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Letter to the Editor

NCI Centers of Cancer Nanotechnology Excellence (CCNEs) – A full story to set the record straight

We live in a 24/7 news cycle world, with opinions often being formed in seconds based on snippets of information from online news services. I believed that science, and news on decisions associated with conducting science would always remain in the realm of complete, factual reporting. Unfortunately, following recent press releases concerning NCI CCNE program, I have found that this is not always the case. I use this opportunity to complete the story here, with all the successes and hope that have not yet been mentioned in recent news.

On May 17, Robert Service wrote a short article in Science [1] titled somewhat alarmingly - "U.S. Cancer Institute cancels nanotech research centers." The Scientist followed with a similar story by Chia-Yi Hou [2] on May 20, and on June 4, Kinam Park wrote a commentary titled 'The beginning of the end of the nanomedicine hype' in Journal of Controlled Release [3], praising the NCI decision on discontinuing the CCNE program, but painting a bleak picture of the overall progress in nanomedicine over last 15 years.

So, what really happened with the NCI funding support of CCNEs? In essence, CCNEs were funded in 2005 by a mechanism designed to support the growth of brand new fields using a limited pool of so called 'set aside' funds. The reason for this set aside mechanism is due to the harsh realities of peer review, where grant applications in emerging research fields may not perform well in the standard peer review process against all other cancer grant applications. This period of 'protection' is designed to last for a limited period of time, after which the field is resilient enough to compete in standard funding mechanisms with other cancer grant applications or simply is not worthy of investment. There have been many programs of this kind at NCI in addition to CCNEs: Integrative Cancer Biology Program (ICBP), Tumor Microenvironment Network (TMEN), Physical Sciences in Oncology Centers (PSOC), and Network for Translational Research in Optical Imaging (NTROI), to mention the few. None of these programs were active for more than two 5-year rounds (10 years).

The CCNE program was unique in that it went on for 15 years, but with gradual reduction of the NCI set-aside budget: \$30 M/year for 8 centers in 1st round of funding, \$23 M/year for 9 centers in 2nd round and finally \$13 M/year for 6 centers in 3rd round. Simultaneous to the lowering of the CCNE budget, overall research interest in cancer nanotechnology grew with the total budget of nanotechnology-associated cancer grant awards increasing from \$100 M in 2008 to \$216 M in 2018 [4]. This aspect can not be overstated enough, since this funding increase was due to growth in both number of cancer nanotechnology grant applications as well as their successful competition for 'general' NCI cancer research funds through primarily R01 grant mechanism. In essence, CCNEs did exactly what they were designed to do – they enabled the seeding of a new field of research and attracting a wide range of investigators to it, followed by a natural ending of CCNE program when the field was mature enough to stand on its own. In addition, the CCNE program sparked so much interest in cancer nanotechnology that the CCNE spending in the last, 3rd funding round constituted less than 10% of overall spending for cancer nanotechnology at NCI. Clearly, CCNEs did not significantly diminish access to these funds for other non-CCNE-participating 'unpretentious scientists who do research, without any fanfare' [3], but rather ignited the expansion of a significant field of study. This is reflected by rapid increase of nanotechnology-related R01 applications, which grew from less than 200 submissions in 2008 to over 700 submissions in 2018, which constitutes ~11% of overall R01 submissions [4].

Dr. Park [3] also states that 'CCNEs produced numerous research articles, all ending with the same lofty conclusion that nanomedicine has great potential'. It is true – the CCNEs produced over 3400 papers overall since 2005, but more importantly, the technologies that the CCNEs were developing resulted in the formation of over 100 start-up companies, which entered over 30 clinical trials (Phase I and Phase II) to-date [5–8]. It is true that some of these trials did not meet their endpoints, but this is not surprising considering the overall success rate (from Phase I to clinical use) for cancer clinical trials which is estimated at ~3.5% [9]. The cost of these trials as well as the cost of additional research stemming from NCI-funded CCNE projects was enabled by very efficient leveraging of NCI funds in the community that combined talented academic investigators and entrepreneurs operating start-up companies. For example, the four CCNEs that were funded in all three rounds of the CCNE program (University of North Carolina CCNE (*Nano Approaches to Modulate Host Cell Response for Cancer Therapy*), Northwestern University CCNE (*Nucleic Acid-Based Nanoconstructs for the Treatment of Cancer*), Stanford University CCNE (*Center of Cancer Nanotechnology Excellence for Translational Diagnostics*), and Caltech-UCLA-ISB CCNE (*Nanosystems Biology Cancer Center*) with the cumulative NCI investment of \$165M, obtained other federally funded grants and contracts at an estimate of more than \$500 M. When including both leveraged grant funds and commercial equity raised from companies spun out from these CCNEs, the total amount of leveraged dollars currently exceeds \$1.48B [7,8]. By any measurable standard, the CCNEs were a highly successful program, with outputs in productivity and translation significantly higher than most other NIH programmatic efforts.

