

Nanotechnology and animal health

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Summary

Nanotechnology, as a new enabling technology, has the potential to revolutionise agriculture and food systems in the United States of America and throughout the world. Examples of potential applications of nanotechnology in the science and engineering of agriculture and food systems include disease treatment delivery systems, new tools for molecular and cellular biology, the security of agricultural and food systems, new materials for pathogen detection, and protection of the environment. Existing research has clearly demonstrated the feasibility of introducing nanoshells and nanotubes into animal systems to seek out and destroy targeted cells. Nanoparticles smaller than one micron have been used to deliver drugs and genes into cells. Thus, some building blocks do exist in isolation and are expected to be integrated into systems over the next 10 to 15 years. It is reasonable to presume over the next couple of decades that nanobiotechnology industries and unique developments will revolutionise animal health and medicine.

Keywords

Drug delivery – Nanoparticle – Nanoshell – Nanotechnology – Nanotube – Pathogen detection.

Introduction

Nanotechnology, as a new enabling technology, has the potential to revolutionise agriculture and food systems in the United States of America (USA) and throughout the world. Nanotechnology can provide new tools for molecular and cellular biology and new materials for pathogen detection, so there are several areas in which nanotechnology could be applied to the science and engineering of agriculture and food systems, e.g. agricultural and food systems security, disease treatment delivery systems, and the protection of the environment (13).

What is nanotechnology? The National Nanotechnology Initiative, a government initiative in the USA (8, 9, 10, 11), describes nanotechnology as: ‘research and development (R&D) aimed at understanding and working with – seeing, measuring and manipulating – matter at the atomic, molecular and supramolecular levels. This correlates to length scales of roughly 1 to 100 nanometres. At this scale, the physical, chemical and biological properties of materials differ fundamentally and often unexpectedly

from those of the corresponding bulk materials’.

In agriculture today, if an animal becomes infected with disease, it can be days, weeks, or months before whole-organism symptoms appear and disease is detected; by which time infection may be widespread and entire herds/fields might need to be destroyed. Nanotechnology operates at the same scale as a virus or disease-infecting particle, and thus holds the potential for very early detection and eradication. Nanotechnology holds out the possibility that ‘smart’ treatment delivery systems could be activated long before macro-symptoms appear. For example, a ‘smart’ treatment delivery system could be a miniature device implanted in an animal that samples saliva on a regular basis. Long before a fever develops, the integrated sensing, monitoring and controlling system could detect the presence of disease and notify the farmer and veterinarian to activate a targeted treatment delivery system. Smart treatment delivery systems are envisioned for biology and bioactive systems such as drugs, nutrients, probiotics, nutraceuticals and implantable cell bioreactors.

In agriculture, the fundamental life processes are explored through research in molecular and cellular biology. New

tools for molecular and cellular biology are needed that are specifically designed to separate, identify and quantify individual molecules. This is possible with nanotechnology and could permit a wide range of advances in agricultural research, such as developments in reproductive science and technology, conversion of agricultural and food wastes to energy and other useful by-products through enzymatic nanobioprocessing, and disease prevention and treatment in animals.

A nanotechnology primer

Nanotechnology is an exciting and rapidly emerging technology allowing us to work at the molecular level, often atom by atom, to create and manipulate tools, materials and functional structures that have nanometre dimensions. Nature has been performing 'nanotechnological feats' for millions of years. Through the arrangement of atoms and molecules, biological systems combine wet chemistry and electro-chemistry in a single living system. We are just beginning to understand the nanoscale methods used in nature to create self-replicating, self-monitoring, self-controlling and self-repairing tools, materials and structures. 'Nano' usually refers to a size scale between 1 nanometre (nm) and 100 nm. For comparison, the wavelength of visible light is between 400 nm and 700 nm. A living cell has dimensions of microns (thousands of nanometres) (Table 1).

The author has identified the following areas as particularly significant to agriculture and food systems and these issues are discussed briefly to assist the reader in understanding some nanotechnology methods.

Microfluidics

On the microscopic scale, fluids in microchannels appear to take on viscous properties and move more like molasses than water. When two or more microfluidic channels are converged into a single stream, the converging streams do

not mix easily (this is a characteristic of laminar flow). Laminar or creep flow at microfluidic level cause living cells to become aligned in single-file order, thus allowing new levels of precision science in cell biology. Other microfluidic applications have the potential for precision 'point-of-care' diagnostics, drug screening and deoxyribonucleic acid (DNA) manipulation. Microfluidics is used today in animal science to significantly simplify traditional *in vitro* fertilisation procedures used in animal breeding. Microfluidics is also an integral part of today's precision miniaturised 'Lab-on-a-Chip' technology, which allows for the analysis and chemical manipulation of small samples. Microfluidics is a science which deals with larger-scale measurements than does nanotechnology, but the merger of the 'dry' world of nanotechnology with the 'wet' world of biology involves the use of microfluidic techniques.

