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# Interview – C4X aims to fix big pharma's drug discovery problems

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It is no secret that big pharma has an R&D problem. A recent analysis by *EP Vantage* found that six of the top 10 drug companies derived less than 20% of their 2015 sales from products developed in-house; the industry is becoming ever more reliant on acquisitions for growth.

But this is a short-sighted strategy, Clive Dix, chief executive of UK-based C4X Discovery, believes. "It works for the person in charge for the period of time they're going to be in charge," he tells *EP Vantage*. However, a deal will only bolster the acquirer's revenue stream for a year or two, he adds. "And once you form a new company with a much bigger revenue stream you've got to produce even more products to keep to growth targets."

**Years of disruption**

Acquisitions typically take two to three years to bed in, he says. "And that's two to three years of non-productivity. When you merge two R&D organisations you disrupt all the thinking and the teams."

This creates a vicious circle. "You've messed up R&D, so you've still got nothing, and all you can do is keep merging," Mr Dix says. And trying to create cost synergies by cutting jobs in the merged company just compounds the problem.

According to the chief executive, what is now happening by default, but not design, is that big pharma are relying less and less on their internal capability for early phase research, and putting more emphasis on acquisitions.

This seems like good news for smaller biotechs, as they can command higher prices from desperate big pharmas. But an acquisition is not always in their long-term interests, especially if R&D budgets are then cut. In spite of this, smaller companies can find it hard to turn down deals, especially if they are in the interests of their investors.

Mr Dix believes that C4X can buck this trend. He is adamant that, while the company will work with big pharma, it is not seeking out a takeover – an apparent U-turn from his previous company, Powdermed, which Mr Dix sold to Pfizer for a reported $400m in 2006.

**New drug discovery model**

C4X has developed technology that could make the drug discovery process faster and more efficient. It aims eventually to start work on four different candidates each year to either take to clinical development itself or to partner.

The company's Conformetrix platform uses nuclear magnetic resonance data to work out quickly the shape in which a molecule sits in solution. "That may sound really trite and simple, but nobody's ever known what shape a drug is," Mr Dix says.

The closest most companies come is seeing a drug's shape when it is interacting with its target. "But molecules adopt many shapes – only one of those is the active shape." The idea is that by identifying the active shape, and creating molecules that stay in this shape, drugs can be more selective and therefore effective.

Meanwhile, conventional drug discovery will test thousands of molecules that have a similar chemical structure to see which ones bind to a particular receptor. But if these form other shapes they could affect other non-target receptors. "If [a drug] can't adopt other shapes, it can't interfere with other things," Mr Dix says.

C4X is testing this theory with its most advanced candidate, a preclinical orexin-1 antagonist for addiction – the same mechanism of action as Pfizer's smoking cessation drug Chantix which, although approved, has been linked with adverse events including suicidal thoughts.

But Chantix also hits the orexin-2 receptor, while C4X's candidate is selective for orexin-1, which could make it

safer. Although this sounds obvious, actually creating an orexin-1-specific candidate was not easy, says the chief executive: “The industry had worked for some 10 years on trying to find an orexin-1 antagonist with no orexin-2 activity. We ended up with a molecule in six months.”

**Improving on known targets**

The rest of the company’s pipeline similarly aims to improve on drugs for known targets. “All of the targets were chosen to prove that the technology could do something that couldn’t be done in other ways,” Mr Dix says.

For example, C4X is also developing an oral GLP-1 agonist for diabetes. These drugs are currently injected but Novo Nordisk is already studying an oral version of semaglutide in phase III, so the company is some way behind (*Novo’s oral GLP-1 looks sweeter, August 27, 2015*).

But it has bigger plans in future. Now it has tested the platform, C4X plans to apply its technology to novel targets, which it will discover through another technology, called Taxonomy3, gained through the March acquisition of Adorial.

This platform carries out “deep data mining” of publicly available genetic data to find new targets, and has already identified genes with previously undiscovered links to diseases including rheumatoid arthritis, according to Mr Dix.

“What’s really exciting is you’re starting with patient data, not with a biologist with a theory around which molecule he likes to work on, and then fitting the data he can find to it and ignoring all the rest – which is how we’ve done it formerly,” he says. The company is starting development of its first pipeline drug with a novel target.

As well as developing its own products, C4X also partners with pharma companies including AstraZeneca and Takeda, and is talking to several others who might use its model for part of their early drug discovery.

“This might be the new model to run in pharma,” Mr Dix says. “Big pharma has got to get out of the mould of acquiring – if we get acquired, everyone will revert back to the old way of doing things. There need to be new models of how the whole thing works.”

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