Plant-Made Pharmaceuticals: An Overview and Update

H. Maelor Davies
University of Kentucky
Lexington, KY

The development of plant genetic transformation in the early 1980s introduced the possibility of having plants express non-native ("foreign") genes, and thereby accumulate non-native proteins in their cells and tissues. Thus the concept of "plant molecular farming" was born, envisaging crop plants as production "vehicles" for useful and/or valuable proteins that originally derived from microbial or animal sources. Several advantages were claimed for such plant-based production, relative to bulk production of the natural source for the corresponding protein, including overall economy of production, lack of need for major capital investment (*e.g.* in fermentation bioreactors), ease and economy of scale-up, lack of risk of contamination with human pathogens, *etc.* (For a background overview of plant molecular farming, see Collins and Shepherd, 1996). Because the case for using plants as the production system became more compelling as the yield of protein per plant increased, proprietary gene-expression technologies were developed specifically for achieving very high concentrations of "foreign" proteins in plant tissues. These technologies, in turn, resulted in the emergence of several agricultural biotechnology companies specializing in plant molecular farming. A wide variety of proteins were expressed in a number of plant species, illustrating the potential of the approach to supply products for pharmaceutical, industrial-enzyme, structural-polymer, *etc.*, markets. Clinical trials in humans were conducted, successfully, with protein pharmaceuticals generated in plants (*e.g.* Ma *et al.*, 1998). A particularly attractive feature of the plant molecular farming concept, which was apparent from its outset, is its potential to provide opportunities for both the agricultural sector and the biotechnology business sector simultaneously.

A variant on the molecular farming theme, which developed contemporarily with it, is the concept of "edible vaccines." In this strategy, the entire plant tissue or organ (such as a fruit) in which the protein pharmaceutical accumulates is also the final delivery device for the protein product, and no extraction of the protein from the plant material

is necessary. Edible vaccines are considered elsewhere in this conference, and will not be discussed further here.

In contrast with the spectacular scientific progress in "proving" the principle, however, the development of significant markets for plant-manufactured proteins failed to happen, so that by the mid-1990s the plant molecular farming field was essentially stalled. The companies that were based on appropriate gene-expression technologies were in a survival-oriented mode rather than in a state of vibrant growth, and little was happening in terms of further technology enhancements. Most troubling was the sense that the end-users of the technology, *i.e.* those companies who owned protein pharmaceuticals, enzymes and other possible product "targets" for plant-based production, appeared to be unconvinced regarding the plant manufacturing platform. Field-level production had been demonstrated on a pilot scale, and some post-harvest bioprocessing capability was constructed. But, in spite of these advances towards scaled-up commercial applications, the plant molecular farming biotechnology sector continue to lack much-needed endorsement by significant clients whose protein medicinals and protein reagents addressed substantial and sustainable markets. The plant-based production "platform" was, in effect, a technology searching for an application.

Fortunately, much has changed in the last 5 years or so, largely as a result of biotechnology's increasing impact on drug development. The fledgling molecular farming industry is ideally placed to address the resulting demand for protein pharmaceuticals, and consequently has re-characterized its technology platform as "plant-made pharmaceuticals" (PMPs). Applications to other proteins such as industrial enzymes, now referred to as "plant-made industrial products," are seen as a future priority.

It now seems much more likely that a new, specialized crop agriculture will be constructed specifically to service the PMP opportunity.

This brief overview will consider the current status of the PMP industry and the challenges facing large-scale implementation of the PMP opportunity today. Using some of our own research at Kentucky Tobacco Research and Development Center (KTRDC) as an example, I will also discuss the interface between the PMP industry and conventional crop agriculture. This is an aspect that has often been neglected in the past, but one that comes sharply into focus when one recalls that conventional crops are not optimized for these new applications and that today's regulatory, containment considerations render them even less suitable. Rather than providing new plant varieties and corresponding new markets for production through existing crop agriculture—as was at one time envisaged—it now seems much more likely that a new, specialized crop agriculture will be constructed specifically to service the PMP opportunity.

