IMMUNOCHEMISTRY

Olympic hopes for chips

A new protein chip for high-throughput drug testing is a promising tool in the fight against doping in sports.

In September of 1988, fans of track and field events were dealt a severe blow when the Canadian sprinter Ben Johnson tested positive for an anabolic steroid and had to return his Olympic gold medal. Unfortunately, this was only one of many similar incidents in the history of sports. Besides the deleterious effects on athletes' health, drug use also causes disillusionment in the eye of the spectator. We are no longer inspired by athletic efforts, but reason—often from a comfortable couch—that it is not training but just the right combination of drugs that stands between us and Olympic glory. One solution to the problem of doping could be systematic controls, whereby everybody entering a competition would be tested. But current doping controls are too cost- and labor-intensive to allow for general screening.

Jing Cheng at Tsinghua University in Beijing was challenged by this bottleneck and presented a first step toward high-throughput drug testing in a recent paper in *Clinical Chemistry* (Du *et al.*, 2005). Sixteen prohibited substrates were immobilized on a chip and overlaid with a mixture of antibodies specific for those targets, along with the sample to be tested. If the test sample did not contain any of the prohibited compounds, the antibodies bound their substrates on the chip and could easily be visualized. If, however, the test sample did contain a forbidden drug, antibody bound this substance before it could bind to its counterpart on the chip, and hence no signal appeared. This detection assay does not require complicated and expensive equipment, and it allows a large number of substances to be rapidly tested at the same time. But there are still a few hurdles in the way of it becoming an internationally accepted doping test. Among other factors, a specific and very sensitive antibody is needed for every prohibited substance, and Cheng is currently working on developing some of these antibodies.

With the advent of systematic and reliable screening for every athlete, doping will hopefully become a thing of the past. Ideally, we will once again be inspired by the performance of top athletes to get off the couch and prove that we are capable of something—even just remotely—similar.

Nicole Rusk

RESEARCH PAPERS
Du, H *et al*. Development of miniaturized competitive immunoassays on a protein chip as a screening tool for drugs. *Clin. Chem.* **51**, 368–375 (2005).

BIOINFORMATICS

Problem solved?

A recent study suggests that the Protein Data Bank (PDB) may contain enough information to develop structure solutions for any single-domain protein—with the right computational tools.

Two strategies currently prevail for predicting the structure of a protein. Comparative modeling (CM) begins by identifying template proteins with strong sequence homology; by determining conserved regions and comparing against the known structure of the template, one can assemble a structure for the query protein. The second strategy, known as threading, extends the idea of CM to potentially evolutionary distant proteins; the query sequence is subjected to a range of possible structural configurations, and once a strong match is found, the tentative fold can be further refined. Thus arises the 'protein structure prediction problem': because both strategies rely to varying extents on the existence of an optimally comprehensive database of structures, the extent to which this database is incomplete limits the potential accuracy of any prediction.

But Jeffrey Skolnick, director of the University of Buffalo Center of Excellence in Bioinformatics, recently came to a rather startling conclusion: the PDB—which currently contains more than 29,000 protein structures—may now be sufficiently complete to comfortably solve this problem for any given single-domain protein. "As the threading algorithms kept getting better," says Skolnick, "I kept finding more and more structures I could fit. If the [PDB] was really incomplete, that left just two possibilities. Either the results are wrong, and we don't understand what's going on; or else it really was that as your algorithm got better, you could recognize the more distantly related structures...and you could build folds."

Skolnick and colleague Yang Zhang addressed this possibility in a new study, assembling a query set of 1,489 single-domain proteins from the PDB, for which they attempted to derive folds from a template library of 3,575 nonhomologous proteins. Using two methods—TASSER, a threading and refinement algorithm, and MODELLER, a CM algorithm—they generated continuous structures for all their queries that were reasonably close to native. After examining the extent to which TASSER could improve alignments of unrelated proteins, they found that for nearly 97% of their single-domain proteins (which had an average sequence identity of 13%), they could actually bring the predicted structure closer to native, within root mean square deviations of 4 Å or less. These findings imply that the PDB could be considerably closer to complete, in terms of fold representation, than expected.

Such findings are bound to rouse controversy. "Most people, when I tell them this, initially are very skeptical," says Skolnick. However, he continues, if these data do reflect the actual state of available information in the PDB, they raise a strong argument for creating databases that can do a better job of matching targets to distantly related templates. "I want to strongly emphasize that the models based on the templates provided by the PDB are imperfect and gappy but can have continuous models built from them—and I would argue that this should suggest a revisiting of the structural genomics fold selection strategy. If it's true, I think it's a very important implication."

Michael Eisenstein

RESEARCH PAPERS
Zhang, Y. & Skolnick, J. The protein structure prediction problem could be solved using the current PDB library. *Proc. Natl. Acad. Sci. USA* **102**, 1029–1034 (2005).