news

death knell for the Canadian drug import industry. Canada's health minister, Ujjal Dosanjh, has announced three options: (1) prohibiting Canadian doctors from countersigning prescriptions from US physicians after reviewing patient charts; (2) prohibiting any non-Canadian from acquiring a Canadian drug unless they are physically examined by a Canadian physician; and (3) devising a protected drug list of any drug deemed in short supply and not permitted for resale to the US. He is expected to announce his decision soon.

If the trade is not stopped, says Trewhitt, the very foundation of research and development is threatened, he says. 'The US pharmaceutical and biotech industry provides 60–70% of the world's new medicines – we think one of the major reasons is that we have competitive pricing.'

But MacKay argues that the notion of drug reimportation posing a threat to R&D funding is faulty logic. He says Canadian sourcing creates customers where they otherwise would not exist. Patients who cannot afford US prices simply won't buy the drug. 'You can't get profit out of a no-sale,' says MacKay. They will buy it, however, if they can find it affordably priced in Canada. The Canadian purchase 'is a new business sale and market for the pharmaceutical company,' he says.

'It's not as if they're losing money,' counters Trewhitt, 'but that profit is much more modest – too modest to sustain the current level of innovation.' It's a trend that he says has been seen many times among drug companies based in Europe and Canada wherever there has been a history of price control. 'You still have a number of cutting edge [companies] in Europe, but what they've done is opened up very large US subsidiaries,' he explains. 'When it comes time to open up a $400 million center, they're opening it up in the US, they don't do it in their home countries.'

Fears

But MacKay argues that the reason the drug companies are fighting this issue tooth and nail – despite reaping profits regardless of whether the drugs are sold in Canada or the US – is because of another unspoken threat. 'Why they want us [Canadian mail order pharmacies] gone is because of the public relations nightmare we create for them,' he says. 'They fear this importation issue will create a huge demand for price controls in the US domestically and eliminate their worldwide cash cow – and we're raising attention to how they're [American consumers] are being gouged,' he says.

Furthermore, he argues, banning the trade will only fuel the illegitimate market that opponents, including PhRMA, cite as the chief threat posed by reimportation. 'They would be creating a Pandora's box,' he says. 'If you kill the only legitimate channel of trade, you have a system where counterfeiters and unregulated products will fill the void of demand. These people will fall into the hands of unscrupulous vendors.'

Getting inside the bug: new targets for TB drugs

Stephani Sutherland, sutherland@nasw.org

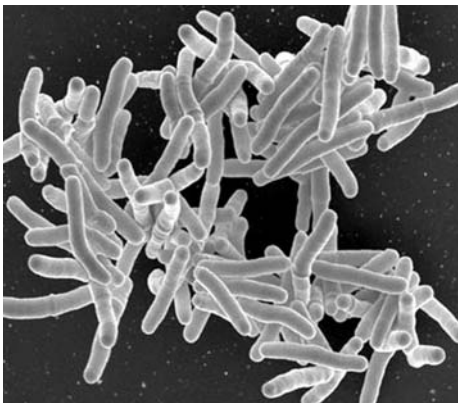
Few of us probably noted the passing of World TB day on March 24 (www.niaid.nih.gov/director/worldtbday_05.htm). But for hundreds of scientists and clinicians working to combat the disease, TB is the focus of every day. Among them are Harvey Rubin and his colleagues at the University of Pennsylvania, who have identified a new drug target in the organism [1].

Global public health crisis

Mycobacterium tuberculosis claims over two million lives worldwide each year– and dwells, hidden, in as many as two billion people. Development of new therapeutics has been stymied for 40 years, and strains of *M. tuberculosis* are gaining resistance to available drugs – a difficult six-month treatment course. The worsening situation has prompted the World Health Organization to declare TB a global public health crisis.

1359-6446/05/$ – see front matter PII: S1359-6446(05)03454-9

news



***Mycobacterium tuberculosis;* image kindly provided by NIAID**

New drugs must travel a long pathway to development, from basic science to clinical trials. Rubin's work takes that first step. He and his group have genetically mapped out the organism's aerobic respiratory chain – how electrons build the force necessary to create ATP. They turned their attention to the first enzyme in that chain, NADH:menaquinone oxidoreductase. After screening over 50 phenothiazine compounds, they identified several that were tuberculocidal *in vitro* and inhibited pathogenesis in a mouse model.

