Interview with senior scientist (MER) Dr Georges Wagnières and PhD candidate Jaroslav Varchola – February 2014

Project title: Micro pO_2 - Monitoring of vascular oxygenation in different tissue compartments by time-resolved micro-spectroscopy in vivo.
Duration: 6 months
Call: 8th Call, no. 13.029
Duration: 1st of October 2013 - 31st of March 2014
Host institution: École polytechnique fédérale de Lausanne EPFL, Switzerland
Home Institution: Pavol Jozef Šafárik University in Košice UPJŠ, Slovak Republic

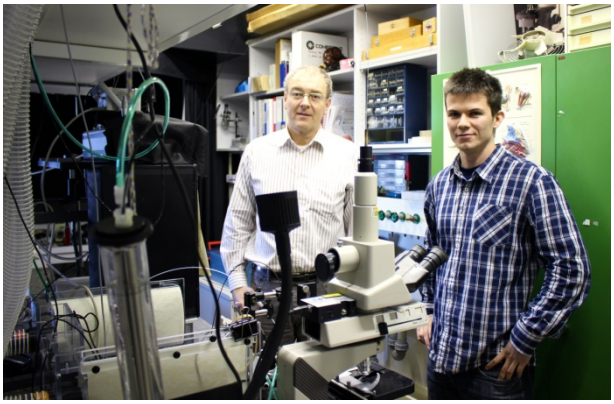
"We have a win-win situation"

What started more than 3000 years ago in broad daylight on the shores of the Nile River is at the origin of new approaches investigated today to calibrate light beams delivered by optical fibres. Slovak Sciex Fellow Jaroslav Varchola (27) and his Swiss Host Mentor MER Dr Georges Wagnières are working on photodynamic therapy PDT– an interesting medical approach to treating various conditions, including cancer or age-related macular degeneration.
The approach consist in administrating a photosensitizer to the patient's affected tissue – a dye which, when excited with light, triggers a photodynamic reaction destroying cancerous tissues.
During this photodynamic reaction, energy is transferred from the dye to the molecular oxygen in the targeted tissue. The resulting excited form of oxygen is very reactive and destroys cells and other tissue components. The level of oxygen thus plays an important role for the effectiveness of the treatment. Therefore, measuring the concentration of oxygen allows to predict the tissue damages and to individualise the light dose.
The development of new approaches based on non-toxic and non-phototoxic molecular probes is currently confined to the laboratory. However, a clinical stage in dermatology will follow. The objective: to fight by means of/with the help of light what is most commonly caused by light – skin cancer.

Sciex: Dr Wagnières, Mr Varchola, you are focussing on tissue and vascular oxygenation in your research project. What exactly are you after in your micro-spectroscopic tests?
G.W.: In this Sciex project we are developing methods to measure the level of oxygen in biological tissues in real time, in order to monitor the light dose used to treat (pre)cancers by photodynamic therapy. Looking at the tissues, we noticed that oxygen concentration with a low resolution leads to important fluctuations. This is due to the fact that tissues are heterogeneous – we have small and large vessels as well as extravascular tissues. Consequently such measurements are quite unstable. This is the reason why Jaroslav performs such measurements at a microscopic scale – hence the project title 'Micro pO_2' – by coupling our existing optical fibre-based time-resolved spectrometer to a microscope. This allows us to measure oxygen in blood vessels with a much higher resolution. As a result, we will be able to assess the relative contribution of the different tissue compartments on the PDT-induced damages. More generally, this project will provide fundamental information on the dynamic processes taking place in the tissues during PDT. These dynamic processes involve the diffusion of oxygen in the tissues as well as its delivery by the blood vessels during PDT.

Does this refining of measurements require the designing of a new apparatus?
J.V.: Yes, indeed. I am improving the existing apparatus and will couple it to a modified microscope. I will have to design new components of this setup, as preliminary calibration measurements will have to be performed in a thermostabilized chamber where pO_2 and humidity can be closely controlled. It's quite challenging, but I have already performed some preparatory measurements demonstrating the proof of concept.

You are currently performing photodynamic measurements on eggs. What are the prospects of having clinical tests in the near future?
G.W.: The idea is to transfer the technology and results to the field of dermatology in order to monitor the treatment of certain precancerous skin conditions. We will measure the level of oxygen in these lesions and then adapt the light dose in order to reduce fluctuations observed between patients or lesions. As the skin is easily accessible for optical methods, we will probably start in dermatology once we have obtained the pre-clinical results.


MER Dr Georges Wagnières and Jaroslav Varchola at the lab.

