POTENTIAL CLINICAL SIGNIFICANCE

Nanomedicine: Nanotechnology, Biology, and Medicine
11 (2015) 1763–1771

nanomedicine
Nanotechnology, Biology, and Medicine

ELSEVIER

Original Article

nanomedjournal.com

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

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Received 31 March 2015; accepted 2 June 2015

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]

We acknowledge support from the US National Science Foundation, Science of Science & Innovation Policy (SciSIP) Program (Award No. 1064146 — "Revealing Innovation Pathways: Hybrid Science Maps for Technology Assessment and Foresight"). The findings and observations contained in this paper are those of the authors and do not necessarily reflect the views of the National Science Foundation. The authors declare there is no conflict of interest regarding the publication of this paper.

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http://dx.doi.org/10.1016/j.nano.2015.06.006
1549-9634/

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

Table 1
Search strategy.

Group	Search terms (note: * is a wildcard, representing any group of characters, including no character)	
T (target and drug)	Brain cancer & pertinent drugs	Keywords: (brain or "central nervous system" or CNS) near/1 (cancer* or anticancer* or tumor* or tumor* or oncology or neoplasm* or carcinoma*) or glioma* or glioblastoma* MeSH: brain neoplasms or glioma or glioblastoma Keywords: temozolomide or procarbazine or carmustine or BCNU or lomustine or CCNU or vincristine or everolimus or irinotecan or cisplatin or carboplatin or methotrexate or etoposide or bleomycin or vinblastine or actinomycin or dactinomycin or cyclophosphamide or ifosfamide
	Alzheimer's disease & pertinent drugs	Keywords: Alzheimer* MeSH: Alzheimer disease Keywords: tacrine or donepezil or rivastigmine or galanthamine or piracetam or memantine
N (nanoparticles and materials)	Keywords: nano* or micelle* or liposome* or dendrimer* or metal complex* or hydrogel* or "quantum dots*" or chitosan* or alginate* MeSH: micelles or liposomes or coordination complexes or dendrimers or hydrogels or quantum dots or chitosan or alginates	
D (delivery systems)	Keywords: "drug delivery system*" or "drug carrier*" or "drug delivery*" or "deliver* drug*" or "delivery system*" or "delivery vector*" or "target* deliver*" or "delayed-action preparations" or "drug release" or "controlled release" or "controlled drug release" or "sustained release" or" sustained drug release" or "brain target*" or "brain delivery*" or "small interfering RNA" or "RNA interference" or" gene delivery*" or "gene vector*" or BBB or "blood brain barrier*" MeSH: Drug delivery systems or delayed-action preparations or drug carriers or RNA, small interfering or RNA interference or genetic vectors or blood-brain barrier	

apply natural language processing (NLP) algorithms to titles and abstracts to extract topical information using *VantagePoint* desktop text analysis software [www.theVantagePoint.com]. After cleaning (using fuzzy matching routines and thesauri), we compile a list of key terms from the titles and abstracts. Then, by combining the results with MeSH terms provided by MEDLINE, we build multi-source keyword lists for BC and AD. We then focus on comparing how NEDD has been developing for each. We especially seek to identify novel findings from BC that could facilitate AD research, or vice versa. Due to different pathologies, most of the keywords for BC and AD are different, but we also look at whether any shared keywords reflect potentially informative similarities and connections.

To extract candidate NEDD topics relating to BC and AD, some 500 top keywords/phrases are selected from their respective key term lists. These are manually examined for further analyses. First, common terms that have no specific meaning for NEDD are excluded (e.g., delivery system, drug carriers, nanotechnology, disease model), and secondly, BC and AD descriptive and pathological terms are excluded (e.g., Alzheimer's disease, brain tumor, degeneration, chemotherapy). That leaves mainly terms related to drug administration and terms pertaining to delivery system. The final lists of 149 BC key terms and 109 AD terms are given in Appendix A (online supplementary material). Principal components analysis (PCA) is then applied to cluster these key terms. The algorithm offers several candidate topics. The PCA results (Appendix A (online supplementary material)) of BC and AD are combined. By discussing with an NEDD specialist, topics with similar meanings are combined and topics that are not constructive are excluded. After checking their related records, we choose 15 topics (i.e., factors that consolidate terms tending to occur together in the publication abstract records). Since some drugs are separately located in different topics, we combined them into two topics based on our lists of drugs for BC and AD. In all, 17 topics are identified on the chosen delivery systems and the drugs used for administration. Further analysis and comparison are conducted based on these specific topics.

