Breaking the Code

In a recent public lecture Harold Varmus, Nobel laureate, former head of the NIH, and president of Memorial Sloan-Kettering Cancer Center admonished the world to be a bit more rational about the near-term prospects for finding "a" cure for cancer.   The tone of his comments was somewhat reminiscent of former Federal Reserve Bank Chairman Alan Greenspan's "irrational exuberance" speech – a speech that has, as of late, proven prophetic.   Why the wet blanket from a champion of biomedical and cancer research? In part, the comments were probably related to some of the attention given the recent trio of publications describing the comprehensive genetic analysis of a large set of human pancreatic and glioblastoma multiforme tumor samples. The findings presented in these studies were somewhat disheartening from a front-line clinician's perspective – though for cancer researchers and geneticists – well, let's just say they won't be out of work soon.

The diversity of genetic alterations present in these panels of carefully selected tumor samples was mind-numbing. In the case of pancreatic cancer, the average number of mutations in a given sample was reported to be 63.   Disappointingly, the overlap between mutations in separate samples was minimal (24 pancreatic cancers held mutations in over 1000 genes). Much the same was found in glioblastoma samples. Each tumor studied held about 47 mutations on average per tumor, and 22 tumors harbored mutations in over 750 genes. Several interesting gene associations fell out of the analysis, including confirmation that the gene associated with neurofibromatosis (NF1) is associated with sporadic glioblastoma, and that mutations in the isocitrate dehydrogenase 1 (IDH1) gene are associated with disease in younger patients and those individuals with secondary tumors . Additionally, patients with IDH1 gene mutations had a considerably longer survival (3.8 versus 1.1 years) than those without IDH1 gene mutations; this fact may lead to the ability to provide a clearer prognosis for at least some glioblastoma patients. One of the brain tumor studies was published as part of the first wave of data from The Cancer Genome Atlas project (TCGA; see http://cancergenome.nih.gov/about/mission.asp) The pilot phase of this project is examining the genetic alterations found in brain, lung and ovarian cancers; if all goes well, the project will be scaled up to tackle and even larger variety of malignancies.

These studies strongly indicate that working out cures for solid tumors is not going to be as straightforward as targeting the BCR-ABL oncogene in chronic myelogenous leukemia. Despite the daunting complexity of genetic alterations exhibited by the tumors in these studies, there is hope for developing effective targeted therapies at a pace greater than one patient at a time. As it turns out, relatively few pathways are affected by the bewildering array of mutations, and these affected pathways overlap considerably between individual cancers. This raises the possibility that drugs targeting critical steps in these pathways might have applicability to multiple tumors of any given type, and perhaps even multiple types of tumors.

Much more information will certainly come from in-depth genetic analysis of cancer tissue samples, and with the ever-decreasing cost of sequencing technologies the pace of

discovery is poised to become exponential.   Network theory is steadily improving our ability to work out complex associations between seemingly unrelated pathways of cellular function. High throughput screening assays for drug discovery are becoming more widely employed to speed drug identification. Yes, Dr. Varmus is correct to point out that cancer is an extremely complicated constellation of disorders. No, there probably won't be "a" cure for most specific types of cancer, much less all types of cancer. However, we finally have the tools to crack the enigma, and more reason to hope for cures (and perhaps prevention) than ever.