Commentary
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Public germplasm collections and revolutions in biotechnology

1. Germplasm collections in a modern economic milieu

State funding of anything to do with the 'public good' has been accepted as something natural in many cultures. However, in free enterprise countries that are at the forefront of modern science, publicly funded activities are widely regarded as legitimate only if they are essential and not addressed by the market place. For-profit companies understandably focus on activities where the relationship between cost and benefit are obvious and hence invest in activities with a well-defined cost–benefit relationship. Collections of living biological materials are an example of an activity where benefits are difficult to associate with cost and therefore have to continually struggle for financial support. Because of its intrinsically speculative nature, basic scientific research is often regarded as having a poorly defined cost–benefit relationship. For-profit entities conduct applied research whose results are likely to augment their coffers, or will sponsor such research via competitive grants. Basic research is more often funded via competitive grants by government agencies, sometimes by private philanthropic foundations, or directly conducted by the very largest private corporations. In most cases of published research, direct public funding provides facilities and training (mostly at universities), while research funds for specific projects are obtained by investigators via competitive grants. Most scientists accept, and adapt to, this situation much as we accept and adapt to the weather.

Boundaries between 'basic' and 'applied' are not rigid or immutable and even the lexicon is fluid. Recently applied research has been re-cast as 'translational', bridging the span between basic research and development of products or processes. In agriculture and botany, the line between basic and applied was probably stronger a couple decades ago: 'Funding for basic (versus applied) research in plant science is very limited and much of what is available comes through the National Science Foundation (NSF)' (Dilcher 1991). Currently, however, 'The line between furthering basic understanding of natural processes and the development of potential applications is hazy and overlapping, and the time from discovery to commercialization can be exceedingly short' (Watson *et al.* 2003). What persists in this changing environment is the necessity for most scientists to obtain research funds via various competitive grants programs.

A major exception to this state of affairs is the maintenance and preservation of large biological collections, which have relevance to both basic and applied research, especially to biotechnology. Government and non-profit entities (the latter usually receiving government assistance) have been critical for creating and maintaining these collections of living organisms, including performing the research necessary to characterize and preserve the germplasm itself. These 'germbanks' are, like bank accounts, savings for both anticipated and unexpected contingencies. In plant research, they provide potential sources of resistance to emerging pests and diseases, genes for drought hardiness or useful metabolic products, as well as other desirable traits. However, these traits are often not readily apparent, and often occur in a genetic background of less desirable properties. Microbial collections are similarly valuable in providing validated material for testing new plant varieties, new anti-microbial drugs, for developing drug targets, and often provide genetic material for development of new enzymes used in every aspect of modern life. Because the value of such biological material is often in its hidden potential, truly

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comprehensive collections are often maintained at public expense or receive governmental subsidies. While preservation of natural environments is an important factor in preserving biological diversity, it is complementary to and not redundant with *ex situ* biological repositories.

The fiscal health (or lack thereof) of germplasm collections has been the subject of frequent review (e.g. Strauss 1998; McCluskey 2003; Babcock *et al.* 2007; Gowans 2009). In the US, 'microbial collections are at risk … because the United States lacks a coordinated national system to protect, preserve and enhance these valuable resources' (APS 2009). In spite of their sometimes insecure budgets, these large biological collections are supremely important. Biological materials from public germplasm collections have been decisive for three of the most significant innovations in modern biotechnology. These innovations are: (i) the commercial production of antibiotics and other drugs, pioneered by penicillin production; (ii) the Green Revolution, commencing with semi-dwarf wheat varieties and (iii) modern molecular genetics, made feasible by the polymerase chain reaction.

2. Microbial germplasm collections and the war on infectious diseases

Successful commercial production of antibiotics was made possible by the genetic and metabolic properties of the strain of *Penicillium chrysogenum* known as NRRL 1951. This strain was isolated from a moldy cantaloupe found at a fruit market in Peoria, Illinois, in 1943 by Mary Hunt on behalf of Kenneth Raper, who was working on a US Department of Agriculture (USDA) project to improve penicillin production (Katz 2006) in collaboration with colleagues at the ARS Culture Collection in Peoria, Illinois (Demain 2006; Raper 1946). The culture collection was able to organize subsequent distribution of increasingly efficient strains and this led to large-scale production of penicillin during World War II, saving 'countless lives' (Harden 2001) and, of course, many lives thereafter.

'The advent of penicillin was not just a turning point in the use of medicines, but also a turning point in the commercial and public significance of drugs … . The growth of companies such as Pfizer, Merck and Glaxo to the highest rank of global companies can be directly attributed to this development' (Bud 2008). Ultimately this has led to a large bio-pharmaceutical industry producing not just antibiotics but also immunomodulatory drugs such as cyclosporine, chemotherapeutics, and some of the most profitable metabolic drugs, exemplified by the cholesterol-lowering statins. Additional impact is seen in the widespread use of microbial enzymes for production and processing of food and fiber as well as for consumer applications such as laundry detergents and personal care products.

Early recognition of the critical importance of microbial germplasm led to the implementation of the Budapest Treaty of 1955, which established a network of International Depository Authorities (IDA): collections responsible for maintaining and distributing the biological materials covered by patent protection. Most countries have at least one IDA in addition to smaller collections emphasizing the *ex situ* preservation of local microbial biodiversity and these collections depend on organizations such as the World Federation for Culture Collections (*http://www.wfcc.info/*) for long-term leadership.

