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Clinical Translation of Nanomedicine

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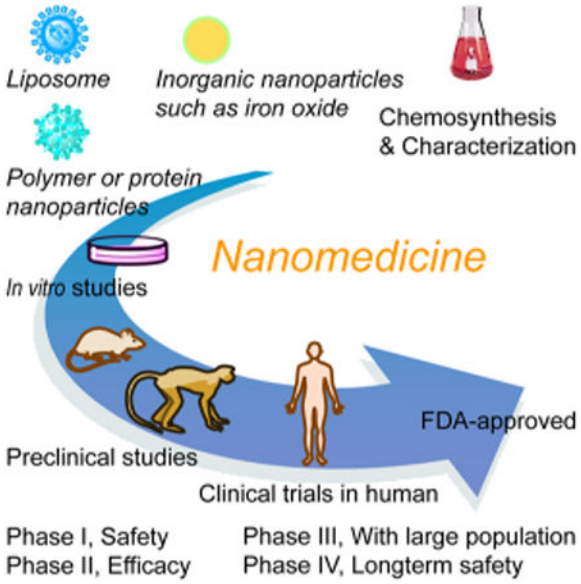
Abstract



1. Introduction

Nanomedicine, the application of nanotechnology to health and medicine, is a relatively new area of interdisciplinary science. The field involves a wide range of scientific disciplines, including physics, chemistry, engineering, biology, and medical science. The term nanomedicine can be traced back to the late 1990s and first appeared in research publications in the year 2000.[1] Despite the wide adoption of the term nanomedicine, its definition varies among experts in this area.[2] Some define nanomedicine broadly as any science that involves matters that are nanoscale. For example, the European Science Foundation in 2004 defined nanomedicine as "the science and technology of diagnosing, treating, and preventing disease and traumatic injury, of relieving pain, and of preserving and improving human health, using molecular tools and molecular knowledge of the human body".[2] While such a broad definition is all encompassing, it can be confusing. For example,

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such a definition would include traditional scientific fields such as molecular biology as part of nanomedicine, because molecules such as nucleic acids and proteins are also nanoscale materials. However, scientists have been studying these molecules decades before the term nanomedicine was even coined, and their research generally does not take advantage of unique properties that only exist for nanomaterials. A narrower definition of nanomedcine is the application of nanoscale material in medicine that takes advantage of the nanomaterial's unique properties.[1] This Review will adopt this narrower definition in our discussion of the clinical translation of nanomedicine.

Nanomedicine has made a rapid and broad impact on healthcare. Despite being only several decades old, research in nanomedicine has already led to the development of a wide range of products including therapeutics, diagnostic imaging agents, in vitro diagnostics, and medical devices. There are more than 200 nanomedicine products that have been either approved or are under clinical investigation.[3] On the other hand, successful clinical translation is a challenging process. It requires extensive preclinical research, carefully selected clinical indication, proper design of clinical trials, and the successful completion of these trials. Mistakes in clinical translation can be unforgiving. Unlike preclinical research where there are many if not unlimited chances of generating a successful study, a single failed clinical trial can doom a drug's translation. Hay et al. recently showed that the eventual success rate of approval for therapeutics entering phase I trial is only about 10%.[4] Because of this sobering statistic, it is important for translational researchers to fully understand the clinical translation process and to develop a successful translation strategy in the early stages of research.

As compared to diagnostics and devices, clinical translation of therapeutics is arguably the most challenging. The typical clinical translation path for a new drug starts with investigators generating robust preclinical data to demonstrate the safety and efficacy of the new drug to enable an investigational new drug (IND) application with the Food and Drug Administration (FDA).[5] Once the FDA has approved the IND, the therapeutic will be evaluated in a first-in-human or a phase I clinical trial. The goal of such a study is to determine the safety profile and pharmacology of the drug. It will result in a dose and schedule for further clinical investigation, or the recommended phase 2 dose (RP2D). The typical phase I trial design used a “3 + 3” cohort expansion design.[6] This design assumes toxicity increases with dose, and it aims to determine the dose level that has less than 1/3 chance of a dose-limiting toxicity (DLT).[7] In general, such a trial starts with a low drug dose. If none of the three patients receiving this dose experiences a DLT, another three patients will be treated at the next higher dose level. If one of the three patients experiences a DLT, then three more patients will be treated at the same dose level. Dose escalation continues until two patients among a cohort of three to six patients experience DLT. The RP2D is the dose level just below this level. Dose escalation typically follows a modified Fibonacci sequence where dose increments decrease as the tested dose increases. Other types of phase I designs include the accelerated titration designs, Bayesian models-based designs, and many others.[7] Each design has advantages and disadvantages, and investigators have to choose the design that best fits the therapeutic.

The goal of a phase II clinical trial is to examine the effectiveness of a drug or treatment. Secondarily, it will acquire more data on the toxicity and tolerability of the therapeutic. Therapeutics will progress to phase III clinical investigation only if they can demonstrate efficacy in phase II. The designs of phase II trials are either single-arm trials or randomized trials.[8] Single-arm trials are cheaper, require fewer patients, and are typically easier to accrue. However, the outcome is less reliable as there is no comparison/control arm, and data are more susceptible to bias. Data from randomized phase II trials are more predictive of phase III results. However, it requires more patients and can be more difficult to accrue. Randomized phase II trials do not replace phase III investigations. Although they are randomized, patients are generally stratified on the basis of very few variables, such as age, sex, and disease status in phase II trials to keep the accrual goal low. Randomized phase III trials stratify patients on the basis of a large number of variables, which leads to less bias and more robust data. Because of the stratifications, the sample size required for phase III investigation is much higher than that of randomized phase II trials.

The goal of randomized phase III trials is to demonstrate that the investigational treatment is more effective than the “gold standard” treatment. In general, phase III data are required for FDA approval. However, in select cases where there are robust data and unmet clinical needs, conditional approval can be granted on the basis of phase II data or interim phase III data. The FDA has a range of programs to speed up the approval process, including accelerated approvals and the recent “break through therapy” designation.[9]

There is a “short-cut” to FDA approval for agents that are based on already approved drugs. This pathway is called the 505(b)(2) pathway. The process of timeline for 505(b)(2) is much more abbreviated when compared to a typical approval process. For nanomedicine, this pathway will typically require that the exact nanoparticle platform is already approved with another agent and the drug being delivered by the nanoparticle is also approved. Past examples of this include the approval of liposomal bupivacaine with the DepoFoam liposome platform.

The FDA was granted the authority to regulate medical devices in 1976.[10] The approval process for medical devices is very different from that of drugs. First, for devices that predate May 28, 1976, these devices can remain on the market without needing approval. For the devices entering the market after that date, they are classified into different classes (I, II, and III) on the basis of their risks (Table 1).[10] Class I devices are of low risk and are generally exempt from premarket notification (referred to as 510(k)) and may even be exempt from compliance with the good manufacturing practice requirement. Class II devices typically will require 510(k) submission before marketing. Class III devices are subject to the most stringent regulatory controls. Their approval will require a premarket approval (PMA) application. The 510(k) pathway is for devices that can be compared to existing, legally marketed “predicate” devices. The new device needs to be shown to be at least as safe and as effective as the “predicate” device. For devices that do not have a “predicate” device with which to compare, they are classified as class III and will need PMA. PMA needs to include scientific evidence that the device is safe and effective for its intended use. Unlike therapeutics where approvals generally require large randomized studies, scientific evidence for devices can include randomized controlled trials, single-arm studies, well-

documented case series, and reports of significant human experience. For new devices that pose significant potential risks, an investigational device exemption (IDE) application is required prior to clinical investigation. Overall, the approval process is much simpler for devices than for therapeutics.

In this Review, we will examine preclinical evidence, chosen clinical path to translation, and clinical data of clinically approved nanomedicine products. We will also discuss the clinical data on nanomedicines that are under clinical investigation or failed clinical translation. Each of these clinical nanomedicine products has a unique clinical translation story. By examining this body of evidence, we aim to formulate important concepts that are keys to nanomedicine's clinical translation and to identify challenges. Such concepts will facilitate the translation of future nanomedicine products.

2. Liposome and Lipid-Based Nanomedicine

The liposome was the first nanoparticle platform in nanomedicine. Because the lipid bilayer is a core component of cell membrane structure, research interest in phospholipid membrane systems began early and predates the field of nanotechnology. As early as 1965, Bangham et al. described “swollen phospholipid systems” in their study on ion diffusion. Initially described as “multilamellar smectic mesophases” and sometimes referred to as “banghasomes”, [11] the term “liposomes” was eventually proposed by Gerald Weissmann, a visitor to Alec Bangham's laboratory, in 1968.[12] Soon after the description, liposomes were utilized in drug delivery for both small molecules as well as protein drugs.[13,14] In the following four decades, research in liposome and lipid nanoparticle drug delivery led to the development of the first FDA approved nanomedicine, DOXIL, as well as 12 additional therapeutics.[15] Moreover, there are 30 liposomal or lipid nanoparticle-based therapeutics currently under clinical investigation.

Liposomes have several favorable properties as drug delivery vehicles. First, they can deliver both hydrophobic and hydrophilic molecules.[15] The core of liposomes is hydrophilic, which can be used to encapsulate hydrophilic therapeutics. Between the liposome's lipid layers, there is also a hydrophobic domain, which can be utilized for the delivery of hydrophobic molecules. Second, liposomal delivery changes the biodistribution and pharmacokinetics of the therapeutic cargo. Such effects can improve therapeutic efficacy as well as reduce toxicity. Third, liposomes can protect its therapeutic cargo from the in vivo environment, which can improve the stability of the therapeutic. Last, for therapeutics needing to avoid the lysosomal pathway, such as gene therapy agents, liposomes can be engineered to escape lysosomes and deliver their cargo into the cytosol.[16]

2.1. Liposomal Anticancer Drugs

Gregoriadis was one of the first to demonstrate the liposome's ability to deliver therapeutics.[17] He also recognized that the liposome's unique properties may improve the therapeutic index of cancer chemotherapy with cytotoxic drugs. To translate the liposome as a clinical drug carrier, further information on its biodistribution and pharmacokinetics was needed. In 1973, Gregoriadis et al. conducted a first-in-man (FIM) study with liposomes containing ^{131}I-labeled human serum albumin in three cancer patients.[18] In addition to

typical pharmacokinetic information obtained from plasma, the investigations were able to obtain tissue biopsies (one from necropsy 5 days post injection and one from surgical biopsy 3 h after injection) to calculate tissue biodistribution. The study showed that the dose to the liver is higher than that of normal tissue (Table 2). It is important to note that such human studies are no longer possible due to the improved, more stringent guidelines of clinical studies. This small FIM study inspired intense efforts in translating liposome as drug delivery vehicles. Despite strong interests from both academia and industry, it was not until two decades later (2/1995) that the first liposome therapeutic (DOXIL, Janssen Products, L.P.) was approved by the FDA.

2.1.1. Liposomal Doxorubicin—Doxorubicin, a member of the anthracycline class of chemotherapeutics, was the first therapeutic evaluated for liposome delivery. As one of the first chemotherapeutics for cancer, doxorubicin was utilized against a wide range of cancers, including breast, lung, gastric, ovarian, sarcoma, myeloma, leukemias, and lymphomas.[19–21] Its wide use made it an attractive candidate for liposomal delivery. More importantly, doxorubicin is known to cause severe cardiotoxicity, which is dose-dependent and cumulative.[22–24] Because of the liposome's favorable biodistribution properties, investigators hypothesized that liposomal delivery could improve doxorubicin's therapeutic index.

The first published phase I trial on liposomal doxorubicin evaluated a “first generation” formulation where the liposome was approximately 300–500 nm in size, with doxorubicin intercalated in the lipid bilayer.[25] 32 patients, most of them with liver cancer refractory to treatment, were given escalating doses (20-120 mg/m^2) of liposomal doxorubicin on a 3-week intermittent schedule. The maximum tolerated dose (MTD) was found to be 120 mg/m^2, with all three patients at this dose level experiencing grade 4 leukopenia and neutropenic fever. While the MTD of this formulation of liposomal doxorubicin is higher than that of free doxorubicin (75 mg/m^2) in the every 3 week schedule, the investigators recognized several issues that would prevent the clinical translation of this formulation.[26] Pharmacokinetic and biodistribution studies showed that liposomal doxorubicin, despite the higher administrated dose, provided lower peak levels of free drug.[27] The liposome was also too large and caused rapid clearance by the reticuloendothelial system (RES) or the mononuclear phagocytic system (MPS). Around the same time as this phase I trial was conducted, preclinical research showed that large liposomes are unable to escape capillaries, and they are rapidly cleared from circulation.[28] This challenged the field of liposome research and translation to identify better and clinically translatable formulations.

Another phase I trial was conducted by Rahman et al. using a different formulation of liposomal doxorubicin.[29] The trial used a 3 + 3 design with a starting dose of 30 mg/m^2. The dose escalations were 45, 60, and 90 mg/m^2. A total of 14 patients were enrolled, and the MTD was found to be 60 mg/m^2. Dose-limiting hematologic toxicity occurred at 60 and 90 mg/m^2 with all 5 patients at 90 mg/m^2 experiencing neutropenia. Two patients experienced hypersensitivity reactions during infusions, which resolved with medication. One patient received a total of 885 mg/m^2 of doxorubicin but did not have any cardiotoxicity. Pharmacokinetic analysis showed liposomal doxorubicin had higher AUC (area under the curve) than that of free doxorubicin.

On the basis of the FIM data from first generation liposomes, Gabizon and Farenholz and their colleagues further improved the liposomal doxorubicin formulation. Key changes included the polyethylene glycol (PEG) surface to create a "stealth" liposome that is not easily detected by the RES system.[26] Another major improvement was remote loading to improve doxorubicin loading within each liposome.[30] The first clinical investigation of this improved formulation (which eventually became the approved DOXIL) was conducted in Israel from 1991 to 1994.[31] The primary end-point of this study was to understand the pharmacokinetics of DOXIL. A total of 16 patients were enrolled in this trial. The study had an unusual design as it had two study arms instead of one. Seven patients in the first arm received free doxorubicin first, followed by a second course of DOXIL. Two doses were studied: 25 and 50 mg/m^2. In the second arm of the study, nine patients received DOXIL upfront. In addition to standard plasma pharmacokinetic studies, patients with malignant effusions were tapped and the doxorubicin concentration was quantified. This study demonstrated that DOXIL had significantly higher AUC when compared to free doxorubicin. DOXIL also had a much smaller volume of distribution (4 L) as compared to that of free doxorubicin (254 L). The clearance of DOXIL was also significantly slower than doxorubicin. These data are consistent with the macromolecular/nanoparticle nature of liposomal formulation. More interestingly, DOXIL resulted in 4–16-fold higher drug concentration in malignant effusions as compared to that of free doxorubicin (Figure 1). This observation was one of the first to support the enhanced permeability and retention (EPR) effect of nanoparticles.

As DOXIL entered the clinical investigation phase, Kaposi's sarcoma (KS) was becoming a common disease due to the epidemic of acquired immunodeficiency syndrome (AIDS).[32] There was a strong need for an effective treatment for this AIDS complication. The DOXIL development team recognized this need and realized that positive clinical trial data would result in rapid approval of DOXIL for this illness. There was also clinical evidence to support the use of DOXIL in this disease, as doxorubicin is utilized in combination chemotherapies for KS.[33] A phase I/II trial was therefore conducted by James et al. to evaluate the safety and efficacy of DOXIL in AIDS-related KS.[34] Patients began treatment with 10 mg/m^2 every 2 weeks. If there was no clinical response, the dose was escalated to 20 mg/m^2 for two cycles before maintenance therapy (10 mg/m^2). Complete response (CR) was defined as no detectable disease, and partial response (PR) was defined as 50% or greater decrease in tumor. A total of 15 patients were assessed in this first publication. 11/15 (73%) had PR, and the remaining had stable disease. No patients experienced a DLT in this study. In a separate phase II study, 21 patients with AIDS-related KS were treated with 20 mg/m^2 DOXIL every 2 weeks.[35] The patients were stratified in low-risk and high-risk groups based on visceral involvement, >25% mucocutaneous KS, progression on interferon alfa, Karnofsky score, symptoms, and CD4 counts. PR was defined as a 50% or greater decrease in the perpendicular diameters of the tumors. Stable disease was defined as no measurable change in five indicator lesions. Ten evaluable patients were in each risk group. All of the low-risk patients had PR. Nine of the high-risk patients had PR and 1 had stable disease. Myelosuppression was the most common adverse event. A third phase II trial was reported in 1995. 34 patients with AIDS-related KS were enrolled (1991–1993) and treated with 20 mg/m^2 DOXIL every 3 weeks. All patients had poor prognosis disease. The overall response

rate was 73.5% with 67.7% PRs and 5.8% (2/34) CRs. Median duration of response was 9 weeks. The primary toxicity was hematologicneutropenia (34%), progressive with each cycle. The collective positive evidence of DOXIL in AIDS-related KS resulted in the FDA accelerated approval of DOXIL for treatment of chemotherapy-refractory KS in 1995.[36] The approval had a phase IV commitment of conducting a randomized trial between DOXIL and DaunoXome (liposomal daunorubicin).

The accelerated approval of DOXIL for KS was further supported by two randomized phase III trials. One of the studies was conducted by the International Pegylated Liposomal Doxorubicin Study Group.[37] 241 patients with AIDS-related KS were randomized between DOXIL (20 mg/m^2) and the combination of bleomycin (15 mg/m^2) and vincristine (1.4 mg/m^2) (BV). Both treatments were given every 3 weeks. Stratifications included prior KS treatment, KS stage, tumor burden, and CD4 count. 121 patients received DOXIL and 120 received BV. The response rate for DOXIL was 58.7% as compared to 23.3% for that of BV ($p < 0.001$). BV was less well-tolerated by patients, with more adverse events and fewer patients completing the full 6 cycles of treatment. A second study compared DOXIL (20 mg/m^2) to a combination of doxorubicin (20 mg/m^2), bleomycin (10 mg/m^2), and vincristine (1 mg/m^2) (ABV).[38] Unlike the prior trial, treatments were given every 2 weeks for 6 cycles. This trial randomized 258 patients between the arms, with 133 in the DOXIL arm. The overall response rate of DOXIL was 45.9% as compared to 24.8% for the ABV arm ($p < 0.001$). There was no difference in overall survival (OS). DOXIL was also found to be better tolerated than ABV treatment. Together, these two studies demonstrated that DOXIL leads to higher response rates than standard chemotherapy regimens, and it is better tolerated in KS. However, there was no overall survival benefit.

The phase IV commitment “A Double-Blind, Randomized Evaluation of Clinical Benefits of DOXIL in Patients with AIDS-Related Kaposi's Sarcoma Treated with DOXIL or DaunoXome” was designed in close collaboration with the FDA and initiated in 1996. The study enrolled 80 patients, and accrual was slow due to the introduction of highly active antiretroviral therapy (HAART) in 1996. The study eventually met accrual in 2000. While the final results of this study were not published, it was presented as abstract and discussed in reviews as well as detailed in the FDA application for full approval by Johnson and Johnson.[39] The results suggested that DOXIL had higher response rates than DaunoXome. However, despite the phase III and IV data, the FDA did not give regular approval due to concerns that HAART has confounded the clinical results. The prospect of regular approval improved when a Spanish group published a study comparing DOXIL + HAART vs HAART.[40] It found that DOXIL + HAART provided significantly higher response for KS than HAART alone (76% vs 20%). However, the company was unable to obtain the detailed data from this study to support the supplemental new drug application (sNDA) filing of DOXIL for KS. By then (2005), HAART therapy had transformed the AIDS epidemic, and any further randomized trial for KS would be extremely difficult to conduct, which the FDA also recognized. On the other hand, DOXIL was the already preferred treatment for KS, and the decreasing incidence of KS resulted in no further pursuit of approval for KS.

Since the accelerated approval of DOXIL for KS, the drug was studied in a number of other indications, including ovarian cancer, sarcoma, glioblastoma, lung, and breast cancer. Three

phase II studies showed promising results for DOXIL in ovarian cancer. Muggia et al. reported a phase II trial of pegylated liposomal doxorubicin (PLD/DOXIL) for the treatment of platinum and paclitaxel resistant ovarian cancer.[41] A total of 35 consecutive patients were enrolled from two institutions. Patients received 50 mg/m^2 of PLD every 3 weeks. In the event of grade 3–4 toxicities, dose was reduced to 40 mg/m^2. The overall response rate was 25.7% and median progression-free survival (PFS) was 5.7 months. Significant side effects included erythrodysesthesia (hand-foot syndrome) and stomatitis. The results were very encouraging in this treatment resistant population. In a separate phase II trial, Goron et al. also evaluated PLD for platinum and paclitaxel resistant ovarian cancer.[42] In this trial, PLD was given at 50 mg/m^2 every 4 weeks. 89 patients were enrolled in this study. The overall response rate was 16.9%, and median time to progression was 19.3 weeks. A third trial was conducted by Markman et al. in platinum/paclitaxel-refractory ovarian cancer.[43] This study used a PLD dose of 40 mg/m^2 every 4 weeks to avoid erythrodysesthesia and stomatitis. 49 patients were enrolled in the study and the response rate was 9%. Less toxicity was observed in this study as compared to the previous two. In 1998, DOXIL received orphan drug designation and a sNDA was filed shortly after. In 1999, the FDA granted accelerated approval to DOXIL for treatment-refractory ovarian cancer based on the three phase II studies and the interim data from the then ongoing randomized, noninferiority phase III study comparing DOXIL and topotecan. The phase IV commitment was to complete this randomized phase III trial. In this study, the PLD dose was 50 mg/m^2 every 4 weeks and the topotecan dose was 1.5 mg/m^2 daily for 5 days every 3 weeks.[44,45] Patients were stratified on the basis of response to initial platinum therapy and presence of bulky disease. The primary end point of the study was total time to progression (TTP) with secondary end points of overall response rate (ORR), response duration, overall survival, and safety. A total of 481 patients were enrolled from 1997 to 1999 at 104 sites in the U.S., Canada, and Europe. The results did not demonstrate superiority in TTP. However, long-term follow-up showed a survival benefit for the PLD arm. (Figure 2). On the basis of the positive survival data, PLD was given regular approval for ovarian cancer. It is important to note that overall survival was only a secondary end point in this study. A second randomized phase III trial was initiated in 2002 to compare carboplatin versus carboplatin+PLD (Southwest Oncology Group SWOG S0200). Unfortunately, the study was closed early due to poor accrual.[46] With only 61 patients, the final results showed no significant impact on survival, but there were fewer hypersensitivity reactions to platinum when PLD was given concurrently. This trial had no impact on DOXIL approval.

The third approved indication for DOXIL was for the treatment of relapsed and refractory multiple myeloma (MM).[47] The approval was primarily based on a randomized phase III trial comparing DOXIL + bortezomib as compared to bortezomib alone in patients with relapsed or refractory MM (DOXIL-MMY-3001). Patients were stratified on the basis of beta2-microglobulin and their response to prior treatment. Randomization was in a 1:1 allocation.[48] The primary end point was TTP, and the study was designed to detect an improvement of 6 months in median TTP. PLD was given at 30 mg/m^2 every 3 weeks. The median TTP was 6.5 months for bortezomib alone and 9.3 months for combination treatment (p = 0.000004). The 15-months survival rate was 76% for combination treatment versus 65% for bortezomib alone (p = 0.03). Combination treatment had higher toxicity.

