

Developing Anti-Cancer Drugs with Computers: Selective, Small-Molecule Inhibitors of JNK2 as Anti-Cancer Drugs

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Drs. Pang and Dong are developing chemicals that can selectively block the function of a cancer-related protein called JNK2. By looking at enormous chemical databases, they are able to assess millions of unique chemical structures that are potential blockers of cancer receptors.

Deep in the basement of the Guggenheim Building on Mayo Clinic's Rochester campus, hum rows and rows computers. They are over ten feet high and each row is embedded with ominous blue lights. The room is cold, and otherwise stark, but there is a looming sense of – excitement. The computers are the Kibbutz100 and the Silvergene – high-performance computers designed for “in Silico Screening” and “Multiple Molecular Dynamics Simulations,” two processes Drs. Pang and Dong have developed to help create models of biological systems. The aim is to use those models to find treatments for cancers and emerging infectious diseases. By looking at massive chemical databases, they are able to assess millions of unique chemical structures that are potential blockers of cancer receptors.

Drs. Pang and Dong's work involves JNKs – proteins seen in cancer-related tissue. These proteins are encoded or enabled by three similarly named genes, JNK1, JNK2 and JNK3. Inhibiting JNK has



been proposed as a means to develop potential anti-cancer drugs. While indiscriminately inhibiting JNKs can have serious side effects, selectively inhibiting JNK2 may offer effective treatment for certain cancers. Using modern chemical synthesis and cancer biology, Drs. Pang and Dong are developing chemicals that can selectively block the function of JNK2.

This work involves three basic components: a high quality database of 2.5 million unique chemical structures; an advanced computer program to identify the inhibitors; and the Kibbutz100 and the

Silvergene computers. In essence, using databases and supercomputers, they are integrating biological data in order to understand how biological systems function.

In Dr. Pang's lab at Mayo Clinic, they will identify tiny molecules that bind to JNK2 using an advanced virtual screening technique. Then they will chemically synthesize selective, tiny inhibitors of JNK2. “This work has the potential to change the way we treat cancer and other deadly diseases by preventing and curing disease, not just treating it after the fact,” says Dr. Pang.

In Dr. Dong's lab at the Hormel Institute, they will take the biochemically characterized inhibitors of JNK2 and work to make them function as potential anti-cancer drugs.

“Successful completion of this work will generate new chemicals that can be used as research tools to further the study on the role of JNK2 in cancers and to ultimately develop anti-cancer drugs,” notes Dr. Dong.

This project has long-term economic benefits for Minnesota. The new data generated will result in more federal funding, which in turn will create jobs for drug discovery research in Minnesota. This work also has immediate licensing opportunities with major pharmaceutical companies to develop JNK2 inhibitors as anticancer drugs – at least 16 companies currently sell a widely used non-selective JNK2 inhibitor and should have a strong interest in selective JNK2 inhibitors.