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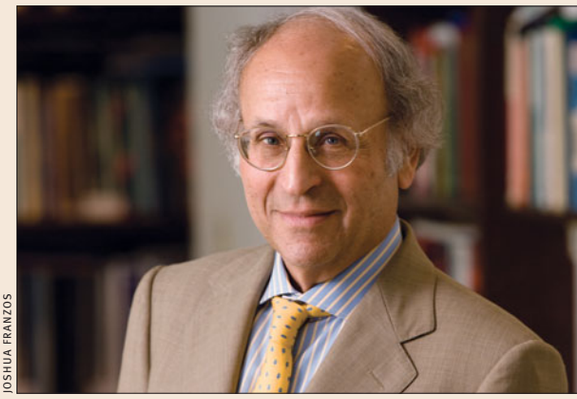
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JOSHUA FRANZOS

If you get to thinking you're a person of some influence, try ordering somebody else's dog around. —Will Rogers

This spring, my wife became enamored with a breed of dog with which I was unfamiliar, the Havanese. She suggested getting one, and I suggested that we dog sit for a weekend for a friend's Havanese, to get a sense of the breed, before making any decisions. A weekend was arranged with the Havanese guest; to protect his privacy, I'll call him Che. Che's owners warned us that the dog was quite affable except that he was insistent about sleeping with his owners in their bed. *Fine,* I thought to myself. *But that isn't going to happen in my house. This dog just needs discipline.* Well, I must have pushed Che out of bed 21 times before he surrendered and curled up on the dog pillow in the corner. Finally, we could rest soundly—until 2 a.m., when we found ourselves sitting bolt upright to earsplitting howling. The dog had rushed downstairs to the front door. *Someone's breaking in!* I rushed downstairs, but as I reached the bottom step, Che rushed up the steps. Having found no one breaking in, I returned upstairs, only to find the dog in my place in the bed. He'd taken advantage of my interest in preserving my territory just as he was attempting to expand his own.

Che exploited opportunities available to him; in an evolutionary sense, so do all organisms—and so do tumors. Case in point: A March 8 paper from British researchers in the *New England Journal of Medicine* shows us, in fine detail, using DNA and RNA sequencing and other methods, the genomic landscape of four primary renal carcinomas. In each case, the investigators found scores of varied and different mutations across spatially separated regions of the same tumor. Pathologists had a sense for some time that this was happening in cancer, but seeing intratumor heterogeneity in this detail is "somewhat frightening," admits Pitt's Adrian Lee, a renowned breast cancer specialist. "When you look at the complexity, it's hard to imagine a targeted therapy working." Gene expression patterns associated with good and poor prognoses were seen in different areas of the same tumor!

The researchers also found convergent evolution taking place—entirely different mutations ended up having the same effect (just as bats and birds independently developed wings)—notably, a loss of function of multiple tumor suppressor genes. "Obviously these genes have a very important function normally," notes Adrian, but "the tumor was going to select for mutations that would delete that function somehow and allow the tumor to survive and grow." Those mutations might have been selected in response to a lack of nutrients in particular areas of the tumor.

Though the challenges it reveals seem daunting, in the end, such research (similar molecular-level studies of tumor cells are going on at Pitt) and a deeper understanding of tumor biology will tell us how to approach personalized medicine. It probably makes sense, for example, to re-biopsy patients after targeted treatments. The group Adrian leads has already found that this may be a useful therapeutic strategy. It may also make sense to biopsy multiple sites in a tumor (and its metastases), given what we now appreciate about tumor adaptation and consequent therapeutic failure.

For the most part, the human species has excelled at adapting to our environment, but it appears the same is true of many tumors. Yet the evolutionary timescale for mutations in tumors is probably months rather than millions of years. This makes the work of Adrian and his colleagues all the more urgent.

A postscript: The affable traits and intelligence shared by the Havanese as a consequence of their Darwinian selection won out. We adopted Sasha, our delightful puppy, in April.

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