



ISB NEWS REPORT

COVERING AGRICULTURAL AND ENVIRONMENTAL BIOTECHNOLOGY DEVELOPMENTS

JUNE 2000

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NEWS AND NOTES

OECD CONFERENCE ON GM FOOD SAFETY

The Organization for Economic Cooperation and Development (OECD) held a conference in Edinburgh from February 28th to March 1st, 2000 on "GM Food Safety: Facts, Uncertainties, and Assessment." The conference followed a request from the G8 leaders at their summit in Cologne in June 1999 that the OECD "undertake a study of the implications of biotechnology and other aspects of food safety." It was the subject of enormous media attention. The organizers subsequently sent participants 97 pages of articles on the conference between February 23rd and March 8th.

The conference was ably chaired by Sir John Krebs, Professor of Zoology at Oxford University and the chairman designate of the future UK Food Standards Agency, and brought together 400 invitees from more than 25 countries. It focused mainly on GM food safety and human health but also covered other issues such as ethics, environmental safety, economic development, and the ownership of intellectual property. The speakers and panelists consisted of, in approximately equal numbers, proponents and opponents of GM food, and those who were essentially neutral on the topic. The presenters were primarily scientists, regulators, NGOs (including Greenpeace, Friends of the Earth, and GeneWatch), and industry representatives. The conference was not aimed at producing a consensus, but rather at identifying areas of greater agreement, divergence of opinion, and uncertainty due to lack of knowledge.

The conference was divided into three sections:

- What is the science of genetic engineering and its potential risks and benefits for food and agriculture?
- What is the science of assessment of food safety, and what, if any, are the special problems posed by GM foods?
- What are the regulatory systems worldwide, and do these require adjusting because of special features of GM foods?

The principal conclusions were as follows:

Food safety

There was consensus that many people are eating GM foods worldwide, especially in the US, Canada, and China, with no adverse effects on human health reported in the peer-reviewed scientific literature. There could, in theory, be long-term effects not yet detected in the approximately ten year span GM foods have been available.

THE ISB NEWS REPORT

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Editor: Ruth Irwin
rirwin@vt.edu

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120 Engel Hall
Virginia Tech
Blacksburg, VA 24061
Tel: 540-231-2620
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Email: isb@vt.edu



Sir John Krebs gave particular emphasis to the lack of evidence to support a negative impact of GM food on health in the final session of the conference. He asked anyone who had any evidence of harmful health effects due to GM foods to come forward with this information. The only example cited was the past case of impurities found in tryptophan capsules originating in Japan; however, this allegation was emphatically explained to result from manufacturing "short cuts" and had nothing to do with the genetic modification process per se.

Decision making

There was consensus that decisions involving GM foods and the assessment of their safety should be more inclusive and open. However, there was no conclusion on how attitudes and beliefs that might become apparent as a result of such consultation should be incorporated into the assessment of GM food safety. The participants were uniformly in favor of GM food labeling but did not agree on its extent.

Assessment of GM food safety

There was accord among attendees that, after six years of using the concept of "substantial equivalence" as a tool, it is time to undertake a more detailed review of this process. There was not agreement about the importance of animal feeding trials (other than toxicity trials), but there was consensus that the methods for testing toxicity and allergenicity need re-examination.

GM technology in developing and developed countries

The majority of speakers from developing countries stressed the crucial importance of GM technology as part of the armory for feeding their populations in the future. There was agreement that the focus of emerging GM technology should be more explicitly determined by the needs of local people rather than of multinational corporations.

After the talks, Prof. Zhang-Liang Chen, director of the National Laboratory of Protein Engineering and Plant Genetic Engineering at Beijing University in China, and Jennifer Thomson were interviewed by a number of European reporters. Prof. Chen indicated that in China, with 20% of the world's population and 7% of the land surface, GM is already playing a major role in food production. Dr. Thomson pointed out the striking increases in cotton yields experienced by small scale farmers in South Africa due to the introduction of the Bt gene.

Concerns about GM technology other than food safety

The principal concerns expressed by opponents of GM technology related less to food safety than to the broader question of why GM food is being produced at all. This sentiment was strongly contested by some, but not all, representatives of developing countries. A second concern discussed was the potential environmental impact of cultivating GM crops.



The way forward

The most significant aspect of the Edinburgh Conference was that it included all sides of the debate surrounding GM foods and nevertheless identified certain areas of agreement. Issues were also identified in which there was disagreement or uncertainty due to lack of knowledge. Progress was made in separating those issues that are subject to scientific analysis from those that are related to politics, beliefs, and values.

