Review

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Plants make galls to accommodate foreigners: some are friends, most are foes

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Summary

At the colonization site of a foreign entity, plant cells alter their trajectory of growth and development. The resulting structure – a plant gall – accommodates various needs of the foreigner, which are phylogenetically diverse: viruses, bacteria, protozoa, oomycetes, true fungi, parasitic plants, and many types of animals, including rotifers, nematodes, insects, and mites. The plant species that make galls also are diverse. We assume gall production costs the plant. All is well if the foreigner provides a gift that makes up for the cost. Nitrogen-fixing nodule-inducing bacteria provide nutritional services. Gall wasps pollinate fig trees. Unfortunately for plants, most galls are made for foes, some of which are deeply studied pathogens and pests: *Agrobacterium tumefaciens*, *Rhodococcus fascians*, *Xanthomonas citri*, *Pseudomonas savastanoi*, *Pantoea agglomerans*, '*Candidatus*' phytoplasma, rust fungi, *Ustilago* smuts, root knot and cyst nematodes, and gall midges. Galls are an understudied phenomenon in plant developmental biology. We propose gall inception for discovering unifying features of the galls that plants make for friends and foes, talk about molecules that plants and gall-inducers use to get what they want from each other, raise the question of whether plants colonized by arbuscular mycorrhizal fungi respond in a gall-like manner, and present a research agenda.

'Only connect!' E. M. Forster, *Howard's End*

I. Introduction

Multicellular organisms have homeostatic mechanisms for keeping cellular growth and development on the straight and narrow (Egeblad *et al.*, 2010; Aktipis *et al.*, 2015). Each cell is expected to cooperate in the making of the organism and its offspring. *de novo* organs, such as tumors, arise when cells at a particular location abandon the cooperative endeavor and embark upon a novel program of growth and development. Cells divide more rapidly. Cells grow larger than normal. Undifferentiated cells differentiate in ways that were not expected. Reactivated differentiated cells

dedifferentiate. Previously existing vascular elements are elaborated. New vascular elements are added. Transfer cells make connections between new vasculature and the new or repurposed cells. The *de novo* complex tissues interface with the entire organism. Normal growth suffers. Developmental plasticity makes all of this possible.

What causes cells to depart from the norm? In humans, the *de novo* growths that receive the most attention are cancers (Aktipis *et al.*, 2015). Some cancers are associated with colonization by a living foreign agent, such as a virus or bacterium. Others are associated with an internal cause: something goes wrong during the organism's growth and development. Somatic mutation is a starting point. Plants provide a contrast (Aktipis *et al.*, 2015). The *de novo* growths that receive the most attention are 'galls' (White, 1951; Braun, 1954, 1958, 1978; Meyer, 1987; Shorthouse & Rohfritsch, 1992; Williams, 1994; Stone & Schönrogge, 2003; Agrios, 2005; Raman *et al.*, 2005; Spooner & Roberts, 2005; Redfern, 2011). Galls have an external cause. The starting point is colonization by a foreigner: a virus, bacterium, protozoan, oomycete, true fungus, parasitic plant, or an animal, including rotifers, nematodes, insects, and mites. The plant is the 'gall-maker'. For want of a better name, we shall call the foreigner the 'gall-inducer'.

Another contrast with cancer is this: cancers are, by definition, not beneficial for the organism that makes them; galls are different because the maker can benefit. Plants make root nodules for nitrogen (N_2)-fixing bacteria, which provide nutritional services for the plant (Oldroyd *et al.*, 2011). Fig trees make galls for the immature developmental stages of a gall wasp, which as an adult provides pollination services (Cook & Raplus, 2003). In these instances, the gall constitutes a reward offered by the plant for services rendered. These relationships are classified as mutualisms, or 'partnerships', because, under most conditions, both parties benefit from the relationship (Bronstein, 1994, 2015; Bronstein *et al.*, 2006).

Symbiosis is defined as a close, ongoing relationship between two 'unlike' organisms (Bronstein, 2015). The relationship can take the form of mutualism, parasitism, or commensalism. Most galls involve two organisms that are very 'unlike', the exception being the galls that plants make for parasitic plants. As we will see, galls as mutualisms are often referred to as symbioses, while galls as parasitism are generally not.

Redfern (2011), who wrote a book about all types of plant galls made for all types of gall inducers, gave this definition: 'galls are growths on plants formed of plant tissue but caused by other organisms'. We have a longer definition: a gall is a manifestation of the reprogramming of plant cellular growth and/or development – possibly harmful, beneficial, or neutral for the plant – that begins at the colonization site of a specific foreign organism, which receives specialized services from the plant and continues to interact with the *de novo* plant tissue or organ as it develops and matures.

This is a checklist for what a gall is: growth and development of plant cells depart from the norm; the departure involves just one small part of the plant; timing and location are precise, as determined by when and where the foreigner starts interacting with the plant cells that are the originators of the *de novo* growth and development; making the *de novo* growth is an on-going process that depends on the foreigner's on-going association with the plant; the foreigner benefits from its association with the *de novo* tissues, evidence for this being successful completion of requisite developmental stages and production of offspring; fitness consequences for the plant are variable, and may take the form of benefits, harm or neither benefit nor harm.

Here are some examples of what a gall is not. Plants sometimes create a 'neoplasm' when a plant-feeding insect deposits an egg (Doss *et al.*, 2000); the egg is lifted off the plant surface by the neoplasm and falls to the ground, where the egg may be eaten. The larva hatching from the egg may fail to return to the plant. The plant neoplasm is meant to harm the plant-feeding insect, and thus it is not a gall – galls always benefit the gall-inducer. If the plant creates a structure that benefits a foreigner but its creation is not strictly tied to colonization by the foreigner, this again does not constitute a gall. Ant colonies protect *Acacia* (Fabaceae) trees by attacking herbivores large (e.g. elephants) and small (e.g. insects) (Bronstein *et al.*, 2006). Plants make little houses called 'domatia' to provide ants with shelters for raising offspring. Plants also make various 'food bodies' to provide ants with carbohydrates and protein. The items are produced by the plant before colonization in order to entice future colonization. While it is true that the plant can create more of each item after it has been colonized by ants, this does not make the item a gall.

Plant galls take myriad forms. Redfern (2011) highlights two distinct types. One is a gall that looks unlike anything the plant species normally makes. This type of gall can either be clumsily-formed (Fig. 1a,b) or a 'tidy' thing that has the pleasing appearance of an ornament (Fig. 1c–h). The second type of gall is comprised of one or more items that the plant normally makes: a root, hair, leaf, stem, twig, bud, inflorescence, seed or fruit. The item is classified as a gall because it is made in a strange manner and is occupied by a gall-inducer. The item can be greatly enlarged. Many copies are made instead of just one. The item appears at a strange time during the plant's lifecycle or in the wrong place on the plant's body. Roots sprout from a stem. Bunches of leaves appear where a flower was expected. The strangeness can be relatively minor – the edge of a leaf is curled (Fig. 1i); a seed is slightly swollen (Fig. 1j) – or the strangeness can be elaborate – growing on a branch of a tree, a dense mass of shoots called a witch's broom (Fig. 1k) looks like a bird's nest from afar.

Many parts of the plant are capable of making galls for many types of organisms (Fig. 2). From the individual gall-inducer's perspective, the changes in growth and development that are elicited from the plant are unique for the most part, being specific to the interactions of one specific type of gall inducer with one specific type of plant. Sometimes there are genotypes within the host plant species that fail to make the gall, presumably by resisting the wiles of the gall-inducer. It seems likely that galls are underreported for the underground parts of plants (Fig. 2). Part of this underreporting may include underground galls as mutualisms. Fig. 2 shows one ecologically important group – nitrogen-fixing, root nodule-inhabiting bacteria. Later we discuss whether responses of plant roots to another ecologically important group – arbuscular mycorrhizal fungi – are gall-like. Nematodes are another gall-inducing group that lives underground, feeding on plant roots. And yet, the very first discovery in 1743 of nematodes as plant parasites

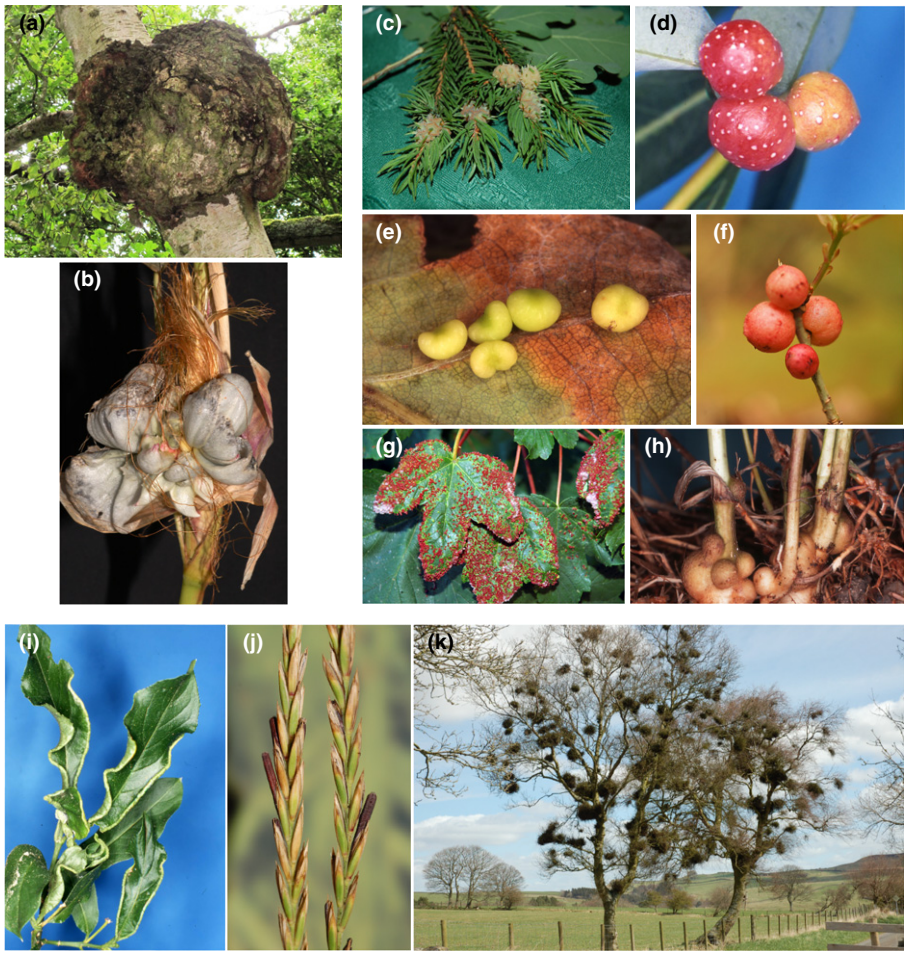

Fig. 1 Examples of types of *de novo* growths created by plants. (a) Tree trunk infected by the bacterium *Agrobacterium tumefaciens*. (b) Maize inflorescence infected by the fungus *Ustilago maydis*. (c) Spruce infected by the aphid *Adelges laricis*. (d) Willow leaves infected by the sawfly *Eupontania viminalis*. (e, f) Oak infected with asexual generation or sexual generation, respectively, of the gall wasp *Trigonaspis megaptera*. (g) Maple leaves infected by the gall mite *Aceria myriadeum*. (h) Goat's beard crown infected by the gall wasp *Aulacidea tragopogonis*. (i) Spindle leaves infected by the gall mite *Stenacis euonymi*. (j) Couch grass inflorescence infected by the fungus *Claviceps purpurea*. (k) Birch trees infected by the fungus *Taphrina betulina*. All photos are from *Britain's Plant Galls* and were used with permission from the book's author, Michael Chinery (2011).

was of a gall-inducing nematode that lives on the aboveground parts of plants (Agrios, 2005). *Anguina tritici* juveniles climb seedling wheat plants by swimming in a film of water, eventually entering the floral primordium. Each seed gall hosts production of up to 30 000 eggs. When the gall falls to the ground, juveniles inside the gall can survive for up to 30 yr.

