

**Could antivirals halt
long COVID?
Plitidepsin:
*Mechanisms of action***

Dra. Nuria Izquierdo-Useros
21 de Abril de 2022

Condición Post-COVID-19: Un largo camino hacia la recuperación

IrsiCaixa

Institut de Recerca de la Sida



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Can drugs reduce the risk of long COVID? What scientists know so far

Researchers are trying to establish whether existing COVID-19 vaccines and treatments can prevent lasting symptoms.

[Heidi Ledford](#)

- Vaccination could reduce the risk of long COVID by about half among those who become infected after vaccination^{1,2}
- It's unclear whether any existing COVID-19 therapy has an effect on long-COVID risk:
 1. Early treatment in non-hospitalized patients (PANORAMIC molnupiravir)
 2. Long-term impact of treatments in hospitalized patients (SOLIDARITY)

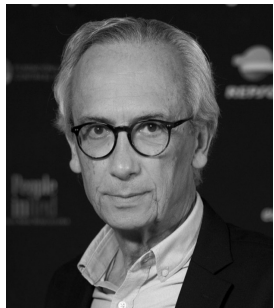
¹Antonelli, M. *et al. Lancet Infect. Dis.* **22**, 43–55 (2022).

²Ayoubkhani, D. *et al.* Preprint at medRxiv <https://doi.org/10.1101/2022.02.23.22271388> (2022).

Ongoing Collaborations

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Identification of Plitidepsin as Potent Inhibitor of SARS-CoV-2-Induced Cytopathic Effect After a Drug Repurposing Screen

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	DRUG	IC ₅₀ / CC ₅₀ μM (Mean +/-SD)	Mode of Action	Previous Clinical Use	Vendor Origen
nM	Plitidepsin	0.06 +/- 0.02 / > 0.1	Targets eukaryotic Elongation Factor 1A2 (eEF1A2)	Multiple myeloma	PharmaMar
	MDL 28170	0.14 +/- 0.06 / > 87	Calpain III inhibitor & Cathepsin B	Pre-Clinical	Merck
	NPO-2142; -2143 & -2260	~ 0.54 / >10	Calpain & Cathepsin inhibitors	Pre-Clinical	Landsteiner Genmed
< 25 μM or 10 ² IU/mL	Remdesivir	2.16 +/-4.1 / > 85	RNA Polymerase inhibitor	Ebola Virus	Cayman Chemical
	Hydroxycloquine	10.9 +/- 11.3 / > 96	Clathrin-mediated endocytosis or pH-dependent viral fusion inhibitor	Malaria	Laboratorios Rubio
	Nelfinavir mesylate hydrate	Not calculated, but active < 10 / > 25	Protease inhibitor	HIV-1	Sigma Aldrich
	Chloroquine	3.86 / > 25	Clathrin-mediated endocytosis or pH-dependent viral fusion inhibitor	Malaria	Sigma Aldrich
	Interferon 2 alpha	8.1+/-0.7 x10 ² IU/mL / >100 x10 ² IU/mL	INF stimulated antiviral proteins	Hepatitis & HIV-1	Sigma-Aldrich
	Interferon gamma	11.2 x10 ² IU/mL / >100 x10 ² IU/mL	INF stimulated antiviral proteins	Granulomatous disease	Sigma-Aldrich
	Fenofibrate	19.8+/- 8 / >100	Activates PPARα	Dyslipidemia	Lacer

Among the **72 compounds** and **28 combinations** tested, we only found 22 compounds with antiviral activity, and only eight families had an IC₅₀ below 25 μ M or 10² IU/mL. These families tackle different steps of the viral life cycle.

Plitidepsin (Aplidin)



