SynTarget: an online tool to test the synergetic effect of genes on survival outcome in cancer

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Dear Editor,

The identification of target combinations with synergistic effects on cancer is at the leading edge of modern cancer research, especially for the development of combined anticancer therapies.[1] However, at present, the basis for selection of beneficial target combinations commonly relies on expert opinion without any systematic rationale. The development of high-throughput technologies has led to the availability of large-scale clinical gene expression data sets.[2–4] Mining of these data sets for identification of gene combinations with synergetic effects on survival outcome in cancer could provide a systematic rationale for the identification of target combinations with potential therapeutic synergy.

Multiple online tools have been developed recently to assess the relationship between expression of a single gene and clinical outcome across a variety of cancers.[5,6] Here we present *SynTarget*, the first tool able to test the cumulative effect of two genes on survival outcome and, therefore, can identify gene pairs with *synergistic* effects. At present, *SynTarget* is based on 15 large-scale gene expression data sets covering eight different cancers with the possibility to select clinically important subtypes (i.e., triple-negative, p53 mutated cancers, K-ras mutated cancers etc.). On submission, the user selects a specific cancer data set and subtype and specifies two genes. Patients in the selected data set (subtype) are split into four groups with respect to the expression of the specified genes (high – high, high – low, low – high and low – low). Next, each group is tested *versus* other samples to find any statistical differences in survival outcome (i.e., high – high *versus* others, high – low *versus* others and so on). This information is accompanied by individual-gene survival effects in order to understand the degree of gene synergy.

Among other drug classes, immunotherapeutic agents have enormous potential for synergistic combinations.[1] Triple-negative breast cancer is the subtype with the worst prognosis among all breast cancer subtypes, with currently no known molecular targets.[7] We used *SynTarget* to search cell surface genes with the synergistic potential on survival, whose high expression leads to significantly negative prognosis. For example, ADAM9 is a membrane-anchored protein and has been implicated in a variety of biological processes, as well as being involved in cancer metastasis. RC3H2 is a membrane-associated nucleic acid-binding protein. High expression of both genes individually was slightly negatively associated (*P*-values $\sim$0.07 and 0.04) with survival in triple-negative patients from the METABRIC data set.[3] The subgroup of triple-negative patients where both genes are highly expressed has a significantly negative shift (*P*-value $<$ 6e – 05) in survival, in comparison with other patients (see Supplementary Materials for details). Therefore, *SynTarget* provides statistical evidence that high expression of both RC3H2 and ADAM9 synergistically affects survival of patients with triple-negative breast cancer.

In summary, *SynTarget* supports the need of biomedical researchers to estimate the synergy of gene expression on survival of cancer patients. To our knowledge this is a first tool of this kind and, as shown by several examples (see Supplementary Materials), *SynTarget* can be used for fast validation of the clinical synergy for two genes. *SynTarget* is incorporated into BioProfiling.de, an analytical portal for high-throughput cell biology,[8] and is freely available at http://www.bioprofiling.de/synergy2G.

Conflict of Interest

The authors declare no conflict of interest.

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