Prof. Krebs recommended formation of an international forum to continue the process started in Edinburgh. The aim would be to provide governments with a state-of-the-art assessment of scientific knowledge about GM technology and to set this assessment in the context of broader societal concerns. This forum would emulate the Intergovernmental Panel on Climate Change (IPCC), but include scientists as well as other stakeholders. It would interact with other international groups such as Codex Alimentarius, include developing countries, and initially focus on food and environmental safety. Two kinds of output are envisaged: a) scientific assessments, and b) inclusive and global debate about the relationship between GM technology and society.

*Jennifer A. Thomson
Department of Microbiology
University of Cape Town
jat@malbiol.uct.ac.za*



PLANT GENETICS OPPORTUNITY

The USDA Cooperative State Research, Education, and Extension Service (CSREES) announces a vacancy for a National Program Leader for Plant Genetics (GS-14/15). The closing date is August 18, 2000. The announcement is available from the USDA Web site at <http://www.reeusda.gov/hrd/SOM-0750.htm>.

PLANT RESEARCH

ENGINEERING HERBICIDE RESISTANCE BY TARGETED MODIFICATION OF A PLANT GENE

A group of researchers from Pioneer Hi-bred International recently produced lines of maize with resistance to the herbicide Lightning (a mixture of imazethapyr and imazapyr)¹. On the surface, this is an unremarkable event.

After all, resistance to these and similar herbicides has previously been produced in maize and other crops using either conventional breeding or genetic engineering strategies. However, what is unusual about the new maize lines is not the fact that they are resistant to these herbicides, but rather the method that was used to confer the resistance: a precise replacement of a single amino acid in the endogenous herbicide target enzyme.

The herbicides imazethapyr and imazapyr are members of the imidazolinone herbicide family, which, along with the sulfonylureas (and a few newer herbicide families), act on plants through the inhibition of the enzyme acetohydroxy-acid synthase (AHAS). AHAS is a key enzyme in the synthesis of the branched chain amino acids—valine, leucine, and isoleucine; so disruption of the activity of this enzyme leads to metabolic disruption and death of plants. However, a very slight alteration in the amino acid sequence of the AHAS enzyme can prevent herbicidal inhibition while preserving its normal catalytic function, a feature that has been exploited by scientists to create crops resistant to AHAS-inhibiting herbicides.

The conventional method for engineering resistance

The conventional method of generating herbicide resistant plants involves isolating a gene of interest (encoding a protein that confers herbicide resistance) and manipulating it in a bacterial-derived plasmid vector. The coding sequence of the gene may have its normal endogenous promoter, or be fused to another regulatory element that will cause it to have a new pattern of expression. This gene is then linked to a selective marker, for example, a gene that encodes antibiotic resistance, which will aid in the selection of cells transformed with the new gene. This entire construct is then introduced into plant cells resulting in its incorporation into the plant genome. Cells that have been transformed with the construct are then selected by their ability to grow in the presence of the antibiotic and surviving plants are regenerated.

This conventional method has two problematic results. First, the transgenic crop plant still contains the antibiotic resistance marker, left over as an artifact of the transformation/regeneration process, which has led some people to worry about the consequences of having antibiotic resistance genes widely expressed in transgenic crops. The second concern is that, because integration of foreign genes into the genome is generally random, the number and location of the transgene insertions into the crop genome cannot be controlled. Transgene insertion can disrupt the function of genes into which they might insert, and the expression of the transgene itself can be influ-

enced by its location in the genome. Some areas of the genome appear to be more actively transcribed than others, and multiple lines transformed with an identical construct can vary widely in their levels of transgene expression. Such issues of transgene copy number, insertion location, and gene stability and expression make the job tougher for plant breeders who are charged with efficiently incorporating the new trait into the latest crop varieties.

An alternative approach

Enter the Pioneer group, led by Chris Baszczynski, who generated herbicide resistant maize lines that avoid these potential problems by specifically changing a single amino acid in the AHAS gene using a chimeric RNA/DNA oligonucleotide. This technique has been used in mammalian systems as a tool for gene therapy, and is now shown to have value in plants. The approach uses an oligonucleotide made up of a combination of DNA and RNA bases, with a 32-base section having nearly exact homology to the target sequence of the endogenous plant gene, except that there is a single base mismatch at the point of the desired mutation. The chimeric oligonucleotide is delivered into target cells using microprojectile bombardment, where it aligns with the endogenous homologous sequence. In certain cases the normal DNA repair mechanism reads the chimeric oligonucleotide as the template gene and “corrects” the mismatched base in the endogenous gene. The result is a direct change in a specific nucleotide in the target gene.

