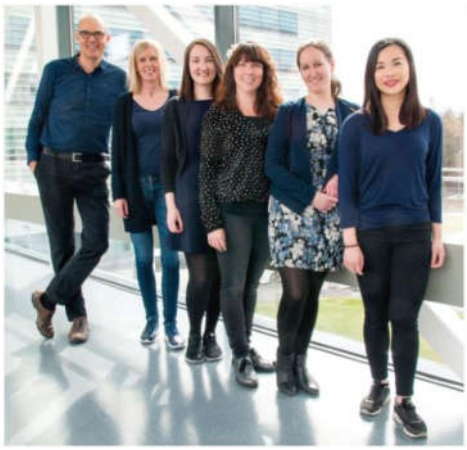
PÅL KRISTIAN SELBO'S PROJECT GROUP



Light-controlled Delivery of Cancer Immunotherapeutics

Sequestration of therapeutic agents in endosomes and lysosomes represents a major barrier to several types of cancer therapies. Another obstacle is notoriously therapy-resistant cancer stem cells (CSCs), which are suggested to be important contributors to tumor heterogeneity. Accumulating evidence proposes CSCs to be drivers of many types of cancers due to their ability to both self-renew and differentiate. Even though the tumor shrinks during cancer therapy it will unfortunately in many cases relapse after end of treatment due to the survival of the CSCs. Hence there is a high need for novel technologies that target and kill CSCs.

We are using the intracellular drug delivery technology, photochemical internalization (PCI) to release immunotherapeutic agents, e.g. CSC-targeting monoclonal antibodies linked to protein toxins (immunotoxins) or cancer vaccine antigens, from endosomes and/or lysosomes into the cytosol of cancer cells. By other words: PCI overcomes lysosome-mediated drug resistance.

The main goal of our project group is to develop and explore novel light-controlled strategies to enhance the efficacy and the specificity of cancer immunotherapies.

ONGOING PROJECTS

PCI of Immunotoxins Targeting Cancer Stem Cells

PCI of Cancer Stem Cell-Derived Vaccine Antigens

RESOURCES AND MORE INFORMATION

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Meet a Scientist: Pål Kristian Selbo, Ph.D.

edited by [Huang Chiao (Joe) Huang and Pilar Acedo Nuñez]

Dear subscribers,

We are glad to present an interview with Dr. Pål Kristian Selbo, a senior scientist and project group leader at the Norwegian Radium Hospital, Oslo University Hospital who focuses on studying light-triggered drug delivery.

Q: Why did you become a scientist?

In my childhood I was deeply captivated by the natural world. I was very interested in everything from the life on earth to the vast universe. The high fascination of biology was narrowed down to cell biology by an excellent and motivating teacher in the high school. She managed to both strengthen my curiosity and the decision to go for a university study.

Q: How did you get involved in photobiology and photodynamic therapy?

My original plan was to get a PhD in the USA directly after I received my M.Sc. degree at NTNU (Norwegian University of Science and Technology) in Trondheim, Norway in 1994. At NTNU, I was involved in a study on inflammation where I established a method to detect the mRNA for the enzyme phospholipase A2 (secreted type, sPLA2) by using *in situ* hybridization in inflamed tissue, including lung sarcoidosis (the favorite diagnosis of Dr. House…) and psoriasis. After this I was shortly involved as a research assistant in a project where we studied the role of sPLA2 in the development of atherosclerotic plaques. I used immunofluorescence for detection of the protein and became very fascinated by the use of fluorescence microscopy. I had no training in photobiology at this point; however, the mix of fluorescence and autofluorescence in the macrophages in the plaques intrigued me. Then, by chance I came over an advertisement from the Berg's lab in Oslo! Prof. Kristian Berg was looking for a PhD student for his PCI (photochemical internalization) project. On the very same day the Norwegian broadcasting channel (NRK) had as one of their breaking news reportage, one from the Norwegian Radium Hospital where photodynamic therapy was used as a promising method to treat skin cancer. I thought wow!, and immediately I sent my application. Kristian called me and invited me for an interview. And so I went down to Oslo, where I "saw the light"!

Q: You have published more than 50 scientific articles - do you have a favorite?

I have several favorites, but if I need to select only one it must be the first paper providing evidence that the PCI method works on established solid tumors: "*In vivo* documentation of photochemical internalization, a novel approach to site specific cancer therapy" (Selbo PK *et al.* Int. J. Cancer, 2001). In a proof-of-concept mouse experiment I decided to go for systemic administration of the PCI-photosensitizer (at that time AlPcS2a) and a direct tumoral injection of the ribosomal-inactivating protein toxin gelonin (detected and characterized at our hospital in 1980!) as

model PCI drug. I got no responses on gelonin alone, weak responses on PDT alone, but the combinatorial treatment group, PCI (AlPcS2a + gelonin + light) eradicated the tumors after only one treatment. I remember the excitement and the joy of making the tumor growth response curves. The first PCI paper (Berg K *et al.* 1999), which was a pure *in vitro* work, was accepted in the Advances in brief section of Cancer Research. It was of course refused in Nature, Science and Nature Biotech., the latter was very positive but asked for *in vivo* documentation...

