themselves. "Do we want to invite scrutiny of patients?" asked Davids. In a press release, the Gay Men's Health Crisis also expressed concern that Frieden's announcement "occurred at a time when HIV prevention efforts in the US are seriously underfunded and increasingly censored…when the federal government is shifting focus toward HIV prevention initiatives that are increasingly based on scientifically discredited abstinence-only approaches, and moving away from effective primary prevention work. […] Research on sexuality and drug use has been under increasing attack by federal government officials" (GMHC, 2005).

But it is not only the federal government who are on the attack. Last year, a right-wing US-based church group, the Traditional Values Coalition (TVC; Washington, DC, USA) drew up what some called a 'hit list' of more than 150 publicly funded scientists who were conducting behavioural research on HIV/AIDS transmission (Brower, 2004). Calling the work "prurient", "smarmy" and "provocative", the Coalition pressured the National Institutes of Health (NIH; Bethesda, MD, USA) and Congress to justify the research, much of which dealt with the motivation behind high-risk behaviour. The TVC asked NIH Director Elias Zerhouni to provide a written explanation for several grants, according to an official at AmfAR.

> There are also questions, and controversy, as to how illegal drug use might have a role in rapid disease progression or drug resistance

However, Cohen and others maintain that research on risk-taking behaviour and psychosocial factors is exactly what is needed to develop effective prevention measures. There are also questions, and controversy, as to how illegal drug use might have a role in rapid disease progression or drug resistance. In addition to its role in the rise of unsafe sex and its impact on neurocognitive health, some research indicates that methamphetamines may affect the immune system by modifying inflammatory cytokine expression and may have additive effects with HIV on brain metabolite abnormalities (Rippeth *et al*, 2004; Chang *et al*, 2005). Other evidence indicates that these commonly used drugs may interfere with anti-viral medicines (Ellis *et al*, 2003).

More information and time is needed to tell whether the New York City case is a harbinger of a more resistant, virulent type of HIV/AIDS, or whether it is an anomaly. "The existence of a cluster of such cases would help determine whether this is a unique virus–host interaction or a new virus type," said AIDS researcher John Moore, from Cornell University's Weill Medical College (New York, NY, USA). "It is also possible that this case may represent a superinfection or dual infection, which a complete sequence of the virus would clarify." Moore and others noted that *in vitro* replication competence would not predict how easily the virus is transmitted among humans. "I am among those considering that this 'superbug' is unlikely to be transmitted at a high frequency, and if transmitted, will have a completely different biological behaviour in a second host," said Luc Perrin, a virologist at the Geneva University Hospital in Switzerland, who recently showed that drug-resistant viruses are transmitted with a lower efficiency than wild-type (Jost *et al*, 2002).

Since the beginning of the AIDS crisis, we may have come full circle. As Shilts described, public health and government officials failed to act proactively to stem the spread of HIV in the early 1980s. However, activists are now criticizing Frieden for doing just that. What is undisputed, though, is that HIV infection is on the rise again, due in part to an increase in unprotected sex and drug use. "We will see more of these cases, though I doubt we have an epidemic in the making," Montaner predicted.

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Vicki Brower
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Common defences

Comparisons between plant and animal immunity can benefit both research communities

At first glance, they have little in common: whereas animals move around, feed on plants and each other, and breathe oxygen, most plants are literally rooted to the spot, draw their nutrients from the air and soil, and produce oxygen. Under the surface, however, things are a bit different. Apart from sharing many cellular structures and processes, plants and animals have evolved similar defences against attacking pathogens. This rather recent discovery has led to greater cooperation between the respective research communities. A flurry of publications over the past few years has identified some conserved

mechanisms of surveillance and defence used by both plants and animals. This in turn has highlighted common research goals, particularly concerning innate immune systems.

Plant and animal immunologists once communicated relatively rarely, but now often attend joint conferences. The Gordon Research Conference on Molecular Mechanisms of Microbial Adhesion, scheduled to take place in Newport (RI, USA) this August, typifies this new spirit, with the delegate and speaker list split almost equally between the two camps. Benefits of this growing cooperation include greater understanding of some immune system disorders, such as Crohn's disease in humans, and new clues to the origins of eukaryotic immunity. There are also other benefits, as animal immunologists can now exploit the huge amount of genetic data on *Arabidopsis*, the 'pet' organism of plant scientists, whose short six-week lifespan enables scientists to test the relationship between resistance and genotype within reasonable timescales.

The cooperation also reflects the rising stock of innate immunity as a field in its own right. Until recently, most animal immunologists regarded innate immunity as the primitive ancestor of adaptive immunity. But this is changing through the work of mammalian immunologists such as Bruce Beutler, a professor at the Scripps Research Institute (La Jolla, CA, USA). Beutler focuses on innate immunity and has been rewarded with a string of discoveries identifying common mechanisms of identification and signalling across several species. Such fundamental work is also relevant to the study of adaptive immunity, as the innate immune system is known to have a crucial role in priming the adaptive response.

