

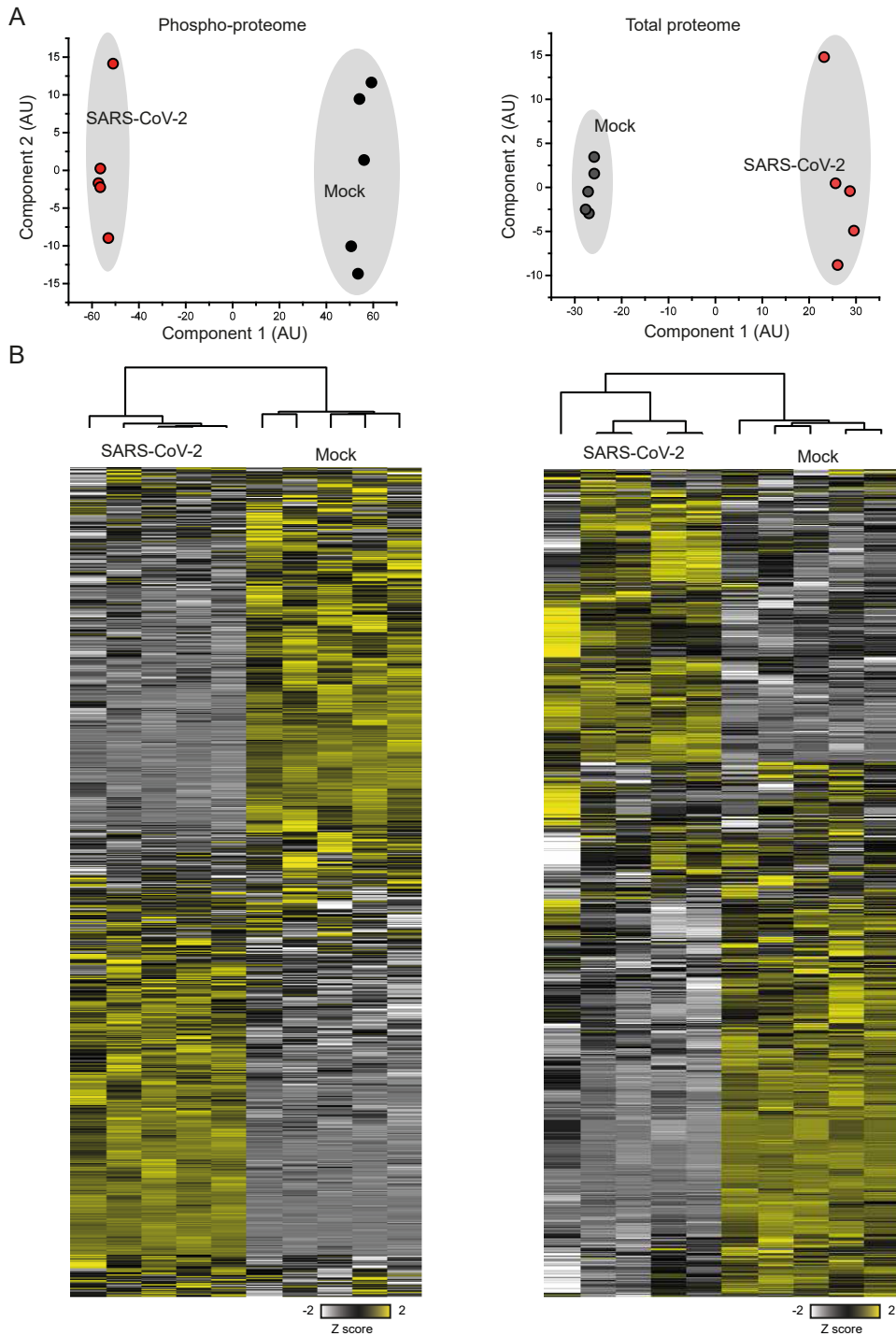
**Molecular Cell, Volume 80**

**Supplemental Information**

**Growth Factor Receptor Signaling