



Exploiting Poliovirus for the Treatment of Cerebral Malignancy

Molecular Determinants of Enterovirus Neuropathogenesis

Tropism

(gr. *τροπος*, to lean toward)

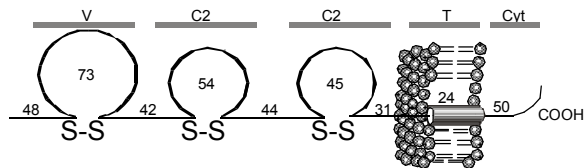
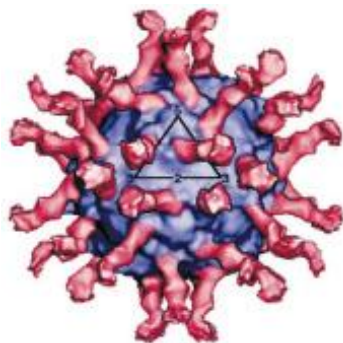
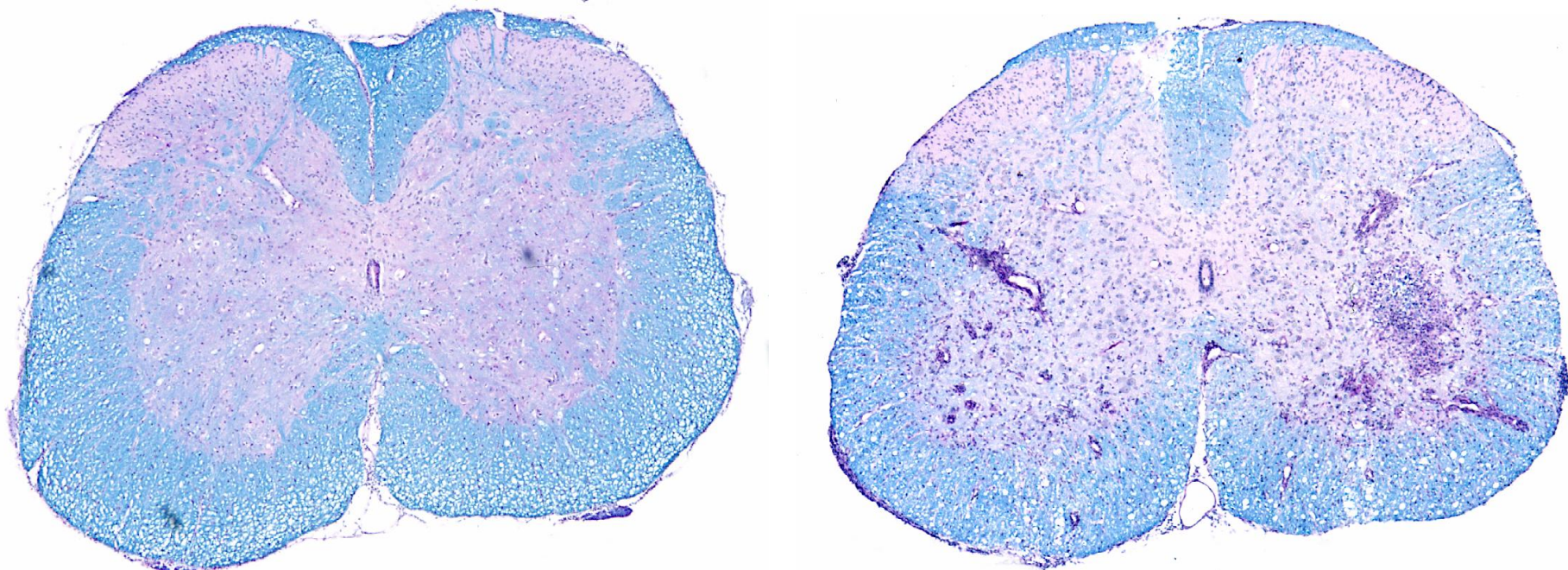
Virulence

(cell-internal factors influencing propagation/spread)

Condition of the host/Circumstance

(opportunity created by accident)

Does the poliovirus receptor CD155 restrict tropism to motor neurons?



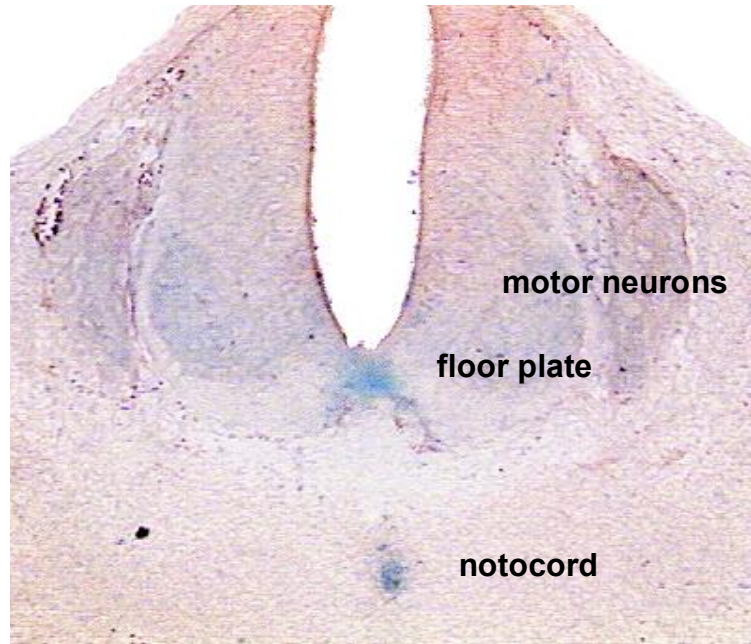
CD155 gene activation in the embryonic anterior neuraxis



