Benign Cell Boosters: Exploring Novel Cancer Therapies Through Simulation

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A quarter century ago, Nowell identified cancer as an evolutionary problem[1]. The cells in a tumor are evolving through mutation and natural selection. There is an emergent \ecology" in the body where tumor cells must compete for the limited resources of a tumor. Any mutant clone with a competitive advantage will tend to spread in a tumor. Unfortunately, this form of natural selection includes selection for resistance to therapies that are imposed on the tumor. Therefore, many of our therapies select for resistant cells and result in a relapse with a drug resistant tumor. In essence, evolution works against us in the case of cancer. Our experimental work traces this evolution in Barrett's esophagus through both genetic and epi-genetic alterations. We are able to track the evolution of mutant clones both in space, across the surface of the esophagus, and in time, over years.

We have developed a set of computational models to simulate the evolutionary dynamics of cancer, both for Barrett's esophagus and in general. We explicitly represent each cell in a section of neoplastic tissue. These cells may suffer mutations that may increase their rate of mitosis, cause genetic instability, or induce resistance to a particular chemotherapy. We can then simulate the evolution of these cells over many years of simulated time. In addition, we have begun to use these models to explore the effects of hypothetical cancer treatments. We are particularly interested in therapies that use the evolutionary dynamics of cancer to our own advantage. Specifically, we have simulated a class of drugs called \benign cell boosters." These hypothetical therapies target the more benign cells in a tumor and seek to give them a competitive advantage over the more malignant cells. The malignant cells are thereby eliminated indirectly through competition with the benign cells for the resources of the tumor. We might then physically remove the benign tumors while suppressing the danger of metastases. Such a therapy should select for a benign state while avoiding the toxicity and resistance that plague traditional therapies. This only works if the therapy's target is causally linked to the benign state. Mere correlation with the benign state is not adequate. The model makes predictions as to the kinds of genes that would best be targeted by a benign cell booster. It also suggests the kinds of regimes that would be most effective. Future work must identify both specific targets and compounds that could be used as benign cell boosters.

References

[1] P. C. Nowell. The clonal evolution of tumor cell populations. *Science,* 194:23-28, 1976.