Results

Developmental trends and interactions

NEDD offers a promising platform for the treatment of various kinds of cancers. NEDD-cancer tools often apply to multiple cancer targets. Approaches and advances in drugs and

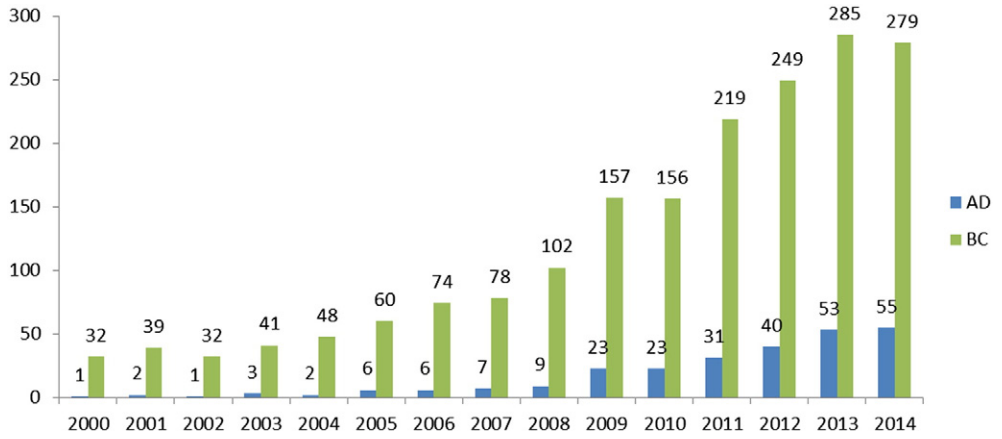

Figure 1. Annual NEDD MEDLINE publications for BC and AD.

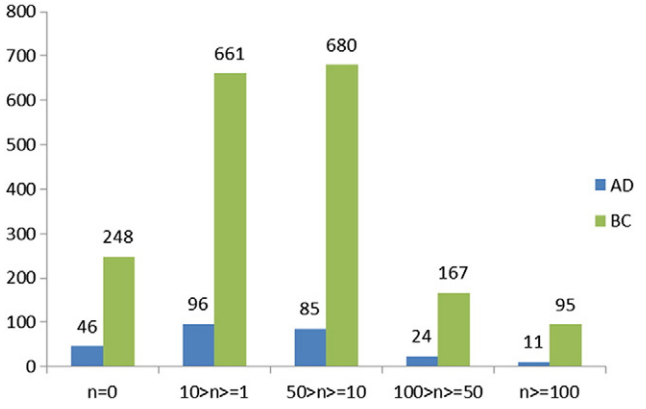

Figure 2. Citation distribution plot (n refers to number of times cited).

delivery systems cross-fertilize richly among cancer types. For AD, NEDD shows promise in delivering agents across the BBB, evidenced mainly in pre-clinical studies. Research publications (indexed in MEDLINE) relating to NEDD approaches for the treatment of BC and AD are increasing (Figure 1). Despite slight dips in 2002, and 2010, the BC upward trend is strong (the drop for 2014 is almost surely due to incomplete MEDLINE indexing; "2014" papers will likely be added for many months). BC publications far exceed AD, and the gap is widening in absolute numbers. However, we note that research attention to AD has accelerated markedly from 2009 onward.

