Human-relevant models are needed to understand and treat human COVID-19 disease

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Outline

- COVID-19 disease
- Drug safety
- Why not use animals?
- Human-relevant models
- Summary

COVID-19 Disease

SARS-CoV-2

100% exposed humans

Upper airway infection

Up to 50%

No symptoms - "asymptomatic carrier"

Tissue injury
Immune cell activation (inflammation)

"Mild" illness

~ 40%

Recovery

Severe immune cell activation (cytokine storm)
Multi-organ damage

~ 10%

Severe illness

~ 9%

~ 1%

Death

Susceptibility factors:

- Age
- Gender
- Ethnicity
- Obesity
- Disease (airway, cardiovascular, diabetes….)
- Smoking

COVID-19 Disease

- A low percentage of infected individuals develop serious illness.

- Serious illness is linked to an uncontrolled immune response.

➢ **Useful current treatments:**

- Dexamethasone (anti-inflammatory)
- Remdesivir (antiviral)

COVID-19 Disease

To develop effective new treatments, we must understand:

- How the disease progresses in susceptible humans
  - design and select and develop effective treatments.
  - cf. key role of inflammation ➡ dexamethasone.
- Why only some humans are susceptible
  - design ways to prevent it.
  - e.g., vitamins K, D and/or C?

Drug safety

- Many hundreds of licensed drugs cause undesired side effects in humans.
- These cause many serious illnesses, including fatality.
- And are not predicted by safety testing undertaken in animals, or in early clinical trials.
- New drugs currently require prolonged testing in large numbers of patients before they are licensed for use.

Data from FDA labels:

WARNING: RISK OF HEMATOLOGICAL TOXICITY, MYOPATHY, LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS
Zidovudine capsules have been associated with hematologic toxicity including neutropenia and severe anemia, particularly in patients with advanced HIV-1 disease *[see WARNINGS AND PRECAUTIONS (5.1)]*.

WARNING: HYPERSENSITIVITY REACTIONS
Serious and sometimes fatal hypersensitivity reactions, with multiple organ involvement, have occurred with abacavir.

➢ **The first effective drug treatments for HIV infection caused severe toxicity in humans….**

Why not use animals?





Advantages

- Many biological similarities to humans.
- Have provided useful disease insights in the past.
- Provide *in vivo* data.

For more details, read this White Paper: https://www.humanrelevantscience.org/white-papers/
and view FDA's Alternative Methods Working Group: *https://www.fda.gov/science-research/about-science-research-fda/advancing-alternative-methods-fda*

Limitations

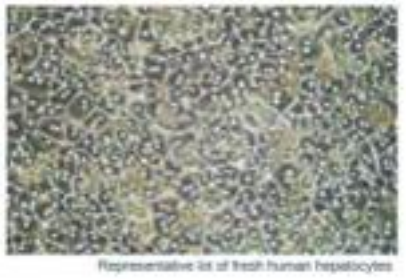
- Many biological differences – including immunology.
- Do not reproduce key features of complex human diseases – infections, cardiovascular, lung, immune, etc.
- No evidence that animals will develop COVID-19 disease.
- Do not address human variability.

- Inadequately address human safety.

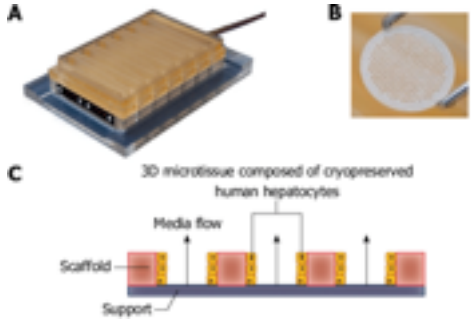
Human-relevant models

- Human-relevant experimental models use cells from human tissues. These are maintained under biologically relevant conditions.
- They are now used routinely to study many different human diseases, to explore disease susceptibility, and to design and test novel drug treatments.
- **And** to predict and avoid human adverse effects of drugs that cannot be detected in animal studies.
- Computational data analysis tools are used to enable accurate prediction of human in vivo relevance of data from human-relevant models.

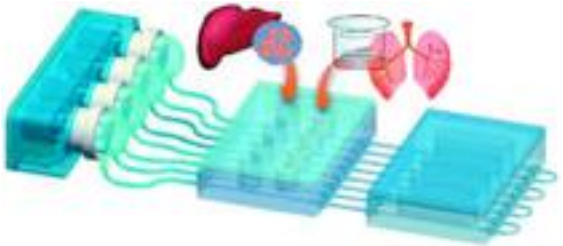
Isolated hepatocytes



3D liver microtissue



Liver and lung cell co-culture



Some human-relevant models

Lung disease:

Sundarakrishnan A, Chen Y, Black LD, Aldridge BB, Kaplan DL. Engineered cell and tissue models of pulmonary fibrosis. *Adv Drug Deliv Rev*. 2018;129:78-94. doi:10.1016/j.addr.2017.12.013

Inflammation in obesity:

Ahluwalia A, Misto A, Vozzi F, Magliaro C, Mattei G, Marescotti MC, et al. (2018) Systemic and vascular inflammation in an in-vitro model of central obesity. PLoS ONE 13(2): e0192824. https://doi.org/10.1371/journal.pone.0192824

Influenza and Staphylococcus aureus super-infection:

Bruchhagen C, van Krüchten A, Klemm C, Ludwig S, Ehrhardt C. In Vitro Models to Study Influenza Virus and Staphylococcus aureus Super-Infection on a Molecular Level. *Methods Mol Biol*. 2018;1836:375-386. doi:10.1007/978-1-4939-8678-1_18

Hepatitis virus infection:

Verrier, Eloi R et al. "Cell Culture Models for the Investigation of Hepatitis B and D Virus Infection." *Viruses* vol. 8,9 261. 20 Sep. 2016, doi:10.3390/v8090261

Cardiotoxicity of drugs:

Colatsky T, Fermini B, Gintant G, et al. The Comprehensive in Vitro Proarrhythmia Assay (CiPA) initiative - Update on progress. *J Pharmacol Toxicol Methods*. 2016;81:15-20. doi:10.1016/j.vascn.2016.06.002

Liver toxicity of drugs:

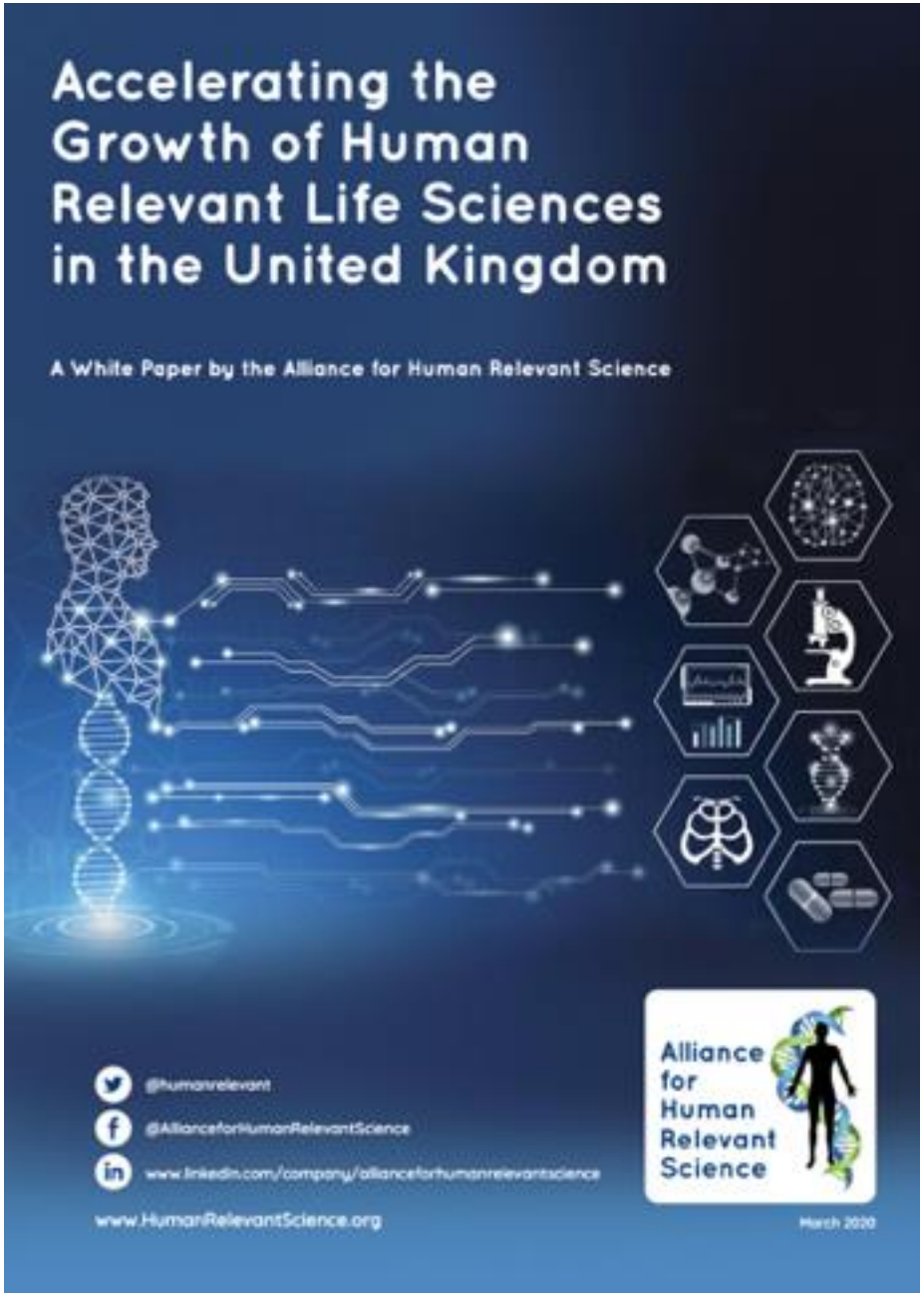
Proctor, W.R., Foster, A.J., Vogt, J. et al. Utility of spherical human liver microtissues for prediction of clinical drug-induced liver injury. Arch Toxicol 91, 2849–2863 (2017). https://doi.org/10.1007/s00204-017-2002-1

Summary

- To understand and treat human COVID-19 disease, we need to use relevant models.
- Experimental animals do not adequately reproduce human biology and human susceptibility, and do not ensure drug safety in humans.
- Development and use of human-relevant COVID-19 models is a realistic opportunity. These must be prioritized for funding.
- Studies undertaken with human-relevant COVID-19 models will complement ongoing human clinical studies.

Disclosure

I declare no conflicts of interest.



https://www.humanrelevantscience.org/white-papers/