CD155 upstream seq. **β -galactosidase** **SV40p(A)**

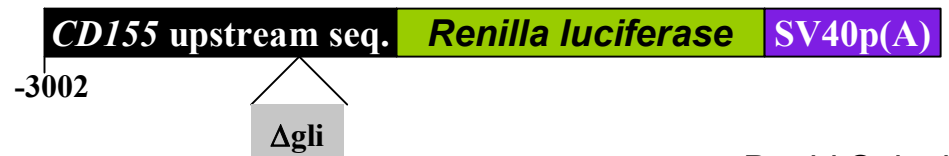
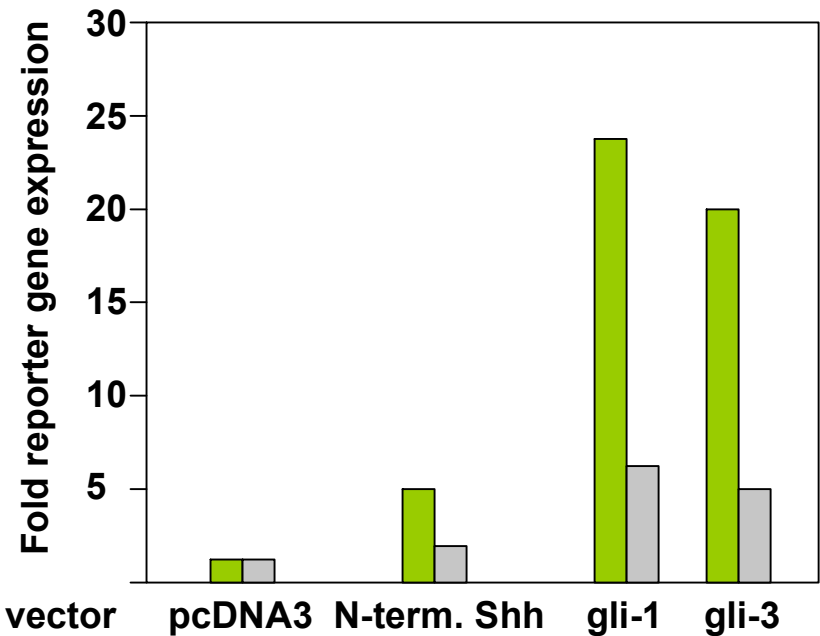
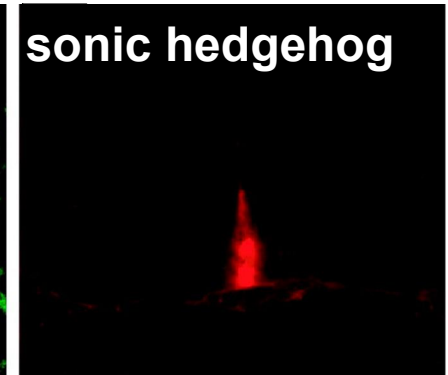
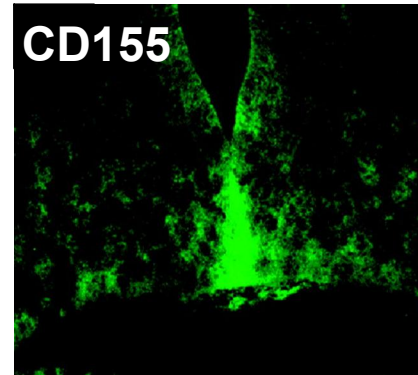
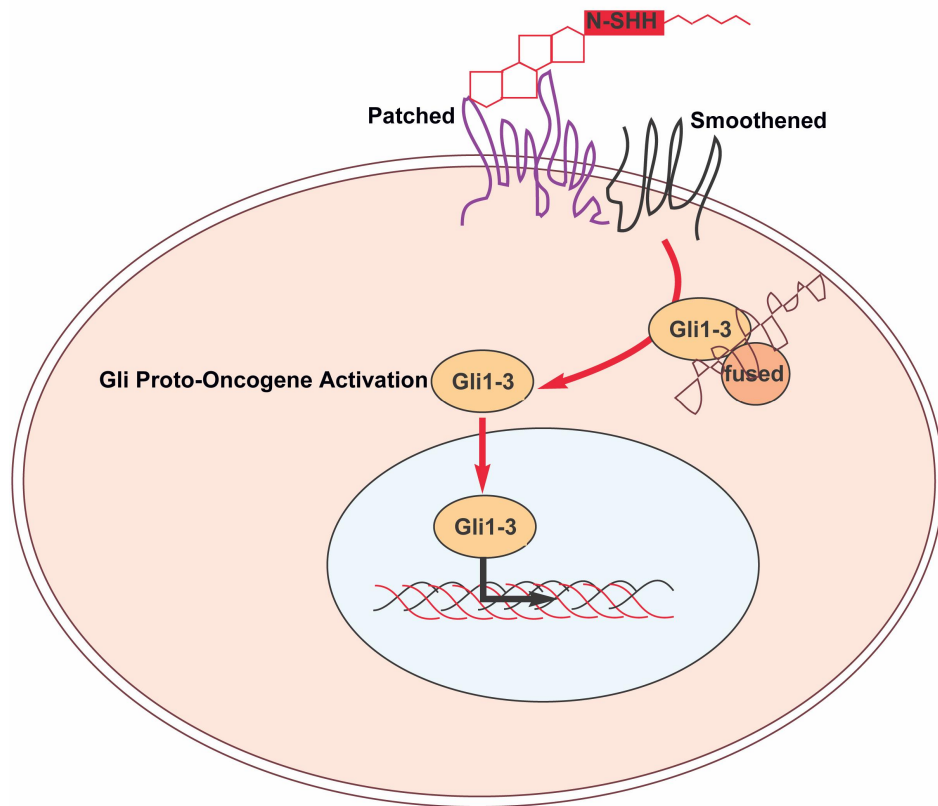
-3002

Sonic hedgehog

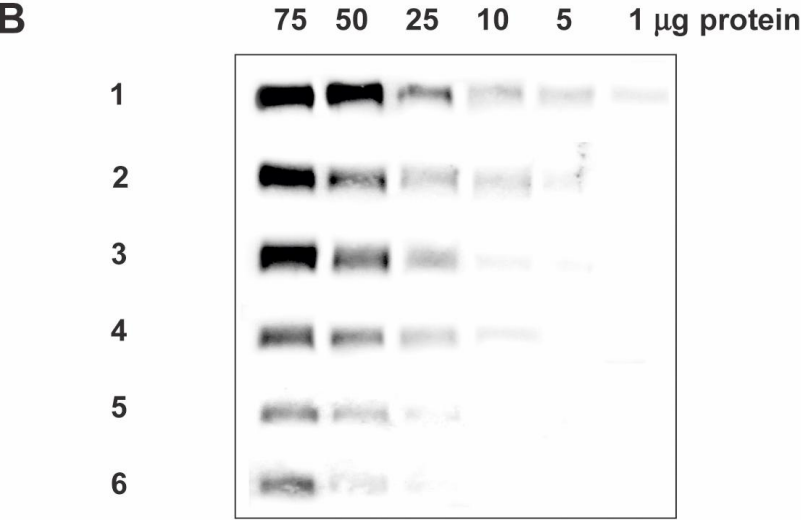
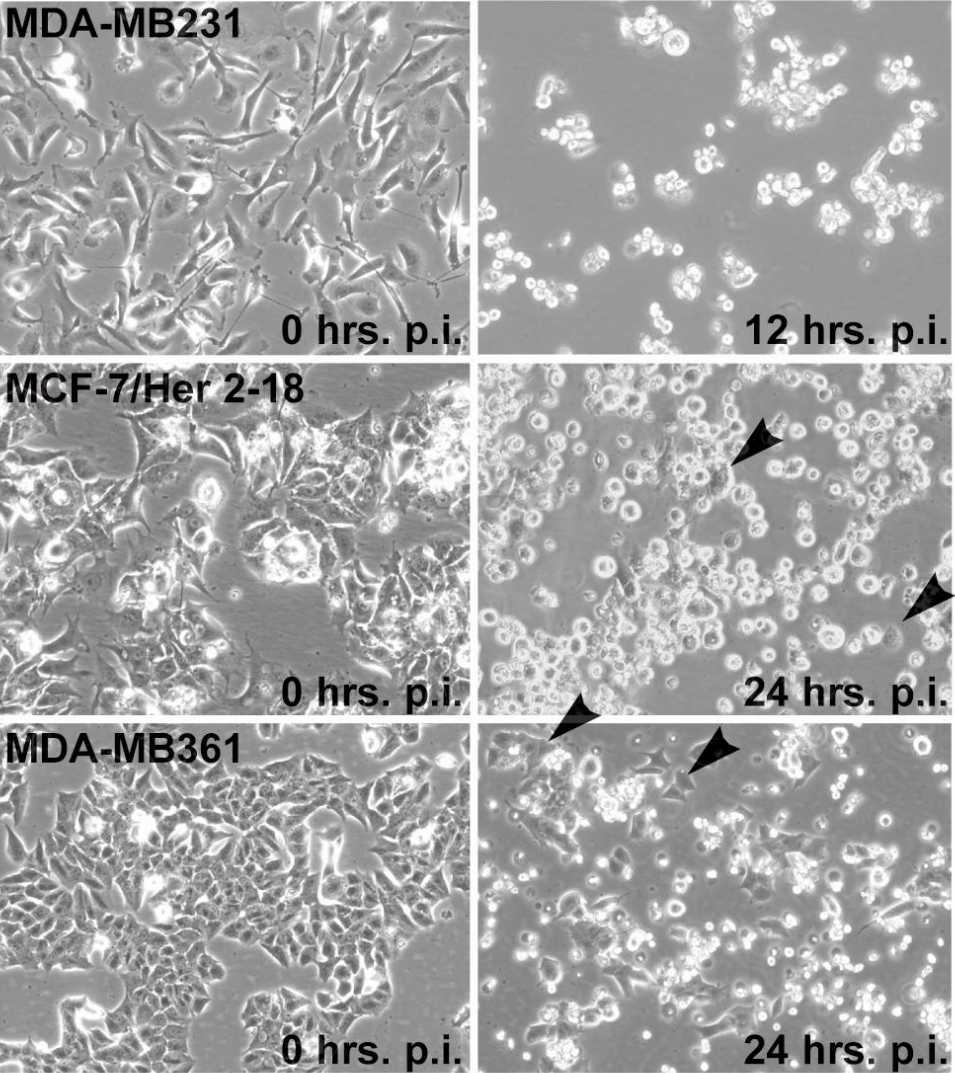
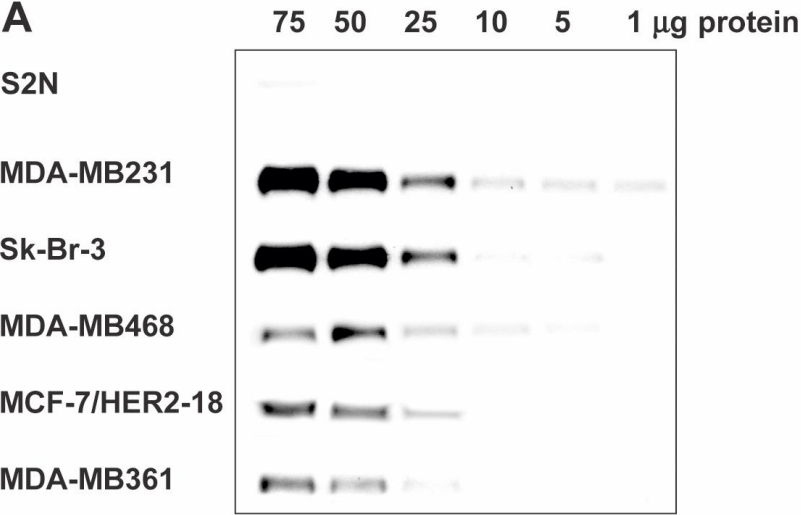


