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"Massive decay" in leprosy genome - massive for research too?

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The sequencing of the genome of *Mycobacterium leprae* has caught the attention of mycobacterial scientists. *M. leprae* doubles so slowly that it takes up to a year to culture - in the nine-banded Armadillo or the footpads of mice because it can't be grown in tissue culture. Michael Glickman, a TB researcher at Albert Einstein College of Medicine in New York, said "One of the first goals of genome analysis is to derive conditions which will allow the organism to be grown in tissue culture."

"This genome tells us what it takes to grow inside a cell - and that's basically all *M. leprae* does, you can't grow it *in vitro*," said Jo Colston, Head of Mycobacterial Research at the UK's National Institute for Medical Research. "So basically it seems to have got rid of everything it doesn't need. Which leads to interest in how it could have evolved."

"It's also very important for research on tuberculosis (TB). The interesting thing about the *M. tuberculosis* genome is exactly the opposite of *M. leprae* - it does much more than we anticipated it would be able to do." For example after the sequence of the M. tuberculosis genome became available 18 months ago (another sequence is available from The Institute for Genome Research) "we found it had genes that would enable it to grow in an anaerobic environment... Now, by comparing it to the leprosy genome, we can say, this is all TB would need to do the basics, and it's got all this other stuff to enable it to be TB."

"And as for leprosy itself, one thing that is unique to the disease is that it invades nerves - Schwann cells - so it has some unique capacity, and maybe the genome will show what that is" said Colston.

Stewart Cole of the Institut Pasteur in Paris, the leader of the *M. leprae* sequencing project, said other obligate intracellular pathogens had been sequenced, including *Rickettsia* and *Chlamydia*, but neither showed gene decay on the same scale. "Probably about 25% of the genome of the typhus agent [epidemic typhus is caused by *Rickettsia pronazekii*] is dead, but the sequencers were unable really to prove that. They couldn't identify any genes in there, but at the same time they couldn't identify any pseudogenes. Whereas we had the TB sequence to compare with." This showed a multitude of TB genes in *M. leprae* that are unused - Cole concludes that genome decay in *Rickettsia* is not on anything like the same scale as *M. leprae*.

Already, "the leprosy sequence has enabled us to do two things," Cole said. "One is, we've been able to identify genes that look like they're specific to *M. leprae*, at least for the present. We will try and produce the proteins for some of those... and see if they are recognized by the immune system. If they are, we'll look at whether they can be used as diagnostic antigens for improving diagnosis in paucibacillary patients... And there is a group of 200 or so proteins that seem to be confined to *M. tuberculosis* and *M. leprae*, so these genes could be responsible for highly specific functions associated with pathogenic mycobacteria, and would be potential drug targets. The main interest here would be for TB."

So what use can the leprosy genome be for leprosy itself? According to Paul Nunn, Disease Coordinator for Tuberculosis and Leprosy at the WHO-based Special Programme for Research and Training in Tropical Diseases (TDR), "The contrasts between leprosy and TB are very revealing. In TB we have a clear-cut test of disease - the sputum smear. Now there may be all kinds of problems with it,

but nevertheless if you've got a positive smear you've got infectious TB. So there's a clear-cut, specific if not very sensitive test for disease. Second, we have a test for infection, the tuberculin skin test, which may not be 100% reliable, but it's quite good enough for most purposes." But in leprosy all there is a clinical observation, of lightened, insensitive skin patches. "And therefore vastly more is known about the epidemiology of TB than is known about the epidemiology of leprosy."

A key aim will be to develop a specific and sensitive molecular diagnostic test. And TDR will be putting a lot of its money in that basket. "One approach that's being taken is to select out sequences of 10-15 peptides that might be useful, get a selection of hopefully unique peptides and put them together, and by using a soup of these get a test that's both specific and sensitive," said Nunn. "This is already being done in one or two places, but with the genome it's going to be very much more efficient to do so."

How long would it take? "This is a complete guess, but I'd say at least 3-4 years." And how much would it cost? " Well we're talking in the region of $1-2 million." And what's TDR giving? "It depends on what we receive, but we're hoping for around $1 million a year for this."

Vijay Pannikar, manager of TDR's Steering Committee on the Chemotherapy of Leprosy hopes the genome can be used to look at resistance to rifampicin, one of the main components of MDT. "This is something we are a bit worried about. We've been using MDT for the last 15 years, and cured more than 10 million patients with that. And the main drug is still rifampicin. It is likely that eventually a resistant strain will emerge. And we want to keep a watch on it. But the current methods are too slow... the mouse footpad takes about a year to get a result. But I believe with the genome information we can do it within a few days.

The leprosy genome project was launched with initial funding from the Victor Heiser Trust of the New York Community Trust for research and training in leprosy and tuberculosis, while Barry Bloom, Dean of Harvard Medical School and long-time researcher on leprosy, was chair of the Scientific Advisory Committee. "They agreed to invade their capital [against their rules] to allow this project to get funded. The Trust people were heroic and really trusted the scientists to use their relatively small funds wisely. They are heroes," Bloom said.

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