PHARMACEUTICAL EVOLUTION: CLINICAL SELECTION VERSUS INTELLIGENT DESIGN

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Charles Darwin's opponents sometimes advance an alternative theory, known as "Intelligent Design". They argue that the human eye, a favourite example, is so exquisite that it cannot be the mere consequence of natural selection acting on random heritable variation. Instead, there must be an Intelligent Designer. Most biological scientists view Intelligent Design as a fallacy. The argument also irritates squid, whose magnificent eyes avoid some bad design features of the human model [1].

There is an analogous divergence when it comes to pharmaceutical innovation. On one hand, many successful drugs appear to have been Intelligently Designed for a specific therapeutic use [2] [3]. Their designers exist, and the few I have met seem ferociously intelligent. Here, Gleevec/imatinib plays the role that the human eye does for creationists. On the other hand, luck is often important and drugs' natural environment, the clinic, can select in a way that the Intelligent Designers would not have anticipated [3] [4].

I think there is a problematic tendency to over-estimate the importance of Intelligent Design versus Clinical Selection in pharmaceutical innovation. Intelligent Design is the public face of commercial R&D. It dominates academic biomedical science. It influences drug regulators and doctors. It aligns with the most valuable kinds of intellectual property, and so influences pricing and reimbursement. In contrast, things are made difficult for late-stage serendipity, for the real-word experiences of patients and doctors, and for creative users, who, in my view, already do much of the innovative heavy lifting. The skew is reflected in relative over-investment in "molecular reductionism" [5], which often lacks predictive validity, and in relative under-investment in optimizing the use of drugs in their natural environment. The skew can also squeeze the pharmacological variation on which Clinical Selection acts, slowing the rate of therapeutic evolution.

