Issues related to environmental use of PGPB
Probability that an organism will cause a deleterious effect in the environment is a function of its:

- Ability to survive
- Ability to multiply
- Dissemination in the environment
- Intrinsic hazard
- Probability of hazardous gene transfer
Bacterial survival and metabolic load
Metabolic load in the environment

- Increasing plasmid copy number and/or size requires increasing amounts of energy
- Overproduction of target and marker proteins may deplete pools of certain aa-tRNAs and drain the host cell of its energy (ATP or GTP)
- Overexpression of secreted foreign proteins may jam export sites and prevent the proper localization of other host cell proteins
- Host cells with unusual metabolic features, such as a naturally high rate of respiration, are more likely to be affected by metabolic perturbations than other host cells
- The foreign protein may interfere with the functioning of the host cell
Consequences of metabolic load for organisms to be released to the environment

1. Presence of foreign DNA may decrease the rate of cell growth; plasmid-containing cells may lose all or part of their plasmid DNA
2. Metabolic load may change host cell size and shape, and increase in bacterial extracellular polysaccharide
3. When an aa-tRNA becomes limiting the incorrect aa may be inserted in its place.
4. Translation uses a lot of GTP and may become limited because of energy depletion from foreign protein overexpression
5. Metabolic load is reduced using a low-copy-number plasmid or integrating foreign DNA into the host chromosome because the transformed host will not waste resources synthesizing unwanted and unneeded antibiotic resistance marker gene products
6. When codon usage of the foreign gene is different from codon usage of the host, depletion of specific aa-tRNA pools may be avoided by re-synthesizing the target gene to better reflect the codon usage of the host
Non-transformed bacterium → Foreign DNA → Transformed bacterium

Non-transformed bacterium:
1. Doesn’t express foreign genes
2. Faster growth
3. Requires fewer resources
4. No tendency to lose plasmid(s)
5. Outcompetes transformants
6. Acts as an effective PGPB

Transformed bacterium:
1. Expresses foreign genes
2. Slower growth
3. Requires more resources
4. Tendency to lose plasmid(s)
5. Easily outcompeted
6. Ineffective as a PGPB
Integrating a foreign gene into the host cell chromosomal DNA to prevent it from transferring to other organisms in the environment.
Protecting Intellectual Property

- Trade Secret
- Know how
- Patent
- Copyright
Patents

- The invention, after having been “reduced to practice” must be “novel”

- The invention must contain an “inventive step” that was “not obvious” to other workers in the field

- The invention must be “useful”

- The patent application must contain a description of the invention that is sufficiently thorough that a person “knowledgeable in the field” can implement it
Patents

- 20 years exclusive rights from date of filing
- In the US, date of invention has precedence over date of filing. In many other countries, a patent is awarded to "the first to file" [To prove that you have the first date of invention, it is essential to keep detailed signed and dated notebooks.]
- In the US, an inventor has one year following publication in which to apply for a patent. In many other countries, patent application must precede publication
- Patents are issued only to individuals, and not to companies
- Patent rights may be assigned to companies. Companies typically own the rights to anything discovered by their employees.
- ~100,000 US patents are issued per year of which ~5-10,000 relate to biotechnology
- ~7 million US patents have been issued to date
Key Elements of the Patent Process

1. Contains a detailed description of the invention
2. Patent holder given exclusive commercial rights for 20 years from the date of filing
3. Patent awarded to first-to-invent or first-to-file, depending on jurisdiction
4. An invention is a product or a process
5. The invention should be reduced to practice
6. The invention should be novel
7. The invention must contain a step that is not obvious to workers who are skilled in the field of the invention
8. The invention should be useful (utility)
9. The application should contain a description sufficiently detailed to allow persons skilled in the field to implement it (feasibility)
10. Products of nature are not patentable
11. Patents are awarded to individuals not corporations
12. Patent rights may be assigned to corporations
Table 22.1 Common types of patent categories with examples of biotechnology inventions

<table>
<thead>
<tr>
<th>Categories</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Product patents</strong></td>
<td></td>
</tr>
<tr>
<td>Substance</td>
<td>Cloned genes, recombinant proteins, monoclonal antibodies, plasmids, promoters, vectors, cDNA sequences, antigens, peptides, RNA constructs, antisense oligonucleotides, peptide nucleic acids, ribozymes, and fusion proteins</td>
</tr>
<tr>
<td>Composition of matter</td>
<td>Multivalent vaccines, biofertilizers, bioinsecticides, host cells, microorganisms, transformed cell lines, and transgenic organisms</td>
</tr>
<tr>
<td>Devices</td>
<td>Pulse-field gel electrophoresis apparatus, DNA sequencing units, and microprojectile gene transfer machine</td>
</tr>
</tbody>
</table>

