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Nano-enabled drug delivery systems for brain cancer and Alzheimer's disease: research patterns and opportunities

Jing Ma, PhD candidate[a,*], Alan L. Porter, PhD[b,c], Tejraj M. Aminabhavi, PhD[d], Donghua Zhu[a]

[a]School of Management and Economics, Beijing Institute of Technology, Beijing, China
[b]School of Public Policy and Technology Policy & Assessment Center, Georgia Institute of Technology, Atlanta, GA, USA
[c]Search Technology, Inc., Atlanta, GA, USA
[d]Department of Pharmaceutics and Pharmaceutical Chemistry, Shree Dhanvantary Pharmacy College, Surat, India

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Abstract

"Tech mining" applies bibliometric and text analytic methods to scientific literature of a target field. In this study, we compare the evolution of nano-enabled drug delivery (NEDD) systems for two different applications – viz., brain cancer (BC) and Alzheimer's disease (AD) – using this approach. In this process, we derive research intelligence from papers indexed in MEDLINE. Review by domain specialists helps understand the macro-level disease problems and pathologies to identify commonalities and differences between BC and AD. Results provide a fresh perspective on the developmental pathways for NEDD approaches that have been used in the treatment of BC and AD. Results also point toward finding future solutions to drug delivery issues that are critical to medical practitioners and pharmaceutical scientists addressing the brain.

From the Clinical Editor: Drug delivery to brain cells has been very challenging due to the presence of the blood-brain barrier (BBB). Suitable and effective nano-enabled drug delivery (NEDD) system is urgently needed. In this study, the authors utilized "tech-mining" tools to describe and compare various choices of delivery system available for the diagnosis, as well as treatment, of brain cancer and Alzheimer's disease.

Key words: Nano-enabled drug delivery (NEDD); Brain cancer; Alzheimer's disease; Tech mining; Technology opportunities analysis

As an emerging nanomedical technology, nano-enabled drug delivery (NEDD) emphasizes targeted and controlled release of therapeutics to improve the efficacy of drug administration to the site of action. NEDD has the potential to enhance medical treatment regimens via tailored drug delivery systems, using nanoparticles, nanocapsules, nanogels, nanotubes, etc., that are increasingly coming available.[1] These NEDD approaches enable the delivery of a great variety of drugs/therapeutics and offer potential advantages over conventional methods for the treatment of many diseases.

Treatment agent delivery to brain cells has been particularly challenging due to the protection of the blood-brain barrier (BBB), coupled with the tight endothelial cells having a narrow diameter (<20 nm), since these restrict the entry of many substances, including most biopharmaceuticals, in reaching targets in the brain.[2-4] Novel strategies are therefore required to deliver agents to brain cells, such as developing surface modified, nano-size devices with the appropriate surface charge and zeta potential.[5] Therefore, the choice of a suitable, biodegradable NEDD system is appealing for successful delivery to the brain regions as the majority of other types of delivery devices have fared poorly.[2,3] A natural choice is to consider using biopolymers (e.g., polysaccharides) as carriers, along with moieties, like ligands, attached to the NEDD device containing a treatment agent. Researchers have chosen such systems based on their biodegradable and biocompatible characteristics, as well as drug encapsulating abilities.[6] Research efforts over the past decade have enhanced the transport of bioactive molecules across the BBB. These include receptor-mediated delivery of bioconjugates, hydrogels, dendrimers, and RNA interference agents.[7-9]

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*Corresponding author at: School of Management and Economics, Beijing Institute of Technology, Beijing, China, 100081.

E-mail addresses: majing881003@163.com (J. Ma), alan.porter@isye.gatech.edu (A.L. Porter), aminabhavit@gmail.com (T.M. Aminabhavi), zhudh111@bit.edu.cn (D. Zhu).

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Alzheimer's disease (AD) and brain cancer (BC) are two major deadly, non-communicable diseases for which treatment is daunting. Every year millions of people are affected by these diseases, yet, unfortunately, no truly effective drug regimens are available.[10,11] In recent years, early detection has been emphasized, but attempts to develop curative methods have met with limited success. Although BC & AD have different pathologies and pathways, the development of NEDD approaches with common elements to deliver drugs through the BBB could possibly advance treatment of both diseases.