The PMP Opportunity Today

To appreciate the current status of the PMP industry, we need to review both the capabilities of the industry itself and the condition of the protein-pharmaceutical markets that it is designed to address.

The basic philosophy of the PMP opportunity today can be stated in the following way:

- there is a substantial, and increasing, worldwide demand for protein pharmaceuticals and therapeutics;
- existing and traditional methods of manufacturing proteins in bulk to the required level of purity and quality are stretched to capacity and will soon become limiting in protein-drug manufacturing;
- specialized plant-based gene-expression technologies are ready to provide an alternative manufacturing platform that can help meet the demand and thus overcome the perceived "bottleneck" in protein production; and
- taken together, these situations make a strong case for commercial development of PMPs.

The following summary reviews each of the above aspects in relation to the current status of PMP commercialization.

Protein Demand

The development of novel protein pharmaceuticals, vaccines, therapeutics and other medically useful molecules is an expected consequence of biotechnology-driven drug discovery. Accordingly, it is not surprising that proteins feature prominently in new drug development today, and that they are predicted to comprise a larger and larger proportion of new medicines over the next decade or so. For example, an estimate of 14% of the pharmaceutical market as proteins in the year 2000 is projected to expand to 40% by 2010 (Price, 2003). A 2004 survey by the Pharmaceuticals Research and Manufacturers' Association (http://www.phrma.org) indicated that 324 "biotech medicines" were in clinical trials or in advanced development (such as preparation for clinical trials) in the United States alone, in that year. Most of these prospective new drugs were proteins such as antibodies, enzymes, peptides, *etc*. Worldwide, many hundreds of monoclonal antibodies and other medicinally active proteins are in all stages of development from discovery through human trials. Moreover, some of these proteins will be administered in large amounts (*e.g.* mg/dose) that will necessitate large production volumes (Garber, 2001), and the prospect of personalized or individualized medicines for some products will pose particularly tough challenges for economical, custom, batch-wise production (*e.g.* Alison *et al.*, 2003). Thus, the demand for pharmaceutical proteins is considerable, and growing, creating a market opportunity that was almost nonexistent when plant molecular farming was conceived in the 1980s.

Protein-Manufacturing Capacity

Next, let's consider the extent to which this demand has created a supply-level crisis that

might stimulate the expansion of PMPs. An increasing demand for proteins creates opportunity for all possible production platforms, including the established way to manufacture proteins to the stringent standards laid down for veterinary and human applications, *i.e.* via fermentation of specialized microbial (bacteria and yeast) and mammalian (*e.g.* Chinese hamster ovary) cell lines, engineered to express the appropriate genes. We can, therefore, expect some expansion in this fermentation industry. While this will represent competition, the increasing need for proteins may also provide a chance for PMP technology not only to prove its fundamental capability but also to illustrate its efficiency in responding quickly, flexibly and perhaps economically to a rapidly evolving demand for product quantity and diversity.

Fermentation facilities require considerable capital investment and have finite capacity so that expansion also requires substantial capital. Such facilities are typically said to cost $300–$500 million to build, with a time frame of 4 to 5 years to cover construction, validation, and licensing (Thiel, 2004). Not surprisingly, therefore, the initial surge of progress in protein drug development stressed existing fermentation capacity, raising serious concerns about a coming "capacity bottleneck." As recently as 2001, a representative from a contract manufacturing organization (CMO) in this field was quoted as saying (cited in Garber, 2001):

> *…the only long-term solution is to shift some production (from fermentation systems) to transgenic animals and plants, which can in theory be scaled up much more efficiently to virtually any level.*

In our opinion at KTRDC, this period of "protein crisis" (Garber, 2001) in the late 1990s and over the last few years generated considerable new interest in the PMP concept. Two more gene-expression technologies emerged as PMP companies during that time, and pharmaceutical companies began to examine the PMP-manufacturing option more seriously. The PMP industry and associated organizations (*e.g.* KTRDC and other PMP-relevant research programs) also became more recognizable as a biotechnology sector in its own right, featuring prominently in the Biotechnology Industry Organization (BIO; http://www.bio.org) and holding a biannual conference (*Conference on Plant-Made Pharmaceuticals*; http://archives.cpmp2005.org).