Making herbicide resistant maize by this method is no simple task, however, and requires a lot of information before even starting. First, it was important to identify the specific amino acid to change, which in maize was to change the serine (coded by AGT) at position 621 to asparagine (AAT). It was also known that maize contains two families of the AHAS gene, with multiple members in each family, so extensive sequencing of various AHAS genes from maize was conducted in order to verify that the region around the target amino acid was not polymorphic. This allowed the researchers to design a chimeric oligonucleotide that would be homologous to all AHAS genes. It was also important to know if genes other than those for AHAS had sufficient homology to this sequence that there would be a chance of introducing an unintended mutation in other genes. Extensive database searching of known maize expressed sequences revealed no sequences that matched the oligonucleotides as well as the AHAS genes.

Cultured maize cells were bombarded with the chimeric oligonucleotides. Previous experiments² using oligonucle-

otides tagged with a fluorescent dye had demonstrated a preferential accumulation of the oligonucleotides in cell nuclei within one hour of bombardment, but the oligonucleotides were degraded rapidly and did not persist beyond 24 hours. Cells that were able to grow and develop callus in the presence of the herbicide imazethapyr were characterized to determine whether the desired mutation had occurred.

Plants were regenerated from nine separate transformation events and tested for susceptibility to Lightning. Of these, three plants were resistant to the herbicide at four times the normal field dose, four others were able to tolerate the normal field dose, and were only slightly injured by the four-fold rate, while two plants (and the untransformed control) were severely injured by the normal field dose of the herbicide. AHAS genes from these plants were sequenced; the highly resistant ones contained the predicted guanine to adenine change that would result in the amino acid conversion. Other regenerated plants had nucleotide conversions different from those predicted, but the mutations were all at, or within a few bases of, the target site. The herbicide susceptible plants did not have the predicted change. When resistant plants were backcrossed to wild-type plants, approximately half of the resulting progeny inherited the resistance, as would be predicted for a dominant trait.

Although the use of chimeric oligonucleotides for the engineering of plants has great potential, it also has some limitations. One problem is the requirement that the trait of interest must be conferred by the alteration of a single amino acid and produce a selectable phenotype to allow regeneration of putative transformants. This is relatively simple to do with herbicide resistance, but it may not be as easily applied to other traits. Another limitation is the need for extensive sequence information on the target gene and crop of interest, which may not be easily performed in less well-studied crops. Finally, the frequency of transformation (10^{-4}) is lower than for conventional transformation events. Nevertheless, the elegance and directness of the technique results in a targeted change in a specific gene, with little or no confounding alterations in the expression of the gene. This technique may become a powerful tool in crop improvement and could allow investigations into the effects of subtle changes in single plant genes.

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Jim Westwood

Department of Plant Pathology, Physiology, and Weed Science
Virginia Tech
westwood@vt.edu



A NEW ERA FOR RICE RESEARCH

The effort to completely sequence the rice genome was given a huge boost recently with the announcement by Monsanto that it will soon release a “working draft” of the genome that covers 80% of the plant’s genetic make-up¹. Monsanto made the announcement in an April 4th press release, stating that the crude sequence map will be made freely available to all researchers. In the press release, the company said that it hoped the release of the information would “. . . accelerate development of improved types of rice.” The announcement comes at a time when a number of significant advances and changes are occurring in the field of rice science and, with the release of the genome map, it seems clear that rice research is entering a new phase.

The physical map of the rice genome is the product of a collaboration between Monsanto and Dr. Leroy Hood, head of the non-profit Institute for Systems Biology. At the time of the collaboration, Dr. Hood was working at the University of Washington, Seattle, where he used BAC (bacterial artificial chromosome) clones to break up the enormous task of sequencing the rice genome into workable fragments. The BAC-based approach was originally developed by Dr. Hood for the Human Genome Project, and he found that, with further refinements for determining the organization of the BACs, the approach worked equally well for rice.

The pleased, but very surprised, members of the publicly funded International Rice Genome Sequence Project (IRGSP) welcomed the announcement². Monsanto and its collaborators had kept the project tightly under wraps until the April press briefing. Few outsiders have seen the data, so there is some concern that not all the sequence is of high enough quality to be useful to researchers. Other researchers have expressed doubt that Monsanto will come through on its promise make the data freely available with no strings attached. As things stand, Monsanto plans to make

most of the information available to the IRGSP within the next few months. However, the company has stated that researchers wanting to generate patents from findings derived from the Monsanto data should give the company an early opportunity to negotiate a non-exclusive license.

