CleanTech Meets BioTech

August 25, 2009
Stanford University School of Medicine
Agenda

• What is the Cleantech Industry?
• How did I become involved in the Cleantech Industry?
• Cleantech and Biotech
• Mendel Biotechnology
What is the Cleantech Industry?

- New technology and related business models that offer competitive returns for investors and customers while providing solutions to global challenges.
- Cleantech addresses the roots of ecological problems with new science, emphasizing natural approaches such as biomimicry and biology.
- Cleantech is driven by productivity-based purchasing, and therefore enjoys broader market economics, with greater financial upside and sustainability.
The Cleantech Industry Includes

• Biofuels
• Green Marketing & Advertising
• Biological Solutions
• Renewable Energy
• Carbon Markets and Trading
• Solar Energy
• Carbon Tracking and Sequestration
• Sustainable Green Programs
The Cleantech Industry Also Includes

• Clean Conventional Energy
• Sustainable Organic
• Energy Efficiency
• Waste Reduction
• Energy Intelligence
• Water Technology
• Fuel Cells and Batteries
• Green Building
My Involvement with Cleantech Industry

• Academic background:
  • Ph.D. in Biochemistry
  • Post-Doc in Molecular Biology at the Harvard Medical School.
  • Looking for an academic job.

• Sound familiar??
Sample Life Science Work

- Novartis
- XDX (Stanford Spin Out)
- Aviir (Stanford Spin Out)
- Calistoga
- Macusight
- Aviir
- UC Berkeley
Cleantech and Biotech

• Energy Biosciences Inc.
• Catchlight Energy Inc.
• Mendel Biotechnology
Cleantech and Biotech

- Energy Biosciences Inc.
- Catchlight Energy Inc.
- Mendel Biotechnology
seeding a sustainable future

Mendel Biotechnology: Biotech to Cleantech

Greg Ikonen
August 25, 2009
Mendel Overview

- Founded April 1997 by 5 renowned plant scientists
- 105 employees
- Major partnerships with Monsanto and BP
- Diverse investor base, including Monsanto, BP and ZAM Ventures as key shareholders
- Extensive IP portfolio covering key regulators of plant genetic pathways
- Building a BioEnergy Seed business for the biofuels and renewable power markets
Mendel’s Trait Business
Mendel was Founded Based on the Power of Transcription Factors

TFs are Master Regulators

Floral symmetry

CYCLOIDEA-related proteins
Luo et al., 1996, Nature 383

Branching pattern

Doebley et al., 1997, Nature 386

Flowering time

CONSTANS Putterill et al., 1995, Cell 80

Trait of Interest
(abiotic, biotic stress tolerance, altered morphology or development)
Screens on Transcription Factors Have Produced Hundreds of Leads

Developmental Traits...
- Branching pattern
- Seed size
- Wild type
- OEX line

Biochemical Traits...
- Glucosinolate composition
- Wild type
- OEX line

Physiological Traits...
- Root vigor
- Wild type
- OEX line
- Flowering time
- N-use
- Wild type
- OEX line
- Drought tolerance
- Wild type
- OEX line
- Disease resistance
- Wild type
- OEX line
Typical Ag Biotech Product Development Process

Typical development timeline & costs: 10 -15 years, $50M – $100M

**Discovery -> Validation**
- High throughput screening; lead validation in model crops.

**Phase I - Crop proof of concept**
- Test gene leads in crop plants; select best candidates.

**Phase II - Early Product Development**
- Field testing in crop Plants. Regulatory assessment started.

**Phase III - Advanced Development**
- Field testing in elite germplasm. Develop Regulatory data.

**Phase IV - Regulatory Approvals**
- Field testing in elite germplasm. Develop Regulatory data.

**Market Launch**

**Mode of Action analysis:**
- define phenotypic basis of the trait
- identify optimization strategies
- the genetic tools in Arabidopsis make it a valuable model

**MOA work supports product development**

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**partners proteins?**

**Trait of Interest**
(abiotic, biotic stress tolerance, altered morphology or development)
Two general trait categories are of high priority

**Intrinsic yield** e.g.
- photosynthetic performance
- enhanced growth and vigor

**Yield stability** (stress tolerance)
- drought tolerance/water use efficiency
  - cold/freezing tolerance
  - N utilization
  - disease tolerance

For recent review see: Century et al., 2008, *Plant Physiology* 147, 20-29
Learning from corn – a recent example of a Mendel biotech trait for yield stability

Plant nuclear factor Y (NF-Y) B subunits confer drought tolerance and lead to improved corn yields on water-limited acres

