ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Using Ligands to Target Cancer Cells

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H&O What are nanoparticle therapeutic carriers?

OF Nanoparticle (NP) carriers typically have a diameter less than 100 nm and can be developed from any number of organic or inorganic materials. Many different classes of NPs have been developed or are currently under development for medical applications. These include NPs that can carry drugs or an imaging modality or a combination thereof, and these NPs can be further engineered with targeting moieties for differential delivery of their payload in a cell- or tissue-specific manner. In this regard, therapeutic NP carriers allow for selective and preprogrammed biodistribution of drugs and control over the kinetic of drug release and duration of drug exposure at the target site. Challenges with modern drug therapy include the difficulty in optimizing the pharmaceutical and pharmacologic properties of drugs. Using conventional drug development approaches, it has always been difficult to create safe and efficacious drugs. The use of NP carriers can drastically facilitate the optimization of both pharmaceutical and pharmacologic properties of drugs (ie, solubility, stability, pharmacokinetics, biodistribution, elimination, efficacy, and toxicity), thus improving the odds of success in drug development.

H&O How might the use of nanoparticle technology renew the potential of once promising drugs, as well as promote the development of new agents?

OF The clinical success of nanoparticle technologies with validated drugs has paved the road for re-exploration of biologically active agents that were previously considered undevelopable due to pharmacologic challenges. I expect that some of these undevelopable compounds could become promising drug candidates when delivered with NP carriers. NPs can offer additional degrees of freedom to aid in the development of drugs. For example, a greater flexibility in the design of drug molecules can be achieved when they are incorporated in the NPs. This is because drug efficacy and safety will no longer be constrained to the same extent by drug properties, but also become in part the function of the properties of the NP. The combination of optimally designed drugs with optimally engineered NPs opens up the possibility of improved clinical outcomes that may not be achievable with the administration of drugs in their conventional form. With these advances in nanomedicine, we will soon be reaching into the toolbox of nanotechnology and utilizing its solutions without thinking twice throughout all aspects of medical science, including drug development. Although nanotechnology remains an exciting field today that some consider futuristic, the idea of developing drugs using nanotechnology will become mainstream within 10–20 years. The field is maturing, and the impact of nanotechnology on medicine will be huge.

H&O What are some other applications of nanomedicine?

OF Drug discovery and development is only one of the many areas that can benefit from nanotechnology. The breadth of the application of nanotechnology to medicine is incredibly broad. In some cases, nanotechnology enables the development and delivery of new therapeutics. This can be seen with RNA interference (RNAi) platforms and other nucleic acid therapeutics. Gene therapy and RNAi are promising treatments for a variety of diseases, yet these

fields have faced considerable challenges. Barriers such as enzymatic degradation, uptake by the reticuloendothelial system, kidney filtration, and limited intracellular entry affect the administration of these therapeutics. Therefore, nanocarriers are often used to encapsulate and deliver these therapeutics to the cell. Nanoparticle teranostics that are capable of co-delivering a therapeutic and an imaging modality for real-time feedback on treatments are a promising platform currently under development. Other promising applications of nanomedicine include lab-on-chip for in vitro diagnostics, nanoparticles for in vivo imaging, and biomaterials for tissue engineering.

H&O What is BIND-014?

OF BIND-014 is a programmable nanomedicine that combines a targeting ligand with a therapeutic nanoparticle. It contains docetaxel, which is encapsulated in biocompatible and biodegradable polymers. BIND-014 is the first targeted polymeric nanoparticle to enter human clinical trials that enables controlled release of the drug. It is targeted to prostate-specific membrane antigen (PSMA), which is abnormally expressed on prostate cancer cells, as well as on the endothelial cells of the microvasculature of virtually all solid tumors. BIND-014 nanoparticles have 4 components: 1) one that carries the drug, 2) one that targets PSMA, 3) one that helps evade macrophages and other immune-system cells, and 4) docetaxel as a pharmacologically active drug.

H&O What are the initial clinical data on BIND-014?

OF Based on promising results from preclinical studies, BIND Biosciences, in collaboration with researchers from the David H. Koch Institute for Integrative Cancer Research at MIT, Brigham and Women's Hospital, Dana-Farber Cancer Institute, Harvard Medical School, and Weill Cornell Medical College, has launched an ongoing phase I study. The study is designed to explore the safety, tolerability, pharmacokinetics, and pharmacodynamics of BIND-014, and to define a recommended phase II dose of BIND-014. The initial clinical results were reported in the April issue of *Science Translational Medicine*. In a poster presentation at the 2012 American Association for Cancer Research annual meeting (abstract LB-452, poster 16), updated data were presented on 17 patients, 6 of whom had disease activity. There was preliminary evidence of anti-tumor activity during dose escalation, with a partial response observed in 1 patient with cervical cancer, and stable disease in 5 patients with pancreatic, colorectal, bile duct, tonsillar, or anal cancer. BIND-014 also demonstrated evidence of anti-tumor activity in tumors for which conventional docetaxel is known to have minimal activity. Phase II studies will be starting later this year.

H&O What has been problematic with the typical process of designing nanoparticles?

OF Nanoparticles are complex structures, so the ability to make and optimize them, and then to scale them up to be manufactured has been a bottleneck for the clinical translation and commercialization of nanoparticles for medical applications. There are many parameters that need to be optimized, including the proper size, surface hydrophilicity, charge, release kinetic, rate of polymer degradation, and drug load. Although targeted nanoparticle technologies have been around for more than 30 years, very few of them have been able to make it to clinical trial. Our research team is excited to have largely solved this problem and bring the first example, BIND-014, to the clinic.

H&O What does the future hold for nanoparticle technology?

OF We are just seeing the tip of the iceberg right now, and a true understanding of the interaction of nanomaterials with the human body will evolve over the decades to come. My prediction is that, in the next 20–30 years, nanotechnology will have a larger impact on medicine, biotechnology, and pharmaceutical companies than any biological class of drugs, such as antibody drugs, have had. Nanotechnology will play a major role in improving the health and lives of patients, and it will create much better diagnostics, therapeutics, and predictive medicine.

Suggested Readings

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