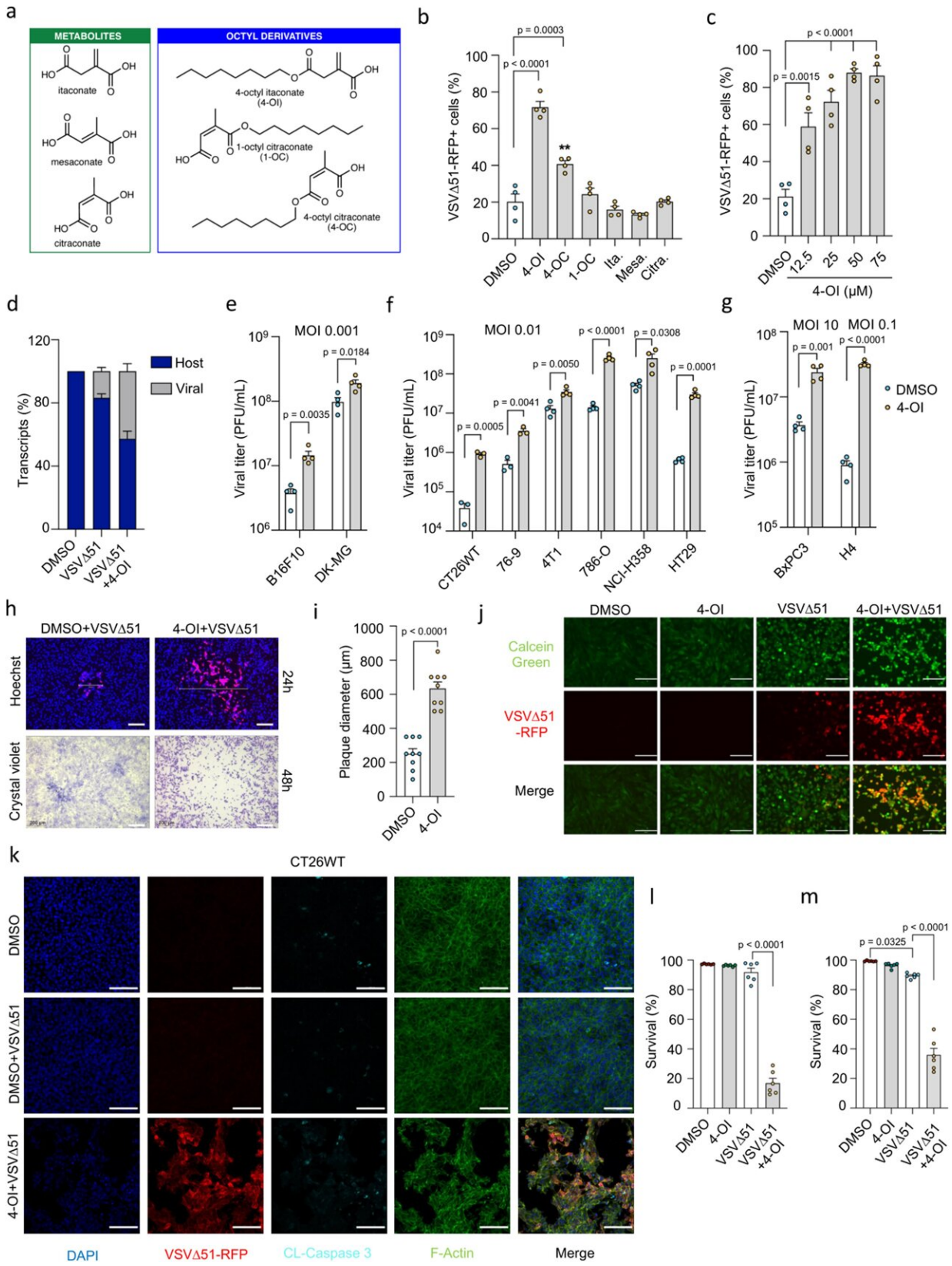
Breakthrough research makes cancer-fighting viral agent more effective