Biomicro-electromechanical systems

Methods of making micro-sized machines or micro-electromechanical systems (MEMS) are already established. Fully functional pumps, rotors, sensors and levers exist at the microscale. Moving from the micro to the nano scale, nano-electromechanical systems (NEMS) devices will present new engineering challenges. However, as with microfluidics, the integration of existing MEMS technology with biological systems has yielded a new class of machines, 'BioMEMS', that can perform functions (such as capture of foreign particles or delivery of drugs to specific locations) at the nanoscale or on nanoparticles. Biochips that are smaller than a postage stamp exist today. These biochips contain sealed channels and wells, electrodes for detection, connectors and fluidic input/output ports. BioMEMS provide the interface between the macro and nano worlds, as well as the interface between the biological and electromechanical worlds of technology.

Nucleic acid bioengineering

Many of the nanotechnology devices of today have been fabricated from pieces of silicon or other material, through etching, much like sculpting away portions of the beginning material block to obtain the final structure. Nucleic acid bioengineering approaches manufacture from the opposite end – a 'bottom-up' approach. Nucleic acid engineering utilises DNA molecules as building blocks, and forms specifically shaped particles that can be used to build larger units. Nanowires and nanomembranes from these basic building blocks are envisioned.

'Smart' treatment delivery systems

On the macro-scale, delivery systems such as postal services, accept items for delivery that are sealed in a

Table 1
Comparison of scales of nanotechnology in the biological world
(adapted from 6)

Biological structures	Size in nanometers
Leukocytes	10,000
Bacteria	1,000-10,000
Virus	75-100
Protein	5-50
Deoxyribonucleic acid (width)	~ 2
Atom	~ 0.1

package and have address instructions written on the outside of the package; both motorised and human carriers transport the package from one location to another. The development of 'smart' treatment delivery systems on the nanoscale uses similar concepts applied at the molecular level. For example, 'smart' drug delivery systems in animals would most likely contain small, sealed packages of the drug to be delivered. The packages would not be opened until they reach the desired location in the animal, e.g. the site of infection. This would allow judicious use of smaller quantities of antibiotics than would otherwise be possible. A molecular-coded 'address label' in the package could allow the package to be delivered to the correct site in the body. Nano- and microscale mechanical systems would serve as the 'carriers' in such a system. Smart delivery systems could also contain on-board chemical detection and decision-making capability for self-regulation that could deliver drug or nutrient treatments as needed. The remote activation and monitoring of intelligent delivery systems will assist livestock producers of the future to minimise antibiotic use.

Nanosensors

Detection of very small amounts of a chemical contaminant, virus, or bacteria in agricultural and food systems is envisioned from the integration of chemical, physical and biological devices working together as an integrated sensor at the nanoscale. Bioanalytical nanosensors are devices or systems with devices that measure or detect a chemical with the use of a biological material or tissue.

Bioselective surfaces

Surfaces are the environment and location on which most chemical and biological interactions occur. A bioselective surface has either an enhanced or reduced ability to bind or hold specific organisms or molecules. Bioselective surfaces are important to the development of biosensors, detectors, catalysts and the ability to separate or purify mixtures of biomolecules.

Nanomaterials

Nanomaterials are materials (either newly created through nanotechnology or that exist in nature) that provide the potential to manipulate structures or other particles at the nanoscale and to control and catalyse chemical reactions. Materials are generally composed of particles of many sizes. The shape, structure and aggregation of particles at the nanoscale influence the properties of the material at the macro-level. Specific examples of nanomaterials are buckeyballs, dendrimers, nanoshells, nanotubes and quantum dots, each of which is described in more detail in the following sections.

Buckeyballs

A buckeyball (also known as a fullerene) is a novel collection of carbon atoms in a spheroid shape in which each carbon atom is bonded to three of its neighbours. Scientists (6) have discovered how to make the metal-filled buckeyballs soluble, bringing them a step closer to biological applications, such as the delivery of medicine or radioactive material to a disease site. The idea of using the 60-atom to 80-atom hollow carbon molecules for drug delivery is what gives added biological functionality to a buckeyball. The aim is to attach water-soluble groups of peptides or hydrophilic chains to get these molecules into the blood stream.

