Simplified Interventional Mapping System (SIMS) : a novel multiplex combinatorial companion diagnostics (Cdx) and strategy to match patient to single drugs and combination of drugs

Vladimir Lazar, MD., PhD *Worldwide Innovative Network for Personalized Cancer Therapy, Paris, France*
www.winconsortiium.org; vladimir.lazar&winconsortium.org

B**ackground** The main limitations of current companion diagnostics (Cdx) are a) multiplicity of drugs that require a large number of tests (and different technologies) to be performed on limited amount of biological samples, and b) inability to prioritize the best therapeutic options for each individual patient. Here we report the Simplified Interventional Mapping System (SIMS), a Systems Biology based novel generation of multiplex combinatorial Cdx which provides biological support to prioritize and to select the classes of drugs that are predicted to be most effective at the individual patient level. The example used is metastatic Non Small Cell Lung Carcinoma (NSCLC), but the method applies to any solid tumor..

Methods: SIMS is based on the use of dual biopsies in order to compare tumor with its histologically matched normal tissue from the same patients. SIMS algorithm integrates data of DNA sequencing, CNV, and the differential expression of mRNA and miRNA between tumor and matched normal tissue from 121 NSCLC patients. SIMS converts thousands of genomic and transcriptomic measurements into a simple and actionable result (a 1 to 10 score) that may be usable by physicians to select the optimal drug or drugs' combinations therapy. One of the most interesting hypothesis being the tri-therapy approaches, following the historical success in AIDS.

Results: Key genes (N = 183) grouped in 24 interventional points forming SIMS were elucidated. The interventional points are defined by genes or group of genes that, when activated, could be blocked by a customized therapy combination. Frequency and trends of co-activation outlined a list of six classes of drugs, predicted to be the most efficient in the vast majority of metastatic NSCLC patients in which classic approaches did not identify druggable oncogenic aberrations such as EGFR mutations, ALK translocations, etc. and are then addressed to classic chemotherapy. The drugs most suitable for combinations are (1) Anti PDL1, (2) CDK4/6 inhibitors, (3) Anti VEGFA, (4) Aurora Kinase A, B, Polo Kinase, (5) PARP or DSB-PK and (6) MEK inhibitors. Using just five of those drugs in tri-therapy combination can result in six combinations that would cover all patients PDL1 positive. Moreover, each patient with metastatic NSCLC may benefit from two or even three tri-therapy combinations that may be rolled over time, to increase survival.

Conclusions:. The way of achieving a biology driven personalized therapeutic solution for all the patients is by including the investigation of transcriptomics.

Comparing tumor and normal tissue biopsies has proven feasible in the ongoing WINTHER trial (NCT01856296) and enables to reduce the noise due to genetic background variability between individuals. SIMS outlines novel therapeutic possibilities by focusing on pertinent classes of targeted therapeutics to be used in combinations, and is a novel generation of combinatorial multiplex companion test enabling to match patients to drugs.