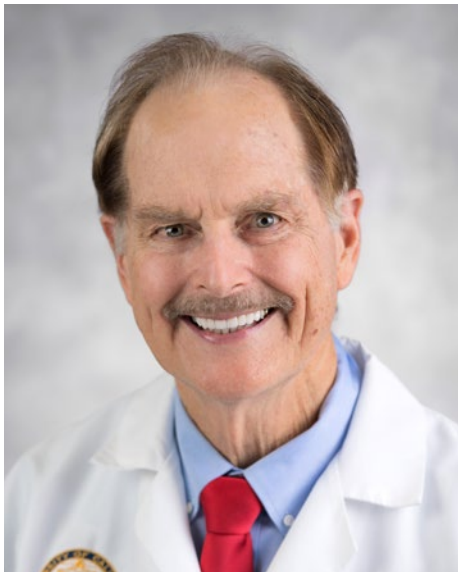
Targeting cancer stemness



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Abstract

ROR1 and ROR2 are highly conserved surface glycoproteins that can serve as receptors for a wingless-related integration site (Wnt) factor (e.g. Wnt5A), which triggers non-canonical Wnt-signaling. Each of these proteins play essential roles during embryogenesis, functioning to maintain cell polarity, enhance chemokine-directed migration, and promote self-renewal of embryonic stem cells that are essential for organogenesis. The receptors become vestigial after fetal development and virtually undetectable on most normal adult tissues. However, we and others have found that ROR1 and/or ROR2 are re-expressed on a variety of human cancers, possibly reflecting cancer cell dedifferentiation to a more primitive, less specialized state. The distinctive expression of these surface proteins by cancer cells makes them potential targets for development of specific cancer-directed therapies. However, in addition to serving as markers for neoplastic cells, we find that the non-canonical Wnt-signaling pathways induced by Wnt-induced activation of ROR1 and/or ROR2 can enhance cancer-cell expression of genes that are important for the tumor-self-renewal, proliferation, migration, and survival of cancer stem cells (CSC). Such CSC are posited to be responsible for cancer relapse after therapy and the development of cancer metastases. We generated highly specific monoclonal antibodies (mAb) for ROR1 or ROR2 that can repress activation of non-canonical Wnt-signaling pathways that are induced by activation of ROR1 or ROR2. The recombinant humanized anti-ROR1 mAb, UC-961 (now known as zilovertamab) can impair engraftment of ROR1-expressing leukemia cells in ROR1-transgenic mice and has been studied in clinical trials. In phase I studies, zilovertamab was found to have anti-leukemia activity in patients with chronic lymphocytic leukemia (CLL), which is a widely metastatic stem-cell-like cancer that expresses ROR1. Transcriptome analysis showed that treatment with UC-961 reduced expression of genes associated with cancer stemness, and repressed target genes induced by activation of ERK1/2, NF-κB, mTORC, STAT3, or NRF2. Noteworthy is the capacity of zilovertamab to repress ROR1-induced activation of NRF2, which is a key regulator of antioxidant genes that can enhance the survival, self-renewal, and resistance to therapy of CSC. Furthermore, we find that cancer cells with mutant *TP53* appear especially dependent on activation of NRF2, which can interact with mutant TP53 to activate transcription of genes that mitigate the oxidative stress induced the altered function(s) of mutant TP53 and therapy promote CSC survival. As such, inhibition of ROR1-induced NRF2 selectively may undermine the survival of CSC with mutant TP53 and thereby enhance their sensitivity to anticancer therapies. Our studies with CLL and other solid tumor neoplasms that express ROR1 and/or ROR2 indicate that surface proteins are not merely markers that help distinguish neoplastic from normal cells, but also function as a surface-receptors that activate signaling pathways that can enhance CSC migration, proliferation, and protection from oxidative/genotoxic stress, including stress induced by aberrant TP53. Research into strategies that target ROR1 and/or ROR2 or their downstream activation pathways may convert these proteins from being a selected advantage for neoplastic cells into cancer's Achilles heel.

Biography

Thomas Kipps, MD, PhD, is Distinguished Professor of Medicine, Evelyn and Edwin Tasch Chair in Cancer Research, Director of the Center for Novel Therapeutics, and Co-Director of the Hematologic Malignancies Program at the University of California, San Diego, Moores Cancer Center. Dr. Kipps is a two-time awardee of a Specialized Center of Research (SCOR) in Leukemia grant from the Leukemia and Lymphoma Society, a two-time awardee of the NIH MERIT Award, and principal investigator of the CLL Research Consortium (CRC), which directed inter-institutional research among the leading investigators in CLL from across the country and abroad. Dr. Kipps is the chair of the international workshop on CLL (iwCLL), and an awardee of the Rai/Binet medal for outstanding contributions to the field of leukemia research.