Understanding the blood brain barrier (BBB)

Fighting brain cancer demands an invitation to the inner sanctum

In this article, Patrys CEO and MD Dr James Campbell compares historical access to a medieval town to the unique properties of Patrys’ PAT-DX1 asset.

Curious? You should be.

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I was talking with a friend recently about the challenges of self-isolation as our society deals with COVID-19. He noted that limited freedom of movement must have been the norm for many people over the course of history. This got me thinking about fortified towns, with their many layers of protection, from sentries and checkpoints to moats, walls, gates and a highly protected inner sanctum. Control points that screen and allow access only to those with the right credentials.

It was a very effective mechanism to protect these places and one that is replicated to protect one of the most important organs in our own bodies – our brain.

The blood brain barrier (BBB) is one of the most important defences our body has. However, the aspects of its biology that make it so effective at doing its job also create hurdles for developing new drugs to treat diseases of the brain. **The ability to cross the BBB is one of the key challenges for new drugs that are being developed to treat brain cancers. This is one of the reasons why Patrys' PAT-DX1 asset, and more broadly the Deoxymab platform, offers so much potential to make a real difference for patients with these devastating diseases.**

Most people think of the BBB literally as a barrier that surrounds the brain with two key functions. First, it needs to stop infectious agents, such as bacteria and viruses from entering the brain. Second it needs to isolate the brain from rapid changes in nutrients and other compounds that are carried in the blood. From this perspective, it is convenient to think of the BBB as a shield or barrier that protects the brain. Common representations in the popular press reinforce this imagery *(see the image in Figure 1 below)* and it does help people to visualise what is happening when they hear statements such as 'almost no large molecules, and 98% of all small molecules, do not cross the BBB'.[1]

FIGURE 1

However, as always, the truth is a little more complicated than this simplistic model. Rather than being a protective, impenetrable barrier that surrounds the brain, the BBB is actually a highly specialised refinement of the circulatory system that tightly controls which compounds are allowed to move through the walls of specialised capillaries and enter into the brain tissue itself. Going back to our castle analogy, it is like we have sentries checking the papers and deciding who can, and who cannot, enter the castle rather than just raising the bridge and stopping everyone.

Generally, the capillaries in the body are an open system which allow most nutrients, proteins and, unfortunately, pathogens to cross from the blood system into the various tissues in the body. The capillaries in the brain, however, have specific, well-controlled crossing points, similar to the gates and guards protecting our fortified town. Only certain, very specific defined molecules in the blood are able to cross this barrier and enter the brain. In a healthy person, this is fine. However, for people who develop diseases in their brain tissue, it provides a real challenge as it can block the very drugs that need to enter the brain in order to effectively treat their disease.

To understand what makes the BBB so special, we need to understand what is different between the capillaries that support all other organs in the body, and the unique, highly specialised capillaries that occur in the brain. Capillaries support tissues by supplying them with the necessary nutrients and oxygen, and by taking away the waste products from those tissues. These interchanges of nutrients, gases and wastes are feasible because, in most tissues, the capillaries are part of an open system where the exchange primarily occurs by simple, unregulated diffusion. In these tissues, the capillaries usually have pores, which are gaps between the cells, that make up capillary's walls. These pores are

[1] Wong, A. D. et al. (2013). The blood-brain barrier: an engineering perspective. Front Neuroeng 6:7.

