Catherine Seed: Welcome to the Inside WIMM podcast: the people behind the science at the MRC Weatherall Institute of Molecular Medicine at the University of Oxford, an institute we affectionally know as the WIMM. Today we have a throw back episode, an interview we release on our Youtube channel back in December 2021. In it we meet Professor Hal Drakesmith from the MRC Human Immunology Unit, and Associate Professor Jon Wade from the Department of Earth Sciences. We explore their collaboration, how they investigated how planetary iron helped shape biological evolution. Enjoy the podcast.

Jon Wade: The conversation started off about football and unfortunately the team I support is mostly useless and we moved on from football to work and that's really where it came across, after the beer had been drunk mostly.

Hal Drakesmith: We suddenly realised that we had something in common, and that thing was iron, although we came to it from entirely different places. But we had a lot of conversations and we realised that we actually had if we put together the concepts that Jon was familiar with and the concepts that I was familiar with and we matched them up we actually came up with something that appeared to be original and exited both of us, and so we turned it into a manuscript.

Jon Wade: My name is Jon Wade. I'm the Associate Professor of Planetary Materials in the Department of Earth Sciences at Oxford. My interests really are understanding how the Earth's core formed, why is the Earth different to say Mars and Venus and Mercury in terms of its' iron contents of its' rocks. That is really where Hal's interest in iron kicks in that is where the overlap is, you know the iron in the rocks becomes the iron that life uses.

Hal Drakesmith: I'm Hal Drakesmith. I'm Professor of Iron Biology at the MRC Weatherall Institute of Molecular Medicine and my lab works on the role of iron in the immune system and how iron deficiency happens and how anaemia happens and how iron influences infectious diseases. Iron is really useful in biology it's absolutely critical for mediating catalysis and metabolic processes. So, it appears when you go back in time and look at very ancient organisms that still survive today you can see that a lot of the basic building blocks of biology are iron dependent. So, things like generation of energy, making DNA, carrying oxygen in the body and in cells, all of those need iron and that is the same for almost every single form of life. The paper kind of comes at this as a narrative tale of the different roles of iron in the evolution of life.

Jon Wade: Iron is cosmo-chemically abundant it's the last things that stars make before they go 'pop' or stop being useful stars. So, it's cosmo-chemically very abundant that is, there is a lot of iron kicking around in the universe at this point in time. The amount of iron in the planet, in the rocks, is really governed by the processes that go on right at the very start of planetary formation. So as the Earth is first forming out of these planetary building-blocks, these meteorites, it's been all falling together and starting to heat up and melt, the amount of iron in the rocks is really governed by the chemical and physical conditions of that process. You then have a very different atmosphere at the dawn of the planet than you have now. It didn't have any oxygen in the atmosphere, and the consequence for that is that in the early seas, in those deep Archean seas, 4 billion years ago when we know we have water around, iron was soluble in seawater. So, there was about 5 orders of magnitude more iron floating around in those seas when life first started to get its' act together and form, than there is now because of the rise of oxygen.

Hal Drakesmith: To begin with, iron is absolutely critical for setting the conditions that life can develop. and it is soluble in water, and it promotes biochemistry, and so simple life can get going. But then, you take the iron away. What happens then? You have to adapt, and any behaviour that enables an organism to get hold of iron when it is difficult to get hold of is going to give a really big selective advantage.

Jon Wade: This event around 2 billion years ago, what we term as the Great Oxidation Event and it wasn't that great but a bit of oxygen ends up in the atmosphere and it's a small amount of oxygen, but actually has a massive consequence for the amount of iron certainly the amount of iron in the surface seawaters of the seas around at that time. because that iron then becomes oxidised, and oxidised iron isn't soluble, it just rains out. We see this in the rocks, we have these called banded iron formations. They occur throughout history, but there is a big peak of them around about 2 billion years (ago). And that is this soluble iron raining out. And that has implications for life, and that is really where Hal's interest and how Hal's research really kicks in. It is around that point you've got this evolutionary driver you've got this resource limitation that the Earth has imposed on life. and to some extent life has imposed on itself.

