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## The rise of micropharma

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The drug discovery pipelines of the major pharmaceutical companies have become shockingly depleted, foreshadowing a potential crisis in the ability of Big Pharma to meet the pharmaceutical demands created by the ever-changing spectrum of human disease. However, from this major crisis is emerging a major opportunity, namely micropharma – academia-originated biotech start-up companies that are efficient, innovative, product-focused and small. In this Feature, we discuss a ‘new ecosystem’ for drug development, with high-risk innovation in micropharma leading to Big Pharma clinical trials; we also identify the ‘five golden goals’ that micropharma must strive to achieve to attain success. Although micropharma will encounter numerous hurdles on this road to success, there is room for optimism that micropharma might have the capacity to address society’s growing, but unmet, need for effective therapeutics over coming years.

Pharmaceutical research is in the throes of an unprecedented crisis. The demise of the ‘blockbuster model’ and the increased demands to satisfy regulatory agencies such as the U.S. Food and Drug Administration (FDA) have taken a dramatic toll on the pharmaceutical business, even before the recent tumult in financial markets [1–3]. The pipelines of the major pharmaceutical companies are shockingly depleted, with the result that, through 2006, 43% fewer new chemical entities (NCEs) have become drugs in the 21st century than did so in the past years of the 20th [4]. The global credit crunch is exacerbating this problem, with layoffs and cuts to R&D spending endemic to the industry.

But major crises produce major opportunities. The opportunity arising from this crisis is the emerging phenomenon of ‘micropharma’ – academia-originated biotech start-up companies that are efficient, innovative, product-focused and small. Indeed, there is room for

optimism that micropharma might have the capacity to address society’s growing, and increasingly unmet, need for effective therapeutics over the coming years.

### A need to change the old regime

The 20th century ended with an explosion of activity in gene-related studies and stem cell research. Although this research has thus far failed to deliver the much anticipated flood of therapeutic advances, the 21st century continues to evoke promise as the ‘Century of Biomedical Research,’ if for no other reason than sheer need [5]. Recently, we have witnessed global threats from H1N1 flu and drug-resistant bacterial infections, emphasizing the ever-looming risk of new infectious disease perils [6]. Previously established disorders such as AIDS and obesity-related health problems continue with significant incidence and prevalence, while long-recognized diseases, such as stroke and

Alzheimer’s dementia, are becoming even more common as a greater proportion of the human population reaches old age. Not surprisingly, the need for drug discovery to address these and other important diseases is increasingly being recognized as a societal priority.

This need for drug discovery is also important from the perspective of global economic health [7]. With the worldwide pharmaceutical market currently valued as \$518 billion per annum and projected to be worth \$800 billion in 2020, the potential for economic benefit is immense. The future growth rate for pharmaceuticals in developed nations is estimated to be 5–7% per year, while in emerging markets such as Brazil, Russia, India and China, the growth rate is estimated to attain 15% per year [8,9].

Regrettably, the time-honored business and science models employed by Big Pharma are failing to address these important health-care and economic needs. The core problem is a lack of innovation from Big Pharma [10,11]. In 2005, Big Pharma research and development costs

exceeded \$55 billion, more than double the amount spent in 1996; however, in 2005, just 22 new drugs were approved by the U.S. FDA compared to 53 new drugs in 1996 [4]. Such evidence suggests that the model is clearly dysfunctional and that the industry is exhibiting the sickness of outdated business and science models.

The blockbuster model worked well in past, but that time has probably come and gone. At present, there is a desperate need to in-license products from external sources, as pipeline failures plague Big Pharma. Accordingly, more companies are declaring publicly that they will obtain up to half of the drugs they develop and market from other sources, mainly through the acquisition of smaller, newer companies. However, where will these new companies come from?

### The new pharma 'ecosystem'

The ecosystem for modern pharmaceutical research has been evolving (Fig. 1) as the tools for drug discovery have become more economical and accessible. Fully integrated Big Pharma companies remain at the top of this new food chain, not because they do all things well, but because of their unchallenged superiority in running clinical trials and regulatory gauntlets. However, these firms are increasingly acting as receivers, rather than originators, of new drug candidates (NDCs). Potential NDCs (especially those with early-stage clinical data) come from a myriad of sources, but increasingly this niche is being satisfied by 'Small Pharma,' corporate

organizations that employ from 25 to 500 employees. Small Pharma has in-house capacity for preclinical and early-stage clinical drug development and is generally more accepting of risk in their drug discovery programs; they are free of much of the overhead of Big Pharma and can therefore focus on diseases and disorders that would not be profitable for Big Pharma to originate. From a financier's perspective, licensing and cross-marketing alliances with Big Pharma represent their most probable exit strategy for their initial investment, and the 'inflection point' for value creation in such deals is at the Phase I/II clinical stage.

