

## BIOBUSINESS BRIEFS

## DEAL WATCH

## Phase III antibody targeting tumour pH acquired in Prometheus deal

Prometheus Laboratories has acquired exclusive rights to commercialize the Phase III-stage clear-cell renal cell cancer (RCC) candidate girentuximab in the United States. Willex will receive US\$19 million upfront plus milestone payments and royalties on sales of girentuximab, if the drug is approved.

Girentuximab is a chimeric monoclonal carbonic anhydrase 9 (CA9)-specific antibody that was originally developed in the 1980s at the University of Leiden, the Netherlands. The high expression of CA9 in solid tumours, and its absence from most healthy tissues, suggested that it could be a promising therapeutic target as well as a diagnostic marker for cancer.

CA9 is a membrane-bound pH-regulating protein that catalyses the hydration of carbon dioxide to protons and bicarbonate at the extracellular surface (*Nature Rev. Drug Discov.* 7, 168–181; 2008). It is highly expressed in cancer cells as they require a slightly alkaline internal pH to survive and proliferate in hypoxic conditions. Studies in mice have shown that inhibition of CA9 has a strong anticancer effect on both the primary tumour and metastases, and in Phase II clinical trials in patients with RCC, girentuximab showed promising results. This antibody is now in Phase III trials and an interim analysis later this year is expected to provide crucial information on the end point of the trial (disease-free survival).

“As CA9 is not present in normal cells and carbon dioxide hydration may also occur without a catalyst, no major toxicity is envisaged when the activity of this protein is completely inhibited,” explains Claudiu Supuran, a professor at the University of Florence, Italy.

Among all of the pH-regulating proteins in cancer cells, CA9 is emerging as the most promising anticancer target, because of its restricted expression. Furthermore, “the elucidation of the three-dimensional structure of CA9 has allowed the development of isoform-specific inhibitors. Some of these compounds, such as coumarins, have shown antitumour and antimetastatic activity *in vivo* (*Cancer Res.* 71, 3364–3376; 2011),” says Supuran.

However, “disrupting the pH regulation in tumour cells will have better success if CA9 inhibition is combined with inhibition of other pH-regulating proteins such as monocarboxylate transporters, Na<sup>+</sup>/H<sup>+</sup> exchanger 1 or CA12, which are also co-expressed at the surface of some tumour cells. In this context, membrane-impermeable sulfonamides, which display inhibitory constants in the low nanomolar range towards both CA9 and CA12, may be preferable,” says Jacques Pouyssegur, a professor at the Institute of Developmental Biology and Cancer Research, Nice, France.

In addition to RCC, girentuximab could be used to treat other highly proliferating solid tumours that express CA9, either on its own or in a combined treatment as a specific drug delivery agent. “Fluorescent sulfonamide CA9 inhibitors (*Radiother. Oncol.* 92, 423–428; 2009) have recently been shown to accumulate in the hypoxic regions of tumours, suggesting that such molecules could also be used for imaging tumours or delivering cytotoxic agents,” adds Pouyssegur.

Since this deal was announced, Nestlé’s Health Science subsidiary has acquired Prometheus Laboratories for an undisclosed sum.



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