

Key information

Access to 2nd generation Antibody-Drug Conjugates (ADC) → innovative and highly effective anti-cancer treatment

The Project:

ADCs combine the well established principle of targeted antibodies (safety and tolerability) with the effectiveness of ultrapotent toxins (anti-tumor efficacy). They consist of a monoclonal antibody conjugated to potent toxins by chemical linkers. The function of the antibody part of the ADC molecule is ‘to guide’ the toxin specifically to the target tumor cells, and to allow healthy cells to be left untouched.

2nd Generation ADCs are designed on the basis of a new class of toxin, that has a mode of action and chemical / biological properties that are entirely new and innovative and that relate to potential clinical benefits of great importance.

The Market:

A general objective in oncology drug discovery and development is to achieve tumor cell eradication, while maintaining at the same time a high level of tolerability to healthy cells and tissues. Currently approved therapeutic monoclonal antibodies, such as MabThera, Herceptin, Avastin and Erbitux have made anti-cancer therapy more effective, safer and better tolerated than with conventional chemotherapeutics and achieved sales of well over 10 billion dollars.

The ADC concept, that combines the targeted therapy approach with ultrapotent toxins for more anti-tumor efficacy and better tolerability, has been taken up by virtually all Big Pharma and Biotech companies such as Amgen, Bristol Myers Squibb, Roche/Genentech, Bayer, Aventis, Biogen Idec and others.

Most of current ADCs have been developed by Immunogen and Seattle Genetics and successfully been marketed to the enterprises named above. They are based mainly on two classes of toxins, the maytansinoids and the auristatins.

Uniqueness of 2nd generation ADCs

Maytansinoids, auristatins and others may effectively induce tumor shrinkage and reduce tumor mass in selected tumor types – by acting selectively on dividing tumor cells. Current opinion however is, that tumor relapse and tumor metastases may be related to “dormant or quiescent tumor cells” that are insensitive to most – if not all - currently approved drugs for the treatment of cancer.

This explains the tremendous demand for toxins and coupling techniques

that result in new ADCs with entirely new properties, in particular to meet the challenges in treating tumor metastases and preventing tumor relapses. In this environment, our unique approach, ADCs that promise efficacy on dividing or quiescent tumor cells alike, may be of unmet value.

The 2nd Generation ADC:

In the past in-depth scientific know-how has been generated respective an unique toxin, and different coupling methods to antibodies. Multiple 2nd generation ADCs have been designed and tested. In addition, ways of producing the toxin in a scalable and cost-effective manner have been identified. The project has now achieved the status of a technology platform, potentially leading to multiple 2nd generation ADCs for treatment of different tumor entities.

The results of extensive scientific and development work so far are supportive for therapeutic claims of significant importance.

Pre-clinical experiments indicate cure potential of 2nd generation ADCs. Non-dividing, slowly dividing and rapidly dividing cells are equally sensitive to minute concentrations of ADCs in the picomolar range. Animals treated with a single dose of selected ADCs were, healthy and tumor-free, long after untreated tumor-bearing animals had died (see figure below).

2nd Generation ADC are expected to be highly effective in therapy resistant cancer. Mechanisms that are made responsible for therapy resistance in tumor patients are not affected by 2nd generation ADC. In specific therapy resistance models, 2nd generation ADC were still highly effective.

2nd Generation ADC potentially have a favourable safety profile compared with current ADC under development. The ADCs are up to $10^3 - 10^4$ (ten thousand times) more potent in killing tumor cells, than the free unconjugated toxin can do damage to few types of healthy cells. 2nd Generation ADC are constructed to avoid even minimum release of free toxin into the blood circulation. But even if minute amounts would be released, its potential to cause damage is limited. On top of that: the free toxin is rapidly removed from the circulation within minutes.

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