

## PERSPECTIVES

scription of *Irfng* in vivo, multiple consensus sites have been identified in the *Irfng* locus, and are likely targets for T-bet-mediated chromatin remodeling, acute transcription, or both (12).

Mice lacking T-bet reveal an unusual feature of T-bet ecology. Although they have a profound defect in  $T_H1$  development, the development and function of CD8 effector T cells remains relatively unperturbed (13). This hinted that a T-bet-independent mechanism might regulate IFN- $\gamma$  expression and cytolytic activity in CD8 T cells even though paradoxically these cells usually express T-bet. CD8 T cells forced to produce more T-bet show increased production of IFN- $\gamma$  and of the cytolytic effector proteins perforin and granzyme B. Why, then, do the CD8 cells of mice lacking T-bet show unabated cytolytic activity and IFN- $\gamma$  production? Is T-bet not the master in the CD8 cell household?

In addressing this question, Pearce, Reiner, and their co-workers discovered a second member of the T-box gene family, *Eomesodermin*, which is expressed in developing CD8 T cells (1). Surprisingly, a dominant-negative form of T-bet that blocks T-bet activity, also suppresses effector responses in CD8 cells from T-bet-deficient mice. This implies that CD8 T cell development is regulated by a T-bet-independent pathway that is sensitive to dominant-negative T-bet. Reasoning that other T-box family members in CD8 cells must be suppressed by a dominant-negative form of T-bet, the authors used degenerate oligonucleotides specific for the T-box domain to amplify cDNAs from recently activated CD8 T cells. Analysis of the amplified cDNAs revealed roughly equal representation of two T-box genes: *T-bet* and *Eomesodermin*. Subsequent gain-of-function experiments established that enforced expression of *Eomesodermin* in T-bet-deficient CD8 cells could restore CD8 effector development, that is, IFN- $\gamma$  production and expression of perforin and granzyme B. Interestingly, enforced expression of *Eomesodermin* in CD4 T cells from T-bet-deficient mice also restored IFN- $\gamma$  production and the  $T_H1$  response. There was a similar response in CD4  $T_H2$  cells transfected with *Eomesodermin*. Importantly, although activated CD4 and CD8 T cells both expressed T-bet, only CD8 cells expressed high levels of *Eomesodermin* transcripts. Thus, although enforced expression of *Eomesodermin* in T-bet-deficient CD4 T cells can restore a  $T_H1$  immune response, it seems unlikely that *Eomesodermin* plays a prominent part in the normal development of CD4 T cells. In contrast, *Eomesodermin* may play a complementary, if not dominant, role in the development of CD8 effector cells.

Although the Pearce *et al.* study offers an explanation for T-bet-independent regulation

of CD8 cells producing IFN- $\gamma$ , it does not preclude a role for T-bet in this process. It does, however, raise important questions about how distinct T-box factors may influence effector T cell development. Why are both T-bet and *Eomesodermin* expressed in developing CD8 T cells when only T-bet is expressed in developing CD4 T cells? Does this simply reflect redundancy and plasticity in the regulation of IFN- $\gamma$ , or is there a division of labor between these T-box factors with respect to the target genes they regulate? The latter possibility is suggested by the greater reduction in expression of genes associated with cytotoxicity compared with those involved in IFN- $\gamma$  production in mice expressing only half the usual amount of *Eomesodermin*. In addition, dominant-negative forms of both *Eomesodermin* and T-bet result in a greater reduction in CD8 cytolytic activity than does dominant-negative T-bet alone. Notably, CD8 T cells from STAT4-deficient mice continue to produce IFN- $\gamma$ . Does *Eomesodermin* amplify and maintain expression of IFN- $\gamma$  through a STAT4-independent mechanism? CD8 T cells acquire effector competency more rapidly than do CD4 T cells; does coexpression of *Eomesodermin* and T-bet facilitate this? Alternatively, does the coexpression of both *Eomesodermin* and T-bet reflect their activation by distinct upstream pathways that are both important for CD8 effector T cell development? For instance, although type I interferons are known to activate STAT1 sig-

naling, they do not induce T-bet transcription (14); does *Eomesodermin* complement this function in CD8 cells, and, if so, to what end? Finally, is the apparent coexpression of T-bet and *Eomesodermin* an artifact of a population-based analysis, and is the true situation that these factors are expressed by distinct subpopulations of activated CD8 cells?

