EHDV-TAU, a novel oncolytic virus

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Clinical Indication: Tumors with defects in IFN/JAK/STAT responses

- Size of target population: ~ 10 % of all cancers are suspected of having inactivating mutations in JAK-STAT signaling.
- Patients which relapse immunotherapy (acquired resistance to checkpoint immunotherapy: currently a population of unknown size) present defects in IFN/JAK/STAT signaling.
- We have identified gene-expression signatures for prediction of susceptibility to EHDV-TAU that may serve to calculate size of target population.
- We have verified the presence of this signature in sizable populations of different cancer cell types: e.g., bladder, melanoma, prostate cancers.

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Modality

- EHDV-TAU is a candidate stand-alone agent for oncolytic immune-virotherapy and promising agent for immunotherapy combinations.

Stage of Development of EHDV-TAU

In vitro experiments with multiple cell lines (human and murine) of tumors of different origins. Experiments show that EHDV-TAU is:

- Specific towards tumors defective in cell-autonomous immune responses;
- Potent;
- Kills cells by different processes including apoptosis and necroptosis,
- Stimulates secretion of immuno-stimulatory cytokines/chemokines.

In vivo experiments in pre-clinical models with immunocompetent and immunodeficient mice show that EHDV-TAU is:

- Safe
- Efficient in inhibition of growth of directly-treated and distant tumors (abscopal effect)
- Capable of enhancing tumor-infiltration of immune-effector cells.

In silico gene expression analyses identify sizeable portions of patients with tumors of different origins that exhibit signature of predicted susceptibility to EHDV-TAU

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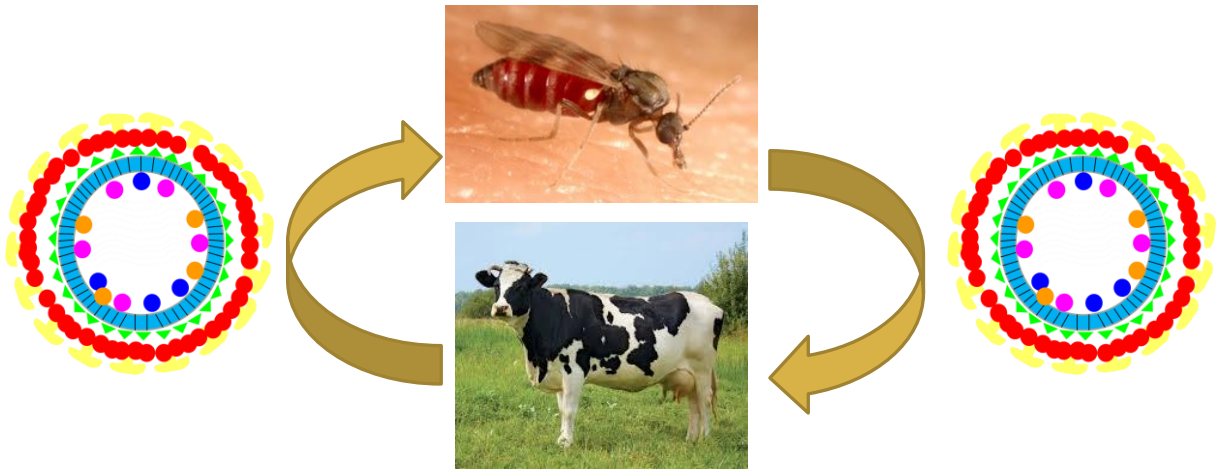
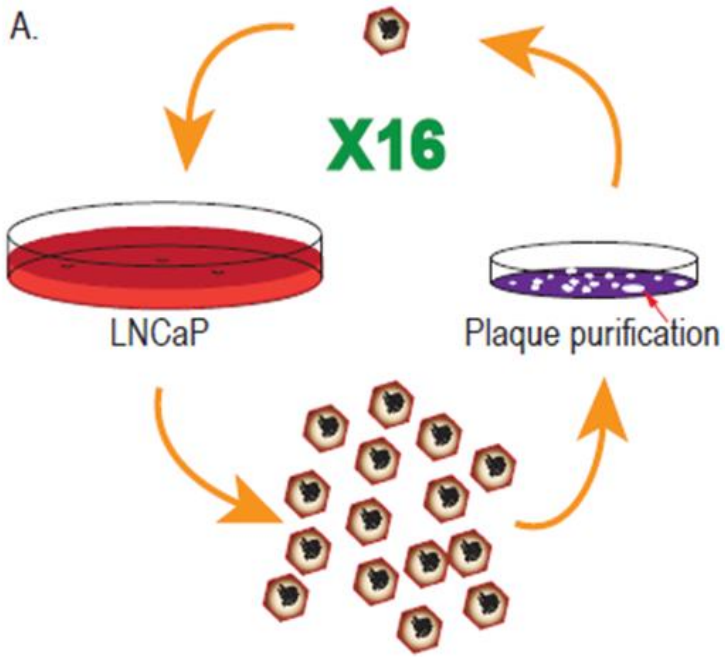
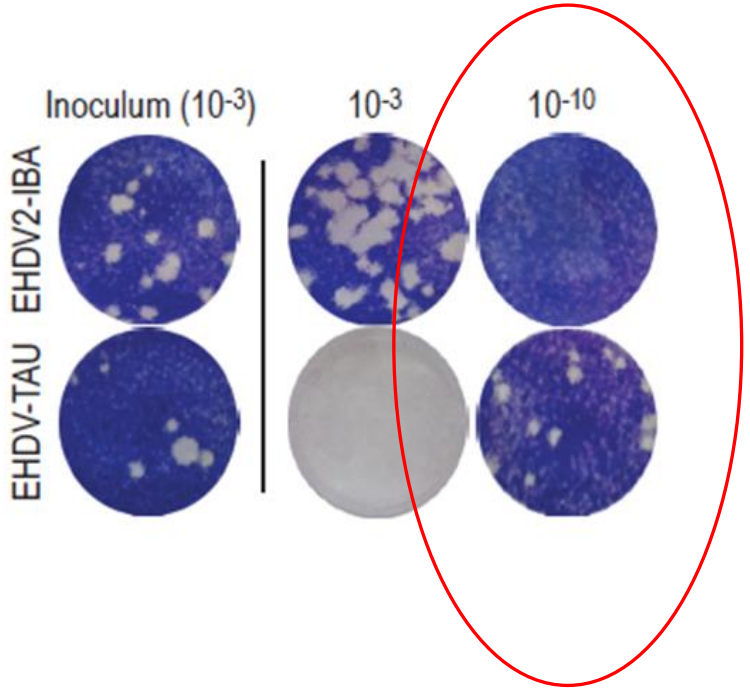
Our novel agent: Epizootic Hemorrhagic Disease Virus-Tel Aviv University



