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Final discussion

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De Boer

I would like to try to summarise a little bit what we have done during the last three days, and I think we have considered conditions for drug transport to the brain and we have considered efflux and carrier mechanisms, we've considered drug delivery technology and we have seen some clinical points of view. And more or less my conclusion is that we are standing almost with empty hands to treat patients, so I ask myself what could be done and since we have heard about four interesting and promising technologies to bring drugs to the brain, I would like to ask a blunt question. I would like to ask, for instance, in the first place Jan Verlooy. What would you like to have from these people who are offering very interesting technologies to treat your trauma, your ischemic or your stroke patients?

Verlooy

As I have already mentioned, maybe it's not only getting drugs into the brain, but also treating secondary effects like leakage of the blood–brain barrier and attention should be paid to cells other than neurons, astrocytes and microglial cells. One should not focus too much on one single way to treat a problem.

De Boer

Maybe the technology people would like to comment on that. For instance, two technologies concerning peptides, would that be a feasible approach to have a quick success by getting some drugs at the right site in the brain or the antibody approach or the CRM197 approach, and the P-97 approach?

Gabathuler

I don't think it's going to be one technology which is going to work for all the approaches, I think it's going to be a bit of everything, but first we have to show if it works, too. That's the main reason why we are working on that, because we have to show that it not only works for the vector, but it works for delivering a therapeutic amount of drugs in the brain and we want to be in the right compartment, not only in the right zone or something like that. So we still have a lot of work in front of us.

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Stanimirovic

I would like to comment on some of the technologies that were presented today. They are mostly based on biologics, such as peptides and antibodies. Moving biologics from an experimental environment into a clinical environment is a big hurdle, because many issues in terms of pharmacokinetics, biodistribution, toxicity etc. need to be addressed. Since we are targeting central nervous system diseases, we have to differentiate between acute states, such as stroke or brain trauma, and chronic diseases such as Alzheimer's. In acute diseases, we need to deliver therapy reasonably fast; we have a therapeutic window to catch. But then, we also have a chronic component of these diseases, and if we add to that Alzheimer's disease and other slow-progressing neurodegenerative diseases, the problem becomes even more difficult because we have to consider multiple applications of the therapy. Currently, some of these diseases could be alleviated with growth factors, another layer of biologics. I think the issue has to be addressed in disease-specific manner, and in the context of particular disease where therapies have to be tailored to the dynamics of the disease; for example, stroke is not just one disease, it has underlying diseases, acute phase and then chronic degenerative phase.

De Boer

So if I translate that, I think we have also an extra problem, because you were mentioning biologics and that is, I think, an extra problem according to drug delivery.

Lemaire

During this meeting very nice strategies were proposed for allowing drugs to cross the blood–brain barrier. However the passage through the blood–CSF barrier was not considered. Do we have a rationale to neglect this possibility of bringing a compound into the brain? In addition, we have to consider the CSF compartment as a possible site of action for some drugs. Therefore, I think that in some cases the blood–CSF barrier could be important for the delivery of drugs to the brain.

De Boer

I think you're right, but I also think that the access that a compound has from the CSF to the brain could be rather limited, particularly when you consider a biological compound. But, please give your opinion.

Lemaire

For a long time the ratio of exchange areas between blood–brain barrier and blood–CSF barrier was estimated to be 4000; recently much lower ratios up to 10 were proposed underlining the growing importance of the blood–CSF barrier.

De Boer

You're right, it's true.

Van Tellingen

If, for example we consider the case of strokes, and we are going to use a neuroprotective agent, we will have some of the technology to get it there, but I have the feeling that we don't really have a target for treating the disease which is coming after it, like the edema. So we should first consider what should be treated in every phase of the process.

Verlooy

That's correct, there are several phases and several targets to consider. I don't know which one you should consider first. Getting the drug somewhere is only one side of

the problem. The drug is targeting only one part of the pathophysiology, not the whole pathophysiology. As I said in the case of neurotrauma, there are lots of diagrams and cascades and they differ a little bit from one another. If you target on one of the first pathophysiological mechanisms, I would say you have a chance of doing a lot of good things in this pathology, without mentioning any specific part of the pathophysiology, not going into that, because there are different theories and different diagrams available. If you could unravel this complex mechanism and target one of those mechanisms, one that is at the beginning of the cascade, then you have the best way to go.

De Boer

I think the other problem which should not be neglected is that new technology needs to be validated in order to come into the clinic. You need a lot of money to see that it works and many companies are not really willing to invest in that kind of technology because it is very costly.

Sugiyama

I want to raise a different issue, that is, the extrapolation from the animal data, or in vitro data, to a human, clinical situation. In the field of pharmacokinetics or drug metabolism, many studies have been done regarding the species differences of metabolising enzymes. People already know that there exists an unbelievable species difference between rodents and humans, and even between monkeys and humans there are great differences. Then people have been developing some methods to extrapolate from animals, or in vitro, to in vivo, so then you know regarding my field, drug transporters, when I try to predict the hepatic clearance or the renal clearance from the animal experiment or the in vitro experiment, we can manage at the moment because in human situations we can somehow get the hepatobiliary clearance or renal clearance by measuring the plasma disappearance and also by measuring the renal excretion. However, in the blood–brain barrier transport field, it is quite different. Just by measuring the plasma disappearance you can never know the uptake into the brain. Therefore it is very important for us to develop some method to extrapolate from animal or in vitro data to in vivo. Using culture systems you can compare the in vitro data with the animal in vivo data, and then somehow you can extrapolate into in vivo. Nevertheless, I have no way of saying that this prediction is good or not, because in humans we can never measure drug concentration in the brain, the only way is the PET or some other methods. So I ask to people in the drug delivery field, developing the antibody or receptor, mediated transcytosis or membrane-breaking peptide.... When you go into the clinical phase, how do you predict that your method may be extrapolated to a clinical situation?

Whittle

I think we can use microdialysis in humans now and some questions such as you have posed will be able to be answered. Certainly if drugs are used in the acute stroke setting or acute post-trauma setting where the patient is in intensive care, and it is quite legitimate to put one or two microdialysis probes into their brain you can actually extrapolate by measuring the extracellular fraction of the compound.

Lemaire

How can one be sure that the blood–brain barrier or the blood–CSF barrier remain intact in such patients? Wouldn't then the microdialysis results be questionable?

Whittle

I agree, there will be variable barrier disruption, but it will give some idea of what is happening with the delivery of the compound.

Abbott

We haven't really concentrated on diagnostic methods, and increasingly we do need to know the status of the blood–brain barrier in these disorders, before we can begin to design a phase-dependent treatment. For example, if the barrier is going through a multiphasic opening and closing, the optimal treatment will certainly differ at different phases, and we need much more accurate methods of diagnosing where in the disease progression the patient is. I think we should concentrate on accurate monitoring of the blood–brain barrier as non-invasively as possible, to help and guide our therapy. If the barrier is open, do we need to seal it up again, or would this actually hamper the treatment if we do it too early? Decisions like this would be easier if we had better and more comprehensive diagnostic assays. It is now possible to combine several of the monitoring methods we have—e.g. MRI, EEG, plasma analysis for S-100 protein and other markers—to get quite a pretty good profile on an individual patient's blood–brain barrier function, and some of the assays can give information on an hour-by-hour basis. If this becomes more routine then you could begin to predict, in a particular patient, what would be the best form of treatment, on day 1, day 2 and so on.