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Heidelberg PHARMA
Focused Cancer Therapies

A targeted cancer chemotherapy with a new mode of action

Combining the precision of antibody targeting with α-amanitin, a novel payload, Heidelberg Pharma has developed a powerful therapeutic platform, with the potential to treat a broad range of cancers.

Heidelberg Pharma's novel targeted chemotherapeutic agent adds the first new mode of action to the arsenal of cancer chemotherapeutics in 20 years. The company, based in Germany, is combining an antibody targeted approach with amanitin, a unique toxin molecule originally identified in the death cap mushroom (*Amanita phalloides*). This new therapy overcomes the problem of resistance that occurs with current cancer therapies and has the ability to kill dormant cancer cells. With the discovery of a biomarker that can identify patients who will benefit the most, Heidelberg Pharma is creating a new therapeutic avenue with wide potential applications in oncology and beyond.

"Almost all fundamental processes have been exploited to kill tumor cells, but there's one missing piece and that's the inhibition of transcription," said Andreas Pahl, Heidelberg Pharma's Chief Scientific Officer. Amanitin is now filling that gap through the inhibition of RNA polymerase II. Whilst the compound is toxic to the liver, Heidelberg Pharma's proprietary Antibody Targeted Amanitin Conjugate (ATAC) platform can successfully deliver amanitin-based therapies by chemically linking the drug to an antibody (Fig. 1). "Just by selection of the antibody we can guide the amanitin payload to different tumor targets and so far, we haven't found a tumor entity that is resistant to this new mode of action," said Pahl.

The company has shown that the amanitin-based drugs kill cancer cells that are resistant to other treatments, including HER2-positive breast cancer cells. A HER2-targeting ATAC was able to achieve complete remission after a single dose, something that could not be achieved with antibody conjugates such as Kadcyla (trastuzumab emtansine).

Another major advance is the induction of cell death in dormant tumor cells, which are responsible for disease relapse. "Even dormant cells undergo some baseline transcription, so if this can be blocked by amanitin, the dormant tumor cell is driven to apoptosis," explained Pahl. Results clearly show that amanitin is able to kill non-dividing tumor cells isolated from bone marrow biopsy samples from patients with multiple myeloma, where auristatin conjugates used by competitors fail.

Biomarker with platform-wide applicability

Together with the MD Anderson Cancer Center in Houston, Texas, the company discovered that the deletion of the *TP53* tumor suppressor gene on chromosome 17 is often accompanied by co-deletion of the neighboring *POLR2A* gene, which encodes for part of the RNA polymerase II complex. Tumor cells with this deletion show a higher risk profile but are also much more sensitive to treatment with ATACs, owing to their lower levels of RNA polymerase II. Heidelberg Pharma has exclusively in-licensed patent rights for this biomarker, which occurs in 20–80% of tumors, depending on type and stage. "We can use this biomarker to identify high-risk patients with a high unmet medical need in order to stratify patients and expedite clinical development," said Pahl.

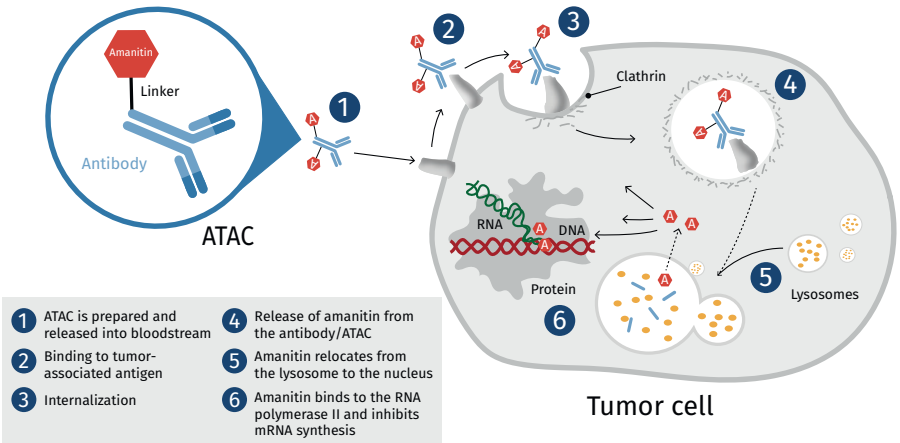

Fig. 1 | ATACs and their mode of action. ATAC, antibody targeted amanitin conjugate.

Therapeutic pipeline

Heidelberg Pharma is building a rich proprietary pipeline of potentially best-in-class drug candidates for both haemato-oncological and solid tumor indications. The lead candidate, HDP-101, is in development for treating multiple myeloma. This bone marrow cancer causes 70,000 deaths annually and has a particularly poor prognosis for patients with chromosome 17 deletions. HDP-101 targets tumor cells expressing the B cell maturation antigen (BCMA) receptor and has higher activity in tumor cells in which chromosome 17 deletions occur. Moreover, preclinical studies show that tumor cell death occurs even when BCMA expression is very low. "Because there are only a few thousand RNA polymerase molecules per cell, you only need to deliver a small number of toxin molecules to achieve cell death," explained Pahl.

Heidelberg Pharma expects to begin clinical studies by early 2021 and hopes the very high medical need for patients with chromosome 17 deletions could accelerate development for this segmented population. Its growing pipeline of proprietary drug candidates includes one that targets the prostate-specific membrane antigen (PSMA) and two others with undisclosed targets.

Partnering and beyond

The strength of the ATAC technology platform has also been leveraged through several partnerships, including one with Magenta Therapeutics aimed at developing conditioning therapies for patients undergoing bone marrow transplantation. The core idea is to replace the very harsh standard conditioning regimens with an ATAC that can selectively eradicate the affected cell population that needs to be replaced by donor cells, not only in oncology, but also in autoimmune and genetic diseases. The company has also entered into a multi-target research agreement with Takeda Pharmaceuticals.

Heidelberg Pharma is now looking for further partnerships to exploit the full potential of its ATAC platform, which can be used to develop safe and effective amanitin-based therapeutics with any specific antibody. "We believe our approach could be a huge step forward in cancer therapy to treat a wide range of tumors and address resistance and dormant tumor cells. This would allow for complete tumor elimination and hopefully even achieve the dream of a cure for cancers that until now relapse and remain incurable," said Pahl.

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