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Editorial Comment

Targeted therapy – How successful has it been?

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The notion of 'targeted' for the actual and future antitumour therapeutic principle implies that the therapy of the past was undirected or lacking targets. This would be to overemphasise what medical oncologists are capable of doing now. Furthermore, it has to be admitted that the therapeutic approaches of the past were not target-less.

Most agents of conventional chemotherapy target tumour-cell DNA synthesis or repair as general principles, exploiting thereby the often only marginal advantage of the relative smaller proliferation rate of many non-malignant transformed cells in comparison to cancer cells. Many alkaloids, derived from plants or of marine origin, function mainly via interference with microtubules and have a negative impact on the functioning of the spindle apparatus. In highlighting the 'target-directed' approach, we base our concept of malignancy on the newer understanding of cancer as a genetic disease with mutations that produce oncogenes, with dominant gain of function, and tumour suppressor genes, with recessive loss of function. Therapeutically, the mutated genes, their gene products such as receptors, or even comprehensive signal-transduction pathways and networks, may be targeted. As with conventional chemotherapy, the absence or the low expression of such genes, their products or entire networks in normal tissues provide the basis for specific tumour targeting.

A model of the physiological circuits of normal cell regulation has been provided by Hanahan and Weinberg [1] in their seminal 'The hallmarks of cancer'. According to Carbone [2], 'hitting a specific target is not therapeutically meaningful unless the tumour depends on the target and equally important, the host does not'. The paradigm of a targeted therapy we are most familiar with is (anti-)hormone therapy, especially in breast cancer. Although it is one that goes back more than a hundred years, we learned only very recently (in 1996) that there exists more than a single receptor mediating the action of oestrogens [3]. Similarly, how to profit from anti-oestrogen therapy even with incomplete knowledge of its mode of action until today, although, in comparison to others, the steroid hormone pathway is among the simplest of the cell's physiological circuits known so far. Nevertheless, it took decades: (1) to determine the target patient population; (2) to standardise the method of determining/measuring the hormone receptor level with various detection methods; (3) to assess the putative therapeutic impact on palliative, curative or adjuvant treatment and prevention. And there are still many open questions to be determined/answered, among them a definitive explanation of its mode of action.

The paradigm of an oncogene-targeted cancer therapy is all-*trans* retinoic acid (ATRA) in acute promyelocytic leukaemia (APL); a condition that is induced by a t(15,17) translocation that generates a PML/RARα fusion protein. ATRA causes degradation of PML/RARα, thereby overcoming the dominant negative effect of this translocation product, ultimately inducing differentiation. ATRA single-agent therapy yields remissions in 87%, among them 81% complete remissions, lasting a median of 12 months. In previously treated patients, complete remissions were observed in 77% [4]. Nevertheless, since combining ATRA with conventional chemotherapy yielded superior survival, only the combination of this highly selective targeted therapy with conventional chemotherapy became state-of-the-art treatment for this rather rare disease [5].

Exactly a 100 years ago, Paul Ehrlich, the founder of chemotherapy, used the term 'magic bullets' for antibodies attacking only the pathogen, thereby leaving the healthy organism unaffected [6]. Rituximab (Mabthera®) was the first (chimeric anti-CD20) monoclonal antibody introduced successfully in haematology; it

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yielded 48% remissions, among them 6% complete remissions, in relapsed and/or refractory patients with indolent and follicular lymphoma [7]. Nevertheless, the treatment of these in principle incurable subentities of the lymphomas with this highly targeted approach has not changed the overall outcome of the disease. Clinical trials to combine the monoclonal antibody with conventional therapies are now envisaged. The ultimate established indication for the drug until now is in the treatment of elderly (i.e., >60 years) patients with diffuse large B-cell lymphoma, where it yields statistically significant longer survival ($P = 0.007$) when added to/combined with conventional chemotherapy in form of the CHOP regimen [8].

The first therapeutically successful humanised monoclonal antibody in solid tumour oncology, trastuzumab (Herceptin®), is directed against the extracellular domain of the transmembrane glycoprotein receptor HER-2. It yielded an objective response rate of 15% (4% complete remissions; based on an intent-to-treat analysis; 95% confidence interval, 11–21%) in a cohort of patients with breast cancers over-expressing HER-2 and progressing after chemotherapy, with a median duration of response of 9.1 months [9]. HER-2 over-expression has a direct role in the pathogenesis of this malignant disease; thus its expression is directly linked to the prognosis of breast cancer. Experimental data suggest that trastuzumab's effect on downregulating HER-2 and/or HER-2-mediated signal transduction are more critical to the clinical activity of the antibody than any effects on antibody-mediated cell killing by activated immune effector mechanisms. The objective response rate of less than 20% led the targeted molecule to be added to conventional chemotherapy, resulting in significantly superior results for the combination with regard to objective response, duration of response, time to progression and survival [10].

