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CAISSON BIOTECH: INNOVATION IN DRUG DELIVERY USING A NATURALLY OCCURRING SUGAR MOLECULE

Thomas Harlan
CEO
Caisson Biotech

"Caisson's HepTune involves the process of conjugating this naturally occurring sugar molecule, heparosan, to drugs. The size of the heparosan and the conjugation method for coupling can vary depending on the drug cargo, the client's/partner's preference, and achievement of optimal performance. Caisson works to meet the partner's clinical performance needs for each drug conjugate."

Motivated by increasingly reported adverse events related to PEGylated drugs and based on the pioneering glycobiology research of Dr. Paul DeAngelis of the University of Oklahoma Health Science Center (OUHSC), Caisson Biotech, L.L.C. has developed and patented a drug delivery technology utilizing naturally occurring sugar polymers to more safely and effectively deliver drugs. Customizable to any currently PEGylated drug or to any other molecule requiring this type of stealth modification, HepTune™, Caisson's drug delivery system, can be used in the treatment of a number of diseases. Caisson's patented delivery system harnesses the naturally occurring sugar molecule, heparosan, as its delivery vehicle. By utilizing proprietary methods to manufacture heparosan and its derivatives, Caisson offers its HepTune as a safer delivery vehicle in general and specifically, as an alternative to PEG (poly[ethylene glycol]). HepTune has many bio-superior attributes over PEGylation, including greater compatibility, lack of accumulation in tissues, extremely desirable PK and safety profiles, and no known toxic effects. Additionally, conjugation of Caisson's heparosan-based reagent affords new and novel intellectual property either for new molecules or to extend the patent life of already-marketed drugs, and also recaptures the percentage of the market due to patients that have developed PEG sensitivity excluding them from current PEGylated formulations. Drug Developemnt & Delivery recently spoke with Thomas Harlan, CEO of Caisson, to discuss how his company is improving the quality and delivery of numerous medications, making life easier for patients, and offering new ways for companies to enhance their drug pipeline.

Q: Can you please provide our readers some background on Caisson Biotech?

A: Caisson is a portfolio company of Emergent Technologies, Inc. (ETI), a leading technology access and innovation management company (www.etibio.com). ETI applies rigorous selection criteria to assess and evaluate technologies emanating from thought-leading scientists in universities and federal research labs. Emergent then builds commercially viable businesses based on those platform technologies. ETI has innovated the start-up company management model, allowing for effective initial technology transfer, rapid ramp-up or scale-back of business (depending on the maturity of the technology), and technical resources in response to market needs, aggressive intellectual property (IP) protection, and IP scope expansion

and G&A expense cost-sharing. ETI scouted the glycobiology research of Dr. DeAngelis, and with him (licensing the technology from OUHSC) built a family of companies to produce and explore applications for three commercially important glycosaminoglycan (GAG) polymers: hyaluronic acid (HA), heparosan, and chondroitin. Collectively, these companies (Hyalose, L.L.C., Heparinex, L.L.C., and Choncept, L.L.C.) have partnered with pharmaceutical and biotechnologyy companies to evaluate GAGs for application areas ranging across rheumatology, ophthalmology, tissue engineering, dermal fillers and reconstructive surgery, drug delivery, biomaterials, medical device coating, and anti-adhesion films. Caisson was formed in 2009 as a wholly owned subsidiary of Heparinex when Dr. DeAngelis' research on heparosan, in particular, began to show bio-superior properties over PEG for drug delivery.

Q: What is it about heparosan that makes it Caisson's drug delivery vehicle of choice?

A: Heparosan is structurally related to heparin, one of the most widely used drugs in the Pharmacopeia. Heparosan was predicted to be biocompatible in the human body as it is a natural precursor in the heparin biosynthetic pathway and also because of the stretches of heparosan that exist in human heparan sulfate chains. In addition, certain pathogenic bacteria even use a heparosan coating to evade the immune system during infection. Caisson's HepTune involves the process of conjugating this naturally occurring sugar molecule, heparosan, to drugs. The size of the heparosan and the conjugation method for coupling can vary depending on the drug cargo, the client's/partner's preference, and achievement of optimal performance. Caisson works to meet the partner's clinical performance needs for each drug conjugate.

Q: Many companies focus on drug delivery technologies. What makes Caisson's HepTune unique, and how does is it differ from PEGylation?

