

## Interferon beta: Star protein in the battle against multiple sclerosis



A few years ago, Serono - a large biotechnical company based in Geneva - commercialized Rebif, a drug for the treatment of multiple sclerosis (MS). It is distributed in 72 countries but its sale was blocked in the States until March 8 last year because of orphan medicine legislation. The Food and Drug Administration (FDA) - who control which drugs are put on the American market - had guaranteed exclusive rights until 2003 to Biogen, a company that had developed a similar drug under the name of Avonex. However, Serono managed to overrule this law - legally - so as to reach the American market, which represents a potential million dollars per year. And it is a protein, interferon beta, which is at the heart of this confrontation between two biotech giants.

### *Multiple sclerosis nibbles away at myelin*

Multiple sclerosis was described for the first time in 1868 by Dr. Jean-Martin Charcot, one of the founders of clinical neurology. It is a chronic disease which develops in young adults (aged 20 to 30) and affects almost twice as many women as it does men. In Switzerland today, about 10'000 people suffer from the disease.

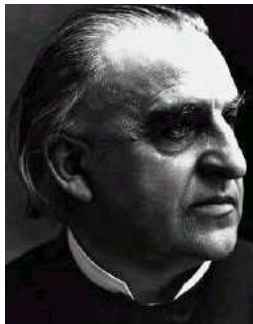


Fig.1 Dr. Jean-Martin Charcot (1825 - 1893)

The principal symptoms of MS are sight and balance disorders, speech problems, a sensation of great fatigue and sometimes paralysis, and are the consequence of damage caused to the optical nerve and the central nervous system. Both are made up of multitudes of "neurons". A neuron is a nerve cell that has a rather peculiar shape: the main "body" is shaped a little like a star from which protrudes a long tail called an "axon" (cf. Fig.2). The axon links one neuron to another, and yet another...until a network is formed. Such a network is comparable to an extremely complex electrical network in which the axons would be the connecting wires between different units.

Each axon is insulated by way of a sheath of "myelin" (cf. Fig.2), which consequently accelerates the nerve impulse along the axons, much in the same way plastic surrounding electric cables does. This sheath is in fact made up of nerve cells called oligodendrocytes which wrap around the axon and thanks to their insulating properties, a nervous impulse can travel at a speed of 120 m/s (432km/h). In multiple sclerosis, the sheath is nibbled away and, as the illness

progresses, various-sized holes appear, sometimes as much as a few centimeters wide. As a result, nervous transmission is disrupted leading to disorders affecting one's sight, sense of touch and movements. Today, MS is thought to be an autoimmune disease (cf. below), which affects the central nervous system.

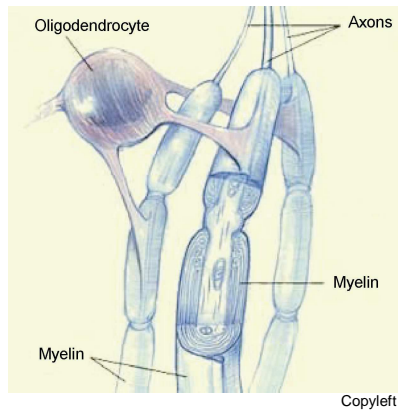


Fig.2 Nervous transmission travels at 400 km/h!

#### ***What is an autoimmune illness?***

When our organism is invaded by a foreign body, such as bacteria or a virus, it responds by triggering off our defense system, or "immune system", to fight it off. Such a system must eliminate the "intruder" without damaging its own organism. This, however, is precisely what happens in the event of an autoimmune disease: something goes wrong in our immune system part of our own body is attacked. In the case of multiple sclerosis, it is the myelin sheath around the axons, which bears the brunt. The factors that set this illness in motion are as yet unknown. Could there be a genetic predisposition to MS? Is there a virus that sets it off? Time will tell.

#### ***Could interferon gamma be the real culprit?***

Our immune system's "riposte" to an infection can take on various forms (cf. box). One of the fastest reactions involves the production of interferons that "interfere" - precisely - with the infection, i.e. they delay its action until our body produces the requisite antibodies to fight off the intruder. Two virologists, Alick Isaacs from Great Britain and Jean Lindenmann from Switzerland, identified these proteins in 1957. They were sorted into three categories according to their size and shape: alpha, beta and gamma.

