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Drug discovery veers off target

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Drug researchers are turning to unconventional sources in an attempt to boost drug discovery programs that fall short of exuberant post-genomic predictions. As drug pipelines stagnate, turning out a succession of 'me too' drugs rather than novel therapies, one potential savior comes in the form of a new scientific paradigm: systems biology, a rather obscure and mystical scientific discipline based on mathematics, computer modeling, and large-scale data processing.

Viewing the larger picture

One company specializing in systems biology is Entelos, Foster City, California. Entelos's technology is based on a set of differential equations that allow users to monitor physiological changes over time. Entelos scientists Lisl Shoda, Huub Kreuwel and colleagues recently reported a systematic analysis of interventions used in non obese diabetic (NOD) mice [1]. The common wisdom regarding this model of human disease is that preclinical evaluation in NOD mice is not helpful because 'everything works'. On the contrary, however, Entelos' mathematical meta-analysis shows that all treatments do not prevent the disease and that some are effective at treating overtly diabetic mice, with the conclusion that the NOD mouse can be a very useful predictor of human response to treatment. Literature surveys and meta-analyses are a hallmark of the systems biology approach, allowing scientists to 'move up' a level and view the larger picture.

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Entelos counts among its clients companies such as Johnson and Johnson and Pfizer. 'A lot of people top-to-bottom in pharmaceutical companies would say they're not happy with the level of productivity in terms of the number of R&D dollars going in and drugs coming out the other end,' says Alex Bangs, cofounder and chief technology officer, '...fundamentally, the way we can help is that we can put things through the pipeline that have higher potential.'

Understanding the pathway

Another voice advocating for a systems approach to drug discovery is Eugene Butcher, a professor of Pathology at Stanford University, who proposes screening potential drug compounds against cell based disease models early in the drug discovery process, thereby allowing whole pathways and biological systems to dictate which compounds achieve lead status, rather than efficacy against a single target, a method that ignores complex interactions between multiple genes. 'The whole idea that you need to look at millions of compounds to identify the best hits and look at all of chemical space that hasn't been validated and seems not to be necessary at all if you look historically', said Butcher.

Millennium Pharmaceuticals, Cambridge, MA, has no plans shift from straightforward single gene target discovery. In response to Butcher's article, Ronen Roubenoff, the Senior Director of Molecular Medicine at Millennium, explains, 'I agree with him that the idea that understanding a gene would lead to understanding a drug was simplistic... The genetic screens are still the first step. You've got to understand the pathway, then understand the regulatory web it lives in.'

Scepticism

Systems biology has not always been received warmly in the pharmaceutical industry, nor in biological research in general. Alex Bangs has seen a great deal of this resistance in the nine-year history of Entelos. 'There are always people who are sceptical of the approach. It's a new technology, a new approach for them. They want to use all the skills they have to probe at this and understand it. What we've been able to do is have enough success in terms of case studies that we can share with people. We've been able to overcome that scepticism. Some organizations have said 'we don't believe in this and won't adopt it'...but I'm seeing a lot of companies that are starting to get very interested in this technology. It's a pretty exciting time for us. We're very busy.'

References

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Frog skin hope for HIV prevention

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Antimicrobial peptides from the skin secretions of frogs that inhibit HIV infectivity *in vitro* could help in the fight against HIV, suggest Derya Unutmaz and colleagues [1]. 'These compounds are clearly toxic to our cells at high concentrations and so are unlikely to be of use as therapeutics,' notes Unutmaz, Associate Professor of Microbiology and Immunology at Vanderbilt University School of Medicine, USA, 'but they may have great potential as preventives in mucosal creams.'

Why frogs?

Frogs and other amphibians secrete chemicals onto their skin to make them distasteful to potential predators. However, explains Robert Lehrer, Professor of Medicine at the University of California, Los Angeles, USA, 'the complex mixture of bioactive peptides found in frog skins also provides a

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first line of defence against bacteria, fungi and viruses.'

'There are hundreds of these antimicrobial peptides, some made by frogs, that are going extinct,' notes Unutmaz. 'Other labs in our department are looking at how these peptides protect frogs against their own pathogens but my interest is in HIV and, because antimicrobial peptides from other species can block HIV infection, we decided to see whether any frog peptides did the same.'

'There are many interesting molecules in frog skin secretions… but identifying peptides that block HIV infectivity is only an early step…'

Peptides with promise

Unutmaz and his team report that caerin 1.1, caerin 1.9 and maculatin 1.1(from the green tree frog, red-eyed tree frog and green-eyed tree frog, respectively) rapidly and completely inhibit T-cell infection at concentrations that are nontoxic to the target cells [1]. Excitingly, says Unutmaz, the peptides also prevent HIV moving from dendritic cells to T cells. 'HIV exploits dendritic cells to take it to the lymphoid tissue, where it can spread into other immune cells. Our discovery that the frog peptides can kill the virus even when it is hidden in dendritic cells suggests that they could be developed as mucosal preventives.'

'There are many interesting molecules in frog skin secretions,' notes Lehrer, 'but identifying peptides that block HIV infectivity is only an early step towards developing an effective HIV preventive. The first compounds one discovers act as templates for a long discovery process that tries to improve their profile.' Toshiyuki Mori of the Molecular Targets Development Program of the National Cancer Institute (Frederick, USA) echoes this sentiment. 'The science in this paper is feasible and interesting but before frog peptides can be used clinically their affinity must be improved and their cytotoxicity reduced.'

Unutmaz is not the only researcher to have turned to frogs for a way to prevent HIV spread. Frédéric Tangy, Director of Research at the Unité des Virus Lents, Institut Pasteur (Paris, France), reported in April 2005 that dermaseptin S4, an antimicrobial peptide from the waxy monkey tree frog, inhibits HIV infectivity *in vitro* [2]. 'We are currently applying for funds to test this peptide in a macaque model,' says Tangy. But, he warns, even if it is effective *in vivo*, ways will have to be found to produce it cheaply before it can be used clinically in the developing countries where HIV preventives are most needed.

'Frog-derived antimicrobial peptides are active against several other pathogens..'

Not just HIV or frogs

Both Tangy and Unutmaz note that frog-derived antimicrobial peptides are active against several other pathogens, which could improve their efficacy in HIV prevention. Demaseptin, for example, is also active against herpes viruses. This broad activity could improve its efficacy as an HIV preventive, says Tangy, because genital herpes infections are associated with an increase in HIV transmission.

In addition, frogs are not the only source of antimicrobial peptides that prevent HIV infectivity. Lehrer is involved in the development of retrocyclins, theta-defensins that are produced by monkeys (but not humans or chimpanzees) and that are active against HIV infection [3]. 'Retrocyclins have been tested *in vitro* and in *ex vivo* models for anti-HIV activity,' says Lehrer, 'but not yet in animal studies.' And Mori is studying cyanovirin-N, an antimicrobial peptide from a cyanobacteria. 'A cyanovirin-N-containing gel inhibits transmission of a chimeric SIV–HIV virus in monkeys', says Mori [4]. 'Three US companies, Biosyn (Philadelphia), Omniviral (Gaithersburg) and Nektar (San Carlos), have taken out licensing agreements with the NIH Office of Technology to develop cyanovirin for clinical use.'

References

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