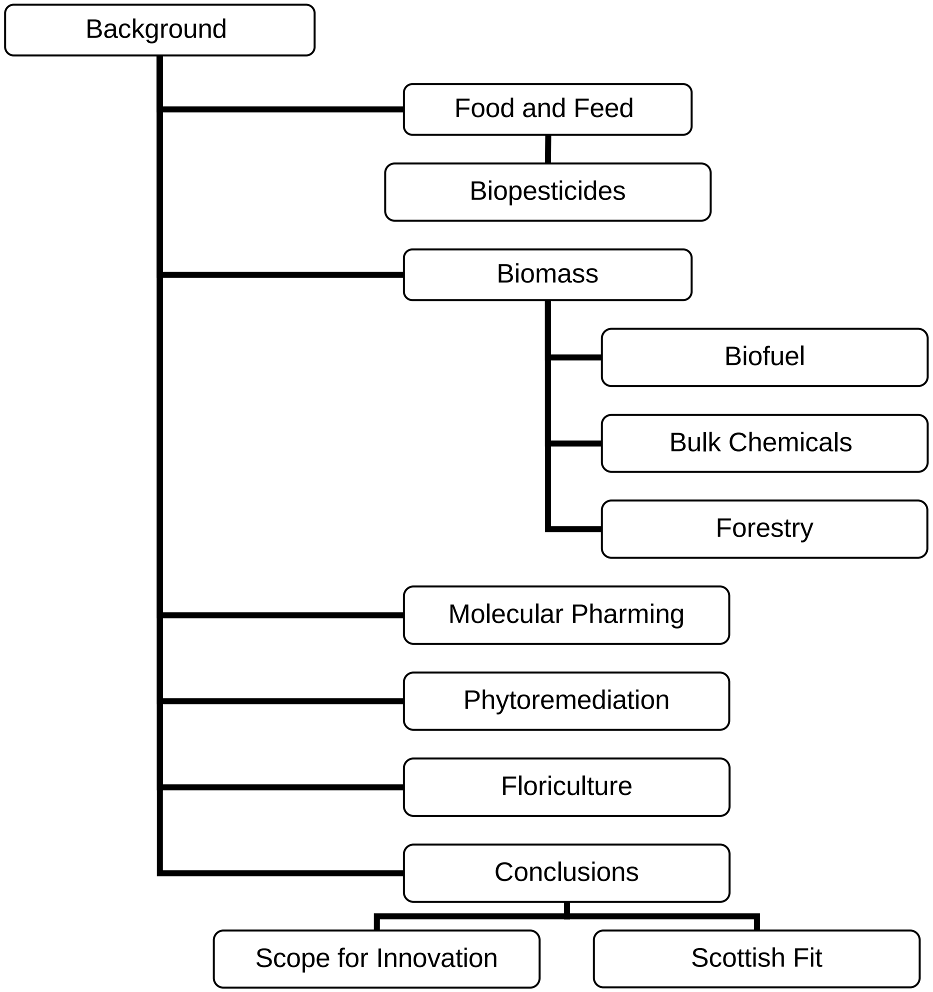
ITI Life Sciences

Plant biotechnology and its many markets

Environmental scan

Technology & Markets
June 2008

Scope of e-scan



This report examines the existing and potential application of modern biotechnology as applied to plant life.

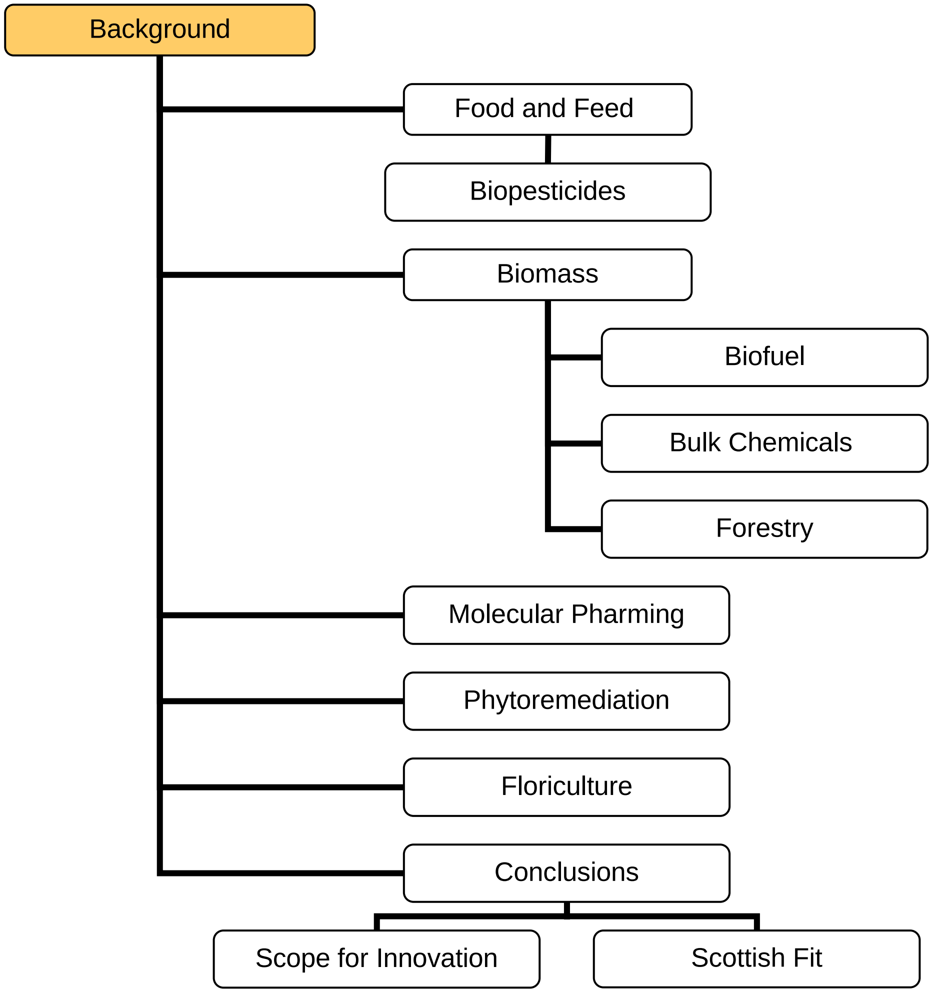
Specifically, it examines the potential role of agricultural biotech in the production of food, fuel and pharmaceuticals from crops in the emerging markets for various chemical feedstocks derived from plant material, and the use of plants in remediation of contaminated land and water.

This report is not an exhaustive examination of the marketplace but offers guidance for future foresighting of areas open for innovation that fit with Scottish expertise.

Executive summary

- Plants are fundamental not only to our global food supply but also to our climate. They have been a source of life-preserving medicines and are used to bring colour, fragrance and flavour to our lives.
- Today we are looking to plants as an environmentally sustainable solution to the “fuel gap” and as feedstock for chemicals previously derived from petrochemicals.
- Modern genetic engineering allows us to selectively modify plants to optimise their value for **all these potential markets**.
- Most efforts to this point have been around enhancing the value of commodity crops for farmers, but today the industry is looking to provide solutions for wider issues such as climate change, new pests, alternative fuel feedstock and nutritionally enhanced foods.
- Agriculture is now looking beyond food to other markets: Biofuels, bioplastics and other chemical commodities such as lubricants, surfactants, fragrances and dyes.
- Underpinning all the markets is the need to be able to both understand and modify plants, stably change them and develop environmentally benign products and processes.
- As a result of this environmental scan, we recommend further investigation of the innovation needs in the following areas:
  - **plant transformation tools and technologies;**
  - **bioplastics and biolubricants – specifically high-value speciality products;**
  - **artificial photosynthesis;**
  - **the application of molecular pharming for emerging therapeutics.**

Background



This section provides the historical context for today's agbiotech industry by briefly explaining the underpinning technology, the status of the industry and the challenges that the technology has faced.

This section does *not* offer a risk–benefit analysis of the genetic modification of plants, which remains a hotly contested issue. However, the issues raised, as they affect the market for agbiotech products, are highlighted.

For ease of reference, genetic modification (or genetically modified) is abbreviated to GM throughout the rest of this document.

From genes to greens

- For centuries, man has guided the development of native plant species by selecting and replanting only those plants possessing desired qualities (e.g. good height, greatest yield, best-tasting fruits).
- Even a rudimentary understanding of Mendelian genetics can equip breeders with sufficient knowledge to assist this “evolutionary” process.
- Modern biotechnology has provided a means to both better control and accelerate this selection process:
  - genetic insights can be used to facilitate traditional plant breeding strategies (non-GM);
  - genes encoding useful traits can be permanently incorporated into a plant’s genome through various transformation techniques (GM).
- A highly volatile mix of commercial, political, regulatory, environmental and ethical issues, alongside profound public distrust, has made the genetic modification of plants a highly controversial area.

The Austrian monk, Gregor Mendel, the grandfather of modern genetics.

Plant technology (I)

The genetic makeup of plants has been altered through a variety of well-established techniques:

Traditional techniques (non-GM)

- **Selective breeding** of plants through cross-pollinating a plant variety with a second plant possessing a desirable trait to produce elite crops.
- **Chemical mutagenesis**. A plant can be modified by treating the embryo with a mutagenic agent. This randomly alters the genotype and generates (potentially) a value-added phenotype.
- **Tissue culture**. Most modern plant development also involves **culture** of plant cells and tissues, allowing the selection of modified plants before they are grown to maturity, saving time and cost.

Transgenic techniques

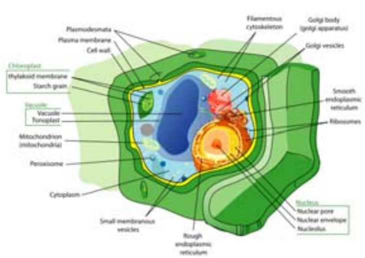
- Infection with ***Agrobacterium tumefaciens*** – a plant pathogen that causes crown gall disease – by splicing novel genes into the pathogen's infective plasmid (so-called T-DNA) and infecting the young plant or tissue culture (see next slide).
- **Biolistics** (aka "gene gun") by shooting DNA-coated gold particles directly into the plant cells for incorporation into the plant genome.

BioRad's Helios Gene Gun

Plant technology (II)

Marker gene | Promoter | Transgene | Termination sequence

1. Transgene to be inserted is linked to a promoter and a marker to regulate its expression and selection, respectively.



2. Transgene inserted into infective plasmid (Ti) of plant pathogen *Agrobacterium tumefaciens* and plant infected with the virus OR transgene may be applied using biolistics.

5. Extensive field trails and safety studies are needed to establish the stability of line and data for regulatory approval.

3. Transfected plants grown in culture. Selection for the transgene carried out using marker selection (often antibiotic selection).

4. Selected plants are grown in greenhouse and phenotype changes studied. Transgene-positive plants are then crossed to establish a stable line.

Plant technology (III)

A comparison of the differences between conventional breeding and transgenics

Selective breeding

- In selective breeding the genetic diversity of a pool of native varieties is used as the source of new traits.
- Genetic markers (if known) for a specific trait are used to probe native plants. Equally, the phenotype of the plant may provide the necessary selection criteria.
- Plant(s) possessing the marker can be selected.
- An elite cultivar (used commercially) is crossed with the trait-positive plant and progeny grown.
- Some of the progeny will carry the new trait. These are then back-crossed with the parent to ensure the original elite traits are not lost.
- The advantage is that the new cultivar is not genetically modified and so suffers less from regulatory scrutiny.
- The disadvantage is that the available natural gene pool may not possess the desired trait.

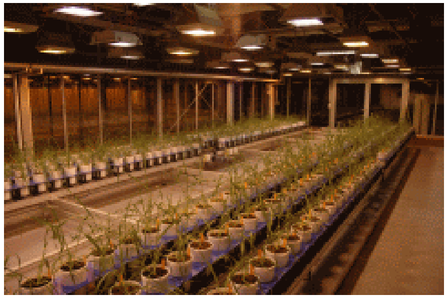
Transgenics

- Transgenics allows the introduction of foreign genetic traits into a plant genome.
- A variety of techniques introduce the gene. In most instances the location at which the gene is inserted is not known.
- Plant(s) possessing the marker can be selected via introduction of a marker gene.
- The selection process can be carried out early and only trait-positive plants grown to maturity.
- Several generations are grown to ensure the transgene is inserted stably in the genome.
- Transgenics offers the benefit of speed but does require knowledge of the genetic basis of the desired trait. There may be obstacles to having a GM crop approved in some regions. The developer may also need to access IP rights to the transgenic technologies used to create the variety.

Plant technology (IV)

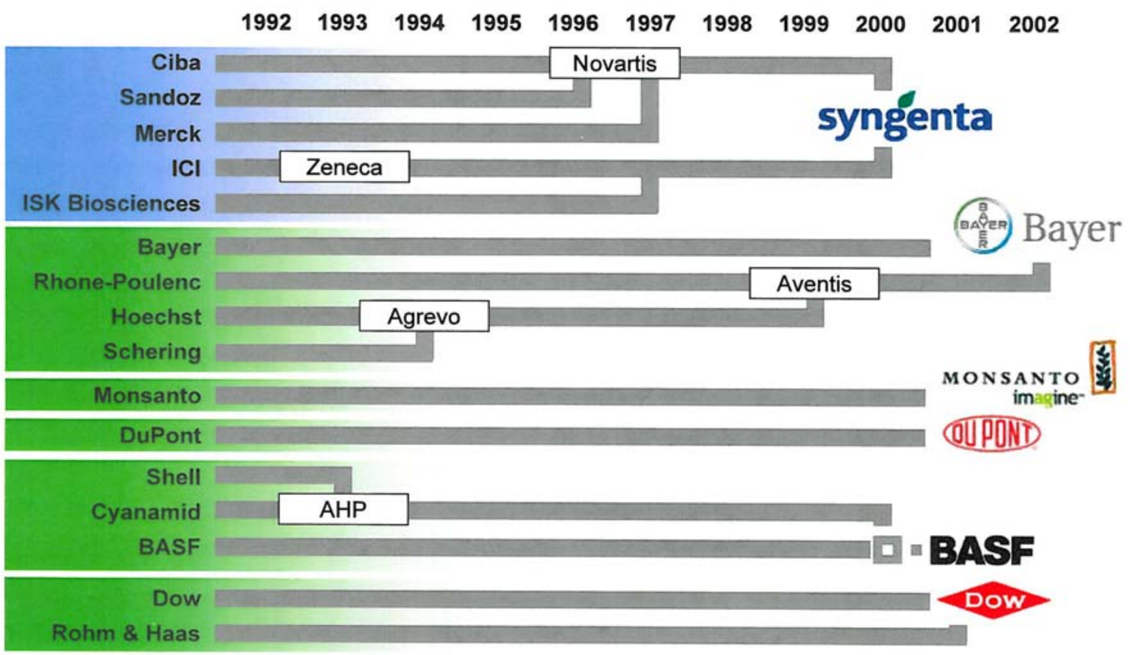
During the past decade, modern genetics has offered means to accelerate the development process of new crops with valuable agricultural traits employing techniques such as:

- **Reverse genetics:** Chemical mutagenesis of native plants to cause changes in the genotype that may be linked to useful phenotypes (traits). **TILLING** (**T**argeting **I**nduced Local **L**esions **IN** **G**enomes) is a reverse genetics technique using natural plant varieties. TILLING® was first developed in the Basic Sciences Division at the Fred Hutchinson Cancer Research Center in late 1999 and licensed to Anawah, Inc.
- **Marker-assisted selection:** DNA tags (or other markers) that are associated with a useful phenotype, whether from the specific species in question or a related species, can provide a valuable tool when selecting hybrids from collections for future cross-breeding of elite cultivars. Today, single nucleotide polymorphisms (SNPs) can be used if the plant genome sequence, or EST map, is available. The advantage here is that the plant can be screened early and need not be grown to maturity, thus saving time.
- **High-throughput phenotyping:** One of the challenges for commercial breeding programmes is a high-throughput means of phenotyping the transgenic plants. Various high-throughput automated image analysis techniques are available, such as that offered by German company Lemnatec.



Agriculture's equivalent to pharma's high-throughput drug screening. Lemnatec facility

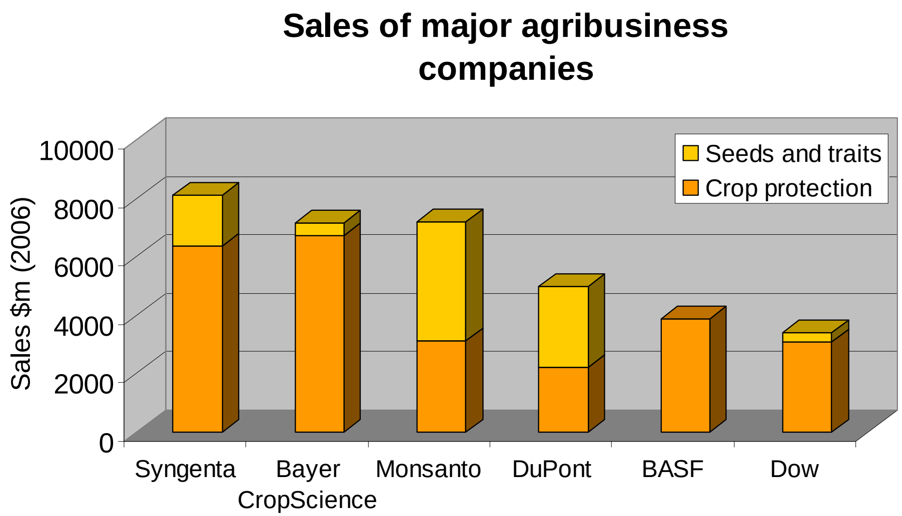
The state of the industry (I)



Courtesy of Syngenta

- Around 20 years ago, stagnating sales and declining profits triggered a wave of consolidation within the agrochemical and seed industry, giving rise to the concept of the fully integrated, large-scale life science company (aka chemicals for all applications).
- But this belief was soon challenged… By the late 1990s, agrochemicals were dragging down share prices and a spate of agrochemical “spin offs” ensued. Wholly agribusiness multinationals such as Syngenta and Aventis emerged from this process.
- The industry shrank through consolidation: Today, around 95% of the global agrochemical market is owned by 20 companies, and the top six players own over 75%.

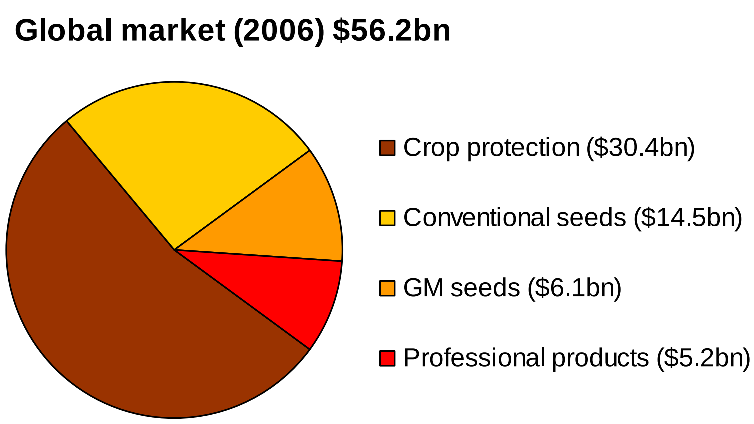
The state of the industry (II)



Source: Syngenta presentation

- The agrochemical industry is **increasingly turning to biotech for new product solutions**. More than half of both Monsanto and Dupont's turnover now comes from the sale of seed and traits rather than chemicals.

