Plants vs. Pathogens
VEGEVADERS™

A card game of infiltration and detection

Prototype 7/18/12
Revised 7/22/13

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Funding from: NSF
As you know, microorganisms – microbes for short – can cause disease
... for example, **The Black Death** – The Plague – began in Europe in the mid 1300s, killing ~25 million people ....

...then, as now, caused by infection with the bacterium called *Yersinia pestis*
...but people also die from starvation due to plant disease – like the potato blight that caused the Irish Potato Famine, 1845-1852...

...1 million died of starvation and a million more emigrated from Ireland
... and the **same pathogen** that killed **potatoes** devastated **tomatoes** just recently in NY state.
But disease resulting from contact with microbes is the exception to the rule...
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Actually, hundreds to thousands of microbes come into contact with larger organisms that could become hosts to these potential microbial pathogens.....
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Actually, hundreds to thousands of microbes come into contact with larger organisms that could become hosts to these potential microbial pathogens.....

...true for humans as well as plants...

... yet only a tiny proportion of these microbes actually become pathogens on hosts – why?
There’s an ongoing battle at the plant’s surface...
There’s an ongoing battle at the plant’s surface...

*Pathogens* are trying to *invade* plants

*Plants* are trying to *detect* these potential invaders and *defend* against them
In the game **VEGEVADERS**, the **battle** is between:

- the **bacterial plant pathogen** *Pseudomonas syringae*  
  (a relative of the animal pathogen that causes Plague and The Black Death)

and

- a **plant** we rely on for food, like a tomato

**Bacteria** on a leaf surface  
**Disease symptoms** on a **plant leaf**
... and they fight it out through **molecular interactions** – how?
Potential **pathogens** (bacteria here) have **FEATURES** = specific molecules that signal potential trouble if a plant recognizes them ...
... for example, *molecules* found in the bacterial *flagellum* (for mobility).
These can be recognized by **PLANT Surface RECEPTORS** via a specific “lock-and-key” match, which then initiates a response from the plant.
Think of these potentially interacting pathogen and plant molecules using the following medieval castle metaphor:
The Plant Cell = a Medieval Castle
Plant **Surface Receptors** = specialized **Lookouts** on the castle’s wall,

The Plant **Cell** = a Medieval **Castle**
Specific Features on a Bacterial Cell = different Flags on a potential Invader

Plant Surface Receptors = specialized Lookouts

Plant Cell = a Medieval Castle

(= a single bacterium)
... and Lookouts can only see matching Flags - Here, Lookouts A or B detect Features A or B

Bacterial Features = different Flags

Plant Surface Receptors = specialized Lookouts

Plant Cell = a Medieval Castle

(= a single bacterium)
Then...

1) Detection by Lookouts A & B

(inside the plant cell)
Then...

1) Detection by Lookouts A & B

→ 2) a Signal sent inside the Castle (cell)

(inside the plant cell)
Then.....

1) Detection by Lookouts A & B

2) A Signal sent inside the Castle (cell)

3) A Defense Response = here, strengthening of the wall

(inside the plant cell)
When **PLANT** Surface **RECEPTORS** detect Microbial **FEATURES**, a signal is sent to the inside of the plant cell ...
... which turns on **Microbe-Triggered Immunity** (or **MTI**), which thickens the cell wall and stops the pathogen
Microbe-Triggered Immunity (MTI) = the first, and most ancient, line of plant defense against pathogen attack
Look at your VEGEVADERS play mat

a single microbe

a single plant cell
Cards played in Row 1 = **different** Microbial **Features** of a **single** microbe
Cards played in Row 1 = **different** Microbial Features of a **single** microbe

Cards played in Row 2 = **different** Plant Surface Receptors in a **single** plant cell
The **Pathogen** player plays **Microbial Feature** cards in Row 1, The **Plant** player plays **Plant Receptor** cards in Row 2, and **Matching letters** (like A with A) = **detection** of a **Microbial Feature** by a **Plant Receptor** (and a resulting **defense response**).
In the game, **2 different pairs** of matching Feature/Receptor cards are required for the **Plant** to **achieve MTI**, and win.
On the mat, here is an example of two matches between Microbial FEATURE cards (or Invader Flags in Row 1) and PLANT RECEPTOR cards (or Lookouts in Row 2), so that Plant achieves MTI and is winning.... so far....
In nature, Pathogens that were detected (via MTI) failed in their invasion attempt...

