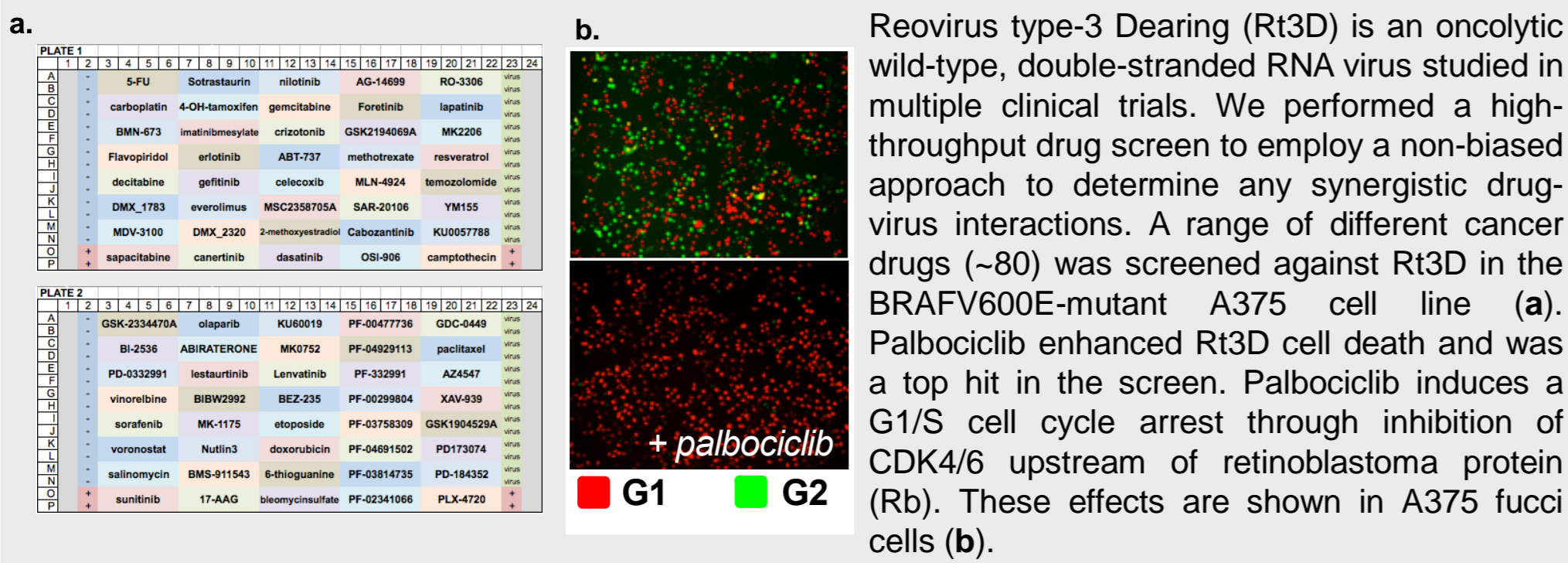


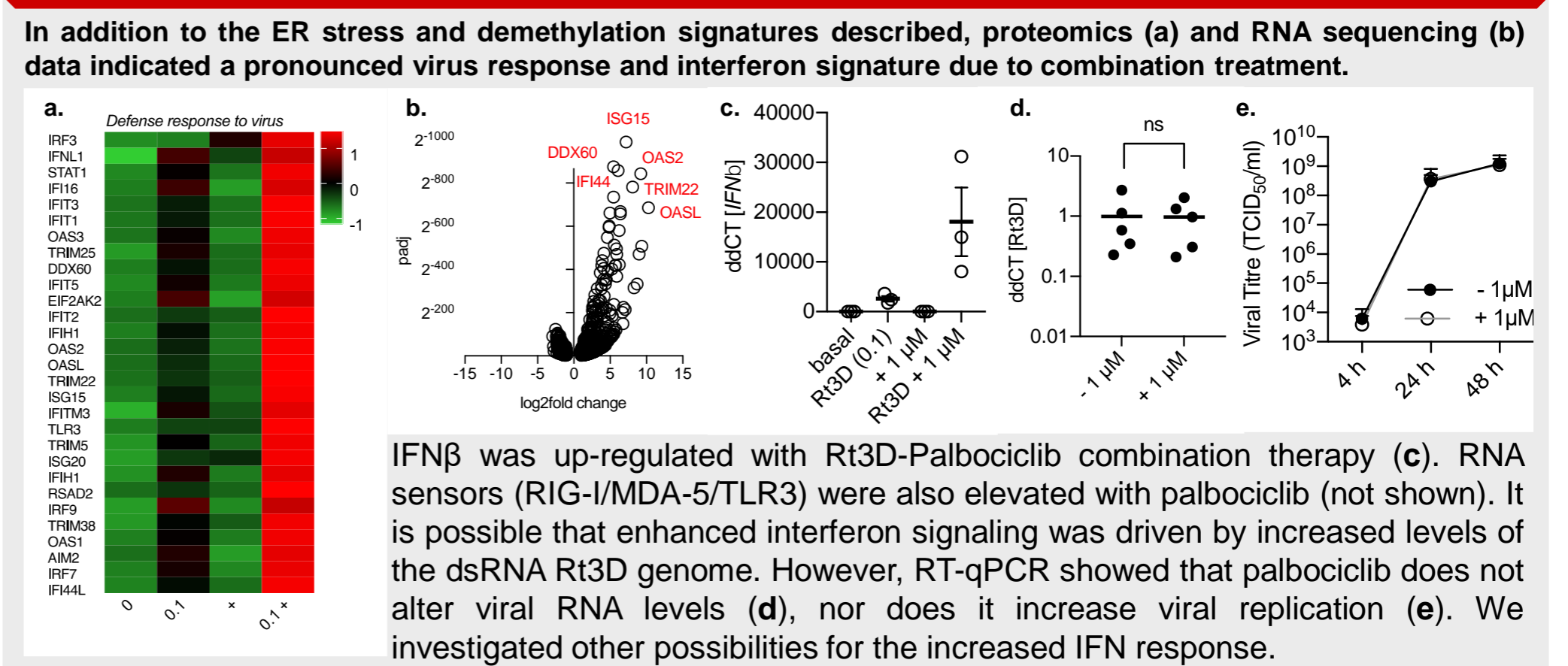
Mechanisms of therapeutic synergy between pattern recognition response agonists and CDK4 inhibitors

Victoria Roulstone*, Joan Kyula*, Richard Elliott, Christopher J. Lord, Nik Matthews, Vicki Jennings, Harriet Whittock, David Mansfield, Jyoti Choudhary, James Wright, Lu Yu, Alan Melcher, Richard Vile, Hardev Pandha, Grey Wilkinson, Matt Coffey, Martin McLaughlin*, Kevin Harrington*. Targeted Therapy Team, The Institute of Cancer Research, London, UK.

