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Implementation of a platform for the identification of broad-spectrum antiviral compounds based on 2D/3D cultures of the central nervous system

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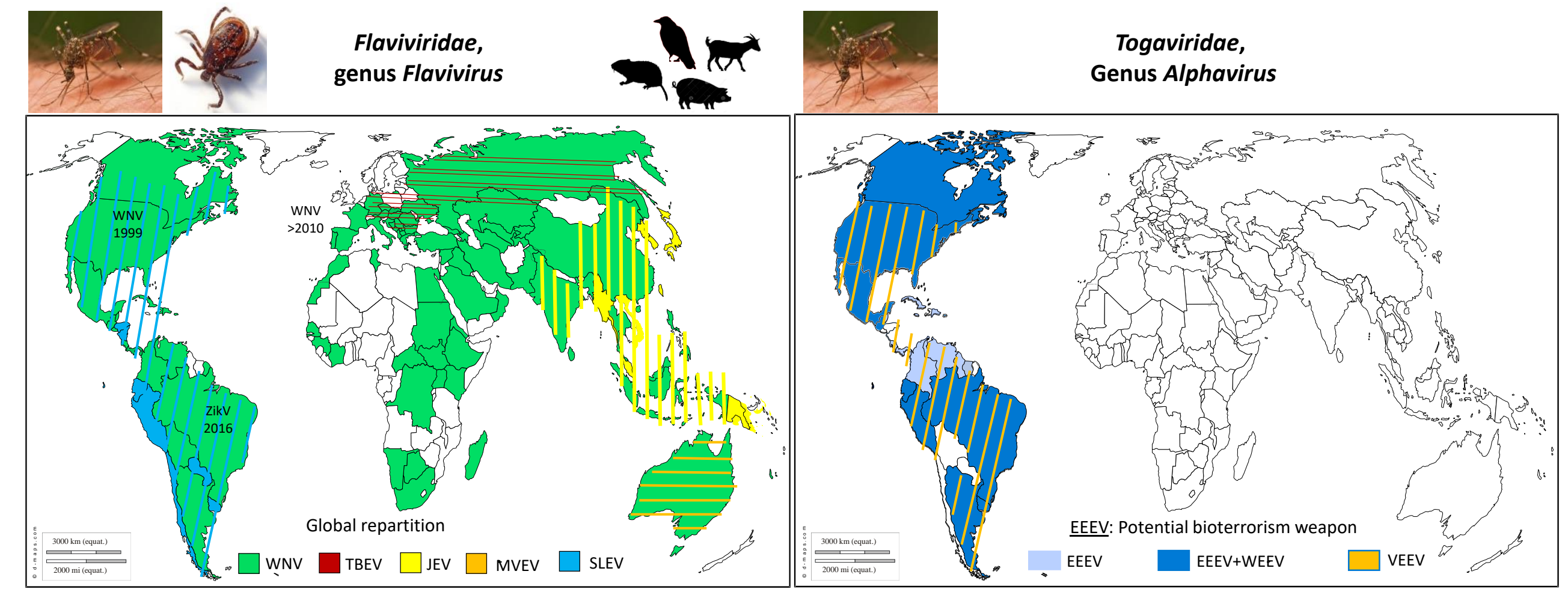


INTRODUCTION

Viral infections of the nervous system are often very serious affections, and can be responsible for fatal encephalitis or severely disabling neurological sequelae. In humans, many viruses are capable of infecting the nervous system; some of them are also responsible for encephalitis in horses. However, there are currently very few antiviral treatments available, and none to block the replication of neurotropic arboviruses (viruses transmitted by mosquitoes and ticks) and limit the damage caused to the brain. Our aim is to identify broad-spectrum antivirals that will be effective against several viral families, in both humans and horses.

