Bench to Bedside

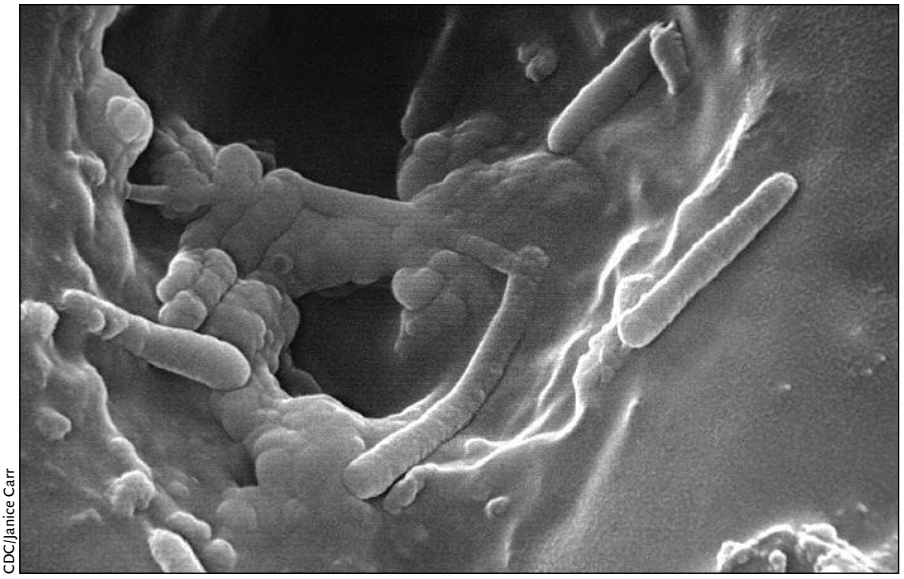
## Chaperoning fungal resistance

Overcoming microbial drug resistance requires not only the design of new drugs but also a better understanding of how resistance develops in the first place. New research reveals that the protein Hsp90 — a molecule that acts like a chaperone to help other proteins fold — enables pathogenic fungi to quickly gain drug resistance (*Science* 2005;309:2185-9).

Drug-resistant fungi like *Candida albicans* are a particular concern: it is difficult to design drugs that work against them because their cellular machinery is similar to our own (*Science* 2005;309:2175-6). It is, therefore, a struggle to uncover new targets for antimicrobial agents.

But work by Leah Cowen and Susan Lindquist points to a new way to tackle this problem. They engineered yeast strains that express either high or low levels of Hsp90 and tested them for both rapid and gradual resistance to antifungal azole agents. The scientists found that Hsp90 enabled diverse new mutations that caused immediate changes in phenotype and allowed organisms to respond to environmental stresses (*Science* 2005;309:2185-9). The protein performed this function in *Aspergillus terreus* as well as in *C. albicans*.

These findings have potential clinical applications. Although azole drugs are fungistatic and not fungicidal, their combination with Hps90 inhibitors is lethal to fungal microbes. This suggests that combination drugs may be the key to killing fungal pathogens while also reducing their resistance to drugs (*Science* 2005; 309:2175-6).



CDC/Janice Carr

Scanning electron micrograph of *Pseudomonas aeruginosa*.

## Cystic fibrosis lung infections detected in breath

The detection of lung infections in cystic fibrosis patients may be only a breath away: new research suggests that bacterial by-products can be detected in the exhaled breath of patients with cystic fibrosis. It is a finding that may lead to welcome alternatives to current invasive bacterial detection techniques.

Patients with cystic fibrosis are particularly susceptible to chronic colonization by opportunistic bacteria like *Pseudomonas aeruginosa* and *Burkholderia cepacia*, which in 80% of patients eventually leads to respiratory failure (*BMJ* 1995;310:1571-2). Early detection of lung infections, which helps to ensure the effectiveness of antibiotic treatment, is therefore an important component of keeping cystic fibrosis patients healthy.

However, current techniques for monitoring bacterial colonization, like sputum or bronchoalveolar lavage analysis, can miss the initial phase of some infections. Michael Kamboures and colleagues therefore sought a new detection technique with the hypothesis that trace gases produced by bacteria could be detected in a patient's breath.

They used a chemical analysis method originally designed for air-pollution testing to monitor the levels of sulfur compounds known to be produced by bacteria like *P. aeruginosa* and *B. cepacia*. Patients with cystic fibrosis were found to exhale almost 2.5 times more carbonyl sulfide than patients without the disease (*PNAS* 2005;doi/10.1073/pnas.0507263102).

Although the results of the study by Kamboures and colleagues do not prove that the carbonyl sulfide comes from lung bacteria, they do suggest that the compound may be a useful noninvasive marker of bacterial colonization. The study also points to the potential of trace gas-breath analysis in the clinical setting. — Compiled by David Secko, Vancouver

DOI:10.1503/cmaj.051493