So - you might wonder - why aren’t the plants always winning???
Bacteria are not all identical. Each has small differences in its DNA, some of which enable an individual to invade and survive.
How? What differences could help bacteria get around the plant’s Microbial Feature-Triggered Immunity (MTI)?
One possibility – the recognized **FEATURE** might be **lost** or 
mutated so it is **no longer detected** by the plant. 
Possible, but some features are really important for the bacteria’s 
survival and their loss would have **serious consequences**
Alternatively, surviving pathogens could have something new and different, like injected **EFFECTOR PROTEINS** that give them a selective advantage...
Indeed, many pathogens that cause disease today inject **EFFECTOR PROTEINS** into the plant cell, where they **shut down** the plant’s MTI...
By analogy, the Invading bacterium injects daggered Invaders (Effectors) through the wall, inside the castle (cell)...
... and Effectors are able to disable, or shut down, specific components of the MTI defense response: B1 shuts down B, A1 (or, alternatively, A2) shuts down A, etc.
On the **VEGEVADERS** play mat, the **cards played in Row 3** represent the different **Microbial Effectors** (= Invading Proteins)
... and a played **EFFECTOR card** in Row 3 that matches the **letter** of a **FEATURE-RECEPTOR** pair in Rows 1 and 2 **disables** that pair.
... and a played **EFFECTOR card** in Row 3 that matches a **FEATURE-RECEPTOR** pair in Rows 1 and 2 **disables** that pair. Here, **Effector D1** in Row 3 **disables** the **D-D pair** in Rows 1 and 2.
... and a played **EFFECTOR card** in Row 3 that matches a **FEATURE-RECEPTOR** pair in Rows 1 and 2 **disables** that pair. Here, **Effector D1** in Row 3 **disables** the D-D pair in Rows 1 and 2. (Alternatively, **Effector D2** could do the same job – only **the letter** needs to match.)
Note that now there is **only one active** FEATURE-RECEPTOR match, so at this point the Pathogen is winning (because the Plant does not have the 2 matches necessary for MTI ......)
Now, let’s lay down some cards and review:

**Pathogen player** – Draw and lay down 4 **Microbial Feature** cards (light orange) in Row #1. (Discard and replace any duplicate card.)

**Plant player** – Draw and lay down 4 **Plant Surface Receptor** cards (light green) in Row #2. (Discard and replace any duplicate card.)
First, on the mat below, are there **2 matches = Microbe-Triggered Immunity (MTI)**?
**NO** – only 1 seen here, so no **Microbe-Triggered Immunity (MTI)**?

**What about on your mat?**  (Tally results from around the class.)
**Pathogen player** – now draw and **lay down** 4 **Effector** cards (dark orange) in Row #3.

**Do you have on your mat** an Effector in Row 3 that **disables** a Feature-Receptor match in Rows 1 and 2 (as seen below)?
Here’s an example on the mat below.
Here’s an example on the mat below..... so now there is now only one active FEATURE-RECEPTOR match, because the D-D match is disabled by Effector D1.
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Therefore, so far the **Pathogen** is winning  (no MTI because only 1 match).
In nature, pathogen **Effectors** are really good at **shutting down** the plant’s **MTI**.

So why aren’t plants **always losing** the battle against microbes?
As with the population of microbes, different plants in a natural population are each slightly different.
And across evolutionary time, plants that survived had something new –
And across evolutionary time, plants that survived had something new – an **R (RESISTANCE) PROTEIN** that recognized an injected Effector ...
... causing activation of a **second, even stronger** plant defense, **Effector-Triggered Immunity (ETI)** – a response that protects the plant from disease...
...at least for the moment....
Here, recognition between 1 Plant Bludgeoner (R Protein) and 1 Effector – by both letter and number (B1/ B1) – sets off Effector-Triggered Immunity (ETI)
... which ends the attack and Plant wins the game! (ETI trumps MTI)
In *VEGEVADERS*, the **cards** played in Row 4 represent the different **PLANT R (RESISTANCE) PROTEINS**...
... and HERE the played **RESISTANCE PROTEIN** card **E2** in Row 4 **recognizes** the matching **E2** **EFFECTOR** (in Row 3) and **induces** the plant’s **ETI**.

