

Description for the general public

Cancer is a disease of the genome. Through multiple genomic changes, cancer cells acquire extraordinary abilities, such as uncontrolled growth or the ability to evade apoptosis and metastasize. The mutational diversity between tumors and limitations of current therapies call for improved, personalized treatment of this disease. With 14 million cases diagnosed globally, and 8.2 million deaths (14.6% of all), cancer remains one of the main causes of death worldwide. Efficient therapies need to be implemented especially in Poland, which has lower incidence, but higher mortality rate due to cancer than the rest of the European Union.

Recently, a strategy exploiting synthetic lethal (SL) interactions among genes was proposed for cancer treatment. SL is a gene interaction where the co-inactivation of two genes results in cellular death, while inactivation of each gene alone is viable. The mechanism behind the SL-based therapy in cancer is that one gene inactivation already occurs via its endogenous mutation in the tumor cells, and not in the normal cells. Thus, applying a drug that targets the SL partner of that gene will selectively kill cancer cells, leaving the rest viable.

An efficient, cost-saving strategy for finding novel medical treatment is drug repositioning. It is worth trying to combine SL with drug repositioning for efficient and relatively cheap development of novel cancer therapeutics. To this end, a map of SL interactions in human cancer needs to be characterized, and confronted with the knowledge of all targets of registered drugs and other compounds. Unfortunately, state of the art approaches to SL identification suffer from severe limitations. Experimental approaches are overwhelmed by the quadratic number of possible pairs, and thus limit their scope. On top of that, when SL screening is conducted with standard experimental techniques, the measurements have low reproducibility. Ideally, SL identification should proceed in two steps. First, a careful preselection of SL candidate pairs by computational predictions, combining evidence from various independent datasets, including genomic data profiling of tumor cohorts, molecular networks, patient survival, or evolutionary history. Second, precise experimental verification of the predicted interactions.

In this proposal, we plan to follow this procedure to generate a list of SL partners of genes mutated in glioblastoma multiforme (GBM), and to screen compounds that target those partners, verifying their cancer-specific essentiality. GBM is known as the most common and the most aggressive malignant primary brain tumor, with median survival of just one year.

We will combine evidence from A) GBM tumor profiling omics data, B) evolutionary history of genes, and C) analysis of gene essentiality screens, to come up with well supported predictions of SL. We plan to systematically investigate and understand to which extent is SL exhibited in various data, and thus which pieces of evidence are the crucial predictors of SL. We will next scan the predicted SL partners for targeting drugs, in this way collecting candidates for drug repositioning. Finally, those candidate drugs will be experimentally verified together with other compounds, which will test the identified SL interactions.

We hope that the SL partners of genes mutated in GBM, delivered from this project, will open a new avenue in cancer drug development. The large number (72 in 2011) of drugs in clinical trials exploiting just a handful of so-far discovered human SL interactions indicates the huge potential of SL in cancer treatment. Although predictions of SL interactions in GBM have been reported previously, a focused and comprehensive study with experimental verification on SL in GBM was so far not performed. Our identified SL interactions will have impact on personalized patient care, where decisions and prognosis can be made based on individual genomic profiles. First, by knowing SL partners of genes mutated in the tumor of a given patient, drugs targeting those partners could be administered. Second, for those patients where both interacting SL partners are inactivated, the survival prognosis is expected to be better than for others.