Biomedical scientists are employing nanomaterials and molecular scale mechanisms to improve delivery systems' targeting and effectiveness. Basically, appropriate drugs (or other therapeutic and/or diagnostic agents) are encapsulated for targeting to a diseased site. We note that nanotechnology offers a range of biomedical possibilities, including direct treatment, but our focus is on NEDD (i.e., nano roles in delivery). In this pursuit, various combinations of drug/delivery mechanism have been developed and employed in laboratory and clinical studies. Literature is both extensive and diverse, making it challenging to compare results from various laboratories around the globe. It is difficult to interpret which agent-carrier systems are most effective, for which ailments (no less to forecast how novel NEDD-agent-disease combinations will fare). There is thus a need to analyze the literature empirically to understand the research activities and their development pathways for early diagnosis and/or treatment of AD and BC.

Recent advances in "tech mining" – computer-aided text analytics applied to science, technology & innovation (ST&I) data resources – offer tools to depict research landscapes, networks, and developmental trajectories.[12] The key data for tech mining are search sets retrieved from global scientific databases that compile research publication and patent abstract records. These means enable rapid processing of the thousands of R&D results published annually to track developments in biomedical fields of interest. Hot topics,[13] fast-breaking developmental pathways,[14] and network relationships can be spotlighted to help advance science. Literature-related discovery and innovation (LRDI) can identify novel methods and discoveries in related fields.[15]

Complex diseases like AD and BC are rarely caused by a single gene (or single signaling pathway) dysfunction. Instead, these diseases are likely a result of disturbed disease networks, involving dysfunction of numerous genes, proteins, and/or signaling pathways. Systems biology suggests that effective treatment of such complex diseases needs to restore disrupted disease networks, which often require simultaneous modulation of multiple proteins (targets)/pathways.

This study compares the evolution of NEDD systems directed at these two diseases through tech mining. Our goal is to identify NEDD assets developed for BC that could contribute to AD, and vice versa. To further such aims, we first lay out developmental NEDD pathways for BC and for AD. We then strive to point toward prospective research knowledge transfer between these brain treatment regimes, thereby identifying cross-fertilization opportunities for biomedical researchers.

This paper contains five parts: 1) refining a search strategy and retrieving MEDLINE data; 2) tracing the developmental trends of NEDD research in BC and AD, and analyzing the interaction between these two fields; 3) identifying research topics mainly from the perspective of nano-enabled drug delivery system components and drugs; 4) profiling selective hot topics in NEDD for BC and AD, and 5) exploring future directions.

Methods

Search strategy and MEDLINE data

Prior tech mining by our research group has addressed nanotechnology broadly,[16,17] moving into the study of NEDD R&D patterns.[13,18] This study focuses on NEDD for the two target diseases (BC & AD). Those prior NEDD studies explored R&D patterns through analyses of fundamental research, compiled in the Web of Science database, and of patenting data, garnered from Derwent Innovation Index. Here, we concentrate on retrieving biomedical research from MEDLINE data on NEDD for BC and AD.

We build our search strategy by considering facets of the delivery of drug-laden nanoparticles or nanocarriers to treat the two chosen brain-related diseases. Our final search framework contains several groups of terms: 1) targets and drugs; 2) nanoparticles and materials; and 3) delivery systems. Each part includes several keywords and relevant Medical Subject Heading (MeSH) terms (Table 1). The first part describes the diseases, BC and AD, and respective treatment agents.

For BC, drugs such as temozolomide, procarbazine, and carmustine are included (http://www.cancerresearchuk.org/about-cancer/type/brain-tumour/treatment/chemotherapy/chemotherapy-drugs-for-brain-tumours, etc.); for AD, drugs include tacrine, donepezil, rivastigmine, galanthamine, piracetam, and memantine.[19] Since several BC drugs are also applicable to other cancer types, using these as search terms widens our search results. The second part is about nano-enabled drug carriers and the relevant materials used in these applications. We use "nano*" as a keyword to generally incorporate different forms, including nanoparticles, nanocapsules, nanogels, nanocarriers, nanodevices, etc. To exclude potentially unrelated records caused by "nano*" or other terms, the third part of this search strategy is introduced. The third part is used to portray the delivery process of the nanocarriers and also to filter out search results reflecting unrelated topics. Besides common drug delivery phrases, we also included BBB in this part, since it is the primary barrier with highly selective permeability for drug-loaded nanocarriers to pass through, to reach brain areas. The search strategy is applied through the MEDLINE interface provided by Thomson Reuters's Web of Knowledge. We collect data from 2000 to 2014. We retrieve 1851 records related to NEDD for BC; for AD, we find 262 records [retrieved through Jan 7, 2015].

Topical analysis

In tech mining, we analyze structured and unstructured text content to ascertain topical patterns and trends. In our study, we