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The Holy Grail Pursued by Medical Research is mostly Unattainable

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Editorial

The term "holy grail" is often used to describe an ultimate objective that everyone desires to achieve. Regarding the investigation of most chronic diseases of uncertain cause, the holy grail involves ascertaining a single molecular cause that, when neutralized, might cure the condition. That this is almost always an unobtainable objective is demonstrated by its never having been achieved for atherosclerosis, rheumatoid arthritis, systemic lupus erythematosus, or other rheumatologic disorder, inflammatory bowel disease, cancer of a particular tissue, most pulmonary diseases, or for either Alzheimer's disease or schizophrenia. Why is it that the holy grail's objective is unattainable for chronic disease? The reason is that it relies upon determining a single molecular cause, i.e., one target, whose neutralization might cure the condition but, as shown above, is almost always ineffective (infectious diseases are exceptions). The alternative approach is combination therapy, which offers a likelier chance for cure but involves choosing amongst numerous mechanisms.

Those mechanisms also may combat drug resistance [1], and include tyrosine kinase inhibitors; monoclonal antibodies; inhibitors of PARP (poly ADP-ribose polymerase) an enzyme involved in DNA repair; inhibitors of mTOR (the mammalian target of rapamycin), that is involved in cell growth, proliferation, and survival; inhibitors of proteasomal function, causing the accumulation of damaged proteins and cell death; inhibitors of the BRAF and MEK proteins in the MAPK/ERK signaling pathway; inhibitors of angiogenesis; chimeric antigen receptor (CAR) T cell therapy; cytotoxic T lymphocytes (CTLs); immune checkpoint pathways, such as the programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) pathways, that regulate the activity of T cells and their responses to cancer cells; cancer vaccines that stimulate the immune system to recognize and target cancer-specific antigens; lymphokine-activated killer (LAK) therapy, that involves the activation and expansion of lymphocytes which induce apoptosis of cancer cells; increasing transition of epithelial-to-mesenchymal cells, improving their ability to migrate; using checkpoint inhibitors to block pathways on T cells, such as those activated when PD-L1 binds to PD-1 causing inhibition of T cells. Overcoming drug resistance, however, has its own problems. One is posed by persistent bacteria, that grow slowly, are antibiotic tolerant, can persist in the host for long periods of time, and may eventually produce a relapse of the infection [2]. A second is that neoantigens, formed by splicing introns after excision of exons, are heterogeneous, which impairs the success of immunotherapy [3].

In brief, even combination therapy, which is the alternative to determining a single molecular cause, i.e., the holy grail, offers no simplistic mechanism because of both the profusion of available approaches, and bacterial persistence and neoantigen formation.

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