Intellectual Property Issues and Plant Biotechnology

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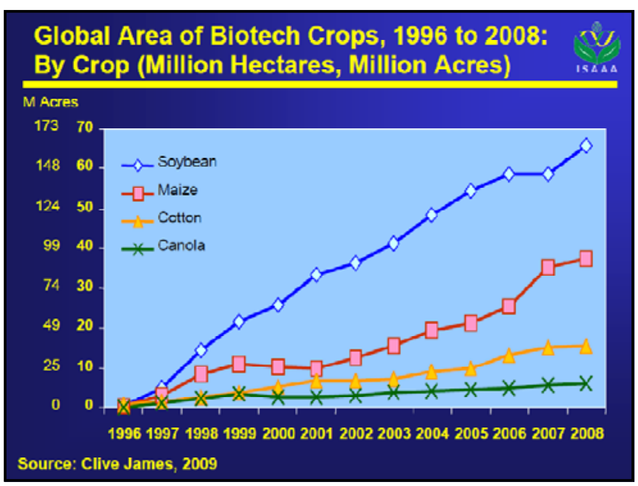
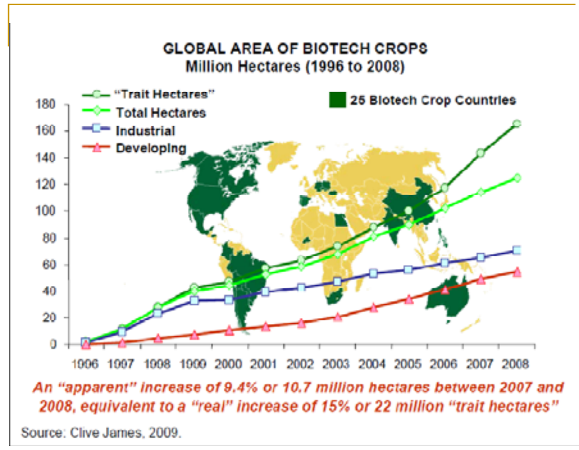
Biotechnology: the predictions

- Will revolutionize plant breeding
- A new "Gene" revolution
- Will feed the world's poor, hungry and nutritionally insecure
- Will make the crops easier and cheaper for farmers to grow
- Consumers will see plentiful food supply that is healthful, cheap and abundant
- The technologies are safe and non-controversial





Biotechnology: the reality

- Only 4 GMO crops (canola, cotton, maize, soybean) grown on significant acreages commercially
- >95% acreage in 6 countries (U.S., Brazil, Argentina, Canada, India, China)
- Two traits (herbicide & insect resistance) account for nearly all acreage
- Six companies (Adventis, Dow, Du Pont, Mitsui, Monsanto & Syngenta) control 98% of global biotech crop market

Biotechnology: the reality (II)

- Traits in commercial use benefit farmers in developed or graduated countries
- Global civil society debate over utility, safety, and ethics
- Only large multinational companies are able to commercialize GMO varieties
- Over half private sector agric. biotech patents obtained from 1982 - 2001 owned by Bayer, Dow, Du Pont, Monsanto, Syngenta

Outline

- Part I Commoditization of seed
  - Commons and anti-commons
  - Plant Patents
  - F_1 hybrids
  - Utility Patents
  - GURTs
- Part II Intellectual property applied to biotechnology
  - Utility patent primer
  - Broad patent example
  - “Patent Thickets” and “Freedom to Operate”
  - Deconstruction of Golden Rice patent
- Part III Global treaties and agreements
  - WIPO
  - ITPGRFA
- Policy reform

Part I Commoditization of seed

Closure of the genetic commons

- Seeds regarded as a public good for the past 10 millennia
- U.S. agriculture is based on introductions in the 19th & 20th centuries
- USDA collecting expeditions & government seed distribution programs
- Farmers saved their own seed & developed new varieties

