s comments:**

Sometimes there is a lot of money for research, but our particular strength is the link we have with the patients. The Association and the cohort of patients are really unique. We began following the patients in 2003, we are now in 2018 and we have an overview of 15 years in our follow-up of certain patients. This database is extremely valuable.
Dr. Anne Joutel’s comments:

The second strength we have is our understanding of the illness from a clinical point of view. Both of us interact enormously, and because I am a trained clinician (I am a neurologist) I have followed the illness from the beginning. We are trying to find therapies which will work in human beings. Our collaboration allows us the hope of reaching solid results and to avoid raising false hopes.

There are three work groups involved in pre-clinical studies.

1) First Group: its scope is the identification of new genes in SVD (small vessels diseases).

Why? CADASIL is an excellent model of SVD but one of the most severe types in the sense that it is sufficient to have the mutation in the gene for developing the symptoms, even if these are variable. Because of that we were able to identify large families as there was little interference from other factors or environmental influences. At present we have identified the most severe forms of SVD from these big families. But they only represents 20% of the forms called “familial”. Therefore, it means that there are still other genes to identify, and these are in all likelihood responsible for less severe forms, in the sense that there will be more variability within families. These smaller families will provide less information. The fact that these genes are not identified is a source of diagnosis wandering for the families carrying them and a source of difficulty. However, the identification of these genes will also allow us to make progress in our knowledge of CADASIL. In particular, it will permit us to show common targets between other brain small vessels diseases and CADASIL, and to prioritize the already identified targets of CADASIL. Professor Elisabeth Tournier Lasserve is therefore in charge of this programme for the identification of these genes, working with another laboratory in Brest. The goal is to try to identify the genes responsible for these family forms of the disease; twelve families have been selected for this study (there are no longer very large families like those at the beginning of the CADASIL research). Sequencing approaches are going to be used: sequencing of the genome has become much less expensive and much quicker; it has been outsourced and is no longer done in laboratories. The DNA is sent to private companies who do the sequencing of all the information-bearing parts of the genome which are called exons. We need then to find a solution for the bio-information analysis, and that is why there is an association with the Brest laboratory, which has the expertise in that area. In order to know the genetic variation responsible for the illness, it is necessary to apply the analysis strategies that are called “bio-information technology” and certain laboratories make it their speciality and their business.

This RHU Programme runs for five years and has substantial funding; we can therefore set ourselves ambitious objectives regarding the knowledge and understanding of the genes involved in SVD.

2) Second Group: its scope is too work on the Notch3 protein and to look for a therapeutic approach.

The first task in this area of work concerns the Notch3 protein: the illness is caused by a mutation in the Notch3 gene which codes for the Notch3 protein, which is a receptor. This receptor, this protein, builds up in the vessels and this abnormal accumulation can be revealed by three different techniques. You all know about GOM. Many of you have had a skin biopsy which has been examined under an electronic microscope. Under these conditions a small round lump can be seen. It is not Notch3 which is seen, but a small round lump which contains Notch3, with some characteristics that one sees under electronic microscopy.

When we apply fluorescent microscopy to vessels which have been “tagged” with an antibody against Notch3 protein, we can see the Notch3 protein which makes small characteristic round lumps.
The third technique uses the brain itself from which proteins from the cerebral vessels are extracted and analysed on a gel where we can see the accumulation of Notch3. Notch3 is therefore the central problem we have to study. The question to be resolved is to determine which type or types of Notch3 are toxic for the vessel and responsible for the illness. In order to work on this, a research engineer has been recruited. He is an expert in biochemistry. One of the difficulties in this RHU project is to recruit competent personnel because we are using techniques which are more and more complicated. We need specialist expertise which is difficult to find. We are using CADASIL mouse models which are different to those I spoke about last year. In these mice we are analysing, in parallel, on the one hand, the accumulation of Notch3 using the above-mentioned techniques, as well as more sophisticated methods, and on the other hand, the symptoms of the illness in order to identify the abnormal types of Notch3 where the quantity increases with age and the aggravation of symptoms. Then, we are going to purify these different types of Notch3 and to test their toxicity on the cerebral vessels in collaboration with colleagues from an INSERM laboratory in Caen. For that process we will be using sophisticated technologies which require much expertise and very expensive equipment, some of which costs about 400,000 euros.