Further inspection of Figure 1 suggests a general lag in AD research activity behind that on BC. However, research on both spurts upward in 2009. Might that reflect improvements in NEDD capabilities pertinent to both forms of brain treatment? The higher publication rates in the most recent 6 years call for attention to developmental pathways. Intelligence on those should provide leading indicators of delivery materials and methods with potential value to improve treatments. In particular, AD drug delivery researchers may gain from tracking advances in BC R&D.

Citation data complements publication data in providing an indicator (albeit imperfect) of quality of published research.[20,21] The citation distribution plot in Figure 2 shows a high proportion

Table 2
Statistics of the highly cited BC and AD papers (> = 100).

	BC	AD	Overlap	Overlap/BC	Overlap/AD
Number of records	1851	262	20	1.08%	7.63%
Highly cited (> = 100)	95	11	2	2.11%	18.18%
Citing highly cited	15,140	2218	493	3.26%	22.23%

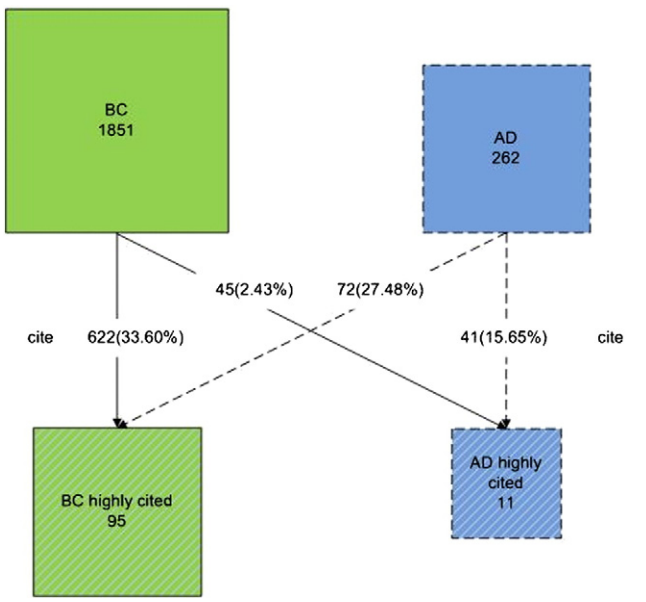

Figure 3. Cross-citing activities of BC and AD.

of well-cited papers for both BC and AD results. Nearly 50% of the papers have been cited over 10 times (e.g., for BC, the middle bar indicates 680 papers each cited between 10 and 50 times). Many papers are cited over 100 times (see the right-most bars with 95 BC papers and 11 AD papers — 5.13% of BC papers; 4.20% for AD).

As per Figure 2, NEDD for BC and AD treatment has received much attention. We don't want to overstate the

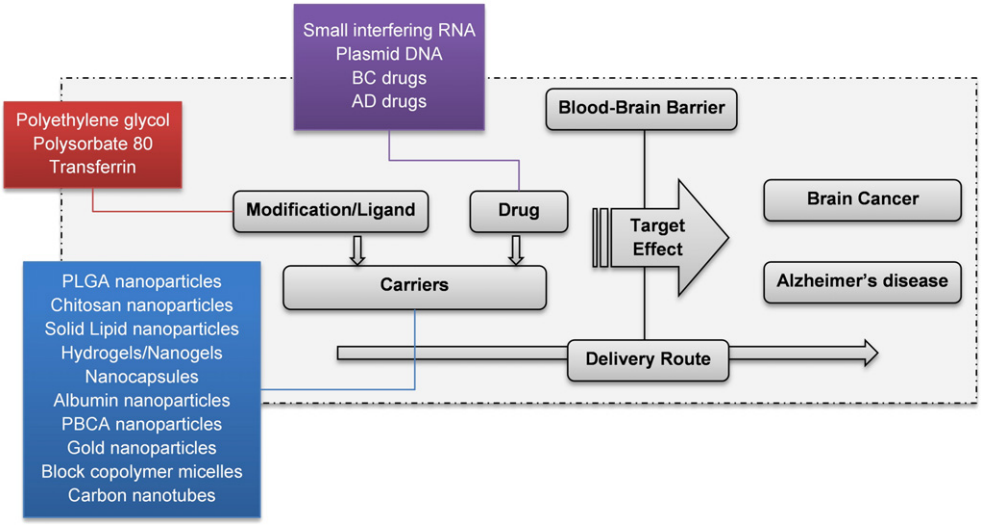

Figure 4. NEDD topics for BC and AD.

