

Q & A – Day 2 Wednesday 26 August 2020

Please find below an overview of the questions and answers for day 2 of the webinar series.

THOMAS HARTUNG

Name: Pilar Samperio Ventayol

- Is there evidence of Covid-19 presence in patient brains?

The number of case reports and studies is increasing. There have been cases of fatal encephalitis. The virus has been shown to infect the brain endothelium, which means PCR of brain tissue cannot distinguish between endothelial and brain cell infection. So, we need confocal or electron microscopy. We and others are on it.

Name: Marcelo Asprea

- Reproduction in animal models for COVID-19 were comparably equal to or better with respect to other viral diseases studied?

I think there is no systematic review. But in general, viruses behave very different in different species if at all. Some models are still considered useful, even if measuring antibody responses where T-cell responses are critical etc.. Work on infection of secondary organs such as in our case the brain is particularly difficult.

Name: Samantha Saunders

- Do you think human challenge trials are a possibility?

Yes, but people need to be aware of the risk they are taking, especially that this could lead to persistent infection with associated risks. I discuss in this paper (open access):

*Calina D, **Hartung T**, Docea AO, Spandidos DA, Egorov AM, Shtilman MI, Carvalho F, and Tsatsakis A. COVID-19 vaccines: Ethical framework concerning human challenge studies. DARU Journal of Pharmaceutical Sciences 2020, doi: 10.1007/s40199-020-00371-8.*

Available at: <https://link.springer.com/article/10.1007%2Fs40199-020-00371-8#citeas>

Name: Penny Hawkins

- Concerns have been expressed that, as brain organoids become more complex, they might become sentient - raising ethical issues. Do you think this is a possibility?

It is a discussion we need to have. We have start to work with Hopkin's bioethicist Jeffrey Kahn on this. However, the current implementation of brain organoids are only about 30,000 cells and have no input or output – so nothing to think about...

Name: Monique Janssens

- Do you use animal-free culture serums in your institute?

I am not aware of any project right now. But I am not in the lab myself, but we have regularly such discussions. We try to avoid and have supported some such initiatives. Sometime difficult, also with ascites-derived antibodies if there is nothing else commercially available.

Name: Franz Lamplmair

- Can we use the Corona-related research on diagnostics, cures and vaccines to progress on refinement, reduction, and in particular replacement?

The whole field is implementing alternatives very slowly, COVID-19 is now calling for acceleration everywhere and some alternatives lend themselves to this. I hope that this is also a door-opener in other areas.

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Name: Valeria Chiono

- Have any vaccine been tested in human multi organ-on chips for better human specificity before animal trials?

Thomas Hartung: Drugs yes, for vaccines I am not sure. Most organ-on-chip still lacks immune systems. But there are for example artificial lymphnodes. However, I have no complete overview of the field and a lot of this will be done in industry without publication.

Jan Willem van der Laan: This would be an interesting approach. We have to be aware that the immunological response of a vaccine depends on the presence of Dendritic cells presenting the antigen to T-cells. I think if there is evidence of any direct effect of COVID-19 infection on a certain organ, than testing with a vaccine carrying the antigens might be informative for a possible direct effect of the vaccine of this organ.

Name: Becky Jones

- Do you think the pressure to skip pre-clinical animal tests and go straight to human trials, for example in the development of the Moderna Covid vaccine, is positive for animal-free science, or a negative as it reflects desperation science potentially putting human volunteers in clinical trials at risk?

Thomas Hartung: It is a trade-off. Animal models only give some protection for the volunteers – especially as many of the arguably more important tox tests occur anyway only in parallel

to testing in volunteers and patients for time reasons. In many instances, I would feel more safe if data from human in vitro tests are available than data in animal tests are partial and in their making. When companies now rethink their safety assessment when going first into humans, they might as well apply this for other drugs in the future.

Jan Willem van der Laan: From a regulatory point of view this is a very interesting question. In vitro data met human iPSC's might help us to think about theoretical possibilities of adverse effects caused by uptake of the RNA-vaccine directly in these iPSC's. We already know a lot about the effects of Oligonucleotides (from previous animal studies). Based upon the specific sensitivity of the human population (compared to most of animal species) this in vitro data on human cells might be more informative about human safety than any animal experiment.

Name: Samantha Saunders

- Do you think human challenge trials are a possibility?

Thomas Hartung: See my answer above to the same person.

Jan Willem van der Laan: The possibility of introducing direct human challenge trials is an ethical issue. It depends on the efficacy of treatment with a therapeutic approach (as a rescue medication) if the vaccine is not preventing the COVID-19 infection.

Name: Sandra Coecke

- What suite of new generation mechanistic Cell and #tissue methods will be needed to understand, prevent and treat the acute but especially the long-term adverse target organ and target system effects of SARS Cov-2 like some of those presented today, brain effects and diabetes type 1

Thomas Hartung: This really depends where they shall be used. For target evaluation, drug efficacy, very tailored assays can be used. For disease models, this will be tailored to the disease and the presence of drug targets. For safety, arguably the broadest battery will be necessary when looking for the "unknown unknowns". We will have likely to compromise looking for frequent things like DILI, likely things associated with the drug class / target, some broad sentinel models like zebrafish and a lot of careful observations in men (micro-dosing, biomarkers / omics) and longer-term observation after market release. The latter will teach us what we need to add to our battery.

Name: Dr. Dipti M Kapoor

- Was there any observation with pre-existing diabetes?

Thomas Hartung: There are studies I saw but not my area. Big risk factor.

Shuibing Chen: *It has been reported that pre-existing diabetes is associated with worse outcome of COVID-19 patients.*

Name: Tom Masding

- What can non-scientists do to contribute to the animal alternatives movement? I left the chemical lab soon after graduating and my recent experience is in sales and supply chain within the chemical/medical industry, my thinking is to work for an animal.

Thomas Hartung: *The spectrum of opportunities is broad requiring very different skill sets. This holds for jobs as well as voluntary activities. Let's discuss in person.*

Name: Anne-Dominique Degryse

- Is the presence of virus in the brain a possible explanation of losing smell and taste in infected patients: will those effects possibly be permanent?

Thomas Hartung: *It has been shown that the virus infects the smell cells directly. The infection of the olfactory nerve is controversial. There could be contribution from brain infection but I consider this unlikely.*

Name: Dr. Sivaprasad R

- Can the present pandemic be regarded as green goo? Is there a means to control COVID-19 using nanorobots?

Thomas Hartung: *I am not sure what a "green goo" is. As any crisis it also is opportunity as it prompts change. Depends on us what we make from it. I cannot speak to nanorobots.*