When did you first become interested in science?

As I recall, I developed an interest in becoming a scientist when I was in primary school. This interest was particularly ignited after my parents bought me Lott’s chemistry set for my birthday. The image on the lid of the box was of a well-equipped chemistry laboratory, and although the contents were less grand, I was sold. Many of the chemicals were supplied in small cardboard tubs with metal lids; in today’s lab some of these are in the poisons cabinet! As a teenager I also developed an interest in ornithology. We lived in the northwest of England, on the coast about 20 miles north of Liverpool, very close to the marshes of the Ribble estuary. This area attracts hundreds of thousands of wintering birds, including geese that use to fly in skeins over our house in the evening. I used to go birdwatching out on the marshes on many weekends particularly in the winter, which led me to briefly consider a career in zoology.

Tell us about your education.

My secondary school education introduced me to more science as I hoped it would. The chemistry classes did not disappoint, colored by the expected combination of noxious fumes and minor explosions in the practical sessions. We also had some classes in biology, which were general in nature. My first experience of looking down a microscope was however discouraging, probably because I hadn’t focused properly on the amoeba we were studying. I had classes in biology only for two years and by the last two years of school I was studying math, physics, and chemistry almost exclusively.

Around this time I read a book by Steven Rose called The Chemistry of Life (first published in 1966). This introduced me to the discipline of biochemistry, and I was immediately impressed with exciting topics that scientists in this area were addressing. This also came at a key juncture when we were to decide the Universities and courses to which we would apply for admission. The Natural Sciences Tripos at the University of Cambridge allowed students with my background subjects to take an introductory course called The Biology of Cells. This seemed ideal as I would be able to study biology but not have to choose a specific degree discipline from the outset. I arrived in Cambridge in 1969.

How did you become a microbiologist?

In the second year at Cambridge I studied biochemistry and chemistry, before focusing on biochemistry for the final year. My final year project was to study the effects of light and wounding on induction of phenylalanine ammonia lyase in potato tuber slices, supervised by Philip Rubery. By this time I was convinced that I wanted to obtain a PhD, and following a brief conversation in the laboratory, Philip agreed to take me on as a graduate student subject to departmental approval. My project was to address aspects of the dimorphism of the fungus Mucor rouxii; hence I was to become a microbiologist.

For my PhD thesis work, I studied cell wall synthesis and composition in Mucor rouxii. This fungus exhibits a yeast–hyphal dimorphism first described by Louis Pasteur and was considered as a possible model for the dimorphic behavior of human fungal pathogens. Despite a
couple of mishaps, which included breaking a half-full Winchester of concentrated hydrochloric acid on my foot, I successfully defended my thesis in 1975.

How and when did you start working on plant pathogens?
For postdoctoral studies Philip had suggested that I might investigate possibilities in the area of plant pathology. In 1975 I joined the laboratory of Jim Callow, at the University of Leeds. At that time, Jim had broad interests in the area of cell–cell recognition in eukaryotes, which included the interactions of pathogenic and beneficial fungi with plants. My work was in the interaction of the fungal tomato pathogen *Cladosporium fulvum* with tomato. A major issue then (as now) was the identification of factors that determine host specificity in such interactions. The approach was to try to identify components in the culture supernatants of different strains of the fungus that induced cultivar specific changes in the different plant varieties. This aim proved to be elusive, although we could demonstrate non-specific elicitation of host defenses by fungal glycoproteins.

In 1979, I returned to working on cell wall synthesis in *Mucor*, this time in the laboratory of Vicente Villa at New Mexico State University in Las Cruces. I studied the synthesis, assembly, and tailoring of the polyuronides that are an important component of the fungal cell wall. This period included a month-long research visit to the laboratory of Arturo Flores-Carreón at the University of Guanajuato, Mexico. On returning to Europe in 1984, I took a short-term EMBO fellowship to study cell wall synthesis in *Schizopyllum* in the laboratory of Jos Wessels at the University of Groningen, The Netherlands. This was to be my last effort in the area of fungal cell wall synthesis, as from Holland I went to the John Innes Centre in Norwich, UK where I shifted gears to use genetics and molecular biology to study a bacterial plant pathogen.

