CCP: Příspěvek ČR k testování léčiv na onemocnění Covid-19:

Unikátní humanizované myší modely ke studiu infekce Sars-Cov-2 a jeho léčby

Unique humanized mouse models to study infection of Sars-Cov-2 and its treatment

Radislav Sedláček

Czech Centre for Phenogenomics Institute of Molecular Genetics











Model Generation



Animal Facility 🔻

Preclinical Testina 🔻

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of the genetic basis for human diseases

Phenotyping v





Model Generation

Genetically modified rodent models have become a key tool in basic and biomedical research. The ability to engineer the mouse genome has greatly transformed biomedical research in the last decade. Find out more >



Phenotyping

The genomes of humans, mice and other species have been completely sequenced, yet the knowledge of genome sequences as such does not shed light on questions concerning the functions of these sequences. Find out more >



Animal Facility

The Animal Facility Module of the Czech Center for Phenogenomics is based on the latest advances in housing, breeding and care of laboratory mice and rats. Find out more >



Preclinical Testing

be Czech Centre for Dhenogenomics can offer a very broad portfolio of highly



Tweets by @CZphenogenomics

Czech Centre for Phenogenomics @CZphenogenomics Novel CRISPR Tool Activates Instead of Editing Human Immune Cell Genes genengnews.com/news/novel-cri.. prostřednictvím @GENbio

(1)



Novel CRISPR Tool Activates Instead of Ed.. A research team used a method called CR. genengnews.com



Czech Centre for Phenogenomics Retweeted



International Angelman Day is February 15. The ASF joins organizations around the world working to raise awareness of Angelman syndrome









Pathophysiology of COVID-19



Host cell

Gupta A. et al., Nature Medicine | VOL 26 | 1032 July 2020 | 1017-1032







Pathophysiology of COVID-19



Gupta A. et al., Nature Medicine | VOL 26 | 1032 July 2020 | 1017-1032







Coronavirus disease 19 (COVID-19): pathogenesis



http://dx.doi.org/10.3390/pathogens9100817







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Coronavirus disease 19 (COVID-19): pathogenesis



http://dx.doi.org/10.3390/pathogens9100817

Animal species used as animal models to study SARS-CoV-2

C.K.F. Rahman et al. / Trends Biomater. Artif. Organs, 34(S3), 78-82 (2020)

Article

Bispecific IgG neutralizes SARS-CoV-2 variants and prevents escape in mice

https://doi.org/10.1038/s41586-021-03461-y

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Check for updates

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Use of adeno-associated virus (AAV) for rapid humanized ACE2 mouse model

Use of AAVs for rapid humanized ACE2 mouse model

Covid-19 preclinical model

(Daniel Ruzek – Department of virology)

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neutralizing properties of CoV-X2 are superior to those of its parental monoclonal antibodies

CoV-X2 fully prevents ACE2 binding to S trimer in ELISA

ACE2 binding to antibody/S trimer complexes is measured either with increasing concentration of the indicated antibody and constant ACE2 (left), or at constant antibody concentration with increasing ACE2 (right).

CoV-X2 neutralizes SARS-CoV-2 pseudovirus and escape mutants generated by its parental monoclonal antibodies

Czech Academy of Sciences

Covid-19 treatment with bispecific antibodies

(CCP & Daniel Ruzek Department of virology)

Histopathology and F4/80 immunohistochemistry (IHC).

(CCP & Daniel Ruzek Department of virology)

hACE2 genetically engineered mouse models:

humanized, variants, and tissues specific models

COVIDAX https://www.covidax.eu/

EBioMedicine

Published by THE LANCET

Monoclonal antibodies targeting two immunodominant epitopes on the Spike protein neutralize emerging SARS-CoV-2 variants of concern

Branislav Kovacech,^{a,b}* Lubica Fialova,^b Peter Filipcik,^{b,c} Rostislav Skrabana,^b Monika Zilkova,^b Natalia Paulenka-Ivanovova,^b Andrei Kovac,^b Denisa Palova,^b Gabriela Paulikova Rolkova,^b Katarina Tomkova,^b Natalia Turic Csokova,^c Karina Markova,^b Michaela Skrabanova,^{b,c} Kristina Sinska,^b Neha Basheer,^b Petra Majerova,^b Jozef Hanes,^{b,c} Vojtech Parrak,^b Michal Prcina,^b Ondrej Cehlar,^c Martin Cente,^{b,c} Juraj Piestansky,^b Michal Fresser,^b Michal Novak,^d Monika Slavikova,^e Kristina Borsova,^{e,f} Viktoria Cabanova,^e Bronislava Brejova,^g Tomas Vinař,^h Jozef Nosek,ⁱ Boris Klempa,^e Ludek Ever,^{i,k} Vaclav Hönig,^{i,k} Martin Palus,^{i,k} Daniel Ruzek,^{JkJ} Tereza Vyhlidalova,^J Petra Strakova,^{Jk} Blanka Mrazkova,^m Dagmar Zudova,^m Gizela Koubkova,^m Vendula Novosadova,^m Jan Prochazka,^m Radislav Sedlacek,^m Norbert Zilka,^{b,c,***} and Eva Kontsekova^{b,c}

Summary & Advantages of the AAV-based model

- Rapid approach compared to transgenic mouse generation
- Generation of experimental cohort can be speed up and large number of animals can be prepared
- Multiple viral receptors can be delivered in once
- Can be used for more pathogens
- AAV based humanized models can serve as rapid first line testing cohorts
- AAV humanization can be used in other pathogens

Extrapulmonary manifestations of COVID-19

Gupta A. et al., Nature Medicine | VOL 26 | 1032 July 2020 | 1017–1032

hACE2 genetically engineered mouse models:

humanized, variants, and tissues specific models

Generation of mouse models to to study biology of SARS-Cov-2

Ready to use:

AAV – hACE2 to infect mouse lung
AAV – tranferin receptors
AAV neuropilin1

GM – mouse models

Ace2 – knockout

- transmembrane serine protease 2 (TMPRSS2) knockout
- □ Kallikreins knockouts
- Serine protease inhibitors knockouts

In pilot: hACE2 conditional - now G2 & prepration of Cre-based models: - cardiocascular, intestinal, neuro (brain), whole body Planned: Tissue specific expression: lung, intestine & endothelial cells

hACE2 genetically engineered mouse models: conditional

tissues specific & inducible models

hACE2 genetically engineered mouse models: conditional

tissues specific & inducible models

Thank you for your attention

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