Weak private sector but strong support for public agricultural research

- Morrill Acts of 1862 and 1890 established the land grant universities
- Hatch Act of 1888 established and funded the state agricultural experiment stations
- Smith Lever Act of 1913 established and funded the cooperative extension service

Scientific basis for plant breeding was established at beginning of 20th century

- Mendel's laws rediscovered
- Many public plant breeding programs initiated
- Public institutions became main source of new varieties

Seed companies sought less public competition

- Governmental seed distribution program was halted
- Lobbied for legislation to strengthen private enterprise in agricultural research
- Private sector could apply discoveries by public sector but needed an incentive
- Strengthened intellectual property protection
- Bayh-Dole Act (1980)
  - Requires Universities to commercialize their technologies

Intellectual Property protection for plants and seeds

- Plant Patent (1930)
  - Asexually propagated crops (except potatoes)
- Plant Variety Protection (1970)
  - Seed propagated crops (& potatoes)
  - UPOV implemented in U.S. in 1994 (global harmonization)
- Utility Patents (first utility patent granted 1790)
  - Diamond vs. Chakrabatry (1980 – microorganisms)
  - Ex parte Hibberd (1985 – USPTO extended to plants)
  - Pioneer vs. J.E.M. (Supreme Court affirmed application to plants)

Trend has been towards an increasing commoditization of seed over time

- F_1 Hybrids
- IP protection
  - Plant patents
  - PVP
  - Utility patents
- Gene Use Regulation Technologies (GURTs)
  - "Terminator technology"
  - Owner controls seed viability

Traditionally, we shrink from permitting small, authoritarian minorities to dictate our social agenda, including what kinds of research are permissible and which technologies and products should be available in the marketplace.

Henry I. Miller, Hoover Institution, and Gregory Conko, Competitive Enterprise Institute (2001)
[Quoted in Kloppenburg, 2004. First the Seed]

Impact on plant breeding and biotechnology research

- Data, germplasm & technology sharing restricted
- Varieties released with IP constraints
- Germplasm access restricted
- Public institutions lack the resources to commercialize transgenic varieties
- A small minority of multinational corporations now controls significant production of several of our staple crops

Part II Intellectual property applied to biotechnology

What is Intellectual Property?

- Technologies
  - Plant varieties
  - Gene sequences
  - Plant secondary products
- Designs
- Processes
  - Transformation
  - Marker assisted selection

What are patents supposed to do?

- Provide incentive to innovate
- State grants limited monopoly in return for disclosure of technology

PVP vs. Utility patents

Provision	PVP	Utility
Breeder's exemption	Yes	No
Permits essentially derived	No	Yes
Farmer's exemption	Yes (narrowed under UPOV)	No
Scope	Cultivars only	Any technology or method
Requirements	Distinct – Uniform – Stable	Novel – Useful – Non obvious – Prior art

WHAT IS PATENTABLE?

- Useful
- New
  - before your invention it was not publicly known or used by others in the United States;
  - before your invention it was not described in a patent or other printed publication anywhere in the world
- Non-obvious
  - at the time of your creation, your invention was not obvious to others in your field, called "persons of ordinary skill in the art"
- Filed by the Inventor

Mary Foley, Tech. Transf. Office, OSU

Do patents on plant biotechnology meet criteria?

(Novel – Useful – Non obvious – Prior art)

- Novel – yes and no (examples of both)
- Useful – yes and no (can't patent DNA sequence w/o knowing usefulness)
- Non-obvious – ? (rigor established by patent examiner)
- Prior art identified? – yes and no
  - Inventors and patent examiners to not always held to a high standard for searching the prior art

Utility patents

- On plant technologies can be quite broad and grant monopolies that interfere with development of varieties using that trait
- Too many patents in an area can impede progress

Examples of problematic patents

- Co-opting germplasm in the public domain
  - Mayocoba (yellow beans) (5,894,079)
  - Basmati rice (5,663,484)
  - Late blight resistance in tomato (5,866,764)
- Fails non-obvious test
  - Popping beans (6,040,503; 6,419,976)

