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Nanotechnology Patents as R&D Indicators for Disease Management Strategies in Agriculture

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Nanotechnology has immense potential for the development of more precise and effective methods for disease diagnosis and treatment in plants and animals. The pan industrial nature of this technology continues to attract all stakeholders involved in issues of diseases management in agriculture. Current investments using nanotechnology in disease diagnostics and drug delivery in India are on the rise. If these are to be profitable, it is essential that transfer processes of nanotechnologies in this sector against the patent portfolios are well understood for developing sound policies and for commercialization. The objective of the present study is to assess the trend of patents of this multifaceted technology and its applications in this sector from the databases such as EPO, USPTO, Delphion and Micropatent. Patent analysis includes bibliographic analysis of the patent timeline such as publication year and priority year, country, main IPC and assignee of the patents and technological analysis of nanoresearch areas and their potential applications in disease management. The study illustrates the potential of patents as indicators of technology to develop a framework for knowledge mapping.

Keywords: Patent, R&D indicators, nanotechnology, agriculture, disease management

Indian agriculture systems, comprising crops, animals, livestock and fisheries, are frequently vulnerable to attacks by pests and diseases of endemic and exotic origin. Biotic stresses are the major limiting factors in realizing the yield potential of crop plants accounting about 25% annual loss of crop produce in India.[1] Infectious diseases in poultry and livestock cause an annual loss of about Rs 50 billion.[2] The rapidly developing aquaculture industry of the country too has suffered setback due to infectious viral diseases resulting in a total collapse of the shrimp farming industry in 1995. In addition, the global trade in agricultural commodities and trans-boundary movement of plants and animals necessitate speedy measures of detection and treatment. Recent threat to biosecurity, and bioterrorism through pandemics of new diseases, viz. SARS, anthrax, avian influenza, H5N1 virus, reiterate the need for rapid detection techniques and treatment protocols for anticipated or unanticipated bio-pests. Often such pandemic threats can transgress and impact all components of ecosystems including humans. Development of an effective, integrated risk and disaster management system for plant and animal husbandry productivity is now essential. This also includes using new techniques and new protocols for detection and management of diseases.

Prominent among the emerging technologies is nanotechnology (NT), which is being visualized as a rapidly evolving technology that can revolutionize food systems[3,4] across the entire agricultural value chain. NT is defined as 'understanding and control of matter at dimensions of roughly 1 to 100 nanometers', where unique phenomena enable novel applications.[5] At this scale, physical, chemical and biological properties of materials differ fundamentally from the properties of individual atoms and molecules or bulk matter. These changes result in unique mechanical, electronic, photonic and magnetic properties of nanoscale materials. The ability to manipulate matter at the nanoscale can lead to improved understanding of processes at this scale and to the creation of improved materials, structures, devices and systems that exploit these new properties which enhance the performance and efficiencies of the processes being used. The first initiative to apply nanotechnology to agriculture was addressed by United States Department of Agriculture in its roadmap published during September 2003.[6] Following several other countries including developing countries have initiated national level programs. In India too, nanotechnology is beginning to be seen as an

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important option for enhancing agricultural productivity, along with other emerging technologies such as, biotechnology, to complement the current conventionally used agricultural technologies.[7] Nearly 30 research areas are known to be related to nanoscience and materials, which can be used through cross-disciplinary/interdisciplinary approaches.[8] This multifaceted technology is more like platform technology providing multiple applications across the agri-value chain, and affording distinct techno-paradigm shifts.[9] Projected applications of nanotechnology in agricultural and food systems for biotic stress management are pathogen and contaminant detection; identity preservation and tracking (e.g. providing information on the origin and movement of crops, livestock or agriculture products); smart treatment delivery systems (e.g. miniature device implanted in livestock or crop variety, that can test for pathogen and or release treatment).

Patent analysis is a known valuable approach that uses patent data to derive information about growth in a particular technology[10] and for planning technology development strategies. Such analysis is also a useful way of examining continuous flow of knowledge from science to technology particularly for emerging technologies where no historic data is available.[11] In the recent past, patent grants in nanotechnology have been used to understand trends in commercialization of research results and to study impact of public funding in nanotechnology.[12]

The objective of this study is to analyse and assess the trend of patents in nanotechnology and its applications in disease management in agriculture. Patent analysis included: (i) bibliographic analysis, and (ii) technological analysis of nanoresearch areas and their potential applications in disease management. Such an analysis can be useful to R&D planners and researchers to prioritize investments in using nanotechnology applications for disease diagnosis and management in a more pragmatic manner.

