Nanotechnology and Prostate Cancer

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Nanotechnology is defined as materials and systems ranging from 1 to 100 nm which exhibit novel and significantly improved physical, chemical and biological properties. In recent years government funding agencies, the biomedical research community and the popular press have shown much interest in the potentially revolutionary impacts that nanotechnology has to offer clinical medicine, particularly oncology.

Numerous proof of concept applications of nanotechnology have been described for high impact diseases such as prostate cancer, which will likely enhance existing diagnostic and therapeutic modalities as well as lead to new ones. Coupled with significant progress in understanding the genetic basis and biochemical pathways of human diseases, nanotechnology is poised to make the management of prostate and other cancers more personalized and predictive.[1]

What makes nanotechnology particularly attractive is that it operates at the same length scale as DNA, RNA and proteins, the building blocks of biological processes. Therefore, nanotechnology offers a unique vantage point from which to gain insight and manipulate biological pathways in complex human diseases. Clinical applications of nanotechnology are the result of the convergence of diverse disciplines including engineering, materials science, chemistry, molecular biology and clinical medicine.

Some of the manufacturing processes of nanotechnology are derived from the computer chip industry, offering high accuracy and mass production at potentially low costs. The biocompatibility of nanotechnology has been made possible by advances in materials science and chemistry, which enable nanotechnology to be used as a tool to address the plethora of biologically interesting molecules and pathways in the era of genomics and proteomics.

Current and near-term applications of nanotechnology in prostate cancer can be broadly divided into 3 categories of *in vitro* diagnostics (biosensors), *in vivo* diagnostics (molecular imaging) and *in vivo* therapeutics (targeted therapy). Because of their nanoscale and biocompatibility, the boundaries for diagnostic and therapeutic applications are frequently blurred, which is a key advantage of nanotechnology. For example, nanoparticles coated with recognition elements such as DNA probes or antibodies can be used to track biological molecules of interest. The same nanoparticles can also be

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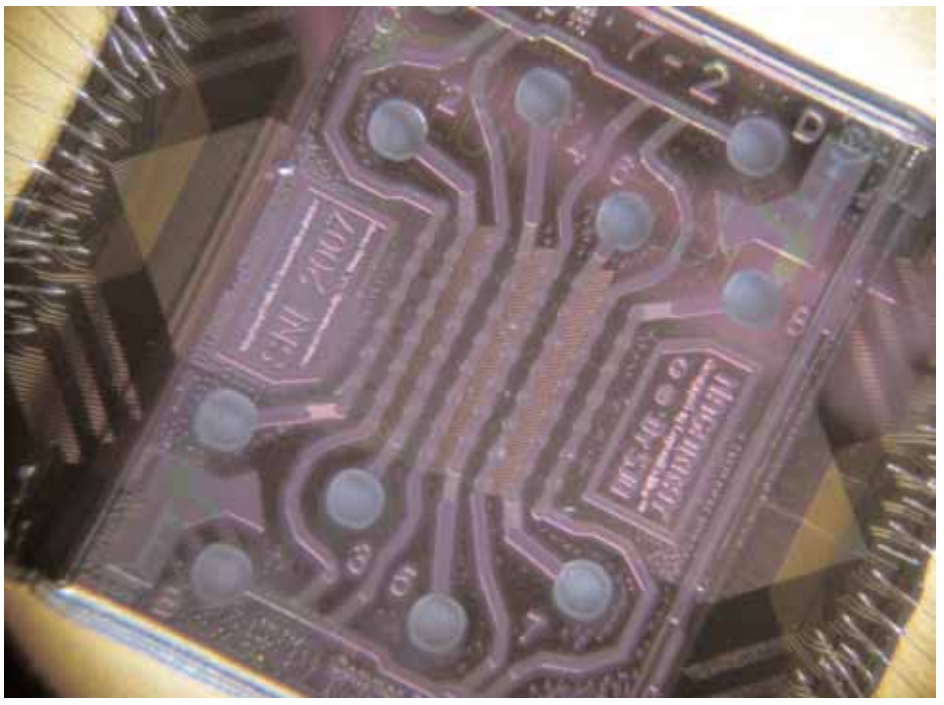

Microfluidic magneto-nano chip with 8 × 8 sensor arrays and 8 microfluidic channels. Chips are being developed to monitor protein profiles in blood samples from patients with cancer to improve therapeutic effectiveness. Key to this technology is use of magnetic nanoparticles to label protein molecules which are then accurately counted by magneto-nano chip. Courtesy of Sebastian J. Osterfeld and Shan X. Wang, Stanford University.

Stem Cells and Urological Tissue Engineering

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results have been validated in a prospective randomized trial comparing periurethral injection of myoblasts and fibroblasts to injection of collagen alone.[15] Unfortunately these studies failed to control for injection technique, thereby limiting our ability to determine if the technique or the myoblasts themselves account for the differences observed. Interestingly the reported results appear to dissipate with time, calling into question the durability of this treatment as well as the role of the myoblasts in urethral reconstruction as the possible mechanism for the improvements seen.

Given the available data suggesting the migratory capacity of most progenitor cells, one would expect myoblasts or any other cell type to migrate similarly when injected into the urethra. Multicenter trials incorporating larger numbers of patients with longer followup are needed to determine whether this treatment modality provides a durable response that may be standardized among centers.

