This is SISS, Science on the ISS, the International Space Station – and today's episode is *Rational drugs.*

If you're any kind of a science buff you'll know that we figured out the double-helix structure of DNA through X-ray crystallography. We fired X-rays at a DNA crystal and the diffraction pattern that bounced off its crystalline framework revealed the 3D geometry of the DNA molecule.

This key finding came from the work of Rosalind Franklin who should arguably have been included alongside Francis, Crick and Wilkins in the 1962 Nobel prize for discovering '*the molecular structure of nucleic acids and its significance for information transfer in living material*'. But, since Rosalind Franklin died in 1958, she couldn't have been included anyway.

What you might not know is that DNA isn't actually a crystal. Fire X-rays at a sample of endogenous DNA and you might create a mutant superhero, but you certainly wouldn't get a clear diffraction pattern that would earn you, or your intellectual-property-thieving lab colleagues, a Nobel Prize.

In order to do X-ray crystallography on organic molecules, you first have to convert those organic molecules into crystals. This was part of Rosalind Franklin's skill set – not only could she diffract X-rays off a DNA crystal, but she could convert DNA into a crystal first. Such a DNA crystal has locked within it a lasting record of all the geometrical relationships that had existed between the elemental components of that DNA molecule in its endogenous form.

Within living cells, DNA is tightly coiled – and those coils themselves are then further coiled into a dense package that is largely impenetrable to external observation. But, kill the cell, isolate its DNA, unravel that DNA and then fix it into a crystalline structure… then the true nature of DNA's underlying molecular architecture can be revealed.

But, long before the ISS was even conceived of, we had pretty much worked out the structure of DNA and X-ray crystallography had moved on to tackle *proteins*. Proteins underlie a much wider variety of complex biological functions than just the recording and reproduction of the genome.

For example, our continued existence is entirely dependent upon some protein-based sewing machines called ribosomes, which can both zip and unzip our multi-coiled DNA genome for the purpose of accessing all the different DNA information templates that we require – to live and to grow and to reproduce. These ribosomes really are tiny molecular-sized machines and we still only have a vague understanding of their 3D structure and of how they do what they do, in a mechanical sense.

If you really want to understand how biochemical processes work, you really do have to start thinking in 3D – and once you start realising how many varied protein structures underlie each and every biochemical action that keeps us alive and well, you might well start wondering why more people aren't investigating the 3D structure of proteins.

Well, in fact, *lots of people* are investigating the 3D structure of proteins. But it's a frontier that we have barely begun to explore. The geometry of DNA was relatively easily since it's the same basic geometry repeated over and over again down a long chain. Proteins are not so easy since they can form much more complex and irregular shapes. It's these very different protein architectures that allow the many different proteins out there to do the many different things that they do.

Back in the 80s and 90s, while we were still just doing space-shuttle-duration missions into microgravity, space-shuttle science demonstrated that proteins can be crystallised in space much

more effectively than they can be on the Earth's surface. The absence of gravity means more opportunity for a growing crystal to achieve a stable and solid framework before it may collapse under its own weight.

Once fully-formed these near-perfect microgravity crystals will retain their structural integrity and can be returned to Earth without collapsing, despite being back in a full 1G of gravity.

It's back on Earth that we can then carry out X-ray crystallography on such space-grown crystals, since X-ray machines are kind of heavy and astronauts orbiting outside the bulk of Earth's atmosphere are already getting enough of a radiation-dose without wanting to deal with the additional burden of working right next to an X-ray emitter.

Using X-ray diffraction, we can effectively map the locations of different atoms within a 3D view of the whole protein. And, with this structural information in hand, we can then determine exactly how the protein works and we can also identify small molecules that might have the ability to either aid or impede that protein's function.

And why does that matter? Because *that* is the basis of nearly all of modern pharmacology. Nearly every drug that we use in science-based medicine does what it does by aiding or impeding the function of a protein.

Penicillin works by binding with the bacterial protein enzyme DD-transpeptidase and blocking its function in building bacterial cell walls. Blocking this function kills the bacteria.

Caffeine, a drug that affects people, interacts with protein gates that are present in membranes of many of the neurons in your brain. Caffeine fits the keyholes that are *supposed to* unlock some of those protein gates. But caffeine is an impostor, it fits the keyhole, but it doesn't open the gate. The real key, adenosine, helps your body to relax and conserve energy.

So, by stopping adenosine from opening protein gates, caffeine makes you vigilant and full of nervous energy.

So, the future of pharmacology is all about protein structures and it's all about *rational* drug design. Irrational drug design – which is essentially *accidental* drug design, involves coming upon a stack of staphylococcus-infected plates that you'd forgotten you'd left in a corner of the lab and then finding the staphylococcus had died on all the plates that had gone mouldy.

This actually happened to Alexander Fleming in the 1920s, who then went on to discover penicillin. He won a Nobel Prize in 1945 along with Howard Florey and Ernst Chain, who realised penicillin's potential as a life-saving drug and also worked out how to mass produce it

But that is not *rational* drug design. Rational drug design involves gaining an in-depth understanding of a protein's 3D mechanical structure and then identifying a small molecule that can interact with that structure. There are a growing number of catalogues full of such protein-interacting molecules, which all have the common feature of being 'drugable'.

For a small molecule to be considered 'drugable', it must be able to do the following:

1. be ingested or injected in a way that does not destroy the molecule nor harm the person who is taking it:
2. be transported to the site where its action can have a therapeutic effect; and

3. have minimal nasty side-effects along the way and be metabolised into oblivion after doing its job.

A good example of such a small molecule, which then became a rationally-designed drug, is Glivec. Glivec was designed and developed to treat a certain form of leukaemia by blocking the action of tyrosine kinase enzyme – which, you guessed it, is a protein. Tyrosine kinase is only active in growing cancer cells and blocking its action leads to the death of those cells, while leaving normal *non*-cancerous cells unharmed. Now, *that* sounds like a rational drug.

So how does the ISS fit in here? Well, building bigger, better protein crystals in microgravity should allow us to gain a better understanding of how proteins work, which should give us a better understanding of how to manipulate those proteins using rationally-designed drugs that will then improve and prolong our lives.

Right now, today, this work is still largely experimental. Most of the focus is still on proving the worth of protein crystallisation in microgravity. We know we can build better protein crystals in space, but just *how much* better, will come down to fully refining the technique. From there, we will then have to determine whether the maximum achievable improvement is really worth all the cost and effort involved. That is the objective and the end point of ISS science in this noble endeavour. Taking the next steps towards rational drug design will nearly all happen back on Earth.

So, it might be a while before we hear that a particular crystal, built on the ISS, led to the design of a particular drug that, back on Earth, saved *countless* lives – or at least *prolonged* countless lives. But we really might hear something like that one day, in the not too distant future, if the ISS science goes on.