Viewpoint

Patents and intellectual property: a salvation for patient-oriented research?

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The UK Medical Research Council (MRC) sent a letter to UK researchers in 1999 informing them that the MRC still supported clinical research and clinical scientists. I wonder how anybody could ever have thought otherwise? The status of clinical science and the widely perceived diminishing strength of clinical science is not confined to the UK, although given the traditional strengths of the UK in this area, it is perhaps more noticeable here. Even in the thriving biomedical community of the USA there is concern about the powerful disincentives to clinical science.[1–3]

Joe Goldstein and Michael Brown won their Nobel Prize for medicine for the discovery of the low-density-lipoprotein receptor. Or, to put it in a more meaningful way, for their ability to take a small child with ischaemic heart disease and hypercholesteraemia and make her condition tractable to basic science.[4,5] They have written with perhaps greater insight than anybody else about the difficulties of clinical science.[1,4–6] Goldstein and Brown classify biochemical research into three types: basic research, disease-oriented research, and patient-oriented research. Basic research would comprise "pure" biochemistry and the like; whereas disease-oriented researchers might include Bert Vogelstein for his work on colorectal cancer and Stanley Prusiner for his discovery of the role of prions in neurodegenerative disease.[1]

Goldstein and Brown are, however, most concerned with patient-oriented research, an activity that characterised their own early research career. They define patient-oriented research by the handshake test—the experimenter shakes hands with those experimented on. Examples of patient-oriented research they cite include the discovery of AIDS,[7] by Gottlieb and colleagues, the delineation of Lyme disease by Steere and colleagues,[8] and Marshall and Warren's championing of *Helicobacter pylori* as the cause of peptic ulcers.[9] Patient-oriented research, they state, is under increasing threat. Those who pursue it being characterised by the four Ps: passion, patients, patience, and (grant) poverty. Furthermore, in an imaginative leap, they argue that one of the reasons the biotechnology industry has had little impact on disease has been the absence of researchers with patient-oriented skills who could provide genuine clinical insight into disease. The rate-limiting step therefore is not the imagination of the basic scientists nor the ability to clone genes or screen for small molecule receptor antagonists, but, rather, the lack of patient-oriented research to point out the Achilles' heel of a disease. Instead, Goldstein and Brown observe that medically qualified researchers take advantage of the abundance of kits and ease of much laboratory experimentation and abandon any hope of solving a clinically relevant problem; instead they choose to pursue second-rate problems in some fast-moving area of basic science. As they say: "ordinary basic research is easier to perform successfully than is clinical research".[1]

Cash and kudos

I wish to build on these arguments and extend them in an unlikely direction. One way of strengthening patient-oriented research is to reconsider the funding base. This type of research still continues as though the intellectual landscape of medical research had not been irreversibly changed by money and corporate strategy, whether that of industry or research councils—yet research needs cash, and without cash there is little kudos.

My research interest is the genetic basis of skin susceptibility to ultraviolet radiation and the causes of melanoma. Scientific attention had focussed on the use of genetic markers to predict melanoma susceptibility, the course of the disease, and response to therapy. If such genetic markers are eventually developed they will be patented and exploited—this practice is routine, and the approach is generic to many different diseases. Yet at present the most useful marker of prognosis in melanoma relies on the measurement of the depth of invasion of the primary tumour with a ruler. Measurement of tumour depth is a simple bioassay for a tumour's life history and likely behaviour. This is classic patient-oriented research: simple and cheap, but nobody else did it until Breslow.[10] Yet this invention is not protected as intellectual property. Depth measurement is used universally by all providing clinical care for patients with melanoma, and is an important covariable in trials of novel agents for melanoma, and yet attracts no income for its inventor.

There are other examples. The best predictors of susceptibility to melanoma do not rely on genotype but on phenotypic scales such as the propensity to sun burn in response to repeated sunshine, combined with factors such as hair colour, family history, sun-exposure history, or the number of moles.[11] Algorithms incorporating these items are likely to be better predictors than any available laboratory tests, although they remain underdeveloped—probably because they are not seen as providing the possibility for profit. They are not even recognised as intellectual inventions. There are many other examples in other areas of medicine—the Apgar score, coma-rating scales, and the myriad of variables used to stratify patients in clinical trials.