Only **1 match** (letter **and** number) is required for **ETI**, and since **ETI** trumps **MTI**, the **plant** wins the game!
... and HERE the played **RESISTANCE PROTEIN** card **E2** in Row 4 recognizes the matching **E2** **EFFECCTOR** (in Row 3) and induces the plant’s **ETI**. Only **1 match** (letter and number) is required for **ETI**, and since **ETI** trumps **MTI**, the plant wins the game!

** (Note that no **Plant Receptor E** (Row 2) or **Microbial Feature E** (Row 1) is necessary.)
... and HERE the played **RESISTANCE PROTEIN** card **E2** in Row 4 recognizes the matching **E2** EFFECTOR (in Row 3) and induces the plant’s **ETI**. Only **1 match** (letter and number) is required for ETI, and since ETI trumps MTI, the plant wins the game!

(And note that for ETI **both** the **letter** and the **number** must match; here RESISTANCE PROTEIN B2 does **not** recognize EFFECTOR B1.)
**Plant Player** – now play 4 dark green cards in Row 4, and see if the Plant wins **by ETI** on your mat.
**Plant Player** – now play 4 dark green cards in Row 4, and see if the Plant wins **by ETI** on your mat.

On this mat, YES!
...... and so the **game** of **invasion** versus **detection** continues in nature... as it has for millions of years ... and **EVOLUTION** ensures that the battle never ends....
...... Here, a **new pathogen** appeared and **was selected for**. The C1 Effector had **mutated** (to C2) so that it is **no longer recognized** by the plant’s C1 R protein.....
...... Here, a new pathogen appeared and was selected for. The C1 Effector had mutated (to C2) so that it is no longer recognized by the plant’s C1 R protein.....
...... and thus the **pathogen** is back on top, defeating the plant’s **ETI** and **successfully invading**...
...... and thus the **pathogen** is back on top, defeating the plant’s **ETI** and **successfully invading**...

.... **until** ... you guessed it ... a **new plant** with a **matching R-protein** (C2 for C2) appears in the population, and survives....
... and thus is selected for ... and so the **game** of **invasion** versus **detection** continues in nature... as it has for millions of years ...
The game *VEGEVADERS* captures this *never-ending* co-evolution between *plant* and *pathogen* in the *EVOLUTION step* between rounds of game play = *different seasons* of game play.

Let’s put this all together in the game....
1) **Lay down** 4 cards in each row, alternating Pathogen and Plant players, discarding and replacing any duplicates.
2) **Score** – assess who has won this season, then **add 1 point** to the winner’s **Victory Point scale**.

Remember:

- **If** the *plant detects* the pathogen (via MTI or ETI), the *plant wins* (and ETI trumps MTI).
- **If** the *pathogen escapes detection*, or *disables* detection, it *invades*, and *wins*. 
QUICK REVIEW for playing the game VEGEVADERS:
a) Matching between $1 + 2 \rightarrow \text{MTI}$ (\textbf{2 letter} matches needed),
b) Matching between $3 + 4 \rightarrow \text{ETI}$ (\textbf{1 letter/number} match needed),
c) Matching of $3$’s letter with a $1$ & $2$ match shuts down (disables) that 1-2 match
Scoring – example #1:

1st – Check for the **strongest plant defense** first = **ETI** = just one letter-number match in Rows 3 & 4 = **Plant detects Pathogen, and wins!** The end. No more scoring steps.

|   | A1 | A2 | B1 | B2 | C1 | C2 | D1 | D2 | E1 | E2 | F1 | F2 | G1 | G2 | H1 | H2 |
|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
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A perfect H1-H1 match = **ETI** = **Plant wins 1 pt!**
Scoring – example #2:

1st – Check for ETI. None seen below.

