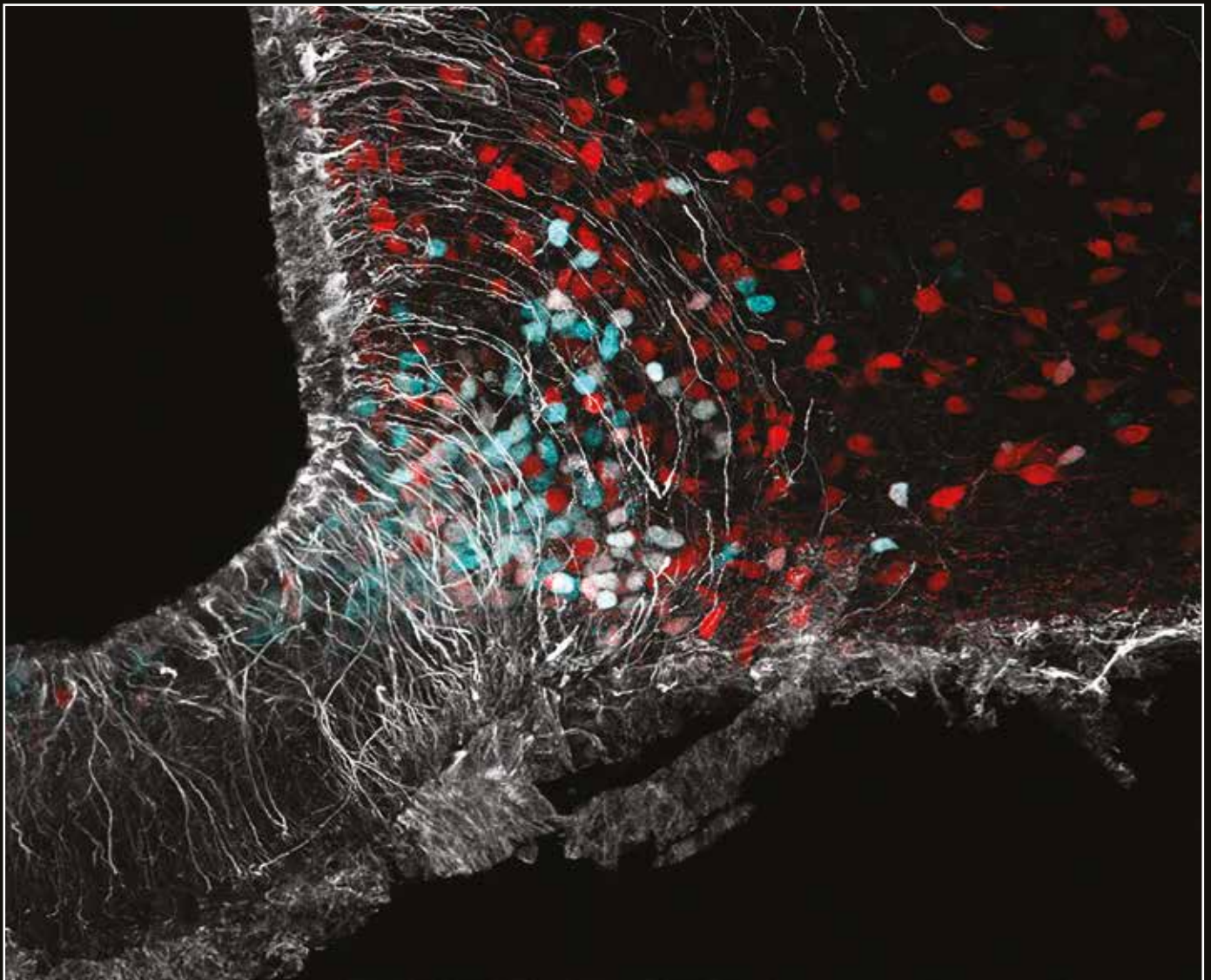