Galls have not received the attention they deserve. They are often seen as quaint oddities rather than as indicators of interesting happenings in the world of plants and their biotic interactions. The quote only connect at the beginning of this review signals our interest in showing how galls are connected to subjects of current interest in biology. Regenerative growth is an example. Broadly speaking, regenerative growth is organismal growth that 'restarts' at a particular location. The easiest way to make organismal growth restart in the laboratory is to injure the test subject by cutting off part of its body. Plants are commonly subjected to this sort of experimental treatment. Gall inducers offer another – far more interesting – experimental treatment for restarting plant growth. This connection makes recent discoveries about plant regenerative growth relevant for galls. Ikeuchi *et al.* (2019) review many things that have recently been learned about molecular mechanisms of plant regeneration.

A different connection is claimed for parasitic gall-inducers (Orlovskis & Hogenhout, 2016). In the world of host–parasite interactions, there is a phenomenon wherein the host – under the tutelage of a parasite – becomes a 'zombie' by turning against its own reproductive self-interest. 'Neuroparasites' have this effect on animal hosts by manipulating their central nervous system (Melhorn, 2017). The protozoan *Toxoplasma gondii* needs multiple hosts to complete its life cycle (Webster, 2007). Intermediate hosts are species of warm-blooded animals. Reproduction occurs in definitive hosts like cats (Felidae). *Toxoplasma*-infected rodents exhibit novel behaviors that promote being eaten by a cat, thereby benefiting the *Toxoplasma* life cycle. Another example: a fungus called *Massospora cicadina* uses infected insects called cicadas as hosts but also as a mechanism for spreading spores (Boyce *et al.*, 2019). Neuro-active chemicals produced by the fungus stimulate infected cicadas to continue flying and to seek mating opportunities. This exaggerated behavior is useless for the cicada because

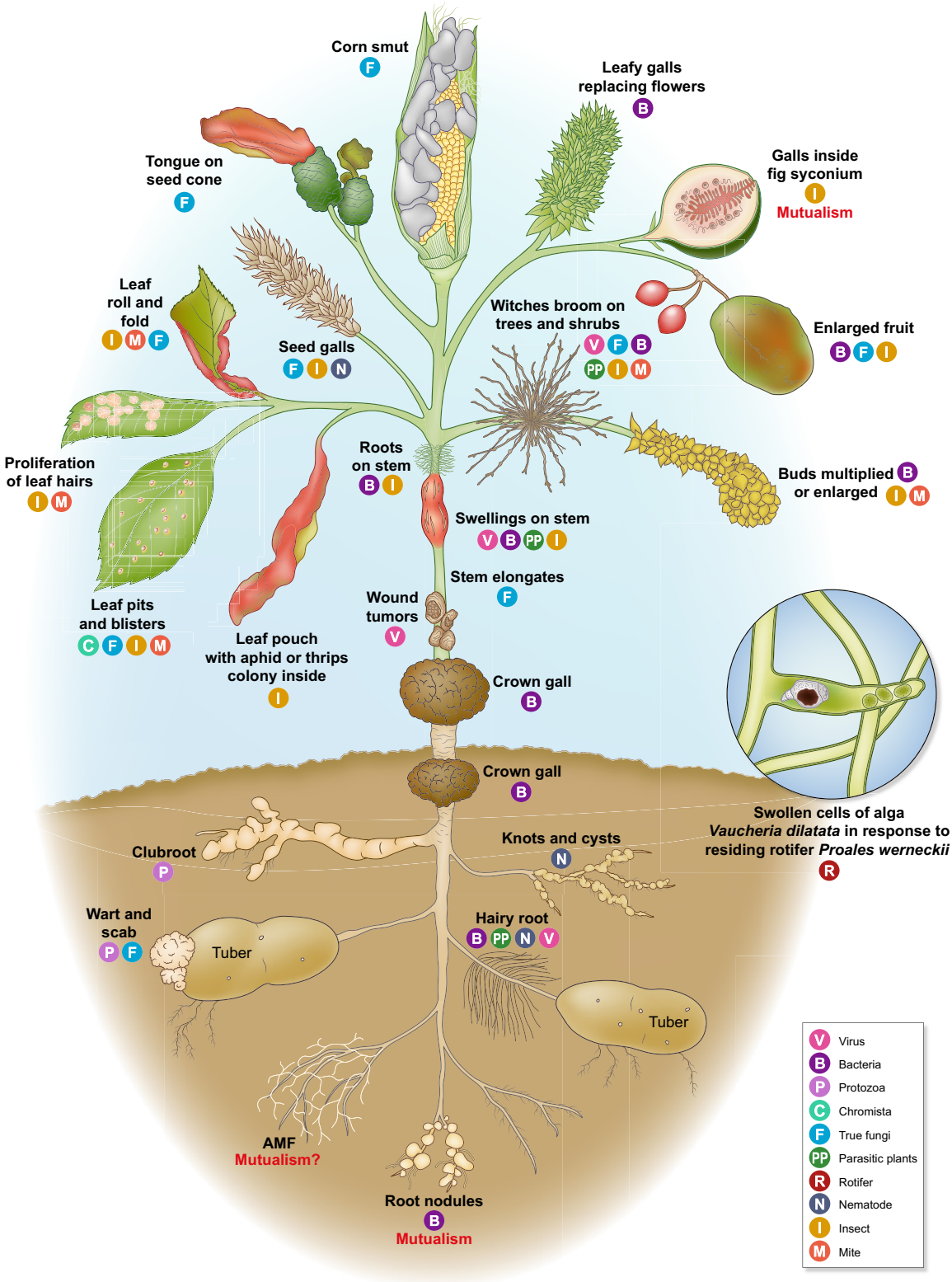

Fig. 2 Many parts of plants make galls for many types of gall inducers. The plant shown here is not drawn to scale and does not represent any one plant species. Rather, the plant represents a compendium of the many types of *de novo* growths that plants are able to make in association with a single gall inducer. A key provides the abbreviation for each group of gall inducers. Next to each gall in the illustration, the abbreviations provide examples of gall inducer groups that can have this sort of effect on this plant item.

reproduction is no longer possible, much of the cicada's body having already been destroyed by becoming a factory for production of fungal offspring.

Plants do not have a central nervous system. Instead gall-inducers turn plants into 'zombies' by manipulating their growth and development (Roy, 1993; Pfunder & Roy, 2000; Goethals *et al.*, 2001; Sugio *et al.*, 2011; Du Toit, 2014). The North American rust fungus *Puccinia monoica* has an outcrossing mating system that requires the bringing together of opposite mating types. The fungus is incapable of achieving this task on its own. Instead, it recruits the services of winged insects (Roy, 1993). Preparations begin in late summer when the fungus infects species of *Arabis*. During the winter, fungal mycelia invade the plant's meristematic tissue. The following summer, the stem of *Arabis* responds by elongating much earlier than is usual. Next a 'pseudoflower' composed of dense brightly-colored yellow leaves is created. The attractiveness of the pseudoflower is enhanced by the fungus emitting volatile chemicals that – together with the visual cues of the pseudoflower – attract bees, butterflies and flies. The fungus also produces a sugary 'nectar', which encourages the insects to search the plant in a manner that facilitates the bringing together of the opposite fungal mating types. When the fungus has achieved its purposes and no longer needs the plant, the pseudoflower turns green. The plant never produces its own flowers, having been 'castrated' by the fungus. A similar cunning scenario unfolds when the European rust fungus *Uromyces pisi* colonizes *Euphorbia cyparissias* (Euphorbiaceae) (Pfunder & Roy, 2000).

Not all gall-inducers have such dramatic impacts on plants. Generally, just one part of the plant is taken over, rather than the whole plant. Sometimes that part is very small. And yet, even the smallest plant gall alerts us to something that is not talked about nearly enough in the field of plant biotic interactions. Consider the self-serving functions of foreigner-produced molecules known as 'effectors' (Hogenhout *et al.*, 2009). Colonization is a time when the body of the foreigner specializes in the production and delivery of effectors. Foreigners have specialized structures and behaviors that enable transfer of effectors from their body to the body of the plant. The most deeply-studied function of effectors is suppression of plant defense mechanisms (Toruño *et al.*, 2016). Galls remind us that effectors have additional functions.

Being a good host is not just about letting down your defenses. The very best hosts create and deliver new and/or improved services for their associates. We do not claim that gall-inducers are the only plant associates that induce plants to create new or improved services – we think it is a common phenomenon. What we claim is that the phenomenon is more obvious for gall inducers. Moreover, the visible changes in plant growth – the gall – remind us to look more closely at microscopic changes in cellular development at the colonization site. Looking for microscopic changes in cell types at colonization sites seems less common for non-galling plant associates, which alter plant cellular development in the absence of noticeable effects on plant growth (Wildermuth, 2010; Chandran *et al.*, 2010).

II. Defining the project

Our intentions are to introduce new audiences to plant galls, update knowledge for those already familiar with plant galls, broaden the perspective of people who know one gall-inducing organism but not the others, stimulate cross-disciplinary research, and inspire efforts to define unifying features of plants as gall-makers and plant associates as gall-inducers, as well as the unique properties that emerge from their biotic interactions.

We begin by showing the phylogenetic diversity of gall-inducers and of plants that make galls. Next, we describe services that galls provide for gall-inducers. Under the topic of galls as mutualistic relationships, we discuss what happens during gall inception and explore whether arbuscular mycorrhizas induce plants to produce gall-like symptoms. Under the topic of galls as parasitism, we introduce a molecular model of parasite offense and plant defense and discuss what happens during gall inception for two gall-inducing bacterial species. Items for a research agenda are mentioned throughout our review and are summarized at its conclusion.

III. Diverse biotic interactions

Redfern (2011) summarizes evidence from the fossil record. One of the oldest known fossil galls was produced by a tree fern living in the middle of North America in the late Carboniferous era, *c.* 302 Ma (Labandeira & Phillips, 1996, 2002). The fossil revealed the overall structure of the gall, as well as an inside chamber lined with enlarged cells and patches of smaller cells that look like callus tissue. The gall appears similar to those produced for modern-day sawflies (Redfern, 2011). However, sawfly fossils first make their appearance later, during the Permian era. Galls became commonplace during the Cretaceous, a time when both flowering plants and herbivorous insects were diversifying rapidly (Redfern, 2011).