Clearly, definitive answers to these and other questions will require further study and better tools for their analysis, such as the production of *Eomesodermin* and *T-bet* conditional knockout mice. Nevertheless, the Pearce *et al.* study provides new insights into transcriptional events that operate during CD8 effector T cell development. Attention can now be centered on comparisons between CD8 and CD4 effector systems, which will benefit our understanding of both.

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## ECOLOGY

# Deciding the Future of GM Crops in Europe

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Three weeks ago saw the publication in the United Kingdom (UK) of the widely anticipated Farm Scale Evaluation (FSE) of the effects of genetically modified herbicide-tolerant (GMHT) crops on farmland biodiversity (1–8). A moratorium on the licensing of these crops has been in force pending a review of their likely impacts on health, the

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economy, and the environment. This delay has infuriated commercial interests in the United States (US), where GM crops are widely grown, and has led to President Bush launching a trade suit against the European Union over its GM policy.

The FSE is the last of a parallel series of reports compiled to enable the UK Government to decide whether or not to lift the moratorium on growing GM crops. The others are (i) an economic evaluation (9), which concluded that the economic viability of GM crops was highly dependent on consumer acceptance. (ii) A science review (10), which concluded that the risks to human health from current GM crops are minimal, that current GM crops are unlikely to pose a threat to UK ecosystems, but that the more effective weed management associated with

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GMHT crops may reduce farmland biodiversity (11). (iii) A public debate (12) involving 675 meetings with 20,000 people, the receipt of 1200 letters and e-mails, 36,557 feedback forms, and interviews with a stratified random sample of 78 individuals. The public debate met with an overall negative response, although markedly less negative for the randomly selected individuals, suggesting bias in the general feedback, with the views of strong anti-GM campaigners contributing disproportionately to the debate (13).

### Farm Scale Evaluation

The FSE was designed to test the hypothesis that there is no difference in biodiversity between GM crops and conventional crops. The study design was carried out over 3 years in 60 fields across England and Scotland. Fields were divided into two, one-half were sown with a conventional crop, and the other with a GM crop (14). The crops grown were sugar beet (including fodder beet), maize, and winter and spring oilseed rape (canola), and the biodiversity recorded included the abundance of weeds and invertebrates. The data were rigorously analyzed, peer-reviewed, and published in a series of eight papers in the *Philosophical Transactions of the Royal Society of London* (1–8). The results on autumn-sown canola are expected to be published next spring.

The primary effects of the use of GMHT crops were, unsurprisingly, on the numbers and biomass of weeds (see the table). In two of the GMHT crops (sugar beet and spring canola), there were reductions of 60 to 80% in weed biomass at the end of the growing season, reflecting increased weed control in these crops. In contrast, there was an increase of 82% in weed biomass in GMHT maize compared with the conventional maize crop. The reason for this is that pre-emergence control of weeds in conventional maize using the herbicide atrazine is extremely efficient, and the GMHT system is unable to improve on this.

There were also a number of effects on the growth and characteristics of weeds during crop development. The GMHT crops were not sprayed with a pre-emergence herbicide, so that initially weed densities were much higher than in the conventional beet and canola. This effect is frequently cited as a benefit of the GM system. However, after herbicide application, these weeds are killed, typically before they are able to set seed. Consequently, by the end of the growing season there are fewer weeds in the GM oilseed rape and beet, and those remaining tend to produce fewer seeds per plant than those surviving in the conventional crop. Thus, short-term increases in weed biomass are likely to be outweighed by longer term declines in weed numbers (15).

The secondary effects of the GM system tend to mirror the effects on weeds. Thus, densities of carabid beetles feeding on weed seeds tended to be higher in conventional beet and canola, as well as in GM maize, because of the greater weed seed production. On the other hand, detritivore (collembolan) densities were higher in the GM beet and canola, as well as in conventional maize. This effect resulted from the increased biomass of weeds during the initial stages of growth, which were then killed by late spraying, providing dead plant material on which detritivores were able to feed. Other trophic groups (pollinators, herbivores, and their natural enemies) showed similar shifts in abundance relative to effects on the abundance of their resources.

