Editorial

Understanding KRAS for better targeting

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Future generations of scientists will only be able to deliver better cancer treatments by gaining detailed knowledge of the cellular mechanisms that underly the disease. There is no better place for the molecular enthusiast to understand Kirsten rat sarcoma virus (KRAS) biology, signaling, and resistance than this review by Santarpia *et al.* (1).

As of 2022, approximately 45% of non-small cell lung cancer (NSCLC) have mutations which can be targeted with approved drugs; the most common abnormality is of the rat sarcoma virus (RAS) oncogene family. Mutations in the RAS pathway are implicated particularly in adenocarcinoma of the lung. The most common RAS isoform mutated is KRAS, which is seen in 25–30% of adenocarcinoma. The KRAS mutation has been famously dubbed "undruggable" largely due to its shape—its smooth structure rendered designing inhibitors to fit onto the surface difficult to achieve and the toxicity of general inactivation of RAS in all cells is unacceptable. This review by Santarpia *et al.* goes above and beyond—it tells us a story about the history of the KRAS protein, its molecular pathogenesis, drug targeting with attention to mutation specific inhibitors, resistance, and hints at the future potential of targeting this pathway which will need to be unlocked with more basic and clinical research (1).

Once a KRAS mutated patient progresses on first line chemotherapy for NSCLC, we now have several targeted options that are preferable to chemotherapy. Docetaxel, a microtubule inhibitor approved by the Food and Drug Administration (FDA) in 1996, has improved overall survival (OS) compared to best supportive care (2). However, the prognosis is poor in this situation, with the median OS approximately 7–8 months. The value of mutation specific inhibitors was seen in the Phase II study CodeBreaK100 (Amgen). In that study of patients previously treated with chemotherapy and immunotherapy Sotorasib produced a duration of response of 11.1 months and median OS of 12.5 months. Grade 3 toxicities were manageable in 19.8%, with the most frequent being diarrhea (Grade 3: 4.0%) and liver enzyme elevation (Grade 3: 11.9%). However, only 3.2% of patients experiencing a Grade 3 toxicity needed to discontinue the treatment (3). Furthermore, KRAS agents such as Sotorasib are given orally, thus decreasing the need for frequent trips to the hospital infusion center. Recent data from the Phase III CodeBreaK 200 Trial, which compared Sotorasib with docetaxel in the second-line setting, demonstrated a significant progression-free survival (PFS) benefit at a median follow-up of 17.7 months. However, OS was not different (4). Cancer patients are now living longer and confounding effects of subsequent treatment makes OS harder to achieve, especially in countries with access to 3rd and 4th line treatments. Recently, the FDA has also granted accelerated approval to another KRAS G12C inhibitor for patients with refractory NSCLC, Adagrasib, based on phase I/II data from the KRYSTAL-1 study, which

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demonstrated an overall response rate (ORR) of 43% and a median duration of response (DOR) of 8.5 months (5). These studies often come with highly publicized press releases and pictures of the pharmaceutical company logos—but the clinical success only resulted after the many years of research and insight detailed in this review.

We appreciated the insight into the limitations of targeted therapies brought to the forefront in this review. Other options to circumvent resistance could be to target downstream in the RAS pathway or to target the phosphoinositide-3-kinase-protein kinase B/Akt (PI3K-AKT) pathway. The latter has already been studied in in breast cancer where protein kinase B/Akt (AKT) has emerged as an attractive therapeutic target for those who have progressed or demonstrated resistance to conventional therapies (6).

Another KRAS signaling mediator is Src homology phosphatase 2 (SHP2) which is encoded by the PTPN11 gene. The SHP2 gene is a tyrosine phosphatase which activates KRAS and has been shown to be a part of the feedback reactivation cascade which contributes to resistance to KRAS. SHP2 has been implicated as an oncogenic driver of multiple types of cancers—head and neck, hematologic, liver, and a few others (7). Interestingly, SHP2 has also received the "undruggable" label in the past, but that has changed recently. At the American Association of Cancer Research (AACR) meeting in July of 2021, multiple oral inhibitors of SHP2 were introduced and shown to have both *in vivo* and *in vitro* anti-tumor activity. One such agent, ETS-001 was shown to have single-agent activity as well as synergy with epidermal growth factor receptor (EGFR) inhibitors, cyclin-dependent kinases 4 and 6 (CDK 4/6) inhibitors, and most importantly for the purpose of this topic, KRAS G12C inhibitors (8).

The tumor immune microenvironment (TME) was discussed in this review and its interaction with KRAS is of particular importance given the widespread use immunotherapy. KRAS mutations have been shown to govern the TME and as a result, affects the anti-tumor immune activity. However, as noted by the authors, tumor mutational burden (TMB) and programmed-death ligand 1 (PD-L1) were found to be high in patients with KRAS mutations due to smoking, which can cause both KRAS G12C mutations and higher mutational burden.

This review is a bridge to understanding the significance of KRAS and is a must-read for not only laboratory scientists but also clinicians aiming to get a better grasp of the drugs they will be prescribing (1).

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