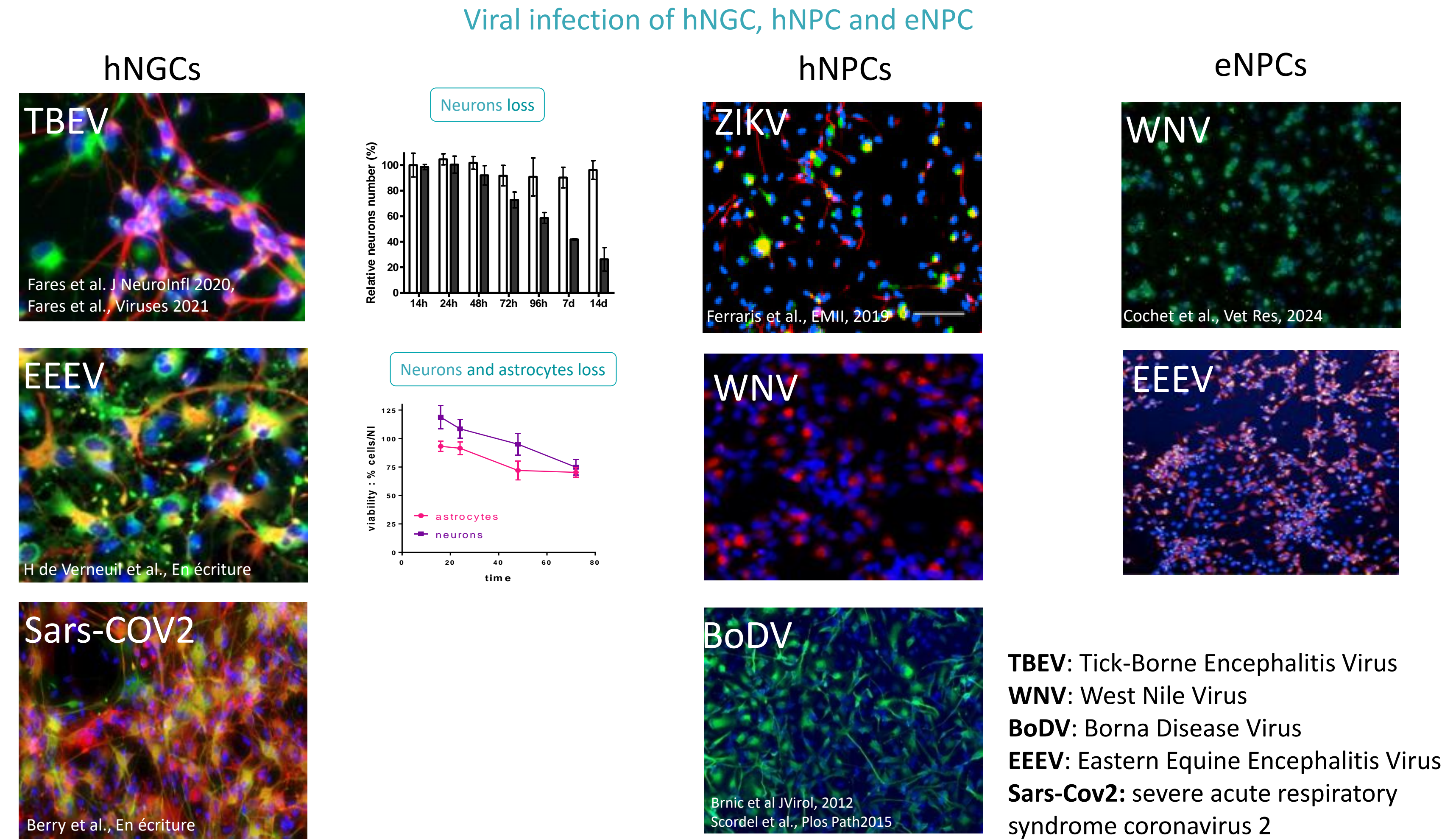
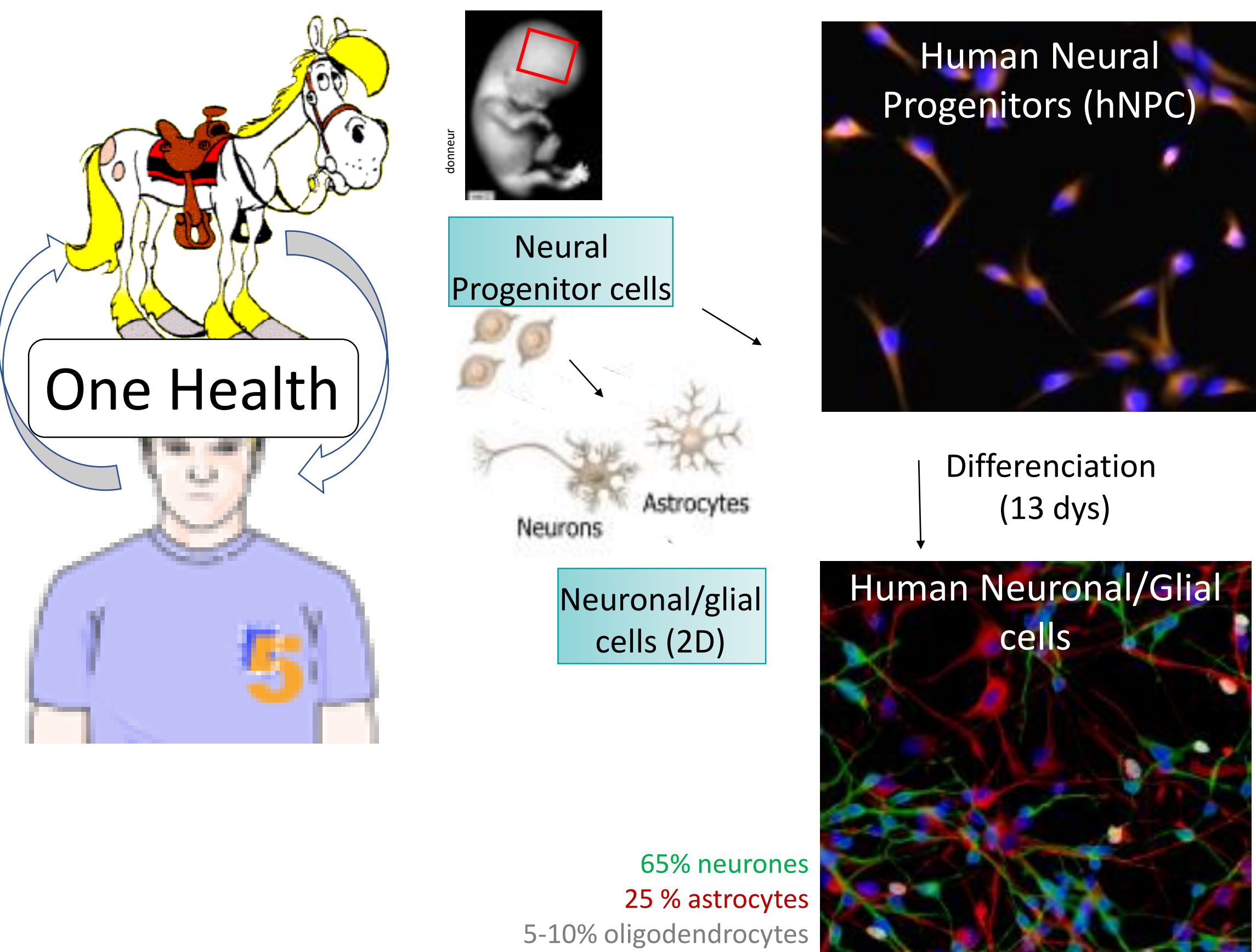
This poster will show the different infection models based on 2D/3D cultures of central nervous system cells that we have developed in recent years, and our strategy for identifying broad-spectrum antiviral compounds active in the nervous system.

