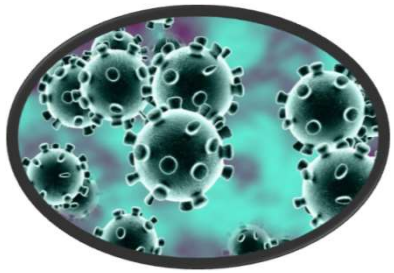

Developing humanized models with an eye on potential for generalizability - what needs to be done?

WHO working group - infection models

Simon Funnell
César Muñoz-Fontela
Bill Dowling
Lauren Schwartz
Ximena Riveros-Balta
Ana Maria Henao-Restrepo

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To develop and standardize animal models to evaluate the potential for vaccine effectiveness and to understand the potential for enhanced disease after vaccination

+379 experts from **+20** countries and +**60** entities convened since Feb 2020

Live deliberations on **results**

Researchers collaborating on **protocols** and processes

Live state of the art **reviews** to guide developers and researchers

Info on **global capacity** to conduct animal studies

→

Facilitate access to global resources for **accelerated** evaluation

Enhanced **access** to animal laboratories for **ALL** developers

https://www.who.int/publications/m/item/global-animal-laboratories-capacities-to-support-vaccine-and-therapeutic-evaluation

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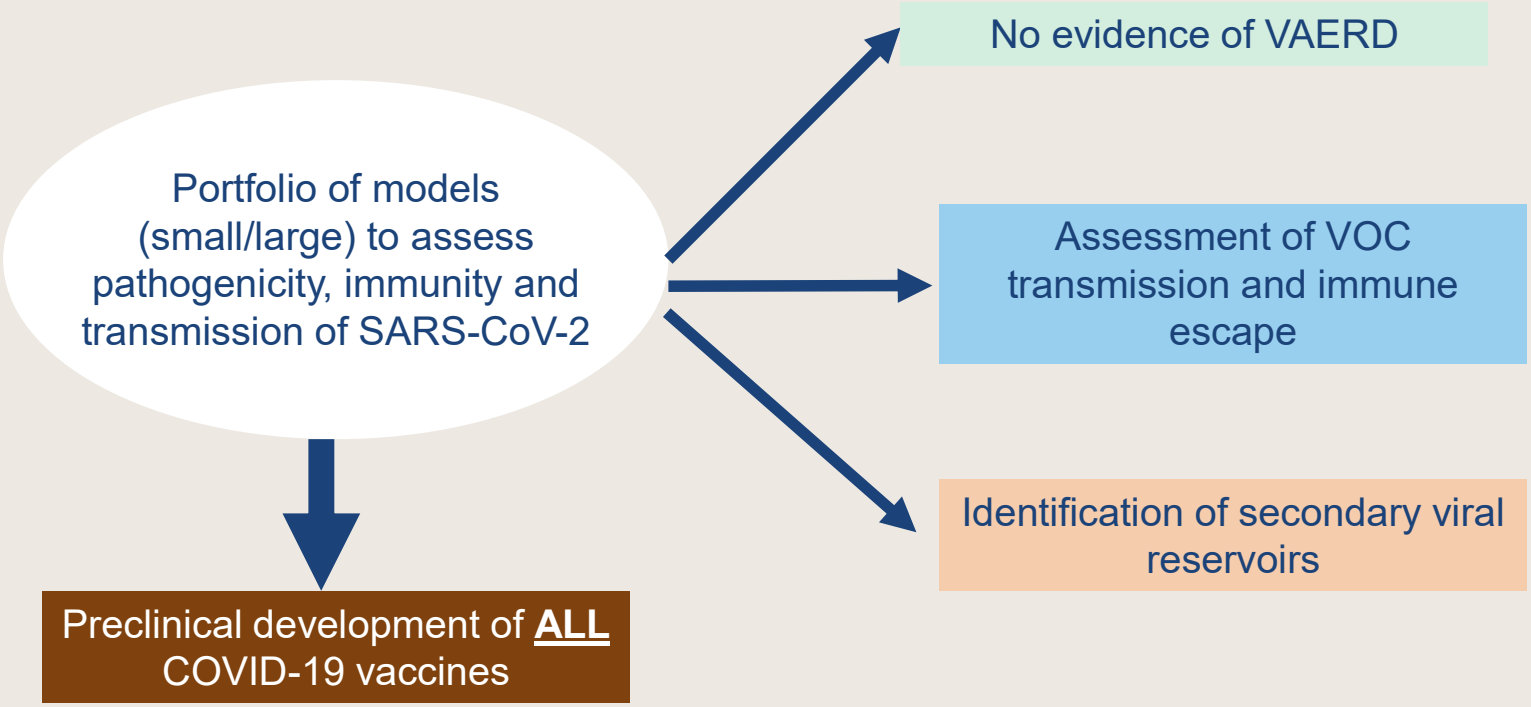
Achievements

