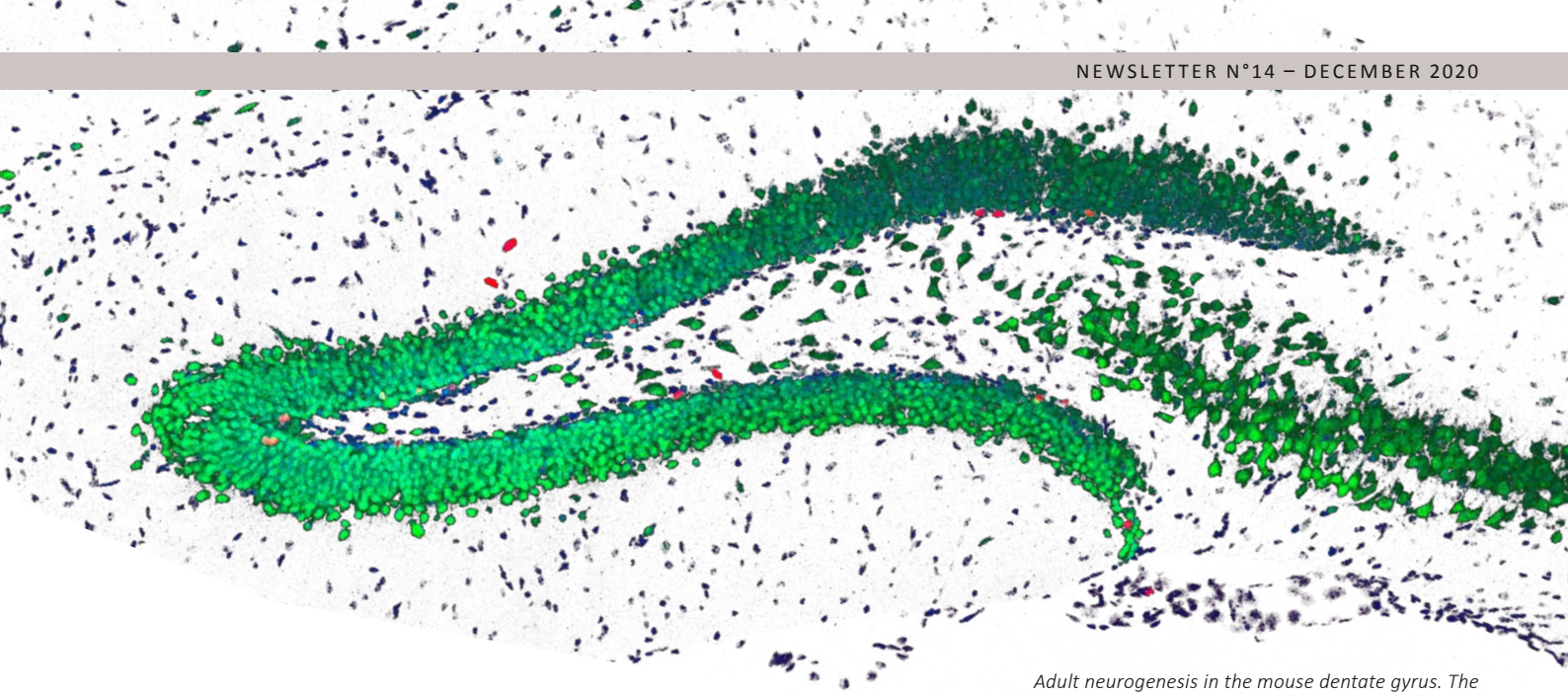

Adult neurogenesis in the mouse dentate gyrus. The newly formed cells are shown in red and neurons in green. Light pink labelled cells are new neurons that will later integrate into neural networks. (See "Lactate, a prospect for the treatment of depression", p. 8-9.)
© Carron/ Toni

EDITORIAL

by Camilla Bellone

2020 has been a challenging year for the Synapsy community and for the whole society.

The impact of the COVID-19 pandemic on health, economy and employment has been unprecedented worldwide. Like many other domains, science has been hit hardly by the spreading of the infection. Laboratories have shut down, clinical studies have been put on hold and the careers of young scientists have been delayed. In addition, Synapsy community lost its director and beloved colleague Alexandre Dayer last summer.

