These findings have provided the basis for seeking inhibitors of macromolecular targets essential to the malignant tumor phenotype but not utilized in vital organs and tissues, which in principle should lead to a better selectivity in comparison to traditional cytotoxic drugs. These anticancer drugs are usually known as "molecularly targeted agents"—a name that is perhaps not completely appropriate because many drugs developed in the first era of cancer chemotherapy, such as the cytotoxic antifolate thymidylate synthase inhibitors, were also molecularly targeted. Alternative names for this new class of anticancer drugs, one of the fastest growing areas of research in cancer chemotherapy, are "signal transduction inhibitors" or "secondary messenger inhibitors."

2 ONCOGENES AND SIGNAL TRANSDUCTION

Mutations in at least several hundred human genes (out of a total of approximately 25,000 genes) become drivers of the abnormal cell growth and division process that generates human cancer. These oncogenes encode the protein components of signal transduction pathways that enable external signals (growth and survival factors) to move from the cell surface receptors to key promoter–enhancer regions along human chromosomes. There, they promote the expression of genes needed for cell growth and division, as well as the evasion of programmed cell death, which is very important in the ever-growing resistance of late-stage aggressive cancer cells to radio- and chemotherapies.

The first human oncogene was discovered in1982,[2] but today more than 500 are known, which can be categorized as follows:

1. Activated oncogenes (e.g., *RAS*, *RAF*, and *PI3KCA*) and deactivated tumor suppressor genes (e.g., *P53* and *PTEN*)
2. Genes that when inactivated or mutated lead to DNA repair defects (e.g., *BRCA1* and *BRCA2*, whose acronym stands for Berkeley, California)
3. Genes that support oncogenic pathways such as those encoding the chaperone HSP90 and histone deacetylases, which are involved in post-translational modification of proteins, chromatin modification, and control of gene expression
4. Genes controlling the tumor microenvironment, including cancer–host interactions

Normal cells undergo genetic alterations at the nucleotide and chromosomal levels as they divide, but as a defense mechanism, they are programmed to undergo cell death in response to such alterations. However, cancer cells evolve by acquiring mutations in genes such as the tumor-suppressor protein p53 (known as "guardian of genome").[3] More than 100 driver genes affected by subtle mutations confer a selective growth advantage to cancer cells through different pathways that participate in cellular processes such as cell fate, cell survival, and genome maintenance.[4]

The precise balance between cell differentiation and division is mainly controlled by the adenomatous polyposis coli (APC), Notch, and HH signal pathways, as well as by genes encoding chromatin-modifying enzymes such as chaperone HSP90 and histone deacetylases. In normal development, the heritable switch from division to differentiation is not determined by mutation but, rather, by epigenetic alterations affecting DNA and chromatin proteins, whereas in cancer cells many genetic alterations favor the division.

Cancer cell survival is dependent on the abnormal vasculature of tumors due to VHL gene mutations, whose product stimulates angiogenesis through the secretion of vascular endothelial growth