How nanomedicine can be used in the treatment of tumors: an interview with Dr Gang Zheng

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Dr Zheng received his PhD in 1999 from SUNY Buffalo in Medicinal Chemistry. Following 2 years of post-doctoral training in photodynamic therapy at the Roswell Park Cancer Institute, he joined the University of Pennsylvania in 2001 as an Assistant Professor of Radiology, where he established the molecular imaging chemistry program and introduced photodynamic molecular beacons and lipoprotein-like nanoparticles. Since moving to Canada in 2006, his research has been focused on developing clinically translatable technology platforms to combat cancer. His lab discovered porphyrin nanotechnology that opened a new frontier in cancer imaging and therapy (*Nature Materials* 2011), which was named one of the 'top 10 cancer breakthroughs of 2011' by the Canadian Cancer Society. Dr Zheng is an Associate Editor for Bioconjugate Chemistry and a Fellow of the American Institute for Medical and Biological Engineering.

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Could you please begin by introducing yourself, your academic background & your work to date?

I am a Professor of Medical Biophysics, Biomedical Engineering and Pharmaceutical Sciences at the University of Toronto, and a senior scientist at the Princess Margaret Cancer Centre. My group has been working on the development of clinically translatable novel agents, both single molecule and nanoparticles, for cancer imaging and multimodal therapies. More recently, my group's focus also includes the emerging approaches that aim to enhance nanoparticle-mediated drug delivery, specifically the use of light, ultrasound and hyperthermia.

Marta Overchuk is my senior PhD student and a Vanier Scholar. A biochemist by training, Marta is now exploring the use of photodynamic therapy to change the tumor microenvironment and enhance the delivery and efficacy of US FDA-approved nanomedicines. She looks forward to applying these findings in the future as she pursues a career in academia focused on improving the clinical utility and versatility of photodynamic therapy.

Are there any colleagues or role models in the field whom you particularly looked up to in your early career or are continually inspired by?

When I was a young assistant professor at the University of Pennsylvania, two persons had major influence on me. One is the great Britton Chance. He advised me on staying true to the spirit of collegiality; to be always humble and willing to share and learn from others. He also asked me to keep exploring, to enjoy the fun of science and be persistent, all life-long lessons that I took deeply into my heart and continuously relied upon. The other is Greg Lanza. I vividly remember our long conversation on a dinner cruise after my talk at the First Society for Molecular Imaging Meeting in Boston in 2003. He encouraged me to embrace and take full advantage of my role as the chemist in a cancer center, and to always challenge myself to develop clinically translatable technologies that can specifically address unmet clinical needs – words of wisdom that served me well ever since.

Please describe the work you are currently conducting on 'Light, heat and sound to enhance nanoparticle delivery to the tumors', which you recently presented at the ACS National Meeting in Boston 2018

The overwhelming growth witnessed in the last two decades in the field of nanomedicine was largely triggered by the idea that nanoparticles, unlike small molecules, can preferentially accumulate in solid tumors due to the enhanced permeability and retention (EPR) effect [1]. Here, leaky tumor vasculature and deficient lymphatic drainage result in the physical entrapment of nanoparticles in the tumor interstitium. Unfortunately, the prevalence of the EPR paradigm has promoted a simplified understanding of the tumor microenvironment, which in turn has created a disconnect between the fields of tumor biology and material development. The vast majority of work to date has focused on perfecting nanoparticle formulations to extend their plasma circulation time, varying nanoparticle size and shape, and developing surface targeting strategies. 30 years after the discovery of the EPR effect, the unprecedented number of papers published in the field of nanomedicine remains disproportionately low relative to the number of nanoformulations used clinically. Such low success can in part be explained by a lack of regulatory guidelines, high costs, and difficulties in material scale-up. However, it has become increasingly clear that the 'ideal' nanoparticle formulation is not likely to provide a meaningful solution over traditional therapies without overcoming obstacles created by the tumor microenvironment.

Recent years have been marked by an increasing number of reports describing the use of 'priming' strategies that alter one or several tumor microenvironment components to enhance the delivery and efficacy of nanomedicines [2]. For example, it has been shown that photodynamic therapy, where focused light is applied in combination with a photosensitizer to induce localized tissue damage, has the potential to enhance nanoparticle delivery to tumors [3]. We took this idea of localized therapy and drug delivery one step further by designing a targeted photosensitizer that can bind specifically to cancer cells and make PDT even more controllable. The thought is to induce just the right amount of vascular and cellular damage to facilitate extravasation and interstitial diffusion of the subsequently injected nanomedicines without causing vascular shutdown.