In what way, though, do these proteins actually interfere with the infection? Well, when a cell in our body is infected by a virus, for example, it produces alpha and beta type interferons, that then act on the neighboring cells. In response,

these cells start up a mechanism which make them more "resistant" to the viral infection. Gamma type interferons are also produced by the infected cell and act like "music conductors", i.e. they modulate other immune system pathways, such as the stimulation of the "cleaning cells" or macrophages (cf. box).

#### ***Our immune system's reactions***

"Self-recognition" is at the heart of any immune system strategy. In the course of its development, it learns to make a difference between the "foreign intruder" and the components of its own organism, i.e. to distinguish its "non-self" from its "self", respectively. Once the intruder has been identified - such as a virus or a bacterium for instance - our immune system can muster various tactical defenses. One of these is the production of antibodies: these are Y-shaped proteins, which bind to the foreign body like so many flags. These flags are sensed by "cleaning cells" (the macrophages), which subsequently destroy the foreign body. A further immune response is ensured by "killer" cells, also known as cytotoxic cells or CTLs. Infected cells are recognized by CTLs and also destroyed. Yet another immune response involves T auxiliary lymphocytes. Once the intruder has been detected, the T auxiliary lymphocytes can "activate" all the system's immune responses. Finally, to add to this strong line of defense, there remains one last row of "soldiers": the interferons, which slow down infection while the immune system prepares for battle.

Interestingly, it seems that interferon gamma itself might be at the origin of the disease. Indeed, the identification of myelin as an "intruder" seems to lead to gamma interferon overproduction. Besides being toxic for our organism, this also starts a host of reactions which will, among other things, result in the production of an excessive amount of "killer" cells (cf. box). These "killer cells" are normally assigned to destroy "sick" cells (cancerous or infected by a virus or a bacterium). And, as a result of incorrect targeting, they destroy the cells which form the myelin sheath.

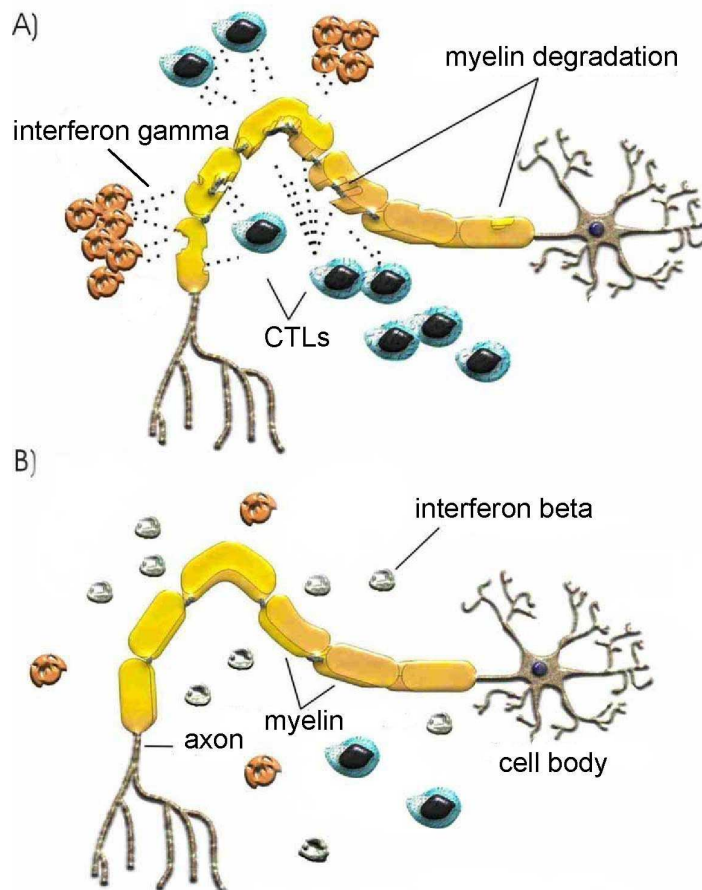
#### ***Interferon beta to the rescue***