- Veterinary Arbovirus (no pre-existing neutralizing immunity, no host-to-host transmission)
- *In vitro* evolution in interferon-defective human cancer cells
- Kills cancer cells through different processes (apoptosis, necroptosis)
- Replicates to high titers in cancer cells but not normal cells
- Potent stimulator of immunity (e.g., via dsRNA genome or cytolytic cell death)
- Kills subset of immunocompetent cells via Oncolysis By Non-Productive Viral Infection (ONPVI)
- Stimulates secretion of immune-modulatory cytokines/chemokines

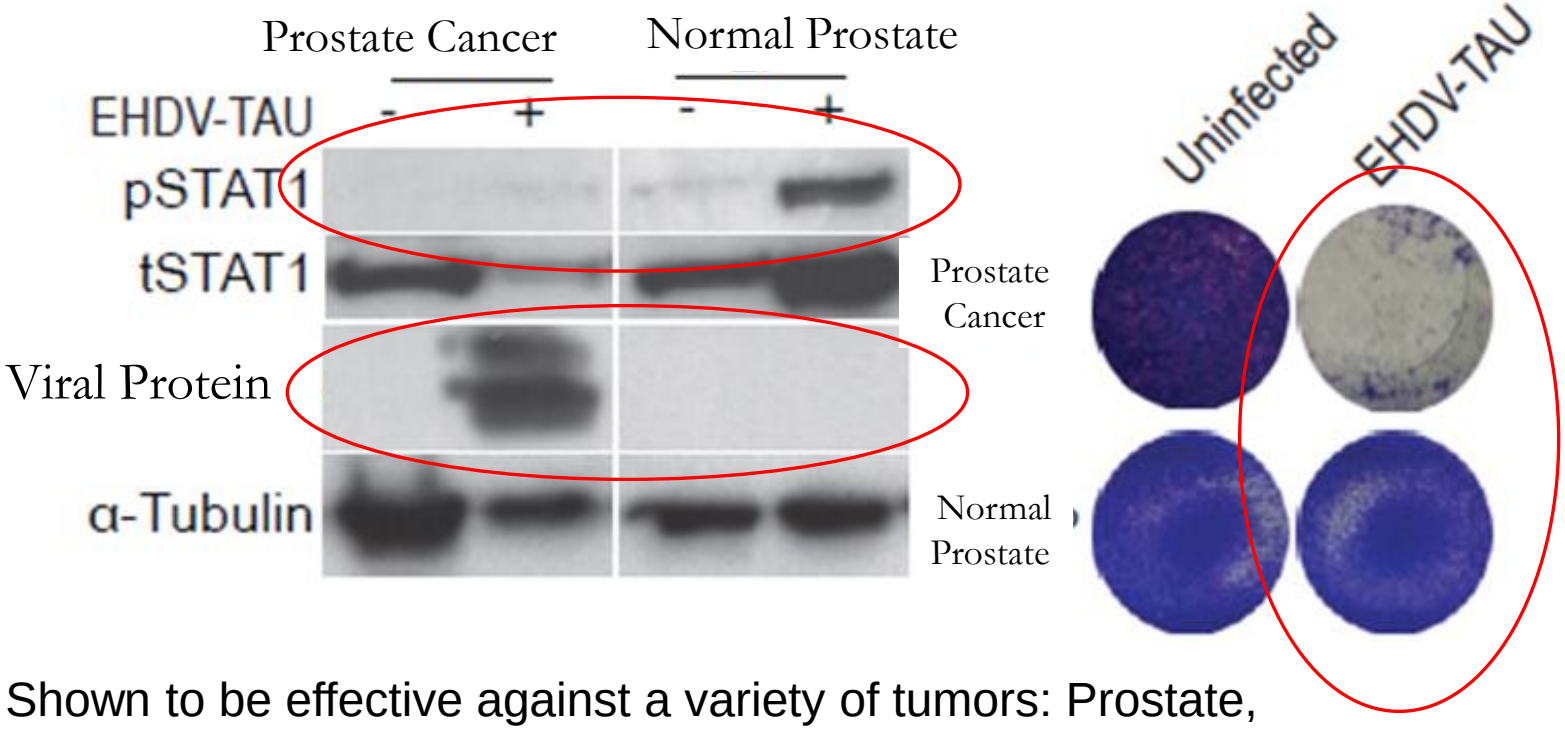
In vitro evolution results in million-fold increase in titer in human cancer cells





Danziger et al., 2016

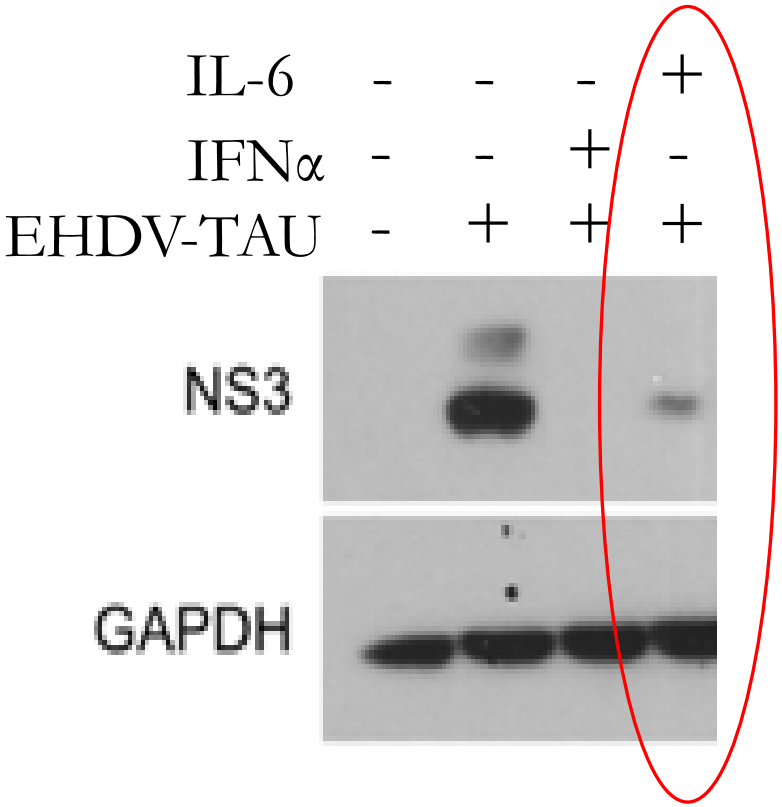
Specificity: EHDV-TAU replicates in, and kills, cancer cells while sparing normal cells

