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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by activating Th-1 cells. The drug is a novel synthetic dipeptide, D-glutamyl-L-tryptophan, dubbed SCV07.

In co-operation with a Russian biotechnology company, Verta, SciClone has recently tested the effectiveness of SCV07 in a Phase II clinical trial. In addition to standard anti-TB therapy, 44 patients with TB (60% with MDR TB) received 10–100 μg d^{-1} of SCV07 for five days. As controls, 27 other patients received standard therapy only.

Among patients treated with SCV07, 57% had negative sputum cultures after one month and 80% were negative after three months (Fig. 1). Among controls, cultures were negative for only 19% and 37%, respectively. These results imply that SCV07 could potentially reduce the length of TB treatment, according to Cynthia Tuthill, SciClone's Vice President for Scientific Affairs. 'The real benefit, however, is that by reducing the time that patients are contagious, there is less opportunity to spread the infection', she explained.

Although these results are encouraging, this was a relatively small study, warns Martin Bachmann, Chief Scientific Officer of Cytos Biotechnology AG (http://www.cytos.com). 'Side effects are always a major concern with non-specific stimulators. It is quite possible that problems may be encountered when patient numbers are increased', he cautioned.

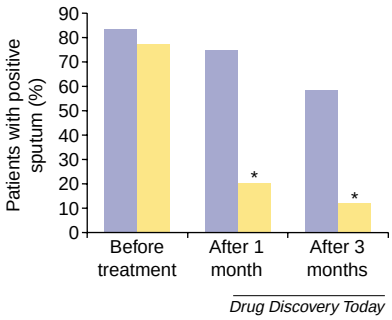


Figure 1. Decreases in positive sputum assays for mycobacteria in Phase II trial of SCV07 (blue bars, controls; yellow bars, patients treated with SCV07. * $P<0.05$). Figure courtesy of SciClone Pharmaceuticals (http://www.sciclone.com).

From missiles to meat

Although it is yet to be tested in Phase III clinical trials, the development of SCV07 could be a significant step in the continuing fight against TB, and perhaps other infectious diseases. This progress might never have occurred without the help of the US Civilian R&D Foundation (CRDF; http://www.crdf.org), which has provided funding for the project and facilitated co-operation between SciClone and Verta.

CRDF is a nonprofit charitable organization that promotes scientific and technical collaboration between the USA and the countries of the FSU. One of its main goals is to give opportunities to scientists and engineers in the FSU (many of whom used to work for the military) to do 'real' science and engineering work, so they would not have to leave their country or their profession to survive, says Tom Owens, a Senior Advisor with CRDF.

According to Owens, any US company is eligible for financial assistance from CRDF 'as long as it has a serious interest and wishes to develop a new relationship with a group in the former Soviet Union on a project in which there could be a decent chance for commercial application in the future'.

'We fund projects up to the time of being commercial', Owens said. Funding might be in the form of travel grants or awards for experiments and other R&D activities that can help people make a decision to enter the commercial market, he explains.

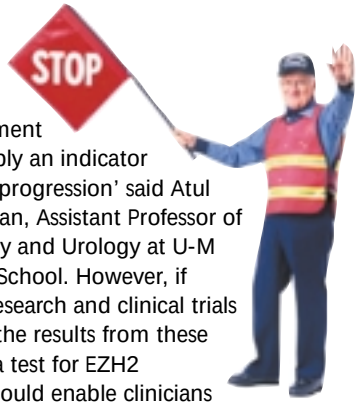
News in brief

Cancer gene expression

EZH2 flags up metastatic prostate cancer

Scientists at the University of Michigan's Comprehensive Cancer Centre (http://www.cancer.med.umich.edu) have shown, through gene expression profiling, that high levels of the polycomb group protein enhancer of zeste homolog 2 (EZH2) could be a warning sign of metastatic prostate cancer [1]. The group compared donated prostate tissue samples and observed that the intensity of EZH2 protein staining steadily increased from benign to clinically localized prostate cancer to metastatic disease. Analysis of EZH2 expression and other clinical indicators, including the Gleason score, tumour stage and prostate specific antigen (PSA) levels, were correlated with clinical outcome and it was found that the most significantly accurate predictor of clinical outcome was EZH2 protein expression in prostate cells.

EZH2 is one of several proteins that control the genetic memory of a cell and can interfere with the transcription of genetic code. 'At this point, it's unclear whether the gene plays a role in cancer's development or is simply an indicator of lethal progression' said Atul Chinnaiyan, Assistant Professor of Pathology and Urology at U-M Medical School. However, if further research and clinical trials reaffirm the results from these studies, a test for EZH2 protein could enable clinicians to diagnose those men who need immediate clinical intervention to prevent the cancer from spreading.



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