

Sanaria Inc. is proud to recognize and celebrate the role of Dr. David Dolberg, Esq. - Sanaria's intellectual property attorney - in helping to shape current approaches to the understanding and treatment of cancer. Prior to launching a career in law, David was a postdoctoral fellow in the laboratory of Dr. Mina Bissell at Berkeley, who was recently highlighted in a New York Times article by Gina Kolata, "Old Ideas Spur New Approaches in Cancer Fight" (December 29, 2009).



As described in the article, inspired by careful reading of older literature, David conducted experiments showing that the Rous Sarcoma Virus, a potent inducer of tumors in adult chickens, does not trigger tumor formation in chick embryos. The results were published in *Nature* in 1984, with David as first author. These findings indicated that genetic alteration alone is not sufficient for tumor formation. This idea was not enthusiastically embraced at the outset, and a prominent cancer researcher visiting the lab soon after publication of the manuscript subjected the paper to a flamboyant and literal trashing. While still in the Bissell laboratory, David's 1985 *Science* article on the role of wounding in Rous Sarcoma Virus-induced transformation was a critical step in the development of a paradigm shift. During the intervening years, research in Mina Bissell's laboratory on breast cancer and later also by others increasingly suggested that the nature of the tissue milieu surrounding a transformed cell could be a potent mediator of progression to an aggressive cancer. Today, Dr. Bissell is recognized worldwide as a pioneer and leader in the elucidation of the microenvironment and tissue architecture as ultimate regulators of cell function, and is the recipient of numerous national and international awards.

Sanaria is delighted that David brings his insight and experience to the current effort to develop a novel malaria vaccine based on whole irradiated sporozoites. David offers the following recollection:

Mina Bissell has always thought outside the box. The safest approach for a scientist is to accept the common paradigm and fill in the blanks. Dr. Bissell has always tried to push the envelope – explain the unexplainable. This approach is apparent in Gina Kolata's recent N.Y. Times article *Old Ideas Spur New Approaches in Cancer Fight* (December 29, 2009). Conventional wisdom said that cancer was a disruption of growth regulation resulting from a single gene alteration. However, it now appears that, the cellular context is crucial in the ultimate phenotype. I used to say to Mina that there's nothing wrong with wearing a swimming suit on a hot summer day, but during a blizzard in the middle of winter it's deranged.

The significance of our first paper in the series, *Inability of RSV to Cause Sarcomas in the Avian Embryo* (Dolberg, DS and MJ Bissell, *Nature* 1984, 309:552) is best understood in the context of the kinetics of tumorigenesis. At that time, cancer genes were being identified right and left based on their ability to 'transform' cells in tissue culture, but each in turn was found to require additional factors to cause tumors *in vivo*. Rous Sarcoma Virus (RSV) was considered the most clear cut example of one-hit tumorigenesis kinetics. RSV is a small RNA virus and a single gene, the *src* gene, seemed to be both necessary and sufficient to cause avian sarcomas. The demonstration that *src* expression in chicken embryos did not cause sarcomas was the final nail in the coffin of the "aberrant gene expression is sufficient to explain tumorigenesis" theory.

Our next paper, *Wounding and its Role in RSV-Mediated Tumor Formation* (Dolberg, DS et al, *Science* 1985, 230:676) was an attempt to explain what other factors might be required. When RSV is injected into chickens a tumor develops at the site of injection, but the virus is circulating throughout the animal. Our theory was that the wound from the injection was necessary for tumor formation and that turned out to be correct. Injecting RSV at one site and wounding at another resulted in tumors at both sites. Later, a graduate student in the Bissell laboratory found that TGF-beta was the responsible cofactor. *Mediation of Wound-Related Rous Sarcoma Virus Tumorigenesis by TGF-beta* (Sieweke, M. H., et al, *Science* 1990 248:1656).

In a sense this paradigm shift in tumorigenesis is not so surprising. Mina makes the point that within an individual, phenotype is dominant over the genotype. After all, all the genes in our 10 trillion cells and various tissues are the same and thus tissue-specificity is dominant. This also explains why different cancers are tissue-specific.

Ms. Kolata's article mentions that I "unearthed papers suggesting that the cancer virus would behave differently in chicken embryos". With regard to revisiting old results to solve current problems, there is a parallel with the Sanaria story. Observations on the inability of RSV to cause tumors in embryos were made 70 years ago (Duran-Reynals, F. *Yale J. Biol Med.* 1940 13:77), but their significance was initially overlooked and subsequently lost in the rush to apply newer technologies and disciplines (tissue culture, cloning and the study of gene regulation) to cancer biology. Similarly, early observations of the immunizing ability of radiation attenuated sporozoites is forty years old, but the significance of those observations with regard to a vaccine were initially overlooked and then forgotten as a result of the advent of biotechnology and the promise of subunit vaccines.

I think there are a couple of lessons here: first, unexplainable observations are easy to dismiss, but frequently turn out to be the most important; second, while new technologies are important tools in research, they can also lead to tunnel vision and narrow one's research focus. It's a bit like the drunk who looks for his lost keys only under that lamp post because the light is better.

Ultimately, there is nothing new under the sun – only new eyes to see and new energy to do.

Finally, I must pay tribute to Professor Mina Bissell. She has given us 40 years of persistent effort: providing more proof, coming up with a mechanism that could replace the old, AND getting people to listen.