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COMMISSION ON GENETIC RESOURCES FOR FOOD AND AGRICULTURE

GENOMICS AND GENETIC RESOURCES FOR FOOD AND AGRICULTURE

By Robin Fears

The Commission has regularly received reports on new developments in biotechnology, in relation to genetic resources for food and agriculture.

This study provides some perspectives on a number of recent advances in the field of genomics and other new biosciences.

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GENOMICS AND GENETIC RESOURCES FOR FOOD AND AGRICULTURE

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SUMMARY

Advances in plant genomics research are opening up a new era in crop plant breeding where the linkage of genes to traits inspires more efficient and predictable breeding programmes. Completion of the first plant genome sequences (*Arabidopsis* and rice) provides models for assigning functions to genes and for hypothesis testing. Improvements in high throughput sequencing and reduction in sequencing costs are bringing many more crop genomes within range of analysis. It is now desirable to establish collective priorities for genome sequencing according to societal as well as technical criteria.

Outputs from genome sequencing are being enhanced by advances in functional genomics technologies, including transcriptomics, proteomics, metabolomics and informatics. Taken together, the new biosciences enable molecular phenotyping, and the integration of multiple datasets provides the foundation for plant systems biology. Progress in the biosciences to underpin discovery of targets for crop improvement now requires the coordination of multi-disciplinary technology platforms to standardise tools and models, and the organisation, validation and sharing of information in community databases that are fit for purpose.

The definition of target genes associated with plant processes and traits is beginning to explain fundamental features in plant growth, development, reproduction, photosynthesis and the response to environmental conditions and pathogens. The characterisation of these molecular determinants will provide valuable tools for tackling a range of goals for improved crops for developing countries, in terms of closing the yield gap, making efficient use of environmental resources, and protecting from biotic and abiotic stress. In order to support a rational process for prioritisation of research on the various problem-oriented goals, there must be concomitant progress in assessing socio-economic value and cost-benefit balance of research outputs.

Advances in microbial genomics will complement the value of plant genomics in elucidating plant-microbe interactions but, because of the very large volume of discovery research data now being generated, innovation target finding requires very efficient agenda-setting, data management and decision systems. A strategy for better coordination and coherence in public sector R&D support must be accompanied by better engagement with private sector R&D to ensure that tractable goals for developing country crop improvement can capitalise efficiently on advances in science and technology, wherever they occur. There would be merit in creating a common resource of a database to share pre-competitive information. Knowledge transfer in the reduction to practice as improved crop breeding also requires the active engagement of the plant breeding and farming communities with the research enterprise in making research choices and translating research outputs.

Molecular marker-assisted crop breeding has already imparted significant improvement to conventional breeding programmes – increasing scope, speed and efficiency of crop selection. Outputs from functional genomics research, characterising specific marker genes rather than the proxy, linked, markers used hitherto, will become increasingly useful in selecting breeding lines. Genomics research will bring a new level of determinism to crop improvement if the current bottlenecks in resourcing, generating, standardising and using the molecular tools can be overcome.

Focused breeding strategies for domesticated crops also require the characterisation of currently untapped genetic diversity in wild relatives, drawing on diverse sources of germplasm. Molecular marker techniques are important in this characterisation and conservation, and in generating increased value for collections of plant genetics resources. There are continuing issues for the funding, management and evaluation of these collections and for their access and benefit sharing. The current technical and ethical challenges are likely to be compounded by the opportunities to capitalise on genome sequencing and by technology development within the collections, in particular the introduction of DNA banking.

In view of the major opportunities for crop improvement now moving into range in consequence of the bioscience advances, it is highly important to reverse the historical decline in public sector agricultural R&D investment and to build new critical mass. A wide range of strategic support mechanisms and

models compete for the attention of the policy-maker but the reduction to practice cannot properly succeed if efforts are excessively fragmented. Effective use of public funding for R&D is also enhanced by provision of appropriate incentives and support to encourage the private sector, particularly smaller companies, to invest in more R&D in ways that do not impede the public sector.

In promoting both public and private sector R&D and joint work, whether in individual collaborations, consortia or other partnerships, it is necessary to do more to make the current mechanisms for benefit sharing effectual, while also exploring new options for promoting access (for example, patent pools, open source licensing, technology brokering) and supporting innovation (for example, public procurement of R&D from smaller companies).

Individual developing countries will vary in the extent to which they decide to generate their own resources in fundamental plant sciences or rely on importing technology and tools. In all cases, there is need to build capacity and competence to benefit from knowledge transfer, requiring greater investment in human and institutional R&D resources and engagement in the processes of global governance for determining priorities, building novel partnerships and sharing benefits. It is recommended that FAO consider further how to develop a framework for concerted international action.

CHAPTER 1: INTRODUCTION TO THE ROLE OF THE BIOSCIENCES IN THE USE OF GENETIC RESOURCES

1.1 The unmet need

More than 800 million people are chronically undernourished. The most recent systematic analysis conducted under the auspices of the WHO Global Burden of Disease Study confirms that undernutrition remains the leading risk factor for health loss worldwide, primarily mediated via underweight, although micronutrient deficiency is also a significant cause of morbidity and mortality (Lopez et al., 2006). Poor nutrition is responsible for nearly six million childhood deaths annually (more than half of all child deaths) and more than a quarter of children younger than five years old in developing countries are underweight. Few world regions are likely to reach the target of the Millennium Development Goals to halve the proportion of young children underweight by 2015 (United Nations Children Fund, 2006).

There have been very significant achievements in global agriculture in consequence of the “Green Revolution” and other initiatives. For example, there has been a three-fold increase in cereal production in Asia in the last 40 years. However, enormous challenges lie ahead to ensure that the projected world population, approximately eight billion in 2025, is adequately and equitably fed, and in environmentally sustainable ways (Borlaug, 2006). Moreover, the productivity achievements have not been uniform; in Africa in the last 40 years, less than 40% of the gains in cereal production came from increased yield. The rest was from expansion of the land devoted to arable agriculture at the expense of forests, soil fertility and water. This expansion cannot continue and in the future Africa must depend more on yield gains than on land expansion to achieve food security (InterAcademy Council, 2004).

1.2 Crop domestication and diversity

Crop domestication has been judged to rank among the greatest human achievements. But while agriculture is some 15,000 years old, structured plant breeding is a twentieth century art (European Commission, 2005). Traditional forms of agriculture have complex structure and high biodiversity – traditional neotropical agroforestry systems commonly contain more than 100 annual and perennial plant species per field. By contrast, modern industrial agrosystems are simplified towards monoculture (Stinner, 2004). Considerable concern has been expressed that the practice of modern intensive, convergent plant breeding leads inevitably to decline in crop genetic diversity (genetic erosion) with severe consequences for the genetic vulnerability of crops and their plasticity to respond to biotic and abiotic challenges[1].

According to IPGRI, there are at least 7,000 plant species that could be cultivated for food but only 150 crops are grown commercially. 30 crops provide 70% of the world's calories and wheat, rice and maize together provide more than 50% of the plant-derived calories. Traditional grain crops such as millet, quinoa and amaranth, together with many types of vegetable and fruit, have been and still are being replaced in Africa, Asia and Latin America. Underused species important for agricultural biodiversity have customarily been little researched but international projects are now doing more to incorporate "neglected" crops into research and breeding programmes (Johns et al., 2006) with potential to improve health status. R&D activities to exploit this potential and to capitalise on the advances in molecular biology that enable improved breeding programmes (as discussed subsequently in this report) may now be facilitated by the International Treaty on Plant Genetic Resources for Food and Agriculture (FAO, 2002a), establishing a multilateral system for access and benefit sharing.

1.3 Advances in plant science

The processes by which plants grow are relatively poorly characterised although the pace of research advance is increasing dramatically (EASAC, 2004). The cutting edge of basic plant research is rapidly evolving from an understanding of the function of single genes to studying networks of genes that control biological processes (European Commission, 2005). Genomics is the study of an organism's entire genome. Initial activity in the field of genomics has employed genome sequencing to identify genes, thus providing the foundation for functional genomics (covering a range of large-scale Omics technologies) to understand gene expression and biological activity. Genomics initiatives are rapidly generating the basic knowledge that is broadly useful for the scientific community – supporting discovery in basic research and applications in breeding and conservation. Advances in genomics and cognate biosciences are beginning to explain the fundamental elements of plant biology with regard to growth, development, reproduction, photosynthesis and the responses to environmental conditions and pathogens. Much remains to be discovered about these key processes and the integrated circuitry that links the different levels of organisation within the phenotype, and of how natural genetic variation creates biodiversity. Subsequent sections of this report will describe how advances in basic science – understanding how plants function – can be used to support improved plant breeding by using molecular markers (short sequences of DNA closely linked to, and indicating, a desirable trait) in marker-assisted breeding.

The reduction to practice encompasses two challenges: the extrapolation from model plant genomics to crop plant genomics (and other Omic technologies) and the translation from scientific advances to breeding programmes, such that technologies and information are presented to plant breeders in a suitably practicable form[2]. As will be described, the new routes to crop improvement accessing greater genetic diversity bring together the advantages of marker-assisted breeding (faster and more targeted) and the understanding of the science underlying attributes of crop domestication, to capitalise on wild species resources.

The reduction to practice in improved crop breeding is by no means just a matter of linear technology transfer from researcher to research user. Knowledge transfer necessitates the active involvement of the plant breeding and farming constituencies and other stakeholders. Impediments to the reduction to practice are often compounded by policy makers taking too narrow a view of the transfer of

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[1] While a recent study using molecular markers indicated no declining trend in genetic diversity in cereal varieties in the UK over the past 60 years, much more research is required using molecular marker-based technologies within a broader scientific framework to monitor changes in genetic diversity and to help quantify the challenges for sustainable agriculture. Such research is now getting started, for example the European Commission Crop Genetic Diversity Project, www.niab.com/gediflux.

[2] Advances in plant biotechnology can also be exploited by genetic modification (GM) – the deliberate transfer of a gene from one organism to another. GM has often over-shadowed non-GM technologies and although GM is not a prime focal point of this report, some opportunities will be reviewed in the context of identifying where there are common policy issues or a need for cohesive strategy.

knowledge; knowledge transfer is as important in evidence-based policy development as it is in product development.

This report reviews needs and activities at the global level, taking an illustrative approach to highlight what opportunities can now be tackled by R&D and what further knowledge is still required in order to bring longer-term opportunities within range. The issues for policy-makers are not confined to R&D funding and prioritisation. Constraints on the effective conduct of R&D, its applications and the governance of innovation must also be tackled if the potential of genomics, allied sciences, and genetic resources is to be realised. The report concentrates on crop plant genomics and genetics but advances in the biosciences will be equally relevant to other agricultural sectors. A recent FAO publication (Ruane and Sonnino, 2006) provides a valuable introduction to the present status of the characterisation, conservation and use of genetic resources relating to the livestock, fishery and forestry sectors and to the exploration of cross-sectoral issues in the use of molecular technologies in breeding and gene banking programmes.

The material importance of the characterisation and utilisation of genomics and genetics resources for food and agriculture can be conceived in terms of the value in achieving three transitions: (a) Genomics to plant biology; (b) Genomics to improved crops and (c) Genomics to society. The following sections of the report are structured to:

- Describe the current status and future opportunities in genomics and functional genomics;
- Provide examples of the elucidation of target genes associated with plant processes and traits;
- Explore the steps translating advances in basic science to crop plant breeding;
- Review the related issues for characterisation and conservation of plant genetic resources;
- Assess R&D investment trends in the public and private sectors and strategic opportunities for new investment, for partnership and collective activity;
- Consider options for addressing Intellectual Property issues, access and benefit sharing;
- Summarise the overall constraints to innovation in plant sciences and the needs for capacity building, strategy formulation and international governance
- Identify key elements that require international discussion in the context of further developing the framework for the FAO Global Plan of Action.

CHAPTER 2: CURRENT STATUS OF GENOMICS AND FUNCTIONAL GENOMICS

2.1 Sequenced genomes – what has been accomplished so far?

Arabidopsis thaliana has received considerable attention by researchers worldwide because of its value as a simple model for crop plants in terms of how it develops, reproduces and responds to stress and disease. *Arabidopsis* has a small genome (Table 1) and was relatively simple to sequence. The first detailed genetic map and sequencing efforts occurred in the 1980s; in the 1990s, *Arabidopsis* mutant collections, gene libraries and genomic resources were developed and shared. The complete genome sequence was published in 2000.

As discussed in the EASAC (2004) report, *Arabidopsis,* as a close relative to crop plants belonging to the *Brassica* genus, serves as an important assembly template for draft sequences of other plant genomes, as a model in assigning function to genes and in formulating hypotheses about possible relationships between specific DNA sequences and phenotypes. Although, the functions of most genes in *Arabidopsis* are still unknown or only poorly characterised, research on *Arabidopsis* as a model system is also helping to elucidate determinants of natural genetic variation. The discovery of genes underlying ecologically important traits provides insight into mechanisms of genome evolution, geographic population structure and selection pressure on DNA in natural populations (Mitchell-Olds & Schmitt, 2006). The new interdisciplinary research field of genomic ecology, at the interface between genomics, evolutionary biology and ecology is now reaching the stage of providing detailed information on the phenotype processes that regulate fitness (for example, www.biol.lu.se/ekologi/CGE).

Oryza sativa Two strains of rice (*indica* and *japonica*) represent the second plant – and first crop – genome to be sequenced (the draft sequence appeared in 2002). The rice genome is significantly larger than *Arabidopsis* (Table 1) and contains about 50,000 genes (compared to about 35,000 genes in the human genome). As all cereal grains are closely related, the rice genome has been used as a model to construct virtual gene maps of very much larger genomes such as wheat.

The initial draft sequences were accomplished by teams of researchers in Beijing Genomics Institute and at Syngenta, Switzerland. The latter was initially criticised for not releasing data into the public domain via the usual route of GenBank, in an attempt to ensure that commercial competitors would have to pay to exploit the information (Syngenta invested $30 million to sequence the rice genome). However, Syngenta has built a relationship with the public sector to develop improved types of rice, as will be described subsequently.

Table 1: Genome size

Plant genome	Estimated size (Mbase pairs)
Arabidopsis	125
Rice	400
Brassica rapa subspecies pekinensis	500
Medicago	550
Poplar	550
Cassava	770
Tomato	950
Sorghum	1,000
Maize	3,000
Barley	5,000
Wheat	17,000

2.2 Current crop plant genomic research initiatives

Many developed countries started research programmes in the late 1990s. There is an accelerating rate of genomics research on crop plants and their botanical models which is generating high quality whole genome sequences, expressed sequence tags (ESTs), genome survey sequences, mutant lines, expression profiling resources and downstream tools (for example, the US National Plant Genome Initiative; www.ostp.gov/NSTC/html/npgi2003/index.htm). The initial expectations and achievements of the cross-Departmental US initiative were reviewed in the EASAC report. Since the time of that analysis (late 2003, published 2004), there has been continuing major commitment in the USA to genome sequencing and translational research to transfer the findings from model systems to plants of economic importance. For example, the intention to fund large-scale sequencing of the maize genome was announced at the end of 2004.