Utility patents that have or may potentially impact my research

- Enola yellow bean (5,894,079)
- Popping beans (6,040,503; 6,419,976)
- Ease of harvest broccoli (2005/0262594)
- Heat tolerant broccoli (2005/0060778)
- Heat tolerant broccoli (2008/0148435)
- Broccoli having detached curds (2007/0118935)
- Broccoli tolerant to hollow stem disorder (2009/0007293)
- High flavonoid tomatoes (2005/0160495)
- High lycopene tomatoes (2008/0184382)

Broadness of patents

- Patent lawyers try to obtain as broad claims as possible
  - 119 claims in 2007/0118935!
- Patent examiners generally limit these but sometimes not
  - Have limited time to review a patent
  - Often not experts in the field of the patent
- Examples of broad patents:
  - Tomato flavonoids
  - Popping beans
  - Heat tolerant broccoli

Example of a broad patent: Heat Tolerant Broccoli (**6,784,345**)

- Claims:
  1. A broccoli plant … center head having a diameter of 3 to 10 inches at maturity … plant is exposed to a maximum daily temperature of 90.degree. F. to 100.degree. F. for 5 consecutive days …plant exhibit no heat stress symptoms including …
  2. Seed produced by the plant of claim 1…
  3. A broccoli plant … exposed to a maximum daily temperature of 95.degree. F. to 100.degree. F. for at least 1 day …
  4. Seed produced by the plant of claim 3…

Example of a broad patent: Heat Tolerant Broccoli (**6,784,345**)

- Claims:
  - 5. A broccoli plant … maximum temperature of at least 85.degree. F. to 100.degree. F. for at least 15 days …
  - 6. Seed produced by the plant of claim 5…
  - 7. A broccoli plant … maximum temperature of 80.degree. F. to 100.degree. F. for at least 20 days …
  - 8. Seed produced by the plant of claim 7…

Example of a broad patent: Heat Tolerant Broccoli (6,784,345)

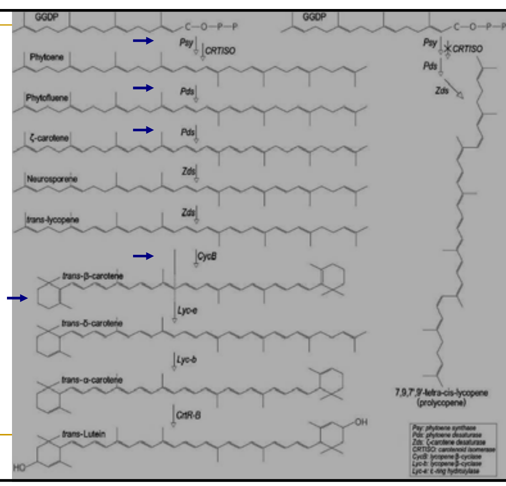
- Any broccoli variety, inbred or F1 hybrid that meet the heat tolerance claims are covered
- Company has an innovative product
- Rather than write a separate patent for each inbred (w/ $$ for each), cover them all

The Patent Thicket

- As patents and MTAs multiply, complexity increases exponentially!
- Creating an anti-commons – numerous IP claims to separate elements required to pursue research & product development
- Patent holders restricting access to upstream discoveries
- Cost – a barrier to becoming a player
- Patenting strategies:
  - Patent clustering (interlocking patents on different components of a product)
  - Patent bracketing (patent clustering around a competitor's patent)

Deconstructing Golden Rice IP thicket

- A rice variety engineered to produce beta-carotene
- Very complex project
  - Required introduction of 3 structural genes in the carotenoid pathway
- The intellectual property (IP) component alone is daunting!