The protein crisis might have become a forceful creator of new end-users and significant markets for the PMP industry. However, sufficient expansion has taken place in the fermentation industry that the crisis appears to be over, at least for now. Indeed, the biomanufacturing news spotlight is now focused on the end of the capacity-expansion boom, and industry analysts opine that "…there is little immediate pressure for companies to move to alternative platforms (*e.g.* PMP) that are as yet commercially unproven" (Thiel, 2004). Whereas just a few years earlier the transgenic animal- and plant-production systems were viewed with new interest as potential ways around the bottleneck, they are again left to make their own case for advantages, economy, *etc.*, relative to the traditional methods of making proteins.

While it seems unlikely that there will be another sudden surge in demand for proteins, the steady growth in demand will continue to apply pressure to the manufacturing

industry. It will be interesting to see if the CMOs will repeatedly be able to raise financing for expansions, and whether the larger pharmaceutical companies that have their own protein products will invest further in fermentation capacity. Another possibility is that protein production will grow sufficiently as a business sector that it will become much more internally competitive, triggering new interest in more economical methods of production and hence, potentially, in PMPs.

For a commercial PMP, an accumulation of product to a level of at least 1% of total soluble protein by weight is considered necessary, with enrichments of 5–10% of TSP being preferable.

PMP Technologies

The need, once again, for the PMP industry to convince the pharmaceutical community that PMPs can become an established route of large-scale production, brings us conveniently to a short overview of PMP technologies, their capabilities, characteristics, strengths and weaknesses. Table 1 lists the more prominently visible PMP companies, together with the kinds of gene-expression technologies on which they are based and the plant species with which they are compatible. The majority, if not all, of these proprietary technologies were derived originally from research conducted in the academic sector. The majority of them share an important attribute, namely the ability to drive protein accumulation in the appropriate plant tissue to very high enrichment levels relative to the native plant proteins in that tissue. Indeed, for a commercial PMP, an accumulation of product to a level of at least 1% of total soluble protein (TSP) by weight is considered necessary, with enrichments of 5–10% of TSP being preferable. With certain gene products that are particularly stable in the plant cell, and/or with certain technologies, enrichments approaching 80% of TSP may be attainable (*e.g.* Marillonnet *et al.,* 2004).

Table 1. Some* examples of PMP companies and technologies

Company name	"Vehicle" plant	Proprietary technology
Large Scale Biology	Tobacco	Viral transfection vector
Icon Genetics	Tobacco	Viral vector (and others)
Chlorogen	Tobacco	Chloroplast-based expression
Planet Biotechnology	Tobacco	Antibody production
SemBioSys	Safflower	Oilseed-based expression
Ventria Bioscience	Rice	Seed-based expression
Medicago	Alfalfa	Expression in forage crop
Biolex	Duckweed	Expression in aquatic plant

*This is necessarily an incomplete list, on account of limited space and scope of this review article; omission of any company or technology does not imply any negative assessment or view.

While sharing a common feature of highly productive gene expression, the PMP technologies otherwise exhibit considerable diversity in regard to other characteristics and perceived advantages. Expression in stably transformed plants contrasts with expression through transfection with modified virus particles. Many of the expression technologies are restricted to certain plant species, but the overall list includes food/feed plants such as corn and canola, feed crops such as alfalfa, and non-food species such as tobacco and duckweed. Depending on the particular technology, expression may occur in the leaf and hence in the bulk of the plant's above-ground biomass, or it may occur exclusively in seed or fruit tissues. Also, expression in the transgenic systems may be from vectors inserted in the nuclear genome or in the chloroplast genome.

