

Nanoncology

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I am with those who believe that nanotechnology will revolutionize cancer medicine¹. One may argue that it already has: Liposomal formulations of doxorubicin (Doxil; Caelyx) have been employed for the treatment of Kaposi's sarcoma for over 10 years, and more recently approved for metastatic breast cancer and recurrent ovarian cancer in the USA². Nanoparticulate paclitaxel enveloped in an albumin chaperone layer (Abraxane) is rapidly becoming a treatment of choice for breast cancer of all stages³. Nanotechnological implements for gene sequencing, biomolecular sensors and proteomic arrays, and components of chromatographic equipment inform therapeutic decisions and fundamental cancer research in laboratories worldwide. Nanoparticulate contrast agents are the norm rather than the exception, in radiological modalities ranging from MRI to CT scans, ultrasound, and nuclear medicine⁴.

Yet, I am with those who believe that what we have seen so far is but the tip of the tip of the tip of the iceberg. Nanotechnology – if engrained within the context of the cancer research and clinical enterprise, as a toolset at the service of it, and never ever as a competing alternative – nanotechnology will transform cancer medicine^{5,6}. On these grounds I am deeply appreciative of the insight of the editorial leadership of *Tumori*, who are dedicating this issue of the journal to the emerging field of oncological nanotechnology. I am gratefully indebted to them, for the kind opportunity to introduce the issue with these modest commentary words.

I had the privilege of developing my views and convictions in the course of an extended role with the National Cancer Institute of the USA. There I served as Special Expert on Nanotechnology, advising its then Director Dr Andrew von Eschenbach, now Commissioner of the Food and Drug Administration, and his Deputy Director Dr Anna Barker on the potential uses of nanotechnology against cancer. Between 2003-2005 we developed a cancer nanotechnology plan, which was refined with the advisement of literally hundreds of leading cancer researchers, clinicians, and nanotechnologists from the communities of physics, chemistry, engineering, mathematics, and biology, together with prominent private sector entrepreneurs, bioethicists, community and patient advocates, and many more⁷.

Particularly vivid in my mind are the excitement and profound impact received from the words of guidance of Nobel Laureates Drs James Watson, Leland Hartwell, Phil Sharpe, David Baltimore, John M Bishop, Harold Varmus, Robert Horwitz – on the biological side – and the carbon nanotechnology Nobel awardees Drs Rick Smalley and Robert Curl. With their help, and that of many others we launched the NCI's Alliance for Nanotechnology in Cancer in year 2005, which remains the world's largest medical nanotechnology program to this date. The process that led to the launch gave me the great personal privilege of reviewing the nanotechnology and cancer programs at a large number of leading laboratory and institutions in the USA and worldwide. It is on this basis that I make the informed, and deeply rooted claim that nanotechnology will revolutionize all aspects of oncology, from basic research to molecular imaging, from laboratory diagnostics to early detection and mass screening⁸, from targeted and personalized therapeutics⁹, to symptom management and end-of-life concerns. My perspectives may be found in greater detail in the cover article of *Nature Reviews in Cancer* in September 2005¹⁰.

First-generation nanotechnologies such as liposomes and albumin nanoparticles have been widely in cancer clinics worldwide, and many second-generation nanovector are in clinical trials. These include biologically targeted particulates, where the

This article is humbly dedicated to the memory of my two generous and visionary mentors, Magnifico Rettore Salvatore Venuta, and Nobel Laureate Professor Rick Smalley, father founder of nanotechnology.

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targeting is accomplished with biomolecular moieties including monoclonal antibodies directed against cancer cell surface epitopes or vascular endothelial biomarkers, aptamers, and peptides. Similar targeting strategies are employed to provide molecular selectivity to radiological imaging agents. Hundreds of nanoparticulate materials are under development. Among the most prominent classes of these are nanoscale polymer assemblies such as PAMAM dendrimers, and biodegradable globules comprised of polylactic and polyglycolic acids. Nanoparticles such as gold nanoshells, magnetic iron oxides, and carbon nanotubes can be remotely activated to release heat into the tumors, so as to provide thermal ablation or trigger heat-shock protein-mediated cancer cell therapy¹¹.

Third-generation therapeutic vectors (multistage particles, or MSP) were recently introduced by our group. Like a rocket directed to the moon, these consist of different stages, each of which is rationally designed to vector the therapeutic and imaging payloads across one or more of the multiple, diverse biological barriers that adversely impact the desired biodistribution of therapeutic agents, conventional and nanotechnological alike. These barriers comprise enzymatic degradation, uptake by the reticulo-endothelial system, hemo-rheology, cellular, endosomal, and nuclear membranes, multi-drug resistance molecular channels, and adverse osmotic pressure in tumor lesions. The debut of these devices earned cover page honors in *Nature Nanotechnology* in March 2008¹². Two Italian researchers figured largely in this accomplishment: My postdoctoral trainee, molecular biologist Dr. Ennio Tasciotti from Scuola Normale di Pisa and ICGB in Trieste was the first author; Applied mathematician and engineer Prof Paolo Decuzzi provided the theoretical modeling for the design of the first stage of the featured MSP¹³.