From: Ho, KS & Scott, MP,
Curr. Op. Neurobiol., 2002

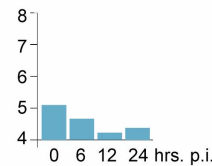
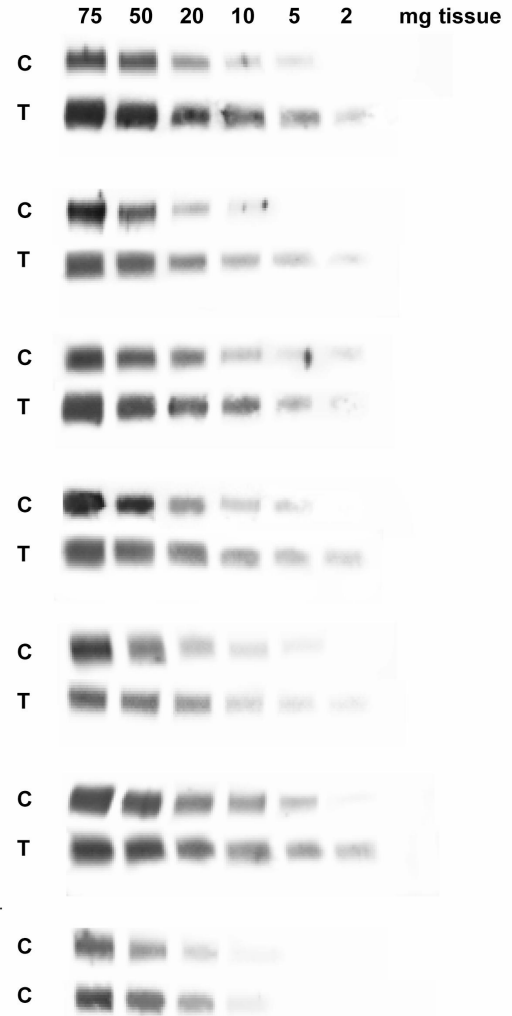
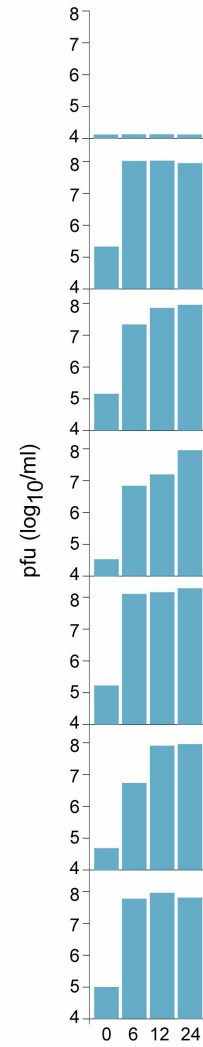
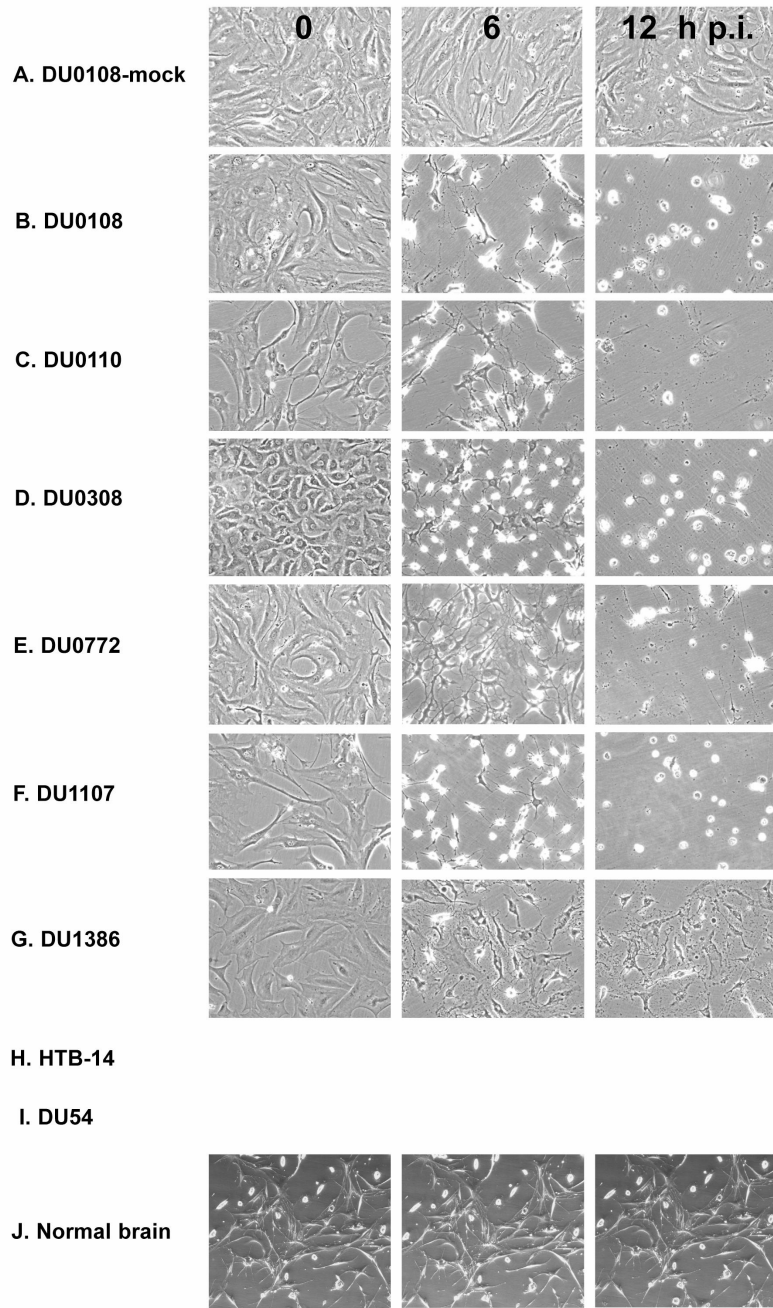
CD155 is regulated by the morphogen *sonic hedgehog*