VIRUSES OF INTEREST

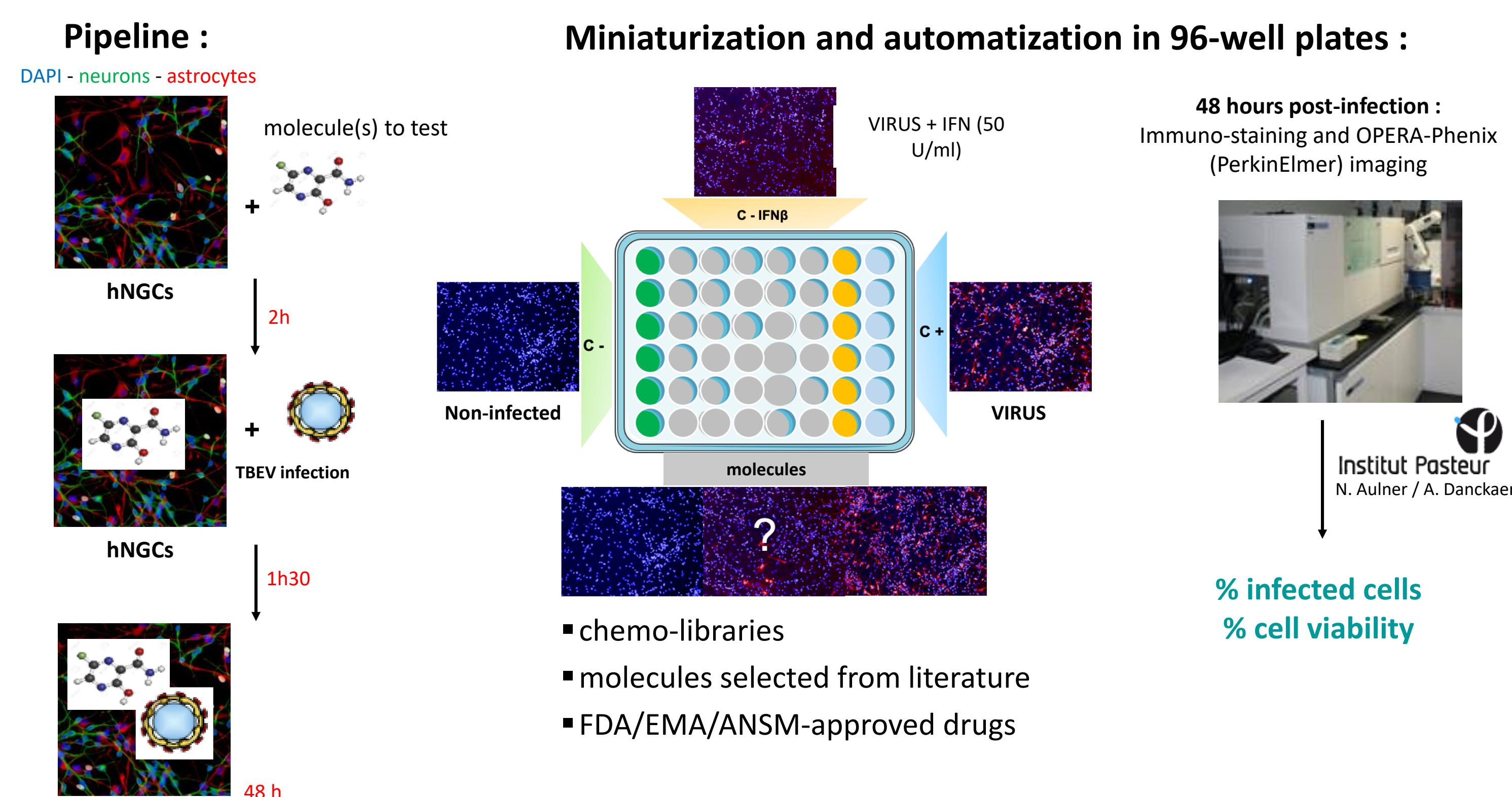


Endemic, emerging or at-risk arboviruses responsible for serious neurological diseases