.



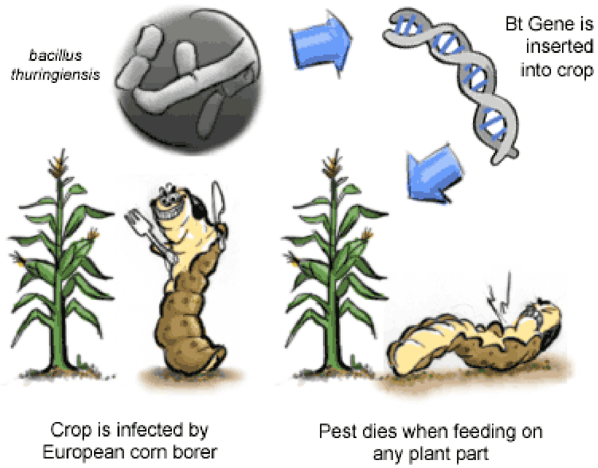
- The trend towards biotech products looks set to continue. The pressure on agrochemical (pesticide and herbicide) sales arising from tighter controls on agrochemical use and impending patent expiry of many of the leading brands will force agrochemical players to seek value from seeds and traits.

IP dominance

- Consolidation within the industry also created a **dominant position over key intellectual assets** including transfection strategies, expression vectors, selectable markers and genes linked to useful traits, etc.
- Indeed, several of the major players have subsidiaries whose sole task is to cross-license these technologies to other players.
- The cost of licensing can, however, have a constraining effect on smaller newcomers to the sector, including those within the public sector.
- Some of the core patents are close to expiry and this could enable some leverage for smaller players and create an environment conducive for creation, protection and adoption of new technologies.
- New varieties of plants are also protected for 20–25 years under **Plant Breeders Rights** (or Plant Variety Rights). The new plant must be tested at a specialist centre and shown to be distinct from other varieties, uniform and stable.
- The breeder of the plant can register the plant as its own property and may sell it exclusively or offer licenses to other users.
- Various exemptions under Plant Breeders Rights can, at times, clash with rights under patent law. For example, a farmer may save the seeds from harvested plants and replant them the following year; a grower may also use a protected plant variety as a source for further plant breeding. Both would contravene patent rights.

GM crops – the early wins

- The first genetically modified (GM) crops that came to market benefited the farmer – so-called **input traits** – by improving the crop's resistance to common pests and their tolerance to herbicides. The goal here was to reduce loss of yield and to reduce the need for costly spraying of herbicides and pesticides. These were simple single gene (single event) traits. The best-known examples included:
  - *bt* maize and cotton (YieldGard, Bollgard): These crops possessed a gene for a fungal endotoxin derived from *Bacillus thuringiensis.* The plant synthesizes the toxin, which then kills the pest but is harmless to native wildlife;
  - herbicide-resistant corn, soybeans, cotton, and canola (e.g. RoundUp Ready). Crops were engineered to possess an enzyme (5-enolpyruvylshikimate-3-phosphate synthase, EPSPS), which is resistant to the toxic effects of the glyphosate herbicide.
- There were clear advantages to the farmer:
  - reduced numbers of pesticide sprays;
  - reduced tilling of fields;
  - improved yields of crops through reduced losses.



Courtesy, *Science Quarterly*

GM fruit & veg – still to come

- **Fruit and vegetables are lower volume but greater profit-margin products than cereal crops as they attract higher farm-gate prices**.
- The first GM fruit to be approved by the US Food and Drug Administration (FDA) was Calgene's *Flavr Savr* tomato. This tomato was engineered to be more resistant to rotting by using an antisense construct that interfered with the production of the enzyme polygalacturonase. Although the modification had the desired effect, it did not slow softening, making the tomatoes difficult to harvest, and it ruined flavour and aroma. The product was not commercially viable.
- Few GM fruits and vegetables have yet to reach the market. Most that are cultivated commercially are virus resistant, such as papaya (Hawaii's fifth largest crop), potato, squash and sweet pepper. India, Brazil and South America are developing transgenic versions of their own staples, such as aubergine, cauliflower and tomato.
- The high cost of new product development and regulatory approval, and the potentially smaller market opportunity, confounded by unpredictable consumer uptake, have (to date) made this an unattractive gamble for companies.

The *Flavr Savr* tomato (top) and virus-resistant papaya (bottom)

It can cost over £100 million and take 8–10 years to get a new crop to market. Around 10% of these costs can be attributed to the regulatory approval process.

Industry reaps a poor PR harvest

- The launch of GM plants coincided with a loss of public confidence in both "industrialised" farming practice and governments' seeming inability to protect consumers (e.g. mad cow disease in the UK).
- Concern surrounded the underpinning science of GM, specifically: The risk of the transgene flow from GM crops to native species through cross-pollination; the health risk of antibiotic selection markers; and the damage caused by the often aggressive use of herbicides and pesticides.
- There was also outrage at the application of so-called terminator technology, whereby a genetic modification could render seeds sterile to prevent the replanting of saved seeds. This was to protect the industry's IP position but it further dented the industry's reputation in the public eye.
- **As a result, there was vehement, if not violent, opposition from European campaigners and consumers, which came to a head in around 1996**.
- In response, by 1998 there was an EU moratorium on new GM crop approvals and strict regulations imposed on labelling and traceability.
- The anti-GM lobby group has had a pervasive effect in Europe during the past decade, contributing directly and indirectly to: Loss of expertise from applied plant science research; reduced funding of agricultural research; and a lack of investment and spinout activity in agbiotech.

EU regulations

- The UK was the first country to pass legislation controlling genetic modification (1978). These regulations were harmonised in 1990 with EC Directives controlling “contained” (laboratory or enclosed system) and “deliberate release” (field trials) of GM organisms into the environment.
- In 1998, largely in response to the public concerns surrounding genetic modification, six EU states imposed an unofficial moratorium on the approval of new GM crops.
- By 2003, the US, Canada and Argentina argued to the World Trade Organization (WTO) that the EU was in breach of fair-trade rules in preventing imports of GM products.
- The EU modified its regulations before the WTO could take action. These July 2003 regulations require labelling of all products containing more than 0.9% approved GM crops and also if the genetic modification has been used in the ***production*** of the food. For example, oil from GM rape and glucose syrup from GM maize must be labelled as GM products, although neither contains any GM material and each is identical to the non-GM product. The US argues that the new regulations have provided even higher hurdles for GM crop producers.
- **No *new* GM crops or plants have been approved for commercial cultivation in the EU for almost a decade.** Around 40 crops are awaiting approval. In part this stems from several EU member states having zero tolerance to GM and voting against all applications; a qualified majority is needed for approval.

There has been concern that if the EU does not approve the importation of new high-yield GM soybean crops grown in the US, Argentina and Brazil by 2010, Europe will face a shortfall of feedstock for domestic animals that could hike the cost of meat production and retail prices.

US and ROW regulations

United States

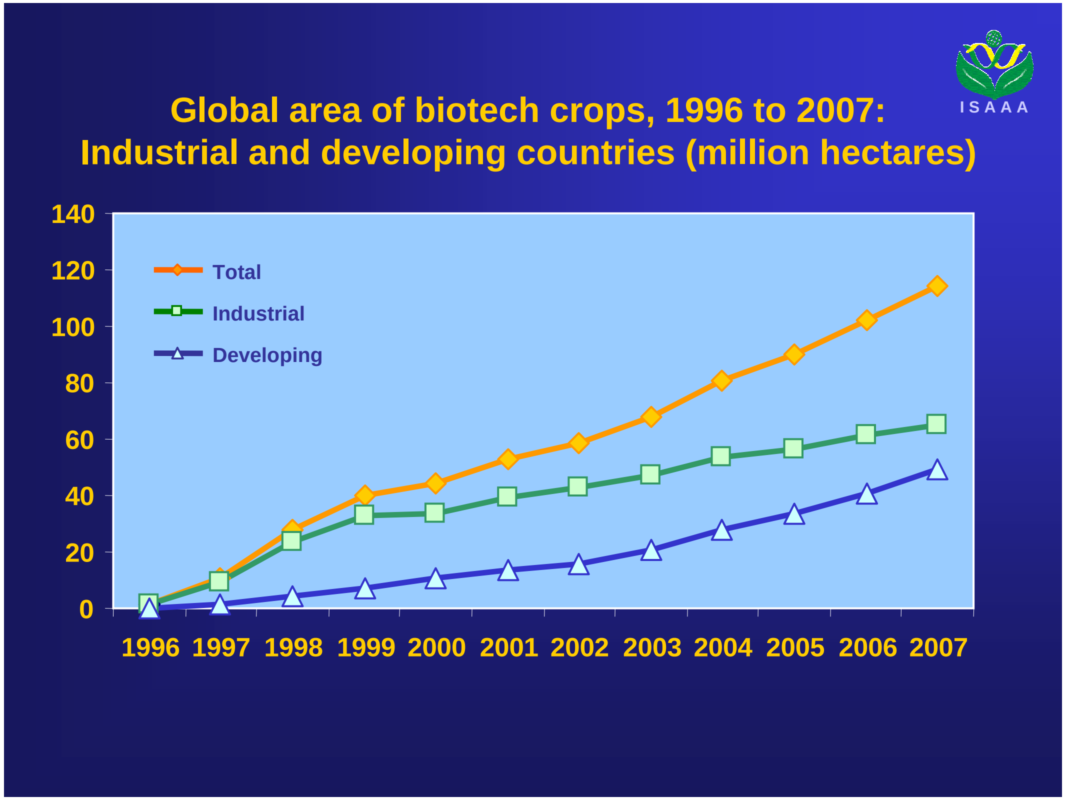
- The US continues to be supportive of GM technology.
- A GM crop destined for food and feed must be approved by both the US Department of Agriculture (USDA) and the Food and Drug Administration (FDA).
- Pesticides and plant-incorporated-pesticides are also regulated through the Environment Protection Agency (EPA). Within the USDA, the Animal and Plant Health Inspection Service (APHIS) oversees biotechnology regulation.
- There is no mandatory labelling of GM foods required by the FDA. The FDA regards GM products (on approval) to be **not substantially different** to the non-GM equivalent.

Rest of the world (ROW)

- Around the rest of the world, attitudes to GM technology vary widely from enthusiastic embrace to outright suspicion.
- Over 50 countries have either approved the import or cultivation of at least one GM crop.
- All countries require some level of safety testing before crops can be planted and many require labelling of GM-containing products.
- Only China, Brazil and the EU currently require labelling of food or feed that has been **derived** from GM processes.

So, who wants GM now?

- Despite the persisting anxieties about GM in some regions, plantings of GM crops have steadily increased during the past decade.
- In total, 114 million hectares of GM crops were planted across 23 countries during 2007 (an increase of 12% from 2006). GM products are sold in over 50 countries. (Source: ISAAA.)
- The global market value of GM crops is around $6.9 billion, equivalent to 16% of the $42.2 billion crop protection market and 20% of the $34 billion seed market. (Source: Cropnosis.) The market is projected to increase to $7.5 billion in 2008.
- GM is now being most rapidly adopted in developing countries, with the notable exception of Africa, which remains wary of the technology.



Reproduced by courtesy of International Service for Acquisition of Agro-Biotech Applications (ISAAA). Source: Clive James, 2008

Globally applied technology

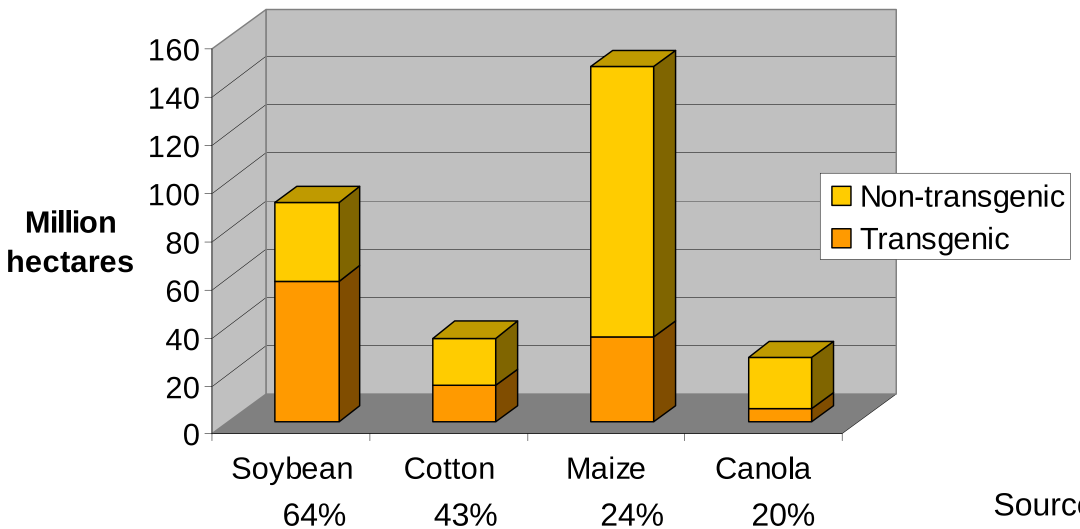
Global area of biotech crops in 2007 by country (ISAAA, Clive James, 2007)

Rank	Country	Area (million hectares)	Biotech crops planted
1	USA	57.7	Soybean, maize, cotton, canola, squash, papaya, alfalfa
2	Argentina	19.1	Soybean, maize, cotton
3	Brazil	15.0	Soybean, cotton
4	Canada	7.0	Canola, maize, soybean
5	India	6.2	Cotton
6	China	3.8	Cotton, tomato, poplar, petunia, papaya, sweet pepper
7	Paraguay	2.6	Soybean
8	South Africa	1.8	Maize, soybean, cotton
9	Uruguay	0.5	Soybean, maize
10	Philippines	0.3	Maize

Technology of choice

- For some crops, GM varieties are now the preferred choice for farmers. For example, in the US almost all soybean planted is genetically modified.
- By global planted area the preferred traits are herbicide resistance (72%) insect resistance (18%) and stacked traits (i.e. two or more traits in the same plants, 19%). A smaller area of virus-resistant crops (squash, papaya) are planted (<1%).
- In Europe, *bt* maize is grown in Spain, France, Czech Republic, Portugal, Germany, Slovakia and Romania. Poland commenced cultivation of GM crops in 2007. Also in 2007, the French government suspended GM crop plantings while carrying out a review.

Global adoption rates for principal GM crops



Source: ISAAA, 2008

Drivers for agriculture

A growing and demanding global community

- Food demand is outstripping supply in many countries, exacerbated by recent poor harvests.
- Demand is set to increase: The United Nations predicts that the population will increase from 6.7 billion today to 9.2 billion by 2050.
- Wealthier nations (e.g. China) now consume more meat, driving the need for animal feedstock.
- Greater health consciousness in the West means consumers demanding quality not quantity.

Impact of climate change and farming on the environment

- Water shortages impact agriculture particularly hard; 70% of all water used globally is used for irrigation.
- Excess use of fertilisers leads to nitrification of soil and water, damaging native wildlife.
- Spread of pathogens and insects into new areas.
- Changes in climate also influence growing seasons and viable crops.

Security of fuel sources

- Security of oil and gas supplies due to political instability.
- Recent price hikes on crude oil impacting on farming, transport and chemicals sectors.
- Government “green” policies driving demand for renewable energy sources.

A green renaissance?

The coalescing of various drivers provides a new impetus for agricultural biotechnology. The aim is to restore confidence in the underpinning science and provide solutions that meet the needs of an expanding global population in an environmentally responsible and ethical fashion.

Struan Stevenson, MEP, Scottish Rural Property and Business Association in Inverurie (April 2008):

"We must relax the rules on biotechnology and ignore the 'Frankenstein Foods' headlines. The reality is that GM foods are harmless and point the way to overcoming global food shortages in the future. Food security in Europe means looking after our home production and not always handing a commercial advantage to our non-EU competitors."

Jim McLaren, President of NFU, Scotland:

"We're not looking for a fight, we just want to have a grown up decision about where GM has a part to play and about retaining research in Scotland…" The Times, Monday 19 May 2008

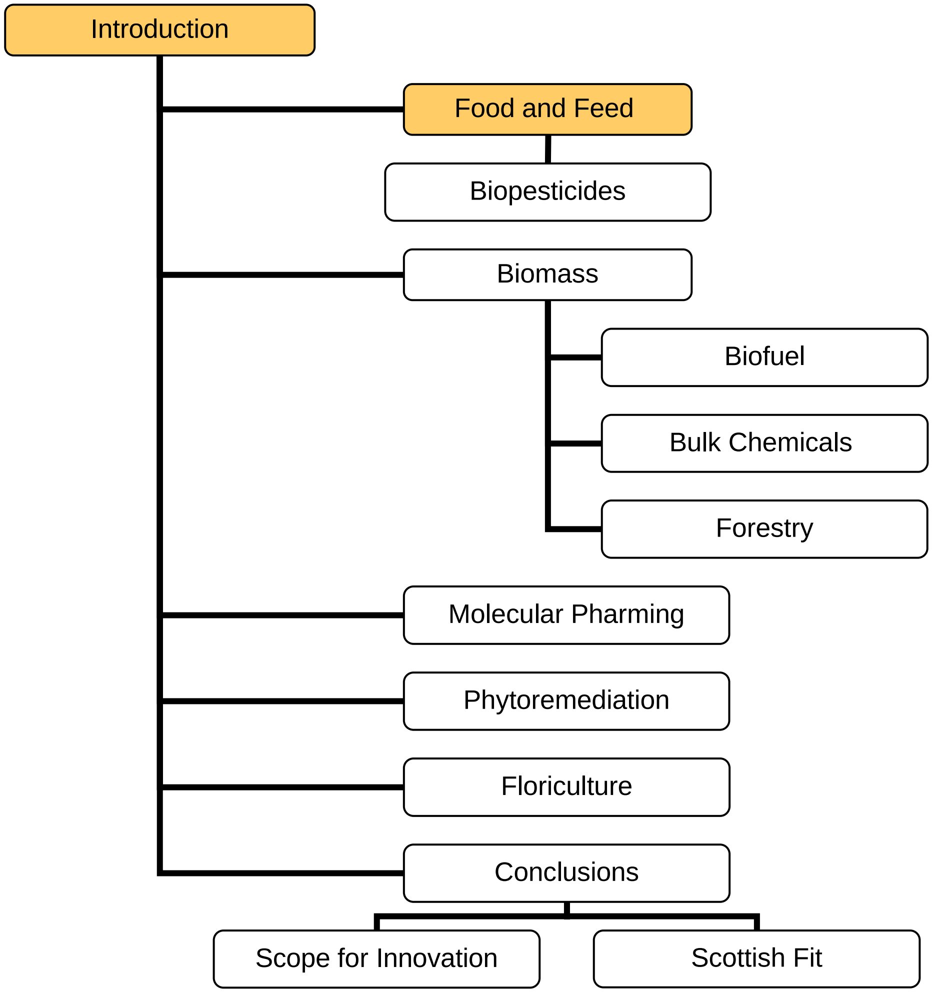
Gordon Brown, in a letter to UN leaders and World Bank (April 2008): The Prime Minister called for the use of genetically modified crops to be reconsidered for the sake of resolving food shortages:

"We must take the initiative to further develop higher-yielding and climate-resilient varieties of crops."