The chimeric monoclonal antibody cetuximab (Erbitux®) blocks the binding of the natural ligands, epidermal growth factor (EGF) and transforming growth factor-α (TGF-α) to the extracellular domain of the EGF receptor (EGFR), thereby increasing receptor internalisation and inhibiting receptor phosphorylation/activation as well as cell proliferation. The objective single-agent activity in patients with metastasised EGFR-expressing colorectal cancer who were resistant to chemotherapy with irinotecan was 11% [11]. Valuable definite survival results from adding cetuximab to chemotherapy in colorectal cancer are not available as yet; time to progression was significantly longer when cetuximab was combined with irinotecan compared to its use alone. In a prospective randomised phase III study in patients with head-and-neck cancer, no significant advantageous impact of adding cetuximab to cisplatin has yet been found with regard to time to progression or survival [12].

The humanised monoclonal antibody bevacizumab (Avastin®) directed against vascular endothelial growth factor (VEGF) was the first representative of the category of anti-angiogenic/antivascular agents proved to have significantly superior results regarding objective response, duration of response, disease-free survival and median survival when combined with standard chemotherapy in general, and with irinotecan/fluorouracil/leucovorin in previously untreated patients with metastasised colorectal cancer in particular [13]. No comparable advantageous effect on survival was found when bevacizumab was compared prospectively with placebo in metastatic renal cell cancer; nevertheless, time to progression was significantly increased [14]. In a prospective randomised phase III study in patients with breast cancers who had failed prior therapy with an anthracycline and a taxane and who were treated with capecitabine alone or in combination with bevacizumab, no advantageous effect on the primary study aim, progression-free survival, was observed for the combination [15].

Let us focus now on the evaluation of the small molecules that were developed as targeted therapies and that have already become available in the clinic. The outcome of a targeted approach is indirectly determined by the identification of an ideal therapeutic target. In this respect, there is probably no better target identified so far than BCR–ABL. It is expressed in the majority of the patients with chronic myelogenous leukaemia (CML) and it has been shown to be the cause of the underlying disease. The BCR–ABL fusion protein functions as a constitutively activated tyrosine kinase and mutagenic analysis has shown that this activity is essential for the transforming function of the protein.

Imatinib mesylate (Glivec®) was developed primarily as an inhibitor of platelet-derived growth factor receptor (PDGFR). It also inhibited all ABL tyrosine kinase variants and c-KIT, the receptor for stem-cell factor (SCF), but no other protein tyrosine kinases. Very recently, it proved to be statistically significant superior to the established combination chemotherapy consisting of interferon-α plus cytarabine with regard to haematological and cytogenetic responses as well as progression to accelerated-phase or blast crisis-free survival [16]. There exist therapeutic limitations to using imatinib in the treatment of the various forms of CML. Several differing mechanisms of resistance can be activated. Therefore, various pharmacological approaches may be, alone or in combination, adequate to tackle this phenomenon. From the clinic, we had to learn that advanced BCR–ABL-positive leukaemias develop DNA mutations at high frequency and dispose on a reduced role for DNA repair. Therefore, preventing resistance from occurring is of utmost importance. Similarly successful was the development of imatinib for the treatment of patients with gastrointestinal stromal tumours (GIST). The constitu-

tive activation of KIT receptor tyrosine kinase was hypothesised to be critical in the pathogenesis of this tumour entity. GIST were found to express the cell surface transmembrane receptor KIT, the protein product of the *c-KIT* proto-oncogene. GIST frequently exhibit gain-of-function mutations in the *c-KIT* gene. The resulting constitutive activation of KIT signalling thereby leads to uncontrolled cell proliferation and resistance to apoptosis. KIT is the receptor for the cytokine known as SCF, representing its natural ligand. The European Organisation for Research and Treatment of Cancer (EORTC) and a collaborative GIST study group reached similarly impressive therapeutic results, yielding partial remissions in 59% and 69%, respectively, with imatinib (formerly STI-571) of patients with metastatic GIST [17,18]. These excellent clinical results in a disease for which a response rate of less than 5% was reported for cytotoxic chemotherapy with doxorubicin led to its 'fast track' registration by the Food&Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products (EMEA) for KIT (CD117)-positive non-operable and/or metastasised patients with GIST [19]. But even this tremendously successful, new, rationally developed therapy has some limitations and drawbacks. Usually the remissions reached are not complete and even if they are complete, tumours tend to recur after several months. About 5% of patients with GIST experience primary resistance to imatinib. Up to now, no optimal immunohistochemical detection method for c-KIT (CD117, stem-cell factor receptor), the therapeutic target, has been established with regard to sensitivity and specificity.