Methodology

To address the objective of this study, two approaches were undertaken:

1 Use of Holistic Systems Framework Developed for a Priority Assessment of the Potential of Nanotechnology for Agriculture

In the present study, patent data was collected through specially designed strategy. Patents related to specific agriculture domain were collected from three resources namely: freely available databases of international/national patent offices (USPTO, EPO and WIPO); no charge providers (Google patents, FreePatentsOnline) and charge providers (Delphion, Derwent, Micropatent). Parsing was done to obtain relevant set of patents of individual agriculture thematic areas with reference to corresponding IPC, USPTO and EPO codes. A set of subject specific keywords and standardized search strings were identified by domain experts and was used to perform full text search of patents (patent titles, abstract, claims and descriptions). Resulting patents were reduced to one patent per family. Duplicates were removed and temporary work sheets were exported in CSV format. After removing repeats, individual patents were later analysed to estimate whether they are truly nanotechnology related patents. Patents that showed 'incidental noises' of nano like $NaNo_3$ (Sodium Nitrate), nanometer, nanolitre, nanosecond, nanospectrometer and others were removed. Units of analysis and representations include inventors, type of affiliations, country, and citation network of patents, nanoresearch area, technology field and timelines.

A framework (Fig. 1) was developed to map nanoresearch area to agriculture thematic areas across the agricultural supply chain, that is, the entire production-consumption system.[12] The information from patents was organized into specially designed MS access patent database, with digital library accessibility. The database facilitated a systematic process of querying, accessing and understanding technological developments in nanotechnology that could be of significant relevance to disease diagnostics, delivery mechanisms and management.

Three of the agriculture thematic areas are of relevance to disease diagnosis and treatment, namely, plant/animal disease diagnosis, delivery mechanism in plants and delivery mechanism in animal systems. For more inclusive identification of patents, these areas were subdivided into six areas: (i) Disease diagnosis in plants, (ii) Disease diagnosis in animals, (iii) Diagnosis in both plants and animals, (iv) Delivery mechanism in plants, (v) Delivery mechanism in animal systems, and (vi) Delivery mechanism in both plants and animals.

2 Knowledge Mapping from Patents in Relevant Fields of Disease Diagnosis and Treatment

From database of more than 1000 agri nanotech patents, 119 relevant patents with claims pertaining to applications in disease diagnosis and treatment were selected. These patents were grouped into 6 key thematic areas in disease diagnosis and treatments in

