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NIPTE: a multi-university partnership supporting academic drug development

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The strategic goal of academic translational research is to accelerate translational science through the improvement and development of resources for moving discoveries across translational barriers through 'first in humans' studies. To achieve this goal, access to drug discovery resources and preclinical IND-enabling infrastructure is crucial. One potential approach of research institutions for coordinating preclinical development, based on a model from the National Institute for Pharmaceutical Technology and Education (NIPTE), can provide academic translational and medical centers with access to a wide variety of enabling infrastructure for developing small molecule clinical candidates in an efficient, cost-effective manner.

Greatly influenced by the success of the Human Genome Project, introduction of the National Institute for Health (NIH) Roadmap for Medical Research in 2004, followed by the initiation of the Clinical and Translational Award (CTSA) program in 2006, and the creation of National Center for Advancing Translational Sciences (NCATS) in 2012, academic biomedical research has been increasingly redirecting its focus toward translational science. Changes in the pharmaceutical industry also had profound effects on this development. Productivity challenges facing industrial research and development (R&D), its focus on nonrare disease targets [1], shifting risks, moving operations to other parts of the world, and commoditization of key elements, whether real or perceived, had a significant role in reshaping the landscape of life sciences. The continuous exodus of highly trained industrial scientists and their shift to academic research significantly increased the technical potential of academia in creating new medicines.

Historically, US academic institutions have been involved in creating a significant number of new drugs [2–7]. Just during the 1997–2005 period, some 60 drugs introduced to the market had academic origins, with over half of them considered novel [2]. Among most known examples are the anticancer drug Alimta® discovered by E.C. Taylor (Princeton) [8], anti-HIV drug Ziagen® (abacavir) designed by Robert Vince (Minnesota) [9], an intravenous sedative-hypnotic agent, Lusedra™, developed by Gunda Georg and Valentino Stella (Kansas) [10], and anti-HIV drugs Emtriva and Lamivudine (epivir) invented by Dennis Liotta (Emory) [5]. More drugs discovered within academia are expected to reach the clinical development stage within the next few years. The perceived gap between academia and industry, in terms of knowledge of pharmaceutical development, is closing and the role of the public sector in pharmaceutical discovery and development has been increasing in recent years.

The current renaissance in academic translational research has been catalyzed by new NIH translational programs, such as the Chemical Biology Consortium (CBC) [11], the Blueprint Neurotherapeutics Network, the Therapeutics for Rare and Neglected Diseases (TRND) program, the Science Moving towArds Research Translation and Therapy (SMARTT) program, initiated in recent years, as well as the most recent creation of NCATS. There are approximately 80 drug discovery centers in US research universities, over half of which were founded over the past decade [12]. Although most centers are focused on cancer and infectious diseases, one-third have orphan disease research programs [12].

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Remarkably, despite significant challenges [13], orphan drugs accounted for 40% of all academia-discovered drugs between 1998 and 2007 [2].

Academic institutions are increasingly investing millions of dollars into new industry – academia collaborative translational centers. A US$110 million University of California San Diego-based Center for Novel Therapeutics [14] and Scripps-based California Institute for Biomedical Research that received US$42 million from German Merck, are just a few examples [15]. Several public–private partnerships with industry and academia participation have been created in recent years [16]. Such collaborations are also actively encouraged by the NIH [17]. Several similar partnerships have been created overseas, such as Cancer Research UK (http://www.cancerresearchuk.org) for anticancer drug development [18] and the UK Drug Discovery Consortium (http://www.ukddc.org). In the European Union (EU), a new industrial – academic collaborative consortium, called the European Lead Factory, was formed early in 2012. It comprises 30 industrial and academic institutions with €196 million in funding [19]. Most recently, the Translational Kinase Tumor Inhibitor Discovery Consortium (TAKTIC), which includes several European and Israeli academic and industrial centers, was created with €1.1 million funding from the EU (www.b3cnewswire.com/20130410884/a-new-eu-funded-industry-academia-drug-discovery-partnership-targets-challenging-kinases.html).

