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REVIEWS

Science & Society

The Case for Basic Biological Research

Isobel Ronai [1,2,3,*] and Paul E. Griffiths [2]

The majority of biomedical and biological research relies on a few molecular biology techniques. Here we show that eight key molecular biology techniques would not exist without basic biological research. We also find that the scientific reward system does not sufficiently value basic biological research into molecular mechanisms.

Many funding agencies around the world see fundamental research as dispensable. While the scientific community has the widespread perception that basic research is vital, the arguments of prominent advocates are often anecdotal [1] and have been criticized as fictional stories [2]. There is a critical lack of systematic studies that provide evidence for the importance of basic biological research. If researchers have evidence for the value of basic research, they will be better able to make the case for continued investment in basic biological research capacity.

We use straightforward case studies from the development of important molecular biology techniques [3] to highlight the critical role of basic biological research for applied research. Key techniques include: restriction enzymes; DNA sequencing; PCR; gene targeting; GFP; RNAi; induced pluripotent stem (iPS) cells; and clustered regularly interspaced short palindromic repeats (CRISPR)–CRISPR-associated protein (Cas) (Box 1 and [3]).

The eight molecular biology techniques are innovations that are used in a wide range of applications that address major global challenges and improve quality of life. For example, the technique RNAi (which is used to inhibit gene expression) has been instrumental for medicine with the creation of therapeutics to fight disease [4–8].

If these molecular biology techniques disappeared today, the majority of biological and biomedical research would cease. For example, the technique PCR (which is used to amplify DNA fragments) enables major advances in knowledge and is a crucial driver of research. PCR has been mentioned in over 650 000 scientific documents (extracted from the Web of Science Core Collection) since its development in 1985 (Table 1).

Basic Biological Research Is Crucial for the Development of Molecular Biology Techniques

Remarkably, the majority of molecular biology techniques not only exist due to basic biological research into evolved natural systems, but rely on naturally occurring mechanisms [3]. For example, the technique CRISPR–Cas (which is used to edit DNA) utilizes a mechanism from bacteria where its biological function is to destroy the foreign nucleic acid of bacteriophages [9].

We have previously shown that all of these molecular biology techniques are developed in a four-stage process: first, a natural molecular mechanism is discovered through curiosity-driven research; second, the 'triggers' (the protein effector and specificity target, which are sometimes the same) of the molecular mechanism are identified; third, the triggers are applied as a technique; and fourth, the technique matures [3].

CRISPR–Cas9 shows the typical four-stage process of molecular biology technique development [3]. First, Ishino *et al*. (Table 1) were conducting curiosity-driven research and discovered, in the genome of the bacterium *Escherichia coli*, the CRISPR motif. A few decades later, Makarova *et al*. (Table 1) identified the key effector protein of the CRISPR–Cas mechanism, Cas 9, in the genome of multiple bacteria. In addition, the nucleic acid sequence specificity of the CRISPR–Cas9 mechanism was found to comprise two components. Brouns *et al*. (Table 1) identified, in *E. coli*, the first component of specificity as CRISPR RNAs (crRNAs) and Jinek *et al*. (Table 1) identified, in *Streptococcus pyogenes*, the second component of specificity as trans-activating CRISPR RNA (tracrRNA). The breakthrough occurred when Jinek *et al*. (Table 1) applied the accumulated basic research knowledge of the CRISPR–Cas mechanism. They combined the specificity of a tracrRNA–crRNA complex (the 'single-guide RNA') with the effector Cas9 into a technique that causes the sequence-specific cleavage of target DNA. In the subsequent 6 years, the technique of CRISPR–Cas9 has been rapidly refined, such as the back-to-back articles by Cong *et al*. (Table 1) and Mali *et al*. (Table 1) that used CRISPR–Cas9 to edit the genome of human cells.

The basic and applied phases of the work that led to the development of each technique have been identified. We classify the discovery and identification phases as basic research, whereas the application and maturation phases are applied research (Table 1). It is important to note that in each case the basic science researchers did not anticipate the later application of their work, but the technological advances relied on this knowledge. Furthermore, almost all of the basic research was funded by government agencies or directly from universities (Table 1).

