Challenges and opportunities for harmonization of regulatory animal Biotechnology

The most <u>diverse</u> and <u>controversial</u> is Biotechnology the most difficult will be the harmonization of the regulatory arena



Source: Fraley (1994)

**BIOTECHNOLOGY STARTED EARLY IN** THE SEVENTIES AND IT IS STILL VERY **CONTROVERSIAL ALTHOUGH** ANIMAL BIOTECHNOLOGY IS NOT YET A MAJOR PLAYER IN THE FIELD

## CHALLENGES OF BIOTECHNOLOGY

## DISTORTED PUBLIC PERCEPTION WHICH RESULTS FROM THE STILL CONTROVERSIAL BIOTECHNOLOGY CONTEXT

Legislations in Brazil came late during the 90s :

# Patents, Biosafety, Variety Protection, Biodiversity, Animal Pre Clinical Law .

Some of these legislations were for a long time under judicial dispute (Biosafety) or are not being properly inforced (Biodiversity) This results from campaigns stimulated by NGOs like Greenpeace, Action Aid e ASPTA, extremely well articulated in all sectors : Judiciary, Legislative, Executive which often support these campaigns like the Ministry of Environment or simply do not react when the Laws are not respected. Example : Institute Royal the only institution competent to do preclinical tests with animals was invaded recently, 200 beagles were stolen : <u>NOTHING HAPPENED</u>

Important "Contributions" for distorted public perception in Brazil

### MAJOR ACTOR

The Judge Prudent single handed with one sentence decreted seven years without transgenics in Brazil. In 1998 he said literally in his sentence:

"Genetic Engineering utilizes alien genes, from which a strange civilization will result with snake faces that will compromise definitivelly, in real terms the survival of future generations in our planet".



The <u>HORROR</u> of Genetically Engineered Food

# Frencery Store

You Can't Avoid It Because It's NOT LABELED!

GREENPEACE

From the LABS of Monsanto to YOUR TABLE! A NEW LIFE FORM Released into the World!

# **GLOBAL REASONS**

# BIOTECHNOLOGY WILL DESTROY THE BRAZILIAN BIODIVERSITY

#### **Deforestation Figures for Brazil**

Year	Deforestation [sq mi]	Deforestation Change	
		[sq km]	[%]
1988	8,127	21,050	
1989	6,861	17,770	-16%
1990	5,301	13,730	-23%
1991	4,259	11,030	-20%
1992	5,323	13,786	25%
1993	5,751	14,896	8%
1994	5,751	14,896	0%
1995	11,220	29,059	95%
1996	7,012	18,161	-38%
1997	5,107	13,227	-27%
1998	6,712	17,383	31%
1999	6,664	17,259	-1%
2000	7,037	18,226	6%
2001	7,014	18,165	0%
2002	8,260	21,394	17%
2003	9,748	25,247	19%
2004	10,588	27,423	9%
2005	7,276	18,846	-31%
2006	5,447	14,109	-49%
2007	4,453	11,532	-47%
2008	4,621	11,968	-47%

All figures derived from official National Institute of Space Research (INPE) data.

#### Causes of Deforestation in the Amazon, 2000-2005



WHEN AS PRESIDENT OF THE NATIONAL BIOASAFETY COMMISSION I ANOUNCED THAT WE WERE GOING TO RELEASE THE RR SOYBEAN IN BRAZIL I RECEIVED FROM THE GREENPEACE:

**REST IN PEACE BIODIVERSITY** 

# SOCIAL REASONS

# BIOTECHNOLOGY IS NOT FOR THE POOR

### Child Development in the Brazilian Semi-arid

Child Mortality Rates are above the average in Northeast which is thirty % above brazilan average which has fallen substantially lately to close to thirty/1000.Still high

Over 50% of the children deathes ocurring before four years of age in the Northeast occur in the Semi Arid .

Only 35 % of the cities in the Semi Arid vaccinate children with DTP.

Almost 60 % of children deathes in the Northeast due to problems during pregnancy occur in the Semi-Arid



## POVERTY AND MALNUTRITION IN BRAZIL<sup>(\*)</sup>

Brazil: 21 million poor people considered as such , families which receive half of the minimum wage : 190 dollars

- Regional Concentration of Poverty in Brazil
  - 50% in the Northeast;
  - 26% in the South East;
  - 10% in the South;
  - 9% in the North; and
  - 5% in the Center West.

