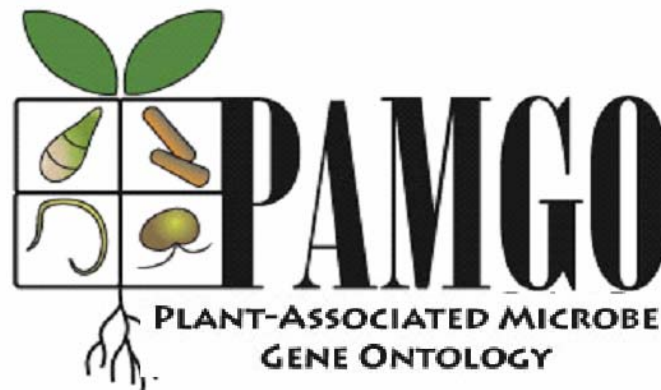


Get GOing with comparative genomics:

**How new terms for the Gene Ontology (GO)
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Outline of the PAMGO Workshop

- Candace Collmer: Getting started with PAMGO – Theory and practice of creating new GO terms
- Magdalen Lindeberg: GO annotation of experimentally characterized genes from *Pseudomonas syringae*
- Marcus Constantine Chibucos: GO annotation of *Phytophthora* genomes – bioinformatic approaches
- Trudy Torto-Alalibo: Overview of ontology-based functional genomics of microbes and their hosts
- **Discussion**: Do currently existing GO terms describe all known processes of microbe-host interactions?
What are useful GO tools?

Questions:

How can comparative genomics facilitate the study of microbial pathogenesis of plants (and animals)?

How is the **Gene Ontology** essential to this effort?

As more and more complete genome sequences of microbes become available,

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e.g. BLAST for single gene comparisons, once a gene is known to be important,

Tools like the Artemis Comparison Tool (ACT) for whole-genome comparisons

2) Would like also to do functional comparisons:

e.g. a) What biological processes differ significantly between a pathogen vs. a non-pathogen?

b) What gene products are used by different pathogens (bacteria, fungi, oomycetes, nematodes) to suppress host defenses?

c) What are all the effector proteins secreted by microbes attacking plants vs. animals?

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******(Here, annotation allows capturing the info you know already, but also finding things you don't know)

But, comparisons of functions of gene products across genomes require that:

1) functions be assigned to genes via annotation,

2) the vocabulary for describing such functions be universally understandable, across organisms

3) annotations be computer searchable

Annotation approaches prior to GO don't allow good functional comparisons:

- 1) Gene names may reflect mutant phenotypes, not functions (and may be obscure to outsiders)
- 2) A protein with same function in different organisms can have different names (e.g. XcpD, OutD, XpsD)
- 3) “Name” or “notes” fields reflect only a subset of the multiple roles of any gene product
- 4) Terminology often has specific and different meanings in different areas (e.g. “attachment,” “adhesion,” “prepenetration activity” could be the same, or not)
- 5) No way to tell the nature or strength of the evidence –
 - low level of BLAST similarity?
 - extensive experimental confirmation?

The solution to the problem:

the **Gene Ontology (GO)** –

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the **Gene Ontology (GO)** –
an international consortium of scientists
working on diverse genome projects

GO is a set of controlled vocabularies

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= carefully defined terms structured in 3
ontologies

The terms of these 3 ontologies, when attached to a gene via annotation, are used to describe 3 aspects of a gene product:

what it does (**molecular function**),

why it does what it does (**biological process**),

and where it does what it does (**cellular component**)

Thus, **GO** allows all biologists to speak the same biological language:

- To describe the what, where, and why of gene products (a k a annotate them)
- To search and compare annotation data across genomes to answer biological questions