India's Minister of Finance (from ISAAA report, 2008):

"It is important to apply biotechnology in agriculture – what has been done with (bt) cotton must be done with food grains. The success achieved in cotton must be used to make the country self sufficient in rice, wheat, pulse and oilseed production."

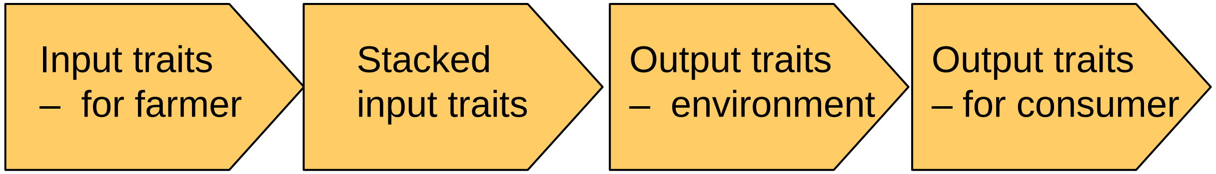
Food and feed



This section examines the current and future role of agricultural biotechnology for sustaining and enhancing crops for food and feed, along with a brief look at the market for biopesticides.

Agbiotech today

- To capture new and commercially attractive markets, the agbiotech sector has begun to invest in second-generation crops that will benefit both the consumer and the environment – so-called **output traits**. New products in development may soon:
  - address the **potential impact of climate change**;
  - generate foodstuffs with **additional nutritional benefit** for animal feedstock and for human consumption (so-called functional foods, a multibillion dollar market);
  - better **protect the environment**;
  - combat **existing and emerging pathogens and pests**.
- In parallel, there is also a growing market for products possessing stacked traits – three or more transgenes – that offer the **convenience of resistance to multiple pests and herbicides**.
- Many agrochemical companies are also investing in developing crops suitable for the biofuel industry and for industrial chemicals thereby further diversifying their portfolio (discussed later).



Second-generation GM crops (I)

Output traits linked to agricultural productivity and the environment:

- Plants that use fewer nitrates to produce similar yields, thus reducing amount of fertiliser needed.
- Crops able to survive and maintain good yields during transient periods of water shortage and temperature extremes.
- Plants that can grow in saline conditions.
- Crops with improved yields.

BUT:

- Question over near-term value for farmers where climate change has not yet impacted.
- Market value in developing countries may be small (with exception of GM rice variants resistant to abiotic stressors).
- May require more complex transformation of plants (metabolic engineering) requiring introduction of multiple genes that would heighten the regulatory hurdles further.

Case study:

Nitrogen fertilisers account for around a fifth of the operating costs for corn producers. In the US, farmers spend around $3 billion on application of fertiliser to crops but plants may absorb less than a half of that applied. This excess is not only costly but damaging to the environment.

Examples of collaborations to improve nitrogen efficiency include:

– Monsanto and Evogene

– DuPont and Arcadia Biosciences

Second-generation GM crops (II)

Output traits of value to the consumer:

- Understanding and regulation of the ripening process to maintain flavour and aroma of GM fruits and vegetables (often lost during genetic modification).
- Enhanced levels of unsaturated fats and long-chain omega-3 fatty acids.
- Plants with reduced levels of common allergens.
- Staple foods with elevated levels of vitamin A and folate.
- Animal feedstocks with enhanced levels of amino acids (e.g. lysine) not normally found in feed.

BUT:

- Experts caution that a true shift in opinion regarding GM may only happen if and when a food can prove medical benefits, posing a cost barrier for developers.
- Complex EU and FDA regulations around food definitions and labelling may also make this a challenging marketplace.

Case study

Transgenic maize expressing high levels of lysine and tryptophan has been developed as animal feed by Monsanto.

Monsanto has also developed soybeans – Vistive brand – containing low levels of linolenic acid, which increases the oils stability at high temperatures (e.g. for baking).

Various companies are working to elevate levels of omega-3 in plants (Monsanto, Solae, etc.).

Innovation today

- Compared with the investment poured into sequencing the human and other mammalian genomes, plants have been poor cousins. To date, only three plant genomes have been sequenced in full (*Arabidopsis*, rice and poplar) and the draft genome of GM papaya.
- Many plant genomes are considerably larger than the human genome (see right) and teasing out the location and sequences of coding regions, especially those attributed to valuable traits, is time consuming.
- Transforming a plant with more than one or two genes – gene stacking – is challenging. At best, only two or three genes can be introduced with current technologies.
- Even when plants have been transformed, there is the labour-intensive task of growing and screening the progeny to evaluate the changes within the plant's phenotype. Methods to render this process more high throughput are needed.
- Innovation needs are examined in more depth later at the end of this e-scan. **Companies noted for offering novel solutions to some of these problems are discussed in the following slides**.

Rice	430 Mb
Human	**750 Mb**
Cotton	830 Mb
Potato	840 Mb
Soybean	1,115 Mb
Maize	2,600 Mb
Wheat	17,000 Mb

Relative genome sizes

Case study: Mendel Biotechnology

- Mendel Biotechnology (Hayward, CA, US) was founded in 1997 based on the premise that control of gene expression would be of value to agricultural biotechnology.
- Mendel scientists have studied the role of 2,000 transcription factors in the model plant *Arabidopsis*, identifying those that control complex valuable traits, such as freezing and drought tolerance, growth rate, disease resistance, nitrogen use efficiency.
- The company has a **broad portfolio of patents around the transcription factors and has been using the know-how to develop plants with valuable commercial traits.** For example, Mendel has received several Small Business Innovation Research (SBIR) grants to investigate the regulators of the production of rubber (from the guayule plant) and cancer drug Taxol (from yew), as well as enhancing disease resistance in commercial crops.
- Knowledge of the role of transcription factors has also provided targets for developing chemicals that could regulate valuable traits. Mendel has a collaboration with Bayer CropScience to identify chemicals that can induce stress tolerance.
- In 2005, Mendel took a strategic decision to branch out into biofuels and is using its platforms to develop proprietary varieties of cellulosic biofuels in collaboration with BP and Monsanto.
- Mendel has collaborations with Monsanto (>$35 million), Bayer, SweTree (Forestry), Seminis and Empressa La Moderna (supplier of premium fruit and vegetable seeds).

Mendel Biotechnology

Case study: Chromatin, Inc.

- Chromatin, Inc. (Chicago, IL, US) was founded in 2000 based on the research of Dr Daphne Preuss at the University of Chicago.
- Chromatin's proprietary technology is based on **an understanding of centromeres and delivery of mini-chromosomes**, autonomous genetic elements that can deliver multiple traits of importance (i.e. gene stacking).
- The centromeres provide stability for the chromosomes ensuring that the genes are inherited in subsequent generations. The lack of inheritance is a common reason for instability during plant transformation.
- Chromatin claims that their technology could accelerate the speed-to-market for single gene modifications by 2–3 years, and a greater time saving for multiple gene (although this has yet to be tested).
- The company has raised more than $12 million in a series A and B round and $3 million in grants.
- In 2007, Chromatin entered into a research and commercial license agreement with Syngenta for its gene-stacking technology.

Chromatin, Inc.

Case study: Arcadia Biosciences

Arcadia Biosciences (Davis, CA, US) uses high-throughput screening, advanced plant breeding and genetic engineering encompassing **TILLING**® – a type of plant “knockdown" or "knockout" technology that enables it to identify genes related to specific traits. The mutant plants can be developed or a GM variant of the native species generated.

- Arcadia accessed the proprietary technology through acquisition of Anawah in 2005.
- The company’s main focus is to provide a new generation of crops that benefits not only growers but also the environment and human health.
- Arcadia has carried out field trials of a canola that uses just a third of the normal amount of nitrogen fertiliser of conventional varieties to achieve similar yields (so-called nitrogen use efficiency; NUE). It is also investigating salt-tolerant varieties of canola, rice, cotton and tomatoes.
- The company is also identifying tomato varieties with enhanced lycopene and natural antioxidant levels.
- The US Department of Defense funded a $2.9 million project with Arcadia in 2005 to look at improving the shelf life of tomatoes and lettuce.
- DuPont, Monsanto, SES VanderHave Seeds, Cal/West Seeds took commercial licenses to NUE during 2005.

Case study: Simplot Plant Sciences

- Caius M. Rommens and colleagues at Simplot Plant Sciences (Boise, ID, US), a research arm of Simplot, Inc. (a private food and agriculture company based in Idaho), have developed a means of transforming plants using vectors and genes derived from plant sources only.
- Although not yet a commercially viable strategy, **cisgenic approaches may help overcome some of the resistance to GM arising from its transgenic elements** (i.e. the use of microbial genes in plants) that were central to the resistance to GM technology from consumer and lobby groups.
- Cisgenic approaches require identifying **plant sequences** that can replace the pathogenic vectors needed to insert genetic material into the plant genome. The gene underpinning the desirable trait is also selected from another plant variant (either the same species or related). So the transformation is "plant with plant" rather than "plant with microbe."
- There have been various debates in the scientific literature (see *Nature Biotech* July 2006) as to whether cisgenic plants should be regulated as natural plant varieties or the more tightly regulated transgenic varieties. If so, a cisgenic approach ***may*** open doors for GM in new markets.

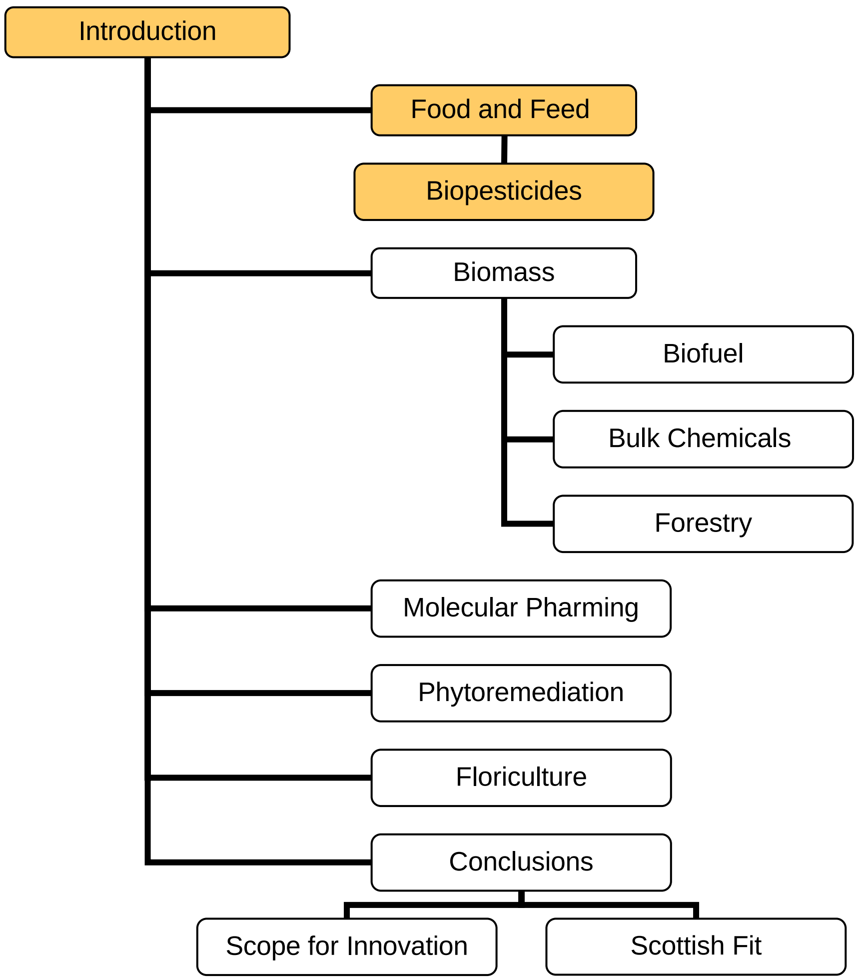
Agbiotech business newsflow

- **Healthy returns**: The agrochemical sector is currently reaping the rewards of the burgeoning food and fuel markets:
  - during 2007, the Burrill & Company Agbio Index gained 40% compared with its Biotech Select Index, up 9% only;
  - shares in Monsanto rose 113% last year and the company generated revenues of $8.6 billion;
  - Syngenta's shares rose 70% and it generated revenues of $9.2 billion.
- **Unprecedented levels of collaboration**: The major players have been joining ranks to share expertise to develop next-generation products. For example, Monsanto has collaborations in place with Dow Agrosciences (for SmartStax, eight-gene stacked corn) and with BASF (for new stress and yield strains).
- **Eastern challenge**: China and India are emerging as key players within agbiotech, resulting from concerted investment in protecting their national food security. The approval of GM rice (pending in China) could further shift the balance. For example:
  - In April 2008, Syngenta announced it would build a new biotech centre in Beijing for a total investment of $65 million. Last year it acquired a 49% stake in a Chinese corn seed business, Sanbei Seed.
  - DuPont created its first biotech research centre outside of the US in Hyderabad, India and has a joint venture with a Beijing company, Weiming Kaituo Agriculture Biotechnology.

Conclusions – food and feed

- The market for food and feed is strong and growing, and larger agbiotech companies are hungry for novel traits that can improve crop productivity and address emerging threats to agriculture.
- The demand for food and improved productivity in agriculture is set to increase with a growing world population and, as discussed later, additional demands on agriculture to meet fuel and chemical needs.
- Changes in climate and spread of new diseases will provide new challenges to which the industry will have to respond quickly.
- There remains a need for innovation at all levels of the plant-discovery process – novel trait identification, understanding plant biology and pathophysiology in response to disease and abiotic stressors, transformation techniques and the ability to validate the new traits by high-throughput precision phenotyping.
- Next-generation GM products will have to appeal not just to farmers but also to end-consumers, and will need to satisfy the stringent requirements of regulatory authorities and policy makers alike.
- **Developers of new products and techniques will find a strong base of deep-pocketed licensees and R&D partners globally, although the market for GM products in Europe may remain tenuous in the immediate future.**

Associated markets - biopesticides



This section examines the market for biopesticides, a category of natural replacements for more conventional pesticides.

Biopesticides

- Biopesticides are those derived from natural materials such as animals, plants, bacteria and certain minerals. There are three main types:
  - microbial pesticides, derived from bacteria, fungi, virus of protozoa. The most commonly used is *Bacillus;*
  - plant-incorporated pesticides (e.g. *bt* corn) where the biopesticide is produced by the plant itself;
  - biochemical pesticides, which control rather than kill pests. For example, pheromones that interfere with pest mating or can be used in traps to lure insects.
- **The global market for biopesticides is around $300 million (2005 figures), around 1–2% of total pesticide sales, but has been projected to grow to over $400 million by 2015.** (Source: CPL Business Consultants, 2006.)
- The main adopters for biopesticides are organic farmers and gardeners, although conventional farmers will also use the products to manage resistance to existing agrochemicals.
- All agricultural biopesticides have to be approved by the UK Pesticides Safety Directorate as safe and effective. A biopesticides scheme was introduced during 2006 to make this process cheaper for the companies, often smaller players, interested in developing these products.
- The US EPA also has a Biopesticide Division that reviews new applications.
- In the EU the regulations are under review as they required harmonisation. At present biopesticides are reviewed along with conventional pesticides.

Drivers & restraints

Drivers The biopesticide market is moving towards reducing the use of older, conventional agrochemicals to ones less damaging to the environment and health encouraged by:

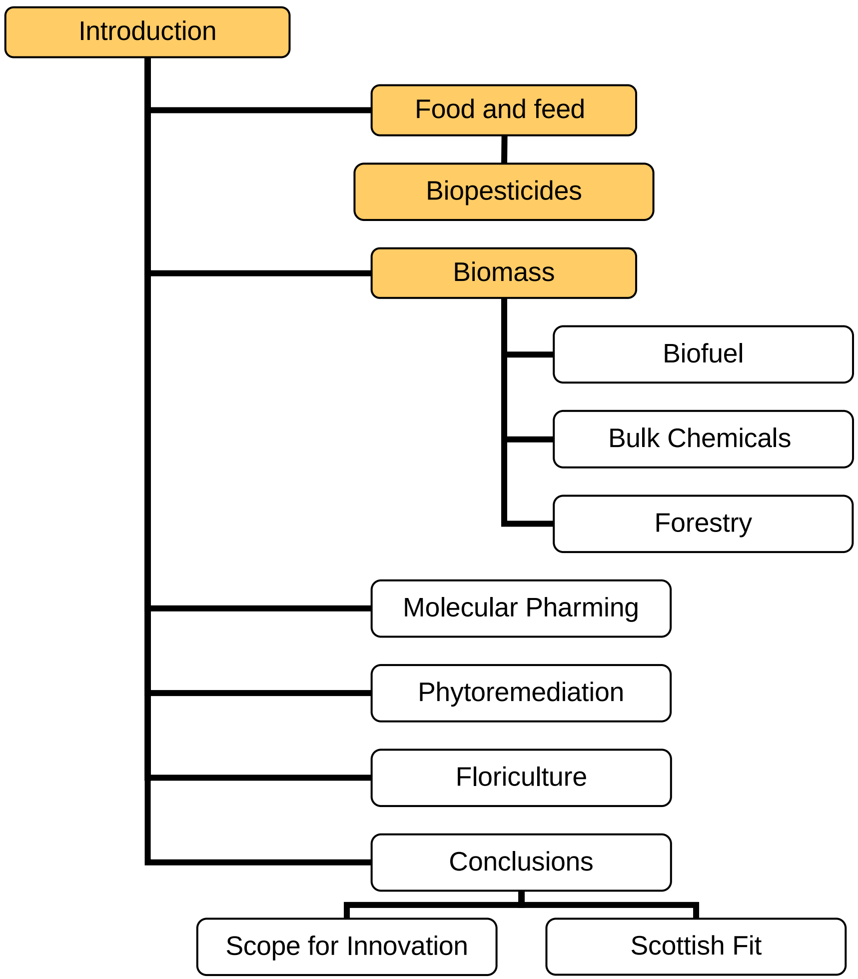
- consumer awareness and concern about pesticide residues on fruits, vegetables and salads;
- government initiatives to reduce pesticide use (e.g. EU Common Agriculture Policy);
- grower and retail initiatives, especially for organic produce;
- shrinking range of conventional chemicals due to industry consolidation and the high cost and risk to industry of bringing new products to market.

Restraints Equally, there are many challenges for those interested in developing biopesticides:

- there is little investment in R&D in this area (compared with the >$2.2 billion spent per annum on conventional pesticides);
- the registration process is expensive and was developed with conventional chemicals in mind and so not well suited for approval of biopesticides;
- there is little support/education for farmers wishing to change to biopesticides.