An in-depth comparative analysis of all these different PMP technologies is beyond the scope of this paper, but suffice it to say that each has particular advantages or unique features. Expression in the chloroplast, for example, may offer advantages in regard to containment and regulatory compliance when deployed in plants that exhibit little or no transfer of chloroplasts through pollen [for a review of chloroplast transformation, see Bogorad (2000)]. Viral transfection systems (Lacomme *et al.*, 2001; Marillonnet *et al.*, 2004) will pose different regulatory approval considerations from those required for transgenic plants, and this may be advantageous in some circumstances. Ease of post-harvest isolation of the protein product, and subsequent bioprocessing is a unique claim made by an oilseed-based system (Moloney, 2000). And at least one system is proven in the production of complex antibody molecules requiring simultaneous and balanced expression of several genes in the same plant cell (Wycoff, 2005). Overall, this diversity of characteristics and features should work to the advantage of the PMP strategy, enabling it to address a wider range of product "targets" and production constraints (*e.g.* growing location, farming know-how, and special regulatory/containment considerations) than might be possible with only one or two gene-expression technologies.

The PMP industry is still working towards its first truly large-scale (100 acres or more), preferably ongoing, provision of a protein drug to a client company or to consumers.

PMP Engagement of Protein Markets

The status of the PMP opportunity today is largely consistent with the ideal philosophy presented at the beginning of this section. Proteins represent an increasing proportion of pharmaceutical products, worldwide. While there is currently less concern about production capacity for those proteins relative to the situation a few years ago, it seems possible that growth in markets for protein drugs, along with dosage and personalization issues, will continue to pose challenges for the capital-intensive, cell-culture-based manufacturing platforms. The PMP platform comprises a range of impressive technologies with a

broad range of capabilities, ready to address these opportunities. But while there have been a few instances of commercial products' being made via the PMP route, most have been small-scale (1–100 acres), one-time, or experimental endeavors. To date, the PMP industry is still working towards its first truly large-scale (100 acres or more), preferably ongoing, provision of a protein drug to a client company or to consumers.

We will next examine the challenges that must be met for the industry to break through into such mainstream protein-drug manufacturing.

Challenges to PMP Development

The basic scientific and technical challenges of making "foreign" proteins in plants were met many years ago. And while it is true that plant-based production may not be feasible for some proteins [*e.g.* on account of different post-translational modifications such as glycosylation (Gomord *et al.*, 2004)], and that technical advances continue to be made in expression levels and other aspects that may improve the range of products that can be made in plants, there is no shortage of viable PMP targets today.

Rather, the factors that most influence the growth rate of the industry at the present time are financial and business related. PMP companies must compete for the attention of investors who also review business models formed around other manufacturing platforms, and who may be more inclined to invest in companies that own the innovative new protein drugs. (PMP companies sometimes own the product target as well as the production technology, but all seek to partner with companies who own additional prospective targets.)

This competition may become easier to beat once the PMP approach is embraced by the pharmaceutical industry as an established production platform. Factors that influence the pharmaceutical community's acceptance of PMPs include the "cultural" differences between the pharmaceutical sector and the agricultural biotechnology sector, an overall lack of understanding of the economics of plant-based production (discussed further below), the lack of familiarity with large-scale purification of proteins from plants to the stringent specifications required for clinical application, and quite possibly a desire not to be the first drug company to adopt the PMP concept. To appreciate the cultural differences, one has only to contrast the highly controlled, highly contained, nature of bulk cell-culture systems in which every cell is almost identical to every other, with the PMP image of a greenhouse or a field of plants; it must be tempting for those engaged in protein-pharmaceutical manufacturing to persist with their established, long-proven, methods for reasons of familiarity and "comfort-level" alone.

