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Inhibitor MEKanisms

By Benjamin Boettner, Assistant Editor

Roche's **Genentech Inc.** unit has figured out why different MEK inhibitors exhibit varying efficacy against BRAF- or K-Ras–driven cancers, which could help in the design of next-generation inhibitors with improved therapeutic indexes.[1] Genentech already has one inhibitor for each kind of tumor in clinical trials.

Mutations in the *K-Ras* (*KRAS*) and *BRAF* genes are responsible for overactivation of the Ras-Raf-MEK-MAPK pathway in many cancers. MEK is a key component of this signaling cascade, but for unknown reasons *BRAF*-mutant tumors thus far have been more sensitive than *KRAS*-mutant tumors to MEK inhibitors.[2]

One hypothesis is that BRAF and KRAS interact differently with MEK. Oncogenic BRAF phosphorylates MEK directly, whereas KRAS acts upstream to activate Raf kinases and other tumorigenic effectors such as phosphoinositide 3-kinase (PI3K).

Consequently, *BRAF*-mutant cancer cells have higher basal levels of phosphorylated MEK than KRAS-mutant cells, rendering the former more sensitive to MEK inhibitors[3] (*see* **Figure 1, "Targeting MEK in cancer"**).

Genentech researchers have now taken a closer look at why three of their inhibitors—cobimetinib (GDC-0973), GDC-0623 and G-573—exhibit differential efficacy. The former is most effective in BRAF-mutant cancer cell lines, whereas the latter two show better results in *KRAS*-mutant cells.

GDC-0973 was discovered by **Exelixis Inc.** and is partnered with Genentech. The molecule is in Phase III trials for melanoma. GDC-0623 and G-573 were discovered at Genentech. GDC-0623, the more potent of the two, is in Phase I testing for solid tumors.

Using a combination of structural, biochemical and physiological data, a team led by Georgia Hatzivassiliou and Marcia Belvin showed that the compounds interacted with MEK in very different ways.

Hatzivassiliou is a scientist and Belvin is associate director of translational oncology at Genentech.

All three compounds are allosteric MEK inhibitors that do not compete with ATP for the kinase's active site but rather bind to an adjacent activation loop. The compounds do so in different ways. GDC-0973 hits a conformation of the loop that is induced by BRAF-mediated MEK phosphorylation. GDC-0623 and G-573 bind to unphosphorylated MEK at the Ser-212 residue and prevent MEK phosphorylation by wild-type Raf.

GDC-0973 showed more inhibition than GDC-0623 or G-573 in mouse xenografts of melanoma or colon cancer harboring a mutated *BRAF* allele. In contrast, GDC-0623 and G-573 showed better results than GDC-0973 in *KRAS*-mutant pancreatic or lung adenocarcinoma xenografts.

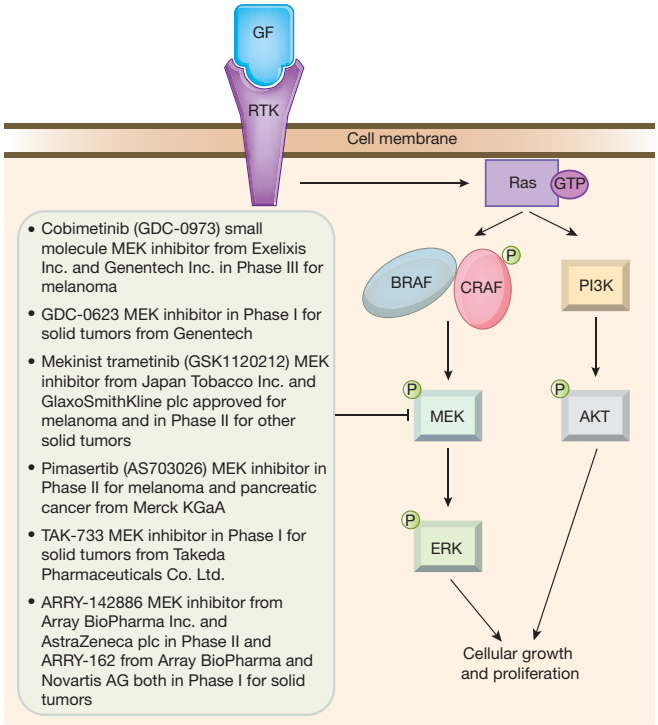

Figure 1. Targeting MEK in cancer. According to findings published in *Nature*, two classes of MEK inhibitors exhibit different effects in *K-Ras* (*KRAS*)- and *BRAF*-mutant backgrounds. In cancer cells, BRAF or Ras proteins often acquire activating mutations that allow them to become independent of growth factor (GF) and receptor tyrosine kinase (RTK) function and to overstimulate their downstream signaling elements. BRAF strongly phosphorylates and activates MEK as its primary downstream target. KRAS activates MEK less strongly than BRAF but also drives phosphoinositide 3-kinase (PI3K) and protein kinase B (PKB; PKBA; AKT; AKT1) signaling. MEK-ERK and PI3K-AKT signaling can cooperate to promote cancer cell proliferation.