Regardless of the doubts, the genome information released by Monsanto will significantly speed up the IRGSP mapping and sequencing effort. It is anticipated that it will already allow for the identification and placement of most of the estimated 30,000 genes contained on the rice genome. This placement information is especially important for traditional plant breeders, who use the information when performing crosses to move traits from one crop variety to another. However, the positional information is useful not just for rice breeders, but also for breeders working with other cereal crops. This is because of a phenomenon known as “synteny.” Many of the cereal crop species, including wheat and corn, have a similar arrangement of genes or gene clusters on their genomes. Therefore, if a researcher knows where a gene of interest is located in the genome of one cereal species, then he will have a pretty good idea of where to look for the same gene in a different cereal species.

A Golden Harvest

The sequencing effort will also identify large numbers of previously unknown genes. It is hoped that the understanding of these genes will lead to the development of recombinant rice strains with improved agronomic performance, thus helping to feed the rapidly expanding segment of the world’s population that depends on rice as a staple dietary component. However, a new recombinant rice variety has recently been developed, quite separately from the Monsanto effort, that goes a long way towards addressing another great need of the rice-dependent poor—malnutrition.

At the 16th International Botanical Congress, Ingo Potrykus described the development of what has since become known as “golden rice”³. Through the introduction and careful regulation of multiple genes from other species, Dr. Potrykus and his fellow researchers have developed a variety of rice that is fortified for both iron and β -carotene, the precursor of vitamin A. Iron deficiency is considered the most widespread form of mineral malnutrition, whereas vitamin A deficiency is the leading cause of visual impairment and blindness in children worldwide.

Previously reported in the journal *Science*, Potrykus described how he and his colleagues first developed a β -carotene fortified rice variety. Rice naturally contains an early precursor for β -carotene, geranylgeranyl diphosphate.

Converting this precursor to β -carotene would require the introduction and expression of four genes; something never successfully achieved in rice. Using an elegant transformation strategy, the researchers were able to introduce the entire conversion pathway by using a gene from the *Erwinia* bacterial species, which was capable of performing two of the conversion steps, along with two genes from daffodil. The highest expressing recombinant rice lines produced 2 $\mu\text{g/g}$ of provitamin A—enough β -carotene to meet an adult's daily vitamin A requirement with as little as 300 g of cooked rice. In fact, these lines accumulated so much β -carotene that the endosperm of these grains appears bright yellow—hence the name “golden rice.”

Work performed by other researchers in the same group led to a different rice strain that was fortified for iron. For the creation of this strain there were two issues that needed to be addressed: iron accumulation and iron availability. Wild type rice contains a phosphate polymer, phytate, which efficiently binds free iron, rendering it unavailable for absorption by humans. The researchers were able to solve this problem by introducing a fungal phytase gene, which breaks down the compound. Two other genes were also introduced: a ferritin gene, which increased iron accumulation in the seed, and a gene encoding a metallothionein protein that aids iron absorption in the human digestive tract.

Once the two strains were established, a series of crosses were required to create the golden rice variety described at the meeting. It will still be several years before golden rice is available for planting by farmers, as it will take time to introduce the new traits into agronomic varieties. However, since none of the group's research was commercially funded, there will be no licensing issues to resolve before the seed can be distributed.

A Change in Focus for the Rockefeller

The work carried out by Dr. Potrykus' group, and also much of the work of the ISRG, has been supported, directly and indirectly, by the efforts of one institution, the Rockefeller Foundation of New York. For the past 15 years, the Rockefeller Foundation has supported the International Program on Rice Biotechnology, a funding initiative that sought to encourage the application of molecular biology to rice research and to develop top-level research facilities in Asian countries. The effort has been immensely successful, with its crowning achievement being the creation of golden rice. However, just when the program's investment really started to pay off, the Rockefeller Foundation decided to shift its agricultural funding focus to support research that will have a more

direct benefit to subsistence farmers⁴.

The Rockefeller's rice initiative was launched in the early 1980s in response to concern that rice would be left out of the revolution in molecular biology. Since then, the foundation has donated over 100 million dollars in support of basic research, development of facilities, and training of young scientists.

The change in the foundation's agricultural focus comes after the arrival in 1998 of a new president—agricultural economist Gordon Conway. Conway instigated an overhaul of the foundation's portfolio, which has led the foundation to change the goals of its support. However, the huge investment that the foundation has made in rice research will hardly pass away. With over 400 scientists trained through the program and the establishment of numerous research facilities, the impact of the Rockefeller program seems set to continue far into the future.