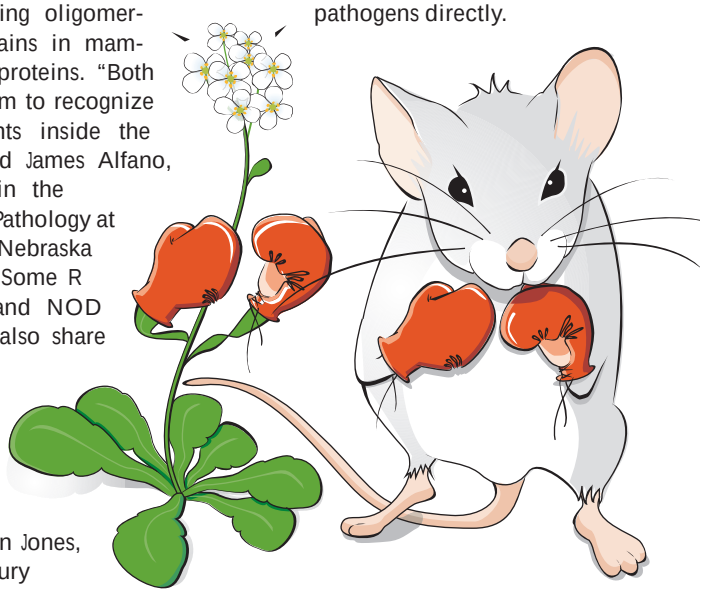
Until the late 1990s, the receptors and pathways responsible for innate immunity were not known, at least in mammals. The first breakthrough came in 1998, according to Beutler, with the identification of Toll-like receptor 4 (TLR4) as a highly specific and unique receptor for lipopolysaccharides, a prominent component of many bacterial membranes (Poltorak *et al*, 1998). This early work led to the identification of other TLRs, numbered 1–3 and 5–9, which recognize different pathogens; TLR3, for instance, is activated by many viruses. Given that viruses and bacteria are totally different in size and structure, it is hardly surprising that they would have distinct receptors in their hosts.

It has been known for some time that, irrespective of the pathogen, the immune system uses common mechanisms of defence and clearance. Part of the explanation for these general responses to different types of pathogen came with the discovery of a single protein, Trif, that is associated with multiple TLR receptors, including those for bacteria and viruses (Hoebe *et al*, 2003). Trif is a signal transducer that induces immune responses after TLRs have detected a pathogen. "Trif's dual role tells us that the type of response the host uses to fight bacteria is also beneficial for fighting viruses," said Beutler. There may even be common aspects to the initial recognition of viruses and bacteria by the innate immune system, Beutler suggested: "There are features shared in common by bacteria and viruses: unmethylated DNA for example." The DNA of higher eukaryotes contains methyl groups to hinder the expression of genes when they are not required and to assist DNA folding, but these are absent from bacteria and viruses.

Despite the progress made by Beutler and others with animals, most of the work on innate immunity still comes from plant research. This led to the discovery of striking similarities between a nucleotide-binding (NB) site found in most plant resistance (R) proteins and nucleotide-binding oligomerization (NOD) domains in mammalian surveillance proteins. "Both of these proteins seem to recognize pathogen components inside the eukaryotic cell," said James Alfano, Assistant Professor in the Department of Plant Pathology at the University of Nebraska (Lincoln, NE, USA). Some R proteins in plants and NOD proteins in animals also share leucine-rich repeats (LRRs), which are able to detect molecular components of pathogens. The interesting aspect, according to Jonathan Jones, head of the Sainsbury Laboratory at the John Innes Centre in Norwich, UK, is that this recognition takes place inside the cell without direct contact with the pathogen. This is the result of a long-range battle in which pathogens, such as bacteria and some fungi, attempt to disable the immune system by suppressing it from a distance.

> …it seems clear that many, if not most, plant pathogens are detected indirectly by the enzymatic activity of their virulence proteins

But the cell, in turn, can detect the presence of distant pathogens by sensing the molecules they use to attack. This is particularly significant for plants, which lack a circulating immune system and leave each cell largely responsible for its own defence. The ability to detect pathogens indirectly also suggests a possible answer to the long-standing puzzle of how plants succeed in combating infection without adaptive immunity and with a relatively small number of R-protein-encoding genes. Plants are able to detect thousands of pathogens using a relatively limited repertoire of just a few hundred R genes, which seems to suggest that the pathogens must have some common features. While there is some truth to this, there is growing evidence in favour of a model called the 'guard hypothesis', which suggests that R proteins do not recognize the virulence proteins of pathogens directly.