Conclusion: The market for biopesticides is an interesting opportunity and – given Scotland's expertise in microbes, plant–pathogen interactions and crop management – this could be an area for further exploration.

Green alternatives to petrochemicals



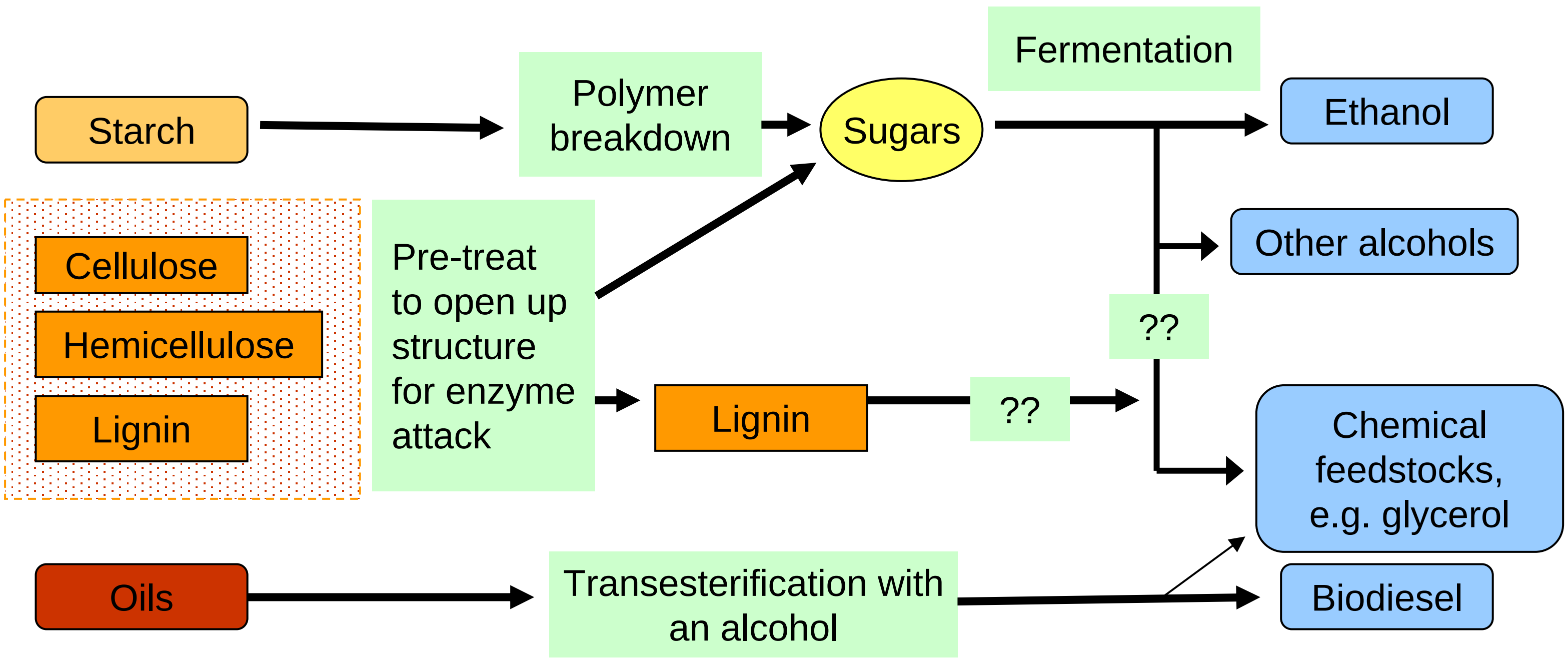
Plant-derived materials and chemicals have been used for centuries for many industrial and domestic applications. Although many are now made cheaply from petrochemical sources, plants still play an important role: Wood is used for construction, fuel and paper making; cork and rubber are natural products with many useful properties; and various plant secondary metabolites are used for flavours, fragrances and dyes.

Plant biomass can also be used as feedstock for the generation bulk chemicals, polymers, surfactants and lubricants.

Here we examine the markets for **biofuels, bioplastics,** several **bulk chemicals** and the **forestry industry**.

Biofuels for transport and energy

The two main biofuels are bioethanol and biodiesel. These are produced by the fermentation of sugars and transesterification of oils, respectively.



?? – Processes still in development

Market drivers

- Biofuels, as a renewable energy source, are seen as a means of ensuring national fuel security while also mitigating climate change by a reduction in greenhouse gases.
- Increased use of transportation and industrial growth may increase the global demand for energy by up to 60% over the next 20 years.
- The global market for both the manufacture and sale of biofuels was around $20.5 billion in 2006, and could grow to $80.9 billion by 2016.

Drivers include:

- The rising cost of fossil fuel: The price of crude oil prices has risen from $20 to over $130 a barrel. This is driven by increased demand for fuel in developing countries, political instability in the Middle East, and the threat of declining reserves in some regions.
- Green policies will also drive demand:
    - UK: Renewable Transport Fuel Obligation (2005) required that 5% of all road vehicle fuel must be from renewable sources by 2010;
    - EU: The EU Biofuels Directive set the goal that by 2010 each member state should have at least 5.75% biofuel use and this should rise 10% by 2020;
    - US: US Energy Independence and Security Act (2007) mandated that renewable fuel use in gasoline US should reach 36 million gallons by 2022 and reducing gasoline use by 20% within the next 10 years;
    - India and China both aiming for >10% biofuel use by 2010.

Emerging restraints

- US studies have suggested that at best only 10% of US fuel demands could be supplied from bioethanol derived from corn. Moreover, the production of biofuels may result in ***more*** carbon emissions than fossil fuels – an undesirable outcome.
- The commercial viability of biofuels is dependent on inexpensive feedstock: Poor harvests and oil-price hikes have forced the price of corn to a 20-year high, making biofuel production commercially unviable for many new start-ups.
- The negative environmental and socioeconomic consequences of using food crops for biofuel feedstock have also raised concern:
  - According to the UN Permanent Forum on Indigenous Issues, 60 million people face clearance from their land to make way for biofuels. The destruction of rainforests and of grasslands and natural carbon sinks is highly detrimental Deforestation accounts for up to 20% of global greenhouse gas emission, more than transport, industry and aviation combined.
  - The International Food Policy Research Institute estimated that biofuel demand has contributed to 30% of recent food price inflation, although other studies suggest a lower figure (<10%). Several confounding factors have contributed (export bans, drought and flooding) but using food crops for fuel feedstock will inevitably impact food price and availability.

"*We have seen that the environmental problems caused by biofuels and also the social problems are bigger than we thought they were. So we have to move very carefully*.“
EU Environment Commissioner, Stavros Dimas, January 2008

"*Biofuels risk failing to deliver significant reductions in greenhouse gas emissions from transport and could even be environmentally damaging unless the Government puts the right policies in place*."
Royal Society Report, Monday 14 January 2008

The cellulosic solution?

- The solution currently being explored is to make use of the non-food components of plant material (sugar-cane bagasse, or the corn stalks, leaves and cobs) or other non-food crops (e.g. grasses and trees) into ethanol. For biodiesel the use of oil palm, jatropha (a tropical oil-rich grass) or alga is an alternative to soya-derived oils.
- The use of so-called **cellulosic biomass** has several advantages:
  - low cost;
  - can be grown on marginal land;
  - requires less fertiliser and water;
  - does not impact on food crop production.
- However, biomass contains cellulose, hemicellulose and lignin, which are less readily processed than starch, posing several technical and economic challenges for biofuel developers.
- Research and development also continues on optimising food-crops to optimise the "energy yield" of the plant grown per hectare – a role for GM.

Processing innovations to optimise energy release from food and non-food crops.

Genetic modification of plant to optimise the "energy yield" of each hectare of crop.

Research - processing

Innovations in cellulosic processing	Activity
Several strategies for improving energy release from "woody" biomass include:	
Enhanced processing Various companies are innovating chemical processes to optimise the release of energy from cellulosic material in a more cost-efficient manner	Companies such as Mascoma, Cilion, Range Fuels have garnered substantial investment from venture capital and US governments in support of developing bioprocessing plants
Improved biocatalysis Improving or developing enzymes better able to release energy from woody plants, achieved through molecular evolution techniques or *de novo* via synthetic biology. Fermentation is carried out using yeast but other microbes, with enhanced properties, are being explored	Syngenta is currently working on developing novel cellulase enzymes for biofuel production. Genencor and Novozyme were recently funded by the US DOE to investigate means of reducing the cost of cellulase enzymes Other companies are using molecular evolution and synthetic biology to develop novel enzymes (e.g. Codexis, Direvo, Dyadic and TMO Biotec)

Research – energy crops

Genetic modification to enhance energy yield	Examples
Improve the **yield of starch or oil** source in the plant	Syngenta is working on varieties of high-starch corn Monsanto is attempting to elevate oil levels in soybeans for biodiesel production Linnaeus Plant Sciences is modifying the oil composition in castor oil plants
Create **plants more tolerant of abiotic stress**, which can be grown in inhospitable regions not currently used for food production	Ceres is generating cultivars of switch grass with stress tolerance and high yields
Improve the **ease of extracting energy** from woody biomass (e.g. crop waste) and trees by altering lignin and cellulose composition	SweTree Technologies have identified genes associated with wood composition and the ease of extracting of lignin from biomass

Case study: Ceres, Inc.

- Ceres, Inc. (Thousand Oaks, CA, US) was founded in 1997 to apply modern genomics to sequence crop and non-food crop plants with a view to developing crops valuable as sources of energy.
- Ceres, the self-named “energy crop company”, has become a leader in understanding the genetics behind some of the non-food crop biomass sources such as switchgrass, sorghum, miscanthus and energy cane.
- The company is focused on **developing varieties with traits that optimise the economics of large-scale production of biofuels, such as stress tolerance, improved yields and reduced need for fertilisers.**
- In April 2002, Ceres signed a $137 million discovery and development deal with Monsanto, which funded its R&D activities until it raised $75 million through a private offering of stock in September 2007.
- Ceres has also branched out into plant-based alternatives to chemicals such as methacrylate monomers in collaboration with materials company Rohm and Haas.

ceres

Algae for biodiesel (I)

- Algae are the most primitive of plants but are a rich source of oils suitable for biodiesel production. Almost half their weight is usable oil and they offer yields around 30 times that of oilseed crops (see table, right).
- The challenge for algal-based biodiesel producers is to optimise the growth conditions to prevent overcrowding of algae that leads to suboptimal yield. The waste material (oxygen) must also be removed and a supply of carbon dioxide secured usually by locating the algal ponds close to a power station.
- There is also research as to which (of many hundreds) of algal species to use, whether to use salt or fresh water species, and whether to grow them in open or enclosed ponds.
- Several groups are investigating the genetic manipulation of algal species to optimise their value as oil producers, but most of the near-term challenge is to prove the commercial viability of this feedstock.

Fatty acid composition of crops

Crop	Oil Yield gallons/acre
Corn	18
Cotton	35
Soybean	48
Sunflower	102
Rapeseed/canola	127
Jatropha	202
Algae	1,200–10,000

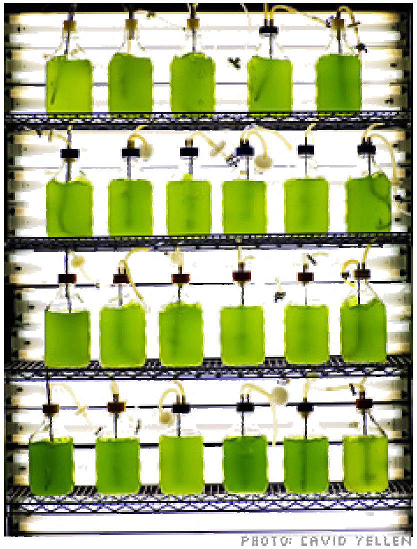
Source: National Renewable Energy Laboratory

Intoxicating algae

US company Algenol is metabolically modifying blue–green algae to **secrete ethanol** at commercially valuable yields. The company raised $70m in investor funding and recently signed a $100m licensing deal with Mexican company BioFields, which will build facilities in the Sonoran Desert.

Algae for biodiesel (II)

- The majority of the companies involved in algal biofuel development are based in the US, where tax credits of $1 per gallon have lowered the barrier for entry into the market. Companies working in algal-based bioreactors include:
  - GreenFuel Technologies;
  - Solix Biofuels;
  - Livefuels;
  - Solazyme;
  - Global Green Solutions.
- Over the past 3 years, >$40 million has been invested in algal start-up and research projects, and the sector in the US has been boosted by tax incentives and subsidies for algal biodiesel production. (Source: New Energy Finance.)
- However, there are many obstacles for algal biofuel: There is a high capital outlay for the bioreactor algal beds; the growth conditions for optimal oil yield are yet to be defined; and the likely commercial return is some 5–10 years off.
- **ITI Energy is currently scoping opportunities in algal-based biofuels. For further information, please contact Gavin Duke or Michael Weston.**



Solar power – photosynthesis

- Solar power is an area of intense research and investment. According to New Energy Finance, during 2007 the global solar power market grew by 40% and venture funding topped $2.8 billion, compared to just $1.8 billion for biofuels. Much of the driver for uptake has been the generous subsidies available to companies operating in this market.
- Photosynthesis, the natural process by which plants harness the energy of sunlight to convert CO_2 and water into fuel (sugars), is therefore an attractive research target. By replicating the energy-conversion machinery researchers hope to transform photons of light into power in the form of either hydrogen (by splitting water), a carbon fuel cell or electric current.
- Plants are relatively inefficient at harnessing solar power and only 1–3% of the sun's energy ends as usable fuel. However, the underpinning process of converting photons into energy is highly efficient and researchers are keen to both understand and replicate this process.
- **There is little commercial activity within artificial photosynthesis as proof of principle that this approach is viable is still needed**.
- However, many well-funded research efforts are underway in this area, for example:
  - Powering the Planet project (US National Science Foundation funding). The goal here is to mimic photosynthesis using synthetic materials such as silicon nanorods to trap photon energy and catalysts to produce hydrogen from water.
  - The EU Solar-H Team is looking more closely at natural photosynthetic elements, such as chlorophyll and related dyes as photo-trapping elements, and metal-complexed enzymes as water-splitting catalysts.

The future is light

- Areas most tractable and under intense research activity today:
  - Development of stable catalysts: To convert water into hydrogen fuel.
  - Using available materials and technologies to replicate components of the photosynthetic process (so-called PSI and PSII systems). For example, G24 Innovations (Cardiff, UK) is using organic dyes to trap light and convert to electric current to power mobile phones.
  - Biomimicry: Trying to recreate photosynthesis in the test tube using biological building blocks.
- Recent developments include:
  - The synthesis of a stable inorganic metal oxide that enables the oxidation of water to oxygen and hydrogen (*Angewandte Chemie*, March 2008). This is one of the key challenges for artificial photosynthesis.
  - Discovery of the plant “dimmer” switch that controls the flow of solar energy through the light-harvesting proteins preventing damage to plants under high intensity light conditions (*Science*, May 2008).
  - Researchers have designed a complex molecule that could prevent the sunlight-induced overload of the photosynthetic pathway via a process called non-photochemical quenching (*Nature Nanotechnology*, 2008).
- **Recreating photosynthesis synthetically will require further long-term research efforts. In the meantime, there is a need to develop a concept of “interim” products where near-term know-how can be applied to increase solar power efficiency.**

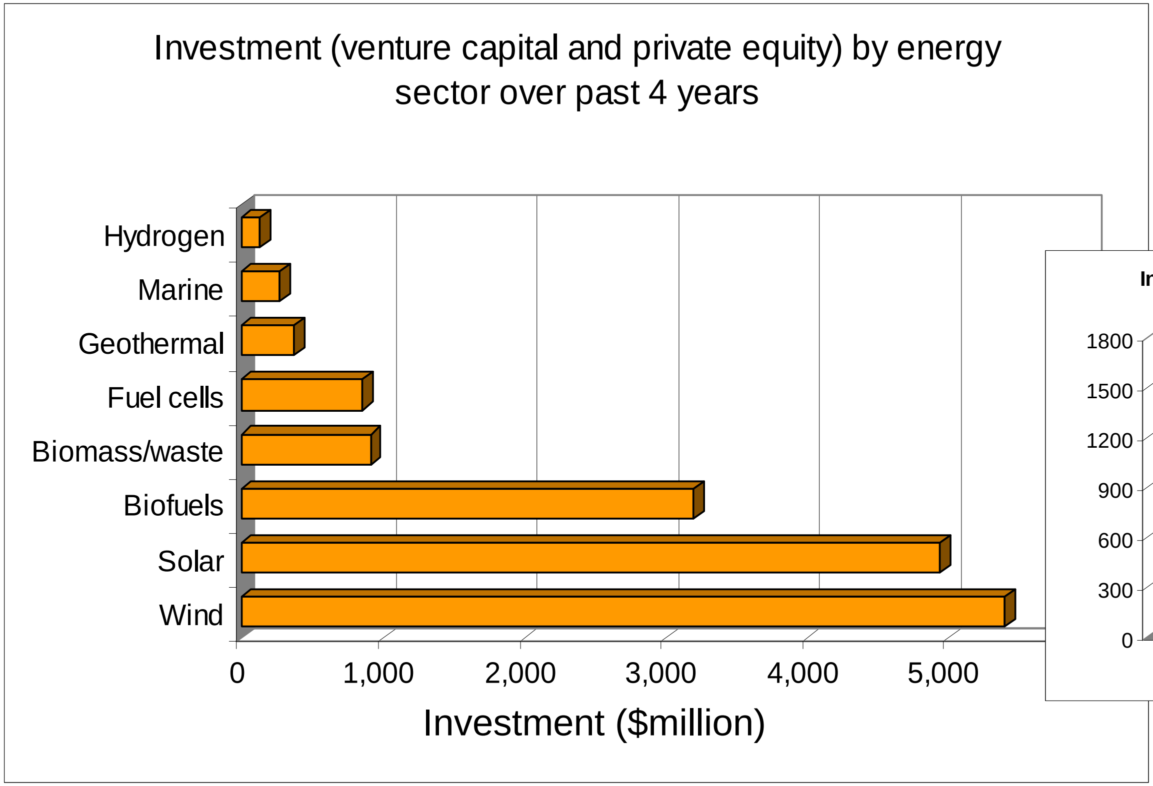
Biofuel news flow

- Total biofuel investment has been in the region of $3 billion during the past 4 years (see next slide and table, below).
- In the UK, BP has unveiled a joint venture with Associated British Foods and DuPont to build a $400 million biofuel plant.
- Many multinationals have forged relationships with research institutes to seek biofuel solutions:
  - Dow Chemical pledged $10 million to launch a sustainable products and solutions programme at Berkeley;
  - BASF pledged $20 million to set up the BASF Advanced Research Initiative at Harvard;
  - Syngenta entered into a research collaboration with Queensland University of Technology and Farmacule Bioindustries (both Australian) to convert sugarcane bagasse to biofuel.

