The Biomedical Mutual Organization: a new approach to developing new medical treatments

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ABSTRACT

Self-experimentation is an efficient, productive and proven way to generate new treatments for mild and serious disease. But it is limited by materials available to the individual and the amount of testing one person can do. I advocate the formation of Biomedical Mutual Organizations, self-funded groups of individuals that provide mutual support for exploring new ideas in medical treatment. Such groups could achieve three things. Firstly, they could pool analytical services to validate the quality of materials and analytical services used in self-testing and self-medication, including verification of the identity and purity of medicine ingredients sourced from non-traditional sources. Secondly, they could pool resources to conduct group experiments in new treatments, interpret the results, and generate new hypotheses which could in turn be tested. Thirdly they could conduct more formal clinical trials on the group as a whole of new, indeed radical, therapies, in effect becoming a self-funded biotechnology company. While many practical objections remain to all of these, especially the last, and the last option may actually be illegal in some countries, some of the ethical objections that prevent such arrangements outside the context of a Mutual Organizations are overcome by the alignment of interests of those involved.

In a previous editorial [1] I pointed to the reliable, useful medical progress that could be made by self-experimentation. There is no-one more motivated to find genuine cures for a disease than the person suffering from that disease, and, with suitable procedural safeguards, that can be translated into a powerful research driver. Self-testing, the 'N=1 clinical trial' could explore far more options for medical advance than the established paths of biomedical innovation. If necessary these can then be plugged into the established medico-industrial process for global dissemination as distinct products.

Two areas of research seemed intractable to this approach. One was surgery. It is hard to see how someone can operate on themselves, especially when they are under general anesthetic. (Radical advances in pain control could address this in theory, but even then it would be a brave person who tried to re-attach their own retina or remove their own appendix.)

The other was where the treatments involved using potential drugs that are not readily available as medicines, especially powerful new therapeutics such as proteins, cells or highly potent small molecules. There are two reasons why this could be beyond the ordinary self-experimenter

> 1) Safety. Such compounds have to be tested to make sure that they will not kill you. At least 99% of compounds synthesized as potential new drugs and found to be active 'in the test tube' never make it to launch as medicines[2], about 1/3 for toxicity reasons, 1/3 for efficacy reasons. Most of the toxicity failures are in early, preclinical research. That means that if you ingest a newly synthesized drug candidate (i.e. a molecule that has good in vitro data) it has about 60 times the chance of being toxic than it has of doing you any good. Few people are willing to take that sort of risk.
> 2) Production. Even if the 'drug' is known to be safe and effective, it has to be made in a way that reliably produces the drug and nothing else. An entire standard of production -

> Good Manufacturing Practice (GMP) - has been formulated to ensure that manufacturing processes make what they are meant to, and for drug manufacture that means defined levels of solvents, starting materials, impurities and other trace materials in all aspects of the medicine's manufacture (including production of the Active Pharmaceutical Ingredient - API - and all the other materials that go into formulating and packaging the final product that you, the patient, can consume). The cost of setting up GMP manufacture of a new medicine varies from a mere $10M - $20M for a small molecule drug to over $50M for a biopharmaceutical, before a single pill emerges from the production line.

So while it is fine to suggest that patients try out new combinations of launched, safe drugs such as aspirin or anti-fungals, new regimes of dosing, and other minor alterations of medical practice, surely trying new use of experimental molecules must remain in the realm of the biopharmaceutical company or the major academic research center.

I do not believe so, for reasons I crib in part from the fiction writing of Bruce Sterling (see, for example [3]).

There are two approaches to narrowing the gap between $750M and the $10k - $20k that some people spend on a 'hobby' each year.

Firstly, as discussed in a previous editorial [1], the huge cost of clinical trials can be reduced radically by overcoming the suspicion that patients have of the motivations of those running the trials. If trial managers and patients are the same, then their motives are aligned. If trial PIs and patients are the same, and patients are assumed to be humans rather than rather large rats, endpoints are easier to define and sequential testing removes most of the variability between trial subjects. This is the reason that many self-experimenters, local GPs and others can come up with new treatments based on small numbers of unfunded observations while pharmaceutical companies spend ever greater amounts to launch ever diminishing numbers of new medicines.

However this relies on observations of people taking existing drugs, and, for the individual who cannot prescribe themselves drugs, taking only over-the-counter (OTC) medication. If I want to try something that is not on sale in the pharmacy, I must get it made, and the cost of actually making drugs is substantial, especially new drugs. If I swallow 10 milligrams of NewDrug, I want to know that it actually is 10 milligrams, it actually is NewDrug, and that there is nothing else in the tablet other than safe, inert materials. A large regulatory infrastructure has grown up to ensure this.