There are significant practical obstacles to research on plant genomes, namely their large and variable size (Table 1), the abundance and distribution of repetitive DNA within the genome and their frequent polyploidy. The opportunities and challenges associated with obtaining and using these genomic sequences were recently comprehensively reviewed by Paterson (2006). As Paterson notes, the decision to sequence a crop genome is "*…a complex equation that balances genome size with scientific, economic and social impact; the phylogenetic distance from previously sequenced plants (that is, the new information that is likely to be yielded); relevant information from previous studies (such as the availability of genetic or physical maps); and the persuasiveness of individual (or groups of) investigators.*"

Angiosperm genomes comprise about 14% of the GenBank sequence data (in 2005) – if this rate of sequencing progress were to be maintained, then sequencing of the current universe of about 200 domesticated plants would be achieved by about 2020. It is likely that technology advances in genome sequencing methods will accelerate and further reduce the cost of this progress: the cost per finished base pair has decreased from $10 in 1990 to 1 cent in 2005 (Service, 2006). The $1,000 genome is in prospect, compared to the current cost of $5-10 million per eukaryotic genome, although the cost and timetable for sequencing must also take account of the time needed in re-sequencing to determine the levels and patterns of polymorphism in each gene in the target species.

The occurrence of polyploidy in many plant genomes and the existence of large amounts of repetitive DNA (assumed redundant, but see section 2.4.3) has led to the introduction of strategies to obtain the gene-related information prior to genome-wide information (reduced-representation approaches) (EASAC, 2004). Paterson (2006) compares the advantages and disadvantages of alternative approaches to gene discovery – EST sequencing, methyl filtration and DNA renaturation kinetic methodologies – as well as the different standard approaches to whole-genome sequencing (shotgun versus clone-by-clone sequencing) as exemplified by rice genome sequencing.

The principal genome sequencing efforts underway using public research investment are listed in Table 2. This list is not exhaustive, and other genome research will be mentioned subsequently, but two conclusions emerge. First, there is a lot of activity now underway, mainly focused on those crops of most commercial importance. The species covered predominantly represent the temperate climates and there has been very much less sequencing effort on tropical crops (although coffee is being sequenced). Secondly, groups of researchers still sometimes compete with each other on the same species.

Table 2: Current plant genome sequencing initiatives

Plant genome	Status of initiative
Arabidopsis thaliana	Sequenced. Databases of genetic and molecular biology data, e.g. Multinational Coordinated Arabidopsis Project, www.arabidopsis.org
Rice (2 subspecies)	Sequenced, e.g. Japan Rice Genome Research Program, http://rgp.dna.affrc.go.jp/index.html and International Rice Functional Genomics Consortium, www.iris.irri.org8080/RFGC/
Grape	Pinot noir cultivar sequenced. Italian Government funding plus Myriad Genetics. Sequence not yet published, www.ismea.it
Populus trichocarpa (poplar)	Sequenced. US Department of Energy Joint Genome Initiative (JGI)[3], http://genome.jgi-psf.org/Poptr1/poptr1.home.html
Medicago truncatula (related to alfalfa)	International consortium, scheduled for completion in 2006, www.medicago.org/genome; genomics also funded by Noble Foundation, www.noble.org
Lotus japonicus	www.kazusa.or.jp/lotus[4]
Sorghum bicolour	US Joint Genome Initiative, scheduled for finish in 2006
Lycopersicon esculentum (tomato)	International consortium, sequencing scheduled for completion 2007 http://sgn.cornell.edu/help/about/tomato_sequencing.html. Tomato Expression Database on http://ted.bti.cornell.edu
Maize	US National Science Foundation/DoE/USDA consortium[5], http://maize.danforthcenter.org and www.maizegenome.org
Brassica rapa	International consortium, www.brassicagenome.org
Solanum (potato)	International consortium (including main producers, China, India, Russia, Poland), possible completion by 2008-2010, www.potatogenome.net. Also, US NSF Potato Genome Project (www.potatogenome.org) and Canadian Potato Genome Project (www.cpgp.ca)
Wheat	International consortium, www.wheatgenome.org
Soybean	US Joint Genome Initiative, www.jgi.doe.gov/sequencing plus other work underway in Canadian Initiative

While there is a case to be made for pluralism in funding and in technical approaches, excessive duplication of work may be wasteful, and indicative of fragmented effort. Agencies in the USA do now manifest some strategic coherence and there is effort to align the funding from the European Commission with that committed by EU Member States. But there is room for further sharing of

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[3] Other JGI plant genome initiatives underway include *Mimulus guttatus* and *Arabidopsis lyrata.* In addition, results for ESTs (transcriptome sampling as a complementary approach to genome sequencing) are compiled for many plant species on the general EST database (www.ncbi.nlm.nih.gov/dbEST/dbEST_summary.html). Other relevant genomic databases are reviewed by Varshney et al., 2005.

[4] Key species *Medicago truncatula* and *Lotus japonicus* with relatively small and simple genomes are important models for legume research and also provide a template more broadly for understanding plant-microbe symbiosis. Essentially complete sequences for gene-rich regions of genome will be available in the near future (Young & Shoemaker, 2006).

[5] Using methyl-filtration and high-Cot selection to analyse gene-rich regions, comparing with BAC approaches, maize will serve as a model for other large genomes and maize genome sequencing will also facilitate development of tools and protocols for the larger genomes (Wessler, 2006).

strategic plans and coordinated technical effort at the global level, for example in terms of individual research groups focusing on chromosome segments most relevant to local interests and expertise, with a coherent shared programme in development of tools and standards and integration of research outputs (EASAC, 2004).

2.3 Future sequencing

As Paterson (2006) observes, angiosperm sequencing has started with detailed studies of model species and is spreading outwards across taxa but the benefits of crop genome sequencing might be obtained more quickly by taking a systematic phylogenetic-based strategy to compare sequences, rather than waiting until all the data from approximately 200 domesticated crops can be accumulated. Thus, sequencing of as few as 16 other angiosperms from different genera from taxonomic orders would cover most of the main branches of the family tree.

A strategy to identify a consensus set of priority plant genomes merits further consideration by researchers, their funders and other policy-makers but this selection strategy would need to be supplemented by other research. Broad phylogenetic coverage is particularly helpful in identifying conserved features but lacks resolving power to relate individual features with biological or evolutionary roles. Thus, for example, the comparison of *Arabidopsis lyrata* sequence with *A.thaliana* (or perhaps *Brassica rapa*) might be anticipated to provide better insight on the association of function with DNA polymorphism. The analysis of diversity represented by genetic polymorphism in crop genes is critically important in progressing understanding of functions in crop domestication and trait selection.

Thus, the options to move forward from current genome sequencing plans (Table 2) include the initial, focused, phylogenetic-based strategy to sequence a relatively limited number of representative plant species as an alternative to the default position, a much larger exercise of systematically sequencing all the domesticated species of interest. But, there is a third option – allocating consortia of international researchers to crop species that would be of most immediate practical value globally as a basis for new breeding programmes. In determining how best to use the existing capacity for genome sequencing, it has been proposed that the crops essential to resource-poor farmers should be given highest priority (Raven et al., 2006). Cassava (*Manhiot esculenta* Crantz) is the third most important source of energy in the tropics, after rice and maize, and The Global Cassava Partnership has indicated that cassava presents a major sequencing opportunity because of the large potential for genetic improvement. A start has been made in generating EST and BAC collections and molecular genetic maps that could form the basis for comprehensive sequence analysis and the comparison with other plant genomes provides a route to exploit the biodiversity within cultivated and wild *Manhiot* species more effectively. However, more generally, it is not just the lack of whole genome sequencing that is an obstacle for “orphan” crop research. There is also a paucity of other sequencing research (ESTs, BACs, molecular maps) for crops such as cowpea, common bean, the millets and tef (Delmer, 2005).

Genome sequencing is only the first step in the translation of plant science research into improved farming practice. In practical terms, plant science is beginning to share in the dramatic transformation of the biosciences from fragmented, gene sequence-focused activities towards system integration approaches (European Plant Science Organization, 2005). And in conceptual terms, it is important to guard against the genome sequence being accorded unwarranted dominant status as the sole determinant of biological function (the “blueprint”). There is greater scope for diversity among genes and their outcomes than can be necessarily accounted for by gene sequence alone (Hughes, 2006b).

It is necessary to consider the greater complexities of genome organisation and to employ other Omics technologies to assess functionality – the concept of molecular phenotyping. The technical detail of these individual methodologies is not considered here (see EASAC, 2004), and all of the technologies are evolving rapidly, but some current examples of their application and implications are now presented as a basis for then discussing their likely future impact on the discovery of new gene-trait targets.

2.4 Other technologies and the new biosciences

In addition to considering the newer Omics, brief mention should also be made of other nucleotide-based evaluation approaches that will help to progress understanding of the genome.

2.4.1 RNA interference (RNAi) as reverse genetics tool

The phenomenon of interference was first studied functionally in plants (flowering in petunias in the 1990s), when it was termed post-transcriptional gene silencing. The use of RNAi to eliminate messenger RNA is a novel approach to understand gene function, as an alternative to conventional chemical mutagenesis or the production of DNA knockout mutants, and is potentially a more specific and controllable technique to tune gene function at particular developmental and physiological stages by contrast with complete gene deletion. RNAi as a tool is currently being used in a broad range of applications, and in plant science it is being used to study host plant-pest interactions ("interactomics"), tolerance to abiotic stress and determinants of growth and development. For example, research at the New Zealand National Centre for Advanced Bio-Protection Technologies is exploring plant molecular defence systems for disease resistance and model symbiotic and pathogenic fungal interactions to determine mechanisms of plant-microbe communication (www.bioprotection.org.nz/agri-biotechnology.html).

2.4.2 Mutagenesis

Chemical and physical mutagens have a long history of use in plant genetic research to introduce novel genetic variation and, potentially, crop improvement. More recently, novel approaches combine mutagenesis with sensitive methods to detect induced DNA sequence variation and are contributing significantly to functional genomics by inducing diversity in model and crop species: one of the pioneering approaches is TILLING (Targeted Induced Local Lesions IN Genomes). A recent review (Waugh et al., 2006) comprehensively lists the current experimental resources in mutagenesis, concluding that "*… it is now feasible and realistic to discover stable and heritable genetic lesions in effectively any gene of interest and to study the impact of these lesions on the process under study directly in the crop.*"

The work of the Plant Breeding Unit of the Agricultural and Biotechnology Laboratory of the International Atomic Energy Agency is exploring a large range of radiation-induced mutations to develop better crop varieties relevant to developing countries. For example, recent research in this joint IAEA-FAO programme is supporting generation of saline-tolerant rice varieties and Black Sigatoka disease-tolerant bananas[6].

2.4.3 Examining non-coding regions

While the strategy for rapidly characterising the larger and more complex genomes relies on preferentially sequencing the gene-rich regions of the genome, attention is also turning to consider the structure and functional roles of plant DNA sequences and variation outside the gene regions. Once termed "junk" DNA, it is becoming clearer that the presumed non-coding regions can carry regulatory and protein-coding information[7]. Thus researchers need to be aware that strategies for sequencing large genomes that select against repetitive DNA sequences to focus on single copy sequence (assumed a gene) may miss regions of the genome that are important for explaining phenotypic variation (EASAC, 2004; Morgante, 2006).

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[6] http://www-naweb.iaea.org/nafa/index.html.

[7] For example, among the DNA in the plant genome that does not code for protein, a proportion is copied into non-coding RNAs, including micro RNAs. Micro RNAs can inhibit translation of messenger RNAs and, hence, may have a critical role in gene regulation.

2.4.4 Transcriptomics

The complete set of RNA transcripts produced by an organism at any one time is called the transcriptome and is the link between the genome, the protein complement and the phenotype. Transcriptomics is the study of gene expression patterns and traditionally has used high throughput DNA microarray methodology.

Over the past decade the cost of doing microarray experiments has decreased by an order of magnitude and the information obtained within a microarray has increased at least several fold. Plant transcriptomic resources were reviewed recently by Rensink & Buell (2005) who provided a comprehensive listing of the databases publicly available from genome-wide expression platforms, including: *Arabidopsis,* barley, *Brassica, Citrus,* grape, maize, *Medicago, Populus,* potato, rice, soybean, sugarcane, tomato and wheat. Most of these research projects are being undertaken by consortia. Rensink & Buell identify several strategic needs that must now be satisfied to accelerate functional discovery and begin the process of translational research:

- Generation of reference expression data sets (according to cell, tissue or developmental stage) for each plant species;
- Addition of gene expression data from mutants and treatments that will help to identify biological regulatory networks;
- Coupling expression and other molecular or phenotypic data to reveal the function of unknown genes;
- Consolidation and analysis of multiple datasets to make cross-species comparisons.

2.4.5 Proteomics

Proteomics research, the large-scale analysis of the protein products of genes, has not advanced as rapidly in plants as in model organisms such as yeast. *Arabidopsis* provides an accessible model to study plant proteomics and the comparison with genomic sequencing and transcript mapping. Key plant science objectives and methodologies were reviewed recently by Bertone & Snyder (2005). Broadly, the scientific challenges are to provide a comprehensive identification of proteins and their isoforms in each tissue; to characterise the biochemical and cellular function of each protein; and to analyse protein regulation. One other major challenge for plant (and other) proteomics is the difficulty in generating quantitative data. The current analytical strategies for quantitative proteomics are of three types: (i) Relative quantification, measuring changes in expression level, subcellular distribution, stoichiometry of protein complexes, and most current data fall into this category; (ii) Absolute quantification, measuring how much protein is present rather than its change in concentration; (iii) Kinetic analysis, measuring protein turnover to understand the balance between synthesis and degradation.

If these methodological issues can be resolved, advances in proteomics are likely to significantly improve the understanding of functional pathways and networks, but the field is still at an early stage.

2.4.6 Metabolomics

Metabolomics is the large-scale study of metabolites produced by a species, again usually explored in terms of a particular cell, tissue or developmental stage. Broadly, metabolic analysis can be considered as a range of technical approaches: from the specific analysis of one or more target molecules, through metabolic profiling (determination of a group of components within a pathway), metabolite fingerprinting (direct comparison of plant samples) to metabolomics (qualitative/quantitative analysis of all metabolites present).

Metabolomic techniques are predicted to have major potential in providing molecular definition of complex quality attributes, in understanding metabolic control and metabolic diversity, the processes of plant development, differentiation, interaction with pathogens and resistance to stress. But there are, again, major methodological challenges, especially in generating, comparing and integrating large datasets and in standardising plant growth under controlled conditions to ensure reproducibility in metabolomics[8].

The application of metabolomics may also find a place in the characterisation of GM plants ("predictive genetic engineering"). Hitherto, the safety of a GM crop can only be established by comparison with a reference species (with a history of safe use) in regard to morphology, agronomic features and chemical composition. Metabolomics has the potential for a more precise analysis of compositional similarity (Rischer & Oksman-Caldentey, 2006): proof of principle has been evaluated by metabolite fingerprinting of GM potatoes. It is also relevant to note that the difference in metabolite profiles between related native tomato species is much larger than when a single exogenous gene is introduced by transgenics (European Plant Science Organization, 2005), providing evidence for the relatively rich diversity in natural gene pools.

One other noteworthy novel application of metabolomics is the use of ambient mass spectrometry to analyse plant tissue *in situ* (Cooks et al., 2006). This application has the potential for rapid, high throughput analysis of plant samples, without preparation, in their natural environment, if coupled with quantitative pattern recognition techniques to interpret fingerprints.

2.4.7 Organising Omics information

The power of Omics technologies will only be realised if data can be integrated to yield complementary views of biological processes and their regulation. Datasets have no ultimate value unless properly annotated, verified, stored and rendered accessible over the long term. Omic data are rapidly increasing in volume and diversity, and there are numerous data integration challenges to be faced in relation to ensuring data comparability, format and quality and to devising rules for standardisation, tracking and access. There has been significant progress made in agreeing standards for reporting Omics data so as to facilitate integration from different sources. For example, standards for microarray gene expression data are on www.mged.org and for proteomics data on http://psidev.sf.net but the procedure for developing standards must be made more inclusive with outreach to the global community of researchers. User and funder perspectives must also be incorporated into the development of robust standards so as to support collaboration and effective knowledge transfer.

