BIO Integration

Voice Series: Interview with Prof. Dr. Sangyong Jon, KAIST Chair Professor

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Foreword

Prof. Sangyong Jon received his Bachelor's, Master's and PhD degrees from Korea Advanced Institute of Science and Technology (KAIST). Now, he has returned to KAIST as the Chair Professor at the Department of Biological Sciences and also as the Director of the Center for Precision Bio-Nanomedicine. His research interest lies at the interface of biomedicine, biotechnology, biomaterials, and nanomedicine. His major research focus is on the development of various platform technologies that may address unmet medical needs. Some of the platforms his team developed over a decade ago include the "Aptide" platform that enables the screening and identification of high-affinity peptides for various protein targets such as antibodies; the "Bilirubin Nanomedicine" platform that provides a universal nanomedicine solution for various inflammatory diseases, and the "Cancer Stem Cell" platform that enables facile generation of three-dimensional (3D) cancer stem cell spheroids from various differentiated cancer cells for basic cancer research and drug development. Prof. Jon has received numerous awards and honors including the 2020 KAIST Innovation Prize and the 2015 College of Fellows at the American Institute of Medical Imaging and Biological Engineering.

His most recent innovation is the development of bilirubin-based nanoparticles, which has demonstrated its therapeutic feasibility in many pre-clinical disease models, including inflammatory bowel disease. More interestingly, he cofounded a start-up company (BiliX Inc) based on the platform technology. In this interview, we learn first-hand about Prof. Jon's exciting innovation and the importance of integrating basic science and translational medicine.

EE: Thank you Prof. Jon for being so gracious in accepting the invitation of *BIOI* to being interviewed. First of all, congratulations on your creation of "Bilirubin-based Nanomedicine". To the best of our knowledge, this is the first bioactive compound derived from the human body that shows immense promise in multiple diseases. Could you please tell us a little bit of background about how this whole idea started?

S Jon: Bilirubin, which you may be heard of it once or are familiar with, is an endogenous organic compound that has been used as a biomarker in blood analysis during regular medical examination at hospitals. The reason for that is it is responsible for causing clinical jaundice as a result of abnormal high level of serum bilirubin, called hyperbilirubinemia, which is sign of severe diseases including hepatitis and pancreatic cancer. For those reasons, most of medical doctors/clinicians have been considering it as a bad guy. However, increasing evidence accumulated so far clearly indicates that bilirubin functions as a potent antioxidant and anti-inflammatory agent and thus plays an important role in protecting our body from oxidative damage. Moreover, numerous epidemiological studies on the relationship between serum bilirubin level and human health revealed that individuals having slightly high serum bilirubin level experience a lot of health benefits such as much lower risk of having major cardiovascular diseases and even cancers. In line with that, many scientists already demonstrated the potent therapeutic efficacy of bilirubin in a variety of animal models of inflammatory diseases. All this evidence strongly suggest the possibility of bilirubin to be developed as a therapeutic to treat various inflammatory diseases. Despite that, little attention was paid to implementation of bilirubin-based therapeutic development. This may be due to its insolubility in aqueous medium and also its potential toxicity such as jaundice-associated adverse effects when it is administered to our body. How to solve the problem associated with bilirubin was relatively easy to scientists trained as organic chemists. What we did is simply attach a hydrophilic PEG to one of two available carboxylic acids of bilirubin and obtain mono PEGylated bilirubin, which could form uniform-sized nanoparticles in aqueous medium via self-assembly. The mono PEGylated bilirubin-based nanoparticle is the bilirubin nanomedicine platform we developed, which does not cause any jaundice while preserving the original biological activity of native bilirubin [1–4]. So far, we have demonstrated the highly potent therapeutic efficacy of bilirubin nanomedicine in various animal models of inflammatory diseases, including the hepatic ischemia–reperfusion injury model, acute asthma, inflammatory bowel disease, and islet transplantation. Based on the validation of proof-of-concept studies, I founded a start-up called BiliX.

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EE: What was your major concern during the progress of this research? Did you face any major stumbling block along the way? How did you overcome these problems?

S Jon: Actually, the bilirubin provided by vendors is obtained from porcine blood. Thus, there is big concern whether animal blood-derived bilirubin is okay to be used to synthesize PEGylated bilirubin and eventually get FDA approval as a nanomedicine. Another issue was that a main form of bilirubin is an IX alpha isomer that has two available carboxylic acids in the asymmetric position for PEG conjugation; for this reason, mono PEGylation always produces two regioisomers of PEGylated bilirubin, which are hard-to-separate from each other. To overcome these two critical issues, we decided to chemically synthesize a bilirubin III alpha isomer (which has a symmetrical structure unlike the IX alpha isomer). After considerable efforts, our BiliX team succeeded in obtaining bilirubin III alpha by chemical means, thus, now we do not worry about an animal source-associated FDA concern. Also, mono PEGylation to bilirubin III alpha does not produce regioisomer either. By doing it this way, we were able to address two key critical concerns hampering our drug development.

