BIO Integration

BIOI Virtual Academic Series PART 2: Frontiers and Multidisciplinarity in Nanomedicine

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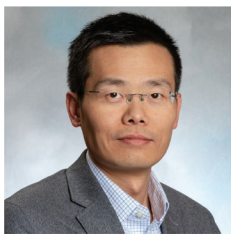
Nanomedicine research which covers many fields including drug delivery, cancer therapy vaccine development, antimicrobial diagnostic imaging, wearable device transplantation, and high-throughput screening, has become an important development direction of modern medicine. On July 29th, 2020, Frontiers and Interdisciplinarity in Nanomedicine, the second session of the online academic exchange: Basic and Applied Science: Transformative Discipline Fusion, held by *BIO Integration* (*BIOI*), had attracted more than 3000 online viewers and won unanimous praise and recognition from its peers. Herein, we summarize the key points of each talk and we hope that the readers can learn more about integration across scientific fields.

Sangyong Jon: Integration of Naturally Occurring Bioactive Compounds into Nanomedicine

Professor Sangyong Jon, from the Korea Institute of Science and Technology, brought us a report entitled Integration of Naturally Occurring Bioactive Compounds into Nanomedicine. Prior to talking about the main point, he introduced his four major current focus of interest in his lab, namely the development of bipodal peptide binders (aptide) that could be used in numerous clinical applications (i.e. targeting ligand, therapeutic) [1–9], the development of surface-cue-induced cancer stem cells [10], the creation of nanoparticles (NPs) using naturally occurring bioactive compounds [11, 12], and the development of endogenous bilirubin NPs for disease treatment [13–18].

In his presentation, Professor Jon spoke about the study of bilirubin NPs as an example to show how nanomedicine could be combined with naturally occurring active compounds. His research group modified polyethylene glycol (PEG) to improve the biocompatibility of bilirubin NPs *in vivo*, added the response characteristics of internal and external sources on the basis of the NPs, designed a new drug delivery system, and finally further improved the delivery efficiency of bilirubin for the treatment of tumor and inflammatory diseases. Being trained as an organic chemist, Professor Jon utilized the integration of organic chemistry, bioconjugation techniques, and an endogenous component to realize a simple yet potent and robust nanomedicine for the treatment of various diseases.



Jinjun Shi: RNA Nanomedicine: Integration of Nanotechnology, RNA Delivery, and Biology

Professor Jinjun Shi, a Professor from Harvard Medical School, shared his paper on RNA Nanomedicine: Integration of Nanotechnology, RNA Delivery, and Biology. Professor Shi introduced the most recent RNA-based therapies and their advances in tumor immunotherapy. The bottleneck of RNA-based therapeutics is first and foremost a delivery issue. Having a short half-life (~5 min), safe and effective delivery of RNAs to a tumor site has been the holy grail in the field. Nevertheless, in-depth study of biomaterials and their properties, their *in vivo* biological interaction, and the properties of the biomolecules (i.e. siRNA, miRNA, and protein) is crucial in the development of an optimal delivery system.

In Shi's lab, they utilized the inherent properties of the tumor microenvironment (i.e. high redox level) and used NPs to deliver mRNA that effectively encoded the phosphatase and tensin homolog (*PTEN*) gene to tumor sites, so as to restore the sensitivity of tumor cells and improve the therapeutic effect of the tumor. This work was published in *Nature Biomedical Engineering* in 2018 [19].

In addition, Shi's lab is also working on targeting macrophages in atherosclerotic plagues using polymeric NPs with stabilin-2 peptide targeting. They proved that this NP system works well to reduce atherosclerotic plagues in the blood vessels and therefore is a promising approach to treat systemic arthrosclerosis [20].

Professor Shi emphasized that the combination of the understanding of tumor biology, RNA technology, and nanomedicine will become an important research direction of clinical disease treatment in the future.