What about nanomedicine as a whole? Since 2005, several cancer nanomedicines have been approved by the US FDA, including Abraxane, Marqibo, Onivyde, and most recently Vyxeos [10,11]. Nanotherm (particles for hyperthermia-based treatment of glioblastoma) was recently approved in Europe. It is true that most of these drugs primarily served to reduce the side effects associated with chemotherapy treatment; however, the last two showed also modest improvement of survival rates for pancreatic cancer and AML, respectively. The sales of Abraxane are now above \$1B/year [12], while Celator, the company that developed Vyxeos, was sold for \$1.4B to Jazz Pharmaceuticals following the successful results of a Phase III trial [13]. In non-cancer arena, recent FDA approval [14] of ONPATTRO™ (patisiran, Alnylam Pharmaceuticals), an RNAi therapeutic agent based on a

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lipid complex injection for the treatment of the polyneuropathy in amyloidosis signaled expansion of the repertoire of therapeutic molecules which can be delivered successfully using nanoparticles, further opening the door for innovative cancer nanomedicines and therapy strategies.

To sum it up - it was the right decision on the part of the NCI to discontinue the CCNE program (effective in 2020). This decision was not a 'cancelation' (as the Science article [1] stated), but rather a measured, judicious decision not to renew the program for what would be an almost unprecedented 4th round. This decision was communicated to CCNE investigators in March. It is also our humble opinion that it is too early to throw nanomedicine under the bus. The development of new technologies usually follows an S-curve model, where after the period of initial development, activities simmer, before further technology maturity is achieved, and significant products emerge. As an example, the New York Times article in 1990 [15] described liposome formulation technology as 'disappointment in terms of doing all the miraculous things it was supposed to do eight or nine years ago'. This technology is widely used now with $2.4B sales in 2017 and is expected to grow to $3.6B in 2020 [16]. Thus, we propose to withhold the judgment on nanomedicine for a bit longer. Time will show if expansion of nanoparticle-based drugs beyond small molecules to include biologics, mRNA, and RNAi, and exercising different treatment modalities including combination therapies, immunotherapy, and intra-operative imaging will produce highly relevant results which will aid oncology in a decisive way. If anything, we believe, this is just the 'end of the beginning' for nanomedicine.

References

[1] R.F. Service, U.S. Cancer Institute Cancels Nanotech Research Centers, https://www.sciencemag.org/news/2019/05/us-cancer-institute-cancels-nanotechresearch-centers, (2019).

[2] Chia-Yi Hou, National Cancer Institute Will Stop Funding Nanotechnology Centers, https://www.the-scientist.com/news-opinion/national-cancer-institute-will-stop-funding-nanotechnology-centers-65907.

[3] K. Park, The beginning of the end of the nanomedicine hype, J. Control. Release 305 (2019) 221 (June 3).

[4] Data obtained from NCI internal grant database using 'nano' as a Research, Condition, and Disease Categorization (RCDC) search term.

[5] S. Chapman, N.J. Panaro, G.W. Hinkal, S.S. Hook, U. Prabhakar, K. Ptak, ... P. Grodzinski, Kindling translational cancer nanotechnology research, Nanomedicine (London, England) 7 (3) (2012) 321–325.

[6] C.M. Hartshorn, M.S. Bradbury, G.M. Lanza, A.E. Nel, J. Rao, A.Z. Wang, ... P. Grodzinski, Nanotechnology strategies to advance outcomes in clinical Cancer care, ACS Nano 12 (1) (2018) 24–43.

[7] P. Grodzinski, C.H. Liu, C.M. Hartshorn, S.A. Morris, L.M. Russell, NCI alliance for nanotechnology in Cancer – from academic research to clinical interventions, Biomed. Microdevices 21 (2) (2019) 32.

[8] C.M. Hartshorn, L.M. Russell, P. Grodzinski, NCI Alliance for Nanotechnology in Cancer – Catalysing Research and Translation Towards Novel Cancer Diagnostics and Therapeutics, accepted for publication in Wiley Interdisciplinary Reviews: Nanomed, Nanobiotechnol (2019) e1570.

[9] C.H. Wong, K.W. Siah, A.W. Lo, Estimation of clinical trial success rates and related parameters, Biostatistics 20 (2) (2019) 273–286.

[10] A.C. Anselmo, S. Mitragotri, Nanoparticles in the clinic, Bioeng. Transl. Med. 1 (1) (2016) 10–29.

[11] S.R. D'Mello, C.N. Cruz, M.-L. Chen, M. Kapoor, S.L. Lee, K.M. Tyner, The evolving landscape of drug products containing nanomaterials in the United States, Nat. Nanotechnol. 12 (6) (2017) 523–529.

[12] Celgene (CELG) Q1 Earnings Beat Estimates, https://www.nasdaq.com/article/celgene-celg-q1-earnings-beat-estimates-on-revlimid-sales-cm1136885.

[13] Jazz Pharma to buy Celator in $1.5 billion deal, https://www.reuters.com/article/us-celator-m-a-jazz-phrmt-idUSKCN0YM0QK.

[14] Alnylam Announces First-Ever FDA Approval of an RNAi Therapeutic, http://investors.alnylam.com/news-releases/news-release-details/alnylam-announces-first-ever-fda-approval-rnai-therapeutic.

[15] A Medical Wonder That Isn't – Yet, https://www.nytimes.com/1990/05/06/business/a-medical-wonder-that-isn-t-yet.html.

[16] Liposome Drug Delivery Market 2018 Global Share, Trends, Segmentation, Analysis and Forecast to 2023, https://www.marketwatch.com/press-release/liposome-drug-delivery-market-2018-global-share-trends-segmentation-analysis-and-forecast-to-2023-2018-09-28.

Piotr Grodzinski

Nanodelivery Systems and Devices Branch (NSDB), Cancer Imaging Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, United States of America

E-mail address: grodzinp@mail.nih.gov.