June 28 2024


a
METABOLITES
OCTYL DERIVATIVES
itaconate
mesaconate
citraconate
4-octyl itaconate (4-OI)
1-octyl citraconate (1-OC)
4-octyl citraconate (4-OC)
b
VSVΔ51-RFP+ cells (%)
p = 0.0003
p < 0.0001
**
DMSO
4-OI
4-OC
1-OC
Ita.
Mesa.
Citra.
c
VSVΔ51-RFP+ cells (%)
p < 0.0001
p = 0.0015
DMSO
12.5
25
50
75
4-OI (μM)
d
Transcripts (%)
Host
Viral
DMSO
VSVΔ51
VSVΔ51 +4-OI
e
MOI 0.001
Viral titer (PFU/mL)
p = 0.0184
p = 0.0035
B16F10
DK-MG
f
MOI 0.01
Viral titer (PFU/mL)
p = 0.0005
p = 0.0041
p = 0.0050
p < 0.0001
p = 0.0308
p = 0.0001
CT26WT
76-9
4T1
786-O
NCI-H358
HT29
g
MOI 10
MOI 0.1
Viral titer (PFU/mL)
p = 0.001
p < 0.0001
DMSO
4-OI
BxPC3
H4
h
DMSO+VSVΔ51
4-OI+VSVΔ51
Hoechst
Crystal violet
24h
48h
i
Plaque diameter (μm)
p < 0.0001
DMSO
4-OI
j
DMSO
4-OI
VSVΔ51
4-OI+VSVΔ51
Calcein Green
VSVΔ51 -RFP
Merge
k
CT26WT
DMSO
DMSO+VSVΔ51
4-OI+VSVΔ51
DAPI
VSVΔ51-RFP
CL-Caspase 3
F-Actin
Merge
l
Survival (%)
p < 0.0001
DMSO
4-OI
VSVΔ51
VSVΔ51 +4-OI
m
Survival (%)
p = 0.0325
p < 0.0001
DMSO
4-OI
VSVΔ51
VSVΔ51 +4-OI

4-OI promotes VSVΔ51 infection and oncolysis. Credit: *Nature Communications* (2024). DOI: 10.1038/s41467-024-48422-x

When a cancer cell doesn't respond to traditional therapies, doctors may turn to a sort of viral biological warfare, by deploying "troops" in the form of viral agents that are specifically engineered to target and eliminate cancer cells. The mode of attack is to transform the tumor into an immunologically "hot" environment, making it more visible and recognizable to our immune system.

Now, researchers from the Department of Biomedicine at Aarhus University have found a way to make one strain of viral agents even more effective. And the results are groundbreaking. Lead researcher, Associate Professor David Olagnier says, "We found that if we administer a specific viral agent called Vesicular Stomatitis Virus (VSVD51) along with a metabolite-drug called 4-Octyl-Itaconate (4-OI), we are able to treat cancers that are considered resistant to viral infections."

The research is published in the journal *Nature Communications*.

In other words, by combining the drug and the viral agent, the researchers have managed to push the door open to possible treatments for cancers that have been immune to nearly all known treatments, including the viral agents. This is because some cancers have antiviral signaling, which enables them to combat the viral agents and resist the treatment.

The results are particularly surprising because the drug 4-OI has, in other combinations, shown to have the completely opposite effect on different types of viruses. 4-OI is normally antiviral—meaning it would actually

stop viruses rather than boost them. But in this specific combination, 4-OI instead helps the cancer fighting viral agents to work better.

"It is the combination of the specific virus and the drug that brings about a completely unique proviral effect, which potentially can have a significant impact on patients affected by cancer that we are currently unable to treat," explains Olagnier.

The new findings are an important step towards a new form of treatment, and they underline the need for consistently working to find new ways to treat the many forms of cancer we face, says Olagnier.

"Cancer is not a single disease but rather a hundred diseases with one name, so it is crucial that we develop multiple ways to eradicate the disease. The use of biologically active viral agents can potentially be a gamechanger for some currently incurable cancers. That's why our findings are so exciting and groundbreaking," he explains.

For the research team, the next step is a more extensive pre-clinical testing of the combinational use of VSVD51 and 4-OI.

"We are especially interested in testing this combination on tumors that have metastasized, which is when the cancer has started to spread, but also on liquid types of cancer like lymphomas," explains Olagnier.

More information: Octyl itaconate enhances VSVΔ51 oncolytic virotherapy by multitarget inhibition of antiviral and inflammatory pathways, *Nature Communications* (2024). Naziia Kurmasheva et al, Octyl itaconate enhances VSVΔ51 oncolytic virotherapy by multitarget inhibition of antiviral and inflammatory pathways, *Nature Communications* (2024). DOI: 10.1038/s41467-024-48422-x