Xiaoding Xu: Nanoparticles (NPs)-meditated LncRNA Silencing for Effective Cancer Radiotherapy

Professor Xu Xiaoding, from Sun Yat-Sen Memorial Hospital, Guangzhou, China, presented a paper titled Nanoparticles (NP)s-

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meditated LncRNA Silencing for Effective Cancer Radiotherapy, and introduced the use of NPs-mediated specific long non-coding RNA (LncRNA) silence to reduce radiotherapy tolerance of patients with triple-negative breast cancer, so as to improve the effect of radiotherapy on the treatment effect and prognosis of patients. In this study, his team first identified a hardcore clinical problem – radioresistance in cancer therapy, for which they investigated the mechanism of this resistance. Using patients' tumor samples, they carried out omics technology to screen out a novel LncRNA (lncarAP1-AS1), which is one of the top candidates that induces radioresistance in patients with triple negative breast cancer (TNBC).

By using an endosome pH responsive NP previously developed by Professor Xu's team [21], they developed an NP system that could sustainably deliver the lncRNA AFAP1-AS1 into cancer cells and subsequently into tumors. In an *in vivo* xenograft model they observed a significant reduction in radioresistance in mice treated with NP(AFAP1-AS1), indicating the feasibility of this nanodelivery system for the clinical intervention of radioresistance.

This elegant work has just been accepted in *Advanced Science* [Nanoparticles (NPs)-meditated LncRNA AFAP1-AS1Silencing to Block Wnt/β-catenin Signaling Pathway for Synergistic Reversal of Radioresistance and Effective Cancer Radiotherapy].

Zhen Yuan: Photoacoustic Imaging Guided Cancer Theranostics

Professor Zhen Yuan, from the University of Macau, China, presented a wonderful academic report entitled Photoacoustic Imaging Theranostics. In this report, he analyzed the research background of photoacoustic (PA) imaging and photothermal therapy [22–24], artificial intelligence [25], and the challenges they faced in the development of these technics; and combined with the research results of his team, put forward his own unique views on its development and challenges.

Yuan's team built triangular bovine serum albumin (BSA)-modified copper sulfide (CuS) nanoprobes with near infrared (NIR) absorption, which were expected to be good nanoplatformms for designing multifunctional nanoprobes that involve the molecular imaging for disease diagnosis and personalized treatment guidance [26].

In another study, they constructed an ultrasmall phototheranostic nanoagent, named DPP-BTzTD Pdots. The unique design of low-bandgap D-A p-conjugated polymer (DPP-BTzTD), together with a modified preparation method, allowed the researchers to fabricate Pdots in ultrasmall particle sizes. Extensive experimental tests have demonstrated that the constructed Pdots exhibit excellent photostability, strong NIR-II absorption, good biocompatibility, bright PA signals, and high photothermal conversion efficiency (53%). The experimental results showed that the photothermal imaging and PA imaging mediated by DPP-BTZTD Pdots could effectively capture the structure and function information of tumors, and achieve A significant tumor ablation effect simultaneously [27]. Based on the these advantages, the DPP-BTZTD Pdots has great potential for clinical translation.

From this virtual academic conference, the take-home message today is this: there are many ways to solve a problem, and the solution might be around us. Nanomedicine is not a magic bullet that could solve all the clinical problems, but by integration of various fields, it becomes one of the most effective ways that could interfere with the many points or pathways in various diseases. We applaud all the researchers and scientist that are working hard today to find new interventions for the betterment of human mankind.