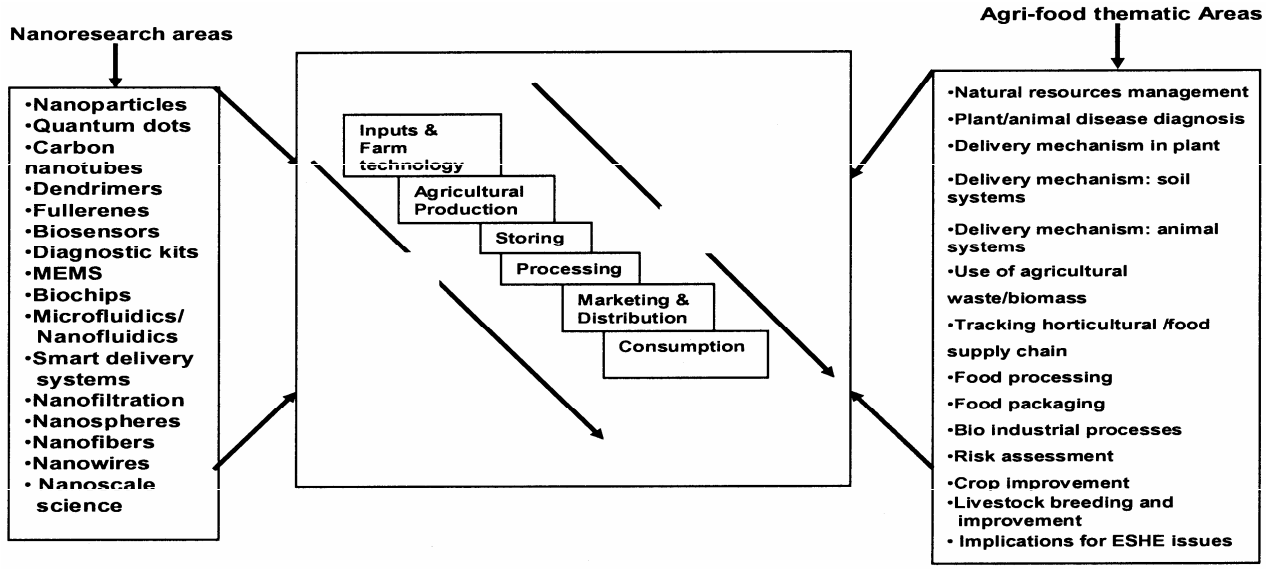

Fig. 1— Framework for integrating nanoresearch areas and agri-food thematic areas[13]

agriculture listed above. Technological assessment and knowledge mapping of nanoresearch areas in disease management was done for the selected patents. Further analysis was carried out based on basic bibliographic and technology trend analysis, which involved analysis of patent timeline, inventors, assignees and geographical distribution; International Patent Classification (IPC) category composition; and possible social, environmental and health risks.

Nanotechnology Patents in Disease Diagnosis and Delivery Systems

The analysis of 119 patents indicates most patents were based on inventions for delivery mechanisms in animal/systems, while no exclusive patents for inventions for diagnosis of diseases in plants were found. However, evidence for this was found in inventions for animal sector where the applications were found for plants too. Considering that animal diseases not only hinder efficient livestock and poultry production but also impact human health, food supply and public health system, R&D efforts are probably being more focused in this sector. Recent experiences with threats of black rust epidemic due to Ug99 race in Africa and Asia; avian influenza, foot and mouth disease (FMD) and bovine spongiform encephalopathy in Europe and the South Asia; swine flu in America evidence the devastating effects of biotic stresses on the economic health of the animal and food industry and consequently, the global economy. Zoonatic diseases are main targets for more research in disease control because of the inherent character of spread to larger range of species including humans.[14] In case of crop plants too; the same principles can be applied for a broad range of uses, in particular to tackle infections. Nanoparticles tagged to agrochemicals or other substances could reduce the damage to other plant tissues and the amount of chemicals released into the environment. Initial work on analysis of core-shell magnetic nanoparticles introduced into plants to work out the correct penetration and transport of the nanoparticles into plants has been reported recently.[15] Thus the technology advancement in the detection and treatment of animal diseases can also be used for supplementing the initial attempts being presently made in disease management of crops. These trends indicate that R&D processes are beginning to be in place for the use of nanotechnology to improve contaminant detection (both chemical and microbial) security of tracking systems and reduce treatment use for enhancing efficiency of animal/crop production, improve health and nutritional status of animals and crop produce and increase food safety.

Analysis of Patenting Activities

The trends in patents were studied on the following parameters:

Basic Bibliographic Analysis

Number of Patents through Reference Dates

Reference dates in patent documents reflect timing of invention, process and strategy of the applicant. In the present study, two indicators, namely, priority

year and publication year were used to gauge trends in inventive activities over a span of 10 years. It is known that priority date/year is the first date of filing of patent application anywhere in the world. It is the earliest and considered closest to the invention date and publication year reflects the time when information is disclosed to the public from statutory offices. Using priority date is most often recommended to reflect inventive performance of technologies, while publication year reflects the rate at which statutory offices are working on these technologies. In case of activities in nanotechnology for disease diagnosis and treatment, it is observed that there are increasing trends on the basis of priority year and publication year from 2001 (Fig. 2). Similar trends have been reported in several other fields of nanotechnology[16,17] indicating the initial investments made since 2000 in several countries in R&D are now resulting in patentable inventions.[18]

Number of Patents by Geographical Scope

The trends in R&D activity are also associated with geographical scope of patent protection, which reflects the market coverage of an invention. Hence, the corresponding patent families of all the 119 patents were also analysed and data normalized to 762 patents. Patenting activity was found to be worldwide with USA (14%) as the leading country with highest number of patents followed by Europe (13%), Australia (11%), Japan (9%), Canada (9%), Germany (5%), Austria (5%), Spain (4%), China (3%) and Brazil (3%). Other countries (24%) include Argentina, Finland, United Kingdom, Hong Kong, India, Iceland, Portugal, Singapore, Slovenia, Slovakia, Taiwan, Denmark, France, Norway, Republic of Korea, Hungary, New Zealand, Israel, Mexico, Greece, Russian Federation, Poland, South Africa, Estonia, Uruguay and Czech Republic.