PLD has also been studied extensively in metastatic breast cancer (MBC).[49] Three different randomized trials compared PLD to either free doxorubicin or other regimens. One randomized phase III trial directly compared PLD to conventional doxorubicin in MBC patients.[50] PLD was given at 50 mg/m^2 every 4 weeks and free doxorubicin was given at a dose of 60 mg/m^2 every 3 weeks. Primary end points were (1) noninferiority of PFS for PLD as compared to doxorubicin and (2) cardiotoxicity rates in the two arms. A total of 509 patients were enrolled and randomized. The investigators found similar rates of PFS and survival. Cardiotoxicity was significantly higher in the conventional doxorubicin arm (Figure 3). However, the rate of palmar-plantar erythrodysesthesia was much higher with PLD (48%) than doxorubicin (2%). These results led to the European Union (EU) approval of PLD (Caelyx/DOXIL) for MBC patients who are at increased cardiac risk. The other two randomized trials, one comparing PLD to capecitabine, the other comparing PLD to vinorelbine or mitomycin+vinorelbine, also showed no survival benefits for either PFS or OS.[49,51] The lack of benefit in terms of efficacy prevented PLD being approved for MBC in the U.S., although it is not uncommon to see DOXIL being used off-label in this patient population, especially if there is a concern for cardiotoxicity.

Following the expiration of the DOXIL patent, there was a recent worldwide shortage of the drug due to closure of the sole supplier of the drug to Johnson and Johnson. It is worth noting that regulations surrounding patents and intellectual property of nanoparticles are quite complex and can result in protection after expiration of the initial patent. This subject has been reviewed in detail by Burgess et al.[52] As a result of the DOXIL shortage, alternative formulations such as Lipodox have been approved by the FDA for temporary importation. Lipodox is also pegylated and has pharmacokinetic properties similar to those of DOXIL.[53]

In addition to PLD, a nonpegylated liposomal formulation (LD) was also clinically translated (Myocet, Enzon Pharmaceuticals). Unlike PLD, which is around 100 nm, Myocet is approximately 190 nm and has a very different structure.[54] Myocet has been approved for the treatment of MBC in the EU and Canada based on results from two randomized phase III trials. Chan et al. compared the combination of LD and cyclophosphamide (MC) with the combination of epirubicin and cyclophosphamide (EC) as first-line treatment for MBC.[55] The LD dose was 75 mg/m^2 every 3 weeks. The primary end point was response rates. 166 patients were enrolled and randomized. The response rates between the regimens were not different, although MC prolonged median time to treatment failure (5.7 vs 4.4 months, p = 0.01). Neither arm showed significant cardiotoxicity. In a separate phase III trial (TLC D-99), LD monotherapy was compared to conventional doxorubicin in MBC.[56] Both arms received 75 mg/m^2 every 3 weeks. 224 patients were enrolled. The only difference between the arms were cardiotoxicity (13% vs 29%) in favor of LD. Median cumulative dose to cardiotoxicity was 785 mg/m^2 for LD and 570 mg/m^2 for doxorubicin (p = 0.0001).

Currently, there is a targeted formulation of liposomal doxorubicin under clinical investigation. MM-302 (Merrimack Pharmaceuticals) is a HER2-targeted LD. Its phase I results were reported in an abstract at the San Antonio Breast Cancer Symposium in 2012. The final results have not been published. The phase I trial found 50 mg/m^2 to be the MTD. This drug is being studied in a randomized phase II trial with an unusual design: comparing

MM-302+trastuzumab to chemotherapy of physician's choice+trastuzumab in HER2-positive MBC (NCT02213744). Target accrual is 250 patients.

Another liposomal formulation of doxorubicin under investigation is ThermoDox (Celsion Corp.). This liposome platform is thermo-sensitive and releases doxorubicin at elevated temperatures.[57] ThermoDox has been studied in eight clinical trials but none has been reported. The largest study, a phase III study of ThermoDox plus radiofrequency ablation (RFA) vs RFA alone for nonresectable hepatocellular carcinoma (HCC), has completed accrual (NCT00617981). Although the results are not reported, the results of this trial were likely utilized to launch the currently active phase III randomized study evaluating ThermoDox with RFA in solitary HCC (3−7 cm) (NCT02112656). The drug is also being investigated for the treatment of liver metastasis, and breast cancer chestwall recurrence.

2.1.2. Liposomal Daunorubicin—Daunorubicin was the first anthracycline developed for cancer treatment.[58] Other anthracyclines such as doxorubicin and epirubicin are derived/synthesized from daunorubicin. For the same reasons that doxorubicin was a good candidate for liposomal delivery, there was also strong interest in the clinical translation of liposomal daunorubicin. The first clinical formulation of daunorubicin (DaunoXome, NeXstar Pharmaceuticals) was developed using a nonpegylated liposome platform.[59] In a phase I trial in multiple tumor types, the investigators identified the MTD for liposomally encapsulated daunorubicin (LED) to be 100 mg/m^2 for previously treated patients and 120 mg/m^2 for untreated patients. The DLT was neutropenia.

Similar to PLD, LED's first clinical indication was AIDS-associated KS. A phase I/II study of LED in KS enrolled 40 patients.[60] The patients received doses of 10, 20, 30, and 40 mg/m^2 given once every 3 weeks, and 40, 50, and 60 mg/m^2 given once every 2 weeks. The MTD was 60 mg/m^2 given every 2 weeks. In the 22 patients who received 50 and 60 mg/m^2, the investigators observed a response rate of 55%. These phase II data were further supported by a randomized phase III trial comparing LED to the ABV regimen.[61] A total of 232 patients were randomized to receive LED of 40 mg/m^2 or ABV every 2 weeks. The ORR was not different between the arms (25% vs 28%), and neither was median survival or median time to failure. ABV caused more alopecia and neuropathy, whereas LED caused more neutropenia. The investigators concluded that LED is comparable to ABV for KS treatment. On the basis of these data as well as two other studies (unpublished), the FDA granted accelerated approval to DaunoXome for KS.[62]

As mentioned above, DaunoXome appeared to be less effective than DOXIL in a randomized head-to-head comparison. Because of the same difficulties that DOXIL faced in regular approval for KS, DaunoXome was also unable to obtain regular FDA approval for KS. In addition, despite evaluation in other cancers, DaunoXome has not shown superior efficacy over standard treatments, and hence has not been approved for other indications.

2.1.3. Liposomal Cytarabine—One of the unique features of liposomes is its long circulating time and slow drug release. The clinical translation of liposomal cytarabine (DepoCyt, DepoTech Corp.) takes full advantage of this liposomal characteristic. Cytarabine, also known as arabinofuranosyl cytidine (ara-C), is a chemotherapeutic

commonly utilized for leukemias and lymphomas. One of the complications of aggressive lymphomas and leukemias is meningeal involvement. Few treatments are effective in this setting. Among the few, intrathecal ara-C (delivering drug into cerebrospinal fluid (CSF)) is one of the options, but it is toxic and requires frequent administration.[63] A liposomal formulation that has slow release may improve efficacy as well as safety of this treatment.

Unlike the previously mentioned liposomal drugs, liposomal cytarabine (LC) was developed using a multivesicular liposome platform.[64] Multivesicular liposomes are larger in size and act as a drug depot. The particular platform used in liposomal cytarabine has been termed DepoFoam and was shown to be able to increase drug exposure in the CSF.[65,66] The phase I study of LC was initiated in 1991.[67] Nine patients were given 1–7 cycles of LC ranging from 25 to 125 mg. Drugs were administered via Ommaya reservoirs. LC was well tolerated, and it had a prolonged half-life as compared to that of cytarabine. 5/6 evaluable patients had clearing (free of tumor cells) of their CSF.

On the basis of the promising phase I trial, two randomized controlled trials were conducted comparing LC to cytarabine. The first study, which was a randomized, multicenter, multiarm study compared 50 mg of LC administered every 2 weeks to standard intrathecal cytarabine administered twice a week to patients with lymphoma or leukemia.[68] 28 patients were enrolled. The response rate for LC was 71% as compared to 15% for cytarabine (p = 0.006). All of the LC patients were able to complete the treatment course, but only 53% of the cytarabine patients completed the regimen. Time to progression and overall survival trended in favor of LC. The second study was a randomized, multicenter, multiarm study involving a total of 124 treated patients with either solid tumors or lymphomas. Twenty-four patients with lymphoma were randomized and treated with LC or cytarabine. Patients received LC 50 mg every 2 weeks or cytarabine 50 mg twice weekly. Patients then received four maintenance cycles of LC or cytarabine 50 mg every 4 weeks. Similar to the first study, response rates were significantly higher in LC with 33% achieving CR as compared to 17% CR in the cytarabine arm. On the basis of the higher therapeutic efficacy and lower toxicity, DepoCyt received accelerated approval for lymphomatous meningitis.

CPX-351 (Celator Pharma) is dual agent liposomal formulation of both cyterabine and daunorubicin. The two drugs are maintained in a fixed 5:1 molar ratio, and multiple preclinical studies demonstrated promising efficacy against hematologic malignancies.[69–71] In this study, 48 patients with relapsed/refractory AML (acute myeloid leukemia) or high risk myelodysplasia were treated with increasing doses of CPX-351. The MTD was determined to be 101 u/m^2 with dose limiting toxicities of hypertensive crisis, prolonged cytopenias, and congestive heart failure reported (all consistent with cyterabine and daunorubicin toxicity). Interestingly, they observed complete responses in 9/43 enrolled patients including 8 in patients with prior cyterabine and daunorubicin treatment. A second phase I study incorporated CPX-351 prior to busulfan and fludarabine conditioned stem cell transplant and found an MTD of 120 U/m^2.[72] With a median follow up of only 205 days, the 1 year relapse free survival was achieved in 40% of patients.

Several phase 2 studies have since demonstrated promising efficacy of CPX-351. The first randomized 126 patients with newly diagnosed AML in a 2:1 fashion to CPX-351 (100

U/m^2) versus traditional 7 + 3 therapy (continuous infusion cyterabine days 1–7 and IV bolus daunorubicin days 1–3).[73] Overall response rates were higher in the CPX treated group (66.7% vs 51.2%). No differences in OS or EFS were observed for the whole group. CPX appeared to be particularly useful in secondary AML where the overall response rate was 57.6% versus 31.6% with a significant prolongation of the EFS in this subset of patients. While the efficacy was promising, toxicity was a problem. Recovery of cytopenias was longer in the CPX treated group (leukopenia recovery 37 vs 28 months), and there were more grade 3–4 infections in the CPX treated group. While not statistically significant, there was a trend toward higher infection-related deaths (3.5% vs 7.3%) and 60 day mortality (4.7% vs 14.6%) in the CPX treated group. A second phase II study randomized relapsed AML patients to CPX (100U/m^2) versus physician preference chemotherapy.[74] Patients were stratified into European Prognostic Index favorable, intermediate, and unfavorable risk groups. The primary end point was overall survival. There was no statistically significant improvement in OS (median 8.5 vs 6.3 months) for all patients, although OS was improved with CPX in the unfavorable risk patients. Several additional phase II studies are currently ongoing (NCT02286726, NCT02019069).

2.1.4. Liposomal Vincristine—Similar to liposomal cytarabine, liposomal vincristine (Marqibo, Spectrum Pharmaceuticals) is also approved for a rare condition and indication: adult patients with Philadelphia chromosome-negative (Ph-) acute lymphoblastic leukemia (ALL) in second or greater relapse.[75]

Marqibo is based on a nonpegylated liposome platform.[76] Preclinical studies indicate the liposomal formulation of vincristine increases the MTD, circulation time, AUC, and therapeutic efficacy over vincristine. Its approval was based on a phase II study evaluating Marqibo in refractory adult Philadelphia chromosome-negative acute lymphoblastic leukemia.[77] 65 patients were enrolled in this multicenter, international trial. Vincristine liposome injection (VSLI) was given at 2.25 mg/m^2 weekly until response, disease progression, toxicity, or pursuit of HSCT (hematopoietic stem cell transplantation). The primary end point was CR or CR with incomplete hematologic recovery (CRi). The CR/CRi rate was 20% and ORR was 35%. Median CR/CRi duration was 23 weeks, and 12 patients were able to bridge to HSCT. VSLI was reasonably well tolerated in this trial. The response rate (no survival benefit) led to accelerated approval (2012) for Marqibo. In a separate phase II trial, VSLI was evaluated in heavily pretreated patients with refractory non-Hodgkin's lymphoma (NHL). Patients received 2 mg/m^2 every 2 weeks for a maximum of 12 cycles or until toxicity/disease progression.[78] A total of 119 patients were enrolled on this trial. ORR was 25%, and 5% of patients achieved a CR. The data suggest that Marqibo may also be effective in treatment refractory NHL.

2.1.5. Liposomal Chemotherapeutics Undergoing Clinical Investigation—In addition to the above-mentioned approved liposomal chemotherapeutics, several others are under clinical investigation, including liposomal cisplatin, liposomal irinotecan, and liposomal docetaxel.

Cisplatin, like doxorubicin, is one of the most commonly utilized cancer chemotherapeutics.[79] Its main limitation is toxicity, which includes neurotoxicity and

nephrotoxicity.[80,81] There has been strong interest in developing nanoparticle formulations of cisplatin, including liposomal formulations.[82] Liposomal cisplatin formulations that have entered clinical stage are listed in Table 3.

Without discussing the details of each clinical study, liposomal cisplatin generally reduces neurotoxicity but does not significantly improve therapeutic efficacy (response or survival end points).[83,84] Because carboplatin has less nephrotoxicity, it is already viewed as the cisplatin alternative in renal impaired patients. Thus, successful clinical translation (approval) of liposomal formulations of cisplatin will require clear demonstration of efficacy end points.

Two liposomal formulations of irinotecan have also been developed and clinically evaluated. Both MM-398/PEP02 (Merrimack Pharmaceuticals) and IHL-305 use pegylated liposomes. Phase I of IHL-305 showed MTD and RP2D is 160 mg/m^2 every 28 days.[85] DLTs were nausea/vomiting and diarrhea. Pharmacokinetic analysis showed high AUC for liposomal irinotecan. No phase II data have been published on IHL-305. MM-398 is much further along in its clinical development. It has been recently (in 2014) granted fast-track status for treatment of metastatic pancreatic cancer that has progressed on or following gemcitabine-based therapy. MM-398 was studied in metastatic pancreatic cancer first in a multinational phase II trial.[86] 40 patients with metastatic pancreatic cancer that progressed following gemcitabine-based therapy were enrolled. MM-398 was given at 120 mg/m^2 every 3 weeks as second-line treatment. The primary end point was 3-month OS. The investigators found that 7.5% of patients had an objective response and 42.5% had stable disease. Interestingly, 31.3% of the patients had a >50% decline of CA19-9, a pancreatic cancer biomarker. The 3-month OS rate was 75%. On the basis of this trial, a three-arm phase III trial (NAPOLI-1) was initiated randomizing patients to MM-398, 5-FU/leucovorin, and the combination of MM-398 and 5FU/leucovorin. The results were reported at the ESMO GI meeting in 2014 and showed that MM-398 + 5FU/leucovorin improved OS (6.1 months vs 4.2 months), PFS, ORR, and CA19-9 response. These findings need to be confirmed upon the final publication of this trial. The reported improvement in survival end points is very favorable to the approval process of MM-398 for this indication. However, it is also important to note that a better trial design would have included a control arm of irinotecan and 5FU.

Liposomal paclitaxel and docetaxel have also been developed for clinical applications. Because taxanes are highly hydrophobic, it is typically delivered using polymeric nanoparticles (discussed later). However, it is possible to encapsulate docetaxel between the lipid-bilayer of liposomes. Two formulations of liposomal paclitaxel have been developed. Liposome-encapsulated paclitaxel (LEP-ETU, NeoPharm Inc.) has been evaluated in a phase I study.[87] Its MTD was 325 mg/m^2 with neuropathy as the DLT. Another liposomal formulation of paclitaxel, a cationic liposomal paclitaxel, is EndoTAG-1 (SynCore Biotechnology, partnered with Medigene).[88] In a phase II trial, EndoTAG-1 plus gemcitabine appears to be superior to gemcitabine alone. Unfortunately, the clinical success of nab-paclitaxel (discussed in a later section) meant the end of clinical translation of these liposomal paclitaxel formulations. For liposomal docetaxel, a phase I trial evaluating liposomal-encapsulated docetaxel (LE-DT) was reported by Deeken et al.[89] A standard 3 + 3

design was used in the study, and the RP2D was 85 mg/m^2 without G-CSF and 110 mg/m^2 with G-CSF. The DLT was neutropenia. No phase II data are available for this therapeutic at this time.

Recently, Gabizon (see DOXIL) et al. developed a liposomal formulation of mitomycin C. The therapeutic is comprised of a mitomycin-C lipid-based prodrug formulated in pegylated liposomes (PL-MLP).[90] It has been shown to be a safer and more effective treatment than mitomycin C in a number of tumor models.[90,91] PL-MLP (Promitil, LipoMedix Pharmaceutical Inc.) is being studied in a phase I trial with expected completion date of June 2015 (NCT017050020).

2.2. Liposomal and Lipid-Based Antibiotics and Antifungals

2.2.1. Liposomal and Lipid-Based Amphotericin B (Abelcet, Ambisome, Amphotec)—Amphotericin B (AmB) is one of the most effective therapeutics against fungal infections.[92] However, its use and efficacy have been significantly limited by its severe and potentially lethal toxicities.[93] It often causes an acute reaction after infusion (1–3 h later) of high fever, chills, hypotension, as well as many other constitutional symptoms. Unlike many other drugs that can cause infusion reactions, premedication does not seem to significantly improve the outcome. Another significant toxicity is nephrotoxicity. It frequently causes elevation of creatinine, a measure of renal function. AmB cause acute tubular necrosis of the kidneys, and the mechanism of toxicity is at least partially due to direct cytotoxicity of the drug to the renal tubular cells. Because of its toxicities, AmB has earned a nickname of “ampho-terrible” among physicians and healthcare givers. More importantly, most physicians were reluctant to prescribe and administer this medication. These toxicities and need for better drug delivery make AmB a perfect drug for liposome/lipid drug delivery.

There are three clinical liposomal/lipid formulations of AmB: Abelcet (Sigma-Tau Pharmaceuticals), AmBisome (Gilead Sciences, Inc.), and Amphotec (Sequus Pharmaceuticals). These three AmB formulations have very different structures (Figure 4) and pharmacokinetics (Table 4).[92,94] Although all are comprised of lipids and AmB, Abelcet, also called AmB lipid complex (ABLC), has a ribbon-like structure, whereas Amphotec, also called AmB colloidal dispersion (ABCD), has a disk-like structure. AmBisome is the only formulation with a “true” liposome structure.

Abelcet was the first formulation to receive FDA approval (11/1995), missing the title of “first approved nanoparticle/liposomal therapeutic” by only 9 months. The preclinical studies to support its development were conducted by Juliano, Lopez-Berestein, and their colleagues.[95–108] The first clinical experiences with ABLC were compassionate use of the drug in cancer patients at MD Anderson (where Juliano and Lopez-Berestein were faculty).[109,110] In both small studies, cancer patients with fungal infections that were refractory to conventional AmB treatment were cured of their infections by ABLC (3/12 in one study and 8/9 in the other). A pharmacokinetics study in healthy male volunteers showed that ABLC had a lower AUC (area under the curve) than AmB's AUC.[111] This is likely due to increased hepatic clearance rather than the increased volume of distribution that the investigators suggested.

Many small phase II and III clinical studies have compared ABLC to amphotericin B in different fungal infections.[94] In general, these studies found ABLC to have equivalent efficacy but significantly less toxicity (especially nephrotoxicity) than AmB.[112–114] A randomized controlled trial compared ABLC to AmB in patients with candidiasis.[94] It randomized 231 patients in a 2:1 design to either ABLC (5 mg/kg) or AmB (0.6–1 mg/kg). This study found response rates to be similar (63% vs 68%) but nephrotoxicity was significantly less in the ABLC arm. On the basis of the collective clinical data on ABLC demonstrating its efficacy in patients who are refractory or intolerant of AmB, Abelcet was approved for the treatment of invasive fungal infections in patients who are refractory to or intolerant of conventional AmB therapy.

Amphotec was the second amphotericin formulation that was approved by the FDA (1996). A phase I study of ABCD in bone marrow transplant patients enrolled 75 patients. It found a MTD of 7.5 mg/kg.[115] At this dose level, there were minimal infusion-related toxicities and no observed nephrotoxicity. Unlike ABLC, which has lower AUC than AmB, the pharmacokinetics study of ABCD found it to have a higher AUC than AmB.[116] Moreover, ABCD has a longer elimination half-life than AmB. This is consistent with the smaller size of ABCD (compare to ABLC), which leads to less RES uptake and clearance.

Several randomized studies compared ABCD to AmB. A randomized, double-blind trial compared the two therapeutics in patients with neutropenic fever.[117] 213 patients were enrolled to receive either ABCD (4 mg/kg) or AmB (0.8 mg/kg). Treatment responses were similar in the two arms (50% for ABCD and 43.2% for AmB). However, the ABCD arm had significantly less infusion-related reactions and nephrotoxicity. In a separate trial, 82 patients with aspergillosis were given ABCD, and the results were compared retrospectively to 261 patients who were treated with AmB.[118] The response rate for ABCD was higher than that for AmB (48.8% vs 23.4%). Fewer ABCD patients developed renal dysfunction as compared to AmB patients (8.2% vs 43.1%). Combined with other open label studies demonstrating that ABCD is effective and less toxic than AmB in treating aspergillosis, the FDA approved Amphotec for the treatment of invasive aspergillosis in patients who have failed or are intolerant of AmB. Following the approval, a double-blind, randomized study comparing ABCD to amphotericin B in invasive aspergillosis enrolled 174 patients.[119] The therapeutic response was similar in both arms (52% vs 51%), but renal toxicity was lower in the ABCD arm (25% vs 49%).

AmBisome is the only “true” liposomal AmB (LAmB), and its pharmacokinetics reflects the formulation differences.[120] LAmB results in a Cmax and AUC that were 8–10-fold higher than that of AmB, respectively. These values are also significantly higher than those of ABLC and ABCD. Importantly, LAmB had a significantly lower volume of distribution, which generally translates into lower normal tissue exposure. The pharmacokinetics differences are shown in Table 4.

LAmB was studied in several clinical indications, including empiric therapy for presumed fungal infection in neutropenic fever patients, treatment of cryptococcal meningitis in HIV patients, fungal infections that are refractory to or intolerant of AmB, and visceral leishmaniasis. As such, it eventually received FDA approval for all of the above

indications.[121] There is a large body of clinical data on LAmB, which is impractical to review in detail here. In general, similar to ABLC and ABCD, AmBisome is significantly less toxic than AmB.[122] However, LAmB did not demonstrate higher therapeutic efficacy of AmB in these studies. For example, two randomized studies comparing LAmB to AmB in neutropenic fever were reported by Prentice et al.[123] A total of 134 adults and 204 children were randomized to AmB 1 mg/kg, LAmB 1 mg/kg, or LAmB 3 mg/kg. There was no significant difference in terms of efficacy between the arms, although the AmBisome arms had significantly lower nephrotoxicity as well as other drug-induced toxicities (2–6-fold reduction).

LAmB has also been compared directly to ABLC in patients with neutropenic fever.[124] In this randomized, double-blind comparative trial, 244 patients were randomized to LAmB 3 mg/kg, LAmB 5 mg/kg, and ABLC 5 mg/kg. While there was no difference in therapeutic efficacy, both LAmB doses were significantly less toxic than ABLC. Specifically, LAmB (3 mg/kg/d and 5 mg/kg/d) had lower rates of fever (23.5% and 19.8% vs 57.7% on day 1; $P < 0.001$), chills/rigors (18.8% and 23.5% vs 79.5% on day 1; $P < 0.001$), nephrotoxicity (14.1% and 14.8% vs 42.3%; $P < 0.01$), and toxicity-related discontinuations of therapy (12.9% and 12.3% vs 32.1%; $P = 0.004$). This is not surprising given the different pharmacokinetics of the two formulations. ABLC's drug release is more rapid, which is the likely cause of increased toxicity. This trial allowed AmBisome to include a claim of superior safety profile over Abelcet in its label.