The second task in this area of work concerns the use of the anti-Notch3 antibody which we have generated for therapeutic purposes. This work is based on our knowledge of other neurological illnesses where there is an abnormal accumulation of proteins, and on the preliminary results of our team which suggest a beneficial effect of an anti-Notch3 antibody on the vascular abnormalities of a CADASIL mouse. What we want to do by the end is to get underway a clinical trial which we think has a good chance of working.

What happened in the case of Alzheimer's disease has made us reflect a lot: the first publication which showed in the case of mice that there was a beneficial effect from an Alzheimer's disease antibody was published in 1998. The first clinical trials in human being took place one or two years later. What had positive result in mice was transposed to man, supposing that it would work in the same way. This was a mistake. So, we are trying to prepare ourselves better, because it is a big thing to launch ourselves into a clinical trial; it mobilises a lot of patients, a lot of energy, and during this time there will be no other clinical trials. So, we must be very sure that there is a large chance that it will work. With Alzheimer's disease, they moved on from mice to humans in a few months, starting by treating severely ill patients, and then the less severely ill ones. They are beginning now to treat families at an earlier stage. We tell ourselves that we will learn from what happened with Alzheimer's disease so as to try not to reproduce these mistakes. It is an important decision to launch a clinical trial. We do not want to raise false hopes; we want to try to set out a treatment which has a big chance of working. That is why there are numerous stages to go through before testing an antibody in man, and why it is equally important to develop markers showing the efficacy of this antibody. The whole of this second task is very much in line with the first. It is in fact very important to understand what effect the antibody has on the different types of Notch3.

The third task in this area of work is aimed at identifying new therapeutic targets, something different from the Notch3 protein itself. In the first instance, that means characterizing the abnormalities of other proteins found in the cerebral vessels. In order to do that, we will use techniques of mass spectrometry in the vessels of CADASIL mice. This work will be done by a post-graduate research student who has helped us in developing new methods of protein analysis.
3) **The Third Group:** its scope is to have a better understanding of the cerebral vessels dysfunction during the illness, and to identify the mechanisms of cerebral strokes in CADASIL

The *first task* consists in perfecting a new technique which will allow us to picture how the cerebral vessels of mice work throughout the whole brain, including the deep regions. This technique, developed by a French physician called Mickael Tanter, uses extremely rapid ultrasound. It will allow us to capture the images in a very rapid sequence (every millisecond) and to have access to everything that is happening inside the brain, including in the deepest regions which are affected in CADASIL.

The *second task* aims at studying the ongoing progression of the abnormalities of the cerebral vessels in the CADASIL mouse, by using this new technique.

The *third task* is: (a) trying to understand why strokes happen when one is suffering from CADASIL. We will be working together in this area with a French laboratory which specializes in coagulation, and we will be testing new hypotheses. (b) (this was not initially in the RHU programme) aims at a better understanding of the mechanisms of lesions in the white matter. The first stage focuses at better understanding the lesions characteristics at a very early stage of the illness in the CADASIL mouse model. To do this, we will use a quite new technique of electron microscopy in which the samples are frozen at very high pressure in order to better preserve the structure of the myelin sheaths.

**Professor Chabriat adds more about clinical matters**

When testing a new medicine on a patient, we have, at the moment, to wait a minimum of two years in order to evaluate its efficacy. We are going to try to shorten this period of time. CADASIL is an illness of the small vessels; these are found in the brain, which is in the cranium, and so we cannot see them directly. When we do an arteriography, an angiography, or when we inject a product in order to see the vessels, we see the big ones, but we do not see the small vessels. The retina, which is a continuation of the nerve tissue, can be considered as a “window” onto the brain. Thanks to the new technology of adaptive optics used in astronomy for telescopes and developed by French engineers, we can nowadays see the back of the retina with a resolution of 300 microns, which allows us to examine the very small vessels of the retina which are 50 microns in diameter. We are associated with the Imagine Eyes company, the “Institut Supérieur d’Optique”, the “Institut d’Electronique”, the research teams of Quinze-Vingts hospital, and with the Institute of Vision, in order to find new markers which could be used if in future we test a new medicine.