Inhibition**

**Prevents SARS-CoV-2 Replication**

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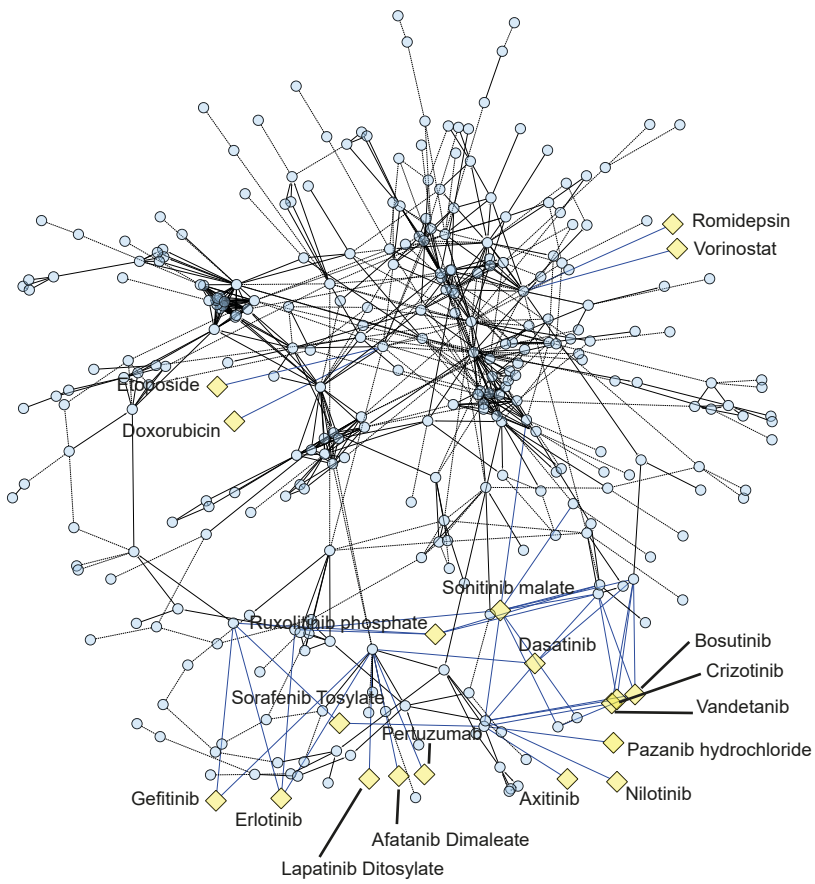