Poliovirus oncolysis mediated by ectopic expression of CD155



The poliovirus receptor CD155 and malignant glioma



CD155/PVR plays a key role in cell motility during tumor cell invasion and migration

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Published: 07 October 2004

Received: 28 July 2004

BMC Cancer 2004, 4:73 doi:10.1186/1471-2407-4-73

Accepted: 07 October 2004

This article is available from: <http://www.biomedcentral.com/1471-2407/4/73>

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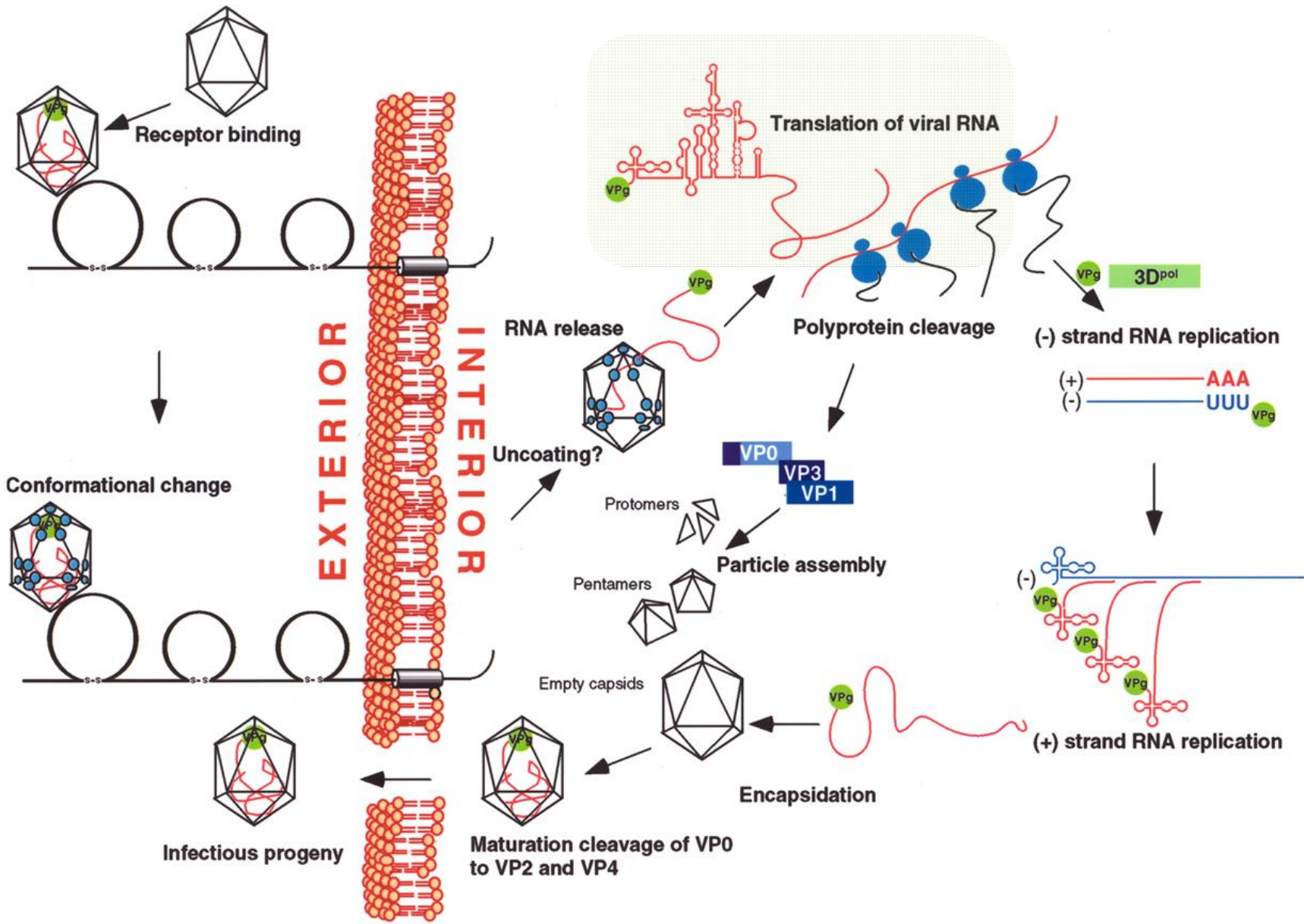
Abstract

Background: Invasion is an important early step of cancer metastasis that is not well understood. Developing therapeutics to limit metastasis requires the identification and validation of candidate proteins necessary for invasion and migration.

Methods: We developed a functional proteomic screen to identify mediators of tumor cell invasion. This screen couples Fluorophore Assisted Light Inactivation (FALI) to a scFv antibody library to systematically inactivate surface proteins expressed by human fibrosarcoma cells followed by a high-throughput assessment of transwell invasion.

Results: Using this screen, we have identified CD155 (the poliovirus receptor) as a mediator of tumor cell invasion through its role in migration. Knockdown of CD155 by FALI or by RNAi resulted in a significant decrease in transwell migration of HT1080 fibrosarcoma cells towards a serum chemoattractant. CD155 was found to be highly expressed in multiple cancer cell lines and primary tumors including glioblastoma (GBM). Knockdown of CD155 also decreased migration of U87MG GBM cells. CD155 is recruited to the leading edge of migrating cells where it colocalizes with actin and α v-integrin, known mediators of motility and adhesion. Knockdown of CD155 also altered cellular morphology, resulting in cells that were larger and more elongated than controls when plated on a Matrigel substrate.