Hal Drakesmith: What Jon and I were realising when we were talking about the oxygenation event the Great Oxygenation Event and then the subsequent one, the Neoproterozoic Oxygenation Event is that this was having an unbelievable effect on the amount of iron available at planetary scale. Gigatonnes of iron were suddenly, relatively suddenly, becoming unavailable to the areas of the planet where there was most life, so the photic zone in the surface of the planet. What effect would that have? ...and it's really hard to know but what we do know is that it was at those times that evolution made enormous bounds, so development of eukaryotic life, multi-cellular life, evidence of predation, infectious events, symbiosis, all of these things appear to occur after the oxygenation events of the planet. So, these are big evolutionary leaps and of course, evolution is really complex, and iron can't possibly be the only thing that really is governing this, but I don't think anybody, as far as we could tell, had really thought about iron in these terms, as kind of a planetary scale event and affecting evolution.

Jon Wade: How life has dealt with these environmental restrictions, it had placed on it this loss of iron, and it's come up with some quite mechanisms like sharing, and cooperating and 'have some of my iron', and 'have some of your iron', but it has also come up with some quite aggressive ones that have also been very successful.

Hal Drakesmith: One of the things that we study in the lab is that these days, iron is actually very hard to get hold of as an organism because it is insoluble and it is not floating around in water, and usually one organism tries to steal it from another. So, you can't get it from the environment you've actually got to steal it from another organism, and that is infection. Infection is essentially you know, if a bug infects you, it isn't interested really in killing you, it's interested in stealing your resources. Using you as a source of food, and a key nutrient that organisms need in that concept of infection is iron. Iron is the most important nutrient that host and pathogens fight over. So, we were really familiar with this concept. It is something that we think about on a daily basis in the lab in terms of an infection in a person and the genes and cells that mediate the response to the infection. And I think that's what I found really really interesting. Life is telling us about events that went on in Earth's rock history that we don't record within the rocks. One of the probably very first interactions that iron has in the context of developing life is with sulphur. Still within us, within our cells, in our mitochondria, you have iron-sulphur clusters. Little tiny, tiny little crystals of iron and sulphur in the middle of our proteins still.

Jon Wade: And those iron sulphides, iron sulphur complexes they are also recording those early reduced oceans. where iron sulphides $FeS$ is much more prevalent than in today’s oceans where it is oxidised. Where you do find it is in things like the bottom of the Black Sea what they call these

Euxinic sort of seas, which are sulphide-rich. But again, it's recording a very very different environment and that is kind of cool. Earth is kind of an annoying planet. in some respects.  If you are a geologist, it is quite annoying because it is really active. There's not many really old, there's bits of rock from all through Earth's history, kicking around the surface but there's not much. The further you go back there is less and less of it. It's the selection pressure for rock, the preservation potential. So actually, we don't have a good record of what the Earth was like in the rock record 4 billion years ago. But it turns out, and I think this is kind of interesting, it turns out that live has recorded at least to some extent, the chemistry of the early seas. We don't have bits of the early sea around but we have it within us. So, the reason life has used iron so extensively is because that is where it learnt iron was available when it learnt its initial programming. back in those Archean seas that contained lots of iron. And then it's had to learn how to deal with an iron loss of 2 billion years and 500 million years ago at that Neoproterozoic event. So, I found that kind of interesting from a geology perspective. You know, we're all into our rocks. We like going out looking at rocks. But it turns out that we don't always have the rocks we want. We might have to look at other evidence of the environment that was around 3.5, 4 billion years ago. and that's where life kicks in, you know, because we record within us some of those grand events.

Often, we're not aware of what goes on in other departments and what their capabilities are. So again, this is one of those areas, we have a common interest, we can tell a common story and then we can bring the tools that we have that we're familiar with, and answer somebody else's problems, or at least try and attack them. And that's exactly what we're doing at the moment.

Hal Drakesmith: Cross-disciplinary research is just really exciting. It actually takes a long time to be able to speak each other's language, where, even the same words that Jon would use, that I would use but we had attached entirely different meanings to them because we're from different fields, so, you know, the intellectual interaction required some lubrication and time but we got there so, we did come up with something that I think is interesting. When I've presented the work to people in my field, in biomedicine, they found it very useful to get this perspective of ok, you know, we've been working on iron for decades, but, why is iron so important? It really does go all the way back to geology, planetary formation, and then the Great Oxygenation Event and taking the iron away. This is where it all comes from.

Jon Wade: Joking aside, it is really important to sort of step outside your comfort zone and talk to other people, and find what they do and actually this is a good occasion of an idle chat over a beer which led to something very interesting.

Catherine Seed: This has been 'Inside WIMM'. If you like the podcast, please subscribe, like or review.