Interuniversity partnerships in the area of drug discovery are also being created. In 2007, a group of academic drug discoverers proposed creating National Medicinal Chemistry Resource Centers, a nucleus for public–private partnerships between academia, industry and the NIH [20]. In 2011, a multi-university Academic Drug Discovery Consortium was initiated by researchers from Johns Hopkins, University of North Carolina, Vanderbilt, Harvard Medical School, and University of California San Francisco (http://www.addconsortium.org).

One significant challenge that is common in both private and public research is to ensure successful conversion of a potent lead molecule resulting from translational research into a viable and efficacious drug candidate and, ultimately, into a new medicine. This challenge lies within the translational gap, which is often referred to as the 'valley of death' [21]. It generally covers a broad range of preclinical and clinical development elements, from target validation through lead optimization, process chemistry and preclinical development to Phase I and II clinical trials [21–23]. Various approaches for bridging this gap have been proposed and are a topic of ongoing national discussion. The most significant factors contributing to the valley of death in anticancer drug development were recently summarized by Adams [23].

Academic drug development partnerships

Much of the discussion related to academic drug discovery and development is focused on medicinal chemistry, high-throughput screening, pharmacology and toxicology, as well as the challenges related to intellectual property, regulatory affairs, funding and commercialization. The role of pharmaceutical science, which includes crucial disciplines such as pharmaceutical formulation, drug delivery, chemical process development and purification, and regulatory science, has not been a focus in academic translational research. These aspects of pharmaceutical science are crucial, often costly and time-consuming elements. Additionally, they often account for significant intellectual property. For example, patents on solid forms and formulations are collectively worth at least US$100 billion dollars. The combination of these elements significantly supports the transition of a molecule with promising *in vivo* efficacy and a desirable safety profile into a clinical candidate with the promise of becoming a new medicine. If successful, these pharmaceutical processes also enable manufacturing of the drug product prototype to be legally tested in human clinical trials. These steps are particularly important because they ensure the quality and consistency of clinical supplies and insure against unnecessary variability in resultant blood drug levels.

It is increasingly important for medicinal chemists to start working with formulation chemists and process chemists at an earlier stage of drug discovery and development. Various 'druggability' challenges, such as aqueous solubility, cell permeability, oral bioavailability and chemical stability, that medicinal chemists most often face, can often be addressed using various drug formulation techniques. In fact, Merck currently has a team of more than 20 scientists led by Allen Templeton and John Higgins devoted to addressing these issues on various families of lead compounds as they are developed [24]. This Merck team begins their accelerated development work with the solid phase of the API as presented. The next step is to understand the solid state properties of the compound and the family to which it belongs. This is because solid-state chemistry has a key role in accelerated development toward IND submission, proof of concept and manufacturing of clinical supplies [25–27]. At the next stage, the solution and formulation properties of the lead compounds are addressed. Of special interest are solubility and/or dissolution properties, which depend on the solid-state structure. The stability of the compound and family are also addressed at this stage. Finally, the pharmacokinetics and absorption (biopharmaceutical properties) are determined. All of this information is used to define the phase and formulation for toxicology and first-in-human studies. Of course, this work must be done on an accelerated basis with very small amounts of compound.

The capabilities of academic research institutions within the drug development arena can be demonstrated using a recent example of the pancreatic drug candidate Minnelide™. All preclinical development and IND-enabling studies for this compound were completed within one university in less than 5 years and without an industry partner (the drug candidate was eventually licensed and transferred to a private company for further clinical development) [28–31]. That success was made possible by unique preclinical infrastructure at the University of Minnesota that few academic institutions have. The model in which such infrastructure, as well as other relevant capabilities, is readily accessible by a broader academic community can include partnerships and consortia that are focused on particular areas of research. A primary example of such multi-university consortia is the NIPTE, created in 2005 and incorporated as a nonprofit academic research organization in 2007. Its membership includes 13 US research universities with world-class expertise in pharmaceutical sciences and engineering. Although being primarily focused on and funded by the scientific arm of the US Food and Drug Administration (FDA), NIPTE has some of the most unique translational capabilities that exist within the walls of academia. As a multi-university consortium, its membership includes eight institutions that are also CTSA sites, and six institutions that are National Institute of Cancer (NCI)-designated cancer centers (including three comprehensive centers). Most of those are located in the Midwest. On the basis of a recent CTSA consortium-wide survey (http://www.ctsacentral.org/reports/cataloging), there are 23 drug discovery centers within its 61 member institutions. The survey also revealed that 22 CTSA institutions have current good manufacturing practice (cGMP) facilities, out of which 16 are FDA registered, and eight are FDA inspected. However, only two of them are involved in small molecule drug development and are located in NIPTE institutions.