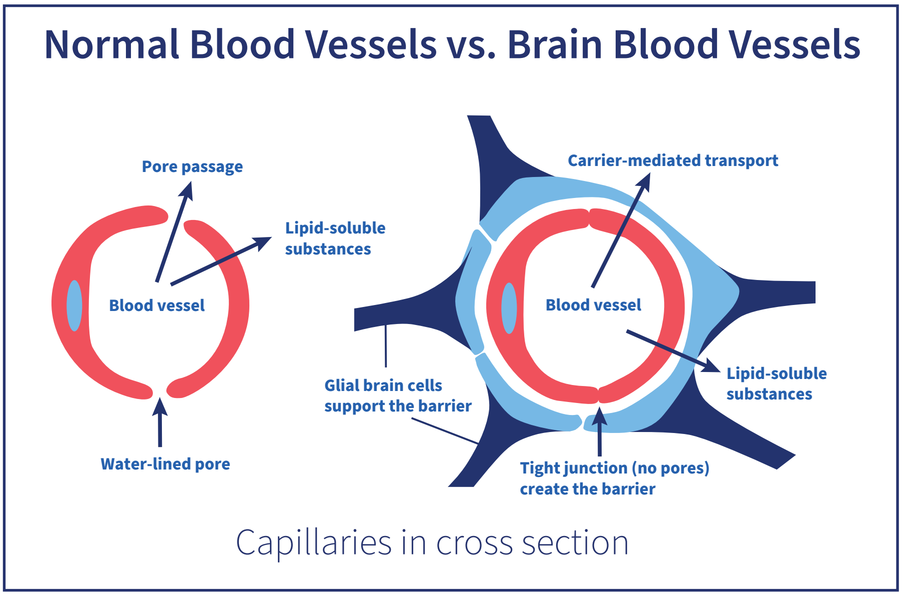

FIGURE 2

big enough to let many substances (such as nutrients, proteins, antibodies, drugs, and even pathogens) to freely transverse the capillary walls, but are not so big that blood cells are able leave the capillaries (*see Figure 2 above*).

In contrast, the capillary cells in the brain are joined by what are called tight junctions. With tight junctions, there are no gaps between cells. Instead, they use a range of highly specialised transporter channels that selectively allow the exit or entry of a select set of essential nutrients, wastes, and proteins. Furthermore, the outside of the capillaries in the brain are reinforced by specialised neural cells called glial cells that strengthen and support the vessel.

Thus, while the capillaries in the body are part of an an open system that allows most molecules to be exchanged between the blood and the organ's tissues, the capillaries in the brain contain check points which allow entry of only a few, select, vital molecules and prevent the entry of circulating toxins and pathogens that could cause brain damage. Unfortunately, in doing this the BBB also often prevents potential drugs that could be used to treat diseases of the brain from actually reaching the brain tissue. Thus, in order to successfully deliver drugs to cancers within the brain, the gatekeeping transporters need to be tricked into allowing these foreign substances to cross the threshold of the brain. **Because of this, one of the pivotal areas of focus in the development of new drugs for diseases of the brain is to find ways to get drugs to be allowed to cross the BBB in order to reach the site of the disease where they can exert their therapeutic effect.**

The reason that our PAT-DX1 antibody is so interesting is that our collaborators at Yale School of Medicine have shown that a protein called ENT2 allows PAT-DX1 to enter cancer cells where it stops DNA repair and causes cancer cell death. This is unusual, as normally antibodies a not able to enter into cells and can only react with proteins, or antigens, that are found on the cell surface. What makes this even more interesting is that ENT2 is also highly expressed in the capillaries of the brain where it allows PAT-DX1 to cross the BBB and access the tissues in the brain. While this ability for a compound to cross the BBB is not at all common, for a large, biological molecule such as an antibody, it is very, very unusual.

Like in our fortified town, what this means is that PAT-DX1 has a special pass that allows it entry to the brain and so the guards let it in. Once it has entered the brain, it is then able to specifically hone into the cancer cells in the brain and trigger their destruction. We have seen this in the experiments that we have conducted with PAT-DX1, which have shown administering this antibody is able to reduce the growth of primary cancers like glioblastoma as well as metastases in the brain.

If you are interested to learning more about the blood brain barrier and promising biotech innovations in this space, check out Denali Therapeutics: https://denalitherapeutics.com/science/engineering

If you'd like to learn more about Patrys' work in this space visit **Patrys.com**