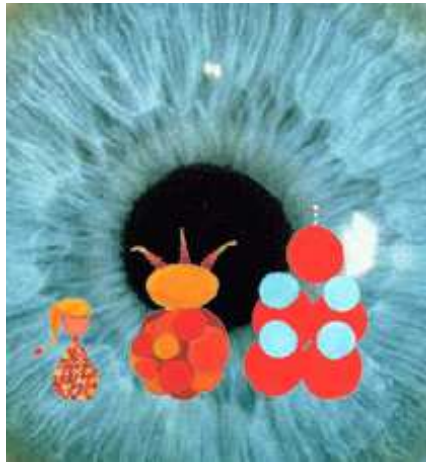


"Journey into a tiny world"



"Journey into a tiny world" (original title: "Globine et Poiétine sur la piste de la moelle rouge") is a tale for children, written and illustrated by Sylvie Déthiollaz and Vivienne Baillie Gerritsen. It was written for a children's science fair where it two actors read it. Its success was such that the Swiss-Prot group decided to turn it into a book. For the time being, the tale only exists in French but the English version should be out by spring 2007.

Lily is suffering from anaemia because she does not have enough red blood cells. Doctor Cruikshank has decided to treat her with EPO - or erythropoietin - which will help her make more... providing it can reach Lily's marrow. Together, Globin (haemoglobin) and Poietin (EPO) leave for their long journey to save the little girl's life. "A journey into the tiny world" is the story of the two heroines and their treacherous adventure into the smallest of worlds. A world scattered with surprises, during which they meet hosts of other proteins that will help them find Lily's marrow and, in the end, save her life.

Globin and Poietin: the heroines

Red blood cells - also known as erythrocytes - are the main blood cells. Their role is crucial since they transport oxygen from our lungs to every other organ. Unlike sugar, oxygen is more than just fuel: it optimizes the production of energy that is essential for the proper functioning of our cells. This is the reason why our brain - which works not only very hard but also full time - cannot go without oxygen for more than a few minutes.

Lily - the little girl in the tale - is not producing enough red blood cells because her kidneys are not working properly. A consequence of this is

anaemia, the symptoms of which are a constant feeling of exhaustion and sluggishness. The production of red blood cells depends directly on the proper functioning of our kidneys. EPO is the link. Kidneys synthesize EPO and then release it into the blood where it reaches the bone marrow found in certain bones such as the pelvis. There, the hormone¹ triggers off the maturation of red blood cells - whose precursor forms reside in the marrow. Hence, EPO is at the heart of the production of the red 'life' cells that ultimately

¹ A hormone is a molecule synthesized by a gland and generally spilled into the blood so that it can reach the organ(s) upon which it acts. As an example, insulin is a hormone produced by our pancreas that regulates the level of sugar in our blood.

provide invaluable energy to an organism. It is hardly surprising then that EPO has been involved with doping scandals - indeed, the intake of EPO can enhance an athlete's performance...

A taxi for oxygen

Were it not for the protein haemoglobin, red blood cells would not be what they are. Haemoglobin is an oxygen carrier. When we breathe in, it grabs a molecule of oxygen in our lungs and distributes it to the other organs. In exchange, haemoglobin is charged with cellular waste, i.e. CO₂. So burdened, haemoglobin then rushes back to the lungs where the CO₂ is freed when we breathe out.

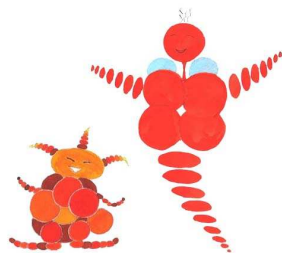


Fig.1 *Globin on the right and Poietin on the left*

« Haemoglobin » is a contraction of « haemo » which has a specific chemical structure of biological importance and « globin » indicating the cell's globular form. Many particularities of our blood are due to haemoglobin: our blood, for instance, is red, and its taste is slightly metallic. Both these properties are the doings of haemoglobin - or, to be more precise, the haem... Haem is a tiny molecular structure, the centre of which is occupied by an iron atom that lends a red blood cell both its hue and its metallic taste. The iron atom is not part of haemoglobin for the sole purpose of aesthetics though: iron is in fact indispensable because, without it, haemoglobin would not be able to carry oxygen. Consequently, without iron, there is no oxygen transfer - which is one of the reasons why iron is given to people suffering from anaemia. What is more, haemoglobin carries not only one molecule of oxygen but four. This is because the protein is in fact a complex of four globins - two α globins and two β globins in humans - each of which embraces a haem...each of which can carry one oxygen molecule...

