Interview with Dr. Johan E. van Lier

Johan E. van Lier received the Thomas Dougherty Award for Excellence in PDT, a lifetime achievement award, presented on the occasion of the Eighth International Conference on Porphyrins and Phthalocyanines held in Istanbul, Turkey, June 22-27 - 2014

Johan van Lier is the Jeanne and J.-Louis Lévesque Professor of radiobiology at the faculty of medicine and health sciences of the Université de Sherbrooke, Québec, Canada. He was born in Amsterdam in 1942, received his basic training in chemical engineering from the Technological University of Delft, the Netherlands (1966) and a PhD in biochemistry from the University of Texas Medical Branch at Galveston, Texas, USA (1969), under the supervision of the late Leland L. Smith. After a year as instructor at the same institution, he joined the new medical faculty of the Université de Sherbrooke where he was appointed full professor in 1981. Co-founder of the MRC group in the radiation sciences (1983), he served as department head of nuclear medicine and radiobiology from 1992-2000 and became founding-director of the Centre d'Imagerie Moléculare de Sherbrooke (CIMS) from 1998-2005. During his career he authored or co-authored well over 300 papers in peer reviewed journals covering topics from synthetic organic, radiopharmaceutical- and medicinal-chemistry, cancer research, through specialized topics in photobiology and nuclear medicine.

We asked him the following questions.

- What do prizes and awards mean for you? What other awards did you receive, any favorites?

I received a Distinguished Alumnus Award from the University of Texas graduate school of biomedical sciences at Galveston, and a lifetime achievement award from the University Hospital Center in Sherbrooke (CHUS). The Thomas Dougherty Award for Excellence in PDT is particularly precious since I consider it a recognition by my peers with whom I share the excitement of the many faces of PDT, from novel synthetic procedures, bioassays to unravel structure-activity relationships, to exploring mechanism of action at the molecular level. A psychologist-friend of mine reminded me that, to be happy, everyone needs once in a while a tap on the shoulder, for me this reward means a solid slap on the back.

- How did you get interested in photodynamic therapy? What was your first approach and how did it evolve? What do you consider your major achievement?

Changing early-on in my career from biochemistry to nuclear medicine and radiobiology meant exploring new avenues for the development of radiopharmaceuticals. In the seventies, Tc-99m was the principal radioisotope available in the nuclear medicine clinic. Since it was known that certain porphyrin derivatives showed preferential uptake by tumour tissues, porphyrins appeared to be logical candidates to tag-on radioisotopes for cancer imaging. Direct labelling with Tc failed since the central cavity cannot accommodate the large Tc-atom. We stumbled on an old Italian patent proposing metal-free sulfonated phthalocyanines as chelators to decontaminate patients exposed to uranium radionuclides. The analogy between porphyrins and phthalocyanines led us to speculate that water-soluble sulfophthalocyanines likewise could show preferential tumour uptake. On such accounts we prepared Tc-99m-sulfophthalocyanine complexes and evaluated their potential as tumour scanning agents for nuclear medicine. Although promising in animal experiments, the complex had certain shortcomings that did not warrant further pursuit to a clinical setting. Having gained some experience in phthalocyanine chemistry we sought to explore other potential applications and I presented our results at one of the early PDT symposia in California. Here it became evident that phthalocyanines could be potent photosensitizers for PDT and I changed my research focus accordingly. Initially we addressed the role of the central metal ion on in vitro PDT efficacy and we published the first results exactly 30 years ago. Realizing that the degree of sulfonation is another crucial factor responsible for the variations in photodynamic activities between different preparations, we purified differently sulfonated metallo phthalocyanines accordingly to the degree of sulfonation and showed that the amphiphilic, adjacently substituted disulfonated derivatives exhibit the best cell penetrating capacity and highest in vivo photodynamic potency. Since disulfonated phthalocyanines are composed of many positional isomers, we explored synthetic routes to prepare phthalocyanines that mimic the disulfonated derivatives, but that can be prepared as pure, single products. This evolved in an extensive project, comparing different synthetic approaches and testing series of new analogs in various in vitro and animal models, from which a trisulfonated derivative, bearing a six-carbon side-