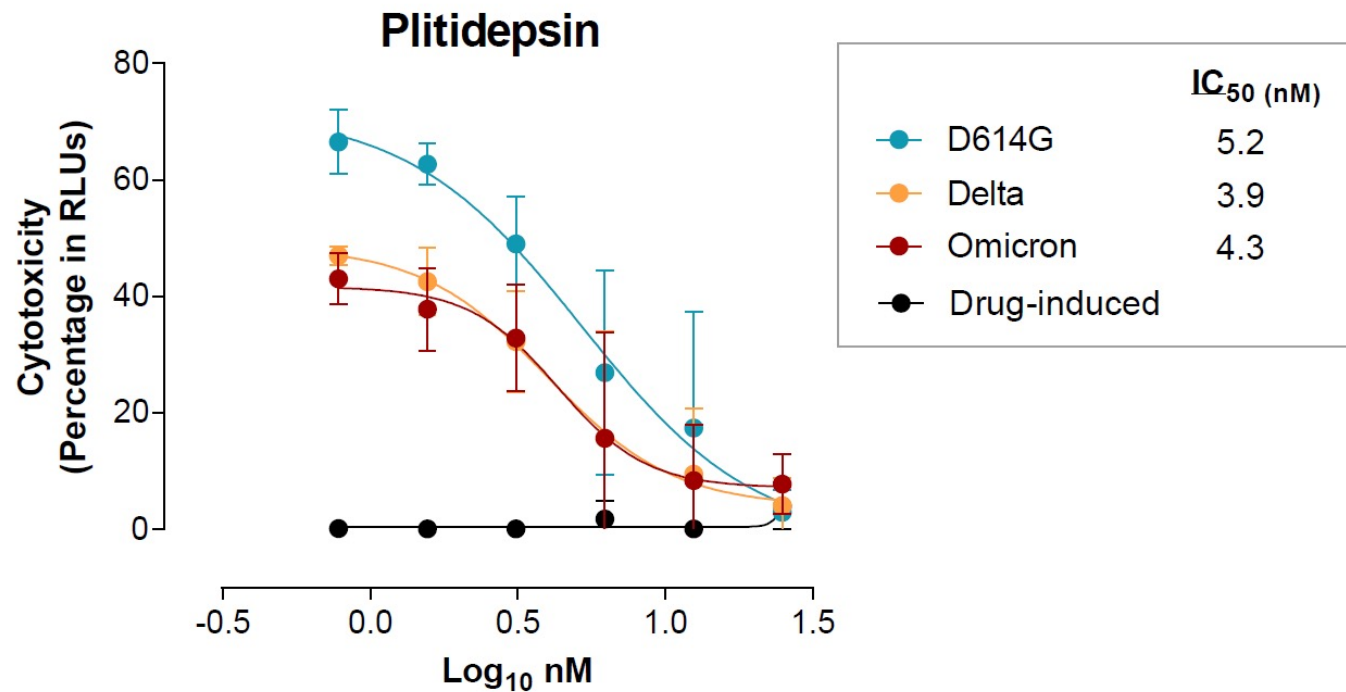
Aplidium albicans

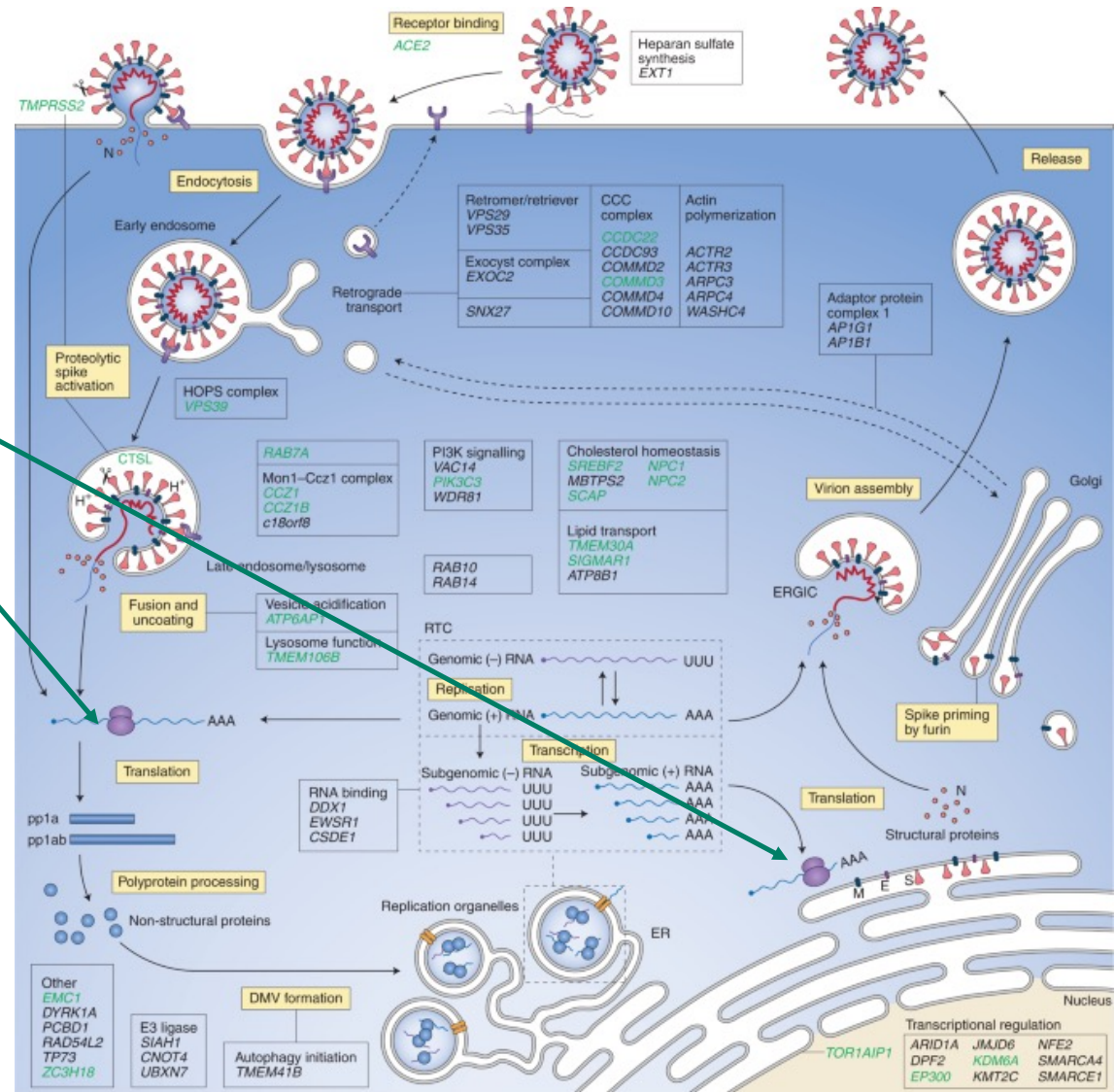
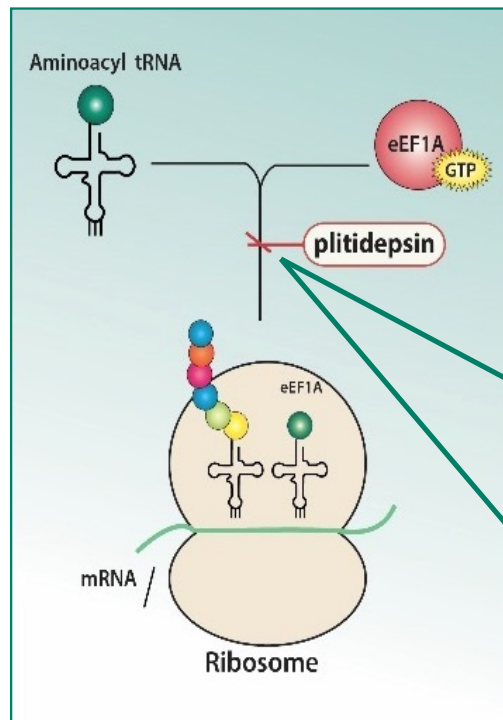
- Marine origin
- Viruses are the most abundant biological particles in the ocean
- 10^6 viruses / mL of water



10^{30} viruses in the oceans > n. stars in the Milky Way!

Plitidepsin is effective against different SARS-CoV-2 variants





Papapanou *et al.* 2021, *J. Pers. Med*

Baggen *et al.* 2021, *Nat. Micro.*



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Unraveling the antiviral activity of plitidepsin against SARS-CoV-2 by subcellular and morphological analysis