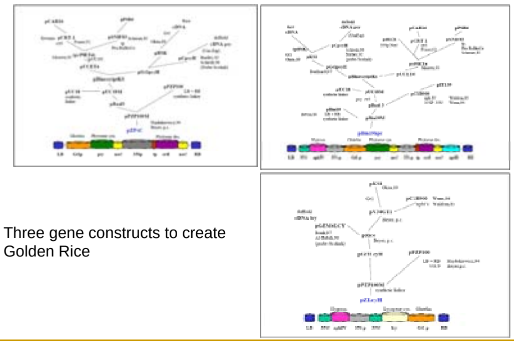


Freedom to Operate Analysis

- A risk management opinion
- Routinely used by corporations to analyze the IP landscape for a new product
- Review of IP and TP (technical property)
- Information to develop strategic deployment plan
- Advice on how to manage IP/TP constraints

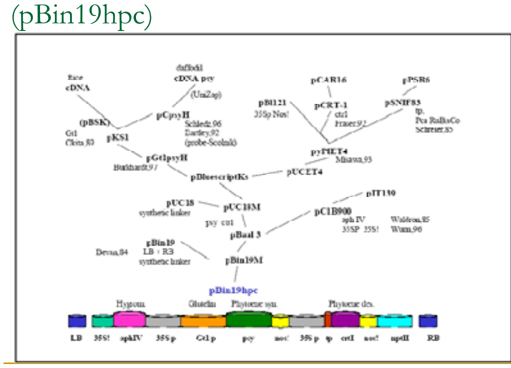
Kryder et al., 2000. The intellectual and technical property components of pro-vitamin A rice (GoldenRice): A preliminary freedom-to-operate review. ISAAA Briefs No. 20. ISAAA:Ithaca 56p. (www.isaaa.org)

Flow chart of tangible property transfers



Three gene constructs to create Golden Rice

Flow chart of tangible property transfers (pBin19hpc)



Product Clearance Profile: Possible Required Licenses and/or Agreements for Golden Rice

Name of Institution	Possible Applicable Patents
1. AMOCO	US5545816, EP0471056, US5530189, WO9113078, US5530188, US5656472
2. Bio-Rad Inc.	US5186800
3. Biotechnica	WO8603516
4. Calgene	WO9907867, WO9806862
5. Centra National de la R.S.K.	WO9636717
6. Cetus WO8504899, U	S4965188, EP0258017
7. Columbia Univ. of New York	US4399216, US4634665, WO8303259
8. DuPont WO9955889,	WO995588, WO9955887
9. Eli Lilly	US5668298
10. Hoffman-La-Roche	US4683202, EP0509612, EP0502588, US4889818
11. ICI, Ltd.	WO9109128,
12. Japan Tobacco	EP0927765, US5591616, EP0604662, EP0672752, US5731179, EP0687730, WO9516031
13. Kirin Brewery	JP3058786, US5429939, US5589581, EP0393690, US5350688
14. Life Technologies	
15. Max Planck Gesell.	EP0265556, EP0270822, EP0257472
16. Monsanto	US5352605, US5858742, WO8402913
17. National Foods RI	JP63091085
18. N.R.C. Canada	WO9419930
19. Novartis AG	
20. Nederlandse O.V.T.	EP0765397, WO9535389
21. Phytogen	US4536475
22. Plant Genetic Systems	US5717084, US5778925, WO8603776, WO9209696
23. Promega	US4766072
23. Rhone-Poulenc Agro	USRE36449, WO9967357
24. Rutgers University	
25. Stanford University	US4237224
26. Stratagene	US5128256, US5188957, US5286636, EP0286200, WO880508
27. University of Maryland	WO9963055
28. University of California	US4407956, WO9916890
29. Washington State University	
30. Yissum R.D.C.	US5792903, EP0820221, WO9628014
31. Zeneca Corp.	US5750865, EP0699765A1

Note that these are the names of the owners or assignees of the rights under the relevant patents. Because of possible subsequent licensing or assignment, these are not necessarily the current entities to approach for licenses.