Table 1 lists many of the species mentioned in this review. It is organized according to the taxonomic affiliation of gall-inducers (Ruggiero *et al.*, 2015). Most of the gall-inducers in Table 1 are associated with land plants. There are fewer examples of galls made by aquatic plants. Galling fungi associate with types of freshwater charophyte algae (Spooner & Roberts, 2005) that are considered paraphyletic to land plants (Lewis & McCourt, 2004). Fungal species belonging to the family Chytridiaceae parasitize desmids, diatoms, stoneworts (Charales) and filamentous algae (Spooner & Roberts, 2005). The rotifer *Proales werneckii* – the only known gall-inducer in the phylum Rotifera – parasitizes *Vaucheria* green algae species (Fig. 2, class Xanthophyceae) (Spooner, 1994). The only ocean plants known to produce galls are seaweeds belonging to the genera *Ascophyllum* and *Fucus* (Coles, 1958). The small, rounded nodules these seaweeds produce contain tylenchid nematodes, either *Halenchus fucicola* in the case of *A. nodosum* or *H. dumnonicus* in the case of *F. vesiculosus* and *F. serratus.*

In Table 1, groups of mutualists are shown in bold type. In a process known as nitrogen fixation, bacteria living inside root nodules convert atmospheric nitrogen into ammonia or related nitrogenous compounds. A single evolutionary innovation enabled the evolution of N_2-fixation in angiosperms (Werner *et al.*, 2014). Today, there are many plant species that make root nodules to accommodate N_2-fixing bacteria (Oldroyd *et al.*, 2011). Gram-negative bacteria belonging to the phylum Proteobacteria have N_2-fixing genera in two classes, referred to

Table 1. Gall inducing taxa include viruses and diverse species spanning the tree of life, as classified by Ruggiero *et al.* (2015).

VIRUS Double-stranded RNA virus, Family Reoviridae, Genus Phytoreovirus, Wound tumor virus **B** (dicots, not monocots)
SUPERKINGDOM PROKARYOTA
KINGDOM EUBACTERIA
SUBKINGDOM NEGIBACTERIA (GRAM NEGATIVE)
Phylum Proteobacteria
Class Alphaproteobacteria:
Rhizobium radiobacter formerly named *Agrobacterium tumefaciens* crown gall **B**
Rhizobium*, *Bradyrhizobium*, and *Azorhizobium – **nodule-inducing nitrogen-fixers on Fabaceae R**
Class Betaproteobacteria – **nodule-inducer *Paraburkholderia mimosuraum* on *Mimosa pigra* (Fabaceae) R**
Class Gammaproteobacteria: *Xanthomonas citri* citrus canker on Rutaceae **R**
Pseudomonas savastanoi olive knot on Lamiales **R**
Pathovars of *Pantoea agglomerans* on Caryophyllaceae (gypsophila) and Amaranthaceae (beets) **R**
SUBKINGDOM POSIBACTERIA (GRAM POSITIVE)
Phylum Actinobacteria – Class Actinobacteria: *Rhodococcus fascians* leafy gall **B**
***Frankia* spp. as nodule-inducers and nitrogen-fixers on *Alnus* and *Myrica* R**
Phylum Tenericutes
Class Mollicutes: *Candidatus* Phytoplasma asteris aster yellows **B**; both plants and insects are hosts
SUPERKINGDOM EUKARYOTA
KINGDOM PROTOZOA – **Phylum Plasmodiophoromycota** – *Plasmodiophora brassicae* – clubroot of brassicas **R**
KINGDOM CHROMISTA – **Phylum Oomycota** – *Albugo candida* – White blister **R**
KINGDOM FUNGI – **Phylum Ascomycota** Class Taphrinomycotina – *Taphrina deformans* – peach leaf curl **R**
Class Sordariomycetes – *Claviceps purpurea* – ergot on cereals **R**
Gibberella fujikuroi – foolish seedling disease in grasses **R**
Phylum Basidiomycota
Class Pucciniomycetes – rust fungus *Puccinia graminis* as a major pathogen of wheat **R**
Class Ustilaginomycetes – *Ustilago maydis* – maize smut on *Zea mays* **R**
Phylum Chytridiomycota – *Synchytrium endobioticum* – potato wart disease **R**
Family Chytridiaceae spp. and galls in desmids, diatoms, stoneworts, and filamentous algae **R**
KINGDOM PLANTAE – **Phylum Tracheophyta** – *Arceuthobium* spp. dwarf mistletoe **R**; *Rhinanthus minor* rattle **B**
KINGDOM ANIMALIA –
Phylum Rotifera – *Proales werneckii* on yellow-green algae *Vaucheria* spp. **R**
Phylum Nematoda – Order Tylenchida – *Halenchus* species on *Ascophyllum* and *Fucus* sea weeds **R**
Meloidogyne incognita root knot nematode on many species **B**
Heterodera glycines cyst nematode on *Glycine max* soybean **R**
Phylum Arthropoda – *SHOWN ARE FIVE ORDERS WITH THE GREATEST NUMBERS OF GALLING SPECIES*
Subphylum Chelicerata, Class Arachnida
Order Trombidoformes; eriophyid mites (Eriophyidae) as specialists on many plant species **R**
Subphylum Hexapoda, Class Insecta
Order Diptera – gall midges (Cecidomyiidae) – *Mayetiola destructor* Hessian fly – major pest of wheat **R**
'Ambrosia' gall midges – expansion of host range in association with fungal symbionts
True fruit flies (Tephritidae) – *Eurosta solidaginis* on *Solidago* **R**
Urophora BIOCONTROL of knapweed *Centaurea* spp. **R**
Order Hymenoptera – Sawflies (Tenthredinidae) – *Euura* species diversification on Salicaceae **R**
Oak gall wasps (Cynipidae) – *Biorhiza pallida* and *Belonocnema treatae* on *Quercus* **R**
Chesnut gall wasp (Cynipidae) – *Dryocosmus kuriphilus* as major pest of *Castanea* spp. **R**
Pollinating fig wasps (Agaonidae) plus various non-pollinating species on *Ficus* R
Pteromalidae – *Trichilogaster acacialongifoliae* BIOCONTROL of invasive *Acacia longifolia* **R**
Order Hemiptera – Aphids (Aphididae) – *Pemphigus* on *Populus*; *Baizongia pistaciae* on *Pistacia* spp. **R**
Phylloxera (Phylloxeridae) – *Daktulosphaira vitifoliae* grape phylloxera as major pest of *Vitis* **R**
Adelgids (Adelgidae) – *Adelges abietus* as pest of Coniferales **R**
Scales (Coccoidea) – *Apiomorpha* (species-rich) and *Maskellia* (species-poor) on *Eucalyptus* spp. **R**
Psylloids (Psyllidae) – *Pachypsylla* spp. on hackberry *Celtis* spp. **R**
Order Thysanoptera – thrips (Phlaeothripidae) – *Austrothrips cochinchinensis* on *Calycopteris* **R**

Taxon is shown along with common name. Groups containing mutualists are indicated in bold type. Host plant range is classified as restricted **(R)** or broad **(B)**, as explained in the text.

as alpha-rhizobia and beta-rhizobia, respectively, or 'rhizobia' collectively. Gram-positive bacteria have N_2-fixing *Frankia* species in the phylum Actinobacteria. At the bottom of Table 1, there is a very different type of gall-inducing mutualist. Fig trees (Moraceae) make galls that feed and house the immature larval stages of fig wasps (Arthropoda-Hymenoptera: Agaonidae), which grows up to be the winged adult that pollinates the tree's flowers (Cook & Raplus, 2003).

Symbionts – regardless of whether they are mutualists, parasites or commensalists – have specialized relationships with hosts and therefore usually have a restricted host range. Gall-inducing species generally meet this expectation, but there are a few exceptions. In

Table 1, species with a restricted host range are indicated by **R**. Many of these have a single host plant species. In Table 1, gall-inducers labelled with a **B** have a broader host range, defined here as the ability to use hosts belonging to two or more plant families. Scientists studying species that have a broad host range have benefited from research tools developed for the model plant *Arabidopsis thaliana*. In the world of bacteria, an example is *Agrobacterium tumefaciens*, which is considered 'promiscuous' because it infects plant species belonging to 140 genera and at least 60 families (De Cleene & De Ley, 1976). In the world of animals, an example of broad host range is the root knot nematode *Meloidogyne incognita* (Berg & Taylor, 2009). A group of insects known as 'ambrosia' gall midges have a broader host range than their gall-inducing relatives (Joy, 2013). Fungi also live in ambrosia galls. They may assist with gall induction or may be the actual gall inducer.

Some gall-inducing species use different hosts during different parts of their life cycle (Redfern, 2011). If the part of the life cycle associated with a particular host is optional rather than obligatory, this alternate host is not used as frequently as the primary host. The stem rust fungus *Puccinia graminis* (also known as black rust) uses wheat *Triticum aestivum* L. as its primary host and barberry species (Berberidaceae) as its alternate host (Zhao *et al.*, 2016). Barberry is where genetic recombination occurs through sexual reproduction (Berlin *et al.*, 2017) and also is the only host that makes a gall for the fungus (Spooner & Roberts, 2005). And yet, there is a connection between what happens on barberry and what happens on wheat: the new recombined genotypes that arise on barberry are often better equipped to overcome wheat defense mediated by *Resistance* genes (Singh *et al.*, 2011). Removal of barberry from the landscape significantly reduces stem rust threats to wheat (Zhao *et al.*, 2016).

One gall-inducer is noteworthy for contributions to basic and applied science (Table 1). In the early part of the twentieth century, the bacterium *A. tumefaciens* became an important model for the study of tumors. Smith & Townsend (1907) were first to demonstrate that tumor-forming symptoms were associated with infection by a bacterium and to experimentally induce tumors in the laboratory, a feat envied by cancer researchers. In the 1970s it was discovered that, during colonization, part of a large *Agrobacterium* plasmid (Zaenen *et al.*, 1974) is transferred into plant cells and integrated into a chromosome (Chilton *et al.*, 1977; Van Montagu *et al.*, 1980). After integrating the transfer-DNA, the plant is guided by instructions from its new DNA. Starting in the 1980s, humans started using *Agrobacterium*'s method to genetically engineer various transgenes into crop plants (Lemaux, 2008; 2009). As we shall see, humans continue to find new uses for *Agrobacterium*.

The fame of the fungus *Gibberella fujikuroi* – the causal agent of 'foolish seedling disease' (Table 1) – comes from being the organism in which gibberellin (GA) was first discovered (Yabuta & Sumiki, 1938). Gibberellin was subsequently discovered in many other organisms, most notably plants, but also in bacteria, including N_2-fixing rhizobia and plant pathogens (Hedden & Sponsel, 2015). Learning how GAs influence plant growth enabled identification of the plant dwarfing genes that were used to increase crops yields during the 'Green Revolution' (Hedden, 2003).

Plants are not necessarily at the mercy of gall inducers. In textbooks, gall-inducing species provide examples of the power of plant resistance (Agrios, 2005; Pedigo & Rice, 2009). Grape phylloxera *Daktulosphaira vitifoliae*, a native of North America, showed up in Europe in the mid-nineteenth century and threatened to destroy the French wine industry (Granett *et al.*, 2001). The problem was solved by grafting vines onto resistant rootstocks and by creating hybrids between French *Vitis vinifera* and resistant American *Vitis* species. For two other gall-inducing species, we know that host plants are protected by '*Resistance* genes', which are discussed in greater detail in section VII, 'Galls as parasitism'. Stem rust is a global pathogen of wheat. New stem rust strains arising on the alternate host barberry are sometimes able to overcome *Resistance* genes deployed in wheat (Zhao *et al.*, 2016). Fortunately, hundreds of *Resistance* genes have been discovered in wheat and its relatives, among which have been found genes effective against new stem rust strains (Singh *et al.*, 2011; Dean *et al.*, 2012; Harris *et al.*, 2014; Lorrain *et al.*, 2019). This is also the case for the Hessian fly, *Mayetiola destructor*, an insect pest of wheat that caused havoc when it invaded North America in the late eighteenth century (Harris *et al.*, 2003). *Resistance* genes have provided effective control of its populations for over 200 yr (Harris *et al.*, 2014). Wheat also has *Resistance* genes for gall-inducing nematodes and mites.