If a protein-supply crisis does not drive a wider adoption of plant-based manufacturing, attractive and superior economics would certainly be expected to do so. Indeed, the PMP industry has recently been challenged to demonstrate the economic advantages of its platform, particularly in regard to production scale-up where the relationship between capital investment and capacity increase may be distinctly advantageous (Thiel, 2004). Unfortunately, many published papers and review articles over the years have misleadingly characterized the PMP technology as a "cheap" way to make a protein. There is, of course, always a finite cost associated with producing a crop, and with PMPs there can

be specific additional costs associated with containment (at least until the plant becomes deregulated), particular harvesting practices, *etc*. Moreover, a complete estimate of cost-of-production for a plant-derived pharmaceutical cannot be made without data on extraction and bioprocessing expenses. For any particular PMP product under consideration, these post-harvest details are usually either unknown or based only on experience at small scale. Thus, the majority of statements in the literature that proclaim an inherent cheapness for PMPs, without justifying that claim, cannot be taken seriously. On the other hand, incremental costs associated with PMP scale-up should be appealing, for the simple reason that planting more acres in the field, or constructing additional contained facilities such as greenhouses, has to be significantly cheaper than building bioreactors for fermentation. (Bioprocessing expansion costs would likely be very similar for all platforms.) It is in this aspect of flexibilty and expansion that the economics of PMPs deserve careful consideration.

Most recently the PMP industry has found that its potential pharmaceutical-industry clients are not the only stakeholders needing to be convinced. The potential use of food/feed plants as the crop species of choice for some PMP systems has drawn criticism from the respective food industry organizations, as well as from environmentalists and biotechnology-opposing groups (*e.g.* see the editorial on page 22 of Nature Biotechnology 133, 2004, for an overview, and http://www.gmabrands.com/news/docs/NewsRelease.cfm?docid=1029 for an example of food-industry perspective). Concern has been expressed over the degree of protection and assurance that could be provided to obviate an envisaged possibility of contamination of the food/feed supply with pharmaceutical proteins from the PMP variant of the crop, either via genetic means (cross-pollination) or by direct mixing of plants or harvested material. Anxiety on this point has generated local/regional opposition to one PMP platform that uses a food plant, resulting in that company's relocation of its pilot production trials and the resulting loss of a new opportunity for farmers at the original site. The fear of food contamination is also reflected in the presently very high level of governmental regulation and risk assessment applied to field releases (field trials, pilot production) of PMP plants (Peterson and Arntzen, 2004).

Despite these concerns, it has been speculated that PMP crops might fare better than most genetically-modified (GM) crops in terms of public perception and acceptance in those countries that are uneasy about GM plants in general [for further discussion and relevant citations see Einsiedel and Medlock (2005)]. The often-heard criticism that input traits such as herbicide tolerance do not provide sufficiently obvious benefit for the consumer no longer applies, and the product is readily understood as a beneficial medicine.

Developing a Dedicated Crop System for PMPs

Concerns about contamination of existing crops with pharmaceutical products coming from the corresponding PMP crops would be moot if PMPs were produced using "vehicle" species that had hitherto not been developed into crops, *i.e.* plants that had not previously been domesticated. However, suitable gene-expression technologies would have to be adapted for use with these previously uncultivated species, or developed from scratch,

and the domestication aspect alone might take many years. Even with the non-food plant, tobacco, there is concern to prevent any possible contamination of the traditional crop; the tobacco-production industry in the United States currently has zero tolerance for GM contamination.

There is an additional reason to consider the development of a dedicated vehicle plant exclusively for PMP applications, namely the lack of desirable characteristics in existing crop varieties. Modern crop cultivars are highly customized to the particular applications for which they are used. Adaptive enhancements continue to be made through advanced breeding and genomics research, improving yield, resistance to pests, and other useful traits. Some of these qualities, particularly the more agronomically oriented ones such as disease resistance, will still be relevant when the plant is used as a protein-production vehicle. However, other traits specific to the PMP application may also be lacking in the commonly grown varieties. Examples include productive response and systemic spread when infected with virus-based PMP gene vectors, sterility or limited (or late) flowering to minimize gene flow via pollen, special morphology and growth habit suited to a specific harvesting method that will be used with the PMP application, absence of certain metabolites that may compromise product integrity or quality during bioprocessing, *etc*. Indeed, the design and development of new plant varieties customized for PMP applications is to be expected, given the general practice of variety development in crop agriculture.

