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NANO-ENABLED DRUG DELIVERY: RECENT TRENDS, EMERGING ISSUES AND FUTURE DIRECTIONS

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ABSTRACT

Nano-Enabled Drug Delivery (NEDD) systems attract attention as a key nano application area. As an emerging scientific and medical field, many researchers and investors want to understand the status and prospects of developments in this domain. Capturing the global developments of NEDD is a challenge, since it is a combination of various technology R&D lines, with a variety of application areas. To help address this challenge, a variety of publication and patent databases provide a reservoir of information on research activities that can be "data mined." The challenge is smart extraction of what is relevant, and how to discern relationships to inform R&D decisions. In this chapter we describe how to do such smart extraction and present a three step process: (1) to articulate the search strategy for the gathering of data, (2) the data capture and sense-making (using the Web of Science and MEDLINE databases) and (3) transformation of these findings into a Technology Roadmap (TRM) tracking NEDD development.

Key words: Nano-Enabled Drug Delivery (NEDD), text mining, tech mining, bibliometric analysis, nanotechnology, subsystem analysis, technology roadmapping (TRM)

INTRODUCTION

With intensified international competition, people have begun to focus on "New and Emerging Science & Technologies" (NESTs) , since they have great potential for innovation and can offer key development opportunities. As one promising NEST, Nano-Enabled Drug Delivery (NEDD) has drawn increasing research attention in recent years.

The first transdermal drug delivery system was introduced in the United States over 20 years ago. Created as an alternative route of administration to improve patient compliance, as well as to reduce side-effects, the transdermal delivery of drugs now represents a multi-billion dollar market. With continuing advances in nanotechnology, NEDD systems are rapidly emerging to meet pharmaceutical industry challenges. NEDD draws on intersecting advances in the fields of medicine, pharmaceutical sciences, and biotechnology. It offers the potential for treating chronic diseases and genetic disorders, and has also been considered a suitable alternative for conventional protein therapy.

For the whole NEDD system, nanocarriers are core to meet several key medical reqirements, including: efficiently entrapping high payload drugs, controlling release, avoiding the "burst effect" (release within the first minutes), and offering potential detectability by imaging techniques (Horcajada, et al. 2009). Besides these, scientists research multi-function nanocarriers to serve both as drug carrier and as diagnostic agent. The advantages of NEDD are strong, but they still have limitations, with multiple research streams ongoing to enhance performance (Horcajada, et al. 2006; Horcajada, et al. 2008;Hinks, et al. 2009; Xiao, et al. 2009). Given this active situation, understanding the NEDD research trajectory is vital to guide R&D portfolio management.

The research of NEDD is diverse. Several subareas like polymer conjugates, nanogels, dendrimers, liposomes, micelles, lipid nanoparticles, nanoemulsions, polysaccharide nanoparticles (such as chitosan), magnetic nanoparticles, gold nanoparticles, ceramic nanoparticles, nanoshells, cyclodextrin nanosponges, and nanocrystals (Loftsson et al., 2005; Peer et al., 2007; Lee et al., 2008; Delcea et al., 2011; Ahmed et al., 2012) are active in recent years. The difficult in identifying the boundary of NEDD gives great challenges in database searching, sub-system specification, and technology innovation pathway identification.

In this chapter, we devise a process to enable smart extraction of information from publication and patent databases to make the route from database to findings reasonably transparent. We focus on major subsystems of NEDD. We will associate Web of Science (WOS) and MEDLINE papers to the major areas, thereby creating intelligence on topical emphases, and track these over time. We then use this content to inform a Technology RoadMap (TRM) for NEDD development.

RESEARCH APPROACH

This chapter strives to profile the multi-dimensional world of NEDD development and extract relevant information (for non-specialists in NEDD or data-mining). Such technical intelligence can inform private sector and public agency R&D decision-making regarding topical priorities in relation to potential markets. We focus on three broad issues:

1. Devising a sound search strategy to provide usable intelligence for specialists and non-specialists.
2. Seeking a way to identify the major NEDD subsystems and figure out major R&D topics in relation to these subsystems.
3. Tracing the technology innovation pathways to characterize current research emphases, identify hot topics, and explore their future developmental directions.

(1) Search Strategy

To develop an NEDD search strategy, we first must charcaterise and classify the NEDD components. Building on a previously developed framework (Robinson et al. 2013). we first identify seven categories and consider those in conjunction with another NEDD search strategy (Porter, 2010). After testing alternative Boolean search phrasing and assessing the implications of alternative formulations in WOS, we generate our final search algorithm (Zhou et.al, 2013). For WOS searching, we have applied one portion within a Georgia Tech nano dataset ("GT nano") to expedite downloading and another portion directly in WOS. For publications from Medline, we search the databases directly.

(2) Subsystems

The driving interest in this research is to answer Management of Technology (MOT) questions regarding the development of NEDD. One big issue is subsystem identification since it can help people perceive the major areas and understand topical relationships in NEDD.

This chapter shares ongoing work to characterize NEDD R&D. We apply our NEDD search algorithm to retrieve abstract records of research publications from Web of Science (WOS) and MEDLINE databases (over 50,000 from each). Initial analyses of the WOS data in conjunction with expert review result in a 4-subsystem model of NEDD development, including some 21 major topics.

Here we explore the progression of NEDD development using this model.

(3) Technology Roadmapping (TRM)

After identifying subsystems and major topics of NEDD, another aim is to use this technical intelligence to inform Technology RoadMapping for NEDD development. The intent is to visualize the R&D effort to advance particular subsystem capabilities and move toward commercial applications (i.e., clinical translation). In this part, we consider previous research on TRM to find a good method to generate NEDD roadmapping.

As defined by Winebrake (2003), TRM is a future-based strategic planning device that outlines the goals, barriers, and strategies necessary for achieving a given vision of technological advancement and market penetration. Nowadays, TRM is considered a flexible, strategic planning technique for collaborative technology planning and coordination for organizations (Garcia and Bray 1998; Gerdsri et al. 2010; Jeon et al. 2011). The approach provides a structured means for exploring and communicating relationships among evolving and developing markets, products, and technologies over time (Phaal et al. 2004). Currently, literature reviews, expert interviews, Delphi, scenario planning, and other qualitative approaches take leading roles in TRM implementation (Phaal et al. 2004; Garcia and Bray 1998). Walsh (2004) modified a model for a disruptive technology roadmapping process and provided an empirical study of the International Industrial Microsystems and Top-Down Nano Systems industry. Gerdsri et al. (2010) constructed a guideline to implement TRM and outlined a case study on manufacturers. Although researchers have introduced quantitative methodology into TRM construction, studies still laregely neglect empirical methods, or struggle to determine how to blend quantitative and qualitative methodologies (Zhang et al. ,to appear).