(Munoz-Fontela et al., Nature 2020; Funnell et al., Nat Commun. 2020; Munoz-Fontela et al., PloS Pathog 2021; Funnell et al, I.NPJ Vaccines. 2021; Krause et al Vaccine. 2022)



Lessons learned

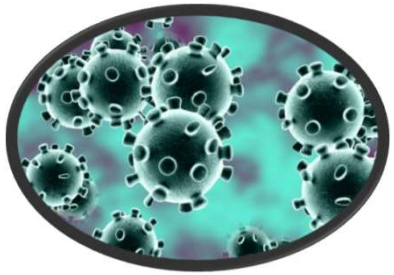
1) Unprecedented data sharing
2) Sharing failures and successes
3) Avoiding unnecessary repetition
4) Value of pre-prints
5) Standardization
6) ‘Proud to be WHO’

Challenges

1) Animal model repositories
2) Standardization (e. g. hamsters)
3) Lack of immune reagents
4) Animal testing protocols and euthanasia endpoints
5) Sharing, sharing, sharing…

Looking at “Pathogen X”

1) Experience can save time and lives (SARS-1, MERS, MPx, Plague, CCHF)
2) Rapid sharing of data, ideas and models will reduce the time to develop vaccines and therapeutics
3) A good understanding of basic pathogenesis and immunology will speed vaccine testing (e. g. T cell epitopes in SARS-CoV-2 spike). Translational approach alone is not enough!



Outcome of WHO R&D Blueprint models questionnaire 20th Dec 2023 - 4th Jan 2024

How can we develop generalised models?
What needs to be done?
How shall we do it?

WHO Headquarters in Geneva
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1202 Geneva
Telephone: +41-22-7912111

World Health Organization

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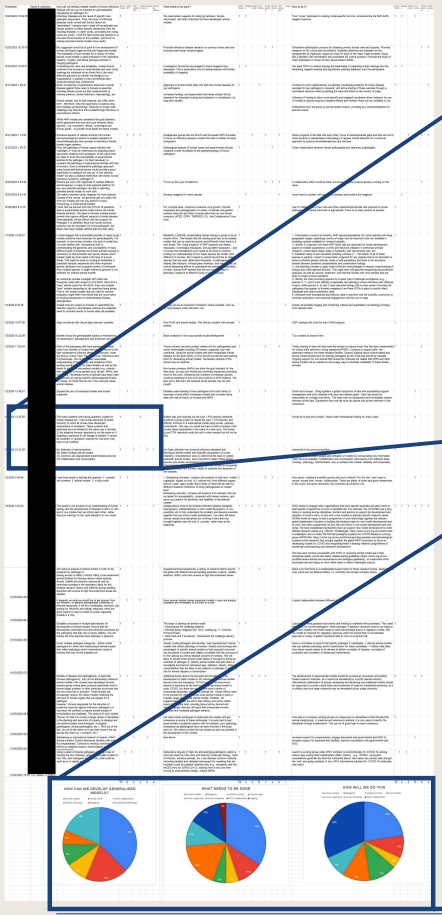
Responses - categorisation