Table 3
Seventeen topics in NEDD for BC and AD.

Category	Topic		AD #	BC #
Delivery system related topics	PLGA nanoparticles		16 (6.11%)	96 (5.19%)
	Chitosan nanoparticles		15 (5.73%)	78 (4.21%)
	Solid lipid nanoparticles		11 (4.20%)	45 (2.43%)
	Hydrogels/nanogels		10 (3.82%)	80 (4.32%)
	Nanocapsules		9 (3.44%)	85 (4.59%)
	Albumin nanoparticles		9 (3.44%)	48 (2.59%)
	PBCA nanoparticles		8 (3.05%)	9 (0.94%)
	Gold nanoparticles		5 (1.91%)	43 (2.32%)
	Block copolymer micelles		3 (1.15%)	50 (2.70%)
	Carbon nanotubes		2 (0.76%)	40 (2.16%)
	Transferrin/transferrin receptor		10 (3.82%)	63 (3.40%)
	Polysorbate 80		10 (3.82%)	23 (1.24%)
	Polyethylene glycol		29 (11.07%)	325 (17.56%)
	Small interfering RNA		12 (4.58%)	141 (7.62%)
	Plasmid DNA		0 (0.00%)	42 (2.27%)
Drug topics	BC drugs	Cisplatin	-	414 (22.37%)
		Methotrexate	-	237 (12.80%)
		Irinotecan	-	70 (3.78%)
		Etoposide	-	68 (3.67%)
		Vincristine	-	66 (3.57%)
		Vinblastine	-	49 (2.65%)
		Carboplatin	-	48 (2.59%)
		Temozolomide	-	35 (1.89%)
		Cyclophosphamide	-	30 (1.62%)
		Carmustine (BCNU)	-	21 (1.13%)
		Bleomycin	-	21 (1.13%)
		Actinomycin (dactinomycin)	-	8 (0.43%)
		Everolimus	-	5 (0.27%)
		Ifosfamide	-	5 (0.27%)
		Lomustine (CCNU)	-	3 (0.16%)
		Procarbazine	-	1 (0.05%)
		Rivastigmine	15 (5.73%)	-
		Tacrine	13 (4.96%)	-
		Donepezil	6 (2.29%)	-
	AD drugs	Memantine	3 (1.15%)	-
		Piracetam	1 (0.38%)	-
		Galanthamine	0 (0.00%)	-