The foundation of the old regime's drug research ecosystem was thought to be embodied in the commercialization of 'academic' or 'basic' research concepts, in which university/hospital-based researchers produced ground-breaking discoveries and technologies for further development by others. The epitome (perhaps caricature) of such work is the creative-but-unfocused professor who accidentally stumbles upon something useful, which the university endeavors to translate into a marketable invention through the euphemistic process of 'tech transfer' [12]. This approach all too often results in underutilized discoveries, generally discarded or bought at fire-sale prices, because they lack sufficient proof-of-concept data to attract significant interest from Small/Big Pharma. We regard this as a tragedy and a course of action that must change.

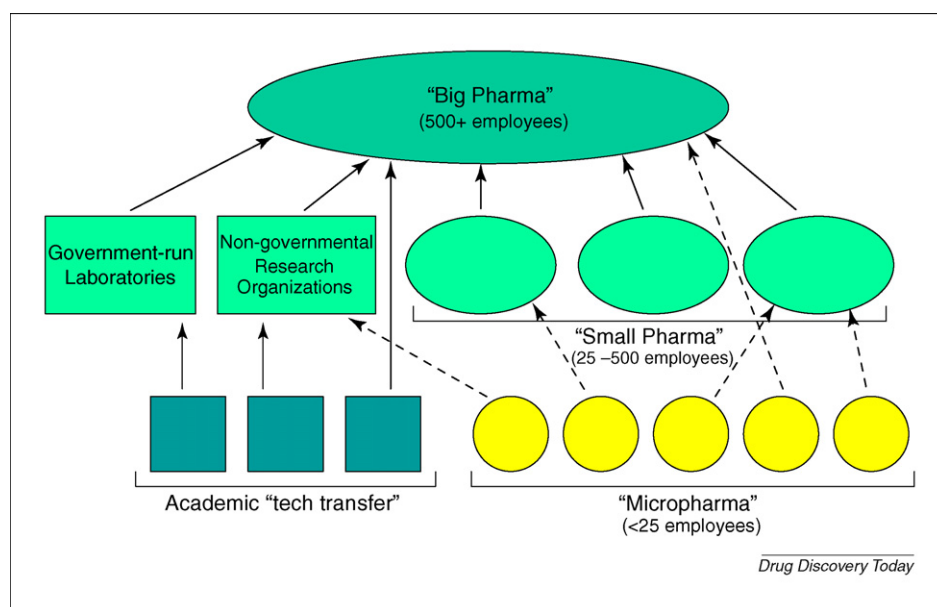
In the new ecosystem, micropharma are gradually supplanting this haphazard process. The

concept of micropharma is not simply a passive 'tech transfer'; it is an active, intentional enterprise that brings together people from science and business departments throughout the academic setting. Micropharma have a longer term, goal-oriented focus that begins with research and survives the initial discovery phase, unlike the conventional academic approach, which tends to focus on short-term licensing or sale of inventions.

### Micropharma: a definition

Micropharma are academia-originated, biotech start-up companies that are efficient, flexible, innovative, product-focused and small (having less than 25, and frequently less than 10, employees). They might arise from universities, hospitals or research institutes. They are created by two or three academic researchers who join forces to design, discover and develop new therapeutics (or diagnostics) for human health disorders. Micropharma are focused typically on one, or perhaps two, related diseases. The model permits high-risk approaches and demonstrates an impressive capacity to absorb both success and failure.

There are numerous advantages to funding such companies within the academic environment. As well as being an obvious source of intellectual capital, universities offer a highly skilled workforce. Universities also offer access to cost-effective infrastructure. Although there are many reasons for micropharma to flourish within an academic environment, participating in such a venture must not be business-as-usual for the



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FIGURE 1

The modern ecosystem of pharmaceutical research. Solid arrows represent established relationships among stakeholders, while dotted arrows represent emerging relationships.

TABLE 1

**The five golden goals of micropharma**

1. To achieve a product (a therapeutic or diagnostic agent) that has efficacy in a recognized animal model of a relevant human disease
2. To have insights into the mechanism of action of this agent at a molecular and/or macromolecular level that enables rational optimization of the agent
3. To have preliminary data pertaining to the pharmacokinetics of the agent
4. To have preliminary data pertaining to the toxicology of the agent
5. To protect the intellectual property embodied within this agent through a patent strategy that optimally includes composition of matter, means of production and use

academic researcher. This is not merely an alternative opportunity for professors to raise funding with which to pursue their habitual basic research activities. Rather, it is a chance for them to develop new goals and to change how they do research, with a focus on translational research and the development of useful products.

To achieve these goals, micropharma must attain certain milestones that eventually enable their technologies to attract the attention of Big Pharma. The 'five golden goals' for a successful micropharma discovery are given in Table 1. Having a new therapeutic entity with efficacy in an accepted animal model of disease is of paramount importance. Having an innovative therapy that works in an equally innovative (and thus unvalidated) animal model is certainly more risky and thus much less desirable. In the realm of drug discovery, being best is of more value than being first [13–15]. Being best also necessitates having molecular level insights into the agent's mechanism of action, thereby permitting product optimization in a rational and insightful way.

