Old drug, new tricks: realising the potential of repurposing

MARK GREENER

Drug repurposing has the potential to bring much-needed new treatments to the market quickly. However, despite many promising candidates, this approach is still underused, with funding and regulatory problems often impeding the development process.

In the 1980s, a drug originally called UK92480 was being trialled for angina. It didn’t work. But men in the clinical studies reported an unusual side-effect: erections. Sildenafil went on to become one of the most successful drugs and, in the mid-2000s, found a new role in pulmonary arterial hypertension. Thalidomide, despite its notorious side-effects, is still marketed for multiple myeloma. Dimethyl fumarate, originally used for psoriasis, is now a highly effective, and commercially successful, disease-modifying treatment for multiple sclerosis. Minoxidil was repositioned for hair growth after patients enrolled in a clinical trial assessing the vasodilator for the treatment of hypertension developed hirsutism.

Recent advances in molecular biology have raised numerous other opportunities for repurposing drugs, including an asthma medicine for kidney cancer, a mainstay of type 2 diabetes management for fragile X syndrome, and a cancer treatment for psoriasis. Yet a lack of investment often stifles innovation. “Repurposing an approved drug has benefits in terms of getting the drug into the clinic much more cheaply and quickly since the pharmacokinetics, pharmacodynamics and toxicity are usually known from previous preclinical and clinical studies,” says Wendy Bollag, professor of physiology, Medical College of Georgia at Augusta University, USA. “Although some repurposed drugs are now primarily used for the repurposed condition, rather than the original indication, we believe that this approach is underused. Usually, this is because the drug structure was patented by the company that developed the medicine for the original indication.

Figure 1. Metformin molecular model. A first-line treatment for diabetes for many years, metformin may now offer hope in the treatment of other conditions such as fragile X syndrome and autism spectrum disorder.
The patent for a repurposed drug covers only a particular use, which is often more difficult to enforce."

From diabetes to fragile X

Because of the lack of investment in repurposed drugs, much needed, relatively inexpensive treatments might fall by the wayside. Metformin (see Figure 1), for example, derives from the French lilac (Galega officinalis; also called goat’s rue), a traditional herbal remedy for the symptoms of diabetes. First synthesised in 1922, it is a first-line treatment for type 2 diabetes.¹ But almost a century later, metformin is finding new roles.

For instance, fragile X syndrome, the most common known cause of inherited learning disabilities, affects around 1 in 4000 males and 1 in 8000 females in the UK (see www.fragilex.org.uk). People with fragile X syndrome may experience a range of social and behavioural problems, developmental delays and learning disabilities. The mutations that underlie fragile X syndrome stop expression of the fragile X mental retardation protein (FMRP). This, in turn, increases the activity of two intracellular signalling pathways – the mammalian/mechanistic target of rapamycin complex 1 (mTORC1) and extracellular signal-regulated kinase (ERK) pathways.²

Previous studies suggested that metformin dampens the activity of mTORC1 and ERK. “We hypothesised that using metformin in fragile X syndrome model mice could reverse the dysregulation of these pathways,” says Christos Gkogkas, chancellor’s fellow and Wellcome Trust Sir Henry Dale fellow at the Patrick Wild Centre, Centre for Integrative Physiology and Simons Initiative for the Developing Brain, University of Edinburgh. “At the moment, there is no ‘cure’ for fragile X syndrome and it is important to identify new compounds that can ameliorate or reverse certain symptoms. Metformin is appealing because we’ve known about it for more than 30 years and it is the most widely used first line of defence against type 2 diabetes, which has led to the accumulation of invaluable data about its safety and tolerability. Thus, if we proved our hypothesis, we would envisage that metformin could be quickly repurposed for fragile X syndrome.”

Indeed, Dr Gkogkas’s team recently reported that metformin can ‘rescue’ the core changes in social, repetitive and other behaviours in a genetically engineered mouse model of the fragile X syndrome. For example, people with fragile X syndrome often show repetitive behaviours, which is reflected in increased grooming by the genetically engineered mice. Metformin reduced the number of grooming bouts, normalised the activity of the signalling pathways and corrected characteristic abnormalities in the neuroarchitecture of the hippocampus.³ “Certain brain circuits are conserved from mouse to humans,” Dr Gkogkas explains. “More importantly, cellular and molecular pathways are highly conserved. Therefore, understanding the circuitry in a mouse for a given behaviour could potentially lead us to identify similar circuits in the human brain, which can also go awry in neurodevelopmental disorders, such as fragile X syndrome.”