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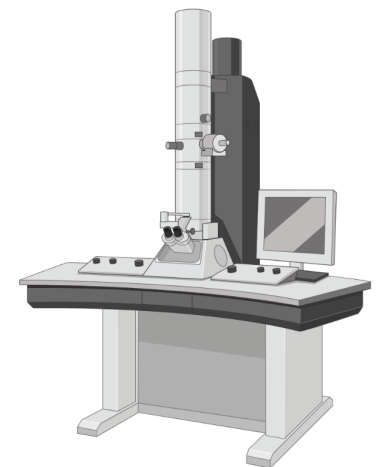
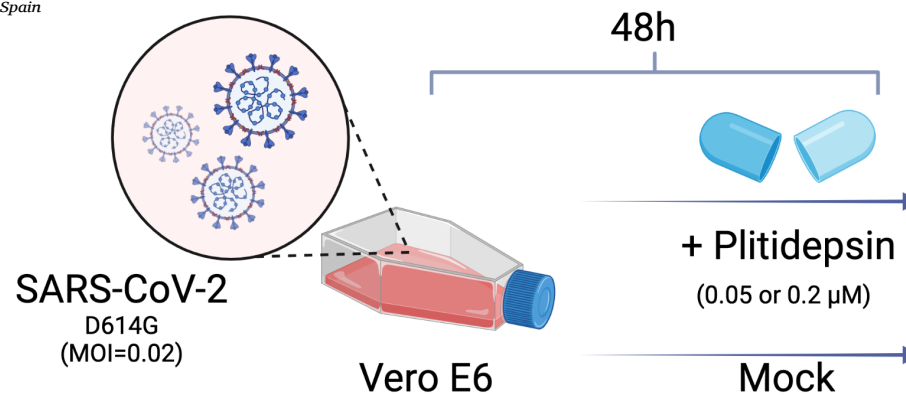
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