References

[1] Kim H, Hwang DB, Choi M, Lee S, Kang S, et al. Antibody-assisted delivery of a peptide-drug conjugate for targeted cancer therapy. Mol Pharm 2019;16:165-72. [PMID: 30521347 DOI: 10.1021/acs.molpharmaceut.8b00924]

[2] Kim D, Jeon H, Ahn S, Choi WI, Kim S, et al. An approach for half-life extension and activity preservation of an anti-diabetic peptide drug based on genetic fusion with an albumin-binding aptide. J Control Release 2017;256:114-20. [PMID: 28457895 DOI: 10.1016/j.jconrel.2017.04.036]

[3] Saw PE, Kim S, Lee I-h, Park J, Yu M, et al. Aptide-conjugated liposome targeting tumor-associated fibronectin for glioma therapy. J Mater Chem B 2013;1:4723-6. [PMID: 32261155 DOI: 10.1039/c3tb20815j]

[4] Saw PE, Park J, Jon S, Farokhzad OC. A drug-delivery strategy for overcoming drug resistance in breast cancer through targeting of oncofetal fibronectin. Nanomedicine 2017;13:713-22. [PMID: 27769887 DOI: 10.1016/j.nano.2016.10.005]

[5] Lee Y, Kim S, Kim D, Jon S. A histone H1-binding-aptide-based apoptosis imaging probe for monitoring tumor responses to cancer therapy. Med Chem Comm 2017;8:390-3. [PMID: 30108755 DOI: 10.1039/c6md00696e]

[6] Kim D, Lee IH, Kim S, Choi M, Kim H, et al. A specific STAT3-binding peptide exerts antiproliferative effects and antitumor activity by inhibiting STAT3 phosphorylation and signaling. Cancer Res 2014;74:2144-51. [PMID: 24576829 DOI: 10.1158/0008-5472.CAN-13-2187]

[7] Kim H, Lee Y, Lee IH, Kim S, Kim D, et al. Synthesis and therapeutic evaluation of an aptide-docetaxel conjugate targeting tumor-associated fibronectin. J Control Release 2014;178:118-24. [PMID: 24462899 DOI: 10.1016/j.jconrel.2014.01.015]

[8] Jeon H, Kim D, Choi M, Kang S, Kim JY, et al. Targeted cancer therapy using fusion protein of TNFalpha and tumor-associated fibronectin-specific aptide. Mol Pharm 2017;14:3772-9. [PMID: 28969419 DOI: 10.1021/acs.molpharmaceut.7b00520]

[9] Jo DH, Kim S, Kim D, Kim JH, Jon S, et al. VEGF-binding aptides and the inhibition of choroidal and retinal neovascularization. Biomaterials 2014;35:3052-9. [PMID: 24388818 DOI: 10.1016/j.biomaterials.2013.12.031]

[10] Choi M, Yu SJ, Choi Y, Lee HR, Lee E, et al. Polymer thin film-induced tumor spheroids acquire cancer stem cell-like properties. Cancer Res 2018;78:6890-902. [PMID: 30352813 DOI: 10.1158/0008-5472.CAN-18-0927]

[11] Saw PE, Lee S, Jon S. Naturally occurring bioactive compound-derived nanoparticles for biomedical applications. Adv Ther 2019;2:1800146. [DOI: 10.1002/adtp.201800146]

[12] Chung CH, Jung W, Keum H, Kim TW, Jon S. Nanoparticles derived from the natural antioxidant rosmarinic acid ameliorate acute inflammatory bowel disease. ACS Nano 2020;14:6887-96. [PMID: 32449857 DOI: 10.1021/acsnano.0c01018]

[13] Kim JY, Lee DY, Kang S, Miao W, Kim H, et al. Bilirubin nanoparticle preconditioning protects against hepatic ischemia-reperfusion injury. Biomaterials 2017;133:1-10. [PMID: 28414974 DOI: 10.1016/j.biomaterials.2017.04.011]

[14] Lee S, Lee Y, Kim H, Lee DY, Jon S. Bilirubin nanoparticle-assisted delivery of a small molecule-drug conjugate for targeted cancer therapy. Biomacromolecules 2018;19:2270-7. [PMID: 29712433 DOI: 10.1021/acs.biomac.8b00189]

[15] Kim DE, Lee Y, Kim M, Lee S, Jon S, et al. Bilirubin nanoparticles ameliorate allergic lung inflammation in a mouse model of asthma. Biomaterials 2017;140:37-44. [PMID: 28624706 DOI: 10.1016/j.biomaterials.2017.06.014]