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Claire Granger
Carnegie Institution of Washington
Department of Plant Biology
alesia_sun@yahoo.com



TRANSGENIC TOBACCO REQUIRES LESS PHOSPHORUS FERTILIZER

Much of plant biotechnology R&D is driven by a need to minimize agricultural chemical applications. In addition to the financial advantages of reducing chemical usage, environmental protection groups worldwide and the growing sustainability movement are shunning current agricultural chemical application practices. Use of modern biotechnology



techniques has been reported to reduce chemical use in some cases by producing plants better able to resist pests, compete with weeds, and take up soil nutrients.

Phosphorus is difficult for plants to obtain because of its low solubility in soil water. In addition, much of the phosphorus applied to crops is lost through runoff and microbial uptake. Phosphorus binds to the aluminum, iron, and calcium ions present in most agricultural soils, making it insoluble and unavailable to the plants. This is especially true in acid and highly alkaline soils because of higher metal ion solubility.

Luis Herrera-Estrella and his research team estimate that 25% of agricultural land contains alkaline soils that prohibit adequate phosphorus uptake. K. G. Roghothama, of Purdue University, calculates that another 30% of the world's crops are grown in acid soils. Extremely acidic and alkaline soils are typical of developing nations^{1,2} and, although adjusting the pH levels to between pH 6 and pH 7.5 encourages better phosphorus uptake, the cost is usually prohibitive. The addition of large amounts of phosphate fertilizers is also expensive, as well as environmentally unsound; consequently, decreased crop yields often must be tolerated in developing nations².

Herrera-Estrella and his team have engineered a tobacco plant that promotes phosphorus uptake in both acid soils and soils high in metals using a technique that could prove economical for developing countries. They exploited the fact that soil organic acids assist roots with phosphorus uptake. Studies conducted by Gardner, Bounty, and others have also indicated that some plants facilitate phosphorus uptake by secreting organic acids into the rhizosphere. Although the secretions are restricted to a zone of soil immediately around the roots, the organic acids may improve phosphorus availability in soil conditions favoring phosphorus loss³.

Alan Richardson and Peter Hocking, of the Commonwealth Scientific and Industrial Research Organization in Australia, believe that organic acids separate bound phosphorus from clay and metals, making it available for plant uptake. In 1988, they reported in a press release that citrate naturally secreted by lupines facilitated phosphorus uptake. (See <http://www.pi.csiro.au/Media/MediaReleases/MR19-02-98.htm>) Phosphorus uptake was also correlated with the uptake of calcium, potassium, and nitrate³.

Drawing on this information, Herrera-Estrella's team engineered a plant capable of over-secreting citric acid in hopes it would enhance phosphorus uptake. They selected tobacco because it does not normally secrete citrate from

the roots, making it simple to quantitate yield improvement from enhanced phosphorus utilization.

The team used *Agrobacterium*-mediated transformation to introduce a *Pseudomonas aeruginosa* citrate synthase gene into tobacco cell cultures. Citrate production was under control of a 35S CaMV promoter. They developed two lines of citrate-overproducing tobacco using this system: CSb-4 and CSb-18, which secrete, respectively, two and four times the level of citrate of transgenic control plants lacking the citrate synthase gene.

Citrate synthase is predominantly expressed in the mitochondria. Herrera-Estrella's group introduced and successfully expressed plasmids carrying the citrate synthase gene in the cytoplasm. Cytoplasmic expression of the gene permits its export from the cell and prevents it from being converted into Krebs cycle intermediates in the mitochondria. Their initial experiments entailed growing plants in naturally alkaline soils with low phosphorus levels. Plant life-cycle completion was evaluated by measuring monosodium phosphate assimilation. The CSb-4 and CSb-18 lines completed their life cycles while the control plants failed to achieve anthesis. Phosphorus accumulation in the plant tissues was also evaluated and correlated with life-cycle analyses.

Differences in shoot and fruit dry biomass were then analyzed under low to high phosphorus conditions (22, 44, and 108 ppm). Other soil conditions were kept optimal. No significant differences in shoot biomass were seen between the CSb and control plants in the 22 and 44 ppm phosphorus groups until the plants reached anthesis. Fruit biomass was significantly greater for the CSb-18 plants under the 22 and 44 ppm phosphorus conditions due to an increase in the number of seeds and individual seed size. Plants grown under 108 ppm phosphorus conditions showed no significant differences in shoot and fruit growth.

Mycorrhizal relationships are also known to enhance fertilizer availability in many plants. Herrera-Estrella's group tested phosphorus uptake by the plants grown in the presence of the mycorrhizal fungus *Glomus fasciculatum*. Again, they showed that the CSb lines were better than the control at capturing phosphorus.