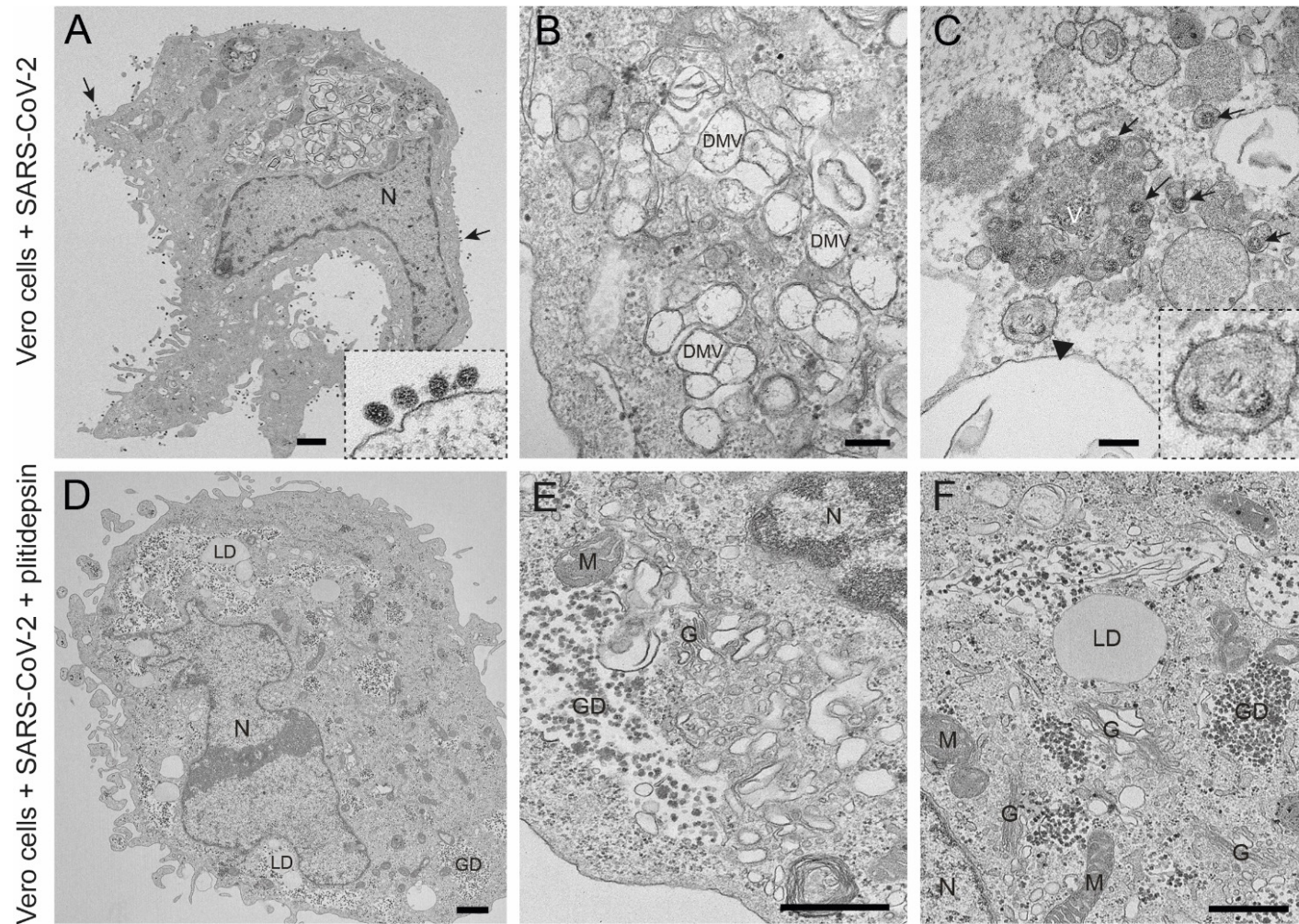
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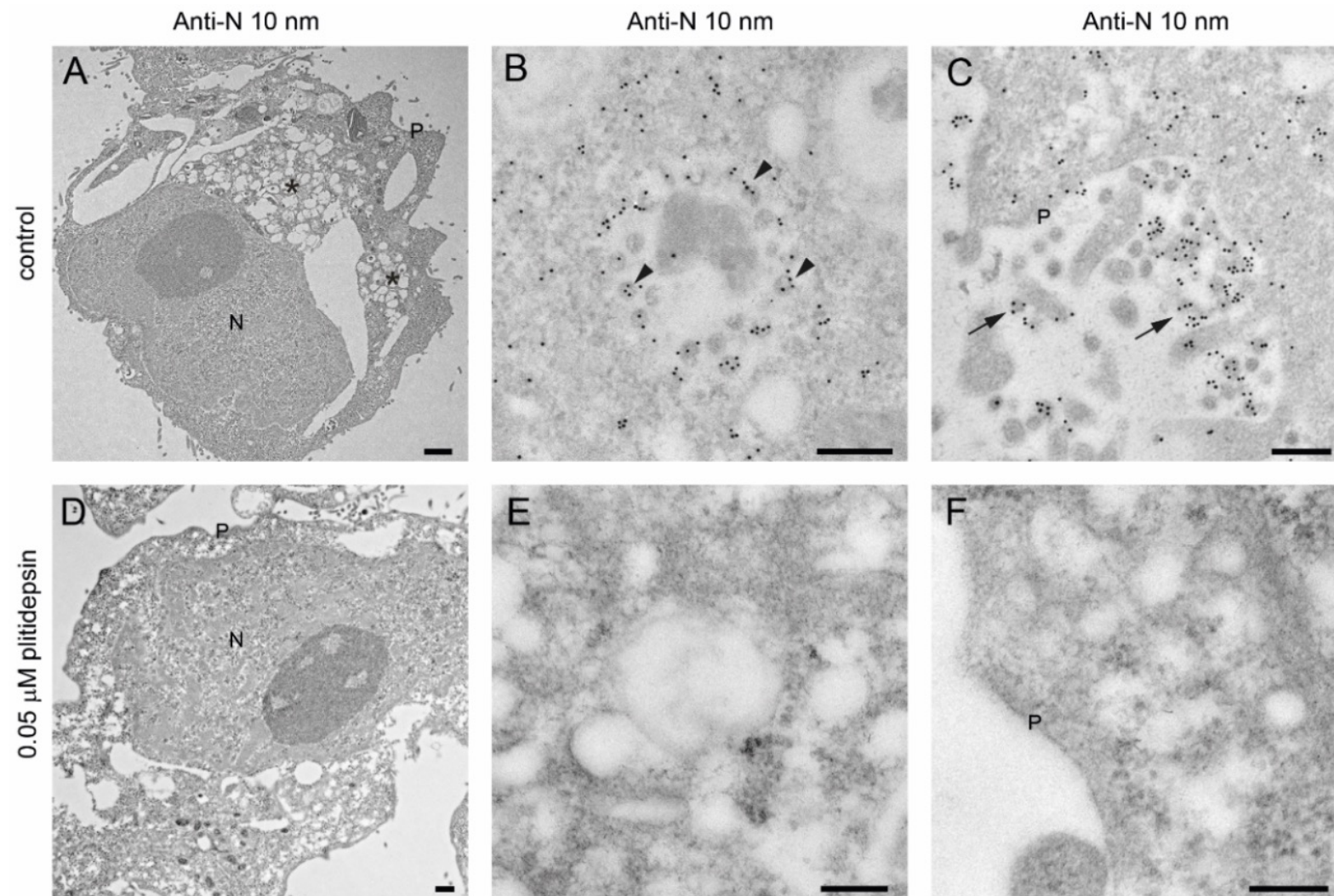