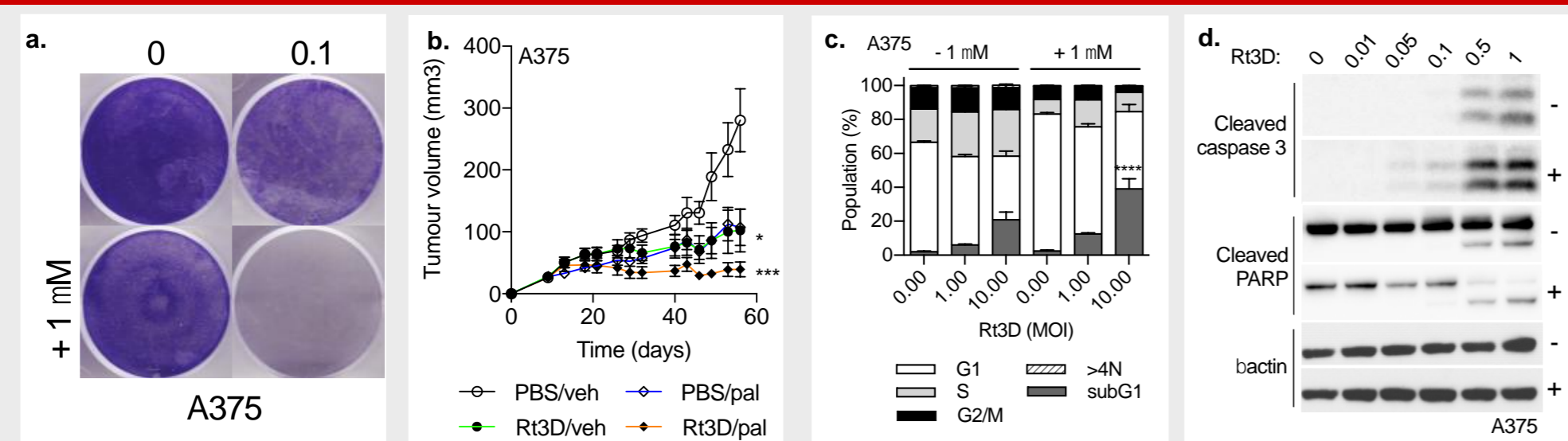
Palbociclib enhances the anti-cancer efficacy of the oncolytic virus Rt3D



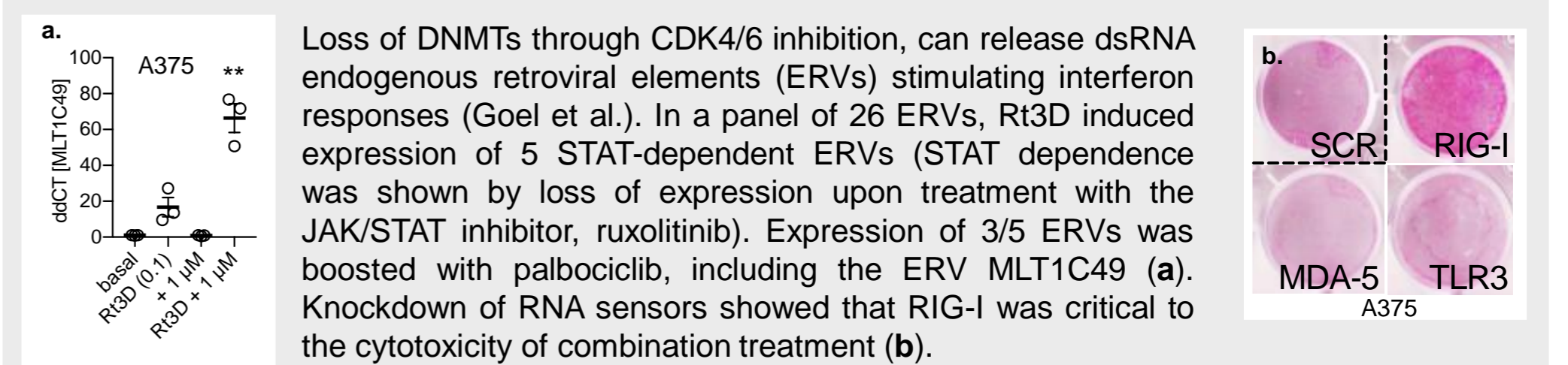
Palbociclib potentiates interferon signalling in A375