Conclusion: These results implicate a role for CD155 in mediating tumor cell invasion and migration and suggest that CD155 may contribute to tumorigenesis.



Receptor binding

Translation of viral RNA

Polyprotein cleavage

(-) strand RNA replication

(+) strand RNA replication

Conformational change

Uncoating?

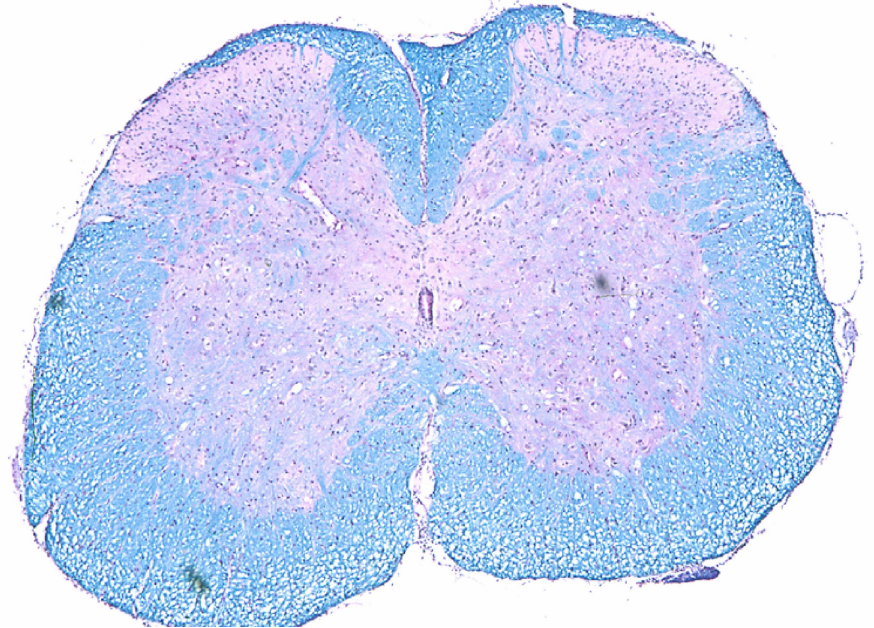
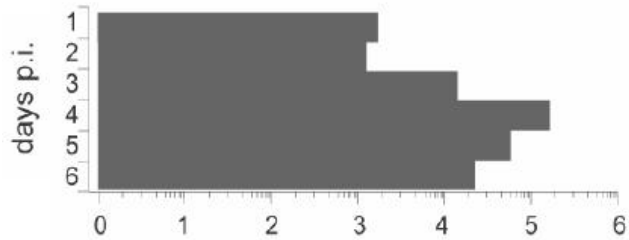
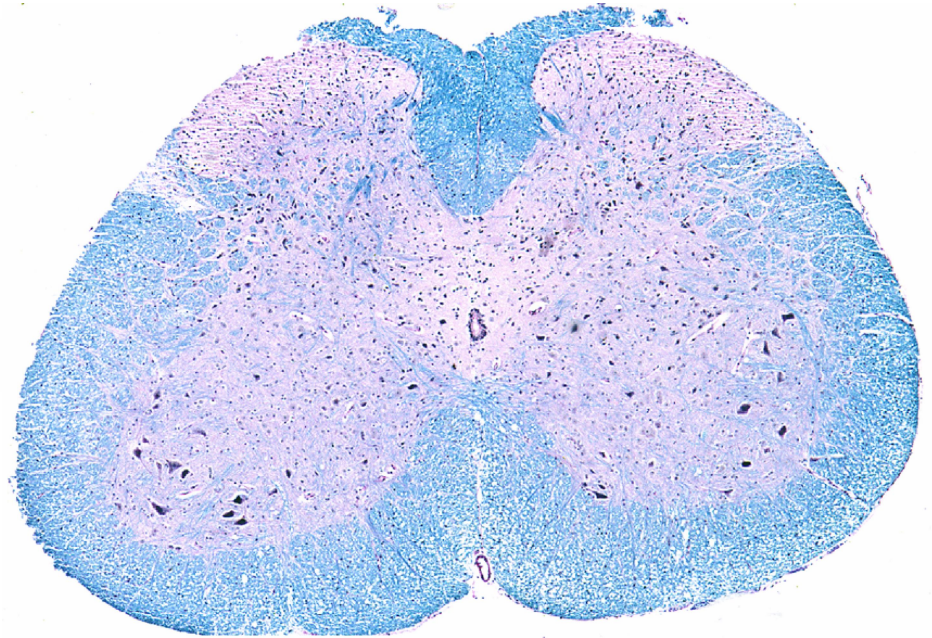
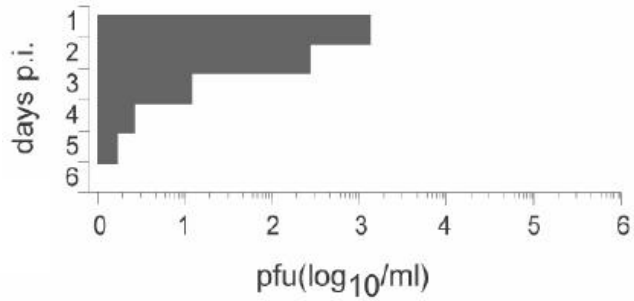
Particle assembly

Encapsidation

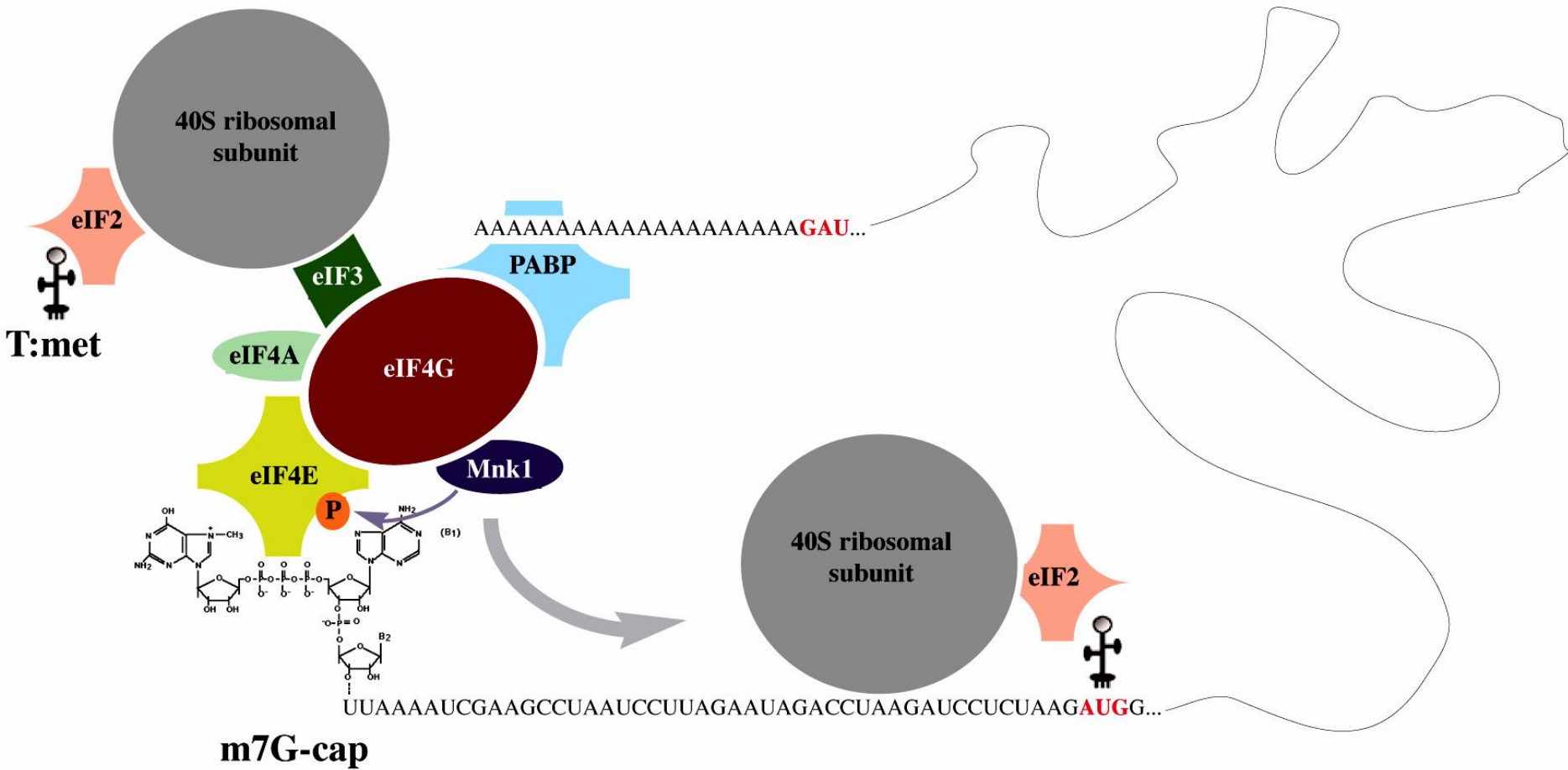
Maturation cleavage of VP0 to VP2 and VP4