Though scientists still do not know why an autoimmune disease breaks out, they do know how

to check its progression. A number of drugs modulate (immuno-modulators) our immune system's reaction, whilst others simply block (immuno-suppressors) its response. Interferon beta acts as an immuno-suppressor in the treatment of MS. Thanks to various biotechnological processes, several types of interferon beta have been produced for therapeutic purposes. The pharmaceutical company Schering were the first to put interferon beta 1b on the market (produced in bacteria) under the name of Betaferon. Its structure differs slightly from natural interferon beta because of a difference in two amino acids. In contrast, interferon beta 1a (produced in mammalian cells) is

100% identical to the natural protein. At the moment, it is commercialized by two companies and under two different names: Rebif (Serono), and Avonex (Biogen). Hence, the rivalry that exists between these two biotech giants and across the Atlantic.

And yet, how exactly the "therapeutic" action of interferon beta works is still not clear. It looks as though it might act on several molecules which bring about a chain reaction, which itself results in a decreasing concentration of interferon gamma. As a result, interferon beta indirectly restores a kind of equilibrium in our immune system (cf. Fig.3).



**Fig.3** Diagram of a neuron. **A.** The "killer" cells (CTLs) of our immune system identify myelin as an "intruder". As a result, they attack it and this is compounded by the activity of interferon gamma. **B.** Interferon beta indirectly decreases interferon gamma action as well as that of the CTLs.

### ***Research still continues***

Although drugs based on interferon beta successfully check the progress of multiple sclerosis, they do not cure it. This is why scientists are searching for a molecule that would have a more direct effect on interferon gamma. But, as you may have realized on reading this

paper, their task is arduous considering the complexity of our immune system!

Pascal Chanson\*

\*Translation: Geneviève Baillie

### ***For further information***

#### **On the Internet:**

- Ligue française contre la sclérose en plaques : [www.lfsep.asso.fr/index.php](http://www.lfsep.asso.fr/index.php)
- Société canadienne de la sclérose en plaques : [www.mssociety.ca/fr/default.htm](http://www.mssociety.ca/fr/default.htm)

#### **In english:**

- Karp C.L., "Interferon-beta in multiple sclerosis: altering the balance of interleukin-12 and interleukin-10?", *Curr. Opin. Neurol.* 14:361-368(2001) PMID: 11371761

#### ***Illustrations:***

- Heading illustration, Source: PDB ID: 1AU1, M. Karpusas, M. Nolte, W. Lipscomb, Human Interferon- $\beta$  Crystal Structure. *Proc. Natl. Acad. Sci. USA* 94 pp. 11813 (1997)
- Fig.1, Source: <http://dicopsy.free.fr/>
- Fig.2, Source: [http://www.lecerveau.mcgill.ca/flash/i/i\\_01/i\\_01\\_cl/i\\_01\\_cl\\_fon/i\\_01\\_cl\\_fon.html](http://www.lecerveau.mcgill.ca/flash/i/i_01/i_01_cl/i_01_cl_fon/i_01_cl_fon.html)

#### ***At UniProtKB/Swiss-Prot:***

- Interferon beta, Homo sapiens (humain): P01574

#### ***Acknowledgements:***

- To Dr Irène Garcia-Gabey from the Département d'immuno-pathologie in the Centre médical universitaire (CMU) in Geneva for her collaboration during the preparation of this article.
- To Sylvie Déthiollaz and Vivienne Gerritsen from the Swiss-Prot group.

*Date of publication: June 15, 2002*  
*Date of translation: November 22, 2005*

---

Protéines à la "Une" (ISSN 1660-9824) on [www.prolune.org](http://www.prolune.org) is an electronic publication by the Swiss-Prot Group of the Swiss Institute of Bioinformatics (SIB). The SIB authorizes photocopies and the reproduction of this article for internal or personal use without modification. For commercial use, please contact [prolune@isb-sib.ch](mailto:prolune@isb-sib.ch).