

## *Trichoderma*—not just for biocontrol anymore

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Received: 1 February 2011 / Accepted: 4 February 2011 / Published online: 29 March 2011  
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### Biography



**Gary Elvan Harman** was born in La Junta, Colorado, USA, in 1944 and spent his childhood in that area. He obtained his B.S. degree from Colorado State University in 1966 in botany. During his junior and senior years, he worked for Professor Ralph (Tex) Baker and conducted independent research that resulted in a sole-authored paper in *Phytopathology*. He then attended Oregon State University, and, in 1970, received his PhD in botany with minors in pathology and biochemistry. After a short postdoctoral fellowship at North Carolina State University, he accepted the position of Assistant

Professor at Cornell University's New York State Agricultural Experiment Station in Geneva, also in 1970. He has been on the faculty of Cornell (Geneva) ever since, and was appointed to the rank of Professor in 1985. He was the first Chair of the Department of Horticultural Sciences. His original appointment at Geneva was to study the physiology of parasitism of seed–microbe interactions, which led to an interest in the biological control of plant pathogens. In 1980 he returned to Colorado State University for a sabbatical leave, and worked with Tex Baker and with Ilan Chet of the Hebrew University of Jerusalem, who also was on sabbatical leave. Baker, Chet and Harman collaborated on *Trichoderma* research. Ever since that time, he has had a very strong interest in both the basic science of biocontrol, especially by *Trichoderma* spp., and the commercial development of these fungi. In the mid-1980s he and his colleagues produced *T. harzianum* strain T22 using protoplast fusion. Shortly after T22 was developed, it became apparent that if this or other strains of biocontrol fungi were going to be commercialized, small companies driven by their discoverers were probably required. To this end, he and two cofounders started TGT Inc., which later became BioWorks Inc. and T22 probably has become the most successful biocontrol strain of these fungi. BioWorks is now a successful company with several million dollars worth of sales each year; and with royalties to Cornell of about \$800,000. He had several roles at BioWorks, including for about a year serving as the CEO before returning full time to his Cornell

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career. More recently, he has become involved in two other companies, Terrenew, LLC – which develops a variety of products using agricultural waste products, and Advanced Biological Marketing – which co-develops, produces and markets the technologies and strains described in this article. He is the primary inventor and product developer for both companies. This complements his basic research and provides a very large source of new information, for example from field trials, that would not be available otherwise. He is frequently asked to speak at international and national meetings and to write invited papers on his work. One such paper in *Nature Microbiology Reviews* set forth a new paradigm for the mechanisms of action and uses of *Trichoderma* that is developed further in this editorial. He, together with Christian Kubicek, wrote a two volume monograph of *Trichoderma* and its uses, which, although now becoming dated, is the standard volume on these fungi. He is the author or coauthor of this and one other book, 136 refereed journal publications, 35 book chapters and numerous other publications. He is the inventor or coinventor of 15 issued patents and has five pending patents. He has received The Award of Merit from the NE division of the American Phytopathological Society (APS), is a fellow of APS and lately received the *Trichoderma* and *Gliocladium* Research Excellence Award from the international *Trichoderma* research community at their recent meeting in Haifa.

Fungi in the genus *Trichoderma* have been known since at least the 1930s as biocontrol agents of plant diseases (Weindling 1932). Since about the 1990s they have been increasingly used in commercial agriculture for this purpose and are reasonably successful in both developed and developing countries (Copping 2004; Harman 2000; Harman *et al.* 2010).

However, we now know that both our knowledge of mechanisms of action and their potential uses was incomplete. As recently as 1998, we believed that principal mechanisms of action of biocontrol were *via* antibiosis and mycoparasitism, although abilities to increase plant growth and induce resistance to plant stresses had been reported (Harman and Kubicek 1998). However, we now know that much or most of the biocontrol activity of these fungi is through their abilities to induce systemic disease resistance; even

“classical” biocontrol by antibiotics (*T. virens* and *Rhizoctonia solani* on cotton seedlings) and classic mycoparasitism (*T. harzianum* control of *Pythium* seed and seedling diseases), when analyzed by genetic or mutational approaches, were found to be due solely to induced resistance (Howell 2006; Shores *et al.* 2010). Viewing biocontrol primarily as a direct effect of *Trichoderma* on the pathogen rather than directly on target pathogens has a huge impact on development of a successful biocontrol system. If we are trying to optimize conditions for the wrong mechanism, then success will be problematic at best.