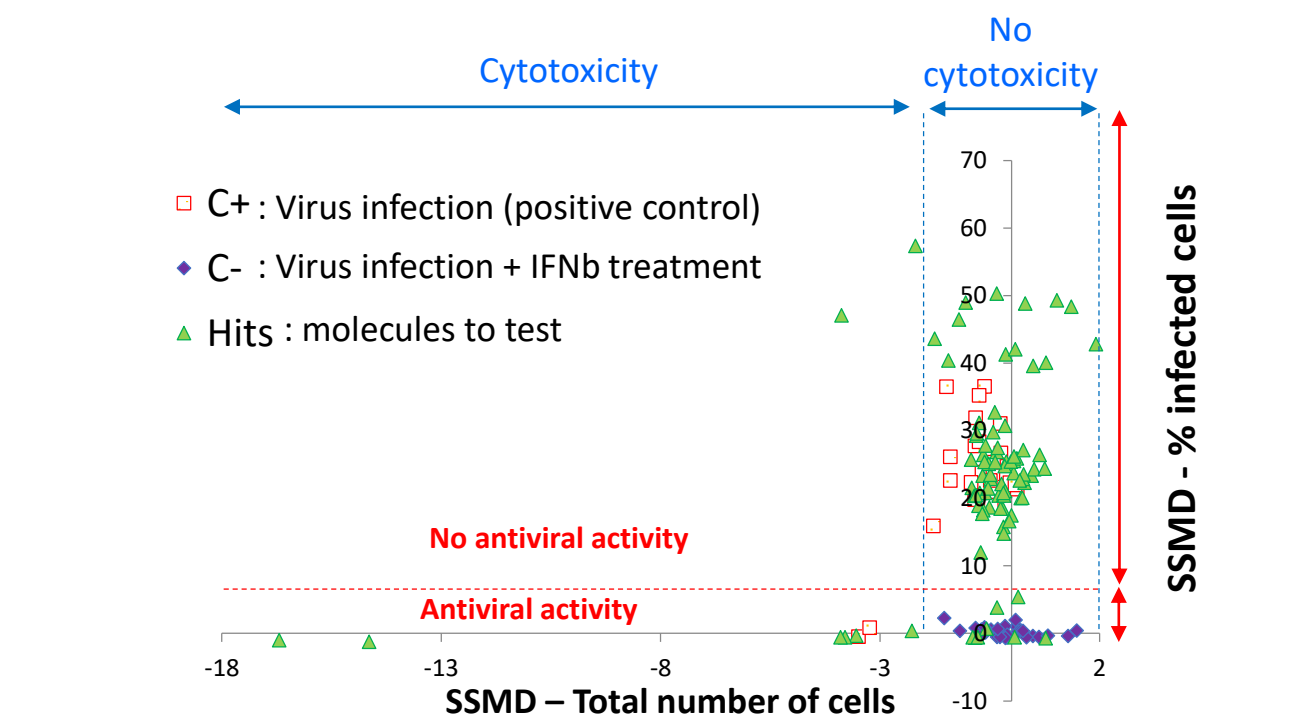
PHYSIOLOGICALLY RELEVANT 2D MODEL TO MIMIC VIRAL INFECTION



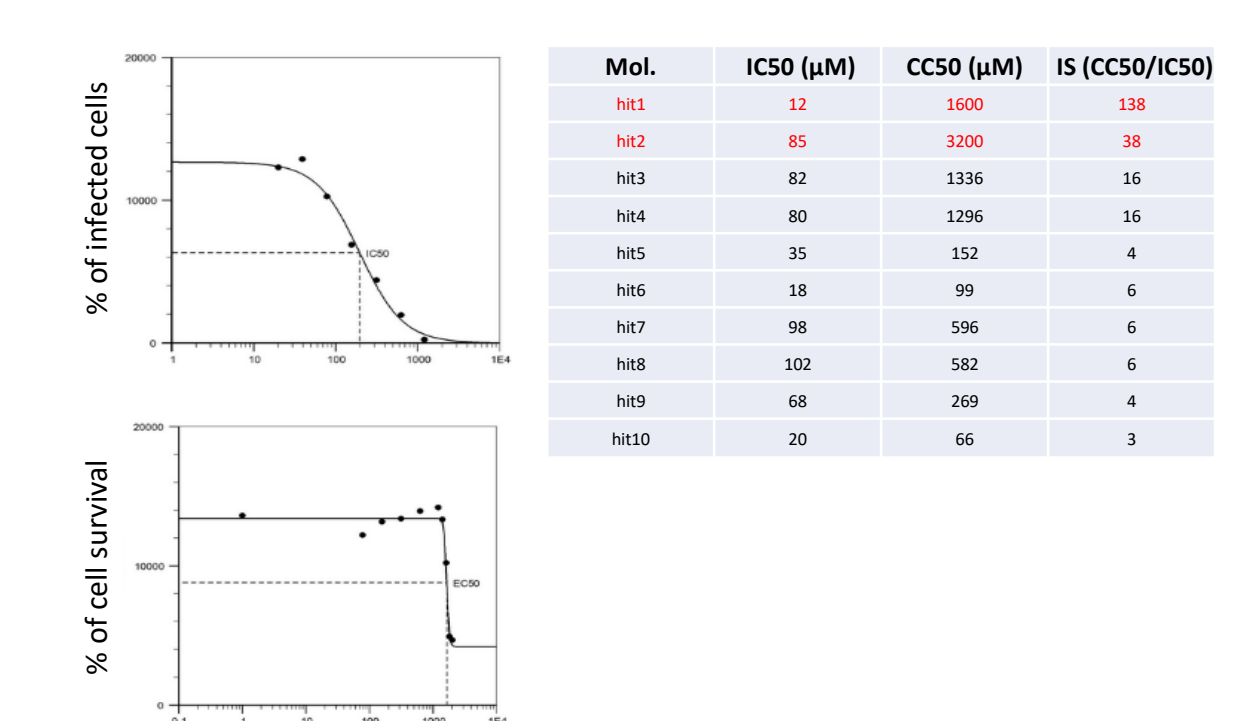
DEVELOPMENT OF A PHENOTYPIC SCREEN BASED ON hNGCs AND IMAGING