So far, Pathogen has escaped detection....
Scoring – example #2:

2nd – If no ETI, then check for MTI in Rows 1 & 2 – if two letter-letter matches = MTI = Plant detects Pathogen, and wins.
**Scoring – example #2:**

2nd – **If no ETI**, then check for **MTI** in Rows 1 & 2 – if **two** letter-letter matches = **MTI** = **Plant detects** Pathogen, and wins.

|    | A1 | A2 | B1 | B2 | C1 | C2 | D1 | D2 | E1 | E2 | F1 | F2 | G1 | G2 | H1 | H2 |
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Next, look here

1 good match
Scoring – example #2:

2nd – If no ETI, then check for MTI in Rows 1 & 2 – if two letter-letter matches = MTI = Plant detects Pathogen, and wins.

But this match is disabled; no good

1 good match

Next, look here
Scoring – example #2:

2nd – If no ETI, then check for MTI in Rows 1 & 2 – if two letter-letter matches = MTI = Plant detects Pathogen, and wins.

But this match is disabled; no good

1 good match

Next, look here

So, only 1 match, Pathogen disables detection, and wins = 1 pt for Pathogen!
after Scoring …

3) **Evolution** – for the **Loser** of the season.

Since only an **altered version** of the loser has a chance for **survival**, the **loser** for the season **evolves** (according to the rules).

**All other cards** for both players, except those involved in evolution, **remain in play** on the board.

**After Evolution, each row** again has **4 unique cards** (no duplicates).
How the Evolution step works....
1) If the **Plant lost**, the Plant evolves – always by **discarding**, randomly, 2 of the 4 **R-protein** cards.

(Pathogen escaped or disabled detection; will reappear next season as is.)

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**Discard, randomly, 2 of the 4 R-Protein cards. Replace them with new cards from deck. Put non-discarded cards back in play.**
2) If the **Pathogen lost**, the Pathogen evolves – by **discarding 1 card** that was **detected** by a match – **either an Effector or a Feature** – according to the rules – see following pages...

One detected card is discarded & replaced with a new card from the deck.
Example a) **Pathogen lost via 1 ETI match** (Rows 3 & 4), so a newly evolved **Pathogen** will appear.

(Plant won, stays the same for next season.)

Discard and replace the 1 detected **Effector** card **B2** in Row 3.
Example b) **Pathogen lost** via **2 MTI matches** (Rows 1 & 2), so a newly evolved **Pathogen** will appear.  
(Plant won, stays the same for next season.)

Discard and replace randomly **1** of the **2 Feature cards** detected in Row 1.
Example c) **Pathogen lost** via **both MTI** (Rows 1 & 2) and **ETI** (doubly, in Rows 3 & 4), so **Pathogen** evolves. Since **ETI trumps MTI**, 1 of the 2 detected **Effector** cards changes.

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Discard and replace 1 randomly – either the B1 or the F1 detected **Effector** card in Row 3 – because **ETI trumps MTI**.
After **Evolution**, **each row** should again have **4 unique cards** (no duplicates).

Then, **Score** that new season.

**Play as long as desired, repeating**  Evolution and Scoring and keeping score of the winner each season.

**Wrap-up** session.
Take-home Messages

• Plants, like animals, have an **immune system** that protects them from infection by a pathogen.
  Protection is based on **recognition** (= detection) of a pathogen molecule by its lock-and-key fit with a plant **receptor**.
  Detection leads to **signaling** and a plant defense **response** – either **Microbial Feature-Triggered Immunity (MTI)** or **Effector-Triggered Immunity (ETI)**.

• Genomes of microbial pathogens **evolve**, changing rapidly over time, both by
  a) **mutation and loss** of recognizable pathogen Features and Effectors, and
  b) the **acquisition of new genes to suppress immunity** (just like drug-resistance genes in animal pathogens), sometimes from neighboring microbes.