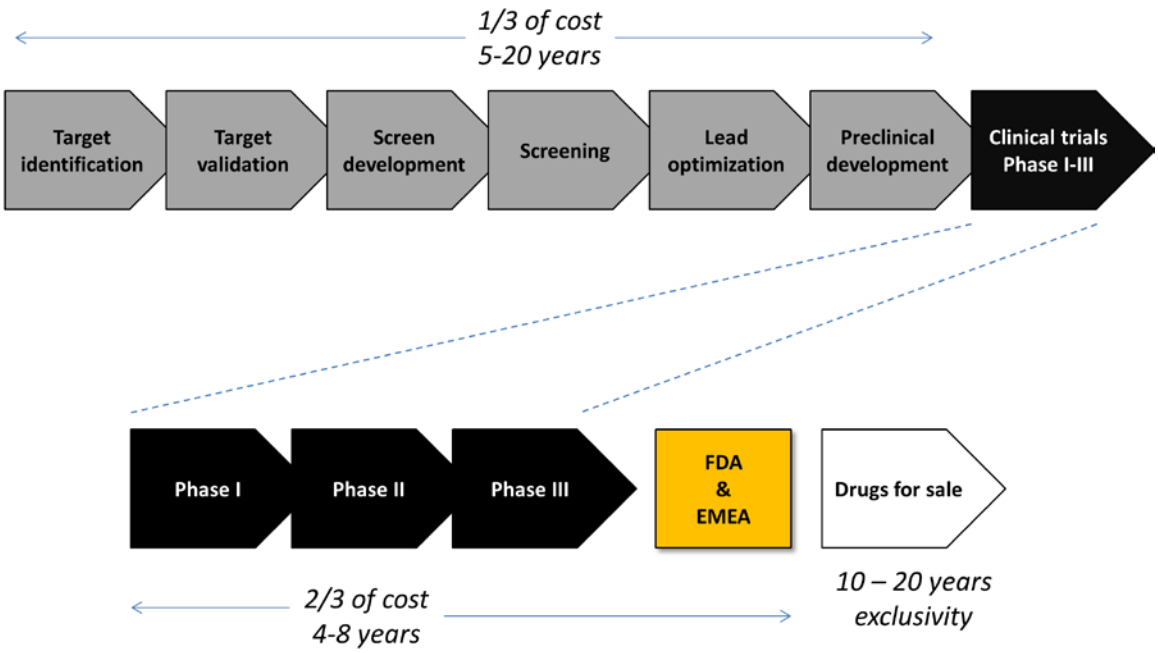
From mechanistic story to creation myth

Nearly all drugs are sold to regulators and prescribers with a mechanistic story: "*Disease phenotype y is caused by the (mis)behavior of molecular component x which can be drugged with drug d. Therefore drug d alleviates disease phenotype y.*" Sometimes these stories are both precise and true (e.g., when *y* = staphylococcal infection, *x* = DD-transpeptidase, and *d* = penicillin). Sometimes they are not (e.g., when *y* = ADHD, *x* = "*something to do with dopamine?*", and *y* = dextroamphetamine) [6].

Mechanistic stories transform into creation myths, around which society organizes both academic and commercial drug discovery. Nearly all drugs enter clinical development with a plausible mechanistic story. Around 10% succeed and emerge with their stories either intact or retrospectively adjusted for commercial consumption[1]. The other 90% fail for reasons on which their stories were silent. People outside of R&D rarely hear the stories of these 90%. It is survivor bias that makes both drugs and human eyes appear more Intelligently Designed than they actually are.

[1] For example, the drug Xalkori/crizotinib is now sold as an ultra-targeted ALK-inhibitor; an archetypical "personalized medicine" for patients with ALK-mutated lung cancers. Crizotinib does inhibit ALK, but it was produced during a campaign to inhibit a different protein, c-MET [48]. For similar comments on Avastin/bevacizumab and Gleevec/imatinib, see later.

Figure 1. Target-based drug discovery version 1.0



The drug industry generally describes R&D to outsiders in terms of Intelligent Design via "target-based drug discovery version 1.0" (Figure 1). This is an academic/industrial process built on a set of assumptions that mirror stories of drug action:

1) Molecular component *x*, the target, (mis)behaves in such a way that it causes disease phenotype *y* (hence the Target Identification and Target Validation chevrons in Figure 1).

2) Molecular component *x* can be drugged with drug *d* in a way that causes an improvement in *y* without an unacceptable decline in other phenotypic traits (hence the Screen Development, Screening, Lead Optimization, and Preclinical Development chevrons in Figure 1).

3) There exists a sufficient number of identifiable and exploitable instances of *x*, *d*, and *y* (hence taxes and philanthropy pay for basic academic biomedical science, and taxes and health insurance premiums incentivize commercial drug discovery).

4) Therefore, the academic/industrial process set out in the grey chevrons of Figure 1 will deliver, with high efficiency, a large number of good drug candidates into clinical trials (black chevrons).

But we have known for years that the academic/industrial process in Figure 1 **has not worked very well** [7] [8] [9] [10] [2]. The cost efficiency and quality of the scientific and technological tools available at each chevron have improved spectacularly. DNA sequencing has become over a billion times cheaper since the 1970s, for better Target

[2] Although there is evidence that enough experience has accumulated that it has started working a little better. See, for example, reference: [49].

Identification; transgenic mice have been invented, for Target Validation; the cost of high throughput screening tests has declined around 10 fold per decade; etc., etc. In contrast, there is a reproducibility crisis in academic biomedical science [11] [12] [13], drug industry R&D spending per approved drug has increased, in inflation adjusted terms, nearly two orders of magnitude since 1950 [8] and the drugs that the chevrons deliver into clinical development are more likely to fail now than in the 1970s. This shows that one or more of assumptions (1) to (4) must have been wrong. Yet Figure 1 remains the standard way of impressing the public and policy makers with the process of drug discovery.