The tyrosine kinase activity of the EGFR can be intracellularly inhibited by blocking its ATP-binding site with a low molecular-weight tyrosine kinase inhibitor (TKI). Among the small TKIs, the reversible EGFR-selective substance ZD1839, now referred to as gefitinib (Iressa®), is the one that actually is most advanced in its development. Gefitinib demonstrated similar antitumour activity in xenograft models with differing levels of EGFR expression. This led to suggest preclinically that factors other than simply the number of EGFR per cell might influence the sensitivity of tumour cells to EGFR-targeted therapy, at least in relation to what concerns small-molecule TKIs or only gefitinib. This led the company not to select for their EGFR status the patients to be entered, for example, in the prospective randomised phase III non-small-cell lung cancer (NSCLC) trials comparing cisplatin/gemcitabine+/-Iressa® (INTACT-1) and carboplatin/paclitaxel+/-Iressa® (INTACT-2) [20,21]. Both studies failed to demonstrate any improvement of treatment outcome. Nevertheless, based on the results from two randomised phase II studies in which 19% (IDEAL-1) [22] and 10% (IDEAL-2) [23] of the patients responded on 250 or 500 mg gefitinib daily perorally, the drug was registered in Japan and got approval by the FDA for patients with NSCLC after the failure of platinum- and taxane-containing prior therapy. But, it is more than questionable to keep apostrophising the above development as a targeted one.

An identical scenario holds true for the development of the small-molecule TKI erlotinib (Tarceva®), which was tested in patients with advanced-stage NSCLC who had not received prior chemotherapy: in the non-US study, chemotherapy consisted of cisplatin and gemcitabine; in the US study, carboplatin and paclitaxel. Final results, which are diffused by media release (http://www.roche.com; October 1, 2003) so far, but not published in a peer-reviewed journal as of yet, are comparably as negative as those for gefitinib in the INTACT-1 and INTACT-2 trials [20,21].

With the exception of imatinib, both in the treatment of BCR/ABL-positive CML and of GIST, the increase in response rates and the prolongation of survival of all the other targeted therapies tested in target-restricted cohorts of patients do not yet go beyond or do not even reach the level of therapeutic impact known from non-targeted conventional therapies. Overall, this is less than should be expected from approaches that merit being classified as 'targeted'. This holds true also if one excludes the highlight of conventional antitumour chemotherapy, i.e., the treatment of advanced stages of Hodgkin's disease [24] and of testicular cancer [25], reaching cure in 75–80% of unselected cases.

What are the underlying causes? There exists insufficient insight about whether, and if so to what extent, clinical effect/response is dependent from the degree of expression of the target. Historically, Baum advocated for decades that all women should be treated after radical surgery for breast cancer with the anti-oestrogen tamoxifen – the first therapy that merits the title 'targeted' – independent of their target-receptor status [26]. It took years to establish clearly that patients with hormone receptor-negative breast cancer are not going to profit from being treated with anti-oestrogens [27]. There is unanimity that there is a clear correlation between the degree of receptor over-expression [10] and/or gene amplification [28] and the anti-tumour effect of treatment with trastuzumab in breast cancer patients.

Although there is a clear target-restricted patient selection in the imatinib trials, a gap between target expression (100% BCR/ABL positivity) and response rate (of only 50%) in CML blast crisis, as well as one between target expression (90% c-KIT positivity) and response rate (of 50–60%) in GIST, should be noticed. Whereas Verweij et al. [29] very recently warned against treating patients with non-GIST soft tissue sarcomas with imatinib without proof of c-KIT positivity, Heinrich et al. [30] cautioned about withholding imatinib from patients whose GIST lack *KIT* mutations or do not express the KIT protein. They based their recommendation on their investigations showing that, in a subset

of GIST lacking *KIT* mutations, gain-of-function *PDGFRA* mutations can account for the clinical response to imatinib [31]. A further example of a false-negative patient characterisation is that of a patient with a c-KIT-negative soft tissue sarcoma (malignant fibrous histiocytoma) responding dramatically on imatinib. Immunohistochemistry demonstrated the absence of c-KIT, but the presence of PDGFRa and its ligand PDGFR-A as well as of the phosphorylated form of AKT [32].