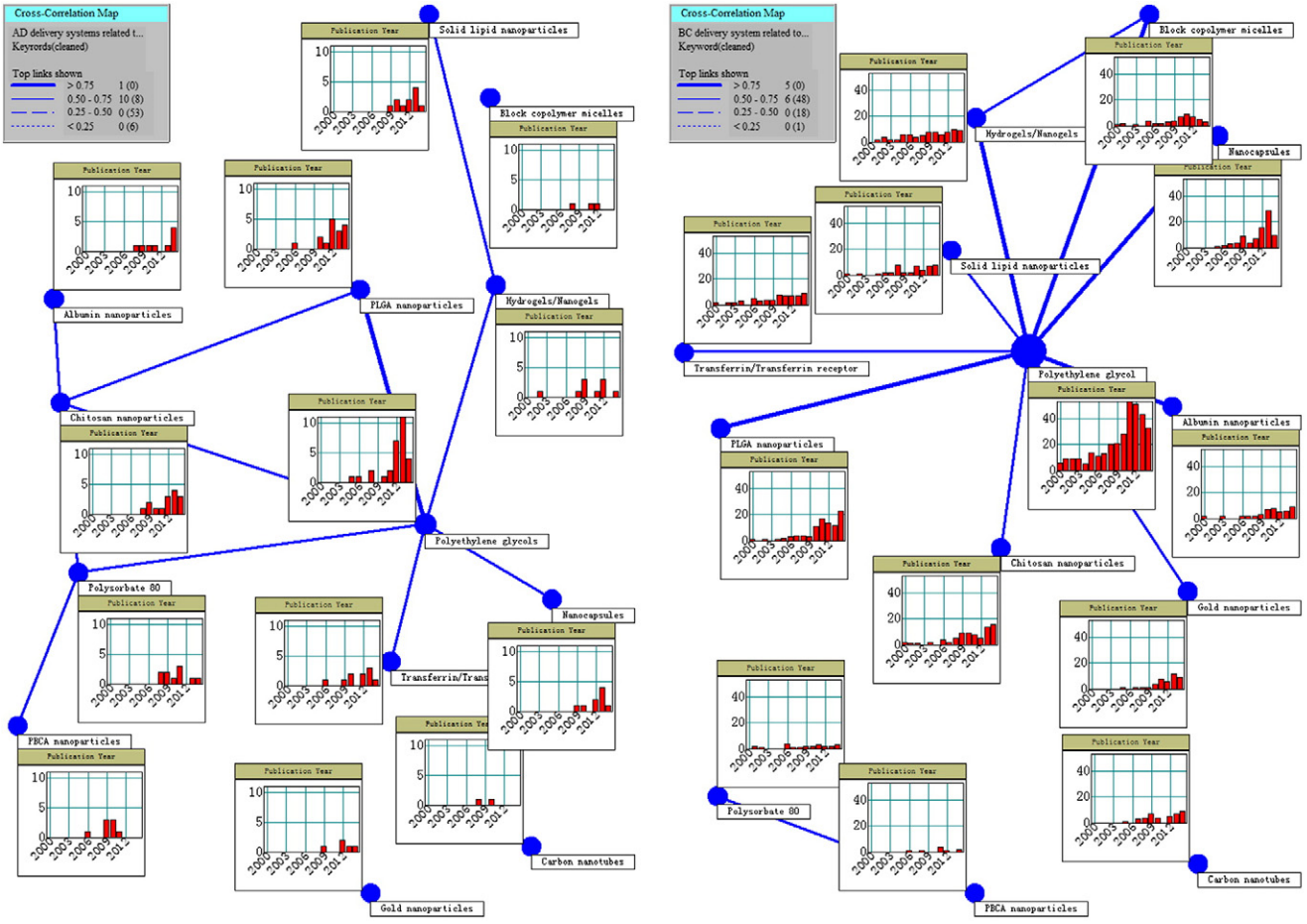

Figure 5. Annual distributions of delivery system related topics.

apparently larger citation numbers for BC. For one, AD research lags BC research in time and citations accrue over time; thus favoring the "earlier field" (BC). One could explore citations/year, but that is not a priority here. Rather we note that this NEDD research is strongly cited, and the distribution shapes are similar (as shown by the five bars of Figure 2).

The strong citation of this NEDD research supports our premise of value in understanding research patterns and trends to identify potential R&D opportunities. In particular, we are interested in potential cross-fertilization between BC and AD R&D. Cross-field citation is a key indicator of connectedness, as it indicates awareness and utility of research findings.[22]

Interaction between NEDD for BC and AD treatments is reflected in their citation networks. As per Table 2, first of all, 20 papers have appeared in both datasets, accounting for 1.08% of BC records and 7.63% of AD records. Of these 20, 2 belong to the highly cited papers set — which is 2.11% of 95 for BC highly cited papers and 18.18% of 11 for AD. Both the papers (one review article and one research paper) discuss brain delivery aspects.[7,23] The research paper deals with the transport mechanism of albumin nanoparticles into the central nervous system (CNS) by transcytosis.