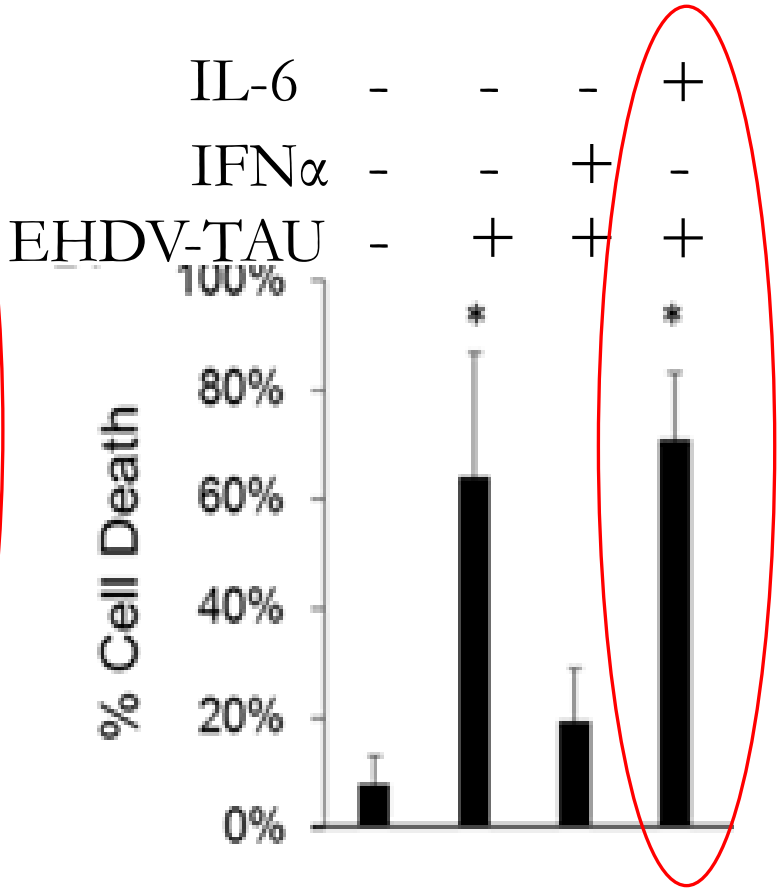


Shown to be effective against a variety of tumors: Prostate, Melanoma, Bladder, Ovarian, Lung, Breast, Glioblastoma, Astrocytoma, Osteosarcoma

Danziger et al., 2016

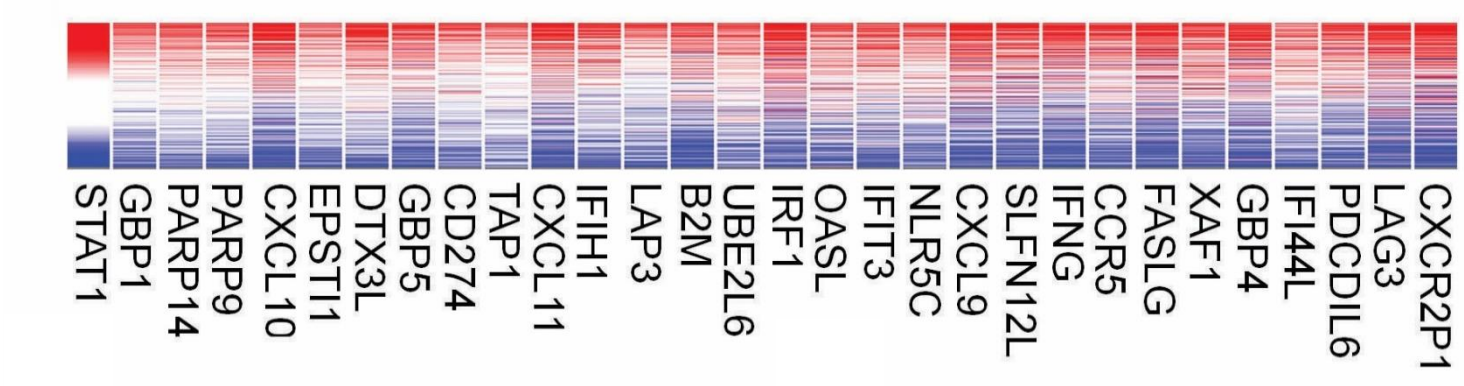
Uniqueness: Kills a subset of cancer cells by Oncolysis by Non-Productive Viral Infection (ONPVI) in presence of inflammatory cytokines