There is a particular responsibility for public research funders to combine and reconcile twin principles – first, that data from public research should be publicly available and secondly, that maximum socio-economic value is derived from the research. In attaining these twin goals, there is a continuing need for the major funding agencies worldwide to agree long-term goals for developing international databases as a community resource, subject to regular appraisal and peer review and incorporating community consensus standards. While funding agencies are often willing to provide initial investment for databases, the greater challenge is to secure continuing funding for their maintenance to be a viable resource rather than an archive.

Many of these issues have recently been reviewed by the US Agencies NSF and USDA in terms of a Needs Assessment for Plant Biology Databases (see Maize Genetics and Genomics Database, www.maizegdb.org). One priority for the plant sciences community in requiring long-lived data repositories where information is actively acquired, organised, maintained and distributed, is to generate the skilled staff to curate complex biological data.

2.4.8 Systems biology and other modelling approaches

The field of systems biology can be regarded as a development from computational physiology, based on the large-scale, high-throughput collection of datasets and their organisation and interpretation, usually through the application of advanced bioinformatics tools. Systems biology aims to understand

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[8] Methodological challenges are probably best addressed by establishing a critical mass of resources to underpin quality assurance, for example the work of Plant Research International (www.plant.wur.nl/expertise/metabolomics) and Rothamsted Research (www.metabolomics.bbsrc.ac.uk/MET-RD.htm).

the behaviour of dynamic networks through coupling molecular biology with advanced mathematical modelling and usually integrates multiple forms of data (for example, metabolites, transcript profiles, kinetic data). Thus, plant systems biology requires standardised functional genomics tools, standardised plant stock material and a common informatics-based vocabulary to integrate and interpret the research streams.

A recent survey by the World Technology Evaluation Center (Assessment of International Research and Development in Systems Biology, 2005 on www.wtec.org/sysbio/welcome.htm) on behalf of US government agencies reviewed the current status of systems biology worldwide and concluded that progress in plant sciences has been relatively slow, primarily because of insufficient funding. Their recommendations to promote plant systems biology included: focusing on model species (*Arabidopsis*), developing sustained research funding programmes at international level and preparing the next generation of researchers by supporting training in quantitative techniques alongside biology. The first of these recommendations is controversial because there is strong political pressure to move plant systems biology funding to crop species at the expense of model systems. WTEC assert, however, that because quality, quantity and correlativity of experimental data together with an iterative cycle of experimental and theoretical work are critical for success in systems biology, it would be premature to lose the model species focus[9]. This general issue – how best to handle the research transition from model species to crop in the reduction to practice – is a pervasive theme across the interface between Omics and the other biosciences.

Systems biology is also being used to understand plant distribution mechanisms, interpreting the response to environmental challenges in an integrated way from molecular to physiological levels. A study of *Arabidopsis lyrata* subspecies *petraea* is ambitiously combining information from research across ecology, physiology, genomics, population genetics, transcriptomics, proteomics and metabolomics (www.petraea.shef.ac.uk) to investigate the extent to which climate and genetics can explain local adaptations in population range limits.

Computational models aid understanding of plant physiology and behaviour in other ways. For example, a consortium of Dutch and British researchers with EU funding is integrating information from observations of plant growth to create models of virtual plant growth in varying environments with long-term simulation to optimise quality of crop production (www.intesys.co.uk).

2.5 Summary of policy issues

There are technical issues to resolve in taking forward the post-genomic technologies; addressing the technical challenges will also enable continuing progress in reducing technology costs, thereby bringing new applications within range. For the policy-maker, there are choices to be made – in apportioning effort between model systems and crop plants, in prioritising crop genome sequencing based on societal as well as technical criteria, in creating shared platforms for technology development and training.

Some may query whether it should be a priority for developing countries to seek to bridge the current “genomics divide” by capacity building in the discipline of genomics itself, perhaps seen as relatively remote as a research area from practical applications. These reservations may be short sighted, for genomics research is a flexible resource. A decade ago, support for genomics would have required major investment and elaborate infrastructure but now genome sequencing is a relatively straightforward activity, relatively easily performed. Investment in fundamental genomics can inform a range of applications and, in terms of the utility of the underlying technology, can address a range of societal objectives, in healthcare as in agriculture.

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[9] Examples of what is currently being done on metabolic networks in model perturbation studies using *Arabidopsis* are illustrated by the leading research groups on primary metabolism at Max Planck Institute of Molecular Plant Physiology in Germany (www.mpimp-golm.mpg.de) and on secondary metabolism at Kazusa DNA Research Institute in Japan (www.kazusa.or.jp/eng/index.html). Researchers are also modelling regulatory networks in developmental processes. For example, The Computable Plant consortium (www.computableplant.org) is attempting to model development of *Arabidopsis* shoot apical meristem (the precursor of leaves and flowers).

Whether or not developing countries chose to build expertise in genome sequencing, there is a growing rationale to invest in molecular phenotyping as a critical local asset in order to understand gene function. For the policy-maker, there is need to support standardisation of tools and resources for the emerging technologies such as proteomics and metabolomics, and to ensure the appropriate management, accessibility and sharing of information within community databases and across disciplines.

CHAPTER 3: CAPITALISING ON ADVANCES IN GENOMICS

3.1 Scientific targets: genes and traits

Plant traits depend on genes and gene networks responding to their environment. Genomics and other Omics technologies can be used to tackle a wide range of problem-oriented goals in order to begin to understand intra- and inter-species variation and to effect rational improvement in crop species. The EASAC (2004) report provides an introduction to some goals for Europe. Many of these goals have a global relevance but it is important also to consider developing country specific needs, not only with regard to crop species but also with regard to current problems and desired traits. In particular, in parts of Africa and some other developing regions, where few farmers have access to irrigation or chemical input, farmers' actual yields are typically a small fraction of the genetic potential: "*In this situation, research may be more efficiently directed at closing the yield gap by focusing on growth- and yield-limiting and growth- and yield-reducing factors*" (InterAcademy Council, 2004).

What scientific opportunities are now coming into range? Advances can be expected across the broad front of plant biology:

- Clarification of cellular processes and architecture underlying plant growth and development, from intracellular protein trafficking and cell-to-cell transport processes through to photosynthesis and reproduction;
- Identification of expressed genes controlling complex plant structures and understanding of their coordinated interactions;
- Elucidation of molecular and homeostatic mechanisms by which plants coordinate their response to external signals such as light, water, ions, pathogens and insects;
- Elaboration of modes and routes by which materials are stored in cellular bodies, including understanding of those processes controlling the nutritional value of plants.

The degree to which knowledge of model systems such as *Arabidopsis* can be generalised to the more complex crop genomes depends on the closeness of the evolutionary relationships. Regulation of many processes, particularly for specialised storage structures (responsible for oil and grain quality) require the direct study of crop species (EASAC, 2004).

Further insight into the association of genes and traits is emerging from research on crop evolution by mapping of the major gene loci implicated in the domestication of species associated, for example, with larger seeds and fruits, trends to annuality, more uniform germination and ripening. It has been observed that many of the specific transitional features in domestication from wild species – such as seed non-shattering to increase the proportion of seed harvested – are regulated by a small number of genes, enabling rapid evolutionary change (Hancock, 2004). One molecular determinant of reduced shattering from rice grains was recently clarified in terms of evolutionary selection undermining the normal development of an abscission layer that controls separation of the grain from the pedical (Li et al., 2006). Plant domestication Quantitative Trait Loci (contributing to major traits) have now been identified for rice, maize and tomato, encompassing six domestication genes, of which five encode transcription factors (acting to regulate other genes). This may represent a broad new opportunity for plant breeders – creating systematic variation in other transcription factors in the genome in order to generate a pool of new trait variation (Doebley, 2006).

Recent examples from key research areas are discussed in Appendix 1 to illustrate the scientific questions that can now be tackled at the interface between functional genomics and the other biosciences, particularly biochemistry and physiology.

3.2 How will molecular techniques improve plant breeding?

Virtually all plant breeding activities can be said to have made at least implicit use of genomic information (Reece & Ejnavarzala, 2006). But there is now the opportunity to use this information much more explicitly. Advances in genetics and genomics are providing the tools to elucidate structure and function, thereby identifying target traits. Molecular markers are identifiable DNA sequences, linked with key genes and thereby associated with particular plant traits, which can be used in breeding programmes to predict the presence of that trait. The practical value of molecular markers is increased by synteny, the similar ordering of genes in different species, so that a marker identified in one species may mark the same trait in other species and an application in orphan crops can capitalise on previous investment in crops of commercial importance (Chataway, 2005). The main benefit of incorporating marker-assisted selection (MAS) into traditional plant breeding is to increase the scope and efficiency and accelerate the programme, in part by reducing the need for time-consuming field evaluation in selection (Reece & Ejnavarzala, 2006). MAS is particularly useful in those conditions where screening the phenotype is difficult or impossible, for example in screening resistance to pests or disease.

The extent to which the genomics revolution will create change in conventional breeding activities will vary according to species but a generic question is applicable to all crops (Koebner and Summers, 2003): *"Anticipating a lifting of the technical and financial limitations to molecular marker- based genotyping, the question of how to bolt-on a small element of MAS to a conventional breeding programme changes into one that asks in what way the field-based activities that characterise the present paradigm will (or should) be adjusted to take advantage of MAS."* For wheat breeding, there has been a relatively slow uptake in the use of MAS. Koebner and Summers warn that if large scale MAS deployment were to dominate wheat breeding programmes then there is danger of losing the holistic advances achieved by previous phenotypic selection and there is risk of generating varieties that then become vulnerable to future shifts in production system, climate or end use. The challenge is to mitigate this danger by interpreting the promise of genomics in terms of the well-phenotyped product. The substantial use of MAS in maize breeding has occurred much faster[10]; rice is an interesting example where the early advances in genome sequencing should promote the application of MAS. Considerable progress has been made in the pyramiding of disease resistance genes, particularly to rice blight and blast. One other recent example of molecular breeding pyramiding traits in rice is the pioneering work of Ashikari and co-workers (2005), combining loci for grain number and plant height in the same genetic background and generating lines exhibiting both beneficial traits.

Delmer (2005) reviews other advances in the use of MAS noting that the USDA Program for Coordinated Agricultural Projects will support translational genomics for crop improvement in cotton, soybean and barley but that public sector funds are lacking in support of efforts to identify and implement connections between upstream science and downstream applications for developing countries. Private, multi-national, company interests mostly do not extend beyond cotton, maize, canola and soybean.

In terms of the possible timetable for the translation of the new research opportunities into improved crops, the European Technology Platform roadmap indicates that significant progress in understanding the molecular determinants and their regulation could now be achieved by the leading research centres within five years; selection and validation of molecular breeding technologies within 10 years and production of novel cultivars within 20 years. Slightly longer (25 years) may be needed for transformation of wild species into new crops through molecular breeding for domestication traits. Proof of principle in selected cases may well be achieved sooner, particularly in light of the

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[10] Koebner, R. MAS in cereals: green for maize, amber for rice, still red for wheat and barley, on www.syngentafoundation.org/syngenta_foundation_plant_genetic_resources_biodiversity.

accelerating pace of technology change but the processes involved in knowledge transfer to farmers in developing countries are likely to remain rate limiting.

More precise breeding strategies will be aided by selection strategies using the DNA sequence within specific genes controlling the desired trait rather than use of a contiguous DNA linked marker sequence, but high costs currently limit the implementation of genomics-assisted crop improvement, particularly for crops that are not considered as commercially of high value. Marker assisted selection will evolve into the more specific genomics-assisted breeding for crop improvement (Varshney et al., 2005). Assuming that high throughput advances in sequencing technology development continue, and building on the accumulation of knowledge on functional polymorphism from comparative plant genomics, it can be predicted that the understanding of gene function "*…will bring crop improvement to a level of determinism that reaches well beyond the …advances that are associated with marker-assisted selection"* (Paterson, 2006).

The potential for capitalising on new genomic information deemed relevant to developing countries has been reviewed by Babu and co-workers (2004). First generation products from the use of MAS included the induction of resistance to soybean cyst nematode and induction of drought stress tolerance in maize as well as the rice pyramiding traits. These applications have progressed relatively fast because of their value to developed countries as well as developing countries. For the future, for developing as for developed countries, use of functional genomics information, in particular the quantitative assessment of gene transcription, based on RNA expression profiles, will be as important, if not more important, in selecting breeding lines than use of marker genotypes (Babu et al., 2004).

Some examples to illustrate this future potential are discussed in Appendix 1.

3.3 Enhancing conservation – molecular markers and characterisation of genetic resources

For strategies to be successful in identifying and studying genes associated with key traits as a tool in improved breeding, a diverse source of germplasm is usually required. Genomic technologies are also of critical importance in contributing to the characterisation, conservation and management of plant genetics resources in national or other repositories of cultivars[11] and those collections of plant genetics resources are vital in enabling plant breeders to respond to farmer's current needs and to prepare for changes in climate, agricultural practice or market requirements. The value of collections in furnishing wild relatives to transfer desirable traits to crops is well exemplified by the work of CIMMYT using *Triticum polonicum* to increase wheat spike size, ICARDA in transferring stripe and leaf rust resistance from wild *Triticum* species and from *Aegilops speltoides* into durum wheat and IRRI incorporating disease and pest resistance traits from wild into commercial rice species[12].

A major international policy goal must be to preserve the current agricultural genetic diversity in germplasm banks, *ex situ* and as growing crops, *in situ*[13]. As most angiosperm seeds can be stored in a viable condition for many years under appropriate conditions (low temperature and humidity), the establishment of well-catalogued seed banks provides a highly valuable archive and resource for research and breeding (Paterson, 2006)[14].

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[11] Genetic resources can be defined as "genetic material of current or potential use". Many countries are now developing a more comprehensive policy on conservation and sustainable use of genetic resources for food and agriculture (e.g. UK on www.defra.gov.uk/farm/geneticresources/index.html), in part to implement international commitments driven by the Convention on Biological Diversity and the International Treaty on Plant Genetic Resources.

[12] www.cgiar.org/monthlystory/july2006.html.

[13] A recent publication (Smale, 2005) describes empirical work for valuing and managing crop biodiversity *in situ* on farms, analysing a set of case studies implemented with international partners, usually IFPRI, IPGRI or FAO. Such work is important to evaluate economic value of biodiversity and help provide a context for the ethical, political and scientific complexity of the issues arising from farmers' rights legislation.

[14] Developing new and better methods of storage is also important for some plants. For example, bananas are a major crop (economically, the world's fourth most important) but cannot be stored in conventional seed banks. A comprehensive collection of banana varieties is an essential resource to help adapt current strains to counter new disease threats such as Black Sigatoka. An international consortium is now capitalising on advances in freezing technology to conserve bananas and other tropical crops such as cassava and taro (that also reproduce without producing seed) (Shanahan, 2005).

Some key issues for maximising effectiveness of current and future banking efforts are described in greater detail in Appendix 1.

3.4 Summary of policy issues

For the policy-maker, it is important to ensure that the efforts to build cross-disciplinary teamwork in the biosciences (section 2.5) extend to include the disciplines involved in target selection and validation. There is a major challenge to be faced in handling the very large volumes of data now being generated in discovery research, in order to ensure selection of the most promising translational research leads that are "fit for purpose" in terms of practical input into crop breeding programmes. The complexity of dealing with the rapidly increasing outputs from crop plant genomics will be compounded by the rapidly increasing outputs from microbial genomics – this is the challenge of interactomics, to decode plant-microbe interactions.