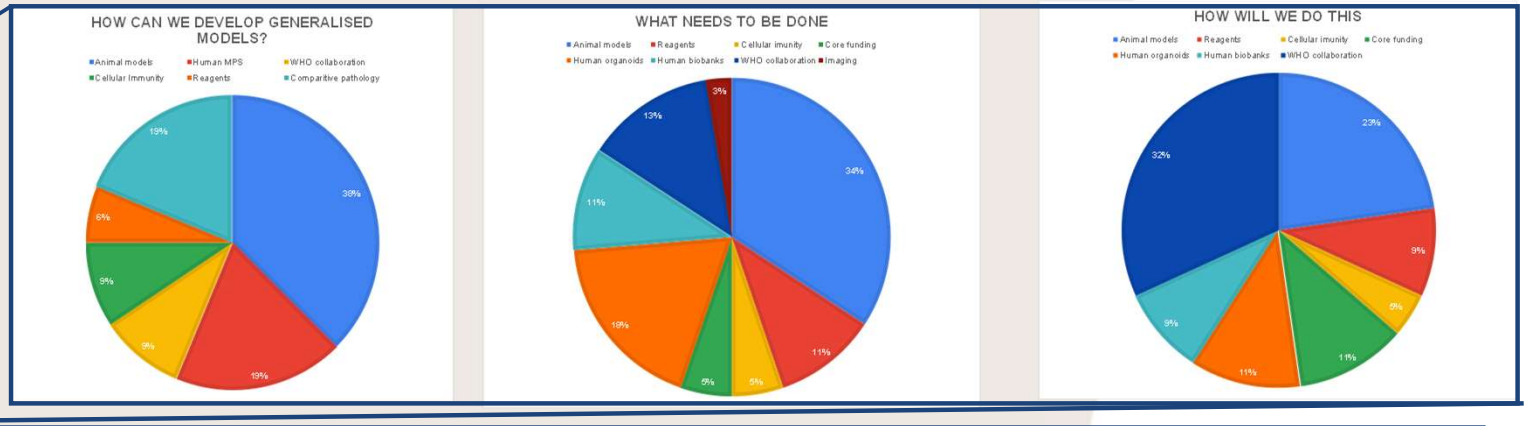


	A	B	C	D	E	F	G	H	I	J	K	L	M
1	Timestamp	Name & Institution	How can we develop reliable models of human infectious disease with an eye on potential for generalizability (developing for pathogen X)?	Animal models	Human MPS	WHO collaboration	Cellular Immunity	Reagents	Comparitive pathology			What needs to be done?	Animal models
17	1/2/2024 14:47:50	[redacted]	The main problems with having authentic models for human disease are 1) the human elements of innate immunity to which all viruses have developed mechanisms of avoidance. These systems and pathways are not inhibited in the same way in animals. 2) the adaptive immune repertoire is not the same so if targeting a particular B cell lineage is needed, it cannot be modeled, 3) receptors required for viral entry may have to be modified.	1			1					Rather than just knocking out the type 1 IFN pathway elements, would be a great project to rebuild the type 1 IFN induction and effector functions in a small animal model using human pathway components. That way you would just have to add a receptor (with correct tissue localization) in the event of a new virus. The human Ig and TCR repertoire could be built in when needed but will not be fast.	
	1/2/2024 23:31:26		1(A) Selection of animal species	1		1		1	1			(A) Data collection from previous infectious diseases and	1

Animal models	Human MPS	WHO collabor	Cellular Immunit	Reagent s	Compari tive	A ni
12	6	3	3	2	6	

Animal models	Reagent s	Cellular imunity	Core funding	Human organoi	Human biobank	WHO collabor	Imaging
13	4	2	2	7	4	5	1

Animal models	Reagent s	Cellular imunity	Core funding	Human organoi	Human biobank	WHO collabor
10	4	2	5	5	4	14