Professor Chabriat displays and comments on different images which have been obtained thanks to this technique.

This equipment, costing 220,000 euros, has been installed in the ophthalmology department of Lariboisière Hospital, thanks to funding from Neurodon. We have 25 patients who have had images of their retina vessels. The intention is that, from now on, all patients who come for their follow up in the CERVCO department at Lariboisiere hospital systematically have images of their retina taken. The purpose is to gather information in preparation for future therapeutic trials.

Another way of gathering information is to study how neurovascular coupling works; some of you have participated in this study. We are looking at how the cerebral blood flow varies in the areas responsible for movement and vision when the subject, equipped with a small EEG (Electro Encephalogram) helmet and during an MRI scan, is shown a black and white chessboard. The subject must close and open his hand each time he sees the chessboard. For this study there is a very complex chain of information processing, which is a specific area of research in the RHU. We are comparing the variations in the cerebral blood flow in the areas responsible for both sight and
movement in the patients and in a control group. A short visual stimulus of 20 seconds does not reveal any difference between the patients and the control group. A longer stimulus of 40 seconds shows a small disconnection which appears after 15 seconds whilst there is no difference in the level of electrical recordings between the patients and the control group. Two different studies have shown the same results. We have managed thus to detect subtle abnormalities in the way the vessels are working in the patients, during a non-traumatic test. The question is knowing whether this marker could be used in a therapeutic study.

Another possible marker is now to study the structure of the brain and to do this by using the movements of water with diffusion imagery. Water is permanently moving within the cerebral tissue. It is the membranes (of the cells, the axons and the myelin) which hinder this movement. These constraints can be measured using different procedures during an MRI scan. We can use sophisticated sequencing to measure the movements of water molecules in the tissues both three dimensionally and at different times. We therefore can have a more precise idea of what is hampering the movements of water in real time. These are complex techniques based on mathematical calculations which have been developed by Cyril Poupon’s team from the CEA, Central commission for Nuclear Energy, with the aim of getting new measurements.

The use of clinical scales to assess the evolution of patients over time. These tests which are presently used in the context of SVDs are the same tests used in Alzheimer’s disease or after a stroke. But they do not take into consideration certain symptoms specific to small vessels diseases. The present scales are not particularly suited to very moderate symptoms, detected in a clinical examination (i.e. a slowing down, troubles with balance). If we use medication alongside crude scales which are not adapted to clinical study, we will not be able to measure their effect. We would like to detect quickly, and with the smallest sample possible, subtle effects in the next clinical trials. A colleague who is a specialist in developing scales, who is both doctor and mathematician, is working with us to identify the most useful information, linked to the patients’ quality of life, with the objective of constructing a new scale of measurements. We will need your participation to develop these new tools; we will have at our disposal a first version of the scale to test, and we will evaluate whether, over time, it is sensitive to the changes noticed by the patients, and how it is linked to their quality of life.

Another project is to use all the clinical data that we have accumulated over time to construct a statistical predictive model about the risks of the illness evolution. It is a prediction which will permanently feed off with new data, in order to make available a very precise predictive tool, which will be used to select very small groups to test out therapeutic hypotheses and to evaluate their possible effect on the course of the illness.