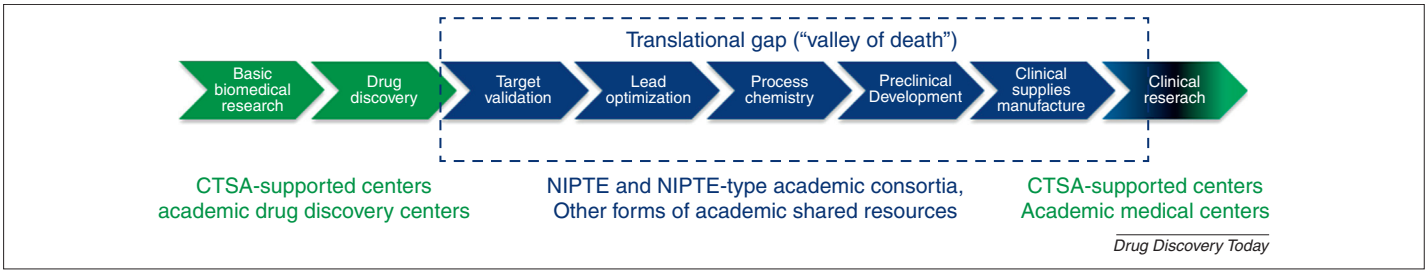

FIGURE 1

Clinical candidate development steps. *Abbreviation*: CTSA, Clinical and Translational Award.

One potential approach to shared resources within academic drug development research is depicted in Fig. 1. Whereas basic biomedical research, clinical research and, to some extent, early drug discovery are based on a well-developed NIH-supported infrastructure, the later-stage translational facilities are uncommon in academic institutions. Establishing and maintaining translational infrastructure is a significant financial, administrative and regulatory challenge. One solution is to make existing, established infrastructural capabilities available to other academic institutions through a network of partnerships, collaborations or consortia. These structures can have a regional or nationwide scale. For example, given that most NIPTE infrastructural capabilities, as well as its CTSA sites, are located in the Midwest, focusing on that particular geographic area would make practical sense for a NIPTE-based translational partnership.

NIPTE could serve as a prototype of regional translational consortia and perhaps a main resource in the areas of lead optimization, chemical process development, formulation development, toxicology, preclinical and clinical supplies manufacturing, and providing chemistry, manufacturing and control (CMC) support for IND applications. Its strength is based on the existing structures of NIPTE, its cGMP manufacturing facilities and drug discovery and development expertise, and scientific, developmental and regulatory capabilities of individual centers and institutes within its member institutions. The main infrastructural capabilities of NIPTE are primarily based on:

- Three centers at the University of Minnesota: (i) The Institute for Therapeutics Discovery and Development (ITDD), a comprehensive drug discovery and development center whose capabilities range from high-throughput screening (HTS) through lead optimization and medicinal chemistry to process chemistry and cGMP drug substance manufacturing; (ii) Center for Translational Drug Delivery (CTDD), which provides support in novel drug delivery and innovative formulations technologies, such as nanoparticulate formulations; and (iii) Center for Translational Medicine (CTM) that supports IND-enabling preclinical studies through GLP toxicology and/or safety studies in rats and dogs.
- The cGMP clinical supplies manufacturing facility of the University of Iowa, University of Iowa Pharmaceuticals (UIP). This is the oldest and largest academic cGMP manufacturing facility in the USA, and provides contract pharmaceutical formulation development, clinical supply, and commercial manufacturing and analytical testing services.
- The ability of Purdue University to use solid state chemistry to carry out accelerated design and development, including its platforms for novel amorphous formulations, co-crystals, coupled with its ability to carry out bioavailability studies in pigs.
- The Waisman Manufacturing Center and Zeeh Pharmaceutical Experiment Station of the University of Wisconsin, which include special strengths in nanoparticulate formulations and vaccine formulation and manufacture.
- The University of Kansas, which has developed novel approaches to the design of medicines and vaccines for many years. The University has deep expertise in vaccine formulation and stability.
- The University of Michigan is a world leader in biopharmaceutics as related to drug development and has special expertise in co-crystal formulation and excipient design.
- Illinois Institute of Technology has outstanding capabilities in modeling diseases and pathways, such as angiogenesis, as well as modeling human biomarkers.
- The top-ranked analytical capabilities of the University of Kentucky include solid state nuclear magnetic resonance (NMR) imaging and expertise in the rapid development of inhalable products.
- The University of Connecticut is a leader in parenteral development and manufacturing science (freeze drying, and formulation of proteins in both solution and solid state).
- The University of Maryland houses one of the two cGMP investigational drug product manufacturing facilities in academia. Additionally, it has a long history of excellence in regulatory science and the development of novel regulatory strategies.
- Duquesne University is among the leaders in quality by design and sensor-based manufacturing.
- University of Puerto Rico has an outstanding record of training scientists for the vast pharmaceutical manufacturing expertise of Puerto Rico.
- Rutgers University has demonstrated excellence in nanoparticles and large scale manufacturing.

The collaborative nature and organizational structure of NIPTE enables access to expertise from other NIPTE schools with 30–50 active NIPTE faculty members and industry partners. The support that NIPTE can provide in various stages of drug development is depicted in Fig. 2.

Implementation of this model within academic partnerships offers a variety of advantages as opposed to outsourcing to private CRO. First, it provides a more synergistic approach, in which academic units involved in discovery, development, manufacturing, regulatory science and clinical research are better integrated as academic partners. Second, owing to the nature of academic research and access to a large pool of academic expertise, this model would undoubtedly result in bringing more innovation into various stages of drug development. One of the stated goals of NIPTE is developing new platforms that would shorten the drug development period and increase the ability to bring drugs to market. Third, the proposed approach offers facile and significantly less expensive routes for academic research to get access to the infrastructure necessary for advancing drug candidates to clinical trials. Unique aspects of NIPTE include its regulatory expertise for preclinical drug development and its access to