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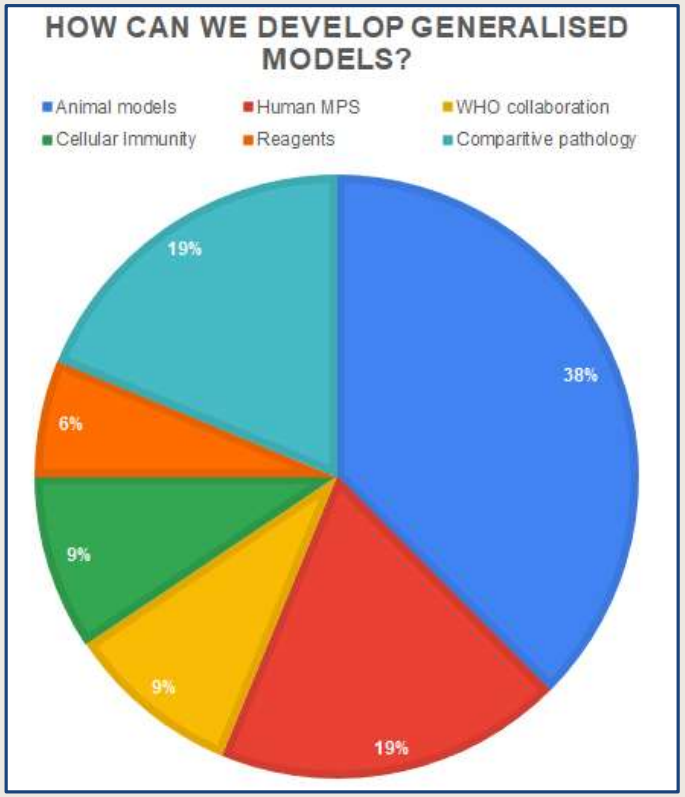
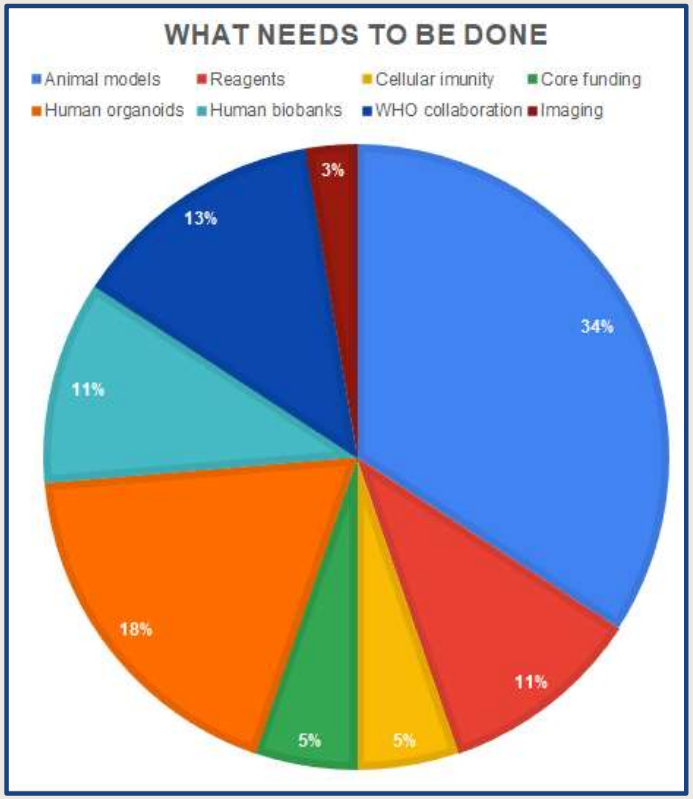
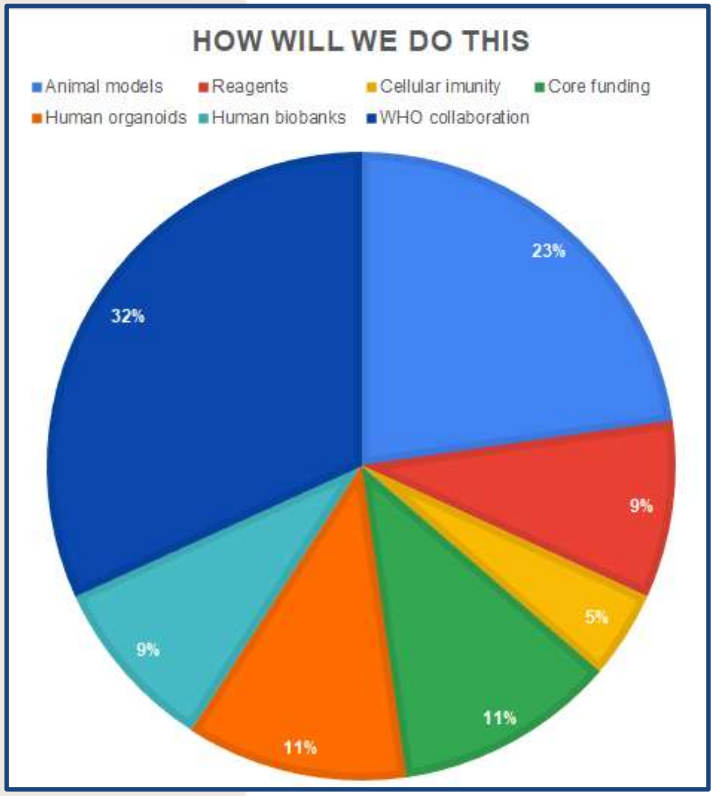
Responses – categorization summary