Interestingly, we find that the time lag between basic biological research and its application as a molecular biology technique is, on average, 23 years (Table 1). The long time lag for return on investment in conjunction with the diversity of benefits from basic research means that it is nearly impossible to precisely quantify the benefit

Box 1. Eight Molecular Biology Techniques That Are Major Scientific Advances

We investigate the scientific achievements of restriction enzymes, DNA sequencing, PCR, gene targeting, GFP, RNAi, iPS cells, and CRISPR–Cas9 (Table 1). The techniques are in chronological order and the development of each technique is split into four phases (adapted from Table 2 in [3]). We classify each phase as either basic or applied research and cite the scientific article where this research was conducted (full references available in the supplemental information online). For each article we first state whether it was published in a high-profile scientific journal (e.g., *Nature*, *Science*, *Cell*, *Proceedings of the National Academy of Sciences of the United States of America*). Second, we obtained the citation count for each article from the Web of Science Core Collection (extracted 7 October 2018). In addition, some of these articles are ranked in the top-100 most highly cited scientific articles [11]. Third, we determined whether any patent holder for the technique is an author of the article. Last, we determined whether any Nobel Prize laureate ('Physiology or Medicine Prize' or 'Chemistry Prize'; www.nobelprize.org/nobel_prizes/) for the technique is an author of the article. We find differential treatment of applied and basic research.

of a specific basic research project, but the rate of return on investment for basic biological research in general is clearly very high [10].

The Development of Molecular Biology Techniques and the Scientific Reward System

The development of each molecular biology technique is a major scientific and technical accomplishment. This research excels on every metric of scientific success. We have found that the allocation of scientific credit is generally bestowed on the applied research phases of molecular biology technique development rather than the basic biological research that enabled these techniques to be developed.

Molecular biology technique development results in landmark scientific articles. The majority of these articles are published in the highest-profile, general scientific journals (Table 1). However, a clear bias is revealed when we compare the applied phases of technique development with those that are entirely basic research. Over 90% of the articles on applied research are published in high-profile journals, compared with approximately 20% of articles on basic biological research (Table 1). In addition, the majority of the scientific articles that detail the development of the techniques are highly cited (i.e., have >1000 citations [11]; Table 1). Three of the techniques have an article ranked in the top 100 most highly cited scientific articles in any scientific area (Table 1 and [11]). However, almost 90% of articles on applied research are highly cited, compared with less than 30% of articles on basic biological research (Table 1).

The researchers who develop these molecular biology techniques receive noteworthy scientific rewards. The majority of the eight molecular biology techniques are patented as methods (Table 1). Perhaps predictably, the patent holders are always the researchers involved in the 'application of trigger' phase [3], but never those involved in the phases of solely basic biological research (Table 1). With the current exception of CRISPR–Cas (which was developed only a few years ago; Table 1), each of these techniques has been the subject of a Nobel Prize, the highest award in science and a leading topic in mainstream media reporting (Table 1). The Nobel laureates associated with each technique always include at least one of the researchers involved in the 'application of trigger' [3] phase, but rarely those who conducted the basic biological research (Table 1).

Our data suggest that the basic phase of molecular biology technique development is systematically less recognized than the applied phase (Box 1). The scientific reward system itself does not sufficiently value basic biological research and it seems that this might be a factor in it being underappreciated outside scientific circles. We advocate that the scientific reward system should give greater recognition to the contribution of the researchers who conduct the initial discovery research that leads to these transformational techniques.

Concluding Remarks

Basic research is not sufficiently valued by the scientific reward system, funding agencies, or the general public. We show that basic biological research is in fact crucial for the development of innovative molecular biology techniques that bring about major scientific advances.

The transformational power of these molecular biology techniques means that there should be strong incentives to develop new techniques and, by extension, for basic biological research. There are many opportunities for future technique development from studying the diversity of nature and its molecular mechanisms. Furthermore, technique development has in the past been serendipitous. We suggest that the identification of natural mechanisms with programmable specificity and effectors with high efficiency (i.e., enzymes) [3] should be prioritized.