Danziger et al., 2018

STAT1 signature correlates with susceptibility to EHDV-TAU: the case of melanoma



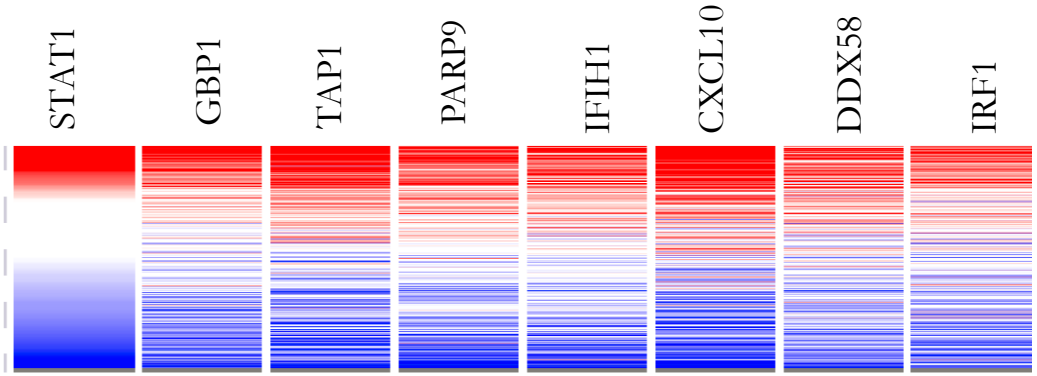
702 genes with Spearman's Correlation Coefficient > 0.5

Correlated Gene	Cytoband	Spearman's Correlation	p-Value
APOL6	22q12.3	0.889842704	4.48E-125
GBP1	1p22.2	0.878994185	3.70E-118
PARP9	3q21.1	0.846922468	4.62E-101
CXCL10	4q21.1	0.829799532	1.80E-93

PANTHER Pathways	**Fold Enrichment**	**+/-**	**raw P value**	**FDR**
T cell activation	9.33	+	1.99E-15	3.27E-13
Inflammation	4.77	+	3.44E-13	2.82E-11
JAK/STAT signaling	10.43	+	2.73E-04	7.45E-03

Dellac et al., 2021

STAT1 signature in Bladder Cancer



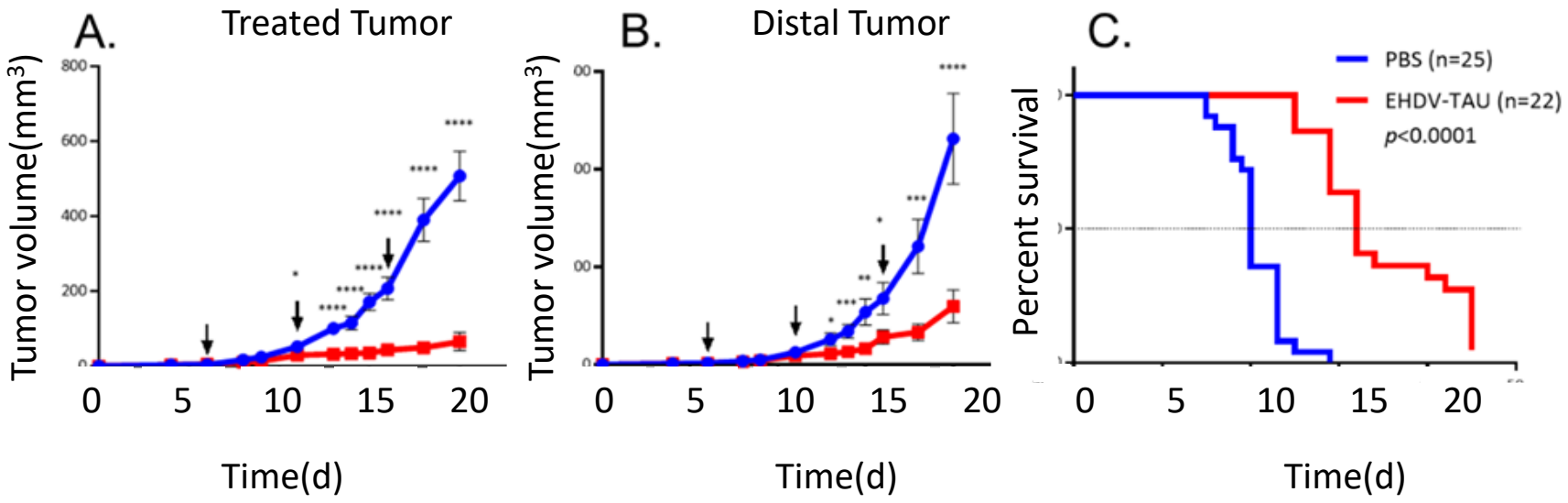
550 genes with Spearman's correlation > 0.5