The reason for this, however, is largely lack of trust in the process. The key to trust is validation. Most drugs (legal and illegal) are available over the internet, but what is the contents of the little blue tablets that arrive from Central America in a brown jiffy bag? Checking that requires a laboratory, which is beyond the single amateur. However it is not beyond several amateurs, which leads me to a solution to the problem of how to extend self-experimentation into the realm of new medicines discovery: the Biomedical Mutual Organization

The Biomedical Mutual Organization.

The most obvious way for a self-experimenter to afford the laboratory services needed to validate the quality of chemical supplies is to pool that requirement with others. The logic is the same as many mutual aid societies, such as the Building Societies which arose in the UK in the 19th Century for workers to pool their investment capabilities to buy houses, a capital investment beyond the means of the individual worker. Many minority groups still do this informally in the UK today. The same logic applied to the origins of most life assurance companies, and today informs communal purchase of boats, holiday homes and other costly luxuries as well as a wide range of charitable activity. Some on-line providers of drugs claim to have a mutual organization for this reason. Any group of self-experimenters could pool resources to have chemicals - whether as

bulk material or as formulated medicines - tested for quality for their own use. These tests could include formal toxicity testing. They key is the trust they have in the testing process, so ideally a member of the group would test the drug themselves - the analytical chemist is one of the people who will be swallowing the pill. There is little better motivation for accurate analysis. The other members of the group should be able to trust their technical ability and motivations: mechanisms for cementing such trust are readily imagined.

This is the simplest model of the Biopharmaceutical Mutual Organization (BMO)[1] - pooling resources to provide a specific quality check. This could be applied to any therapeutic - a generic drug provided over the internet, a known drug active ingredient (API) provided by a contract synthesis company, a novel biopharmaceutical grown in an academic laboratory or in someone's kitchen. There is no need to limit this approach to what can be bought at high-street pharmacies.
The second level is implicit in the concept of self-experimentation. It is rare that a one experimenter can dream up and execute a novel, rigorous experimental programme themselves. Most programmes can benefit from more experimental subjects and more intellectual input. So the second level could pool self-testing as well as materials validation. To make this work the co-operative would need to be composed of people with some knowledge of the scientific method, lots of time, intellectual ability (although not necessarily academic qualifications), enough money to buy some basic supplies, and an interesting selection of poorly treated diseases. This suggests that a group of retired pharmaceutical and biotech company scientists. If following Seth Roberts' approach to self testing[4] they would track a wide range of physiological and pharmacological parameters over months or years to generate new hypotheses about therapeutic approaches, and then test those on themselves. Intellectual Property (IP) arising from their work would be the property of the collective, and such a group of people would be ideally placed to identify pharmaceutical companies who might be interested in buying such IP off them, so funding the cooperative further. The cooperative could extend its activities to meetings, publications or anything else, but the essence must remain that they test their ideas on themselves: once they leave that principle and start testing on other people, then the cycle of mistrust described in the previous article starts and you end with GLP, GMP, 5000-person clinical trials and venture capital investors demanding quarterly returns and closing the company down when they not get them.

(Interestingly, patent law in many countries provides that research into the subject of a patented invention is not an infringement of the patent on that invention, and that clinical trials of drugs are considered as research into those drugs. So the BMO is not legally prevented from running clinical trials of drugs that are still on patent, including drugs not yet launched. This could include drugs in Phase II or Phase III clinical trial, which will have undergone GLP safety and animal efficacy testing at a company's expense. The BMO is not, of course, entitled to sell the resulting data, or the drug itself, but as it is not intending to do so that should not be a limitation. Should the BMO concept take off, we can expect strong pressure from pharmaceutical companies to change the law in this respect.)

The last level takes this concept further, to have a BMO test new therapeutics rather than new uses of existing, well-known molecules. Here we enter less certain ground.

The cost of getting a new drug to Phase II clinical trials (i.e. testing on patients, the stage I have defined as what the BMO will do) is variously estimated as $10M - $30M. This is beyond the means of almost everyone, especially as most of those drugs fail to have any noticeable effect. Those familiar with research outsourcing will know, however, that it need not be like this. Animal model studies of new anti-cancers show results for a few thousand dollars. Animal models of pain are more expensive, maybe $20,000. Screening for receptor binding costs $200 - $1000, screening for 'off-target' effects similar amounts. In other words, actually getting a good idea whether a new chemical might work as a drug can cost as little as $50,000, and if you are really

[1] -for historical consistency this should be Biomedical Mutual Society, but BMS is the abbreviation of a well known drug company])

lucky less than $20,000. To put is more concretely, by buying a Nissan Micra instead of a BMW M series you could save enough to discover a new drug, providing you were willing to test the result on yourself.