The dark side of haemoglobin

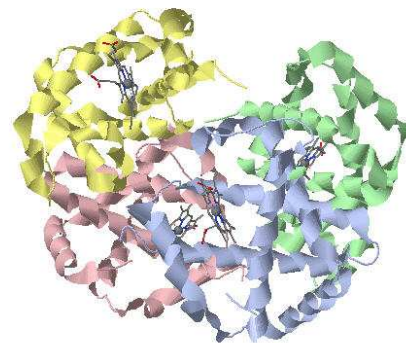
Haemoglobin is therefore crucial to the circulation of oxygen in organisms and has a major role in sustaining life. Like so many things though, it also has a dark side... Much in the way that all sorts of people take a taxi, haem can also carry

substances other than oxygen. And even poisons...simply because it cannot tell the difference. Carbon monoxide (CO), for example, can replace oxygen. Carbon monoxide is a gas which can seep out of maladjusted coal stoves, blocked ventilation systems or certain heating systems that have not been well-maintained. Since carbon monoxide has neither colour nor smell, we are at a loss to detect it. As a consequence, every year there are many carbon monoxide-related accidents. Emile Zola, for instance, who was famous for his literary talents and political commitments, died from carbon monoxide poisoning in 1902 in his sleep, because of a clogged chimney.

On the molecular level, what happens is that haemoglobin is quite happy to carry carbon monoxide instead of oxygen. As a consequence, the oxygen level in the blood subsides, and headaches and nausea are the first symptoms to follow intoxication. If the dose is increased, the organism suffocates 'from the inside' unless the victim is rapidly removed from its presence.

A universal protein ?

Haemoglobin is not only a very widespread protein but one that has been around for a very long time, which is hardly surprising since it does ship a molecule essential to life - which brings us to the origin of the word 'protein'... from the Greek 'prôtos' meaning first and essential - as proteins are for all living organisms. The term 'protein' was used for the first time by the Dutch chemist Gerardus Johannes Mulder in 1838 to denote - precisely - the essential character of the chemical constituents he was referring to. For the record, Mulder may well have used the designation 'protein' following a suggestion which had been made to him by the Swedish chemist Jöns Jacob Berzelius shortly before.



Fabrice David, ISB Genève

Fig.2 *Structure of haemoglobin. The four chains are coloured differently. The four haems resemble a grid with the iron atom in its centre.*

If the fatherhood of the word is debatable, there is not one species that can claim exclusivity over haemoglobin. Haemoglobin is found not only in animals and plants but also in fungi and bacteria. Besides its universality, it is also more or less complex and comes in many shapes and sizes! Remarkably, despite the many different versions of haemoglobin, the iron structure which is so important in oxygen transport is preserved in most

cases. And it is thanks to the accumulation of oxygen on Earth - which appeared over one billion years ago - that organisms have been able to evolve and diversify.

S  verine Altairac*

*Translation: Vivienne Baillie Gerritsen

Excerpt from « Journey into a tiny world »

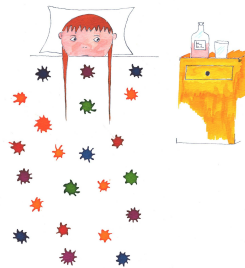
[...]

Instead of getting better, things just seem to be getting worse. It's been three days since Lily last visited the doctor. She's had three days of injections but she's still feeling just as tired and down in the dumps as ever. Her friends come to see her every day, bringing presents and laughter with them. Cheshire - her tomcat - spends his time stretched out on her bed, purring and nuzzling up against her just as she loves... yet nothing seems to cheer her up. She just dozes her day away, drifting in and out of wild, colourful dreams.