Humans have found many uses for gall-inducers, which are reviewed by Redfern (2011). Table 1 lists gall-inducing species that have been heroes of biological control programs for invasive weeds (Redfern, 2011; Winston *et al.*, 2014). In the prairie grasslands of North America, the knapweeds *Centaurea diffusa* and *Centaurea biebersteinii* are managed through releases of *Urophora* tephritid species (Diptera). In South Africa, invasive *Acacia longifolia* is managed by releases of the gall wasp *Trichilogaster acacialongifoliae* (Hymenoptera).

For centuries, galls have been used by practitioners of folk medicine, in part because of their high tannin content (Redfern, 2011). Today galls are important for drug discovery. An example: ergot fungal species belonging to the genus *Claviceps* (Table 1) produce the famously harmful chemicals that cause gangrenous and convulsive ergotism in humans and domestic animals. However, *Claviceps* fungi also produce useful chemicals such as ergotamine, which is used to treat migraines. Recently, the genetic engineering skills of *A. tumefaciens* were used to create *Claviceps paspali* strains that produce only the chemicals that are useful (Kozák *et al.*, 2018).

Many gall-inducing animals – nematodes, insects, mites (Table 1) – are similar to N_2-fixing bacteria in that they live inside a chamber fabricated by the plant. Specialized feeding cells typically line the walls of the chamber. Cells comprising this and other layers of the gall generally exhibit a 'syndrome' of cytological features that is unique to the species of gall-inducer (Bronner, 1992; Westphal, 1992; Rohfritsch, 1992; Berg & Taylor, 2009). In addition to the creation of novel cells for feeding and protecting the gall inducer, the plant creates novel vasculature and transfer cells in order to make connections with its gall-inducing 'friend' or 'foe' (Melnyk, 2016).

The very large animal phylum Arthropoda (Table 1) contains the vast majority of described gall-inducing species. It is estimated there are as many as 30 000 gall-inducing insect species (Raman *et al.*, 2005). As many as 15 000 vascular plant species make galls for diverse Arthropods (Meyer, 1987). The table shows the five orders of Arthropoda that have the greatest numbers of galling species. Two other orders of insects have gall-inducing species – Coleoptera (beetles) and Lepidoptera (moths and butterflies) – but are not listed because gall-inducing species are so rare. The rarity of gall-inducers in these two insect orders is surprising. There are 393 415 described species of Coleoptera and 158 570 species of Lepidoptera (Zhang, 2013). About half of these species feed on plants (Strong *et al.*, 1984). This leads us to a question: why are there so few gall-inducing species in these two very large insect orders that have so many plant-feeding species?

Insect gall-inducing species have been subjects of famous long-term ecological studies (Table 1): true fruit flies (Tephritidae) on *Solidago* (Abrahamson & Weis, 1997), *Euura* and *Pontania* sawflies on *Salix* (Price, 1992; Hardy & Cook, 2010), *Pemphigus* aphids on *Populus* (Whitham, 1992; Larson & Whitham, 1997), and cynipid oak gall wasps on *Quercus* (Stone & Schönrogge, 2003; Egan *et al.*, 2012; Hearn *et al.*, 2019). Galls of oak gall wasps are attacked by parasitic plants (Egan *et al.*, 2018). *Euura* sawfly species on *Salix* provide examples of the exceptional species diversification that can occur in association with plants (Hardy & Cook, 2010).

IV. Comparing galls and gall inducers

Table 1 shows why the task of comparing gall-inducing species is so much harder than comparing plants as gall-makers. Plants are built along similar lines and share options for dealing with foreigners. By contrast, gall-inducing species are wildly different (Redfern, 2011). Their sizes and bodies are hopelessly different. Their actions are different. In particular, gall-inducing animals and microbes seem very different. By having flight as adults and the ability to walk during plant-feeding stages, insect gall-inducers have the opportunity to find and choose between a variety of habitats, plant species, individual plants, and locations within plants. Gall-inducing mites and nematodes lack wings but can walk or crawl. They also seem to exhibit some degree of choice. Many gall-inducing animals – having already found a host plant – seek out naturally occurring growing points where meristems already exist (Redfern, 2011), including growth zones in leaves and buds and the cambium of leaf veins, stems, and roots. Gall-inducing microbes presumably have fewer options for finding plants and seeking out particular locations, the exception being when they recruit winged insects to do this work for them (Sugio *et al.* 2011; MacLean *et al.*, 2014).

By reading Redfern (2011), we learn that the actions of gall-inducing animals and microbes become more similar during gall inception. At this time, what they have in common is the habit of 'staying put'. This may come naturally for bacteria and fungi, but it is not natural for plant-feeding animals. Most animal species, while feeding on plants, move about freely over the surfaces of the plant. Some move between multiple plants. Gall-inducing animals are different. By 'staying put' during colonization, they interact with relatively few plant cells. The scale of their interactions is made even smaller by deploying a very small part of their body, which is used to introduce effector molecules to plant cells and to inflict specific patterns of wounding. Needle-like mouthparts called stylets are a typical example of such a body part, and these are connected to the glands that make effectors. A tiny eriophyid mite attaches its stylets to a single plant cell and may not move for days (Westphal, 1992). The longer it stays, the bigger the gall. A different body part, deployed by gall wasps and sawflies (Table 1; order Hymenoptera), is a needle-like apparatus called an ovipositor which is used to introduce eggs to specific groups of plant cells, but also serves to wound cells and introduce effectors (Martinson *et al.*, 2015). The fact that both microbial and animal gall-inducers 'stay put' during gall inception narrows the research focus to a small group of plant cells, which are more easily compared across galls and gall inducers than the diverse end products (the galls).

V. Galls provide services

The services plants give to gall inducers appear under six themes (Table 2). The first is nutrition. Better nutrition takes many forms. One is production of a food that can only be eaten by the gall-inducer. Crown galls produce opines that can only be catabolized by the *A. tumefaciens* strain causing the infection. The plant metabolome is remodeled to produce the novel food, as is the primary metabolic response of *A. tumefaciens* to catabolize the novel food (Gonzalez-Mula *et al.*, 2019).

A second theme is protection. Shelters provide greater stability of abiotic and biotic conditions. These benefits are generally assumed for all gall-inducers that are surrounded – entirely or partially – by gall tissue (Stone & Schönrogge, 2003; Redfern, 2011). If you live in an enclosed space, waste disposal becomes a problem. Galls that accommodate gall-inducing aphids have a solution: the liquid waste produced by hundreds of aphids living inside the gall is absorbed by the inner surface of the gall (Kutsukake *et al.*, 2012). Further removal of the waste occurs via the plant's vascular system.

A third theme is transportation. This can be as simple as transport from inside the plant to the outside world. The bacterium citrus canker *Xanthomonas citri* (Table 1) moves from the plant interior to the plant surface when the outer layer of the gall dies and cracks open (Brefort *et al.*, 2009). Galls associated with rust fungi are designed to create a force that expels fungal spores into the airstream (Spooner & Roberts, 2005). More sophisticated transport occurs when the gall attracts winged insects, as occurs with leafy galls induced by the phytoplasma *Candidatus asteris* (Sugio *et al.*, 2011; MacLean *et al.*, 2014). Leafhoppers oblige phytoplasmas by providing transport to new plant hosts, but they also serve as hosts themselves.

A fourth theme is reproduction. The gall's effect on reproduction by adults is generally a function of greater production of offspring or better accommodations for immature stages. For gall-inducers that produce multiple generations inside a single gall – bacteria, aphids, and thrips – numbers of offspring generated inside galls can be enormous. A large leaf pouch gall (Fig. 2) housing 10 000 or more individuals is produced for the pistachio aphid *Baizongia pistaciae* (Wool, 2004).

The fifth theme is space for communal functions. In communities, different groups specialize in different tasks. In the insect orders Hemiptera and Thysanoptera (Table 1), soldier castes only

Table 2. Services galls provide for gall-inducers.

NUTRITION (expected for all gall-inducers)
Plant food of higher quality or greater quantity than what the plant normally offers
Food that can only be eaten by the gall associate (e.g. opines as food for *Agrobacterium tumefaciens*)
Food that is available over a longer period (e.g. delayed senescence of gall tissue)
Food produced inside plant cells becomes accessible to organisms that live outside cells
(e.g. wall of nutritive cell autolyses, releasing cell contents to insects and mites)
(e.g. sugars exported out of plant cell to *Xanthomonas* species living in extracellular spaces)
PROTECTION (expected for most gall-inducers)
Protection against biotic stress (e.g. predators, parasites, pathogens and competitors)
Protection against abiotic stress (e.g. extreme temperature, humidity, light, salinity)
A suitable place to cultivate fungal symbionts (e.g. gall midges in tribes Asphondyliini and Lasiopterini)
Removal of gall-inducer waste from enclosed chambers (e.g. galling aphids)
TRANSPORTATION (possible for gall-inducers that lack sufficient self-locomotion)
Escape from plant interior to surface (e.g. citrus canker) where other modes of transportation await (e.g. water)
Propulsive escape from plant interior into airstream (e.g. spores ejected from aecial cups of fungal rusts)
Galled tissue recruits winged insects via food rewards or other attractive cues:
(e.g. move gall associate (bacteria, fungi, nematodes, mites) to a fresh host of the same host species)
(e.g. move gall associate (such as phytoplasmas) to a different host plant necessary for completion of life cycle)
REPRODUCTION (expected for all gall-inducers)
Place to build body as an immature form in order to produce many offspring as a free-living adult (insects)
Place for creating generations of descendants that live in and elaborate the gall (e.g. aphids, thrips)
Place to produce infective stages that proceed to attack other plant parts or other plants (e.g. bacteria, fungi)
Place where sexual recombination occurs, giving rise to more virulent host races (e.g. rust fungi on alternate hosts)
A PLACE TO OPTIMIZE COMMUNITY INTERACTIONS (only species living in groups)
A place where division of labor can occur (e.g. soldier castes in gall-inducing aphids and thrips)
Greater opportunities for gaining useful DNA via horizontal gene transfer (HGT) from foreign plant associates
Divide up responsibilities for producing plant-manipulating effectors (e.g. Buonaurio *et al.* (2015))
A place to share signals for coordinating timing of activities (e.g. attack of host cells and reproduction)
(e.g. signaling by pheromones in bacteria, smut fungi and insects), (e.g. signaling by quorem sensing in bacteria)
(e.g. signaling by quorum sensing within and across bacterial species)
A BETTER WAY TO CONTROL THE PLANT'S OTHER BIOTIC INTERACTIONS
The gall as a 'stronghold' in the plant, from which the gall-inducer can exert greater influence over future colonization of the plant by other species, perhaps beneficial or harmful to the gall-inducer

appear in species that induce galls (Stern & Foster, 1997; Crespi & Worobey, 2016). Soldiers of the gall aphid *Nipponaphis monzeni* specialize in two tasks: stinging caterpillars that eat the gall and deploying 'social immunity' to plug holes made by caterpillars by communally exploding their bodies (Kutsukake *et al.*, 2019). Galls provide spaces where bacterial communities benefit from quorum sensing and horizontal gene transfer (Jacques *et al.*, 2016).