Together, the three liposomal/lipid formulations of AmB are arguably the most successful nanotherapeutics to date, as they have largely replaced the use of AmB. This is despite the fact that none of the formulations have demonstrated superior efficacy over AmB, and they are much more costly.[125] The wide adoption of liposomal/lipid formulations of AmB is based on safety and convenience of administration. Clinical AmB administration generated high anxiety in clinicians due its significant toxicity. It generally required high levels of care and monitoring after drug administration that lasted hours. In contrast, clinicians are able to administer liposomal/lipid formulations of AmB similar to other therapeutics without extra clinical monitoring. Although the clinical translation model of liposomal/lipid formulations of AmB is one to emulate, there are few therapeutics that possess the high toxicity profile of AmB.

2.2.2. Liposomal Antibiotics—Clinical formulations of liposomal antibiotics have been studied, but none have been approved. Gentamicin is a aminoglycoside antibiotic that is highly effective against Gram-negative organisms.[126] Its main toxicities are ototoxicity and nephrotoxicity. A liposomal formulation of gentamicin (TLC-65) was studied clinically for the treatment of mycobacterium in AIDS patients.[127] In this phase I/II study, patients were given escalating doses of liposomal gentamicin (1.7, 3.4, and 5.1 mg/kg). A total of 21 patients received the treatment with the only significant toxicity being renal insufficiency (1 patient). Blood mycobacterium colony counts decreased with treatment, suggesting therapeutic efficacy. However, this therapeutic did not succeed in its development program. Without published reports, it is unclear whether it failed due to lack of efficacy or lack of toxicity reduction.

Another antibiotic, amikacin, has been formulated with liposomes, mainly for inhalation delivery for patients with cystic fibrosis (CF). The rationale for liposome delivery is to increase the half-life of amikacin.[128] Liposomal amikacin (ARIKAYCE, Insmed Inc.) has been studied in a phase II trial, which enrolled 105 CF patients, for the treatment of *Pseudomonas aeruginosa*, one of the most common pathogens in CF.[129] The trial used a randomized, double-blind, placebo-controlled design. The primary end point was safety and tolerability, and secondary end points were lung function, *P. aeruginosa* in sputum, and CF quality of life questionnaire. Subjects were randomized to once-daily ARIKAYCE (70, 140, 280, and 560 mg; $n = 7$, 5, 21, and 36 subjects) or placebo ($n = 36$) for 28 days. The drug was found to be relatively safe with no difference in toxicity between experimental arms and placebo arms. The 560 mg dose group had improved lung function (FEV1) at days 28 and 56 as compared to placebo ($p = 0.033$). Sputum *P. aeruginosa* also decreased more than one log in the 560 mg group when compared to placebo ($p = 0.021$). These data suggest that liposomal amikacin may be a viable treatment for CF.

2.3. Liposomal/Virosomal Vaccines

Liposome structure resembles viral envelopes, which are typically derived from host cell membranes. Taking advantage of this property, investigators incorporated viral membrane proteins or peptides into liposomes to formulate virosomes, and utilized these virosomes as vaccines.[130] The advantage of virosomes is that they contain key viral proteins that can generate immune response, but they lack the genetic information on viruses that make them safe to administer. Another key advantage of virosomes lies in the fact that they contain low levels of ovalbumin and are thus less allergenic than traditional vaccines. Two virosome-based vaccines have been approved for clinical use. Inflexal V (Crucell, Janssen Pharmaceuticals) is a virosome influenza vaccine that is formulated by incorporating hemaglutinin and neuraminidase, key influenza antigens, into liposomes.[131] Since its introduction to clinical use in 1997, a large number of clinical trials have evaluated its safety and efficacy.[132] Clinical data showed that it is safe and efficacious. In a direct comparison between Inflexal and a nonvirosome influenza vaccine, 453 children were randomized 1:1 between the formulations.[133] The seroconversion is similar between the arms except Inflexal has a higher seroconversion rate for the H3N2 strain (88.8% vs 78.3%). Inflexal is the only adjuvanted influenza vaccine that is approved for all age groups.

Epaxal (Crucell, Janssen Pharmaceuticals) is a virosome-based hepatitis A vaccine. It is formulated by adsorbing inactivated hepatitis A virus onto liposome surface.[134] Clinical studies showed that a two-dose Epaxal regimen can lead to long-term (at least 9–11 years) protection against hepatitis A with a median duration of protection of 52.1 years.[135] An even more impressive statistic is that >95% individuals will have protection for at least 30 years. The safety profile of this vaccine also appears to be excellent.[136]

2.4. Liposomal Anesthetics

The same DepoFoam platform used to deliver cytarabine (mentioned above) has also been used to deliver anesthetics. Liposomal formulations (DepoFoam) of morphine and bupivacaine have both been approved by the FDA. Liposomal morphine (DepotDur, Pacira Pharmaceuticals) has been approved for epidural administration for the treatment of pain

following major surgery. The fact that DepoFoam has been used in both the approved liposomal cytarabine and the approved liposomal morphine makes the translation path of DepotDur easier than most therapeutics. In a randomized, controlled, dose-ranging trial comparing extended-release epidural morphine (EREM/Depodur) to morphine, 441 patients were randomized to 1 of 6 epidural treatments.[137] The treatments were single dose 5 mg of morphine sulfate (MS), 5 mg of EREM, 10 mg of EREM, 15 mg of EREM, 20 mg of EREM, and 25 mg of EREM. The primary end point was to compare the efficacy of single dose EREM at escalating doses (5, 10, 15, 20, and 25 mg) versus single dose MS 5 mg for postoperative pain management. At 48 h after treatment, significantly more single-dose EREM patients (13%) than MS patients (2%) had excellent pain control (defined as not requiring any IV fentanyl for breakthrough pain control) ($p < 0.01$). Moreover, patients in the single-dose EREM 15, 20, and 25 mg groups reported significantly lower pain-intensity scores and greater satisfaction with their pain relief. Further, EREM showed a typical dose–response relationship with patients requiring the least breakthrough fentanyl in the 25 mg group (683 vs 982 and 985 μg fentanyl for 15 and 20 mg groups). In another study evaluating EREM for pain relief in total hip arthroplasty, 200 patients were randomized to receive 15, 20, or 25 mg EREM or placebo.[138] All EREM groups had improved pain control, and 25% of EREM patients did not need supplemental analgesia (as compared to 2% for placebo). DepoDur has been studied in a number of other surgical procedures such as cesarean section and colorectal surgery, and the results are similar to the above-mentioned studies, excellent pain control with less need for breakthrough pain medications.[139]

Liposomal bupivacaine (EXPAREL, Pacira Pharmaceuticals) is approved for administration into the surgical site for postsurgical analgesia. It is a treatment particularly helpful in patients who are intolerant of or at high risk of complications from opioids. In one study, bupivacaine extended-release liposome injection (BELI) was compared to placebo in patients undergoing hemorrhoidectomy in a randomized double-blind trial.[140] BELI was found to reduce opioid pain medication use (opioid free from 12 h (59%) to 72 h (28%) after surgery as compared to patients receiving placebo (14% and 10%)). In a small phase IV health economic study, 27 surgical patients undergoing ileostomy reversal were followed and their pain management costs were calculated.[141] BELI use was associated with less opioid use, shorter length of hospital stay (median, 3.0 days versus 5.1 days), and lower hospitalization costs ($6482 versus $9282, respectively; $p = 0.01$). These pharmacoeconomic considerations further illustrate the potential of controlled release anesthesia in postoperative analgesia.

2.5. Liposomal Verteporfin

Visudyne (Bausch and Lomb) is a liposomal formulation of verteporfin, a hydrophobic photosensitizer, which has been approved for the photodynamic treatment (PDT) of “wet” age-related macular degeneration.[142] The rationale for liposomal delivery is because verteporfin is known to self-aggregate in aqueous environment, which can limit its bioavailability. Visudyne, combined with PDT, prevents the growth of the destructive blood vessels. In this treatment, patients are administered Visudyne through intravenous injection followed by light therapy (to the eyes). Two multicenter, double-blind, placebo-controlled, randomized trials compared Visudyne to placebo in patients with age-related macular

degeneration.[143] A total of 609 patients were randomized 2:1 to Visudyne or placebo. The primary end point was proportion of eyes with fewer than 15 letters lost. At 12 months after the procedure, 246 (61%) of 402 eyes assigned to verteporfin ascompared to 96 (46%) of 207 eyes assigned to placebo had lost fewer than 15 letters of visual acuity from baseline ($p < 0.001$). The Visudyne treatment group also had better visual acuity, contrast sensitivity, and angiographic outcomes (secondary end points). There were few adverse events associated with Visudyne treatment. On the basis of this result, Visudyne was approved for treatment of wet macular degeneration. The drug has also received orphan drug status for the treatment of central serous chorioretinopathy (CSC), a rare condition where serous fluid accumulates between the retina and the retinal pigment epithelium, causing retinal detachment.[144] A recent randomized clinical trial compared two doses of Visudyne in CSC.[145] This noninferiority trial attempted to demonstrate that 30% dose would be as effective as the 50% dose. However, noninferiority was not achieved and it found that the 50% dose of Visudyne is superior to 30% dose. Importantly, it showed that PDT with Visudyne is an effective treatment for CSC. Visudyne has also been studied for the PDT of cancers, although it is unclear what the clinical translation path will be given PDT's limited role in cancer.[146]

2.6. Liposomal/Lipid Nanoparticle Delivery of Nucleic Acids

Liposome and lipid nanoparticle formulations are excellent delivery vehicles for nucleic acid therapeutics, such as gene therapy agents and small interfering RNAs (siRNAs).[147] These nanoparticle formulations, especially cationic lipid formulations, protect the nucleic acid agents from degradation and can also facilitate their endosomal escape, a critical step in achieving success for nucleic acid therapeutics.

Several phase I clinical trials have evaluated liposomal (cationic) formulations of gene therapy agents. In one study, liposomal formulation of E1A gene therapy was injected into the thoracic or peritoneal cavity of 18 patients with advanced cancer of the breast ($n = 6$) or ovary ($n = 12$).[148] The treatment was well tolerated with treatment-related toxicities of fever, nausea, and vomiting. Importantly, E1A expression was detected in tumor cells, indicating successful gene therapy. A separate phase I trial evaluating the same agent for intratumoral delivery in recurrent breast and head and neck cancers showed similar results.[149] Another phase I study examined the delivery of p53 gene therapy in advanced solid tumors.[150] The transferrin-targeted liposomal formulation was administered systemically in 11 patients. The treatment was well tolerated with only 1 patient experiencing serious side effects of chest pain and tachycardia.

Liposomes have also been used to deliver antisense therapeutics. Dritschilo et al. reported the results of a phase I study of liposomal c-Raf antisense in conjunction with radiotherapy in advanced cancer.[151] 17 patients who were receiving palliative radiotherapy were administered the agent. Side effects included mostly infusion reactions such as fever, chills, and dyspnea; these side effects were improved by premedication.

Recently, there has been strong interest in the clinical translation of siRNA therapeutics.[152] The most successful effort has been the lipid formulations of siRNA for the treatment of transthyretin amyloidosis. In a report of two phase I studies, two lipid nanoparticle

formulations, ALN-TTR01 and ALN-TTR02 (Patisiran, Alynlam Pharmaceuticals), were given to 32 patients with transthyretin amyloidosis (ALN-TTR01) and 17 healthy volunteers (ALN-TTR02).[153] Infusion reactions were seen in approximately 20% of the patients. Although efficacy is not a key component of phase I studies, this trial showed provocative and exciting data. There was a rapid and dose-dependent lowering of transthyretin levels in both patient cohorts. For ALN-TTR02, the mean reductions in transthyretin levels ranged from 82.3% to 86.6% and reductions remained at 56.6%–67.1% at 28 days ($p < 0.001$). These data suggest high potential for therapeutic success of these agents. Several other RNAi (RNA interference) agents are also under clinical investigation, and these are listed in Table 5.[154]

3. Protein Nanoparticles

3.1. Nab-paclitaxel

The most successful protein nanoparticle therapeutic has been nanoparticle albumin-bound (Nab) formulation of paclitaxel (Nab-paclitaxel). ABI-007, marketed as Abraxane (Abraxis corporation), is an albumin-bound formulation of paclitaxel that is devoid of any solvents including Cremephor or ethanol. Paclitaxel is a naturally occurring compound extracted from the bark of the western yew tree, *Taxus brevifolia*.[155] The mechanism of action is very well established and reviewed elsewhere.[156,157] Paclitaxel is a widely used chemotherapeutic agent with FDA approval for the treatment of a number of different solid tumors including breast, lung, head and neck, gastrointestinal, and ovarian cancers.[158]

Small molecule paclitaxel has limited aqueous solubility. To improve solubility and in vivo delivery, paclitaxel was initially prepared as a Cremophor/ethanol-based (Cremophor EL, now marketed as Kolliphor EL) preparation (marketed as Taxol). There are several major drawbacks to Cremophor EL-based delivery systems. First, they are associated with a well-described acute hypersensitivity reaction resulting in severe and sometimes fatal allergic or anaphylactic responses.[159–161] These hypersensitivity responses have been observed in up to 20–40% of patients.[158] While premedication with steroids or antihistamines can reduce the frequency of hypersensitivity responses, severe and fatal reactions still occur. Second, they can form plasma micelles, which are capable of entrapping paclitaxel and other coadministered drugs such as anthracy-clines.[162] Plasma trapping is problematic as it results in decreased drug clearance and decreased volume of distribution.[163,164] The aqueous solubility of paclitaxel is so poor that it requires a very high concentration of Cremophor EL. In fact, the amount of Cremophor EL needed to deliver recommended doses of paclitaxel is higher than any other marketed drug, which results in plasma concentrations of up to 0.4% after a typical dose of 175 mg/m^2.[165] While Taxol is undoubtedly efficacious as a chemotherapeutic agent, the therapeutic index was clearly limited by its Cremophor EL delivery system, which increased toxicity.

There was a lot of interest in exploring alternative delivery methods to try to improve the clinical efficacy of paclitaxel, and a number of systems were explored. Perhaps the most logical, and by far the most successful of these, was the conjugation of paclitaxel to albumin. Albumin serves as a natural carrier protein for paclitaxel once in solution in the plasma. Conjugating paclitaxel to albumin prior to administration was a relatively

straightforward way of greatly enhancing its overall solubility and in vivo transport process. Abraxane is a formulation of 130 nm particles in the bottle, which rapidly dissociates into approximately 8 nm paclitaxel coated albumin molecules in the plasma.

Abraxane has a lower treatment volume and time required for administration. One of the first phase I trials of Abraxane involved 19 patients with solid tumor malignancies, which had failed standard therapy.[166] Patients were treated every 3 weeks with increasing doses ranging from 135 to 375 mg/m^2. Dose-limiting toxicities (including neuropathy, stomatitis, and superficial keratopathy) were observed in 3 out of 6 patients at the 375 mg/m^2 group. Thus, the MTD was determined to be 300 mg/m^2, which was significantly higher than the 175 mg/m^2 range reported for Cremophor-EL paclitaxel. Importantly, not a single acute hypersensitivity reaction was observed. Pharmacokinetic analysis showed that values of maximum concentration and area under the time–concentration curve increased linearly over the tested ranges and correlated very well with toxicity in individual patients.

An additional phase I study was completed by Nymen et al. utilizing a weekly treatment schedule (3 weekly doses of drug followed by 1 week of rest per cycle).[167] This study included 39 patients with advanced solid tumor malignancies. Patients were treated with Abraxane weekly at doses ranging from 80 to 200 mg/m^2. Pretreatment to reduce hypersensitivity reactions was not recommended in this study. Treatment was relatively well tolerated. Major toxicities were again hematologic and peripheral neuropathy, and 33% of patients tolerated at least 6 cycles of therapy. MTDs were 100–150 mg/m^2, depending on previous chemotherapy and radiation treatments. In patients with heavy pretreatment (defined as >6 cycles of previous anthracycline, irradiation of >25% of bone marrow, etc.), no DLTs were seen at 80 or 100 mg/m^2, whereas 2 episodes of grade IV neutropenia occurred at 125 mg/m^2. In patients with light pretreatment, there were two episodes of grade III peripheral neuropathy observed after 6 or 7 cycles of Abraxane 125 mg/m^2, but this was controlled with dose reduction. There were also 2 episodes of grade III neuropathy after just 2-3 cycles of 175 mg/m^2, and the MTD was determined to be 150 mg/m^2. This was significantly higher than the previously reported MTD of 80 mg/m^2 for weekly dosed Cremophor EL-based paclitaxel. The authors also noted partial responses in five patients with breast, lung, and ovarian cancers, who had been previously treated with paclitaxel. The promising results of this and other phase I trials led to further clinical investigations in a number of different disease sites.

Subsequent preclinical and clinical studies demonstrated that Abraxane had greater antitumor efficacy than Cremophor EL-based paclitaxel. Mechanistic evidence to explain the increased efficacy of nab-paclitaxel was demonstrated well in preclinical work by Desai et al.[168] They assessed antitumor activity, intratumoral paclitaxel accumulation using mice bearing human tumor xenografts of lung, breast, ovarian, prostate, and colon cancers treated with nab-paclitaxel or Cremophor EL-based paclitaxel. Nab-paclitaxel had significantly greater antitumor activity than Cremophor EL-based paclitaxel in most tumor types tested. This difference was most striking in breast (MX-1) and ovarian (SK-OV-3) xenografts. There were more tumor-free survivors (100% vs 20% for breast, 24% vs 0% for ovarian), and time to recurrence was significantly longer (103 vs 22 days for breast, 63 vs 26 days for ovarian) in the Nab-paclitaxel treated mice. Time to recurrence was also increased in

prostate (PC-3; 48 vs 26 days) and colon (HT29; 36 vs 26 days) cancer xenografts. They then measured intratumoral paclitaxel levels by treating animals bearing MX-1 tumors with tritium-labeled paclitaxel in both preparations and measuring tumor radioactivity at seven time points over 24 h. Following equal doses of paclitaxel (20 mg/kg), intratumoral accumulation was significantly higher in the nab-paclitaxel treated mice. Nab-paclitaxel had an absorption constant that was 3.3-fold higher than Cremophor EL-based paclitaxel (0.43 vs 0.13/h), and the tumor area under the curve (AUC) was 33% higher in the Nab-paclitaxel treated tumors. Finally, they demonstrated that Nab-paclitaxel had significantly greater binding affinity and transcytosis in human endothelial cells than Cremophor EL-based paclitaxel. Fluorescent-labeled Nab-paclitaxel showed 9-fold greater binding of paclitaxel in human umbilical vascular endothelial cells, and transport across human lung endothelial cells was 4.2-fold higher than Cremophor EL-based paclitaxel. Transcytosis of Nab-paclitaxel was indeed through active transport, as it was completely blocked by methyl-β-cyclodextran, an inhibitor of caveolar-mediated transcytosis. Further, Cremophor-EL diluent decreased paclitaxel binding to both albumin and endothelial cells in a dose-dependent manner. These studies provided mechanistic evidence that Nab formulation can improve the therapeutic index of paclitaxel by decreasing toxicity and improve antitumor efficacy by improving intratumoral delivery.

3.1.1. Nab-paclitaxel in Metastatic Breast Cancer—Several clinical trials subsequently demonstrated the efficacy of Abraxane for the treatment of metastatic breast cancer. A phase II study by Ibrahim et al. included 63 women with metastatic breast cancer.[169] Slightly more than one-half of the patients (48) had been treated with prior chemotherapy. Patients were treated with 300 mg/m^2 Abraxane by intravenous infusion every 3 weeks without any premedication to prevent acute hypersensitivity reactions. Treatment was relatively well tolerated with expected paclitaxel toxicities of neutropenia (24% grade IV) and neuropathy (11% grade III). However, no severe hypersensitivity reactions were reported. Treatment appeared efficacious, as the overall response rate was 64% in patients treated with first-line therapy and median time to disease progression was 26.6 weeks.

The superiority of Abraxane to Cremophor EL-based paclitaxel in the treatment of metastatic breast cancer was established in a phase III randomized controlled trial in 2005.[170] This study randomized 460 patients with metastatic breast cancer who were candidates for single-agent paclitaxel. Eligible patients had to have received either no prior treatment with paclitaxel or docetaxel or not experienced relapse or progression within 1 year of discontinuing paclitaxel or docetaxel in the past. Patients were randomized to Abraxane (260 mg/m^2) without premedication or standard paclitaxel (175 mg/m^2) with IV premedication every 3 weeks. Abraxane was more efficacious and had a more favorable toxicity profile than Cremophor EL-based paclitaxel. Overall response rates were 33% versus 19%. Time to progression was significantly longer in the Abraxane arm (23 weeks vs 16.9 weeks). Time to progression was significantly longer in patients getting first-line therapy than second-line or greater therapy, and Abraxane increased the time to progression in both groups (24.0 vs 19.7 weeks for first-line, 20.9 vs 16.1 weeks for second-line or greater). Median overall survival was significantly higher with Abraxane than standard

paclitaxel in second-line or higher patients (56.4 vs 46.7 weeks) and trended toward improvement in first-line patients (65 vs 55.7 weeks). Treatment was relatively well tolerated in both groups with 97% and 93% of patients in both groups completing all planned doses without dose reduction or delays because of toxicity. Despite receiving a 49% greater average paclitaxel dose-intensity, there were no grade III acute hypersensitivity reactions in the Abraxane group as compared to 2% in the standard paclitaxel group. Further, there was significantly less grade IV neutropenia in the Abraxane arm (9 vs 22%). The higher dose intensity with Abraxane treatment did translate into a higher incidence of grade III neuropathy (10% vs 2%). However, these all improved to grade I or II with treatment interruption or dose-reduction. Overall, there were no measurable differences in quality of life between the two groups. On the basis of the results of this and above-mentioned trials, the FDA approved Abraxane for the treatment of metastatic breast cancer in patients who have failed combination chemotherapy for metastatic disease or relapsed within 6 months of adjuvant therapy. As discussed below (Table 6), there are many more completed and ongoing clinical trials, to expand the approval of Abraxane for the treatment of breast cancer at virtually all disease stages including early stage operable disease.

3.1.2. Nab-paclitaxel in Non-Small Cell Lung Cancer (NSCLC)—Despite years of clinical research and advances in systemic therapies, long-term survival in locally advanced and metastatic lung cancer is exceedingly poor with 5 year overall survival rates of less than 5%. Paclitaxel is efficacious in the treatment of lung cancer and frequently given in combination with other drugs, most commonly carboplatin.[171,172] Given the encouraging results of improved efficacy and decreased toxicity as compared to Cremophor-EL paclitaxel, there was strong interest in investigating the use of Abraxane for the treatment of advanced NSCLC.

Green et al. conducted a single-arm phase II study investigating the efficacy and safety of q3 week monotherapy Abraxane (260 mg/m^2) in patients with inoperable, locally recurrent, or metastatic NSCLC.[173] 43 patients were enrolled, and 84% had visceral dominant disease. Monotherapy Abraxane showed promising efficacy, with ORR of 16.3%. Median time to progression was 6 months, and median overall survival was 11 months. Treatment was well tolerated, and 95% were treated per protocol without dose reduction or delays because of toxicity. Nine patients (21%) experienced a grade III toxicity, of which four were neutropenia and two were peripheral neuropathy. There were no grade IV toxicities. These results compared very favorably to previously published studies with single agent Cremophor EL-based paclitaxel.[174]

Rizvi et al. subsequently conducted a phase I/II study investigating the use of weekly single agent Abraxane in patients with inoperable advanced or metastatic disease.[175] Patients could have received neoadjuvant or adjuvant chemotherapy but no prior systemic therapy for their metastatic disease. The dose escalation (100–150 mg/m^2) portion of the study determined the MTD to be 125 mg/m^2 after no DLTs were observed at 100 and 125 mg/m^2; there were DLTs of febrile neutropenia and grade III neuropathy in 2 of 6 patients at 150 mg/m^2. Forty patients were then enrolled on the phase II portion and treated with weekly Abraxane on days 1, 8, and 15 followed by a 1-week break. Of these, 77% had received no prior chemotherapy. The ORR was 30% with median time to progression of 5 months and median

overall survival of 11 months. Similar to previous studies, treatment was well tolerated. 85% of patients completed therapy as planned. There were no treatment-related deaths and only two episodes of grade IV toxicity (both neutropenia).