Third-generation nanotechnologies provide for a complexity of functions that cannot be attained by individual molecules or individual nanoparticles. Well aware of the advantages but also the limitations of the carbon nanotechnologies he had discovered, Nobel Laureate Dr. Rick Smalley referred to the need to encapsulate nanotubes for in-vivo applications inside of polyethylene glycol (PEG) shells as “the PEG-EGG” – a concept that he developed in the final days of his life, in the most dramatic moments of his own battle against cancer. In reality, all nanovectors require “PEG-EGGs” to ensure sufficient circulation time to provide concentration in target lesions. With the introduction of the MSP, we are honored to expand Dr. Smalley’s PEG-EGG concept into multiple, multifunctional stages that deliver the “EGG” across multiple biological barriers. We are small children on the shoulders of a giant.

Nanomedicine and nanoncology are global challenges, with active programs worldwide. Italy itself is home to a broad spectrum of individual laboratory, institutional, and regional initiatives. The Country howev-

er lags behind other leading Nations in that an Italian National program has not been developed yet, and appears to be a remote possibility indeed. I consider myself very privileged for having had the opportunity over the years to start several collaborative programs with leading Italian laboratories, and to assist in the development and launch of important larger-scale initiatives. Most recently I participated in the establishment of the Center for Nanomedicine of the Regione Lombardia, where cancer experts from IEO-IFOM and the Istituto Nazionale Tumori join forces with leading academic laboratories in nanotechnology from Politecnico di Milano, the Università di Pavia and Università Statale, together with chip manufacturing giant ST Microelectronics and a host of start-up firms. This Center epitomizes a fundamental requirement of nanotechnology: The necessity for inter-institutional, interdisciplinary partnerships.

The world of nanomedicine will belong to those that are capable of bypassing the traditional institution-centric, myopic views, and will be able to forge veritable alliances. This was message from the NCI’s program of 2005, and this determined the funding priorities. Lombardia appears to have embraced the message. However, Italian science has traditionally resisted the formation of major interdisciplinary thrusts, and has been handicapped in its pursuit of novel frontiers by a stifling National mechanism of academic appointment and promotion that severely punishes interdisciplinary endeavors. On the positive side, a major factor in favor of Italy’s participation in the nanomedical overhaul is the National tradition of creative innovation. The Country is home to world-leading programs such as those in nanophotonics, proteomic technologies and biomaterials in Lombardia among others, and in robotics and microtechnology in Pisa. Regional programs focusing on nanotechnology have emerged in Regione Veneto with a State-funded “Technological District”. I had the privilege of part-taking in the launching of programs in Friuli-Venezia Giulia, at the Politecnico di Torino, and a splendid, world-leading initiative at the Università Magna Graecia (UMG) in Catanzaro, Calabria.

Inspired by the leadership and visionary insight of its founding Rettore, famed cancer researcher Professor Salvatore Venuta, UMG rapidly developed a world caliber program in nano-oncology. With his untimely death the program at UMG has suffered irreparable damage. Professor Venuta was a great personal friend and cherished mentor of mine. His pioneering views and perspectives on nano-oncology reached across the ocean and synergized with Dr. Andrew von Eschenbach’s, in a mutually beneficial interweaving of visions and programmatic implementations. His acute intellect, energy, and enthusiasm were silenced by cancer. His legacy will endure in the hearts of all those who met him, or were touched by his vision. He will be profoundly missed by all of good will.

Despite its traditional creative strength, and wealth of local and regional initiatives, Italy has not been able to develop a National program in nanotechnology that is worthy of its role as a leading industrialized nation. At the request of the Presidenza del Consiglio dei Ministri I chaired the Gruppo di Lavoro sulle BioNanotecnologie of the Commissione Nazionale Biosicurezza e Biotecnologie in 2005-2006. The Gruppo comprised leading researchers from many Italian institutions, and developed a report with a funding recommendation for a 400 Million Euros over 5 years. Caught in political transition, it never had a realistic chance of being funded, but it can still be viewed on the website of the Presidenza del Consiglio dei Ministri. An important lesson reconfirmed in this occasion is that science must be kept separate from politics, and that Countries that fail to do so place themselves at a competitive disadvantage.

Cancer needs not be the scourge it has been for humankind throughout history. Cancer needs not be a death sentence for anyone, nor a sentence to suffering. The conquest of cancer is within reach – it will involve the revision of our collective thinking from ‘eradicating cancer’ – a veritable impossibility – to ‘living with cancer with no loss of quality or length of life’. This is a realistic goal, which may be attained with a combination of prevention, screening, early detection, personalized diagnostics, personalized intervention, and continuous monitoring. Nanotechnology is a fundamental implement for all of these – but success in any of them can only be attained by the synergistic integration of nanotechnology within the more customary disciplines of clinical oncology and biological research¹⁴.

These modest words of introduction to the present issue of Tumori are humbly offered as an encouragement for the effort of integration across disciplinary boundaries. Working together we can make the ultimate difference against cancer – and since we can, we

have a moral obligation to do so. Let’s again roll up our collective sleeves, and get to work with renewed enthusiasm.

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