A sixth theme is greater control over who else is allowed to colonize the plant. Having taken up residence in the plant, the plant associate can either make the plant more susceptible or less susceptible to subsequent invaders. Gall inducers have been shown to have this sort of influence (Zgadzaj *et al.*, 2016; Lamovšek *et al.*, 2017; Kyndt *et al.*, 2017). Effectors provide a mechanism for this type of control (Snelders *et al.*, 2018). The gall-inducing citrus canker *X. citri* secretes effector proteins that kill other bacterial species (Souza *et al.*, 2015; Sgro *et al.*, 2018). An open question is this: are gall-inducers better than other types of plant associates at controlling future access to either the whole plant or the small part of the plant they occupy?

VI. Galls as mutualism

1. Rhizobia and nodule inception

'Rules of engagement' in the legume–rhizobial symbiosis were described by Oldroyd *et al.* (2011) and are illustrated in Fig. 3(a). After detecting plant-secreted flavonoids (Perret *et al.*, 2000), bacteria produce the 'Nod factor', a rhizobial-signaling molecule discovered more than 20 years ago (Freiberg *et al.*, 1997). Recognition by the plant occurs via cognate host receptors (Kawaharada *et al.*, 2015) and triggers organogenesis. Plant cell divisions (indicated by dotted lines in Fig. 3a) lead to nodule primordium formation in one of two places (Hirsch, 1992). *Lotus japonicus* produces a determinate nodule originating in the inner cortex. It has a transient meristem. *Medicago truncatula* produces an indeterminate nodule originating in the pericycle. It has a persistent tip-growing meristem. The idea that a diffusible signal travels between the root surface where the Nod factor is recognized and the site where cell divisions begin is suggested by the cell layers that separate the two events (Fig. 3a).

Uptake of bacteria into living plant cells is a unifying and distinctive feature of the N_2-fixing root nodule symbiosis (Parniske, 2018). Entrapment of the bacterium begins with curling of the root hair (Fig. 3a). Localized lysis of adjoining cell walls is necessary for creation of the infection chamber, which is modified when curling is completed. Live-tissue imaging has revealed radial expansion of the infection chamber, along with increases in exocytosis and cell wall-associated markers (Fournier *et al.*, 2015). Remodeling of the cell wall coincides with increases in numbers of bacteria. After this, the infection thread is initiated and continues to develop, following the path determined by the pre-infection thread. Bacteria are guided towards the developing nodule primordium.

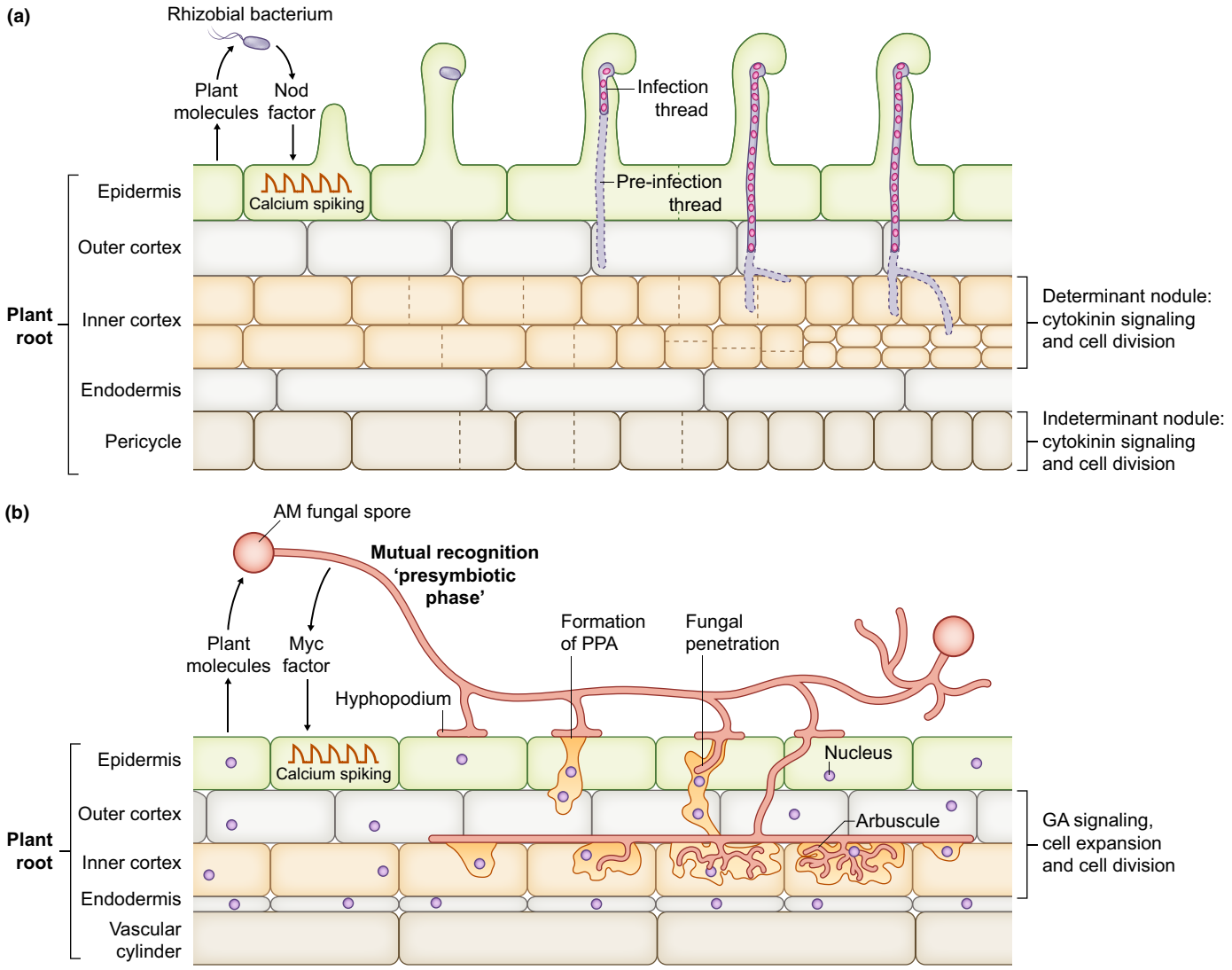

Fig. 3 Plant roots make accommodations for (a) rhizobial bacteria (based on Oldroyd et al., 2011) and (b) arbuscular mycorrhizal (AM) fungi (based on Parniske, 2008). Nodules made for rhizobia are considered to be galls, but accommodations for AM fungi are not. Interactions start with the plant releasing exudates, which stimulate bacteria to make the Nod factor, and fungi the Myc factor, both of which cause calcium spikes in plant cells. In (a), a root cell incorporates the bacterium and then makes a pre-infection thread that guides the growing colony of bacteria through cells to the location where cell divisions (dotted lines) are preparing the nodule primordium. In (b), a root cell contacting the hyphopodium produces a pre-penetration apparatus (PPA) that guides the fungal hypha towards the cortex. PPA-like structures are induced in inner cortical cells. The hypha enters these cells and branches, forming the arbuscule. See text for further explanation. GA, gibberellin.

Uptake of rhizobia into the plant is not inevitable. Specificity between N_2-fixing bacteria and plants occurs at species and genotypic levels (Perret *et al.*, 2000). Partnerships between roots and N_2-fixing bacteria are less common when soil nutrients are plentiful (Parniske, 2008; Oldroyd *et al.*, 2011). Failure to colonize has various causes, including failure of recognition events. Active resistance by the plant occurs via induced immune responses mediated by TIR-NBS-LRR *Resistance* genes (Yang *et al.*, 2010), discussed in Section VII.

Even after the nodule has been built, the plant is able to control its association with the N_2-fixing bacteria that live inside the nodule (Oldroyd *et al.*, 2011; Parniske, 2018). Differentiation into N_2-fixing bacteroids can be prevented by the plant; alternatively, the plant can deploy a nodule specific cysteine-rich (NCR) peptide, which causes bacterial cell death and early nodule senescence in a manner that is allele-specific and rhizobial strain-specific (Yang *et al.*, 2017).

The usefulness of an organismal habit is suggested by its gains and losses over evolutionary time. The legume family and nine other plant families participate in N_2-fixing root nodule (NFN) symbiosis. The NFN clade includes both nodulating and non-nodulating species. Genome-wide comparative analysis of 37 plant species – 13 of which were non-nodulating – has provided evidence for multiple independent loss-of-function events of the symbiotic regulator NODULE INCEPTION (Griesmann *et al.*, 2018). This suggests that the current distribution of nodule-forming plant species in the NFN clade is the result of multiple losses of the nodule-forming habit, rather than multiple gains. Selection

pressure against plants maintaining the NFN symbiosis may be greater than previously thought. This seemingly has implications for the proposal that a wider range of valued plant species – including cereals – could be made more self-sufficient by enabling mutualisms with N_2-fixing bacteria (Beatty & Good, 2011).

2. Mycorrhizal fungi and arbuscule inception

There is mounting evidence that the plant pathway to nodulation is derived from the more general pathway for arbuscular mycorrhizal (AM) fungi (Parniske, 2008; Op den Camp *et al.*, 2011; Kereszt & Konorosi, 2011; Oldroyd *et al.*, 2011; Martin, 2008; Martin *et al.*, 2018, 2016, 2017; Strullu-Derrien *et al.*, 2018). Fig. 3(b), based on Parniske (2008), shows what happens when AM fungi start interacting with plant cells. In place of the Nod factor of rhizobia, there is a mycorrhiza (Myc) factor (Fig. 3b). The Nod factor and Myc factor are both lipochito-oligosaccharide (LCO) signals and both induce calcium oscillations in root epidermal cells and activation of 'plant symbiosis-related genes' (Oldroyd *et al.*, 2011; Parniske, 2008). Symbiosis Receptor-like Kinases (SYMRK) are crucial, acting in both types of root mutualisms. Ectopic expression of SYMRK genes induces spontaneous nodule organogenesis in the absence of rhizobia (Ried *et al.*, 2014).

The fungal hyphopodium (Fig. 3b) is a member of a class of fungal infection cells called appressoria that exert physical forces to breach the plant cuticle and secrete effectors (Ryder & Talbot, 2015). Hyphopodia contact root epidermal cells and stimulate the plant's production of a pre-penetration apparatus (PPA), which subsequently accommodates the fungal hypha, guiding it through root cells to the inner cortex (Fig. 3b). The hypha enters intercellular space and grows laterally. The plant's inner cortical cells then develop an internal structure through which hyphal strands enter the cells. The 'arbuscule' – created inside the plant cell as the hypha branches out within its self-contained PPA – provides the interface for delivery of resources – mostly phosphate but also water – collected by the hyphal network of the fungus, which can be vast (Miller *et al.*, 1995).

Like rhizobia, AM fungi receive protection as well as nutrients in the form of carbohydrates (Solaiman & Saito 1997; Bago *et al.*, 2000). It was recently discovered that AM fungi are entirely reliant on plants for their supply of lipids (Lanfranco *et al.*, 2018). This discovery has changed ideas about energy balance during plant–AM partnerships: the plant's responsibility for biosynthesis of organic carbon compounds is far greater than was previously thought.