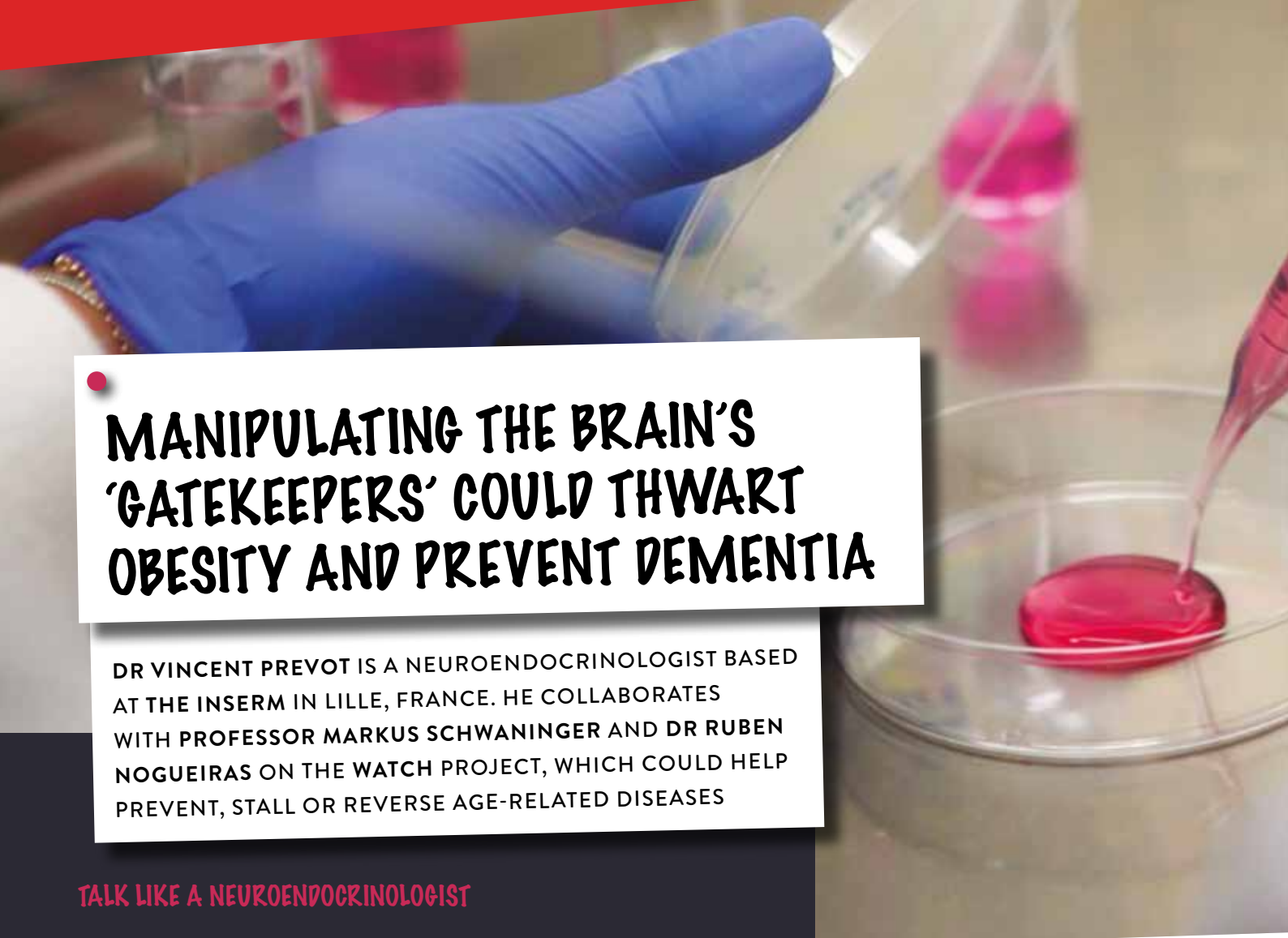