In this situation, bibliometric methods, tracing back to Derek Price in 1963, offer promise. Bibliometrics offer capabilities for observing scientific activity patterns and instruments for systematic analyses (van Raan, 2005). Bibliometrics use counts of publications, patents, or citations to measure and interpret scientific and technological advances (Porter and Detampel,1995), summarize scientific activities (Kajikawa and Takeda, 2009), explore basic scientific efforts and technological capabilities (McMillan and Hicks 2001), and indicate research performance over time (van Raan 2003). In this chapter, we apply bibliometric methods to construct a hybrid visualization model for technology roadmapping.

We use Principal Components Analysis (PCA) to get potential major topics. We also add expert judgement to revise these topics. Then, based on text mining results, we trace topical developmental trends. We believe this makes a useful contribution to understanding emerging technology application pathways. That information, in turn, can inform drug R&D management and research policy.

ANALYSES

SEARCH STRATEGY

Our study of NEDD originates from doctoral thesis research in the Netherlands (Robinson, 2010). Later, a separate study which led by North Carolina Biotechnology Center's (NCBC) also gave great support in this research (Porter, 2010). Commencing in 2008, under the help of knowledgeable colleagues in the US and Europe,a boolean, term-based search algorithm for NEDD is devised. We advanced a conceptual framework to approach NEDD (Appendix Table 1), informed by various reviews and "foresight" pieces. This led us toward categorization to frame our current NEDD search (Table 1).

Table 1. Nano-Enabled Drug Delivery: Related Terms

No.	*Category*	*Keywords*
1	B (biological processes)	(bioavailab*or biodistrib* or biocompatib* or cytotox* or biodegradab*)
2	I (imaging)	Image* or imaging
3	T (target)	(Cancer or tumor* or tumour* or "RNA interference" or RNAi)
4	H (helpers)	("polyethylene glycol" or pegylate or PEG or molecule* or polymer* or polyethylenimine or PEI or polyspermine or polypropylenimine or "poly lactic-co-glycolic acid" or PLGA or cyclodextrin or dendrimer* or chitosan* or atelocollagen* or "hyaluronic acid" or polypeptid* or peptid* or lipid* or ligand* or or Micelle* or Liposom* or conjugat* or Viral* OR Virus* or nonvira* or non-vira*)
5	P(pharmaceutical)	(1) (agent* or Drug* or pharmac* or formulation*) (2) (siRNA or "short interfering RNA")

		(3) microRNA (4) DNA or gene (5) (Dox or Doxorubicin*) (6) actives or adjuvant
6	D(delivery approach)	(1) (deliver* or vehicle* or carrier* or vector*) (2) (treat* or therap*) (3)("control* releas*" or transduct* or transfect* or transport* or translocat*)
7	N(nano-delivery vehicle)	This category means GT nano Database or some approximation of its search terms; also consider viral or virus or dendrimer or colloid

Table 1 notation: * allows for any following characters in the term.

When we search in database, the key terms should be used in combination. But identifying the potential combinations is hard. Here, our aim is to balance retrieval (i.e., capturing a high percentage of the relevant records) with precision (i.e., without undue noise). Since the boundaries of NEDD are murky---on one side, "all" drug delivery is molecular biology and chemistry; on the opposite side, relatively few delivery mechanisms are based exclusively on some "distinctly nano" property---in this chapter, we look for a middle ground to profile general NEDD research activity. We choose pharmaceutical/cargo (P), nano-delivery-vehicle (N), characteristics of the delivery approach (D), and the target for the drug cargo (T) and largely set aside B (biological processes), I (imaging), and H (helpers) categories since these categories can bring high complexity and confounding issues (e.g., where to draw the line on imaging research?). Because this strategy does not focus on “disease”, we only selectively incorporate "T" terms.

After considerable consultation, we key on two general search strategies:

(1) D + P + N;

(2) D + T + N.

In test and evaluation, we try to search these combinations for one sample year in Web of Science and Medline. We use WOS nano dataset at Georgia Tech (Arora et al., 2012) to cover the "N" element and facilitate experimentation with alternative search phrasing. We assess particular search elements by examining 10-record samples and judging whether 70% were on target, sometimes accepting 60%; then determined whether to accept, exclude, or revise (and retest) the search string. This approach reflects a "Tech Mining" perspective that favors high recall at the expense of some precision (Porter and Cunningham, 2005) . The logic is that later cleaning and text analyses can remove noise. Development and refinement of our NEDD search strategy is further detailed elsewhere (Zhou et al., 2013; Zhou et al., under review).

We applied search strategies in the Georgia Tech nano dataset (from WOS), the full WOS, and Medline. The NEDD search tallies are shown in Table 2.

Table 2. NEDD Datasets

Data type	*Database*	*Number of records*	*Total number for different data type*
Publication data	*WOS*	**61,465**	85311(54.6% overlap between WOS and Medline)
	Medline	52,529	

For this paper, we focus on publication data. Although there is a high overlap between WOS and Medline data, the significant difference between these two data sources is clear. For WOS data, one advantage is the quality of papers is high. In order to support this view, we divide our NEDD publication dataset into three parts: the overlapping publications between WOS and Medline, WOS non-overlaping publications, and Medline non-overlaping publications.

We choose the 100 most highly cited journals from the overlapping publications dataset, then compare their coverage by WOS and Medline. One surprising finding is none of the Medline-only journals belongs to the highly cited subset, but most of the WOS-only journals do. Furthermore, if we compare the publication trends for the three subsets of journals, we see that WOS coverage (WOS-only plus overlapping journals) dominates (Figure 1).