There are a number of important differences in the management of GM crops versus conventional crops, which could have important environmental effects. Notably, herbicide use is typically far lower in the GM system than in the conventional one. In the GM system, there is usually a maximum of only two herbicide applications per growing season. In conventional crops, particularly sugar beet, this number can be trebled when weed infestations are large. Consequently, the amount of active herbicide ingredient used in the GM system may be much lower than in the conventional one. In extreme cases, some farmers using the GM system actually applied no herbicides, presumably because of an already highly depleted weed flora. This could reflect an agronomic advantage of the GM system: Because weed control is extremely effective using broad-spectrum herbicides in GM crops, farmers have the flexibility to act responsively to weed problems, whereas with conventional crops (particularly sugar beet) control is often difficult and farmers have to act preemptively. A huge caveat, of course, is that changes in practice of this sort will only be possible if yields or profits are maintained, but it is impossible to judge this from the FSE results.

The FSE results show large negative impacts of growing GMHT crops on weeds in sugar beet, smaller but consistent negative effects on weeds in oilseed rape, and positive effects on weeds in maize. The change in timings of herbicide applications leads to shifts in invertebrate resource abundance during the growing season, and the invertebrates respond to this change. The management of GMHT crops is dramatically different from that of conventional crops and could lead to

major reductions in herbicide applications if yields from GMHT crops can be maintained.

### Limitations

The FSE is one of the most extensive and impressive ecological studies ever conducted. However, it is not without limitations. One of the most serious limitations is that for logistical reasons crop yields were not measured. Without yield measurements it is not possible to judge the effectiveness of GM technology and whether GM crops can deliver increased yields. This is particularly significant given that farmers vary enormously in the number and timing of herbicide applications to their GM crops, which could have a major impact on weed numbers and yield (16) and consequently on invertebrate biodiversity.

The most serious limitation of the FSE from the standpoint of public policy is that

### SUMMARY OF THE MAIN RESULTS

Differences in biodiversity between crops exceed differences between GMHT and conventional crops (3–8).

Higher early season weed numbers and biomass in all three GMHT crops (3).

Higher weed mortality in GMHT sugar beet and canola resulting in lower late-season biomass and seed rain of weeds in those crops, but lower weed mortality in GM maize (3).

More detritivores (collembola) in all three GMHT crops as a result of higher weed detritus (5, 6).

Lower numbers of bees, butterflies, and Heteroptera in GMHT sugar beet and canola as a result of reduced weed populations; generally higher numbers of invertebrates in GM maize (5, 6).

Lower herbicide inputs in GMHT crops (2).

the study has no predictive component. Forecasts of the likely impacts on biodiversity 10, 20, or even 50 years into the future and at a landscape scale are needed if policy decisions are to be made. However, the FSE was not designed with the goal of estimating parameters for the development of predictive models, but was tied to a rather narrow hypothesis test and constrained to a field scale. Therefore, the current results are inadequate to make long-term policy evaluations; a modeling framework (11) would seem to be necessary to achieve this.

Although the FSE is extremely comprehensive, the results are not adequate to evaluate effectively the likely long-term impacts of growing GMHT crops, and further evaluations of the results will be necessary.

### The Future

The current debate about growing GM crops in the UK contrasts with the situation in the US where GM crops are widely grown. Two differences help to explain these contrasting attitudes. First, the major epidemics of BSE (bovine spongiform encephalopathy) and foot-and-mouth disease in the UK led to a breakdown in public

confidence in politicians and scientists over food safety. Second, the UK relies on farmland for recreation. Whereas in the US, National Parks such as Yellowstone and Yosemite are largely unmanaged, equivalent beauty spots in the UK are predominantly agricultural landscapes. The environmental impacts of farming are also of increasing concern (17). Farming practices over the past 30 years have had an enormous impact on the biodiversity of farmland (18). There is consequently an attitude of extreme caution to technological changes in farming practice.

