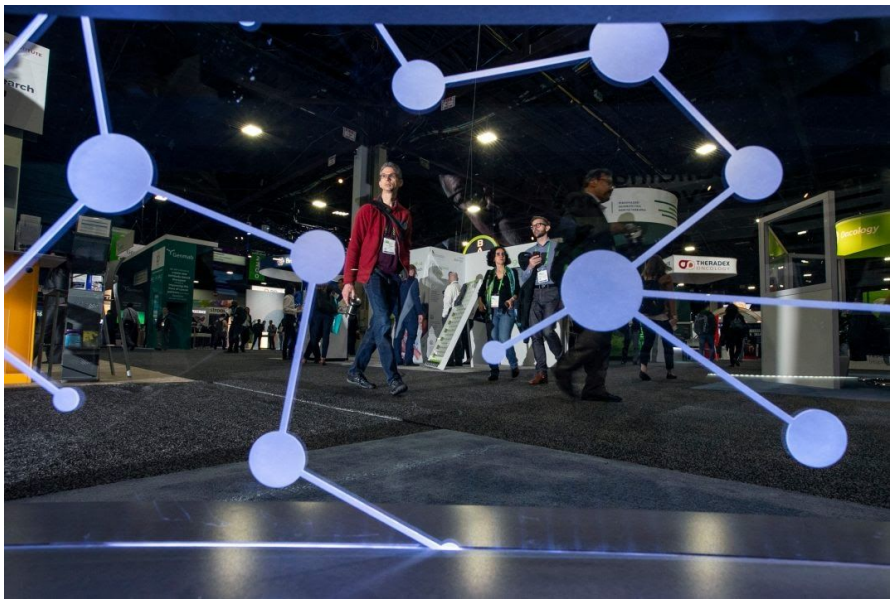
Anti-CD99 Targeted Nanosphere Shows Potential in Ewings Sarcoma

By **Peter Hofland, Ph.D** - April 3, 2019



Despite key-advances in the development of novel anti-cancer therapeutics, off-target, adverse, effects plague drug developers. One reason is that standard chemotherapeutic agents are not specific. This, inevitably, leads to off-target toxicity.

Today, patient-specific targeted therapies are considered the holy grail of anti-cancer therapeutics. In most cases, these therapies allow potent tumor depletion without detrimental off-target toxicities. This approach has resulted in the development of *antibody-drug conjugates* or *ADCs.* But even these uniquely designed targeted agents may fail to achieve a sufficient therapeutic window due to target-mediated or off-target toxicities. For example, results from a recent study published in *Chemistry* describes how, in clinical trials, some of these ADCs have failed, showing off-target toxicities. [1]

To overcome the problem of off-target side effects, researchers at NanoValent Pharmaceuticals (Bozeman, MT) have developed a new class of of pharmaceutical agents called *targeted nanospheres or TNS.*

NanoValent's first in class *targeted nanospheres,* which incorporates the company's highly optimized *Hybrid Polymerized Liposomal Nanoparticle* or HPLN technology, developed in collaboration with *Children?s Hospital Los Angeles* (CHLA), is expected to provide a vast improvement in flexibility and choice for patients restricted by current

treatment options, including immunotherapy and antibody-drug conjugate-based anti-cancer agents. This improvement is the result of repositioning existing therapies such as chemotherapeutics and by optimizing the delivery of emerging candidates including small molecules and therapeutic nucleic acids.

Targeted Nanosphers

Considered a novel class of therapeutic agents, targeted nanospehers are true 'nano'-size particles covalently linked to a tumor specific monoclonal antibodies or peptides. The unique matrix-structure enables chemotherapeutic agents to be loaded to high concentrations without leaking.

Encapsulating irinotecan

One of the company's drug candidates offers a unique form of therapy with an anti-CD99 TNS encapsulating irinotecan, a *topoisomerase I inhibitor* with a mechanism of action aimed at interrupting DNA replication in cancer cells, the result of which is cell death. Irinotecan or CPT-11 is a semi-synthetic derivative of camptothecin, and approved in the United States for the treatment of colorectal cancer. The water-soluble drug is metabolized mainly by the liver to *7-ethyl-10-hydroxy-camptothecin* or SN-38.