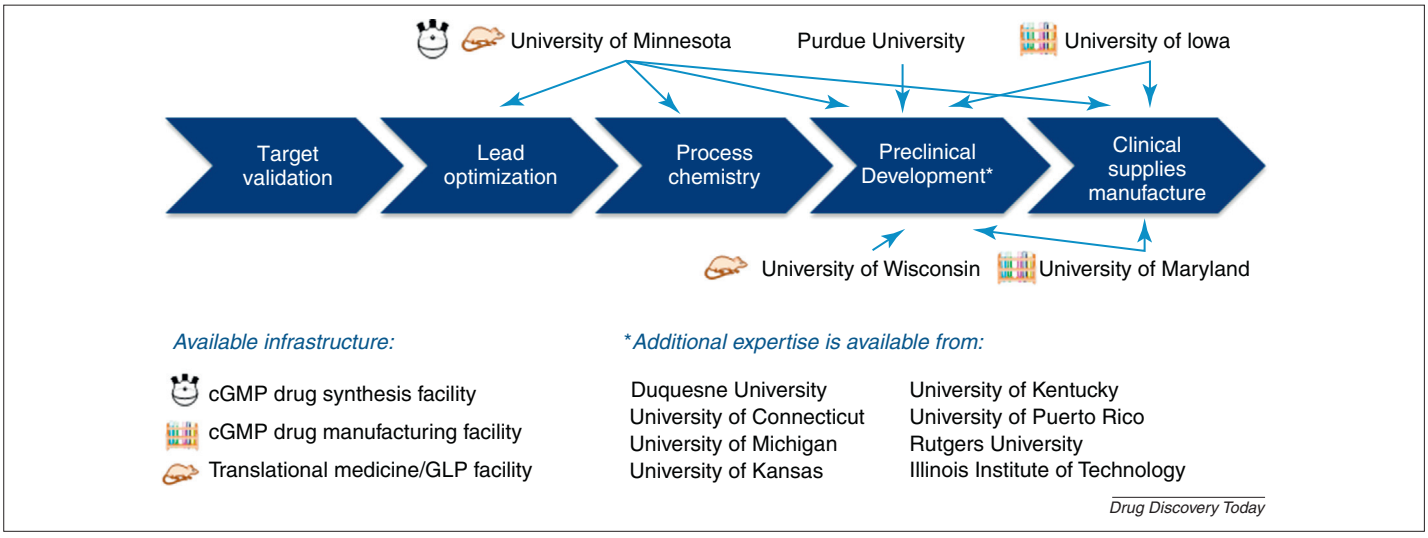

FIGURE 2

National Institute for Pharmaceutical Technology and Education (NIPTE) support for key clinical candidate development stages. *Abbreviations*: cGMP, current good manufacturing practice; GLP, good laboratory practices.

highly regulated cGMP infrastructure that is rarely available in the academic world. Fourth, the integrated approaches to drug development will make the projects more attractive to industry, large and small alike, and potential investors. Most NIPTE scientists either have direct industrial experience or have a long history of collaborating with industry. They bring together the best practices of both worlds and can help create partnerships with industry to commercialize the academia-initiated drug products. Thus, the approach offered by NIPTE can accelerate commercializing academic discoveries that are eventually transferred to industry, to the market and, ultimately, to patients.

Clinical supplies concept

Access to high-quality clinical supplies is crucial to first-in-human clinical research. Manufacture of clinical supplies requires three steps: (i) synthesis and/or sourcing of the drug (API); (ii) conversion of the drug to a bioavailable formulation; and (iii) manufacture of clinical supplies and placebo (Fig. 3). Additionally, regulatory support and IND-enabling studies, such as process development, analytical method development, stability studies for drug substance and drug product, are crucial parts of this drug development stage.

The drug, either small molecule or macromolecule, must be synthesized or sourced in large enough quantities to enable preclinical toxicological testing and manufacture of clinical material. It requires a combination of organic chemistry, process chemistry, analytical chemistry and chemical engineering skills, as well as regulatory support, to make the clinical candidate cGMP ready. Quality control and quality assurance are crucial from the beginning of this process, because the quality of the GLP toxicology material should often exceed that of the clinical batch. The Therapeutics Process Development Facility, Institute for Therapeutics Discovery and Development, University of Minnesota, has capabilities for chemical process development, scale up and cGMP manufacturing of small molecule and protein-based drug substances. Additionally, the program leaders have extensive experience in all aspects of pharmaceutical consulting and have access to a wide range of other options for API synthesis if required.

In many cases during modern drug development, a formulation must be developed to render the drug soluble. It has been estimated that over 60% of the drugs under development are poorly soluble, and that approximately 40% of newly developed drugs are abandoned by the pharmaceutical industry and will never benefit a patient owing to poor bioavailability resulting from low water solubility and/or cell membrane permeability [32]. NIPTE scientists have extensive experience in formulation approaches, including amorphous formulations, cocrystals and salts that solubilize small molecule drugs. They can also design formulations for achieving optimal blood levels of the API.

Once a bioavailable formulation has been discovered, it must be scaled up to manufacture clinical supplies. Two NIPTE schools, the University of Iowa and the University of Maryland, have facilities capable of manufacturing clinical supplies. Additionally, NIPTE researchers have extensive expertise in clinical supply manufacturing and also work with several other contract laboratories. Therefore, NIPTE is ideally positioned to provide assistance in a wide range of clinical supply needs, including regulatory expertise, analytical methods development, stability studies and FDA submissions.