Better coordination and coherence in public sector R&D support must be accompanied by better engagement with the private sector R&D efforts to ensure that tractable objectives for developing country crop improvement can capitalise efficiently on the spill-over from advances in science and technology elsewhere. A strategy to tackle research bottlenecks in the areas covered by chapters 2 and 3 would benefit from establishing a common resource of a database to share pre-competitive information – to prevent wastage of resource in unnecessary duplication of endeavours and in following discredited research leads. It is a challenge for public sector policy-makers to convince private sector companies to share their pre-existing pre-competitive data and to embark on concerted work in new pre-competitive areas. This issue will be discussed further in the final chapter: there are significant opportunities for public-private sector consortial work in plant genome sequencing, determination of polymorphism, analysis of gene transcripts, proteins and metabolites and target finding for orphan crops.

In order to build consensus on genotype-phenotype target priority setting, policy-makers also need to do better in standardising and using methods for assessing socio-economic value of the targets. But there is a dilemma. Estimating value is most difficult in areas of uncertainty, perhaps particularly in seeking preparedness for climate change (Appendix 1). Yet, the R&D strategy must be implemented before the uncertainty is resolved.

The public policy issues associated with the maintenance and use of conservation resources have already been well described by FAO. All collections require continuing attention in terms of their funding and management issues and their access and benefit sharing issues. Some of these issues are accentuated by the developments that will make the collections most useful as a resource to support the biosciences advances described. Introduction of standardised molecular marker technology-based characterisation of the genetic resources and the inception of DNA banks (Appendix 1) to complement seed/plant collections bring new pressures for both resource management and for benefit sharing.

CHAPTER 4: TRENDS IN INVESTMENT

4.1 Public sector investment in agricultural R&D

A comprehensive account of agricultural R&D investment was published relatively recently, based on ASTI analysis (CGIAR, 2005) although systematic data comparison is only available up to the year 2000. Among key points emerging were:

- Worldwide, public investments in agricultural R&D increased by 50% in inflation-adjusted terms between 1991 and 2000. During the 1990s, for the first time developing countries as a group conducted more public agricultural research than developed countries.
- Two countries, China and India, account for 40% of developing country expenditure; sub-Saharan Africa continued to decline in relative terms (and some countries were spending less in absolute terms over the decade). Agricultural R&D had become increasingly concentrated

in a few countries, primarily USA, Japan, France, Germany, China, India, Brazil, Thailand and South Africa. Growth in spending has been relatively robust in the Asia-Pacific region and in Latin America.

- There had been a relative contraction in public funding for agricultural R&D in developed countries, particularly in Japan and Europe. In part this reflects the shift from public to privately performed R&D and in part a change in government priorities. Furthermore even where developed countries are spending public money on agricultural R&D, priorities are changing away from a focus on increasing productivity in staple crops and towards a focus on environmental effects and food quality.
- In 2000, 94% of private agricultural R&D spending was performed in developed countries where, on average, 55% of total spending is by the private sector. In developing countries, on average only 6% of agricultural R&D is in the private sector (with large variations, from 8% in the Asia-Pacific region to 2% in sub-Saharan Africa).
- Aid funding priorities over the period up to 2000 show a withdrawal of support from agricultural R&D, particularly so for sub-Saharan Africa.
- The CGIAR system accounts for only a small fraction (1.5%) of global agricultural R&D expenditure although CGIAR spending more than doubled over the period 1980-2000 in real terms. Since 2000, CGIAR funding has grown moderately but with a continuing trend to hypothecated support for specific projects that involve multiple CGIAR or other research centres.
- At the national agricultural research level, there is an increasing tendency to focus on systems rather than research institutes, to include universities, the private sector and other stakeholders. National research systems have begun to organise within regional networks and to provide linkages with those involved in downstream applications.

The CGIAR 2005 report augments the earlier ASTI report "Slow Magic" (Pardey and Beintema, 2001) sounding an alarm call – that at the time of the new millennium, public investment and institutional initiatives for R&D in some developing countries were declining. The trends in funding may actually have understated the gap in scientific knowledge between developed and developing countries because science is a cumulative endeavour and there is need to have policies, precepts and practices to increase the stock of knowledge and accumulate innovations. Discoveries and data tacit to the individual researcher, if inadequately recorded, are lost to the next generation. The authors of "Slow Magic" called for a sizeable and sustained effort to reinvigorate support for science in under-performing developing countries.

4.2 Addressing fragmentation of research and lack of critical mass in public sector R&D

The enthusiasm for investment in genomics and cognate biosciences is too recent to be measured in the ASTI data and plant genomic sequencing represents only a relatively small part of the total plant sciences/agricultural R&D enterprise. Indeed, genomics and other fundamental research may not be conventionally counted together with the applied sciences in calculating net investment. What is clear is that private sector investment, both in basic genomics and in technology development and applications, continued to be comparatively dynamic and there is ongoing risk that public policy makers lose control of the research agenda.

The EASAC report (2004) discussed some of the funding challenges for Europe and, to a significant extent, the EASAC conclusions can be extrapolated globally. There is need for increased funding to generate and capitalise on the scientific advances but it is also important to reverse the fragmentation of research activity that has led to duplication of effort, waste of resources and neglect of important areas. At the European level, there is now prospect of better allocation and coordination of research resources in consequence of the ERANet Plant genomics programme and the European Technology Platform "Plants for the Future". These initiatives may also serve as models for international collaboration – developing good practice for coordination between current programmes and for initiating joint work in priority areas.

Data on some of the leading research initiatives are summarised in Table 3. In addition to government sources of funding there is significant investment by some Foundations, for example the Rockefeller, Noble and Syngenta Foundations, in generating and using genomics research outputs.

Table 3: Examples of government expenditure on research in plant genomics and allied biosciences

Funder	Scope[15]	Funding
Member States of EU (data from www.erapg.org)	Mainly wheat, maize, barley, rye, oat, rice, sorghum, millet plus grape, forage grass	Total approx $600 million over period 1999-2004. Currently about $130 million year (not counting all staff costs)
European Commission	ERANet Call for proposals in plant genomics Plants for Future Technology Platform	$40 million in current round Funding to be determined but significant company contribution anticipated
US National Plant Genome Initiative (multi-agency)	Major programme on genomics (e,g. maize), functional genomics (*Arabidopsis*), application of technology to crop plants and training	Estimated $1.3 billion over 2003-2008
Canadian Crop Genomics Initiative[16]	Canola, wheat, soybean, corn	$70 million for plant genomics
Australian Centre for Plant Functional Genomics[17]	Wheat, barley	$40 million over 5 years (part funded by grain companies)
South Korea	Crop Functional Genomics Centre	Plant genomics $50 million, plant sciences $160 million
Japan	RIKEN plant science and plant genomics centres	Plant genomics $80 million

Some developing countries have indicated significant plans for growth in public sector research in the general area. For example, South Africa is committed to increase total public spend on R&D from a current level of 0.8% of GDP to >1% and plant biotechnology is a designated priority. While details remain to be clarified, this intention to spend more can be contrasted with the decline in R&D in South Africa in the period up to 2000 as noted by ASTI. Nigeria is planning to create an endowment fund for science and technology worth up to $5 billion, enabling $500 million to be spent annually on research, with agricultural biotechnology as one priority area; this funding may prove to be especially valuable if, as indicated by initial news reports, the money is allocated via a relatively independent national science foundation according to a peer reviewed, competitive grant scheme. Public sector R&D budgets for China are not differentiated in terms of plant science/genomics but total R&D spending is expected to quadruple from 2005 to 2020 and genomics/proteomics is a stated priority. Vietnam will spend >$60 million over the next 15 years on agricultural biotechnology including GM-crops and part of this investment will be used to train scientists. Mexico recently allocated $250 million to agricultural R&D, focusing on alliance building between national research centres and producers.

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[15] See Table 2 for corresponding scientific detail where applicable.

[16] http://res2.arg.gc.ca/science/genome2_e.htm

[17] www.arc.gov.au/grant_programs/centre_plant.htm

4.3 Private sector R&D and its support

The commercial world seed market is currently assessed at about $30 billion (Smolders, 2005). Systematic compilation of data on private sector investment in specific R&D projects is difficult, but there can be no doubting the scale of private sector activity. For example, in one company, Pioneer (Dupont), a worldwide germplasm base in the winter, spring and durum wheat classes is used to make more than 3,000 new genetic combinations per year[18]. The R&D budget of each of the leading multi-national companies is greater than the total budget of CGIAR (Chataway, 2005).

In the annual survey of publicly traded biotechnology companies, 309 firms collectively spent $16 billion on R&D but, of these, only 3% are agribiotech companies. Monsanto, Pioneer and Syngenta are regarded as the market leaders as biotechnology-agrochemical companies. For example, Monsanto total R&D spending in 2004 was $511 million (Lahteenmaki & Lawrence, 2005), representing 9% of net sales (seeds and genomics products account for approximately 60% of net sales; www.monsanto.com). Syngenta R&D spend in 2003 on seeds was $127 million and on plant sciences $146 million (by comparison with $454 on crop protection).

Apart from a dominant role for the multinational biotechnology-agrochemical companies, the industrial sector encompassing plant genomics and breeding is complex and segmented. Cereal breeders tend to invest heavily in research, including genomics, but developers of fruit and vegetable varieties have historically not invested in genomics (www.erapg.org)[19]. Agrifood company research rarely covers plant genomics (Nestle is an exception) possibly because of concern about consumer hostility, conflating genomics and GMOs. Specialised bioscience companies, often starting as spin outs from universities or public research institutes perform a range of functions in supplying technology (genomics, other Omics) or specific tools (such as mutagenesis or data mining)[20].

As noted previously, investment by the private sector in developing countries is usually limited. Among recent initiatives is one by The Rockefeller Foundation and other donors to establish Africa Agricultural Capital in Uganda to invest in small agriculture-related businesses that show potential to expand in developing products and services for small-scale farmers in East Africa (www.rockfound.org/Agriculture/Announcement/134). UNESCO recently reviewed the role of Technology Business Incubators in developing countries to provide a link between knowledge production and knowledge diffusion, by state-sponsored provision of physical space, shared facilities and support for other private sector innovation activities (Lalkaka, 2006). Sharing examples of good practice in incubating technology in smaller companies and supporting national and international networking between incubators are also important elements in any strategy to create more sustainable enterprises in developing countries. Other countries might also benefit from adopting the US Small Business Research Initiative in which government departments are required to spend 2.5% of their R&D budget in procuring research from smaller companies.

4.4 Cost-benefit issues in setting the research agenda

The investment data from the public and private sectors illustrate some of the trends in R&D input but, of course, it is also highly important to make best use of the funding available by wise choice of R&D projects, by flexible management of the science, using appropriate methods, tools and technologies, and by ensuring that research outputs are disseminated by engaging with all relevant stakeholder groups.

How should research priorities be chosen? A societal need may not yet be soluble. Choice of research project must be determined by the scientific opportunity – in terms of creative ideas, talented

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[18] www.pioneer.com/usa/research/whefacts.htm.

[19] This situation may be changing. For example, the not-for-profit international vegetable research institute AVRDC (www.avrdc.org) has an annual budget of approximately $10 million from donors. Its medium term strategy involves MAS to create new inbred lines, populations and hybrids to expedite variety development by both private and public sectors.

[20] The small company sector is dynamic and companies with specialised functions will collaborate. One recent example is Evogene and Biogemma, both engaged in genomics and genetics research who are collaborating on developing commercial maize lines with improved drought tolerance.

researchers, and advances in technology. Research funding is often most successful when responding to investigator-led research proposals and researchers can be deterred by excessive specification of targets, yet there is need for strategic prioritisation according to societal need in an environment of finite financial resources. In setting the research agenda, it is equally important for policy-makers to guard against an excessive enthusiasm for technological novelty, the influence of vested interests and short-term political pressures.

While debate concerning R&D in both developing and developed countries is dominated by pleas to increase investment substantially, socio-economic impact is rarely considered. The implicit assumption is that additional R&D expenditure will command a sufficiently high rate of return in agricultural productivity (Roseboom, 2003). In reality, the selection of R&D projects will never be perfectly efficient because of imperfect information and distortions in the selection process. Moreover, as selection efficiency tends to be lower in developing countries, improving the selection process would help to reduce under-investment in agricultural R&D.

CGIAR has an unrivalled reputation and a long track record in supporting science for better crops (approximately $7 billion in 1990 dollar-equivalents since its inception). According to CGIAR impact assessment, a plausible scenario of benefits achieved, yields a return on investment of approximately nine-fold, presumed to be an under-estimate since much of CGIAR work has not been subjected to large-scale *ex-post* economic assessment (www.impact.cgiar.org). Looking to the future, concern has been expressed (Hughes, 2006a) that the Generation Challenge Programme ($8 million a year; www.generationcp.org) is severely under-funded if it is to capitalise effectively on the advances in molecular biology. This is a concern that needs to be addressed because it is important for efforts to be optimally effective as well as economically efficient.

4.5 Regional and other partnerships to tackle the needs of developing countries

The value of improved selection of research projects and programmes (and decreased research duplication) could be augmented by more coordination at regional and international levels. As an example of what is becoming possible in consequence of genomics research, the leading international crop research centres in rice (IRRI) and maize/wheat (CIMMYT) recently announced a linked research programme to compare genetic and biological data to provide integrated information on all three crops to plant breeders. At the regional level, it has been suggested that South Asian countries could do more to cooperate in agricultural research perhaps via a South Asian Union, modelled on the European Union and a regional collaboration may also then form a stronger basis for partnership with international bodies such as CGIAR (Padma, 2006).

Ayele and co-workers (Ayele et al., 2006) recently surveyed crop biotechnology partnerships (including those using MAS) in Africa, mainly Kenya but including some other sub-Saharan countries. The main features of these partnerships are found to be: (i) Projects are usually small, loosely organised and financed by donors, bilateral, multilateral or private sector (such as Rockefeller and Syngenta Foundation); (ii) Profit-making private sector participation is rare; (iii) Some partnerships develop a significant advocacy role (for example AfricaBio and the Kenyan African Biotechnology Stakeholders Forum); (iv) Partnerships tend to be science-driven not user-led, they often do not prioritise need assessment and delivery systems and are only weakly linked to food production innovation; (v) Biotechnology partnerships tend to originate outside national agricultural systems and are not clearly linked to national development goals; (vi) Donors tend to select countries with some existing capacity in agbiotechnology, countries with a weak science base may be excluded. Taken together with other analysis (for example, Chataway, 2005; Hall, 2005) this survey provides some important lessons for policy-makers in terms of what is still needed to provide a coherent framework for research investment priority setting and the coordination of projects to help mobilise resources.

Now is a particularly opportune time to learn those lessons and avoid repeating earlier mistakes on a larger scale. As noted previously, external interest in investment in agricultural development in Africa declined during the 1980-1990s but there is now some resurgence of interest although this interest may not yet be matched by a significant increase in spending on agriculture (according to analysis by the Future Agricultures Consortium, www.futureagricultures.org/hot_topic.html).

Pluralism in R&D funding is highly valuable and it is necessary to experiment with different approaches to linking researchers, breeders, farmers and policy makers in order to identify good practice for technology transfer in differing circumstances. However, it is also important to be aware of the risk of a plethora of competing, overly ambitious, under-resourced initiatives proceeding in an uncoordinated manner.