#### • Out of 100 poorest Counties in Brazil 78 are in the Northeast

- There are 4 million children up to six years of age living in the Semi- Arid, more than 17% of the equivalent brazilian population.
- (\*) Geografia da pobreza extrema e vulnerabilidade à fome. Sonia Rocha e Roberto Cavalcanti Albuquerque. INAE - Estudos e Pesquisas, nº. 54. Setembro, 2003.

### GENETIC ENGINEERING MUST DEMONSTRATE THAT CAN RESOLVE IMPORTANT SOCIAL PROBLEMS

### **Bioscience for a less hungry world**

It is imperative and urgent a global science based effort towards a <u>less</u> <u>hungry world</u> focussing on major constraints for agriculture development in the tropics , that can be <u>resolved</u> by the modern bioscience . We must focus on <u>plants resistant to drought</u>, <u>pests and to soil aluminum toxicity which</u> <u>affect more than half of tropical soils</u>. Grasses capable of fixing nitrogen from the air, to allow poor people to save the cost of oil derived urea which pollutes the soil and the water .

We in Brazil have the best genetics for the tropics .Gene sources are available- We can make the Gene Revolution to work in the same direction as the Green Revolution did decades ago with a difference . We have a much more powerful science in our hands.

# **OPPORTUNITIES FOR** HARMONIZATION OF REGULATORY ANIMAL BIOTECHNOLOGY MUST **CONSIDER THE** CHANGE OF PARADIGMS THAT WILL OCCUR IN A NEAR FUTURE

http://www.blogsnature.com/tradesecrets/author/lbarreto

## A potential change of paradigm Gene expression in the milk of "caprinos"

# rEVO BIOLOGICS

### **Biosimilars MAb Opportunity**

World-wide sales of biologics by patent expiration year







78,125 – 156,250 L Cell Culture Facility\* Mean CapEx = \$550M – \$1,100M (includes DSP) 1,500 Goat Milk Production Facility\* (Annual Output 3,750 – 7,500 Kg)

Cell Culture CapEx @ 35% = <u>\$200M - \$400M</u>

Actual Investment to date = <u>\$25M</u>

\* Assumes 2 g/L productivity

\* Based on actual productivity (5 g/L and 10g/L)

### Bioreactor

11

A BUL

180 Acres 2000 Goats

**Raw Materials** 

Personnel

Vehicles

Clinic Personnel

Hand?

-

4

Founder Production

Dairy

#### F.D.A. Approves Drug From Gene-Altered Goats



A goat at GTC Biotherapeutics' farm.

#### **B**ioengineering on the Farm

Egg

IMPLANTING THE DNA

The modified DNA is

injected into the nucleus

of a fertilized goat egg,

which is then implanted

into a female.

The Food and Drug Administration has approved the first drug produced in the milk of genetically engineered animals.



MODIFYING THE DNA A human gene that produces the blood protein antithrombin is inserted into a short strand of goat DNA.

Sources: GTC Biotherapeutics

The second secon

TESTING THE OFFSPRING Kids born from the modified eggs are tested for the presence of antithrombin in their milk. Promising kids are bred normally to create a herd of modified goats.



EXTRACTING THE PROTEIN Milk from the herd is filtered and purified. Annually, each goat can produce as much antithrombin as 90,000 human blood donations.



First transgenically-produced therapeutic protein used in humans First approval of a marketing authorization for a recombinant therapeutic protein made in transgenic animals (EU 2006, FDA 2009) Provided a recombinant form of Antithrombin that can be used EU and US

### Adalimumab

- Binds to TNFα preventing activation of TNF receptors
- Important in down regulating the inflammation associated with autoimmune diseases
- Third TNF inhibitor to be approved in US
  - after infliximab (Remicade) and etanercept (Enbrel)
- Abbott Labs Humira approved by FDA in 2002
  - #1 global biologics therapy: \$9.2B in 2012
- Generated transgenic goat lines in 2010
  Expression ~20 g/l



