

## Commentary: Jérôme Van Biervliet

# Oncurious – a paediatric oncology company

The French novelist Victor Hugo is often remembered for his remark that ‘perseverance is the secret of all triumphs.’ This is as true in drug discovery as it is in art, where an initial insight can take years of work to produce a product of lasting value. Academic science often leads to a breakthrough.

This is the story behind Oncurious NV, a company launched in April to develop a new therapeutic indication for the compound TB-403, which has a long and unusual history. Oncurious is a joint venture between ThromboGenics NV and VIB.

TB-403 is a humanised monoclonal antibody against placental growth factor (PlGF), a member of the vascular endothelial growth factor (VEGF) sub-family. PlGF has been the subject of top academic science and company interest for many years. The therapeutic potential of PlGF has shown differential effects in studies in mouse models, where blockade of PlGF has resulted in anti-angiogenic and anti-tumour effects in some models.<sup>1,2,3,4</sup> but less so in others<sup>4,5</sup> in part due to context-dependent effects, modulated by differences between tumours in the expression level or the type of receptor, levels of tumour-secreted VEGF affecting VEGF/PlGF ratios and homo/heterodimer formation.<sup>4,6,7</sup> Based on its potential in anti-angiogenic paradigms, TB-403 was tested in healthy volunteers and patients with advanced solid tumours in 2008, where it was shown to be well tolerated with minimal side effects.

However, in a landmark paper between R. Jain’s laboratory at Harvard Medical School and Peter Carmeliet, an alternative signalling mechanism for PlGF was documented and hence a new therapeutic mode of action was envisaged in a new indication, medulloblastoma. PlGF was shown to be up-regulated in the majority of medulloblastoma cancers regardless of the genetic subtypes. To a large degree, the growth factor was produced by the stromal cells surrounding the tumour cells. The functional model relies on PlGF-Neuropilin 1 binding and signal transduction towards pro-survival pathways in the tumour cells. This effect is independent of its effects on angiogenesis.

To corroborate this thesis, it was shown that the expression of Neuropilin 1 correlates with poor overall survival in medulloblastoma. A model akin to addiction behaviour emerges, whereby medulloblastoma cells induce production of stromal PlGF to sustain a pro-survival state through paracrine secretion of signalling molecules. This becomes a self-enforcing cycle. Disruption of this cycle through PlGF blockade resulted in direct anti-tumour effects *in vivo*, including tumour regression, decreased metastasis and increased survival.

Whereas the initial development plan for the compound was for advanced solid tumours, the new indication is specifically for medulloblastoma, a life-threatening brain tumour.

Medulloblastoma is the most common malignant brain tumour in children, accounting for 20% of all paediatric brain tumours. Current treatment consists of brain surgery

followed by radiation and/or chemotherapy. Long-term survival can be achieved in approximately 80% of patients, but the combination of radiation and chemotherapy is highly toxic to the developing brain and associated with significant long-lasting detrimental impact on these children. Approximately 20% of these children experience relapse of the primary tumour and consequently have a very poor prognosis with a median survival of only 14 months.

TB-403 represents an opportunity to establish a new, targeted therapy in paediatric patients with medulloblastoma, particularly for those with relapsed disease, with the aim of improving outcome and survival. In the longer term, it may help to avoid some of the detrimental sequelae of the current radiotherapy and chemotherapy regimens and lead to better functional outcomes for first-line treatment medulloblastoma patients. Such an impact would translate to a long-lasting impact on these children’s lives. Additionally, there are indications that PlGF and Neuropilin 1 are overexpressed in some other paediatric tumours where TB-403 may have additional applications.

Oncurious now plans to start a Phase 1/2a programme with TB-403 in relapsed or refractory medulloblastoma patients. Enrollment of the first patient is expected before the end of 2015. Beyond TB-403, the company aims to extend its impact in paediatric oncology indications based on scientifically novel therapeutics – because cancer shouldn’t be allowed to destroy innocent victims and their families.

### References:

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