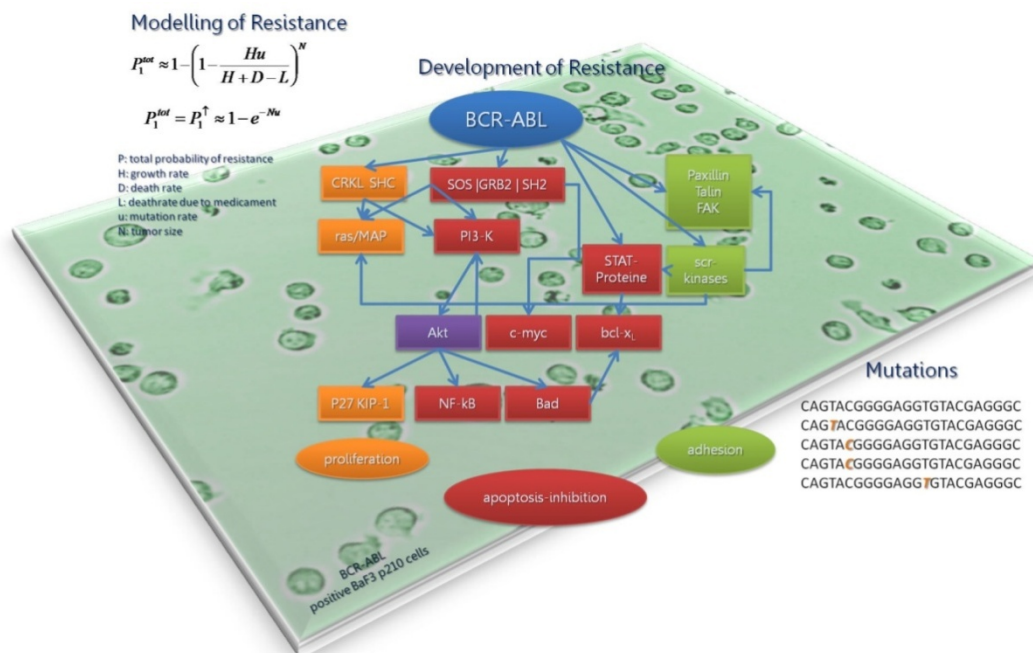


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Description

Drug and multidrug resistance is a frequent clinical problem for cancer patients. Many mechanisms of drug resistance have been found. For example, drugs can be prevented from entering the cells; drugs can be pumped out of cells; drug binding can be prevented by mutation or altered expression of the target; and defects in apoptosis, senescence, and repair mechanisms can contribute to resistance. In this study, we established Imatinib resistant BCR-ABL positive BaF3 p210 cell clones by using two ways: a concentration-time gradient (step width 1/10 of IC50 for Imatinib) and by adding of 5fold and 10fold of IC50 for 60 days. We set out to mathematically model and experimentally analyze the resistance to TKI in these clones. To achieve this goal, we will apply a tightly integrated experimental (e.g. proteomics, genomics and metabolomics) and modelling approach at different molecular and cellular levels, wherein the clinical aspects included from the very beginning. For the modelling, we combine network-based global analysis with detailed dynamic modelling of emergence of resistance and systems theory analysis. The source data will be initially the existing data on gene/protein expression as well as resistance spectra and kinetics under TKI treatment *in vitro* and *in vivo*. The network-based analysis consists of three major steps: the very reconstruction of molecular networks using databases and/or data from large-scale experiments, a structural analysis of the networks, and the study of network dynamics. The structural analysis allows identifying components or pathways for detailed dynamic modelling. Based on results from the TKI-CML system, the project intends to develop systems biology methods and algorithms for the modelling and simulation of drug resistance in cancers in general.



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