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In addition, evidence of the durability of stem cells in the region of interest, as well as evidence of their ability not only to repopulate in vivo but also to function, needs to be determined. Thus, although the use of stem cells to treat SUI offers new and exciting possibilities, the jury is still out. Ultimately what needs to be determined is whether these are only sophisticated new bulking agents or if they truly are capable of restoring normal urethral function. ◆

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HEY *Bob!*

You're Too Old

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The United States Preventive Services Task Force (USPSTF) says that if you are 75 years old or older, you are too old to have prostate cancer screening.[1] They recommend that doctors do not screen such patients or those who have a life expectancy of 10 years or less, which is the time required to experience a mortality benefit. Their technical reason is the psychological harm of false-positive test results.

In addition, increased prostate specific antigen (PSA) screening tests could lead to the discomfort of a prostate biopsy, which in turn could lead to treatments that could cause more harm than good. That is their position, evidently based on the general health and life expectancy of those 75 years old or older since according to USPSTF, there are "competing causes of death" for this age group.

However, not even testing for prostate cancer takes "ignorance is bliss" to another level. As a 76-year-old patient with recent prostate cancer who just received a good report during his 6-month checkup after proton therapy, I cannot agree with them. Although they have statistical data to overwhelm my anecdotal evidence, in this era of equality shouldn't everyone have an equal opportunity to use available medical resources?

Or is this perhaps another, not so subtle example of allocation of such resources? Perhaps "someone" has concluded that it is a waste of Medicare money not only to treat those older than 75 years with prostate cancer, but also to even bother testing them to see if they have it.

I do understand that prostate cancer can be slow moving and, yes, my urologist gave me the option of doing nothing except watchful waiting after my biopsy revealed 2 cancerous cells. He asked me, "Do you feel you are going to live more than 5 years?" My affirmative answer triggered my review of treatment alternatives.

If I would not have had my yearly PSA test, there would have been no biopsy and no need to look for treatments. That is what the USPSTF is suggesting would have been best for me, although I am in an increased risk category that includes older men, black men and men like me with a family history of prostate cancer.

Who would be liable for not allowing me the opportunity to monitor the condition of my prostate and take precautionary action? What if the can-

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rendered multifunctional as a vehicle to deliver highly selective cytotoxins.

Nanoscale biosensors hold great potential for *in vitro* cancer diagnostics, primarily due to their exquisite sensitivity and capacity to simultaneously detect multiple biomarkers ("multiplexing"). Advances in nanomanufacturing techniques offer label-free detection techniques such as nanocantilevers, nanowires and nanopores.

Recent examples of nanowire arrays demonstrated multiplexed detection of prostate specific antigen (PSA), PSA-α1-antichymotrypsin, carcinoembryonic antigen and mucin-1 down to subpicogram per ml sensitivity in undiluted serum samples.[2] Furthermore, there is wide interest in developing microfluidic and nanofluidic "lab-on-a-chip" technology capable of complex sample processing steps, including cell concentration, lysis, reagent mixing and target detection using minute quantities of clinical specimens.[3] An example of an integrated magnetic nanosensor array is shown in the figure.

For cancer imaging, quantum dots (QDs) represent a new class of fluorescent probes that have been shown to be powerful tools in animal and *in vitro* models of prostate cancer. QDs are semiconductor nanocrystals with unique optical properties that offer significant advantages, including increased brightness, reduced background noise, photostability and capacity for multiplexing compared to conventional organic fluorescent probes. The emission wavelengths of QDs are tunable, which means that different emission colors can be achieved by varying the size of the QDs.

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Immunohistochemistry of ex vivo clinical specimens (eg prostate needle biopsy cores) using multicolored QDs to simultaneously localize multiple biomarkers may be the most promising clinical application in the near term.[4] Potential *in vivo* human applications of QDs are currently limited due to the potential toxicity of their heavy metal core, although significant research efforts are under way to overcome this limitation.

Another class of nanoparticles called ultrasmall superparamagnetic iron oxide particles (ferumoxtran-10) has recently been demonstrated to be useful in differentiating between benign and malignant lymph nodes in a variety of urological cancers including prostate cancer.[5] Because of their small size (30 to 50 nm) nanoparticles are able to cross the capillaries and localize in lymph nodes where they are phagocytosed by macrophages of the reticuloendothelial system. Tumor infiltrated lymph nodes show differential uptake in images before and after contrast administration, thus enabling identification of metastatic diseases in otherwise normal size lymph nodes. This technology may facilitate preoperative surgical planning as well as followup for early recurrence.

Lastly, nanoscale multifunctional nanoparticles hold the potential to allow targeted delivery of molecular cancer therapies with enhanced efficacy and reduced systemic toxicity.[6] Nanoscale drug delivery vectors including dendrimers, micelles, liposomes, nanocapsules, nanospheres and nanotubes are under active investigation. The small size of these nanovectors enables passive passage through the leaky cancer vasculature as well as active molecular targeting through surface modification with biological ligands.

While there are numerous animal studies showing different configurations of multifunctional nanoparticles, currently there are no Food and Drug Administration approved nanoparticle based drugs for urological cancers. Abraxane™ is a nanoparticle albumin bound formulation of paclitaxel approved for metastatic breast cancer which enables higher intratumor drug concentration with improved side effect profiles. Taxanes (paclitaxel and docetaxel) have been shown to prolong survival in patients with hormone refractory prostate cancer. Numerous clinical trials are currently under way evaluating Abraxane for hormone refractory prostate cancer.

The emergence of nanotechnology promises to benefit the management of the most common urological cancers including that of the prostate. While significant progress has already been made in basic engineering, chemistry and biological laboratories, much work remains to be done translating the findings into the clinical arena. As the primary care providers for patients with prostate cancer, urologists are urged to become acquainted with the basics of nanotechnology and join colleagues in other disciplines to actively participate in making this exciting technology a reality. ◆

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