

nature biotechnology

Where have the flagships gone?

There was a time when flagship biotech companies looked very different from pharma.

At the dawn of the biotech industry, companies like Genentech and Cetus in California, Biogen in Switzerland and Genetics Institute on the East Coast were flagships. These were pioneers standing behind the mast and proudly hoisting their biologic colors in the face of the prevailing winds of chemistry. Like the starry ships they were, they biologically went where none had gone before. Over the years, the sparkling navy grew, adding icons such as Genzyme, Amgen, Millennium, Gilead and a host of others, many now defunct and forgotten.

They were joined by national flagships: in the UK, Celltech, then British Biotech, then Celltech again (after British Biotech's demise on the stock exchange); for a while, Genset shone in France and Lion Bioscience in Germany, until they, too, disillusioned their bourses; then there was ES Cell International in Singapore and Macrogen in South Korea; and now we have Genmab in Denmark and Actelion in Switzerland and several potential flagships in Belgium (as is much in the nature of things Belgian).

The stock markets in many smaller countries still have great expectations for their flagships. Indeed, in some countries, the idea persists that flagship biotechs, particularly the largest companies, must be supported to ensure a critical mass of talent that retains and attracts necessary scientific and management expertise to the region. They are portrayed as bellwethers for the local sector's health.

But this defensive idea is an anathema to free markets. Any flagships must remain competitive in the global market to remain afloat. And if governments attempt to artificially intervene, defend and keep a flagship working in the name of supporting their national sector, then they are doomed to fail.

Thus, today the age of biotech flagships seems to be passing. Some have simply sunk. Some were subsumed into large pharmaceutical companies, often providing innovative engines for these increasingly slow-moving behemoths. In fact, the lines of demarcation between multinational pharmaceutical firms and so-called flagship biotechs are now so blurred it is hard to differentiate the two.

But neither business failure nor pharmaceutical assimilation is the principal cause of the flagships' demise. The problem is that these days most flagships no longer compete with pharma. They are now very much all part of the same phleet, steaming, sailing or rowing phuriously in the same let's-make-better-drugs direction. There are phlotillas of service companies, pherrying traditional cost-plus goods, such as manufacturing, or drug development, or sequencing to drug companies. Most of the health biotech sector is so thoroughly aligned with pharma that it no longer represents a different force pushing in a different direction. Like good lieutenants, biotech companies provide pixes to satisfy phar-madmirals' desires. (Ed: EnoughPh already!)

What led to this intimate coalition of biotech and pharma? The simplest explanation is that the two sectors now draw funds from the same treasure chest.

Venture capitalists and drug companies are part of the same ecosystem. When the bottom dropped out of the initial public offering market for most biotechs, venture capitalists sought safety from the storm. Acquisition by pharma firms has become the primary exit for investors.

To maximize their exit chances, biotechs are now shaped preemptively for acquisition. New startups have been reinvented as lean drug-asset development vehicles. Pharma corporate venture arms act as technology-validating coinvestors. Pharma also became a source of founding money, putting cornerstone finance into new venture funds.

Nominally, limited partners and corporate coinvestors do not influence short-term investment decisions. But most investors know on which side their ship's biscuits are buttered. And pharma has a hand in the hatching and dispatching (and matching) of biotech firms. No wonder then that the biotech flagship charting a course counter to pharma strategy is such a rarity.

But perhaps that is about to change because the rules of engagement are about to change.

In the US healthcare market and elsewhere, the era of constantly expanding healthcare budgets that have fed the pharma economic model is coming to an end. The world is working out how to build health technology assessment muscles, and thus very soon an impasse will be reached where the business models and tactics of the existing pharma fleet no longer apply.

It is in this context that innovation will become paramount as a tool for carving out market share from the same limited healthcare pie. The original biotech pioneers were not flagships because they were smarter or earlier or more successful, but because they were contrarian. Their flags were rallying points for those who wanted to do or invest in something different. Supported by a source of funding that was independent of pharma, they innovated in ways that challenged pharma's momentum. Recombinant proteins were not more of the same; antisense oligonucleotide therapeutics and gene therapies opened up new targets and promised (at least partial) cures.

As Clayton Christensen and his co-authors write in their book *The Innovator's Prescription*, companies with "lower cost business models emerge at the bottom of the market in simple applications and gradually move upmarket to disrupt the established competitors." At the moment, it is not yet clear what that new generation of disruptive flagships will look like. This is because it is not yet clear how governments and payers will provide the funding directions that incentivize biotech innovators to spring up and challenge the current pharmaceutical model.

But with the pressures so great for governments and payers to balance budgets, it is not a question of whether this will happen, but when. All it takes is for reimbursers to provide the right incentives to fund disruptive innovation. And when they do provide that mechanism, a new wave of biotech flagships will set sail. Whatever emerges will likely blow the pharmaceutical fleet's existing business model right out of the water. **LB**