We are today in the age of the internet and long-distance communication. It is therefore necessary to find new approaches. We can thus consider some evaluations at a distance, remote examinations (tele-medicine), and perhaps even re-education at a distance. We are associated with the Genious group, which is developing games which allow an evaluation and rehabilitation of cognitive functions. Our patients have troubles with focusing their attention, with the speed of processing information, with their mental agility and with difficulties of memory, of slowing down and of tiredness, problems with walking, with their balance and with behavioural problems (apathy). We hope to be able to measure these disturbances with these new tools. For this work we have joined up with physiotherapists’ teams: the team of Prof Yelnik who is a specialist in problems of balance, those of Professors Pradat-Diehl and Azouvi, specialists in cognitive re-education, and that of Prof Godefroy, who is a specialist in cognitive tests and who is developing tests and norms. One of the problems is the absence of knowledge about the values for normal people, the effect of age and the impact of sport on their performances.

The project is trying to create games for the patients in order to evaluate and improve them clinically, and to produce norms. We hope to develop re-education through play, at a distance and over time, and to be able to let the patients themselves test out these games. The idea is to create
an internet platform which will allow patients to test themselves and to use it for re-education purposes.

Here are the links to the websites which allow access to examples of these games:

https://www.youtube.com/watch?v=JXVREkhDfoY

https://www.curapy.com/

We will perhaps be able in the future to imagine remote re-education. Like in the pharmaceutical industry, those selling the products and those evaluating them must be independent from each other.

A small precision however: those who sell these tools say that the process of evaluation for the games is identical to the medicines evaluation, which is not the case. Unlike these games, a medicine cannot be commercialised unless it has proved its efficacy. Are these games to be considered as medical devices or as games? The intention is that they should be evaluated as medical devices and prescribed by doctors. The question of standardised norms is also very complex. The “challenge” is to leave the recreational industrial sector moving towards the evaluated and solid therapeutic domain.

Annie Kurtz: “the current presentation of these sites is not respectful towards the patients: we must put a lot of thought into this”.

Prof Chabriat: There is a certain amount of necessary advertisement in this presentation, to show that tools will be made available and that a platform is going to be created on which these tools will be developed. And in parallel with this, there must be all the preparatory work with the authorities.

What we are doing today, with the speech therapist or the neuro-psychologist in a re-education department will perhaps be done tomorrow remotely, but with tools which will have been tested by professionals, and evaluated and validated by the authorities. The remote evaluation of patients is of great interest. We are trying to develop tools that can be used at a distance with the neuro-psychologists of Lariboisière and Amiens hospitals.

A sociology team has joined the RHU Project. The objective is to better understand what you expect for from the researchers, to evaluate how we are working together, and, in conjunction with the CADASIL France association, to think about the ethical problems of diagnosis in the context of research.

Madeleine Akrich (sociologist): “Last year we were presented to you during CADASIL France general assembly and some of you were present. On the one hand, we are working to put together a bibliography of the research into what has been said on similar cases. On the other hand, we are working by having discussions with the people concerned by CADASIL. We have begun the interviews and we have met up with five people who replied to us after an article was posted in the Association’s newsletter. There are two additional people who have contacted us, whom we have not been able to meet yet. We must meet up with a larger number of people. These are not interviews by questionnaire. We are asking you to tell us about your experience of this illness, and that of your family, and how you were led at certain times to take certain decisions; for example, whether or not to get a diagnosis; why at that very moment and not another, what was the impact of the diagnosis, and what it is like to live every day with this illness? All these research programmes are in the process of changing the configuration of decisions around getting a diagnosis. If we project ourselves forward a few years from now, and we imagine we will have then managed implementing certain treatments which could be used even before any symptoms appears, that would put a different aspect on the question of getting a diagnosis.

The length of the interview depends on you. Up to now, no interview has lasted less than two hours. It is the interviewees who have decided how long it should be. It is a time when people
reflect about their illness with somebody who is not directly implicated (a doctor or someone in the family…) and who is there to listen as attentively as possible; it is a time for discussing in detail what they think about what has happened. We not only meet up with people who actually have the illness, but also those within their close family who might themselves have been affected but who in fact didn’t inherit from the defective Notch3 gene, or also people close to those affected (parents, husbands and wives), because we realize that it is an illness which has a very big effect on all those around them. The encounters remain anonymous. We will also meet up with researchers, clinicians, and people who work in the laboratories”.

