

Professor Tom Brown***Nucleic Acid Therapeutics: Present and Future Prospects***

Q: Is the reason that cystic fibrosis is dominant that only requires those two Gs have to become As?

A: Everyone with CF will have two faulty or 'mutated' CF genes. These mutations may also be known as 'variants'. There are **over 2,000** known mutations that can cause CF. The two genes could be the same mutation, or you could have two different ones. In my slide the two highlighted G-bases were separate examples of alternative single base mutations that are known to cause CF when present as two copies (i.e. homozygous).

Q: Although the viral RNA can be destroyed by the bonding of the oligonucleotide and be destroyed by the enzyme, won't the viral DNA still be inside the host's genome? Therefore the viral genes would be still transcribed continuously, thus a large amount of oligonucleotides would be required constantly which doesn't really 'cure' the cell so won't be delaying the virus or any kind of abnormal proteins created by the cells?

A: A virus particle cannot survive for very long inside a human cell, it will be degraded by the host's defence mechanisms so it relies on being able to quickly make key proteins that allow it to be copied and leave the cell to invade other cells. The oligonucleotide is designed to intercept a key component of this copying process.

Q: When inserting this foreign RNA, are patients a risk of an unfavourable immune response - e.g. too much of an immune response or weakening of the immune system in any way?

A: Yes this is possible, particularly if repeated injections are required for a therapeutic application. It is an area of ongoing research. For vaccines it is not a major problem as an immune response is actually needed, provided that it is not too strong. Did you notice that the Nobel Prize in medicine announced on 2nd October was for RNA vaccines?

Q: Surely if the oligonucleotide is made in such a way the cell cannot recognise it, the cell would believe it's foreign and destroy it. So how did they work around that?

A: To avoid this potential issue the chemical modifications in therapeutic oligonucleotides have been designed to avoid setting off an immune response in human cells. One example of this is the use of methylated cytosine in the oligonucleotide which is less immunogenic than cytosine.