Would you swallow the result? Clearly that depends on the nature of the condition I am trying to treat and the nature of the risk inherent in the treatment. But it also depends on my personal attitude to risk. The huge cost of drug discovery and development is driven by an extremely conservative, risk-averse approach to risk, driven by the motivations described in the previous article. If I think that MegaPharm is trying to get me to take a novel cadmium-containing analogue of aspirin because it will boost their share price, I am disinclined to acquiesce. If my friend is trying to get me to take the same drug because she took it and it cleared up her eczema, I am more inclined to trust her. If it is melanoma instead of eczema I am even more inclined to trust her. If it is an ethyl ester of aspirin rather than a cadmium chelate, then I will almost certainly try it. Risk, reward, and perception of the reality and validity of the measures of risk and reward are critical. This requires an informed co-operative, not a company pushing drugs on a public that it regards as only semi-sentient.

But in reality, it is unlikely that the BMO will design new small molecule 'chemical' drugs and have them made, because pharmaceutical companies are actually quite good at that. What they are not good at is radical treatments - biopharmaceuticals (although these are moving into the mainstream), gene therapy, siRNA, stem cell therapy, complex tissue engineering approaches, or polypharmacy. These are hard to test on animals, and the liability issues of testing them on people scare off companies and many academics.

The most radical form of the BMO is therefore a group of people who are willing to try genuinely groundbreaking therapeutic approaches on themselves. Ironically, such treatments have a better safety record than potent small molecule drugs - TGN-1412 was shocking because it proved so dangerous, whereas 'bad' monoclonal antibody drugs before have generally proven no worse than mildly toxic or ineffective. There are already many people who use hGH, FGF, IGF and EPO on themselves, so the idea of doing so systematically, with scientifically justified rationale and properly validated materials and outcomes measures is an improvement on current practice. The role of 'freelance' chemists in providing new drug molecules for use (or abuse, depending on your view) by athletes is also well known (e.g. [5]). Quite apart from the legality of use of drugs in sport, there are ethical issues around this which mostly derive, at root, from the information asymmetry between the pharmacologist who designs the agent, the chemist who makes it and the athlete who uses it. This is why it is important that the BMO is a cooperative, with all the members participating in the testing and use of the product, thus aligning their interests. Once one member becomes the producer and another the consumer, we are back to the requirement for complex ethical and legal oversight, regulation at every step and the conventional biopharmaceutical development process.

The costs of this would be significantly higher than just validating drugs bought on the internet for their quality, and the BMO members would have to invest significant cash as well as their bodies in the scheme. The BMO would in effect become a biotechnology company, one in which the shareholders are also trial participants, with the difference that, rather than promising shareholders 'we will make you rich' (a promise almost never fulfilled for private biotech companies in Europe), the participants are promised the still risky but attainable goal of 'we will make you well'

Perceived problems with such an approach are more to do with the law and with ethics. In some territories, encouraging others to take compounds that have not been approved for consumption is illegal. It is also illegal in some cases for shareholders in a biotechnology company to participate in company clinical trials. So it may be necessary to conduct some tests while vacationing in a suitable legislative environment. To be blunt, these are details: if the BMO is

composed of educated, informed, intelligent adults then they can chose to risk damage this way just as they do every time they drink, smoke, eat too much or go out in the sunshine.

The ethical issues are, to many, more worrying. The idea that the people who manage a clinical trial are the same as the people who invest in it and the people who take part in it tramples a host of current 'ethical standards' underfoot - that trial managers should be disinterested in the result of the trial, that trial participants should not be paid, and shouts 'conflict of interest' at every point. But the 'conflict of interest' rules have been created because of the mistrust engendered by the cycle described in Figure 1 of the previous editorial [1]. If the shareholders in pharmaceutical companies are the only beneficiaries of my being injected with a new therapeutic, then of course I mistrust them. If the doctor urging me to take the pill was looking as much to their consultancy income or their publication record as to my wellbeing, then I will be highly suspicious. But such conflicts vanish (or at least diminish) in a BMO.

There are of course huge barriers remaining to realizing this last, most radical version of the BMO. Who is liable if something goes wrong? Who picks up the pieces of a TGN-1412-type disaster? What if the material costs $10M but the BMO only has $1M? Who decides what to test? How does the BMO balance the risk:benefit ratio for different members with different attitudes towards risk and different life expectancies to put on the line? What rules can you impose on the BMO members to prevent them confounding your clinical trial with other drugs or adverse lifestyle? Rather than speculate on these points endlessly, I invite readers to comment . But in the face of the collapse of the biotechnology industry in the UK (private biotech investment in the UK in 2006 was down to the levels last seen in 1993), investor pessimism and timidity, growing regulatory barriers and growing public mistrust of industry, the BMO is, in principle at least, a route by which the 21st Century can have better drugs than the 20th.

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