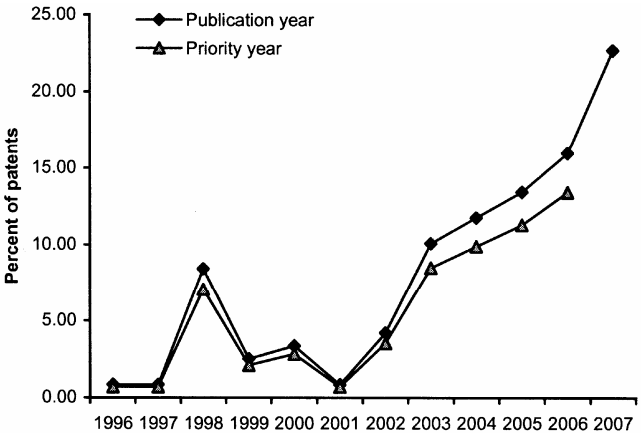

Fig. 2— Patent timeline analysis

Significantly, about 13 percent of the patents were PCT filings reflecting that applicants for these technologies also considered applying through PCT route. These trends indicate the trends of patent applications in several countries by inventors with possible markets in most places including developing countries. It is well known that nearly 62 countries including developing countries[19] like China[20], India, Brazil and South Korea have initiated major programmes in nanotechnology with funding at national or international levels.

In view of the enabling nature of nanotechnology, investments are being made by several developing countries in this sector, to 'leapfrog' their way to leadership and also to 'catch up' in global economic terms. However, having large groups of researchers working on similar subjects may lead to overlapping of patents creating patent thickets and rendering difficulties for commercialization.

Number of Patents by Profile of Assignees

The patent data was classified in the following categories: Corporate sector comprising of industrial organizations and corporate bodies, institution sector comprising academic institutions, government sector and public funding agencies and individuals with no institutional affiliation. The analysis indicated that industrial organizations registered maximum patents (64%) followed by institutes in public domains including universities, R&D centres etc., (24%), independent investors (6%) and collaborations between public and private organizations (6%). Considering the projections of rapid growth of nanotechnology and expected market volume of one trillion dollars by 2015[21], the interest of industry in building a portfolio of patents is justifiable. In the sector of disease diagnosis and delivery systems too, it is obvious that industry continues its interest. Even in the US, which is a leading country with R&D interests in this area, 90% of patent applications are held by the private sector, with the remainder split amongst the public sector.[22]

A further analysis of major assignees in each of 5 fields of this sector (Table 1) reveals players like Bayer AG, Nanobio Corporation, Galderma Research & Development SNC, Prion Developmental Laboratories Inc, Naturalnano Inc, as major assignees in each field.

Table 1— Major assignees in individual sector of disease diagnosis and delivery mechanisms in agriculture

Individual sector	Major Assignees in individual sector
Disease diagnosis in animals	Prion Developmental Laboratories Inc University of Florida Research Foundation Inc
Delivery mechanism in plant systems	Naturalnano Inc
Delivery mechanism in animal systems	Galderma Research & Development SNC Independent Inventors
Disease diagnosis in both plants and animals	Bayer AG
Delivery mechanism in both plants and animals	Nanobio Corporation

These trends are new for agriculture R&D where the research contributing to the green revolution including its dissemination of technologies was not concerned with acquiring intellectual property rights[23] and was largely conducted in the public domain. The predominance of the private sector and its ownership of IPR, presents new challenges to the agriculture sector, particularly in developing countries[24] where R&D programmes are still in public sector institutes. For these institutes to gain access to the new technologies in their R&D programmes, new policy decisions and governance models for sharing research tools and research outputs would be needed.

Technology Trend Analysis

Number of Patents Depicting Various Nanoresearch Areas

Use of nanoparticles, nanospheres, nanotubes, nanocapsule, nanocrystal and nanostructure is mentioned in most of the patents. In nanoresearch area, nanoparticles (61%) ranked first followed by nanospheres (17%), nanotubes (8%), nanoscale phenomena and processes (5%), quantum dots (3%), Nanosensors/ biosensors(3%), Dendrimers (2%) and nanofibres (1%).