Another direction our lab is pursuing is the use of focused ultrasound in combination with gas-filled microbubbles to overcome natural delivery barriers, such as the blood–brain barrier. Upon exposure to low-frequency therapeutic ultrasound, microbubbles have been shown to induce transient, safe and localized opening of vasculature, which has been exploited for the delivery of either microbubble-loaded or co-injected therapeutic agents. Moreover, our group discovered that, under similar ultrasound exposures, porphyrin microbubbles can undergo an *in situ* conversion into nano-sized bubbles [4]. This discovery enables the development of a novel EPR-independent nanoparticle delivery strategy in which co-administration of ultrasound and systemically injected microbubbles would both locally generate porphyrin nanoparticles while also increasing vascular leakiness, allowing for combined tumor imaging and therapy [5]. Both light and ultrasound-enabled strategies described above offer an alternative to the EPR-centered delivery paradigm used ubiquitously thus far, promising more predictable and controlled tumor nanomedicine delivery.

What are the implications of this work on the nanomedicine field?

Combination therapies are effective in most cancers. Finding combination regimens that allow the full potential of nanomedicines to be unleashed is a highly promising avenue toward delivering therapeutic advantages to cancer patients who will receive these treatments. For example, photodynamic therapy is already applied clinically for esophageal, prostate and non-small-cell lung cancer treatment, so maximizing its efficacy in combination with drug-carrying nanoformulations could markedly improve therapeutic outcomes. Similarly, better understanding of the effects of focused ultrasound in combination with microbubbles holds promise to change the way we manage deep-seated untreatable solid tumors like glioblastoma.

What do you see as the biggest area of growth for nanoparticle delivery in nanomedicine?

There are two major positive trends in nanomedicine that we would like to highlight. First, after the field has become saturated with studies describing overly complex systems, a shift has occurred toward more simple systems. This shift has multiple implications: simpler systems have better reproducibility, lower costs and are more easily translatable. The second trend is the increasing number of attempts to integrate novel therapeutic approaches with currently existing treatment paradigms. For example, radiation therapy can enhance nanomedicine, and conversely nanomedicine itself can enhance the effects of radiation therapy. In the first paradigm, radiation treatment has been shown to change intratumoral pressure dynamics, leading to enhanced nanoparticle tumor uptake [6]. In the

second case, established immune-mediated effects of radiation can be boosted by specially designed nanoparticles that can capture tumor antigens and deliver them to antigen-presenting cells [7]. It is thus evident that these techniques, when applied in a complimentary approach, create symbiotic pathways. Overall, marrying materials and engineering perspectives with biological and clinical needs will help to eliminate the disconnect between the biology, material design and clinical reality.

What do you hope to achieve in your career? What are your long-term scientific goals?

For me, the most important goal of my research is to develop and implement safe and effective treatment options that will benefit cancer patients. Another long-term scientific goal is to place the field of porphyrin nanomedicine, which I help to cultivate, into the center of nanotechnology inventions and clinical breakthroughs. Perhaps equally important is to nurture my students, aka my ‘Gangsters’, into becoming independent thinkers and doers, and to enjoy seeing their career blossoming.

Marta is hoping to synergize her knowledge in biology, materials design and biomedical engineering to make photodynamic therapy a robust therapeutic option used primarily or adjunctively to treat a greater variety of cancer types than it is approved for currently. Ultimately, she hopes to better establish photodynamic therapy as a mainstay clinical treatment option much in the way that radiation, chemotherapy and surgery are used ubiquitously alone or in combination to maximize patient outcomes. She looks forward to working alongside and sharing ideas with diverse scientific, clinical and industrial collaborators to achieve her career goals.

Do you have any final comments for the readers of *Nanomedicine*?

Cancer nanomedicine field is now at the tipping point of its development and, based on our experience and the evidence that field has accumulated over the past few decades, we can make two major conclusions:

- The simpler the designed agent is the better its chances are to be translated into the clinic;
- Making the unmet clinical needs your starting point and tailoring the technology for the specific application will help to find the most meaningful solutions to the existing problems.

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