# MANIPULATING THE BRAIN'S 'GATEKEEPERS' COULD THWART OBESITY AND PREVENT DEMENTIA

DR VINCENT PREVOT, DR RUBEN NOGUEIRAS  
AND PROFESSOR MARKUS SCHWANINGER



*Tanycytes (in white) and some of the neurons they directly interact with in the hypothalamus: the neurons promoting appetite (NPY neurons – in blue) and the neurons inhibiting appetite (POMC neurons – in red)*  
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# MANIPULATING THE BRAIN'S 'GATEKEEPERS' COULD THWART OBESITY AND PREVENT DEMENTIA

DR VINCENT PREVOT IS A NEUROENDOCRINOLOGIST BASED AT THE INSERM IN LILLE, FRANCE. HE COLLABORATES WITH PROFESSOR MARKUS SCHWANINGER AND DR RUBEN NOGUEIRAS ON THE WATCH PROJECT, WHICH COULD HELP PREVENT, STALL OR REVERSE AGE-RELATED DISEASES

## TALK LIKE A NEUROENDOCRINOLOGIST

**DEMENTIA** – a syndrome that affects memory, language, problem-solving and other thinking abilities severely enough to interfere with daily life

**HYPOTHALAMUS** – a small region of the brain located at the base, near the pituitary gland. It plays a crucial role in many important functions, such as releasing hormones and regulating body temperature

**LEPTIN** – a protein made in the fat cells, which circulates in the bloodstream and goes to the brain

**MEDIAN EMINENCE** – a small swelling on the underside of the hypothalamus that gives rise to the pituitary stalk

**METABOLISM** – all the chemical processes that go on continuously inside your body to keep you alive and your organs functioning normally, such as breathing, repairing cells and digesting food

**TANCYTES** – specialised cells with long processes that are found along the walls of the third and fourth ventricles of the brain

There is an adage that states we know more about the Universe than we do the human brain and, while that is not strictly true (it has to be understood in context), it is perhaps fair to say that relative to the opportunity for discoveries in the future, we do know much more about the Universe than we do our own minds!

Fortunately, some of the very best minds are engaged in the Well-Aging and the Tanycytic Control of Health (WATCH) project. The project sees a collaboration between Dr Vincent Prevot, a neuroendocrinologist based at the Inserm in Lille in France, Professor Markus Schwaninger, a neurologist at the University of

Lübeck in Germany, and D Ruben Nogueiras, an expert in molecular metabolism at the University of Santiago de Compostela in Spain. The team wants to understand more about the role that peripheral hormones play in proper brain functioning, and how a lack of communication between the brain and the periphery may lead to cognitive decline in adulthood. The WATCH project is focusing on tanycytes, cells found in certain areas of the brain.

### TANCYTE TRAITS

Tanycytes, a type of nerve cell known as glia, line the walls of the third ventricle in the hypothalamus. Some tanycytes still divide in

the adult brain, giving rise to new neurons, a phenomenon that only occurs in two or three other brain regions. They also have several other fascinating and unique features. In particular, tanycytes of the hypothalamic median eminence have a special advantage – they dip their ‘end-feet’ (the expanded tips of their processes) directly into the blood circulation, since the capillaries underlying this region have fenestrations or ‘windows’ in their walls. This sets them apart from capillaries in most other parts of the brain, which have leak-proof walls to separate brain cells from circulating molecules, constituting a ‘blood-brain barrier’. “The fact that the tanycytes in this region contact both the blood and, at their other end, the ventricular liquid or ‘cerebrospinal fluid’, which constitutes a kind of canal system connecting different parts of the brain, is why they are part of our focus,” explains Vincent. “It means that they are peculiarly qualified to sense what is going on in the rest of the body, and to allow messages from other tissues to bypass the blood-brain barrier and, thus, gain access to brain circuits.”

### DISCOVERIES

Through experiments in animal models over the last few years, the team has shown that tanycytes are not passive bridges between the



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**FIELDS OF RESEARCH**

Neuroscience, Neuroendocrinology



**PROFESSOR  
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University Of Lübeck, Germany

**FIELD OF RESEARCH**

Neurology



**DR RUBEN NOGUEIRAS**

University Of Santiago  
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**FIELD OF RESEARCH**

Molecular Metabolism

**JOINT RESEARCH PROJECT**

Well-Aging and the Tanycytic Control of Health (WATCH): Studying the tanycytic hormonal shuttle and whether it is the missing link between impaired brain function and metabolic imbalances, with the aim of preventing or reversing age-related conditions such as obesity, diabetes and dementia

**FUNDER**

European Research Council (ERC)

two liquids but play a handful of very active and peculiar roles. Firstly, tanycytic end-feet, by alternately advancing and retreating, participate in a complex ‘dance’ with the terminals of hypothalamic neurons, which need to get close enough to the fenestrated capillaries during certain periods to secrete their hormonal signals into the blood circulation. Secondly, although tanycytes replace the blood-brain barrier by forming another barrier at the ventricular wall, this layer, made up of their cell bodies, is more or less tightly sealed depending on whether the biological state of the animal requires signals from the blood to enter the brain or not. Thirdly, tanycytes themselves actively transport some of these signals into the brain, allowing them to reach responsive neurons that would otherwise be insulated from them.

“It is because of this very special role as controllers of the access of signals from other tissues to the brain that tanycytes are often referred to as the ‘gatekeepers’ of the brain,” explains Markus.