Looking to build on these favorable results, Socinski et al. then undertook a phase I trial investigating the feasibility of combining Abraxane with carboplatin.[176] 175 patients with stage IIIB or inoperable metastatic disease with no prior treatment for metastatic disease were enrolled. They were separated into seven cohorts of 25 patients each receiving different doses of weekly (100–140 mg/m^2) or q3 week (225–340 mg/m^2) Abraxane. Carboplatin (AUC = 6) was infused q3 weeks in all treatment arms. Treatment toxicity was an issue, but the combination of Abraxane and carboplatin was feasible. The most common toxicities were hematologic, and the most common nonhematologic toxicity was peripheral neuropathy. Overall, 22% of patients required discontinuation because of treatment-related toxicities without evidence of disease progression. In the weekly treatment arms, the 100 mg/m^2 dose was best tolerated as only two patients (8%) required discontinuation for treatment-related toxicities as compared to six patients and seven patients (24–28%) at the higher dose levels. In the q3 week arms, unacceptable toxicity rates ranged from 16% to 44% (lowest in the 260 mg/m^2 arm and highest in the 340 mg/m^2 arm). ORRs ranged from 24% to 56%, with higher ORRs seen in the weekly infusion arms (36–56%) than the q3 week arms (24–40%). Notably, there was no dose–response relationship in either the weekly or the q3 week treatment arms. Maximal ORR was observed at 125 mg/m^2 (weekly) and 225 mg/m^2 (q3 week) doses. Median PFS and OS ranged from 4.8–6.9 months and 8.3–15 months, respectively. Neither differed by treatment schedule or showed a dose response relationship. However, when the investigators analyzed patients based on histology (squamous vs non-squamous), they observed significant and opposite differences. In patients with nonsquamous histology, weekly treatment was associated with a significant increase in PFS and OS of more than 2 months. However, q3 week treatment appeared to be better in patients with squamous histology as it was associated with a greater than 3 month increase in PFS and greater than 2 month increase in OS in that cohort of patients.

Following these results, Socinski et al. initiated a phase III trial seeking to demonstrate the superiority of Abraxane over Cremophor EL-based paclitaxel in combination with carboplatin for the treatment of advanced NSCLC.[177] This trial randomized 1052 patients (521 to Abraxane and 531 to solvent based) with advanced (stage IIIB or IV) NSCLC to weekly Abraxane (100 mg/m^2) with q3 week carboplatin (AUC = 6) versus standard of care q3 week Cremophor EL-based paclitaxel (200 mg/m^2) with q3 week carboplatin (AUC = 6). By almost all metrics, Abraxane had superior efficacy over solvent-based paclitaxel. Radiographic and clinical ORR were significantly higher (33% vs 25% and 38% vs 30%, respectively) as were median PFS (6.3 vs 5.8 months) and median OS (12.1 vs 11.2 months). By histology, Abraxane had a significantly higher ORR in squamous cell tumors (41% vs 24%), and equivalent ORR were observed in nonsquamous histologies (26% vs 25%). Overall, the median number of cycles received was 6 in both treatment arms. Dose reduction for toxicity was required in 46% of the Abraxane arm and 23% of the Cremophor EL-based arm. Abraxane was associated with significantly fewer grade III or IV peripheral neuropathy (3% vs 12%) and neutropenia (47% vs 56%) but more anemia (27% vs 7%) and thrombocytopenia (18% vs 9%). Subjective measurements of taxane-associated toxicities

were assessed using a FACT-taxane assessment scale, and 94% of patients had follow up assessments. Abraxane was associated with significantly smaller changes from baseline for neuropathy, pain, and hearing loss as compared to Cremophor EL-based paclitaxel. On the basis of the results of this study, the FDA approved Abraxane in combination with carboplatin for the first-line treatment of patients with advanced NSCLC in October 2011. See Table 6 for further details on ongoing investigations.

3.1.3. Nab-paclitaxel in Pancreatic Cancer—Pancreatic exocrine carcinoma is one of the most lethal malignancies. In the metastatic setting, survival is generally less than 6 months. As of 2011, gemcitabine was the only approved single-agent chemotherapy for the treatment of metastatic pancreatic cancer. However, median overall survival is still only 5.7 months, with less than 20% 1-year survival rate. A number of phase III trials had tried different combination therapies with gemcitabine, but only the combination of gemcitabine and erlotinib showed a significant improvement in overall survival.[178–182] The search for new combination therapies to improve survival continued. Molecular profiling of human pancreatic tumors suggested that nab-paclitaxel may be a rational selection as pancreatic tumors secreted high levels of the albumin-binding protein SPARC (secreted protein acidic and rich in cysteine). This protein is also overexpressed in breast and lung cancers, which respond favorably to nab-paclitaxel as described above. Van Hoff et al. initiated a phase I/II trial of gemcitabine (1000 mg/m^2 on days 1, 8, 15, q28 days) in combination with Abraxane in patients with metastatic pancreatic cancer.[183] Patients could have received prior 5-FU or gemcitabine as a radiosensitizer but not for metastatic disease and must have had at least 6 months of stable disease following therapy before relapse or progression. 67 patients were enrolled on the dose-finding portion of the study (100, 125, or 150 mg/m^2). DLT was observed in all three patients treated with 150 mg/m^2 including one fatal infection, so 125 mg/m^2 was selected as the MTD. The clinical efficacy in patients treated at the MTD was very encouraging. Median PFS was 7.9 months with a median OS of 12.2 months, and 48% of patients were alive at 1 year. Tumor metabolic activity as measured by PET-CT scan was available for 55 patients. The median decrease in FDG activity after 12 weeks of therapy (4 cycles) was 69%. Seventeen patients obtained complete responses on PET CT, and these patients had significantly increased median OS as compared to those with partial or no responses (20.1 vs 10.3 months). Survival was also significantly longer in those with high SPARC versus low SPARC expression (17.8 vs 8.1 months).

Within the same study, the authors also analyzed treatment responses, stromal content, and tumoral drug concentrations in 11 patient-derived xenografts. Gemcitabine monotherapy resulted in regression of 2 of 11 xenografts. Abraxane alone only induced regression in 4 of 11 xenografts. However, the combination of gemcitabine and Abraxane caused regression in 6 of 11 patient-derived xenografts. When they examined the stroma of two gemcitabine resistant tumors, they observed a profuse desmoplastic stroma. In contrast, treatment of these same tumors with Abraxane resulted in a decrease in desmoplastic stroma with an increase in the glandular density and increased endothelial cell content accompanied by dilated blood vessels. These rearrangements facilitated tumoral delivery of gemcitabine; intratumoral levels of gemcitabine increased 2.8-fold from approximately 2500 ng/g with gemcitabine alone to nearly 7000 ng/g with the addition of nab-paclitaxel.

With these very promising clinical and preclinical data, these same authors then undertook a randomized phase III study of gemcitabine (1000 mg/m^2 on days 1, 8, and 15) versus the same dose of gemcitabine with Abraxane (125 mg/m^2) to demonstrate the clinical superiority of combination therapy over single agent gemcitabine.[184] A total of 861 patients with metastatic pancreatic adenocarcinoma were randomized (431 to combination therapy and 430 to gemcitabine alone). Patients were not allowed to have had any prior cytotoxic doses of chemotherapy for metastatic disease. Combination therapy with Abraxane was clinically superior in terms of median OS (8.5 vs 6.7 months), 1 year OS (35 vs 22%), 2 year OS (9 vs 4%), and median time to progression (5.5 vs 3.7 months). Subgroup analysis demonstrated that risk of death appeared to be reduced in patients with markers of more aggressive disease including liver metastases, multiple sites of metastatic disease, and greatly increased CA19-9 levels. As for toxicity, there were 16 treatment related deaths (4%) in both arms, all secondary to sepsis. The most common grade III toxicities were hematologic and more frequently occurred in the combination therapy arm. This was most notable for neutropenia (38% vs 27%) and leukopenia (31% vs 16%). Nonhematologic toxicities were also more frequent in the combination group including peripheral neuropathy (17% vs 7% grade III). However, no grade IV peripheral neuropathy was reported in either group. Time to resolution to grade I or less was no longer in the combination therapy group. Overall, 41% and 47% of patients in the combination therapy group required dose reductions in Abraxane or gemcitabine (respectively). 33% of patients treated with gemcitabine monotherapy required a dose reduction. This study clearly demonstrated the clinical superiority of gemcitabine plus nab-paclitaxel as compared to gemcitabine alone with an acceptable increase in toxicity. On the basis of these results, the FDA granted approval for the combination of gemcitabine and Abraxane as first-line therapy for the treatment of advanced pancreatic cancer.

3.1.4. Additional/Ongoing Studies of Nab-paclitaxel—As detailed in Table 6, there are many ongoing trials examining the combination of Abraxane with other existing agents to expand the approved indications for Abraxane. Current early stage (phase I–II) clinical studies are investigating uses in all stages of breast cancer (early operable through metastatic) as well as a host of other primary cancers, including ovarian, lung, pancreatic, melanoma, GI, and GU cancers. Outside of breast cancer, the majority of these investigations are investigating use in advanced stage disease. There are also several ongoing phase III trials as detailed in Table 7. Given the previous successes with Abraxane in multiple different cancers, it seems likely some of these trials will prove successful, and new indications for Abraxane will be identified and granted.

3.2. Nab-rapamycin

The phosphatidylinositol-3-kinase (PI3-K)/AKT signaling cascade is intimately involved in tumor cell survival, proliferation, stress-response, and metabolism. The mammalian target of rapamycin (mTOR) protein is downstream of PI3-K and is a critical regulator of many of these processes.[217] Inhibitors of mTOR, including rapamycin and its analogues (including everolimus and temsirolimus), are effective anti-tumor molecules used in the treatment of several solid tumor malignancies including breast, RCC, and neuroendocrine tumors.[218–220] Unfortunately, rapamycin is plagued by poor solubility, bioavailability, and significant

gastrointestinal side effects.[221] Similar to cremophor in Taxol preparations, the solvents used to deliver mTOR inhibitors are associated with toxicity and acute hypersensitivity reactions.

Following the success of nab-paclitaxel, a nab formulation of rapamycin, ABI-009, was developed. This formulation produces NPs of approximately 100 nm in size. Preclinical data have been promising, and clinical studies are ongoing. One published study demonstrated cytotoxic effects of nab-rapamycin with perifosine in multiple myeloma cells.[222] A phase I dose-finding study of q3 week ABI-009 in patients with advanced solid tumor malignancies was undertaken.[223] Dose was escalated from 45 to 125 mg/m^2. Treatment was overall well tolerated. Two grade III toxicities (suicidal ideation and hypophosphatemia) were seen at 125 mg/m^2. There is an ongoing phase I/II trial of ABI-009 for the treatment of BCG refractory or recurrent nonmuscle invasive bladder cancer (NCT02009332).

4. Polymer–Drug Conjugates

The use of biological molecules such as proteins or peptides as active agents is a well-established therapeutic technique. Replacement of a deficient enzyme, such as adenosine deaminase in severe combined immunodeficiency (SCID), can reverse the toxic effects of metabolic disorders. Alternatively, the administration of active enzymes or proteins can have therapeutic effects. These can include growth factors (GM-CSF), hormonal antagonists (GNRH antagonists), active enzymes (arginine deaminase), and many other potential applications. However, the systemic administration of synthetic or exogenous drugs or biomolecules is often hampered by physical and biological limitations. The half-life of exogenous molecules in circulation is usually quite short for a number of reasons. Small molecules generally have rapid renal clearance. Enzymatic degradation is frequently an issue for proteins, peptides, and nucleic acids. Many proteins also induce immunogenic responses, which increase clearance rates. In addition to clearance issues, many therapeutics have significant systemic toxicities. Many compounds are poorly soluble and require the use of solvents, which themselves have well-established toxicities. In some instances, the most clinically significant acute reactions of some formulations are actually related to the solvents as opposed to the active drug.

Polymer–drug and polymer–protein conjugation has provided a successful solution to many of these issues and has resulted in improved delivery and clinical utility for a number of approved agents (Table 8). The most frequently utilized polymer has been polyethylene glycol (PEG), although others, such as polylactic acid (PLA), polygultamic acid, and *N*-(2-hydroxypropyl) methacrylamide (HPMA), have been successfully utilized and moved into clinical trials.[224,225] The conjugation of PEG (or other polymers) to a drug, protein, or peptide imparts a number of biological and pharmacological advantages for systemic delivery. Because polymers like PEG are hydrophilic compounds, they improve the solubility of conjugated agents and can eliminate the need for potentially toxic solvents. Conjugation greatly increases the size of the drug of interest, which can decrease exposure of nontarget tissues and decrease systemic toxicity. The increased mass also improves circulation times by decreasing renal clearance and primarily limiting the uptake of small molecules to the endocytic route. Polymer-conjugation can further increase circulation time

by decreasing immune-mediated clearance and enzyme-mediated degradation. Additionally, some polymer drug conjugates (such as CRLX-101 and polyglumex) can be used to form self-assembling nanostructures. As demonstrated in Table 8, polymer–drug conjugates have been successfully utilized and approved for the treatment of many different medical conditions. The literature supporting approved polymer–drug conjugates is quite large, and has been reviewed in detail many times before.[226–230] We will discuss the clinical development of several of these newer compounds in more detail here.

4.1. Poliglumex Paclitaxel

Polyglutamic acid conjugated (poliglumex) paclitaxel is another NP formulation of paclitaxel. This formulation produces slow, controlled paclitaxel drug release by hydrolysis of ester bonds. Early preclinical studies were promising. Li et al. demonstrated that polyglutamic acid paclitaxel formulation potently diminished in vivo xenograft tumor growth.[231] Mice bearing ovarian (OCA-1) xenografts received equal doses of paclitaxel (at the solvent-based MTD of 80 mg/kg) and demonstrated significantly greater delays in tumor growth with polyglutamic acid NP formulation than solvent-based preparation. Further, at the MTD of NP formulation (160 mg/kg), they observed complete tumor regression. In a rat primary mammary adenocarcinoma model (13762F), they observed complete tumor regression at the MTD of NP paclitaxel (60 mg/kg) and at lower doses (40 mg/kg). In contrast, at the MTD of solvent-based paclitaxel (20 mg/kg), they observed tumor growth delay, but not regression. NP administration caused significantly more tumor necrosis than solvent-based paclitaxel. Several other preclinical studies confirmed the improved efficacy and prolonged tumor paclitaxel concentration of polyglutamic acid-formulated paclitaxel as compared to Cremophor EL-based paclitaxel.[232–235]

Early clinical studies with poliglumex paclitaxel demonstrated unexpectedly high rates of toxicity. The first published phase I study involved seven patients with advanced solid tumor malignancies treated every 3 weeks with doses escalated from 235 to 275 mg/mg^2.[236] Grade III/IV neutropenia was seen in 2 of 5 patients at 235 mg/m^2 and one-half of the patients (1 of 2) at 275 mg/m^2. More surprising were the rates and severity of peripheral neuropathy. Two out of seven patients developed grade III neuropathy, which persisted between 8 and 18 months. A second phase I study also demonstrated DLTs of neutropenia and peripheral neuropathy and determined the MTDs of q3 week and q2 week administration were 266 and 177 mg/m^2, respectively.[237]

Commercially available forms of polyglutamic acid paclitaxel, initially under the trade name Xyotax, subsequently changed to Opaxio (CTI Biopharma), went on to be tested in a number of different clinical settings. Results in some sites were disappointing, but others have appeared very promising and phase III studies are currently ongoing.

Several studies in NSCLC patients with Xyotax have been completed. In contrast to Abraxane, the results of clinical trials of Xyotax in patients with advanced NSCLC were disappointing. Richards et al. performed a single-arm phase II study of Xyotax as first-line treatment for patients with advanced or metastatic NSCLC.[238] Twenty-six patients were treated with 175 mg/m^2 on a q3 week dose regimen. Toxicity was tolerable as there were only two events of grade IV neutropenia (neither febrile) and only three patients experienced

grade III peripheral neuropathy. Response rates were modest as there were only two patients with a partial response (7%) and transient stable disease was achieved in 57% of patients with a median duration of 9 weeks.

Three subsequent phase III trials failed to consistently demonstrate a benefit of Xyotax as compared to standard therapies for advanced NSCLC. The first randomized 849 patients with advanced NSCLC previously treated with platinum-based chemotherapy to either Xyotax (175 or 210 mg/m^2) or docetaxel (75 mg/m^2).[239] There were no differences in median OS (6.9 vs 6.9 months). Time to progression was also unchanged (2 vs 2.6 months). The toxicity profile was different but not necessarily more favorable with Xyotax. NP formulation was associated with less grade III/IV neutropenia or febrile neutropenia, but it was associated with more grade III peripheral neuropathy and more patients in the Xyotax arm had dose reductions or discontinued therapy because of toxicity. A subsequent trial by O'Brien et al. randomized chemotherapy naïve patients with advanced NSCLC and a performance status of 2 (poor performance status) to single agent Xyotax (175 mg/m^2) or single-agent venorelbine or gemcitabine.[240] Grade III/VI hematologic toxicity was reduced in the Xyotax arm (2–3% vs 8–10%). Peripheral neuropathy was more common in the NP-paclitaxel arm but was limited to 3% of patients in that arm. There was no difference in median OS (7.3 vs 6.6 months). Finally, Langer et al. attempted to demonstrate superior survival of carboplatin plus Xyotax over carboplatin plus solvent-based paclitaxel in advanced NSCLC patients.[241] Patients in the NP paclitaxel + carboplatin group had significantly less alopecia, arthralgias, myalgias, and cardiac events. However, they had more grade III/IV neuropathy and hematologic toxicity. Further, there were no differences in median PFS (3.9 vs 4.6 months) or OS (7.9 vs 8 months). The results of these trials were largely disappointing, and interest in the use of polyglutamic acid conjugated paclitaxel for lung cancer has largely subsided. There is a completed phase II study investigating the combination of Xyotax (Opaxio) and pemetrexed (NCT00487669) in advanced NSLC patients, and results are pending. Otherwise, there are no ongoing trials in the lung cancer setting.

Ovarian cancer is a disease for which improvements in the therapeutic ratio of paclitaxel may be particularly useful. The management of epithelial ovarian cancer includes a combination of paclitaxel and platinum (generally carboplatin).[242] Despite intensive therapy, long-term survival for ovarian cancer remains quite poor and treatment can be fairly toxic. There has been excitement that the use of NP formulated paclitaxel could lead to improved outcomes for patients with ovarian cancer.

Several phase I studies have demonstrated the feasibility of polyglutamic acid NP formulated paclitaxel with platinum drugs. Nemunaitis et al. conducted a phase I study of q3 week CT-2103 (Xyotax) (175–250 mg/m^2) with carboplatin (AUC 5-6) in 22 patients with treatment refractory advanced solid tumors.[243] The only observed grade IV toxicity was neutropenia, which was seen in nine patients. Several patients had significant thrombocytopenia, which was attributed to carboplatin and resolved with dose reduction of carboplatin. No patients required dose reductions of Xyotax, and the MTD was determined to be 225 mg/m^2. Three patients demonstrated partial responses on this therapy. Interestingly, all three of these patients had advanced ovarian cancer, which had previously

failed taxane therapy. Another study treated 44 patients with advanced solid tumors with q3 week cisplatin (75 mg/m^2) in combination with Xyotax and made similar observations.[244] Combined therapy was relatively well tolerated, and they observed partial responses in nine patients.

Morgan et al. conducted a Gynecologic Oncology Group (GOG)-sponsored phase I study of patients with chemotherapy naïve ovarian, peritoneal, or fallopian tube carcinoma.[245] All patients were postsurgical but optimal resection was not required. All patients were treated with q3 week carboplatin (AUC 6) and poliglutamex paclitaxel. The first 11 patients were involved in a dose finding study. Dose was initially 225 mg/m^2. However, two out of three patients at this dose experienced grade IV neutropenia, and the dose was reduced to 175 mg/m^2 and then to 135 mg/m^2 when two of five patients also had grade IV neutropenia. No DLTs were observed in the three patients treated at 135 mg/m^2, and this dose was then used in the feasibility study. Twenty patients then completed the feasibility study. Hematologic toxicity was significant but manageable. 95% (19 of 20) of patients experienced grade IV neutropenia, but only three of these lasted longer than a week or involved febrile neutropenia. There were three cases of grade II and only one case of grade III peripheral neuropathy. Overall, 16 of 20 patients completed 6 cycles of therapy. Response to therapy was encouraging. Of the 20 patients treated, 16 had measurable CA-125 and 10 had measurable disease at the start of chemotherapy. There was one radiographic complete response and three partial responses. In terms of CA-125, 75% of patients had complete responses, and the remaining 25% had partial responses to therapy. A subsequent phase II study from the GOG in recurrent/persistent ovarian or primary peritoneal cancers demonstrated that q3 week single agent-poliglumex paclitaxel had some efficacy in tumors that were taxane or platinum resistant.[246] One additional phase II study involving patients heavily pretreated with prior chemotherapy demonstrated promising efficacy but higher than expected (15%) grade III peripheral neuropathy.[247] There is currently an ongoing GOG (GOG-0212) phase III trial comparing the efficacy of maintenance Taxol versus poliglumex paclitaxel or observation in patients who have an initial complete response to taxane + platinum therapy (NCT00108745).

Polyglutamic acid conjugated paxlitaxel NPs have also shown clinical promise as radiosensitizers. Chemotherapeutics are frequently used in combination with radiation to improve the efficacy of radiation. The combined use of radiation with chemotherapy has improved clinical outcomes in a number of diseases including head and neck cancer, rectal cancer, and esophageal cancer. Radiation causes cell killing principally through the generation of oxidative damage to cellular structures including DNA. The concurrent use of cytotoxic agents can render cells even less capable of surviving the toxic effects of radiation. Unfortunately, traditional drug delivery methods do not preferentially deliver drug to tumors. Normal tissue cells are also exposed to drug and are rendered more sensitive to radiation, which results in increased normal tissue toxicity. This lack of tumor specific drug delivery has largely limited the clinical translation of radiosensitizers. NP drug delivery offers several advantages over traditional drug delivery, which positions these agents well to improve the clinical utility of concurrent chemoradiation. First, NPs preferentially accumulate in tumors and not normal tissues because of irregular tumor vascularity and relative lack of lymphatic drainage. Second, the slow, controlled drug release with NP

formulation can work synergistically with radiation to improve the efficacy of radiation-induced toxicity.

Preclinical work by Li et al. demonstrated the potential advantage of NP polyglutamic acid formulation of paclitaxel.[248] Mice bearing OCa-1 xenografts were treated with free or NP paclitaxel 24 h after tumor irradiation. Paclitaxel potentiated the effects of radiation and improved tumor growth delay in both formulations. However, at equal doses (60 mg/kg) tumor growth delay was significantly longer following the administration of NP formulated drug than free drug. As compared to radiation alone, the enhancement ratios (tumor growth following radiation and drug treatment/tumor growth following radiation only) for NP formulated and free paclitaxel were 4.4 and 1.6, respectively. They confirmed the improved antitumor efficacy at several doses of radiation (5–15 Gy). They further demonstrated that irradiation increased tumor vasculature permeability (via extravasation of Evens blue dye), which correlated with increased uptake of tritiated paclitaxel following treatment with NP formulated drug. A second preclinical study confirmed that polyglutamic acid-conjugated paclitaxel was a potent radiosensitizer to both single and fractionated radiotherapy in mouse xenograft models.[249] This study further demonstrated NP paclitaxel did not increase radiation-induced hair, skin, or jejunal toxicity (assessed with crypt survival assays). As expected, these preclinical studies demonstrated that NP formulation can improve the therapeutic ratio of paclitaxel chemoradiation.