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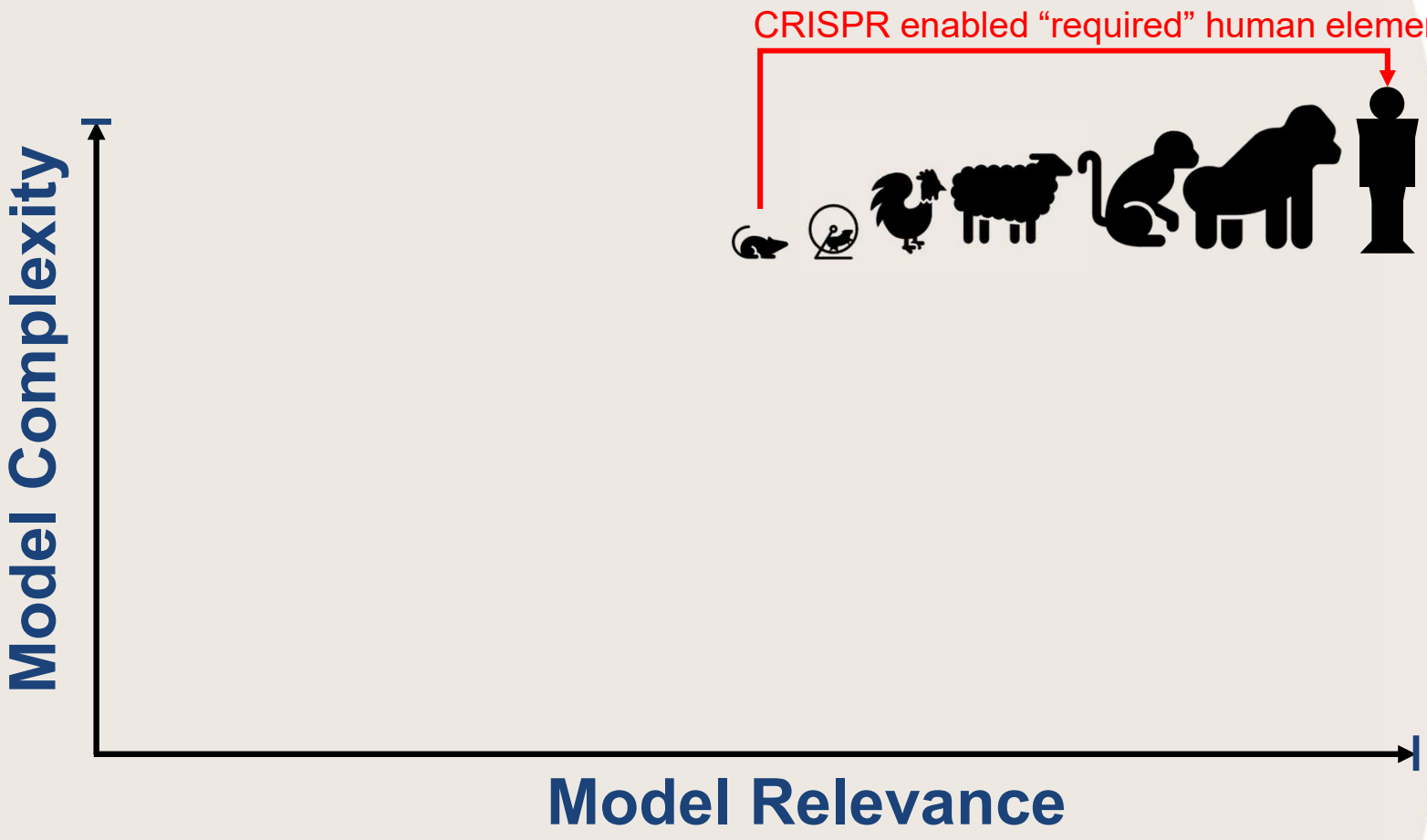

