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Precision medicine for colorectal cancers

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The advent of the EGFR-targeted monoclonal antibodies cetuximab and panitumumab paved the way to the individualized treatment of metastatic colorectal cancer (mCRC). In the last 5 years it has become evident that mCRCs respond differently to EGFR-targeted agents and that the tumor-specific response has a genetic basis. After the initial response, secondary resistance invariably ensues, thereby limiting the clinical benefit of anti-EGFR therapies. Understanding the molecular bases of secondary resistance to cetuximab and panitumumab is required to design additional therapeutic options. We found that molecular alterations in KRAS, NRAS, BRAF and MET are causally associated with the onset of acquired resistance to anti-EGFR blockade in colorectal cancers. Preclinical models of relapse including cell lines and patient-derived xenografts (xenopatients) allowed us to assess new lines of therapy. We believe that acquired resistance is a fait accompli and time to recurrence is simply the interval required for the resistant subclone to re-populate the lesion. We are currently assessing if combination therapies targeting different genes in the pathway effectively delay the onset of resistance. Overall our results support the initiation of innovative, molecularly driven clinical trials.