Intense efforts are underway to develop synthetic Wnt signaling modulators, including small molecules (XAV939, pyrvinium), peptides (SFRP1), and blocking antibodies. FDA-approved lithium chloride stimulates CTNNB1, while NSAIDs like celecoxib inhibit CTNNB1-dependent transcription. Wnt-blocking antibodies show promise in targeting colon cancer and HCC cells, with WNT3A-neutralizing antibodies reducing prostate cancer proliferation in vivo. Regarding TGF-□ signaling, while no definite clinical role exists, SMAD4 expression correlates with prognosis and 5-FU response. Clinical trials investigate 18qLOH for adjuvant therapy and the impact of chronic NSAID use on Notch pathway activity. Several clinical trials target pathways including IGF-1R, Wnt, Notch, Hedgehog, and TGF-□, with some showing promise (e.g., □-secretase inhibitor RO4929097, vismodegib). MSI status is a reliable biomarker for immunotherapy response, with checkpoint inhibitors like pembrolizumab and nivolumab showing efficacy in metastatic CRC. Combination therapies (e.g., pembrolizumab/ipilimumab, nivolumab/ipilimumab) are also being investigated. Other PD-1/PD-L1 inhibitors are in phase I trials. Targeting the CIMP pathway involves anti-EGFR monoclonal antibodies (cetuximab, panitumumab) and TKIs. Cetuximab is effective but ineffective in tumors with RAS, BRAF, or PIK3CA mutations. Panitumumab shows improved OS and PFS in combination with FOLFOX or 5-FU/LV. There are no approved therapies for KRAS-mutated CRC, but AMG 510, targeting KRASG12C, shows promise, along with other agents targeting G12C and G12D mutations. While BRAF inhibitors have shown limited success alone in CRC, combinations with EGFR inhibitors (e.g., vemurafenib/cetuximab, encorafenib/cetuximab/alpelisib, dabrafenib/trametinib/panitumumab) show improved outcomes. Anti-VEGF/VEGFR therapies, such as bevacizumab, improve PFS and OS in metastatic CRC, including in KRAS-mutant patients. Further research is needed to clarify the role of molecular classification in therapeutic interventions and to identify reliable biomarkers for CRC risk. The future of CRC treatment likely involves personalized medicine using novel drug combinations and specific targets to minimize toxicity. Understanding CRC's .underlying mechanisms will be crucial for developing novel diagnostic and therapeutic strategies