Talkative microbes
A route to new antibiotics

Suzy Moody

Streptomyces bacteria – the red colour shows the presence of a membrane-bound antibiotic which is released into the growing media when the cells get old.

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When you think of bacteria and fungi, you don't tend to think of them being particularly talkative, social organisms. In fact, microbes are constantly communicating with each other, their neighbours and the environment. ***Suzy Moody*** *explains.*

Microbial communication happens by small bioactive molecules which the cells release into and receive from the environment. In this way, they gather valuable information about what is going on in the world around them and then respond appropriately. While our knowledge of the phenomenon of microbial signalling is not new, the impact this constant stream of information has on medical microbiology and the hunt for new antibiotics is only just being understood.

Professor Dame Sally Davies (the Chief Medical Officer for the UK) recently described the threat from antibiotic resistant infectious disease to the welfare of UK citizens as on a par with the terrorist threat. The indiscriminate use of currently available antibiotics in agriculture and predominantly in

In response to its environment, this colony of Streptomyces coelicolor *has produced beads of bioactive compounds (molecules that have an effect on living cells).*

Morbidity means the rate of incidence of a particular disease.

medicine has led to many common pathogens developing multi-drug resistance, making their treatment and eradication from the body impossible. The mortality and morbidity rates associated with multi-drug resistant infection are increasing steadily as a result, and new classes of antibiotics are urgently needed to treat people effectively. How can microbial signalling help in this situation?

Growing together

In the laboratory, microbes are usually grown in monoculture. i.e. one species is grown in isolation in a flask or on a plate. This is a very artificial scenario as in nature microbes are do not live on their own; they form mixed communities of several different species in one ecological niche. These communities signal to each other, and produce all sorts of compounds in response to their neighbours and changes in the immediate environment. Scientists have now realised that many of the pathways microbes have for production of useful compounds are switched on as a result of this interactive lifestyle, and indeed many of the signalling molecules themselves, when purified, act as potent antibiotics. By growing microbes in monoculture in the laboratory, we have missed a whole raft of bioactive molecules that are only produced when the microbes are grown in mixed culture.

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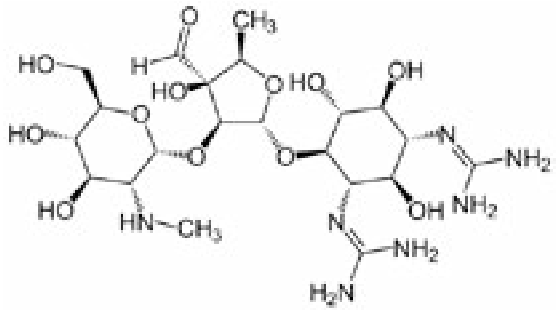
A microbiologist plating bacteria. Using single colonies of bacteria have led to many interesting compounds being missed.

Over 60 % of all clinically used antibiotics are derived from a single genus of bacteria, the *Streptomyces*. These bacteria have been intensively studied following the discovery, more than sixty years ago, that *Streptomyces griseus* produces an antibiotic, streptomycin, which was the first successful anti-tuberculosis antibiotic. It is still in use today.



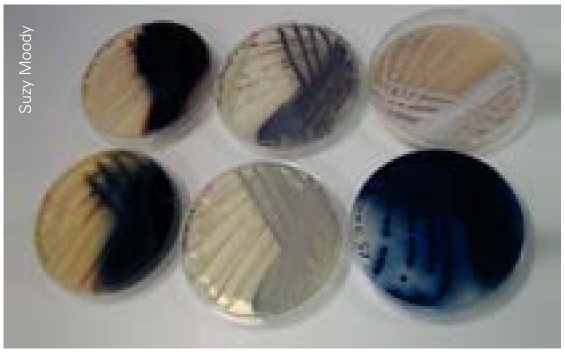
The molecular structure of streptomycin, the first anti-tuberculosis antibiotic. It was discovered by a student, Albert Schatz, in 1943.

Since then, many *Streptomyces* species have been found to produce bioactive molecules useful to humans. Many of the compounds have applications in both medicine and veterinary use, and include antibacterial, antifungal, antiprotozoal, and anticancer drugs, as well as immune suppressants. Yet even in this well-studied genus, growing these bacteria in mixed culture has already proved fruitful with novel compounds being produced.

