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DRUG DISCOVERY

Better, safer, small molecule drugs

CATH O'DRISCOLL

Scientists say they have hit on a new way to make safer, more versatile small molecule drugs that could pave the way to treatments for a slew of currently hard to treat or untreatable diseases.

Traditional drug discovery efforts have focused on finding small molecules that bind directly to proteins, but an estimated 80% of proteins are considered difficult to target or even 'undruggable' by these approaches, according to Yochi Slonim, CEO of NJ-headquartered Anima Biotech. Instead, Anima's strategy is to discover small molecules that work much earlier in the process – by binding to various other regulatory proteins that control protein production or translation in cells.

In 2018, the company announced a collaboration with Eli Lilly for the discovery and development of translation inhibitors of several undisclosed target proteins – a deal worth up to $1bn in milestone payments.

'Our *Translation Control Therapeutics* technology is the first platform for the discovery of small molecule drugs that specifically control mRNA translation as a new strategy against many diseases,' says Slonim. 'The technology not only allows to reduce production, but also to ramp up production of the targeted protein – something that has never previously been possible,' he explains.

Protein translation occurs by cellular machines called ribosomes that decode the genetic information in strands of messenger RNA and use it to assemble the corresponding proteins. But despite its fundamental importance in biology, Slonim says 'you won't find a textbook today that will tell you how the regulation of translation works in a specific way to control individual proteins'.

Anima's breakthrough has been to develop a way to visualise and monitor the production of proteins as they are being made, he explains – by attaching fluorescent tags to pairs of transfer RNA molecules that carry the coded-for amino acids to ribosomes for protein assembly. Light pulses emitted when two labelled tRNAs are brought together in the ribosome reveal when, where and how much of the target protein is being made in the cells – in real time.

It's this light output that Anima has put to work in its platform technology for automatically screening hundreds of thousands of small molecules for their ability to decrease or increase the production of a range of target proteins associated with disease.

'One key point is the approach is totally unbiased,' Slonim says. 'We simply do the screening in live cells to see which compounds increase or decrease production of the protein. The outcome can be we find 30 or 40 different compounds that are chemically very diverse that can do this.' AI technology is then used to select the compounds that should be most effective.

Another advantage of this screening platform is that the small molecules identified are inherently more tissue specific and therefore safer than conventional small molecule drugs, he says. This is because the regulatory proteins controlling protein translation tend to be specific to each tissue or organ in the body. In screening for small molecules that control collagen production, for example, he notes that Anima researchers have found compounds that reduce protein production in the lungs but are not active in skin or liver cells.

Anima's lead programme is in lung fibrosis, with other programmes in fibrosis, scleroderma, respiratory syncytial virus infection, and against cMyc protein – which is overexpressed in most types of cancer and Huntington's disease.

MATERIALS SCIENCE

Light trapping pixels

ANTHONY KING

The smallest pixels yet have been created by trapping light with gold nanoparticles. They could be used to change the colour of buildings while consuming very little energy.

The gold nanoparticles are coated in a sticky conductive polymer and sit on top of a reflective, mirror-like surface, which traps light (*Science Advances*, doi: 10.1126/sciadv.aaw2205). 'We deployed potential to control the redox state of the polymer, and that in turn changes the refractive index and essentially the light colour,' says Hyeon-Ho Jeong, a co-author of the research at Cambridge University. 'We don't need a backlight or much energy to operate the light, just ambient light.'

The polymer, polyaniline, and nanoparticle are sprayed onto the flexible mirror-coated plastic. Initial applications include lighting up buildings, or as electrical panels in supermarkets. Gold absorbs light in the blue region, so 'we are currently operating colours tinted from red to green, but we are looking to see what type of material could generate blue,' Jeong says. Aluminium and silver nanoparticles are other possibilities.

The nanoparticle mirror system is based on gold particles that possess well understood 'surface plasmon resonances', says Martyn Pemble, materials chemist at the Tyndall National Institute at University College Cork, Ireland, commenting on the research. These are oscillations of electrons that occur at wavelengths linked directly to their size, shape and – importantly for this application – the spacing between the particles and the underlying mirror. 'This work represents a potential paradigm shift in terms of the design and fabrication of colour displays, which could have enormous commercial potential,' notes Pemble.

The nanoparticle on mirror, or NPoM, structure, he says, 'opens up huge possibilities in terms of the construction and manufacture of ultra-thin colour changing devices, which show changes in colour and response times suitable for most display applications, yet would be perhaps 100 times thinner than comparable conventional displays.