Tobacco is convenient for illustrating vehicle-plant customization. The *Nicotiana* genus contains a large number of species that are found in diverse regions of the world and which exhibit a wide range of morphological and other relevant characteristics. Most importantly, many of these undomesticated species are already large, bushy and productive plants, in contrast to the "wild" relatives of many crop plants, which so often exhibit small, low-yielding forms. Moreover, many *Nicotiana* species have disease-resistance traits not found in the traditional, commercial *N. tabacum* cultivars. Thus, there is an extensive and useful germplasm resource, and the domestication breeding path is conveniently short. Most of this germplasm has been ignored in breeding traditional tobacco types, presumably because the exotic species and associated variants are unsuited to the manufacture of traditional products such as cigarettes. Naturally, these issues have no relevance in the new PMP applications of the plant.

Table 2 provides a listing of the most desirable characteristics to be incorporated into the new vehicle plant that we are constructing at KTRDC for use with all tobacco-specific PMP gene-expression technologies. In order to achieve optimal compliance with federal regulations concerning limitation of gene flow (genetic "containment"), we have adopted a hybridization strategy. Thus the plants set out in the field for production will be interspecific hybrids that exhibit a high degree of sterility. One parent of the hybrid is an appropriate cultivar of *N. tabacum*, whereas the other is a different species of *Nicotiana*. Each parent also contributes different characteristics that are important features of the final custom hybrid. For example, for transgenic PMP strategies one parent will be expressing the PMP transgene via the appropriate high-level expression system. For chloroplast-based expression, this would be the maternal parent. The other parent may also be transgenic for other characteristics such as herbicide tolerance, *etc*.

Table 2. Desirable traits and characteristics of a new crop plant customized for use with tobacco-based PMP gene-expression technologies.

Performance traits	Production-related traits
Transformable	Eonomical production*
Regenerable from cell culture	Vigorous regrowth*
PMP-vector-system compatible	Disease resistance
Sterile	Herbicide tolerance
Identity-preserved	Insect resistance
Desirable metabolite profile	High biomass-yield*
Bioprocessing-optimal	Good protein production
	Suited to mechanized harvesting

*Vigorous regrowth (for multiple harvests) and high biomass-yield contribute directly and importantly to economical production, but the latter is listed separately as well so as to include improved economy of seedling production, transplanting, and many aspects of crop maintenance, as well as economical disposal of waste material post-bioprocessing, *etc.*

It will be noted that the table of characteristics includes economy of production. One disadvantage of conventional tobacco for PMP applications is the very high cost of production of the traditional crop, resulting from the use of transplants, wide plant spacing, and considerable manual labor even pre-harvest. In developing the customized *Nicotiana* hybrids for PMPs, we can also take the opportunity to address the cost-of-production issue. For example, mechanized harvesting enables the crop to be produced by sequential harvesting and regrowth, unlike traditional tobacco, which is (manually) harvested once. This contributes significantly to improved production economics, so productive regrowth becomes an important performance trait for the new PMP hybrid lines.

Along with the development of new hybrid *Nicotiana* plants, much can be done to usefully customize the production practices, further reducing the cost of production for PMPs. The mechanized harvesting mentioned above, using plants grown much closer together and employing three or four rounds of growth from the same plants over an extended growing season, are good examples. Eliminating transplants, and producing the crop by direct seeding into the field, would also lower production costs. However, at the present time transplanting is actually viewed advantageously relative to direct seeding for PMPs, as it further reduces the possibility of volunteer plants' emerging in the following year. Accordingly, we are examining the possibility of achieving more economical raising of transplants in the greenhouse, and good progress is being made with higher densities of transplant production.

We are hopeful that the increasing market opportunity (demand) and the demonstrated production capability (PMP technology) will soon converge.

In Conclusion

The continuing development of protein-based medicines worldwide bodes well for the future of the PMP concept. Gene-expression technologies for plant-based production are proven and productive. We are hopeful that the increasing market opportunity (demand) and the demonstrated production capability (PMP technology) will soon converge to achieve large-scale, and ongoing, manufacturing of valuable proteins from one or more plant-based platforms. Meanwhile, much can be done to enhance the agricultural interface with PMPs, as I have illustrated above with reference to our work with *Nicotiana*. Existing crops and associated production methods are frequently sub-optimal for application to PMPs, but the use of related germplasm that remains compatible with PMP gene-expression technologies can not only enhance production economics and facilitate regulatory compliance, but also mitigate potential conflict with traditional food and other applications of that plant.