Donald E. Nelson‡, Peter P. Repetti‡, Tom R. Adams‡, Robert A. Creelman‡, Jingrui Wu*, David C. Warner†, Don C. Anstrom‡, Robert J. Bansen‡, Paolo P. Castiglioni‡, Meghan G. Donnarumma‡, Brendan S. Hinche‡, Roderick W. Kumimoto‡, Don R. Maszlo†, Roger D. Canales‡, Katherine A. Krolkowski‡, Stanton B. Dots Neal Gutterson*, Oliver J. Ratcliffe*, and Jacqueline E. Heard*‡

*Monsanto Company, 62 Maritime Drive, Mystic, CT 06355; and ‡Mendel Biotechnology, Inc., 21375 Cabot Boulevard, Hayward, CA 94545
Communicated by Maarten J. Chrispeels, University of California at San Diego, La Jolla, CA, August 29, 2007 (received for review December 10, 2007)

Commercially improved crop performance under drought conditions has been challenging because of the complexity of the trait and the multitude of factors that influence yield. Here we report the recent release of a transgenic maize line expressing two nuclear factor Y subunits (AtNF-YB1 and AtNF-YB2). These proteins that belong to the AP2/ethylene-responsive binding protein family (11, 12). These factors enhance the expression of genes with a CBF/DRE box in their promoters, which are involved in ABA biosynthesis and response pathways. These plants have improved drought tolerance, and transgenic maize plants expressing ZmNF-YB2 are in the right flat or row. Fig. 1. Constitutive expression of AtNF-YB1 confers drought tolerance in Arabidopsis. Representative pots of transgenic plants (Left) and controls (Right) are shown at the end of a dry-down period (Upper) and at 5 days after rewatering (Lower).

Fig. 5. Transgenic maize plants in greenhouse and field have visibly observable improved drought tolerance. In both photographs, controls in the left flat or row, and transgenics expressing ZmNF-YB2 are in the right flat or row.
Mendel’s BioEnergy Seeds Business
Federal mandates for biofuels were increased late 2007.
Domestic biomass demand

Domestic demand for biomass
Millions of dry tons per year

Liquid biofuels  Power Generation (RPS 15)  Power Generation (RPS 25)
Yield drives cost of feedstock and land required for planting of energy crops

- Increasing yield from 6 to 12 DT/acre reduces the cost by ~40% and acreage required by 50%
- To compete with cheap feedstock such as wood and agricultural waste ($45-$55 delivered), energy crops need to reach yields of 10+ DT/acre

* Delivered at refiner’s gate, Southern Illinois

* Preliminary*
Optimal Cellulosic Feedstock Crops

- High Yield (>15 tons/acre/year)
  - ~ 20% of 25 mi radius = 300M gal/year
- Low Input (fertilizer, water, tillage, pesticides)
- High conversion efficiency
- Stable quality from year to year
- Satisfies sustainability demands

\[ Miscanthus \times giganteus \]
\[ Zea mays \]
\[ Spartina cynosuroides \]
Miscanthus is a premier perennial grass

- Switchgrass is a commonly studied, model perennial grass native to North America
- Miscanthus, originally from East Asia, is a popular perennial crop used for energy and pulp production but also as an ornamental
- Little effort so far to improve Miscanthus performance – opportunity for rapid gain from technology effort

<table>
<thead>
<tr>
<th>Region</th>
<th>Miscanthus</th>
<th>Switchgrass</th>
</tr>
</thead>
<tbody>
<tr>
<td>North Illinois</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Central Illinois</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>South Illinois</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>Average</td>
<td><strong>13</strong></td>
<td><strong>5</strong></td>
</tr>
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* Miscanthus and Switchgrass Trials in Illinois; Frank G. Dohleman, Emily A. Heaton, Stephen P. Long, courtesy of the authors
** Assuming 16GJ or 15.2 MMBTU per short ton of dry matter (15% moisture content)
Learning from corn - yield progress

- Mass selection for large ears did not increase yield.
- Actual Breeding plus Cultural Practice Gain
- Heterosis & replicated testing

Graph showing the trend of average corn yields (kg/ha) from 1865 to 2005, with different lines for open pollinated, single cross, double cross, and biotech GMO, each with a slope indicating the rate of increase.
Biotech in Energy Crops

Key lessons from current ag biotech industry

- Biotechnology/genomics provides a platform for improved core genetics and new biotech traits

Current molecular biology tools can dramatically accelerate energy crop domestication

- Efficient development of dense genetic maps
- Efficient, cost-effective development of informative markers for key traits
- Deployment of biotech traits used in today’s crops in tomorrow’s biofuel crops
Mendel
BIOTECHNOLOGY

seeding a sustainable future