Infectious progeny

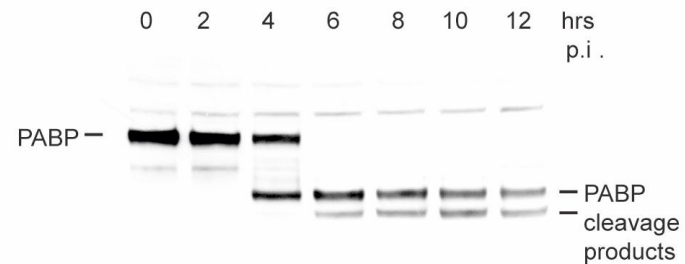
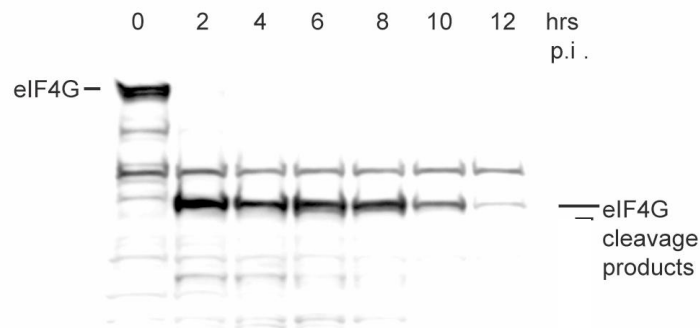
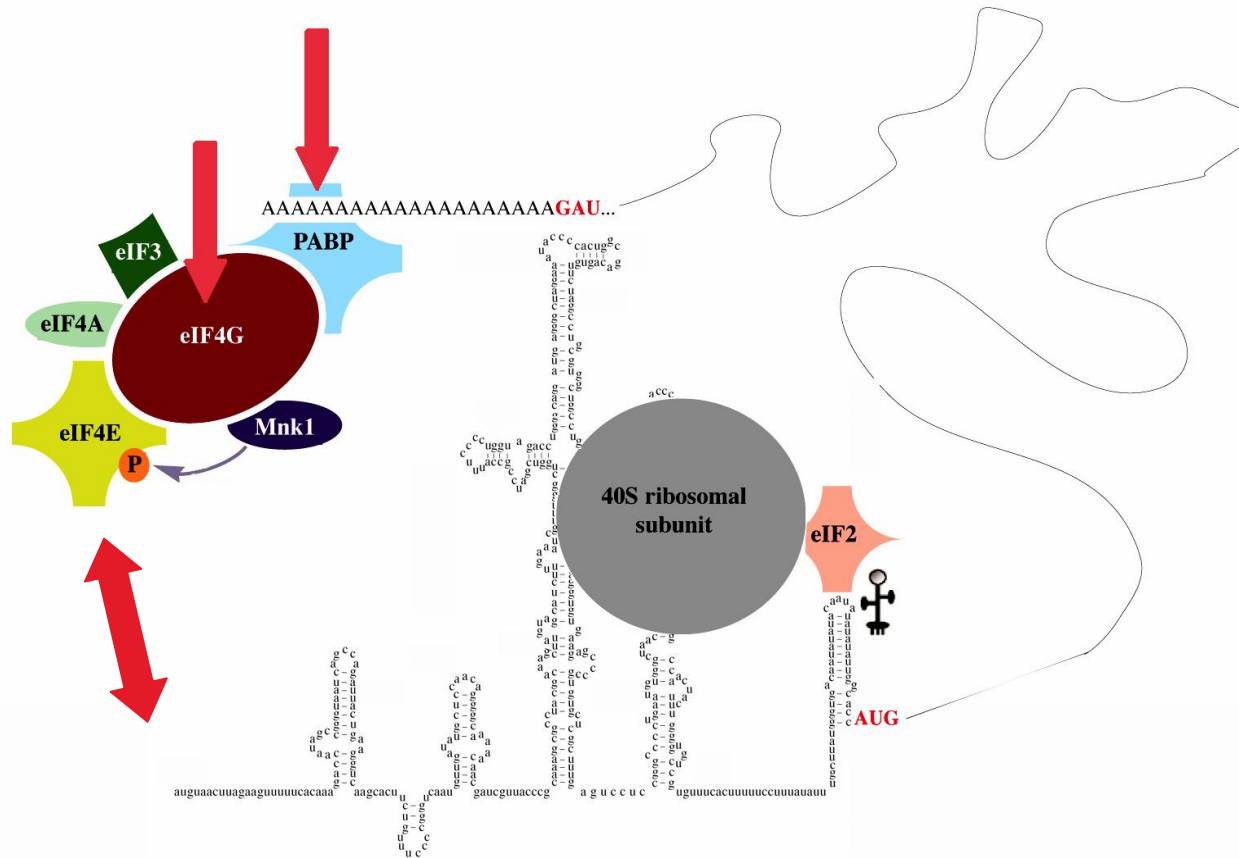
The IRES determines neurovirulence