The struggle for existence

While the story of drug discovery is framed in terms of Intelligent Design, the way money is spent points to a reality that Darwin would recognize; the production of variation followed by selection: "*… as more individuals are produced than can possibly survive, there must in every case be a struggle for existence...*" [14] The struggle is shown in R&D attrition statistics (e.g., 24 targets to hit projects, 15 lead optimization projects, 12 preclinical projects, etc., per approved drug) [15] and in the clinical development of successful drugs.

Avastin/bevacizumab, for example, is a monoclonal antibody that scavenges VEGF-A, an endogenous signaling molecule that stimulates the growth of new blood vessels. The drug has 7 FDA approved indications in oncology[3]. The FDA prescribing information cites 10 clinical trials on which these approved indications are based. The drug is used off-label in several other cancers, in eye diseases including age-related macular degeneration (AMD), and in a handful of other conditions.

I guess that a perfectly efficient, cost-conscious, Intelligent Designer could have got 7 indications approved by the FDA with 20 clinical trials or fewer (the 10 "pivotal" trials plus associated Phase I and Phase II efforts). If I go to the standard clinical trials database, clinicaltrials.gov, I can search for trials involving Avastin/bevacizumab. Limiting my search to interventional studies, I find not 20 trials, but 1,662. Now, many of them used Avastin/bevacizumab almost incidentally (e.g., as the standard of care on top of which to add a new treatment). Others were testing off-label uses that Roche/Genentech might not welcome (e.g., AMD where Avastin/bevacizumab competes with another drug, sold by Roche/Genentech, that is both more lucrative and FDA approved). However, Roche/Genentech had a hand in 506 trials, sponsoring 153 and collaborating on another 353.

If one skims through these 506 trials, and compares them with the 7 approved indications, one gets the strong impression of a selection process, albeit one that was highly directed and commercially astute. Roche/Genentech had no good way of predicting what Avastin/bevacizumab would do in patients, particularly in drug combinations – critical in oncology – where synergistic or cumulative efficacy and toxicity can both occur. The intellectual property clock was ticking. Other drugs were competing to capture valuable markets. Therefore, it made sense to run multiple trials in parallel,

[3] Two indications in metastatic colorectal cancer, and a single indication in each of non-squamous cell lung cancer, glioblastoma, metastatic renal cell carcinoma, cervical cancer, and ovarian cancer.

many of which could never inform the other development streams, and many of which led nowhere. Only now do we know that Avastin/bevacizumab was a relative success in some areas (e.g., metastatic colorectal cancer) but a relative or total failure in others (e.g., breast cancer, adjuvant colorectal cancer). At the same time, of course, the huge development program raised Avastin/bevacizumab's profile among oncologists. The drug was ubiquitous at cancer conventions for the best part of a decade.

Interestingly, while Avastin/bevacizumab struggled for existence, indication by indication, its mechanistic story has been up for debate. The drug was Intelligently Designed to **starve** the growing tumours of their blood supply [16]. It may, in fact, work in an entirely different way, by normalizing tumour blood supply [17] [18].

Similar comments apply to Gleevec/imatinib, although here there is the impression of a more narrowly focused selection process. There are 10 FDA approved indications; four in leukaemia that depend primarily on inhibition of bcr-abl, the target for which the drug was Intelligently Designed, and 6 others. The other indications depend on proteins that happen to be similar to bcr-abl, and which Gleevec/imatinib **fortuitously** inhibits. Clinicaltrials.gov shows 517 interventional trials involving Gleevec/imatinib. As with Avastin/bevacizumab, the drug is a control or background treatment in many of these trials. However, Novartis sponsored 86 and collaborated on another 84. The drug has seen development failures (e.g., glioblastoma) and results that may yet lead to unexpected successes (e.g., pulmonary arterial hypertension). As with Avastin/bevacizumab, the mechanistic story has shifted over time. In 2002, fresh from its first FDA approval, Gleevec/imatinib was "*a **selective** inhibitor of the BCR-ABL tyrosine kinase causative of chronic myeloid leukemia.*" [19] Now that the drug works in diseases that have nothing to do with bcr-abl, it has conveniently transmuted into "*a **broad-spectrum** tyrosine kinase inhibitor.*" [20] [my emphasis]

