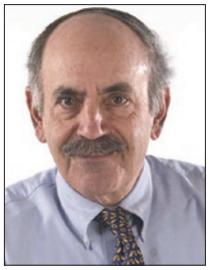
Robert Weinberg



A decade after publishing the seminal "The hallmarks of cancer" paper in *Cell* with Doug Hanahan, Robert Weinberg reflects on where we stand in the fight against cancer.

The discovery of the first oncogene, *Ras*, and the first tumor suppressor, *Rb*, are just two of many seminal contributions of Robert Weinberg to our understanding of cancer. The founding member of the Whitehead Institute for Biomedical Research and Daniel K. Ludwig Professor for Cancer Research at the Massachusetts Institute of Technology talks about the successes and failures of cancer research in recent years.

How has your thinking changed since the 'hallmarks' paper was published in *Cell*?
Robert Weinberg: The six hallmarks Doug Hanahan and I described in the year 2000 are, we think, still central. The question is whether there are additional properties of cancer cells that we need to consider. For example, there are enabling characteristics that make the acquisition of the six hallmarks possible. One of them is enhanced mutability and destabilization of the genome. Another may be chronic inflammation. There are also "emerging hallmarks," specifically immune evasion and the altered metabolism of cancer cells that Otto Warburg first described. There has also been an explosion of information indicating unambiguously that the tumor microenvironment has strong effects on the behavior of tumors.

Is this one of the reasons why most experiments done in animal models never really translate to humans?
RW: It could be that the interactions with the stroma are indeed captured in the animal models, but there are more fundamental problems with the mouse models of cancer, which preclude them from being very effective at present. For one thing, the cancer cells that are used in most mouse models, most often from the NCI-60 cell line collection, are poor representatives of the cells in actual tumors.

Are you excited about the contributions of large-scale genomics cataloging initiatives to understanding cancer?
RW: One consideration is how much bang we get for the buck. But as the cost of sequencing and data analysis comes down, that will be less of a consideration. We now begin to focus more on the intrinsic ability or the inability of sequencing to provide useful information. Are we learning more about human tumors? We have certainly learned a lot more about the sources and the extent of genetic instability within tumor cell genomes. Still, the question is whether these kinds of studies contribute to understanding the physiology of a cancer cell. The insights gained to date have been real but, relative to the effort expended, modest.

What about the role of stem cells in cancer?
RW: My lab works a lot on cancer stem cells, and the more we look the clearer their existence becomes. The controversy has already begun to subside. A question that remains is whether cancer stem and non-stem cells are interconvertible. We find the bidirectional interconvertibility between stem cells and non-stem cell populations to be real. The recognition of the existence of cancer stem cells is critical to developing new kinds of therapeutics, if only because cancer stem cells often turn out to be more resistant to conventional therapeutics.

How soon before progress in understanding metastasis translates into advances in treatment?
RW: We still don't understand all of the fundamental properties of metastatic cells. We may nevertheless empirically stumble across antimetastatic drugs without understanding why they are working. But if we wish to embrace rational drug design, we're still in the awkward position, because we don't understand all of the biochemical distinctions between primary cancer cells and their metastatic offspring. On the positive side, metastasis research has exploded over the past five years and our understanding of the molecular mechanisms that enable the physical movement of cancer cells from the primary tumor to distant organs has improved enormously. The next major challenges concern the complex programs that allow cancer cells to adapt to foreign tissues.

What about the contribution of epigenetics and microRNAs in cancer?
RW: At one level, epigenetics and microRNAs represent additional components in the already complex circuitry of signaling pathways. An interesting question, which I cannot answer, is whether the study of microRNAs and histone modifications is going to generate entirely new conceptual paradigms. I think there could be surprises in both areas, because certain microRNAs and histone modifications are surprisingly specialized in affecting very discrete processes.

What are the other biggest breakthroughs in cancer research over the past five years?
RW: I might be prejudiced, but I think the discoveries of the importance of the epithelial-mesenchymal transition, the EMT, and cancer stem cells have profoundly altered many peoples' thinking about the way tumors arise and disseminate. Many other discoveries have been interesting, but to my mind in a conceptual sense incremental.

If you could set the priorities for cancer research for the coming years, what would be on the top of your list?
RW: Something many people would probably not be interested in hearing. The big advances in our understanding of cancer have come year after year, decade after decade from small, independent research groups, rather than large research consortia. I'm hoping that the people who run the funding agencies come to recognize that much of the monies that are spent on multicenter collaborative initiatives—I'm not talking about clinical research—are not spent very effectively. Funds should be diverted instead to fostering young investigators to start their own groups and to move out in their own directions. I feel very passionate about this. We are losing generation after generation of young researchers. On the technology side, I think developing better xenograft models is going to be critical. Right now, to my mind, the major logjam in moving drugs ahead is that the preclinical testing of drugs is still so primitive.