She can't wait to get better. She's dying to play elastics with Susan. She promised she would tie Leo to a tree, and she misses the chats and the giggles she has with her friends behind the teacher's back. But she's stuck in bed.

The medicine Doctor Cruikshank prescribed for her is on her bedside table. And, as far as she is concerned, it's not doing her much good. Surely he should be giving her more... The worst part is that she has to wait for him to come to give it to her. "You can't swallow this," he has told her. "Since the molecule is a protein, your stomach will just digest it and that would be of no use to you. We have to inject it straight into your blood."

Really...? What if she took one gulp? Just one? It wouldn't do her any harm... And she would get better faster... Lily glanced at the bottle of medicine. Only one gulp... There wasn't a sound in the house. She sat up in her bed, grabbed the bottle and swallowed the lot in one go...



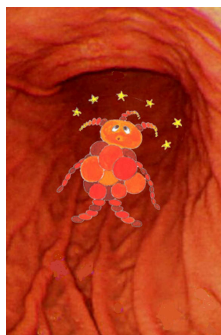
There seemed to be no end to Poietin's fall as she plummeted down a twisty, narrow, pitch-dark tunnel. She could feel its slimy walls squeezing against her, pushing her down further still. Then the tunnel suddenly widened and she landed upside down with a thump on a flat clammy surface. Stunned, she had a look around. She seemed to have ended up in a cave. A huge moist cave... that was very warm and... very smelly...

"Where am I?" she wondered, gathering her senses and holding her nose. "It's not at all the way I was told it would be." She rose and flicked some gooey stuff off her leg. "Right. No time for dreaming. I have a job to do!" And she slipped a second time and fell with a splotch on her bottom. Furious, she rose and rubbed her bruises.

"Who's there?" rang out a thunderous voice.

"Who's there? Who's there?" repeated its echo.

Too frightened to answer, Poietin didn't say a word. For a while, nothing stirred. And then she heard a chop ... chop ... chopping sound. She tiptoed to where the noise was coming from, which seemed to be from behind a mound. As she approached, the sound grew louder and louder. She had a look over the top... and was relieved to see another protein. Just like herself. A giant one but a friendly one, she was sure. "Perhaps he can show me the way" she wondered as she clambered over the top and skipped towards him. But her carefree skip soon turned into a terrified hop when she realised what the giant was up to: he was hacking away at another protein. Albumin! She was lying outstretched on the table! Lily must have eaten an egg that morning. Albumin lives in the white of an egg and here is the butcher protein cutting her into tiny little bits!



Poietin didn't know what to do. Stay? Run away? If she hung around too long, he might do the same to her! But where could she run to? She had no idea where she was. Trembling with fright, she managed a "Hello..." The only answer she got was a grunt. And the butcher protein continued his gruesome task. Perhaps it's just his way of saying hello, thought Poietin. So she cleared her throat and continued: "Excuse me, could you tell me where I am?" He grunted a second time. Poietin watched him chop methodically, wondering what to do next. She decided to try once more. "Excuse me... Sir... I'm on a mission... quite an important one... Lily's life depends on it actually..."
[...]

Translation: Vivienne Baillie Gerritsen

English version on: http://www.expasy.org/prolune/pdf/cont_e_en.pdf

You can purchase the tale in book form at the following address:

<http://www.lulu.com/content/855527>

For further information

On the Internet:

- From Protéines à la Une, "EPO, a stupefying hormone":
http://www.expasy.org/prolune/pdf/prolune002_en.pdf
- From Protein Spotlight, "The man behind the molecular lung":
http://www.expasy.org/spotlight/back_issues/sptlt021.shtml

At UniProtKB/Swiss-Prot:

- Haemoglobin subunit alpha, Homo sapiens (human): P69905
- Haemoglobin subunit beta, Homo sapiens (human): P68871
- Erythropoietin, Homo sapiens (human): P01588

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