AUTHOR COMMENTARIES - From Special Topics

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Roland Brosch
From the Special Topic of Tuberculosis

In our Special Topics analysis of Tuberculosis (TB) research over the past decade, the work of Dr. Roland Brosch ranks at #4 by total cites and #2 by cites/paper, based on 23 papers cited a total of 3,931 times. He is also a coauthor on the papers ranked at #1 and #11 on the list of the most-cited papers from the past 10 years.

His record in Essential Science Indicators℠ *from Thomson Reuters includes 36 papers, the majority of which are classified in the field of Microbiology, cited a total of 4,670 times between January 1, 1998 and December 31, 2008. Dr. Brosch the Head of the Integrated Mycobacterial Pathogenomics Unit at the Institut Pasteur in Paris, France..*

In the interview below, he talks with ScienceWatch.com *about his work related to TB.*

SW: Would you tell us a bit about your educational background and research experiences?

I did my studies in biology at the Universities of Graz and Salzburg in Austria and received a Ph.D. from the University of Salzburg. As part of my postdoctoral work, I studied the genomic and phenotypic diversity of the food-borne pathogen *Listeria monocytogenes* at the Institut Pasteur in Paris, France, and the University of Wisconsin, Madison, USA, before I became interested in *Mycobacterium tuberculosis* and joined the group of Professor Stewart Cole, who was leading an *M. tuberculosis* genome-sequencing project at the Institut Pasteur in collaboration with the Sanger Institute (Hinxton, UK) in order to decipher the genetic bases of this major human pathogen.

It was an extraordinary experience, scientifically and socially, to be part of the team who got the first broad insights into the gene content of this key pathogen. In the following 10 years I had the great opportunity to continue working in the lab of Stewart Cole. I used comparative genomics of *M. tuberculosis* and Bacille Calmette-Guérin (BCG), the attenuated vaccine strain, and undertook functional analyses to extract the biological and evolutionary information contained in the genome data.

Recently, Stewart took on a new position at the EPFL in Switzerland. In 2008 I became head of the new research Unit at the Pasteur Institut that is dedicated to integrated mycobacterial pathogenomics. In addition, several other units on the Pasteur campus are working on various other

+larger view

M. tuberculosis culture on agar plate.

aspects of tuberculosis research, such as genetics, structural biology, immunology, histo-pathology, and host-susceptibility, which makes the Institut Pasteur a very stimulating place to do mycobacterial research.

SW: What influenced your focus on tuberculosis?

Tuberculosis has had a huge impact on human history, and continues to claim millions of lives at the beginning of this 21st century. The emergence and spread of multi- or extensively drug resistant (MDR, XDR) strains of *M. tuberculosis* represent an additional threat. Thus, further research on this pathogen and its interaction with the host is absolutely crucial to cope with this problem in the future. Many novel tools of molecular biology have been developed in recent years and their adaptation to mycobacteria open new exiting insights into the biological properties of *M. tuberculosis*.

SW: The majority of your papers in our analysis deal with research into the *Mycobacterium tuberculosis* genome. What important discoveries have been made about this genome, and how has this knowledge helped with the disease?

The genome of *M. tuberculosis* contains all the information this organism needs to persist and multiply in the host. The genome information together with functional genomics studies now allow us to determine the weak points in the metabolism of the bacterium, which is, for example, important for the development of novel anti-tuberculosis drugs.

SW: Your most-cited paper in our analysis is the 1998 *Nature* paper, "Deciphering the biology of *Mycobacterium tuberculosis* from the complete genome sequence," which has been cited close to 3,000 times. Would you walk our readers through this paper and why you think it is so highly cited?

This landmark paper has indeed changed the way in which scientists look at *M. tuberculosis*. The genome of *M. tuberculosis* contains large regions of particularly high GC content and repeated motifs that have posed an enormous challenge for the finishing phase of the sequencing project. It was the use of large insert size clone libraries, which finally enabled us to bridge the gaps in the shotgun libraries and to establish a reliable genome sequence.

"Tuberculosis has had a huge impact on human history, and continues to claim millions of lives at the beginning of this 21st century."

The next major challenge was the annotation and interpretation of this raw sequence. About 4,000 genes have been identified in the genome of *M. tuberculosis* including several from new gene families, many of which are now the subject of intense and focused research. The availability of this information has enabled a variety of novel approaches that include studies of the transcriptome, the proteome, protein structures, and/or metabolic reconstruction.

The information content of the genome sequence of *M. tuberculosis* benefits many different disciplines of mycobacterial research, and that is why the paper is so highly cited. Indeed, biological and medical research without access to genomic data is difficult to imagine nowadays.

SW: Another paper you coauthored that is receiving citation attention is the 1999 *Tubercle and Lung Diseases* paper, "Analysis of the proteome of *Mycobacterium tuberculosis in silico*." Please tell our readers about this paper and its significance.

This paper published in *Tubercle and Lung Diseases* (now named *Tuberculosis*) contains an extensive bioinformatic analysis of the *M. tuberculosis* genome, which identified large gene families that seem to play important roles for the bacterium. Some of these families, such as the ESAT-6 family or the MmpL family, have since then been shown to be essential for the pathogenicity of the organism.

SW: In 2008, you coauthored a paper in *Genome Research*, "Insights from the complete genome sequence of *Mycobacterium marinum* on the evolution of *Mycobacterium tuberculosis*." Would you talk a little bit about this paper—its goals, findings, and implications for the field?

The results presented in this paper are based on the collaborative work of groups from several institutions. This work nicely demonstrates that during the early evolution of *M. tuberculosis*, both genome downsizing and gene acquisition via horizontal gene transfer seem to have played major roles for *M. tuberculosis* becoming a pathogen.

SW: What are your hopes for progress in TB research over the next decade?

My hopes for the TB research of the next decade are focused on the functional analyses of the genes that have been identified to be involved in the pathogenicity of *M. tuberculosis*. Knowledge of how *M.*

tuberculosis uses these genes during the infection process is important to find new ways to target this major pathogen. In addition, due to more and more genome sequence information becoming available, information on the origin, evolution, and specific adaptation of *M. tuberculosis* to its host should help to find factors that are crucial for *M. tuberculosis* being such a successful pathogen.

SW: What would you like the "take-away lesson" about your research to be?

I think that the research to which I have contributed within the last 10 years has allowed important new insights into the biology and evolution of *M. tuberculosis* and closely related members of the *M. tuberculosis* complex. This knowledge will be exploited within the next years for novel prophylactic and/or therapeutic interventions.

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Roland Brosch's current most-cited paper in *Essential Science Indicators*, with 2,793 cites:

Cole ST, *et al.*, "Deciphering the biology of *Mycobacterium tuberculosis* from the complete genome sequence," *Nature* 393(6685): 537-+, 11 June 1998. Source: *Essential Science Indicators* from Thomson Reuters.

Additional Information:

Stewart Cole Interview for Special Topic of Tuberculosis.

KEYWORDS: TUBERCULOSIS, TB, MYCOBACTERIUM TUBERCULOSIS, COMPLETE GENOME SEQUENCE, VACCINE, MULTI-DRUG RESISTANCE, EXTENSIVELY DRUG RESISTANT, GENE FAMILIES, GENOMICS, PATHOGENICITY.

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