

# Drug resistance in cancer: principles of emergence and prevention

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While targeted therapy is yielding promising results in the treatment of specific cancers, drug resistance poses a problem. We present a new mathematical framework which can be used to study the principles underlying the emergence and prevention of resistance in cancers, treated with targeted small molecule drugs. We consider a stochastic dynamical system which is based on measurable parameters, such as the rate at which resistant mutants are generated, and the turnover rate of tumor cells (we define the turnover rate as the ratio of the natural death rate and the replication rate of cancer cells in the absence of treatment). We find that resistance against nontoxic small molecule inhibitors arises mainly before the start of treatment, rather than in the course of therapy. In other words, resistant mutants pre-exist treatment, they are naturally generated during tumorigenesis.

We apply the mathematical framework to chronic myeloid leukemia, CML. Early stage CML was the first case to be treated successfully with a targeted drug, Imatinib. This drug specifically inhibits the BCR-ABL oncogene which is required for progression. While drug resistance is preventing the successful treatment at later stages of the disease, our calculations suggest that, within the model assumptions, a combination of several targeted drugs with different specificities might overcome the problem of resistance. We also address the problem of cross-resistance (that is, the situation where a single mutation makes a cell resistant to two or more drugs simultaneously); this is a relevant issue in the context of the three currently used drugs for CML: Imatinib, Nilotinib and Dasatinib. We will finally talk about various scheduling strategies including cyclic treatments and a treatment where the number of drugs used is reduced after a period of time.