Microbes interacting

What makes this so very interesting is that the mixture of compounds produced by some species depends on which other species it is cultured with. In other words, these bacteria send out different signals and produce different molecules depending on who is in the neighbourhood. For a microbiologist, it is really exciting to realise how interactive these organisms are and how much detail they can detect in their environment.

Streptomyces are often used in antibiotic discovery programmes because the genomes of *Streptomyces* species that have been sequenced show coding for numerous proteins needed to make all sorts of antibiotics and other interesting compounds. While genome sequencing has revealed the possibility of making these molecules, it does not tell us how to switch on the pathways to produce these bioactive molecules in the laboratory. Mixed



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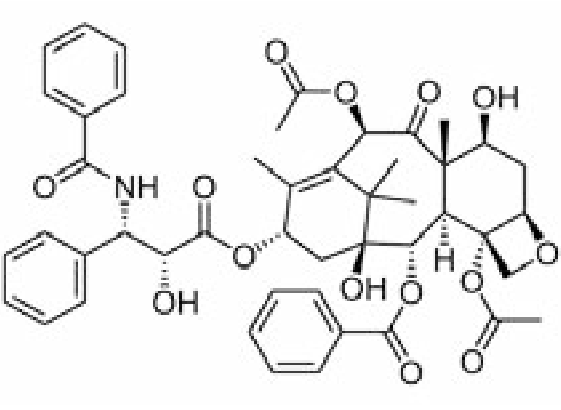
Streptomyces coelicolor *produces a range of coloured antibiotics depending on the medium it is grown on. Changing the content of the medium has been a key part of antibiotic discovery. The red and blue pigments seen here are coloured antibiotics, and whether they are produced depends on what they are grown on.*

culture techniques, where more than one species is grown on a plate at a time, may now give a new approach to activating some of these mysterious pathways so that new molecules are produced by the bacteria. Mixing *Streptomyces* with more distantly related bacteria can also prompt novel antibiotic production. Bacteria such as *Rhodococcus* and *Corynebacteria* contain an unusual molecule, mycolic acid, in their cell wall. Mixing these mycolic acid-containing bacteria with *Streptomyces* has also led to the production of novel antibiotics by the *Streptomyces* species.

Some of the compounds produced by Streptomyces *that are used in medicine. Compound names are shown in black, the class of compound is shown in blue.*

Fungi talking

The role of signalling in switching on the production of new molecules is not only found in bacterial species – fungi exhibit the same properties. *Paraconiothyrium* is a fungus that inhabits yew trees and it is responsible for production of the potent anti-cancer drug paclitaxel. Using two other fungi that also live on yew trees in a mixed culture has led to large increases in the amount of paclitaxel produced.



The molecular structure of paclitaxel (tradename Taxol). The complex structure of many bioactive molecules prevents them being made synthetically. We rely on bacteria and fungi to make many of our pharmaceuticals.

Streptomyces bacteria – *the blue pigment is an antibiotic produced by the bacteria which is released into the growing media.*

Another fungal example is *Candida albicans*. This is a yeast which sometimes lives on human skin and can cause disease. This fungus was cultured with some fungi that live on the skin and do not harm the person. In the mixed culture, *Candida albicans* produced a whole selection of known and new compounds, some of which have potent antimicrobial activity.

A promising approach

This new approach to switching on antibiotic production pathways is really promising. Not only does is tell us a huge amount about the ecology and social life of microbes, it promises a relatively easy way of searching for new antibiotics. Traditional approaches to antibiotic discovery have involved large screening programmes, trial and error with culture conditions, complex genetic engineering or isolation of new organisms from increasingly inhospitable environments. The mass of genome sequencing data being accumulated, while useful in identifying possible antibiotic pathways, has also become a source of frustration to scientists as switching these biosynthetic pathways is very difficult.

The mixed culture approach is offering a new, simple way to explore the bacterial world for compounds that can be used as pharmaceuticals. Most of the species mentioned here are common organisms worked on by many laboratories. Mixing appropriate 'neighbours' in the laboratory and analysing the compounds made has already led to the discovery of new bioactive molecules. By recognising that microbes are social organisms, designed to communicate with each other, we can harness their signalling and response behaviour in our search for much needed new antibiotics.

Suzy Moody is a microbiologist at Swansea University who has worked on both bacteria and fungi.

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