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ProLynx's linker technology releases drugs at pre-programmed rates

ProLynx: Hitting the links

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ProLynx LLC has developed conjugate linkers that increase a drug's duration of action by releasing active therapeutics at consistent, preprogrammed rates. By doing so, the company thinks it can overcome the drawbacks of other conjugate technologies.

First-generation conjugates increase duration of action by covalently attaching active drug to a macromolecular carrier, such as PEG or serum albumin. But these bound carriers often reduce a drug's biological activity and preclude intracellular action, according to ProLynx co-founder and President Daniel Santi.

Second-generation technologies typically use linkers that are cleaved by esterases, releasing the drug to act unencumbered by the carrier. However, Santi said, ester-containing linkers have a maximum half-life of one or two days, which limits their ability to continuously keep the drug concentration at or above target levels. Esterase activity also varies between individuals and across species, making the release rate of active drug unpredictable, he added.

Santi and Gary Ashley, co-founder and CSO, reasoned they could improve the predictability of drug release by designing linkers that are cleaved based on pH-dependent ionization and release drug at a rate proportional to the amount of conjugate ionized at a physiological pH. They also hypothesized they could control that rate by adding different modulators to the linkers.

"Gary and I thought it out and filed for provisional patents before doing any of the chemistry work," Santi said. "And the technology worked out the way we hoped it would."

The company is focused on partnering the platform technology. Last year, it announced a deal with **Johnson & Johnson**'s Janssen R&D Ireland unit (formerly Tibotec Pharmaceuticals Ltd.) to evaluate ProLynx's linker technology with undisclosed Janssen compounds. Financial details were not disclosed.

To show proof of concept, ProLynx used its linkers to join PEG to either a peptide or a small molecule - exenatide and SN38, respectively. SN38 is the active metabolite of cancer drug irinotecan.

The linkers provided predictable, tunable release rates of ligands from PEG *in vitro*, with half-lives spanning from hours to more than one year at physiological pH.

In rats, linkers conjugated either to PEG or a hydrogel delivered exenatide at a rate sufficient for dosing once every week. Data were published in the *Proceedings of the National Academy of Sciences* on April 2.

The company plans to perform additional preclinical studies to demonstrate *in vivo* POC of every-other-week dosing with the PEG-exenatide conjugate, as well as a subcutaneous hydrogel implant that would allow for once-monthly dosing.

According to COO Peg Horn, ProLynx has unpublished data showing its PEG-SN38 maintains drug serum levels at or above target levels for "extraordinarily long periods - about as close to a continuous infusion as you can get from a single injection."

The company would like to license both molecules. "We do not intend to be a product-focused company," Horn said.

ProLynx has seven patent applications covering the company's linkers, modulators, supports and conjugates.

The company has raised an undisclosed amount of funds from its employees, and has enough cash to continue developing the linker technology and conduct preclinical testing.

COMPANIES AND INSTITUTIONS MENTIONED

Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.

ProLynx LLC, Hayward, Calif.