Good target

Rubin is under no illusions about the long road to new therapeutic drugs. 'To be honest, these compounds aren't going to become active anti-TB agents. But this enzyme is a good target, and this class of drugs is a good candidate.' Christine Sizemore of the National Institute of Allergy and Infectious Diseases (NIAID) agrees. 'The targets they're going after represent a new direction: oxygen metabolism.' She describes the work as 'an important biochemistry paper,' with the compounds' activity as 'a little bit of a carrot at the end.' Even if they never become drug candidates, she adds, they might have immense utility as tools to understand the inner working of the microbe.

Rubin characterizes the experiments 'as a proof of principle that this enzyme, and even the whole chain, is a good target.' Work from another laboratory [2] has also honed in on this oxidative machinery – specifically ATP synthase. 'They targeted the last enzyme of the pathway, and now we've targeted the front end, the first step that sends electrons down the chain.'

The Holy Grail

The success of *M. tuberculosis* as a pathogen arises from its tenacity. Even deprived of oxygen and nutrients, it can survive for years in the body of its host by entering a dormant state. When resources become available, the bug awakens with devastating effects for its host. But the transition between these states remains mysterious.

Although there's no evidence yet that the reductase plays a direct role in entering or leaving dormancy, Rubin and his team 'believe in our heart of hearts that it might.' Understanding how Mtb survives on lower oxygen levels is critical to learning how to kill the bug. The answer may lie in the oxidative enzymes' high affinity for oxygen. 'We believe that how the bug up- or down-regulates these enzymes is key to whether it stays dormant.'

Sizemore says, 'The Holy Grail is to find drugs that will kill the bug dead rather than force it into its dormant state – to find something that will kill it in any state.' She cautions that, as with development of any drug, 'the realities of economy play into TB treatment.' Next-generation drugs might not be around the next bend, but hopefully we won't have to wait another 40 years for them. And with new targets, hard work, and a bit of luck, maybe we won't have to.

References

1 Weinstein, E.A. *et al.* (2005) Inhibitors of type II NADH:menaquinone oxidoreductase represent a class of antitubercular drugs. *PNAS* 102, 4548–4553

2 Andries, K. *et al.* (2005) A diarylquinoline drug active on the ATP synthase of *Mycobacterium tuberculosis*. *Science* 307, 223–227

Looking for new sepsis targets

Vida Foubister, vfoubister@optonline.net

A nitric oxide synthase inhibitor that showed initial promise for the treatment of sepsis was found to be associated with increased mortality in a large clinical trial last year. Now scientists are looking at the many pathways involved in the disease for clues that might lead to new targets.

Rising incidence

The incidence of sepsis, the body's response to a bacterial infection, has increased during the past decade from about 80 per 100,000 population to 250 per 100,000 population and is expected to continue rising as the population ages. The disease, which has a mortality rate of about 25%, costs US hospitals alone nearly $17 billion annually [1].

'One of the principal causes of death is severe hypotension, and much of the therapy is based on reversing this extremely low blood pressure that leads to fluid extravasation, inadequate tissue and organ perfusion, and ultimately organ failure and death,' explains Adrian J. Hobbs, Wellcome Trust Senior Research Fellow, Wolfson Institute for Biomedical Research, University College London.

Although pharmaceutical companies have been funding research in this area for years, Xigris, a recombinant human Activated Protein C marketed by Eli Lilly and Company, is the only therapy approved for treating high-risk severe sepsis.

Nitric oxide levels

NG-methyl-L-arginine held promise as a therapeutic for sepsis due to its ability to inhibit the overproduction of nitric oxide, a vasodilator that at sustained high levels can cause systemic hypotension. But, a multiple-center clinical trial found the nonspecific nitric oxide synthase inhibitor increased mortality in patients with septic shock and was prematurely halted [2].

There are, in fact, three isoforms of nitric oxide synthase: inducible (iNOS), endothelial (eNOS), and neuronal (nNOS). It's iNOS that has been long linked to the increased nitric oxide levels triggering septic shock, and research has focused on inhibiting its expression.

However, recent work led by Hobb shows that mice lacking eNOS, an enzyme found predominantly in endothelial cells lining the

1359-6446/05/$ – see front matter PII: S1359-6446(05)03437-9