We now know much more about the interactions of plants and *Trichoderma*. In most cases, efficient strains (and most are not very efficient, so strain selection is critical) infect and colonize the outer layers of plant roots, and establish chemical communication with the plant. This results initially in an induction of resistance mechanisms that wall off the *Trichoderma* strain and prevent further plant colonization (Harman *et al.* 2004; Yedidia *et al.* 1999). However, a few plants, such as cocoa, respond to such fungi by permitting their ramification throughout their structure, but the strains involved, when applied to other plants, function only as root colonists (Bae *et al.* 2011). The chemical factors that elicit plant responses are numerous and range from hydrophobin-like proteins, peptides, and smaller molecules. These still are being discovered and known active metabolites have been summarized (Harman *et al.* 2004; Lorito *et al.* 2010). Once efficient strains colonize plant roots and establish chemical communication, then they are likely to persist and provide benefits to plants for the life of at least an annual plant. The best strains also will fully colonize roots as they expand and grow (Harman 2000). Thus, they function much more like mycorrhizae than the ways that we thought they acted before about 2004. They clearly are endophytic plant symbionts that also have the ability to proliferate and grow in soil.

The establishment of root colonization and chemical communication by *Trichoderma* strains strongly affect plant physiology by changing plant gene expression, as documented by several groups (Alfano *et al.* 2007; Bae *et al.* 2011; Djonovic *et al.* 2007; Marra *et al.* 2006; Shores and Harman 2008; Shores *et al.* 2010). There are several hundred separate plant genes or proteins known whose

expression is altered by root colonization by *Trichoderma* spp. Interestingly, even though the fungi are generally confined to the roots, the changes in expression are substantially greater in the shoots than in the roots (Shoresh *et al.* 2010).

These changes in plant gene expression generally improve plant performance. One of the benefits is systemic resistance to plant diseases *via* plants' innate defense systems. Activation of these systems reduces disease caused by a wide variety of pathogens, including fungi, bacteria, and even a virus (summarized in Harman *et al.* 2004). Further, the data are clear that this induced response is widespread across both monocots and dicots (Harman *et al.* 2004). The downside, as was described in a recent Guest Editorial (Walters 2010), is that innate defensive systems are only partially effective and seldom, if ever, approach immunity. This, however, is counter-balanced in the case of *Trichoderma* by two factors: (1) the resistance induced is long-lasting, with protection occurring for months after application and (2) *Trichoderma* spp. are resistant to most chemical pesticides, which facilitates integrated control. An excellent strategy, exemplified most strongly by commercial seed treatment systems, is to apply a chemical pesticide with the effective *Trichoderma* strains. Chemical protectants provide relatively short-term, but a highly effective level of pathogen control, while the *Trichoderma* colonizes roots and provides season-long benefits to plants.

Some strains of *Trichoderma* spp. provide other benefits. They enhance not only resistance to biotic stresses (diseases) but also to abiotic stresses such as water deficits and salt (Fig. 1) and temperature (Bae *et al.* 2009; Mastouri, F. 2010, Ph.D. thesis, Cornell Univ.; Shoresh *et al.* 2010). Similar results, although with somewhat different symptoms, occur in the presence of 75 mM NaCl in the water used for irrigation. Resistance to these stresses also has occurred in field experiments. One principal mechanism by which resistance to abiotic stresses is conferred is *via* higher levels of expression of the enzymes involved in scavenging of reactive oxygen species (ROS) (Shoresh *et al.* 2010). Plants exposed to biotic or abiotic stress may produce high levels of damaging ROS (Mittler 2002) and some of the symptoms of these stresses are due to this toxicity. Enhancement of enzymes in pathways such as the glutathione-ascorbate cycle will recycle



**Fig. 1** Tomato plants grown in the presence of a strain of *Trichoderma harzianum* incorporated into the planting mix ( $10^4$ - $10^5$  cfu per cc of potting mix) (**pot at right**) and without the organism (**pot at left**), following several days in which water was withheld. The resistance to drought is obvious

antioxidants more rapidly and thereby reduce effects of stresses.