**Process patents**

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Process of preparation</td>
<td>DNA isolation, synthesizing double-stranded DNA, vector-insert construction, polymerase chain reaction (PCR) applications, and purification of recombinant protein</td>
</tr>
<tr>
<td>Method of working</td>
<td>Nucleic acid hybridization assays, diagnostic procedures, and mutation detection systems using PCR</td>
</tr>
<tr>
<td>Use</td>
<td>Applying biofertilizers and bioinsecticides, fermentation of genetically modified microorganisms, and nontherapeutic animal treatment systems</td>
</tr>
</tbody>
</table>
Patenting Issues

• Different countries - narrow vs. broad claims (e.g. Japan vs. US)

• DNA sequences are not patentable, unless what they encode is useful

• Multicellular organisms (animals) are patentable in the US but not in Canada

• What constitutes authorship?
Some Important Patent Cases

- 1880s and 1890s Louis Pasteur
- 1980 Diamond vs. Chakrabarty
- 1980 Cohen and Boyer
- 1988 Oncomouse
- 1991 Application to patent 315 partial human cDNAs
- 1997 Human Gene Therapy
- 2010 Human genes are a “product of nature”
Abstract of the Cohen and Boyer 1980 patent

A method for replicating a biologically functional DNA, which comprises: transforming under transforming conditions compatible unicellular organisms with biologically functional DNA to form transformants; said biologically functional DNA prepared in vitro by the method of: (a) cleaving a viral or circular plasmid DNA compatible with said unicellular organism to provide a first linear segment having an intact replicon and termini of a predetermined character; (b) combining said first linear segment with a second linear DNA segment, having at least one intact gene and foreign to said unicellular organism and having termini ligatable to said termini of said first linear segment, wherein at one of said first and second linear DNA segments has a gene for a phenotypical trait, under joining conditions where the termini of said first and second segments join to provide a functional DNA capable of replication and transcription in said unicellular organism; growing said unicellular organisms under appropriate nutrient conditions; and isolating said transformants from parent unicellular organisms by means of said phenotypical trait imparted by said biologically functional DNA.
2009 lawsuit claims that DNA is not patentable

- The ACLU and the Public Patent Foundation (PUBPAT) filed a lawsuit against Myriad Genetics, the University of Utah Research Foundation, and the USPTO. It challenged the USPTO’s authority to issue patents that relate to products of nature and the legitimacy of claims issued to Myriad Genetics that relate to isolated DNA encoding the breast cancer markers BRCA1 and BRCA2 and to methods of detecting alterations in BRCA1 gene sequence to diagnose cancer.
- The lawsuit charged that the patents stifle diagnostic testing and research that could lead to cures and that they limit women's options regarding their medical care. The District Court in the Southern District of New York ruled in March 2010 that the patents on BRCA1 and 2 are invalid. Myriad is appealing.
- The court held that genes are products of nature and thus not patentable. Diagnostic methods that involve analyzing and comparing gene sequences were also found to be not patentable, as were methods for identifying cancer therapeutics by comparing growth rates of engineered cells. This ruling calls into question the validity of patents now held on approximately 2,000 human genes. The court also held that diagnostic and screening methods that utilize gene sequence information are also not patentable.
- The USPTO has issued ~35,000 patents including a gene sequence in their claims. These gene patents protect isolated or purified DNA sequences, RNA sequences, vectors, nucleic acid-based vaccines, cells engineered with gene sequences, and various uses of gene sequences.
University/Government Research

• Who owns the rights?
  – U of W policy #73 (see next overhead)

• Basic versus applied research
  – Encouraging secrecy/duplication of efforts
  – Encouraging mediocrity?
  – Channeling researchers
  – Matching funds
  – University entrepreneurs and conflict of interest
“Ownership
Except as stipulated below, it is University policy that ownership of rights in IP created in the course of teaching and research activities belong to the creator(s).

The exceptions are:

* The University normally retains ownership of IP rights in works created as 'assigned tasks' in the course of administrative activities.
* Owners of IP rights in scholarly works created in the course of teaching and research activities grant the University a non-exclusive, free, irrevocable license to copy and/or use such works in other teaching and research activities, but excluding licensing and distribution to persons or organizations outside the University community. Any such licensing and/or distribution activity would be authorized only by an additional license from the owner(s).
* In sponsored or contract research activities, ownership of IP rights may be determined in whole or in part by the regulations of the sponsor or the terms of the contract.”
Questions:
1. What factors need to be considered before deliberately releasing PGPB to the environment?
2. Why are transgenic PGPB, including rhizobia, often found to be not especially competitive with indigenous soil bacteria?
3. What is metabolic load and how might it affect the functioning of a PGPB?
4. How can one produce transgenic PGPB while keeping the effect of metabolic load to a minimum?
5. How can foreign genes be integrated into the chromosomal DNA of a host PGPB?
6. What is a patent and why is it useful?
7. What are the criteria for deciding whether something is patentable?
8. What sorts of changes might one need to make when patenting the same invention in two different jurisdictions such as the US and Japan?
9. Why is it difficult to patent complete or partial DNA sequences when the function that these sequences encode is unknown?
10. Why is patenting of scientific discoveries good (or bad) for the further development of science?
11. Is it better for a university or for a researcher/inventor to own the rights to inventions made during the course of research activities at the University? Why?