**TRANSPORTING MESSAGES**

Any gatekeeper has the ability to allow or deny entry. But a properly functioning brain needs neural circuits in the brain to detect the state of the rest of the body and direct appropriate functional or behavioural responses. In the case

of hunger, for example, the hormone ghrelin is secreted in the stomach that sends a message telling us we are hungry, while the hormone leptin tells us we are full. However, in some instances, the messages do not get through, so an individual’s brain might never receive leptin, letting the person continue eating, eventually becoming overweight. It is believed that tanycytes play a role in our ability to transport the messages to the appropriate neuronal circuits.

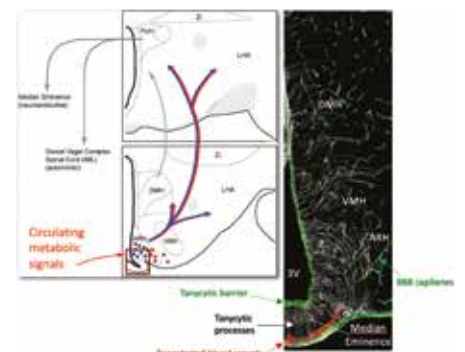
Although this example is specifically related to a metabolic disease like obesity, it shows there is a tangible link between brain function and metabolic state. If tanycytes play the role of ‘gatekeeper’ in conditions such as obesity, they could also play a role in the onset of dementia or other cognitive issues – because the processes involved are essentially the same.

**LOOKING AHEAD**

In order to see whether the tanycytic hormonal shuttle is the missing link between impaired brain function and metabolic imbalances, and how exactly this link works, the team needs to be able to see two things. “We need to know what happens when we deliberately disrupt the transport of hormones into the brain, and also determine what happens if, in individuals where the transport has already been disturbed, we

use drugs or other methods to restore the function,” says Ruben. “To do this, we will use genetically-modified mice or cultured cells to investigate the functions of certain genes or cellular processes.”

If the team can show that restoring the transport of hormones into the brain has a positive effect, it may be possible to restore cognitive function in patients that have experienced a decline. Ultimately, the team wants to find a cure for obesity, as well as prevent cognitive decline – ambitions that the mechanisms they have uncovered could facilitate. WATCH this space.



Tanycytes of the hypothalamic median eminence have a special advantage – they dip their ‘end-feet’ directly into the blood circulation.



# ABOUT NEUROENDOCRINOLOGY

The endocrine system is the collection of glands in the body that produce hormones that regulate a range of different functions, such as metabolism, growth and development, tissue function, sexual function, reproduction, sleep, and mood. The brain also produces hormones, through which it controls the activity of other organs and glands. Neuroendocrinologists study the interaction between the nervous system and the endocrine system. Neuroendocrinologists are especially

focused on how the two systems communicate together – a principle that is the backbone of the WATCH project.

“In terms of concepts, the biggest challenge facing the field is connecting the dots linking neuroendocrine dysfunction (that is, defects in the way the hypothalamus works) and various psychiatric and metabolic diseases as well as pathological ageing,” explains Vincent. “From the point of view of the tools and technology

needed, I would say that it is understanding how to exploit and interpret big data efficiently, accurately and productively.”

## EXPLORE A CAREER IN NEUROENDOCRINOLOGY

- The Endocrine Society’s website is comprehensive. We recommend taking your time to read through relevant sections, especially the one dedicated to careers and professional development: [www.endocrine.org/our-community/career-and-professional-development/endocareers](http://www.endocrine.org/our-community/career-and-professional-development/endocareers)
- The Society for Endocrinology is a wonderful resource, including lots of information about career pathways: [www.endocrinology.org/careers/career-pathways](http://www.endocrinology.org/careers/career-pathways)
- According to Indeed.com, the average salary for an endocrinologist in the UK is £96,000.
- You can explore salaries on offer across Europe on the careers section of the BMJ website: [www.bmj.com/careers/jobs/diabetes-and-endocrinology/europe](http://www.bmj.com/careers/jobs/diabetes-and-endocrinology/europe)

## PATHWAY FROM SCHOOL TO NEUROENDOCRINOLOGY

Vincent recommends that students consider taking neuroscience, endocrinology and the biology of reproduction modules during their time at university. These will provide budding neuroendocrinologists with a broad understanding of the matters at hand.

You will need to study biology or chemistry at an undergraduate level, before moving on to scientific research or medicine. In the WATCH team, Vincent and Ruben are scientists and Markus is a medical doctor.

