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RNA but not as we know it

Aptamers—artificially generated three dimensional strands of RNA—might revolutionise therapeutics, says **Ryan Hobson**

The holy grail of modern medicine is the inhibition of the molecules and biochemical pathways involved in generating disease. Cancer, for example, would be a thing of the past if you could therapeutically inhibit the aberrant pathways that enable unregulated cell division. For longer than a century the medical world has sought "magic bullets" that might perform these functions.[1 2]

Monoclonal antibodies

Monoclonal antibodies are antibodies that have been engineered to target particular molecules and to block their functioning. This method of inhibition is similar to the way in which an enzyme is inhibited when its active site is blocked. With their natural specificity and tight binding ability, monoclonal antibodies were thought to be ideal for the role of magic bullets. However, despite the introduction of a number of treatments based on antibodies, they have yet to fulfil their early promise.[1 2]

Within the past 15 years or so, another class of molecule has emerged to rival or complement monoclonal antibodies: aptamers. These are artificially generated single strand RNA molecules that have three dimensional globular structures, similar to tRNA. Through an in vitro selection process, known as SELEX (systematic evolution of ligands by exponential enrichment), aptamers can be isolated that bind essentially any molecular target with even greater specificity and affinity than monoclonal antibodies. Further to this, aptamers have other properties that make them more attractive as magic bullets than monoclonal antibodies.[3-5]

Aptamers are small molecules, with typical molecular weights of 8000-15000. Antibodies on the other hand are large (155000) and as a consequence take a long time to enter the affected tissues when used as therapeutic agents. In theory this could result in unwanted clinical side effects–for example, bone marrow toxicity if the antibody is coupled to a compound that kills cells.[2] In contrast, aptamers are present in the blood for only a few minutes. They can be easily modified to increase this time or to carry other molecules to a specific target, depending on clinical requirements.

Monoclonal antibodies rely on mice for their initial production, so the human immune system recognises them as foreign.[2] Although this problem was largely overcome in 1986, with the advent of humanised monoclonal antibodies, prolonged use can still result in immune reactions in patients. A new technology using bacteriophages (viruses that replicate in bacteria) genetically modified with human antibody genes that can produce fully human antibodies has much potential.[1] After prolonged use in animal models and clinical trials, aptamers have not elicited an immune response.[5]

Success stories

Aptamers have already entered the drug market with the successful completion of clinical trials of pegaptanib (Macugen, OSI Eyetech and Pfizer). This aptamer based drug has been successfully used to treat exudative age related macular degeneration, one of the leading causes of severe visual loss in people older than 55 in the developed world.[6] In a phase III clinical trial, 1208 patients were randomly assigned to receive pegaptanib every six weeks over a period of 48 weeks. About 70% of actively treated patients achieved the primary endpoint, defined as visual loss of fewer than 15 letters of visual acuity, compared with 55% of the controls.[6]

Aptamers that neutralise the infectivity of the HIV virus in peripheral blood mononuclear cells in vitro have also been developed. They bind to a protein known as gp120 that has so far been difficult to target with monoclonal antibodies because of their size and the protein's antigenic diversity.[7]

Aptamers can provide solutions to many of the problems encountered by monoclonal antibodies. Although much more expensive than conventional drugs, aptamers have the potential to be at least 10 times cheaper than monoclonal antibodies because they are chemically synthesised. These properties give aptamers a considerable clinical and market advantage over monoclonal antibodies. The introduction of pegaptanib and the successful completion of clinical trials for other aptamers should increase the profile of this promising new class of targeting and treatment agents, leading to further interest in this exciting emerging field.

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