**Supplementary Fig. 1. Quality control of proteome datasets, Related to Figure 1.**

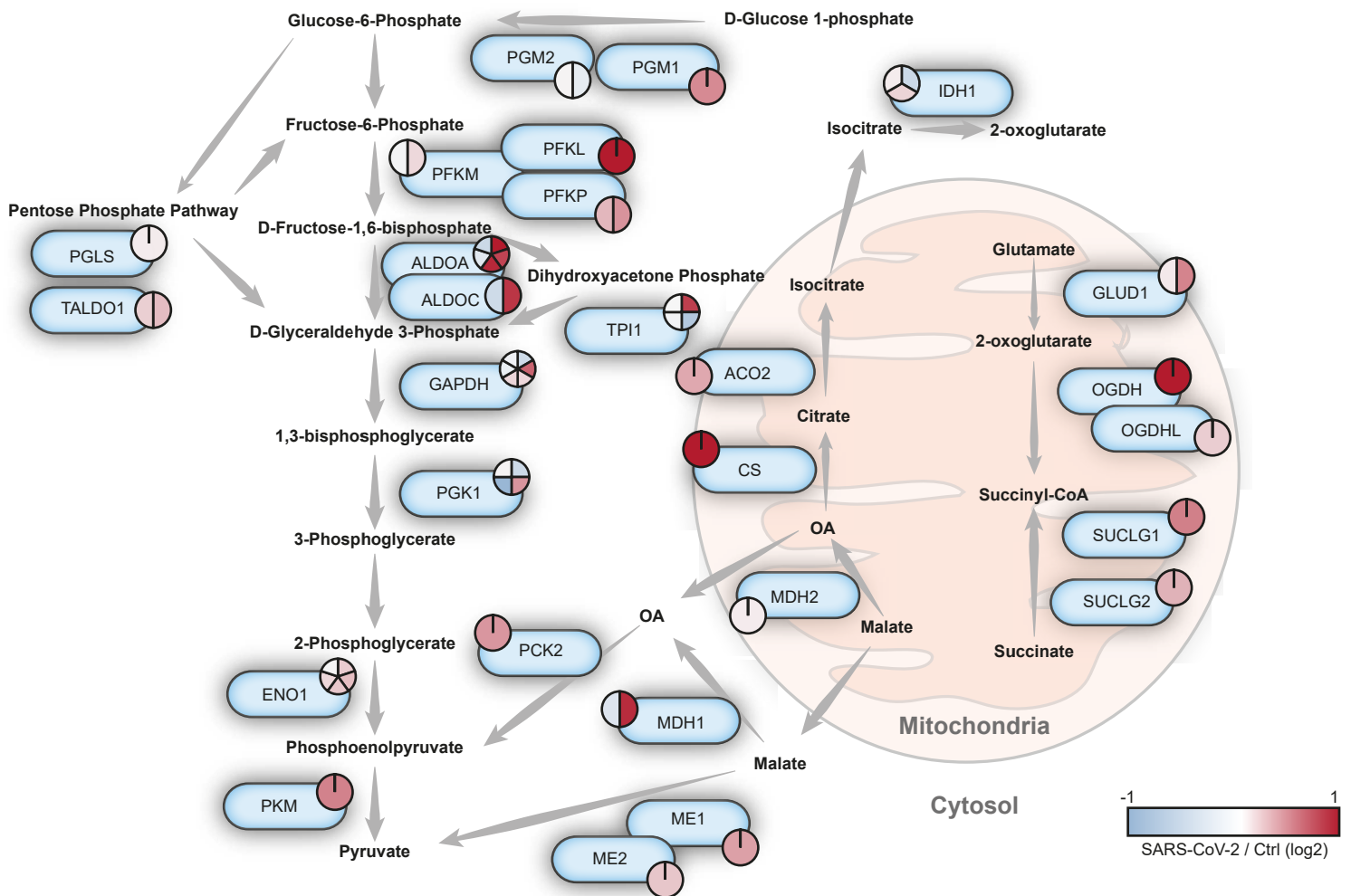
(A) Principal component analyses for phospho- and total proteomes. All quantified phosphopeptides or proteins were log<sub>2</sub> transformed and principal component analysis performed in Perseus. Projections were exported and plotted.

(B) Heatmaps for phosphoproteome (left) and total proteome (right). All quantified measurements were Z scored and hierarchical clustering carried out with Euclidean distance measure.

A

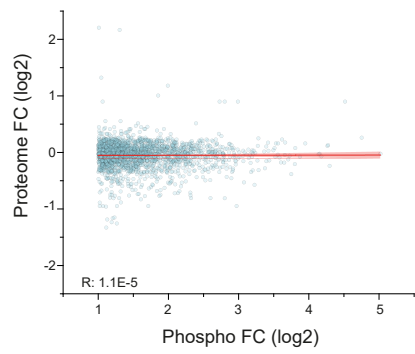


**Supplementary Fig. 2. Drug-target network analysis of proteins with significantly decreased phosphorylation, Related to Figure 2.** ReactomeFI network was built from all proteins found significantly decreased in phosphorylation ( $\log_2 < -1$ ,  $FDR < 0.05$ ) and overlaid with available drugs. Blue circles indicate proteins, yellow rectangles identified drugs, and lines functional interactions.