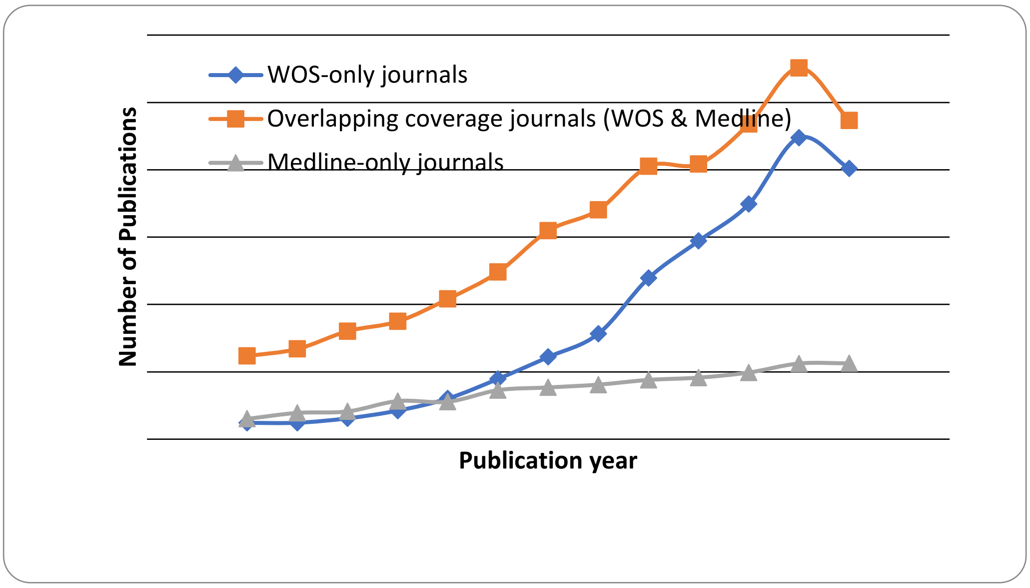

Figure 1. NEDD publication trends by Database Journal Coverage

These findings show that publications indexed by Medline, but not by WOS, have less influence on recent NEDD research. However, the Medline database also has advantages. Medline abstract records include MeSH index terms, reflecting a highly developed, tree-structure (hierarchical) classification. Indexing is at the article level, drawing on more than 5,500 journals (Leydesdorff et. al, 2012). MeSH terms are updated annually (http://www.nlm.nih.gov/ mesh/ mtr_abt.html).

The MeSH classification has 12 levels. The first level includes 16 categories that represent 16 research topics, such as Chemicals & Drugs [D], and Diseases [C]. In each major topic, several sub-topics follow. For example, “Inorganic Chemicals” and ”Organic Chemicals” are located in the second level of the “Chemicals and Drugs” category. We note that, with the development of technologies, new sub-categories are added into this hierarchical classification. For example, the "liposome" was added into MeSH in 1999.

Compared with WOS subject categories, MeSH terms might be more appropriate classifiers to help understand topical emphases (Bornmann et al., 2008).

Considering these features, we choose WOS as our target database since it covers most important articles. But we also use MeSH terms to refine some NEDD subsystems and related major topics which we draw from WOS abstract records.

Subsystems

In this part, we try to find a way to identify the main NEDD subsystems and elucidate linkages among them. We extract noun phrases from titles and abstracts (since they provide topical content) using the Natural Language Processing (NLP) routine (tailored to scientific writing) of VantagePoint desktop text mining software (www.theVantagePoint.com). After several "term clumping" steps (Zhang et al., under review) ,we choose 424 frequently occurring and interesting terms and group them by VantagePoint's Principal Components Analysis (PCA) routine. The output of this step is 19 topical groups and their highly related terms. After checking by expert (see Acknowledgements), the total topical groups expand from 19 to 21 topics.

Besides aiding by text mining results, the "review the reviews" method can help us to gain perspective on the filed. We have a logic way to select NEDD reviews. After getting NEDD dataset, we chose 7247 documents tagged as reviews by WOS. Then we whittled these down to 169 based on recency, journal impact, citations received, and topical diversity. These reviews show great value for subsystem and major research area identification.

Based on literature study (reviews) and text mining of WOS search results, we separate four major areas for NEDD: drug, nanocarrier, delivery outcome, and disease. Our conceptual model appears as Figure 2.

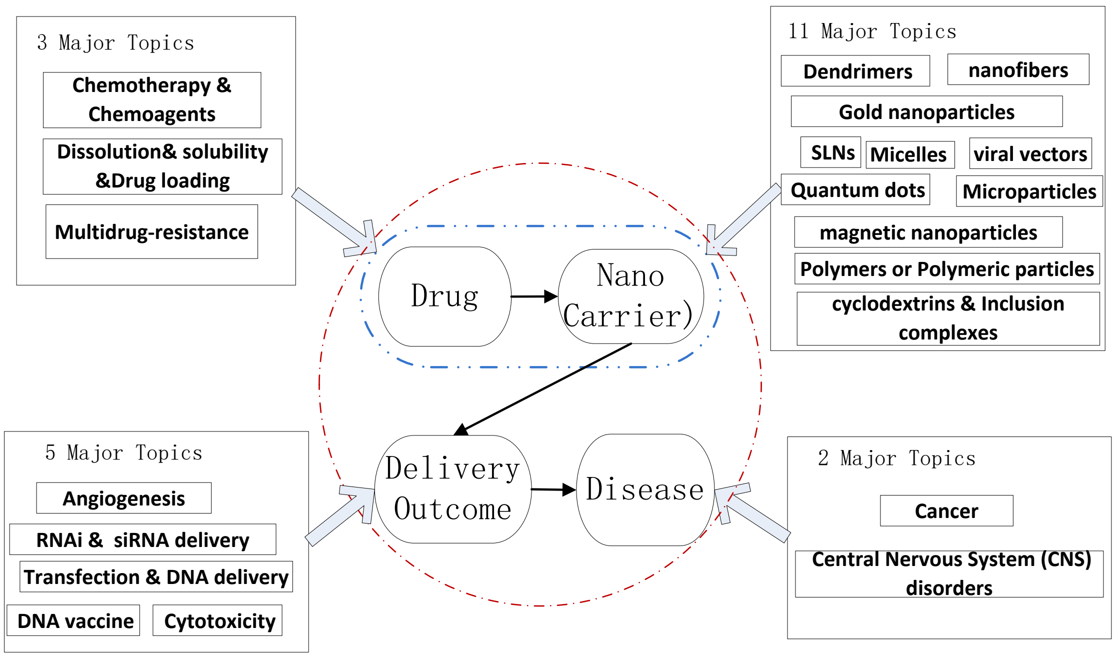

Figure 2. NEDD Model

Since we get these four subareas and classify the major topics mainly by literature study and expert judgement, the results may be difficult to reproduce exactly. To offset this subjectivity, we use the MeSH classification system to provide a complementary tool to check these topical classifications. In Medline, there is a deep tree structure (12 levels). The 16 first level categories can help us to identify NEDD subsystems.