3. Plant germplasm and the Green Revolution

Publicly funded germplasm collections also led to the Green Revolution, which began with 'high-yielding, short-statured wheats' that can trace their origin to a Japanese-US variety known as Norin-10 (Qualset and Shands 2005). This variety was crossed with Washington State winter wheat varieties by Orville Vogel, a USDA breeder, and resultant lines were shared with plant breeder Norman Borlaug, who combined them with germplasm from the collection at CIMMYT (International Maize and Wheat Improvement Center) (Iwanaga 2009) to produce high-yielding, short-statured wheat varieties. The genes present in these varieties enabled introduction of 'dwarfing traits' (reduction in plant height) such that stems could support the heavy weight of high-yielding heads of grain, thus avoiding the falling over (lodging) of the crop. This success has led to the Green Revolution, widely credited as preventing certain famine, and led to Dr Borlaug receiving the 1970 Nobel Prize for Peace. Because of the ability to access material from multiple collections it is well acknowledged that 'genebanks were crucial to this success' (Qualset and Shands 2005). The crucial importance of plant germplasm has led to the establishment of a number of plant germplasm repositories, including the USDA National Center for Genetic Resource Preservation in Fort

Collins, Colorado, and, more recently, the Svalbard Global Seed Vault in Norway. While appropriations for the US National Plant Germplasm System (NPGS) are relatively stable, significant reductions in both operations and research expenditures have occurred subsequent to the economic downturn of 2008. The NPGS budget has been just above $40 million since 2003, with a high of more than $43 million in 2007 (Bretting 2009). Despite the relatively secure situation for plant germplasm, even venerated collections are at risk. In 2010 the Russian Pavlovsk Experimental Station of the NI Vavilov Institute of Plant Industry near St. Petersburg was threatened with destruction, despite a history of over 80 years as a pioneering plant germplasm repository (Parfitt 2010). This collection, made famous by the staff's refusal to eat potatoes and seeds from the collection during the siege of Leningrad (Raeburn 1996), maintains plant varieties native to Russia and available nowhere else.

4. Microbial germplasm and the revolution in molecular genetics

Another Nobel Prize–winning invention finds its roots in a microbial germplasm repository. That is the development of the polymerase chain reaction (PCR), whose essential ingredient taq polymerase is a metabolic product of a thermophilic bacterium, *Thermus aquaticus*. PCR, which is not practical using thermo-labile enzymes, was developed by Kerry Mullis at Cetus Corporation. Initial experiments required the addition of polymerase enzyme at each cycle, and so the investigators at Cetus obtained a sample of the bacterium *Thermus aquaticus* ATCC 25104 from the American Type Culture Collection (ATCC), then located in Rockville, Maryland (Mullis *et al.* 1986; Innis *et al.* 1988). Most readers of these paragraphs will have one or more thermal cyclers in their laboratories, and all will recognize the impact of PCR on every aspect of modern biological inquiry, and on biotechnology and healthcare. Had the strain of *T. aquaticus* not been available in a public repository, the experiments that made PCR a practical application might not have been conducted.

5. Future prospects

Such revolutions are unanticipated by all but the most perspicacious (or clairvoyant!). It may seem folly to predict the next revolutions in biotechnology. However, there are two candidates from agriculture that bear inspection:

The first is the long-sought ability to harvest cereal crops without yearly sowing. While any commercial production of perennial wheat is in the distant future, perennial cereals have been created via hybridization from wheat and closely related grasses (e.g. PI 550713 *Agrotriticum* sp.) using germplasm from the collections of the NPGS, the Wheat Genetics Resource Center and other germplasm collections. These crosses and their parent materials are also highly resistant to a number of diseases attacking wheat (Cox *et al.* 2002). Scientists are actively screening other publicly available germplasm materials for use in perennial wheat breeding, especially those germlines potentially adapted to dryland farming (Murphy *et al.* 2007).

The second candidate is found at the interface of microbial genetics and agriculture. Beneficial fungal endophytes of plants have the possibility of being the cornerstone of an incipient agricultural revolution. One such symbiosis is already in commercial production, and is derived from NPGS material. This tall fescue forage grass contains a fungal endophyte that is non-toxic to livestock but deterrent to insects (Clement *et al.* 2009). The grass, on the market as MaxQ (North America) and MaxP (Australia and New Zealand), is produced under US Patent 6111170. Other research, also using the NPGS material, has produced endophyte-containing forage grass under US Patent 7465855.

Perennial wheat or endophytes in forage grass may or may not become the next wave of agricultural biotechnology. However, the critical importance of germplasm collections to medicine, to agriculture and to biotechnology is not speculative. Germplasm from publicly funded collections was critical for launching the three biggest biotechnological revolutions of the 20th century.

6. Conclusions

While these examples demonstrate the clear value of germplasm collections, support for living *ex situ* collections is perennially inadequate. The US National Science Foundation supports fewer than 20 collections of living material, and these are mostly genetic in emphasis. Among them are stock centres for fungal genetics (McCluskey *et al.* 2010), *E. coli, Dictyostelium*, *Chlamydomonas* and *Drosophila*. The ATCC has a broad variety of materials, but because of the independent and non-profit nature of its collection, ATCC cannot accept the large numbers of unique isolates being used in modern scientific research. The US National Institutes of Health and US Department of Defense support collections of materials relevant to human and veterinary health. There is no collection, however, that is prepared to accept and maintain the wide variety of material being isolated and characterized by researchers around the US or around the world. There is no comprehensive, publicly supported collection of plant-associated microbes, although some collections of plant-associated bacteria, yeasts, and other functional groups of plant-associated microbes receive public support. International efforts, such as the Global Biological Resource Center Network (Smith 2010), will help in promoting germplasm collection activities, but national efforts, in every country, will be needed to maintain the germplasm resources that could spur the breakthroughs leading to the next revolution.

The authors strongly advocate that public funding for germplasm repositories be sufficient for the collection, preservation and distribution of these organisms, and that curatorial and research staff be adequate in numbers and training.

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