and breast cancer (51). Interferon, in combination with a small molecule (ribavirin), is the gold standard for treating hepatitis C virus infections (52).

### 3. TLR-agonists

The term "TLR agonist" refers to a chemical that stimulates a toll-like receptor (TLR). The cited references in the following narrative identify oncology clinical trials using TLR agonists.

The toll-like receptors consist of a class of ten proteins. Each of the toll-like receptors responds to a different agonist or ligand. For example, CpG-oligodeoxynucleotides stimulate TLR9 (53,54). TLR9 recognizes unmethylated CpG sequences in DNA molecules. CpG sites are relatively rare on vertebrate genomes in comparison to bacterial genomes or viral DNA. Synthetic CpG-oligodeoxynucleotides are analogues of naturally occurring viral and bacterial DNA. Coban et al. (55) provide a diagram showing the cell signaling pathway induced by administered CpG-oligodeoxynucleotides.

The immune system responds effectively to most viral and bacterial infections for two reasons. The first is that viruses and bacteria contain foreign antigens, while the second is that viruses and bacteria provide naturally occurring TLR agonists. In contrast to the situation with infections, the immune system generally fails to respond effectively to tumors. This failure results from the fact that tumor antigens are self-antigens (or closely resemble self-antigens), and also from the fact that tumors do not express TLR agonists. For this reason, TLR agonists have been used as drugs and administered to cancer patients, in conjunction with a chemotherapy, as in the clinical study of Manegold et al. (56). The actual CPG molecule that was used was identified as

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