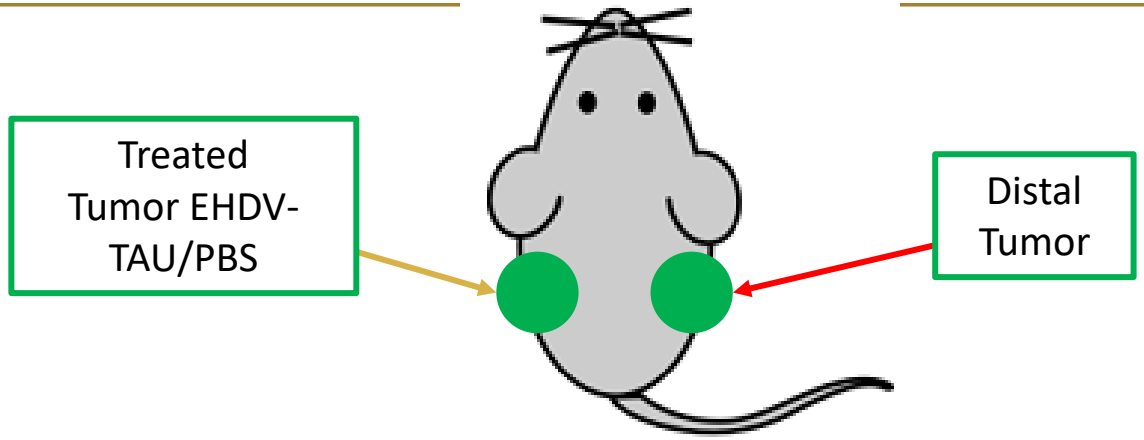
GBP1	1p22.2	0.856195	8.85E-117
PARP9	3q21.1	0.855037	3.89E-116
IFIH1	2q24.2	0.847893	2.74E-112
CXCL10	4q21.1	0.828691	7.35E-103

PANTHER Pathways	**Fold Enrichment**	**raw P value**
T cell activation	10.18	2.86E-16
Inflammation mediated by chemokine and cytokine signaling pathway	5.06	1.46E-13
Interleukin signaling pathway	5.21	9.07E-06
JAK/STAT signaling pathway	13.65	1.75E-05

In-vivo oncolysis and safety:

Direct and abscopal anti-tumor effects that prolong survival



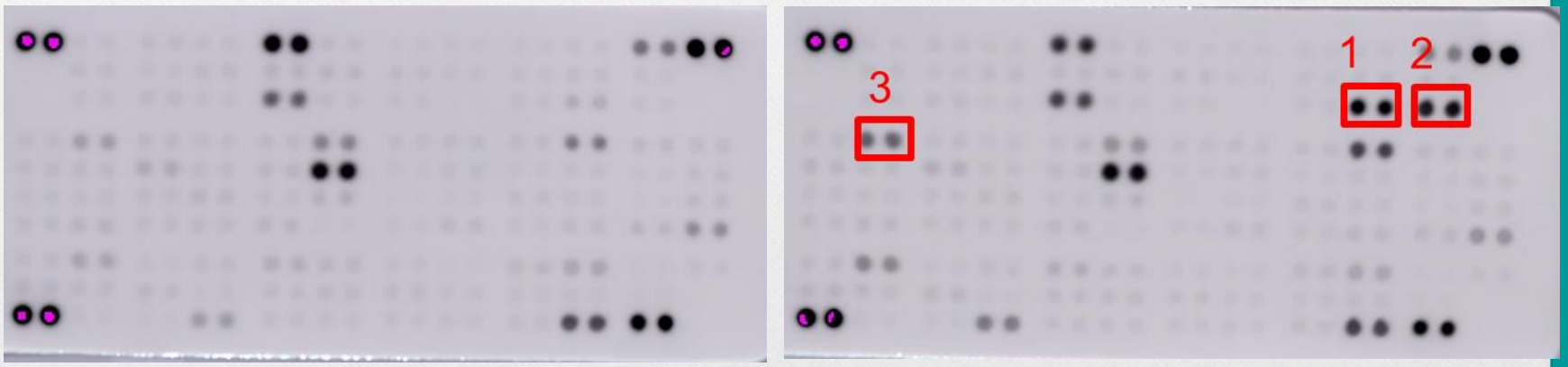


Dellac et al., 2021

Immuno-stimulation: Induces secretion of NK, Neutrophil and T-cell activating chemokines from infected cancer cells. Activates immune *cells ex-vivo*

Uninfected

Infected



Cytokine array identifies: CXCL1, CXCL2 and CXCL10 secretion by infected cells

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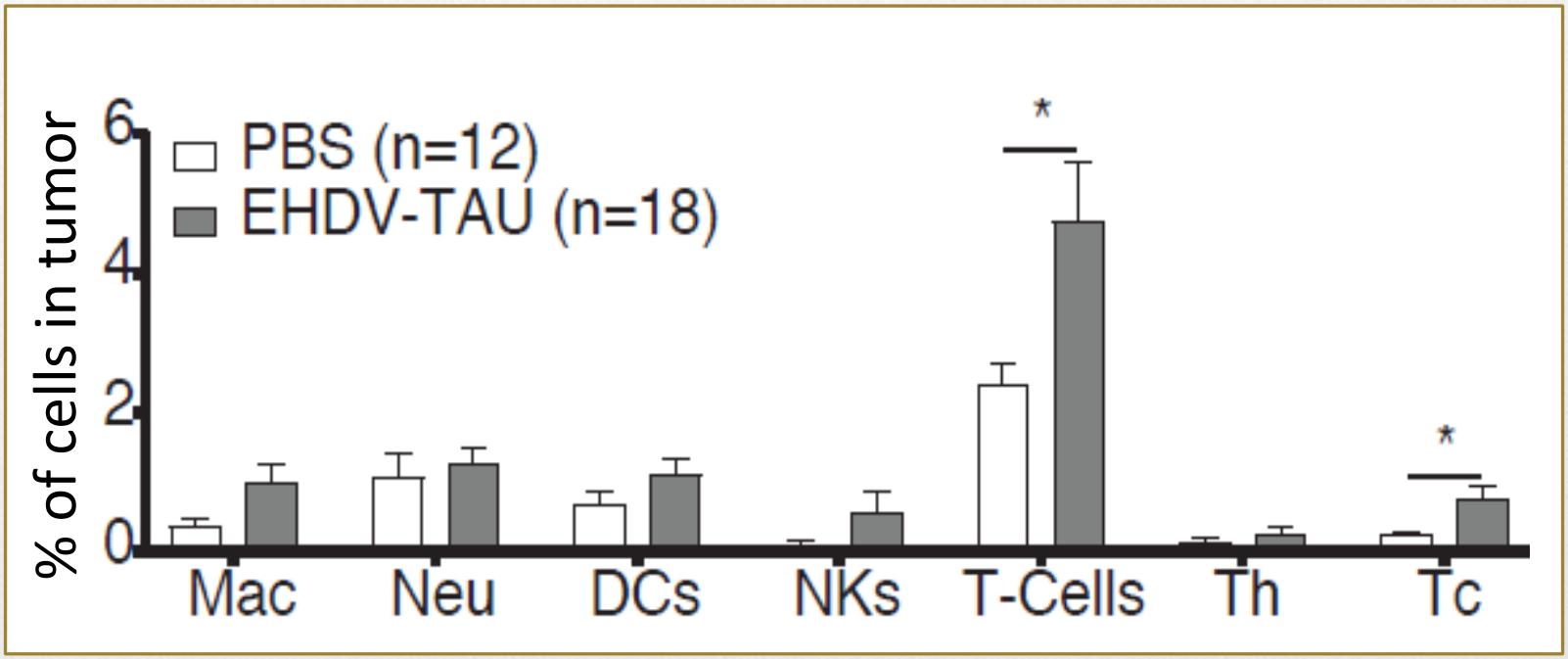
EHDV-TAU enhances immune-infiltrate (e.g. cytotoxic T-cells) in treated tumors



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Dellac et al., 2021

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