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Cover story

The beginning of the end of the nanomedicine hype

The U.S. National Cancer Institute (NCI) has announced that it will stop funding its Centers of Cancer Nanotechnology Excellence (CCNEs) [1]. The official reason is that an emerging field of nanotechnology has become mature enough to compete head to head with other types of cancer research. Regardless of the actual reasons, this decision is timely. After 15 years of support, CCNEs have produced numerous research articles, all ending with the same lofty conclusion that nanomedicine has great potential.

When CCNEs began in the United States, the whole world followed, and naturally, scientists all around the world got into the nanomedicine field. It is understandable that scientists follow research funding, and readily available funding has produced thousands of research articles on various aspects of nanomedicine. Competing for research funding resulted in fabrication of more complicated nanoparticles which appeared elegant on paper. The sad part of the nanomedicine history is that nobody knew exactly what nanomedicine meant, and that remains true even today. In the early days of nanomedicine, simply changing the name from conventional drug delivery systems, such as liposomes, polymer micelles, and other colloidal particles, to nanomedicine was enough to receive research funding. The nanomedicine hype, which was fueled further by sensational media coverage, may not be necessarily bad, as hype may motivate risky research that may not be clear at the outset, and thus, some hype can be productive [2]. The issue, however, is how to identify such useful hype and how long it can be treated as a necessary investment. If the hype is decades old, it may just be that the potential of the hype is probably not going to be realized anytime soon.

The nanomedicine hype has caused another conundrum. If nanomedicine is such an enabling technology with great potential for curing diseases, what can explain that nanomedicine research has almost exclusively focused on tumor-targeted drug delivery, when cancer is responsible for only about 25% of all deaths [3]. Even for cancer, there are more than 100 types, and each cancer requires different treatments [4]. Lora Kelly vividly described her painful journey as a cancer survivor at the annual Controlled Release Society meeting in July 2018 in New York [5]. Over the years, she received 12 Neulasta injections causing long bone pain, 12 atropine injections causing disabled speech, 62 chemotherapy infusions, more than 28 CT scans with radioactive dye, 31 trips to the ER, 72 experimental pancreatic vaccines, 225 min of high dose radiation, 360 lovenox injections, 420 lab draws, and more than 230 doctors' appointments. It is inconceivable to expect that such pancreatic cancer and 100 other forms of cancers can be cured by simply placing anticancer agents in nanoparticles. The limitations and false hope of nanomedicine became clear as more quantitative data were obtained and analyzed. Nanomedicine reaching a tumor is usually at the level of 1% of the intravenously administered dose [6], and at that level, any expectation of the clinical efficacy is wishful thinking.

We should be more critical to what we are doing in nanomedicine, as our job is to do meaningful work for all patients, instead of focusing on publications [7].

It is time to review the progress made in nanomedicine, and examine the sources of difficulty in clinical translation, and move forward. CCNEs have received about \$330 million over the past 15 years, and this can be simply considered tuition for learning that nanomedicine is not as useful as we had hoped. Development of each new drug is known to cost more than \$1 billion [8], and thus, spending \$330 million does not sound too bad. But the loss is much more than what the dollar amount indicates. It is the time and resources spent on nanomedicine that could have been used in other research efforts for finding cures for heart diseases, Alzheimer's disease, Parkinson's disease, macular degeneration, opioid addiction, to name several. Even more important are the missed opportunities of training the next generation of scientists to be better scientists. Quoting William Faulkner, "There is no such thing as bad 'scientist'. Some 'scientists' just happen to be better than others." Instead of focusing on the senseless, pointless pursuit of new and innovative nanomedicine, i.e., more complex and fancier looking nanoparticles, we could have trained young scientists to open their eyes to see, open their ears to listen, and open their heart to feel what is important.

We need to rely on data, i.e., relevant and accurate data [9]. It is time to accept that what we wish is not the same as what we can actually achieve. Jina Choi, Director of the San Francisco Regional Office of the Securities and Exchange Commission commented on the Theranos story, "Innovators who seek to revolutionize and disrupt an industry must tell investors the truth about what their technology can do today, not just what they hope it might do someday [10]." The investors of our research are ourselves who pay taxes, and we need to be honest about what nanomedicine can do today, not just what it might do someday. French wine was considered to be superior to American wine, but this idea was changed by the blind taste test at the 1976 Judgement of Paris [11]. Top honors for both red and white wines went to California wines by the most prestigious wine experts in France. French judges were disgusted with their own result of blind wine testing, because their conclusion was based on their unjustified criterion that "These must be French wine because they are so good". The nanomedicine field may have experienced the Judgement of Paris moment in 2019.

Doing research is like a painter trying to capture a beautiful sunrise reflected on water on canvas. The difficulty is that it lasts only 5 min and it is too short to capture it by painting. Only repeated attempts to capture the moment will lead the painter to reproduce the image. Claude Monet said, "I have done what I could as a painter". Scientists do what they can do without exaggeration and hype. Science is hard and it does not become easier simply because someone comes up with

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trendy names with a lot of promotion. To avoid this problem, the current funding systems have to change to support conservative scientists who have diverse, meaningful research ideas. The recent NCI's announcement is encouraging, as it marks the beginning of shifting resources to nurture unpretentious scientists who do research, without any fanfare, on what matters in real life.

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