4.6 Summary of policy issues

For the policy-maker, there is a wide range of strategic support mechanisms that compete for attention. There is need to increase public sector R&D investment to capitalise on the new era of R&D opportunities. Commitment to increased funding must be accompanied by resolution to reduce fragmentation. An effective use of public funds may also be accomplished by provision of appropriate incentives and support mechanisms to encourage the private sector to spend more on R&D in ways that do not impede the public sector. The various models of consortia (for example, EU Technology Platform and ERANet, US multi-agency approaches) may provide new options for the effective use of research budgets.

In order for these strategic choices to be properly informed by the evidence, there is need for better statistics on current trends in R&D spending, to cover all relevant science disciplines and sectors. The momentum to spend more on R&D should also be accompanied by improved procedures and evaluation methods for research agenda setting and measuring impact.

CHAPTER 5: FACING THE CHALLENGES TO ACHIEVE FOOD SECURITY AND SUSTAINABLE DEVELOPMENT

5.1 Genomics and the public provision of global goods

Much is being accomplished scientifically to provide valuable tools for plant breeding but there is still need for better delivery mechanisms to address the major challenges for crop improvement inherent in the Millennium Development Goals. The relationship between plant genetic resources and the biological technologies that use them, and the juxtaposition between the International Treaty on Plant Genetics Resources for Food and Agriculture, the Convention on Biological Diversity and the systems for protection of Intellectual Property Rights have been comprehensively reviewed by Esquinas-Alcazar (2005). Genomics research represents a long-term investment in R&D, it requires multi-disciplinary expertise and its outputs are of global value. Therefore, genome sequences (and their functional characterisation) may be deemed to be international public goods, particularly for those crops covered under the multilateral system of the International Treaty on Plant genetic Resources (FAO 2002a Annex 1). What then are the implications for freedom to operate, intellectual property rights and benefit sharing?

It may be that the strategic management of plant genomics R&D in delivering public goods can benefit from experience gained in other sectors, in particular in the health care research sector. Sequencing the human genome was a very considerable research undertaking. Once the potential value and technical feasibility of sequencing the human genome was grasped, discussion between research funders, and at the political level, led to consensus that the information generated must be available to all in the scientific community. This assumption – that data should be shared – extended to subsequent initiatives exploring the value of variation in sequence data for therapeutic purposes (for example the HAPMAP project to map and make freely available data on DNA sequence variation, www.hapmap.org). One initiative was particularly noteworthy – the Single Nucleotide Polymorphism consortium – because the private sector (pharmaceutical companies) as well as the public sector participated (and led) the consortium, engaged in collective research and dissemination of the results to all.

During the last decade in the health care research sector, the concept of shared pre-competitive knowledge has expanded – extending downstream from the most basic of research towards potential areas of application. For example, in pharmaceutical R&D, companies are now engaging collectively together with the public sector to explore determinants of biological efficacy and safety in specific therapeutic areas as illustrated by the recent inception of the joint European Commission-industry funded Innovative Medicines Initiative. Collective effort and the sharing of results can be viewed as mutually beneficial for all involved (outweighing the temporary loss of competitive advantage occasioned by disseminating the results freely) – in progressing research more rapidly, in capitalising on expertise in complementary areas and in setting the standards that will dictate future research directions.

Other recent biomedical research initiatives that help to define and promote collaborative research to deliver public goods include:

- Mouse mutagenesis – a new international project to generate at least one mutation in each of the more than 20,000 genes in the mouse and to make available to all researchers. This represents the largest international research collaboration in biology since the Human Genome Project.
- Guidelines for sharing data in large-scale biological research – bringing together the perspectives from the producers of genomic data, their funders, users and scientific journals to standardise principles for community resource projects (www.wellcome.ac.uk/doc_wtd003208.html). It is likely that there will also be a global code of conduct for data sharing, developed in consequence of current discussions with others including WHO and the Gates Foundation.
- Global initiative on sharing avian influenza data – a joint effort by FAO and OIE will systematically make avian influenza virus sequences accessible to the entire scientific community (www.fao.org/newsroom/en/news/2006/1000374/index.html) as a critical part of the global work on the surveillance and control of the highly pathogenic H5N1 virus, and support for preparation of human vaccines. A multidisciplinary consortium of researchers (spanning the areas of human and veterinary medicine and Intellectual Property) to improve the sharing of H5N1 data and analyse findings has jointly created the Global Initiative on Sharing Influenza Data (www.gisaid.org) - and this is being hailed as a model for future initiatives.
- The Biomarkers Consortium – a recently announced (October 2006) collaboration in the USA between the NIH, FDA, nine pharmaceutical companies plus trade bodies and patient groups with an initial investment of $5 million to find and validate disease markers. The Consortium has published its general Intellectual Property and data sharing principles[21] to cover both pre-existing data and Intellectual Property and new data/inventions produced by the Consortium (when a non-exclusive research license for the inventions will be made available to those outside the Consortium).

5.2 Making products available to society – freedom to operate and benefit sharing

The consortial initiatives described in the previous section have had one other impact – in beginning to change thinking on what is patentable. This comes at a time when progress in technology practice (for example, the increasing ease of sequencing) is already changing the effective standard for patent protection – raising the threshold for what is now considered obvious and cannot be patented. Before considering the broader issues for Intellectual Property Rights, one other point should be emphasised. Knowledge transfer is often considered primarily – if not exclusively - in terms of the formalised ownership of information (IPRs). Yet it is important to realise that the transfer of knowledge is best carried out by the movement of people. The implications for training and mobility to support knowledge transfer will be covered subsequently and a case can be made for developing a new role in R&D, that of "translator" of research, to catalyse the reduction to practice.

5.2.1 Public commons, private domains and effects on innovation

In terms of the formal mechanism for claiming and transferring property rights, IPRs in the area of plant sciences take several forms: patents, plant variety protection certificates, plant breeder's rights

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[21] www.fnih.org/Biomarkers%20Consortium/IP_Policies.pdf

and trade secrets. The criteria for eligibility for protection vary between countries according to cultural, historical and economic factors although there is increasing harmonisation of laws and rules[22]. Ideally, the legal protections bring certainty to innovation processes, secure an efficient distribution and transfer of technical knowledge, create an efficient market in ideas and facilitate networks, from invention to innovation to market.

All members of the World Trade Organisation are committed eventually to complying with the Trade-Related Aspects of Intellectual Property (TRIPS) although the status of plants as patentable subject matter remains controversial. Rights to intellectual property are confined to the jurisdictions where they are granted. Currently there are relatively few plant patents in developing countries so that the researcher's freedom to operate in these countries is not necessarily the main issue (Pardey & Beintema, 2001). However, the lack of established IPR systems in some developing countries may then present a major barrier to creating partnership between the public and private sectors and to knowledge transfer more generally. The initiative by the World Intellectual Property Organisation (WIPO) to pay greater attention to the interests of developing countries in support of sustainable development, to encourage participation by local communities in WIPO activities may be helpful (Shetty, 2005). Although the processes of implementation of IPR regimes, like other regulatory regimes, can be costly for developing countries and for their public research institutes and smaller companies, there are opportunities for coordinated action at the regional level, "*Public-good agricultural research in Africa will miss the opportunities of the new genetics without concerted regional efforts to economize on the requirements of establishing the regulatory regime.*" (InterAcademyCouncil, 2004).

While IPRs do provide incentive to innovate and to reveal knowledge, a proliferation of patents makes it increasingly difficult for both public institutions and private start-up companies to participate in research. Moreover, the aims of companies may be difficult to reconcile with the rights of farmers who maintain many of the landraces on which improved varieties depend (Pardey & Beintema, 2001). As patenting become prevalent, the number of separate rights needed to construct an innovation proliferates and multilateral bargaining can become difficult (discussed in Knight, 2003 and EASAC, 2004). If multiple owners each have the right to exclude others from use of the resource then no one has an effective privilege of use (Verbeure et al., 2006). In consequence, there is danger of under-exploitation of the totality of the IPRs obtained, termed the "tragedy of the anticommons" (Heller & Eisenberg, 1998). While there are actually few, if any, well-validated examples of this problem, it would seem to present a particular obstacle for resource-poor communities and decentralised partnerships.

5.2.2 Models of access and appropriation

What then are the potential solutions for devising proportionate regulation; that is, how can the conditions for freedom to operate be improved? There are several instructive models:

Patent pool – multiple patent holders could enter a patent pool (by analogy with a model established for the electronics and communications industries), to agree to licence patents to each other and to third parties. Guidelines have now been established by US antitrust agencies and the European Commission to deal with any anticompetitive potential of multiparty licensing agreements (Verbeure et al., 2006). One specific application of this model is illustrated by the history of Golden Rice.

Technology brokering – initiatives such as AATF are helping to find new ways of transferring patented technologies from companies in developed countries to the public research sector in Africa. Such initiatives aim to do more than provide access, on a royalty-free basis, to IPRs by also providing the matchmaking, stewardship and guidance necessary to ensure success of technology transfer (CGIAR, 2005). Other technology brokering initiatives, for example the Public Intellectual Property Resources for Agriculture (www.pipra.org) support open access databases of patented material (originating from either public or private sector).

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[22] The resource portal supported by the International Centre for Trade and Sustainable Development (www.ictsd.org) provides comprehensive coverage of IPR issues in food and agriculture on www.iprsonline.org/resources.

The impediment for knowledge transfer is not, however, confined to lack of sharing of patented information but also the uncertain free exchange of all scientific information. Scientists in developing countries are often not able to access published scientific data however it is generated. A recent initiative from ICSU proposes an open access database of all scientific data to be provided for research and education purposes although there may still be problems in providing equitable access to computerised databases[23].

Open source licensing – the concept of open access technology has been well developed by the Centre for the Application of Molecular biology in Agriculture in Australia (www.cambia.org). This initiative on Biological Innovation for an Open Society (BIOS) provides open source licensing, "the dynamic protected technology commons", via an extensive patent database and support for use of intellectual property, on condition that any improvements made on the patented discovery must remain in the public domain. There is growing demand for the open source model to be applied in the biosciences but a common problem is that there may be too many patents to circumvent in any given area and there is, again, a need for more international funding to drive the initiative. There are some conspicuous opportunities for open source molecular sciences as a new paradigm (for example, alternative methods of gene transfer, Chung et al., 2006) and the analogy between open source molecular agronomy (Knight, 2003) and the open source practices of the software industry is superficially compelling. However, there is a major difference between the industry sectors – writing software is cheap but biosciences R&D is expensive and resource-intensive, currently requiring significant profit to repay the investment (Bains, 2005).

Research funder policy - it is helpful if research-funding bodies stipulate that researchers should act to share their outputs for both further research and commercial use in developing countries, via a royalty-free licence. For example, the Kirkhouse Trust (www.kirkhousetrust.org/ipPolicy.html) has developed a standard model adopted from the McKnight Foundation on collaborative crop research (www.mcknight.org/science/ipstatement.asp).

Academic exploration of new options – there is continuing scholarly analysis of the options for change. The European project on Property Rights in Plant and Animal Genomes (www.propeur.bham.ac.uk/theme3ws/rep.htm) is evaluating a range of approaches to the regulation of genetic biodiversity with a view to developing new, harmonised models of governance in IPRs. A project on the ethics of plant genomics benefit sharing at Wageningen University in the Netherlands (www.society-genomics.nl/include/print.inc.php?page=190) will also compare models of benefit sharing. As this project proposal noted, it can be useful to categorise models of sharing as "downstream" (at the level of transfer/implementation of the technology) or "upstream" (at the level of decision making on research priorities). Other new options for benefit sharing have been discussed at the FAO email conference in 2003 and it is important for the academic community to engage with industry and policy-makers in debating the ways to move forward on benefit sharing.

In summary, there are various new models emerging for managing access and appropriation, which have diverse objectives and means to integrate the various stakeholders in R&D. It would be valuable to review progress in these different models and assess their potential impact, within the next few years.

Traditional perspectives on benefit sharing must now be extended to incorporate the more recent developments – based on the standard Material Transfer Agreement adopted at the First Session of the Governing Body of the International Treaty on Plant Genetic Resources for Food and Agriculture.

The International Treaty on Plant Genetic Resources (FAO, 2002a) has been widely welcomed as a comprehensive agreement aiming to conserve resources for food and agriculture, facilitate their sustainable use and share the benefits derived from their use (recognising Farmer's Rights for free access to genetic resource and to be involved in the decision-making processes). The International

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[23] The ICSU committee CODATA has a broad mandate to improve the quality, management and accessibility of data and covers issues relating to IPR and exclusivity, data archiving and preservation, equality of access regardless of geography or business practice, and data use standards.

Treaty is particularly valuable in emphasising the special nature of agricultural biodiversity and in reinforcing the concept of the multilateral approach to access and benefit sharing.

The recent work by Visser and colleagues (2006) is helpful in exploring some of the options for non-monetary benefit-sharing arrangements in the implementation of the International Treaty. Options for the multi-lateral approach pioneered by the Treaty can be classified in terms of information exchange, capacity building and technology transfer. The recommendations (Visser et al., 2006) help to build a conceptually integrated model of global information sharing embedded in a strengthening of regional networks and national capacities.

5.2.3 Summary of policy issues for product protection

For the policy-maker, while encouraging exploration of new options for promoting access and benefit sharing, at the same time it is a priority to optimise working of the current situation to avert any tragedy of the anticommons, and to support good practice in developing consensual approaches. Models of access and benefit sharing are often developed locally and may be in areas outside of agriculture; therefore, analysis, synthesis and communication must be key elements of the policy function.

The issues for access and appropriation are often not distinct from other R&D/innovation policy issues. For example, a lack of confidence by the private sector to invest in R&D, in consequence of privatisation, or because smaller companies are deterred by the complexity of patent rules and patent proliferation, may be overcome to some extent by public policy initiatives such as the procurement of R&D from smaller companies.

5.3 Setting the global policy agenda

The mood of pessimism about agricultural R&D noted previously (Pardey and Beintema, 2001)) reflected significant concerns about declining public sector investment in R&D, the prospect of losing scientific and plant breeding capabilities and excessively proprietorial attitudes in the private sector. While these concerns have by no means disappeared and public funding for translational research and plant breeding activities is still inadequate, arguably there is now room for more optimism measured in terms of the dramatic advances in science and technology, an increasing culture of commitment to partnership and a renewed recognition of the importance of this area by some policy makers. What is needed to assure this optimism?

5.3.1 Identifying the constraints to innovation

Innovation bottlenecks can be classified generally as technical, human capital, financial, regulatory or societal. Technical constraints may be at the level of generating knowledge by scientific research (for example, inadequacy of public sector research systems and infrastructure) or in sharing knowledge (for example, weak institutional links between government, industry and academia). Societal impediments may arise from weak stakeholder dialogue processes and disquiet on ethical dimensions, including the issues for equity, guardianship of the commons and globalisation[24]. Individual technical, financial and regulatory challenges have been discussed in previous chapters. Taking a cross-cutting view of the emerging issues helps to identify priorities for action, as described in the final sections.

5.3.2 A framework for the translation from genome sequence to new product

To reiterate, the bioscience revolution in plant genomics has opened up novel opportunities for plant breeders to capitalise on molecular technologies to assess and enhance diversity in their germplasm collections; to identify genes that influence key traits, and to introgress valuable traits from new sources. The use of MAS in those cases where phenotyping presents a particular difficulty or where it is important to trace the history of gene determinants will increasingly become a core part of breeding

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[24] Ethical issues in food and agriculture are reviewed in the publication in the FAO Ethics Series (FAO, 2001) that also provides an outline of the steps required for creating a mechanism to balance interests, resolve conflict and encourage stakeholder participation.

programmes (Delmer, 2005). As described previously, a range of applications for crop improvement is now coming within range of the science push. However, for this research to be translated into practice it is also necessary for policy makers to provide the right conditions for the access and use of research, matched to user needs, capabilities and resources.