A reminder of her details: madeleine.akrich@mines-paritech.fr

Prof Chabriat: in order to do all these clinical studies, we definitely need the participation of your Association, of patients suffering from CADASIL and of people prepared to be in control groups (individuals who do not have any disease of the cerebral small vessels). We have several studies and we will recruit various sub-groups according to the different studies. Jocelyne Ruffié and Abbas Taleb have put a lot of work into updating details of the cohort of patients; at the moment we have 376 persons identified on our database. For some studies we will use for example large cohorts of 150 patients, and, for others, small groups of 25 or 30. In parallel, we will also need other patients who have had strokes but who do not have CADASIL. So, we really need all those who wish to take part, patients, families, in order to contribute to into this project. It is essential for the future development of treatments for these illnesses.

For the RHU project, we need definitely the help of the CADASIL France association!

Catherine Surjous, President of the CADASIL France association:

“We have decided to try and support you more. This morning we decided during our general assembly to increase our research subsidy to you from 15,000 euros (last year) to the sum of 18,000 (this year), and we hope to reach 20,000 euros for our 20th anniversary next year”.

Professor Chabriat: this sum will also allow us to partially pay for Abbas Taleb’s post which I am trying to defend because the part-time hospital position of this clinical research assistant is regularly under threat. The situation at the hospital is difficult at the moment. It recently led to a renewed reduction of resources. All this work has only been possible because we have a database which is managed by our clinical research assistant, whose role is essential. All this would not have been possible without your precious help.

Thank you from the bottom of my heart.
Questions and Answers

Q: "An American and a French researchers have set up a biological process to interchange within a strand of DNA a gene with another. This technique, known as CRISPR-cas9, raises many ethical challenges, particularly in France. I wonder if some researchers, in countries where ethical rules are less restrictive than in France and where this type of method would be authorized for therapeutic purposes, had not considered, even only intellectually, replacing the defective Notch3 gene with a healthy gene. Is it biology-fiction or a real future possibility?"

A: (Prof. Chabriat and Dr. Joutel) "This gene modification technique is limited to laboratory animals in order to produce a mutation. It makes it possible to obtain a mouse model more quickly than via genetic crossover. Its application at the human level is absolutely not being considered. In France, the use of human cells is strictly regulated and bioethical laws do not allow such experiments. This topic raises ethical questions comparable to those of cloning."

Q: "When a person is a non-symptomatic patient (or at the very onset stage of the illness), which procedures must be followed in terms of access to health care when one does not live in France? What facilities or services must be available quickly? Which foreign services could be requested for a repatriation to France?"

A: (Mrs. Morel, social services assistant at CERVCO) "If the question is about patients’ rights to care benefits when the person is not in France, the answer varies depending on whether one is a French citizen entitled to rights to the Health Insurance Program in France or who is the holder of a valid French residence permit, or not.

For a French citizen or beneficiary of a valid French residence permit:
- If the person is on holiday abroad, one can request repatriation via his/her travel insurance (if he/she subscribes to one) and get then normal care provided by the health insurance program under which he/she was covered before the trip.
- If the person is working abroad, one may be covered (via individual contribution or employer-funded contribution) by the public insurance fund for French citizens abroad or by private insurances (depending on the country of residence). They would be responsible for the initial charges and perhaps could ask for a repatriation, subject to prior agreement with the French National Health Insurance program. After returning in France, the person’s entitlements to the French Health Insurance will have to be re-opened, subject to conditions of conformity status and length of stay.

For a person whose nationality is outside the European Union and without a valid French residence permit (or of EU nationality but having not worked and contributed in France), there is no coverage under common law, applicable either to "Repatriation" or care in the country. This person might benefit, under certain conditions and after several months, from care by the public Medical Assistance, which will in any case not entitle him/her to get either a residence permit or access to subsidies, allowances, or path to normalization"

For more specific information concerning a particular case, please find the CERVCO details on its website under the “Consultations - Contacts” heading. (https://www.cervco.fr/en/content/consultation)

Q: "Is there a detailed list (in French and English) of medications to avoid when carrying the CADASIL mutated gene?"