Herrera-Estrella's findings indicate the possibility of reducing supplemental phosphorus applications for crop production. However, further investigations are needed before applying this procedure in the field. Cost effectiveness studies must be evaluated separately on fruit, leaf, and root crops, as well as effects of citrate overproduction on crop

taste and appearance. Studies also need to be conducted on the influence of other organic acids on phosphorus uptake. Herrera-Estrella's study does not address phosphorus uptake under acid soil conditions, a significant problem for many agricultural areas.

The group is currently investigating citrate overproduction to improve phosphorus uptake in corn and rice. These two crops have large phosphorus requirements and are responsible for significant phosphorus depletion from farm lands. Perhaps using transgenic citrate-overproducing plants, these crops will one day be better able to use natural phosphorus soil reserves and require smaller applications of fertilizer.

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Brian R. Shmaefsky
Department of Biology and Environmental Sciences
Kingwood College
bshmaefs@nhmccd.edu

ANIMAL RESEARCH

CLONING REVERSES CELLULAR SENESCENCE

One of the important issues facing cloning technology is whether animals that are cloned by the transfer of nuclei from aging somatic cells will prematurely age. Normally, somatic cells undergo only a finite number of cell divisions in culture until the culture reaches senescence and dies. One question that needs to be addressed is whether the properties of senescent cells will be retained in cloned animals generated from late-passage somatic cells or not. In the April 28 issue of *Science*, Lanza and coworkers investigated this question by analyzing six cloned calves derived from the transfer of nuclei from senescent somatic

cells. A somatic cell line was established from a 45-day old female bovine fetus. These cells were cultured until greater than 95% of their life-span was completed and the cells displayed typical characteristics of senescent cells. These senescent cells were subsequently used as nuclear donors. From a total of 1896 bovine blastocysts reconstructed with these senescent cells, six calves were delivered by caesarean section.

Dermal fibroblasts isolated from these cloned animals were analyzed for a biochemical marker of non-senescent cells called EPC-1 (early population doubling level cDNA-1). The RNA levels of EPC-1 were higher in dermal fibroblasts isolated from cloned animals compared to dermal cells from age-matched controls. These results suggest that fibroblasts derived from cloned animals show a biochemical property not of the donor cells but of non-senescent cells. Thus cloning was able to reprogram nuclei to a "young" state.

To verify these findings, an assay measuring the number of population doublings until senescence was used to compare fibroblasts from cloned and control animals. Dermal fibroblasts were obtained from adult Holstein steers and grown in culture. When the fibroblasts were near senescence, nuclear transfer was performed to generate cloned fetuses. At six-weeks of gestation, cloned fetuses were removed and fetal fibroblasts were isolated and cultured until senescence. Cells isolated from cloned fetuses underwent an average of 93 population doublings in culture as compared to 61 population doublings for cells isolated from control six-week fetuses. These results indicate that nuclear cloning is capable of extending the life span of somatic cells.

As a final test, the lengths of the telomeres, which are the ends of chromosomes, were measured and compared in the cloned calves and age-matched controls. The telomere hypothesis of aging proposes that telomeres shorten as cells age. Consistent with this hypothesis, normal cattle showed a shortening of telomere length with age. However, telomere lengths in the cloned animals were elongated relative to age-matched controls and even newborn calves. Thus, cloning likely reactivated telomerase activity in these cells, resulting in a lengthening of telomeres.

This result contrasts with a previous report that evaluated the telomere lengths in Dolly, the first cloned sheep. In the case of Dolly, her telomeres were shorter than age-matched controls and more closely reflected the telomere lengths of the nuclear donor cells. Currently, the reason for the differences between measured telomere lengths in cloned sheep and cattle is not clear. It could be due to



differences in species or donor cell types used (mammary for sheep versus fibroblasts for cattle).

The ability of nuclear transfer to reprogram nuclei from a senescent state to a phenotypically youthful state is an important finding. This should begin to alleviate the concerns that the transfer of nuclei from adult animals will generate prematurely aged animals.

Source

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Eric A. Wong
Department of Animal and Poultry Sciences
Virginia Tech
ewong@vt.edu

REGULATORY NEWS

ADMINISTRATION ANNOUNCES SWEEPING ASSESSMENT OF FEDERAL AGRICULTURAL AND FOOD BIOTECH REGULATIONS

On May 3, the Clinton Administration announced a broad-ranging assessment of Federal environmental and food safety regulations regarding agricultural biotechnology¹. The intent of the assessment is to strengthen the scientific basis for regulations and to improve consumer access to information on food products. A number of agencies were directed to strengthen existing regulatory roles or to assume new roles.