Are the accommodations (Fig. 3b) plants make for AM fungi a gall? Cell expansion and cell division are well-known features of gall inception. Plants infected by AM fungi express a novel GRAS transcription factor, MIG1, which triggers cell expansion in the root cortex (Heck *et al.*, 2016). The effect of MIG1 on growth is achieved through gibberellin (GA) signaling. In addition to cell expansion during AM accommodation, a recently published article reports observations of cell division in the root cortex (Russo *et al.*, 2019). Lateral root growth and development are stimulated by LCO signals, which are produced by both AM fungi and rhizobia (Felten *et al.*, 2009; Maillet *et al.*, 2011). If N_2-fixing bacteria are gall-inducers, perhaps AM fungi should be too.

3. Plant hormones

Scientists studying galls have focused on the effects of the canonical growth hormones. Auxin, cytokinin and gibberellin have received the most attention (Yamaguchi *et al.*, 2012; Mitchum *et al.*, 2013; Davière & Achard, 2017; Tooker & Helms, 2014; Gohlke & Deeken, 2014), but brassinosteroids and strigolactones may also be important. Canonical stress hormones – salicylic acid, jasmonate, ethylene, and abscisic acid – are pivotal in antagonistic plant interactions (Howe *et al.*, 2018) but are not talked about as much when it comes to plant galls. It seems possible that this binary view of hormone function – either for growth or immunity – may prove overly simplistic (Robert-Seilaniantz *et al.*, 2011; Vanstraelen & Benková, 2012; Pieterse *et al.*, 2012). We are learning that 'growth' hormones can have effects on immune signaling and that 'stress' hormones can have effects on plant growth and development.

Nodules provide an example of how gradients of auxin and cytokinin influence which item the plant chooses to make in a particular location (Oldroyd *et al.*, 2011). The root apical meristem has four zones. Signaling pathways regulate cell proliferation in the stem cell niche, cell division in the meristematic zone, and cell expansion in the elongation zone. The differentiation zone is where plant cells decide which organ will be made – the options being a lateral root or a nodule primordium (Oldroyd *et al.*, 2011). At sites of localized high auxin, a lateral root is initiated. At sites of localized strong cytokinin signaling, a nodule primordium is made.

Gall-inducers have various options for influencing the plant's hormone levels (Pertry *et al.*, 2009; Chalupowicz *et al.*, 2009). In Section VII, *Rhodococcus fasciens* provides a sense of these options, which include introduction of self-made hormone analogs or self-made hormone-metabolizing enzymes. Many hormones are derived from universal metabolites, and this allows their synthesis by myriad non-plant organisms. Hormone production can also be a 'joint venture', as illustrated by the role of gibberellin (GA) in the initiation of determinant nodules made for N_2-fixing rhizobial bacteria.

GA_4 is the form of GA that provides classical gibberellin growth activity in plants. Multiple steps are required for GA_4 biosynthesis (Zi *et al.*, 2014; Nagel & Peters, 2017). Alpha-rhizobia (Table 1) carry out many of the steps leading to biosynthesis of GA_4 by having an operon – a linearly-arranged functional unit of transcription and genetic regulation – containing genes encoding the enzymes that together enable the reactions that create the penultimate precursor, GA_9 (Nett *et al.*, 2017b). However, because GA_9 lacks classical gibberellin activity, one more step is needed to produce GA_4. The plant has that ability, taking the rhizobia-produced GA_9 and turning it into GA_4.

Why might plants want to maintain control over the final step of GA_4 production? An answer is suggested by the function of GA_4 for gram-negative pathogenic Proteobacteria belonging to the Class Gammaproteobacteria (Table 1). They are able to carry out all of the steps necessary for making bioactive GA_4 (Zi *et al.*, 2014; Nagel & Peters, 2017; Nagel *et al.*, 2017, 2018) and use their GA_4 for a

different purpose – to suppress jasmonic acid-induced plant defense (Robert-Seilaniantz *et al.*, 2011; De Bruyne *et al.*, 2014). Given the dual actions of GA_4 – one good for the plant and one bad – it makes sense that plants might want to control when and where deployment of GA_4 increases the risk of invasion. It is interesting that there are beta-rhizobial species, such as *Paraburkholderia minosarum* (Table 1), which are similar to pathogenic bacteria in that they are able to carry out all of the steps leading to GA_4 synthesis (Nett *et al.*, 2017a; Nagel *et al.*, 2018). What are the fitness consequences of rhizobia being able to produce their own GA_4 – as is the case for beta-rhizobia – vs only producing the penultimate GA_9 and leaving GA_4 production to the plant – as is the case for alpha-rhizobia?

VII. Galls as parasitism

1. Molecular framework

A framework we find useful for discussing antagonistic molecular interactions – including those involving gall inducers – is the 'zigzag' model proposed by Chisholm *et al.* (2006) and Jones & Dangl (2006). Their model is being refined as advances are made (Cui *et al.*, 2015) and may eventually be simplified (Thomma *et al.*, 2011).

In Fig. 4, Panel 1 introduces pattern-triggered immunity (PTI), the plant cell's first layer of defense. 'Danger signals' warn the plant that invasion is occurring. The signal is either a plant feature that is created during invasion (so-called damage-associated-molecular-patterns, DAMPs) or a parasite feature, typically a conserved structural feature of the invader, such as flagellin of bacteria or chitin of fungi. The parasite feature is called a MAMP, PAMP or HAMP depending on whether it originated from a microbe, pathogen or herbivore, respectively. The plant has pattern-recognition receptors (PRRs) that trigger signaling pathways. Signaling is amplified by mitogen-activated protein kinases (MAPKs; Pitzschke *et al.*, 2009). What all this eventually leads to is creation of a plant feature that contributes to defending the cell against attack. Fortification of the cell wall is one example.

PRRs (Fig. 4) are transmembrane receptor-like kinases (RLKs) that have an extracellular perception domain and an intracellular signaling domain (Zipfel, 2014). RLKs function in intercellular communication, linking the world outside the plant cell – where the antagonist typically resides – with the world inside the cell – where defense is mounted (Michelmore *et al.*, 2013). Genome sequencing of plants reveals RLK-encoding genes: Arabidopsis has at least 600 RLK-encoding genes (Michelmore *et al.*, 2013).

Panel 2 in Fig. 4 introduces the antagonist's strategy of effector-triggered susceptibility (ETS). For altering host-cell function and structure (Hogenhout *et al.*, 2009), antagonists have 'effector' molecules encoded by '*effector* genes' (also called 'virulence factors' encoded by '*Virulence* genes'). As we explained previously, the best-studied targets of effectors in plants are involved in plant defense, with defense suppression being the ultimate aim. However, there is growing interest in effectors that force the plant to deliver better services to the parasite. In this case, the effector targets a particular 'plant susceptibility trait', which is a normal function of the plant which, when manipulated by the antagonist, turns the plant against its own self-interest (Lapin & Van den Ackerveken, 2013; van Shie & Takken, 2014; Presti *et al.*, 2015). The Hessian fly – a member of a large gall-inducing insect clade (Cecidomyiidae, Table 1) –

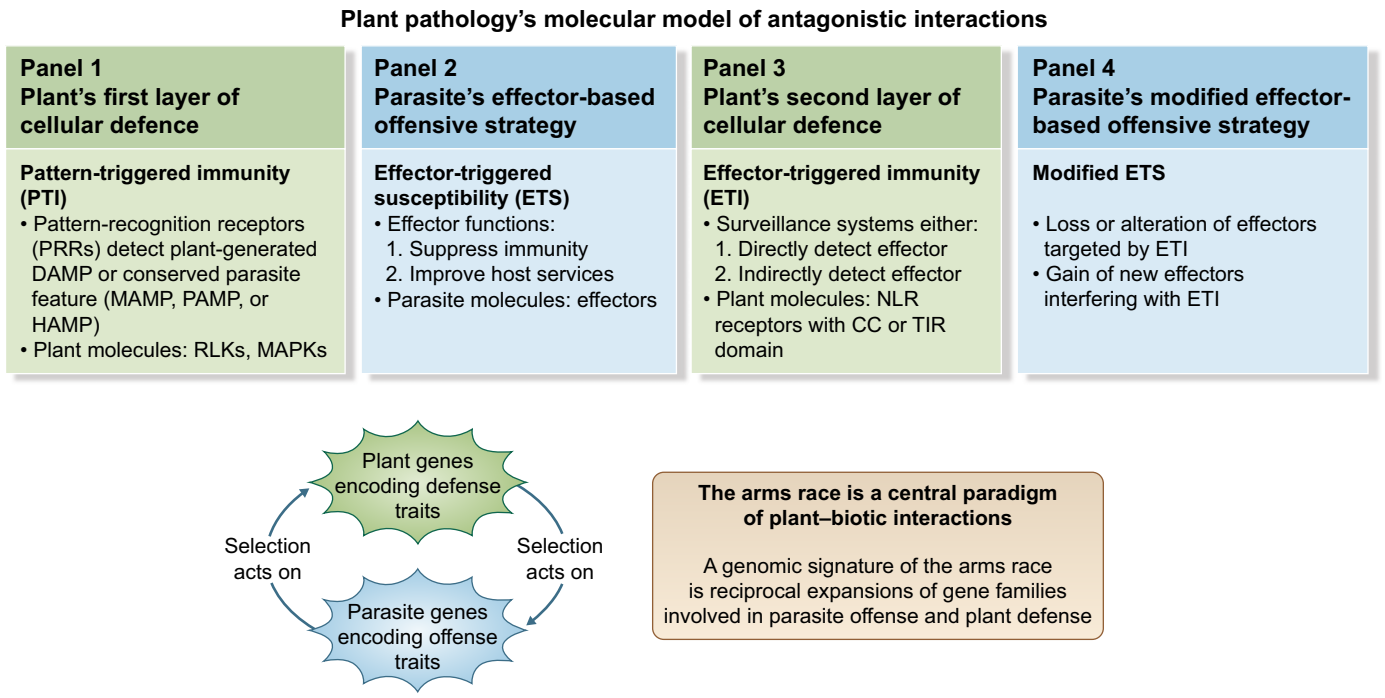

Fig. 4 Key features of plant pathology's molecular model showing two plant features involved in immunity and two parasite features involved in offense and counter-defense. The model is based on work by Chisholm *et al.* (2006) and Jones & Dangl (2006). See text for further explanation.

upregulates expression of the wheat susceptibility gene Mds-1 (Liu *et al.*, 2013). This appears to be an essential feature of Hessian fly colonization inasmuch as silencing of the Mds-1 gene makes colonization impossible.

Genome sequencing of antagonists of plants predicts 'effector candidates' based on screening of *in silico*-translated products for presence of an N-terminal signal peptide, protein size, and homology to known sequences (Sperschneider *et al.*, 2015; Thordal-Christensen *et al.*, 2018). Predictions of which effector candidates are most important for colonization – as well as which effectors are encoded by parasite *Avirulence* genes – are being refined by 'effectoromics', which involves high-throughput *in planta* expression screen approaches (Lorrain *et al.*, 2019). Fungal rust species – among which are many gall-inducing species – are noteworthy for having thousands of genes that encode secreted proteins that are strongly expressed during colonization (Lorrain *et al.*, 2019). The genome of the Hessian fly, a member of a large gall-inducing insect clade, predicted 1400 effector candidates (Zhao *et al.*, 2015). Several of the effector candidates strongly expressed during colonization have been cloned. Each is associated with the ability of Hessian fly larvae to colonize plants expressing a specific *Resistance* gene (Aggarwal *et al.*, 2014; Zhao *et al.*, 2015; Zhao *et al.*, 2016).

