Drug research needs serendipity

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The molecular revolution was supposed to enable drug discovery to evolve from chance observation into rational design, yet dwindling pipelines threaten the survival of the pharmaceutical industry. What went wrong?

The answer, we suggest, is the mismeasure of uncertainty, as academic researchers underestimated the fragility of their scientific knowledge while pharmaceuticals executives overestimated their ability to domesticate scientific research.

For all the breathless headlines proclaiming breakthrough discoveries, the truth is that we still do not understand what causes most disease. Even when we can identify a responsible gene or implicate an important mutation, we have made only limited progress in turning these results into treatments.

Medical research is particularly hampered by the scarcity of good animal models for most human disease, as well as by the tendency of academic science to focus on the "bits and pieces" of life – DNA, proteins, cultured cells – rather than on the integrative analysis of entire organisms, which can be more difficult to study.

Nevertheless, real scientific progress has occurred, inviting the question: why do pharmaceutical companies, which spend billions of dollars each year trying to turn advances into treatments, have so little to show for their efforts? Answer: spreadsheets are easy; science is hard.

Like most corporations, pharma companies seek to identify the largest markets they can find and develop products for these customers – an approach quite sensible in theory, but less so in practice. First, drug sales are notoriously difficult to foresee even at the time the medicine hits the market, so predicting sales a decade or more ahead of registration, when the research and development process typically begins, is generally a fool's errand, yielding more false precision than true insight. Yet much of contemporary pharma R&D is driven by this sort of rigid planning.

Second, the process of drug development is also very difficult to predict, because of both our limited understanding of disease and our inevitably imperfect understanding of the effect any new compound will have on the body. While design played a pivotal role in the development of effective HIV drugs, other modern medications were discovered in the old-fashioned way: by accident. Viagra, for example, was originally developed as a treatment for chest pain.

In the face of **declining productivity**, pharma companies have been trying to boost output by increasing efficiency, narrowing their focus to a handful of disease areas, shelving safe but ineffective compounds without fully exploring their scientific potential and trying to ensure that each project the company is working on is carried out with a clearly defined market segment in mind. Unfortunately, for new medicines in particular, this strategy often fails significantly to reduce exposure to negative uncertainty – all the bad things that can happen during drug development – and eliminates much of the exposure to positive uncertainty (serendipity) that remains so vital.

So intent are managers on maintaining focus that important opportunities for novel discovery are lost, as is the intellectual space for tinkering and capitalising on the chance observations and unexpected directions so important in medical research. Instead, pharma executives are creating an ever-more-rigid environment and then wondering why their productivity is going down, and why they have such difficulty attracting and retaining talent.

Fortunately for patients, hope may lie just round the corner. As pharma companies cut costs by outsourcing large parts of their operations, service providers have sprung up around the world to fulfil these functions. This is good news: while the pharmaceutical industry is ripe for disruptive innovation, the barriers to entry have been far too high for anyone new to break through. If the trend to outsourcing continues and if the main competence of pharma companies becomes (as some have suggested) simply their ability to orchestrate the entire process, it is not difficult to imagine that an innovator – particularly an innovator with a greater appreciation of the nuances of science – might be able to do this a lot better.

The next-generation pharma company will create a lean, agile organisation able to capture, consider and rapidly develop the best scientific ideas in a wide range of disease areas and aggressively guide these towards the clinic. Small market size will not deter their pursuit of promising drugs with a clear and comparatively inexpensive path to clinical development; their ideal portfolio will consist of an extensive collection of such molecules, cheap options that may offer unexpected benefit to patients and provide disproportionately large returns to investors.

If pharma companies want to stay in the game, their leaders will need to resist the false comfort of revenue predictions and valuation spreadsheets, and instead resolve to look uncertainty in the face, acknowledge its presence and embrace the opportunity it represents.

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