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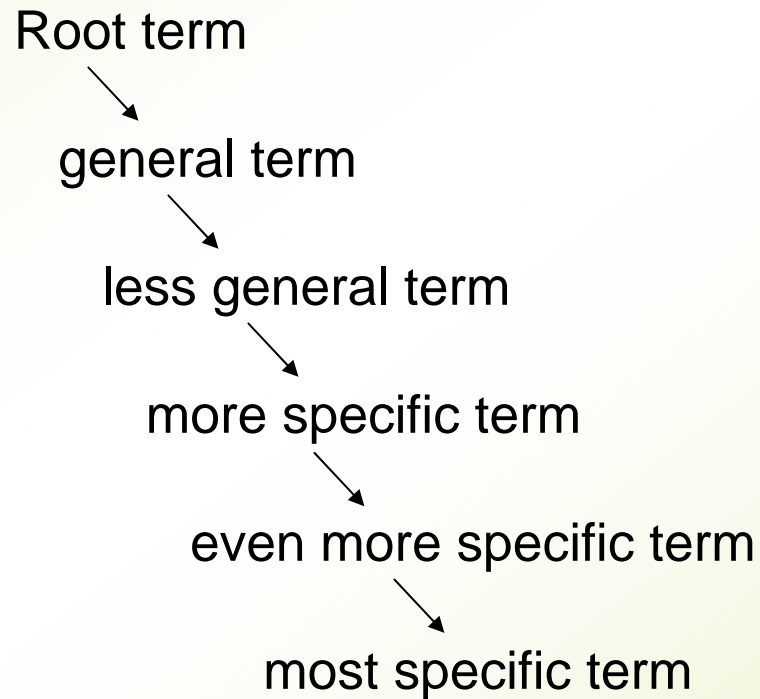
Each term also has a unique id number - this makes the term easily understandable and searchable by a computer.

Each term is related to other terms in a “parent-child” relationship where the child term is more specific than the parent term.

Elements of a GO term

- **ID number:** GO:0012501
- **Ontology:** biological process
- **Name:** programmed cell death
- **Definition:** Cell death resulting from activation of endogenous cellular processes. [source: GOC:lr]
- **Synonyms:** related: necrosis
- **Parent term:** cell death
- **Child terms:** apoptosis, autophagic cell death, hypersensitive response; etc. (many more)
- **Comment:** (None at present)

General GO tree structure



- ⊕ all : all [218166]
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 - ⊕ ⓘ GO:0009626 : hypersensitive response [30]
 - ⊖ ⓘ GO:0035096 : larval midgut cell programmed cell death [2]
 - ⊕ ⓘ GO:0016244 : non-apoptotic programmed cell death [24]
 - ⊕ ⓘ GO:0043067 : regulation of programmed cell death [1638]
 - ⊕ ⓘ GO:0046666 : retinal cell programmed cell death [35]
 - ⊖ ⓘ GO:0010343 : singlet oxygen-mediated programmed cell death [1]
 - ⊖ ⓘ GO:0010198 : synergid death [1]

GO annotation of a gene:

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3) Requires citation of a Reference (PMID #) supporting the annotation and the evidence code

GO and the Start of PAMGO

- GO began as a collaboration among scientists working on eukaryotic model organisms: mouse (MGI), fruit fly (FlyBase), and baker's yeast (SGD)
- Terms relevant to prokaryotic organisms added later, spearheaded by scientists at TIGR (now JCVI)
-- Michelle Gwinn-Giglio
- GO term development is a continuous process (and GO is continually evolving)

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- Bacteria
- Fungi
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- Nematodes

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We realized the power of GO annotation for asking important biological questions across organisms

e.g. What gene products in different pathogens are involved in suppressing host defenses?

But few GO terms were available for annotating genes involved in the different processes of pathogenesis.

Only these GO parent terms:

“pathogenesis”

“host-pathogen interaction”

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Only these GO parent terms:

“pathogenesis”

“host-pathogen interaction”

Insufficient to address questions like:

What gene products in different pathogens are involved in suppressing host defenses?

In early 2004, formation of the **Plant-Associated Microbe Gene Ontology (PAMGO)** interest group

Collaborators from:

Cornell University

North Carolina State University

TIGR

University of Wisconsin at Madison

Virginia Bioinformatics Institute (VPI)

Wells College

.... working on genome projects of plant pathogens:

bacteria -- *Pseudomonas syringae* pathovars,
Erwinia chrysanthemi
Agrobacterium tumefaciens

oomycetes -- *Phytophthora sojae*
Phytophthora ramorum

fungus -- *Magnaporthe grisea*

nematode -- *Meloidogyne hapla*

Original goal of PAMGO:

To develop higher order GO Biological Process terms for annotating genes of microbes implicated in plant pathogenesis

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(All face similar challenges vis-à-vis the host)
- plant and animal hosts
(Some microbial processes used for both – e.g. type III secretion system in bacterial pathogens of plants and animals; similarities in Plasmodium/oomycetes)
- all intimate relationships (mutualistic to parasitic)
(Attachment to host is necessary for both a mutualistic Rhizobium [nitrogen fixation] or a pathogenic Agrobacterium [plant disease])
























The last realization –

that we wanted terms appropriate for the full range of intimate interactions between microbes and their hosts –
led to much discussion among GO members,