In this part, our logic is as follows:

(1) Check Medline NEDD data to identify which of the 16 branches hold most of our records. These categories may represent major research areas of NEDD.

(2) Add topics that are not included in our 21 major topics, but show as highly related to NEDD research, to the most suitable subsystems. Since Medline publications are distributed in different research categories, we can find hot research areas that are not included in our previous conceptual model.

(3) Search these topics (21 old topics and new ones) in MeSH database and identify the major areas to which they belong.

(4) Revise the final classification and ask our experts to check.

We should note here that some topics belong to multiple research areas, so they can be located in more than one category. Such topics could have special value in indicating multidisciplinary research integration.

In our NEDD Medline dataset, the top categories match our conceptual model well. The Chemicals and Drugs category("D" for short); Techniques and Equipment category ("E") and Technology, Industry, Agriculture category ("J"); Phenomena and Process category ("G"), as well as Disease ("D"), correspond with "Drug," "Nanocarrier," "Delivery outcome," and "Disease" subsystems (Figure 2). According to MeSH classification, we reorganize 21 topics into four subsystems. We should note, there are four additional "hot topics" (enzymes and coenzymes; cellular physiological phenomena; cardiovascular disease, and virus-based disease) from Medline to incorporate into the four subsystems. The total number of major topics of NEDD increases to 25. After checking by experts (Robinson et al., 2013), Figure 3 presents our final NEDD subsystems & topics model.

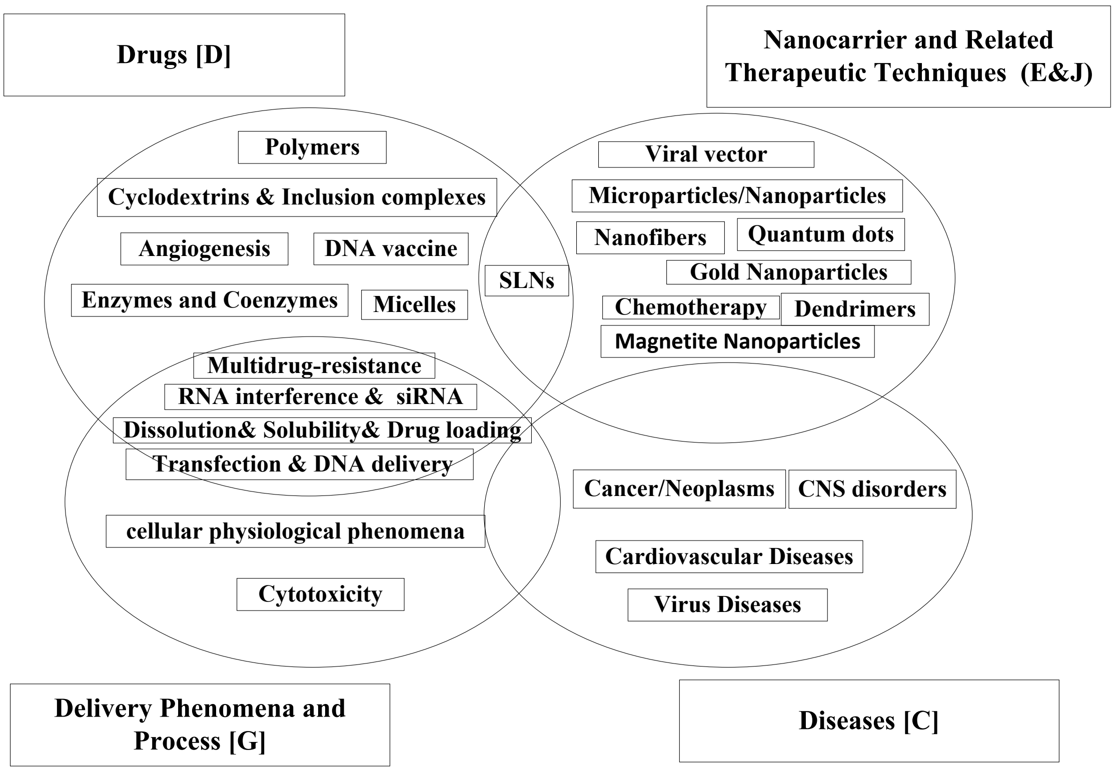

Figure 3. NEDD Subsystems

Drug (or genes or other active agents) can be considered as the cargo of the Nano-Enabled Drug Delivery system. Drug (D) links tightly with the other three subsystems. The second subsystem focuses on Nanocarriers and Related Therapeutic Techniques. This reflects our search algorithm, keying on "nano-enabled" to distinguish from traditional drug delivery endeavors. For the other areas, Diseases are the main targets, and Delivery Phenomena and Process show the delivery process and related effects of NEDD.

Under these four subsystems, we identify 25 major topics, 6 of them belong to the "Drug" subsystem; 8, to "Nanocarrier and Related Therapeutic Techniques"; 2, to "Delivery Phenomena and Process"; 4, to "Disease" subsystems. Solid lipid nanoparticles (SLNs) have close linkages with "Drug" and with "Nanocarriers," so we associate them to two subsystems. We locate Multidrug-resistance, RNA interference, siRNA, DNA delivery, and Dissolution & Drug loading, in the "Drug" and "Delivery Phenomena and Process" categories.

If one considers the publication trends for the four NEDD subsystems, "Nanocarrier and Related Therapeutic Techniques", which account for 45% of NEDD publications, show rapid increase in research activity. "Disease"," Delivery Phenomena and Process," and "Nanocarrier and Related Therapeutic Techniques" share similar developmental trends. The total publication counts increase notably since 2009. Some interdisciplinary topics like RNAi are growing fast. Trends for the four subsystems and the cross-system (interdisciplinary) topic sets are compared in Figure 4.