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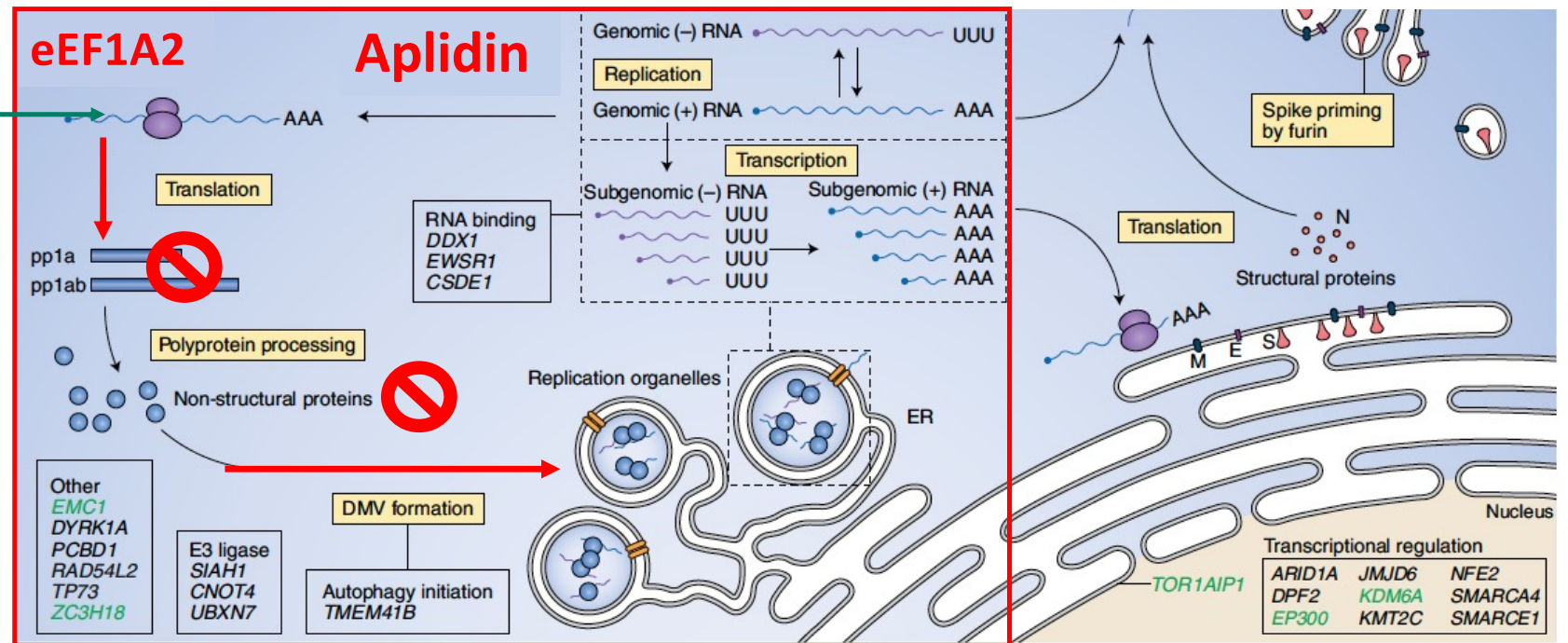
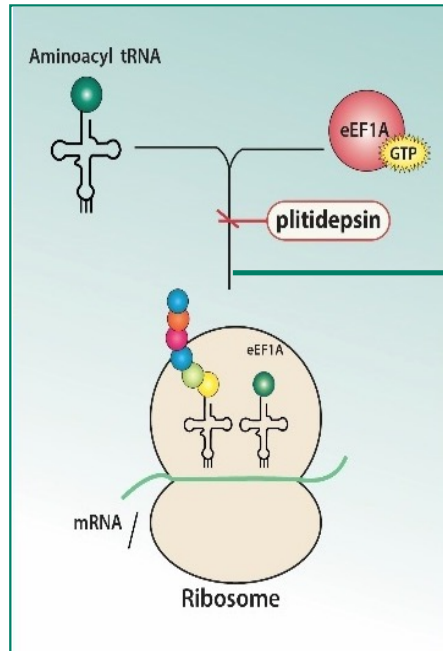
Electron Microscopy & Immunogold staining







