The Rice Genome and the Minor Grains

RONALD P. CANTRELL AND TIMOTHY G. Reeves ("The cereal of the world's poor takes center stage," Perspectives, 5 April, p. 53) correctly point out that the availability of the rice genome sequence has the potential to contribute to food security through the improvement of rice, the staple crop in the diets of half the world's population. They also point to its contribution to future improvement of maize, wheat, and other major commercial grains. A further boon will be felt through its contribution to improvement of the "minor" grains such as tef, sorghum, and the millets.

The world's commercial grain crops have been the focus of enormous public and private investment. The minor grains also feed millions and are a key to food security for the poorest in Asia and Africa. These grains are culturally valued, adapted to harsh environments, nutritious, and diverse in terms of their genetic, agroclimatic, and economic niches. Research on these crops, however, has been severely underinvested, receiving minimal attention by advanced laboratories relative to their importance for the world's poorest regions.

Sorghum, one of the so-called minor grains, is important for food security.

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As a result, and because of the close evolutionary relationships among all of the domesticated grain crops [a point well made by Jan Leach *et al.* ("Why finishing the rice genome matters," Letters, 5 April, p. 45) and Jeffrey Bennetzen ("Opening the door to comparative plant biology," Perspectives, 5 April, p. 60)], it is in these crops, too, where the rice sequence will have a significant food security payoff.

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Altered Peptide Ligands and MS Treatment

THERE ARE SERIOUS DISCREPANCIES IN Jennifer Couzin's article "Gently soothing a savage immune system" (News Focus, 19 April, p. 456) regarding a trial using altered peptide ligands in patients with multiple sclerosis (MS). She quotes Roland Martin of the National Institutes of Health (NIH) about a trial that he participated in with a drug termed an altered peptide ligand (APL), produced by Neurocrine Biosciences. She writes that "three of the eight volunteers suffered exacerbated MS [multiple sclerosis] symptoms apparently linked to the peptide-targeting drug supposed to temper immune attacks."

Couzin fails to note that the NIH trial cited by Martin using the Neurocrine drug was published back to back with a placebo-controlled, double-blinded, multicenter trial on 144 patients (*1*, *2*). Not only did the bigger placebo trial fail to show any signs of worsening caused by the peptide, the trial also demonstrated improvement on magnetic resonance scans in both the volume and number of contrast-enhancing lesions at one of the doses of altered peptide that approached statistical significance. Moreover, there was evidence of a desirable Th2 shift in T cells responding to myelin basic protein (*2*).

The NIH trial involved only eight patients and was not placebo-controlled or blinded (*1*). Moreover, of the three patients who worsened, one had inflammatory demyelinating peripheral neuropathy, rendering the diagnosis of MS questionable. Another patient who worsened had a total clearance of T cells reactive to myelin basic protein, after treatment with the altered peptide, making it difficult to blame the peptide for the patient's worsening. Couzin states that another "patient began the trial with a few brain lesions and ended up with 91." This is inaccurate. The patient had over 20 lesions at baseline and had no contrast-enhancing lesions before starting beta interferon treatment, which was given to the patient after withdrawal of APL therapy and a "course of standard intravenous steroid therapy" (*1*, p. 1170). This is quite different from concluding that the patient ended up with 91 lesions after APL therapy. It is unfortunate that the figure accompanying the article was labeled "Backfired," because there were no contrast lesions at all at the conclusion of altered peptide therapy and before beta interferon was administered [see fig. 1c of (*1*)].

Overall, the results of the two trials with APLs in MS show that there was "no substantial improvement or worsening in the whole cohort of 8 MS patients treated at NIH" (*1*, p. 1169), and there was improvement on magnetic resonance imaging in the placebo-controlled, double-blinded study involving the same drug (*2*).

APLs are a promising therapy for autoimmune disease, and further trials, with sponsorship from the NIH-funded Immune Tolerance Network, are planned. It would be unfortunate indeed if these conflicting matters were not clarified and if the successful early use of APL was not mentioned (*1*, *2*). To state only one side of the story is regrettable.

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Response

IT IS CORRECT THAT THREE OUT OF EIGHT multiple sclerosis (MS) patients participating in the National Institutes of Health (NIH) study suffered from exacerbations during the trial of an APL (*1*); however, extensive immunological testing linked the disease exacerbations to APL treatment in 2/8 (25%) of the patients.

The result of both trials (*1*, *2*) was identical in that neither study demonstrated a statistically significant difference between treated and untreated patients (*2*) or baseline versus treatment (*1*) with respect to the clinical and magnetic resonance imaging (MRI) parameters.

It is correct that the NIH trial was not placebo-controlled or blinded; however, an analysis of the adequacy of blinding was not performed for the Kappos *et al.* study (*2*), and 8/8 patients in the NIH trial had substantial skin reactions at the injection site, i.e., induration, pain, and/or reddening, rendering effective blinding unlikely.

Conlon and Steinman refer to the three patients that worsened in our trial. They doubt the diagnosis of MS for patient MS601, yet we are unaware of data that would question the diagnosis of MS in this patient. Furthermore, this patient did not suffer from an inflammatory demyelinating neuropathy, but from a clinically silent hereditary neuropathy.