Paradoxically, although the results of the FSE may appear detrimental to those supporting GM crops, they might actually be beneficial. Applications to grow GM crops can only be rejected on health or environmental grounds. Using the FSE results as a justification to adopt a cautious approach, for example, by not licensing sugar beet or oilseed rape but permitting the planting of maize, might be the politically expedient way to introduce GM crops to a skeptical public while clearly showing responsible concern. There is, however, the complex issue of cross-pollination between

GMHT maize and conventional maize that still has to be resolved.

The FSE has not produced evidence for any new environmental damage as a result of GM technology. The reductions in biodiversity result solely from increased control of weeds, and the FSE appears to show that introducing GMHT crops is equivalent to the development of a new, very efficient herbicide. Such changes in technology occur routinely and without public debate. Although the impacts of GMHT crops on biodiversity may be negative, future technological developments could also yield effects of this sort, and there is no reason to make a special case for GM crops. On the other hand, environmentalists might argue that if biodiversity is to be conserved in farmland habitats, the negative effects of farming technology need to be halted, and GM crops may be the place to start. Thus, the FSE will, inevitably, provide ammunition for both sides of the debate.

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## PHYSICS

# Nonlinear Optics in Fibers

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Silica fibers are at the heart of modern telecommunications. In that context, both their dispersive and nonlinear properties are of paramount importance. The recent development of photonic crystal fibers has enabled new and useful combinations of those properties, often in previously inaccessible ranges of wavelength.

Fused silica glass is called “nonlinear” because its index of refraction depends, if only slightly, on the light intensity. Thus, as a light pulse travels down a fiber, it acquires a phase shift that varies according to the instantaneous intensity across the pulse. This “self-phase modulation” eventually leads to a substantial broadening of the pulse’s spectrum. At the same time, (linear) chromatic dispersion creates a phase shift that broadens the pulse in time. In data transmission, the latter effect can cause severe overlap of pulses from adjacent bit slots, resulting in loss of information. If the fiber’s dispersion is “normal” (higher optical frequencies travel more slowly than lower ones), self-phase modulation can accelerate the dispersive pulse broadening.

In contrast, if the fiber’s dispersion is “anomalous” (higher frequencies travel faster than lower ones), for pulses of the right peak intensity and shape, the nonlinear and dispersive phase shifts are complementary, that is, they sum to a constant across the pulse (1). Because the constant phase shift has no influence on the shape of the pulse, no broadening occurs. The resultant invariant pulse is known as the soliton. A special version of the soliton is the basis for the most sophisticated commercial ultralong-haul fiber optic transmission systems (2).

When light pulses of two distinctly different optical frequencies travel down the fiber together, the fiber’s nonlinearity produces the growth of two new frequencies, or “sidebands,” one above and one below the two original frequencies. This phenomenon is known as “four-wave mixing.” In a fiber with low dispersion, the new frequency components can grow to large intensity. They may cause interference in multichannel transmission, but also provide a convenient technique for frequency translation from one wavelength or frequency channel to another.

The phenomena discussed thus far have involved “instantaneous” nonlinearity,

where the response time is short compared with one cycle of the optical field. But there is also a “slow” response (on the order of some tens of femtoseconds), which leads to the Raman effect. In this effect, an optical pump produces a broad band of optical gain, whose frequency peaks at about 13 THz less than that of the pump itself. Because of its ability to turn the transmission fibers into their own optical amplifiers while generating a minimum of spontaneous emission noise, the Raman effect is the preferred mode for optical amplification in transmission systems.

In ordinary fibers, however, both the chromatic dispersion and the nonlinearity are subject to certain limitations. First, the region of anomalous dispersion, required for solitons, is limited to wavelengths greater than 1300 nm. Second, for single-mode fibers (which support only one spatial pattern of variation of optical field across the fiber core), core cross-section areas (where most of the light is confined) are limited to a rather narrow range, roughly from 10 to 100  $\mu\text{m}^2$ . This limitation in turn restricts the range of intensities, and hence the strength of nonlinear effect, that can be achieved with a given optical power.

The recently developed photonic crystal fibers (see the figure) overcome both restrictions (3, 4). Solitons and soliton-related phenomena can now exist at much shorter wavelengths, because photonic crystal fibers can be made with anomalous disper-

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