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

Upper airway infection

100% exposed humans

Tissue injury

Immune cell activation (inflammation)

"Mild" illness

Severe immune cell activation (cytokine storm)

Multi-organ damage

Severe illness

Recovery

No symptoms - "asymptomatic carrier"

100% exposed humans

Susceptibility factors:

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

~ 50%

~ 40%

~ 9%

~ 10%

~ 1%

Death
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.

**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.

For more details, read this White Paper: [https://www.humanrelevantscience.org/white-papers/](https://www.humanrelevantscience.org/white-papers/)

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.
Some human-relevant models

**Lung disease:**

**Inflammation in obesity:**

**Influenza and Staphylococcus aureus super-infection:**

**Hepatitis virus infection:**

**Cardiotoxicity of drugs:**

**Liver toxicity of drugs:**
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.
Accelerating the Growth of Human Relevant Life Sciences in the United Kingdom

A White Paper by the Alliance for Human Relevant Science

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