Stepping Back
How can we improve regulatory reviews to promote innovative and safe uses of genetically modified trees?

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Goals for today

• Rationale for change
  • Urgent need and context for genetic innovation
  • Impressive record of research accomplishment from field studies of GE trees
  • Severe constraints to research and breeding from preclusion of gene flow

• Regulatory revisions
  • Exemptions of the familiar and similar
  • Tolerances for gene flow and management

• Stepping back
Billions are struggling now, and it’s a very scary future – agriculture and forestry of all kinds will become much more difficult.
No-analog communities (communities that are compositionally unlike any found today) occurred frequently in the past and will develop in the greenhouse world of the future.

How do you study an ecosystem no ecologist has ever seen? This is a problem for both paleoecologists and global-change ecologists, who seek to understand ecological past or future, is heavily conditioned by our current observations and personal experience. The further our explorations carry us from the present.
Constraints to breeding with trees are great – GE methods offer very significant additional tools

**Constraints include**

- Difficulty to inbreed / introgress new genes
- Long breeding cycle
- Common use of asexually propagated varieties of high value
GE proven to be of diverse value for forest trees
All demonstrated in the field

- Resistance to insects and diseases
- Tolerance to salinity and temperature stress
- Phytoremediation of environmental toxins
- Modified properties to improve processing for biofuels or pulp
- Tolerance to herbicides to reduce the environmental impacts, improve efficiency, or reduce costs of weed control treatments
GE proven to be of diverse value for trees
All demonstrated in the field

- Accelerated flowering for faster breeding and research
- Fertility control for reduced spread and improved growth rate
- Synthesis of new, renewable bioproducts
Yet there is hardly a trickle of commercial GE tree products compared to its scientific potential – why?

Social / market and regulatory barriers are great
Global admixture of GM and non-GM crops/food create immense coexistence, trade problems under current regulations

Many costly cases of trade disruption and lawsuits with corn, soy, and rice – billions in lost value

Oregon GMO “wheat-gate” shows the huge risk in doing research

An agreed safe, well studied, extremely rare GMO left over from earlier research nearly crippled Pacific Northwest trade in wheat, led to lawsuits.
The problem much worse for most trees
Field studies essential for complex trits

The case of the magic lignin-reduced trees

- Nature Biotechnology 1999 – antisense 4CL genes generated much excitement
- Increase of growth rate, halving of lignin content, no obvious ill effects in greenhouse
Its totally different in the field
The core problem: Presumption of harm from GE method during research and breeding

- All gene flow must be prevented during research
  - But movement from mature trees will occur due to incomplete domestication, wild and feral relatives, wide pollen and often seed movement

- Impedes or prevents stress resistance and other complex trait development
  - Require extensive field trials, through to tree maturity, to test many concepts and insertion events

- Increasingly an anachronism in the era of precision breeding, cisgenics, intragenetics
An additional issue: Event-specific decisions and costs

- Slowness/difficulty of introgression – essentially unused in forestry
- Need diverse genes and genotypes transformed during breeding program
- Small economic benefits to pay back regulatory costs from single events
- Gene flow and AP/LLP a nightmare during research and breeding with many genes, genotypes, and events
A serious regulatory problem under USA system

Far-reaching Deleterious Impacts of Regulations on Research and Environmental Studies of Recombinant DNA-modified Perennial Biofuel Crops in the United States

STEVEN H. STRAUSS, DREW L. KERSHEN, JOE H. BOUTON, THOMAS P. REDICK, HUIMIN TAN, AND ROGER A. SEDJO
International regulatory pressure in wrong direction due to Cartagena Pr.

Strangled at birth? Forest biotech and the Convention on Biological Diversity

Steven H Strauss, Huimin Tan, Wout Boerjan & Roger Sedjo

Against the Cartagena Protocol and widespread scientific support for a case-by-case approach to regulation, the Convention on Biological Diversity has become a platform for imposing broad restrictions on research and development of all types of transgenic trees.

The Convention on Biological Diversity (CBD) has become a major focus of activist groups that wish to ban field research and commercial development of all types of genetically modified (GM) trees. Recent efforts to influence CBD recommendations by such groups has led to the adoption of recommendations for increased regulatory stringency that are inconsistent with the views of most scientists and most of the major environmental organizations. We suggest that the increasingly stringent recommendations adopted by the CBD in recent years are impeding, and in many places may foreclose, much of the field research needed to develop useful and safe applications of A convention co-opted

Negotiated under the United Nations (UN) Environment Program, CBD was adopted in June 1992 and subsequently entered into force in December 1993. The CBD has been signed by 191 of the 192 members of the UN, making it one of the largest international treaties. The aim of the CBD is to promote the conservation and sustainable use of biodiversity, and the fair and equitable sharing of benefits from the use of genetic resources. Because transgenic organisms have the potential to affect biodiversity, special provisions of the CBD cover the use and trade in living modified organisms (LMOs, also known as genetically modified organisms; GMOs).