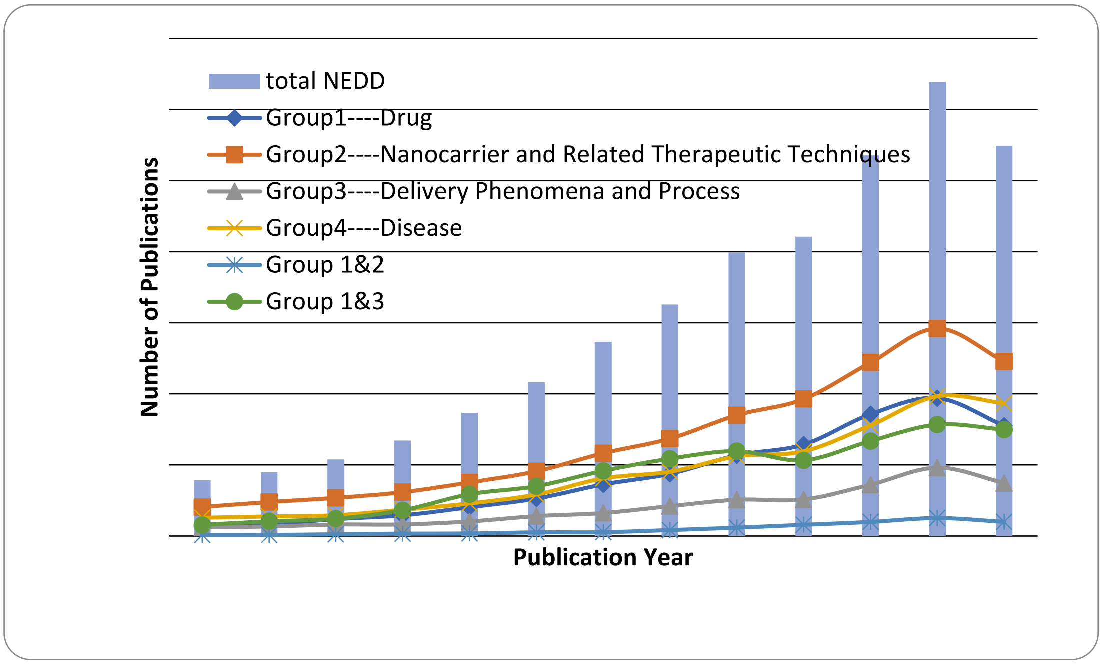

Figure 4. Research Publication Trends for each NEDD Subsystem (WOS)

As presented, we find the topic classification is somewhat different between our initial NEDD conceptual model based on study of WOS records and expert judgement, and MeSH category consideration. That's not surprising since NEDD is a strongly connected system; each subsystem strongly connects with the others; likewise, research on major topics intersects. Each of the 25 topics is closely linked with one subsystem, but is also strongly related to the others. So it's hard to identify cleanly to which subsystem they belong.

MeSH classification incorporates domain expert judgment, and this scheme is well-accepted by medical research organizations. Table 3 compares the classifications to show their similarities and differences.

Table 3. NEDD Subsystem Comparison

Medline Classification	NEDD Model	Topics	The Sequence of Topics
Drug	-----	enzymes and coenzymes	25
Drug	**Nanocarrier**	**polymers**	**6**
Drug	**Nanocarrier**	**micelles**	**15**
Drug	**Nanocarrier**	**cyclodextrins & inclusion complexes**	**21**
Drug	**Delivery Outcome**	**DNA vaccine**	**7**
Drug	**Delivery Outcome**	**angiogenesis**	**14**
Nanocarrier and related technique	Nanocarrier	viral vectors	3
Nanocarrier and related technique	Nanocarrier	microparticles	9
Nanocarrier and related technique	Nanocarrier	magnetic nanoparticles	17
Nanocarrier and related technique	Nanocarrier	dendrimers	12
Nanocarrier and related technique	Nanocarrier	gold nanoparticles	19
Nanocarrier and related technique	Nanocarrier	quantum dots	18
Nanocarrier and related technique	Nanocarrier	nanofibers	20
Nanocarrier and related technique	**Drug**	**chemotherapy & chemoagents**	**2**
Delivery Phenomena and Process	Delivery Outcome	cytotoxicity	5
Delivery Phenomena and Process	-------	cellular physiological phenomena	8
Disease	Disease	cancer(neoplasms)	1
Disease	Disease	CNS disorders	24
Disease	-------	cardiovascular disease	22
Disease	-------	virus disease	23
Drug & Nanocarrier	Nanocarrier	SLNs	16
Drug & Delivery Phenomena and Process	Drug	dissolution& solubility& drug loading	13
Drug & Delivery Phenomena and Process	Drug	multidrug-resistance	10

Drug & Delivery Phenomena and Process	Delivery Outcome	RNA interference & siRNA delivery	11
Drug & Delivery Phenomena and Process	Delivery Outcome	transfection & DNA delivery	4

We note some significant differences in Table 3. Chemotherapy belongs to the "Drug" subsystem under the NEDD conceptual model, while it locates in "Nanocarrier and Related Therapeutic Techniques" under the MeSH classification. Both classifications are meaningful since chemotherapy is a strongly connected topic. On one hand, because of its effectiveness as a cancer therapy, it has direct linkage with auti-cancer drugs. On the other hand, the nature of chemotherapy is a therapy technique. so allocating it to the "Nanocarrier and Related Therapeutic Techniques" subsystem is reasonable.

As for micelles, they are particles consisting of aggregates of molecules held loosely together by secondary bonds. Liquids that contain large numbers of suspended micelles are referred to as emulsions, and these link with the drug assembling process. Under this condition, micelles lean toward the "Drug" subsystem. The same situation holds for polymers. As for cyclodextrins, they form inclusion complexes with a wide variety of substances that can be used in drug production.

For angiogenesis and DNA Vaccines, the first one is related to physiological effects of drugs and the latter can encode antigens administered for the prevention or treatment of disease. Accordingly, both of them are assigned to the "Drug" subsystem.

We should note here, some nanocarrier related topics also suit the "Drug" subsystem. Actually, it's hard to isolate "Drug" and "Nanocarrier" since, in an NEDD system, these appear together. Because some topics, like multidrug-resistance and solid lipid nanoparticles, are so inherently multi-disciplinary, we place them in multiple subsystems.

TECHNOLOGY ROADMAPPING OF NEDD

In this chapter, one aim is to use technical intelligence to inform a Technology RoadMap for NEDD development. Since we believe TRM can contribute to understanding emerging NEDD application pathways, we visually represent the R&D effort, observed in the previous section, in order to explore how to advance a particular subsystem's capabilities and move towards commercial applications (i.e., clinical translation).

The logic for building a Technology RoadMap is as follows:

- First step: According to the publication year, we divide publication records into several time intervals. Our aim is to trace the 25 major topics over time, believing that research activity on these can represent the main research situation of NEDD. For each time period, we use a threshold of 100 or more publications for that topic to be included in the TRM.
- Second step: After identifying the subordinate research areas in different time intervals, the next step is finding the linkage among the topics. In addition, since each topic belongs to one or more subsystems, we can also trace subsystem evolution using the topical trends.

Figure 5 presents the resulting TRM.

We should note that, on this map, shapes, arrows, and location have different meanings.

- Number: each number represent one of the 25 main NEDD topics.
- Shape: different shapes represent different subsystems. Here we use six shapes to represent topics in the 4 subsystems, as well as the two overlapping domains (Drug + Nanocarrier; Drug + Delivery Phenomena and Process). Circles indicate topics in the "Drug" system. Triangles mean they are in "Nanocarrier and related therapeutic techniques." Stars belong to "Delivery Phenomena and Process." Seven-point stars mean "Disease." Pentagons mean topics belong to "Drug" and "Nanocarrier and Related Therapeutic Techniques" subsystems. Squares represent topics belong to "Drug" and "Delivery Phenomena and Process" subsystems.
- Arrow: The arrows between topics show the developmental path for a certain topic.

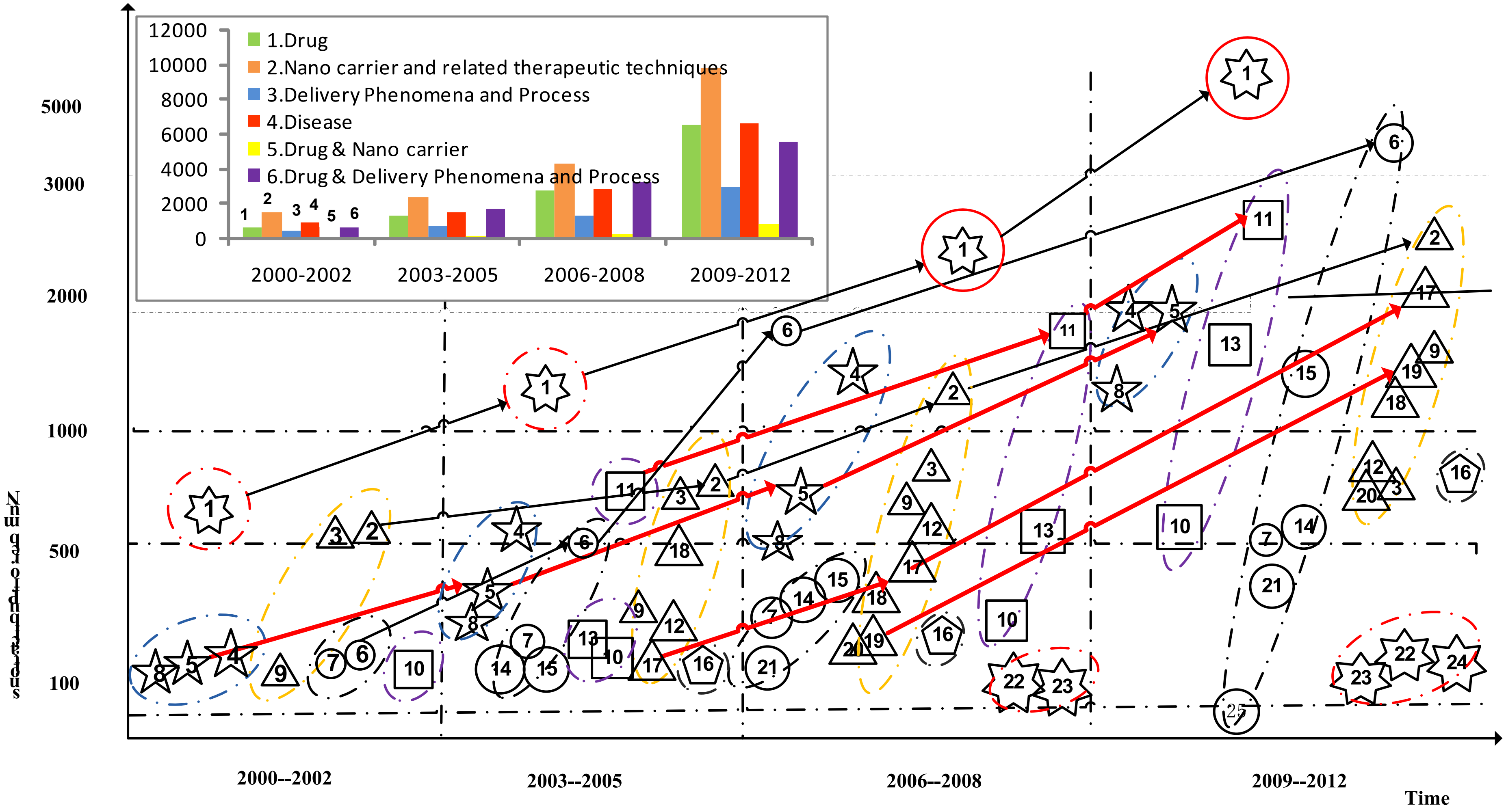

Figure 5. The Macro Level Technology Roadmapping for NEDD coming from our data

In Figure 5, we divide publication years into four time intervals in order to trace the developmental path for each subsystem and its related topics. In order to see the sequence of each topic, the last column of Table 3 shows the sequence number.

We consider the TRM at a macro level to investigate the development of topics in different stages. In the first time period (from 2000 to 2002), the sub-technologies of "Nanocarrier and Related Therapeutic Techniques" are more active. Chemotherapy & chemoagents and viral vectors, which account for 46% of this subsystem's publications in this period, are representative areas. Other subsystems show relatively less research activity than "Nanocarrier."

In the second time interval (from 2003 to 2005), Nanocarrier-related technologies show strong research activity. At the same time, the research for the other three subsystems begins to increase. Polymers (No. 6), related to drug production, increases a lot. With the development of "Drug" and "Delivery Phenomena and Process" research, interdisciplinary research emphases on topics like RNA interference & siRNA delivery (No.11) plays an increasing role in NEDD research. There are 774 publications belong to RNAi in this time interval.

In the last two periods, research on NEDD consistently increases, especially on interdisciplinary topics like dissolution & solubility & Drug loading (No.13). However, viral vector (No. 3) is the exception, showing a recent decline. In contrast to the viral vectors, the research activity with regard to nonviral vectors, such as plasmid DNA (62 publications in 2000 vs. 215 in 2010), shows a rapid increase in recent years. Nonviral vectors likely receive increasing focus because they offer substantial safety advantages over viral vectors (Thomas et al.,2003; Luo and Saltzman, 2000).

From technology roadmapping of NEDD, we find cancer (No.1), polymers (No. 6), and chemotherapy (No. 2) hold the top three places (some 18,440 WOS journal publications). Besides these, we also want to investigate "hot" topics as these can indicate current research opportunities and suggest directions for future development. From Figure 5, we now explore four topics which show the greatest increase in research activity in the recent two time intervals.

RNAi (No.11) research has increased sharply since the second time interval. US, China, and Japan lead in this area. Just to illustrate analytical potential, we note that one can "zoom in" to observe that Harvard has been particularly active and scholars like Lieberman and Langer stand out. Cytotoxicity, magnetic nanoparticles, and gold nanoparticles increase sharply in the third time interval, especially from 2007.

In cytotoxicity (No.5), besides some US and Chinese organizations, Seoul National University appears especially strong. Magnetic nanoparticles (No.17) have been the focus of much research recently. Chinese Academy of Sciences (CAS) publishes most, with the University of Washington, Harvard, and Michigan also strong.

Gold nanoparticles (No. 19) have been widely explored for diagnostic applications (Daniel and Astruc, 2004; Love et al., 2005). Their high biocompatibility and facile functionalization have enabled biocompatible drug delivery after conjugation with various therapeutic agents (Ghosh et al., 2008; You et al., 2010; Gu et al., 2012). The US leads here (University of Massachusetts, Washington, and Georgia Tech are noted). China is the second biggest research contributor here and CAS occupies its leading position. South Korea is the third nation with Seoul National University prominent in gold nanoparticles. Several literatures have highlighted the enormous developments of functionalized gold nanoparticles and magnetic nanoparticles as effective nanotheranostics, enabling simultaneous therapy and diagnostic imaging (Xie et al., 2010; Shubayev et al., 2009; Mura and Couvreur,2012).

In Figure 5, in order to see the general trends of subsystems, we draw a dashed line (oval) around topics that belong to the same subsystem. But this way cannot reflect the micro developmental path. In Figure 6, we focus on three levels. The first level consists of newly emerging technologies of each topic in a certain time interval; the second level is leading organizations for these technologies; the third level is countries. To avoid excessive chapter length, we do not map the other 5 subarea micro technologies; we just take "Drug" as an example.