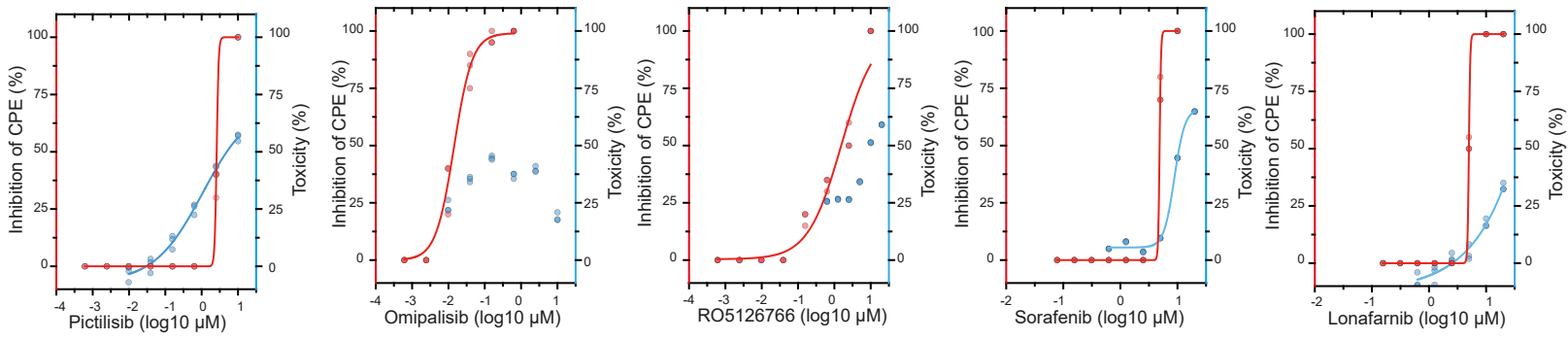
### Supplementary Fig. 3: Reprogramming of carbon metabolism upon SARS-CoV-2 infection, Related to Figure 2.

Representation of carbon metabolism pathways. All proteins for which changes in phosphorylation upon SARS-CoV-2 infection could be quantified were indicated. Pie charts show fold changes in individual phospho-sites, colour coded according to the extent to which individual phosphorylation site increased or decreased.



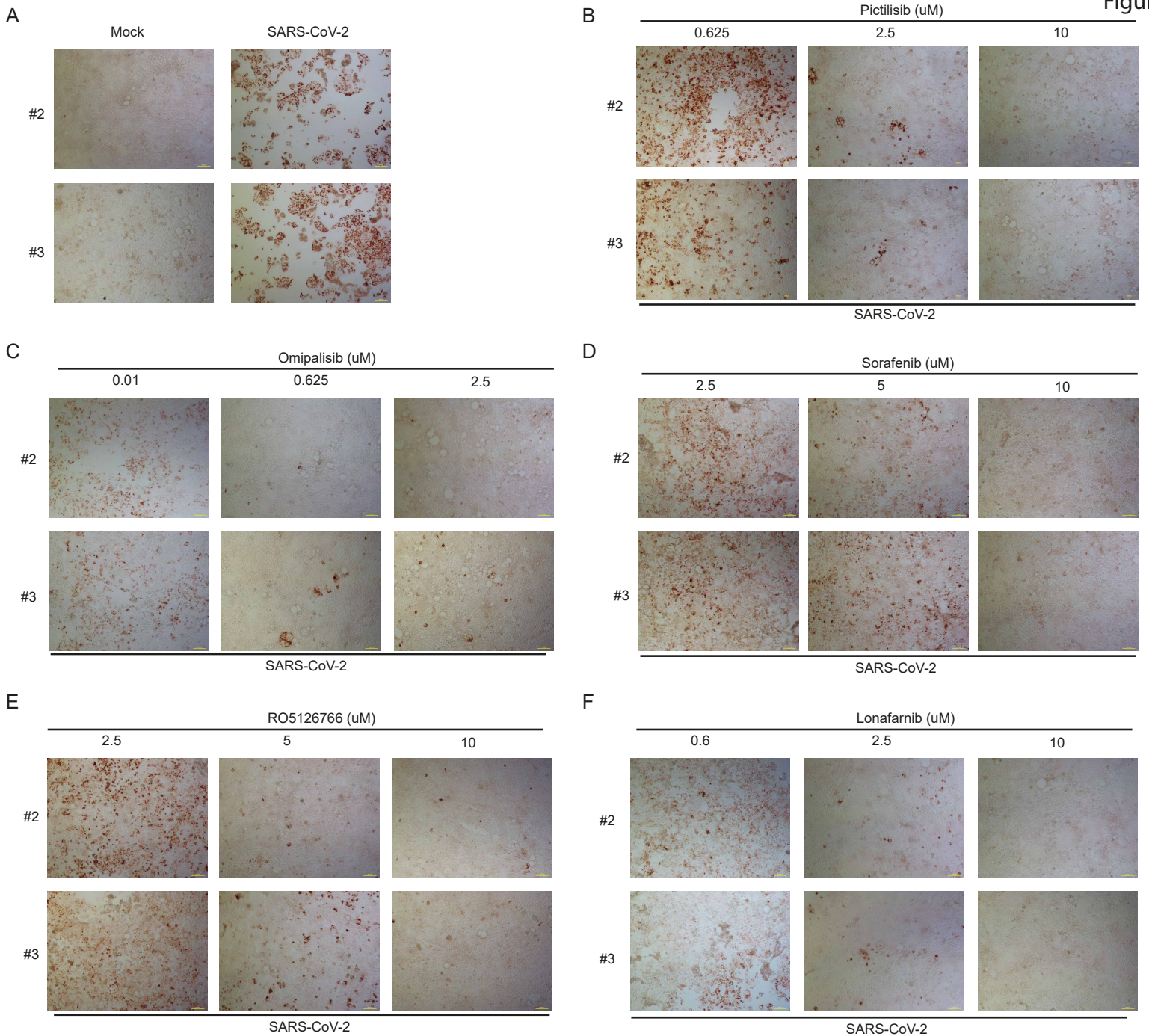
**Supplementary Fig. 4. Scatter plot showing phosphopeptide fold changes in comparison to corresponding protein changes for proteins part of the EGFR network, Related to Figure 3.**