Recent data has shown that in some cases, low concentrations of insoluble drugs in a nanoparticle form can be more active than previously thought, offering the potential to administer drugs in low dosages without reducing effectiveness of the treatment. The new technology allows more scope to develop new drugs by converting currently available drugs into a nanoparticles form.[25] Cancer, keratinization, dermatological, ophthalmologic, rheumatic, respiratory, cardiovascular disorders in animals are some of the diseases being treated using nanoparticles. Nanoemulsions are used for treatment of bacterial, fungal and viral diseases in both plants and animals. Only nanospheres were considered for treatment of keratinization and dermatological disorders.

Further analysis was done using Aureka Themescape, a text mining and visualization tool with contour map display capabilities giving users a bird's eye view of the common concepts from a given document set. The program reads full text documents, identifies themes that occur throughout the reference, and employs clustering algorithms to organize documents by co-occurrence of the identified themes.

The analysis based on title and abstract of patents showed that the main focus is on disease diagnosis and treatment. Pharmaceutical and cosmetic compositions and biosynthesis of nucleic acids were the other two areas of work, which were simultaneously covered in the patents. In the area of nanotechnology for diagnosis and treatment, frequently used are various forms of nanoparticles including lipid nanoparticles, metallic nanoparticles and polymer coated nanoparticles. These were used as bioimaging probes, delivery devices and surface recognition. These findings substantiate the trends observed earlier from basic bibliographic data (Fig. 3).

Mapping of Nanotechnology Applications to Disease Diagnosis and Treatment

A more detailed techno-analysis of patents in the sector of disease diagnosis and delivery of treatments was done by text mining of title, abstract and claims. Attempt was made to link to each of 5 fields i.e disease diagnosis in animals; diagnosis in both plants and animals, delivery mechanism in plants; delivery mechanism in animal systems, and delivery mechanism in both plants and animals. A tabulated synopsis of potential applications using nanotechnology for enhancing disease diagnosis and treatment made through analysis using the framework is presented in Table 2. Nanoparticles were found to have applications in all fields followed by nanotubes. Most of the research is focused on biosensor technology. It is known that this technology has progressed rapidly during recent years because of demands from homeland security for rapid detection methods in bioterrorism.[26] Several functions in nanogenomics, nano fabrication, instrumentation, devices are used for developing this technology. The other applications found include nanoformulations

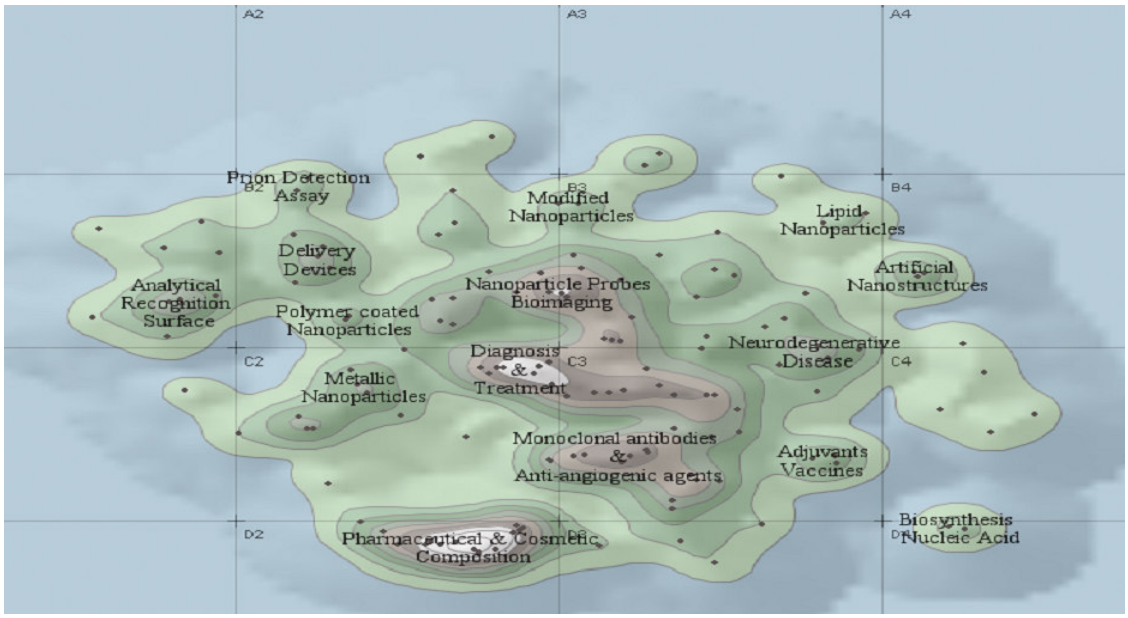

Fig.3— Aureka Themescape map indicating nanoresearch areas

Table 2— Potential nanotechnology applications for enhancing disease diagnosis and treatment in agriculture

