

EMERGING COMPANY PROFILE | REPRINT FROM JUN. 22, 2023

## Tagworks: using click chemistry to make ADCs more applicable and radiotherapies safer

BY RICHARD GUY, BIOPHARMA ANALYST



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Netherlands-based Tagworks is using click chemistry to simultaneously accomplish on-target activation of ADCs and off-target deactivation of radiopharmaceuticals. After spinning out of Philips Healthcare in 2011, the company has announced a \$65 million series A round co-led by Ysios Capital and Gilde Healthcare.

Tagworks Pharmaceuticals B.V. CEO Marc Robillard told BioCentury that antibody-drug conjugates (ADCs) are limited by a paucity of receptors that are selectively over expressed on cancer cells and capable of internalizing the ADC into the cell.

Tagworks solves this problem by increasing the number of targetable receptors to include those that don't internalize ADCs. The company's click chemistry-based technology is based on the sequential administration of a pair of molecules that react only with each other. When they do, they release a cytotoxic payload that enters the cell via passive uptake.

The first molecule is a targeting antibody bearing a trans-cyclooctene moiety bound to the cytotoxic payload

monomethyl auristatin E (MMAE), which is commonly used in ADCs. The second is a tetrazine-bearing trigger. After the first molecule binds to the target, and the second molecule binds to the first, their respective trans-cyclooctene and tetrazine moieties click together to release the MMAE.

Robillard said that in addition to increasing the scope of possible targets, the approach has the advantage of induced a bystander effect. "The drug doesn't have to go into the cell that has the receptor," he said, "It could actually go into a neighboring cell with no receptor." That, he added, is useful in the context of solid tumor indications, which are "notoriously heterogeneous."

The company has also adapted its technology to improve the safety of radiopharmaceuticals, which Robillard said persist in the body too long to permit dose levels high enough for efficacy.

"You can't inject enough into the patient to get efficacy because you have dose-limiting toxicity due to irradiation of the bone

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marrow,” he said. “We realized that if you could use click-to-release to release a payload in the tumor on demand, you could also potentially unlabel radioactively labeled antibody off target and not in the tumor.”

In this use case, the targeting antibody bears a trans-cyclooctene bound to a therapeutic isotope. “You allow this to circulate,” said Robillard. “You allow the binding receptor to internalize the antibody into the cell. After that has happened, you inject the trigger molecule. That is cell impermeable, so it will click release anything it finds in the extracellular space, in the blood and other tissues. In one shot you unlabel the activity off-target, and not touch the activity on-target.”

The cleaved portion is “a small chelator” that is “peed out in 10 minutes,” he added.

The company has three on-target activation and two off-target deactivation programs in its pipeline. The company’s lead program is on-target activation program TGW101, which is targeting TAG72 to treat solid tumors and is at the preclinical stage.

Robillard said the series A financing would be sufficient to advance TGW101 into the clinic.

He added that the company’s technology could also be applied to immuno-modulators comprising a tumor-targeting protein bound to a T cell, to stop the off-target activation of T cells. However, the company has not disclosed any click-to-release immuno-modulators in its pipeline.

Robillard cited CytomX Therapeutics Inc. (NASDAQ:CTMX), Werewolf Therapeutics Inc. (NASDAQ:HOWL) and Amunix Pharmaceuticals Inc., now part of Sanofi (Euronext:SAN;

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## COMPANY PROFILE TAGWORKS PHARMACEUTICALS B.V.

Nijmegen, The Netherlands

**Technology:** Click-cleavable ADCs and radiotherapeutics

**Origin of technology:** Philips Healthcare

**Disease focus:** Cancer

**Clinical status:** Preclinical

**Founded:** 2011 by Marc Robillard, Raffaella Rossin and Zach Taylor

**Academic collaborators:** names of universities

**Corporate partners:** names of cos

**Number of employees:** 20

**Funds raised:** \$74 million

**Investors:** Gilde Healthcare, Lightstone Ventures, New Enterprise Associates, Novartis Venture Fund, Ysios Capital

**CEO:** Marc Robillard

**Patents:** 12 issued covering the composition of matter on several generations of the click-to-release reaction and click cleavable therapeutics ; as well as product-focused IP

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NASDAQ:SNY), as examples of other companies developing cancer prodrugs designed to activate only after reaching their target.

The products of all three companies are unmasked by proteases over expressed in the tumor microenvironment.

Novartis Venture Fund, New Enterprise Associates and Lightstone Ventures participated in Tagworks’ series A.

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