As well as being efficacious, the agent must also have good pharmacokinetics (PK) and good toxicology if it is to transcend the barrier from being merely drug-like to attain the lofty designation of 'drug.' If a micropharma lacks the resources for a whole-animal-based PK study, then surrogate data can be meaningfully obtained from *in vitro* studies of relevant cell lines. For example, Caco-2 studies can be used to predict the absorption rate of candidate drug compounds across the intestinal epithelial cell barrier [16]. Rather than performing PK studies 'in-house,' micropharma companies often elect to farm such studies out to contract research organizations. Similarly, preliminary toxicology data are also important when endeavoring to promote a micropharma product.

Securing patent protection might be the last entry in Table 1, but it is decidedly not least in priority [17]. Without an effective intellectual property policy, even the most impressive NDC will 'die on the vine.' Typically, academia has

been driven by the 'publish or perish' mantra – a process which ironically can cause potentially life-saving technologies to perish because of failure to patent. Indeed, arguably it is unethical to disclose a significant new discovery in the published scientific literature before patenting if it has applicability for pharmaceutical use.

The long-term goal of micropharma is not to do multicenter Phase III clinical trials, manufacturing, or drug marketing – these are activities that Big Pharma will always do better. Rather, micropharma aims to discover therapeutics and to add value to these discoveries by performing preclinical evaluations of the agents and by advancing them, perhaps to the level of a Phase I human clinical trial through effective partnering with Small Pharma.

**Obstacles to micropharma**

To be scientifically successful, micropharma require truly multidisciplinary research. Historically, this has been a major barrier in academia. A molecular biologist in a Department of Anatomy collaborating with a molecular biologist in a Department of Physiology is not really multidisciplinary. Real multidisciplinary research necessitates overcoming the silo mentality of academia and requires biologists talking to chemists (and vice versa). Both sides must remember that this is a partnership of equals – not one group of scientists treating the other like they are supportive technicians. Each needs the other in micropharma.

To be financially successful, micropharma require funding, ranging from the initial seed funding (\$250,000–500,000) to later, more substantive Series A funding (\$1–5 M). Acquiring such funding frequently requires interacting with venture capitalists. A good venture capitalist is absolutely invaluable to the success of micropharma and is often more efficient, knowledgeable and responsive than any government funding agency. However, both sides must remember that this is a partnership of equals. The venture capitalist needs scientists just as the scientists need venture capitalists. The venture capitalist is offering money, but the

scientist is offering a product that is worth money. Moreover, too often venture capitalists will expect the scientists to be exactly what they themselves are not – innovative and creative. They will frequently demand that the scientist produce products that are cutting-edge and unique, while they themselves imprison this exciting technology in a one-size-fits-all approach to business models. Accordingly, the scientist must do 'due diligence' on the venture capitalists, just as the venture capitalist performs due diligence on the scientist.

To be ultimately successful, micropharma require long-term partnerships with Small/Big Pharma. Increasingly, Pharma needs the expertise and strengths of micropharma as much as micropharma needs the expertise and strengths of Pharma. However, both sides must remember that this is a partnership of equals (well, almost). Pharma offers funding, developmental know-how and unparalleled experience in human clinical trials; micropharma offers scientific innovation, flexibility and a model that enables cost-effective risk-taking. An industrial researcher pontificating to an academic researcher 'that's not how it's done in industry' is not helpful. Conversely, but similarly, there is nothing more annoying than an academic researcher offering platitudes rather than products, preaching to the industrial researcher about the need for industry to be an altruistic patron of basic science. This underscores the need for would-be micropharma founders to carefully consider the five goals in Table 1 and remember the goal is a product that helps people with disease.

Certainly there are those who could take issue with micropharma, in that this trend might have the potential to turn academia into a mere clone of industry. Academics have traditionally resisted what they view as the siphoning of resources away from fundamental research, which rightly is considered the heart of academia. For our part, we believe helping humankind can be tangible and concrete, not merely a vague and rarely fulfilled comment in the first paragraph of a manuscript or grant application. Frankly, there is

a crisis in drug development that threatens to overwhelm us. This is not the time for dogma, but a time for innovation and collaboration.

And to those who would say that academics have no business doing research that Big Pharma can do better, our answer is blunt: Big Pharma is failing to deliver. For reasons stated above, Big Pharma has been exhibiting a systemic lack of risk-taking, a corporate culture of emulation rather than innovation, and a neglect of some of the diseases and disorders of developing nations that humankind wants to eradicate.

### Micropharma: a bright future?

The growth of micropharma within academia is an exciting development. It promises a chance for society to reap additional benefits from the sizeable investment made in academia, while at the same time providing a solution to the woes of Big Pharma. The evolution of the micropharma concept is not going to be easy: it demands that researchers think about interdisciplinary problems and seek multidisciplinary solutions; that granting agencies and tenure committees become more receptive to valuing and supporting commercial outputs such as patents and start-up companies; that universities and hospitals open their doors to business; and that financiers remember they are called 'venture' capital for a reason! These requirements

become all the more important in this climate of financial uncertainty – the decline of Big Pharma R&D success threatens to halt progress in medicine, unless perhaps a plentitude of micropharma can be called upon to fill the growing niche.

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