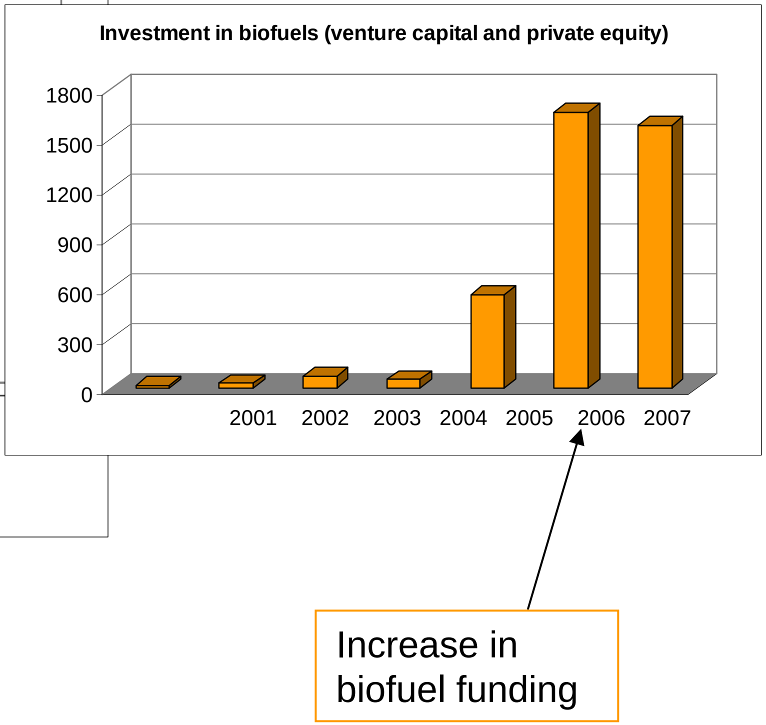
Selected biofuel venture capital (VC) investments

Company	Description	Funding
Amyris Biotechnology	Synthetic biology, enzymes	$90 million
ASA Alliances Biofuels	Ethanol production plants	$94 million
Cilion	Ethanol plants in US	$209 million
Codexis	Biocatalysts for production of biofuels	$75 million
Mascoma Corp	First switchgrass cellulose ethanol plant	$61 million
Range Fuels	Waste from pine-tree harvesting into ethanol	NA
Renewable Energy Group	Biodiesel and bioethanol	$122 million

Investment activity



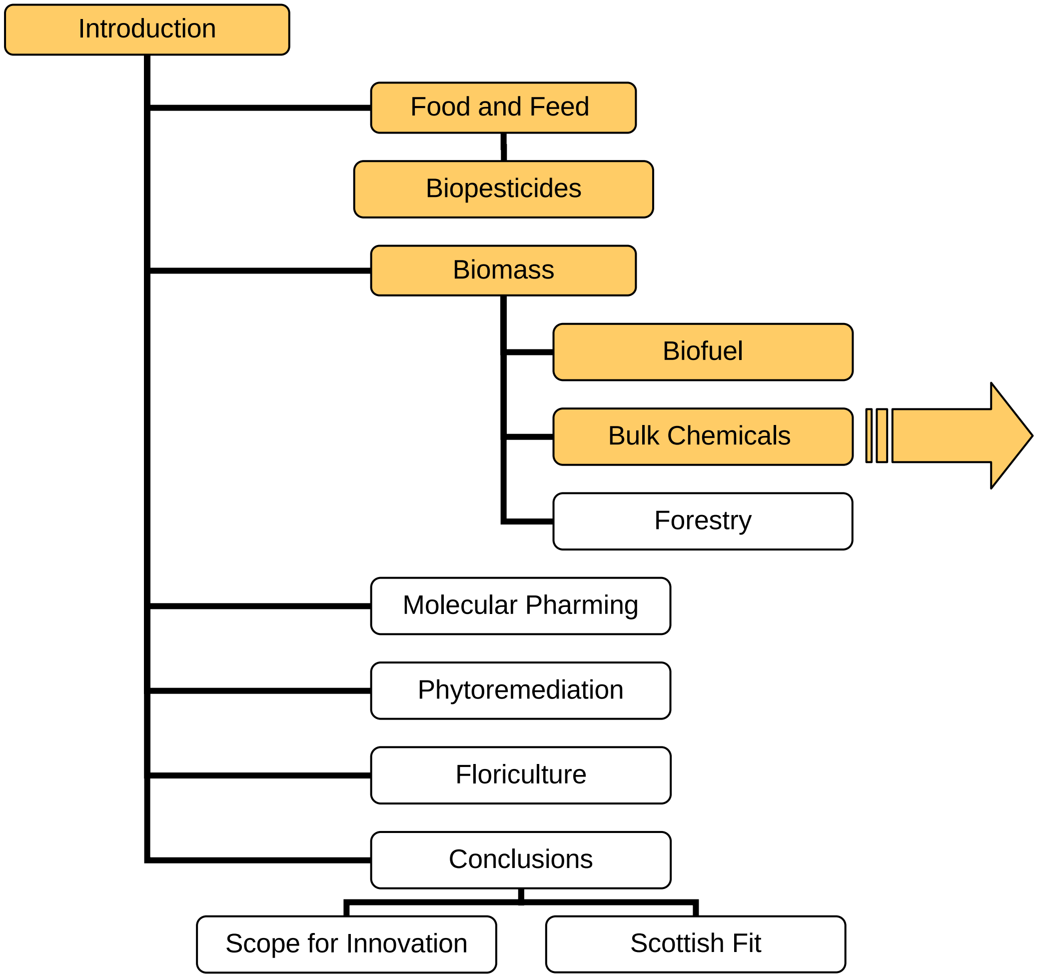
Wind, solar and biofuels have received most funding among renewables over the past 4 years. (Source: New Energy Finance.)



Conclusions – biofuels

- Despite recent controversy over the negative impact of biofuels on food prices and the environment, the market for biofuels is certain to grow in the future.
- Cellulosic plant material is the only viable alternative to food crops but processing needs optimisation.
- There is a role for plant biotechnology to optimise the “bioenergy yield” of both food and non-food crops feedstocks.
- Plants may be modified to either increase the energy content of the plant (i.e. starch and oil yields) or to render extraction more cost-effective. Many of the major agrochemical players are investing in this area and can apply know-how learnt from GM food crops.
- The need for superior energy crops may become more acute as the competition for land for food and fuel heats up. However, GM plants will still require regulatory approval and so run the risk of similar regulatory constraints in GM-sensitive zones.
- Algae, which can be contained and are naturally energy rich, may provide a more acceptable biofuel feedstock and the modification of algae is an active area of research. However, in the near term, basic questions over how to optimise algal oil production still need to be addressed.
- Another exciting area is artificial photosynthesis, to harness solar energy. This emerging area requires fundamental research but might provide a rich source of innovation that may help, in the near term, to enhance existing solar power technology.

Bulk chemicals



In this section we look at some of the bulk chemical markets, traditionally met by the petrochemical industry, that can be met by plant biomass.

- Bioplastics
- Biolubricants
- Surfactants
- Fragrances & flavours
- Dyes & pigments

Bulk chemicals from plants

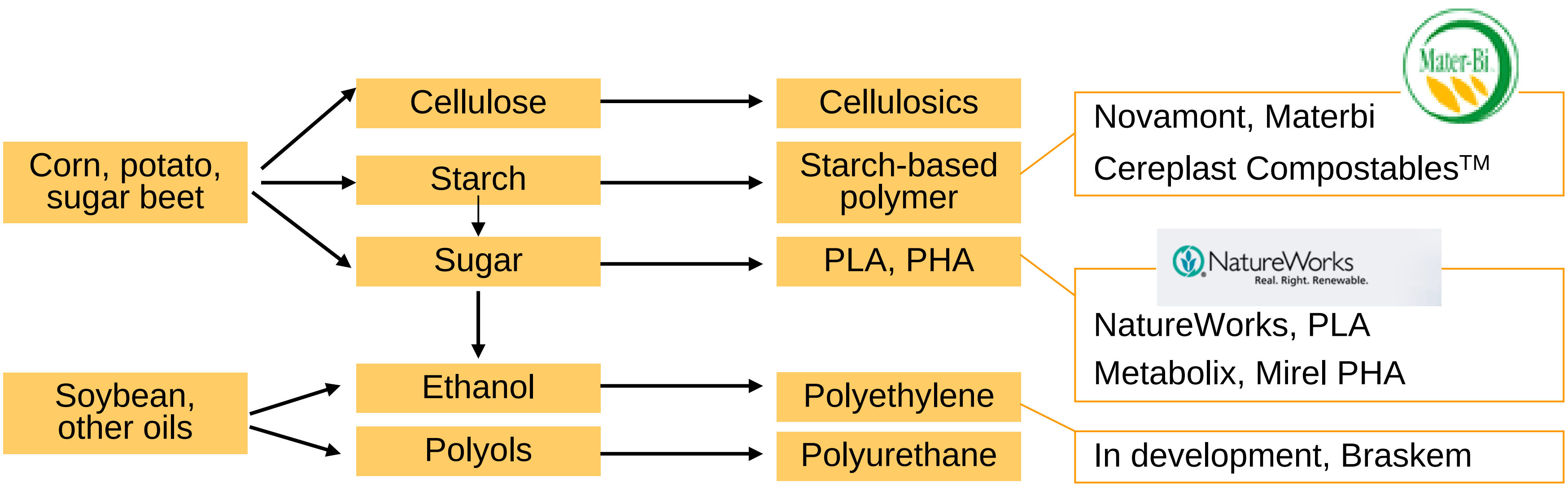
Around 13% of petrol is actually used as a starting material for products as diverse as textiles, resins, surfactants, paints and plastics. (Source: US DoE.)

Industry sectors	Approximate market size	Comments
Bulk chemicals including solvents	$trillion	Major bulk chemical feedstocks include: glycerol (used in drugs, cosmetics, food and drinks industries); epichlorohydrin (for epoxy resins (76%) and paper, textiles, inks and dyes) and 1,3 propanediol (for polymers, cosmetics, laminates, paints and glues). Glycerol is a by-product of biodiesel
Polymers and fibres	Polymers total $1.6 trillion Plastics $250–350 billion	Bioplastics could capture around 2.5% of the market for conventional plastics market in the medium term Other polymers include starches (used in paper and glue making)
Surfactants	$7 billion	Around 10% of the surfactant market is derived from plant-based materials, most commonly rape, oil and palm
Lubricants	$36 billion	Around 90% of lubricants could be replaced with biolubricants
Fragrances and flavours	$6.4 billion	Many originally derived from plant materials but now made synthetically. There is a move toward use of natural extracts in food products
Dyes and pigments	$2.5 billion	As above

Market data – various sources.

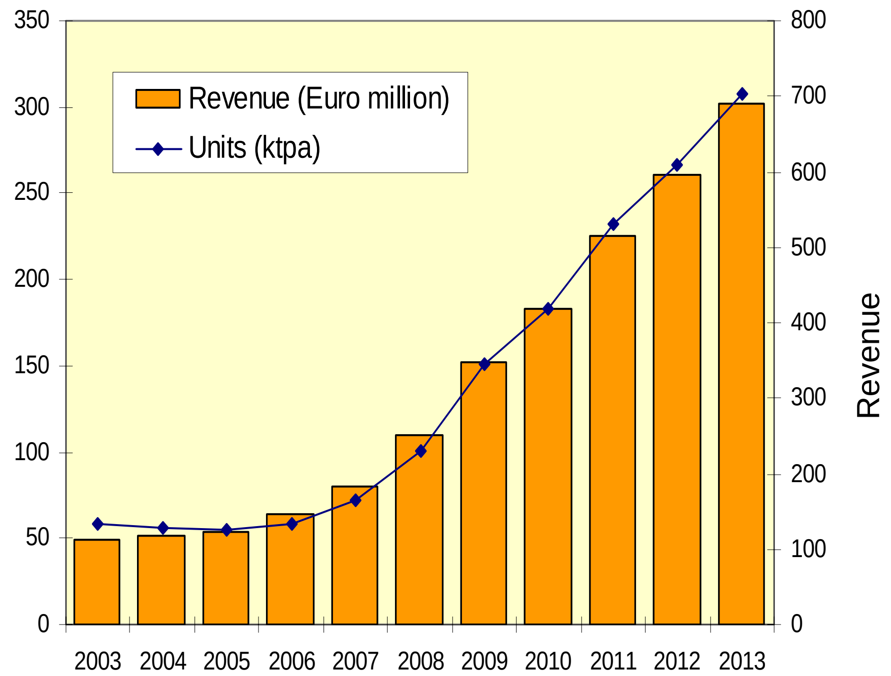
Bioplastics

- Bioplastics were first developed in the 1970s (just after the last oil crisis) when ICI-UK began to look for alternative routes for the manufacture of plastics.
- ICI developed a thermoplastic polyester called polybetahydroxyrate-PBH called “biopol” through fermentation. The IP around biopol was acquired by Monsanto and subsequently by Metabolix in 2001.
- Three main types of bioplastic are currently available: Starch-based polymers, polylactic acid (PLA) and polyhydroxyalkanoates (PHA). Various others are in development.



Europe leads the market

European bioplastic market



Source: Frost and Sullivan, 2007

- Currently, the **global plastics market is worth around $350 billion**.
- The market for bioplastics is very fragmented, making accurate estimates difficult. Consumption was around 85,000 tons (2006), which was approx. 0.7% of the total plastics market. This is predicted to increase to around 2.5% of the total market within the next decade. CAGR for bioplastic in Europe is predicted to be around 26.7% (2006–2013; Frost and Sullivan, estimate).
- At present, most of the market for bioplastics is in Europe, where there is greater market pull.

Bioplastics in production

Plastic	Manufacturer, Brand	Comments
Polyhydroxy-alkanoates (PHA)	Procter and Gamble, Nodax™ (co-polymer) Metabolix, in development	Metabolix has dominant IP position in this area Highly versatile plastics
Polylactides (PLA)	NatureWorks (Cargill) PLA production plant in US makes commercial quantities Manufacturers in Germany and Japan	Main feedstock is US corn (posing a problem for marketing this product in Europe) Readily degraded and could be recycled Limited by high water permeability and heat distortion
Starches	BASF – Amflora (for paper industry, pending approval), Ecoflex Novamont, Materbi (Italy)	Thermoplastic starch can be produced at high temperature GM approaches viable with better understanding of starch biosynthesis Other polysaccharides could be explored (pectins, alginates, chitin)
Plant oils	Cara Plastics Arkema, Rilsan B (a polyamide)	Most plant oils are unsaturated triglycerides and contain ester linkages suited for polymerization. These could form the basis of many useful polymers or as co-polymers with vinyl esters and polystyrene
Cellulosics	Innovia Films	Could be used directly or esterified derivatives for plastics – cellulose acetate and derivates Can be generated from waste

Case study: Metabolix, Inc.

- Founded in 1992, Metabolix (Cambridge, MA, US) is developing a proprietary platform technology to co-produce plastics, biofuels and chemicals in energy crops such as switchgrass, oilseed and sugar cane through metabolic engineering of entire pathways.
- Metabolix first product is a biodegradable plastic – Mirel – derived from corn sugar digested using genetically modified bacteria. Mirel is suitable for injection moulding, extrusion coating, etc. and is commercialised through a joint venture, *Telles*, with Archer Daniels Midland Company (ADM).
- Metabolix is developing advanced oilseed crops for bioplastic and biofuel production in conjunction with the Donald Danforth Plant Science Centre in St Louis, Missouri.
- The company has a dominant IP position for production of PHA with patents covering the genes that encode the PHS pathway, methods of isolation, purification and processing and novel compositions
- **Metabolix also has an interest in generating biodegradable plastics within the leaves and stems of GM sugarcane and switchgrass.**
- The company floated successfully in 2006 at $14 and is currently trading at around $11 a share.

METABOLIX
where nature performs™

Case study: BASF

- BASF Plant Sciences has genetically optimised potato to produce pure amylopectin, the pectin of most value to the paper and adhesive industries.
- Standard potatoes contain a mix of 80% amylopectin and 20% amylose starches. Amylopectin is a thickener and amylose a gelling agent. Amylose has to be modified chemically to prevent it gelling inappropriately.
- BASF modified a gene controlling starch synthesis in the potato so it produces 100% amylopectin.

Around 75% of the world's starch is produced in Europe; the market is worth around €1.5 billion annually.

- BASF estimates that Amflora will generate more than €100 million for the industry and farmers in Europe.
- Amflora was approved by the EU Food Safety Authority in 2006 but it is still pending final approval by the European Commission. If successful, Amflora could be the first new GM approved for commercial cultivation in Europe for nearly 10 years.

BASF
The Chemical Company

Drivers and restraints

Drivers:

- **Oil prices**: In the past, bioplastics have cost substantially more than conventional plastics, but rising oil prices have reduced the price difference and will encourage bioplastic uptake in the future.
- **Legislation**: New legislation will drive the uptake of biodegradable plastics. For example, France and China have banned plastic bags, and the UK is following this lead. Many cities in California have banned styrofoam packaging and are looking for renewable alternatives.
- **Environmental awareness**: “Green” labels sell products (food, cars, appliances, etc.). This is particularly pertinent to the organic, high-value produce sector: Tesco and Sainsbury have both switched to biodegradable packaging for their organic food ranges.

Restraints:

- **Relative costs**: The relatively high price of bioplastics may deter many end-users looking to manufacture short-lived disposable items such as cutlery and carrier bags. The advantages of bioplastics will have to be clearly communicated to justify higher costs.
- **Supply and demand mismatch**: At present, capacity for bioplastics is not high and there is a risk that the industry will fail to meet demand.
- **Processing problems**: As with any young industry, there are still processing challenges that may take time to resolve.
- **Inadequate waste handling**: The main benefit of bioplastics (their potential for rapid degradation) can be lost if they are not processed correctly. It will be necessary to ensure that communal composting facilities are available, currently not the case across much of Europe.

News flow

- Production capacity is being increased rapidly:
  - In 2007, Metabolix joined with Archer Daniel Midland to build a plant in Iowa to produce 110 million pounds of PHA a year, making this a commercially viable product.
  - Dow Chemical and Brazilian sugar and ethanol producer Crystalev have built a facility in Brazil to manufacture linear low-density polyethylene for films and food packaging.
  - Brazilian petrochemical company Braskem announced that it had developed a route to manufacture high-density polyethylene (HDPE) derived from cane sugar, and will introduce commercial quantities of the same in 2010.
- Basic research has begun to highlight ways in which synthetic enzymes can be engineered to optimise processing of the plant material as well as a better understanding of the pathways that can lead to bioplastic feedstock. For example:
  - In June 2007, chemists reported in *Science* that they had found a means of using metal chlorides to transform sugars into hydroxymethylfurfural, which can be easily transformed into plastics.
  - In April 2008, CSIRO researchers announced that they had found a way to boost a plant's production of oils suited for plastic production.