Validation of Rt3D in combination with palbociclib

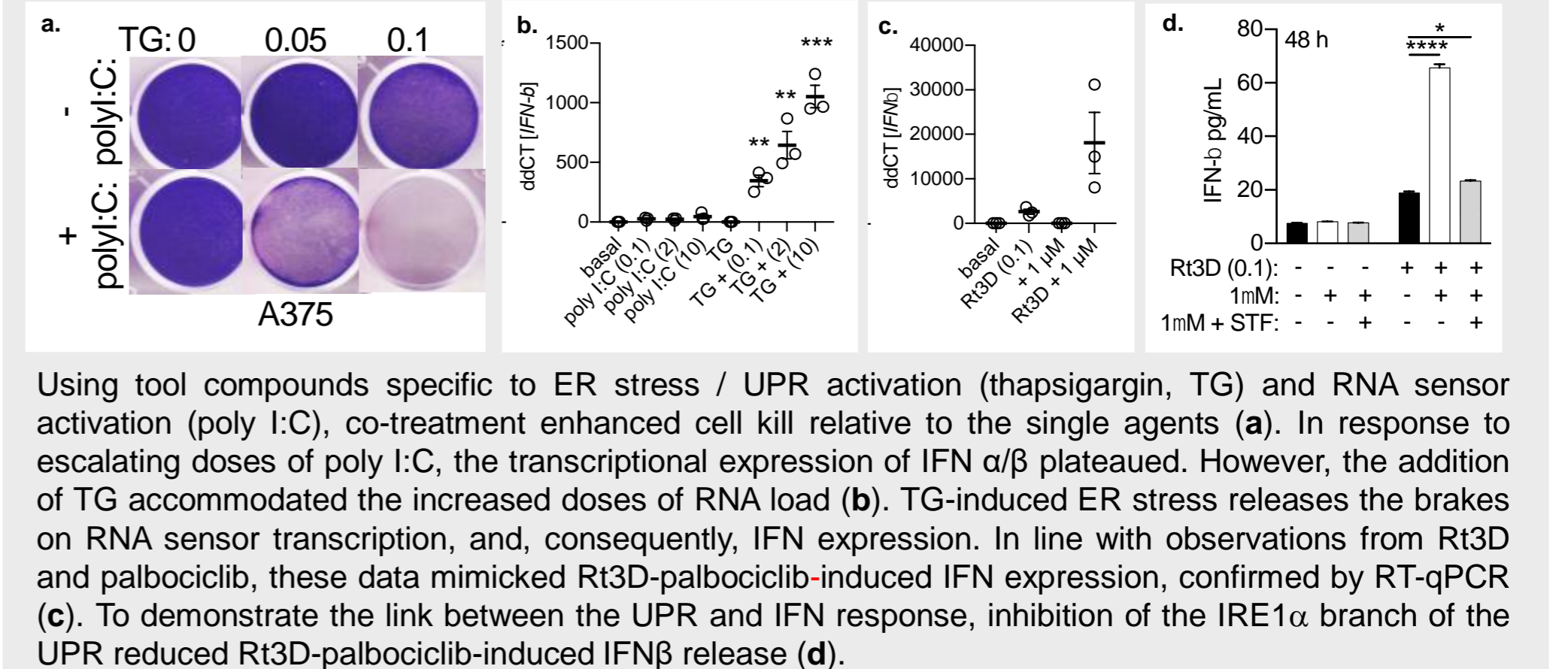


Rt3D plus palbociclib therapy enhance ERV expression



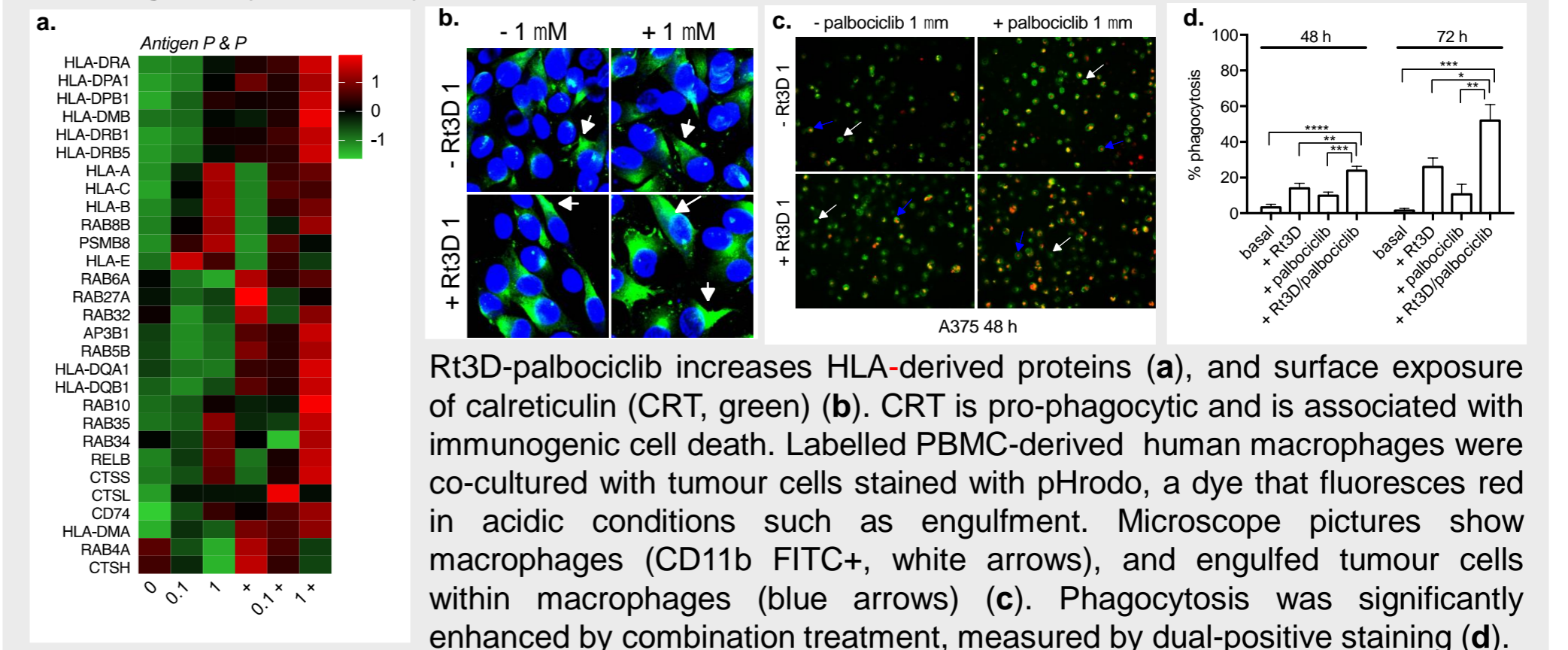
ER stress enhances RNA sensor-driven interferon responses

At this point we suspected a link between the unfolded protein response (UPR) and cytoplasmic dsRNA sensing. Complicating this, each single agent impacted multiple cellular processes.



Combination therapy enhances innate immune activity

We hypothesized that enhanced dsRNA sensing and ER stress may also enhance the immunogenicity of therapy.