[16] Lee Y, Lee S, Jon S. Biotinylated bilirubin nanoparticles as a tumor microenvironment-responsive drug delivery system for targeted cancer therapy. Adv Sci 2018;5:1800017. [PMID: 29938184 DOI: 10.1002/advs.201800017]

[17] Lee DY, Kim JY, Lee Y, Lee S, Miao W, et al. Black pigment gallstone inspired platinum-chelated bilirubin nanoparticles for combined photoacoustic imaging and photothermal therapy of cancers. Angewandte Chemie Int Ed Engl 2017;56:13684-8. [PMID: 28869355 DOI: 10.1002/anie.201707137]

[18] Kim MJ, Lee Y, Jon S, Lee DY. PEGylated bilirubin nanoparticle as an anti-oxidative and anti-inflammatory demulcent in pancreatic islet xenotransplantation. Biomaterials 2017;133:242-52. [PMID: 28448818 DOI: 10.1016/j.biomaterials.2017.04.029]

[19] Islam MA, Xu Y, Tao W, Ubellacker JM, Lim M, et al. Restoration of tumour-growth suppression in vivo via systemic nanoparticle-mediated delivery of PTEN mRNA. Nature Biomed Eng 2018;2:850-64. [PMID: 31015614 DOI: 10.1038/s41551-018-0284-0]

[20] Tao W, Yurdagul Jr. A, Kong N, Li W, Wang X, et al. siRNA nanoparticles targeting CaMKIIgamma in lesional macrophages improve atherosclerotic plaque stability in mice. Sci Transl Med 2020;12:eaay1063. [PMID: 32718990 DOI: 10.1126/scitranslmed.aay1063]

[21] Xu X, Wu J, Liu S, Saw PE, Tao W, et al. Redox-responsive nanoparticle-mediated systemic RNAi for effective cancer therapy. Small 2018;14:e1802565. [PMID: 30230235 DOI: 10.1002/smll.201802565]

[22] Hu Z, Lam KF, Yuan Z. Effective connectivity of the fronto-parietal network during the tangram task in a natural environment. Neuroscience 2019;422:202-11. [PMID: 31682954 DOI: 10.1016/j.neuroscience.2019.09.021]

[23] Wang M, Yuan Z, Niu H. Reliability evaluation on weighted graph metrics of fNIRS brain networks. Quant Imaging Med Surg 2019;9:832-41. [PMID: 31281779 DOI: 10.21037/qims.2019.05.08]

[24] Wang MY, Lu FM, Hu Z, Zhang J, Yuan Z. Optical mapping of prefrontal brain connectivity and activation during emotion anticipation. Behav Brain Res 2018;350:122-8. [PMID: 29752969 DOI: 10.1016/j.bbr.2018.04.051]

[25] Ieong HF, Gao F, Yuan Z. Machine learning: assessing neurovascular signals in the prefrontal cortex with non-invasive bimodal electro-optical neuroimaging in opiate addiction. Sci Rep 2019;9:18262. [PMID: 31797878 DOI: 10.1038/s41598-019-54316-6]

[26] Gao D, Sheng Z, Liu Y, Hu D, Zhang J, et al. Photoacoustic imaging: protein-modified CuS nanotriangles: a potential multimodal nanoplatform for *in vivo* tumor photoacoustic/magnetic resonance dual-modal imaging (Adv. Healthcare Mater. 1/2017). Adv Healthc Mater 2017;6. [DOI: 10.1002/adhm.201770001]

[27] Men X, Wang F, Chen H, Liu Y, Men X, et al. Ultrasmall semiconducting polymer dots with rapid clearance for second near-infrared photoacoustic imaging and photothermal cancer therapy. Adv Funct Mater 2020;30:1909673. [DOI: 10.1002/adfm.201909673]