Conclusions – bioplastics

- At present, the production of bioplastics from plant material is not impacting food crops negatively. However, if the market expands rapidly, and food-pricing pressures continue, the advantages of using GM crops for bioplastics may become more pertinent.
- Much of the current research is focused on optimising the processing of the bioplastic feedstock, although there appears to be an opportunity to optimise plants as sources of plastic monomers.
- Few companies appear to have experience in this area offering an opportunity for innovation. In particular, the optimisation of oil-derived plastics seems untapped. High-value specialist markets (e.g. medical plastics) also need to be investigated.
- Will consumers who are keen to buy green, eco-friendly (organic?) produce welcome their products packaged with GM-derived plastics? This will be an interesting marketing challenge!
- The main market for GM-derived bioplastics may therefore lie in Asia and the US, where there is less resistance to GM-derived products.

"The ubiquitous media coverage would indicate there is much more antipathy towards global warming and pollution resulting from petrochemical plastics than there is for the use of GM technology."
Brian Igoe, Metabolix (*Biopack* magazine)

Wise counsel or wishful thinking?

Biolubricants

- Biolubricants are vegetable-oil-based lubricants used for hydraulic fluids, chainsaw oils, concrete release agents and niche oils.
- In 2006, the European market for biolubricants was just 2.6% of the total European lubricant market but this is expected to rise at around 6.6% CAGR. The total market for lubricants is around $40 billion globally.
- The main drivers for the market are:
  - increasing awareness of environmental impact of lubricants especially in safe disposal;
  - legislation forcing a reduction in use of conventional products (such as the EU Eco-Label introduced in 2005 and REACH);
  - greater demand for eco-friendly products by consumers;
  - rising crude oil prices.
- Limitations on the biolubricant market to date have included their high cost and their poor performance (e.g. oxidative stability, behaviour on heating), which may not match that of conventional oils.
- However, companies active in crop commodities – Cargill, Oleon – and agbiotech companies are beginning to investigate the market potential of oil crops. The multinational oil companies such as Shell, Exxon-Mobil and Statoil have also taken an interest.

Case study: FUCHS is working with Monsanto, the National Non-Food Crop Centre (York, UK) and TAG to evaluate how growing conditions may effects the oil content of conventional crops.

Case study: Linnaeus Plant Science

- One of the few companies looking into specialist oils is Linnaeus Plant Sciences (Vancouver, Canada), which specialises in castor oil used in the manufacture of some lubricants, plastics, surfactants, paints and dyes, and in the preparation of imitation leather. It could also be used as a feedstock for fuel.
- The castor oil plant contains many highly toxic and allergenic compounds (including ricin), making the harvesting of the plant hazardous to workers in the main growing regions of India, China and Brazil. The lack of consistency in supply, and resulting price fluctuations, have restricted the expansion of markets of this oil, which currently stand at around 600–800 million pounds weight each year.
- **Linnaeus secured rights to IP from Stanford University surrounding the castor hydroxylase gene and has eight issued patents on means to produce hydroxy fatty acids in oilseeds.**
- Work is focused on transforming plants to express fatty acid hydroxylase genes so as to synthesise a range of fatty acids in their seeds. Linnaeus is also interested in the genetics of a desert plant able to elongate ricinoleic acid.
- Linnaeus has partnered with the world's fifth largest chemical company, Atofina, to look for alternatives to the existing supply of castor oil.

Castor oil plant pods

Surfactants

- Surfactants are chemicals that lower the surface tension of liquids, allowing substances to dissolve more readily. They are used in many industries, including agriculture, road surfacing, emulsions and paints, metal-working and textiles. They are also found in cosmetics and household detergents.
- Surfactants are largely derived from petrochemical sources, although around 10% is supplied from plant-based materials. The major crops are oilseed rape oil and coconut palm (which contain lauric acid used to manufacture the detergent laureth sulphate).
- Surfactants are a relatively mature market, with most growth seen in the speciality markets such as personal care. Products are distinguished on the basis of price, performance and safety
- As an indicator of market size, the European industrial surfactants markets was around €500 million in 2003 and is expected to grown to €579 million by 2010. The US speciality surfactant market is predicted to reach $3.4 billion by 2009.
- One of the main technology trends is the drive for using environmentally friendly surfactants triggered by rising oil prices and stricter environmental regulations.
- There is some activity in this space: Huish Detergents, Inc. (US) manufactures methyl ester sulphonate from renewable resources at commercial volumes. But otherwise there are few players looking a GM plants for this application.

Flavours & fragrances

- **The global fragrances and flavor market was valued at around $6.37 billion in 2006**. The industry is highly consolidated: Collectively, Givaudin, International Fragrances and Flavours, Symrise and Firmenich cover more than 50% of the market.
- Many plant extracts were traditionally used to provide flavour and fragrance but, because of cost and (large) market demand, most are now produced synthetically.
- Synthetically produced flavours and fragrance are costly to make (energy wise) and the end product lacks the authentic taste or smell of the original. However, extraction of natural extracts is costly and provides small yields.
- With consumer concerns around the health impact of artificial additives there is a clear swing back to natural products as noted by several retailers (e.g. recent M&S advertising campaign).
- Here, agbiotech can provide assistance through the identification of the genes in plants that encode flavours and fragrances:
  - researchers at the HortResearch company in New Zealand announced that they had identified the gene encoding the scent of apples and roses. Other scents are more complex combinations of multiple compounds (sometimes up to 30) and these are being investigated;
  - researchers at the Max Plank Institute have cloned genes for the decarboxylase enzymes that convert phenylalanine to 2-phenylethanol, better known as rose oil.
- Once the gene or genes are known, these can be generated synthetically using fermentation techniques to produce the flavour or fragrance in bulk.

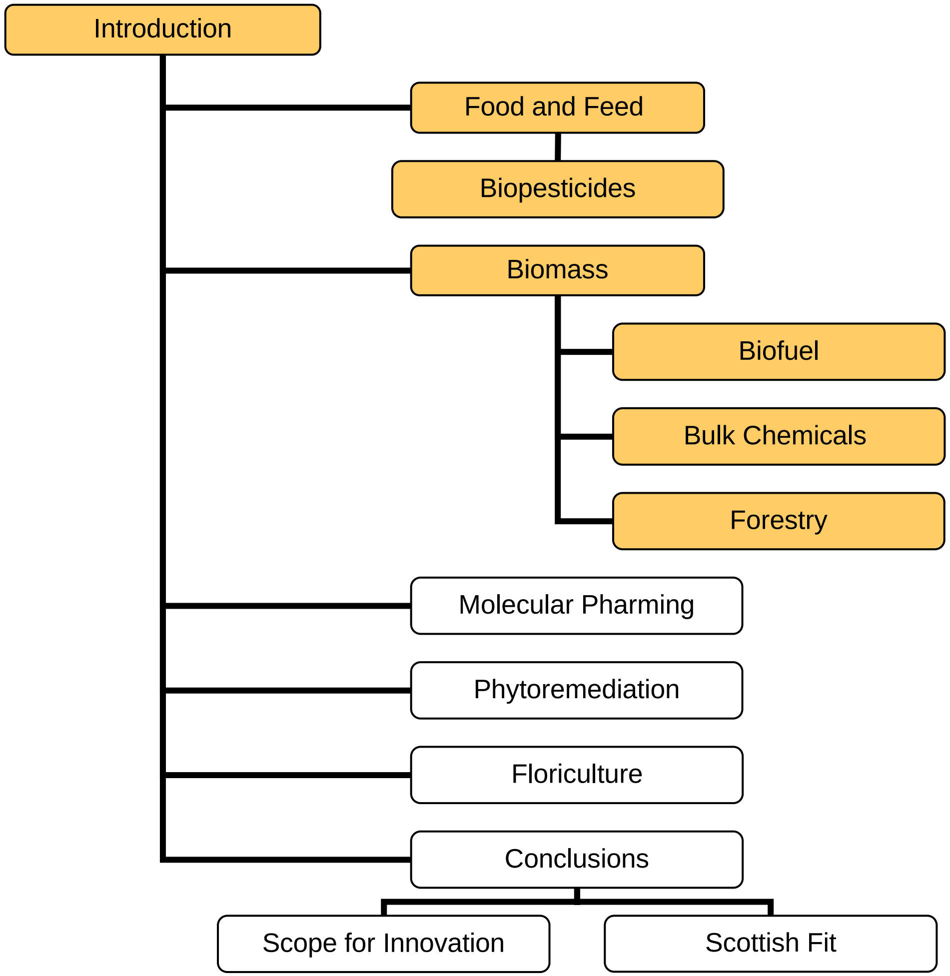
Dyes & pigments

- The market for dyes is around $2.5 billion but, as yet, only a small fraction are derived from natural sources.
- Natural dyes are often less toxic than synthetic alternatives. Natural dye processes can reduce pollution and have a smaller carbon footprint than synthetic dyes.
- Today, the demand for natural colours for clothing, food, paints and other applications is increasing.
- The biggest limiting factor in the large-scale use of natural dyes is cost. They are more expensive than synthetic dyes, and establishing natural dye-processes in place of existing processes would incur capital costs.
- In a similar manner, researchers are looking at the genes responsible for imparting colour to fruits and vegetable. The only colour-modified product on the market is Florigene's blue carnations. It took the company many years to introduce the gene that imparts blue to these flowers.

Conclusions – bulk chemicals

- There is a substantial opportunity to optimise the yield and quality of the chemical feedstocks derived from plants.
- Chemicals such as glycerol, a by-product of biodiesel production, offer an additional lucrative market for bioenergy producers.
- Bioplastics offer the most attractive opportunity (by market value) as they are welcomed by consumers and encouraged by government policy. **Few companies are optimising food and non-food crop as sources of bioplastics and there may be an opportunity to explore novel bioplastic feedstocks for high-value niche applications, which do not compete with commodity crop-derived PHA and PLAs**.
- Biolubricants also offer another attractive opportunity. **Niche markets for high-value, low-volume speciality oils may well offer an attractive market opportunity for novel plant oils, including those derived from GM plants or algae**.
- The drive for more environmentally friendly products will also impact on the market for surfactants, which, although a mature market, might still offer opportunities for niche surfactants derived from plants.
- It would be worth further investigating the natural extracts market for flavours, fragrances, dyes and pigments. One of the barriers to growing the sector is cost so means to improve yield may be attractive.

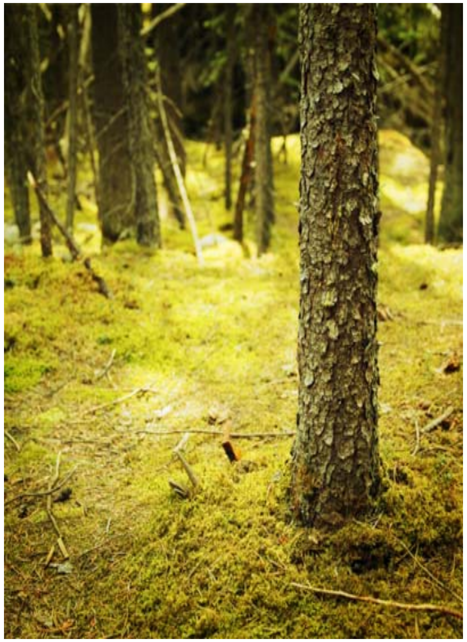
Forestry



This section looks at whether there is an opportunity for the application of biotechnology within the forestry industry.

Forestry

- The world's forests not only create a beautiful landscape but also combat global warming; provide wood for construction, paper and fuel; and generate income and jobs for millions of people. The global forestry market is estimated to be worth ~ $750 billion.
- Following concerted inward investment, the UK forestry industry has been a success story. Increasing demand from China and India has driven up timber prices, and last year UK timber sales were around £300 million.
- More than 70% of UK timber is processed in Scotland and forestry supports 26,000 jobs and generates £500 million gross to the local economy. Scotland is almost self-sufficient in wood-related material.
- The value of UK woodlands has more than doubled within the past 4 years and more investors have been attracted by favourable tax regimens.
- Although it would seem an obvious and highly attractive target for agbiotech, there are several fundamental barriers that make the genetic modification of trees difficult.
- Arguably, GM could be used to engineer faster-growing trees better suited for either construction or paper making, or resistant to emerging diseases.



The genetic challenges of wood

- The richness in the genetic diversity among native trees underpins their ability to adapt to changing environment. There is thus significant risk inherent in the manipulation of this genetic pool, which has deterred activity in this area
- Trees are generally slow growing. This poses a challenge for cloning trees, where a cutting is taken from a parent plant and cryogenically preserved. It can take up to 6 years to determine whether the parent plant has the desired properties and, by then, the frozen cuttings might no longer be viable.
- Trees have not been subjected to domestication, as experienced in our food crops, and so have not lost genetic variation. This makes trees very genetically diverse but also means that the linkage between markers and genes might not be consistent among populations, making marker-assisted selection a less predictable application.
- Trees are also not well suited to clonal propagation because they suffer from inbreeding depression, the result of homozygosity for recessive traits that arises from their genetic diversity.
- Several thousand *bt* poplar trees have been planted in China, but most work is concentrated on selective breeding of elite varieties of commercial trees. There is little GM tree planting elsewhere and most forest research is focused on traditional breeding to identify elite species.

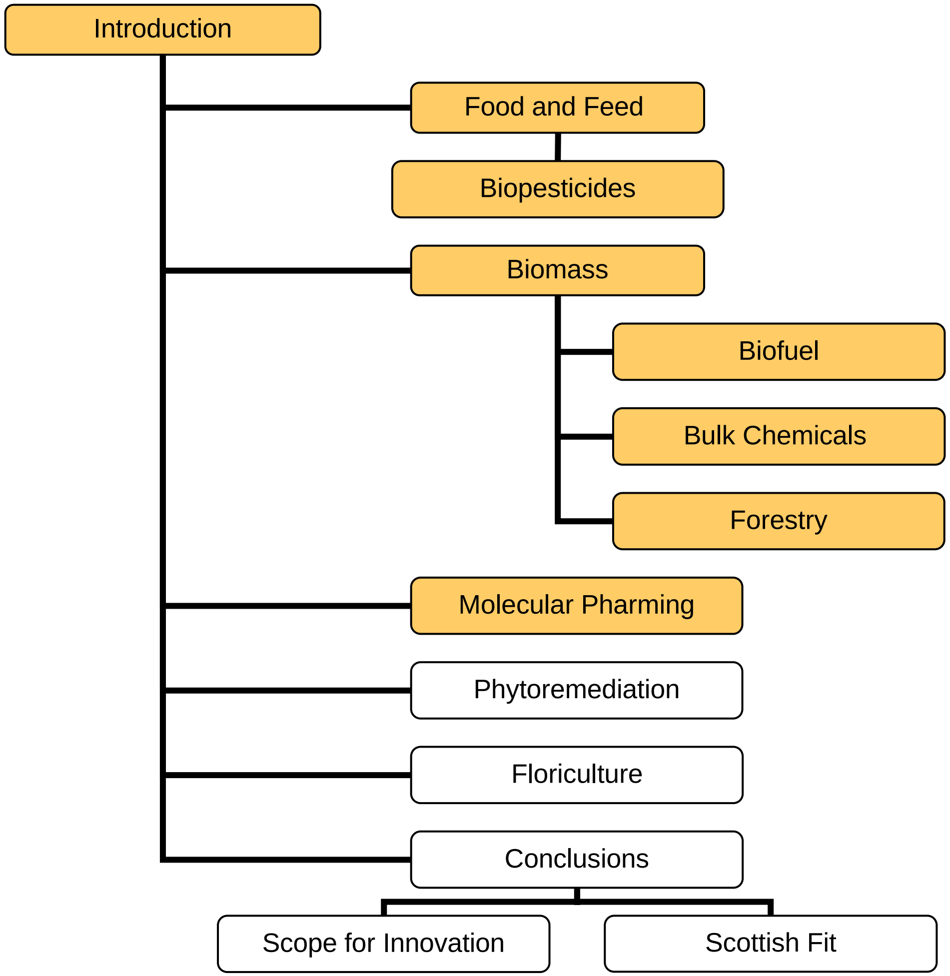
Case study: SweTree Technologies

- Although there has been a number of GM tree field trials across the globe, there do not appear to be any commercial plantings and few companies are hoping to build a business on GM forestry. One exception is SweTree Technologies.
- SweTree is a Swedish research and development company founded in 1999 as a joint initiative between the foundation of technology transfer (Teknikbrostiftelsen) in Umea and the company, Woodheads AB. The company is associated with 45 renowned research leaders in plant and forest biotechnology in several universities around Sweden.
- SweTree's main interest is in the genes expressed in the growing regions of trees, which might be linked to the growth of trees and their fibre properties.
- Trees contain high levels of lignin, the rigid polymer used to strengthen plant cell walls. Understanding the lignin biosynthetic path and genetic controls may be of value for improving the energy yield of woody biofuel feedstocks and producing superior timber for the construction and related industries.
- SweTree has identified a number of genes that can influence the levels of lignin in trees and a technology that can reduce levels of a pectin, making the wood more readily pulped and energy extracted.

Conclusions – forestry

- Forestry is big business, generating products for fuel, construction and paper industries in a sustainable and environmentally acceptable manner.
- Demand for wood and its products will continue to grow as the world's expanding population needs fuel and housing.
- The application of modern genetics to forestry is being done with some caution, as not only is it challenging technically but, compared with other plant life, there is seemingly much more hesitation about tampering with the genetic makeup of our forests.
- No GM trees have been planted within the UK and the Forestry Commission currently has a non-GM policy.
- However, the United Nations recently announced that it would not implement a global ban on the cultivation of GM trees. It will be up to individual nations to decide whether to permit application of this technology. This decision was met with concern by opponents of GM, as tree pollen can carry over hundreds of miles, breaching national boundaries.

Molecular pharming



This section looks into the progress made in the manufacture of medicines in plants, so-called molecular pharming.

Pharmaceuticals from plants

- Plants are a rich source of bioactives: Around 50% of modern medicines were originally derived from native plants.
- **Molecular pharming** is a novel **manufacturing process** by which plants are genetically modified to generate bioactives such as simple chemicals, lipids, recombinant proteins and vaccines for use as therapeutics or nutritional supplements.
- The transformation of the plant involves the insertion of a gene/s encoding the desired agent into the plant.
- The plant or plants cells are then grown in enclosed environments or in the field, and the bioactive is extracted using conventional processes.
- Proponents have been very bullish about the potential of molecular pharming but, over the past two decades, many companies have tried and failed (e.g. Large Scale Biology, Prodigene).
- Several pharmaceutical companies have closed down their pharming programmes (e.g. Monsanto, Dow Plant Pharma), although note Bayer's recent acquisition (see later).
- However, as some of the first products enter the clinic, the potential of molecular pharming might be realised at last.

A green advantage?

Suggested benefits of manufacturing drugs in plants

- ✓ Cost: Speed and cost-advantage in the scale up of production.
- ✓ Green issues: Renewable stock material that is environmentally friendly.
- ✓ Safety: Plants are free from material infectious to humans.
- ✓ Royalties: Circumventing the complex royalty stacking in use of proprietary mammalian systems.
- ✓ Capacity: Unlimited, at least in theory.
- ✓ Versatility: Plant material could be given as the therapeutic (e.g. oral vaccines) reducing storage and transportation costs. Stability may also be enhanced in this manner.
- ✓ Processing: Plants are capable of folding and modifying protein after translation in a manner not possible with mammalian and bacterial cells.