Summary

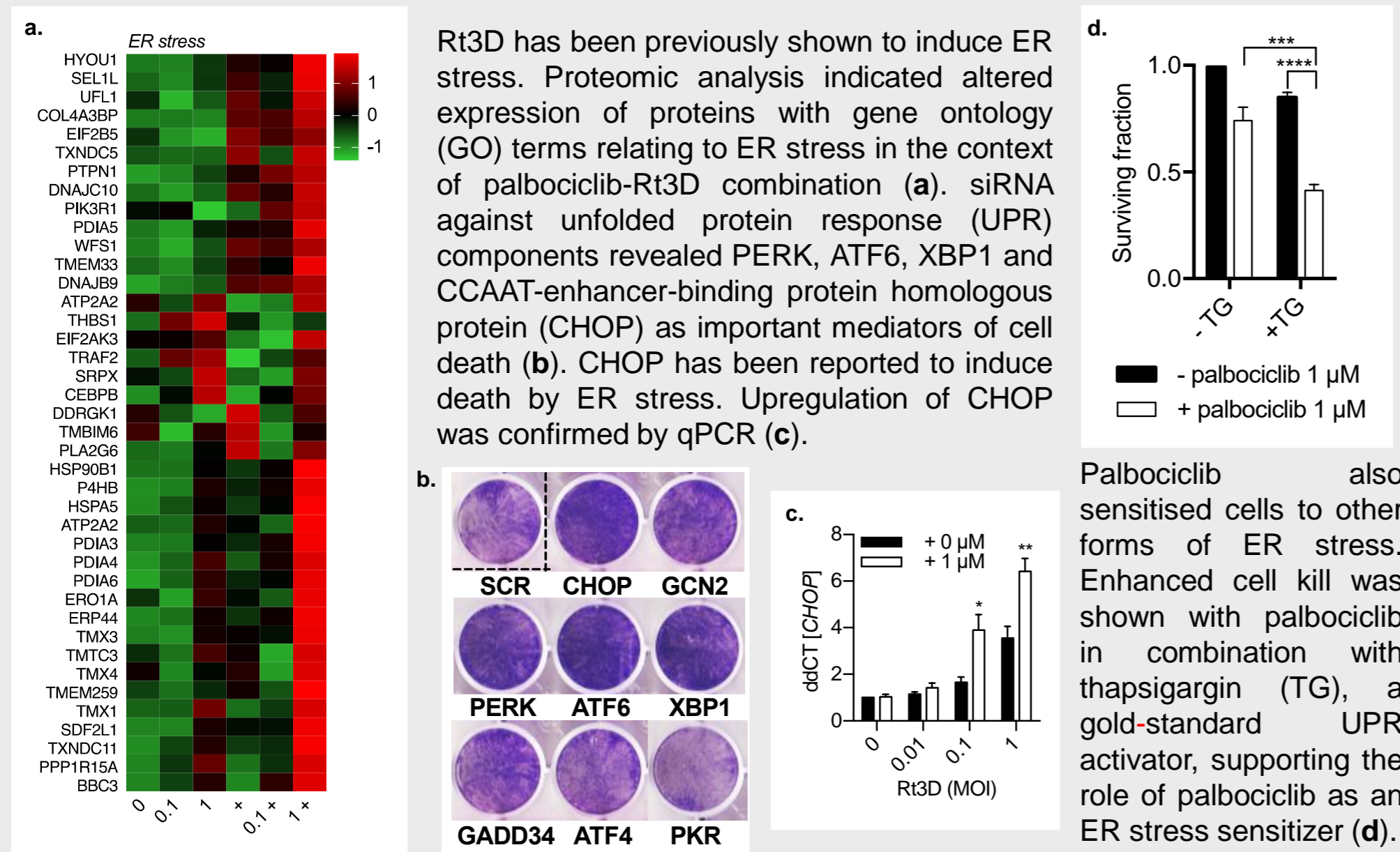
Oncolytic viruses are an attractive treatment option because they are self-amplifying, kill through multiple mechanisms and have good potential to promote anti-tumour immune responses.

- Combinatorial therapy of Rt3D plus palbociclib was identified by a high-throughput drug screen.
- Palbociclib altered cell cycle dynamics and DNA methylation, while Rt3D activated interferon signaling via RIG-I. In addition, both agents appeared to have non-overlapping ER stress profiles.
- The combination, however, enhanced ER stress, potentiated ISG-induction, ERV liberation and phagocytosis *in vitro*.

Our pre-clinical data show a strong rationale for the combination of Rt3D with novel pharmacological inhibitors, such as the CDK4/6 inhibitor palbociclib.

Palbociclib aggravates ER stress.

To understand the mechanistic interaction, we analysed the proteome in A375 BRAF-mutant melanoma treated with Rt3D plus palbociclib.



Palbociclib causes extensive DNA modification

