Drug repurposing discovery for Alzheimer's disease research

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Dr. David Chambers is a systems biologist and consultant to the life sciences sector who specializes in the biomarker discovery research pipeline and the associated bioinformatics challenges. He has an established academic research career that spans 15 years and currently holds a lectureship at King's College London, where he runs both a dedicated research group and a genomics-focused drug discovery facility. The emphasis of his research is to accurately profile the set of genetic instructions required to define cellular identity and behavior at single-cell resolution and to apply this information to future drug repurposing strategies for diseases of the central nervous system. He has extensive experience of commercial and laboratory-developed high-resolution genomic profiling methodologies, is an early adopter of innovative technologies, and has worked alongside many biotechnology and software companies to help develop and refine their products for various life science markets.

Thermo Fisher Scientific: You are approaching the fight against Alzheimer's disease from a different angle; can you please tell us about CMap?

David Chambers: Sure. In general, the drug discovery process works by having a target, something that is dysregulated or dysfunctional in a disease, and then you aim to get a drug against that target. One of the big issues in neurodegeneration, and of course particularly Alzheimer's disease, is that there are a number of problems associated with it. So, it's very complex; there are poly-proteinopathies; there are inflammation issues. It's very hard to get a drug to identify one target. We've taken a completely different approach in our research where we've looked at the transcriptomic changes that are associated with Alzheimer's disease and tried to find drugs that in the future could modulate those based on a whole new scientific release by the Broad Institute called the "Connectivity Map" (CMap) [1].

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Thermo Fisher: What is drug repurposing and how does it relate to your research?

David Chambers: Generally speaking, drug repurposing discovery is about finding drugs that were designed to do one thing for a particular disease or disorder and researching whether they can do something equally clinically effective in a different disease or disorder. Genomic drug repurposing was really pioneered by the Broad Institute, and they did something that had never been done before with CMap: they took the entire suite of FDA-approved drugs and developed a gene expression profile of them on some MCF-7 cancer cells. What that really means is they took each drug and independently added some to cancer cells, and then they used the Applied Biosystems™ GeneChip™ Human Genome U133 Plus 2.0 Array to research what genes were upregulated or downregulated by each of those drugs. That then gives you a huge database of genes that can be regulated by specific drugs. So, if you now have a disease or a disorder—such as cancer in this example—you can then ask what genes changed in the disease or disorder, and research if a drug will do the opposite. Will it bring those genes back to normal?

There is enough proof-of-concept data to say that this is a useful tool for drug repurposing research. It's just one way of identifying potential drugs, among many other ways possible.

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Thermo Fisher: What key challenges do you face?

David Chambers: The challenge for us, of course, is that Alzheimer's disease is not a cancer; it's a neurodegenerative process, which means that you have your gene expression changes happening in neurons. Now, we all know that different cells behave in very different ways. So our difficulty was, how do we take a change in the neuronal gene expression and compare that to a database of drug profiles that were generated in cancer cells? What we chose to do at this point was to regenerate part of the CMap by taking a set of those FDA-licensed drugs and analyzing gene expression not onto cancer cells to get their profile, but onto human iPSC–derived cells, which had a much more cortical-like phenotype. That means that our database of gene expression changes that are associated with drugs are generated in a neuronal cell line. Then we can start to ask a more specific question: how do gene expression changes associate with disease signatures in humans, such as early Alzheimer's disease, and how can that pair up with the gene expression changes that have been generated in actual human neurons themselves? So, there's much greater synergy.

And to try and maintain consistency between our approach and the Broad Institute's approach, we did the exact same thing. Our drug profiles were also generated on GeneChip Human Genome U133 Plus 2.0 arrays. So, we have a very similar database of gene expression changes for our drug profiles that we can then use to research correlations or anticorrelations with our disease signature. The challenge was effectively taking something that we know works very well, but modifying it, so it's more specific to our research question—in this case, repurposing drug discovery for Alzheimer's disease.

Thermo Fisher: And so that explains the differences between Nmap and CMap?

David Chambers: Exactly. We are "Network Mapper" (Nmap), a neuronal connectivity map. Nmap is very much the same as CMap, but rather than researching an individual drug's effect on a cancer cell line, you research the effect on a neuronal cell line, something that has a cortical character, which of course is particularly relevant to Alzheimer's disease because that's where we're seeing some of the cell and synaptic loss. CMap is based on MCF-7 cells, so it's a cancer-focused initiative.

Thermo Fisher: What is the link between neurodegenerative diseases and gene expression? How does this relate to drug repurposing discovery?

David Chambers: For many diseases and neurodegeneration in particular, there are very characteristic changes in the expression of a specific set of genes. You have a set of genes that are upregulated in response to the disease or the degeneration and a set of genes that are downregulated, and those sets of genes may well change based on whether it's something like Alzheimer's disease. And of course, they will change over the period of that disease progression. So, you have genes that are characteristic of early Alzheimer's disease or even mild cognitive impairment, and then genes that are also associated with severe Alzheimer's disease. The way that works is that we want to use those characteristic disease signatures as a fishing tool to research drugs that can correct those changes in gene expression and drive them back to where they should be, and that really describes the principle of genomic drug repurposing discovery.

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Thermo Fisher: How did you decide on the best approach to uncover your insights?

David Chambers: I am very fortunate to be part of a large team that put together an application to the Wellcome Trust to be able to drive the Nmap initiative. We have access to some excellent bioinformatic approaches that could generate unique disease signatures from the public databases. We then have the ability to run this whole project in a laboratory that was set up for high-throughput

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GeneChip microarray expression profiling and pair that up with all of the cell culture work that we have access to for the human iPSC–derived cortical neurons. So, what we had was the availability to put every aspect of this initiative together in one research institute, from the bioinformatics through to the gene expression profiling on the human cortical neurons, and also the subsequent bioinformatic analysis. Additionally, once we have started to identify compounds that are more likely to be able to ameliorate some of the things that we see in Alzheimer's disease, then we will have access to the same animal models. So, what this became was a one-stop shop to go from a disease signature that we had uniquely generated through to getting drugs *in vivo*, all within the same place and relatively cheaply compared to the initial identification of one target/one drug and going through that discovery process.

Thermo Fisher: What are the future directions?

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David Chambers: I think we are standing on the precipice of genomic drug discovery. This is really one of the very first initiatives where we've tried to research what a drug can do in terms of gene expression with what's happening with the disease. The amazing thing about CMap is that it works. I think that alone is worthy of comment. So, secondly now: what does this mean in terms of the future?

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Single-cell genomics—it's not just on the horizon; it's here, it's happening. What we now can do is try to get a much more refined understanding of what's happening in any given disease at the single-cell level. I think refinement levels are where we're going in the future; we have to show this works. We have to get some repurposed drugs into the clinic and into use, have some patient benefit in some way, and then ask how we can further refine it with all of the new genomic technologies in the future.

And then we'll also continually update and refine our drug profile libraries. We'd like to think that genomic drug reprofiling research has a place alongside all of the other more traditional drug discovery methodologies, and that it will have some genuine patient benefits in the future. This will clarify our insights into what drugs are doing in terms of gene expression.

Reference

1. Lamb J et al. (2006) The Connectivity Map: using gene-expression signatures to connect small molecules, genes, and disease. *Science.* 313(5795):1929-1935.

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