Until now, conventional treatments of skin tumours imply surgery or cryotherapy. Is there some change to be expected?
G.W.: Compared with standard treatments, PDT is of interest in particular with regard to the cosmetic results of the treatment. This is due to the fact that PDT induces an apoptosis in the tissue. The fact of having this type of cell death leads to a much better cosmetic outcome after the treatment.
J.V.: Aside from this obviously big advantage, PDT has also less malicious side effects than chemotherapy because of its more local and targeted treatment.

Are there going to be clinical tests in Switzerland and Slovakia?
G.W.: Well, it has not been defined up to now. Possibly, given the links we have with different university hospitals here in Switzerland in the Leman Lake Area, the first tests will probably be done here.

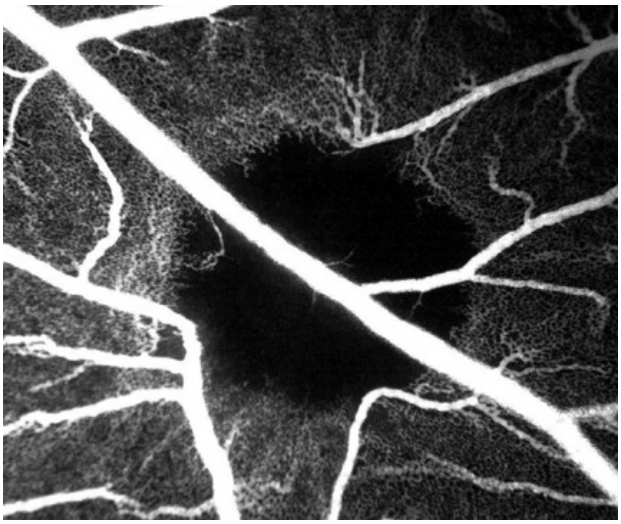
PDT's first therapeutic approaches were discovered around 1900 and it still took nearly a century until it could be applied. What were the challenges?
G.W.: In fact PDT was discovered much earlier, as papyri found in Egyptian archives testify to the use of sunlight in ancient Egyptian civilization to treat depigmentation of the skin by staining the lesions with plant extracts. Those contained, as we know, another type of photosensitizer – as you can imagine, the patent protection is not a concern {laughing}! But, as a matter of fact, scientific progress only took place when the so-called enabling technology evolved. Very bright light sources such as lasers capable of coupling high optical power in optical fibres. It was only then that PDT could be applied more successfully in other organs, like the bladder, the retina, the oesophagus or the tracheobronchial tree. It is also only in the last decades that effective drugs with acceptable side effects have been discovered. Several of them are now getting on the market.

The pO2 project with Jaroslav Varchola is the second Sciex project you lead with the same Home Mentor Prof Miskovsky. Has this also led to a larger European co-operation within an FP7 project?
G.W.: Yes, we have a joint FP7 project called CELIM connecting the Home Institution (Kosice University, Slovakia) with EPFL and different other research groups in Europe. It is about fostering excellence in multiscale cell imaging.

How do you, Mr Varchola, experience working at EPFL in the context of this pan-European research project?
J.V.: It is of course a great opportunity to be part of one of the globally leading universities. I am also very proud of my lab at the University of Kosice, as due to European grants, we are fortunate to have modern equipment. In many respects, however, it is different from my lab in Slovakia. Here at EPFL I enjoy a great working atmosphere, as it is a large campus attracting researchers from all over the world. Personally I am happy to get to know different experimental setups and to gain insights in scientific methods or approaches. I am very much looking forward to integrating these results into my PhD thesis.

Would you say that your Home Institution is less internationalized and still in the process of opening up to a global community of researchers?

Yes, and the main reason for that is that Switzerland is a wealthier country than Slovakia. We cannot offer salaries that can successfully compete and attract researchers from all over the world. We are of course co-operating with international universities and many Slovak students head abroad for an internship or a short stay, but it is mostly people from Slovakia gaining experience abroad and not the opposite. However, in our lab, the situation is now changing due to the CELIM project.
GW: Programmes like Sciex aim at fostering collaborations and establishing networks. In our case, this led to the creation of the FP7 CELIM project. It was not the only factor but it played a very important role.


Microscopic view of a tissue with dark spot in the centre where cells were destroyed by photodynamic action

Unequal funding opportunities in a competing European and international research community and the issue of brain drain are problems worth discussing in the context of transnational collaboration projects?
J.V.: I think salaries in science and engineering are one of the main reasons why people are leaving Slovakia. On the one hand, projects like CELIM try to bring Slovak researchers back to Slovakia with a European-standard salary. There are now six new co-workers, one of them being a former Sciex Fellow. On the other hand, every one of these researchers had to gain some experience abroad. With this salary policy, the brain-drain issue is being tackled and returning researchers can bring in their international experience into Slovak academia and improve science in Slovakia.