A: (Prof. Chabriat) Recap of answers given in 2017: "Some medications are not advised, especially those contracting the vessels. For example, some anti-migraine drugs like Triptans are vasoconstrictors. So, in principle, because blood circulation is presumably precarious in the brain, we try to protect the patient and avoid these drugs. This is also the case for nasal drops that contain vaso-constrictors. There are no absolute contraindications for other drugs."

Further information can be found on the HAS -High Authority for Health (www.has-sante.fr)- website, by searching the “PNDS CADASIL” term. This National Protocol for Diagnosis and Care (PNDS) document provides detailed guidelines and information on care that may be prescribed. Information on the disease is also available on the CERVCO website (https://www.cervco.fr)
A: (Prof. Chabriat) "It has not been observed that pregnancy is a triggering factor for symptoms or worsening of the disease. On the other hand, it has been observed that after the birth, during the postpartum period, some women may experience severe migraine attacks with aura. For young women, migraine attacks can be the first symptom that leads to diagnosis.

A more precise study could be the subject of a scientific research and for example a thesis based on a posteriori interviewing of women patients which are part of the group followed by CERVCO, on particular events during their past pregnancies or as a result of childbirths."

Q: "Can you explain to me in detail the risks involved in general anesthesia for a surgical operation I have to undergo and for anesthesia in the case of a tooth extraction?"

A: (Prof. Chabriat) "There is no particular risk, except at the time of induction because the onset of anesthesia can cause a decrease in blood pressure. For a person with CADASIL who has a reduced blood flow and a decreased flow rate, this decrease should be monitored because it can induce an event. It is recommended that you inform the anesthesiologist of the disease so the doctor will monitor changes in blood pressure before, during and at the end of the anesthesia period".

Recap of answer given at the 2017 GA: "There is no contraindication to general anesthesia. The only recommendation is the control of blood pressure during anesthesia. People diagnosed with CADASIL can show their patient card to the doctor (card available from CERVCO and the Association). In this document, it is explained that small vessels that provide the perfusion in the brain are fragile, that blood irrigation is perhaps less optimal and that we must pay more attention to the blood pressure. This is a precautionary measure that all anesthetists are familiar with but it needs to be monitored even more closely."

Q: "Pregnancy: Are there any proven risks for the mother if she has CADASIL disease? Do we know if pregnancy has the potential to accelerate the symptoms of the disease? Are there any special precautions that must be taken daily during pregnancy and at the time of delivery? Should the patient get a more regular and/or specific medical monitoring during pregnancy?"

A: (Prof. Chabriat) "It is not possible to give an answer to this question because there has never been any study or therapeutic trial carried out with this substance."

Q: "I have been taking Kardegic (Aspirin) 160 mg for six years. Does this dosage present a risk to hemorrhage in the long run or does it have other health implications? Meanwhile, the neurologist lowered my dosage to 75 mg. But the disease had a recurrence. He decided again to prescribe me back at 160 mg. Does it make sense?"

A: (Prof. Bousser) "It is the benefit/ risk ratio of the dosage which matters. If the doctor thinks there is a benefit to prescribing aspirin in order to avoid an ischemic stroke or a clogged artery, the prescription is justified.

The risk of cerebral hemorrhage due to aspirin is very low and is not dosage-related. Aspirin is a blood thinner. It is therefore justified after an ischemic accident. After such an event, it is especially necessary to prescribe the right dosage to prevent an artery from becoming clogged. It is not advised to go below 75 mg. The important thing is to prevent the arteries from clogging up. A higher dose does not increase the risk of bleeding, but it can cause stomach aches."

Q: "Can Ginkgo Biloba supplement improve blood circulation in the brain?"

A: (Prof. Chabriat) "It is not possible to give an answer to this question because there has never been any study or therapeutic trial carried out with this substance."