## THE IMPORTANCE OF COLLABORATION

Science is carried out at a level of detail which makes it impossible for any single laboratory or team to study all aspects of a problem. A project as ambitious and wide in scope as WATCH is only possible with the combined and synergistic efforts of several groups with complementary interests, expertise and skills. The three groups involved in WATCH (Vincent’s team in France, Markus’ in Germany, and Ruben’s in Spain), have a common interest in deciphering the role of the hypothalamus, and of the tanyocyte in the functions necessary for bodily homeostasis, as well as normal cognitive function and ageing-associated changes and disorders. However, each specialises in the study of different biological processes, using different models and techniques, so when they join forces, they manage to obtain results and insights that each group would be unable to achieve on its own.

## THE TEAM’S TOP TIPS

- 01** Try your best to develop a passion for something. I have always been curious about biology and it has helped me enormously throughout my career.
- 02** Taking courses in your native language can be a big help. So much of scientific work relies on effective communication and taking some language classes will certainly help with that.
- 03** History is another important subject to consider studying – even if only in your spare time. It can help put things into context, which is very important within science.

# MEET THE TEAM



**PROFESSOR  
MARKUS SCHWANINGER**

**I enjoyed Latin and ancient Greek in school,** but I loved the sciences and conducted chemistry experiments on my own at home.

**Several people inspired me to become a scientist,** but my main inspiration was the supervisor of my thesis, Willhart Knepel.

**The best way to overcome obstacles in my work is to consult with others,** talk with colleagues and read their scientific papers.

**I am amazed by the endless complexity of life.** Evolution has brought up such a magnitude of ingenious and stunning mechanisms.

**There have been eureka moments in my career** when I have been able to predict how cells or organisms will behave.

**I'm proud of research papers I've written** and the tools my group has produced that have helped

the wider scientific community. Most importantly, I'm proud of seeing the people I've worked with progress.

**You should always keep in mind that science is a craftsmanship that can be learned.**



**DR RUBEN NOGUEIRAS**

**As a child,** I loved being with my friends and playing basketball. In terms of school subjects, biology was my favourite by far.

**I spent extra hours in the lab during my degree.** Then I did my master's and loved the lab work – and decided to become a scientist.

**Any successful scientist needs three qualities.** Motivation (because science can be frustrating), perseverance (because hard work is essential, no matter how talented you might be), and the ability to choose the right environment to work in (because being part of a good team is vital).

**Patience enables me to overcome challenges.** It allows scientists to spend time looking for new solutions to old problems.

**Many aspects of my career are rewarding.** I enjoy it when my colleagues find my work interesting, but I love to see the career progression of former students.

**Convincing reviewers and panels can be challenging.** Part of a scientist's work is explaining why your work deserves funding more than many other excellent proposals.

**I am proud of securing an ERC Starting Grant, and becoming part**

**of the Synergy Grant was pleasing.** Contributing to our understanding of how the brain and peripheral organs are communicating is something I am very proud of.

**Enjoy what you do.** It is so important to get up each morning and want to go to the lab. Such a mindset will help you throughout your career.

**Many experiments do not work.** The important thing is to realise that and to keep going. Thankfully, Vincent and Markus make working together fun, so we can overcome any challenges we face.



**DR VINCENT PREVOT**

**Living in Perú as a child, I raised caterpillars and watched them become butterflies.** When I was ten, I collected scorpions and insects with my father in the Andes. At 14, with very permissive parents, I built a zoo at home with snakes, turtles, geckos, scorpions, piranhas, salt-water fishes, a ferret and a dog! I was breeding snakes and became a member of the French Herpetology Society at the age of 16. With my interest in breeding reptiles and the obstacles that often arise, I wanted to understand the mechanisms that control how animals reproduce

and became fascinated with neuroendocrinology.

**Passion for my subject,** perseverance, open-mindedness, willingness to question dogma and acceptance of the fact that I do not know everything have made me successful. Surrounding myself with competent and well-disposed people who possess a strong team spirit has also been key.

**It sounds simple, but to overcome obstacles, I sleep on them!** I usually find that the solution presents itself in the morning.

**I practise martial arts, avoid talking science at night with my family,** and engage in constructive activities like gardening or doing odd jobs around the house.

**I am proud of having been able to make real contributions to our understanding of how the brain controls reproduction and metabolism.** I am also proud of having been able to build a top-notch laboratory and an ERC Synergy consortium with internationally renowned scientists and a real spirit of teamwork.

# NEUROENDOCRINOLOGY WITH THE WATCH PROJECT

## TALKING POINTS

### KNOWLEDGE:

1. What are tanycytes?
2. Can you list some of the ways in which tanycytes are unique?

### COMPREHENSION:

3. Why are the properties and functions of tanycytes of particular interest to the WATCH team?

### APPLICATION:

4. How might the team's research help prevent obesity and cognitive impairments?
5. In what ways can slight changes to the processes within the brain have major negative impacts on individuals?

### SYNTHESIS:

6. There is some discussion on the challenges of justifying research for funding above other brilliant ideas. Can you list some of the reasons why you believe the WATCH project was awarded funding? Can you see the greater purpose that the team's work might have?

### EVALUATION:

7. What might a world of the future look like if we can find a way to ensure that messages relating to hormones arrive at their intended destination? Can you see other potential benefits besides curing obesity and preventing dementia?

## MORE RESOURCES

### BRAIN GAMES

We can all use a little brain training! These games from Lumosity are backed by science and will help you discover your strongest brain training area: [www.lumosity.com/en/brain-games/](http://www.lumosity.com/en/brain-games/)

### THE BRAIN VS. THE UNIVERSE

Read this fascinating article from Universe Today, and see what you make of what is being suggested: [www.universetoday.com/148966/one-of-these-pictures-is-the-brain-the-other-is-the-universe-can-you-tell-which-is-which/](http://www.universetoday.com/148966/one-of-these-pictures-is-the-brain-the-other-is-the-universe-can-you-tell-which-is-which/)

## ACTIVITIES YOU CAN DO AT HOME OR IN THE CLASSROOM

### APPLYING FOR FUNDING

Obtaining a grant is always a big achievement for a researcher. Imagine you are a researcher applying for funding to conduct a similar project to the one that Vincent, Markus and Ruben are doing. Write a letter or speech or prepare a presentation to give to a funding body. You will need to:

- highlight what your research is setting out to achieve
- outline the main focus of your research
- outline the main benefits of the research for individuals
- explain the wider societal impact your research will have
- explain why your research should receive funding above your competitors.

### THE HYPOTHALAMUS

Vincent describes the hypothalamus as, "a window to the brain." Challenge yourself to find out as much as you can about this fascinating part of the brain:

- Where is it located?
- What functions does it perform?
- How is it connected to blood circulation?
- What is the median eminence?
- Which signals does the hypothalamus control?
- Which 'higher' brain functions does it play a part in?

Now, to what extent do you agree with Vincent's description?



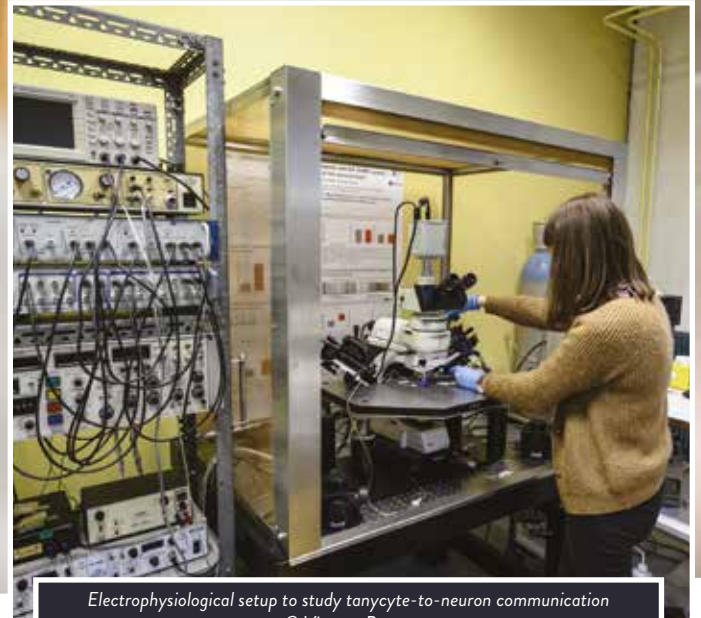
Scientific discussion in the lab between the three principal investigators (Vincent, Markus and Ruben) © Vincent Prevot



WATCH team members working at the bench © Vincent Prevot



Electron microscopy to visualise tanyocytes and neurons © Vincent Prevot



Electrophysiological setup to study tanyocyte-to-neuron communication © Vincent Prevot



Slicing brains at the cryostat © Vincent Prevot



The WATCH project team, including (on the left) Markus, Vincent and Ruben © Vincent Prevot

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