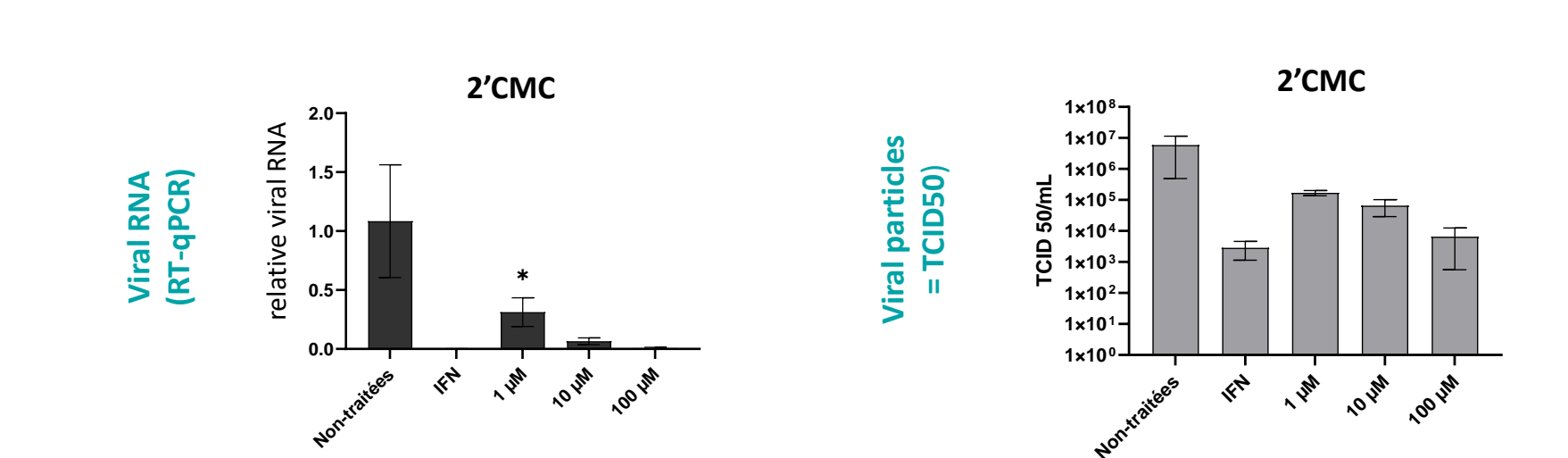
Statistical analysis for hits identification



Selectivity index



Hits confirmation by quantification of viral RNA/titer



COMPARISON OF THE ANTIVIRAL ACTIVITY OF SELECTED MOLECULES

- 8 molecules selected from the literature (already described for their anti-flavivirus activity).
- Cells: hNGCs + two others *in vitro* models with different levels of relevance (A549: human alveolar basal epithelial cells; hNPCs: human neural progenitor cells) – all permissive to TBEV infection.
- Read-out: % of infected cells and % cell viability by an automatized imaging approach.