chain, emerged as a lead. More recently, we explored the use of phthalocyanines as theranostics, e.g radiolabeled analogs for PET imaging and radiotherapy, in addition to fluorescence imaging and PDT. Access to PET isotopes and animal scanners allowed us to explore FDG-PET to monitor real-time tumour response to PDT, providing a rapid test to predict action mechanisms and long-term tumor response, using a minimal number of animals.

- You worked in another research field, in parallel to PDT, and in which you have been even more successful, which is a rare situation. Can you present it, as most of our readers may not be aware?

As an alternative to laboratory assays on biopsy material, non-invasive nuclear imaging of estrogen receptor densities in breast cancer patients has been researched by many groups. This was, and still is, perceived as a valid tool for early detection of metastases to guide treatment and follow-up. In the seventies the most suitable radioisotope to label estrogens, approved for human use, was I-131, while for chemistry and preclinical testing commercially available I-125 was most convenient. Many efforts were made to develop radiolabeled estrogens featuring a stable C-I bond to avoid in vivo de-iodination, while additional substituents were explored to optimize receptor binding affinity and target selectivity. We likewise prepared series of new analogs, tested various in vitro binding affinities, established biodistribution pattern in animal models and developed structure-activity relationships, from which we concluded that the addition of a non-radioactive F atom at the 4-position of estradiol should further improve receptor-mediated tumor-uptake. With the introduction of medical cyclotrons and PET cameras in the nineties, short-lived F-18 became available and 17β-[F-18]fluoroestradiol (FES) was introduced in the USA for PET imaging in breast cancer patients. Our prior experience led us to the prepare a 4-fluoro,11β-methoxy derivative of FES (FM-FES) and its improved imaging potential was confirmed through preclinical assays. FM-FES is currently in a Phase II trial in our PET clinic, and direct comparison with FES reveals that FM-FES is capable of imaging smaller receptor-positive lesions and could be adopted as a routine clinical breast cancer scanning agent. I believe this is a need example where drug development in an academic setting went all the way from the lab-bench to the patient's bed site.

- What would you do differently if you could modify the past?

After finishing my graduate studies in Texas, and once I had decided to move on, there were many options. Largely due to the publishing-fury of my thesis director I had an overblown CV and it would have been no problem to join some top laboratory for further postdoctoral training. Another option was to move to the pharmaceutical industry and make some money. However, discoveries I made during my graduate research had ignited this strange ambition to strike out on one's own, to explore something revolutionary like the evolutionary link between cholesterol autoxidation and steroid hormone biosynthesis, and when I was offered a junior faculty position in Sherbrooke with an open slate for my research aspirations, but with the understanding that I would teach biochemistry to medical students in French, I replied without hesitation "pas de problème", which at the time was about the extent of my fluency in Napoleon's language. Once established in Sherbrooke I had the fortune to work with great, young, enthusiastic colleagues, who's complementary scientific interests allowed me to explore new research directions, to attract ambitious students, while leaving no time to look back or elsewhere, I guess I had found my niche.

- What are the five words coming to your mind when you hear "research"?

Passion, dedication, challenge, euphoria, satisfaction, and I'll throw in frustration, not necessarily in that order.

- Is there anything you wish to add?

Apart from PDT being a gratifying topic for my own career, it has proven rewarding for training graduate students, exposing them to basic synthetic chemistry procedures, in vitro assays, tumor response studies in animal models and molecular imaging techniques. Meetings, like the ICPP8 organized this year in Istanbul, bring together many complementary disciplines connected through common interests in porphyrins and phthalocyanines, providing an unique opportunity for students and faculty to interact and explore new avenues for their future endeavors.