Dr Gkogkas now plans to explore further metformin’s action in the brain and examine whether it improves symptoms in other neurodevelopmental conditions, particularly autism spectrum disorders. “There is a momentum for clinical trials with metformin in fragile X syndrome and autism, especially because metformin is approved for use in the paediatric population,” he says. “We could see the results of clinical studies of metformin in neurodevelopmental disorders coming out as early as the next one to two years.”

A common pathology

Traditionally, ideas for repurposing drugs have arisen serendipitously: a side-effect or clinical observation prompts the investigation. Increasingly, however, researchers draw inspiration from basic biology. For example, immune dysfunction contributes to diseases as diverse as cancers, arthritis and psoriasis. Indeed, Cancer Research UK and Arthritis Research UK are collaborating on a project looking at immune homeostasis – how immune pathways operate in steady-state conditions. Aberrations in immune homeostasis seem to contribute to some cancers and musculoskeletal diseases. “We’re looking at the cross-talk between immune cells and how changes can affect both conditions,” explains Nigel Blackburn, director of drug development at Cancer Research UK.

Like metformin for fragile X syndrome, the repurposing of vorinostat – also called suberoylanilide hydroxamic acid (SAHA) – for psoriasis was inspired by a deep understanding of the molecular biology. Vorinostat, which is approved in the USA for cutaneous T cell lymphoma, inhibits an enzyme called histone deacetylase.

Almost all of the trillions of cells in the human body contain about two metres of DNA, which is tightly coiled and wrapped around proteins called histones (see Figure 2). “Histone acetylation ‘loosens’ the DNA so that transcription machinery can more readily access genes to trigger their expression,” Professor Bollag explains. “Histone deacetylase ‘tightens’ the DNA structure. Therefore, histone deacetylase inhibitors tend to promote gene expression. However, the name ‘histone deacetylase’ is something of a misnomer. These enzymes also deacetylate a number of other proteins, including transcription factors, that are also important for gene expression.”

This action on gene expression stimulated investigations of histone deacetylase inhibitors in cancer and psoriasis, both of which are typified by excessive cell proliferation. “Psoriasis is characterised by excessive proliferation of keratinocytes in the epidermis,” says Professor Bollag. “Psoriasis also exhibits aberrant keratinocyte maturation as well as inflammation. Although the immune system clearly plays a key role in psoriasis, accumulating evidence points to the involvement of keratinocytes in the initiation, maintenance or both of the inflammatory response. Psoriasis shows a vicious cycle whereby activated keratinocytes produce cytokines that stimulate the immune system, which produces cytokines that activate keratinocytes and so on. Therefore, we anticipated that agents that improve keratinocyte homeostasis might improve skin diseases, such as psoriasis.”

Professor Bollag’s team is focusing on a protein called aquaporin-3, which transports water and glycerol, and so...
maintains skin hydration, aids epidermal wound healing and repairs barrier function. Psoriatic lesions show low levels of aquaporin-3, which is also abnormally expressed in the cytoplasm rather than in the membrane.4 “We also found evidence that aquaporin-3 inhibits keratinocyte proliferation and promotes differentiation,” she adds. “Therefore, in addition to inhibiting cell growth in many cancer cells, SAHA’s effect on aquaporin-3 levels should counteract several of the abnormalities observed in psoriatic skin.”

Professor Bollag’s team recently reported that SAHA increased aquaporin-3 expression in cultures of normal human keratinocytes and mouse skin organ culture.4 “Psoriasis is a complex disease that is not adequately modelled in a petri dish,” she explains. “Therefore, before applying this result to the clinic, additional experiments in animal models of psoriasis will need to be performed. However, topical histone deacetylase inhibitors are in development for cutaneous T cell carcinoma and psoriasis. We believe that these trials will show positive results in psoriasis and would support development of related drugs. Once we confirm an ability of histone deacetylase inhibitors to ameliorate psoriasis-like skin lesions in mouse models, clinical studies can be initiated. We are planning to perform and finish these experiments in the next year and see if we can go from there.”

A similar approach could pay dividends in other areas. “We think that matching the pathway and drug action on a molecular level will apply to other conditions, although more than one approach can be used to develop novel and effective drugs for treating diseases,” Professor Bollag says. “One such approach is to identify a key enzyme or protein underlying a particular cellular response, such as proliferation, differentiation or cell death, and then to target that particular enzyme or protein to alter its activity. This strategy has worked for a number of diseases, including psoriasis, with some of the new biological drugs developed based on research suggesting the importance of the pathways targeted.”