Drivers

- Predicted capacity crunch in biomanufacturing capacity.
- Suited to smaller batch production, so possibly better suited for personalised medicines.
- Some complex molecules are hard/impossible and costly to make synthetically.

Restraints

- It's GM, so resistance from public and regulators is still a risk.
- Eliminating plant toxins or agrochemicals used in producing crops.
- Regulatory system largely untested although guidelines are available.

Pharming reaches the clinic

Company	Plant	Products	Indication	Status (Partnered)
Biolex	Lemna	Interferon-a CR (Locteron)	Hepatitis C	Phase 2a (Octoplus)
		Anti CD20 mAb		Preclinical (Medarex)
		HGF antagonist	Cancers	Preclinical (Kringle Pharma)
		Human plasmin	Blood clots	Preclinical
Medicago	Medicago (Alfalfa)	Aprotinin	Coronary artery bypass surgery	Developmental
		Virus-like particles (VLPs)	H5N1 avian influenza VLP vaccine	Developmental
Planet Biotechnology	Tobacco	CaroRx	Dental caries	Phase 2b
SemBioSys Genetics	Safflower	Insulin	Diabetes	IND filed
		APO A1	Cardiovascular disease	Preclinical
		Immunosphere	Fish-feed additive	Development (AquaBounty)
		Hydresia	Skin-care products	Market
Ventria Biosciences	Rice	Lactoferrin	Topical therapy and GI health and cystic fibrosis	Phase 1
Dow Agrosciences	Tobacco	Veterinary vaccines (Concert™ plant-cell-culture system)	Newcastle disease (poultry virus)	Approved but not marketed
Greenovation	Moss	Service offering only at present		
Chlorogen	Tobacco	TGF-β	Cancers	Preclinical (Phase 1 2009)

Case study: Biolex

- Biolex (Pittsboro, NC, US) uses duckweed (*Lemna*) as a manufacturing platform. This simple aquatic plant grows fast, doubling its mass within 36 hours, generates no seeds or pollen, and can be grown in an aseptically sealed vessel to GMP standards. There is therefore no risk of gene flow and capital set-up costs are low.
- *Lemna* is transformed using RNAi to enable the expression of recombinant proteins many of which have been hard to produce in bacterial or mammalian culture systems.
- Moreover, *Lemna* can correctly fold and glycosylate recombinant proteins such as monoclonal antibodies. Indeed, Biolex have produced an anti-CD20 antibody with superior antibody-dependent-cell-cytotoxicity to that of the marketed anti-CD20 blockbuster, Rituxan (*Nature Biotechnology*, 2006).
- Biolex has credibility with investors closing a $30 million Series C round in May 2007 (JNJ Development Partners, Dow Venture Capital, JP Morgan) after previously raising $60 million in Series A and B round. It has manufacturing and R&D agreements with leading antibody players Genmab and Medarex, plus interest from Merck, Bayer and Merial.
- Biolex consolidated its *Lemna* IP position through acquisitions of Lemnagene and Epicyte during 2005.
- Most likely to get the first “plant pharmaceutical” to market with Locteron™, a controlled-release interferon alpha, currently in Phase 2 for hepatitis C.

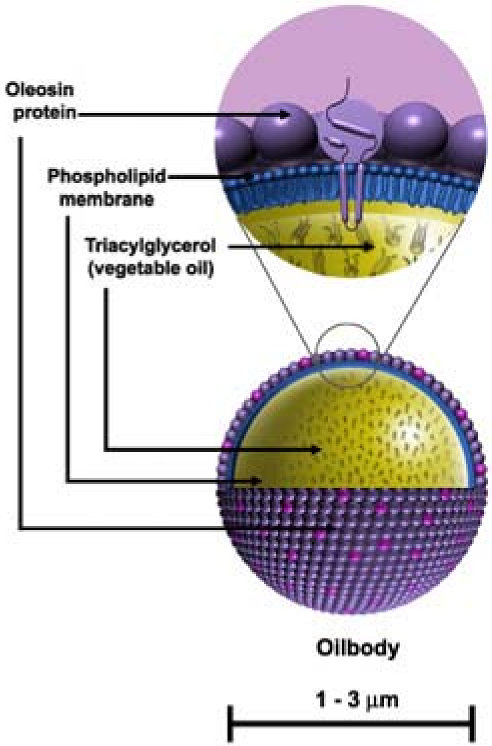
Case study: Chlorogen, Inc.

- Chlorogen, Inc. (St Louis, MO, US) specialises in the production of pharmaceutical proteins within the chloroplasts of tobacco plants.
- Chloroplasts are the organelles that carry out photosynthesis. Each plant cell may carry around 100 chloroplasts and each of these can hyperexpress genes (up to 100 copies) during plant leaf development. Chloroplasts are inherited maternally, in seeds rather than pollen, and so there is a low risk of gene flow through cross-fertilisation with other species.
- Chlorogen's intellectual property resides in a genetic regulatory signal that controls chloroplast gene expression in seeds only.
- Chlorogen's technology is less well developed than many of its competitors but it captured the interest of Dow Agrosciences for application in plant cell culture and animal healthcare.
- To date, Chlorogen has raised ~$12 million (Burrill & Co is an investor).
- The first product is a member of the TGF-beta superfamily for application in gynaecological cancers with possible entry to the clinic during 2009–2010. Chlorogen is also looking at cholera vaccines and insulin-like growth factors for diabetes.
- Processing and extraction remain an obstacle and Chlorogen has established an alliance with a local bioprocessing facility.

Chlorogen The future of protein production

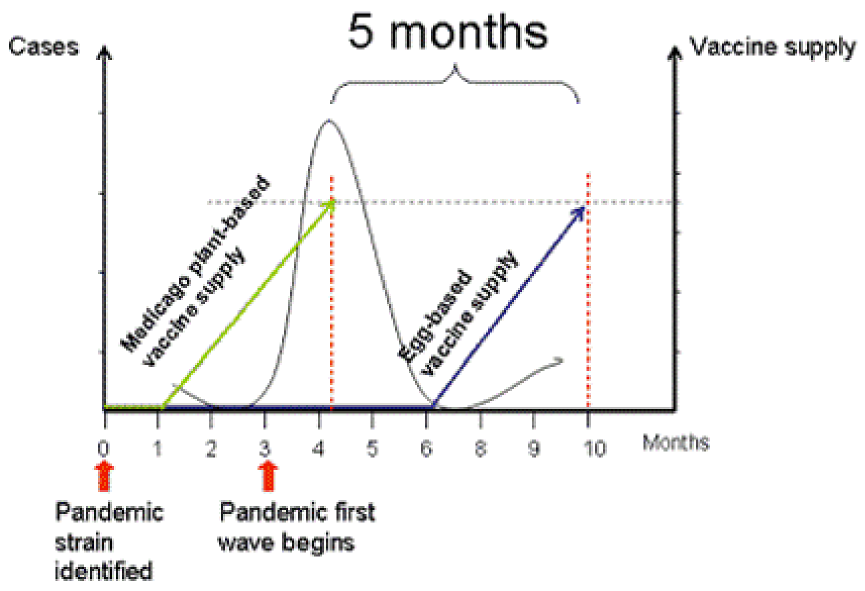
Case study: SemBioSys Genetics

- SemBioSys Genetics (Calgary, Canada) uses safflower as a host plant for its oilbody technology to produce recombinant proteins.
- Oilbodies are protein-coated lipospheres that naturally form in plant seeds to store triglycerides (see right).
- SemBioSys developed a method to engineer an oilbody-associated protein to carry recombinant proteins.
- Non-transgenic oilbodies have been marketed as fish feed (Immunosphere) with AquaBounty and as skin products (Hydresia) via SemBioSys' Botaneco subsidiary.
- The lead product is insulin, which may enter Phase 1 trials later in 2008. SemBioSys claims to get a 1.2% per weight accumulation of insulin within the seeds, extrapolating to 1 kg per acre (enough for 2,500 patients).
- SemBioSys claims that the plant could reduce the capital costs of production by 70% and product costs by 40%.
- The company has generated around $9.4 million in investment and has a number of other proteins available for co-development. It secured a processing and purification deal with Cangene for insulin.



Case study: Medicago

- Medicago (Quebec, Canada) is a publicly traded company that is focused on producing recombinant proteins in genetically engineered alfalfa using a transient expression system.
- Alfalfa is a fast-growing, high-yield plant that can be readily contained. It provides several advantages over field-based crops (including glycosylation).
- **Medicago claims to be able to produce virus-like particles (VLPs) suited for testing within 1 month of the identification of the genetic sequence of the new virus strain (see right).**
- Medicago is developing a VLP against H5N1 avian influenza virus (“bird flu”). This was effective in preclinical mouse studies against a range of strains of the virus.
- Medicago has partnerships with Acambis and InterveXion Therapeutics, and with an anonymous Fortune 100 company.



Source: www.medicago.com

Case study: Bayer/Icon Genetics

- Bucking the trend of big pharma to exit the molecular pharming scene, Bayer acquired Icon Genetics during 2006. Icon has developed techniques to transiently express complex proteins, such as antibodies, using multiple plant viruses in tobacco plants.
- Stably transformed tobacco plants can produce functional antibodies (plantibodies) but yields are low (1–40 mg/kg plant tissue) and it can take several years to secure a stably transformed plant (see table, below).
- Transient expression is faster but the common vector used (*A. tumefaciens*) cannot co-express more than one polypeptide at high levels. Instead, Icon uses two non-competing viruses encoding separate polypeptides to infect tobacco plants. The entire young plant is infected by immersion in virus-containing solution and grown to harvest. Yields are up to 0.5 g/kg of plant.
- **Bayer claims to be interested in using the technology to produce vaccines where a fast response time could mean meeting the needs *ahead* of an emerging epidemics.**

Relative yields and time to scale-up with different techniques

Expression system	Time to milligram of mAb	Time to gram of mAb
Transient techniques	14 days	14–20 days
Mammalian cell culture	2–6 months	6–12 months
Stable transgenic plant	12 months	>24 months
Transgenic animal	>12 months	>12 months

Source: PNAS 2006 Vol 103, 14645

Biologics capacity crunch?

- Biologics – including recombinant proteins and monoclonal antibodies – have been among the fastest growing and most successful class of therapeutics: They have a higher rate of success in the clinic and many have become blockbuster products (e.g. Rituxan).
- Driven by a need to cut costs, many large companies are increasingly contracting out the manufacture of biologics. The worldwide market for contract biomanufacturing reached $2.4 billion during 2007, a 14% increase from the previous year. (Source: HighTech Business Decisions.) CMOs are anticipating 14–15% growth during 2008.
- Several years ago there was a predicted capacity crunch in biologics manufacture, which appears not to have been realised: Improvements in cell lines, development of high-capacity resins (for separation), single-use technologies and smaller bioreactors have improved the cost efficiency of fermentation and cell culture. Capacity was bolstered with companies and regional initiatives developing additional biomanufacturing capabilities (e.g. Manchester's National Biomanufacturing Centre).
- However, the process of setting up a cell culture facility can take 5–6 years and cost up to $300 million. Arguably, a plant-based production system would be faster and cheaper to commission.
- The relative cost-effectiveness of mammalian and plant-based production system is difficult to prove because, as yet, there is no commercial production of plant-derived pharmaceuticals and companies are reluctant to share their estimates.

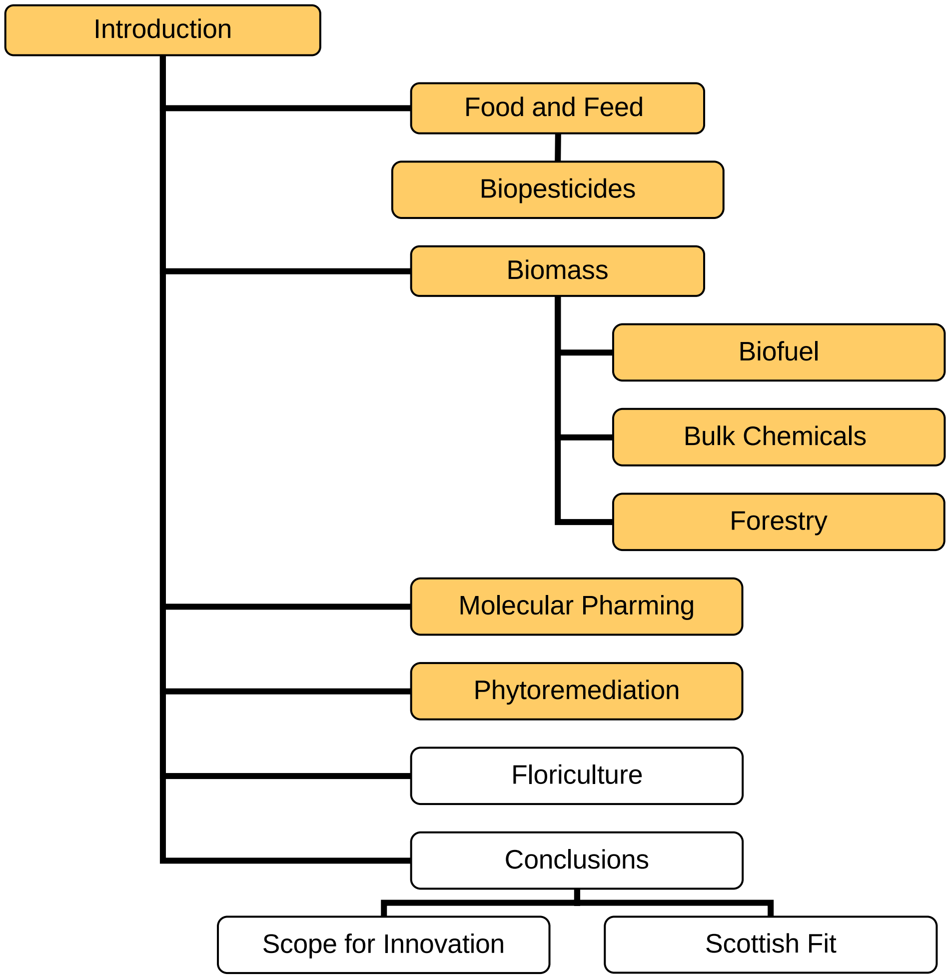
Regulatory hurdles

- In the US, the FDA and USDA both regulate drugs derived from plants and issued a guidance document "*Drugs, Biologics and Medical Devices Derived from Bioengineered Plants for Use if Humans and Animals*" around 6 years ago. Containment of the transgenic crop was a key concern.
- First FDA-approved vaccine for Newcastle disease in poultry was developed by Dow Agrosciences using their Concert™ plant system. Dow has not commercialised the vaccine, although it claims this is not due to lack of confidence in the product.
- The US FDA have now granted Investigational New Drug status for several other plant-based agents.
- The situation in the EU is largely untested, but there would need to be dual control both for the release of the genetically modified plant (by the EU Food Safety Authority and Environmental Protection Agency) and the usual approvals for a medicine (EMEA).
- No plant-based medicines derived from a GM crop have yet been tested by the EU system so, as yet, it is not clear whether there will be similar resistance to that experienced by GM food crops.

Conclusions – molecular pharming

- The FDA approval of the first tobacco-plant-generated vaccine in 2006 provides some confidence in the regulatory acceptance of plant-derived medicines. With several products in mid-stage clinical trials, the first pharmed products could reach the market within the next 3–5 years.
- The application of GM for molecular pharming ***may*** not meet with the same public resistance seen within the food sector, but regulators will still need to be assured of safety.
- Enclosed culture systems of simple plants might be preferred route, eliminating the risk of gene flow and the usual crop management headaches (pests, chemical application, etc.).
- The main threat to plant-based manufacture will be improvements in traditional biomanufacturing techniques, which might further drive down the cost and speed of cell-based systems.
- As yet, it is simply not clear that molecular pharming is a compelling story purely on cost. The technology needs to find a unique selling proposition through:
  - superior speed of scale-up, e.g. for vaccine production to combat fast-emerging epidemics;
  - products with properties that provide a distinct clinical benefit (e.g. enhanced efficacy, selectivity, reduced side effects);
  - production of novel and emerging therapeutics where conventional techniques are not meeting growing needs.

Phytoremediation



This section looks into the application of plants to remediate contaminated land and water.

Phytoremediation

- Bioremediation is the degradation of organics present in contaminated soil or water with the help of living organisms, such as microbes, fungi, plants or their components (e.g. enzymes).
- **Phytoremediation** is the use of plants to clean up soil, sediment and water contaminated with metals and/or organic contaminants such as crude oil, solvents, heavy metals and polyaromatic hydrocarbons.
- Phytoremediation has the following advantages:
  - economical, does not require expensive equipment or trained personnel;
  - eco-friendly, avoiding use of cleaning chemicals that can be toxic themselves;
  - can be used on the site of contamination;
  - the end products are non-toxic.
- Some plants are natural hyperaccumulators of heavy metals. For example, Alpine pennycress can accumulate cadmium and zinc to levels than would kill other plants; sunflowers can remove arsenic and uranium; ragweed and hemp can remove lead.
- **There are few assessments of the market for phytoremediation, which in part reflects its small size. The US phytoremediation market is worth around $100–150 million per year, just 0.5% of the total remediation market.**
- The market for phytoremediation in Europe is negligible but is likely to grow, especially in Eastern European countries and China, where many contaminated sites require clean-up.