Despite this particularly difficult situation, we saw some positive developments: the Year 10 site visit received positive reviews from panel members, and the 3rd Conference on the Neurobiology of Mental Health at Campus Biotech was a great success.

We now look forward to 2021 as an exciting new year for the Synapsy community. Taking advantage of the virtual platforms, we will initiate a virtual Synapsy seminar series starting in January, and will resume Synapsy happy hours and organize online training events. At the same time, we will closely monitor the epidemiological situation, hoping that our annual meeting in Villars can still take place, as planned, during Year 11.

In this newsletter, you will find out more about the recent advances in WP#5 on mood disorders, with interviews and portraits of researchers and clinical scientists and special highlights of exciting new findings.

Happy reading, best wishes for the holiday season and 2021. Stay safe! ●

N°14 – DECEMBER 2020 (ENGLISH)

NEWSLETTER

NATIONAL CENTRE OF COMPETENCE IN RESEARCH (NCCR) SYNAPSY

synapsy
Bringing Together Brain Research and Psychiatry
National Centre of Competence in Research

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Genetics to stratify the WP#5 cohort

Giorgio Pistis is profiling polygenic scores to understand whether genetic risks associated with particular pathophysiological pathways are higher in specific sub-groups of patients of the mood disorder cohort. Synapsy met him to find out more about his project.

Giorgio Pistis is a geneticist, working as a postdoc at the Centre d'épidémiologie psychiatrique et de psychopathologies (CEPP) of the CHUV, in Martin Preisig's group, under Synapsy WP#5.

His role in the Preisig lab is to apply Polygenic Risk Score (PRS) analyses to patients and healthy controls involved in three high-risk cohorts — the Lausanne-Geneva Study, the Canadian Flourish Study and the population-based CoLaus|PsyCoLaus study — to quantify the genetic contribution to mood disorders.

Giorgio's current work involves examining the hypothesis, formulated in 2016, by among others, Martin Preisig, that the offspring of early onset bipolar disorder parents would have a higher chance of developing the disorder themselves. It has been suggested that offspring of patients with bipolar disorder that emerged before the age of 21 years of life are 8 times as likely to develop the same disorder as healthy controls, whereas this risk was not significantly elevated in the offspring of patients with bipolar disorder that emerged after the age of 21 years.

In Search of Genetic Risk Variants

The PRS is a number that quantifies risk variants identified in the DNA that can contribute to the onset of a given disease, in this case bipolar disorder or depression. A patient experiencing mood disorder would have a higher score (number of risk variants) than a healthy control.

In these three studies, genetic data from some 4500 individuals, patients and healthy controls has been collected. This data is analysed against the background of wider studies of the human genome, named genome-wide association studies (GWAS). GWAS provide lists of genetic variants associated with a given disease, which can be used to calculate the PRS of the participants of the three studies.

> "One study we looked at in the literature produced a list of genetic variants associated with major depression from a cohort of 800,000 individuals (patients and healthy controls). We look to see if, using those variants, we can split our depressive patients from our controls. We also investigate whether specific depression subtypes overlap with aggregates of genetic variants that influence biological pathways known to be relevant to depression."
>
> Giorgio Pistis

Giorgio Pistis

The study expects to find that early onset probands will have a higher polygenic score for bipolar disorder or depression disorder, and that a lower score will be seen for late onset patients.

The Holy Grail of Modern Psychiatry

The PRS are analysed for their potential to stratify, and identify subgroups of patients in the mood disorder cohort. This is a hot topic in psychiatric genetics because the diseases involved are very heterogeneous. While identifying genetic markers for other diseases might be relatively easier, for highly heterogeneous entities like depression, or bipolar disorder, the constellation of symptoms is vast and the overlap of contributing factors highly complex.

As work proceeds, Giorgio and his colleagues are discovering that within the main group of people suffering from mood disorder, there are subgroups that can be distinguished by genetics.

The next important aspect is to hypothesise about the link between the PRS and specific symptoms and pathways.