Nanotubes

Nanotubes are essentially buckeyballs that have been opened on two sides with additional atom groups added in the characteristic hexagon shape to form a hollow carbon tube (cylinder). They can be thought of as a sheet of graphite (a hexagonal lattice of carbon) rolled into a cylinder (14).

Dendrimers

Dendrimers (polymers) are a new class of three-dimensional, man-made molecules produced by an unusual synthetic nanofabrication route that incorporates repetitive branching sequences to create a unique novel architecture (2). Exceptional features of the dendritic architecture include a high degree of structural symmetry, a density gradient displaying an intra-molecular minimum value and a well-defined number of terminal groups, which may be chemically different from the interior. These features create an environment within the dendrimer molecule to facilitate an avenue for reliable and economical fabrication and manufacturing of functional nanoscale materials that can have unique properties (electronic, optical, optoelectronic, magnetic, chemical, or biological) that can be the basis of new nanoscale technology and devices. Dendrimers can be designed to aggregate to form cylinders or spheres depending upon the nature of the fundamental building unit.

Quantum dots

Quantum dots are nanometre-scale crystals that were originally developed in the mid-1980s for optoelectronic applications (1). They are created with nanometre precision during chemical synthesis and are composed of hundreds or thousands of atoms of an inorganic semiconductor material, which gives them intriguing optical properties. When a quantum dot is excited with a beam of light, they re-emit light (fluoresce) with a narrow and symmetric emission spectrum that depends directly on the size of the crystal. This means that quantum dots can be fine-tuned to emit light at a variety of wavelengths simply by altering the size of the core, and they therefore

constitute a set of multicoloured molecular beacons for use in imaging. A 3 nm particle made from cadmium selenide, for example, radiates green light at 520 nm, while a slightly larger 5.5 nm particle of the same material radiates red light at 630 nm.

The core of the quantum dot is usually contained within a protective inorganic shell such as zinc sulphite, which has a higher electronic band gap than the core. This increases the intensity of the fluorescence. However, until recently the hydrophobic nature of this outer shell prevented quantum dots from being used in aqueous biological environments, but some scientists have produced new, biocompatible quantum dots (4). There is considerable debate among biological scientists whether the technology for coating quantum dots adequately alleviates toxicity issues.

Nanoshells

Nanoshells are a new type of optically tunable nanoparticle composed of a dielectric (for example, silica) core coated with an ultra-thin metallic (for example, gold) layer (5). Gold nanoshells possess physical properties similar to those of gold colloid, in particular a strong optical absorption due to the collective electronic response of the metal to light. The optical response of gold nanoshells depends dramatically on the relative sizes of the nanoparticle core and the thickness of the gold shell. By varying the relative core and shell thicknesses, the colour of gold nanoshells can be varied across a broad range of the optical spectrum that spans the visible and the near-infrared spectral regions. Gold nanoshells can be made to either absorb light or to scatter it preferentially by varying the size of the particle relative to the wavelength of the light.

Scientists can create nanoshells that carry molecular conjugates to the antigens that are expressed on cancer cells or in the tumour microenvironment. This second degree of specificity preferentially links the nanoshells to the tumour and not to neighbouring healthy cells. It is then possible to externally supply energy to these cells. The specific properties of nanoshells allow for the absorption of this directed energy, creating an intense heat that selectively kills tumour cells. The external energy can be mechanical, radio frequency or optical – the therapeutic action is the same (5).

Application to animal health

Animal health is an increasingly important issue, both for animal agriculture and pet owners. Feneque, a veterinarian, writes that nanotechnology has the potential to significantly affect the way veterinarians practice veterinary medicine (3). Food security and safety and an increasingly aged pet population, along with heightened

costs for medication and veterinary care create a need for new solutions. Nanotechnology has the potential to provide these solutions, since the possible applications of the technology in medical and veterinary applications are almost mind-boggling. Although much research and major company developments are necessary before nanotechnology is common place in veterinary medicine, there are numerous glimpses of the future in applications for drug delivery, disease diagnosis and treatment, breeding and identity preservation (IP). Some exciting applications are discussed further below.

'Smart' drug delivery

Today, antibiotics, probiotics and pharmaceuticals are delivered to animals primarily through feed or injection systems. Delivery of medicines is either provided as a preventative measure or as a treatment once the disease organism has multiplied and symptoms are evident. Nanoscale devices are envisioned that will have the capability to detect and treat an infection, nutrient deficiency, or other health problem, long before symptoms are evident at the macro-scale. This type of treatment could be targeted to the affected area. 'Smart' delivery systems can have multifunctional characteristics to avoid biological barriers to successful targeting and they may also be:

- time-controlled
- spatially targeted
- self-regulated
- remotely regulated
- pre-programmed.