How and when did you start working on bacterial pathogens?
In 1985 I joined the laboratory of Mike Daniels, which was first located at the John Innes Institute and after 1988 at the newly formed Sainsbury Laboratory. When I arrived Mike’s lab was primarily interested in the molecular genetics of *Xanthomonas campestris* pathovar *campestris*, the causal agent of black rot of crucifers. Chris Barber in Mike’s lab had already cloned two clusters of genes involved in *Xanthomonas* virulence and Pete Turner, a postdoc, had created transposon insertions in these genes in the chromosome. I decided to try to identify phenotypes of the mutants that we might inform the functions of the genes products. Graham Scofield and I were able to show that mutations in one gene cluster affected export but not the synthesis of a number of extracellular enzymes. This supported information derived from sequencing by Frans Dums to indicate that one of this gene cluster encoded a Type II secretion system.

The phenotypes of strains with mutations in the second gene cluster indicated an impaired synthesis of extracellular enzymes, but no effect on their export. Mike named these *rpf* genes, for regulation of pathogenicity factors. Gradually details of the nature and function of these Rpf proteins emerged. Sequencing by a PhD student Tang Ji-Liang showed that RpfC was a complex two hybrid sensor kinase. Chris Barber and a postdoc, Greer Wilson, implicated several of the Rpf proteins in a cell–cell signaling system mediated by a fatty acid diffusible signal factor which we called DSF. A graduate student, Holly Slater, showed that the sensing and transduction of the DSF signal required RpfC and the regulator RpfG, which is an HD-GYP domain protein. Bioinformatic analysis by Michael Galperin at NIH suggested that the HD-GYP domain is a phosphodiesterase (PDE) active against the second messenger cyclic di-GMP (Fig. 1). This led to the hypothesis that cell–cell signaling mediated virulence in *Xanthomonas* through modulation of the cyclic di-GMP levels. A postdoctoral fellow, Lisa Crossman, showed that expression of a PDE of a different class could revert the phenotype of an *rpfG* mutant back to wild-type, consistent with the predicted function of the HD-GYP domain.

How did you start working on plant host responses?
At the same time that the work on *Xanthomonas* signaling, we were also interested in the role that other factors may have in plant–microbe interactions. Mari-Anne Newman and I began to study the effects of lipopolysaccharides (LPS) on plant defense responses. This work revisited experiments first described in the 1970s by several labs in the US. Although LPS did directly induce some defense responses in some plants, one major effect was to prime plants to respond more rapidly to a challenge by a pathogen. One of these primed responses was the rapid synthesis of hydroxycinnamoyl-tyramine conjugates and another postdoctoral fellow, Edda von Roepenack-Lahaye described

**Figure 1.** The bacterial second messenger cyclic di-GMP is synthesized by diguanylate cyclases with a GGDEF domain and degraded by two classes of phosphodiesterase, with either EAL or HD-GYP domains. Topics of interest in Dr Dow’s laboratory (indicated by question marks) are the signals that can activate the GGDEF, EAL, or HD-GYP domain proteins and the mechanisms by which the level of cyclic di-GMP (or the proteins) control virulence and biofilm formation.
the family of THT genes responsible for their synthesis in tomato.

How and when did you start working on human bacterial pathogens?