Panel 3 in Fig. 4 introduces the plant's strategy of Effector-Triggered-Immunity (ETI), wherein the plant exploits effectors as 'danger signals' (Cui *et al.*, 2015). In this context, the effector acts as an 'elicitor' of plant defense and makes the parasite avirulent (i.e. unable or less able to colonize the plant). A parasite gene that encodes an effector that elicits this type of plant defense is an '*Avirulence* gene'. The plant gene that encodes the ability to detect the *Avirulence* effector is a '*Resistance* gene'. Presumably effectors encoded by *Avirulence* genes have functions that benefit the parasite in a different context, such as when the parasite attacks a plant that does not have the matching *Resistance* gene (Hogenhout *et al.*, 2009).

During ETI (Fig. 4), nucleotide-binding domain leucine-rich repeat (NLR)-containing receptors detect perturbations in the plant cell, either directly as a receptor–ligand interaction, or indirectly via changes in a plant cellular process targeted by the effector (Cui *et al.*, 2015). The cellular process that is monitored can be real or a 'decoy' created by the plant to entrap the effector. After the effector is detected, it is proposed that the NLR undergoes nucleotide-dependent conformational changes, with this exposing its N-terminal coiled-coil (CC) or Toll/interleukin-1-receptor (TIR) domain, which then is able to participate in higher-order signaling complexes (Mestre & Baulcombe, 2006; Bernoux *et al.*, 2011; Maekawa *et al.*, 2011; Schreiber *et al.*, 2016; Cesari *et al.*, 2016; Casey *et al.*, 2016).

Panel 4 (Fig. 4) shows that parasites can defeat ETI by modifying ETS (Cui *et al.*, 2015). This is why a single *Resistance* gene deployed in agriculture may eventually fail to provide control of the pathogen or pest population (Michelmore *et al.*, 2013; Harris *et al.*, 2014). Sexual recombination as well as somatic exchange – genetic exchange between two haploid nuclei – contributed to the emergence of the virulent *AvrSr50* stem rust *P. graminis* race that was able to overcome wheat resistance encoded by the *Sr50* gene (Chen *et al.*, 2017). DNA insertion and sequence divergence also contribute to the creation of virulent stem rust races. As might be expected given the effector functions shown in Panel 2 (Fig. 4), loss of an effector or alteration of its function may create fitness penalties for the parasite (Leach *et al.*, 2001).

Fifty years ago, Erlich and Raven (1964) proposed that coevolution between plant defensive chemicals and herbivore detoxification mechanisms gives rise to an 'arms race' (Fig. 4). The 'arms race' was highlighted as a major driver for species diversification in plants and insects. A recent gene editing study showed just how easy it can be for insects to evolve immunity to plant toxins (Karageorgi *et al.*, 2019). On a par with host-adapted monarch butterflies (*Danaus plexippus*), fruit flies (*Drosophila melanogaster*) edited for just three genetic changes were transformed into creatures able to withstand plant toxins called cardiac glycosides, which are found in milkweeds (*Asclepias* spp.) and other plants.

The 'arms race' is a central paradigm for plant biotic interactions (Fig. 4). Relationships between the plant's NLR-containing receptors and the parasite's cognate effectors provide one example. A genomic 'signature' of the arms race in plants is the expansion of gene families encoding traits that play a role in their most important biotic interactions (Meyers *et al.*, 2003; Harris *et al.*, 2014; Plomian *et al.*, 2018; Hipp *et al.*, 2019). Likewise, the genomic 'signature' of the arms race in parasites is expansion of gene families encoding traits that enable colonization and maximal exploitation of the plant (Zhao *et al.*, 2015; Lorrain *et al.*, 2019).

2. Crown galls made for *Agrobacterium tumefaciens*

We know a lot about *Agrobacterium*. Nevertheless, we begin by mentioning a few things mentioned by Nester (2015) that are not known. Little is known about how *Agrobacterium* functions outside the laboratory in the natural world. Also lacking are time-course studies of tumor development, similar to what is shown in Fig. 3. And while we know there are many plant species and genotypes that are able to resist colonization by *Agrobacterium*, we don't fully understand how they are able to do this (Pitzschke, 2013; Gohlke & Deeken, 2014). Twenty years ago, reclassification of *A. tumefaciens* as *Rhizobium radiobacter* (Young *et al.*, 2001) pointed to its close taxonomic relationship with N_2-fixing alphaproteo-rhizobia (Table 1).

What makes *A. tumefaciens* and others of its kind (Lacroix & Citovsky, 2016) unique is export of a single-strand form of Transfer (T)-DNA to the plant cell, which is integrated into the plant's chromosomal DNA. Fig. 5, based on Gelvin (2017), illustrates the sequence of events. Recognition of plant-released phenolic and sugar molecules by a two-component bacterial regulatory system triggers induction of *virulence* (*vir*) genes and the making of Vir proteins. Two of the Vir proteins – the endonucleases VirD1 and VirD2 – excise the T-DNA region from the tumor-inducing (Ti) plasmid. A complex is formed by VirD2 attaching to the 5′ end of the T-DNA strand. The T-VirD2/T-DNA complex and Vir effector proteins are secreted into the plant cell via the T4SS secretion system (Aguilar *et al.* 2010). The T-DNA is transported into the nucleus through nuclear ports. Stable integration of the T-DNA into the plant genome and gene expression lead to the

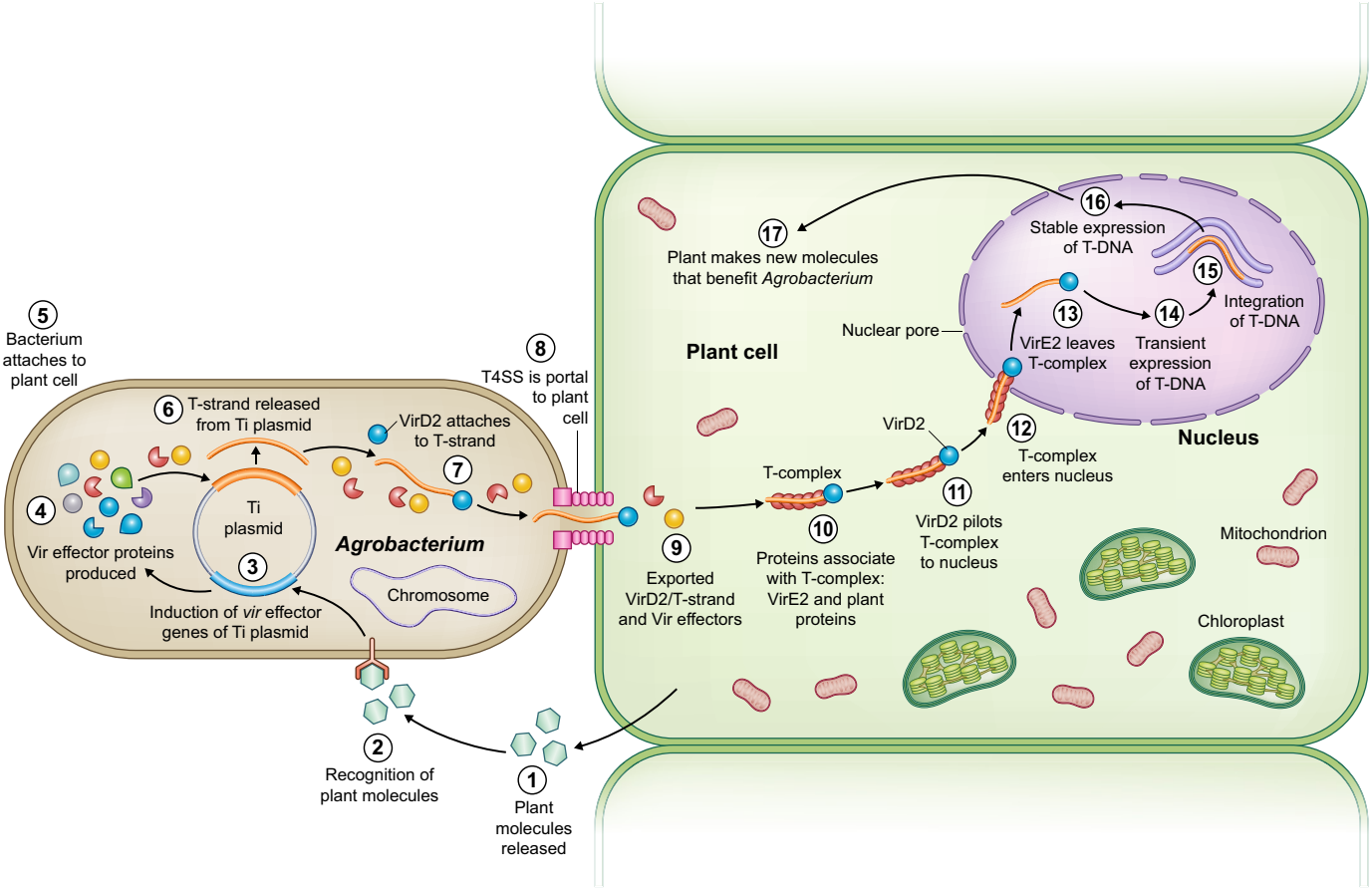

Fig. 5 Model based work by on Gelvin (2017) showing interactions between a plant cell and *Agrobacterium* that lead to gall inception. Many steps in the model are still under investigation. (1) Plant cells release molecules. (2) Recognition of plant molecules by *Agrobacterium*'s two-component sensory system induces (3) expression of *vir* genes encoded by the tumor-inducing (Ti) plasmid and (4) production of Vir effector proteins. (5) Attachment of the bacterial cell to the plant cell occurs simultaneously to *vir* gene induction or afterwards. (6) Among the Vir effector proteins that are produced are VirD1 and VirD2, which together act to release Transfer DNA (T-DNA) from the Ti plasmid. (7) VirD2 attaches to a single-strand form of T-DNA (T-strand) and acts as a pilot, both in *Agrobacterium* and in the plant cell. (8) *Agrobacterium* has created a portal into the plant cell via its Type IV secretion system (T4SS). (9) The VirD2/T-strand complex and Vir effectors enter the plant cell. Effectors exported into the plant cell comprise the 'exportome'. (10) Inside the plant cell, other proteins associate with the VirD2/T-strand complex – including bacterial VirE2 and possibly plant proteins. (11) The VirD2/T-strand/VirE2 complex travels through the plant cytoplasm and (12) enters the nucleus through a nuclear pore. (13) VirE2 disassociates from the T-complex. (14) Transient expression of T-DNA-encoded transgenes can occur. (15) T-DNA is integrated into a chromosome of the host cell. The locus where T-DNA is integrated is random, and integration rarely occurs without mistakes (e.g. deletions and insertions). Integration of T-DNA results in (16) 'stable transformation' (i.e. stabilization of T-DNA-encoded transgene expression). (17) The genetically transformed plant cell produces molecules that benefit *Agrobacterium*. These include special foods known as opines, as well as phytohormones involved in the making of the crown gall. See text for further explanation.

changes in cellular growth and development that result in gall (tumor) formation (Gohlke & Deeken, 2014; Nester, 2015). The T-DNA contains genes that encode for production of auxin, cytokinin and opines. Manipulation, mimicry and hijacking of plant functions by *Agrobacterium* are implicated (Djamei *et al.*, 2007; Pitzschke & Hirt, 2010). The role of plant proteins in integration of T-DNA into the chromosome is under investigation (Gelvin, 2010; Shi *et al.*, 2014).