… both animals and plants attack pathogens with bursts of superoxide, hydrogen peroxide, nitric oxide and toxic antimicrobial metabolites

According to the guard hypothesis, proposed by van der Biezen & Jones (1998), R proteins guard the targets of virulence proteins. R proteins sense damage caused to these target proteins, which are significantly outnumbered by pathogens. According to Roger Innes, Professor of Genetics of Plant–Pathogen Interactions in the Department of Biology at Indiana University (Bloomington, IN, USA), support is increasing for the guard hypothesis. The strongest evidence comes from the plant bacterium *Pseudomonas syringae*, which grows in the spaces between leaf cells. *P. syringae* has an effector protein that attempts to subdue the defence system in *Arabidopsis* by cleaving a host protein kinase. But this cleavage stimulates resistance, which is mediated by an NB-LRR protein (Shao *et al*, 2003). This, argues Innes, provides compelling evidence that the NB-LRR protein acts as a guard protein by sensing specific damage to the host protein kinase.

Even if the guard hypothesis is not wholly correct, it seems clear that many, if not most, plant pathogens are detected indirectly by the enzymatic activity of their virulence proteins. The question is whether the same holds true for animal immunity. It is known that plants rely totally on innate immunity and that they must be able to identify a huge range of pathogens through their R proteins. But animals also rely on innate immunity for the initial detection of infection. When bacteria infect animals, they also produce virulence proteins that are designed to subdue host defences, once again providing a potential early warning of pathogenic attack.

Most of the known virulence factors produced by Gram-negative bacteria are secreted through the type III secretion system, which seems to be absolutely essential for pathogenicity—bacteria without it rarely cause infection. The type III secretion system comprises a needle-like protrusion from the membrane that provides a channel to deliver proteins either directly into host cells or into intercellular spaces. Unlike in plants, evidence that type III effector proteins elicit an immune response in animals was lacking until recently. The discovery that a translocator protein generated by the type III secretion system of *Yersinia pseudotuberculosis* triggers an immune response in humans via the NOD proteins was therefore a highly significant development (Viboud *et al*, 2003). "I think it is likely that other examples will begin popping up where NODs recognize virulence proteins such as type III effectors," said Alfano. Such findings suggest that animal immunity researchers should look harder at how NOD proteins are activated, and in particular should be more open to the idea that activation may not occur through direct contact with pathogen molecules.

Animal research has already benefited directly from plant immunity studies. The best-known example is Crohn's disease in humans, which, along with some other autoimmune disorders, has been linked to NOD proteins that were identified through their similarity to plant R proteins (Ogura *et al*, 2001). It is now known that one of these proteins, NOD2, recognizes a specific polymer in the bacterial membrane called muramyl dipeptide (MDP). However, mutations in *NOD2* can render it insensitive to MDP and so unable to induce the NF-κB pathway, which normally enhances the production of inflammatory mediators. This renders the intestine susceptible to chronic inflammation, the hallmark of Crohn's disease, although the exact mechanism is still unclear.

While there has been great interest in similarities between the intracellular detection of pathogen molecules by plants and animals, common ground has also been identified in extracellular perception. The LRR domains in some plant R proteins are also found in receptor kinases that can detect pathogen-derived molecular patterns outside the cell. The *Arabidopsis* receptor kinase FLS2, for example, can recognize the flagellin protein extracellularly, and according to Alfano, acts similarly to LRR domains in animal TLRs. Flagellin is the principal component of the helical flagellum that extends from the bacterial body.

There is also overlap in the mechanisms that plants and animals use to disable pathogens. Plants often invoke the hypersensitive response when an infection is detected, leading to rapid programmed cell death (PCD) in the vicinity of the invasion site. This is thought to inhibit the pathogen from spreading further. Recent molecular studies suggest that animals invoke PCD by similar regulatory mechanisms. In both cases, the signals seem to be processed by the mitochondria, which initiate the death execution pathway. Moreover, both animals and plants attack pathogens with bursts of superoxide, hydrogen peroxide, nitric oxide and toxic antimicrobial metabolites.

Views vary on the evolutionary significance of the similarities between plant and animal immunity. "The fact that there's conservation of [sequence] motifs but quite a bit less in terms of real biochemical pathways suggests that there's divergent rather than convergent evolution," Beutler said. However Jeff Dangl, a plant biologist in the Department of Biology at the University of North Carolina (Chapel Hill, NC, USA), believes that most of the similarities have arisen through convergent evolution. Dangl cites a famous review by Elliot Meyerowitz (2002), which argued that plants and animals evolved multicellularity independently and therefore provide truly comparative models of development. Having inherited common molecular tools from their single-celled ancestors, both plants and animals have evolved to use some of them for immune defence. "For example, if MAPK pathways are commonly used in eukaryotic signalling, there is no surprise that they are used in both the plant and animal immune systems," Dangl said.

