

Foreword

a report by

Mauro Ferrari

*Professor, Brown Institute of Molecular Medicine and Chairman, Department of Biomedical Engineering,
University of Texas Health Science Center*

The operational frontiers of medicine remain the early detection of disease and the deployment of directed therapeutic action against it. Early detection affords the ability to intervene at a time preceding the spiralling of pathologies into their forms that are most damaging. For diseases that evolve as a progression through sequential stages – i.e. outside of the realm of trauma and accident – the asymptotic form of early detection trespasses into the domain of prevention, once coupled with suitably directed therapeutic countermeasures. The expression ‘suitably directed’ conceals perhaps the most daunting aspects of the challenge: the ability to intervene with negligible adverse impact on the quality of life of the patient. If – or, rather, when – early detection and directed therapy become reality, medicine will fully transform from a discipline of reaction, focusing on averting catastrophe, to an endeavour of monitoring, and imperceptibly modifying, trajectories through the space of health and deviation from it. While it is impossible to predict how long it will take to achieve these epochal transformations in different branches of medicine, or for specific diseases, it is substantially easier to identify their critical mission tasks, and the strategic advances that underlie success. As a paradigm, the case of cancer may be considered – the ultimate pathology, or rather, family of pathologies, both in terms of multi-stage, sequential progression to the most damaging phenotypes and in terms of astronomical diversity in its molecular presentations.

There is a large window of opportunity for early detection in cancer: 10–15 years of successive genetic transformations typically precede the clinical identification of a neoplasm, which all too often happens at a stage when effective, curative treatment is no longer an option. Early detection in cancer, in the most desired form of mass screening, available to the entire population, may only be envisioned through the analysis of molecular profiles present in biological fluids such as serum, plasma, sputum and others, yet the serum proteome may contain as many as one million different molecular species, or even more, and the low molecular weight markers on which quantitative attention must be focused are typically eight to 12 orders of magnitude less concentrated than the most abundant ‘noise’ proteins. This defines the most exceptionally complex, yet high-impact, needle-in-the-haystack problem in human history. In order to reach its conquest, it will be necessary to develop platforms that can separate, recognise and quantify individual molecules, acting in realtime and at extraordinary throughput. Multiple nanotechnological approaches are under development to address these needs: nanotextured surfaces for mass spectrometry; the bio-barcode approach; biologically gated nanowire transistors; reverse phase protein nanoarrays; nanocantilever beam sensors, and others. Whether any of these, or their combinations, will yield the ultimate proteome monitoring solution, the recognition of the fundamental fact remains: only nanotechnology can provide the key platforms for the conquest of the biofluid, proteome-based early detection objective.

The problem of directing therapy with precision, against the background of extraordinary and time-variable diversity, is not only an issue of biological recognition of target, or biological specificity of therapeutic action. A dominant concern is the overcoming of the biological barriers that govern the distribution of agents of therapy. Among these barriers are those of endothelial and epithelial nature, but also biophysical ones such as adverse oncotic pressure states, preferential sequestration by immune cells, protective degradation processes and many more. These barriers act sequentially and, thus, must be addressed sequentially. It is arguably too much to ask of any ‘classical’ or pre-nanotechnological therapeutic agent to be able to perform such a combination of duties: biological target recognition; cytotoxicity; and the avoidance of several, sequential barriers. Yet, the notion of incorporating multiple functionalities in suitably small carriers of therapeutic actions – or nanovectors – maps exactly onto the strengths of nanotechnology. Many different generations of nanovectors are under development worldwide that offer advantages in multi-modal (not only biological) targeting and recognition, and the ability to overcome biological barriers. Whether any of these will be the ultimate solution to precisely engineering bio-distribution, the fact remains that only through nanotechnology can the problem of directing therapy be resolved in broad generality. This *Nanobiotechnology Supplement* examines several areas more closely, and serves as a key tool to update readers on some of the most exciting developments in the field. ■



Mauro Ferrari is a founder of biomedical nanotechnology/micro technology, especially pertaining to drug delivery, cell transplantation, implantable bioreactors, and other innovative therapeutic modalities. In these fields, he has published approximately 100 papers and six books. He is the inventor of more than 20 issued patents, with about 30 more pending in the US and internationally. His career research and development portfolio totals over US\$30 million, including support from the NIH, NSF, DARPA, DoE, as well as the Board of Regents of the State of Ohio, The Ohio State University, and private enterprises. Currently, Dr Ferrari serves as Professor, Brown Institute of Molecular Medicine; Chairman, Department of Biomedical Engineering, University of Texas Health Science Center; Professor of Experimental Therapeutics, University of Texas M.D. Anderson Cancer Center; Professor of Bioengineering, Rice University; Professor of Biochemistry and Molecular Biology, University of Texas Medical Branch; and President of the Texas Alliance for NanoHealth.