One aspect of T-DNA transport and integration that requires further investigation is the question of whether the T-DNA targets chromosomal sites that are already damaged or whether *Agrobacterium* itself induces the damage, which is then exploited for the purpose of T-DNA integration (Gelvin, 2017). Song & Bent (2014) documented the increased incidence of double-strand breaks in the chromosomes of Arabidopsis plants attacked by the bacterial pathogen *Pseudomonas syringae*. The same was seen in tomato and potato plants attacked by pathogenic fungi. This is now being investigated for *Agrobacterium* (Gelvin, 2017).

The 'exportome' is the set of foreigner-produced effector proteins that is exported into host cells (Fig. 5). Methods for defining 'exportome' functions and host targets are being developed for many parasites, including bacteria that challenge human health such as *Mycobacterium tuberculosis*, the causative agent of tuberculosis (Perkowski *et al.*, 2017). The endeavor as regards *A. tumefaciens* might appear simple because it exports only five effectors into the plant cell (Nester, 2015; Gelvin, 2017; Lacroix & Citovsky, 2018). Several things make the endeavor more complicated than it might seem. For example: each effector can have multiple targets – rather than a single target – in the plant cell (Lapham *et al.*, 2018; Wang *et al.*, 2018).

Table 3. A research agenda for plant galls.

A greater focus on the plant as gall maker
Move beyond binary view of relationships with gall associates as beneficial or harmful to the plant:
For galls primarily viewed as beneficial to plants, quantify tradeoffs of accommodating the gall associate
For galls primarily viewed as harmful, define the harm and explore plant responses that mitigate the harm
Establish 'signature' features of plant cells during gall inception, development and maturation
Are particular plant developmental programs activated by gall inducers? (Schultz *et al.*, 2019)
Establish the boundaries of the galler's zone of influence on plant cell growth and development
Compare processes plants use to make galls vs callus tissue (Sugiyama, 2018; Guiguet *et al.*, 2018)
Compare processes plants use to enhance localized growth (e.g. galls) vs overall growth
Compare the plant's style of defense against gallers vs necrotrophs or other biotrophs
Are plants really better at suppressing *de novo* growth than animals? (Aktipis *et al.*, 2015)
Compare gall zones to non-gall zones in terms of susceptibility/resistance to subsequent invasion
Determine how a single plant genome can create so many different plant galls, each seemingly unique
Continued exploration of individual cases of each gall associate
Enrich gall systems having a primarily genetic/molecular approach with ecology, physiology and behavior,
Enrich gall systems having a primarily ecological/behavioral approach with genetics, molecular biology and physiology
Sequence genome of gall associate: identify effector candidates and other genes involved in biotic interactions
Define the exportome (i.e. molecules made by gall associate and applied to plant cells)
Define the plant cellular target(s) of each member of the exportome
For each plant cellular target, compare its function in normal plant cells vs cells interacting with galler
Establish chronology of exportome production relative to developmental events in plant cells
Define roles of plant hormones – those produced by plants as well as those produced by gall-inducers
Determine the contribution of physical interactions ('wounding') to gall inception (Jayaraman *et al.*, 2014)
Is cooperation between galling and non-galling bacteria common? e.g. *P. savastanoi* (Buonaurio *et al.*, 2015)
For insect gallers, explore contribution of bacterial endosymbionts to the making of galls
For insect gallers having fungal symbionts, determine roles during plant interactions
Define benefits of gall for galler – if there are special foods, explore remodeling of galler's primary metabolism
Explore idea that gall confers on gallers more control over plant's associations with other organisms (Table 2)
Establish determinants of gall-inducer host range, both traits of the plant and the gall-inducer
Compare plant interactions of individual cases of gall associates
Phylogenetic perspective (Gilbert & Parker, 2016): has each galling clade evolved its own way of altering of plant growth or have galling clades converged on tactics and cellular targets?
Explore what happens when a plant is simultaneously attacked by two or more gall-inducers – who wins?
Explore what happens when a single plant part (e.g. a root) is simultaneously colonized by friends and foes
Compare plant interactions of closely-related gall-inducing rhizobia and *A. tumefaciens* (Wood *et al.*, 2001)
Compare tactics and cellular targets of gall associates having a restricted vs broad host range
Compare galls with other types of plant biotic interactions (relatives or same plant if possible)
Compare plant interactions of gall-inducers with those of close relatives that are not gall-inducers
What advantages and disadvantages do gallers have over non-galling biotrophs?
Do gallers have unique genomic/genetic/transcriptomic features not seen in non-gallers?
Explore whether gallers have a greater ability than non-gallers to manipulate biotic interactions of plants
Are subtle alterations of cellular growth and development more common than previously recognized in non-galling biotrophs?

A gene cluster is a contiguous unit of the genome associated with a single trait. Regulation within the cluster is integrated, complex and redundant (Temme *et al.*, 2012). This makes genetics of the gene cluster hard to decipher. Synthetic biology offers the opportunity to rebuild a gene cluster from the bottom up, using synthesized, fully characterized parts. The gene cluster associated with nitrogen fixation in *Klebsiella oxytoca* was 'refactored' to improve the ability of the bacterium to produce fertilizer (Temme *et al.*, 2012).

Synthetic biology could be used to refactor the Ti plasmid of *A. tumefaciens* (V. Citovsky, pers. comm.). Advantages include elimination of all pathogenic and transformation-unrelated abilities, such as bacterial conjugation. The newly synthesized Ti plasmid could include nonbacterial (e.g. plant) genes that may facilitate plant transformation and/or transgene expression. By refactoring for optimal expression of effectors in bacteria and export to the host, it may be possible to enlarge the set of eukaryotes that can be genetically transformed by *Agrobacterium*, with this including a greater number of plant species as well as a greater number of non-plant species (Lacroix *et al.*, 2006; Lacroix & Citovsky, 2018).

3. Leafy galls made for *Rhodococcus fascians*

Plants produce 'leafy galls' for *Rhodococcus fascians* (Goethals *et al.*, 2001; Stes *et al.*, 2011). In leafy galls, shoot meristem creation is ongoing. The gall – as a permanent sink – never converts to being a source tissue (Depuydt *et al.*, 2009; Dhandapani *et al.*, 2017). Growth suppression ('stunting') occurs elsewhere in the plant. Like *A. tumefaciens*, *R. fascians* has a broad host range – mostly dicotyledonous herbaceous perennials, but also monocots.

The *R. fascians* pathosystem is a model for the interplay between plant- and antagonist-produced molecules. The *R. fascians* strain D188 has a number of essential *Virulence* genes, which are typically

organized in 'operons' located on a linear virulence plasmid (Crespi *et al.*, 1992; Stes *et al.*, 2011). The 'attenuation' (*att*) operon encodes an autoregulatory system. Under the auspices of *att*, D188 switches from a harmless epiphytic lifestyle to that of an antagonist (Maes *et al.*, 2001). Additionally, the *att* operon partially controls the expression of the *fas* operon, which encodes enzymes that produce a mixture of regular and highly modified synergistically-acting cytokinins (Stes *et al.*, 2011, 2013; Radhika *et al.*, 2015). The *fas* operon is considered a key virulence factor for *R. fasciens*. Some plants resist *R. fascians* colonization by producing a compound that quenches activation of the *att* operon (Rajaonson *et al.*, 2011).

It is frequently said that agricultural yields must increase throughout the twenty-first century to feed the world's burgeoning populations. What agriculture needs is promotion of plant growth that is balanced and multi-directional. Harnessing the potential of microbes is posed as a solution (Busby *et al.*, 2017). The growth-promoting abilities of rhizobia and mycorrhizas are recognized in this context. Parasitic gall-inducers are not considered to be part of the solution because the unidirectional growth they promote is harmful to the overall growth of plants.

Might the growth-promoting skills of harmful gall-inducers be put to a better purpose? Plasmid-free *R. fascians* derivatives and other *Rhodococcus* species now are being explored for their potential to promote multi-directional balanced plant growth (Francis *et al.*, 2016; Savory *et al.*, 2017; Francis & Vereecke, 2019). A different way to exploit parasitic gall-inducers is to use knowledge about their plant interactions to discover plant features that we might target in order to increase crop yields. Phytoplasma gall inducers seem particularly interested in MADS box proteins (MacLean *et al.*, 2014), which are key regulators of plant pathways involved in growth and development (Theissen *et al.*, 2000). A recent report showed how scientists were able to increase maize grain yields in the field by increasing and extending the expression of MADS-box transcription factor *zmm28* (Wu *et al.*, 2019).

VIII. Research agenda

We have raised questions throughout this review. Many appear in Table 3, where they are organized under four themes: a greater focus on plants as gall-makers, continued exploration of individual gall-inducing species, and two comparative endeavors – one to compare plant galls to discover their unique and distinctive features, and the other to compare plant galls to other types of plant biotic interactions. The first comparative endeavor has already started: Damiani *et al.* (2012) used laser-assisted microdissection and transcriptomics to compare genes involved in plant roots accommodating beneficial rhizobia and harmful root-knot nematodes.

Throughout this review, we have emphasized our interest in gall inception. Scale is a problem. We sit in the uppermost rows of a very large theatre, watching a drama that has a complicated plot and which unfolds on a tiny stage with players who use miniscule tools to interact with each other. Powerful new techniques are forthcoming for visualizing what is happening on that small stage. Novák *et al.* (2017) describe technologies which enable tissue- and cell-specific analyses of plant hormones. This includes real-time simultaneous identification and quantification, and continuous monitoring and visualization of localized distributions of hormones via biosensors. The journal *Science* awarded the '2018 Breakthrough of the Year' (Pennesi, 2018) to a trio of techniques that allow scientists to track when genes in individual cells are turned on and follow what happens over time as the cells multiply and specialize. The trio of techniques was developed to track what happens during embryonic development (Harland, 2018; Wallingford, 2019) but will also be useful for studying plant development. Advances in understanding of plant growth were evident in a recent paper reporting on a growth-based framework for leaf shape development and diversity (Kierzkowaski *et al.*, 2019). The authors asked the following question: 'how do genes modify cellular growth to create morphological diversity?' The 'growth maps' and 'fate maps' created in this paper for the different leaves of Arabidopsis and *Cardamine hirsuta* will have applications for plant galls.

IX. Conclusions

We were asked to review the subject of plant galls. This sounded like a good idea when we started. As time went on, we asked ourselves: is this really a subject? To use a modern term, galls are more of a 'mashup', a loose confederation of disparate elements that someday might be organized into something more coherent. It became one of our goals to make galls more of a subject and less of a mashup. Advancing this goal in the future will require a greater public exchange of ideas.

We join other scientists in claiming plant galls as portals of discovery. Barbara McClintock (1984), in her acceptance speech for the Nobel Prize, marveled at the precision of the plant genome, which, in the case of galls, summons forth entirely new structures that are unique to the organism that issued the summons. In a recent book, the developmental biologist Alessandro Minelli (2018) pointed to galls as one of two areas in plant evolutionary developmental biology that have not been 'seriously addressed'. Galls, by having their own specific development, result in easily recognizable phenotypes that are amenable to experimental manipulation. Clearly, much is left to be discovered.

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