Red line with shade indicates linear fit. No correlation between the two datasets could be observed.



**Supplementary Fig. 5. Cytotoxicity data for all tested inhibitors overlaid with CPE data from Figure 4B, Related to Figure 4.**

Cells were plated and incubated with dose series of different inhibitors. Cytotoxicity was assessed by rotitest vital (N = 3 biological replicates). Red points/axis indicate inhibition of CPE through different inhibitor concentrations. Blue points/axis represent percentage of dead cells compared to control.

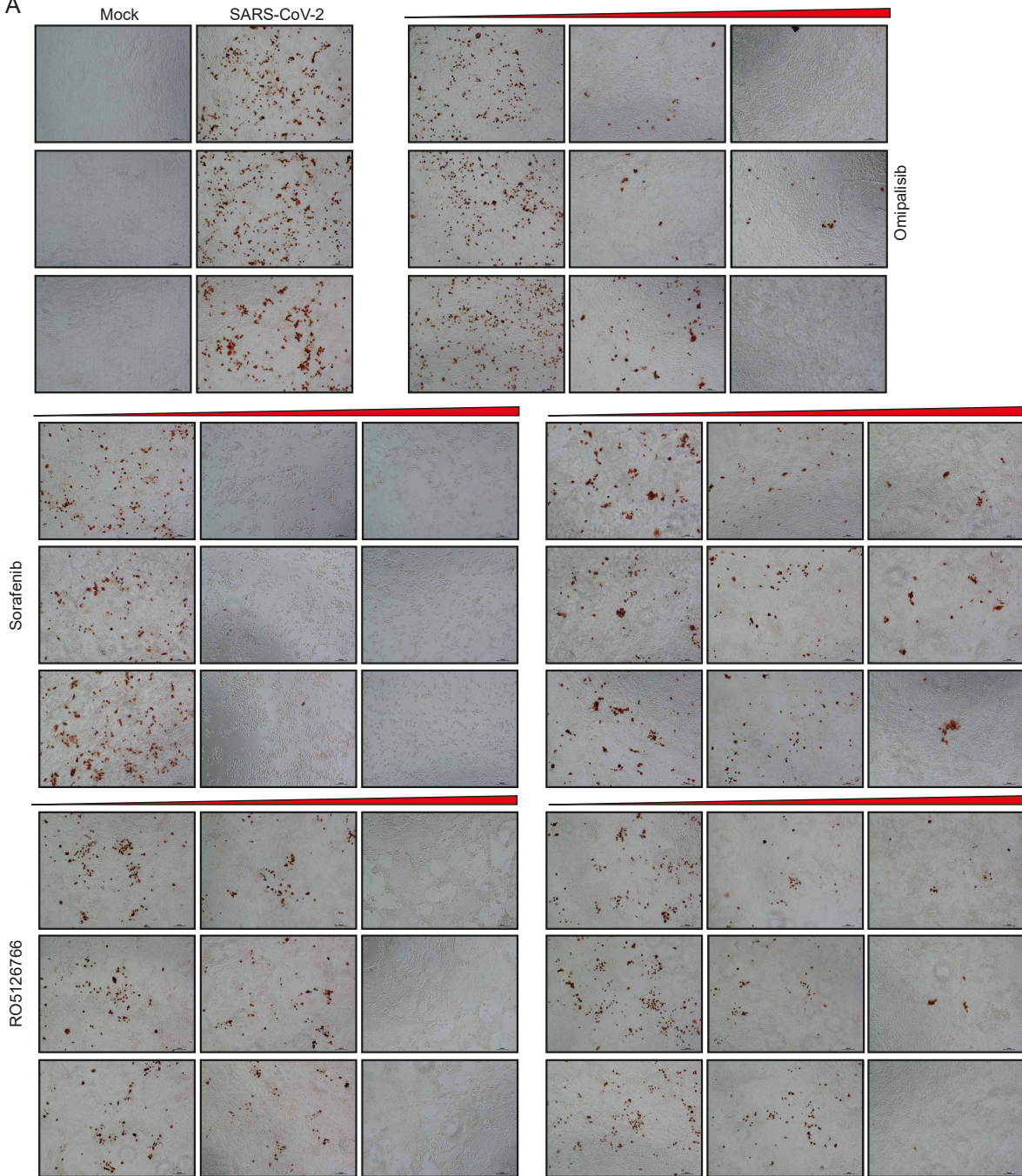


**Supplementary Fig. 6. Replicate stainings of dsRNA of SARS-CoV-2 infected cells with and without different inhibitors of GFR signalling, Related to Figure 4.**

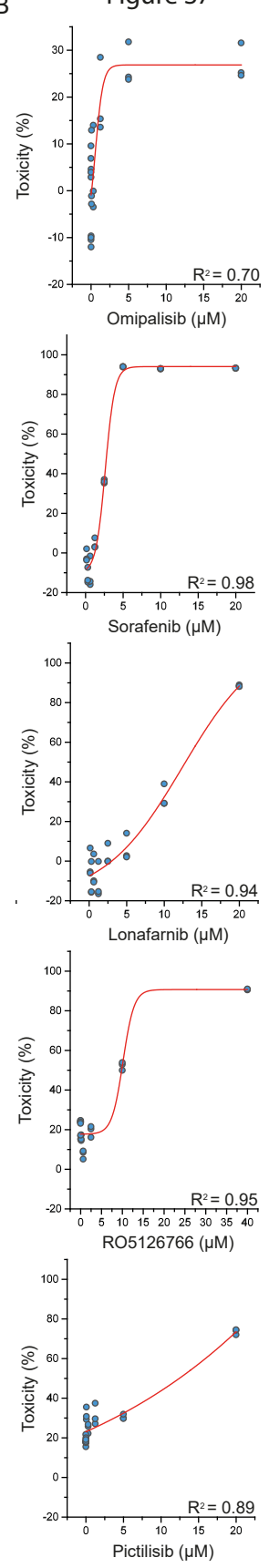
(A) Mock and infected cells after 24 hours of incubation.

