It’s a familiar refrain. The vast majority of cancer deaths in the US come about not because of a lack of treatment, but because the treatments themselves stop working in the patients receiving them. Accordingly, the emergence of drug resistance is now widely regarded by oncologists as the biggest challenge in cancer therapy. Insensitivity to drugs may arise due to changes in gene expression that allow a cancer cell to rewire its metabolism to circumvent the targeted pathway. Resistance also arises through genetic mutations, which, provided they offer a survival or growth advantage, can come to dominate a population of replicating cancer cells much as they would a population of organisms undergoing adaptive evolution in a new environment. (See “Resist or Desist,” The Scientist, April 2017.)

Growing appreciation of cancer’s capacity to evolve drug resistance is revealing fatal weaknesses in the drug-treatment strategy that dominates cancer treatment and drug discovery efforts, says Mel Greaves, director of the Centre for Evolution and Cancer at the Institute of Cancer Research (ICR) in the UK. During traditional drug screening, for example, oncologists “take a drug, put it in a test tube with a cell culture or cell line of cancer, and ask if it kills the cells,” says Greaves. At the ICR, which launched its Centre for Cancer Drug Discovery last summer, “we’re saying, that’s just wrong.”

Instead, several groups of cancer biologists are looking for therapies and treatment strategies that target cancer evolution itself, says Rossanese, now head of biology at the new center, which claims to have the “world’s first Darwinian drug discovery program” specifically designed to tackle drug resistance. This can take the form of manipulating the course of cancer evolution to clinicians’ advantage, or putting the brakes on the processes that drive it in order to limit a tumor’s capacity to adapt. In taking this approach, researchers “just assume resistance from the start,” Rossanese says. “If you do that, and you change your mindset that way, then how would you design drugs?”

**Cornering cancer**

The emergence of resistance to potent inhibitors such as dabrafenib isn’t surprising, says Rossanese. By the time of diagnosis, a typical tumor might already comprise more than 1 billion cells, each of which has the entire human genome at its disposal. During the tumor’s development up to that point, the accumulation of mutations in replicating cells will have led to heterogeneity, the substrate for evolution, among different subpopulations of cancer cells.

When a clinician administers high doses of a drug that blocks an important cellular pathway, “the pressure on the cells to come up with a resistance mechanism is quite strong,” Rossanese says. Any mutation conferring an advantage in that scenario, even if it’s present in just a few cells, offers an escape route, and can quickly sweep through the population to produce a drug-resistant cancer that thwarts further treatment.

One way to try to block cancer’s evolutionary escape routes is to use drug combinations that target multiple oncogenic pathways at once. For example, the combination of dabrafenib and trametinib—a drug that targets another central protein in cellular signaling, MEK—was approved in 2014 for certain types of melanoma and later for other cancers after showing improvement in survival rates compared with dabrafenib treatment alone. However, many cancers eventually go on to evolve multidrug resistance. There’s also the issue of toxicity: generally, the more drugs a clinician administers, the higher a patient’s risk of side effects.

An alternative strategy is to set a sort of evolutionary trap by administering a combination of drugs in a particular order. The aim is to select for resistance to the first therapy before hitting surviving cancer cells with a second therapy designed to target a vulnerability created by the very mutations that conferred resistance to drug 1. Known as evolutionary hedging, the method exploits the fact that any biological adaptation often involves trade-offs, being better at surviving in one environment may mean being worse at surviving in another. As part of an announcement last year about the ICR’s new drug discovery center, computational biologist Andrea Sottoriva likened the approach to sending cancer “down dead ends and to its own destruction.”

To turn the idea of evolutionary hedging into practical cancer therapies, oncologists are using computational and experimental techniques to predict which combinations of drugs, and in what order, are most likely to work. In one 2016 study, MIT researchers exploited the evolution of drug resis-