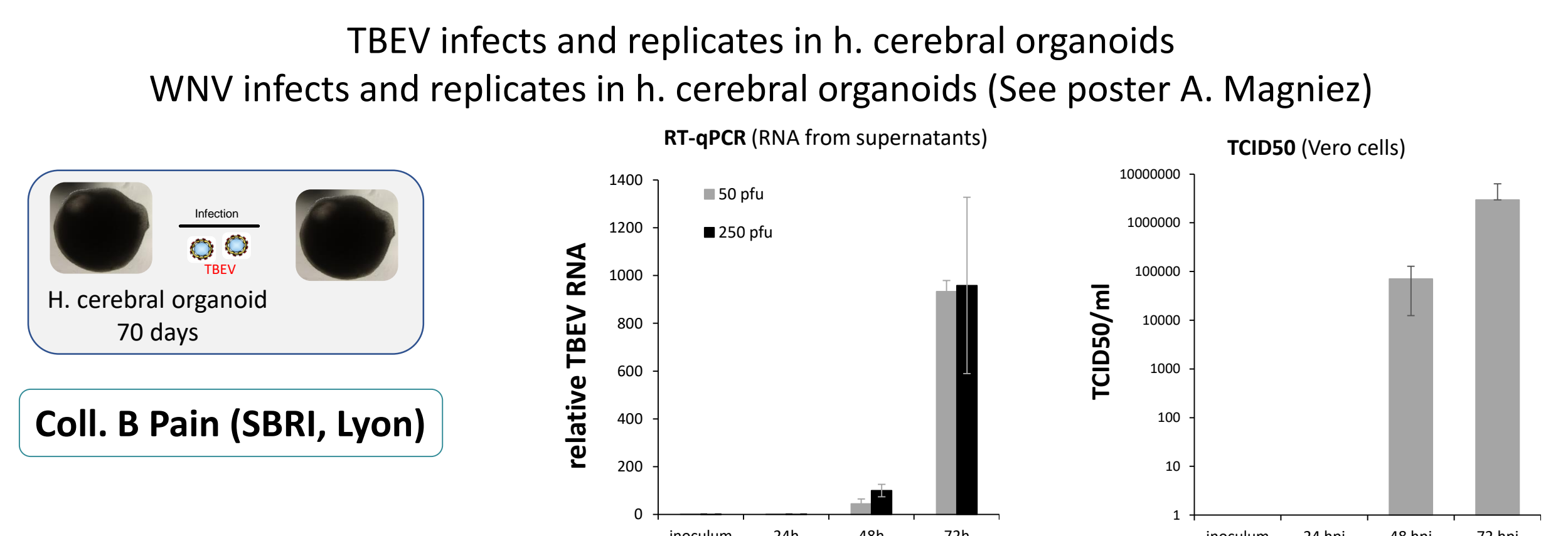
Molecules	A549	hNPCs	hNGCs
Cyclosporine A	✓	✗	✗
Alisporivir	✓	✗	✗
2'C-methylcytidine	✓	✓	✓
Ribavirine	✓	✗	✗
Bréquinar	✓	✗	✗
Mycophenolic acid	✓	-	✗
Ivermectin	✓	✗	✗
Arbidol	✗	✗	✗

→ Importance to choose the most physiologically relevant *in vitro* model to screen antiviral drugs.

CONCLUSION

- Our pipeline allows to test the antiviral potential of chemical compounds on a panel of physiologically relevant *in vitro* models representative of the human and equine infected brain.
- Cytotoxicity of molecules for human/equine brain cells can be assessed and their selectivity index can be calculated.
- Hits identification is statistically determined.
- The diversity of our models allows the identification of broad-spectrum antiviral compounds.
- Whether the compounds act on neurons and/or astrocytes (antiviral effect/cytotoxicity) may be resolved.

USING HUMAN CEREBRAL ORGANOID (3D MODEL) TO VALIDATE OUR HITS



Validation of the « hits » using TBEV-infected human cerebral organoids:

