# Bialy Replies to a comment from Walter Gilbert

## From: Oncogenes, Aneuploidy and AIDS…, Notes/Chapter 7 "An Idea Whose Time Had Come"

16. Pihan, G., and Doxsey, S. J. 2003. Mutations and aneuploidy: co-conspirators in cancer? *Cancer Cell* 4:89–94.

In the words of one scientist who read these pages in manuscript, "It might appear, especially to people who read books with references," as though I "have given short shrift to exciting new developments in clinical oncology with drugs such as Gleevec" and to "a large literature that shows specific mutations in genes like *rb, p53* and *BRCA1* and *BRCA2* generate polyclonal tumors and are sufficient for cancer." For those readers, I offer the following by way of explanation.

The efficacy of such drugs is transient and partial (see below), and it is always dangerous to draw genetic and biochemical conclusions from clinical data. With respect to the second point: The relevant mutational data are exceedingly fragile, and this is especially true for tumor suppressor genes. Most genes are functionally described in terms of the biochemical activity of an implicated protein, but tumor suppressors are defined by a process whose phenotype is the output of an entire metabolic network. Since this is the case, genetic background is of extreme importance, as the definition of the endpoint depends on the entire output of that particular genome. By way of example, mutational inactivation, in the well studied case of *PI3Kgamma,* may predispose already perturbed cells to cancer in one genetic background, and not lead to any cancers whatsoever in a different one (Barbier, M., et al. Tumour biology (Communication arising): Weakening link to colorectal cancer? *Nature* 413:796, 2001).

These constantly moving, but never really changing, tepid waters of oncogene-mutation theory are well illustrated by an essay that appeared in *The Scientist* at the end of 2003 entitled. "A Cell-Cycle couple loses its luster" (Steinberg, D., *The Scientist,* Dec. 23, 2003). The piece pointed out, in no uncertain language, that after more than ten years in which cyclinE and cyclin dependent kinase 2 were held to be prime movers in driving cancer cell proliferation, five recent papers totally demolished this (for oncogene theory at least) long-held view. "Everything flows" wrote the philosopher. Or, as it is more often paraphrased, "You never step in the same river twice."

As with the various epicycles devised to make Ptolemaic descriptions of the solar system fit the facts, interest in these single gene entities as *agents provocateurs* of cancer will fade. The Copernican replacement will be a perspective derived from quantitative analyses of network perturbations based largely on the central idea of aneuploidy-catalyzed, continuous genomic rearrangements instead of an endless parade of multi-problematic mutations. This perspective is exemplified in: Duesberg, P., Stindl, R., and Hehlmann, R. 2001. Origin of multidrug resistance in cells with and without multidrug resistance genes. *Proc. Natl. Acad. Sci. USA* 98:11283–11288.

*Recent literature provides an ideally controlled example in support*

*of the chromosome reassortment hypothesis. In an attempt to control the diploid and chronically hyperplastic phases of chronic myeloid leukemia as well as the aneuploid and malignant phase, or blast crisis (19), the same cytotoxic drug, STI-571, was developed (66, 67). According to a "News and Views" article in Nature, the "newage drug" was "rationally designed" to inhibit the putative common cause of the chronic and malignant phases, a tyrosine kinase encoded by the BCR-ABL hybrid gene that "drives the cells . . . to become cancerous" (66). But, contrary to expectation, only patients suffering from the diploid chronic phase showed lasting responses, whereas "most" patients suffering from the aneuploid blast crisis "relapsed within a few months, despite continued treatment" (66). In searching for an answer, some investigators have quickly offered several mutations of the BCR-ABL gene that would render the encoded kinase resistant against STI-571 without affecting its putative oncogenic kinase function (67). But, as the "News and Views" article points out, this answer generates at least one new question: "Why do drug-resistant cells emerge from blast crisis and not from the earlier phase?" In addition, one wonders why mutations of the active site of the kinase, which prevent the competitive inhibitor from binding, would not also prevent the kinase from maintaining transforming function. Our hypothesis suggests simple answers to both questions. The blast crisis is caused by aneuploidy rather than by the kinase (19), and aneuploidy also generates drug-resistant variants by chromosome reassortments. Indeed, drug-resistant blast cells without mutations of the active site have already been observed (67). By contrast, the diploid hyperplastic leukemia cells cannot generate drugresistant variants by chromosome reassortments.*