First Ebola vaccine approved

The world's first vaccine against Ebola virus gained conditional approval from the European Commission in November. Merck's Ervebo vaccine has already been given to hundreds of thousands of people to help control the current outbreak in the Democratic Republic of the Congo (DRC). The approval will now speed up licensing by African country regulators and enable rapid patient access in at-risk countries.

The vaccine is a vesicular stomatitis virus–based vaccine expressing the glycoprotein of a Zaire Ebola virus (rVSV-ZEBOV). It has been given as one dose during an outbreak to individuals who have been in contact with infected people and the contacts of those contacts, as well as to front-line healthcare workers, in a so-called ring vaccination strategy under an expanded-access compassionate use protocol. Preliminary analysis of 90,000 vaccinated individuals in DRC estimates an efficacy rate of 97.5% when individuals are exposed ten days or more after vaccination, according to World Health Organization (WHO) data.

Another vaccine, made by Johnson & Johnson, began testing in DRC in November. The company in the same month applied for European approval. The Johnson & Johnson vaccine regime consists of two vaccines: an adenovirus type 26–vectored vaccine encoding the glycoprotein of Zaire Ebola virus (Ad26.ZEBOV) and a booster shot with a modified vaccinia Ankara–vectored vaccine encoding glycoproteins and a nucleoprotein from several types of Ebola virus (MVA-BN-Filo) given 56 days after the first immunization. The trial will vaccinate at-risk individuals living close to, but outside, the current outbreak zone in an effort to prevent virus spread.

The WHO says the Merck vaccine meets the organization's quality, safety and efficacy standards, which allows United Nations agencies and the vaccine alliance Gavi to stockpile the vaccine for future outbreaks.

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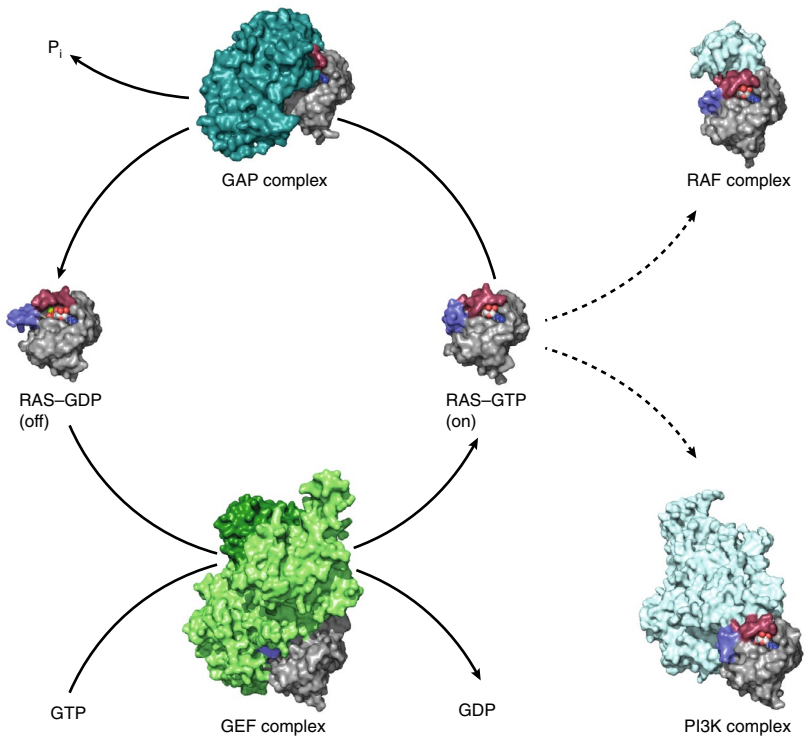
"We are being whipsawed by a failure to understand a fundamental economic principle." Kenneth Moch, CEO of Cognition Therapeutics, referring to the drug pricing bill before the US House of Representatives. More than 100 biotech execs penned a letter to the leaders of the US House of Representatives. (*STAT*, 5 December 2019)

Grail of RAS cancer drugs within reach

The first KRAS inhibitors to reach the clinic show preliminary but promising safety and efficacy.

Several decades of basic research on RAS signaling in cancer are finally starting to pay dividends. Amgen and Mirati Therapeutics recently reported early clinical data on their respective first-in-class small molecules, AMG-510 and MRTX849, in a range of solid tumors carrying the $KRAS^{G12C}$ mutation. These KRAS inhibitors not only disrupt cancer cell growth but also appear to promote T-cell infiltration into the tumor microenvironment: important first steps in addressing a vast area of cancer biology. But much effort is still needed to embed these agents in durable combination therapies. "Everyone is thinking very strongly in terms of what's next with these," says Julian Downward, of the London-based Crick Institute. "We have to think ahead." Tackling other KRAS oncogenic mutations that are also important cancer drivers is still wide open territory. A couple of firms are developing promising approaches to get beyond $KRAS^{G12C}$, but none of these is yet in the clinic.

Despite the caution, there is a palpable air of excitement among scientists focused on RAS signaling, given that *RAS* mutations are implicated in about one third of all human cancers. RAS proteins — of which there are three isoforms, KRAS, HRAS and NRAS — have been notoriously difficult to drug because their smooth surfaces lack obvious binding pockets to target with a drug. Although KRAS is the most clinically significant of the three, all are involved in relaying external growth signals to the nucleus through the mitogen-activated protein kinase (MAPK; also known as extracellular signal-regulated kinase, or ERK) pathway or through the phosphatidylinositol-3-OH kinase (PI3K)–AKT–mTOR pathway. The whole cascade is initiated when a ligand binds a receptor tyrosine kinase, leading to RAS activation,



RAS cycles between an 'on' state bound to GTP and an 'off' state bound to GDP. The active and inactive conformations of RAS differ, which controls the interactions between RAS and its binding partners. Credit: Reproduced with permission from *Nature Reviews Drug Discovery*, Springer Nature.