upregulated about 40-fold in anaerobic biofilms. The protein was also in the sera of chronically infected patients. The authors showed that with increasing chronicity of the infection, progressively more antibodies against OprF were formed. Thus, Fuqua thinks OprF is a promising target.

Although he is personally more excited by the quorum-sensing target, Shirtliff mentioned some successful attempts by other authors to develop a vaccine against the OprF protein [4]. The vaccine protected mice fromchronic pulmonary infection with *P. aeruginosa* and could also be applied in this case.

Meanwhile, Hassett is happy with both potential targets and is prepared to talk with companies that he expects will be interested in these results. 'We have a surface-exposed drug target and we have the talking-machinery drug target,' he said. 'It's very exciting.'

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Chemical geneticists unify their data

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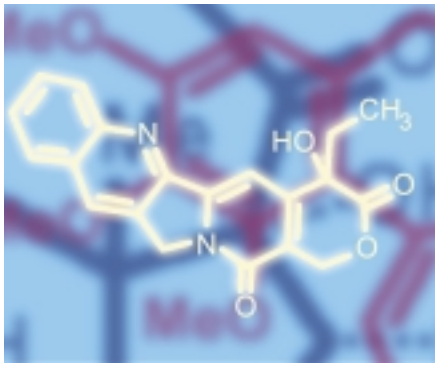
The first large-scale database of small molecules, to be released shortly, will be a boon to the field of chemical genetics, says Brent Stockwell, a researcher at the Whitehead Institute (http://www.wi.mit.edu/home.html). The collection promises to help researchers rapidly test thousands of mechanisms in mammalian cells, which have been beyond the reach of traditional genetics.

The annotated compound library (ACL) will be available to the public once the details have been finalized and published, Stockwell said at a recent conference at the New York Academy of Sciences (http://www.nyas.org).

A special challenge

Chemical geneticists – who study the effects created when specific small-molecule chemicals are added to cells – have to overcome several disadvantages that classical geneticists do not encounter, as they study the effects of random (or even intentionally induced) mutations [1]. Where other geneticists can trace a phenotype back to the mutated gene with relative ease, identifying the specific target of a small molecule can be challenging.



Unlike site-directed mutagenesis, it can also take 'years and years, if [it is] at all possible, to make one small molecule that's specific for a single target,' said Kevin Shokat, Associate Professor of Cellular and Molecular Pharmacology at the University of California in San Francisco (http://www.ucsf.edu).

When researchers do have success with a specific molecule, they have to plough through reams of literature to match it with the relevant molecular mechanisms [2]. Creating a GenBank-like database of small molecules can overcome some of those handicaps, says Stockwell. For example, he says, if scientists screen 2000 compounds, and find that 50 can actively inhibit angiogenesis, the ACL website can calculate statistically relevant themes among those compounds. Based on the mechanisms that are enriched among the molecules, the researchers can form a 'mechanistic hypothesis,' he said.

A range of chemical space

There are currently two main types of small molecules: drug-like synthetic compounds that are simple and of low molecular weight, and novel natural products of unknown mechanism that are more complex and have higher molecular weights [3].

The ACL lists both simple and complex compounds, which have known mechanisms and targets and span a greater range of chemical activity, explained Stockwell. 'We're sampling a great range of chemical space,' he said.

The database currently lists nearly 2000 compounds, but Stockwell and his colleagues hope to expand that number to 5000. The compounds are annotated in a systematic fashion with 138 molecular descriptors and 12,700 different mechanistic terms. Over time, Stockwell says, the number of terms could be expanded to 60,000.

In one demonstration of the database's power, the researchers tested

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1760 compounds on normal lung fibroblasts and lung carcinoma. After a thorough analysis, they found that 12 compounds specifically kill tumour cells, while 14 specifically target normal cells.

They also tested the compounds in a tumour cell line, derived from normal cells by adding telomerase, large-T oncoprotein, small-T oncoprotein and Ras. Again, the researchers found nine compounds that selectively kill tumour cells but not normal cells. The researchers found that compound NSC259968 is 16-fold more potent when telomerase and large-T are introduced, but has no effect with small-T or Ras. Another compound, echinomycin, is 2048-fold more potent when large T is added, and the effect of camptothecin increases only with addition of the oncogene Ras.

When the researchers further investigated the effects of camptothecin, they found that the effect is mediated through topoisomerase (TOP1). When Ras is introduced, TOP1 increases, and cells that lack TOP1 are resistant to camptothecin.

Power tools

According to Stockwell, these results are an 'important demonstration that such information can be used to selectively validate a specific molecular alteration' – in this case, that cells expressing TOP1 are more sensitive to camptothecin.

Some biotech companies and academic labs are now creating thousands of small molecules using combinatorial chemistry [4]. Others are developing tools to identify proteins that have a key role in a given cellular process [5,6], and still others are building a genome-wide collection of small interfering RNA (siRNA). For decades, mammalian geneticists have been 'jealous' of yeast or worm geneticists because their tools do not have the same power, Stockwell, said. But by combining all the tools now in development, he says, scientists can 'finally do genetics in mammalian cells'.

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Cold war adversaries team up to conquer TB

Thomas S. May, freelance writer

Peaceful co-existence and co-operation between the USA and the countries of the former Soviet Union (FSU) have, undoubtedly, contributed to a greater sense of security throughout the world over the past decade. Now it seems that this co-operative atmosphere could also help conquer one of the deadliest and most widespread diseases – tuberculosis (TB).

Among infectious diseases, TB is the second greatest contributor to adult mortality, responsible for approximately two million deaths per year worldwide, according to statistics from the World Health Organization (WHO; http://www.who.org), which estimates that one-third of the world's population is infected with *Mycobacterium tuberculosis*. (http://www.who.int/gtb/publications/globrep02/).

Although TB can sometimes be cured with a six-month course of antibiotics, various forms of multidrug-resistant TB (MDR TB) have been on the rise in certain areas of the world, and people infected with MDR TB often require extensive chemotherapy for a period of up to two years. In Russia, for example, after decades of gradual decline, the incidence of TB (especially MDR TB) has been increasing steadily over the past 10 years, largely as a result of widespread poverty and homelessness.

Migration from parts of the FSU with high TB rates has exacerbated the problem. Furthermore, 'a shrinking health budget resulted in an erratic supply of anti-TB drugs and laboratory supplies, reduced quality control in TB dispensaries and laboratories, and inadequate treatment led to drug resistance', according to a recent WHO country profile (http://www.who.int/gtb/Country_info/pdf/Russian_Fed.pdf).

Immune booster?

One possible approach to defeating TB, besides the use of antibiotics, is to try to strengthen the immune system of TB-infected people. This is the approach taken by a small US company, SciClone Pharmaceuticals (http://www.sciclone.com), which claims to have developed a drug that stimulates the immune response

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