Nanoresearch area	Application
	Disease diagnosis in animals
Nanoparticles	Rapid prion-detection assay for neurodegenerative diseases such as transmissible spongiform encephalopathy in bovine, sheep and cats. X-ray contrast agents
Nanoparticles bound to anti-calprotectin antibody	Assay method to detect cardiovascular disease
Luminescent nanoparticles	Bioanalytical sensing platform
Magnetic nanoparticles of a metal oxide and a polymer	Diagnostics for infectious diseases
Radioactive nanoparticles	Diagnostic imaging and disease treatment for tumors, microbial disease, bone metastasis, AIDS associated cancer, vascular malformations and functional disorders.
Magnetic quantum nanoparticles	Multifunctional contrast agents or probes for in vivo bioimaging
Nanodevices, Microdevices and sensors	Monitor chemical or physical changes in the body fluids.
Biosensors	For detecting the hybridization of natural nucleic acids (DNA/ RNA) of specific sequences
Nanobioprocessor	For protein and cell therapy, diagnostic in biophotonics and nanomedicine
Nano-dot	MRI enhancer
Biofunctionalized quantum dots	Biological imaging
Fluorescent nanocrystals	Diagnostic and non toxic therapeutic applications
Nanocells	Diagnosis and treatment for brain tumor, Asthma
Bioconjugated nanostructures	Detecting and treating diseases
	Delivery mechanism in plant systems
halloysite / other mineral-derived nanotubes	Controlled or timed release of agents for treating agricultural materials, crops
	Delivery mechanism in animal systems
Peptidic nanoparticles	Drug delivery and antigen display systems
Nanosilver-containing antibacterial and antifungal granules	Inhibitory effect for broad-spectrum of bacteria and fungi
Engineered silver nanoparticles	For malaria, fungal and bacterial infections of the skin, pelvic inflammatory disease, pharyngitis

Contd.

Table 2— Potential nanotechnology applications for enhancing disease diagnosis and treatment in agriculture

Nanoresearch area	Application
Nanoparticles comprising a platelet-derived growth factor (PDGF) receptor tyrosine kinase inhibitor	For Restenosis, Atherosclerotic vascular disease, vein graft failure
Biodegradable controlled release nanoparticles	Sustained release bioactive agent delivery vehicles include surface modifying agents to target
Nanocrystals, Nanoparticles-Solid lipid nanoparticles (SLNs)	For dual action, inhaled formulations providing both an immediate and sustained release profile for severe acute respiratory syndrome (SARS), influenza, mumps, croup, sinusitis, bronchitis, angina, laryngitis
Nanospheres	Pharmaceutical/cosmetic compositions for dermatological, rheumatic, respiratory, cardiovascular and ophthalmological disorders
Nanocapsules	Lipid-derivatized bisphosphonic acid for bone diseases
	Helicobacter proteins, nucleic acids administered as vaccines
Metal cluster nano-compounds	Tumor diseases
Nanotubes	Anti-microbial peptides and compositions for treating farm animals
Nanotubes and nanoparticles	For delivering anti-cancer agents
Arnphiphilic nanotubes and micelles	Delivery of biologically active agents
Dendrimer, nano-machines	Cancer, viral diseases, allergies (Hay fever), viral (AIDS), bacterial, protozoal, toxin contamination
Nanocells	Allows the sequential delivery of two different therapeutic agents with different modes of action or different pharmacokinetics.
	Disease diagnosis in both plants and animals
Luminescent nanoparticles	Veterinary diagnostics for determination of antibodies, antigens, pathogens /bacteria, for symptomatic and pre-symptomatic plant diagnostics
	Multianalyte determination system
	Analytical platform and method for generating Protein expression profiles of cell populations
Nanotubes and nanoparticles	Process to make high quality DNA in a cell-free system, free of bacteria contaminants, and optimally free of flanking bacterial gene coding sequences which can minimize or silence gene expression when used for expression inside a target cell
Nanocrystals	Bioimaging
	Delivery mechanism in both plants and animals
Nanoemulsion vaccines	Against a variety of environmental pathogens
Nanoforrmulations	Agrochemicals, pharmaceuticals, catalysts, and other active ingredients
Nanostructured surface materials	For catalytic, therapeutic, herbicidal, pesticide, antibacterial and antifungal applications
Lipophilic and hydrophilic nanoparticles	Used in pharmaceutical products, food additives, cosmetics, agriculture, pet foods and veterinary products

for delivery of pesticides, vaccines and drugs in plant/animal systems. These include conventionally used materials and also novel compositions.