Another major benefit conferred by these endophytic plant symbionts is induction of increased nitrogen use efficiency (NUE) in plants. One estimate of the amount of applied nitrogen fertilizer taken up by plants is low (approximately 33% in small grains) (Arnall *et al.* 2009), so there is substantial room for improvement. Data from field trials on several different crops indicate that it is possible to reduce N application rates by 30–50% with no reduction in yield (Harman 2011; Shoresh *et al.* 2010). If this reduction was applied to the 30 million hectares of wheat in the USA, the savings in nitrogen application would total more than a billion kg of N annually. The mechanisms by which NUE is induced in plants is not fully known, but one contributing factor probably is the ability of the fungi to increase deep rooting, and thereby increase the volume of soil colonized by plant roots.

One clear paradox with *Trichoderma*, and other endophytic plant symbionts, is that the effects induced by them all require energy. Thus, these abilities would logically reduce plant growth, but instead, we frequently observe increased plant growth. The only source of energy for plants is sunlight and photosynthesis. The fungi have the abilities to increase photosynthetic efficiency (Mastouri 2010, Ph.D. thesis; Vargas *et al.* 2009).

*Trichoderma* spp., especially newer strains selected with the newly discovered attributes in mind, have significant advantages in both the developed and developing world. First, since they grow with plant roots, only small amounts of inoculum need to be

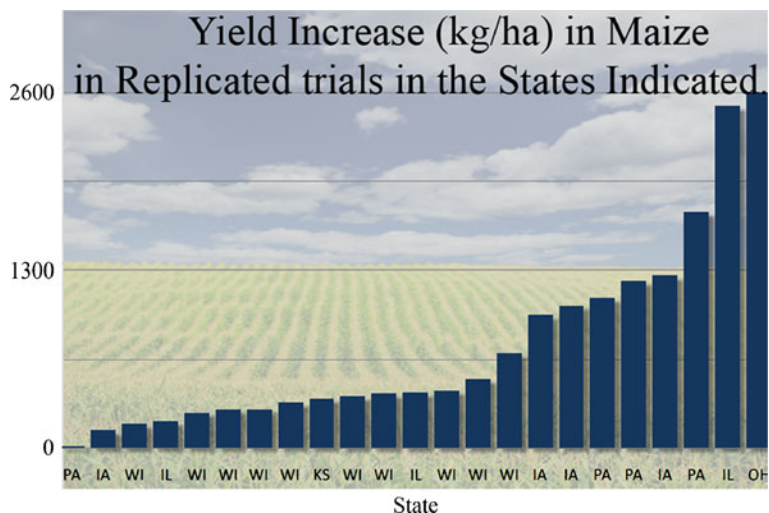
provided for long-term benefits. For seed treatments, only about 500 mg ha<sup>-1</sup> of highly concentrated commercial preparations need to be applied. For addition to greenhouse potting soils, only 10<sup>4</sup>–10<sup>5</sup> colony forming units (CFU's) per cc are necessary; preparations with CFU levels of more than 10<sup>10</sup> g<sup>-1</sup> are routine in commercial production. For developing countries, inoculum can be produced under very high quality control in developed countries, and provided to growers economically since only small amounts have to be shipped.

Inducing plants to cope more effectively with biotic and abiotic stresses and inadequate fertilizer levels has significant environmental advantages, including reducing nitrogen pollution in water and air. Furthermore, as a consequence of these advantages, the net result even in the developing world is an improvement in crop yields. Figure 2 gives data on yield improvements on maize in heartland of the USA using standard production practices. The yield improvements average about 820 kg ha<sup>-1</sup>, which at today's prices equal about \$442. The price per hectare for the *Trichoderma* is about \$8, so there is a large return on the farmer's investment, not including any savings from reduced N application. This yield improvement is presumed to be the sum net improvement in plant efficiency by reduction in plant responses to stresses. Availability of staple foods is expected to decrease in the future and this improvement in yields will help to avoid the worst effects. In developing countries, smallholders and others are being trained to apply seed treatments,

thus improving the economics for them. Since many smallholders cannot afford inputs such as fertilizers and pesticides, providing these products at low costs can assist global food security (Harman 2011; Shoresh *et al.* 2010).