Of course the principal invention on which all therapy is predicted is that of diagnosis. Goldstein and Brown[1]

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remind us that the description of syndromes or classification of apparently heterogeneous clinical material is rate limiting for advances in clinical care. This insight remains neglected, difficult, and notable by its absence from discussions of how to fund biomedical advance. For instance, trials of patented therapies for AIDS all depend upon the intellectual insight provided by Gottlieb and colleagues.[7] AIDS is therefore an intellectual invention. However, when therapeutic studies are done, no financial recognition is made of the intellectual property rights of those who actually discovered the disease; meanwhile royalties accrue to those who, for example, invented the PCR technique that is used to assess HIV viral load. The point is not that royalties or patents are unreasonable—rather that there needs to be a more widespread recognition of primary acts of clinical creativity.

Another area where patient-oriented research fares badly is when agents developed for one purpose are found in the clinic to have other therapeutic uses—for example phototherapy in dermatology. An example would be the use of TL01 phototherapy originally developed for psoriasis and now being used to treat eczema and even primary photosensitive dermatoses. The continued evolution of the clinical roles of sildenafil, selective serotonin reuptake inhibitors, β-blockers, immunosuppressives, and angiotensin-converting-enzyme inhibitors all show that this pattern of clinical discovery is real and the norm. Instead there is a tendency to degrade such clinical innovation as mere serendipity, or to imagine that rational drug development will supersede this type of discovery. But the increased cost of developing new therapeutic agents will, if anything, put an even greater value on strategies that define all the therapeutic opportunities a compound may offer at an earlier stage. Indeed, it is frequently the discovery of a new therapy that provides the fresh mechanistic insight into a disease that determined the pattern of future basic research. An example from my own speciality illustrates these points.

Seborrhoeic dermatitis is a common rash mainly affecting the scalp, face, and upper torso with some similarities to psoriasis. The cause of the rash was long debated. A particular yeast, *Pityrosporum ovale*, can be found on the skin, but it was unclear whether it was primary or merely present in increased amounts as a result of a putative primary abnormality of epidermal proliferation. Although this debate has simmered inconclusively for over half a century, Sam Shuster exploited ketoconazole, a new drug developed for other reasons, to test the causal link.[12] The rash resolved suggesting that the yeast is indeed causally implicated in this chronic inflammatory disease. With little project funding, and over 2 years, the cause of a common chronic disease had been discovered, a treatment invented, and clinical practice changed. Yet, because the work was unrelated to any basic science it remained largely invisible at the level of grant funding or of intellectual property.

Biotech: the market within us

We are living through a commercially driven expansion in the biological sciences—the reason being the belief held by many corporations that one of the major commercial markets of the future lies within our own bodies. If patent and intellectual property rights are only applied to laboratory discoveries and procedures, patient-oriented research will continue to fare badly. What I am suggesting is that inventions such as Breslow's technique of measuring melanoma prognosis by assessing depth, or Gottlieb's delineation of the AIDS diagnosis, are conceivable as intellectual property and amenable to patenting in the same way that kits for measuring melanoma markers or HIV load are regarded. And the injection of resources that this shift would allow would provide exactly the kind of encouragement needed to revive the dying science of patient-oriented research.

Seeking intellectual-property protection for a syndrome or disease as if it were an invention may seem strange, but it is no more absurd that patenting DNA of unknown function. Critics may label this proposal as just another unnecessary burden on the cost of health—leading to the need for royalty payments for reporting a particular diagnosis, or the use of a clinical rating scale. In practice charges may only be levied when novel commercial therapies are being introduced or during clinical trials to establish the value of new therapies. By such means, real clinical science—such as syndrome delineation, understanding of clinical heterogeneity, and discovery of new uses for drugs developed for other reasons—are all in principle capable of generating income. This income may in turn encourage institutions and funding agencies to focus on clinical science, develop appropriate career structures, and allow patient-oriented research to interact with biotechnology as an equal partner. If, as Goldstein and Brown and others have argued,[1,13,14] patient-oriented research is a rate-limiting factor on new discovery, the thought experiment I propose requires consideration.

References

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