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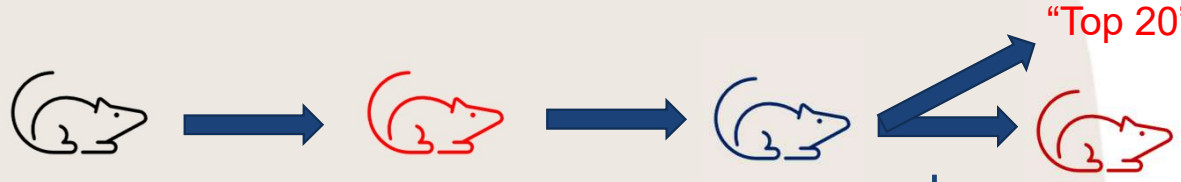
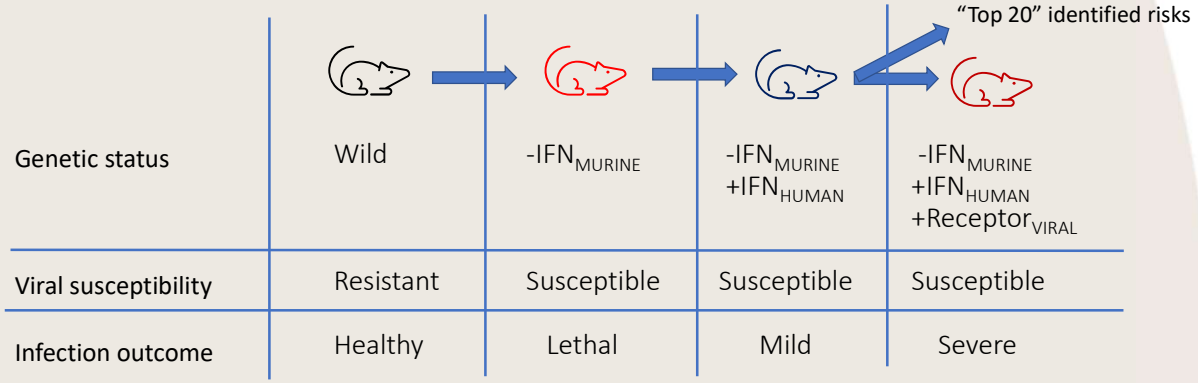
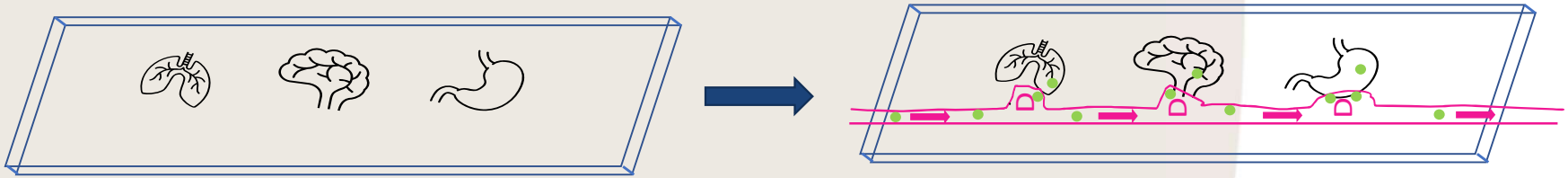


Genetic status	Wild	-IFN$_{MURINE}$	-IFN$_{MURINE}$ +IFN$_{HUMAN}$	-IFN$_{MURINE}$ +IFN$_{HUMAN}$ +Receptor$_{VIRAL}$
Viral susceptibility	**Resistant**	**Susceptible**	**Susceptible**	**Susceptible**
Infection outcome	**Healthy**	**Lethal**	**Mild**	**Severe**