1) Plant source		
Taipei 309 *Oryza sativa* var. *japonica*	IRRI	No agreements or patents
2) Gene constructs (16 patents)		
pGEM4	US4766072	Vectors for in vitro production of RNA copies of either strand of cloned DNA sequence
pBluescriptKS	US5128256	DNA cloning vectors with in vitro excisable plasmids
	US5188957 EP0286200 WO8805085	Lambda packaging extract lacking beta-galactosidase activity
CAMV 35S promotor	US4407956	Cloned cauliflower mosaic virus DNA as a plant vehicle
	US5352605 US5858742 WO8402913	Chimeric genes for transforming pant cells using viral promoters [sic]
Gt1 promotor	JP63091085 WO9916890	Rice glutelin gene and preparation thereof
Transit peptide	US5717084 US5728925	Chimaeric gene coding for a transit peptide and a heterologous peptide
	USRE36449	Chimaeric gene for the transformation of plants
npt II	EP0927765	Method for selecting transformed cells
aph IV	US5668298	Selectable marker for development of vectors and transformation

3) Structural genes (24 patents)

psy (phytoene synthase)	US5545816	Phytoene biosynthesis in genetically engineered hosts
	US5705624	DNA sequences encoding enzymes useful in phytoene biosynthesis
	US5750865	Process for modifying the production of carotenoids in plants, and DNA, constructs and cells therefor
	EP0471056	Biosynthesis of carotenoids in genetically engineered hosts
	JP3058786	DNA strand useful for synthesis of carotenoid ([sic]
	WO9109128	DNA, constructs, cells and plants derived therefrom
	WO9806862 WO9907867	Methods for producing carotenoid compounds and specialty oils in plant seeds
	WO9955889	Carotenoid biosynthesis enzymes
crtI (phytoene desaturase)	US5530189 WO9113078	Lycopene biosynthesis in genetically engineered hosts
	WO9955888	Carotenoid biosynthesis enzymes
lcy (lycopene cyclase)	US5429939 US5589581	DNA sequences useful for the synthesis of carotenoids
	US5530188 US5656472	Beta-carotene biosynthesis in genetically engineered hosts
	US5792903 EP0820221 WO9628014	Lycopene cyclase gene
	EP0393690	DNA sequences useful for the synthesis of carotenoids
	EP0699765	DNA, constructs, cells and plants derived therefrom
	WO9636717	DNA sequences encoding a lycopene cyclase, antisense sequences derived therefrom and their use for the modification of carotenoid levels
	WO9955887	Carotenoid biosynthesis enzymes
	WO9963055	Genes of carotenoid biosynthesis and methods of use thereof

4) Transformation (23 patents)		
Agrobacterium vectors (general)	US4536475 EP0265556 EP0270822	Plant vector stable binary agrobacterium vectors and their use
	WO8504899	Methods and vectors for transformation of plant cells
	WO8603516	Plant transformation vector
Agrobacterium vectors (monocotyledons)	US5591616 EP0604662	Method of transforming monocotyledons
	EP0257472	Transgenic monocotyledonous plants, seeds, thereof and process for the preparation of the plants
	EP0672752	Method of transforming monocotyledon by using scutellum of immature embryo
	WO8603776	Process for preparing genetically stably transformed monocotyledonous plant cells
	WO9209696	Process for transforming monocotyledonous plants
	WO9419930	Enhanced regeneration system for cereals
	WO9967357	Agrobacterium mediated transformation of monocots

4) Transformation (continued)		
Co-transformation	US4399216 US4634665	Process for inserting DNA into eukaryotic cells and for producing proteinaceous materials
	WO8303259	Method for introducing cloned, amplifiable genes into eukaryotic cells and for producing proteinaceous products
	US5731179	Method for introducing two T-DNAs into plants and vectors therefor
	EP0687730 WO9516031	Method of transforming plant and vector therefor
Electroporation	US5186800	Electroporation of prokaryotic cells
	EP0765397 WO9535389	Method for introduction of genetic material into microorganisms and transformants obtained therewith
Transformation (general)	US4237224	Process for producing biologically functional molecular chimeras