The Council on Environmental Quality (CEQ) and the Office of Science and Technology Policy (OSTP) will conduct a six-month inter-agency assessment of Federal environmental regulations concerning agricultural biotechnology. Focusing on domestic environmental issues, CEQ and OSTP will approach the assessment by preparing case studies to identify strengths, weaknesses, and potential areas of improvement in the existing regulatory structures.

The Food and Drug Administration (FDA) will propose a rule to ensure that it is informed at least 120 days before genetically modified crops, food products, or animal feeds are introduced into the market². FDA will require submission of specific information to support determination of whether the item poses food safety, labeling, or adulteration issues. The new rule would replace the current voluntary practice of

consulting with the agency. The rule will propose that, consistent with applicable disclosure laws, the information submitted and FDA's decision will be posted on the agency's Web site. FDA also will develop guidelines for voluntary labeling of foods as containing or not containing genetically modified ingredients. To support these efforts, FDA will add scientists with agricultural biotechnology expertise to its food and veterinary medicine advisory committees.

The US Department of Agriculture (USDA) will work with farmers and industry to develop reliable testing procedures and quality assurance programs for differentiating genetically modified from unmodified commodities. Working closely with the State Department, USDA will inform farmers of domestic and overseas market information to assist in their planting decisions and provide information on the best practices for producing genetically modified varieties.

The USDA, FDA, and the Environmental Protection Agency will support an expanded program of competitive grants focusing on biosafety issues. USDA was specifically directed to support risk assessment research under its Initiative for Future Agriculture and Food Systems program.

The USDA, FDA, and the State Department will initiate domestic and international public education and outreach programs to communicate how genetically modified foods are regulated in the United States and how the regulations protect human health and the environment.

Response to the new proposals was mixed³. Representatives of food-producing and marketing industries were generally supportive of the increased Federal role, when previously they had opposed it. Critics faulted key aspects of the proposed policy changes, for example, the voluntary approach to labeling of foods as free of genetically modified ingredients, as opposed to mandatory labeling of foods containing them. Critics also pointed out that the administration could be out of office before new rules are finalized.

Ultimately, the key test of rule changes stemming from the policy review process will be whether consumers prove more willing to trust the safety and environmental sustainability of genetically modified products.

Sources

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*Eric M. Hallerman
Department of Fisheries and Wildlife Sciences
Virginia Tech
ehallerm@vt.edu*



T25 GM MAIZE: THE KERNEL OF UK BIOPOLITICS

The controversy over GM herbicide tolerant maize, namely T25 GM maize, has moved from Lord Melchett's Greenpeace raids on Norfolk fields to the corridors of power in Westminster, Cardiff, and beyond. The Ministry of Agriculture, Fisheries, and Food (MAFF) placed an advertisement in the March edition of *Plant Variety and Seeds Gazette* indicating their intention to place 'Chardon LL' (Liberty Link) on the UK's National Seed List. Placement on the National Seed List allows a GM variety to be sold commercially. This particular variety of T25 GM fodder maize is resistant to the herbicide glufosinate-ammonium (GA), the active ingredient in Liberty®, which is sold by Aventis (formerly AgrEvo). As fodder maize, it is likely that 'Chardon LL' will be used primarily for silage.

GA has been used internationally since 1984 as a successful non-selective foliar herbicide marketed under the commercial names Basta®, Ignite®, Finale®, and Challenge®. GA blocks glutamine synthase, the only enzyme that detoxifies ammonium in plants, causing death.

The GA herbicide can be detoxified enzymatically. A gene that codes for the phosphinothricin acetyl transferase (PAT) enzyme was isolated from the same bacterium, *Streptomyces viridochromogenes*, in which glufosinate was discovered. When the PAT gene is introduced into a plant, it produces an enzyme that inactivates the GA molecule via an acetylation reaction, thereby making the plant glufosinate resistant. The transformation construct that contains PAT gene also contains the CaMV 35S promoter and an antibiotic resistant marker gene.

The biopolitical problems with T25 GM maize have been twofold. First, at the EU level there has been a breakdown of the Council Directive (90/220/EEC) of April 23, 1990 on

the deliberate release into the environment of genetically modified organisms in relation to T25 maize. This is because Austria refused to allow trials, even though the EU had finally approved T25 GM maize in 1998 after a two-year delay. In December 1999, the Italian Government suspended T25 maize (along with six other GM products) following opinions from the Italian Health Institute and the Health Council. Furthermore, the Swiss Federal Bureau for the Environment, Forests and Landscape has also banned the T25 maize stating, "harmlessness to humans and the environment has not been adequately proven and the risk cannot be sufficiently reduced by taking technical measures."