Reducing tumor burden

The initial results of the first-in-class CD99-targeted nanoparticle (CD99-TNP/Ir), presented at the annual meeting of the American Association for Clinical Research (AACR), held March 29 – April 3, 2019 in Atlanta, Ga, indicate that the drug candidate can efficiently reach implanted Ewing's sarcoma tumors in xenograft mice and dramatically reduce and/or eliminate the tumor burden.

Researchers at NanoValent confirmed that complete tumor ablation has been observed at doses as low as 1 mg irinotecan/kg, treated twice per week. In other cases, animals who failed untargeted treatment showed complete tumor ablation after "salvage" treatment with a CD99-targeted TNS.

The CD99 targeted formulation, called NV103, showed better efficacy than the commercial untargeted *liposomal irinotecan* (Onivyde?; Ipsen Biopharmaceuticals) and doxorubicin (Doxil?; Janssen Oncology). Toxic side effects, normally associated with systemic administration of free irinotecan, were minimized or undetectable. NV103 showed excellent bioavailability. Even the

untargeted HPLN/Ir improve drug bioavailability six-fold in a comparison experiment with the drug in liposomal form, with no discernible systemic toxicity.

Experiments using human an anti-CD99 antibody targeting TNS demonstrated these novel agents can be used for delivery of therapeutic nucleic acids including siRNA, ASO or functional CRISPRCas9 systems against EWS-FLI1. One of the observations confirms that TNS/siRNA and ASO against EWSFli1 reduced the protein expression of EWS-Fli1 by 35% and 65%, respectively.

NanoValent's results of TNS/CRISPR-Cas9 systems further showed substantially improved efficient delivery of CRISPR-Cas9 components and a 70% knockdown of EWS-FLI1 expression in vitro. The initial animal study showed the systemic administration of a human monoclonal anti-CD99 TNS encapsulating CRISPR-Cas9 against EWS-Fli1 could reduce the tumor growth of Ewing tumor successfully.

Varied therapeutics

Based on these results, Jon Nagy, PhD, the Chief Scientific Officer and co-founder of NanoValent, expects that targeted nanosphers can be used as a clinically viable method for the targeted delivery of varied therapeutics, including chemotherapeutic agents such as doxorubicin and irinotecan, therapeutic nucleic acids (siRNA and ASO) and CRISPR-Cas9 systems.

"The next big step is to prove that our carefully developed and optimized technology can provide highly advantaged product candidates that can be validated in the clinic. With this data in hand, we should be on the cusp of translating the massive potential and flexibility of targeted nanosphers based technologies," Nagy explained.

Ultimately, after development of other tumor-specific targeting agents and varied encapsulated therapeutics, NanoValent's technology can be usefully adapted for the treatment of various cancers as well.

"Once NV103 is clinically validated in Ewing sarcoma, we will explore additional indications in patients with hepatocellular carcinoma, prostate cancer and neuroendocrine tumors as well as advancing other developmental candidates,? noted Timothy Enns, Chief Executive Officer of NanoValent Pharmaceuticals.

The company's promising strategy is expected to augment the efficacy of current therapeutic strategies while, at the same time, decreasing off-target toxicities leading to undesirable adverse events associated with non-targeted anti-cancer treatments.

Reference

[1] Lerchen HG, Stelte-Ludwig B, Berndt S, Sommer A, Dietz L, Rebstock AS, Johannes S, Marx L, J?ri?en H, Mahlert C, Greven S. Antibody-prodrug conjugates with KSP inhibitors and legumain mediated metabolite formation. Chemistry. 2019 Mar 14. doi: 10.1002/chem.201900441. [PubMed]

[2[Gyoo Kang H, Nagy J, Mitra S, Triche T. Targeted therapy of Ewing?s sarcoma by human anti CD99 targeted hybrid polymerized liposomal nanoparticles (HPLNs) encapsulating anticancer agents. Annual Meeting American Association of Cancer Research; April 2, 2019. Session PO.TB08.01 – Targets and Therapies in Pediatric Cancer [Presentation]

Last Editorial Review: April 2, 2019

Featured Image: General during the American Association for Cancer Research Annual Meeting, at the Georgia World Congress Center, Sunday March 31, 2019. **Courtesy:**? 2010 ? 2019 AACR/Al Diaz. Used with permission.