as well as numerous other antibacterial substances. Throughout the years, Waksman had numerous colleagues who were interested in the antibiotic properties of soil bacteria, including a graduate student named Rene Dubos. After graduating from Waksman's lab, Dubos joined the faculty at The Rockefeller University in New York in 1927. His work led to the discovery of tyrothricin and gramicidin from *Bacillus brevis*, which were both potent against gram positive bacteria but were too toxic to use in humans. In 1939, encouraged by Dubos' results and those from his own lab, Waksman began a more comprehensive study of the production of antibacterial chemical substances by soil microorganisms, in the hope of finding substances useful against such devastating human pathogens as *Mycobacterium tuberculosis*.

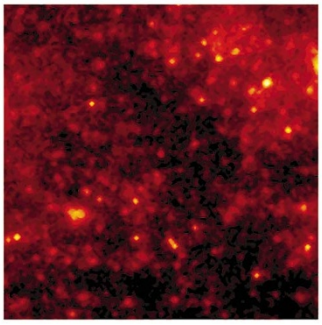
In 1943, another graduate student in Waksman's lab, Albert Schatz, began a project on the antibiotic properties of *Streptomyces griseus*, and from this work he identified streptomycin. Waksman and Schatz noted streptomycin's activity against many different bacterial species *in vitro*, including *M. tuberculosis*. Subsequently, Waksman and Schatz collaborated with two physicians, William Feldman and Corwin Hinshaw at the Mayo Clinic, to administer streptomycin to animals infected with tuberculosis. Although only a small amount of streptomycin could be made for use in the trial (and thus only a small number of animals could be tested) the results were unprecedented: treated animals seemed to have been almost completely cured of the infection.

Soon after this animal trial, the Merck Company in New Jersey, not far from Rutgers University, began to produce large quantities of streptomycin, in anticipation of its usefulness in treating human infections. (One cannot help thinking that the large pharmaceutical presence currently in New Jersey results in part from the success of this collaboration.) The first clinical use of the drug was in 1944, in a young female tuberculosis patient in Minnesota. An initial dose of 0.4 grams per day of streptomycin had almost no effect, but an increased dosage of 1.2 grams per day worked well, and she was later discharged from the hospital with no remaining symptoms. Larger, more controlled clinical trials followed, both in the USA and in the UK, and the results were impressive, with a majority of patients showing improvement after antibiotic treatment. The biggest problem encountered was one the world still wrestles with today — the emergence of strains resistant to the antibiotic (as discussed in last month's editorial). The use of multiple drug treatments began a few years later, as additional compounds effective against tuberculosis were developed. Impressively, in a single decade, the basic research on antibiotic properties of soil bacteria had dramatically improved human health. In 1952, Waksman was awarded the Nobel Prize in Physiology or Medicine in recognition of his achievements. *Tracy Smith*

picture story

Seeing double in living cells

Many signal transduction pathways depend on a cascade of events that begins with the dimerization of cell surface receptors. In the case of epidermal growth factor (EGF) receptor, binding of EGF and receptor dimerization is followed by a conformational change in the receptor that results in autophosphorylation and activation of the receptor tyrosine kinase. While biochemical experiments, such as crosslinking and immunoprecipitation, have been used to study receptor dimerization, these techniques are limited by the fact that they require disruption of the cell. More recently, methods such as fluorescence resonance energy transfer (FRET) and complementation of β-galactosidase have opened the way to studying protein interactions in living cells. Now a report in the March issue of *Nature Cell Biology* (**2**, 168–172) shows how single molecule imaging technology can be used to watch the movements and interactions of individual EGF receptor molecules on the surface of cells.



The fluorescent dye Cy3 was conjugated to EGF and added to living human cells. Within one minute, two classes of fluorescent spots appeared at the cell surface (Figure). The fluorescence intensity of the minor class is about twice that of the major class. By monitoring the formation of spots, Yanagida and coworkers found that in most cases the fluorescence intensity of a spot suddenly increased by a factor of two. They interpreted the spontaneous doubling of fluorescence as the binding of a second molecule of EGF to a preformed receptor dimer complexed with a single EGF molecule. Using a monoclonal antibody that preferentially recognizes the phosphorylated (activated) form of the EGF receptor, they show that EGF receptor dimerization precedes the autophosphorylation of the receptor. Thus, they conclude that receptor dimerization occurs before receptor activation and signal transduction and that the receptor dimer bound to EGF is formed before a second molecule of EGF binds.

These types of single molecule experiments in living cells allow one to monitor individual members of a heterogeneous population and to identify and quantitatively compare the different subpopulations. Moreover, individual molecules can be studied under physiological conditions and monitored over time in a way that is difficult or impossible to do in standard experiments that yield information only on the average properties of a mixed population. By combining this exciting new method with manipulation techniques such as atomic force microscopy, and optical and magnetic tweezers, it should be possible to study the dynamic properties of more and more complicated biological systems in the future. *Boyana Konforti*