It should be noted that several beneficial microbes, including plant growth-promoting rhizobacteria, mycorrhizal fungi and the basidiomycete *Piriformospora indica* have at least qualitatively similar effects on plants (Shoresh *et al.* 2010). All of at least some strains, along potentially with other organisms that colonize roots without disease, have evolved mechanisms to increase NUE, increase resistance to drought and other abiotic stresses, and induce systemic resistance to plant disease, all by their effects on plant gene expression (see Shoresh *et al.* 2010 for a summary). This remarkable concordance of effects must be an example of convergent evolution, because the organisms are totally unrelated. Our hypothesis is that these effects are possible within the genetic composition of plants, but that these symbiotic microbes have evolved separate mechanisms to induce plants to simply be more efficient. This has advantages to the microbes, since a larger number of healthy roots enable greater proliferation of the organisms within roots. There are no comparative data yet on the comparable abilities of these dissimilar plant symbionts; however, *Trichoderma* spp. have advantages in that they can be easily manipulated or selected since large numbers of strains can be grown and tested relatively simply and because they have reasonably good shelf life, which aids commercialization.

**Fig. 2** Yield Increase (kg/ha) in maize in replicated trials in the states indicated. Data are courtesy of Advanced Biological Marketing, Van Wert, Ohio, and resulted from tests run by independent farm consultants. IA, Iowa; IL, Illinois; KS, Kansas; OH, Ohio; PA, Pennsylvania; WI, Wisconsin





It must be emphasized that strains of *Trichoderma* spp. differ greatly in the effects on plants. Furthermore, benefits are mostly strain-specific, so it is not possible to generalize on the abilities of one strain and to assume that others of the same species will work equally well or give the same advantages. For example, strain T22 of *T. harzianum* in most cases provides NUE and, frequently, improved yields in maize. However, with a few genotypes of this crop, application of T22 results in no improvement or even a yield reduction (Harman 2006). This does not occur with wheat, where yield improvements are nearly always noted, or in the greenhouse, where the strain is widely used. However, our new strains of the same species seem to provide no such problems with maize (Fig. 2) or any crop we have tested. This points up the essentiality of a very robust screening program. In our case, this begins with initial selections, including evaluation of various improvements in plant performance in the greenhouse, including rapid and precise evaluations using plant gene expression assays. After this, however, extensive field trials are essential, with 10–15 separate and individual trials across a range of environmental conditions and genotypes, are essential for every crop. For our new strains shown in Fig. 2, well over 100 trials on a wide variety of crops in very diverse environments were completed before commercialization was implemented. It is important also to note that statistical analysis of any single trial is of much less importance than uniform positive responses across a wide range of trials. This usually is beyond the scope of university research and a commercial entity is necessary. For example, more than 80 separate field trials on maize and 50 on wheat were conducted with T22 in contract before it was concluded that seed treatments with this organism were inappropriate for maize but desirable for wheat. A minimum time for evaluations of a new strain from first analyses to full field trial programs usually requires a minimum of 5 years, including at least 2 years of commercial field trial evaluations. Even then, continued testing and data collection are essential as new uses are contemplated or even if new plant genotypes of established uses are introduced into the field. Thus, a wide range of continued trials is essential. With our new strains, for example, we need greater testing in plants exposed to water deficits and other stresses. Occasional negative

effects of *Trichoderma* spp. are similar to those effects that may occur with any agricultural input, including chemical pesticides and fertilizers.

The value of these strains and products is large. There are around 238 million hectares of maize, wheat and soybeans in the USA; if the new products were applied to 2% of the total acreage, the net return to US growers is \$184 million (assuming a 10x return on farmer's investment, which is conservative) and used on 10% of the US acres the increase in farm income is over \$900 million. This does not include the value of the treatments to other large crops such as rice, or the value of crops outside the USA.

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