Set up multiple human organ MPS

Add cellular immunity component

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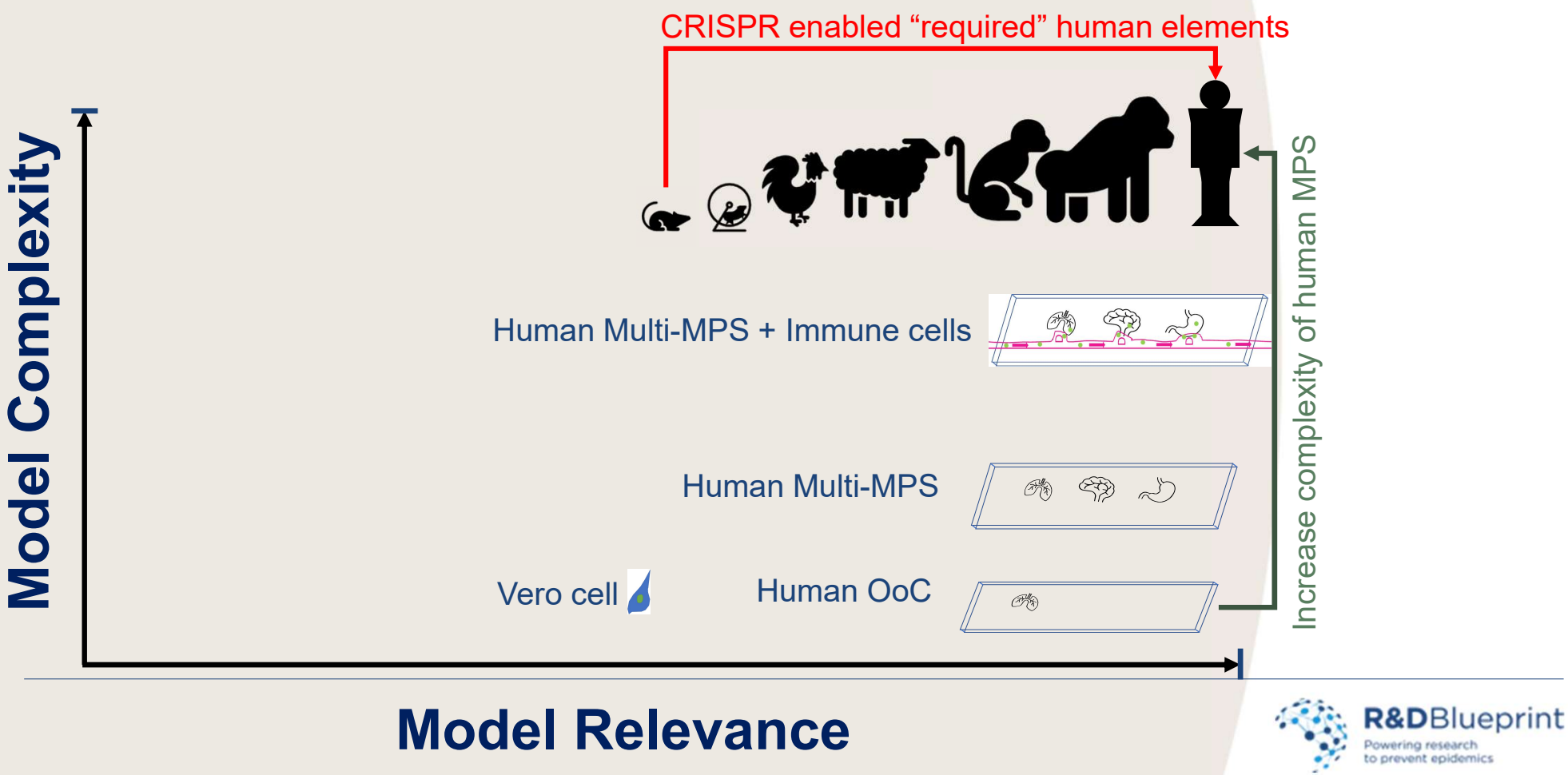

