From the Editor

Targeting RAS: The Elusive Prize

This CCR Focus examines a prized target in oncology—inhibition of RAS, the GTPase signaling protein known as a molecular signaling switch and found to be mutated in many common cancers. These mutations, typically in one of three key hotspots, keep the protein always on, signaling proliferation and survival. This CCR Focus examines the intense quest under way to develop a molecule or therapeutic strategy that will inhibit RAS. The articles, guided by Guest Editor Frank McCormick, discuss various aspects of targeting RAS:

- Downward discusses "synthetic lethal" approaches to RAS inhibition.
- Marcus and Mattos forecast direct inhibition of the "undruggable target."
- Cox, Der, and Phillips revisit blocking its critical membrane attachments.
- Kimmelman offers RAS metabolic reprogramming as a therapeutic target.

Together, these articles demonstrate a multipronged effort to block RAS, known for over 30 years to be mutated in cancer, and express cautious optimism that it is just a matter of time before we can affect RAS activity in human cancer.

After reading this CCR Focus, we no longer ask whether we "will ever have" an agent to inhibit aberrant RAS function in the clinic. Rather, we now ask "how much benefit" can we affect RAS activity in human cancer.

Text Box 1. Brief timeline of key milestones in RAS research

1964/1967: Harvey and Kirsten rat sarcoma viruses isolated
1979: RAS is a 21-kDa GDP- and GTP-binding protein
1981: Viral Hras and Kras genes have a normal human cellular counterpart
1982: HRAS and KRAS identified as activated oncoproteins in human cancer cell lines
1982: Bladder cancer HRAS gene is activated by a codon 12 mutation
1983: KRAS and NRAS activating mutations identified in human cancer cell lines
1983: Mutant HRAS transformation of primary cells requires cooperating genes
1984: Mutant HRAS has defective intrinsic GTPase activity
1988: HRAS crystal structure determined
1989: RAS membrane association and function are dependent on farnesylation
1990: NF1 tumor suppressor gene encodes a RasGAP
1992: MEK signaling discovered
1993: Farnesyltransferase inhibitors (FTI) block growth of HRAS-transformed cells
1993: RAF identified as the first mammalian RAS effector
1994: PI3K identified as a RAS effector
1997: Alternative KRAS4B and NRAS prenylation discovered in presence of FTI
2005: The FDA’s Oncologic Drugs Advisory Committee votes against approval of the FTI tipifarnib
2005: The FDA rejects tipifarnib
2008: Tumors with KRAS mutation do not benefit from the EGFR antibody cetuximab
2009: Synthetic lethal interactors of mutant KRAS are identified
2012: FDA approves KRAS mutation test as a companion diagnostic for cetuximab
2012: First direct inhibitor of KRAS protein function identified
2013: A direct inhibitor of a specific KRAS mutant protein (G12C) is identified
2015: Tipifarnib to be revisited in HRAS cancers

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See all articles in this CCR Focus section, "Targeting RAS-Driven Cancers."

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