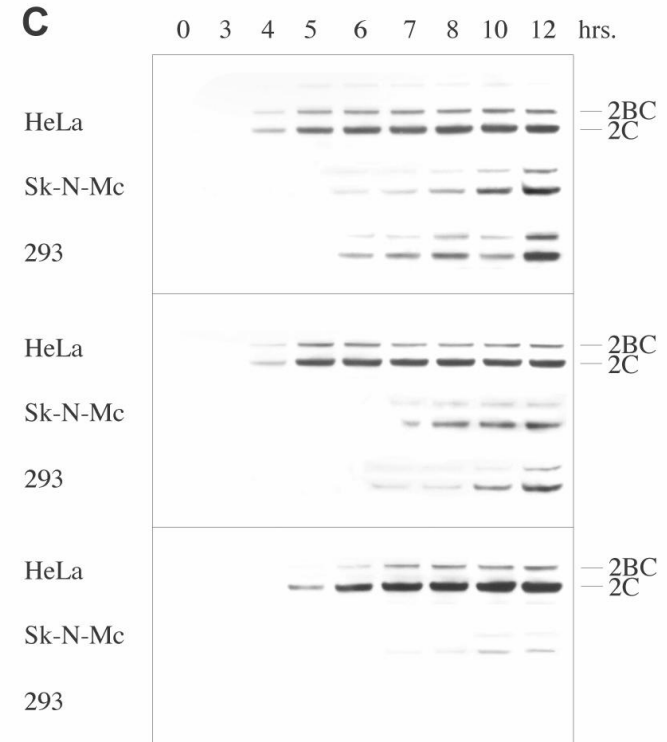
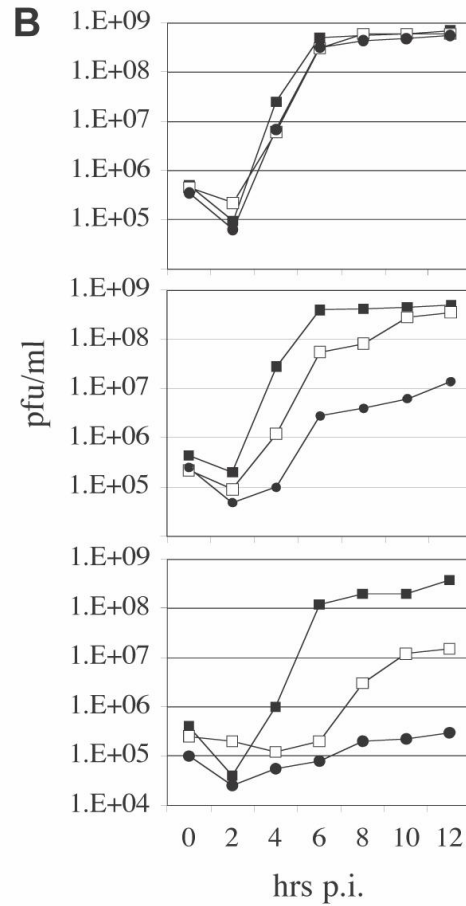
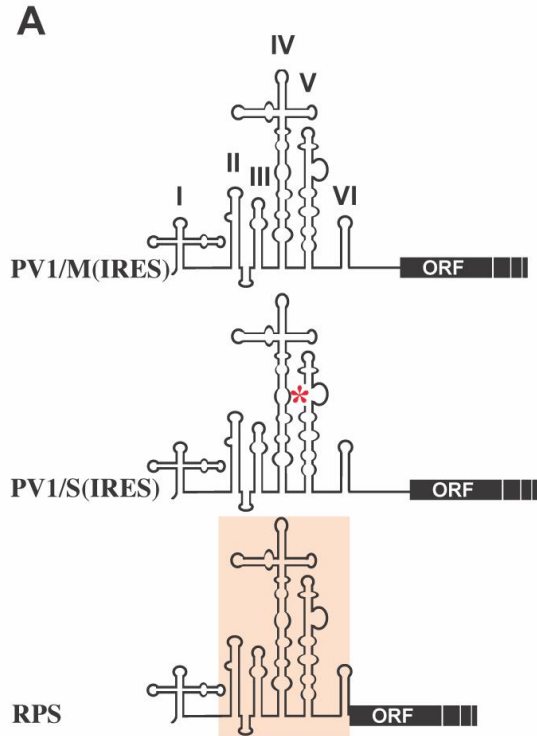
Cap-dependent translation initiation



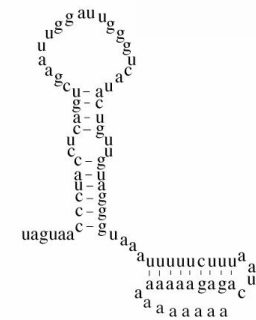
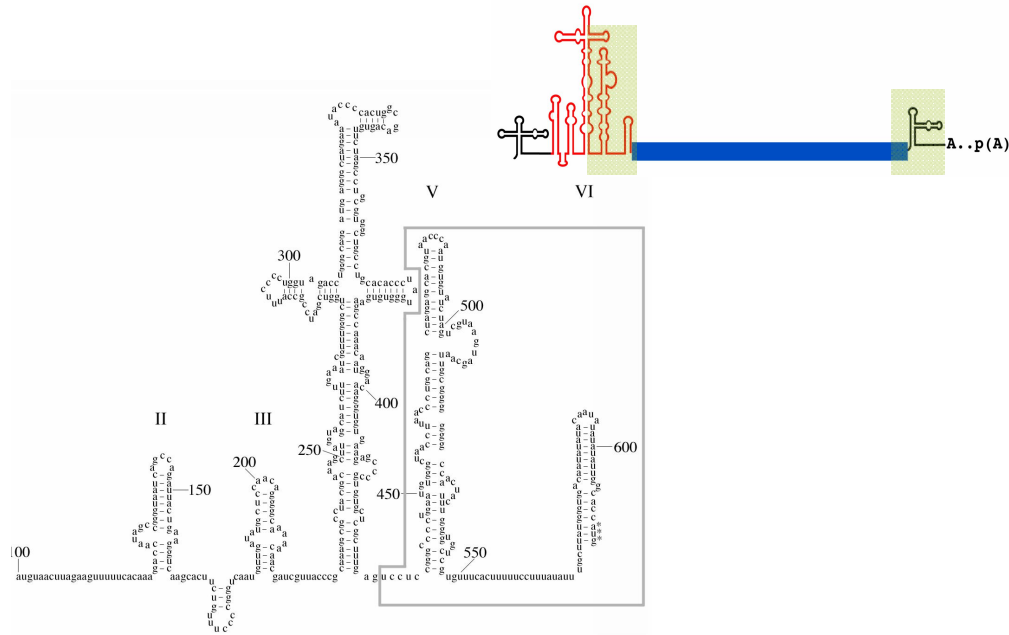
Translation initiation by internal ribosomal entry