5) Regeneration		
Regeneration of rice	US5350688	Method for regeneration of rice plants
	WO9419930	Enhanced regeneration system for cereals
6) Molecular techniques		
PCR technique	US4683202 US4683195 US4965188 EP0509612 EP0502588 EP0502589	Process for amplifying nucleic acid sequences
Taq polymerase	US4889818 EP0258017	Purified thermostable enzyme and process for amplifying detecting, and/or cloning nucleic acid sequences using said enzyme

MTAs, Licenses, Documents and Agreements Relevant to Golden Rice

Product Component	Source of component
1. Rice germplasm transformed with gene construct(s)	Taipei 309, obtained from IRRI
2. PGEM4	Promega
3. PbluescriptKS	Stratagene
4. PCIB900	Ciba-Geigy Limited (now Novartis Seeds AG)
5. Camv35S Promoter (component of pCIB900)	Monsanto
6. Camv35S Terminator (component of pCIB900)	Monsanto
7. AphIV gene: hygromycin Phosphotransferase (component of pCIB900)	Ciba-Geigy Limited (now Novartis Seeds AG)
8. PKSP-1	Thomas Okita, Washington State University
9. GT1 Promoter: glutelin storage protein (component of pKSP-1)	Thomas Okita, Washington State University
10. PUCET4	N. Misawa, Kirin Brewery Co., Ltd.
11. Pea Rubisco transit peptide (component of pUCET4)	N. Misawa, Kirin Brewery Co., Ltd
12. CrtI gene: phytoene desaturase (component of pUCET4)	N. Misawa, Kirin Brewery Co., Ltd
13. PPZP100	Pal Maliga, Rutgers University
14. pYPIET4	Clontech, but now marketed by Life Technologies
15. Electroporation Apparatus	Bio-Rad Corp., Gene Pulser II SystemÒ
16. Miroprojectile Bombardment Apparatus	Bio-Rad Corp.

The numbers:

- 15 Technical property components (MTAs)
- About 70 patents overall (not all apply in all countries)
- 44 patents in US; 40 in EU
- Negotiations with 12 – 20 entities

Fewer patents in developing countries

- China (10)
- India (5)
- Indonesia (6)
- Bangladesh (0)
- Vietnam (9)
- Thailand (0)
- Myanmar (0)
- Japan (21)

- Process patents:
  - Claims cover process only in country where patent is issued.
- Export considerations:
  - Must negotiate license for product patents even if not covered in country of development – if product is exported to country with patent

IP management strategies

- Invent around current patents
- Re-design constructs
- IP/TP owners relinquish claims
  - (Zeneca & Monsanto already have)
- Ignore all IP and TP claims
- Seek licenses on all IP and TP
- Mix of all options

Golden Rice wrap-up

- Negotiations nearly complete
- Some major IP holders have donated licenses
- Progress made in introducing into adapted varieties & increasing expression levels
- Field tested in 2008
- "…may be available to farmers as early as 2011…"

"…FTO opinion, including the information presented in this report:"

- "**Varies on a country-by-country basis** because most statutory protection is founded in national law, and patents are issued by national governments;
- Is **dynamic** because patent status is dynamic (new patents are issued or expire daily, sold or licensed, disputed or rendered invalid by courts. therefore ownership changes, and the impact of specific claims are constantly changing); and
- Is always an opinion and **never a definitive answer**."

New business opportunities!