Having inherited common molecular tools from their single-celled ancestors, both plants and animals have evolved to use some of them for immune defence

Convergence may have also been driven by pathogens through their use of common mechanisms, such as type III effectors, to subdue the host immune response. "There are some type III effectors that are conserved in plant and animal pathogens, and they might target some highly conserved host proteins," said Ulla Bonas, a professor in the Institute of Genetics at Martin Luther University in Halle, Germany. This convergence also

suggests that there must be some pathogens that affect both plants and animals. Indeed, one such example is the bacterium *Pseudomonas aeruginosa*, which attacks both *Homo sapiens* and *Arabidopsis*.

Perhaps more significant are the common conditions that arise when the immune system malfunctions. There are many known autoimmune diseases in humans, but plants also suffer from them. In lesion mimics, the hypersensitive response that triggers cell death is initiated in the absence of a pathogen. In extreme cases, the whole plant dies from multiple lesions, although this is not a major problem for horticulture or agriculture. The exact mechanisms involved are still unknown, but there is common ground for plant and animal immunologists to study the pathways involved in autoimmune disease, especially where PCD is concerned.

Much work still remains to elucidate the immune response in detail, particularly the steps after the pathogen is detected. Nevertheless, cooperation between plant and animal researchers has already yielded important insights into these mechanisms. It is becoming increasingly clear that these two communities, who for so long communicated so little, can pool their resources to investigate immunity.

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Philip Hunter

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Adopting an orphan

Incentives to develop drugs for rare disorders raise hopes and controversy

The spectrum of ailments that haunt mankind is depressingly vast. Major chronic and infectious diseases, such as malaria, AIDS, cardiovascular diseases and cancer, claim millions of lives every year, and exact a heavy toll in both the developed and the developing world. These big killers, however, do not have a monopoly on pain, suffering and death—diseases that affect comparatively few people can have the same result. According to the World Health Organization, some 5,000 such rare disorders exist. Other estimates push the number up to 8,000, depending on the specific classification criteria used. In Europe, a rare disease is defined as one that affects one person in 2,000, whereas in the USA and Japan, the definition of a rare disease is one that afflicts fewer than 200,000 and 50,000 patients, respectively.

> Due to their relatively low prevalence, rare diseases as a whole have traditionally been neglected by large parts of the scientific, medical and political communities

Regardless of the precise definition, rare diseases are a serious problem for human and public health. Although each case involves a relatively small number of individuals—from just ten to hundreds of thousands—together, rare diseases affect a major subsection of the population in developed countries, including 25 million US residents and about 6%–8% of the population of the European Union (EU), equivalent to 24–36 million people. But it was not until the early 1980s that various countries, the first being the USA, introduced legislation and incentives to make the development of drugs for rare diseases more attractive for pharmaceutical companies. These have been a major success, and have led to the approval of hundreds of new drugs, but they have not been without criticism. Whereas some critics decry the often extremely high costs of these drugs, patient advocacy groups push for a wider awareness of rare diseases and for better training of physicians.

About 80% of identified rare diseases have a genetic origin, and the remainder are caused by infections, allergic and autoimmune disorders or poisonings, or have unknown causes (National Organization for Rare Diseases, 2003). In some instances, symptoms manifest at birth or early in childhood, as happens in several lysosomal storage disorders, some neurological disorders such as Rett syndrome, or in osteogenesis imperfecta and related collagen and bone diseases. Many rare diseases, however, appear only in adults. Unfortunately, despite variable aetiology, rare diseases share similar traits: they are usually chronically debilitating, degenerative and often life-threatening.

Due to their relatively low prevalence, rare diseases as a whole have traditionally been neglected by large parts of the scientific, medical and political communities. With the exception of a few conditions that occur more frequently on a global or regional scale, such as cystic fibrosis and thalassaemia, knowledge and awareness of the vast majority of rare diseases is still scant or totally absent, and the medical and social consequences for victims and their families are often devastating. Delay in diagnoses, lack of relevant information and difficulty in finding specialized physicians are common problems, and many patients go completely undiagnosed. Most importantly, even when recognized, thousands of rare diseases cannot be treated, simply because no medicines, therapies or protocols for good clinical practice exist. This is not due to scientific or medical difficulties in tackling rare diseases, but rather lies in their inherent lack of attraction for pharmaceutical companies, which are more interested in developing drugs for common disorders that affect millions than in treating a handful of patients. Thus, the drugs needed to treat these 'orphan' diseases "are