• As microbes evolve to escape detection and infiltrate plants, plants are selected via **artificial** or **natural selection** to acquire new Resistance genes:
  a) via plant breeders introducing new Resistance genes into plant cultivars (using **selective cross breeding** or **genetic engineering**), or
  b) via **cross pollination** and **genetic recombination** in nature.
Wrap-Up and Reflection

**Evolution:**

You’ve seen it in action in the game *VEGEVADERS*, as molecular repertoires change over time due to selective pressure. The *same game* has been playing in nature for millions of years, with remarkable similarity among different kinds of pathogens, ensuring that no resistant plant cultivar in the field stays resistant to microbial infection for long...
Some Possible Discussion Questions

1) What did you learn about plants from playing VEGEVADERS? Did you learn anything new you didn’t know before?

2) What did you learn about evolution from playing VEGEVADERS? Anything you didn’t know before? How is a farmer’s field different from the natural world, and how might that affect pathogen or plant evolution?

3) Based on what you’ve learned from playing VEGEVADERS, are there questions you have about plant-pathogen interactions? Was there anything that seemed confusing? Is there anything you’re curious about, and would like to learn more about?

4) If a plant cultivar can detect the presence of a potential pathogen, it is normally resistant to attack by that organism. What kind of selective pressure does this exert on this potential pathogen, and how specifically is the pathogen likely to change in response?

5) There is evidence in the DNA sequences of pathogens for mutation and loss of genes for specific effectors. But if effectors are lost, the bacterial pathogen needs to acquire a new effector to suppress plant immunity – how does this happen? (HINT: consider the increasing problem of microbial resistance to antibiotics seen in hospital settings.)

6) How do plants acquire a new Resistance gene, whose protein product can recognize a new pathogen molecule (such as a new bacterial effector)?
The **same game** has been playing in nature for millions of years, with **remarkable similarity** among different kinds of pathogens ...

And, similar molecular strategies are used by **animal pathogens**, including the bacterium *Yersinia pestis*, causal agent of the Plague, today as yesterday.... (recently, a husband and wife contracted the Plague in New Mexico – the husband was in a coma for months and nearly died; he lost both legs from gangrene)

Worst of all, in this molecular arms race, the pathogens keep winning! We **need more options, more ideas**...
... for smarter pathogen control to stop the stem rust fungus Ug99, the “red menace” threatening the world’s wheat since 2010...
The End
Plans for the future include a **website** where teachers/students can find links to:

1) the Introductory PowerPoint and homework exercises
2) an online version of the classroom game (with additional levels and extra add-ons)
3) FAQs with links to more info, *e.g.*:
   - primary literature papers,
   - figures showing molecular components of plant immunity,
   - figures showing comparison of pathogen genomes where effector genes have been mutated/lost in some pathogens,
   etc.
We welcome your comments and suggestions! Please send any you may think of later to Candace Collmer, cwc6@cornell.edu


VEGEVADERS™: A fun way for teaching/exploring diverse high school topics

- Food for the Future: Challenges in world-wide agriculture
- How immunity works in plants & animals
- Genes, mutation, recombination & evolution
- Our Health: How microbes become resistant to antibiotics
- Molecular recognition → signaling → cellular response
- New biotechnologies for crop protection

by B. Adams, A. Collmer, C. Collmer, M. Lindeberg; Cornell University & Wells College
(contact Candace Collmer: cwc6@cornell.edu)
Take-home Messages

Plants, like animals, have an **immune system** that protects them from infection by a pathogen. Protection is based on **recognition** of a pathogen molecule by its **lock-and-key fit** with a plant **receptor**. Detection leads to intracellular **signaling** and a **plant defense response** — either **Microbial Feature-Triggered Immunity (MTI)** or the **hypersensitive Effector-Triggered Immunity (ETI)**.

Genomes of microbial pathogens **evolve**, changing rapidly over time, both by

a) **mutation and loss** of recognizable pathogen Features and Effectors, and

b) the **acquisition of new genes to suppress immunity** (just like drug-resistance genes in animal pathogens),

As microbes evolve to escape detection and infiltrate plants, **plants** are selected via **artificial** or **natural selection** to acquire new Resistance genes:

a) via plant breeders introducing new Resistance genes into plant cultivars (using **selective cross breeding** or **genetic engineering** and **biotechnology**), or

b) via **cross pollination** and **genetic recombination** in nature.