Patient MS503 showed a disappearance of MBP (83-99)–specific T cells after APL administration, and we therefore stated (*1*) that the MS exacerbation in this patient cannot be linked to APL therapy, even though the lesions of this patient were very different from all her previous lesions. Furthermore, the disappearance of MBP (83-99)–specific T cells does not prove that the drug had no relation to her atypical MS exacerbation.

Patient MS502 had an average baseline MRI activity of 13.5 contrast-enhancing lesions per month (median = 12). During APL administration, the average number was 55.5. During over 100 consecutive monthly MRI scans at the NIH, the second highest peak outside the APL treatment phase was 26 lesions, compared with the peak of 91 lesions during APL treatment. This is well above 3 standard deviations of the average. In addition, we have documented that the number of both APL- and MBP (83-99)–specific T cells increased more than a thousandfold, that most of these T cells had a proinflammatory phenotype, that most of them cross-reacted with both peptides, and that the increase in frequency was observed in the peripheral blood and the cerebrospinal fluid.

Conlon and Steinman mention that this patient had a total clearance of lesions, "making it difficult to blame the peptide for the patient's worsening." However, this "clearance of lesions" was observed after the second exacerbation of this patient and after 10 days of high-dose intravenous steroids followed by an oral taper, as shown in fig. 1c of our article (*1*). Both episodes of "clearance of lesions" are obviously attributable to steroid therapy and not APL treatment as they suggest.

With respect to the Kappos *et al.* trial (*2*), Conlon and Steinman fail to mention that one of the patients presented with three MS exacerbations in ≤4 months. This is equal to a yearly exacerbation rate of about 12 exacerbations, roughly 12 to 20 times the average exacerbation rate in relapsing-remitting MS. Therefore, it is not correct to state that exacerbations due to APL therapy were not observed in that trial (*2*). In addition, Kappos *et al.* did not study by immunological measures whether these exacerbations were related to APL therapy.

Conlon and Steinman mention that there was evidence for a desirable Th2 shift in the multicenter trial of the APL. This notion is based on ELISA measurements of interferon-gamma and IL-5 in primary cultures of peripheral blood cells in 7 of 144 patients [4.9%; only four are shown in (*2*)].

In summary, our data do not show clinical efficacy or lack thereof; however, they indicate that the treatment of MS patients with this particular APL is not safe at the dose that we administered. The fact that about 10% of the patients in the multicenter trial and the NIH trial showed signs or symptoms of generalized hypersensitivity—and this observation was made at all doses—underscores that this APL is not safe, probably not even at the lowest tested dose. The data and safety monitoring boards of both trials were concerned enough by these observations to terminate both clinical studies. We have discussed in detail the potential causes of the side effects upon APL treatment (*3*). Conlon and Steinman are correct that some of the immunological findings suggest that the potential efficacy of APL in autoimmune diseases should be pursued further. How this should be done and which APL should be used are not clear in the moment.

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Reassessing Research Assessment in the UK

JONATHAN ADAMS'S EDITORIAL "RESEARCH Assessment in the UK" (3 May, p. 805) paints an unduly selective and congratulatory picture of the Research Assessment Exercise (RAE). There is a strong belief among academic researchers that the apparent increase in UK research performance illustrated in his graph is mostly due to "grade inflation," as academics learn how to play the RAE game and tell the assessors what they want to hear. As a consequence, the recent RAE deemed more than half of the UK's academic departments to be of "international quality" in research, a figure that is manifestly ludicrous. This is why the "funding differentials are being flattened": If too many departments get the top grade, there is insufficient money to reward them all. An unfortunate side effect is that genuinely top-grade departments can no longer be distinguished from those of lower rank, so the truly top departments cannot be rewarded either. In short, the RAE has comprehensively destroyed the rationale for its own existence.

It is possible that the RAE has helped to improve the UK's research in some respects. It has certainly helped to increase the salaries of some researchers, by creating a "transfer fee" mentality in which academics who are likely to score well on the RAE are paid higher salaries to entice them to other institutions or to prevent them being so enticed. But Adams fails to mention the downside of this exercise, which is the amount of academic time and effort expended in preparing the required documentation. This was justifiable when the exercise produced tangible rewards, but it is a complete waste of time when it does not, and this is the real reason why the RAE has now pretty much run its course.

The RAE is not the only such exercise inflicted on UK academics. The worst example is the Teaching Quality Assessment (TQA), which would be better called the Document Quantity Assessment. This immense and tedious bureaucractic exercise consumes vast amounts of time and energy and achieves very little, aside from damaging academic morale, wasting time that could better be spent on actual teaching, and piling up mounds of unnecessary paperwork. The TQA is universally detested by the UK's academic community, whereas the RAE has been tolerated—until now. This tendency toward overassessment has done enormous damage to the whole of the UK's public sector, including police, teachers, nurses, doctors, and higher education. Workers in many of these areas are now leaving in droves.

I would like to think that the real reason why a system like the RAE is "a rarity internationally" is that other countries have observed the sheer stupidity of the UK's assessment procedures and vowed not to make the same mistake. Certainly, the RAE should be seen as a ghastly warning rather than as a model for other countries to follow. Unfortunately, I expect to see other countries heading down the same destructive path, seduced by the same simplistic arguments. Uncritical and selective reports like the one written by Adams will certainly encourage them to do so, and for this reason alone it is important for opposing views to be heard.

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