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that we wanted terms appropriate for the full range of intimate interactions between microbes and their hosts –
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and to the decision to define a new GO term,
“symbiosis”, according to the broad definition that
encompasses mutualism through parasitism,
with current GO term “pathogenesis” as a child of that
broad term

- [-] all : all [179191] 
- [-]  GO:0008150 : biological_process [138785]
 - [-]  GO:0051704 : interaction between organisms [1595]
 - [-]  GO:0044419 : interspecies interaction between organisms [953]
 - [-]  **GO:0044403 : symbiosis, encompassing mutualism through parasitism [951]** 
 - [-]  GO:0051816 : acquisition of nutrients from other organism during symbiotic interaction [1]
 - [-]  GO:0051825 : adhesion to other organism during symbiotic interaction [88]
 - [-]  GO:0051832 : avoidance of defenses of other organism during symbiotic interaction [312]
 - [-]  GO:0051821 : dissemination or transmission of organism from other organism during symbiotic interaction [12]
 - [-]  GO:0051828 : entry into other organism during symbiotic interaction [75]
 - [-]  GO:0051827 : growth on or near surface of other organism during symbiotic interaction [0]
 - [-]  GO:0051831 : growth within other organism during symbiotic interaction [10]
 - [-]  GO:0051701 : interaction with host [297]
 - [-]  GO:0051702 : interaction with symbiont [0]
 - [-]  GO:0051708 : intracellular protein transport in other organism during symbiotic interaction [3]
 - [-]  GO:0051817 : modification of morphology or physiology of other organism during symbiotic interaction [66]
 - [-]  GO:0051814 : movement within other organism during symbiotic interaction [3]
 - [-]  GO:0044399 : multi-species biofilm formation [0]
 - [-]  GO:0009877 : nodulation [5]
 - [-]  **GO:0009405 : pathogenesis [455]**
 - [-]  GO:0051824 : recognition of other organism during symbiotic interaction [0]
 - [-]  GO:0051836 : translocation of molecules into other organism during symbiotic interaction [54]

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.... appropriate for prokaryotic or eukaryotic microbes

.... appropriate for plant or animal hosts

.... appropriate for mutualistic to pathogenic interactions

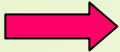
Original PAMGO-developed Biological Process GO terms

- GO:0044403 : symbiosis, encompassing mutualism through parasitism
 - GO:0051701 : interaction with host
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 - GO:0044406 : adhesion to host
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 - GO:0044415 : evasion or tolerance of host defenses
 - GO:0044414 : suppression of host defenses
 - GO:0044007 : dissemination or transmission of organism from host
 - GO:0044409 : entry into host
 - GO:0044408 : growth on or near host surface
 - GO:0044412 : growth within host
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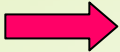

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As genome annotation using the new GO terms began in 2005-2006 for genes implicated in the virulence of the plant pathogens:

- 3 *Pseudomonas syringae* pathovars
- *Erwinia chrysanthemi* 3937
- 2 *Phytophthora* spp.

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It soon became evident that additional, more specific GO terms were necessary to capture information available in the published literature

Some needs were quite complex, and required more general GO discussion

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Related terms did exist in GO, i.e.

GO:0012501 – programmed cell death

GO:0009626 – hypersensitive response

But their current definitions indicated they were to be used to annotate host genes, not microbial (symbiont) genes

“programmed cell death” = "Cell death resulting from activation of endogenous cellular processes"

“programmed cell death” = “Cell death resulting from activation of endogenous cellular processes”

and

“hypersensitive response” = “The rapid death of plant cells in response to invasion by a pathogen”

Again, this need led to a broad discussion among GO Consortium members,
via email
and at the GO Consortium meeting in March, 2006,

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via email
and at the GO Consortium meeting in March, 2006,

.... and the decision that new children terms for GO term
“interspecies interaction between organisms” had to be
created

For example, the new PAMGO term,

“induction by symbiont of host programmed cell death”

for annotating microbial genes

that induce PCD in a host cell

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 - ⊕ ⓘ GO:0051701 : interaction with host [271]
 - ⊕ ⓘ GO:0044003 : modification of host morphology or physiology [92]
 - ⊕ ⓘ GO:0044004 : disruption by symbiont of host cells [63]
 - ⊕ ⓘ GO:0001907 : killing by symbiont of host cells [63]
 - ⊕ ⓘ GO:0052042 : positive regulation by symbiont of host programmed cell death [0]
 - ⊕ ⓘ **GO:0052044 : induction by symbiont of host programmed cell death [0]**



Thus, terms for genes of host having an effect in host:

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vs. terms for genes of microbe having an effect on host:

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PAMGO members wanted to propose as children of
“interspecies interaction between organisms,”

we held a 3-day PAMGO term jamboree in July, 2006, at
TIGR with

- 5 PAMGO members
- 2 members of GO editorial board

to expedite the creation and integration of new, more
specific terms within GO

Many of these new terms are children of
GO:0044003, “modification of host morphology or
physiology”

e.g. “induction by symbiont of defense-related host
cell wall thickening,”

“modification by symbiont of host morphology or
physiology via protein secreted by type III
secretion system,”

“catabolism by symbiont of host cell wall
pectin”

Examples of some more specific GO terms (see handout):

GO:0044003 : modification of host morphology or physiology

GO:0044004 : disruption by symbiont of host cells

GO:0044005 : induction by symbiont in host of tumor, nodule, or growth

GO:0052002 : metabolism by symbiont of substance in host

GO:0052046 : modification by symbiont of host morphology or physiology via secreted substance

GO:0052111 : modification by symbiont of host structure

GO:0019054 : modification by virus of host cellular process

GO:0052031 : modulation by symbiont of host defense response

GO:0052162 : modulation by symbiont of defense-related host calcium ion flux

GO:0052090 : modulation by symbiont of defense-related host calcium-dependent protein kinase pathway

GO:0052090 : modulation by symbiont of defense-related host callose deposition

GO:0052161 : modulation by symbiont of defense-related host cell wall thickening

GO:0052077 : modulation by symbiont of defense-related host ethylene-mediated signal transduction pathway

GO:0052082 : modulation by symbiont of defense-related host jasmonic acid-mediated signal transduction pathway

GO:0052080 : modulation by symbiont of defense-related host MAP kinase-mediated signal transduction pathway

GO:0052084 : modulation by symbiont of host ethylene-mediated defense response

GO:0052553 : modulation by symbiont of host immune response

GO:0052032 : modulation by symbiont of host inflammatory response

GO:0052088 : modulation by symbiont of host jasmonic acid-mediated defense response

GO:0052089 : modulation by symbiont of host salicylic acid-mediated defense response

GO:0052037 : negative regulation by symbiont of host defense response

GO:0052509 : positive regulation by symbiont of host defense response

GO:0052019 : modulation by symbiont of host hormone or growth regulator levels]

GO:0052038 : modulation by symbiont of host intracellular transport

GO:0052190 : modulation by symbiont of host phagocytosis

GO:0052040 : modulation by symbiont of host programmed cell death

GO:0052018 : modulation by symbiont of host RNA levels

GO:0052027 : modulation by symbiont of host signal transduction pathway

GO:0052026 : modulation by symbiont of host transcription

GO:0052091 : modulation by symbiont of nutrient release from host

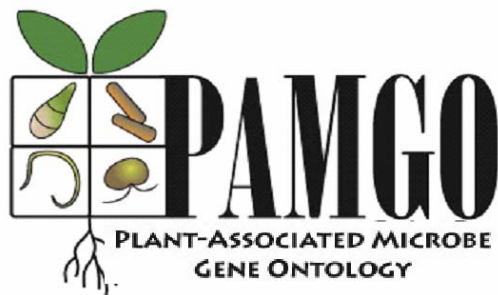
GO:0019087 : transformation of host cell by virus

This is where we need your input,

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to look at the terms and send us suggestions for any that
are needed in your system.

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to look at the terms and send us suggestions for any that
are needed in your system.

Contact us at pamgo-discussion@vbi.vt.edu



(<http://pamgo.vbi.vt.edu>)

Current PAMGO Collaborators

Dr. Candace Collmer (Wells College and Cornell University)

Dr. Magdalen Lindeberg (Cornell University)

Dr. Marcus Constantine Chibucos (Virginia Bioinformatics Institute)

Dr. Trudy Torto-Alalibo (Virginia Bioinformatics Institute) – **Coordinator**

Dr. Brett Tyler (Virginia Bioinformatics Institute) – **PI**

Dr. Michelle Gwinn-Giglio (TIGR)

Dr. Alan Collmer (Cornell University)

Dr. Nicole Perna (University of Wisconsin)

Dr. Jeremy Glasner (University of Wisconsin)

Dr. Joao Setubal (Virginia Bioinformatics Institute)

Dr. David Bird (North Carolina State University)

Dr. Ralph Dean (North Carolina State University)

Dr. Linda Hannick (TIGR)

Dr. Owen White (TIGR)

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The Kauffman Foundation for partial support of a sabbatical leave for CWC, 2003-2004, when PAMGO began

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