User-led innovation

Clinical trial sponsors pick which battles to fight and how to fight them, and – importantly – which battles to avoid. Trials are "*a messy mixture of science, regulation, public relations and marketing*" [8] which often lack what might be called ecological validity. This leads to another important Clinical Selection step that happens when drugs are released into their natural environment. They often do better or worse than expected when they meet real patients in the real world, with their comorbidities, concurrent medications, variable adherence, and given the fact that the things that patients find important are often not measured in trials. This real world step is not merely passive. Users, patients and doctors, are themselves important innovators.

User-innovators have been studied in a variety of technical fields, from mountain biking to scientific instruments. To quote from DeMonaco *et al.* [21], one of the few studies of user-led innovation in pharmaceuticals:

- "*Traditionally, it has been assumed by innovation process scholars, that product manufacturers would be the developers of all or most new products … However, empirical research during the past two decades has now shown that product users rather than manufacturers are the actual developers of many of the commercially important new products in fields studied to date… Users, it has been found, tend to develop products and applications involving functional*

novelty. In contrast, manufacturers tend to develop products and applications that address well-understood needs."

This makes sense. It is hard for most manufacturers to invest to satisfy uses that are not obvious at the point at which the investment is made. Pharmaceutical R&D decisions often require "target product profiles" against which to judge drug candidates. How can one produce a target product profile for medical needs that one does not understand?

DeMonaco *et al.* go on to argue that one should expect to high rates of innovation among the users of pharmaceuticals [21]:

- "*Clinical practitioners carry out a much higher volume of formal and informal experiments than do manufacturers and universities. In the case of laboratories and formal clinical trials, the total volume of experiments going on in humans per new molecular entity probably only numbers in the hundreds or thousands of subject exposures for each new indication or use. In the case of clinical practice, the total volume of formal and informal experiments going on is equivalent to the number of prescriptions generated for the product…* "
- "*Information asymmetries exist in the case of discovery of new applications for existing drugs. As a consequence, many of the potential applications of an approved drug* ***cannot be predicted on the basis of data available to laboratory researchers****. Instead, it seems reasonable that many will only be discovered via "learning by doing" during widespread testing and use in the field.*" [my emphasis]

This prediction seems to be born out. DeMonaco *et al.* [21] examined the cohort of 29 new molecular entities (NMEs) approved by the FDA in 1998. Over the next 5 years, 144 new and effective off-label uses were found for drugs in the cohort. Eighty five of the 144, nearly 60%, were field discoveries by practicing physicians, made independently of researchers at Universities and of the drug industry[4].

DeMonaco *et al.*'s work resonates with my reading of history. R&D seemed remarkably efficient and productive, though ethically problematic, during the "golden age" of drug discovery (~1945 to ~1975) when something akin to user-led innovation often blended seamlessly into a very different discovery processes, in which clinical practitioners were more heavily involved than they are now [3] [22] [23] [24] [25] [8].

It also strikes me that discovery by clinical observation tends to have high predictive validity versus the scientific push of Intelligent Design [26] [27]. The screening model of the human patient is another human patient, not an isolated protein. Furthermore, the sample sizes on which field discoveries are based are generally small, often a single serendipitous observation. Small, noisy, therapeutic signals are not detectable when n = 1, so the effects that can be discovered in the field will tend to be large. I find it ironic that there is such little overt support for a discovery model that, *a priori*, will detect therapeutic effects that are likely to be both large and valid, yet so much support for the model that is shown in Figure 1.

[4] Of course, there are regulatory constraints that may discourage the industry from being too interested in off-label uses

“I know he is a good general, but is he lucky?”

Clinical Selection means that the real-world adoption of drugs, indeed their therapeutic significance, is very hard for Intelligent Designers to anticipate. Important drugs change medical practice. The Chief Executives of drug companies don’t seem to know which of their products will win and which will lose [28]. Wall Street analysts’ pre-launch forecasts are notoriously unreliable, though often better than the forecasts of the companies themselves [4] [29].