What would you say is the main added value of a Sciex project for the EPFL?
G.W.: For us it is definitively the fact that we have access to complementary know-how, infrastructure, equipment and scientific set-ups. This is why this collaboration between EPFL and Kosice University is that fruitful. We are working on similar fields, which are partly overlapping but mostly complementary. In addition, of course, the fact of having supplementary human resources helps the collaboration to progress.

What are in your view the different added values brought in by the project partners in Kosice and at EPFL?
G.W.: There's a chain of mechanisms during PDT that needs to be investigated. The Kosice group knows how to measure the quantity of singlet oxygen produced in a cell, whereas our know-how and infrastructure for this specific type of measurement is not yet that developed here at EPFL. On the other hand, at EPFL we are capable of measuring the lifetime of the excited state of photosensitizing. This makes our skills and instrumental set-ups complementary. My lab does not have the resources to do all these tasks alone.

How sustainable will this co-operation be?
G.W.: It is not in the following 2 or 3 months that Jaroslav will solve all problems with PDT... {Laughing}. Seriously, the tests we are currently conducting with one specific

molecular probe will open new research areas of interest not only in our field, but also for other types of cancer or diseases. We will first address the field of dermatology, but PDT is of interest in ophthalmology, as well as for the treatment of cancers affecting the prostate and other organs. So I definitely see a long-term future for such collaboration in order to optimize PDT as an application and understand the basic mechanisms taking place during the photosensitization process. Additionally, our work on tissue oxygenation is not only of interest in PDT but also for other treatment procedures. Of course, the know-how transfer between the two institutions takes time, is quite complex and evolving. We have identified new projects, which have nothing to do with PDT, so I would rather say that the collaboration is developing rather than staying at the level we have established during the past years.

You have made use of the Short-term visits Sciex offers to Home and Host Mentors. Was it a good experience?
G.W.: Well, these visits are crucial to conducting and reviewing the project. These things cannot be done in a Skype conversation, in particular when addressing experimental issues. It is also an opportunity to give lectures and seminars. Co-workers from Kosice University gave three at EPFL and I have given two and am preparing a 3rd one for Kosice. These exchange visits are really important in order to have the common project progressing. It is also an opportunity to write joint articles, at least two are being submitted at the moment and more will follow.
J.V.: It was also on the occasion of one of his Short-term Visits during the former Sciex project that I had the chance to meet Dr Wagnières personally and participate in his lecture about the scientific projects of his EPFL group.

What will you do after your Sciex project?
J.V.: Of course being a 2nd year PhD student, I have 2.5 years to go. I would definitely like to continue as a scientific researcher and maybe become a university teacher.

How did you prepare your Sciex Fellowship? What were the challenges you had to face?
J.V.: Our project being the second Sciex-project conducted by Dr Wagnières, it was easier for me than for others I guess. However, finding accommodation in Lausanne for 6 months was quite a challenge. Fortunately the secretary of the lab was a real help! I was also a little afraid of the usual bureaucratic hassle with permits and stuff, but it all went quite smoothly.

How would you compare the Sciex Fellowships to other funding instruments? Would you say that Sciex requires a different commitment towards your partners than other funding programmes?
G.W.: I don't think that the commitment is less strong in other projects. With Sciex, the idea is, however, to support know-how transfer of scientists rather than just financing projects.
I definitively think that the Sciex Programme is very positive. As far as our collaboration is concerned, the objectives are achieved. We have a win-win situation, as the EPFL is profiting from this programme for the reasons mentioned before and I'm convinced that this is also the case for the Slovak side. The intention is to support countries that have recently joined the European Union in the development of their academic institutions and I think this is one key aspects of the Sciex Programme. I am really confident that such an initiative helps those countries by sharing know-how, improving the exchange of information and broadening their networks. And I'm sure it will have consequences in short time on the attractiveness of, for instance, the Slovak Republic. Not only to attract Slovak researchers from abroad and reduce brain drain, but also to attract scientists like me. Maybe I will settle in Bratislava or Kosice, who knows? {Smiling} This sort of initiative definitely helps countries to reach academic levels corresponding those of high-ranked Western countries.

Mr Varchola, what will be in your baggage when returning to Kosice University? What experiences will you take back to your Home Institution?
J.V.: Well, for sure a lot of new knowledge and new methods acquired here. A different approach to doing science, a different style of working. Of course I will bring back a lot of results that will improve the experiments planned for my PhD thesis. The results from this project will be published in a new joint article and I am going to present them at a conference. And, in addition to the many pros of this project, I have a great chance to enlarge my scientific network here.

Thank you for the interview!

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