A phase I study demonstrated the feasibility of weekly polyglutamic acid-conjugated paclitaxel NPs with concurrent radiation in patients with gastric and esophageal cancers.[250] This dose-finding study enrolled 21 patients. All patients were planned to receive 50.4 Gy of radiation. The initial dose of NP paclitaxel was 40 mg/m^2 and was increased in increments of 10. Toxicities, as expected, included gastritis, esophagitis, and neutropenia. Dose-limiting toxicities were seen in three of four patients at 80 mg/m^2 so the MTD was determined to be 70 mg/m^2. Efficacy appeared promising. Twelve of the patients were treated with concurrent therapy for control of loco-regional disease, and, of these, four achieved complete clinical responses.

Promising clinical results were also seen in a phase II study of polyglutamic acid NP paclitaxel concurrent with neoadjuvant cisplatin-based chemoradiotherapy for the treatment of localized esophageal cancer.[251] Forty patients were treated with weekly NP paclitaxel (50 mg/m^2) and cisplatin (25 mg/m^2) concurrent with 50.4 Gy of radiation followed by surgical resection. Treatment was very well tolerated. Grade III esophagitis, nausea, and fatigue occurred between 5% and 7% of patients. Three patients had complete clinical responses to chemoradiation and refused treatment. Of the remaining 37 patients, there were 12 pathologic complete responses to neoadjuvant therapy.

A recent phase II study also attempted to combine polyglutamic acid NP paclitaxel with Temozolomide and radiation for the treatment of grade 3 or 4 gliomas.[252] Twenty-five patients were treated with daily Temozolomide (75 mg) and weekly NP paclitaxel (50 mg/m^2) with daily radiation (6000 cGy in 200 cGy fractions). Seventeen of the patients had GBM, and the median PF and OS were favorable at 11.5 and 18 months. However, seven patients experienced grade IV neutropenia, and the duration of hematologic toxicity lasted

up to 5 months. The authors concluded that toxicity with combined Temozolomide and NP paclitaxel was unacceptably high. However, given the favorable PFS in GBM patients, there is currently an ongoing phase II trial of polyglutamic acid NP paclitaxel with concurrent radiation for the treatment of non-MGMT hypermethylated GBM (NCT01402063). Further, the FDA granted orphan drug status for Opaxio in the treatment of glioblastoma in 2012.

The above studies demonstrate the clear potential for the use of NP formulated paclitaxel as a radiosensitizer. There is an additional ongoing phase I/II trial investigating the combination of polyglutamic acid NP paclitaxel with cetuximab and concurrent radiation in patients with HPV negative SCC of the head and neck (NCT00660218).

4.2. PK1 and PK2

HPMA (*N*-(2-hydroxylpropyl) methylacrylamide) is another polymer that has been utilized for NP formulation. Two versions of HPMA-copolymer-doxorubicin have been developed and completed early phase clinical trials. The first, PK1 (Pfizer Inc.), is doxorubicin conjugated to HPMA by a Gly-Phe-Leu-Gly peptidyl linker. The peptidyl linker is very stable under physiologic pH but is effectively cleaved at low pH's following lysosomal uptake. This drug showed promising results in preclinical animal studies when compared to free doxorubicin.[253–255] A phase I study including 33 patients with metastatic solid tumor malignancies showed the MTD to be 320 mg/m^2.[256] The dose-limiting toxicities were febrile neutropenia and mucositis. Interestingly, common anthracycline-specific toxicities such as cardiotoxicity were not observed despite cumulative doses of 1680 mg/m^2. The plasma half-life was 93 h. Responses were seen in 4/36 patients. A phase II study involving 62 patients with metastatic breast, NSCLC, or colorectal cancer treated patients with 280 mg/m^2 PK-1.[257] The toxicity profile was quite favorable. There were no episodes of grade IV neutropenia, and there was no evidence of cardiotoxicity in any of the patients. However, the clinical efficacy was quite modest. In all, only 6/62 patients showed any clinical response to treatment. All six were partial responders, and all were chemotherapy naive at the time of enrollment.

PK2 (Pfizer Inc.) is a compound similar to PK1 except that it contains additional galactose residues to facilitate hepatic targeting. Preclinical work in rats demonstrated less cardiotoxicity with PK2 than free doxorubicin.[258] A phase I study was completed, which included 31 patients with liver tumors (25 primary, 6 metastatic).[224] Patients were treated with IV infusions every 3 weeks, and dose was escalated from 20 to 160 mg/m^2. The dose-limiting toxicities were again neutropenia and mucositis (in addition to severe fatigue). I^{123}-labeled polymer was also given to patients to measure biodistribution. 24 h following administration, 16.9% of the dose was targeted to the liver with 3.3% in the tumor. Targeting was not observed in particles lacking the galactose residues. The above studies demonstrate the potential for HPMA-conjugated drug–polymers to decrease the systemic toxicity of anthracyclines. To our knowledge, there are no ongoing studies with either PK1 or PK2 at this time.

4.3. CRLX101

Camptothecin is a promising anticancer drug, which works through the inhibition of topoisomerase 1. However, the clinical translation of camptothecin was initially limited by poor drug solubility, poor stability, and high rates of toxicity.[259] To address these issues and improve clinical translation, efforts were made to generate a NP formulation of camptothecin. A cyclodextran-PEG copolymer conjugated to camptothecin has shown a lot of preclinical and clinical promise. Initially marketed as IT-101, this compound is now marketed under the trade name CRLX101 (Cerulean).

Many preclinical studies have been completed showing promising antitumor activity, prolonged drug release, and favorable toxicity profiles.[260–263] Schluep et al. demonstrated that IT-101 had favorable pharmacokinetic and biodistribution profiles as compared to free and unconjugated camptothecin in mice bearing colorectal LS174T xenografts. Maximal AUC plasma concentrations of conjugated polymer were 100-fold higher than unconjugated or free drug, and the plasma half-life was increased from 1.3 to 17–20 h. Further, tumor concentrations of camptothecin were 160-fold higher in mice treated with conjugated drug. Conjugated drug was also more efficacious against several tumor lines in vitro as well as multiple lymphoma xenografts in vivo.

Feasibility in humans was established during an initial phase I/IIa clinical study of patients with heavily pretreated advanced solid tumor malignancies.[264] Patients were initially treated with weekly escalating doses of CRLX101 (6, 12, or 18 mg/m^2). Pharmacokinetic data suggested that biweekly dosing would be better tolerated, and dosing was switched to biweekly drug administration at doses of 12, 15, and 18 mg/m^2. The most common toxicity was myelosuppression. Several patients treated with weekly drug experienced grade IV hematologic toxicity, whereas only one grade IV hematologic toxicity was observed with biweekly dosing. The MTD was determined to be 15 mg/m^2 biweekly, and 44 patients were treated at this dose for the phase IIa portion of the study. CRLX101 showed some efficacy as 64% of patients had transiently stable disease with median time to progression of 3.7 months. An additional study correlated CRLX101 treatment with decreased expression of multiple genes (including topoisomerase 1, K_i-67, VEGF, etc.) associated with decreased survival in multiple human tumors.[265]

A number of ongoing clinical trials are now trying to build upon the early preclinical and clinical success of CRLX101. There are phase I/II studies of CRLX101 in combination with bevacizumab in patients with advanced RCC (NCT01625936, NCT02187302) or recurrent ovarian/tubal/primary peritoneal carcinoma (NCT01652079). There is a two-arm phase II study comparing CRLX101 and topotecan for the treatment of recurrent small cell lung cancer (SCLC) (NCT01803269). Several studies are investigating CRLX101 as single agents in the treatment of advanced NSCLC (NCT01380769) or unresectable gastric or esophageal tumors (NCT01612546). Finally, there is also an ongoing phase I/II trial of neoadjuvant CRLX101 and capecitabine combined with concurrent radiotherapy for the treatment of advanced rectal cancers (NCT02010567). The phase I dose-finding studies have been completed, and phase II studies are currently ongoing.

4.4. CRLX301

Cerulean, the same company that developed CRLX101, has also developed CRLX301, a polymeric nanoparticle conjugate of docetaxel (Taxotere). The company has undertaken preclinical studies looking at tumor responses of seven xenograft models of human cancers and reported greater inhibition of tumor growth in 5/7 tumor lines treated with CRLX301 compared to Taxotere.[266] Toxicity is also reduced in CRLX301 as compared to Taxotere. An Australian phase I/II trial in patients with treatment refractory advanced solid tumors is set to begin enrolling patients in the near future.

5. Polymeric Micelles and Nanoparticles

5.1. Polymeric Micelles

5.1.1. Genexol-PM—Genexol-PM (Sorrento Pharmaceutics) is a polymeric micelle formulation of paclitaxel devoid of Cremophor-solvent. This product is also marketed in several countries under the name Cynviloq. The biodegradable amphiphilic diblock copolymer is comprised of monomethoxy poly(ethylene-glycol)-*block*-poly($_{D,L}$-lactide) (mPEG-DDLLA). The first published preclinical study compared the in vivo toxicity, efficacy, and distribution of Genoxel-PM to Cremophor-based paclitaxel.[267] Genoxel-PM was much less toxic as both the MTD and the LD_{50} were markedly increased in Genoxel-PM as compared to solvent-based paclitaxel (60 vs 20 mg/kg and 205–221 vs 8.3–8.8 mg/kg, respectively). Given at equal paclitaxel doses, there was no difference in the plasma AUC between the two formulations. However, Genoxel-PM treated animals had 2–3-fold higher paclitaxel concentrations in heart, lungs, kidneys, and spleen. Importantly, Genoxel-PM also resulted in 2-fold higher levels of paclitaxel in tumors (B16 melanoma). Genoxel-PM also showed more significant delays in growth of SKOV-3 and MX-1 tumor xenografts in vivo. These studies demonstrated Genoxel-PM, similar to Abraxane, is more efficacious and less toxic than solvent-based paclitaxel.

A phase I clinical trial involving 21 patients with advanced solid tumor malignancies refractory to standard care investigated the toxicity and pharmacokinetics of every 3 week dosing.[268] Doses were escalated between 135 and 390 mg/m^2. Genoxel-PM appeared to have linear kinetics over this range. The most frequent toxicities were myalgia, neutropenia, and neuropathy. No hypersensitivity reactions were noted. Grade III myalgia was noted in 1 patient at 230 mg/m^2 and another at 300 mg/m^2. The MTD was established at 390 mg/m^2 as two out of three patients developed grade IV neutropenia or grade III polyneuropathy. A second phase I trial investigated weekly dosing in 24 Asian patients with solid tumors refractory to standard chemotherapy.[269] Drug was given once weekly for 3 weeks followed by a week of rest. Dose was escalated between 80 and 200 mg/m^2. Grade IV hematologic toxicity was observed at doses of 200 mg/m^2 and the MTD was established at 180 mg/m^2. Clinical efficacy appeared promising as 14 of the patients had partial responses or stable disease.

Several phase II trials have been conducted and have demonstrated generally positive results. Lee et al. conducted a single-arm trial of every 3 week Genoxel-PM (300 mg/m^2) in patients with metastatic breast cancer.[270] The overall response rate was 60% and median

time to progression was 9 months. Grade III neuropathy was noted in 51% of patients. Two patients also had grade III acute hypersensitivity reactions. A second phase II study involved 69 patients with advanced NSCLC who had not received prior chemotherapy for their lung cancer.[271] Patients received Genoxel-PM (230 mg/m^2) and cisplatin (60 mg/m^2) on every 3 week cycles. Genoxel-PM dose was escalated to 300 mg/m^2 on subsequent cycles in patients not experiencing grade III or higher toxicity (47% of patients). Overall response rate was 37.7% and median time to progression was 5.8 months with median OS of 21.7 months. Toxicities were generally mild. Peripheral neuropathy was the most frequent grade II toxicity (13.0%). It is worth noting that two patients experienced grade IV hypersensitivity reactions. A third single-arm phase III study investigated Genoxel-PM + gemcitabine as first line treatment for advanced NSCLC.[272] Forty-three chemotherapy naive patients were treated with Genoxel-PM (230 mg/m^2) and gemcitabine (1000 mg/m^2) on days 1 and 8 of a 3 week cycle. Median number of cycles received was 4, with an overall response rate of 46.5%. Median progression free survival and overall survival were 4.0 and 14.8 months, respectively. Grade III/IV neutropenia was observed in seven patients (16%) with two fatal pneumonias reported.

Given these favorable results, and those with Abraxane, Genoxel-PM has been approved for the treatment of metastatic breast cancer and advanced NSCLC in South Korea. Preliminary data from a South Korean phase III trial appear to demonstrate superior efficacy over solvent-based paclitaxel in the treatment of metastatic breast cancer. Genoxel-PM has not been approved by the FDA, although additional trials are ongoing in the United States.

5.1.2. NK012—NK012 (Nippon Kayaku Co. Ltd.) is a polymeric NP formulation of SN-38, a biologically active metabolite of CPT-11 (irinotecan). The conversion of CTP-11 to SN-38 is mediated by hepatic carboxylesterases, with a metabolic conversion rate of under 10% of the total volume of CPT-11.[273] With such a low conversion rate, the generation of SN-38 was quite attractive. NK012 is formed by the aqueous self-assembly of amphiphilic block copolymers of PEG-poly glutamic acid covalently bound to SN38 by an ester bond. The hydrophobic SN-38 bound PGA (poly(L-glutamic acid)) forms the core of the micelle and is protected from uptake and degradation. Cleavage of SN-38 from PGA occurs slowly by the process of hydrolysis under physiologic conditions leading to stable, prolonged drug release over many hours. A number of preclinical studies have demonstrated activity against a number of tumor types including pancreatic cancer, glioma, NSCLC (non-small-cell lung cancer), RCC (renal cell carcinoma), and gastric cancer.[273–277] NK012 has been studied in two phase I trials. The first examined pharmacokinetics and toxicity in 24 patients with advanced solid tissue malignancies refractory to standard therapy.[278] Patients were treated every 3 weeks. Dose was escalated from 2 to 28 mg/m^2. One of nine patients in the 20 mg/m^2 arm experienced transient grade IV neutropenia. No grade IV toxicity was seen at 24 mg/m^2 and 2/8 patients had grade IV neutropenia at 28 mg/m^2, which was determined to be the MTD. SN-38 release was slow and controlled with a terminal phase half-life of approximately 210 h independent of dose. A second phase I study found similar results with an MTD of 37 mg/m^2. Several other phase I trials have been completed with results pending. In the U.S., there is an ongoing single-arm phase II trial of NK012 (28 mg/m^2 every 28 days) as single agent therapy in relapsed, metastatic triple negative breast

cancer patients (NCT00951054). Another single-arm phase II study in patients with relapsed SCLC has completed accrual (NCT00951613). There is also an ongoing phase II colorectal trial in Japan.

5.1.3. NK105—NK105 (Nippon Kayaku Co. Ltd.) is a polymeric micellar formulation of paclitaxel consisting of PEG and modified polyaspartate as a hydrophobic block. Similar to Abraxane, NK105 is a NP formulation of paclitaxel which is devoid of solvents including Cremophor EL. NK105 was developed to improve the therapeutic index of paclitaxel therapy. This preparation has shown promising potential in several preclinical studies.[279,280] As compared to solvent-based paclitaxel, NK105 showed greater radiosensitization in lung tumors and greater cytotoxicity for several cancer cell lines in vitro. Further, plasma paclitaxel AUC was 90-fold higher with NK105 than solvent-based preparations with a 25-fold higher tumor AUC. Neurotoxicity was also decreased in mice treated with NK105 as compared to Taxol. A dose-finding phase I study was undertaken by Hamaguchi et al.[278] Nineteen patients were treated every 3 weeks with doses escalated from 10 to 180 mg/m^2. Neutropenia was the most common toxicity and occurred in three patients at the 180 mg/m^2 dose (1 grade III, 2 grade IV). There were no events of peripheral neuropathy. There was one episode of grade 2 acute hypersensitivity reaction. Maximum plasma AUC and Cmax increased in a dose-dependent manner. A phase II study demonstrated clinical efficacy in patients with advanced gastric cancer that had failed at least one line of chemotherapy. 57 patients were treated with q3 weeks NK105 (150 mg/m^2). The ORR was 25% with median PFS of 3 months and median OS of 14.4 months. In the U.S., there is currently an ongoing randomized phase III trial of NK105 versus Taxol for the treatment of advanced or metastatic breast cancer (NCT01644890).

5.1.4. SP1049C—Another polymeric NP currently under clinical investigation is a polymeric formulation of doxorubicin called SP1049C (Supratech Pharma Inc.). This NP consists of a mixture of proprietary block copolymers (Pleuronic L61 and F127). Doxorubicin is quite hydrophobic and readily encapsulated in the hydrophobic core of the micelles. Several preclinical studies have demonstrated improved antitumor efficacy as compared to doxorubicin in mouse models of myeloma and leukemia.[281–283] The drug was found to be well tolerated in a dose-finding phase I study.[284] In this study, 26 patients with tumors refractory to other therapy were treated with escalating doses of SP1049C (5–90 mg/m^2). The primary toxicities were hematologic. Grade III–IV neutropenia was seen in one of seven patients at 35 mg/m^2 and increased to four of seven patients at 90 mg/m^2. The recommended MTD for future phase II studies was 70 mg/m^2. It is worth noting that four patients also had >20% fall in their EF while on trial. Pharmacokinetics followed an appropriate linear dose–response increase. This was followed by a phase II study in patients with advanced chemotherapy naive esophageal and GE junction tumors.[285] Twenty-one patients were treated with every 3 week SP1049C (75 mg/m^2). The overall response rate was 47% with median PFS and OS of 6.6 and 10 months, respectively. Toxicity was primarily hematologic. Measurable declines of at least 15% in left ventricular ejection fraction (LVEF) were noted in four patients, but none of these were symptomatic or resulted in a LVEF of <45% of baseline. SP1049C has been granted orphan drug status for gastric cancer by the FDA, and phase III trials are under development.

5.1.5. BIND-014—Most available NP carriers are nonspecific in that they do not directly target any specific tissues. They are semiselective in that they take advantage of abnormal tumor physiology, including tumor vasculature, to preferentially accumulate in tumors with limited access to normal tissues. In an effort to improve specificity, a number of groups have attempted to generate targeted NPs, and possess some inherent cell type specificity. This can be accomplished by the conjugations of epitopes/biologically targeted ligands to the NP surface. One such nanoparticle that has entered clinical development is BIND-014 (Bind Therapeutics). It is a polymeric NP formulation of docetaxel, which is conjugated to a ligand targeting the extracellular domain of prostate-specific membrane antigen (PSMA), a protein specific to prostate cancer cells. An initial study by Hrkach et al. investigated the development of PSMA targeted docetaxel NPs.[286] They used a combinatorial approach to optimize the biodistribution and pharmacokinetics of PSMA targeted docetaxel NPs for chemotherapeutic benefit in metastatic prostate cancer. Biodistribution and drug release studies demonstrated controlled drug release with lower concentrations in liver and bone marrow than in plasma. Toxicity studies demonstrated no increased risk of hypersensitivity reactions or toxicity to high dose targeted versus nontargeted NPs in rats. Mice bearing LNCaP prostate cancer xenografts demonstrated greater delays in tumor growth following the administration of targeted docetaxel NPs than with either untargeted docetaxel NPs or solvent-based docetaxel. When tested against nonprostate tumor xenografts, they observed a similar efficacy between targeted and nontargeted NPs, both of which appeared more efficacious than solvent-based docetaxel. An additional study has also demonstrated improved antitumor efficacy of targeted versus nontargeted docetaxel NPs in several prostate cancer cell lines.[287]

The clinical translation of BIND-014 is ongoing. Interim data from a phase I study (NCT01300533) in patients with advanced solid tumors have demonstrated some antitumor activity at doses of 75 mg/m^2.[288,289] Several phase II studies are also ongoing in patients with metastatic prostate cancer (NCT01812746) or NSCLC (NCT01792479, NCT02283320).

5.1.6. Nanoplatin (NC-6004)—As mentioned above, cisplatin (*cis*-diamminedichloroplatinum, CDDP) is a frequently utilized chemotherapeutic agent. NP formulation provides a rational approach to improve the therapeutic index of platinum therapy. Nanoplatin (NC-6004, NanoCarrier Co. LTD) is a polymeric micellar formulation of cisplatin. Several preclinical studies demonstrated the potential advantages of Nanoplatin over free cisplatin. One early study demonstrated a more favorable pharmacologic and toxicity profile in rats.[290] The plasma AUC for Nanoplatin was 65-fold higher with a clearance value 1/19th that of free cisplatin. Tumor efficacy was equivalent. However, nephrotoxicity and neurotoxicity (sciatic nerve injury) were significantly reduced by NP formulation. Notably, there was transiently increased hepatotoxicity noted in the rats treated with Nanoplatin, which was not observed in cisplatin treated rats. A second study demonstrated reduced ototoxicity in guinea pigs.[291] Unlike cisplatin, Nanoplatin did not induce changes in auditory brainstem responses, sensory hair cell loss, or platinum distribution in the organ of Corti. Another study demonstrated improved in vivo tumor

growth delay with less nephrotoxicity in mice with OSC-19 bearing human oral SCC xenografts.[292]

Published results are available for a phase I study of Nanoplatin.[293] This study included 17 patients with advanced solid tumor malignancies treated with escalating doses (10–120 mg/m^2) of NC-6004 given as every 3 week treatments. The drug was relatively well tolerated. However, after noting evidence of nephrotoxicity and hypersensitivity reactions early in the phase I trial, all remaining patients were treated with aggressive hydration and premedication (dexamethasone, chlorphenamine, and ranitidine). Despite this, two transient grade II renal toxicities were observed at 90 mg/m^2, and several grade II/III renal and hypersensitivity reactions were noted at 120 mg/m^2. The recommended dose for additional phase II studies was 90 mg/m^2. Pharmacokinetics were linear and dose responsive, and Nanoplatin showed delayed and sustained release of cisplatin. There are currently several ongoing clinical trials of Nanoplatin. There is an ongoing phase I/II study of Nanoplatin and gemcitabine for advanced solid tumor and NSCLC (NCT02240238) and two phase III trials of gemcitabine versus gemcitabine + Nanoplatin with advanced or metastatic pancreatic cancers (NCT00910741, NCT02043288).

5.1.7. NC-4016—Oxaliplatin, like its other platinum siblings cisplatin and carboplatin, is a DNA cross-linking agent with potent antitumor activity to a broad range of tumors.[294] NC-4016 (NanoCarrier Co. LTD) is a polymeric NP formulation of oxaliplatin that has demonstrated promising preclinical data and is under further clinical development.[295] The investigators demonstrated that NP formulation improved in vivo tumor growth delay in xenograft models when compared to small molecule oxaliplatin. Further, free oxaliplatin induced significant peripheral neuropathy as measured by cold hyperalgesia and allodynia, whereas NP-formulated oxaliplatin did not. This study demonstrated an improved therapeutic index of oxaliplatin by NP formulation. Similar results were obtained in a second preclinical study.[296] A phase I dose-finding study in patients with advanced cancers or lymphoma is currently underway (NCT01999491).