In 2002 I came to University College Cork, first as a Science Foundation Ireland Walton Visiting Fellow and then as an SFI Principal Investigator. I wanted to continue the work on DSF signaling and the HD-GYP domain in Xanthomonas, but political considerations suggested that some focus on human bacterial pathogens would be expedient. Consequently I proposed to study the function of HD-GYP domain proteins in Xanthomonas and in Pseudomonas aeruginosa, which has a particular importance in Ireland because of the high incidence of cystic fibrosis in the population. Yvonne McCarthy and Robert Ryan (a postdoctoral fellow) joined my lab in 2004. They were able to demonstrate that the HD-GYP domain of RpfG was a PDE active on cyclic di-GMP, thus adding a piece to the understanding of cyclic di-GMP signaling in bacteria. At the same time we began to put an increasing emphasis on the study of human pathogens. Yvonne showed that DSF signaling regulates virulence of Stenotrophomonas maltophilia, an emerging nosocomial pathogen related to Xanthomonas. Following this, a graduate student, Karen O’Donovan, showed that HD-GYP domain proteins controlled biofilm formation and virulence factor synthesis in P. aeruginosa.

How did you become interested in interspecies interactions?

We had noted that the genomes of several bacterial species including Pseudomonas aeruginosa encode histidine kinases with input domains similar to the DSF sensor RpfC of Xanthomonas. This suggested the possibility that these bacteria may be able to sense DSF, although they did not apparently synthesize it. In collaboration with Tim Tolker-Nielsen, University of Copenhagen, Robert Ryan demonstrated a DSF-mediated interaction between S. maltophilia and P. aeruginosa that modulated biofilm architecture and tolerance to polymyxin. At around the same time, the group of Lian-Hui Zhang in Singapore showed that Burkholderia cenocepacia, a cystic fibrosis pathogen, also produced a DSF-like signal. Shortly after this, Robert went on to set up his own laboratory with a program to study DSF-based interspecies signaling in the context of polymicrobial infections associated with cystic fibrosis.

Do you have partners that are important for your research projects?

I have a long-standing collaboration with the group of Prof Tang Ji-Liang at Guangxi University, Nanning, PRC, who was formerly Mike Daniels’s graduate student at the John Innes Centre. His group has developed considerable expertise in functional genomics of virulence in Xanthomonas. I have made a number of visits to Nanning since 1991 and several Chinese scientists have visited my lab. The most recent visitor was a co-supervised graduate student, Shi-Qi An, who was studying the regulatory action of the Rpf proteins using RNAseq. This particular project had other key partners in Melanie Febrer and colleagues at The Genome Analysis Centre, Norwich.

Members of my lab also make research visits to other institutions to learn new techniques. Robert Ryan was funded for a visit to the lab of Ute Römling at the Karolinska Institute, Stockholm to learn about cyclic di-GMP quantitation, to Chuck Farah’s group in the University of São Paolo to study the role of protein–protein interactions in Rpf-mediated signal transduction in Xanthomonas and to the laboratory of Judy Armitage at the University of Oxford to study these interactions within living Xanthomonas cells. A graduate student, Aileen O’Connell, went to the laboratory of Karsten Niehaus at the University of Bielefeld in order to utilize proteomic technologies to study Rpf regulatory processes.

We are involved in a collaborative project with Martin Walsh and Domenico Bellini at the Diamond Light Source UK aimed at determining the structure and function of HD-GYP domain proteins from Pseudomonas aeruginosa. A postdoctoral fellow, Delphine Caly, was largely responsible for the work in my lab on this project, in which we determined the first structure of an enzymatically active HD-GYP domain PDE.
**What is your mentoring style?**

My lab runs along the same lines as that of my mentor Mike Daniels. The postdoctoral scientists are encouraged to develop their own projects, as a stepping stone toward establishing themselves as independent scientists. I am always accessible to the graduate students, so that they can discuss their work informally. Although I have a professional attitude to the work and associated mentoring, I don’t take myself too seriously, as befits someone who got the plastic end of a ballpoint pen stuck in his ear!

**What is your philosophy in scientific pursuits?**

I have been climbing and mountaineering in the UK, the Alps, the Andes, the Rockies, New Mexico, Yosemite, the Karakoram, and the Himalayas and played football (soccer) in teams around the world. I adopt the team ethics of these pursuits both in my scientific collaborations and within the group in the lab. In the words of Bill Shankly, the Liverpool FC manager of legend, “The socialism I believe in is everyone working for each other, everyone having a share of the rewards. It’s the way I see football, the way I see life.”