

THE RIGHT HAND-HOLD

In recent years, researchers around the world have confirmed ERKs' role in the generation of cancer. In 2001, for example, scientists working in Chicago, New York and Israel found that one of the most used cancer-fighting drugs, Taxol, has its effect through interaction with ERKs. Such intriguing finds help to suggest the prospect of drugs that selectively target particular sites within the complexly coiled structure of ERKs.

You can think of a protein as a big machine with many functions, says MacKerell, and some of them may not be good. "You can break the machine in many places, but that might mean you'd lose some of the good things the machine does. So our job is to be extremely specific about how we break the machine, and to do that you have to understand exactly how the machine is built, its precise shape."

ERKs, notes MacKerell, can be thought of as a crossroad protein. They are activated by a range of different signaling molecules and in turn can communicate with (via a reaction called "phosphorylation") up to 70 different proteins.

"We want to block just a subset of those 70 proteins — so that we block one pathway and not others. This work falls into the realm of 'chemical biology,' an important area right now in biomedical research, and it helps us to understand in detail how ERKs function."

Across the atomic landscape of ERKs are specific places — "docking domains" — where other molecules can link up. For ERKs, a partner protein first docks and then a chemical change occurs at the ERK's "active site." The method to MacKerell's and Shapiro's madness is that experiments show different parts of the docking domain link with different proteins.

"It's like if you jump into a moving truck," says MacKerell. "You've got to latch onto it, and then you can pull yourself in. Basically, 70 different proteins can latch onto ERKs, and one part of an ERK is involved in the latching on, and another part handles the phosphorylation. And that hand-hold where proteins latch on involves different parts of the ERK docking domain for different proteins."

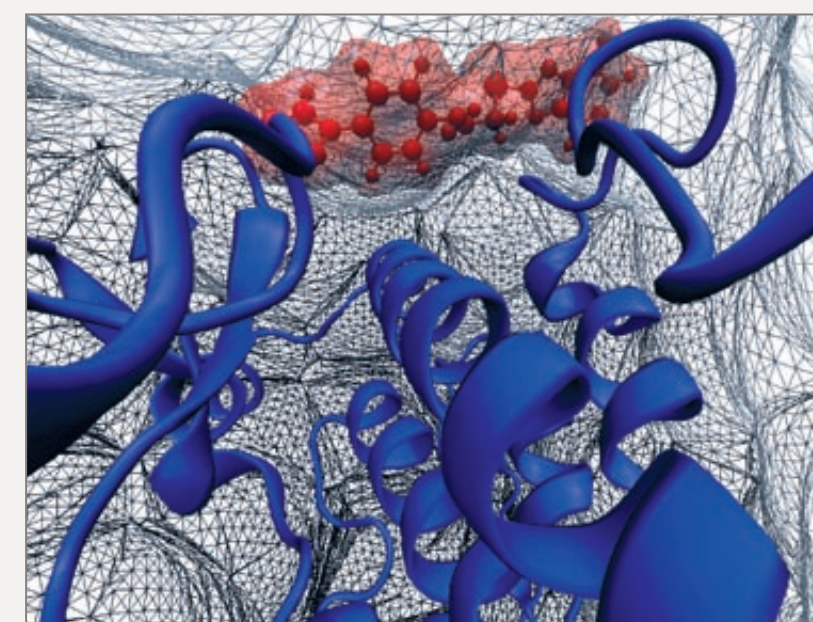
Each of the hand-holds — better known as binding pockets — represents the start of a distinctive

biochemical pathway that controls a specific task in cellular life. Finding these pockets is a first step. The next is to find a compound that can fill the right pocket and block a cancer-causing pathway. Ultimately, such compounds have the potential to become new drugs that can treat certain types of cancer.

THE PREDICTION BUSINESS

The trick is to find molecules that are the right size, shape and electronic charge at the right places to latch on and fill the pockets. This quest puts MacKerell squarely into the prediction business, and it would be impossible without computational tools. With "molecular dynamics" — simulations that track the atom-by-atom position of a molecule as it changes its shape over time, MacKerell identifies likely binding pockets.

The next step is to use this computer-drawn blueprint to search through a database of small organic compounds to find candidates that are likely fits to a binding-pocket target. To match a single molecule with a single binding-pocket within an ERK's docking domain requires screening nearly a million compounds one-by-one. When a promising compound is found, it takes up to 20 "docking runs" — computational screens that test to see how snug is the fit, how well the compound matches structurally and biochemically with the pocket. Each of these runs can require up to 100-billion calculations.



View from the interior of the ERK protein with a bound inhibitor (red), where the ribbons represent the protein backbone and the mesh represents the protein surface.

From 100 compounds, 10 showed promise as molecules capable of turning off taps of cancer at their source.

Without massively parallel systems — such as PSC's BigBen — that make it possible to employ hundreds of processors simultaneously, this work would not be feasible. "What PSC does," says MacKerell, "by allowing us access to so many processors, is make it possible for us to screen through our database multiple times in a very short period of time." Searches that otherwise would take months can be done in as little as a couple of hours.

When the data storm of the first round of screening settled, MacKerell had found about 100 compounds worth focusing on — his best picks for Shapiro to take into his laboratory for *in vivo* biological testing with cancer cells. "Alex gave me a list of 100 or so compounds," says Shapiro, "and I bought a small amount of each of them. In my lab, we have several cancer (cell) lines that we use for our preliminary studies and then the most biologically active compounds are tested in animal models. Here's where we evaluated whether the compounds Alex predicted could actually be useful by biological standards."

From the original round of 100 compounds, Shapiro found 10 that showed significant promise

as ERK inhibitors, molecules capable of turning off taps of cancer at their source.

"It's exciting," says Shapiro "that some of these compounds are showing they have an effect on stopping cancer cell proliferation."

Shapiro counts the computer-based methodology as highly "cost and person-power effective." His findings to date led two years ago to renewal of NIH support for his work with MacKerell's lab. "Computational modeling has identified a number of compounds with biological activity," says Shapiro. "Some of them are now under patent protection." (FS)

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