Key attributes for the translational framework from plant genome sequence to new product include:

(i) Maintaining excellence in basic research and creating a balanced portfolio across the basic-applied research spectrum, for model systems and crop plants and from genome sequencing through to systems biology;

(ii) Retaining the flexibility to capitalise on the increasing speed and power of biosciences research;

(iii) Increasing multi-disciplinarity (in particular, across molecular sciences, physiology, ecology and taxonomy) and teamwork within the research enterprise;

(iv) Investing in research infrastructure – this may require new organisational models of resilience as universities often resist change; Centres of excellence are needed to leverage new sources of funding and to provide comprehensive coverage of all relevant disciplines, there may be options for doing this via virtual networks as well as within a physical entity;

(v) Building scientific capabilities in translational biology, validating proof of concept and using molecular phenotyping to link discovery research to downstream applications;

(vi) Addressing business development and commercial partnership issues, recognising, rewarding and integrating roles for the private sector and attracting new sources of finance (for example from Venture Capital);

(vii) Dealing with IPRs, access and regulatory issues;

(viii) Introduction of innovation into routine practice – re-creating organisational linkages between research, plant breeding and farming, while addressing the tension between centralising tendencies (to capitalise on economies of scale and the current concentration of expertise) and decentralising goals for local R&D and its applications;

(ix) Identifying and reversing skill deficits, particularly in phenotypic characterisation, field studies and management of innovation;

(x) Responding to increasing societal expectations and ensuring accountability of the research community.

Elements within this framework, linking laboratory to field, have frequently been perceived to be in a state of disconnect (EASAC, 2004; Delmer, 2005; Reece & Ejnavarzala, 2006). Until these disconnects are remedied, the promise of the biosciences cannot be effectively realised. These challenges for the innovation framework and its funding broadly apply in all countries[25]. However, the problems in developing countries are exacerbated[26] by grossly insufficient government investment in research; by a weak private sector and weak coordination and regulatory framework; and by high costs of delivery to small farmers that limits access to both finance and technical information. One necessary first step in addressing these weaknesses is to develop a better understanding of the private sector’s role in agricultural innovation in developing countries (for example in Latin America, Pomareda & Hartwich, 2006). The policy-maker does face difficult choices (Chataway, 2005). To what extent should funds be allocated to building scientific capabilities and to what extent should resources be devoted to the range of functions that sustain technological capacity, regulation, networking and market support mechanisms?

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[25] Increased efficiency and productivity cannot be realistically achieved without long-term commitment to R&D funding. Usually, governments only respond to calls for funding if they have the means of measuring success. While more should be done to agree what is meant by success, there is a clear need to develop better metrics of R&D success at the local, national and regional level. Metrics can be a mixture of quantitative and qualitative indicators, measuring both basic and applied research outputs (rather than R&D processes), and are most useful when providing a measure of socio-economic value.

[26] According to analysis by the Future Agricultures Consortium (www.future-agricultures.org/hot_topic.html).

The difficulty in tackling the translational challenges and market weaknesses tends to be compounded by specific problems in valuing genetic resources as the basis for crop improvement. In a background study paper for the FAO Commission on Genetic Resources for Food and Agriculture, a review of commercial practice in the use of plant genetic resources for food and agriculture was undertaken by Smolders (2005), who identifies additional impediments in the reduction to practice, ascribed to the uncertain value of the initial asset (Box 1).

Box 1: Valuing plant genetic resources as a source of innovation
(adapted from Smolders, 2005)

- There are problems in estimating the value of a plant genetic resource because of uncertainties regarding its commercial utility and market demand. Value resides partly in characterisation of germplasm and in proof of concept regarding putative traits. Value increases with characterisation and evaluation.
- Estimates of the future value of a trait have rarely been successful.
- Exotic germplasm or landraces are perceived as having little practical value for seed companies, and their introgression into breeding lines is time-consuming and risky.
- Genetic resources that simply widen a company’s gene pool without specific properties of interest have essentially no commercial value and require long-term, risky, R&D investment.
- It is difficult to identify commercial practice in relation to raw materials that are conserved and released from *ex situ* genetic repositories.
- Even once a trait has been identified, the gene sequenced and cloned, there is still high risk for development until proof of concept is established.

Taken together, these weaknesses and challenge for the innovation framework may seem daunting but the recent roadmap and timetable set by the European Commission for its Technology Platform provides a practical structure for what may be achievable (Box 2).

Box 2: **Translating research into practice – the European Technology Platform roadmap**
(adapted from European Commission, 2005)

Next 10 years

- Create integrated programme in basic plant sciences, coordinating existing centres of excellence.
- Ensure prioritisation of genomics research for main crops of global interest.
- Build translational research capacity to capitalise on genomics and other plant sciences, to identify molecular determinants for characterising genetic resources and supporting improved crop plant breeding programmes.
- Promoting public-private partnership in all activities.

10-20 years

- Establish comprehensive genomics knowledge base for all economically and strategically important crops and their related genetic resources.
- Develop enhanced phenotyping tools and models to exploit genetic diversity.
- Identify and address remaining issues for crop genomics to promote developing country sufficiency and sustainability.

This timetable can be viewed as offering a stretch goal for corresponding efforts in developing countries in association with centres of research excellence in the EU, USA and elsewhere. While the timelines for the developing countries roadmap are likely to prove somewhat longer in many cases, the same strategic requirements apply, subject to consideration of the extent to which individual developing countries should build their own capability in fundamental science or rely on importing technology and tools (EASAC, 2004). In all cases there is need for developing countries to build capacity and competence to benefit from knowledge transfer.

5.3.3 Human and institutional resources

Rapidly evolving fields of science and technology are driven by active and talented scientists. The proper management of this talent – through support for training and mobility – will determine success. Coordination of effort is crucial to achieve the necessary critical mass of resources across three different interfaces: between research institutions, between academia and industry, and at the international level.

The InterAcademy Council Report (2004) provides a detailed analysis of what human and organisational resources are needed to build impact-oriented research in Africa. Among the reforms proposed by the InterAcademy Council are the redesign and support of national agricultural science systems; the encouragement of institutions and mechanisms to articulate science and technology strategies and policies; the development of African centres of agricultural research excellence; and the strengthening of international research linkages.

Masiga and Isokpahi (2004) review the specific opportunities and challenges in Africa for training in genome science, with reference to computational biology and bioinformatics. Various examples of degree-level, short-term training workshops and partnership activities are described, the majority focusing on healthcare applications of genomics, although similar approaches can often also be enlisted for the plant sciences. While significant progress can be discerned in initiatives supported by international funding agencies and not-for-profit institutions, increased commitment from governments is now required in order to provide the infrastructure to establish and sustain networks. The FAO email conferences also specifically draw attention to the lack of financial, human and infrastructure resources in developing countries for the application of molecular methods in the characterisation and conservation of genetic resources for crop improvement.

Generally, these capacity-building problems are not biotechnology-specific but they do crystallise the key issue of the degree to which developing countries should themselves invest in new technologies or rely on the acquisition of technological advice imported from elsewhere. This question cannot be answered in a generalised way because countries are at different stages of technology development in national agricultural research systems and will benefit from a range of partnership activities in knowledge transfer (EASAC, 2004). Case studies on capacity development in agricultural biosciences have been well described by Hall (2005) and Ayele and colleagues (2006) and the general conclusion from these analyses is that policy makers need to take a multi-dimensional approach to capacity development. Encompassing not just the development of human capital and resource infrastructure, but also developing capacity to use the knowledge productively through institutional innovation, networking and regulatory reform. One other element should be emphasised as a common factor conducive to capacity building: the imperative for scientists to provide the local leadership and advocacy that is essential to raise the profile of the contribution that R&D can make. This leadership can be expressed in various ways; in seeking international collaboration, in arguing the case for a longer-term strategic (rather than short-term, project-based) approach in international research centres and in adopting better mechanisms for the management of innovation (Masiga and Isokpahi, 2004; Reece & Ejnavarzala, 2006).

5.3.4 Public and private sector cooperation

Delmer (2005) observes the importance of private sector influences, not only in delivering commercially important crop improvements but in two additional ways. First, in providing a model for the public sector to work at the interface between basic and applied biology and secondly through novel forms of public-private partnership to support R&D in relatively neglected areas. Examples of individual partnerships have been described previously but agricultural R&D strategy is relatively rudimentary in some respects by comparison with the situation in tackling developing country healthcare needs[27]. Recent analysis indicates that public-private partnerships in biomedicine can be superior to industry or public sector efforts alone. Efficacy might be further improved by introducing a mechanism to allow partnerships to merge where appropriate (currently difficult because of their legal construction). There may be further room for improvement – in that leading partnerships are currently dominated by private endowed foundations and have relatively little input from either public funding or private commercial entities.

There are significant differences between the agriculture and health sectors that may determine how partnerships can support innovation. In particular, there is a major difference in market structure (Chataway, 2005): in health, major neglected diseases potentially constitute large, undifferentiated markets whereas targets in agriculture in poorer developing countries are distributed in local and regional markets with different social and environmental conditions. The adaptation of innovation to local needs requires local knowledge and increases R&D translation costs. Notwithstanding the differences, this is an opportunity for the multinational companies to display leadership and the area may now begin to evolve rapidly in consequence, for example, of the significant levels of funding available from the Gates Foundation Grand Challenges.

The Gates initiatives aims to make a large amount of R&D funding available through its commitment to engage with all relevant parties, in a mission-oriented approach using standardised research methods, that enforces collaboration rather than waiting for collaboration to arise spontaneously. There have been additional recent developments whereby the Gates and Rockefeller foundations will jointly invest ($150 million) in an initiative (Program for Africa’s Seed Systems) to improve seed varieties in developing countries, particularly in sub-Saharan Africa. This programme will also invest in graduate level education for general capacity building in crop breeding.

The new partnership models are timely in offering a means to capitalise on information on genes and traits arising from private sector research on commercial priorities that will now become available for application to breeding programmes for locally adapted germplasm or neglected crops. In turn, the public sector will have to regain its sense of purpose to share responsibility for generating and delivering new products while, at the same time, rewarding the private sector for its contribution.

One other strategic approach that might be adapted from healthcare innovation is support for orphan applications whereby the public sector in the USA, EU and Japan provides financial support to companies for research, plus incentives for development, in areas that would otherwise be deemed commercially unattractive.

5.4 Global governance and FAO instruments

5.4. Summarising priorities for the genomics transition

As noted in the introduction, the value of the interplay between the new biosciences and genetic resources can be construed in terms of three transitional themes: (a) Genomics to plant biology; (b) Genomics to improved crops; and (c) Genomics to society.

To be effective, the three transitions must each enshrine the principles of collaborative R&D effort, capacity building, international cooperation and benefit sharing:

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[27] It is reasonable to desire to draw analogies between plant sciences and medical sciences because the two areas share societal goals in terms of both health and wealth creation. The implementation of public-private medical R&D partnerships for developing country diseases is now a very active area characterised by different models of partnership. For example: (i) Novel start-up organisations to identify market opportunities and map R&D and delivery strategies (www.bvgh.org, composed of bioindustry, Gates and Rockefeller Foundations; (ii) Donated patent plus not-for-profit company (www.oneworldhealth.org, The Institute for One World Health, funded by the Gates Foundation); (iii) Pharmaceutical company-academia consortia, for example Medicines for Malaria (www.mmv.org), Global Alliance for Tuberculosis Drug Development (www.tballiance.org), Drugs for Neglected Diseases Initiative (www.dndi.org).

Genomics to plant biology – prioritising genomes for sequencing; supporting development of shared technology platforms, particularly in molecular phenotyping; ensuring generation and use of accessible and standardised databases; increasing collaboration across scientific disciplines.

Genomics to improved crops – improving evaluation and communication of socio-economic value and use in strategic decision-making; building international collaboration in selecting R&D priorities for reduction to practice and preparedness for new threats (in particular, climate change); engaging between research, plant breeding, conservation and farming constituencies; creating open access systems for pre-competitive data.

Genomics to society – developing new models for access and benefit-sharing; establishing evidence-based priorities for allocation of resources to public sector R&D, for support of private sector R&D and for Public-Private Partnerships.

The challenges for global policy-making and for the global governance of initiatives should not be underestimated (Stannard et al., 2004). Effectively capitalising on the opportunities for international cooperation and oversight requires reaching consensus on those areas that can benefit from international agreement and collective activity, necessitating inclusive discussion across all constituencies and clarifying the organisational structures and procedures required at international level.

5.4. Developing FAO Instruments

FAO may wish to address further at the level of policy formulation those points that are amenable to international discussion in the context of its Commission on Genetic Resources for Food and Agriculture. In creating a framework for concerted international activity in support of the Millennium Development Goals, FAO might discuss with governments the need to take into account the following:

(i) The value of agreeing a “declaration on plant genomics” as a first step to a “declaration on genomics”, proposing guidelines on how relevant policy should be formed and the research priorities defined.

(ii) The importance of mobilising scientific effort to address opportunities for those crops included within the ambit of the International Treaty on Plant Genetic Resources.

(iii) Strategies for building scientific capacity in developing countries to support new crop breeding. In quantifying the issues relating to analysing and building capacity in the biosciences, FAO may want to consider updating the 2005 inventory of developing country use of molecular marker and other technologies (www.fao.org/biotech/inventory_admin/dep/default.asp). Further work on this database would be particularly useful if it additionally distinguishes between the use of molecular techniques for genetic improvement (MAS) and for genetic characterisation associated with conservation of resources. Such analysis should include documenting the current use of Omics technologies. Furthermore, in the context of FAO preparing for the second Report on the State of the World’s Genetic Resources for Food and Agriculture (due 2008) and implementing the Global Plan of Action in priority areas, there is further need to consider how genomics and other Omic technologies might contribute to the background studies for the second Report, particularly in terms of the indicators of genetic diversity and methodologies for crop improvement (Fraleigh, 2006).

(iv) Managing the knowledge commons - informing future discussion on sharing of benefits requires more effort to identify ways to measure the impact of current IPR protection systems in the sector. More generally, the effort already committed by the FAO Commission on Genetic Resources for Food and Agriculture on drafting a Code of Conduct for plant biotechnology as it affects the conservation and utilisation of plant genetic resources (FAO 2002b) is highly relevant in the emphasis on ensuring access to resources and exchange of scientific information. As the more recent gap analysis of the draft code of conduct (FAO 2004b) notes, there is no international policy instrument that makes an explicit link between access and benefit sharing and products or processes generated by modern technologies (a theme that is discussed in detail by Esquinas-Alcazar, 2005). The Commission on Genetic Resources for Food and Agriculture may, therefore, wish to consider further the options for developing an international policy instrument on how agricultural IPR policy could be managed to ensure that biotechnologies can better meet the needs of the poor for food security and sustainable development[28].

(v) Drawing on lessons learned in other scientific fields to assess new approaches to freedom to operate and, potentially, developing generic principles and precepts applicable to global, collaborative R&D effort (including Consortia, Technology Platforms and Public-Private Partnerships). A reasonable starting point is that the focus for patenting should emphasise the protection of end products, where there is less likely to be a detrimental impact on new research, by comparison with patenting of early/intermediate outputs that may act (perhaps inadvertently) to deter new research.

(vi) Clarifying where additional work is now required. For example: (a) to maintain an updated account of the types of research advance and the opportunities for application coming into range – capturing the current state of the art in science and technology; and (b) to extend from this analysis of crop plants to cover other species (livestock, fisheries, forestry, micro-organisms) as they relate to food and agriculture, to promote the use of Omics as a cross-sectoral collaboration and, where relevant, in cross-sectoral (ecosystems) integration.