Smart delivery systems can also have the capacity to monitor the effects of the delivery of pharmaceuticals, nutraceuticals, nutrients, food supplements, bioactive compounds, probiotics, chemicals and vaccines. Thus, in the future, further technological advances will make it possible to:

- develop delivery systems (potentially using buckeyballs, nanotubes and dendrimers, etc.) for biological and bioactive systems (drugs, nutrients, probiotics, pharmaceuticals, nutraceuticals and implantable cell bioreactors) for targeted site delivery capability
- develop integrated sensing, monitoring and controlling capabilities, including the ability to be self-regulating
- develop large animal health monitoring and therapeutic intervention
- develop small animal health monitoring and therapeutic intervention
- develop nucleic acid (e.g. DNA) delivery systems through a bottom-up approach using DNA molecules to build nanowires and nanotubes for assisted reproduction, animal vaccines and animal control agents.

The nanotechnologies described above will only reach their full potential through integration. Thus, 'smart systems integration' is similar to designing and building the logic of a 'nervous system' that will allow the individual parts to work together. Integration of the nanotechnologies into a working control system (whether remotely controlled or under automatic control) will require electronic communication between several technologies, including the sensing systems, reporting systems, localisation systems and control systems. The logic to control the subsystems (control algorithms) must be developed and eventually translated into a computer language. Research needs to be undertaken to:

- integrate NEMS with remote receive/transmit systems (embedded on the chip, satellite interaction, global positioning systems, remote powering, biopower)
- develop integrated sensing, monitoring and controlling capabilities including self-regulation and remote activation
- design and develop automated integrated networks for the monitoring and control of animal systems and food safety and security
- develop a 'smart herd system' that detects, identifies, reports and treats the illness of a single infected animal in a herd prior to the onset of symptoms.

Disease diagnosis and treatment

Imagine the possibility of injecting nanoparticles into an animal and then a week or so later being able to run a light over the animal's body to activate cancer-killing agents to destroy the tumour. Researchers at Rice University (5) are doing just this by using nanoshells injected into the animal's bloodstream with targeted agents applied to the nanoshells to seek out and attach to the surface receptors of cancer cells. Illumination of the body with infrared light raises the cell temperature to about 55°C, which 'burns' and kills the tumour. Others have been experimenting with 'smart' superparamagnetic nanoparticles. These nanoparticles when injected in the bloodstream target tumour receptor cells. These nanoparticles are made from iron oxides that when subjected to a magnetic field enhance the ability of the nanoparticles to locate tumour cells. At the site of the tumour the nanoparticles emit an attached drug to kill the cancer cells.

Quantum dots may also be injected into the bloodstream of animals and they may detect cells that are malfunctioning. Because quantum dots respond to light it may be possible to illuminate the body with light and stimulate the quantum dot to heat up enough to kill the cancerous cell.

Nucleic acid engineering-based probes and methods (7) offer powerful new ways to deliver therapeutic or

preventative treatment for particular diseases. The greatest challenge is to develop a nonviral DNA delivery system that has high levels of efficiency and specificity but low toxicity and cost. Therefore, future DNA delivery may depend on a hybrid system that combines the benefits of both viral and nonviral components.

Identity preservation

An identity preservation (IP) system is a system that creates increased value by providing consumers with information about the practices and activities used to produce an agricultural product. Today, through IP it is possible to provide stakeholders and consumers with access to information, records and supplier protocols regarding the farm of origin, environmental practices used in production, food safety and security, and information regarding animal welfare issues. Each day shipments of livestock and other agricultural products are moved all over the world. Currently, a lack of finances limits the number of inspectors that can be employed at critical control points of the production, shipment and storage processes.

Quality assurance of the safety and security of agricultural products could be significantly improved through IP at the nanoscale. Nanoscale IP has the potential to continuously track and record the history of a particular agricultural product. We envision nanoscale monitors linked to recording and tracking devices to improve the IP of food and agricultural products. The keys are biodegradable sensors for temperature and other stored data containing the history of stored food for both physical and biological parameters. The future of the meat industry may well depend on an ability to track all stages in the life of the product, including the birth of the animal, its medical history, and its movements between the ranch, the slaughterhouse and the meat-packing plant, right through to the consumer's table. Of course, a major issue exists with regard to biodegradable nanoparticles in the steak!

Animal breeding

Management of breeding is an expensive and time-consuming problem for dairy and swine farmers. One solution that is currently being studied is a nanotube implanted under the skin to provide real time measurement of changes in the level of estradiol in the blood. The nanotubes (12) are used as a means of tracking oestrus in animals because these tubes have the capacity to bind and detect the estradiol antibody at the time of oestrus by near infrared fluorescence. The signal from this sensor will be incorporated as a part of a central monitoring and control system to actuate breeding.