5.1.8. NK911—NK911 (Nippon Kayaku Co. Ltd.) is a polymeric formulation of doxorubicin. It has shown promising preclinical results of improved tumor accumulation of doxorubicin as compared to free drug with improvements in antitumor activity in vivo.[297] When compared to liposomal doxorubicin (DOXIL), NK911 appears to be less stable with more drug release with accumulation of doxorubicin in both spheroid outer layers and centers.[298] One interpretation of these data is that DOXIL may be more efficient at delivering drugs to tumors near the vasculature, whereas NK911 may better expose cells further removed from the blood vessels by improved diffusion. A phase I dose-finding study in 23 patients with advanced solid tumors has been completed.[299] Neutropenia was the predominant toxicity, and several instances of grade IV neutropenia were observed in patients treated with 67 mg/m^2. The recommended dosing for phase II studies was 50 mg/m^2. Other side effects included nausea and vomiting. Pharmacokinetics demonstrated dose-dependent increases, as expected. Ongoing phase II studies in solid tumors have been proposed, but to our knowledge there are no trials actively accruing patients at this time.

5.1.9. Paclical—Paclical (OAS-PAC-100, Oasmia Pharmaceutical AB) is a micellar formulation of paclitaxel encapsulated in the proprietary retinoid compound XR-17 and devoid of Cremophor EL. Preclinical studies demonstrated promising results, and the FDA granted orphan status in 2009 based on the hypothesis that Paclical was safer than Taxol. Paclical has completed a phase III trial in patients with recurrent ovarian, primary peritoneal, or fallopian tube carcinomas (NCT00989131). The parent company, Oasmia, has filed for application in Russia pending results of the completed phase III trial. No publications or public information are available on this therapeutic.

5.2. Dendrimers

Dendrimers are likely to become a very important class of NP delivery vehicles as they represent a chemically interesting and burgeoning field. The term dendrimer refers to branched or dendrimeric polymers. Dendrimers are comprised of conventional monomers generated by the iterative addition of concentric branched layers (frequently referred to as generations) around a central core. The addition of successive generations results in highly amplified, organized, and mathematically defined surface sites. The resulting overall structure has four principal regions: a core scaffold, interior layers, terminal surface groups attached to interior layers, and void spaces. The highly controlled generational growth process allows for the generation of NPs with precise control over size, shape, elemental composition, and surface properties. Several recent reviews very nicely detail the process of dendrimer generation and chemistry.[300,301]

Given the precise control over specific NP properties afforded by dendrimer generation, it is unsurprising that these highly adaptable platforms represent an active area of research as drug delivery vehicles. Dendrimers can be formulated for delivery via parenteral, transdermal,[302] intraocular,[303] and oral[304] administration routes. Dendrimeric platforms have been developed to target inflammation, infectious disease, cancer, wound healing, and ocular diseases as well as for use in theranostic applications. A detailed review of preclinical studies is beyond the scope of this Review but was outlined very nicely in a recent review.[300] To date, one dendrimeric NP formulation, Vivagel, has completed phase III investigation, and we will review that here in more detail.

5.2.1. Vivagel—Preclinical work from the 1990s–2000s demonstrated the proof of principle that polyanionic compounds, including sulfated polymers, can have potent antiviral activity against enveloped viruses including HIV and HSV.[305,306] The generation of synthetic polyanionic compounds by traditional chemical processes is fairly difficult. However, the controlled generation of many such compounds as dendrimers was undertaken by Starpharma (Melbourne, Australia) in the early 2000s. They generated a library of polyanionic dendrimers with the goal of identifying effective antiviral compounds for the clinical development of drugs to prevent the transmission of sexually transmitted infections (STI). A number of these dendrimeric compounds showed potent antiviral activity. The lead compound identified was SPL7013, an anionic G4-poly(L-lysine)-type dendrimer displaying 32 napthalene disulfonate groups on the surface.[307] This was formulated as a topical vaginal gel. Early preclinical studies in pig-tailed macaques demonstrated that 5% (w/w) SPL7013 protected 100% of the monkeys from infection via intravaginal infection of simian-human

immunodeficiency virus (SHIV).[308] Further preclinical studies demonstrated activity against HSV1 and HSV2 in vitro.[309] In June 2003, an FDA investigational new drug application was submitted for SPL7013, marketed as Vivagel. This was the first IND application submitted for a dendrimeric compound.

The first phase I study of Vivagel demonstrated that intravaginal administration was well tolerated.[310] Thirty-eight women were treated with 0.5%, 1%, or 3% Vivagel or placebo daily for 7 days. Mild symptoms including mild abdominal pain, vaginal burning, and vaginal itching were observed between 11% and 25% of patients in each group (including 25% in the control group). A second phase I study attempted increasing to twice daily administration of 3% gel.[311] Again, this was fairly well tolerated but mild symptoms were more frequently reported in the Vivagel than control groups (71% vs 53%) as were more frequent mild colposcopic irregularities (83% vs 53%) including cervical erythema. The latter observation is quite concerning as any degree of mucosal breakdown or lymphocyte recruitment could be potentially problematic as loss of mucosal integrity could favor viral transmission. Indeed, a follow up phase I study demonstrated small but reversible increases in markers of vaginal inflammation including vaginal mucosal cytokine and lymphocyte levels during a 14 day course of twice daily 3% Vivagel.[312] While inflammation following twice daily administration is potentially concerning, another study demonstrated potent antiviral activity in cervicovaginal fluids collected from women treated with 5 doses of 3% Vivagel with at least 5 days between doses.[313] At up to 3 h post-treatment, >95% of samples showed near complete antiviral activity. At 24 h, >90% inhibition was observed in 6 of 11 patients. There were no patient-reported vaginal, cervical, or vulvar irritative complaints, although no colposcopic evaluation was made. While these early studies demonstrate that Vivagel can retain antiviral activity in cervicovaginal fluids and is relatively well tolerated, there are no data demonstrating reduced HIV transmission to date. Currently, Vivagel has been formulated as a condom lubricant intended to reduce viral STI infections and is available in Australian markets. Further studies are ongoing to try to expand use in other markets.

Clinical studies performed by Starpharma also demonstrated efficacy against the polymicrobial infection bacterial vaginosis. Results of a phase II study in 2011 demonstrated high rates of clinical cure and confirmed test of cure. However, the results of two phase III trials in 2012 were inconclusive (NCT01577537 and NCT01577238). The primary end point of both trials was test of cure with secondary end points of clinical cure (resolution of symptoms). Patients were treated with 1% Vivagel or placebo daily for 7 days. Clinical cure was achieved in 50% and 57% of women treated with Vivagel as compared to just 17% and 21% of placebo treated patients. However, test of cure showed no difference between Vivagel and placebo treated patients in either study (27% vs 21% and 28% vs 28%). Given the lack of statistical benefit in test of cure, a NDA was not filed with the FDA for a bacterial vaginosis indication. However, the increased rates of symptomatic improvement were encouraging, and ongoing studies are underway to attempt to demonstrate significant improvements in decreased risk of bacterial vaginosis recurrence with Vivagel treatment.

6. Inorganic Nanoparticles

6.1. Magnetic Iron Oxide Nanoparticles

Iron oxide nanoparticles exemplify the unique properties that can result from formulating materials on nanoscale. Iron oxide nanoparticles possess a superparamagnetic property, which is not present in other iron oxide materials.[314] In the presence of an external magnetic field, superparamagnetic iron oxide nanoparticles (SPIONs) can provide strong paramagnetic signals at very low doses (Figure 5), which make them excellent contrast agents in magnetic resonance imaging (MRI). In addition, these agents can also produce heat and have been evaluated as clinical hyperthermia agents.[315]

6.1.1. Ferumoxtran-10—Ferumoxtran-10 (AMI-227, AMI 227CN, AMI 27, G 53425, BMS 180549, Combidex, Sinerem) is an ultrasmall SPION (USPIO) that has been extensively studied as a MRI contrast agent. The agent is comprised of an iron oxide core, which is 10–20 nm in diameter, coated by dextran T-10.[316] Ferumoxtran-10s preclinical development started in the late 1980s and early 1990s. In one study in rats and rabbits, the investigators demonstrated that Ferumoxtran-10 can differentiate tumor deposits from bone marrow.[317] Subsequent preclinical studies showed that Ferumoxtran-10 is an excellent agent for MR lymphography, which established its clinical translation path forward as a lymphotrophic MR contrast agent.[318] For this clinical application, Ferumoxtran-10 is a negative contrast agent as it enhances the normal tissue (lymph nodes) and identifies the disease process (no enhancement) by negative contrast.

In an open-label, placebo-controlled phase I investigation of Ferumoxtran-10, 41 healthy volunteers were given Ferumoxtran-10.[319] The investigators reported no postdose change in physical exams, vital signs, or electrocardiogram. In addition, they did not see any significant changes in clinical laboratory results. However, they did note 14 adverse events that were considered “not serious”.

One of the first clinical experiences of Ferumoxtran-10 studied its safety and effectiveness as a MR contrast agent in patients with urologic and pelvic cancer who had suspected lymph node metastases.[320] 30 patients underwent standard MR imaging followed by repeat imaging with Ferumoxtran-10. 60 histologically confirmed lymph nodes were correlated/analyzed on MRI images. The investigations found that Ferumoxtran-10 was well tolerated and it detected 10 additional pathologic nodes than standard MR imaging. The sensitivity of Ferumoxtran-10 imaging was 100% but specificity was 80% in this study. Over the following decade, Ferumoxtran-10 has been studied for MR imaging of multiple body sites, including liver,[321,322] pelvis,[322] cardiac imaging,[323] mediastinum,[324] and head and neck.[325] The general findings are that Ferumoxtran-10 can improve the sensitivity of lymph node MR imaging.

The most high profile clinical study of SPIONs was a trial evaluating Ferumoxtran-10 in detection of lymph-node metastases in prostate cancer.[326] 80 patients with high risk (clinically localized) prostate cancer underwent Ferumoxtran-10 MR imaging before and after surgical resection of the prostate with lymph node biopsy or dissection. 334 lymph nodes were identified on surgery. 63 nodes (18.9%) from 33 patients had pathologically

confirmed metastases. Of these 63 nodes, 45 (71.4%) did not fulfill the usual imaging criteria for malignancy. MRI with lymphotropic superparamagnetic nanoparticles correctly identified all patients with nodal metastases, and a node-by-node analysis had a significantly higher sensitivity than conventional MRI (90.5% vs 35.4%, $p < 0.001$). More importantly, Ferumoxtran-10 significantly improved the positive and negative predictive values of identifying a malignant lymph node, which are the most clinically relevant test characteristics.

Because of the large number of clinical trials with Ferumoxtran-10, its safety profile is also well established. In a comprehensive analysis of 37 clinical trials that included 1777 patients, 23.2% of patients reported some kind of adverse event.[327] The most commonly reported treatment-related adverse events were back pain, pruritus, headache, and urticaria. Only seven serious adverse events (SAEs) (0.42%) were considered to be treatment-related (anaphylactic shock, chest pain, dyspnea, skin rash, oxygen saturation decreased, and two cases of hypotension). There were 12 deaths, only one of which (anaphylactic shock) was considered to be related to ferumoxtran-10, which was administered by bolus injection of undiluted product, a mode of administration that is no longer recommended.

Despite the strong clinical data, Ferumoxtran-10 was not approved by the FDA. Instead of requesting approval for a narrower indication, Ferumoxtran-10 application requested broad approval for imaging lymph nodes throughout the body. While the clinical data mostly support this request, the broad indication caused concerns from the regulatory body. Another issue was the single patient who died from anaphylactic shock. This raised safety concerns even though the data indicate the drug is quite safe (see above). Last, the low level of financial incentive for contrast agents prevented the agent from further development after the initial rejection. To this day, there is no approved SPION for MR imaging.

6.1.2. Dextran-Coated Iron Oxide NPs (Sienna+)—Similar to Ferumoxtran-10, Sienna+ is also a dextran coated SPION that is lymphotropic. Instead of systemic administration, Sienna+ is given locally for detection of sentinel lymph nodes (SLN). It is combined with a hand-held device that can detect Sienna+. It competes with radioisotope and dye-based SLN detection technologies and is marked as a device. In a clinical study on detection of SLN in breast cancer, Sienna+ was compared to the "gold standard" radioisotope (^{99m}Tc).[328] The study was a multicenter prospective trial with a noninferiority design. It accrued 150 patients and detected 291 SLNs, with a detection rate per patient of 97.3% (146/150) for ^{99m}Tc versus 98.0% (147/150) for Sienna+. The investigators concluded that Sienna+ can be performed easily and is noninferior to ^{99m}Tc for SLN detection. The agent has been approved by the European Commission (CE) in 2011, and U.S. studies are ongoing.

6.1.3. Aminosilane-Coated Iron Oxide NPs (MFL AS1)—As mentioned earlier, SPIONs can also be used for hyperthermia therapy, a potential treatment modality for cancer.[329] One SPION formulation, an aminosilane coated SPION (MFL AS1), has been studied clinically for this application. Preclinical data showed that MFL AS1 can produce sufficient elevations in temperature under a magnetic field, and the hyperthermia effect can reduce tumor growth.[330,331]

MFL AS1 has been studied clinically in locally recurrent prostate cancer and recurrent glioblastoma multiforme (GBM). In a prospective phase I study, MFL AS1 was injected into the prostates of 10 patients with biopsy proven locally recurrent prostate cancer.[332] Maximum temperature of 55 °C was achieved. However, the agent also caused high skin temperatures (up to 44 °C), which led to patient discomfort. No systemic toxicity was observed, although four patients had urinary retention. Median duration of PSA-control was only 4.5 months.

In a single-arm phase II study, 66 patients with recurrent GBM received intratumoral instillation of MFL AS1. Hyperthermia sessions were sequenced immediately before or after fractionated radiotherapy.[333] The primary study end point was overall survival following diagnosis of first tumor recurrence (OS-2), while the secondary end point was overall survival after primary tumor diagnosis (OS-1). Median OS-1 was 23.2 months and only tumor volume at study entry was significantly correlated with ensuing survival ($P < 0.01$). The only significant toxicity appeared to be grade 1–3 thermal stress in six patients. MFL AS1 remains under clinical investigation for GBM.

6.1.4. Siloxane-Coated Iron Oxide NPs (Ferumoxsil)—Siloxane-coated SPIONs have demonstrated clinical utility as oral MRI contrast agents. AMI-121 is a NP formulation of iron oxide crystals (each 10 nm), which aggregate to form 300 nm particles. These particles are coated in the inert siloxane, which helps to prevent iron absorption by interfering with the uptake of iron from the GI tract. The microcrystalline structure retains its supraparamagnetic properties, including loss of signal in the presence of an external magnetic field and shortening of the T2 relaxation time.

The preclinical studies of Ferumoxsil (AMI-121) appeared positive, as they did not show any evidence of mutagenicity in rats using the Ames test. The drug appeared safe, as the MTD in rats and dogs was approximately 1000 times the dose that was ultimately used in the clinical trial. The first clinical study conducted with Ferumoxsil (AMI-121) included 15 healthy adult men.[334] This study also incorporated preclinical data of the potential for mutagenicity, MTD, and fecal clearance. Approximately 91% of the material was recovered in stool, with 87% being recovered within 72 h. In the clinical portion, healthy volunteers were given doses of AMI-121 ranging from 22.5 to 225 mg and imaged with abdominal MRI of 0.6 or 1.5 T. AMI-121 proved a successful oral contrast agent in this study. Delivery throughout the stomach and small bowel (proximal through distal) was achieved in every subject. The enhanced images showed improved delineation of nonbowel organs (comparing pre vs post contrast enhancement) including the pancreas (both head and tail), paraaortic lymph nodes, and anterior kidneys. Importantly, this formulation did not appear to produce any noticeable artifacts. AMI-121 was relatively well-tolerated, producing transient diarrhea in 5 out of 15 patients, but no serious adverse events. Subsequent results from a small multicenter phase III study were positive as well.[335] The phase III study included 20 patients with gynecological indications for pelvic MRI, including cervical cancer staging, suspected recurrent ovarian cancer, or other gynecological malignancies. Patients were given 600–900 mL of Ferumoxsil over a 60 min interval. Of note, 13 patients were treated with hyoscinbutyl bromide to decrease artifact by decreasing peristalsis. As compared to precontrast, Ferumoxsil contrast significantly improved contrast scores in the small bowel

and cecum. However, improvement in the colon was more limited and only significant on T2 weighted imaging. There was improved delineation of pelvic organs, including the uterus and adnexa. Improved delineation of the bladder was limited to the T2 weighted images. Lesion delineation, including identification of local lymphadenopathy, was significantly improved, and MRI diagnosis matched surgical diagnosis in 17 patients. There were no serious adverse events. Interestingly, there was no vomiting or diarrhea within 24 h of consumption. The main patient complaint was the contrast flavor, which limited 19 out of 20 women from consuming all 900 mL (although all completed the minimum of 600 mL).

A subsequent study compared the sensitivity and specificity of Ferumoxsil with oral contrast enhanced CT scan for the detection of suspected gastrointestinal tract lesions.[336] Thirty patients with known or suspected GI disease enrolled in this study. All patients received MRI with Ferumoxsil oral contrast and CT with oral contrast media (Gastroview solution (Mallinckrodt Medical, Inc., St. Louis, MO) or E-Z-Cat (E-Z-EM, Inc., Westbury, NY)). As compared to oral contrast CT, Ferumoxsil-enhanced MRI was less sensitive (67% vs 83%) but more specific (89% vs 68%). A total of eight confirmed abnormalities were detected by both modalities. Eleven abnormalities were detected only on CT and four were detected only on MRI. All four lesions detected on contrasted MRI only were in the duodenum and small bowel. Surgical diagnosis demonstrated six false positives on CT as compared to only 2 on Ferumoxsil-contrasted MRI. Therefore, FDA approval was granted for oral Ferumoxsil to image the upper GI tract in 1996.

Looking to improve the efficacy in the lower GI tract (sigmoid colon, rectum) and pelvis, another group used Ferumoxsil as a rectal contrast to image pelvic organs with promising results.[337] This phase III study included 20 patients (16 women, 4 men) with suspected rectosigmoid or ovarian masses. After a precontrast scan, 300–600 mL of contrast was given rectally (average of 481 mL). Delineation was significantly improved for all images of the rectum, rectosigmoid, and sigmoid colon. Delineation of all pelvic organs, including lymphatics and vessels, excluding the prostate ($N = 4$ for male patients), was significantly improved with Ferumoxsil contrast. There were no adverse events reported. Correctness of diagnosis was enhanced with Ferumoxsil contrast. Six of 13 patients with ovarian cancer had bowel involvement at time of surgery; noncontrast MRI correctly predicted three of the six (50%), whereas contrasted MRI correctly predicted five of the six (83%). Peritoneal implants were detected in six out of seven (86%) and seven out of seven (100%) patients with contrast-unenhanced and enhanced MRIs, respectively. Four patients had colorectal tumors, of which noncontrast MRI only detected two (50%) as compared to all four (100%) with contrast MRI. Readers reported improved diagnostic confidence with postcontrast enhancement in 14 of the 20 patients. To our knowledge, no additional studies have investigated Ferumoxsil as a rectal contrast, and there is no FDA indication for this purpose.

6.1.5. Carbohydrate-Coated Iron Oxide NPs (Ferumoxytol)—Chronic anemia is a symptomatic problem for many adults, particularly those with chronic kidney disease (CKD). The etiologies of anemia in CKD are multifactorial and very well established. These etiologies include loss of endogenous erythropoietin production, blood loss from hemodialysis, and vitamin deficiencies. Chronic anemia tends to worsen as renal function declines. The management of chronic anemia generally involves iron administration, which

is most frequently accomplished with oral iron tablets. However, oral iron replacement is often suboptimal due to its poor absorption and bioavailability.[338] Oral iron causes abdominal discomfort and cramping and is poorly tolerated in some patients. The combination of toxicity and multiple daily dosing often translates to poor patient compliance. For many patients, parenteral (intravenous) iron replacement has been utilized to circumvent these issues, particularly in patients with CKD. Unfortunately, parenteral iron replacement is not without its own limitations. Iron dextran, the first available IV iron formulation, was associated with mild side effects including arthralgias, chills, and myalgia. However, there were also rare incidents of immediate anaphylaxis, which were sometimes fatal.[339–341] Lower molecular weight formulations decreased the incidence of anaphylaxis but not entirely.[342] Newer generations of IV iron formulations include iron sucrose and iron gluconate, which have fewer toxicities but require multiple infusions over relatively long periods of time.

The search for alternative IV iron delivery eventually focused on supramagnetic iron nanoparticles. One of these was ferumoxytol (marketed as Feraheme in the U.S., Rienso in the EU). Ferumoxytol is a supramagnetic iron oxide coated in a carbohydrate shell of polyglucose sorbitol carboxymethyl ether. The resultant colloidal particle ranges in size from about 20 to 30 nm. Ferumoxytol is formulated with mannitol and administered via intravenous injection.[343] It was initially developed as an IV MRI contrast agent. It was well-tolerated and showed promise as an MRI contrast agent in large blood vessels.[344,345] However, it was also recognized that ferumoxytol could also be a useful delivery vector for parenteral iron replacement. The main pharmacologic advantages of ferumoxytol are related to the carbohydrate shell. This helps to physically isolate the iron from other components in the blood. The particles are recognized and taken up via the macrophages in the RES, where the iron is released from the shell within vesicles. From there, free iron can either be transferred to transferrin and utilized by erythroid precursor cells, or the iron can be incorporated into intracellular stores.

The safety and efficacy of ferumoxytol for the treatment of anemia associated with nonhemodialysis-dependent CKD was established initially in a phase II trial.[346] This trial included 21 patients with stage I–V CKD who were either dialysis free (18) or on peritoneal dialysis (3) and were either not receiving EPO-stimulating agents or on stable dosing. Patients had to have hemoglobin (Hb) less than 12.5 and transferrin saturation less than 35%. Patients were dosed with either 4 doses of ferumoxytol 225 mg every 2–3 days or 2 doses of 550 mg separated by 1 week. For safety evaluation, vital signs were monitored at baseline, 15, 30, and 60 min after the injection, and then weekly. Both groups showed significant increases in Hb, reticulocyte counts, ferritin, and transferrin saturation. Peak Hb was observed at 4 weeks for the group treated with 4 doses of 225 mg (median Hb increased from 10.9 to 11.9) and at 5 weeks for the group treated with 2 doses of 550 mg (median Hb increased from 10.0 to 11.0). At 2 weeks, ferritin increased from 252 to 988 and 212 to 885, respectively, for the two groups. Seven patients reported mild symptoms including nausea, pain at injection site, chills, and constipation, but there were no reports of anaphylactic responses. This small study suggested that ferumoxytol could be well-tolerated as a rapid injection and was effective in treating anemia in non-hemodialysis patients with CKD. A subsequent crossover phase III trial compared the safety of IV ferumoxytol (510 mg as a

single injection) versus placebo in 750 patients with stages I–V CKD with Hb between 9 and 12.5.[347] Patients were treated with either ferumoxytol or placebo, followed by the other treatment 1 week later. This study did include dialysis patients who had been on dialysis for at least 90 days prior to randomization. Ferumoxytol was well tolerated. Any adverse event was observed in 21% of patients following ferumoxytol and 16% of patients following saline placebo. The majority were minor, nonspecific toxicities including itching, site reaction, and chills. Serious adverse events were seen in 2.9% of patients after ferumoxytol and 1.8% of patients after placebo. Only one patient had a serious acute anaphylactic reaction to ferumoxytol.