- Brokering patents
- Patent portfolios are becoming very important assets to corporations
- Very fluid business
- Some companies derive primary support from managing their patent portfolio

Patent issues

- When first issued in a new area, utility patents tend to be overly broad
  - Patent examiner needs access to relevant prior art (database of the gray literature)
  - USPTO draw on research community through non-disclosure contracts
- Patents are being used to claim germplasm in the public domain

Patent issues (II)

"…if today's intellectual property practice had been in place 30 years ago, then it would be very unlikely that US corn yields would have reached today's level." –Gouache (2004)

- Creating restricted-access genetic populations
  - Two tiers: public domain unimproved & proprietary elite
- Restricted germplasm exchange
  - Esp. developing countries
- Reduced rate of genetic improvement
  - Cannot cross with just anyone's material

Part III Global perspective

Differences between U.S. and International Patents

- First to invent (U.S.) vs. first to file
- Cannot patent a living organism under international system (no variety patents)
- Can patent a method or technique that uses a particular living organism
- PVP: commercial sale only when variety is on national registry list

International consequences of intellectual property rights

"In an uncertain farmer's rights environment, the traditional exchange of genetic materials could be curtailed." –Everson (1999)

- World Intellectual Property Organization: strong IP on a global level
- Access to germplasm from some developing countries restricted due to perceived imbalance
  - Germplasm obtained for free from developing countries; germplasm in modified form sold back to them with unfavorable trade agreements imposed
  - Trade-Related Aspects of Intellectual Property Rights
  - Convention on Biological Diversity
  - International Treaty on Plant Genetic Resources for Food and Agriculture

International Treaty on Plant Genetic Resources for Food and Agriculture

- Establishes a Standard Material Transfer Agreement
- Provides for remuneration if germplasm is used to develop commercial product
- But…
  - Early germplasm collections not grandfathered in
  - Certain crops excluded for political reasons

Efforts to reform the IP system

Recommendations for changes in IP

- USPTO should re-focus on promoting innovation
- Raise the bar on novelty, non obvious, prior art criteria
- Patent examiners should establish a peer reviewer system
- Patents should be limited in scope
- Prohibit patenting of public domain technologies
- Conditionally exempt traits that are in the interest of national food security

Community Patent Review

- Pilot program applies to: Computer Architecture, Software and Information Security, Business Methods and E-Commerce
- http://www.peertopatent.org/
- http://www.uspto.gov/web/patents/peerpriorartpilot/

PIPRA - the Public Intellectual Property Resource for Agriculture

- http://www.pipra.org/
- "…improve agriculture in emerging economies by decreasing intellectual property barriers and increasing technology transfer."
- Resources:
  - IP policy analysis
  - IP landscape analysis on particular technologies
  - **Biotechnology resources, e.g. the pPIPRA vector**
  - Research consortia support, e.g. Pierce's Disease
  - IP management workshops at public institutions
  - Regional IP Resources, mainly in Latin America and Southeast Asia
  - IP handbook

"…patent system has come to be increasing about protecting investment rather than promoting innovation…"

"…the loosening of the definition of 'utility', the way inventive step and novelty are applied in patent applications, and an apparent willingness to leave it to the courts to decide the validity of patents are bring the system into disrepute. Some see a risk of the US system turning into a patent application registration system as opposed to a patent granting one."

"Since crop genetic improvement is a derivative process, each incremental improvement made through biotechnology now comes with a number of IP constraints, with new IP added with each … further improvement."

Future Control of Food

Resources:

- USPTO database: http://patft.uspto.gov/
- USDA PVPO: http://www.ams.usda.gov/AMSv1.0/ams.fetchTemplateData.do?template=TemplateC&navID=PlantVarietyProtectionOffice&rightNav1=PlantVarietyProtectionOffice&topNav=&leftNav=ScienceandLaboratories&page=PlantVarietyProtectionOffice&resultType=&acct=plntvarprtctn
- WIPO database: http://www.wipo.int/patentscope/en/
- Google Patents: http://www.google.com/patents

Points to ponder:

- As an end user, what rights should you have to patented material?
- As a researcher how should you be allowed to use patented plant germplasm?
- How do we increase rigor at the patent office?
- How do we prevent patent thickets?
- How do we create a workable system to compensate the originators of technical property (germplasm) in developing countries?
- Has the IP system created a "science anti-commons?"
- For anyone doing research: Who owns your work?