IPC Category Composition

A more detailed assessment on the fields of technology was made by analysing the distribution pattern of the patents in various subfields of categories under IPC.[27] The patents were found in about 16 IPC classes (till subclass level or the third hierarchical level of classification) covering a large domain of sectors. It is known that a patent application can be associated with more than one IPC class and one patent may occupy more than one subclass. It was found that there are maximum number of patent records in IPC classes A61K and A61P which cover preparations for medical purposes and therapeutic activity of chemical compounds or medicinal preparations (Table 3). This was followed by records in IPC classes, G01N and C07D with applications for characterized materials for the purpose of drug delivery or compounds for imaging based on their properties. The trend also indicates that several patents are being filed for technologies, which have applications extendable to the field of disease diagnosis and treatment in agriculture. However, the wide breadth of the field being applied gives opportunity for broad patent coverage. It is apprehended that intellectual property litigation over patents covering applications in diagnosis or treatments of diseases can

Table 3— Distribution of patents in top 10 IPC subclasses

IPC code	Description	% Patents*
A61K	Preparations for medical, dental, or toilet purposes	35
A61P	Therapeutic activity of chemical compounds or medicinal preparations	14
G01N	Investigating or analysing materials by determining their chemical or physical properties	11
C07D	Heterocyclic compounds	8
A61Q	Use of cosmetics or similar toilet preparations	7
C07C	Acyclic or carbocyclic compounds	5
C07K	Peptides	4
C12Q	Measuring or testing processes involving enzymes or micro-organisms; compositions or test papers therefore; processes of preparing such compositions; condition-responsive control in microbiological or enzymological processes	4
C12N	Microorganisms or enzymes; compositions; propagating, preserving, or maintaining microorganisms; mutation or genetic engineering; culture	3
A61L	Methods or apparatus for sterilizing materials or objects in general; disinfection, sterilization, or deodorization of air; chemical aspects of bandages, dressings, absorbent pads, or surgical articles; materials for bandages, dressings, absorbent pads, or surgical articles	2
C07H	Sugars; derivatives thereof; nucleosides; nucleotides; nucleic acids	2

*Total set of 260 patent records

be expected to emerge and the complexities seen earlier in agricultural biotechnologies may assume even a higher level in this field.

Conclusion

Nanotechnology is a highly interdisciplinary field, and when interfaced with technologies of agriculture, it leads to complexities in technology diffusion processes. This necessitates need to interlink different knowledge domains using a multifaceted search approach from different patent databases. Several approaches are in vogue[28] especially in other field of sciences. This study is probably one of the first attempts in linking agriculture research with nanoresearch areas using patents as R&D indicators. Through the specially developed framework and database, an attempt was made in this study to link theme areas, nanoresearch and application in disease diagnosis and treatment schedules over a variety of areas of agriculture including crops, veterinary fields, poultry, fisheries, and related areas.

The results indicate that the majority of the agri-nanotech patents are in different fields with various IPC codes and applications extendable to the field of disease diagnosis and treatment in agriculture. Current quantum increase in agri-nanotech patents is similar to nanotech patents in other fields[29], which can lead to overcrowded patent thickets. It is well known that patent thickets in turn hinder critical innovation and continued product development. Such a situation in disease diagnosis and treatments in agriculture may hinder an effective integrated risk and disaster management system. Hence it is essential to form licensing[30] and patent pools for making the invention available to the public. Keeping in perspective, the emphasis on issues of IP and technology transfer in the National Agriculture Research Systems in India[31], the transfer processes of nanotechnologies in this sector against the patent portfolios may need to be well understood and policies developed before the commercialization cycles are put in. It is suggested that policies for developing open access models or encouraging use of propriety ownerships on humanitarian licensing models[32] be part of technology transfer models for nanotechnologies based research in disease management.

Any new technology in agriculture not only affects agricultural systems but also will have major impact on humans and ecology. The study indicated that most of patents researched indicate a dearth of real data on the risks involved by utilizing either these products or processes at the field level. It is essential that risk assessment protocols be worked before technology diffuses into more markets.

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