Into the valley of death

Despite the clinical potential, a lack of investment often hinders repurposing. For example, a growing body of epidemiological and experimental evidence suggests that statins may reduce mortality in breast cancer.5 But this remains controversial. “There is no financial incentive to invest in studies to determine the value of statins in breast cancer despite promising and intriguing epidemiological studies,” Dr Blackburn explains. “It is really difficult for a drug company to make the money back that they invested in phase 2 and 3 trials from a repurposed medicine, especially if the drug is active in a rare cancer. It’s really frustrating.”

Researchers often approach Cancer Research UK with an idea for a phase 1 study of a repurposed drug. “However, we often need to decline potentially promising repurposed drugs as no one will pick up the bill for phase 2 and phase 3 trials. We might need a philanthropic approach, such as the Gates Foundation in vaccine research, to unlock the potential,” Dr Blackburn adds.

Certainly, academic centres’ pockets are not deep enough to fund clinical research. “We looked into developing another molecule that we think could be used to treat skin diseases and found that such research would cost well over a million dollars – money that most institutions of higher learning do not have and often cannot access,” Professor Bollag says. “Indeed, as the avenues to fund the required studies are limited, this stage of drug development is often called ‘the valley of death’.”

Part of the answer is for companies to consider repurposing earlier in the lifecycle. “We’ve worked with several companies on a drug that might have an effect in cancer, but that was originally developed for a different indication,” Dr Blackburn remarks. “As the drug is still covered by patent, the company has the opportunity to recoup the investment.”

For example, AstraZeneca discontinued development of the investigational drug AZD2098 for asthma. However, AZD2098 targets CCR4, a receptor for chemokines (messengers that control the movement of cells). Renal cancer cells seem to overexpress CCR4. So Cancer Research UK is looking at repurposing the AZD2098 for kidney malignancies. “We’ve worked on several similar examples. If successful, there is sufficient patent life to move such drugs

Figure 2. DNA tightly coiled around histone proteins to form nucleosomes. Gene expression is regulated by the acetylation and deacetylation of histones, and histone deacetylase inhibitors, which can promote gene expression and inhibit cell proliferation, are currently being investigated for the treatment of both cancer and psoriasis.
forward either with the original company or another licensee,” Dr Blackburn says. “These drugs offer new hope for these malignancies.”

Indeed, drug companies have huge libraries of biologically active drugs that never reached clinical studies or even animal models, forming a huge and largely untapped resource. “People have talked about this a lot and some companies have opened their libraries to researchers,” points out Dr Blackburn. “There may well be a pharmacological gem hidden in there, but until we have a systematic investigation of these libraries, we won’t know.”

Importantly, repurposing drugs can reduce development costs. This should, in turn, reduce the price of the medicine once on the market. Reducing costs is especially important in cancer where drugs costing hundreds of thousands of pounds extend life by a few months. “Something has to change,” Dr Blackburn remarks. “The cost isn’t sustainable and there is a crisis in funding coming, I don’t know when, but it’s coming. So, we need to work with regulators and companies to make repurposing easier and cheaper.”

“It would be irresponsible to ignore the high translational value of repurposing existing compounds,” Dr Gkogkas adds. “Validating the effectiveness of existing compounds can have a positive ripple effect in clinical and preclinical research by helping to design targeted animal studies, by reducing the time in which a compound can be available to doctors and families and by reducing the overall cost of clinical and preclinical validation. However, without a doubt, basic drug discovery is also key in biomedical research. Irrespective of the profitability of a compound, a combination of new drug discovery and the repurposing of existing ones is the ideal way to move forward.”

**Conclusion**

So whether by accident or design, drug repurposing can result in commercial blockbusters, offer new hope in difficult-to-treat diseases and provide new insights into drug mechanisms. Moreover, advances in molecular biology mean that there are more opportunities for repurposing than ever. However, making the most of the new opportunities means finding new ways of funding and developing drugs. “Drug development is, traditionally, a very linear process,” Dr Blackburn concludes. “Companies need to follow that process for regulatory and commercial reasons. Other researchers can take a step back to look at repurposing and other innovative ways of finding drugs. We now need to find the mechanisms that can bring these innovations to the clinic.”

**References**


**Declarations of interest**

Mark Greener is a full-time medical writer and, as such, regularly provides editorial and consultancy services to numerous pharmaceutical, biotechnology and device companies and their agencies. He has no shares or financial interests.

*Mark Greener is a freelance medical writer*