In 2000, the Cartagena Protocol on Biosafety entered the CBD
An example of the perverse risks of method-based regulation: “Catkin-gate”
The strange case of the upright summer catkin
Regulatory confusion, obstacles at national and international levels

The Phantom Forest: Research on Gene-Altered Trees Leaps Ahead, into a Regulatory Limbo

STEVE NASH

At an industrial park in Walnut Creek, California, technicians and robots are sorting through the 550 million base pairs of genetic code in poplar DNA to sequence a tree genome for the first time.

They are poised to unlock a fine, full toolbox for the work of genetic engineering in trees.

In Vermont, a group called Action for Social and Ecological Justice has just kicked off a national campaign to pressure companies to ban research on genetically engineered (GE) trees. The Sierra Club, the World Wildlife Fund, and the American Lands Alliance, among others, have called for a moratorium on commercialization of GE trees.

In Washington, a federal agency with key responsibility for judging the biological safety of GE trees is preparing its response for Congress to a report by the

More than 200 notices of field trials have been filed with federal regulators for lab-engineered fruit, nut, and forest trees—also known as genetically modified, biotech, or transgenic trees. But aside from a virus-resistant, bushlike papaya tree grown in Hawaii, no one has yet sought regulatory approval for commercial use of a gene-altered tree.

"Maybe soon," said codirector of the group at North Carolina State. "Like others in the industry, we feel little certain.

Westvaco Corporation, and two New Zealand firms. Arborgen estimates that, if tests go very well, the product could be ready for the market in a decade.

Cloned cathedrals
Tinkering with tree DNA presents some issues for research and for public policy, however. Casting an uncertain light over

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Lignin-modified trees

Concept proven, but much refinement needed

Type of gene, promoters, extent of modification, environment, stand management, genotype modified

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**Improved saccharification and ethanol yield from field-grown transgenic poplar deficient in cinnamyl-CoA reductase**

Rebecca Van Acker, Jean-Charles Legrel, Dirk Aert, Véronique Storme, Geert Goossens, Bart Ineens, Frédéric Legue, Catherine Lapierre, Kathleen Piens, Marc C.E. Van Montagu, Nicholas Santoro, Clifton E. Foster, John Ralph, Wim Sleutels, Gilles Pilate, and Wout Boerjan

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Contributed by Marc C. E. Van Montagu, November 28, 2013; reviewed March 24, 2014

Lignin is one of the main factors determining recalcitrance to enzymatic processing of lignocellulosic biomass. Poplars (Populus tremula $\times$ Populus alba) down-regulated for cinnamyl-CoA reductase (CCR), the enzyme catalyzing the first step in the monolignol-specific branch of the lignin biosynthetic pathway, were grown in field trials in Belgium and France under short-rotation coppice culture. Wood samples were classified according to the intensity of the red systol coloration typically associated with CCR down-regulation. Saccharification assays under different pretreatment conditions (saccharification and fermentation assays showed that wood from the most affected transgenic trees had up to 16% increased ethanol yield. Fermentations of combined material from the complete set of 20-mo-old CCR-down-regulated trees, including bark and less efficiently down-regulated trees, still yielded ~20% more ethanol on a weight basis. However, strong down-regulation of CCR also affected biomass yield. We conclude that CCR down-regulation may become a successful strategy to improve biomass processing if the variability in down-regulation and the yield penalty can be overcome.

Bioenergy [G1H, second-generation bioenergy]

**Global warming and the depletion of fossil fuels provide a major impulse for the increased interest in renewable energy sources. Liquid biofuels, bioethanol in particular, are currently produced from food crops. Enhanced energy crops will be needed.**

**Significance**

In the transition from a fossil-based to a bio-based economy, bioethanol will be generated from the lignocellulosic biomass.
Cold tolerant *Eucalyptus*

Concept proven, much refinement needed

*Type of gene, promoters, extent of modification, environment, stand age, genotype modified*

Provided by Arborgen
Forest pest epidemics increasing with travel and climate change

Regulations make timely use impossible

Examples

1892 - White pine blister rust
1904 - Chestnut blight
1923 - Port-Orford-cedar root disease
1920s - Beech scale complex
1930 - Dutch elm disease
1967 - Butternut canker
1976 - Dogwood anthracnose
2000s - Sudden oak death
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Proposed regulatory solutions – tiered regulation, product vs. process

Genomics, Genetic Engineering, and Domestication of Crops

Steven H. Strauss

Genomic sequencing projects are rapidly revealing the content and organization of crop genomes (1). By isolating a gene from its background and deliberately modifying its expression, genetic engineering allows the impacts of all genes on their biochemical networks and organismal phenotypes to be discerned, regardless of their level of natural polymorphism. This greatly increases the ability to determine gene function and, thus, to identify new options for crop domestication (2). The organismal functions of the large majority of genes in genomic databases are unknown. It is important to agricultural goals, but poorly represented in breeding populations because they are rare or deleterious to wild progenitors.