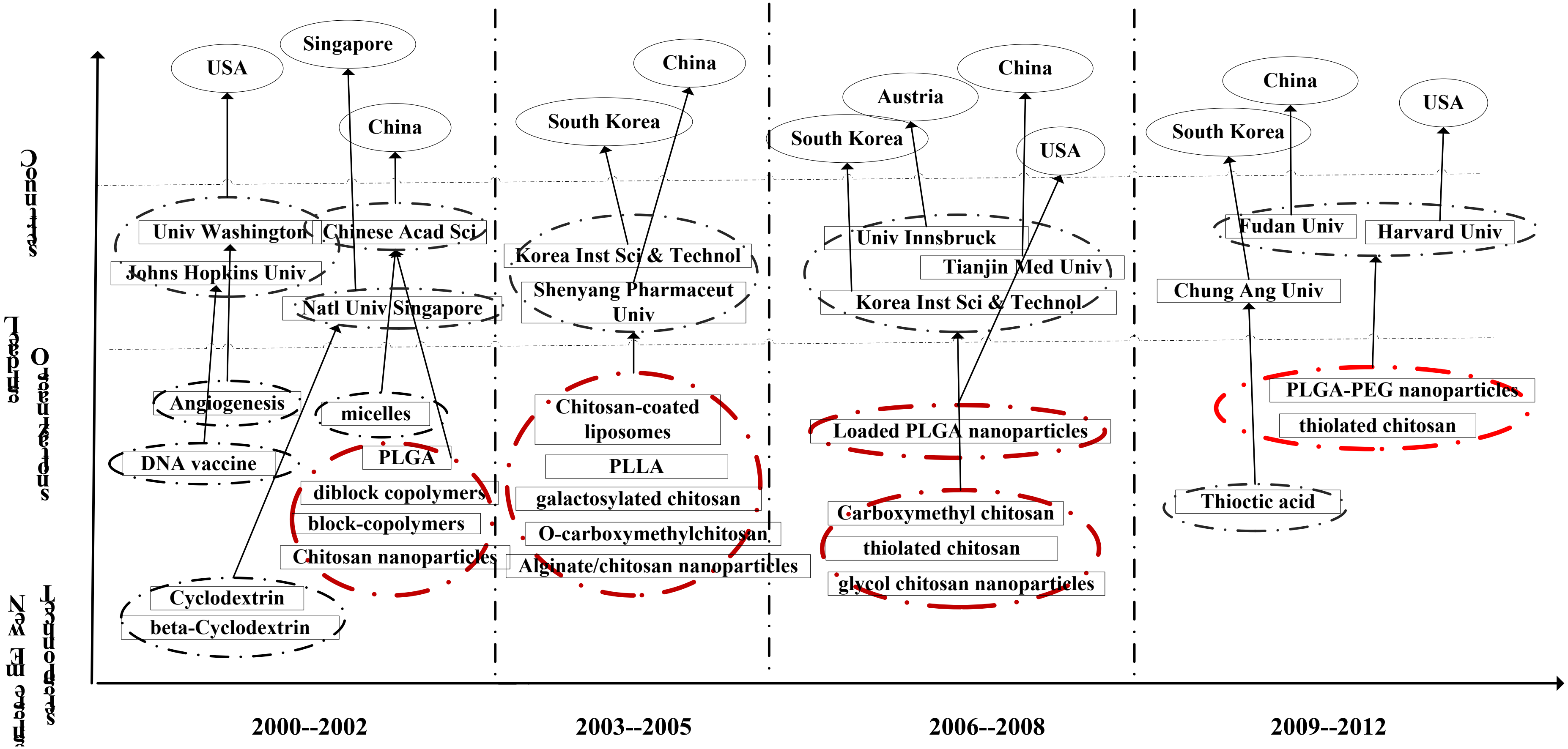

Figure 6. The Micro Level Technology Roadmapping for "Drug" subsystem

Figure 6 shows micro level TRM for the "Drug" subsystem. We use VantagePoint to get new drug related terms in each time interval and choose the top ones. Then we compare the chosen key words with all terms that are included in 6 drug topics. In such a way, we can get which term belongs to which topic.

In Figure 6, we found most of the new terms relate to the topic "Polymer." These include block-copolymers in the first period, glycol chitosan in the second period and carboxymethyl chitosan in the third period. At the organization level, Chinese Academic Science and Seoul National University hold the leading positions. At the country level, China and South Korea lead the development of polymer science.

In addition, with the development of drug related technologies, this area fuses with other subsystems. From 2006 to now, some researchers focus on loaded PLGA nanoparticles and PLGA-PEG nanoparticles that use new polymers to improve the function of nanoparticles.

DISCUSSION AND CONCLUSIONS

NEDD is emerging on a variety of R&D fronts to address a large variety of challenges, for example in the pharmaceutical industry with regard to solubility, cost-reduction, higher success rate for targeting diseases, and patent lifecycle extension.

This chapter profiles this increasing NEDD research activity. We develop a multi-module search strategy to construct an NEDD dataset from Web of Science (also, from Medline and Derwent Innovation Index for future analyses). We categorize NEDD related terms into seven categories (Table 1). After testing and evaluation, plus expert review, three categories ("B" – biological processes; "I" – imaging; and "H" – helpers) were set aside. We focus on P (Pharmaceutical), N (Nano), and D (Delivery), with limited incorporation of "T" (Target) terminology to comprise our NEDD search.

We also peruse multiple literature reviews to help identify four NEDD subsystems: "Drug," "Nanocarrier and Related Therapeutic Techniques," "Delivery Phenomena and Process," and "Drug" systems. We apply "term clumping" steps to consolidate topical content from four text fields in large sets of abstract records to suggest possible major topics. Furthermore, since MeSH categories are arguably more reliable classification tools, we add them to adjust our subsystems and refine 25 related topics. In this part, we find NEDD to be a strongly interconnected system (i.e., subareas are not highly isolated).

The next step, which we aspire to, is to forecast innovation pathways (Robinson and Propp 2008, Robinson et al. 2013) for NEDD by breaking down to the subsystem level, to track advances. We find that the development of the subsystems includes considerable inter-system topics, like RNA interference & siRNA delivery. In addition, among 25 major topics, four hot topics -- RNAi, cytotoxicity, magnetic nanoparticles, and gold nanoparticles -- show great prospects in recent years. We track their developmental trends and identify some leading organizations in these areas, to illustrate the potential for further in-depth probing. One can perform "tech mining" to address a range of questions concerning "who is doing what research, where, and when?" Such technical intelligence can inform researcher or research manager decisions on whether to invest in fundamental R&D on a particular topic or possibly seek collaborators already so engaged.

A further step would be to look at the actual commercialization strategies, product development, and clinical trials. One has to fish in different reservoirs and apply slightly different techniques from those outlined in this chapter. But following a similar logic, one could explore patent data for indicators of potential commercial applications of types of NEDD (patents do not indicate commercialization per se). We intend to combine analyses of our WOS, Medline, and Derwent patent search results to forecast developmental pathways for NEDD.

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Appendix

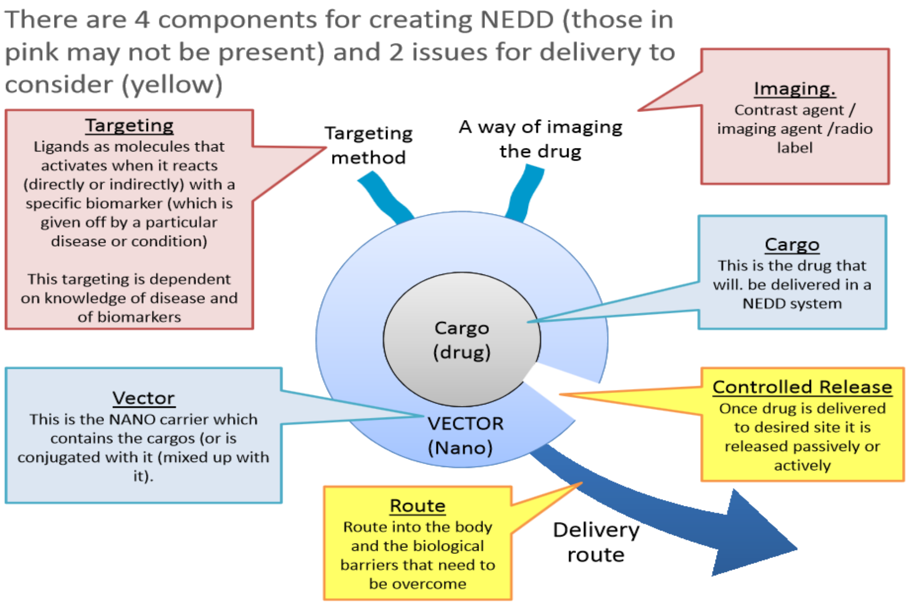

Figure 1. the conceptual framework for NEDD