## Trastuzumab

- Humanized antibody that binds selectively to the HER2 protein
- Cancers usually develop resistance to trastuzumab
  - Combination of trastuzumab with chemotherapy has been shown to increase both survival and response rate
- Treatment cost up to \$100,000 per year
  - Sales: >\$6.4B in 2012.
- Transgenic production:
  - Transgenic goats:
    - 50 g/l
    - Equivalent binding to Her2
    - Equivalent ADCC
    - CDC under evaluation



#### Cetuximab



- Indicated for the treatment of Metastatic K-Ras wild-type Colorectal as well as for Head and Neck (squamous cell carcinoma) cancers.
- Typical treatment cost: ~\$80,000 (~\$10,000 per month)
  - Worldwide Sales: ~\$2 Billion in 2012
- Transgenic goats:
  - 10 g/l
  - Equivalent binding to EGFR
  - ADCC and CDC under evaluation
  - Transgenically-derived product is free of  $\alpha_{1-3}$  Gal residues which cause anaphylaxis observed with Erbitux



#### Camila e Tinho – First "caprinos" genetically modified in Latin America to express filgastrima GCSF in the milk of Camila



### <u>Granulocyte colony stimulating factor</u>, a citokinin that **boosts neutrophil counts**, can save patients of Melioidosis with sepsis Science vol 317 1024 2007



Globe-girdling threat. Although melioidosis is endemic to parts of Southeast Asia and northern Australia, cases have occurred on all continents except Antarctica.

## THE CHANGE OF PARADIGM IN CROP BIOTECHNOLOGY WILL CONTRIBUTE FOR THE <u>DIVERSITY</u> OF THE FIELD AND REQUIRE SPECIFIC LEGISLATIONS

### WHO BUILT AGRICULTURE IN BRAZIL ?

- Romeu Kihl Soybean
- Ady Raul da Siva Wheat
- Ernesto Paterniani e Ricardo Magnavaca Corn
- Alcides Carvalho Coffee
- Marcilio Dias e Flavio Couto Vegetables
- Silvio Moreira e Dalmo Giacommetti Citrus
- Clibas Vieira Beans
- Raul Moreira Banana
- Eleuzio Curvello Cotton

### IN THE WAKE OF THE DOUBLE HELI FROM THE GREEN REVOLUTION TO THE GENE REVOLUTION

#### BOLOGNA . May 27 to 31, 2003

#### SPEAKERS

P. Arús	D. Delmer	T. Helentjaris
L. B. de Castro	G. Ejeta	D. James
R. Beachy	N. Ellis	D. Kamanga
J. Bennett	D. Frisio	G. Khush
J. Bennetzen	M. Gale	A. Kilian
E. Benvenuto	C. Gessler	M. Koornneef
R. Bertram	J. Giovannoni	P. Langridge
N. Borlaug	G. Morelli Gradi	H. Le
S. Briggs	S. Grandillo	M. Maluszynski
W. Broekaert	S. Grando	S. Masini
R. Cantrell	A. Graner	S. Mayer
P. Christou	E. Guiderdoni	M. van Montagu
P. Cunningham	P. Gustafson	M. Morgante
P. De Castro	T. Hash	M. Motto

B.S. Ngubane M. Pages A. Paterson A. Pellegrineschi M. Pezzotti R. Phillips A. Piatti P. Pingali E. Porceddu I. Potrykus C. Qualset A. Rafalski G. Rizzioli M. Ronconi

F. Salamini S. Salvi G.T. Scarascia Mugnozza O. Smith M. Swaminathan M. Thomas F. Trifiletti A. Tsaftaris G. Valè K. Vandenberghe L. Vingiani M. Yano M. Zabeau R. Zeigler









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INTSORME



# FROM THE GREEN TO THE GENE REVOLUTION gene expression in plants

# Method to Silence Genes Earns Loud Praise

Over beer and coffee, in labs and at scientific conferences, the speculation has been intense for years: Who in the RNA interference (RNAi) field, biologists wondered, would win the Nobel Prize, and when? Science's ultimate accolade was considered increasingly inevitable as the gene-silencing method revolutionized genetics, spurred

development of new medical treatments, and transformed our understanding of cellular behavior. But, under Nobel rules, the prize can go to no more than three people. Yet many had made seminal contributions to the discovery and understanding of RNAi.