No correlation was found between the target expression of the VEGF levels and tumour response under exposure with the VEGF antibody bevacizumab, neither preclinically [33] nor clinically [15].

There is overwhelming unanimity in the judgement that there is no correlation between the expression of EGFR as a target and the antitumour activity of anti-EGFR-directed therapies, notably gefitinib, neither at the preclinical level [34] nor at the clinical [35,36], independent of the tumour type. Although Natale et al. [37] describe a correlation between tumour gene expression and response to monotherapy with gefitinib in NSCLC, the levels of EGFR RNA were not predictive of treatment outcome.

As a consequence of the above findings and analyses, the recommendations for future studies with targeted therapies range from target-restricted [38,39] to target-non-restricted patient selection [40]. In order to round off target-related/-dependent pharmacodynamic associations, it has to be stated that there is no unequivocal interpretation concerning any positive correlation between specific targeted therapy-dependent (skin) toxicity and response to target-directed therapies.

Summarising the differing developmental scenarios in the actual targeted-therapy arena, we can principally discriminate between the following.

Successful development because of:
- a clear hypothesis,
- relevant preclinical data,
- rational development,

resulting in clinical utility in well-characterised cohorts of patients.

Examples: imatinib mesylate (Glivec®), trastuzumab (Herceptin®).

Successful development despite of:
- only a vague idea about the putative impact of the function of the target; target not restricted to the malignant cell clone, i.e., a situation identical to the 'pre-targeted era',
- rational development,

resulting in clinical utility in well-characterised cohorts of patients.

Example: rituximab (Mabthera®).

(Successful) development because of:
- a clear hypothesis,
- target specificity not existing to the expected degree,
- sticking to a developmental pattern routinely used for conventional non-targeted therapies,

resulting in a clinical situation that cannot be overlooked as of yet.

Examples: farnesyl protein transferase inhibitor(s) (R115777, Zarnestra®).

Development because of:
- a clear and attractive hypothesis,
- preclinical data not sufficiently supporting this hypothesis,
- fast-track development,

resulting in a clinically questionable therapeutic offer for a not-characterised cohort of patients to be exposed to a therapy named 'targeted'.

Examples: gefitinib (Iressa®), erlotinib (Tarceva®).

The above analysis led us to conclude this account by raising questions about how to understand better the reasons for failing targeted approaches and how to promote strategies to overcome the present obstacles to a higher clinical impact of targeted therapies.

What are the common features of so-called targeted therapeutic approaches?
- Targeted therapies are mainly cytostatic, but not tumour eradicating.
- Targeted therapies effect almost no cures.
- Only a percentage even yields objective tumour regression and symptom relief.
- Development of resistance compromises long-term antitumour effectiveness.

What are the reasons for the ineffectiveness of targeted therapeutic approaches?
- Knowledge about measuring the expression of relevant target parameters within tumours for the selection of cancer patients to be treated and its standardisation is lacking.
- Cancer cells may escape from growth inhibition by using alternative growth pathways.
- Constitutive activation of downstream signalling effectors, targeting proximal events may be ineffective because of redundant inputs to downstream convergence sites.
- The majority of tumours are driven by more than one pathway.
- Since cancer cells are genetically unstable, treatment with antisignalling drugs might also produce resistant cells.
- Most malignancies are heterogeneous and are driven by several genetic and epigenetic deviations.

How can we render our most targeted therapies more effective?
- By identifying disease causative/maintaining structure(s)/pathway(s) to be targeted that are not of equal importance for the host.
- By identifying surrogate parameters for functional activity of the target guaranteeing high predictive accuracy.

- By validating the determination/measurement of targets.
- By developing methodologies that allow us ultimately to abandon taking multiple sequential biopsies of tumour- and non-tumour tissue, and their substitution by non-invasive pharmacokinetic and pharmacodynamic endpoints.
- By better selecting candidate patients for selectively acting therapies (e.g., based on genotyping) and assessing individual comprehensive signal-transduction pathways and networks, resulting in the identification of so-called signalling nodes.
- By combining them with:
  - conventional antitumour therapies such as chemo- and radiotherapy,
  - other targeted therapies to form poly-targeted therapies (comparable to poly-chemotherapy).
- By optimising the right sequence of application.
- By using them as continuous therapies of low toxicity in different/earlier clinical scenarios including the adjuvant setting and possibly in chemoprevention.

Conflict of interest statement

The author indicates no potential conflicts of interest.

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