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CAMBRIDGE SOCIETY FOR THE APPLICATION and APPRECIATION of RESEARCH

"Antibiotics, 75 years on"

(Creating new antibiotics, using genes clones from *Streptomyces* spp.)

Professor Sir David Hopwood, FRS
Department of Molecular Microbiology, John Innes Centre, Norwich

Monday, 20th February, 7.300 - 9.00 p.m.
The Wolfson Lecture Theatre, Churchill College, Cambridge

Chair: Dr L F Wright, ThinkSmith Limited
Vote of Thanks: Dr Richard Freeman, Scientific_Generics Ltd

About the lecture:

David Hopwood writes…….

During the Golden Age of natural product discovery, in the 1950s and 1960s, dozens of antibiotics were developed to treat bacterial and fungal infections, mostly natural products produced by the soil-living, filamentous actinomycetes (for example tetracycline, erythromycin, kanamycin, rifamycin, candicidin, streptomycin to name but a few)

After the Golden Age, the search for anti-microbial agents became increasingly fruitless. New antibiotics are again in urgent need, especially to combat the rise of multi-drug resistant *Staphylococcus, Enterococcus* and *Mycobacterium* infections, as well as those caused by Gram-negative pathogens.

One approach to the challenge is to harness the power of *Streptomyces* genetics to develop '**unnatural** natural products' by genetic engineering, especially using the large and supremely important chemical family of polyketides, whose synthesis on giant protein templates programmed to introduce variation into their products lends itself to combinatorial biosynthesis. The scope for such an approach is being widened as large numbers of novel gene clusters are found through large-scale genome sequencing. Often such genes are not expressed under typical culture conditions in the laboratory, but are available through genomics, and the challenge is to find generic ways to switch them on.

About the speaker:

David studied botany at the University of Cambridge, with a particular interest in genetics, especially the embryonic field of microbial genetics. When he graduated in 1954 it was suggested that the streptomycetes might make an interesting subject for genetic analysis. These microbes seemed to be intermediate between bacteria and fungi, two microbial groups with apparently very different genetics. During his doctoral studies at Cambridge he harnessed natural gene exchange to make the first chromosome map of a streptomycete. With Audrey Glauert, he showed that the streptomycetes are in fact true bacteria in their cellular organisation, and that their resemblance to fungi must have arisen independently. Nevertheless they revealed many genetic novelties.

More than 45 years later, after posts as Assistant Lecturer at Cambridge, Lecturer in Glasgow, and finally head of the Genetics Department at the John Innes Centre and Professor at the University of East Anglia, Norwich (now Emeritus), he is still working on the same microbe – *Streptomyces coelicolor* – as on day one of his PhD studies!

However, much water has flowed under the bridge in the meantime. Through the efforts of many scientists, this organism became genetically the model for the actinomycetes, with versatile *in vivo* and *in vitro* genetics. David's interest in antibiotics developed largely by accident, spurred on by studying the genetics of actinorhodin, the blue polyketide antibiotic pigment that gives *S. coelicolor* its name. After the complete gene cluster was cloned, segments of it were used to produce the first hybrid antibiotics by inter-species cloning. This was a catalyst for the development, again through the efforts of many scientists in several countries, of the currently burgeoning field of 'combinatorial biosynthesis of unnatural natural products'.

He is involved in this field as a visiting fellow at Kosan Biosciences Inc, in Hayward, California, where he spends a couple of months each year. Meanwhile he coordinated the project to sequence the large (8.7 Mb) linear chromosome of *S. coelicolor.* The sequence, completed at the Sanger Institute in July 2001, was described in *Nature* in May 2002. The chromosome contains the largest number of protein coding sequences (7825) so far reported for a micro organism.

Interpretation of the sequence throws a powerful light on microbial adaptations to life in the complex soil habitat. In a biotechnological context, it, and those of other actinomycetes currently under study, provides a versatile toolbox of 'spare parts' for combinatorial biosynthesis of drug candidates. See

The CSAR Organising Secretary adds……

David Hopwood was my PhD supervisor! My Doctorate was in Streptomyces genetics, at the John Innes (Institute, as it was then). Fascinating micro-organism! David took the supervision of his students very seriously, and as a result I emerged with (though I say it myself) a good command of genetics!

I left Genetics behind some years ago; but I have very fond memories of when I used to earn my living doing real work with real micro-organisms!

Coffee and biscuits available, as usual, in the foyer outside the lecture theatre from ~7.00 p.m. Once again, we shall be charging non-members a nominal sum for entry.

Richard Freeman *CSAR Organising Secretary*