EE: Would you say that you have found the "magic bullet" of nanomedicine-based drugs? What are the obstacles that you might face down the road?

S Jon: No, I don't think so. The bilirubin nanomedicine we are developing for clinical trials is just a feasible option for treating multiple intractable inflammatory diseases that do not have appropriate drugs yet. Nanomedicine has some advantages over conventional small molecular drugs, including a longer blood circulation half-life and targeting the disease site in a passive manner. However, on the other hand, quality-controlled manufacturing of nanomedicine on a large scale is the critical issue with most nanomaterials-based therapeutics. In addition to the critical issue, the documentation required for FDA approval may be different for nanomedicine from conventional drugs, which is also another issue that needs to be addressed.

EE: From your CV, we understood that you came from a pure chemistry background. When did you start transforming chemical studies into nanomedicine and now into translational studies? Is the integration of these fields difficult?

S Jon: Yes, I majored in Chemistry and received my PhD in Organic Chemistry, more specifically, in the development of methodology in organic synthesis. Around the time I received my PhD, I thought about changing my research field to a research area to which I can apply my strong ability to synthesize organic compounds and materials. That thought drove me to join a laboratory focusing on "supramolecular chemistry" as a postdoc, in which I learned a lot about the principle of molecular recognition between organic and biomolecules. After I finished the first postdoc experience in supramolecular chemistry, I decided to expand my research interests further to more real application-related research fields. Thus, I started my second postdoc position in the Langer Lab at the Massachusetts Institute of Technology (MIT) where I learned a lot of biomaterials and nanomedicine-related knowledge and research trends, which made possible the foundation of my own lab. The most important thing I would like to emphasize through a career of mine is that my expertise in organic chemistry and the ability to be able to synthesize "target desired compounds" has contributed substantially in designing and creating novel materials for biomedical applications.

EE: How did you manage to have a start-up company? What preparation is needed for "bench-to-clinics" transition? Would you advise other scientists to do the same?

S Jon: First of all, critically analyze whether a platform or a technology of yours can create value in the area of business the technology will be used. In that way, it is critical to give weight to what other established technologies and companies can't do and only yours can do. Is there any niche area or market your can create and compete with? Novelty and innovativeness of your science and technology cannot guarantee the success of your start-up in the business. Second, find and make the best team, including a CEO and a CTO/CSO. Especially a professional CEO is the most important, who is able to dedicate his/her best endeavor for the company. Because you can act as a CSO/CTO, the position is not an necessity in an early-stage start-up. For my experience, we faced a lot of unexpected obstacles, including scalability, manufacturing issues, and quality control of the nanomedicine. Over the course of R&D, I realized that development process is more rather difficult than research.

EE: What advice do you have for the young generation of scientists today?

S Jon: I would like to say scientists regardless of generation should try to think outside the box and have critical views on research findings or published discoveries. As an example of mine, as I said it in the beginning, although considerable evidence of its clear-cut therapeutic outcomes in many disease indications has been accumulated in recent decades, none of scientists have been trying to overcome the solubility issue on bilirubin and develop it as a therapeutic. Why is that? Because medical doctors and scientists have maintained the long-standing stereotype on bilirubin, which is, it is a waste product and may be a harmful compound. If we did not break the stereotype, bilirubin nanomedicine and a start-up BiliX could not be born.

EE: Do you have any advice for *BIO Integration* as a new journal?

S Jon: As you know, a considerable number of journals including highly reputed traditional journals and even newly launched journals have already covered multidisciplinary research areas and continue to expand their scope to fields they have not covered before. Why? It is presumably because fusion between different research disciplines or technologies is a general trend in science and technology at present as well as for the future. Under the circumstances,

the *BIO Integration* journal needs to appeal its own uniqueness that can differentiate it from other already well-established multidisciplinary journals. What would such a uniqueness be that *BIO Integration* can sell? A suggestion of mine is your journal may be able to benchmark the approach of the *Journal of Visualized Experiments* (*JoVE Journal*) that is the first journal publishing a video manuscript, not in print. I would say such a unique approach is needed for *BIO Integration* to be successfully launched or to become popular in our scientific society.

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