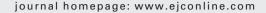


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Upcoming techniques in drug development

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ABSTRACT: Under development are new techniques that have the potential to define subpopulations of patients which may or may not respond to targeted therapy. Better definition of resistance mechanisms against monoclonal antibodies or tyrosine kinase inhibitors will be one approach to achieve this goal. Progress has been made in the detection of these mechanisms when targeting the epidermal growth factor (EGF) receptor family. Proteomics either performed by imaging techniques or by methods such as matrix-assisted desorption/ionisation time-of-flight (MALDI-TOF) mass spectrometry requires further standardisation and validation. A mass spectroscopy-based pre-treatment patient selection system is under development that is highly reproducible and capable of classifying patients by survival.

Keywords: Epidermal growth factor receptor; Resistance mechanisms; Proteomics; Imaging MALDI-TOF; Mass spectrometry

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DEFINITION OF RESISTANCE MECHANISMS

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Only a fraction of patients respond initially to therapy (primary resistance), and those who do, often lose their response to targeted therapy with time (secondary resistance). The postulated mechanisms behind targeted therapy and development of resis-

tance were explored and the epidermal growth factor receptor (EGFR) family was used as an example. The ErbB or epidermal growth factor (EGF) family of receptor tyrosine kinases consists of four members: EGFR (Erb1/HER-1), HER-2 (ErbB1/neu), HER-3 (ErbB3), and HER-4 (ErbB4). ErbB receptor tyrosine kinases are attractive targets for therapy. They initiate multiple signalling pathways, and they are conveniently accessible on the cell surface where they can be targeted with monoclonal antibodies.1 They have an ATP-binding site and are amenable to enzymatic blockade. Mutations - often single amino acid replacements and short deletions - in ErbB receptor genes can occur, as is the case with non-small-cell lung cancer (NSCLC). Likewise, overexpression of ErbB proteins occurs in a fraction of carcinomas, including ErbB-2 overexpression in about a third of breast cancers. Cetuximab (Erbitux®), panitumumab (Vectibix®) and trastuzumab (Herceptin®) are all examples of anti-ErbB monoclonal antibodies in clinical use. The potential mechanisms of trastuzumab action include

- recruitment of natural killer (NK) cells to Her-2 overexpressing tumour cells;
- reduction of Her-2 signalling to the phosphatidylinositol-3 kinase (PI3K), Src, or mTOR pathways;
- inhibition of angiogenesis and vasculature normalisation, thereby improving delivery of chemotherapeutic drugs such as paclitaxel (Taxol®);
- enhancing receptor endocytosis and degradation;
- other hypothesised mechanisms.

Perhaps the main mechanism of action is antibody-dependent cellular cytotoxicity (ADCC) of tumour cells. Antibodies attach to the tumour cell, then NK cells move in and destroy it. Clynes compared knockout and wild-type mice and showed that preferential activation of inhibitory Fc receptors enhanced tumour responses to trastuzumab treatment.² Mice without Fc receptors were unable to recruit NK cells, hence the antibody displayed only partial inhibition of tumour growth.

Spiridon and colleagues used mice with severe combined immune deficiency (SCID) to demonstrate synergistic antitumour effect of a combination of monoclonal antibodies against Her-2 that do not bind to the same epitope. The speaker presented studies performed in his laboratory, in collaboration with M. Sela, showing that single monoclonal antibodies lead to some down-regulation and degradation of EGFR, but certain combinations completely destroy the receptor. A single monoclonal antibody leads only to dimer formation, yielding inefficient