Acknowledgments

The Kentucky Tobacco Research and Development Center is funded by the Commonwealth of Kentucky, and is administered by the Kentucky Tobacco Research Board and the University of Kentucky (College of Agriculture). Research on the development of new *Nicotiana* hybrid plants and associated production methods, described above, is conducted by Orlando Chambers, David Zaitlin, Baochun Li, Richard Mundell and colleagues at KTRDC.

References

Alison A *et al*. (2003) Individualized human scFv vaccines produced in plants: humoral anti-idiotype responses in vaccinated mice confirm relevance to the tumor Ig. Journal of Immunological Methods 278 95–104.

Bogorad L (2000) Engineering chloroplasts: an alternative site for foreign genes, proteins, reactions and products. Trends in Biotechnology 18 257–263.

Collins GB Shepherd J (eds.) (1996) Engineering Plants for Commercial Products and Applications. Annals of the New York Academy of Science 792.

Einsiedel EF Medlock J (2005) A public consultation on plant molecular farming. AgBioForum 8 26–32

Garber K (2001) Biotech industry faces new bottleneck. Nature Biotechnol. 19 184–185.

Gomord V *et al.* (2004) Production and glycosylation of plant-made pharmaceuticals: the antibodies as a challenge. Plant Biotechnology Journal 2 83–100.

Lacomme C *et al.* (2001) Plant viruses as gene expression vectors. In: Genetically Engineered Viruses (Ring CJA and Blair ED eds.). Oxford: BIOS Scientific Publishers Ltd., pp 59–99.

Ma J K-C *et al.* (1998) Characterization of a recombinant plant monoclonal secretory antibody and preventative immunotherapy in humans. Nature Medicine 4 601–606.

Marillonnet S *et al.* (2004) *In planta* engineering of viral RNA replicons: Efficient assembly by recombination of DNA modules delivered by *Agrobacterium* Proceedings of the National Academy of Sciences of the USA 101 6852–6857.

Moloney MM (2000) Molecular farming using seeds as hosts. In: Seeds Technology (Bewley D Black M eds.). Sheffield: Academic Press, pp 226–253.
Peterson RKD Arntzen CJ (2004) On risk and plant-based biopharmaceuticals. Trends in Bioechnology 22 64–66.
Price B (2003) Personal Communication.
Thiel KA (2004) Biomanufacturing, from bust to boom….to bubble? Nature Biotechnology 22 1365–1372.
Wycoff, K (2005) Secretory IgA antibodies from plants. Current Pharmaceutical Design 11 11–19.

Maelor Davies is director of the Kentucky Tobacco Research and Development Center (KTRDC) at the University of Kentucky. He received his graduate and postgraduate education at the Universities of Oxford and London (United Kingdom), respectively, then undertook postdoctoral research at the Plant Research Laboratory at Michigan State University. Prior to joining KTRDC, he was a senior scientist with Calgene Inc., a pioneering agricultural biotechnology company in California. During his 14 years with Calgene, Dr. Davies played key roles in R&D programs that produced some of the world's first genetically engineered crops. His Calgene work focused on, *inter alia*, crop use of fertilizers, herbicide tolerance, improved fruit quality, and novel natural products.

Since 1996, Davies has been responsible for designing and overseeing the transition of KTRDC from health-related research to its present mission of facilitating the development of new crops for Kentucky agriculture. The research in plant-made pharmaceuticals (PMPs) emphasizes the development of a new, PMP-dedicated crop plant and an associated agricultural production system that will be useful to all companies using tobacco-based gene-expression technologies for protein production. The Center also supports unique research into natural products, anticipating that the development of new applications for intrinsic, small-molecule plant metabolites will, in turn, create new crop opportunities for growers.