At this moment in history, basic research lacks adequate funding and is in a vulnerable position [10]. We have shown that basic biological research (the characterization of natural molecular systems) should not have to be constantly justified by researchers. Policymakers and those in power must understand that the outcomes of basic biological research cannot be compared with applied research; rather, it is the foundation of applied research. Basic biological research is a long-term investment in knowledge seeking that does not have immediate payoffs, but the longer-term payoffs are immense. We argue that funding agencies need to maintain their investment in basic biological research capacity to ensure that future scientific progress and technical innovations occur.

Table 1. The Scientific Achievements of Eight Molecular Biology Techniques

Molecular biology technique	Phase of development	Type of research	Refs	Published in high-profile scientific journal	Citation count (and top-100 rank)	Number of patent holders as authors (and patent number)	Number of Nobel Prize laureates as authors
Restriction enzymes	Discovery	Basic	Luria and Human (PMID: 12999684)		237	N/A	0
			Dussoix and Arber (PMID: 13888713)		170	N/A	1
	Identification of specificity/ effector	Basic	Smith and Welcox (PMID: 5312500) Kelly Jr and Smith (PMID: 5312501) (paper in two parts)		597 428	N/A	1
	Application of trigger	Applied	Danna and Nathans (PMID: 4332003)	✓	308	N/A	1
	Maturation	Applied	Feinberg and Vogelstein (PMD: 6312838)		21 655 (#40)	N/A	0
DNA sequencing	Discovery	Basic	Watson and Crick (PMID: 13168976)		645	N/A[a]	2
			Matthaei and Nirenberg (PMID: 13768264)		22	N/A[a]	1
	Identification of effector	Basic	Kornberg *et al.* (1956)[f]		No data	N/A[a]	0
	Identification of specificity	Basic	Atkinson, *et al.* (PMID: 4312461)		159	N/A[a]	0
	Application of triggers	Applied	Sanger, *et al.* (PMID: 271968)	✓	66 986 (#4)	N/A[a]	1
	Maturation	Applied	The *C. elegans* Sequencing Consortium (PMID: 9851916)	✓	2821	N/A[a]	0
			International Human Genome Sequencing Consortium (PMID: 11237011)	✓	13 360	N/A[a]	0
PCR	Discovery	Basic	Watson and Crick (PMID: 13168976)		645	0	2
			Meselson and Stahl (PMID: 13635537)	✓	872	0	0
	Identification of effector	Basic	Kornberg *et al.* (1956)[f]		No data	0	0
	Identification of specificity	Basic	Kornberg, *et al.* (PMID: 13363894)		157	0	0
	Application of triggers	Applied	Saiki, *et al.* (PMID: 2999980)	✓	7360	6 (US4683202 and US4683195)	1
	Maturation	Applied	Saiki, *et al.* (PMID: 2448875)	✓	15 712 (#63)	5[b] (US4683202 and US4683195)	1[b]
Gene targeting	Discovery	Basic	Gluzman, *et al.* (PMID: 199739)		15 16	0	0

Table 1. (continued)