Q: What is your philosophy for establishing and running a thriving research lab?

My number one rule is that I will have an "open door" philosophy. Members of the team should have the opportunity to come to me at any time to ask for advice. Equally important is that there should be fun and openness among the team members. Putting together a team were all can collaborate and not compete is important. Using the whip is not my style of management. Instead, I value very much the democratic and empathic way of management. I think also it is important to not have a micromanagement style, as this is damaging for the relationship. And too much pressure kills the creativity. If there are technical problems or lack of man power in the lab I roll up my sleeves and join them in the lab. I also strive to address the importance of integrity. This is obvious, but I always stress the importance of replication of results. We can only be proud of the novel findings if they can withstand the future tests by others. I also remind them by the very motivating factor that research at our hospital has resulted in worldwide approval of two PDT/PD-based drugs (Metvix® and Hexvix®, Photocure ASA). In the end here I would like to acknowledge my previous mentors and supervisors Professors Kristian Berg and Tayyaba Hasan. I just try to follow their ways to foster a right environment to grow.

Q: Can you tell us about something from your work that is exciting to you right now?

Recently, we have shown in collaboration with PCI Biotech, collaborators in Zürich (UHZ) and in Trondheim (NTNU) that we can strongly enhance the efficacy of protein and peptide-based vaccines. By using the PCI method we are able to release vaccine antigens into to cytosol before they are degraded and go to the MHC class II presentation (CD_4 activation). Instead, PCI activates the MHC class I presentation pathway resulting in robust cytotoxic T cell (CD8) activation in different experimental models. This has resulted in a clinical trial on healthy volunteers. In parallel with this I have to mention the project on using the PCI method to overcome therapy resistance including targeting of cancer stem cells.

Q: What, in your view, are the key challenges for translation of PCI/PDT into clinical practice?

Regarding PCI: PCI Biotech is working on this, as they are the owners of the PCI patents. They recently selected bile duct cancer (Cholangiocarcinoma) as a target indication. In Europe, this is a rare cancer with no efficient therapies, except surgery and stenting. However, most patients are unresectable at time of diagnosis. Hence, one major challenge is to recruit enough patients during the limited time of the study. However, the company has been very lucky to have several active sites in Germany, and the hope now is that more hospitals will join the coming phase II clinical trial both in Europe and in the USA.

Regarding PDT: We know that for some non-malignant and malignant indications, PDT has been or is a very good alternative. Except a few examples (such as Photofrin, Visudyne, Metvix/Levulan, Hexvix, Tookad) there is a lack of large clinical trials showing that PDT is the very best option for cancer therapy on specific cancer indications. This may have prevented the worldwide clinical success of PDT. A major challenge for PDT is also the competition with other emerging treatments such as checkpoint inhibitors and targeting therapeutics. A future trend may be to combine these treatments with PDT?

Q: As Senior Researcher at Oslo University Hospital and a member of the ESP Education and training committee, how do you advise scientist to approach their careers? Any tips to young photobiologists?

You should have realistic ambitions combined with a strong scientific curiosity. Seek to or stay in photobiology labs that are doing well (there are many worldwide). After training or obtaining a degree, have a stay in another photobiology lab abroad to widen up your knowledge and skills. Become a member of a professional photobiology association. Several of them have programs that are designed to foster the carrier of young photobiologists. As a member of the executive committee of the ESP I have to mention the "5th ESP Photobiology School" in Brixen/Bressanone, Italy. This summer school provides an excellent introductory overview of all main aspects of photobiology, including photodynamic therapy, presented by experts in each area. Next possibility is 10-16 June, 2018. For more information, go to: http://www.photobiology.eu/photobiology_school

Another important thing: go to international photobiology meetings and present your work and make new contacts. You need to be visible. E.g. ASP, ESP and IPA have young investigator awards and dedicated poster sessions where you can present your work if you are not selected for an oral talk. Make the posters as good as possible – you may get an award. Some societies have also dedicated sessions for grant writing and career advice. Remember to apply for travel awards. Some societies are active on social media: follow them!

Q: What do you like to do in your spare time?

With 3 kids (2, 6 and 9 years), the spare time goes mostly to family fun and activities. When it comes to books we are currently reading everything from Norwegian/Swedish children books (there are many excellent, not only Astrid Lindgren) to J.K Rowling's Harry Potter. Winter has arrived in Oslo, so skiing is a natural thing to do in the weekends. If bad weather, we go to the swimming hall. Late night TV is currently Game of Thrones. When the kids are getting more independent I plan to join the hospital volleyball team again and the hospital choir Coradium (which I co-initiated 20 years ago).