Originally, when Aventis applied through France for EU marketing approval in 1996, the UK government told the European Commission that it had no objection to placing T25 on the European market. Most member states voted in favor of marketing consent in 1997, except for France, which followed in 1998 after a national debate on GM crops. The fact that Directive 90/220 is currently under repeal, and only recently moved past the EU co-decision procedure's second stage reading at the EU parliament, allows those opposed to the marketing of T25 to argue for a freeze in its marketing process. Interestingly, many of the new changes to Directive 90/220 have been proposed by the UK-based Labour MEP, David Bowe.

Second, on March 1, Environment Minister Michael Meacher wrote to all English MPs, outlining the new environmental assessment tests aimed specifically for herbicide tolerant GM crops under a program of farm scale trials. With this in mind, the moves by MAFF to place 'Chardon LL' on the Seed List has caused yet more controversy.

A further twist occurred when the Welsh Agriculture Secretary Christine Gwyther recently approved use of the T25 GM maize seed in the UK. In a statement, Ms. Gwyther said she had given her approval to include the seed in the UK National Seed List despite her earlier support for a GM-free Wales. She stated, "I have concluded that the only reasonable, legal way forward is for the application to be approved." This opinion reverses a previous statement in which Ms. Gwyther said, "I certainly have problems with GM in that I think to have a GM-free Wales would be such a wonderful marketing opportunity for Welsh produce, and I've always made that quite clear." The move also went against the wishes of the Assembly's agriculture committee, which had earlier urged her to vote against the listing because, as a whole, it had previously said it too prefers that Wales be a GM-free zone. The Welsh assembly continued on its collision course with



Westminster (UK's Parliament) when on Wednesday, May 24th members in Cardiff unanimously voted to ban GM crops in Wales (54-0 ballot). The issue of GM crops has allowed the new Welsh assembly to define its independence in a dramatic manner by clashing publicly with Britain's Government. As a result, it has now pushed GM technology into the political arena where more often than not, under such biopolitical conditions, scientific fact can be the first fatality. The implications for biotechnology policy and the resulting biotechnology regulatory affairs boils down to the fact that GM technology has become political. However, it is important to note, as the Irish American politician Tip O'Neill once famously stated, "All politics is local." The current debacle in the UK between the Welsh assembly members and their Westminster counterparts is a case in point of how such local biopolitical forces can operate.

Shane Morris
Dept. of Chemical and Environmental Sciences
University of Limerick
Shane.Morris@ul.ie

UPCOMING MEETINGS

More meetings can be found at: <http://www.isb.vt.edu>

3RD INTERNATIONAL CONFERENCE ON TRANSGENIC ANIMALS (ICTA)

Oct. 16-21, 2000
Beijing, China

Topics include:

- Transgene Expression in Animals
- Transgene Expression in Plants
- Transgenic Disease Models
- Alternative Transgenic Models
- Transgenic Transplantation Models
- Transgenic Safety
- Transgenic Techniques
- Transgenic Bioinformatics
- Gene Targeting and Knockout
- Manipulation of ES Cells and Embryos

Contact:

BILONG Transgenics

Tel: 86-10-6256-0561, 800-810-0797

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Email: info@bilong.com

<http://www.hum-molgen.de/meetings/meetings/0853.html>

FOURTH INTERNATIONAL RICE GENETICS SYMPOSIUM

October 22-27, 2000
Makati City, Philippines

Participants of the Symposium will discuss the latest developments in rice molecular biology, systematics and evolution, cytogenetics, classical genetics, tissue and cell culture, genetic engineering, and genomics. Discussions will lead to a better understanding of the genetic architecture of traits and their manipulation, modification of gene expression, genome sequencing, functional genomics, and gene discovery.

Contact:

Gurdev Khush

Email: g.khush@cgiar.org

<http://www.cgiar.org/irri/RGS.htm>

AGBIOTECH 2000: INNOVATION IN ASIA

November 15-18, 2000
Singapore

Offered by Nature Biotechnology and the Institute of Molecular Agrobiolgy, this conference will offer the opportunity to explore the potential of the new molecular technologies for improving the nutritive value of food, creating more productive and environmentally friendly crops, and engineering plants to produce valuable products like plastics and pharmaceuticals. The conference will also provide an opportunity to discuss the business infrastructure of the agbiotech sector and the challenges of bringing products from the research laboratory to the marketplace.

Contact:

The Secretariat

Tel: +(65) 299-8992

Fax: +(65) 299-8983

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**ISB News Report
120 Engel Hall
Virginia Tech
Blacksburg, VA 24061**