Early Monday morning, several years earlier than many expected, the guessing game came to an end. Two Americans—Craig Mello of the University of Massachusetts (UMass) Medical School in Worcester and Andrew Fire of Stanford University in Palo Alto, California—learned that they had won this year's \$1.37 million Nobel Prize in field, "I feel slightly guilty to be here," Phillip Zamore, who works with Mello at UMass, calls the award "one of the most well-deserved Nobel Prizes ever given." The *Nature* paper, Zamore notes, prompted him to leap into the RNAi field at the end of his postdoc 8 years ago, much as it inspired many other young researchers. Mello, he says, "is a scientist's scientist. ... He's seeking to a tions as div using the me shut down v Meanwhile, I test the funct erate animal RNAi to siler While RN



**Silence is golden.** Andrew Fire (*left*) and Craig Mello learned this week that they'd won the Nobel Prize for their groundbreaking discovery of RNAi's gene-quelling power.

Experimento com feijão transgênico resistente ao vírus do mosaico dourado (Embrapa, janeiro de 2008)



## THE BRAZILIAN AGRICULTURAL REVOLUTION IN THE XXI CENTURY-CHANGING PARADIGMS IN BIOTECHNOLOGY

### How Brazil will feed the world?

How the agricultural revolution will build a pharmaceutical industry in Brazil ? – Changing paradigms

## **GREEN VACCINES**

- Vaccine site for Medicago secures \$3.5M DARPA milestone
- Vaccine developer <u>Medicago</u> (<u>TSX:MDG</u>) has secured a <u>\$3.5 million milestone payment</u> from the federal government for progress on a vaccine manufacturing site intended to respond to pandemic threats.
- The milestone is the fourth Medicago has received from the <u>Defense Advanced Research Projects Agency, or</u> <u>DARPA</u>. Quebec, Canada-based Medicago has received \$19.8 million in milestones to date out of a potential \$21 million for the project. The company opened the 97,000-square-foot Research Triangle Park, North Carolina vaccine facility last fall.
- Medicago has developed proprietary technology that makes virus-like particles, or VLPs, from tobacco leaves. VLPs mimic the structure of a virus and prompt an immune response from the body. But because the particles are not the actual virus, they cannot infect people and they are unable to replicate.
- Medicago's RTP facility is seen as playing a role in quick responses to viral threats. The company's technology can develop a vaccine from tobacco leaves in about 30 days, considerably faster than the traditional method of incubating virus in chicken eggs, a roughly six-month process. DARPA was seeking scalable manufacturing capabilities for vaccines to respond to virus outbreaks, both natural and terrorism-related. DARPA's <u>Blue Angel project</u> has been seeking new ways to produce large amounts of influenza vaccine in under three months.
- Nature Bioentrepreneur | Trade Secrets
- MEDICAGO now belongs to MITSUBISHI PHARMA

#### ZMapp Ebola Treatment: What To Know About The Experimental Drug Made From Tobacco

By Treye Green@TreyeGreen t.green@ibtimes.com

on August 06 2014 2:34 PM

Dr. Kent Brantly and missionary Nancy Writebol are both recovering at Atlanta's Emory University Hospital in a special isolation unit. The pair were the first humans to receive doses of the experimental ZMapp Ebola treatment after they contracted the virus in Liberia. Reuters Two U.S. citizens infected with the Ebola virus while in Liberia were the first recipients of ZMapp, an experimental treatment created by Mapp Biopharmaceutical and LeafBio to help fight the sometimes-deadly virus. The patients, both aid workers, appear to be improving after receiving ZMapp, but questions remain about the drug, <u>created with tobacco plants</u>, which had previously been tested only on primates.

How Does The ZMapp Ebola Treatment Work?

Why paradigms are hard to change ?

Corporations are happy when they profit after the investments they make. They question is if they will perform well with new paradigms including nascent regulatory frameworks.

Harmonization require adopting new laws

## Laws are hard to build and to inforce

Are there harmonized laws for biosimilars ?

WE WILL HAVE TO HARMONIZE MAB **BIOSIMILARS PRODUCED BY CHO** CELLS WITH MAB BIOSIMILARS PRODUCED BY THE MILK OF MAMMALS WITH MAB BIOSIMILARS PRODUCED BY NICOTIANA