The MEDLINE data provide no citation information, so we retrieved datasets on highly cited papers using a connector provided by the Web of Science Core Collection. From this effort, as shown in Table 2, we find that 15,140 papers cite the 95 highly cited BC papers; and 2218 papers cite the 11 highly cited AD papers. There we find an overlap between these two datasets of 493 records. Comparing with the original BC and AD datasets, the proportion of overlapped records is bigger. Citation activities increase the diffusion of knowledge, since the results of prior studies are referenced by subsequent papers in other fields (in addition to citation in their own field). The result in Table 2 suggests that the knowledge conveyed by the cited papers diffuses between NEDD research for BC and AD.

Finally, such fusion can be further illustrated by cross-citing activities. Reverting back to the original NEDD-BC and NEDD-AD datasets, 622 out of the 1851 BC papers cite 95 highly cited BC papers, while 45 BC papers cite 11 AD highly cited papers; and the numbers for AD are 72 and 41 out of 262 records, as shown in Figure 3. Especially for AD, 27.48% of the NEDD-AD papers cite BC highly cited papers. However, in these 72 papers, only 8 of them are from the 20 overlapped papers of BC and AD. For the other 64 AD specific papers, we find NEDD-BC treatment papers referenced, implying some influence of the notions from these BC papers. The interaction between these two brain diseases in the NEDD domain and the possibility for them to learn from each other, especially for AD, are indicated by such cross-citing activities.

# Records	Show Values >= 1 and <= 74 Cooccurrence # of Records	Cisplatin	Methotrexate	Small interfering RNA	Irinotecan	Etoposide	Vincristine	Vinblastine	Carboplatin	Plasmid DNA	Temozolomide	Cyclophosphamide	Bleomycin	Carmustine	Dactinomycin	Everolimus	Ifosfamide	Lomustine	Procarbazine
325	Polyethylene glycol	74	33	15	15	11	15	12	7	16	4	2	6	1	1	1	1		1
96	PLGA nanoparticles	19	5	2	4	8	7	2	2	3	4	2		1					
85	Nanocapsules	18	7	8	2	6			4	1	1		2						
80	Hydrogels/Nanogels	32	11	3	5	3	1	2	3	1	4	2	6	1					
78	Chitosan nanoparticles	11	24	7	2	1	3	1	4		3	5	1	1			1	1	
63	Transferrin/Transferrin receptor	5	3	9		1				9	3			2					
50	Block copolymer micelles	21	9	1	2	5	1		1			1							
48	Albumin nanoparticles	4	15	1		1	1	3	3	1		2		1		1			
45	Solid lipid nanoparticles	7	6	1		5	1	3			2			1			1		
43	Gold nanoparticles	15	6	2	2				1		1				1				
40	Carbon nanotubes	15	5	2	1	2			5	1									
23	Polysorbate 80	2	2								1								
9	PBCA nanoparticles	2					1				1	1							

Figure 6. Connections between delivery systems and drugs in BC.

NEDD topics in BC and AD

The 17 topics, which are identified on the chosen delivery systems and the drugs used for administration, are linked to a NEDD framework that we proposed.[24] The entire NEDD brain delivery framework (Figure 4) is constructed of several parts. Normally nanoparticles and other nanocarriers are loaded with different agents and then ligands are attached to assemble a fully workable delivery system. By using various delivery routes, like intravenous or intranasal administration, these delivery systems are able to cross the BBB through transcytosis or other effects, to finally arrive at the disease sites. The 17 topics we identified mainly focus on developing delivery systems. These 17 topics certainly do not cover all developmental efforts, but they should capture many major sub-technologies of NEDD for BC and AD, especially for delivery systems.