(B-F) SARS-CoV-2 infected cells with different concentrations of different signaling inhibitors. (B) pictilisib, (C) ompalisib, (D) sorafenib, (E) RO5126766 and (F) lonafarnib. Stainings were performed for dsRNA. Scale bar represents 100  $\mu$ M. Replicates represent technical replicates to visualize a larger area.

A



B



**Supplementary Fig. 7. Compound assays with SARS-CoV-2 infected UKF-RC-2 cells, Related to Figure 4.**

(A) dsRNA staining of UKF-RC-2 cells mock infected, infected with SARS-CoV-2 alone or in combination with three different concentrations of the indicated drugs. Different dosages are indicated left to right (omipalisib: 0.08, 0.3, 1.25; sorafenib: 1.25, 2.5, 5; lonafarnib: 1.25, 2.5, 5; RO5126766: 0.6, 2.5, 10; pictilisib: 0.3, 1.25, 5; All concentrations are given in [μM]). Replicates represent technical replicates, to visualize a larger area. Scale bar represents 100 μm.

(B) Cytotoxicity assays of UKF-RC-2 cells treated with increasing concentrations of omipalaisib, sorafenib, lonafarnib, RO5126766 or pictilisib (N = 3). Red line indicates curve fit. R2 values for curve fit are given.