The superiority of ferumoxytol to daily oral iron in nonhemodialysis-dependent patients with CKD was demonstrated in a phase III trial of 304 patients by Spinowitz et al.[348] Eligible patients had stage I–V CKD and iron deficiency anemia with Hb less than 11, ferritin less than 600 mg/dL, and transferrin saturation less than 30%. Patients were randomized 3:1 to receive IV ferumoxytol (510 mg × 2 doses separated by 5 ± 3 days) or oral iron 200 mg daily for 21 days. The primary end point was the increase in Hb on day 35. IV ferumoxytol was more efficacious as the average increase in Hb at day 35 was 0.82 vs 0.16 g/dL with oral iron supplementation. This difference was even more pronounced in patients getting erythropoietin-stimulating agents (1.16 vs 0.19 g/dL). Adverse events were more common in the oral iron group (24% vs 10.6%) with the majority being GI-related (nausea, constipation, etc.). Dizziness was the only adverse event more frequently seen in the ferumoxytol group but was only observed in 1.8% of patients. There were no serious acute events or anaphylactic reactions. Comparable results were obtained in a similarly designed European phase III study.

An additional phase III study demonstrated the superiority of IV ferumoxytol to daily oral iron in 232 hemodialysis-dependent CKD patients with iron deficiency anemia.[349] This study was very similar to that of Spinowitz et al., except that it only included dialysis (stage 5 CKD) patients and patients were randomized 1:1 as opposed to 3:1. The mean Hb increase at 35 days in the ferumoxytol arm was 1.02 g/dL as compared to 0.46 g/dL in the oral iron arm. This difference persisted after adjustment for other factors, including baseline hemoglobin content. As expected, there were more acute mild toxicities in the oral iron group (56% vs 49%) with most of those in the oral group being GI related. Serious adverse events were reported in 12% of patients in each group. There were two episodes of transient hypotension in the ferumoxytol group and none in the oral iron group.

On the basis of positive results in the above trials, the FDA granted approval for ferumoxytol (Feraheme) in the treatment of CKD patients with chronic iron deficiency anemia in 2009. The EMA also granted approval in 2012. Since then, there have been several phase III studies looking to expand the use to patients with iron deficiency anemia of any cause, not only those with CKD. The first compared ferumoxytol in two doses of 510 mg to placebo and showed a favorable toxicity profile.[350] The second compared two different IV iron formulations, ferumoxytol and iron sucrose, in patients who had failed or could not tolerate oral iron therapy.[351] This noninferiority study included 605 patients randomized 2:1 to receive 2 doses of 510 mg ferumoxytol or 5 doses of 200 mg iron sucrose (over 14 days). The primary end point was change in Hb at week 5. Ferumoxytol showed a

superior mean increase in Hb (2.7 vs 2.4 g/dL), and a comparable number of patients achieved an increase of at least 2 g/dL in Hb (84% vs 81%). Patient-reported adverse events were similar (41% and 44%), as were treatment-related side effects (14% and 16%). There were slightly more serious adverse events in the ferumoxytol group (4.2 vs 2.5%), but there were no differences in the rates of expected serious adverse events, including acute cardiovascular complications. Patient-reported quality of life metrics were similar between the groups. A supplemental new drug application has been filed to try to gain FDA approval of ferumoxytol for the treatment of iron deficiency anemia from any cause.

6.1.6. Polystyrene-Coated Iron Oxide NPs (Ferristene)—Another oral magnetic particle formulation utilized clinically was Ferristene. This formulation consisted of ferrite-type iron oxide particles coated with a nondegradable polystyrene resin carrier. The resultant nanoparticles had a mean diameter of approximately 300 nm. Preclinical studies demonstrated that the central moiety retained its supraparamagnetic properties, which were predominantly negative enhancement on T2. The first phase I study demonstrated that Ferristene could be used safely as an oral contrast agent for abdominal imaging but also demonstrated the need for careful dosing.[352] Patients were given 1 L of contrast ranging from 0.05 to 2.5 g/L in concentration. Contrast agent progressed from the stomach to the colon at expected time intervals. The lowest concentration (0.05 g/L) was not sufficient as there was no signal reduction as compared to precontrast, and the highest concentration (2.5 g/L) provided too much iron, which resulted in blurring and metallic artifact. Intermediate doses were somewhat improved but not without problems. The 0.1 g/L concentration only produced minor artifact in one out of nine patients, but it was only sufficient as a contrast agent in two out of nine cases. In contrast, the 1.0 g/L concentration produced artifact in four out of seven cases but was sufficient as a contrast agent in six out of seven cases. These results demonstrated that while Ferristene had potential as a contrast agent, the signal-to-noise ratio (enhancement vs artifact) is somewhat steep. There was no significant toxicity, including GI upset or diarrhea, observed in any patients. Furthermore, blood and urine tests demonstrated no change in iron levels, suggesting that no or minimal absorption occurred.

A large, multicenter phase II study then addressed some of the imaging concerns raised in the phase I study discussed above. This trial included 216 patients at seven centers.[353] Patients ingested media with a concentration of 0.5 g/L. They further examined two separate preparations, one aqueous and one viscous. This was an important distinction, as the investigators demonstrated significantly improved homogeneous distribution throughout the bowel with the viscous solution. This translated to decreased susceptibility artifacts, improved general contrast effect, and improved organ delineation. In all, raters reported improved diagnostic information in about 70% of cases with the viscous formulation. There were no cases of worse image quality with the contrast reported. Again, the formulation was well tolerated. Less than 5% of patients reported any toxicity, which primarily included nausea and vomiting. There were no reported serious adverse events. Similar results were obtained in a second phase II study by Rinck et al.[354] These authors reported improved diagnostic information from postcontrast images in 52% (16/31) of patients with no major side effects. There was minimal blurring or metallic artifacts with either the 0.25 or 0.5 g/L concentration of viscous Ferristene. The utility was further demonstrated by Van Beers et

al.[355] They evaluated overall image quality and target/organ delineation in 30 patients with small bowel or pelvic lesions treated with viscous Ferristene. In their observation, postcontrast images showed better delineation of lesions, small bowel, and the paraaortics lymph nodes. However, there was no improvement in delineation of the colon or other pelvic organs including the iliac vessels, bladder, or genital tract. They concluded that perhaps inclusion of rectal contrast could potentially improve the utility for delineating pelvic organs and large bowel.

Ferristene, marketed as Abdoscan (Nycomed Imaging), was approved in Sweden for use as an oral contrast agent in 1993. Several other clinical studies have been completed with Ferristene.[356–359] However, it never progressed to widespread use, and approval was never obtained outside of Europe. Manufacturing was discontinued by Nycomed in 2002.

6.2. Gold Nanoparticles

As evidenced from other formulations in this Review, most delivery systems in clinical use (particularly those for drug delivery) are based on liposomal or polymer platforms. However, colloidal elemental particles, such as gold, are also being investigated as clinical delivery systems. Gold is a naturally occurring, relatively inert (depending on the oxidation state) compound. Following absorption, 90–95% is bound to albumin or globulin where it can remain for several months. Excretion is primarily in the urine and feces. Faraday initially described the synthesis of nanosized gold particles in the mid 19th century. In the 1950s, there was interest in utilizing radioactive colloidal gold for the treatment of cancer. While this was not successful with hematologic disease, two studies demonstrated some activity in the treatment of liver tumors, including disseminated reticulum cell sarcoma.[360,361] Colloidal gold has also been used in the treatment of rheumatoid arthritis and more recently has been used fairly extensively for diagnostic purposes. We will not be reviewing diagnostic agents here. Instead, we will focus on the therapeutic translation of gold nanoparticles.

Preclinical studies demonstrated several potentially useful properties of gold nanoparticles, particularly in cancer therapy. Much of the preclinical literature highlighting NP gold as an anticancer therapy has been previously reviewed.[362] Gold is a high-Z element (having a high number of protons and neutrons in its nucleus), and several studies have demonstrated that high-Z elements can improve the efficacy of radiotherapy. When exposed to electromagnetic radiation, excitation of electrons produces strong surface fields, which produce significant localized heat upon relaxation. This heat is sufficient to destroy surrounding tissues including tumors. One study has demonstrated that 1.9 nm gold NPs accumulate in EMT-6 mammary carcinomas in mice and significantly increased the radiosensitivity of the tumors.[363] Excitation of high-Z elements does not require high energy photons from a linear accelerator. A number of preclinical laser-based strategies, referred to as plasmonic photothermal therapy, have coupled different gold nanoparticle platforms (including nanospheres, nanoshells, nanorods, and nanocages) with phototherapy to produce antitumor effects.[364–366] While these preclinical data are promising and exciting for the future translation of nanomedicine, there are no clinical studies that have successfully utilized gold NPs as a radiosensitizer or photothermal therapy agent. However, the potential utility of

gold NPs as drug delivery vehicles has been tested clinically. Gold nanoparticles can easily be conjugated to macromolecules, including proteins (TNFα),[367] nucleic acids,[368] and drugs (such as paclitaxel, doxorubicin, and cisplatin).[369–371] Preclinical studies have demonstrated good intratumoral delivery of several different agents with expected therapeutic outcomes. While these preclinical results are promising, to date, only one (gold-conjugated TNF) has completed clinical testing.

6.2.1. CYT-6091 (Aurimune)—Tumor necrosis factor (TNFα) is a potent anticancer molecule. Signaling through TNFα results in the induction of a number of antitumor functions, including cell lysis, apoptosis, and pro-inflammatory pathways.[372,373] Unfortunately, exogenous administration of TNFα results in extreme side effects (hypotension, septic shock, etc.), which have largely limited its clinical utility, except in isolated limb perfusion.[374] As reviewed in Paciotti et al., one solution to this problem was the conjugation of TNFα to colloidal gold NPs.[367] While this reduced the toxicity of TNFα and improved tumor cell killing, the particles were quickly cleared by macrophages in the RES. To reduce detection, uptake, and clearance by the RES, a new formulation was created, which conjugated a thiol-derivitized PEG and recombinant TNFα on the gold NP surface. The resulting NPs have a mean diameter of approximately 30 nm. The new vector (PT-cAu-TNF) showed promising preclinical results. Paciotti et al. demonstrated that the addition of thiol-PEG improved the biodistribution (away from liver and spleen) of gold-TNFα NPs. The combination NPs also had the greatest antitumor effect in mice bearing MC38 colon tumors with the lowest toxicity. A second study further demonstrated that in animals dosed with doses of NPs effective at shrinking tumors, TNFα rapidly and preferentially accumulates in the tumor, whereas the gold colloid gradually accumulates in the liver over 4–12 h and is slowly cleared over a period of months without significant toxicity.[375] Yet another preclinical study also demonstrated that CYT-6091 potently improved hyperthermia-mediated tumor killing in mice bearing fibrosarcomas without increasing toxicity.[376]

Subsequently, a phase I study has been completed, which demonstrated the safety and feasibility of CYT-6091 in humans.[377] This study included 30 patients with advanced or metastatic solid tumor malignancies refractory to standard therapy. Dosing was escalated from 50 to 600 $\mu g/m^2$. The first two patients did not receive prophylactic antipyretics, and both experienced post-treatment fevers, which were self-limited (resolved without further treatment). Neither patient experienced hypotension or a severe side effect. All subsequent patients were pretreated with antipyretics. Transient hypotension was experienced in 62% of patients following treatment. However, this was mild, and all but two of the patients had diastolic blood pressure measurements in the normal range. Two patients had single diastolic blood pressure measurements outside of the normal range; however, these were transient and spontaneously resolved. There were no episodes of severe hypotension or other side effects, even at the highest doses tested. Other common side effects were mild and included lymphopenia, hypoalbuminemia, electrolyte disturbances, and increased plasma liver enzymes. As for efficacy, a partial response was observed in one patient and stable disease was observed in another four patients. The drug, marketed as Aurimune, is being

manufactured by Cytimmune (Chicago, IL), which is planning to continue development with future phase II studies to further demonstrate clinical efficacy.

6.3. Hafnium Oxide Nanoparticles

Hafnium oxide is another example of an inorganic metallic compound emerging as a unique nanoformulation. Nanoparticles of hafnium oxide possess unique properties, which are being utilized to enhance the therapeutic effectiveness of radiotherapy. Hafnium has a high atomic number ($Z = 72$), which makes it an attractive candidate as a radiosensitizing agent. When activated by radiation, hafnium oxide increases the electron density, and thus absorption, of the high-energy dose deposited within irradiated tissues. In addition, preclinical data have demonstrated that these particles are chemically inert with excellent local and systemic tolerance,[378,379] thus potentially improving the therapeutic window of radiotherapy.

6.3.1. NBTXR3—NBTXR3 is a nanoparticle of hafnium oxide crystals currently in clinical development as a nanoradioenhancing agent. It is engineered as a 50 nm sphere, functionalized with a negative surface charge, and stabilized in an aqueous solution at pH between 6 and 8. It is unique among other nanoparticles in that it is directly injected into the tumor.[379] As the tumor is irradiated, high energy photons from external beam radiotherapy are absorbed by tissues and generate electrons, which then activate the hafnium oxide nanoparticle. Once activated, NBTXR3 also emits high energy electrons, increasing the production of free radicals and other reactive oxygen species, and thus enhancing the ability of radiation to target and destroy cancer cells through double-stranded DNA damage. NBTXR3 is an inert particle, as it only emits high energy electrons during exposure to ionizing radiation.

Preclinical studies of NBTXR3 have shown that it enhances radiation doses 9-fold when compared to water exposure alone, and confirm dispersion and clustering of the nanoparticles within cancer cells, both at the periphery and in the center of the tumor. Importantly, there was persistence of the nanoparticles within the tumor, with little leakage outside the tumor to normal tissue. Furthermore, the combination of radiation and NBTXR3 in the HT1080 cell line (a human fibrosarcoma model) showed enhanced antitumor activity, as demonstrated in vitro by the clonogenic cell survival assay and in vivo with HT1080 xenograft tumors in nude mice. These findings were confirmed in both radioresistant and radiosensitive human cancer cell lines, although there was differential uptake of the nanoparticles observed between epithelial versus mesenchymal and glioblastoma cells.[380] Most importantly, there was no increase in toxicity in the treated xenograft animal models as compared to control animals.[379]

The above studies demonstrate the clear potential for the use of NP formulated hafnium oxide as a radiosensitizer. Currently, NBTXR is being studied in phase I clinical trials in combination with concurrent radiation for the treatment of soft tissue sarcomas (NCT01433068) and head and neck cancer (NCT01946867). NBTXR3 nanoparticles first entered clinical development in France in 2011. The hafnium oxide nanoparticles were injected directly into extremity soft tissue sarcomas. As the tumors are treated with

NBTXR3 and preoperative radiation prior to resection, this study will allow for pathologic evaluation of the tumor and surrounding normal tissue.[381] In the head and neck cancer trial, patients 65 years and older with T3 or T4 squamous cell carcinoma of the oral cavity or oropharynx will receive either an intra-arterial or an intratumor injection of NBTXR3, followed by radiation therapy 24 h later, to assess dose limiting toxicity, safety, and tolerability of the nanomedicine. Both studies are currently recruiting participants and await published results.

7. Summary and Outlook

Nanomedicine has made a significant impact on the treatment of many human illnesses. However, we are still in the early stages of the clinical development of nanotechnology. Today, there are many nanotechnology-based diagnostics and therapeutics under clinical development. Furthermore, extensive preclinical research has provided key information on critical design criteria for nanomedicine development.

Although we are highly optimistic about the future of nanomedicine, the clinical translation of nanomedicine products faces several challenges. First, nanoformulations already exist for the "easy" drugs for nanoparticle drug delivery, such as amphotericin, doxorubicin, and paclitaxel. It would be very difficult to engineer new formulations of these drugs to provide additional clinical benefit. To reformulate other approved therapeutics, investigators must identify clear translation pathways where the nanoformulation can provide superior therapeutic efficacy over their small molecule counterparts. Overall, the clinical benefits of even the most successful nanoformulations of existing drugs (including Abraxane) have largely been realized through decreases in toxicity. Improvements in therapeutic efficacy have been much more modest, particularly when compared to the small number of very successful small molecule inhibitors and antibodies (including crizotinib and erlotinib for mutated NSCLC or Gleevec for (9:22)-translocated chronic myelocytic leukemia), which tend to target driver mutations as opposed to general cellular pathways. While nanoformulation can improve the delivery of existing drugs to tumors, it may not be able to circumvent many of the well-established mechanisms of chemoresistance, which limit the effectiveness of traditional chemotherapeutics. Because of the higher cost of nanoformulations, one must also consider conducting cost effectiveness analyses when devising the clinical translation strategies. A potential for nanomedicine is to utilize nanoparticle platforms in the development of new drugs. Instead of chemically modifying a lead compound to address drug delivery challenges such as solubility, the compound can be formulated with a nanoparticle. Another exciting area for nanomedicine is the delivery of nucleic acid therapeutics where a delivery vehicle is necessary. In addition to siRNA, several groups are working on the delivery of messenger RNA (mRNA) for treatment of genetic diseases such as cystic fibrosis. The success of these clinical programs can have paradigm-shifting effects on clinical medicine.

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Abbreviations

ABCD	AmB colloidal dispersion
ABLC	AmB lipid complex
ABV	doxorubicin
AIDS	acquired immunodeficiency syndrome
ALL	acute lymphoblastic leukemia
AmB	amphotericin B
AML	acute myeloid leukemia

ara-C	arabinofuranosyl cytidine
AUC	areas under the curve
BELI	bupivacaine extended-release liposome injection
BV	bleomycin and vincristine
CDDP	cisplatin/*cis*-diamminedichloroplatinum
CE	European Commission
CE	cysticfibrosis
CI	confidence interval
CKD	chronic kidney disease
CPT-11	irinotecan
CR	complete response
CRi	CR with incomplete hematologic recovery
CSC	central serous chorioretinopathy
CSF	cerebrospinal fluid
DLT	dose limiting toxicity
DPC	dynamic polyconjugate
DMPC	dimyristoyl phospitidylcholine
DMPG	dimyristoyl phospitidylcglycerol
DSPG	distearoyl phosphitidylcholine
EC	epirubicin and cyclophosphamide
EPR	enhanced permeability and retention
EREM	extended-release epidural morphine
EU	European Union
FDA	Food and Drug Administration
FIM	first-in-man
GBM	glioblastoma multiforme
GOG	Gynecologic Oncology Group
HAART	highly active antiretroviral therapy
HCC	hepatocellular carcinoma
HD	hemodialysis
HF	hemofiltration
HPMA	*N*-(2-hydroxypropyl)methacrylamide

HR	hazard ratio
HSCT	hematopoietic stem cell transplantation
HSPC	hydrogenated soy phosphatidylcholine
IND	investigational new drug
IDE	investigational device exemption
KS	Kaposi's sarcoma
LAmB	liposomal AmB
LC	liposomal cytarabine
LD	nonpegylated liposomal formulation
LE-DT	liposomal-encapsulated docetaxel
LED	liposomally encapsulated daunorubicin
LEP-ETU	liposome-encapsulated paclitaxel
LNP	lipid nanoparticle
LVEF	left ventricular ejection fraction
MBC	metastatic breast cancer
MC	LD and cyclophosphamide
MM	multiple myeloma
mPEG-DDLLA	monomethoxy poly(ethylene-glycol)-*block*-poly($_{D,L}$-lactide)
MPS	mononuclear phagocytic system
MRI	magnetic resonance imaging
mRNA	messenger RNA
MS	morphine sulfate
MTD	maximum tolerated dose
mTOR	mammalian target of rapamycin
Nab	nanoparticle albumin-bound
NabP	Nab-paclitaxel
NDA	new drug application
NHL	non-Hodgkin's lymphoma
NP	nanoparticle
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival

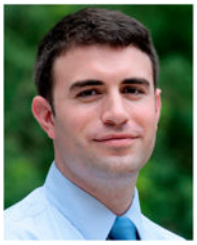
PDT	photodynamic treatment
PEG	polyethylene glycol
PFS	progression-free survival
PGA	poly(L-glutamic acid)
Ph-	philadelphia chromosome-negative
PI3-K	phosphatidylinositol-3-kinase
PLA	polylactic acid
PLD	pegylated liposomal doxorubicin
PL-MLP	mitomycin-C lipid-based prodrug formulated in pegylated liposomes
PMA	premarket approval
PR	partial response
PSMA	prostate-specific membrane antigen
RCC	renal cell carcinoma
RES	reticuloendothelial system
RFA	radiofrequency ablation
RNAi	RNA interference
RP2D	recommended phase 2 dose
SAEs	serious adverse events
SCID	severe combined immunodeficiency
SCLC	small cell lung cancer
SHIV	simian-human immunodeficiency virus
shRNA	short hairpin RNA
siRNAs	small interfering RNAs
SLN	sentinel lymph nodes
sNDA	supplemental NDA
SPARC	secreted protein acidic and rich in cysteine
SPIONs	superparamagnetic iron oxide nanoparticles
TLC-65	liposomal formulation of gentamicin
TNF	tumor necrosis factor
TTP	time to progression
VSLI	vincristine liposome injection
USPIO	ultrasmall SPION

Biographies

Yuanzeng Min was born in Jiangsu, China, in 1982. He received his Ph.D. at the University of Science and Technology of China. His Ph.D. work focused on platinum prodrug synthesis and delivery to overcome the drug resistance. After completing his Ph.D. studies in 2012, he joined the Division of Chemistry and Biological Chemistry at Nanyang Technological University as a research fellow conducting nanoparticle-based activated imaging for drug efficacy evaluation. Now he is working with Dr. Andrew Z. Wang in the field of nanomedicine with a special emphasis on cancer treatment.

Joseph M. Caster received his Ph.D. in pharmacology from Duke University in 2008 and his M.D. from the University of North Carolina at Chapel Hill in 2012. He is currently completing his clinical training in radiation oncology at UNC—Chapel Hill. He was awarded entry into the B. Leonard Holman research pathway by the American Board of Radiology to continue training as both a physician and a scientist. He is interested in the development and translation of nanotherapeutics to improve the efficacy of chemoradiotherapy. He is currently being mentored by Dr. Andrew Wang and completing research in his laboratory within the Carolina Institute of Nanomedicine.

Michael J. Eblan received his B.A. in Biology and Economics from The University of Virginia in 2004. He then completed a postbaccalaureate research program at the National Human Genome Research Institute of the National Institutes of Health. He received his M.D. from The University of Pennsylvania School of Medicine in 2011. Now, he is completing clinical training in radiation oncology as chief resident at The University of North Carolina at Chapel Hill. Currently, he is working with Dr. Andrew Z. Wang to develop nanotherapeutics to improve radiotherapy and cancer care.



Andrew Z. Wang received his M.D. from Harvard Medical School in 2004. He then completed clinical training in radiation oncology in the Harvard Radiation Oncology Program. After completing a postdoctoral fellowship at Massachusetts Institute of Technology and Brigham and Women's Hospital at Harvard Medical School, he became faculty at University of North Carolina—Chapel Hill in 2009. Currently, he is Associate Professor of Radiation Oncology and a member of the Carolina Center for Cancer Nanotechnology Excellence, Carolina Institute of Nanomedicine and Center for Nanotechnology in Drug Delivery. His research interest is in the preclinical development, evaluation, and clinical translation of nanomedicine.