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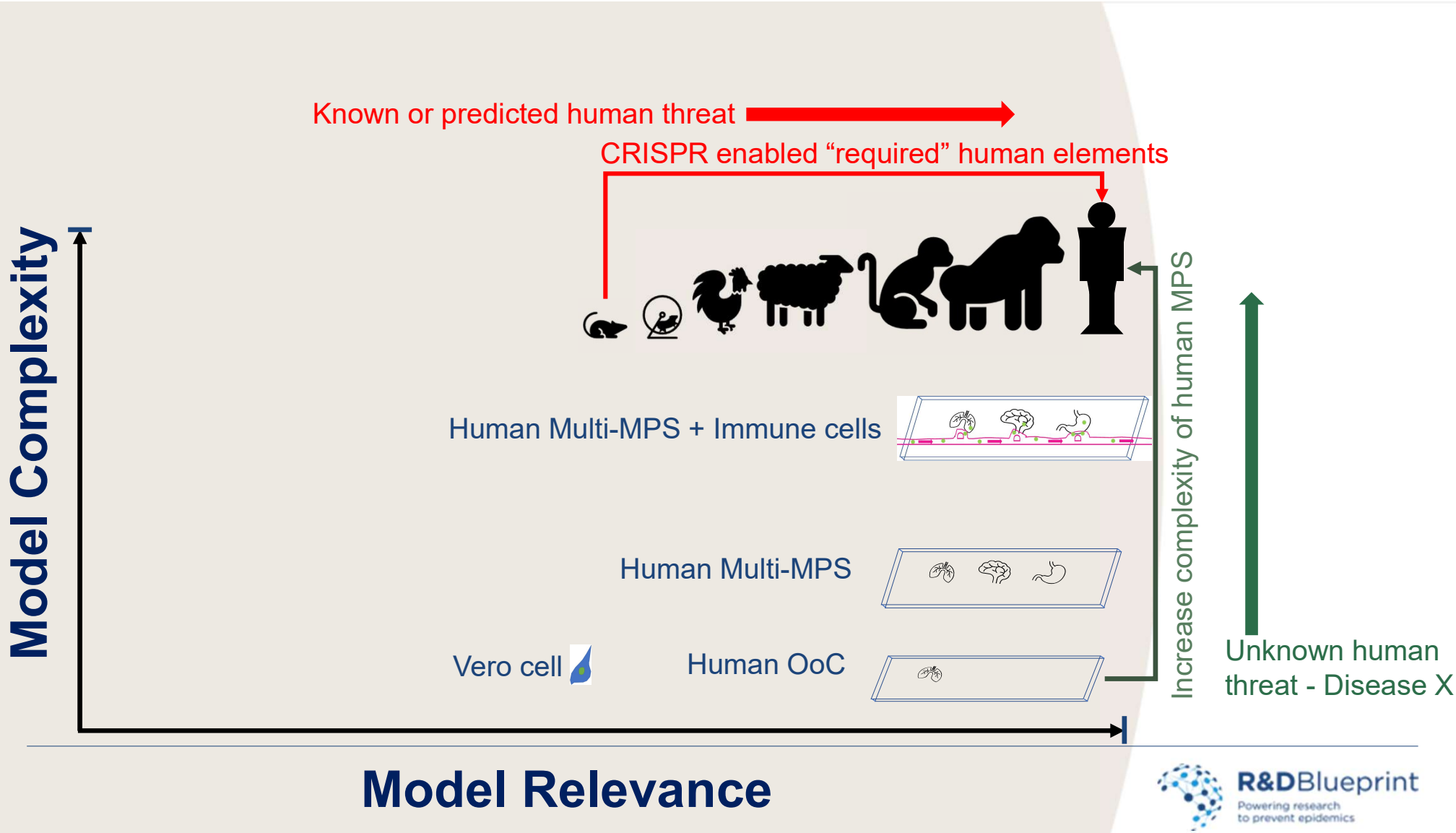
Known or predicted human threat
CRISPR enabled “required” human elements
Model Complexity
Human Multi-MPS + Immune cells
Human Multi-MPS
Vero cell
Human OoC
Increase complexity of human MPS
Unknown human threat - Disease X
Model Relevance
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Responses *– Summary outcome -* ***"What needs to be done?"***

Sharing data and resources to accelerate development of drugs, therapeutics and vaccines especially standards, reagents, pathology data, clinical samples and methodology.

Simultaneous development of animal models refined for each of the known high-risk groups of pathogens along with simultaneous development of microphysiological systems which may complement or support *in vivo* approaches.

A large percentage of responders valued the continuation of international data sharing