Molecular biology technique	Phase of development	Type of research	Refs	Published in high-profile scientific journal	Citation count (and top-100 rank)	Number of patent holders as authors (and patent number)	Number of Nobel Prize laureates as authors
			Vogel, *et al.* (PMID: 199740) (paper split)				
	Identification of specificity	Basic	Hinnen, *et al.* (PMID: 347451)	✓	1871	0	0
	Application of trigger	Applied	Smithies, *et al.* (PMID: 2995814)	✓	639	1 (US5416260)	1
	Maturation	Applied	Thomas and Capecchi (PMID: 2822260)	✓	1667	0	1
			Doetschman, *et al.* (PMID: 3683574)	✓	480	1[b] (US5416260)	1[b]
			Mansour, *et al.* (PMID: 3194019)	✓	1381	0	1[b]
	Identification of effector	Basic	Multiple effectors	–	–	–	–
GFP	Discovery	Basic	Davenport and Nicol (https://doi.org/10.1098/rspb.1955.0066)		51	0	0
	Identification of effector	Basic	Shimomura, *et al.* (PMID: 13911999)		1306	0	1
	Identification of specificity	Basic	Prasher, *et al.* (PMID: 1347277)		1490	1 (US5491084)	0
	Application of trigger	Applied	Chalfie, *et al.* (PMID: 8303295)	✓	4532	2[c] (US5491084)	1
	Maturation	Applied	Heim, *et al.* (PMID: 7854443)	✓	1104	0	1
			Cormack, *et al.* (PMID: 8707053)		2158	0	0
RNAi	Discovery	Basic	Napoli, *et al.* (PMID: 12354959)		1500	0	0
	Identification of specificity (component) and application of trigger	Basic and applied	Fire, *et al.* (PMID: 9486653)	✓	8740	6 (US6506559)	2
	Identification of specificity (processed component)	Basic	Hamilton and Baulcombe (PMID: 10542148)	✓	1812	0	0
	Identification of effector	Basic	Hammond, *et al.* (PMID: 10749213)	✓	1934	0	0
	Maturation	Applied	Elbashir, *et al.* (PMID: 11373684)	✓	6618	0	0
iPS cells	Discovery	Basic	Gurdon (PMID: 13951335)		516	0	1

Table 1. (continued)

Molecular biology technique	Phase of development	Type of research	Refs	Published in high-profile scientific journal	Citation count (and top-100 rank)	Number of patent holders as authors (and patent number)	Number of Nobel Prize laureates as authors
	Identification of specificity/ effector and application of trigger	Basic and applied	Takahashi and Yamanaka (PMID: 16904174)	✓	11 952	2 (US8058065)	1
	Maturation	Applied	Takahashi, *et al.* (PMID: 18035408)	✓	9494	2[b] (US8058065)	1[b]
CRISPR–Cas9	Discovery	Basic	Ishino, *et al.* (PMID: 3316184)		423	0	N/A[d]
	Identification of effector	Basic	Makarova, *et al.* (PMID: 11788711)		178	0	N/A[d]
	Identification of specificity (component A)	Basic	Brouns, *et al.* (PMID: 18703739)	✓	916	0	N/A[d]
	Identification of specificity (component B) and application of triggers	Basic and applied	Jinek, *et al.* (PMID: 22745249)	✓	3384	4 (US20140068797)[e]	N/A[d]
	Maturation	Applied	Cong, *et al.* (PMID: 23287718)	✓	4407	1 (US8697359)[e]	N/A[d]
			Mali, *et al.* (PMID: 23287722)	✓	3228	0	N/A[d]

[a]For background on why DNA sequencing was not patented, see [12].
[b]Author(s) also awarded for an earlier publication.
[c]One author also awarded for an earlier publication.
[d]Developed as a technique only 6 years ago.
[e]Under a long-running patent application battle [13,14].
[f]Kornberg, A. *et al*. (1956) *Fed. Proc.* 15, 291–292.

Acknowledgments

We thank Michael Holmes, Josh Christie, Kate Lynch, Jun Tong, Tim Dean, Ben Oldroyd, and members of our groups for their thoughtful comments on this article I.R. was financially supported by an APA and P.E.G. is the recipient of an Australian Research Council Australian Laureate Fellowship (FL170100160), both funded by the Australian Government.

Supplemental Information

Supplemental information associated with this article can be found online at https://doi.org/10.1016/j.molmed.2018.12.003.

[1]Charles Perkins Centre, The University of Sydney, Sydney, NSW, Australia
[2]School of Life and Environmental Sciences, The University of Sydney, Sydney, NSW, Australia
[3]Department of Ecology, Evolution and Environmental Biology, Columbia University, New York City, NY, USA

*Correspondence: isobel.ronai@sydney.edu.au (I. Ronai).

https://doi.org/10.1016/j.molmed.2018.12.003

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