For each topic, we list the number of related records in our BC and AD datasets separately, as given in Table 3. These numbers don't cover all related studies, since we only use MEDLINE data in these analyses. The results given in Table 3 are able to profile the general distribution of these research topics. Then, 13 out of these 17 topics are specific delivery elements including carriers and modifications/ligands, shown in Figure 4, such as PLGA nanoparticles and chitosan nanoparticles. These topics may overlap and could be used in combinations. Generally, these delivery systems are more widely developed in research for BC treatment, as reflected in the number of records. Only poly(butyl cyanoacrylate) (PBCA) nanoparticles are more represented in AD datasets. Delivery systems with transferrin or anti-transferrin receptor antibodies attached as ligands seem to offer high potential to facilitate the transport of pharmaceuticals through the BBB to reach brain regions. The surfactants, such as polysorbate 80 or even polyethylene glycols, are used to improve the efficiency of transport of drug candidates to the brain.

	# Records	15	13	12	6	1
# Records	Show Values >= 1 and <= 3 Cooccurrence # of Records	Rivastigmine	Tacrine	Small interfering RNA	Donepezil	Piracetam
29	Polyethylene glycols	1		2		
16	PLGA nanoparticles	1			1	
15	Chitosan nanoparticles	3	3	2	1	1
10	Hydrogels/Nanogels		1	1		
10	Polysorbate 80	2	2			
10	Transferrin/Transferrin receptor			1		
9	Albumin nanoparticles	1	1			
9	Nanocapsules			2		
8	PBCA nanoparticles	1				
3	Block copolymer micelles	1				

Figure 7. Connections between delivery systems and drugs in AD.

The majority of BC drugs are mentioned together with delivery system related topics in the publication abstracts. Not all these studies are specific to brain delivery; some of them concern general neoplasm treatments or other cancer types, but these may have potential for brain delivery as well. In the case of AD, the most studied drugs are rivastigmine and tacrine. RNA interference technology (small interfering RNA — siRNA) has been tried for both BC and AD treatments. However, plasmid DNA has been mainly applied to BC.

Comparison of major topics

Figure 5 displays a combined network and trend analysis of the 13 delivery system elements used for BC and AD. For AD

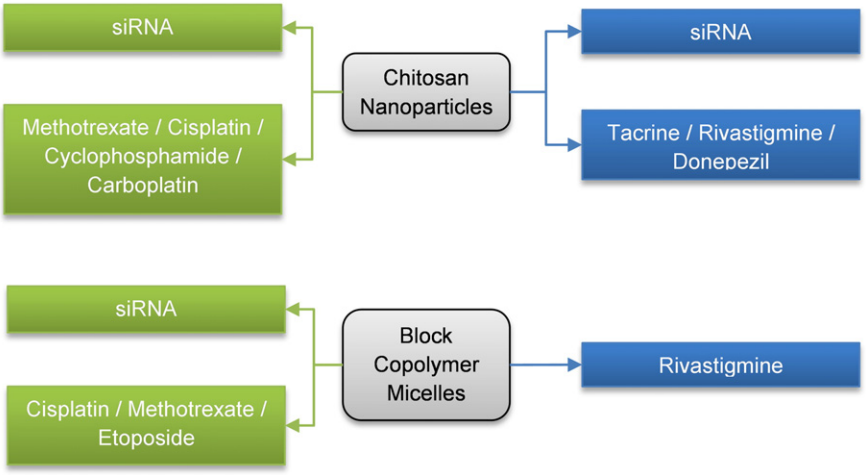

Figure 8. Chitosan nanoparticles and block copolymer micelles.

(left side of Figure 5), most of the elements increase rapidly from about 2009 — similar to the trend shown in Figure 1. For instance, chitosan nanoparticles, solid lipid nanoparticles, nanocapsules, and PLGA nanoparticles grow sharply, while the trend for other elements is fluctuating with a lower number of research publications addressing those. At the same time, PLGA nanoparticles, nanocapsules, and chitosan nanoparticles have shown a rapid increase for BC (right side of Figure 5). On the other hand, block copolymer micelles have shown a decline in research attention recently, while other BC-related topics increased relatively smoothly.