In cancer cells that develop resistance to BRAF inhibitors like Zelboraf vemurafenib, BRAF trans-activates wild-type CRAF (RAF1), and the BRAF-CRAF complex is further stimulated by elevated Ras activity. Ras activity can be enhanced by *de novo* mutation of *neuroblastoma Ras viral (v-Ras) oncogene* (*NRAS*) or hyperactive RTKs.

The findings were published in *Nature*.

According to Hatzivassiliou, the results point to the need for assessing the impact of BRAF and KRAS mutation status on clinical efficacy of individual allosteric MEK inhibitors.

"Conclusions with one inhibitor don't necessarily translate to conclusions about MEK as a target in general. For example, past clinical trials with MEK inhibitors that didn't demonstrate strong clinical efficacy need to be revisited with new compounds with known mechanisms of action," she said.

Kevin Koch, president and CSO of **Array BioPharma Inc.**, told *SciBX*

that "this is one of the nicest examples of drug discovery where chemical structure is related to target structure. At a high level there are not many examples where minor changes in drug interactions with their targets are shown to create novel biology resulting in different drug efficacies."

Array's MEK inhibitors for solid tumors include ARRY-142886, which is in Phase II testing and is partnered with **AstraZeneca plc**, and ARRY-162, which is in Phase I trials and is partnered with **Novartis AG**.

Levi Garraway, an associate professor at **Harvard Medical School**, an assistant professor at the **Dana-Farber Cancer Institute** and a principal investigator at the **Broad Institute of MIT and Harvard**, said that the study may open up more fine-tuned therapeutic approaches to BRAF- and KRAS-driven cancers.

"This preclinical study should definitely heighten interest in clinical trials for MEK inhibitors. There is the potential that distinctions made in the work could eventually lead to cancer drugs that offer additional treatment options to the ones available right now," said Garraway.

Gaining traction

In addition to helping fine-tune patient selection, the study's mechanistic insights could spur the development of MEK inhibitors with improved efficacy.

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—Kevin Koch, Array BioPharma Inc.

According to Garraway, "The findings reveal new binding mechanisms and may offer a new pharmacological rationale for a subset of MEK inhibitors that could provide a way to get traction in *KRAS*-mutant cancers. Of course, it will be crucial to find out whether so-called KRAS-selective MEK inhibitors have any activity in patients carrying *KRAS*-mutant tumors."

Gary Johnson, chair of the Department of Pharmacology at **The University of North Carolina at Chapel Hill School of Medicine**, told *SciBX* that "increasing the allosteric selectivity through high-affinity interactions like those described with Ser-212 in this study is predicted to ensure greater selectivity of these kinase inhibitors. Moreover, the unique contacts formed may further increase the durability of inhibitor responses by slowing the dissociation of the inhibitor compound from its target kinase."

Koch said that it will be important to explore different MEK inhibitor categories across multiple tumor types.

Another important question is whether inhibitors with efficacy in *KRAS*-mutant cancers can interfere with the growth of *BRAF*-mutant tumors resistant to Zelboraf vemurafenib, an oral small molecule inhibitor of the oncogenic BRAF V600E. *BRAF*-mutant cancers that are resistant to BRAF inhibitors could be targeted by MEK inhibitors that are particularly active in a *KRAS*-mutant background.

For example, Zelboraf resistance arises when mutant BRAF forms a complex with wild-type CRAF (RAF1). CRAF's kinase activity is triggered by Ras overactivity, which originates with *de novo* mutations of the *KRAS* homolog *neuroblastoma Ras viral (v-Ras) oncogene* (*NRAS*) or elevated receptor tyrosine kinase (RTK) activity[4] (*see* **Figure 1, "Targeting MEK in cancer"**).

Roche has rights to Zelboraf from Plexxikon Inc., which **Daiichi Sankyo Co. Ltd.** acquired in 2011.

Lee Graves told *SciBX*, "It would make sense to test KRAS-specific MEK inhibitors against BRAF inhibitor–resistant melanomas since they appear to depend on high Ras activity. My prediction is that these may be superior to the MEK inhibitors exhibiting comparatively higher activities in *BRAF*-mutant backgrounds."

Graves is an associate professor in the Department of Pharmacology at the UNC at Chapel Hill School of Medicine.

Garraway agreed. "The addition of MEK inhibitors with elevated potential in *NRAS*-mutant conditions may conceivably help prevent escape from mutant BRAF inhibition and the development of resistance," he said.

The authors did not disclose patent and licensing status of the findings described in the *Nature* paper.

The most advanced MEK inhibitor is Mekinist trametinib (GSK1120212) from **GlaxoSmithKline plc**. The drug, which GSK in-licensed from **Japan Tobacco Inc.**, is approved for melanoma and is in Phase II testing for other tumor types.

Other MEK inhibitors include **Merck KGaA**'s pimasertib (AS703026), which is in Phase II testing for melanoma and pancreatic cancer, and **Takeda Pharmaceutical Co. Ltd.**'s TAK-733, which is in Phase I trials for solid tumor indications.

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COMPANIES AND INSTITUTIONS MENTIONED

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