There is a wonderful paper by Kesselheim and Avorn from 2013 [30], which hints at this point. The paper identifies drugs that have had huge clinical significance, those that physicians believe have been most “transformative” over the last 25 years. I would love to know the detailed discovery and development history of all the drugs in the paper. Fortunately, Kesselheim and colleagues are working on this [2] [31]. However, in the meantime, I think I know a little of the history of several of them (many readers will certainly know much more).

The anti-TNF biologics were first developed for septic shock but failed in Phase II trials before finding uses in rheumatoid arthritis and other auto-immune diseases. Roche licensed its anti-TNF, Enbrel/etanercept to Amgen, presumably because it saw minimal commercial opportunities itself. Enbrel now generates sales of around $5 billion per year and the anti-TNFs have become the World’s most lucrative drug class. SmithKlineBeecham patented a class of Viagra/sildenafil-type drugs but stopped work on them, seeing no real medical need and fearing the reputational risk from treating a “lifestyle” condition [32]. This was several years before Pfizer’s allegedly serendipitous discovery of Viagra/sildenafil’s priapic effects during a Phase I trial. The precarious development of Gleevec/imatinib is well known [2], with the project nearly expiring in the merger between Ciba-Geigy and Sandoz which created Novartis. Mevacor/lovastatin had a bumpy ride [33]. Merck halted clinical development in 1980, after Sankyo stopped trials of a similar drug, probably spotting an animal toxicity signal. Mevavor/lovastatin was resurrected in a physician-led study in high risk patients in 1982, after which Merck revived its own program. The drug was approved on the basis of surrogate endpoints in 1987. Whether lowering cholesterol was beneficial or not remained controversial until 1994, when another statin (simvastatin/Zocor) was shown to improve overall mortality. Diprivan/propofol is an anaesthetic. It appears to have been transformative because its launch coincided with the introduction of the endotracheal mask and complemented the development of day case surgery [31]; not something that could have been anticipated by its Intelligent Designers. Diprivan/propofol has also found a use at sub-anaesthetic doses as an antipruritic; the serendipitous discovery of an anaesthetist [21]. Ceredase/alglucerase may be important, in part at least, because it led to the discovery of far more Gaucher Disease patients than anyone believed possible, and a market of far lower price sensitivity than anyone believed possible. This transformed the industry’s investment in ultra-orphan diseases. I understand that GlaxoWellcome started with modest expectations for its flucitasone/salmeterol combination (Advair or Seretide), but ended up with annual sales 10 times higher than forecast. Botulinum toxin was approved in 1989 as an orphan drug for use in strabismus, hemifacial spasms, and blepharospasm. Its widespread cosmetic application followed from clinical observations made during on-label use [21]. Etc., etc.

Getting more from Clinical Selection

Since pharmacological innovation involves more Clinical Selection and perhaps less Intelligent Design than most people believe, things should be organized differently [29]. Rapid and cost-effective progress requires more drugs brought into the real world more cheaply. The role of R&D should be to provide the maximum quantity of acceptably safe chemical diversity on which real-world Clinical Selection then acts. As Mao Tse Tung said: "*Letting a Hundred Flowers Blossom and a Hundred Schools of Thought Contend is the Policy for Promoting Progress.*" Regulation, intellectual property rights, and pricing should incentivize the creation of acceptably safe diversity, its **unbiased** real-world selection by patients and doctors, and diffusion of users' discoveries. Furthermore, it is a mistake to insist on too much "evidence" on drugs' efficacy prior to real-world use, as such evidence evidently fails to support accurate predictions of drugs' ultimate utility. In particular, Phase III trials of low ecological validity inflate R&D costs and reduce pharmacological variation.