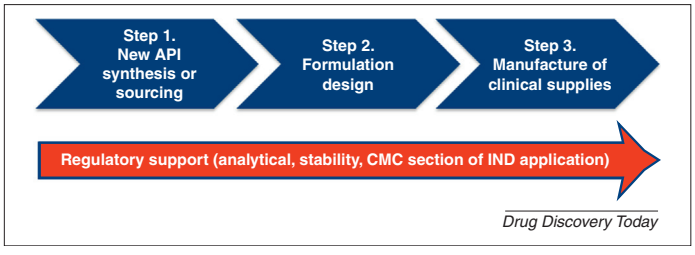

FIGURE 3

National Institute for Pharmaceutical Technology and Education (NIPTE) clinical supplies concept. *Abbreviations*: API, active pharmaceutical ingredients; CMC, chemistry, manufacturing and control; IND, investigational new drug.

Platforms for accelerating drug development

NIPTE scientists have developed several platforms for accelerating therapeutic development. Chorus, a previous Eli Lilly division that is now independent, has established that it is possible to rapidly move compounds to proof of concept. Chorus statistics indicate that the costs to develop a compound to proof of concept using an accelerated model are less than US$10 million and the timeline is approximately 3 years [33]. By contrast, the industry average cost to reach proof of concept is in the range of US$40 million and the average industry time is 4.5 years [33]. The approach of NIPTE is similar to that of Chorus. Its platforms include: (i) advanced strategies for formulation design using amorphous forms, co-crystals, salts and polymorphs; (ii) unique strategies for developing dissolution tests that are rank-order related to blood levels and can be used to design the best formulation without requiring animal studies; (iii) a porcine model for human pharmacokinetics; and (iv) close working relationships with clinical trial manufacturing experts. For example, Aptuit used a platform similar to that available at NIPTE to develop a model compound (itraconazole) for a first-in-human clinical trial within just 52 weeks [34]. Finally, eight NIPTE schools are also CTSA sites with the capability to carry out clinical trials rapidly and economically. This helps ensure a smooth transit from preparation of clinical supplies to the initiation of clinical trials.

Coordinating center

NIPTE headquarters can serve as a coordinating center helping with the contractual, legal, administrative and financial arrangements, as well as project management and coordination. As a one-stop shop, it can provide academic researchers with easy access to various capabilities and infrastructure in its member institutions. The projects have multiple points of entry that vary from HTS and assay development, through hit to lead and lead optimization to process chemistry, formulations, manufacturing and preclinical studies. To a great extent, NIPTE has been fulfilling this role as a scientific partner for the FDA Office of Pharmaceutical Sciences, most recently handling an FDA-funded U01 grant with up to US$35 million in funding and 24 ongoing projects. NIPTE also serves as a TRND contractor for Lead Optimization and CMC development. In addition to their collaboration with the FDA through the Critical Path Manufacturing Sector Research Initiative and other programs, NIPTE schools also have significant regulatory expertise. For example, Purdue University has a MS degree program in regulatory and quality compliance that includes lecturers from the pharmaceutical industry and the FDA. This program includes the filing of an IND as one of its projects and extensively discusses NDA filings. This regulatory expertise enables NIPTE to provide collaborators with regulatory guidance during the development of new drugs. Active faculty members, commitment from university administrations, a proven track record of success of collaborative projects and several FDA approved facilities all ensure that NIPTE is well positioned to undertake this task.

Concluding remarks

The primary goal of academic translational research is to accelerate translational science through the improvement and development of resources for moving discoveries across translational barriers to clinical development. To achieve this goal, access to drug discovery expertise and preclinical development infrastructure is imperative. The proposed use of, and ready access to, collaborative centers for coordinating preclinical development, based on a NIPTE model, stands to provide academic translational research institutions with access to a wide variety infrastructure for developing novel small molecules primed to become clinical candidates. This infrastructure includes lead optimization, process chemistry and scale up, preclinical toxicology, analytical method development, development of suitable formulations, bioavailability, stability testing, regulatory support and manufacture of clinical supplies to support Phase I and II trials.

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