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[28] It is also worth noting that the possible development of international policy instruments to encompass other key Articles in the draft Code of Conduct, particularly relating to promotion of appropriate biotechnologies that apply to genetic resources, will need to take account of the new Omics technologies described in the present Report.

Appendix 1

R&D OPPORTUNITIES AND REDUCTION TO PRACTICE: EXAMPLES OF CAPITALISING ON ADVANCES IN GENOMICS

(i) Advances in science: matching discovery to societal needs

Exploring fundamental processes in plant biology

The breadth of this research can be seen as a strength for a vibrant research community. It is also a potential source of weakness if the research community is not well connected and able to integrate the disparate research advances. There is need for better connectivity between researchers working in different disciplines and on different species. The discoveries cited here are not necessarily yet at a stage ready to translate into downstream applications, but the knowledge is needed to open up the longer- term opportunities and to catalyse the transition from model plant to crop research.

Controlling stomatal aperture Plants need to respond to many different environmental signals and require complex integration of information via signalling networks. The control of stomatal pores mediates the exchange of gases and water vapour from the atmosphere to leaf interior, controlling leaf temperature via transpiration, and contributing to the ability to withstand drought. Recent elucidation of the regulation (by abscisic acid) of *Arabidopsis* stomatal aperture architecture may provide a basis to improve plant varieties with enhanced water usage efficiency and drought tolerance (Mishra et al., 2006).

Controlling root development Microarray-based evaluation of capillary root formation in *Arabidopsis* under controlled conditions and by comparison with dysfunctional mutants identified genes crucial for the formation of new roots (involved in the processes of cell division, growth and differentiation; http://europa.eu.int/comm/research/headlines/news/article_05_11_11_en.html). As capillary root formation is adaptable to soil changes, understanding these processes may help to develop crop varieties that absorb water and minerals more efficiently.

Controlling photoperiod Barley is a very adaptable crop that can be grown over a wide area from the Arctic Circle to subequatorial regions, in part because different strains vary in response to changes in photoperiod (an environmental cue that regulates development and time of flowering). Identification of a regulator class of genes involved in circadian clock function in barley helps to clarify how cereals develop in response to environmental cues, potentially allowing plant breeders to tailor crops to specific environments and to new conditions, perhaps especially climate change (Turner et al., 2005).

Controlling light capture It has been postulated that cultivars with erect leaves increase light capture for photosynthesis and, hence, increase grain yield. Brassinosteroids influence both plant height and leaf erection in rice. Proof of principle was recently obtained using a rice brassinosteroid mutant with erect leaf phenotype and enhanced grain yields under field conditions (Sakamoto et al., 2006). Potentially, understanding this trait is relevant to improvement of other cereal crops, reducing requirement for artificial fertilisers.

Understanding and combating major constraints to crop production

Research advances are now occurring in the general area of plant abiotic and biotic stress (Delmer, 2005), an area where there are immediate needs for practical applications in improved crop breeding.

Abiotic stress It has been estimated that up to 80% of the potential yield of annual crops is lost because of abiotic stress (Jenks & Hasegawa, 2005). Progress on key topics includes:

- Soil salinization - approximately 20% of total irrigated land is presently affected by salinity. The challenge of developing salt-tolerant crop plants (influencing osmotic and ionic homeostasis and damage repair) is being addressed by exploitation of natural genetic resources both through direct selection in stressful environments and through mapping of Quantitative Trait Loci and marker assisted selection[29].

- Non-optimal temperatures - too cold for efficient crop production in far northern and southern regions and too warm in equatorial regions. Much research has been performed using *Arabidopsis* and tomato model systems. Other research is underway on developing drought resistance in both the private sector (for example, BASF Plant Science, www.corporate.basf.com/en/produkte/biotech/plantscience) and in the public sector. An example of the latter is the work at CIMMYT on maize (drought reduces worldwide yield by >15%), funded by the Rockefeller Foundation to produce a composite genomic map identifying DNA regions involved in conferring drought tolerance (www.rockfound.org/Agriculture/Announcement/116,Nov2005).
- Non-optimal pH, soil too acid or alkaline. Understanding the problem of soil acidity is important in combating aluminium toxicity (EASAC, 2004). Recent CSIRO research identified a wheat gene that enables roots to exude malate (a normal constituent of plant cells) that sequesters aluminium and prevents root damage. The gene is currently used as a marker for tracking aluminium tolerance in wheat breeding trials (Sustainable farming on www.csiro.au/csiro).

There is significant progress in understanding the acclimation to individual stress conditions, and efforts to combat abiotic stress will benefit from other research leads discussed previously (for example, the control of stomatal aperture) but it is becoming increasingly important to integrate the knowledge from diverse abiotic stress signalling pathways. In particular, research is needed to clarify molecular mechanisms in the response to combination of different stresses that simulate field conditions (Mittler, 2006), typically drought plus heat or cold plus high light intensity (in northern latitudes), for it may not be possible to extrapolate from the response to individual stresses.

Biotic stress and plant-pathogen relationships Plant disease epidemics can incur very large national economic costs as well as the costs to individuals in developing countries. Soybean rust in Brazil was estimated to have caused $5 billion in accumulated losses since 2001; groundnut rosette virus in sub-Saharan Africa to have caused 15 episodes of up to $400 million per episode since 1900 and cassava mosaic disease in Uganda to cause an annual loss of $70 million since 1990 (Office of Science & Innovation, 2006).

A comprehensive review of the options for future control of infectious diseases in plants, with an emphasis on sub-Saharan Africa was published recently by a joint Africa-UK foresight project (Barker et al., 2006). Conventional breeding for genetic resistance to disease has enjoyed some significant successes, for example in conferring resistance to cassava mosaic virus disease, maize streak virus disease, sorghum and bean anthracnoses and pearl millet downy mildew. However, many other diseases have not yet been controlled by conventional resistance breeding (Delmer, 2005) either because of lack of knowledge about pathogenesis or lack of investment to translate knowledge of the pathogen into improved plant varieties, for example cassava brown streak disease, finger millet blast, tomato late blight and maize grey leaf spot.

A significant impetus to understanding plant-pathogen relationships was achieved by the sequencing of the genome of the bacterium *Pseudomonas syringae* in 2003. *P.syringae* causes the plant disease bacterial speck and one of its host plants is *Arabidopsis.* Taken together, the data from host and pathogen genomes provide a valuable model for research on infection and host resistance, with the prospect of harnessing a plant's natural ability to defend itself as an alternative to chemical pesticides.

Recent research has also begun to characterise some key crop-pathogen interactions (Delmer, 2005). For example, the parasitic fungal pathogen responsible for rice blast disease, *Magnaportha grisea* – estimated to destroy enough rice annually to feed 60 million people - employs a specialised secretion system to deliver proteins directly into host plant cells where they evade and suppress defences and

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[29] However, as salt tolerance is a complex trait involving many genes (Yamaguchi & Blumwald, 2005), transgenic plant generation may offer an alternative approach to molecular marker-based breeding.

facilitate tissue invasion (Gilbert et al., 2006). The discovery of the key pathogen protein, an aminophospholipid translocase enzyme, could become the basis for targeting new fungicides or for breeding new resistant strains.

Advances in microbial genomics to elucidate conserved pathogen genes and identify host resistance genes will provide new resources for breeding strategies. The Global Rust Initiative is mounting a coordinated effort to tackle wheat stem rust fungus: strain Ug99, discovered in Uganda in 1999, is feared to spread globally and is capable of severely damaging perhaps half of the world's bread wheat (Borlaug, 2006). One promising research lead is to use wheat varieties from the Kenya-Ethiopia region to search for genes enabling wheat to resist Ug99. The USDA has also recently announced a new public sector consortium (funded with $5 million) to identify marker genes that provide resistance to wheat rust, serving as the molecular basis for high throughput strain development and breeding programmes with multiple disease resistance genes.

There is continuing need for better monitoring systems so that a faster response can be mounted for emerging diseases. Advances in pathogen genomics will provide new diagnostic opportunities through the development of microarray-based combined diagnostics on a chip. For example, recent work by a European consortium to create a microarray for potato pathogens may help to select improved crop breeding material and also promote international trade with less onerous quarantine conditions (www.diagchip.com).

Research on plant-microbe relationships is not confined to the study of pathogens. There is also great interest in deciphering the role of microbes in crop utilisation of nitrogen and phosphorus. Mexican researchers have sequenced the genome of the bacterium *Rhizobium etli* that some crops use to obtain nitrogen, and this will help to expound functionally conserved features in diverse symbionts (Gonzalez et al., 2006). A Chinese-European consortium is studying the genetic basis of the activity of Arbuscular Mycorrhizal fungi that are symbiotic with crop plant roots, improving phosphate uptake. Selecting the most effective fungal strains as a basis for field trials has increased crop yield and quality (www.dijon.inra.fr/bbceipm/Mychintec/). The beneficial endophytic fungus *Pyriformospora indica* that also colonises plant roots has been found to improve defence readiness in barley, by elevating antioxidative capacity (Waller et al., 2005). This action helps to account for the known effects of the symbiotic fungus on increasing barley yield, enhancing salinity tolerance and disease resistance and also furnishes a model system to study systemic disease resistance and grain yield in cereals, with potential to discover molecular traits to exploit in new breeding programmes.

(ii) Reduction to practice in improved crop breeding

As noted in the EASAC report (2004), progress in genomic technologies alone is insufficient to bring about the reduction to practice. There is concomitant need for well-phenotyped biological resources, for integration of knowledge from across other scientific disciplines and for the involvement of research end users – and these are likely to be the rate-determining steps in capitalising on the genetic knowledge underlying desired traits. Some recent examples of the future potential will be described but there is already a significant accumulation of experience on MAS that needs to be taken into account when evaluating whether novel claims are realistic or over-optimistic. This accumulating experience is well reviewed in the summary document of the FAO email conference in 2003 (FAO, 2004a); it is difficult to generalise further from the broad range of expert perspectives contributed but some key points of consensus emerged (Box 3).

Box 3: **Technical, economic and strategic issues in the use of MAS as a tool for the genetic improvement of crops**[30]

Selected issues emerging from FAO email conference 2003:

- Many researchers in developing countries view MAS as an important "downstream technology" tool for crop improvement, to be deployed alongside conventional methods to select optimal variants.
- The application of MAS is much less controversial than GM.
- In order for MAS to become a strategic priority for developing countries, it is necessary to clarify objectives for an acceptable return on investment (and this also requires better estimates of costs involved[31]) and MAS should not distract attention from research on under-utilised species and crop diversification. There must be better evaluation of the potential economic gains from MAS in comparison with conventional improvement programmes.
- Costs will decrease as the technology matures and developing countries could economically capitalise on MAS through collaborative ventures (within national and regional frameworks).
- Criticisms of MAS often stem from poor R&D management strategies and lack of operational integration in breeding programmes rather than from deficits in the technology. MAS will not be successful without an established breeding strategy as well as focused research on trait biology.
- Historically, success of MAS depends on the extent of the linkage between molecular marker and target gene (if too far apart there is increasing probability of recombination events resulting in loss of association); further work is needed in many cases to create better molecular marker maps.
- Traits controlled by a single gene are most amenable to MAS; fewer tightly linked markers are available for Quantitative Trait Loci.
- The major technical problem is lack of DNA polymorphism when MAS cannot be applied to trait selection.
- Current impact of MAS on farmers is assumed to be relatively small. For example, experience in India demonstrates that most molecular research has not been translated into plant breeding. This may indicate that findings in the laboratory do not equate with success under field conditions but it is also the case that efforts to trace and document impact may be relatively rudimentary.
- Other key issues for the uptake of MAS technology in developing countries relate to Intellectual Property Rights (IPRs), skills, training and capacity building, the role of international organisations and public-private sector linkages (issues to be considered subsequently).

While many of the general points raised in the FAO forum in 2003 remain very valid, some of the more recent technical and organisational achievements are resolving previous uncertainties and bringing new opportunities within reach. To reiterate, when genomic sequences are available, diversity analysis can target genes directly rather than via the proxy markers that have been necessary for the past couple of decades.

(iii) Recent research on major crops

Recent work on major crops is beginning to actuate the translational linkages from biology to breeding. As well as establishing the basis for specific improvements in crop breeding, these activities help to strengthen the translational research system ready for future applications from discovery:

Maize Research is identifying the genes that account for the striking improvement in yield and nutritional quality that accompanied the domestication of maize from teosinte (Yamaskai et al., 2005).

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[30] Recent draft reports on national plant breeding and biotechnology surveys conducted by FAO are on www.fao.org/biotech/detail_event.asp?event_id=34209.

[31] The costs, human and infrastructural resources required to identify and apply molecular markers are discussed by Reece & Ejnavarzala (2006).

These gene loci may represent excellent candidates for introgression from wild relatives to increase the diversity for exploitation by breeders in further enhancing agronomic performance, palatability and quality. This research is particularly noteworthy in demonstrating the value of a population genetics approach (based on analysis of DNA Single Nucleotide Polymorphisms) to select genes contributing to agronomic traits when other methods are ineffective. One consequence of stringent selection for desirable traits during domestication and, thereby, reduction in diversity, is that conventional Quantitative Trait Loci and association analysis methods will miss the most interesting class of genes – those that lack genetic diversity because of the history of their selection.

Wheat A major chromosome pairing locus in polyploid wheat, Ph1, regulates the pairing of its six subsets of chromosomes but, in so doing, prevents the pairing of wheat and wild relative chromosomes, precluding the introduction of new genes. Molecular characterisation of Ph1 (Griffiths et al., 2006) has now provided the information necessary to devise ways to inhibit the control exerted so that wheat breeders should be able to access a much greater range of genetic diversity and to transfer traits such as disease and drought resistance from wild species.

Tomato As with many crop plants, cultivated tomatoes carry only a small fraction of the genetic variation that is available in related wild species and landraces. Mapping Quantitative Trait Loci to compare the domesticated tomato (*Solanum lycopersicum* var. Roma) and wild tomato species (*S.pennellii)* has shown the importance of comprehensive screening for “metabolic genomics” (genetic, metabolic and morphological characterisation) of wild genetic resources in the identification of valuable traits that can then be introduced into modern varieties by streamlined breeding programmes (Schauer et al., 2006)[32].

Rice More than half the world’s population depend on rice as a staple crop. China is the largest producer and consumer of rice, and pioneered hybrid rice technology. Completion of the rice genome enables study of gene function on the genome-wide scale and identifiable genes provide resource for breeding programmes. The China Rice Functional Genomics Program (funded by the Chinese Ministry of Science and Technology) is developing tools and resources to characterise essential genes for crop improvement for a wide range of traits relating to grain yield and quality, growth and development, disease and pest resistance and abiotic tolerance (Wang et al., 2005). One recent publication illustrates very well the potential for genomics research in rice breeding, in characterising genetic variation underlying the ability of some rice varieties to tolerate prolonged immersion in water and, thereby, survive seasonal flooding (Xu et al., 2006).

Millet 30% of the Indian pearl millet crop is lost when an epidemic of downy mildew occurs. An improved resistant hybrid version of pearl millet employed MAS, representing the first time that a crop variety produced in this way has been promoted in India (Hash et al., 2004).

Cowpea A programme of work funded by the Kirkhouse Trust is using modern genetic methods to sequence the cowpea genome and use MAS to introduce desirable traits (Southern, 2005). This work is also of interest in illustrating how collaboration between Indian and UK scientists provides a model for technology transfer and training for developing countries (www.kirkhousetrust.org/projects/2005_11_Bangalore.html).