Greener cleaners

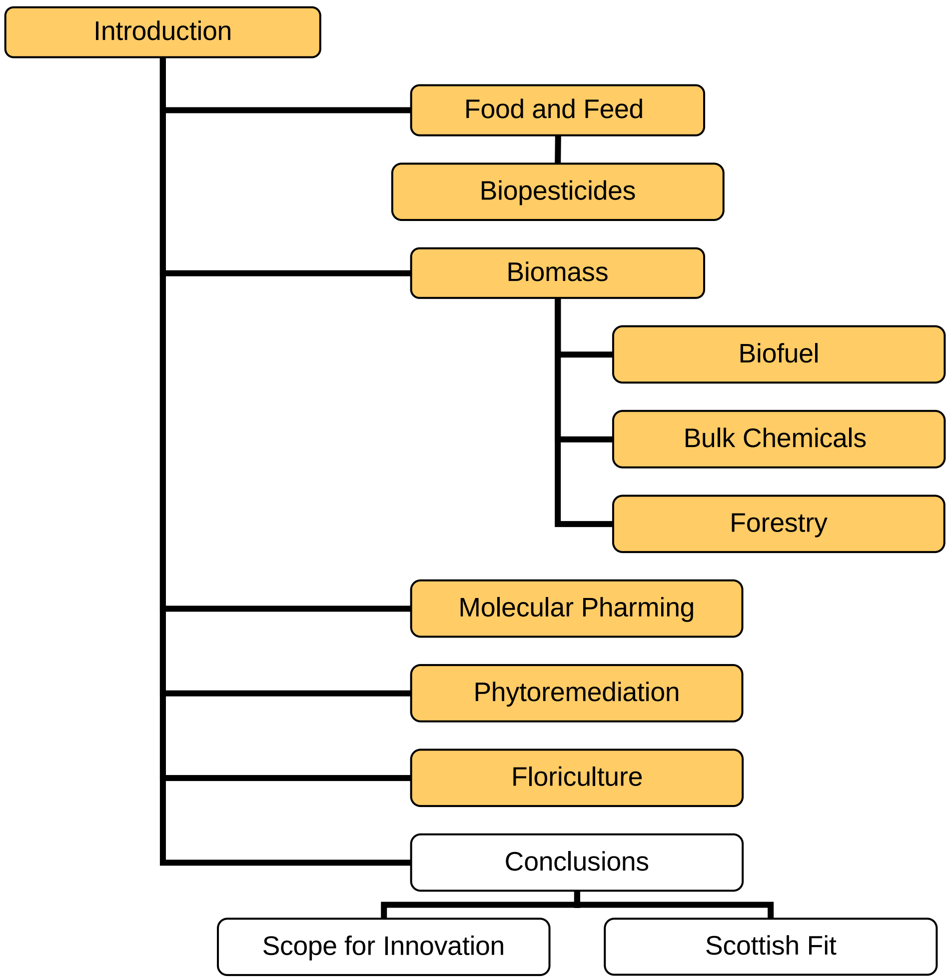
- Much of the work carried out on phytoremediation has been done within academic laboratories to better understand the mechanisms that underlie the uptake, transport and detoxification of pollutants, and also the interaction between plants and microbes within the root system. The sequencing of the genomes of model plant species has enabled this process.
- Another line of investigation has been the development of transgenic plants that show higher tolerance, accumulation and/or degradation of various pollutants. For example:
  - a gene encoding a nitroreductase from a bacterium was inserted into tobacco and the plant showed faster removal of TNT and greater resistance to this toxin;
  - Neil Bruce (York, UK) genetically modified *Arabidopsis* to remove the military explosive hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX) by incorporating a bacterial cytochrome P450 enzyme;
  - Indian mustard has been modified to overexpress enzymes involved in sulphate/selenate uptake.
- Novel techniques should enable gene expression in specific plant structures (e.g. root rather than leaves) and for generating transgenic phytoremediators that cannot contaminate native species (e.g. by engineering the chloroplast only).

Conclusions – phytoremediation

- Phytoremediation is an environmentally attractive solution for remediation of contaminated sites.
- It does have some disadvantages: It can only occur as fast as the plant can grow (for trees, this can be many years) and extends only to the depth of root penetration; in highly contaminated sites plants simply might not grow at all.
- The products of phytoremediation companies are often common plants, which may not attract a premium market price. Many companies generate income through the associated consultancy provided.
- As yet, no transgenic plants have been approved for phytoremediation and the sector would face the same issues for GM approval arising as with any transgenic crop.

In February 2008, Florigene applied to the Australian Office of the Gene Technology Regulator for a license to release genetically modified *Torenia* (a flowering pot plant also called wishbone flower) to conduct proof-of-concept studies of ability of the GM plant to absorb phosphates from polluted water and to slow or repress growth of algal blooms.

Floriculture



This section looks at the market for biotechnology as applied to ornamental plants and flowers.

Flower power

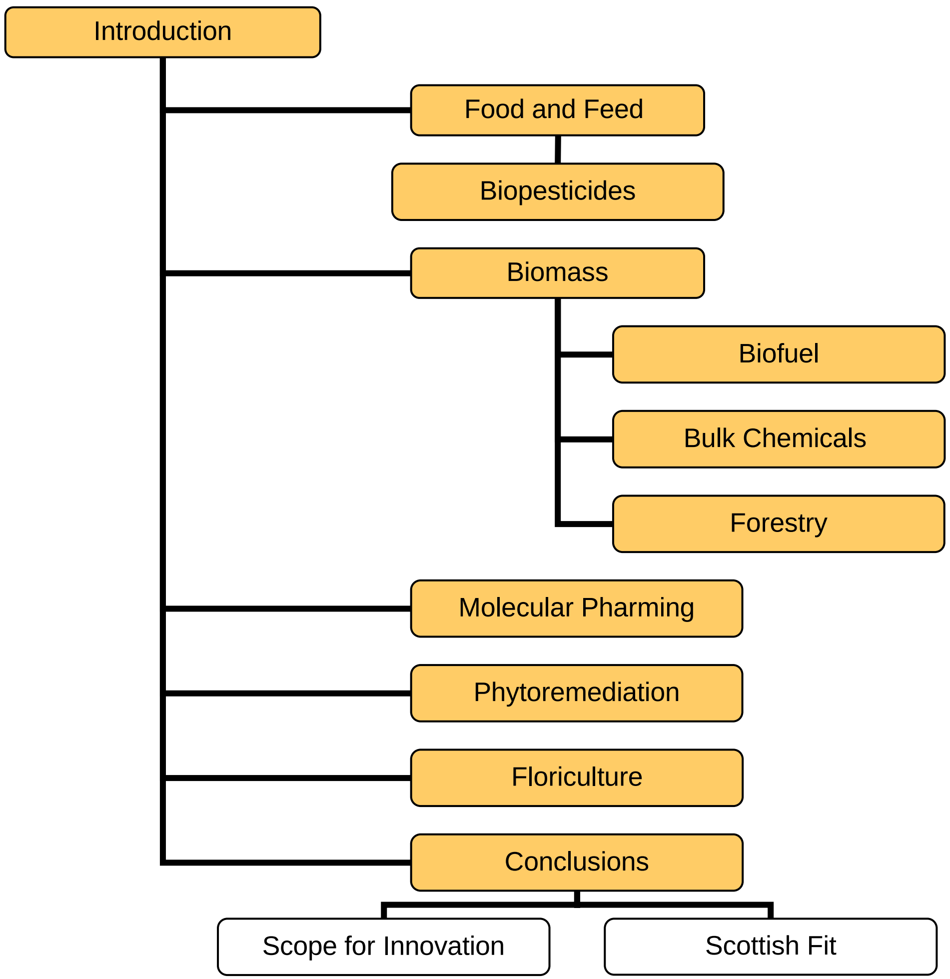
- According to the Society of American Florists, **per capita spending on floral products is around $20 billion per annum in the US alone**. Among growers, floriculture production contributes over $5 billion in value – around 7% of all agricultural sales.
- The only GM flowers approved for cultivation are Florigene's range of blue carnations (right). Melbourne-based Florigene (Australia) claims to have sold 75 million blue carnations in the US, Japan and Australia.

- Although GM ornamentals still need to be approved by government regulators, the standards are less strict than for food. However, the cost of R&D, licenses and regulatory approval may deter most horticulture companies from investing in this area.
- Basic understanding of the genetics and biology of ornamentals is also missing, and many horticultural businesses may be deterred from investing in such research. Colour and scent, in particular, are sophisticated systems to unpick and replicate.
- However, the future for GM ornamentals may be easier to predict. The public's opposition to GM ornamentals might be less vehement than to GM food as flowers are a voluntary, non-essential purchase.

Last year Mendel Biotechnology and German plant breeder Selecta Klemm forged a functional genomics collaboration in the form of joint venture Ornamental Bioscience to create a new range of ornamental plants that could adapt to the changing climate – specifically the ability to cope with drought and resistance to common plant pathogens

ornamental bioscience

Conclusions

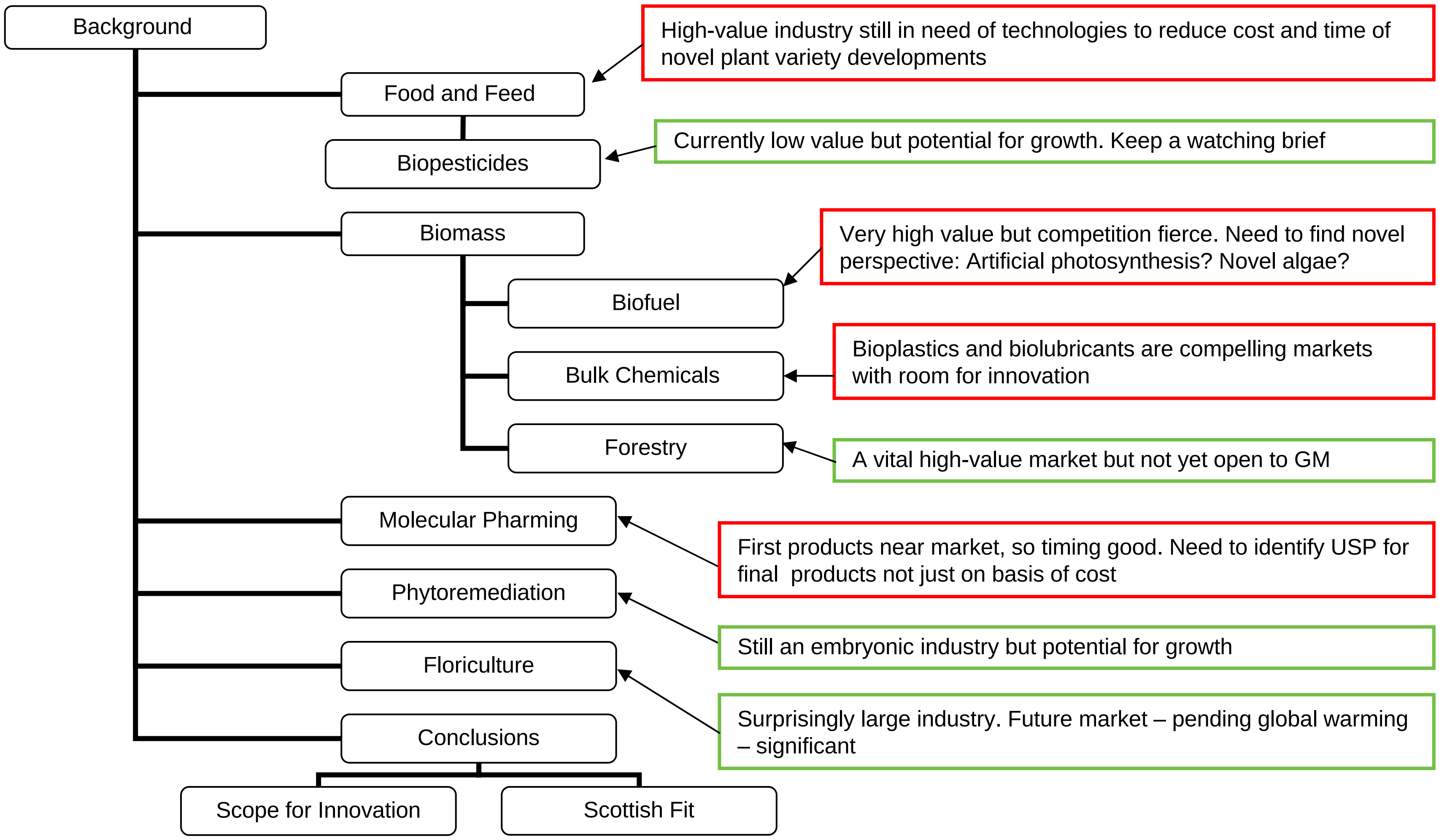


Here we summarise our findings, explore the need for innovation, Scottish research and commercial strengths, and recommend areas for further due diligence.

Scope for innovation

- Plants offer an environmentally attractive means of meeting many global needs – whether for food, fuel or consumables – in an environmentally sustainable manner.
- With suitable safeguards in place, modern genetic engineering allows the selective modification of plants to optimise their value for **all these potential applications** or as a tool to optimise conventional plant breeding.
- Concerns around GM will not disappear in the immediate future but global macro-economic changes might shift opinion (e.g. based on price, reducing carbon footprint, environmental impact) on the perceived risks–benefits of the technology.
- There are technology platforms that underpin all plant-based markets, and herein lies an opportunity for innovation.
- The markets that appear to have most traction and are most open for innovation are summarised in the following slide.

Markets of interest



Technology needs (I)

Plant genomics

- In contrast to the investment poured into sequencing the human and other mammalian genomes, plants have been poor cousins.
- The lack of access to comparator genome databases has slowed gene selection and breeding programmes in crop plants – most work has focused on model plants such as *Arabidopsis*.
- Many plant genomes are considerably larger than the human genome and teasing out the location and sequences of gene coding regions is therefore more complex.
- Even more challenging is identifying value-added traits in plants.
- Tools such as plant DNA arrays, as developed by Affymetrix and other gene-chip providers, may assist in this market.
- Various genetic approaches should lead to a better understanding of plant biology, plant–pathogen interactions to identify novel targets for pesticide development.
- An understanding of plant stressors and master controllers of key pathways would also provide valuable insights into means to modify plant phenotype.
- Finally, there is a need to apply bioinformatics and systems biology to remove the serendipity from the process.

Technology needs (II)

Transformation technologies (1)

- **Efficiency**: Although existing transformation systems work well for some plants, many potentially commercially valuable varieties are resistant to genetic modification. Improvements in the efficiency of existing technologies are also desirable.
- **Predictability**: Also of value would be means to control where the transgene inserts in the genome to ensure stability of the transformation. For example, gene insertion may disrupt the promoters of other native genes causing unpredictable consequences.
- **Novel strategies**:
  - Novel techniques, including the application of RNAi for modulating gene expression, are of interest.
  - Non-transgene strategies (as seen with Simplot techniques): Alternatives to using bacterial modification systems and introducing plant-derived genes using plant-derived vectors and plant transgenes.
  - Marker-free methods: Strategies to avoid leaving antibiotic selection markers within the plant genome or avoid their application in the first place may help alleviate public concern over the use of antibiotic resistance markers.
  - Various transient high-expression systems may suffice for some applications and markets (see Molecular pharming).

Technology needs (III)

Transformation technologies (2) – gene stacking for complex traits

- Most of the early GM plants carried a single modified gene, but it is desirable to introduce multiple traits in a single plant (e.g. multiple herbicide and pesticide resistance). This will become more important when engineering more complex changes such as stress resistance.
- Although there has been some success at introducing two genes, it is technically challenging to introduce more than one, and various strategies are being developed. The *Agrobacterium* transfection system for example is limited in the size of transgene that can be incorporated.
- An additional challenge is ensuring the coordinated expression of multiple genes and maintaining expression rates for each gene in parallel.

Technology needs (IV)

High-throughput precision phenotyping

- One of the most challenging and time-consuming processes in a commercial breeding programme is phenotyping the transgenic plants. The impact of a genetic modification can be subtle (e.g. not a visual alteration but a metabolic change) and its advantage for agriculture may not be obvious. It is also important that the plant is tested within a “real field” environment.
- The phenotyping of thousands of plants is both labour intensive and also time consuming. Any means of automating and “industrialising” this process is therefore valuable.
- LemnaTec is one company that has attempted to standardise and automate an image-based analysis system. Larger companies (e.g. Dupont Hy-Bred’s FAST system) have developed in-house systems.
- In addition to digital imaging, other techniques, such as near-infrared spectroscopy and spectral reflectance, have also been explored, although these are not yet commercially viable.

Emerging techniques

Various genetic techniques, largely arising from human genetic research, are now being applied to plants. Examples include:

- RNA: Antisense and RNA interference are being used to probe gene function.
- Epigenetics and its effects on plant behaviour are also of importance.
- Metabolomics and proteomics: This has provided insight into more complex interactions between plants genes and/or proteins that underpin complex traits such as yield, resistance to stress, flowering and fruit formation. The first plant proteome (*Arabidopsis*) was published in the journal *Science* in May 2008.
- Gene-modification techniques from human medicine (zinc fingers, directed nuclease editor) are being applied to improve the plant transformation process.
- Microarrays: Gene chip makers such as Agilent and Affymetric are generating products for the agriculture market including plant gene arrays.

Scottish fit – research

- Plant sciences and biotechnology is a **particular area of strength in Scotland** with world-leading research teams at universities in Glasgow, Edinburgh, Dundee and Abertay, Strathclyde and Aberdeen. Areas of expertise exist in:
  - basic plant biology – control of development, metabolism, photosynthesis, lipid biology, etc.;
  - interaction of plants with pathogens;
  - plant ecology;
  - microbiology;
  - applied crop technology;
  - forestry and phytoremediation.
- Dundee is home to the Scottish Crop Research Institute, which – uniquely – has crop-breeding capabilities and expertise in barley, potatoes and soft fruit. These crops are of high value and relevance within Scottish agriculture.
- The Scottish plant science community has in recent years worked hard to provide a **strong, cohesive and supportive network**. It recently sought funding to create a "Plant Pool" for Scotland, for which a communal plant transformation resource would be created at SCRI.
- Scottish plant scientists are well networked and make profitable use of their contacts oversees to help carry out fieldwork not possible in the UK.
- However, there is not a critical mass of agbiotech companies in Scotland (indeed, this is a UK-wide issue). However there is some expertise within the various markets, which could provide a foundation for growth in the future (see next slide).

PSS Plant Science Scotland

Scottish fit – industry

	Food	Biofuels	Bioplastics and polymers	Forestry	Molecular pharming	Phyto-remediation
Academic	Dundee/SCRI Aberdeen Glasgow Edinburgh Rowett Institute Aberdeen	SCRI (poplar, biomass and microbes) SAMS (algae, microbes) Aberdeen (energy crops)	Good materials and chemistry expertise in several universities could be applied	Forestry Commission (Roslin) SCRI Aberdeen Abertay (forest genetics)	None directly but basic plant biology could be applied	Glasgow (Susan Rosser) Aberdeen (ecology group) Abertay
Industry	Kerry Bioscience* CropTech? Mylnefield Research Services	Energy companies	Various plastic and polymer producers such as Devro, Giltech, Biofilm	Many timber and processing companies in Scotland In 2007, SE announced a biomass action plan with a total of £10.5m funding	None	Few

* Denotes local subsidiary of non-Scottish company

Recommendations

- From our analysis of the markets, we believe that there continues to be opportunities for improved understanding and technologies within the following sectors:
  - **New plant "discovery" techniques:** The need to significantly enhance the speed and efficiency of plant transformation and to permit more complex genetic changes to be implemented. In addition, more efficient methods to screen both for novel genetic traits and plants carrying those traits are required.
    - *We recommend foresighting in this area.*
  - **Novel bioplastics and biolubricants:** Both substantial markets with room for further innovation to develop, in particular, specialist products for high-value applications.
    - *We recommend foresighting in this area.*
  - **Molecular pharming:** Here, the need is to better identify the unique opportunity for plant-production systems: Is this speed of production (e.g. vaccines), production of emerging therapeutic agents (RNAi?) or engineering novel properties in biologics not possible with existing manufacturing systems?
    - *Here, further assessment of specific opportunities is needed.*
  - **Artificial photosynthesis:** Although still in its infancy, the question here is how know-how of photosynthetic processes today can impact on solar power in the medium term.
    - *Here, there is a need to create a view of what near-term success (or products) would look like in this area.*

Please talk to us!

- We very much welcome dialogue with our members in this area. If you would like to discuss the report findings and associated opportunities with us further, please contact ITI Life Sciences at:

  foresighting@itilifesciences.com
  +44 (0)1382 568060

  For more information on ITI Life Sciences, please visit:
  http://www.itilifesciences.com/