Q: "I have lost a lot of weight, 10 kg, since last summer and I am very weak. My primary physician says that genetic diseases make you lose weight. Is it true? And does CADASIL cause depression?"

A: (Prof. Chabriat) "It is wrong to say that genetic diseases make you lose weight. With regard to depression, indeed all diseases of small vessels responsible for lesions of the white matter double the risk of depression. These lesions are a factor leading to depression, regardless of other symptoms. They can disrupt connections. They are not the direct cause of depression but they make people more fragile and sensitive. This symptom was observed during follow-up visits at CERVCO. A specific medical care must be provided to patients presenting it."
Q: "Have you noticed a narrowing effect of the capillaries following the disease?"

A: (Dr. Anne Joutel) "Capillaries, like other brain vessels, are the site of deposits of Notch3 and GOM. There is research currently being done on the possible existence of morphological or functional abnormalities of these capillaries."

Q: "Have stem cell research been successful?"

A: (Dr. Joutel) "Eight patients at CERVO underwent a skin biopsy from which fibroblasts were prepared and sent to a partner lab in England who deprogrammed them into stem cells and then reprogrammed them into smooth vascular muscle cells. A post-doctoral student working in Dr. Joutel’s laboratory has been studying whether these cells reproduced abnormalities such as the accumulation of Notch3 protein. Under basic conditions, the results are inconclusive and we did not observe any accumulation of Notch3 protein. This study has been put on hold, but it is not a failure because it allows us to understand that a cell containing a Notch3 receptor with a CADASIL mutation is not a sufficient condition to develop the deposits. New questions arise. In addition to identifying different toxic species of Notch3, we must also understand the mechanism of this accumulation. The single expression of the receptor with a Notch3 mutation is not enough. Intervention of other elements remains to be identified. These questions are the subject of ongoing research works. We are testing new ideas and hypotheses, thanks in particular to new techniques developed over the last year. Among the technological improvements, MRIs of thick brain slices have been developed in order to visualize the vascular network in three dimensions. This requires time, resources and staff. But postdoctoral research work contracts in France have a maximum five years duration, while projects require expertise and skills in specific technology. The research team regularly loses members, and must constantly recruit and train new ones.”

Q: "Are the results of 7-Tesla MRI study being taken into account in current and future projects?"

A: (Prof. Chabriat) "This study led by Professor Eric Jouvent has deepened our knowledge of the disease. This technology has resulted in two important results: - Very small infarcts, not visible with other techniques, have been found in the cerebral cortex of patients. - It is possible to better identify different categories of white matter lesions. Some are associated with small infarcts and others are mostly associated with spaces around small vessels. This sophisticated technology is a tool for understanding and differentiating CADASIL with other diseases. It can decrypt the lesions but it is not adapted to produce a marker to assess the evolution of the disease in the brain or to measure the effectiveness of a future therapeutic trial. The standard 3-Tesla MRI is easier to use and is more widespread. The 7-Tesla equipment is very rare, it is technically complex to carry out examinations and patients must absolutely not move. It is mainly a tool in the research field to study characteristics of lesions with resolutions that it is not possible to obtain with other equipment. Thanks to another funding, a 7-Tesla MRI study will be conducted in order to compare several small vessels diseases. For example, small white matter lesions will be examined, so as to try to better understand how they differ."

Q: Is fatigue a characteristic of the disease?"

A: (Prof. Chabriat) "Fatigue is linked to the slowdown and deficit of attention often observed during the illness. Doing a task then requires more effort. This symptom will be evaluated with a CADASIL-specific rating scale which is in a definition stage."

Q: "Do you need brain donations and what are they used for?"

A: (Dr. Joutel) "The answer is yes, even though we already have in our laboratory some samples from France and other European countries. Their interest is twofold: - When we find something on mice, we must be able to check it on human samples. - In human beings, we observe the advanced stage of the disease, which we cannot reproduce in mice. The brains of deceased patients are therefore useful in helping to answer these questions and in performing tests. We also need brain donations from patients who do not have vascular diseases, and it is paradoxically more difficult to obtain these control brains samples.”