Biofortification It has been estimated that up to 80% of the world’s population is iron deficient, 30% zinc or iodine deficient, 15% selenium deficient; and some diets may also be deficient in calcium, magnesium and copper. Traditional interventions to tackle mineral malnutrition (supplementation, food fortification, dietary diversification) are often ineffective and there is considerable interest in exploiting natural genetic variation to breed mineral-efficient crops with increased content in edible material (White & Broadley, 2005). The work of HarvestPlus as part of the CGIAR Global Challenge

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[32] The tomato is often regarded as a model organism for fruit-bearing plants, to identify determinants of fruit quality (flavour and nutrition). The focus on the quality phenotype, requiring an integrated strategy to link molecular and crop output traits, provides a good illustration of the model for using characterised, currently untapped, genetic diversity in native varieties to identify and map loci for a focused plant breeding strategy (Giovannoni 2006). Metabolite profiling is, to a large extent, species-independent and so can be used to progress general understanding across crop species, exploiting natural diversity and underpinning selection of breeding stock for improved quality.

Program is providing a coordinated approach to the problem (www.harvestplus.org). Feasibility studies on micronutrient biofortification are underway for six staple crops, beans, cassava, maize, rice, sweet potato and wheat, with a priority to increase iron and zinc levels. This research is evaluating genetic variability and heritability of mineral traits, their stability across diverse soil conditions and climatic zones, and whether it will be feasible to breed for increased concentration of several minerals simultaneously without affecting other quality characteristics.

(iv) The challenges of climate change

Climate change is widely predicted to have major impact on global agriculture and food security (for example, Royal Society, 2005). Different crops have different weather sensitivities. Drought-resistant varieties of staple annual crops need further development, as discussed previously, but global warming will have deleterious consequences other than drought (for example, high temperatures, flood, other extreme weather conditions) that require research now.

It has been estimated that rice yields in Asia would need to double over the next 50 years to overcome the challenges set by climate change (IRRI workshop, March 2006, www.scidev.net/News/index.cfm?fuseaction=readNews&itemid=2754&language=1).

The International Rice Research Institute (IRRI) in the Philippines is setting up a consortium to search for tolerance genes in rice protecting against heat, drought, ozone and other pollutants (the important example of tolerance to submergence in flooding has already been noted; Xu et al., 2006).

The Intergovernmental Panel on Climate Change estimates 23% increase in surface ozone by 2050. Simulation studies predict an impact on yield and nutritional quality of soybean, a crop particularly susceptible to high levels of ozone; further research is needed to understand the effect and to develop ozone-resistant varieties. However, climate change modelling also suggests that other adverse effects on crops of increasing temperature and decreasing soil moisture might be offset to some extent by the direct fertilization effects of increasing carbon dioxide concentration. Further research is needed to develop crop varieties that can take advantage of the increasing atmospheric carbon dioxide.

It is judged that Africa is the region whose agriculture is most vulnerable to climate change (InterAcademy Council, 2004) and a crop science programme is necessary to mitigate the predicted problems (Slingo et al., 2005). The potential effect of climate change on plant diseases in Africa has been subject to analysis by African experts participating in the UK foresight programme (Rweyemamu et al., 2006) with a view to identifying scientific priorities for crop resistance breeding programmes. Disease vectors might be anticipated to increase with higher temperatures but some effects may be offset by declining rainfall and slowed pathogen development. Some fungal diseases will be favoured by hotter and drier conditions. For example, in areas where maize is being replaced by sorghum – some of which are already marginal for maize cultivation – sorghum head smut (*Sporisorium holci-sorghi)* is likely to become a more serious constraint to crop production.

(v) The interface between molecular biology, taxonomy and conservation

There are now more than 1,300 *ex situ* crop genetic resource banks worldwide (Koo et al., 2005). Individual countries may create substantial germplasm collections, often concentrating on crops of national priority. CGIAR-maintained collections, as an input for breeding programmes, now comprising more than 600,000 samples, are pivotal to global conservation efforts (including rice, wheat, maize, cassava, millet, sorghum, cowpea). A background study paper for the FAO Commission on Genetic Resources for Food and Agriculture (Visser & Smolders, 2004) analyses critical success factors for the effectiveness of plant genetic resources networks. A recent FAO email conference provides a comprehensive perspective on current issues for the use of molecular markers in characterisation and conservation efforts (Box 4). The recent FAO publication (Ruane & Somino,

2006) further collates some important perspectives for exploring and protecting agricultural genetic resources in developing countries using the modern molecular methods[33].

Box 4: Role of molecular markers in characterisation and conservation of crop genetic resources

Selected issues emerging from FAO email conference 2005:

- There is increasing value for molecular marker technologies to characterise the extent of genetic diversity within a collection, for the development of collection management strategies (identification of gaps, redundancies, contaminants) and identification of locations suited for establishing *in situ* conservation sites.
- Molecular markers must be used alongside phenotypic (agronomic and morphological) data.
- Various molecular marker technologies are in use (for example, fragment length polymorphism, microsatellite repeat techniques, Single Nucleotide Polymorphism, ESTs). It is important for the individual methods to be reproducible and for researchers to adopt a common approach with community standards in order to generate and exchange directly comparable data and, in time, create a universal curated molecular marker database. There is a valuable role for the CGIAR Generation Challenge Programme in providing standardised microsatellite kits.
- There is growing interest in the potential of DNA itself as a means for long-term conservation of genetic material, supplementing seed banks[34].
- Some experts are sceptical that many developing countries are in a position to employ advanced techniques. In that case, primary effort should be on ensuring that existing research findings reach rural populations. There are current problems associated with lack of financial, human and infrastructure resources in developing countries for characterisation and conservation of genetic resources. Nonetheless, developing countries must not become “technologically excluded”; there is agreed priority for training and skill development and opportunities to support at regional (for example, Asian Maize Biotechnology Network) as well as at national level.
- Research and the application of results to characterisation and conservation of germplasm will also benefit from regional collaboration and pooling of resources (for example, BECA, Biosciences Eastern and Central Africa) as well as partnership between developing and developed country institutions. Public-private partnerships are feasible where the economic impact of characterisation and conservation can be demonstrated.

In summary, the use of molecular markers is able to determine genetic variation within a population and, thereby, provide a management tool to accumulate different accessions with maximum genetic variation. If applied and interpreted correctly, DNA analysis techniques give an objective evaluation of the genotype, independent of growth conditions or development state of the plant. Although the FAO email conference concentrates on public sector activities, collections are also an important resource for industry. For example, industry accounts for 40% of the use of the National Cereal Collection in the UK.

(vi) Improving and using conservation capabilities

Examples of recent research advances supported by these collections are discussed in the FAO email conference. Two other examples illustrate the range of current research supported and the potential for collections to amplify the value of genome sequencing efforts.

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[33] News on the use of molecular markers in the characterisation of plant genetics resources is collected on the IPGRI Plant Genetics Resources Newsletter portal on www.ipgri.cgiar.org/pgrnewsletter/default.asp.

[34] Very few banks of DNA extracts have been established and most taxonomic collections are inadequate for long-term high quality DNA preservation and extraction (Savolainen & Reeves, 2004). Funding agencies will need to do more to support global efforts in DNA banking. A recent IPGRI publication (Carmen de Vicente, 2006) surveyed the current global status of DNA banking, its potential in the conservation and use of genetic resources and the associated technical and policy issues. The rules and procedures governing access and exchange of sequence information and sharing of benefits accruing from further research on DNA samples, require further consideration.

Papaya Researchers at the Institute for Plant Biotechnology for Developing Countries (Belgium) in partnership with researchers in Ecuador and Columbia are investigating genetic diversity in papaya with goals for increasing papain production and for planting in colder, subtropical areas. The genome sequencing of papaya (completion of approximately 5% of the papaya genome by Lai et al., 2006) is beginning to provide a systematic basis for these and other improved crop objectives as well as characterising a model organism for other fruit-producing tree crops.

Potato The importance of maintaining potato genetic resources is comparatively well recognised and will provide highly valuable material with which to capitalise on the sequencing efforts (Table 2). The genus Solanum contains more than 1,000 species, with more than 250 species bearing tubers. Potato production worldwide is dominated by *S.tuberosum* but local Andean communities cultivate a range of species within the *S.brevicaule* complex with a wide diversity of tuber types (www.cipotato.org). The wild potato species inhabit a range of mountain environments, adapting to a relatively extended range of biotic and abiotic stresses by contrast to the domesticated varieties which have been adapted to relatively few habitats (Mullins et al., 2006). Hence, the semi-wild mountain taxa that show diverse disease and frost resistance qualities are a major genetic resource in germplasm collections.

Box 5: US Department of Agriculture Action Plan on Plant Genetic Resources Management (www.ars.usda.gov/research/programs)

Critical factors in safeguarding and using collections:

- Avoiding risk of loss of collection – duplicating storage sites; maintaining conditions for preservation of viability on long-term storage; implementing reliable methods for regeneration of genetically representative samples.
- Documenting genetic resources – ensuring updated information management system and linkage with other databases (structure, function and genomics).
- Expanding germplasm evaluations – many accessions have little characterisation and there is need for evaluation of traits in terms of DNA sequence of specific genes or genomic sequence as useful measure of genetic diversity and divergence.
- Technology transfer of genetic resources – issues for physical transfer (such as quarantine regulations) and for IPR and usage conditions.

Optimism on individual research initiatives is tempered by continuing concern expressed about the status of global genetic conservation efforts. Some collections fail to meet the necessary criteria to store accessions for the long term, to duplicate and regenerate material as required and to document and store information in the collection. This is not a problem confined to developing countries and the challenges are discussed in detail in the current USDA Strategy Plan (Box 5).

There is an ambitious initiative underway to finance international crop conservation efforts by an endowment fund (Global Crop Diversity Trust) to assure the utility of CGIAR collections (Koo et al., 2005). Any future strategy must also assess the extent to which a central genetic resource bank, providing long-term conservation, should be duplicated by local resources facilitating ongoing active collection[35]. The issues for implementing the Global Crop Diversity Trust with regard to involving the private sector, for sharing of germplasm, technologies and training and for capacity building, require concerted effort. Therefore, the recent FAO proposal – the Global Initiative for Plant Breeding Capacity Building[36] – as part of the ongoing implementation of the International Treaty on Plant Genetic Resources for Food and Agriculture is to be welcomed.

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[35] There is also an important initiative represented by the agricultural crop seed bank in Svalbard in the Arctic, intended to be the most complete collection in the world. Even though the secure nature of this collection creates a significant asset, there are unresolved issues for training to preserve and manage the collection. Without this expertise, much of the utility of the collection could be lost.

[36] www.fao.org/ag/magazine/0606sp1.htm.

While the global standardisation and consolidation of inventory effort is vital, concern has also been expressed recently that CGIAR gene bank policy is changing as a result of the procedures agreed in the International Treaty on Plant Genetic Resources for Food and Agriculture. In one cited case (Jayaraman, 2006) it was feared that wheat-breeding programmes in India would suffer from what is perceived as a more restricted supply of elite germplasm because Material Transfer Agreements are being devised to suit the needs of multinational seed companies. While this concern has not been fully substantiated, it is clearly important for the International Treaty Governing Body to monitor the impact of the recently finalised Material Transfer Agreement.

(vii) Genomics and GM Applications for Improved Crops

As noted in the FAO statement (www.fao.org/biotechnology/stat.asp) the definition of biotechnology covers many of the tools and techniques that are commonplace in agriculture and food production. While there is little controversy about some aspects of biotechnology and its applications (in particular, MAS) GM plants are viewed as controversial in terms of feared impact on human health and the environment.

However, although the use of genomic technologies can accelerate rational plant breeding by non-GM routes – the focus of this report - there may be some goals where only GM technologies are feasible (Royal Society, 2000). Some crop species have few or no wild relatives with which to cross breed or a desirable characteristic may only be available by using an unrelated species. Important traits such as pest and herbicide resistance are most necessary where no inherent resistance has been demonstrated within the species.

While it is not now possible to review all the emerging GM opportunities, some representative very recent scientific advances will be mentioned to illustrate the range of current research opening up new applications, that would be difficult to achieve by non-GM routes (Box 6).

Box 6: **Examples of recent research in GM crops**[37]

- Enhanced starch production in cassava – by modulating rate-limiting step in starch biosynthesis in tuberous roots by introducing enzyme from *E.coli* with reduced feedback regulation (Ihemere et al., 2006).
- Identification of silicon transporter (aquaporin) in rice – providing transgenic strategy to increase silicon in dicotyledonous species where insufficient silicon has been linked with stress (Ma et al., 2006).
- Improvement of seed yields under boron-limiting conditions – genetic modification of *Arabidopsis* with transporter protein controlling uptake of boron (widespread micronutrient problem for crops, particularly in China and Pakistan) (Miwa et al., 2006).
- Increasing absorption of zinc and iron – genetic modification of wheat with thermostable phytase increases potential for phytate hydrolysis in cooked cereals and hence improves phosphate and mineral bioavailability (Brinch-Pedersen et al., 2006).

Another field where GM crops are gaining attention is bioenergy. The potential application of crops to generate bioenergy has implications for international R&D, for partnership models and for food crop priorities. With regard to the current global status of biofuels, biomass productivity is highest in tropical environments and the production costs of biofuels, notably ethanol, are comparatively low in various developing countries. For example, bioethanol produced from sugarcane is currently competitive with fossil fuels in Brazil, the world's leading producer of bioethanol. Developing

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[37] There are also significant advances in non-food applications for GM-crops. For example: (i) Plant-derived pharmaceuticals – European Commission is funding public-private sector consortium (including South Africa), www.pharma-planta.org. Plant-derived proteins are in clinical trial evaluation but commercialisation prospects are overshadowed by regulatory uncertainty; (ii) Bioremediation – Chinese Academy of Sciences has completed screening programme of 5,000 native plants to absorb heavy metal pollutants with prospect of gene transfer to design GM plants. Other applications of phytoremediation include removal of organic pollutants, particularly explosives, where investment is now highest in Pacific Rim countries (Rylott et al., 2006).

countries such as Malaysia, Indonesia and the Philippines, that currently produce biodiesel for their domestic markets, could develop export potential. Nigeria is considering the use of cassava for bioethanol production, other feedstocks such as sorghum (for bioethanol) and *Jatropha* (for biodiesel) may have applicability in many regions. Fiji is aiming to replace diesel fuel imports with coconut oil from local copra production.

The issues for developing GM-biomass crops as part of the future strategic development of biofuels have been noted recently in the European Commission vision for 2030 and beyond (www.europa.eu.int/comm/research/energy/pdf/draft_vision_report_en.pdf). The Chief Scientist at British Petroleum (BP) recently suggested (Koonin, 2006) that the size of the prize in biofuels is too large to ignore, "*The combination of modern breeding and transgenic techniques should result in achievements greater than those of the Green Revolution in food crops, and in far less time*".

It is, of course, possible that some of the same scientific advances required for more efficient bioenergy production also underpin improved food crop breeding. One long-term goal is to improve the efficiency of photosynthesis (and to increase the adaptability of photosynthesis to the environment, for example shading within a leaf canopy). This goal is coming into range in terms of experimental modification of the initial step in photosynthesis catalysed by the enzyme ribulose biphosphate carboxylase-oxygenase (Griffiths, 2006)[38].

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[38] A recent IRRI proposal also aims to explore the feasibility of increasing photosynthesis efficiency in rice by transferring genes from wild relatives or maize, converting from C3 to C4 photosynthetic pathway (C4 plants have an additional enzymatic step prior to RuBisCo, increasing the efficiency of photosynthesis at the expense of photorespiration).

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