Ethical issues

Nanotechnology is a part of the future of animal health. Clearly, this technology has a high potential to benefit animal agriculture and food systems. However, as with any new technology, we have an ethical responsibility to apply it wisely and to recognise that there are potential unforeseen risks that may come with the tremendous positive potential.

Nanotechnology and nanomaterials have the potential to play a significant role in risk reduction for animal agriculture and food systems' security. Of major importance to the development of nanotechnologies will be a thoughtful, thorough and balanced assessment of the benefits and risks of nanotechnologies. The public should be educated through television, the internet, and point-of-sale informative bulletins that explain the added value and increased safety and food security that the application of nanotechnology provides. In addition to improving contaminant detection and the security of tracking systems, the use of nanotechnology can increase the efficiency of animal agriculture and food systems processes and help to reduce the use of antibiotics, thus increasing food safety for the consumer.

Final comments

Is nanotechnology being over hyped? Will it change the world of animal health and veterinarian practice? The author believes that it will have a profound impact, but not in the immediate future. Existing research has clearly demonstrated the feasibility of nanoshells and nanotubes for introduction in animal systems to seek out and destroy targeted cells. Nanoparticles smaller than one micron have been used to deliver drugs and genes into cells. Thus, some building blocks do exist in isolation and it is reasonable to believe integrated system capability can be developed over the next 10 to 15 years to meet many of the applications addressed herein. Nanotechnology, although still in the early stages of its development, is beginning to equip scientists, engineers and biologists to work at the cellular and molecular levels for significant benefits in healthcare and animal medicine. It is reasonable to presume over the next couple of decades that nanobiotechnology industries and unique developments will be revolutionising animal health and medicine.



Nanotechnologie et santé animale

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Résumé

La nanotechnologie, en tant que nouvelle technologie de base, pourrait révolutionner l'agriculture et les systèmes alimentaires aux États-Unis d'Amérique et partout dans le monde. Les systèmes d'administration des traitements à visée thérapeutique, les nouveaux outils de la biologie moléculaire et cellulaire, la sécurité des systèmes agricoles et alimentaires, les nouveaux matériels de détection des agents pathogènes, la protection de l'environnement sont autant d'exemples d'application possible de la nanotechnologie dans le domaine de la connaissance scientifique et de la conception des systèmes agricoles et alimentaires. La recherche existante a clairement démontré qu'il était possible d'introduire des nanocapsules et des nanotubes dans les systèmes animaux pour rechercher et détruire les cellules ciblées. Des nanoparticules d'une taille inférieure à un micron ont été utilisées pour acheminer des médicaments et des gènes à l'intérieur de cellules. Il existe donc des unités élémentaires isolées qui devraient être intégrées dans des systèmes dans les 10 à 15 prochaines années. On peut raisonnablement prévoir que dans une vingtaine d'années, le secteur de la nanobiotechnologie et les nouvelles découvertes à venir révolutionneront la santé animale et la médecine.

Mots-clés

Administration des médicaments – Détection des agents pathogènes – Nanocapsule – Nanoparticules – Nanotechnologie – Nanotube.



Nanotecnología y sanidad animal

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Resumen

Como nuevo conjunto de técnicas instrumentales, la nanotecnología puede llegar a revolucionar los sistemas de producción agropecuaria y alimentaria en los Estados Unidos de América y el mundo entero gracias a su empleo en la ciencia y la ingeniería aplicadas a dichos sistemas. Entre otros ejemplos en este sentido cabe citar su aplicación a los sistemas de administración de tratamientos contra enfermedades, la creación de nuevas herramientas de biología molecular y celular, la seguridad de los sistemas de producción agrícola y alimentaria, los nuevos instrumentos para detectar patógenos y la protección del medio ambiente. Las investigaciones realizadas hasta ahora han demostrado que es posible introducir nanocápsulas y nanotubos en sistemas animales para localizar y destruir determinadas células diana. Por otra parte, se han utilizado nanopartículas (de diámetro inferior a una micra) para introducir fármacos y genes en las células. Ya existen pues los ingredientes aislados, y es de prever que en el plazo de 10 a 15 años se consiga ensamblarlos para que formen sistemas coherentes. Es razonable pensar que en los dos próximos decenios el sector de la nanobiotechnología aportará novedades sin precedentes que revolucionarán la sanidad animal y la medicina veterinaria.

Palabras clave

Administración de fármacos – Detección de patógenos – Nanocápsula – Nanopartícula – Nanotecnología – Nanotubo.



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