Even though most NEDD systems are developed to load various kinds of agents, there are still many differences, probably due to the nature of the drug molecules and their solubility patterns, as well as their physio-chemical interactions with the surrounding media and with the carrier matrix. Correlations between particular NEDD systems and drugs reflected in Figures 6 and 7, for BC and AD, respectively, show preferences for some drugs in terms of delivery systems. For instance in the BC-related publications, cisplatin shows strong association with hydrogels/nanogels (32 records, of 80 total for hydrogels/nanogels), while cisplatin with block copolymer micelles show up together in 21 records (out of 50 total for block copolymer micelles). Methotrexate for BC is more often encapsulated using chitosan nanoparticles (24 records), followed by albumin nanoparticles (15 records). The preference of delivery systems is less clear in AD, due to the low number of records, but chitosan nanoparticles have the most direct relationships with the AD drugs (Figure 7). In BC, transferrin, as a ligand which attaches to the delivery vehicle, shows strongly in transporting or mediating the delivery of siRNA and plasmid DNA.[25]

The differences among NEDD system-drug associations suggest future opportunities for researchers. For instance, chitosan nanoparticles are often used as drug carriers for brain delivery based on our data. But block copolymer micelles are only popular in BC treatment. Chitosan nanoparticles can be prepared by using emulsification, chemical crosslinking, and ionic gelation methods, accompanied with other modifications or coating with biomaterials, such as PLGA, polyethylene glycol, and polysorbate 80. Cargo types, such as siRNA or drugs, can be loaded into the chitosan nanoparticles. But for block copolymer micelles, situations are quite different in the sense that the loading of drug molecule cargo is done by in situ methods during the process of polymerization. As per Figure 6, chitosan nanoparticles have been connected mostly with methotrexate delivery, while block copolymer micelles are used more for cisplatin. Furthermore, we did not find evidence for using block copolymer micelles for siRNA delivery in AD treatment (Figure 8). The only anti-Alzheimer drug employed with block copolymer micelles of note in these data is rivastigmine. Hence, the question: is there a possibility for block copolymer micelles to play a more important role in AD treatment?

Discussion

NEDD enables the delivery of a great variety of drugs and genetic agents. It holds great potential for the treatment of many diseases. In this study, we compare the developmental pathways of NEDD systems for BC and AD treatments. Even though these two diseases have different pathologies and challenges, and different pathways, NEDD studies about them hold some developmental elements in common. In particular, drugs need to be delivered through the BBB. Our study indicates that NEDD for BC treatment has a more developed history than for AD, as more studies have been completed for the former. Notions applicable to AD might be learned from BC NEDD studies. These might include research findings on NEDD system-drug combinations, preparation issues, delivery interactions, and brain region differences.

By analyzing the citation interactions and relevant topics of NEDD in these two fields, we have identified commonalities and differences between BC and AD on a macro level to reveal some potential applications and substitutes. These studies could provide a global view of the developmental pathways of NEDD in BC and AD treatments, as well as for future potential solutions. For example, is there any way to introduce plasmid DNA into AD treatment or to apply block copolymer micelles

more widely for AD? The gaps and differences between NEDD use in BC and AD treatment may offer further consideration for researchers working in either area.

There are several similarities in other types of drugs where the nanocarrier systems are useful in target area such as breast cancer, where the drug-loaded carrier has to cross over a tissue barrier. Other efforts may include insulin with (peptide)-loaded nanocarriers, like pH sensitive hydrogels, that can deliver drugs to the small intestine by protecting the peptide in gastric stomach media. Exploration of such research cross-opportunities covers potential for future tech mining analyses.

For us, examining research patterns for NEDD for these two brain diseases furthers our ongoing interest in understanding ST&I developmental pathways. We believe that profiling R&D patterns, as pursued here, can suggest research opportunities. We are pursuing development of "emergence" indicators – in the form of topical trend patterns – that could serve as leading indicators. In this case, the earlier research concentration in NEDD for BC suggests less potential for those researchers in exploring AD research thrusts. On the other hand, NEDD-AD researchers might well consider both macro and micro-level findings from NEDD-BC studies to better formulate their research strategies.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.nano.2015.06.006.

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