A: A significant challenge in the pharmaceutical industry exists in which drugs are excreted too quickly from the body. This can cause patients to endure an increased number of treatment injections (requiring repeated, either multiple injections in a single day or daily injections over an extended period of time) and generate strong immunogenic responses. Currently, PEG is the most widely used drug delivery agent for protein-based drugs to overcome these problems, but suffers from liabilities, including detrimental accumulation in organs and antigenicity of its own. Furthermore, higher doses and/or lifetime treatments using PEG could amplify these problems because the liver detoxification system creates a variety of reactive PEG metabolites that are cytotoxic. There is a rising occurrence of PEG immunogenicity. In 1984, anti-PEG antibodies were detected in 0.2% of naïve patients sampled, but as of 2001, stunningly 22% to 25% of healthy blood donor samples (n = 350) had anti-PEG antibodies.[1] It is thought this increase of anti-PEG antibodies in the general population is due to the increasing use of PEG in consumer products, such as toothpaste, laxatives, vitamin pills, and many other products commonly used on a daily basis. Indeed, some childhood leukemia patients no longer respond to their PEGylated asparaginase (Oncaspar®) medication due to anti-PEG antibody levels.[2] In contrast, the natural heparosan polymers of Caisson's HepTune have the superior synergistic combination of biocompatibility, lack of immunogenicity, and long half-life in the bloodstream. Caisson's heparosan-reagents are degraded into normal sugars and even recycled into other molecules the body uses and thus possess substantially lower toxicity.

Furthermore, the quality control of PEG polymer synthesis (ie, the drug delivery vehicle) with respect to molecular weight distribution is less than optimal. The length of the linear polymer is not uniform and typically a preparation of linear PEG polymers greater than 10 kDa, a portion (~3%) of chains might have branching. This unplanned branching can yield a series of cross-linked complexes containing multiple cargo molecules because every branch has a reactive group for coupling to the cargo. On the other hand, linear heparosan reagents are substantially uniform in length, even for masses up to 800 kDa. In addition, due to an innovative synthesis method involving enzymatic polymerization, Caisson's heparosan drug delivery vehicles cannot be branched and can never have more than a single reactive group. The attachment of the heparosan vehicle to drug cargo, has many other superior attributes over PEGylation, including ease of generating a larger size range of polymers, higher water solubility, greater biocompatibility of degradation products, lack of accumulation in tissues, and new intellectual property. In a 2008 *Current Opinions in Drug Discovery & Development* article, it was predicted future drugs will use higher molecular weight PEGs and/or be given at higher doses for long periods.

Caisson predicts heparosan will be the preferable therapeutic vehicle based on supporting preliminary study results and due to PEG's intrinsic limitations and emerging immunogenicity.

Q: What impact do you see Caisson Biotech's HepTune technology having in the market?

A: Caisson Biotech is well positioned to have a significant impact in the market in a number of ways. Caisson has entered into the market with a naturally occurring sugar polymer drug delivery vehicle, HepTune, with many superior performance benefits when compared to current existing competitive drug delivery systems. Supporting this technology is a very strong patent portfolio. Caisson owns or has rights to 13 patents, 4 of which are issued. Caisson's aforementioned patents are a subset of patents within Dr. DeAngelis' total patent portfolio for carbohydrate production consisting of over 200 patents and patent applications.

The Caisson patent claims consist of multiple and distinct heparosan production methodologies, the use of heparosan as a biomaterial and also the use of heparosan conjugated to therapeutics. PEG, the base material for the PEGylation platform, is a publicly available material. Unlike the innovators of the PEGylation technology, Caisson retains rights to the composition-of-matter and methods-of-manufacture of the heparosan conjugation reagent. This includes the production of monodisperse heparosan materials. The ability to have claim coverage related to the production of the base material (ie, heparosan) provides added protection and exclusivity around the ultimate conjugated materials and therapeutic products. In addition, Caisson benefits from the rights to the control of production and supply of the heparosan material.

With the many advantages outlined, Caisson believes it is well positioned to make a significant impact and contribution to the current drug delivery market, greatly benefiting pharmaceutical companies and ultimately patients.

Q: What makes Caisson Biotech an ideal partner?

A: Caisson Biotech has a commercially proven drug delivery technology, a highly motivated and committed staff, and a track record of meeting milestones specified in contracts, both commercial and grant sourced. Caisson's employees have a combined 66 years of experience in the Glycobiology field ranging from the discovery and manipulation of enzymes responsible for synthesis of GAG polymers (heparosan, chondroitin, and hyaluronic acid) to production and validation of heparosan for use in drug delivery. Caisson's founding scientist, Dr. Paul DeAngelis, is highly recognized in the Glycobiology field for various contributions, both scientifically and for his commercial success, and is still actively engaged with Caisson on a daily basis. Companies interested in evaluating HepTune will find the management easy to work with, the cost of evaluation very affordable, and the process whereby conjugates are specified and procured for evaluation and testing easy to comprehend and comply with. The corporate management has developed a simple, timely, and effective engagement protocol for companies interested in evaluating the technology.

Q: What can we expect to see from Caisson in the market?

A: In May, 2012 Caisson announced Novo Nordisk as its first commercialization partner. The recently executed Developmental License Agreement focuses on development of a number of heparosan-conjugated drugs. One or more of these drugs are projected to enter into clinical trials between 2013 and 2014.

Caisson is also developing an internal drug pipeline with several products currently progressing through preclinical trials. The company is gearing up for commercial-scale production to handle multiple new clients and expects to see active sales and marketing efforts by its partners in the US and Europe in the near future. Caisson looks forward to the rapid advancement of its clinical pipeline and the opportunity to work with additional industry partners to bring novel therapeutics to patients in need.

References

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