Sasche *et al.* 2022, **Antiv. Res.**



Research Article

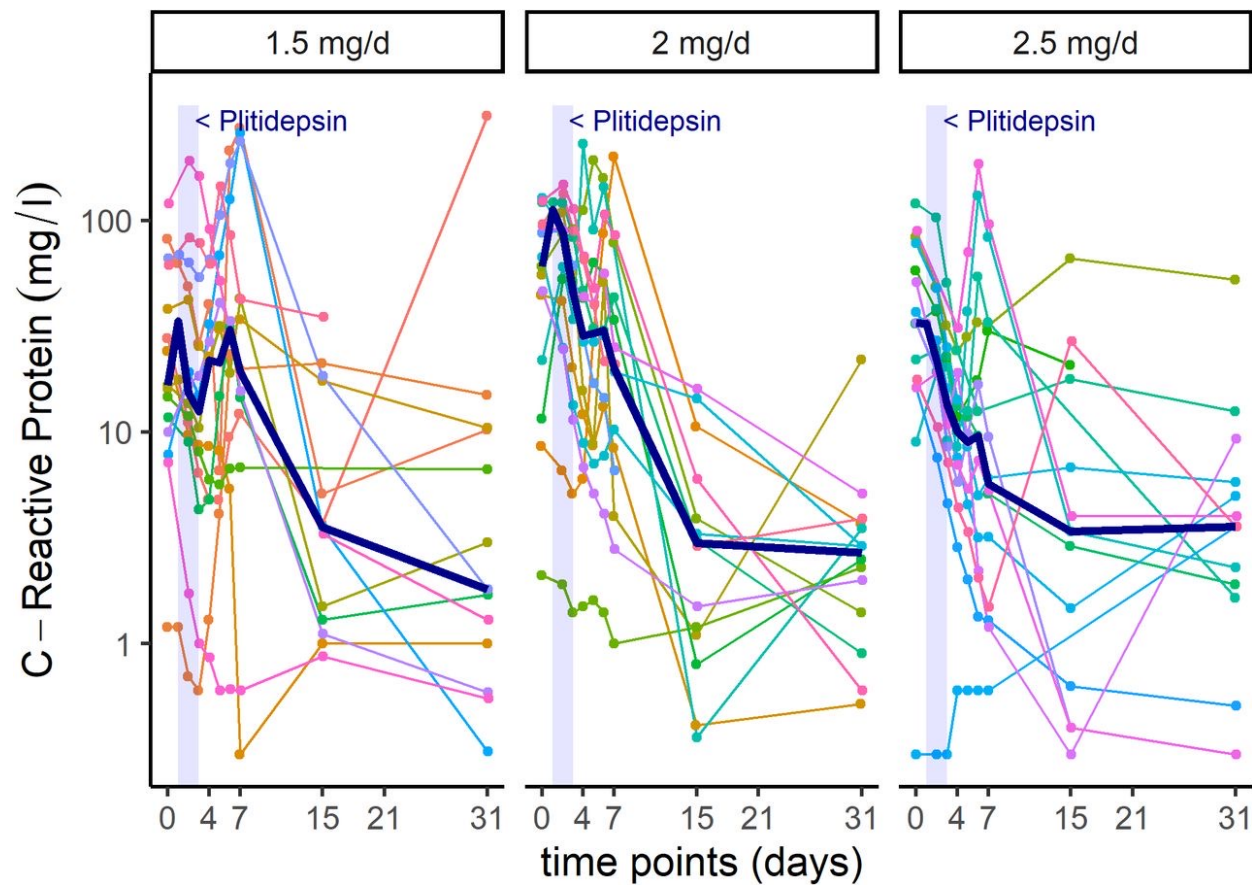


Preclinical and randomized phase I studies of plitidepsin in adults hospitalized with COVID-19

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- Plitidespin showed to be **safe** in CoVID-19 patients at 1.5mg, 2mg or 2.5mg per day for 3 days.
- **Viral load** was reduced.
- **Phase II/III** studies currently running

Intra-patient time-course variation in C-Reactive Protein, per dose-cohort.



Jose F Varona et al. LSA 2022;5:e202101200

Understand if Plitidepsin has an effect on long-COVID risk

1. Early treatment in non-hospitalized patients
2. Long-term impact in hospitalized treated patients



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