One advantage of the teams involved in Synapsy WP#5 is that they already have a deep knowledge of these diseases and their symptoms. Hypotheses about the relevance of the variants identified for mood disorder can thus be formulated more convincingly. ● *by PH*

A psychologist in a clinical research team

Ryan Murray's work within Synapsy WP#5 focuses on measuring brain reactivity to and recovery from psychosocial stress within clinical patients and healthy controls. He talked to us about his role as a psychologist in a clinical research group and his projects.

After psychology-related studies, research and practice in Geneva over a 10-year period, Ryan earned a Master of Science in Neuroscience in 2012 from the University of Geneva, which he holds in addition to complementary bachelor and master degrees in Psychology from the UNIGE. He received his doctorate in Psychology in 2018, from the Swiss Centre for Affective Sciences in Geneva, working on mapping the neural correlates of emotion processing.

Ryan is currently working as a postdoc researcher and data analyst in Camille Piguet's team at UNIGE/HUG, where his principal activity is acquiring and analyzing fMRI data for both patients and healthy controls in response to psychosocial stress.

Seeking Markers of Vulnerability

The study uses a modified version of the MIST method (see box), which is a codified way to elicit a small but discernable psychological stress in patients while they are in the MRI scanner. The intent is to get a picture of what is occurring within the brain during the performance of stress-inducing tasks.

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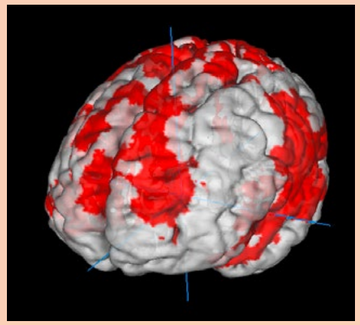

Neural activations correlating with emotion dysregulation in healthy individuals during recovery after psychosocial stress ©Murray/Piguet

The MIST (Montreal Imaging Stress Task)

Stress is elicited by having participants complete five blocks of arithmetical calculations of varying difficulty under time constraints. In between blocks, they are given feedback on the results of their calculations and on how they compare to their (fictive) peers.

This team introduced two innovations to the MIST. The first is the inclusion of a recovery period of 90 seconds immediately after the feedback is given, during which neural stress recovery can be observed. The second innovation is the addition of a positive feedback (previous standards included negative and neutral feedback only) on the idea that this can itself be a source of stress in people uncomfortable with compliments or experiencing the fear of future expectations.

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So far, this task has been applied to more than 200 subjects, healthy controls, as well as bipolar, ADHD and borderline personality disorders patients. Initial results in healthy subjects have been published (Murray et al. *Journal of Affective Disorders*, 2020), illustrating the significant influence of maladaptive emotion regulation traits on brain activity within regions associated with self-regulation and stress coping. The next paper will most probably concern borderline and bipolar patients, and more specifically their offspring: the initial hypothesis was that offspring of psychiatric patients presenting increased stress reactivity and emotion dysregulation would show altered patterns during this task, that could represent a marker of vulnerability.

Ryan's long-standing interest in psychological stress in children and adolescents is kindled by the implications of data seen by the team. The team is discussing interpretations of the clinical implications, how the findings can relate to different types of mood disorders — and specifically bipolar and borderline personality disorders— and what might be potential avenues for clinical intervention, such as mindfulness training.

Role of the MRI operator

Ryan is a certified MRI operator and can capture data in connection with any number of enquiries.

The role of the fMRI operator is first, and foremost, to capture reliable data from a monitoring of MRI scans, both structural and functional, of the brain during the performance of specific tasks.

Ryan explains that while MRI operators are not neurologists —they don't diagnose— they do know brains. They have a responsibility to scrutinize structural images of brains and to signal any abnormalities that might be apparent. They will have seen MRIs of hundreds of brains and can understand what might be significant. ● *by PH*

Ryan Murray

From science... ...to yoga — and back to science

After initial studies in science, Zeynep Knight-Celen opts for a life practicing and teaching yoga. Ten years later her interest in the workings of the mind rekindles her scientific curiosity and leads her to a PhD position in the Mindfulness study.

Zeynep is currently a PhD candidate in Camille Piguet's group. She is working on the Mindfulteen project (www.minfulteen.ch) (read previous Synapsy article www.nccr-synapsy.ch/news/11936/). After earning a bachelor's degree in Molecular Biology and Genetics in Istanbul and a neuroscience research experience in New York with Professor Bruce McEwen, where she understood that working with animals was not for her, Zeynep returned to Turkey in 2002 where she completed a master's degree in the genetics of plants.

"Then I became a yoga teacher."

She then practiced yoga for 10 years, qualifying as a teacher and giving yoga lessons to thousands of people in Turkey, and training numerous apprentice yoga teachers. This practice gifted her many observations about people: the fact that yoga was not just for the body, but also for the mind; it helps focus attention, makes a person more aware and helps people function better in life in general. This rekindled Zeynep's scientific curiosity to know more about how the mind was working.

She explains: "Mindfulness is an ancient practice and has been studied in science since the 1970s. In my early work as a yoga practitioner and teacher in Istanbul, I never used the term. We practiced and talked about awareness, bringing attention to the senses, listening, watching the thoughts as they happen … "

Back to Science

Seeking opportunities in Europe, in 2015 Zeynep found a Masters programme in Geneva (UNIGE) she was able to join and where she earned her degree in neurosciences, working under Professor Patrik Vuilleumier. When, at the age of 40, she secured a PhD position to explore the workings of the mind in the Mindfulteen study in the group of Camille Piguet, it felt like a dream come true.

The Mindfulteen study is examining the possible benefits of mindfulness, a practice of bringing attention to the present moment in a non-judgemental manner, on the management of stress in young people aged 13 to 15 years. Changes in the brain induced by mindfulness practices are monitored using physiological data, magnetic resonance imaging, biological markers and questionnaires on anxiety and stress.

Zeynep's role in the Mindfulteen study is to compare the data before and after the intervention of mindfulness training. This is the focus of her PhD research. At the moment she is analysing the before data. She does meet all the participants, though without knowing whether they are the group practicing mindfulness training or the control group.

Still Practicing Yoga

In Geneva, Zeynep continues to practice yoga, giving one yoga session a week and doing one teacher training each year, over seven weekends. "The weekly practice is like a one-hour meditation for me. Grounding, being with people, is very balancing for me", she explains.

Zeynep's stays in touch with yoga practitioners in Turkey and elsewhere through her YouTube channel (13,000+ followers) and her Instagram account (5000+ followers). While these accounts are connected to her yoga practice, she does mention her science pursuits and is pleased to receive questions about a career in science from young women to which she unfailingly responds with encouraging words. ● *by PH*

Zeynep Knight-Celen

CLINICIAN SCIENTIST

A career at the intersection of physics and psychiatry

Pierre Marquet's career path has been rather untypical. Combining qualifications in physics and psychiatry-psychotherapy, he is a clinical researcher "par excellence", engaged for over 20 years in the development of knowledge about the biological dimensions of mental disorders.

His career began at the EPFL where he obtained a Master's degree in physics (medical engineering) at a time when the technology was just beginning to prove its relevance to the medical field.

Pivotal encounters

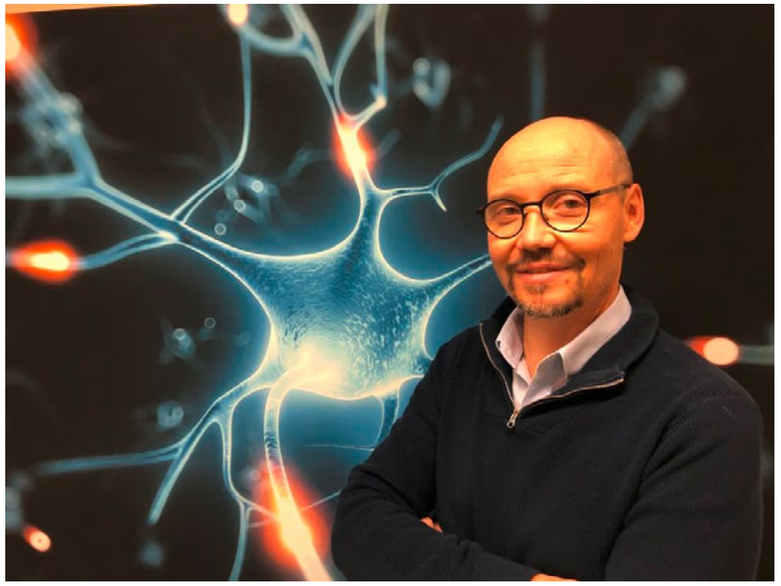
Several subsequent encounters influenced both his collaborations and his professional choices. The first of these, with Professor Christian Depeursinge at the EPFL, «a visionary professor» in Pierre's own words, led him to work on applications in optics to analyse both tissue and cellular material of the brain, the workings of which he found fascinating.

"I pursued medical studies with the intention of working on the brain, all the while continuing my research projects at the EPFL ", which paid for his medical studies and allowed him to stay connected to microscopic imagery research. He then met Professor Pierre Magistretti at the University of Lausanne and convinced him to apply new optics technology to elements of cellular imaging. "He was exceptionally open-minded and immediately found linkages with the neurosciences." This then led to a MD-PhD with Pierre Magistretti at UNIL/CHUV, while also continuing in the team of Christian Depeursinge at the EPFL. He was well positioned to find linkages between the two, with his two mentors providing advice in their respective areas of expertise.

Opening up new paths

"At the time, digital microscopic holography — a pioneering technique applied to the observation of cellular behaviour — was being developed." This technique opened a path towards a concept of computational imagery, the construction of digital images, which is particularly well suited for neuronal cells. The articulation with psychiatry and mental disorders came about a dozen or so years ago, when pluripotent stem cells appeared: "my two areas of expertise, with their common denominator in neurosciences, allowed me to investigate".

Once his MD-PhD was completed, his fascination for the workings of the brain undiminished, and his interest in understanding people and mental pathologies sharpened, pushed him to specialise in psychiatry, and especially psychotherapy. He then began his internship in psychiatry, a move that was greatly facilitated by his retention of a 50% research post in Pierre Magistretti's lab.



Pierre Marquet

The clinic to give meaning

By 2014 optical imagery applied to the neurosciences became known as neurophotonics. Pierre Marquet was named to the Canada Research Chair for neurophotonics, attached to the University of Laval (ULaval) in Quebec, to apply this imagery to psychiatry. This opportunity gave rise to the creation of an international research unit involving UNIL, the CHUV and ULaval, "thanks to the support of the Vice-Chancellor François Bussy and Professor Jacques Gasser".

Currently, with support from Synapsy and in synergy with the research groups within WP#5 (cf. next article, p. 7-8) Pierre Marquet is working on investigating cellular biomarkers by combining digital holography and stem cell technologies.

Pierre Marquet would not want to have to choose between physics and psychiatry. It is precisely in the nexus of the two that he finds the pertinence of his work. "The discovery of the two principal classes of medication currently used in psychiatry, neuroleptics and antidepressants, was fortuitous" he reminds us. The search for biomarkers will alter this trend. Knowing that mental disorders have a biological component will have an impact on the way patients are cared for and will contribute to reversing the stigma attached to these conditions. Both of these are key concerns at the heart of Synapsy. ● *by LB*

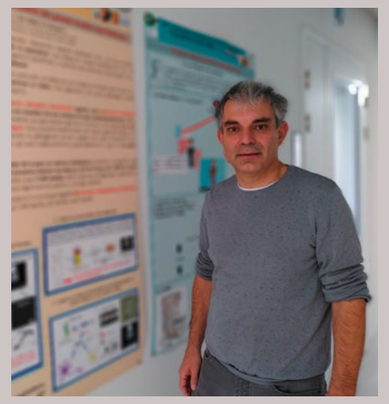
NEWSLETTER N°14 – DECEMBER 2020

RESEARCH HIGHLIGHT

Holography and cellular reprogramming in the quest for biomarkers

Bipolar disorders affect some 2% of the population. Patients present a wide variety of clinical symptoms of which many can be especially handicapping. A new approach to find biomarkers, driven by Pascal Jourdain, could change the game by improving treatment and diagnosis.

Therapeutic options for the treatment of bipolar disorder caused by both environmental and genetic factors are limited, with current options restricted to stabilising the moods of affected patients. It has been shown that children of bipolar parents are much more likely than children of healthy parents to develop the disorder. The identification of biomarkers of bipolarity in patients and their children would accelerate the diagnosis and the development of effective treatments. Such advances would also facilitate the implementation of preventive measures and improve knowledge of the biological component of the disorder. This is the focus of Pascal Jourdain's work – a biologist in the group of Pierre Marquet – within the mixed international unit involving UNIL, the CHUV and ULaval, and in collaboration with Pierre Magistretti at UNIL/CHUV.



Pascal Jourdain

Imaging chlorine

His project combines two approaches: digital microscopic holography and the reprogramming of induced pluripotent stem cells (IPSC). «Holographic imagery allows us to measure the phase changes in light as it passes through a cell. The phase change is in most cases correlated with a change in volume of the cell, which is itself linked to ionic and water exchanges on either side of the cellular membrane. "Using this tool, we have been able to show that it is possible to measure the activity of certain co-transporters involved in psychiatric disorders, especially those transporting chlorin" explains Pascal Jourdain. In a first instance, with the support of the Fondation de Préfariger, the researchers in P. Marquet's group studied fibroblasts– skin cells – taken from adult bipolar patients and healthy controls of the Synapsy WP#5 cohort managed by Professor Martin Preisig at the CHUV. The fibroblasts were cultured so as to determine their pharmacological profile and the specific role played by chlorine.

A human neuron bank

In order to observe neuro-developmental stages, the project is now seeking to re-programme the fibroblasts taken from adult bipolar patients and

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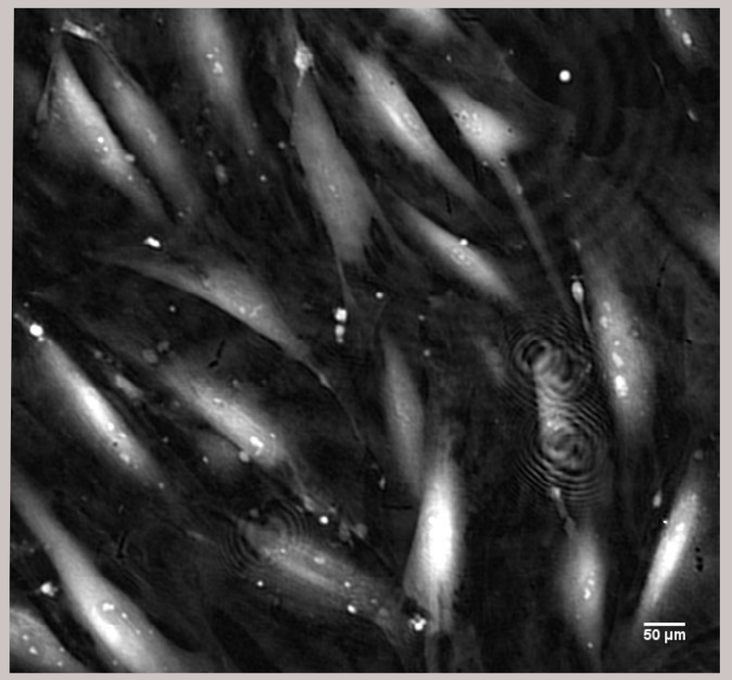
their healthy controls as IPSC cells, which can then be differentiated into a variety of neuronal options. The reprogramming can also be carried out from urothelial cells, which are easier to obtain from children. The objective is to identify, using in vitro cultivation, functional neuronal networks that carry the genetic heritage of each patient. Currently the project has reprogrammed cells from some 50 patients. Using the information gathered from the work with fibroblasts, Pascal Jourdain is on the lookout for anomalies in the pharmacological profiles of IPSC neurons that he can correlate with the formation of neuronal networks during development. Results are confidential for the moment while they are being written up, but Pascal Jourdain describes them as «very encouraging»!

In the future this research could lead to a personalisation of care and treatment specified to the biological profile of each individual bipolar patient and contribute to lifting the stigma associated with mental disorders by highlighting their biological component. ● *by LB*



Phase image of in vitro fibroblasts culture. Fibroblasts come from human skin. ©Mermin

Lactate, a prospect for the treatment of depression

According to WHO, more than 264 million people in the world suffer from depression, a disorder that has a major impact on all facets of the lives of those it affects. It became the first cause of invalidity in 2020. The work on lactate carried out by Anthony Carrard, a biologist in the neurobiology of depression research unit of the CHUV/UNIL, is opening new and promising perspectives involving the metabolism of lactate.

In a preceding study you observed the antidepressant effects of lactate.

Yes, indeed, we identified the antidepressant effects of lactate and showed that these effects were characterised by changes in the expression of genes implicated in neurogenesis.

What is the link between neurogenesis and depression?

That's precisely what we want to find out. We are particularly interested in the hippocampus, a part of the brain known to evidence neurogenesis in adults. In order to identify a mechanism, we are focussing on two stages of neurogenesis: the proliferation of stem cells and their survival.

What experimental model are you employing to answer these questions?

The model we are using is depression induced by corticosterone. The goal is to reproduce in mice the high rate of cortisol (the equivalent of corticosterone in humans) found in the blood of certain depressive patients. When the mice are treated with corticosterone, the survival and proliferation of stem cells decrease. We have been able to show that this inhibition is reversed by lactate. In addition, the inhibition of neurogenesis eliminates the antidepressant effects of lactate.

Which means that adult neurogenesis is necessary for the antidepressant effects of lactate?

Yes, at least for the adult neurogenesis taking place in the hippocampus. But that still doesn't say anything about the mechanism by which lactate acts to regulate neurogenesis. In order to understand this, we are monitoring its metabolism. As lactate is first oxidised into pyruvate before entering the process of cellular respiration, we tested the pyruvate. As no effect was observed, the key must therefore be found in between the lactate and the pyruvate.

This is where the famous NADH factor, at the heart of your latest study, comes in?

Indeed. We postulated that the NADH, a molecule produced during the oxidation of lactate into pyruvate, plays an important role in the regulation of neurogenesis by lactate. In order to test this hypothesis, we initially worked with cultures of stem cells and confirmed the effects of treatments conducted in vivo. Then, in order to test the potential of NADH, we studied the production of ROS (Reactive Oxygen Species), a marker of oxidative stress within cells. The corticosterone increases the production of ROS reflecting the oxidative stress. A co-treatment with lactate reduces the production of ROS to basal values. This is not the case with pyruvate. We then treated the stem cells with NADH and observed that NADH leads to the same effect as lactate.

What is your working hypothesis, and what are the potential applications?

The oxidation of lactate into pyruvate is accompanied by the production of NADH. We are currently examining whether NADH reduces the oxidation of key proteins induced by corticosterone.

These results are currently under review. They allow us to improve our understanding of the molecular mechanisms involved in the antidepressant action of lactate. We shall now attempt to identify the proteins upon which NADH acts. These could be the targets for future treatments. ● *by LB*

Anthony Carrard

CAREER

From academia to entrepreneurship – seizing an opportunity to make a significant contribution to the treatment of neurological disorders

We spoke with Charles Finsterwald, PhD, Chief Scientific Officer and co-founder of the start-up Gliapharm about his career path and his decision to switch from fundamental research to application.

An interest in neuroscience

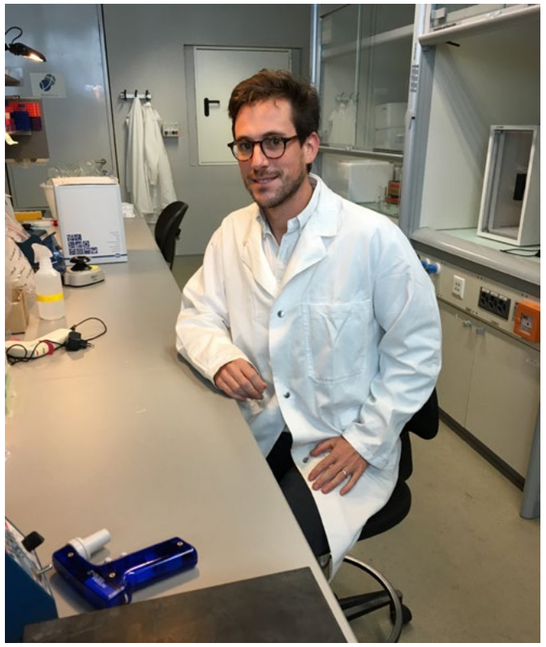
After a bachelor in biology and a master's in biomedical studies from UNIL, Charles Finsterwald earned his PhD in neuroscience from the Lemanic Neuroscience Doctoral School where he worked in the lab of Dr Jean-Luc Martin at the Centre for Psychiatric Neuroscience on understanding the mechanisms underlying neurotropic factors during brain development. After his PhD, Charles accepted a postdoc position, funded by the Swiss National Science Foundation, to work in the lab of Professor Cristina Alberini at New York University (NYU), where he investigated the role of stress on memory formation, in particular in post-traumatic stress disorder (PTSD). While pursing his postdoc, Charles also graduated in project management at NYU, gaining experience in the field of management and underlying business perspectives that he found to be very complementary to fundamental science.

Entrepreneurship opportunity knocks

When Charles returned to Switzerland, he was invited by Professor Magistretti in 2014 to join a team at EPFL to work under the terms of an Innosuisse grant to explore the viability of launching a start-up that would seek clinical applications derived from the discovery that glial cells and specifically astrocytes play a fundamental role in the control of brain metabolism. This could represent an innovative target for new therapeutic solutions as brain metabolism is reduced in a number of neurological disorders. Over the same period, Charles completed EPFL's classes on entrepreneurship, gaining a theoretical and practical overview of issues in company management, business development, funding strategies, and intellectual property matters. These different courses provided Charles with the tools of entrepreneurship, which he was able to combine with his lifelong passion for science.

Gliapharm was subsequently incorporated in 2016. Charles, fascinated by the potential of this line of work to make a major contribution to treatment of neurological pathologies, joined the new company as co-founder, board member and Chief Scientific Officer.

Gliapharm aims at targeting glial cells in order to stimulate their activity and boost the metabolism of specific brain areas and for different indications that have an impaired brain energy metabolism. Gliapharm believes that glial cells - astrocytes in particular – offer unique and important perspectives in the treatment of neurological pathologies such as amyotrophic lateral sclerosis (ALS), Alzheimer's disease and depression. The metabolic boost that astrocytes allow could also be applied in a preventative approach in specific cases. ● *by PH*



Charles Finsterwald

Gliapharm: Milestones

1980s, 1990s, 2000s

Fundamental science, looking at characteristics of glial cells, leading to an understanding of the therapeutic potential of glial cells, by various research institutes and universities, with strong leadership by Prof. Pierre Magistretti of EPFL.

2014 – 2015

Funding from Innosuisse to develop the concept and look at business planning, intellectual property issues, human resources aspects, engaging with investors. Coaching provided through Innosuisse proved very useful in setting up systems and operations. Gliapharm also set up an independent scientific advisory board, which provides key guidance in drug development and clinical aspects.

2016 – present

Co-funding by Innosuisse and the Puccini Foundation has allowed Gliapharm to establish an operational base and lab at Campus Biotech, conduct research and development, and cultivate technical, academic, industrial and financial partnerships, mainly with USA, France, Switzerland and indeed Campus Biotech based actors.

2019

Gliapharm raised an additional CHF 2 millions from diverse business interests. This allowed Gliapharm to intensify data collection and put together a full team with the requisite expertise. Biology is kept in house, while medicinal chemistry is out-sourced. Gliapharm also works with a number of CROs (contract research organisations) on regulatory aspects or preclinical pharmacology for example.

2021 and beyond (planned)

Raising CHF 10-20 million to intensify work aiming at producing a clinical candidate within 2 years, and conducting proof of concept clinical studies in an orphan neurological indication. Continue research and development of molecules to trigger brain metabolic activity for specific indications.

2023 and beyond

Be in a position to begin Clinical trials. ●

Synapsy seminar series

We will invite speakers from all over the world to present basic or clinical work to our community and we will at the same time promote the Synapsy network. The seminars will take place over Zoom on a monthly basis, the last Monday of the month at 5PM (see dates below) and each talk will consist of one 45min presentation, followed by 15min discussion.

- **WP1: January 25th 2021**
- **WP2: February 22nd 2021**
- **WP3: March 29th 2021**
- **WP4: April 26th 2021**
- **WP5: May 31st 2021**

More information soon on https://nccr-synapsy.ch/programs/synapsy-seminar-series/.

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