<table>
<thead>
<tr>
<th>Confinement level</th>
<th>Type 1 field trials (exploratory)</th>
<th>Type 2 field trials (precommercial)</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Biological and physical confinement—detailed data</td>
<td></td>
<td>Highly toxic or allergenic pharmaceuticals and proteins</td>
</tr>
<tr>
<td>Medium</td>
<td>FSC, basic data</td>
<td>FSC, detailed data</td>
<td>Novel pest-management genes, low toxicity pharmaceuticals and proteins</td>
</tr>
<tr>
<td>Stress tolerance</td>
<td>FSC, basic data</td>
<td>FSC, detailed data</td>
<td>Genomics-guided transgenics</td>
</tr>
<tr>
<td>Low Domesticating</td>
<td>Petition for exemption?</td>
<td>FSC, basic data</td>
<td></td>
</tr>
</tbody>
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Categories of confinement and monitoring for small- and large-scale transgenic field trials. Biological confinement includes genetic mechanisms to preclude spread and/or reproduction. Physical confinement requires use of geographical isolation or physical barriers. FSC, farm-scale confinement; use of spatial isolation within and between farms and border crops, combined with monitoring. Detailed data include surveys of gene flow away from the site. Basic data include assessment of confinement mechanisms.
Regulating transgenic crops sensibly: lessons from plant breeding, biotechnology and genomics

Kent J Bradford¹, Allen Van Deynze¹, Neal Gutterson², Wayne Parrott³ & Steven H Strauss⁴

The costs of meeting regulatory requirements and market restrictions guided by regulatory criteria are substantial impediments to the commercialization of transgenic crops. Although a cautious approach may have been prudent initially, we argue that some regulatory requirements can now be modified to reduce costs and uncertainty without compromising safety. Long-accepted plant breeding methods for incorporating new diversity into crop varieties, experience from two decades

Regulatory costs also play a role in the growing disparity between the expanding global adoption of the large-market transgenic maize, soybean, cotton and canola crops⁴ and the so-called ‘small-market’ or ‘specialty’ crops, for which field trials and commercial releases of transgenic food crops have all but stopped⁵. In 2003, fruits, vegetables, landscape plants and ornamental crops accounted for more than $50 billion in value in the United States, representing 47% of the total US farm crop income⁶. Of this, the only transgenic commodities currently mar-
Gene targeting, genome editing, coming along fast
= increased precision, safer than breeding

**PLANT BIOTECHNOLOGY**

**Zinc fingers on target**

Matthew H. Porteus

The existing methods of creating genetically modified plants are inefficient and imprecise. Zinc-finger technology offers the prospect of opening up a swifter and more exact route for crop improvement.

**CRISPRs**

**TALENs**
Suggested exemptions – a start

• Approved, familiar markers and gene transfer systems based on approvals in other crops
• Mutagenesis of transformation system
• Cisgenic (or functionally cisgenic) transfers from similar or closely related species (e.g., congeneric gene sources)
• Modification of expression of native genes and pathways (intragenic)
• Genome editing or mutagenesis
Suggested exemptions – a start

• Well understood products with urgent ecological or humanitarian value, and non-toxic
  • USA: Early consult with FDA re. low level admixture

• Gene dispersal into the environment and associated AP/LLP during research and breeding, or when crop-appropriate mitigation methods are employed

• Best management practices (BMPs) not zero-tolerance
Exemptions and lower tiers of regulation do not mean all GMOs unregulated

- Companies to choose regulatory reviews where desired, or with high novelty or risk
- Right of agencies to challenge based on trait novelty and scientific reviews
- Food safety, environmental benefit vs. hazard, trade hazards beyond newly set AP thresholds
- Presumptive value of innovation and safety, vs. presumption of harm due to method
  - Comparator is conventional breeding and plant domestication practices
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In summary

• Growing population, living standards, and climate change pose existential challenges to civilization, economics, and livelihoods everywhere
• Ecosystems in the near future (one or a few tree generations) will change radically
• Breeding and genetics are not panaceas, but are powerful tools to help manage these threats
In summary

• GE has proven itself a very powerful new genetic tool for both crops and trees

• Demand precaution, not the precautionary principle
  • We need all major tools if we are to be able to cope with a frightening future

• Develop and use GE methods based on product familiarity, benefits, and safety
  • Not based on the method or unworkable method-based AP/LLP rules
Voltaire was right….

The perfect is the enemy of the good