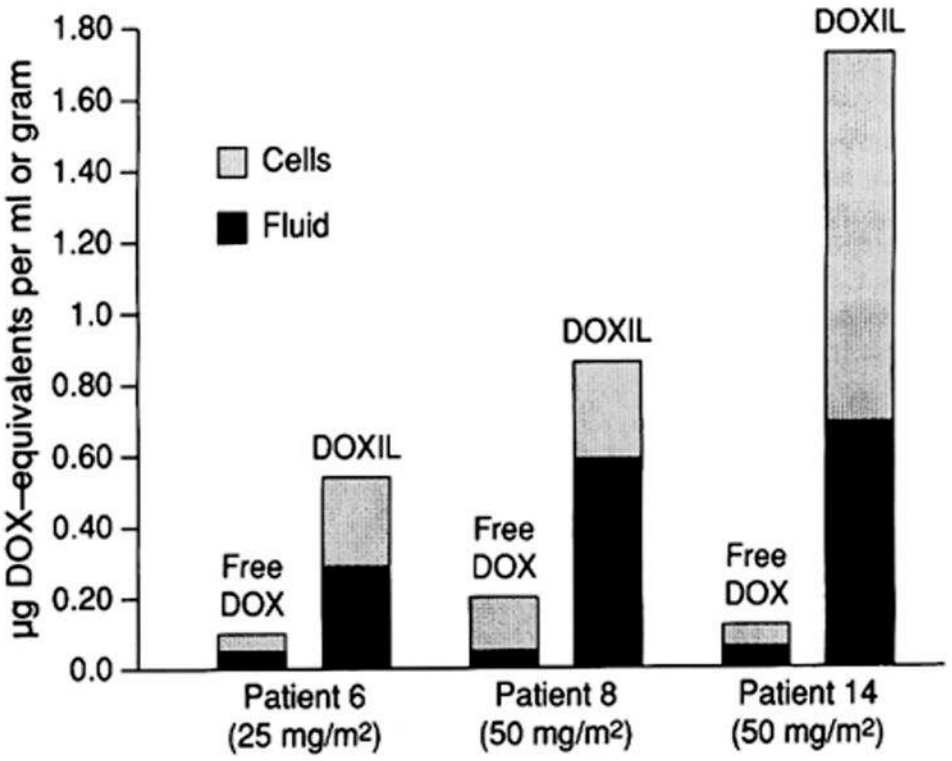


Figure 1.

Doxorubicin levels in patients' tumor biopsies, comparing free DOX and DOXIL. Reprinted with permission from ref 26. Copyright 2012 Elsevier Ltd.

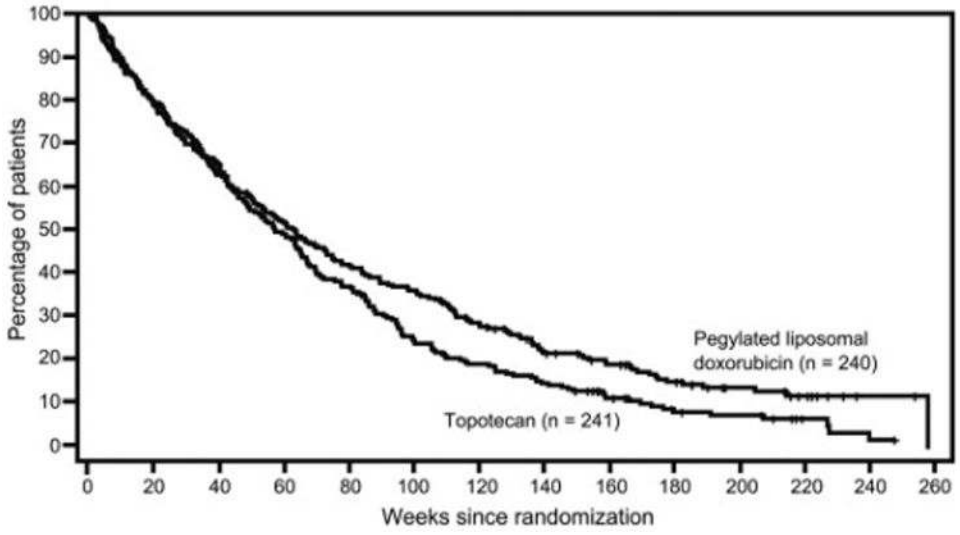


Figure 2.

Kaplan-Meier curves of survival for all randomized patients assigned to treatment with pegylated liposomal doxorubicin or topotecan. Reprinted with permission from ref 45. Copyright 2004 Elsevier Ltd.

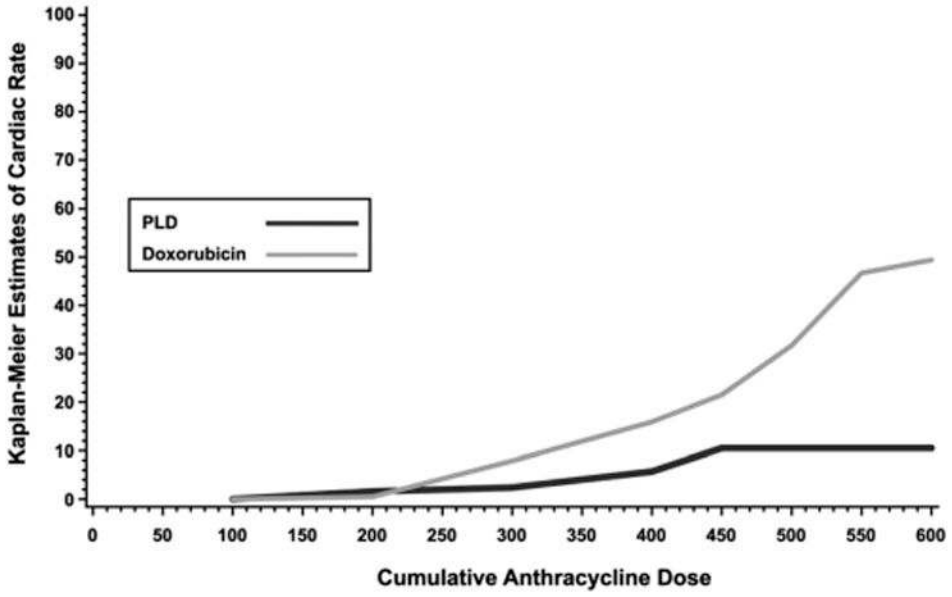


Figure 3.

Rate of cardiac events versus cumulative anthracycline dose. Patients who had a baseline and at least one additional multigated blood-pool imaging (MUGA) scan during treatment. Cumulative percentage of events versus cumulative anthracycline dose, protocol-defined cardiac events. Reprinted with permission from ref 50. Copyright 2004 Oxford University Press. hazard ratio (HR) = 3.16; 95% confidence interval (CI) 1.58–6.31; $P < 0.001$; PLD, $n = 254$; doxorubicin, $n = 255$.

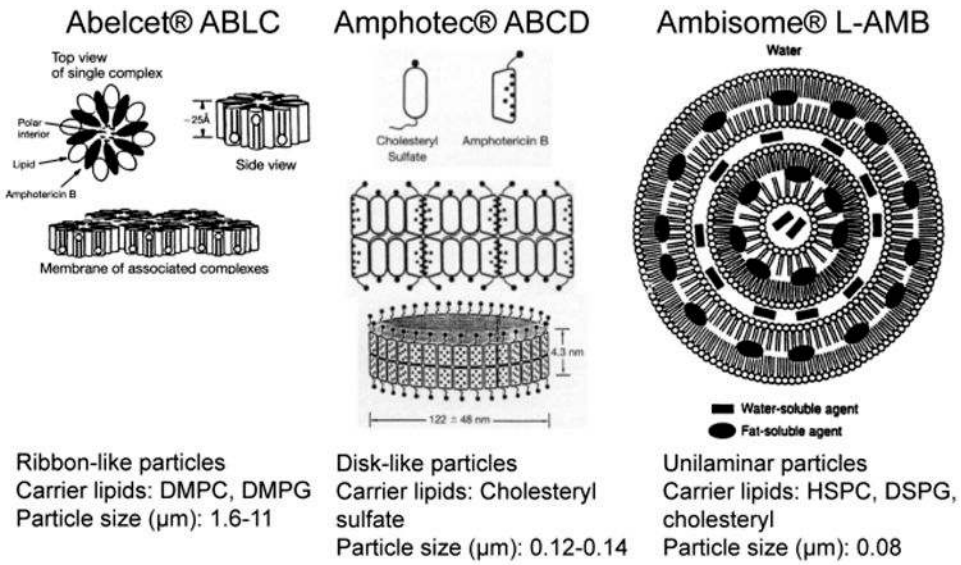


Figure 4.

Lipid amphotericin B formulations. DMPC, dimyristoyl phospitidylcholine; DMPG, dimyristoyl phospitidylcglycerol; HSPC, hydrogenated soy phosphatidylcholine; DSPG, distearoyl phosphitidylcholine. Reprinted with permission from ref 94. Copyright 1996 Oxford University Press.

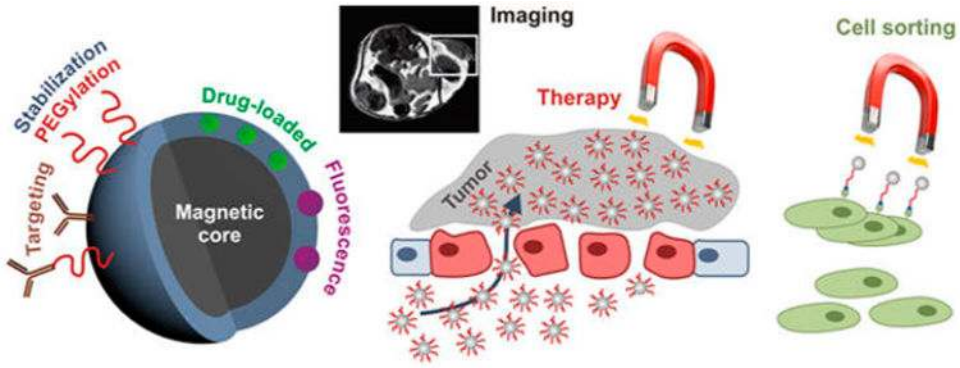


Figure 5.
SPIONs for biomedical application. Reprinted with permission from ref 316. Copyright 2012 American Chemical Society.

Table 1

Summary of the FDA Device Regulation Process[a]

step 1	determine whether the product is a medical device	defined in section 201(h) of the FD&C Act
step 2	identify the device class	class I
		low risk of harm to the user
		subject to general controls
		typically exempt from premarket notification (i.e., “510(k)”)
		class II
		moderate risk of harm
		subject to general and specific controls
		typically requires 510(k)
		class III
		high risk of harm
		typically requires premarket approval (i.e., “PMA”)
step 3	identify the premarket pathway	510(k) process
		“substantial equivalence” to a legally marketed predicate device
		PMA process
		“reasonable assurance of safety and effectiveness” based on submitted studies
		de novo request
		for low-to-moderate risk devices that do not have a legally marketed predicate device
		risk-based classification into class I or II
		future devices of this type are reviewed in the 510(k) process
step 4	if clinical data need to be collected before commercialization, submit an investigational device exemption (IDE) application	allows manufacturers to collect safety and effectiveness data on an investigational device to support a future marketing submission (510(k), PMA, or de novo)
		purpose of the IDE review is to ensure the safety and welfare of human research subjects

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Table 2

In Vivo Uptake of Liposome-Entrapped ^{131}I-Labeled Albumin by Normal and Malligant Human Tissue[a]

	patient A		patient B	
tissue	radioactivity[b] (cpm/g tissue)	trichloroacetic-acid precipitable radioactivity (% of total)	radioactivity[b] (cpm/g tissue)	trichloroacetic-acid precipitable radioactivity[c] (% of total)
normal liver[d]	7504	21.5	13 200	45.0
tumor in liver	10 267	24.6	15 400	33.3
normal right kidney	9173	29.3		
tumor in right kidney	441 000	95.0		
normal spleen	4900	25.0		
tumor in spleen	11 700	32.6		
normal colon			13 200	32.8
tumor in colon			29 800	20.4

[a] Reprinted with permission from ref 18. Copyright 1974 Elsevier Ltd.

[b] Dosages injected were 21.0×10^7 cpm in patient A and 8.8×10^7 cpm in patient B as assayed from the injected preparation at the time of tissue counting.

[c] Plasma radioactivity was more than 95% trichloroacetic acid precipitable at 10 min and 82.6% precipitable at 3 h when tissue was obtained (patient B).

[d] Hepatic uptake of radioactivity (% of the injected dose) as measured by the hybrid whole-body scanner technique as follows: patient A, 81.0% at 10 min; patient B, 75.0% and 66.0% at 2 and 50 min, respectively; patient C, 70.5% at 3 min and 41.0% at 6 h. There was no evidence of radioactivity uptake by bone marrow.

Table 3
Clinically Evaluated Liposomal Formulations of Cisplatin

	formulation			
	L-NDDP	**SPI-77**	**lipoplatin**	**LiPlaCis**
particle size	1–5 μm	110 nm	110 nm	NA
half-life in human (h)	$t_{1/2}\alpha$ = 0.8–21 min, $t_{1/2}\beta$ = 14–36	80–145	60–117	$t_{1/2}\alpha$ = 3–5.5, $t_{1/2}\beta$ = 80–141
MTD (mg/m^2)	312.5	420	300	120
clinical status	phase II	phase II	phases II, III	phase I

Table 4

Pharmacokinetic Parameters of Amphotericin B and AmBisome[a]

compound, patient no.		dose (mg/kg)	C_{max} (μg/mL)	V (L/kg)	CL (mL/min)	$T_{1/2\beta}$ (h)	AUC (μg·h/mL)
amphotericin B	1	1.0	1.7	2.14	0.76	32.6	21.9
	2	1.0	1.7	1.34	1.57	9.9	10.6
	3	1.0	2.1	4.32	1.91	26.2	17.4
	4	1.0	1.5	2.68	0.84	37.0	19.9
	5	1.0	1.6	4.07	1.71	27.4	9.7
	6	1.0	2.1	1.12	0.59	21.9	28.3
	median [range]	1.0	1.70 [1.5–2.1]	2.41 [1.12–4.32]	1.20 [0.59–1.91]	26.8 [9.9–37.0]	18.65 [9.7–28.3]
AmBisome	7	3.0	7.7	0.825	0.636	15.0	89.2
	8	1.2	41.6	0.052	0.032	18.6	622
	9	3.0	10.3	0.616	0.559	12.7	89.5
	10	2.3	23.5	0.276	0.554	5.76	70.4
	11	3.0	6.4	0.932	0.942	11.3	53.1
	12	3.0	20.5	0.253	0.253	8.7	197
	13	3.0	73.4	0.055	0.044	14.5	1,140
	14	2.3	2.9	2.69	2.40	12.9	16.1
	15	3.0	89.0	0.130	0.036	41.4	1,380
	16	2.1	12.0	0.539	0.391	15.9	89.5
	17	4.2	10.2	0.163	0.254	7.40	65.6
	17 plus HD[b]	4.2	18.9	0.103	0.591	10.8	88.2
	17 plus HF[c]	4.2	13.8	0.190	0.641	8.5	74.9
	18	4.0	17.8	0.642	0.671	11.1	123
	19	3.0	14.0	0.393	0.438	10.4	228
	20	3.0	10.8	0.609	0.277	25.4	372
	21[d]	1.4	10.0	0.288	0.258	12.9	90.5
		2.8	18.0	0.369	0.322	13.2	145
		4.2	24.1	0.286	0.363	9.1	193
	22[e]	2.0	11.8	1.44	0.348	47.7	95.7
		3.0	14.7	0.450	0.403	12.9	124

compound, patient no.	dose (mg/kg)	C_{max} (μg/mL)	V (L/kg)	CL (mL/min)	$T_{1/2\beta}$ (h)	AUC (μg·h/mL)
22 plus intralipid[f]	3.0	15.9	0.388	0.307	14.6	152
	4.0	25.5	0.266	0.548	6.71	146
median [range]	3.0 [2.8–3.0]	14.4 [6.4–89.0]	0.421 [0.055–0.932]	0.363 [0.036–0.942]	13.05 [8.7–41.40]	171 [53.1–1,380]
Pg		<0.001	0.001	0.006	0.03	0.001

[a] Reprinted with permission from ref 120. Copyright 1997 American Society for Microbiology.

[b] HD, hemodialysis.

[c] HF, hemofiltration.

[d] AmBisome dose increased from 1.4 to 4.2 mg/kg.

[e] AmBisome dose increased from 2.0 to 4.0 mg/kg.

[f] Parallel infusion of 20% intralipid (50 mL/h).

[g] Statistical comparison by Mann–Whitney U test of median values of patients receiving amphotericin B with those of patients receiving 2.8–3.0 mg/kg of AmBisome.

Table 5

RNAi-Based Drugs in Clinical Trials[a]

drug	target	delivery system	disease	phase	status	company	ClinicalTrials.gov ID
ALN-VSP02	KSP and VEGF	LNP	solid tumors	I	completed	Alnylam	NCT01158079
siRNA-EphA2-DOPC	EphA2	LNP	advanced cancers	I	recruiting	MD Anderson Cancer Center	NCT01591356
Atu027	PKN3	LNP	solid tumors	I	completed	Silence Therapeutics	NCT00938574
TKM-080301	PLK1	LNP	cancer	I	recruiting	Tekmira Pharmaceutical	NCT01262235
TKM-100201	VP24, VP35, Zaire Ebola L-polymerase	LNP	Ebola-virus infection	I	recruiting	Tekmira Pharmaceutical	NCT01518881
ALN-RSV01	RSV nucleocapsid	naked siRNA	respiratory syncytial virus infections	II	completed	Alnylam Pharmaceuticals	NCT00658086
PRO-040201	ApoB	LNP	hypercholesterolaemia	I	terminated	Tekmira Pharmaceutical	NCT00927459
ALN-PCS02	PCSK9	LNP	hypercholesterolaemia	I	completed	Alnylam Pharmaceuticals	NCT01437059
ALN-TTR02	TTR	LNP	transthyretin-mediated amyloidosis	II	recruiting	Alnylam Pharmaceuticals	NCT01617967
CALAA-01	RRM2	cyclodextrin NP	solid tumors	I	active	Calando Pharmaceuticals	NCT00689065
TD101	K6a (N171 K mutation)	naked siRNA	pachyonychia congenita	I	completed	Pachyonychia Congenita Project	NCT00716014
AGN211745	VEGFR1	naked siRNA	age-related macular degeneration, choroidal neovascularization	II	terminated	Allergan	NCT00395057
QPI-1007	CASP2	naked siRNA	optic atrophy, nonarteritic anterior ischemic optic neuropathy	I	completed	Quark Pharmaceuticals	NCT01064505
I5NP	p53	naked siRNA	kidney injury, acute renal failure	I	completed	Quark Pharmaceuticals	NCT00554359
			delayed graft function, complications of kidney transplant	I,II	recruiting	Quark Pharmaceuticals	NCT00802347
PF-655 (PF-04523655)	RTP801 (proprietary target)	naked siRNA	choroidal neovascularization, diabetic retinopathy, diabetic macular edema	II	active	Quark Pharmaceuticals	NCT01445899
siG12D LODER	KRAS	LODER polymer	pancreatic cancer	II	recruiting	Silenseed	NCT01676259
Bevasiranib	VEGF	naked siRNA	diabetic macular edema, macular degeneration	II	completed	Opko Health	NCT00306904
SYL1001	TRPV1	naked siRNA	ocular pain, dry-eye syndrome	I,II	recruiting	Sylentis	NCT01776658
SYL040012	ADRB2	naked siRNA	ocular hypertension, open-angle glaucoma	II	recruiting	Sylentis	NCT01739244
CEQ508	CTNNB1	*Escherichia coli* carrying shRNA	familial adenomatous polyposis	I,II	recruiting	Marina Biotech	unknown
RXi-109	CTGF	self-delivering RNAi compound	cicatrix scar prevention	I	recruiting	RXi Pharmaceuticals	NCT01780077
ALN-TTRsc	TTR	siRNA-GalNAc conjugate	transthyretin-mediated amyloidosis	I	recruiting	Alnylam Pharmaceuticals	NCT01814839

drug	target	delivery system	disease	phase	status	company	ClinicalTrials.gov ID
ARC-520	conserved regions of HBV	DPC	HBV	I	recruiting	Arrowhead Research	NCT01872065

[a] DPC, dynamic polyconjugate; LNP, lipid nanoparticle; NP, nanoparticle; shRNA, short hairpin RNA. Reprinted with permission from ref 154. Copyright 2013 Nature Publishing Group.

Table 6

Completed Phase I/II Trials

cancer			
tissue	**stage**	**treatment**[a]	**studies/refs**
breast	metastatic	NabP+Cisplatin	185
		NabP+Bevacizumab	186
		NabP+Gemcitabine	187,188
		NabP+Lapatanib	189
		NabP+Capcitabine	190
		NabP+Bevacizumab+ddAC	191
		NabP+Trastusimab	192
		NabP+Trastusimab+Carbotaxol	193
	locally advanced	NabP+Gemcitabine+Epirubicin	194
		NabP+5FU+Epirubicin+Cyclophosphamide	195
		NabP+Carboplatin+Bevaciszumab+Herceptin	196
	early stage operable	NabP+Cyclophosphamide+Herceptin	197
		NabP+Lapatanib	198
		NabP+Bevacizumab+ddAC	199
		NabP+ddAC	200
ovarian	advanced	NabP	201,202
		NabP+Carbotaxol	203
		NabP+Bevacizumab	204
lung	advanced	NabP+Gemcitabine	205
		NabP+Pematrexid	206
		NabP+Carboplatin+Bevacizumab	207
melanoma	advanced	NabP+Carboplatin	203,208
		NabP+Carboplatin+Bevacizumab	209
		NabP+Oblimerson+Temazolamide	210
pancreas	advanced	NabP+Gemcitabine+Capcitabine	211
		NabP+Gemciabine+Bevacizumab	212
gastric	unresectable	NabP	213
GU urothelial		NabP	214
bladder		intravessicular NabP	215
prostate		Pre-RP NabP	216

[a] NabP: Nab-paclitaxel.

Table 7

Ongoing Phase III Trials

cancer and stage	treatment	ClinicalTrials.gov ID
melanoma	Nab vs Decarbazine	NCT00864253
operable breast	Nab vs Paclitaxol based neoadjuvant chemotherpay	NCT01583426
operable breast	Nab vs Paclitaxol based neoadjuvant chemo	NCT01822314
operable breast	Nab+EC or AC vs Paclitaxel+EC or AC	
elderly operable breast	EC vs CMF vs Capcitabine+Nab-Paclitaxel	NCT01204437
recurrent or metastatic breast	Bevacizumab+Pacliatxel vs Bev+ Nab-P vs Bev+ixabepalone	NCT00785291
metastatic breast	Nab-Paclitaxel+Gem Carbo vs Gem Carbo	NCT01881230
advanced NSCLC	Maintenance Nab-Paclitaxel following Nab-Pac+Carbo	NCT02027428
unresectable pancreatic	Nab-paclitaxol+FOLFIRNIOX+Gemcitabine+Capcitabine ±Algenepantucel-L	NCT01836432
resected pancreatic	Gem+Nab-Paclitaxel vs Gem	NCT01964430

Table 8
Polymer–Drug Conjugates in Clinical Use

drug (trade name)	indications	approval
PEG-adenosine deaminase (Adagen)	severe combined immunodeficiency disease	1990
PEG-asparaginase (Oncaspar)	acute lymphocytic leukemia	1994
Glatiramer Acetate (Copaxone)	multiple sclerosis	1996
PEG-interferon alpha-2b (PegIntron)	Hepatitis C	2001
PEG-interferon alpha-2a (Pegasys)	Hepatitis B, Hepatitis C	2002
PEG-filgrastim (Neulasta)	chemotherapy-associated neutropenia	2002
PEG-Visomant (Somavert)	acromegaly	2003
PEG-aptanib (Macugen)	wet age-related macular degeneration	2004
PEG-Fab' fragment of a humanized anti-TNF-alpha antibody, CERTOLIZUMAB PEGOL (Cimzia)	Crohn's disease, rheumatoid arthritis	2008
PEG-loticase (Krystexxa)	chronic gout, adults refractory to conventional therapy	2010
PEG-interferon beta-1a (SYLATRON)	adjuvant treatment of melanoma with microscopic or gross nodal involvement within 84 days of definitive surgical resection including complete lymphadenectomy	2011
PEG-inesatide acetate (Omontys)	erythropoiesis-stimulating agent for anemia due to chronic kidney disease in adults on dialysis	2012
PEG-interferon beta-1a (Plegridy)	relapsing multiple sclerosis	2014
zinostatin stimalmer	HCC	approved in Japan 1994