There are, no doubt, practical problems with this Maoist vision. It may be unacceptably dangerous for patients. It does not sit well with current drug regulation, nor intellectual property laws, nor reimbursement practices, nor the questionable dogmas of "evidence-based" medicine. However, absent a revolution which I do not expect, there are some small steps being made in the right direction, and other steps that could be taken rather easily.

One step is the European Medicines Agency's Adaptive Licensing (AL) pilot [34] [35] [36] [37] [38] [39] [40]. As I have written elsewhere [40], "*AL structures clinical development around the graded introduction of a new drug as evidence on its risk-benefit profile accumulates by a variety of means [34] [37] [38]. Perhaps, for example, commercial sales in a high-need subset of patients can be permitted on the basis of the results of Phase II trials, while further evidence is collected that allows a broader label and wider use in a larger patient population. The emphasis shifts away from large pre-approval trials and towards more diverse and perhaps more ecologically valid evidence of real-world utility (e.g., patient registries for safety data).*" The initial implementation of AL will probably replicate some of the problems that exist in the current system. Its emphasis on prospectively planned evidence generation has the whiff of Intelligent Design. If things are too inflexible, AL will discard drugs that do something useful, but not the precise thing that the Intelligent Designer hoped. The commercial incentives for trial sponsors don't change. Sponsors still pick which battles to fight and which to avoid. Nor is it clear that AL will appear attractive to trial sponsors, except under a narrow set of circumstances [40].

However, I am hopeful because the experience and infrastructure that AL generates may provide an environment under which more acceptably safe chemical diversity can be released into the real world. AL may also provide evidential tools that, in the long run, make it easier for doctors and patients to decide which of the diversity is useful and which is useless.

Looking well beyond of the pharmaceutical mainstream, user-led innovation has seen an internet-enabled resurgence. At the "ultra" end of the ultra-orphan diseases, I know of one group, representing few tens of children worldwide with NGLY1-deficiency, which appears to be making progress via self-experimentation (or sometimes parent-experimentation) [41] [42]. Their approach reminds me of more mainstream R&D in the

1940s and 1950s [22] [3]. I know another group that systematically collates and shares patients' experiences of prescribed medicines, including negative side effects and unexpected benefits [43]. They are second only to the FDA in terms of the number of adverse event reports they collect. I am sure there are other similar initiatives that I have missed [44] [45].

I am going to finish by suggesting two further steps. The first is to mitigate what innovation economists call "*market failure in the peer-to-peer diffusion of user-innovations*" [46]. There is a huge infrastructure that provides financial incentives for drug producers to innovate and then to spread their innovations far and wide [47] [46]. Incentives include intellectual property rights, R&D subsidies and tax breaks, and a relative, if not absolute, tolerance for high drug prices. We would not have 1,662 Avastin/bevacizumab trials listed on clinicaltrials.gov if it were a cheap generic. Governments put these incentives in place because they believe the benefits of innovation and its efficient diffusion outweigh the incentives' cost. In contrast, there are small-to-zero financial incentives for user-innovators to spread good therapeutic news. Most of the time, it is too much effort for a busy physician or patient to rigorously test and then "market" their discovery, even when they believe it is important [46].

I propose that health systems promote the "diffusion" of user-led innovation to a greater degree. The National Health Service in the UK, the Centers for Medicare and Medicaid Services in the US, and other major payers should each award two annual prizes; big enough to hit the headlines. One prize is for the user-led innovation with the greatest health benefit over the previous 5 years. The other is for the most effective proselytization of an important user-led innovation.

My second proposal is an assault on survivor bias in stories of R&D. This will help shrink Intelligent Design to its rightful – still large – size in public and policy consciousness. From now on, any eminent discoverer of any drug should be allowed to talk about his or her great discovery only on the condition that she or he dedicates an equal amount of time to a case-control project. The case-control must have involved the discoverer. It should have appeared prospectively similar to the great success, but must have been an abject failure. There should then be time for impertinent questions on whether anything other than luck distinguished the two.

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