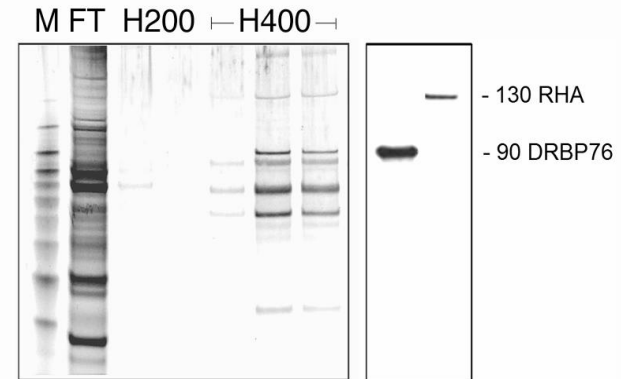
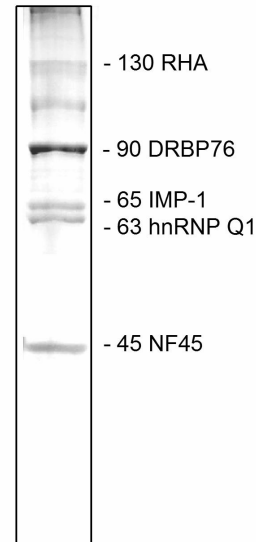
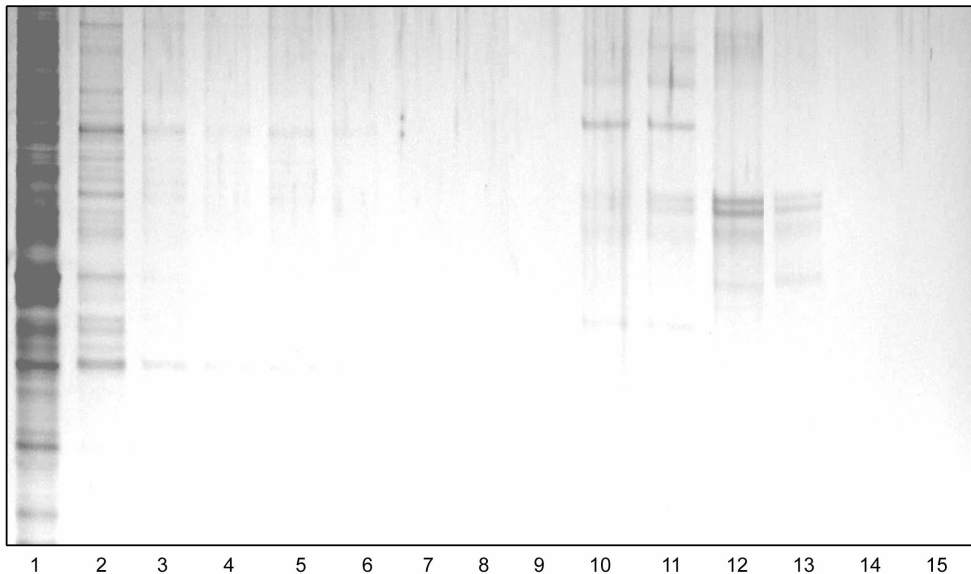
Neuronal incompetence of the HRV2 IRES



The NFAR complex bridges the IRES and 3'UTR

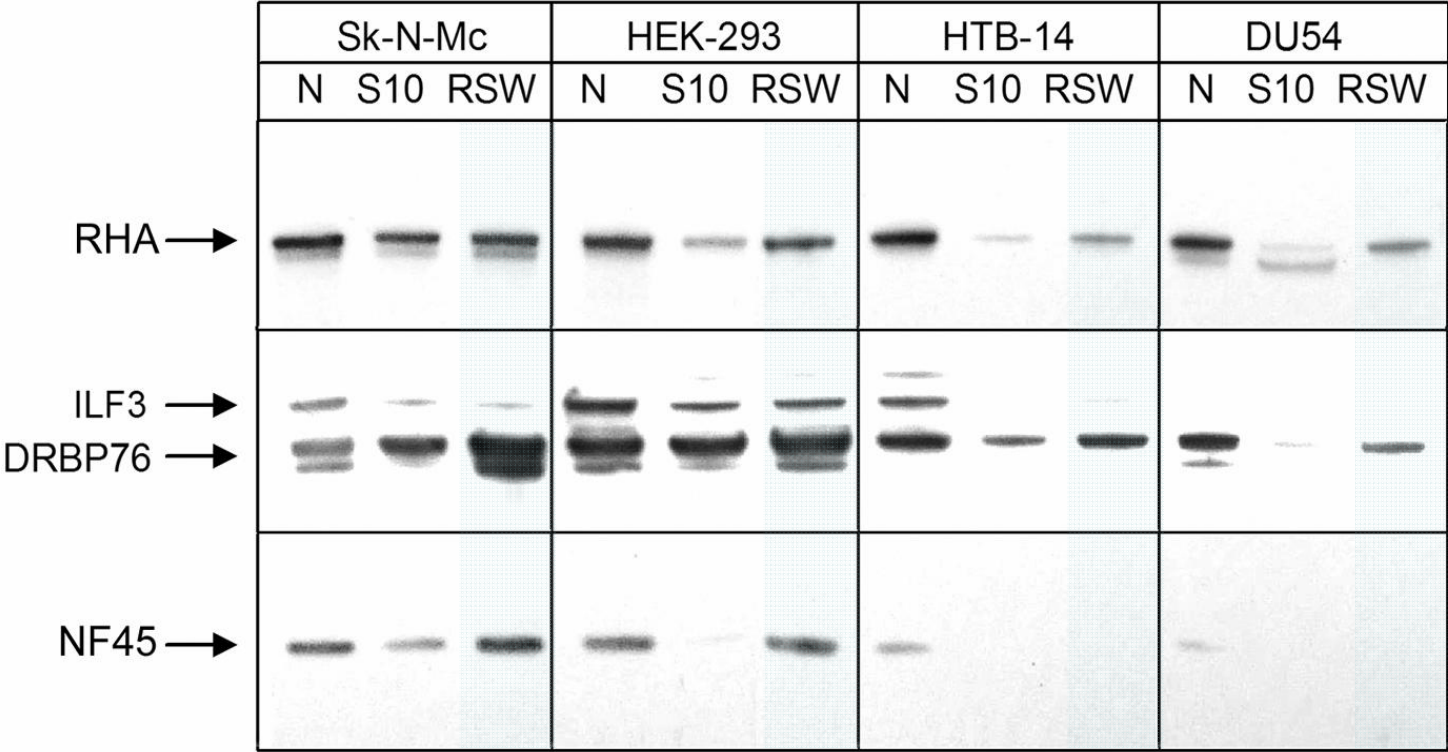


CE FT H200 Washes H300 H400 H500 H600 H700 H800 H1000

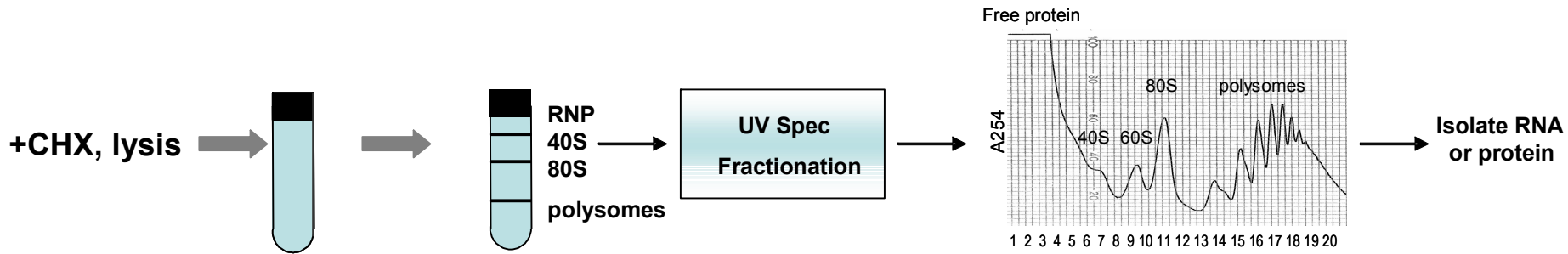


Melinda Merrill
Paola Florez

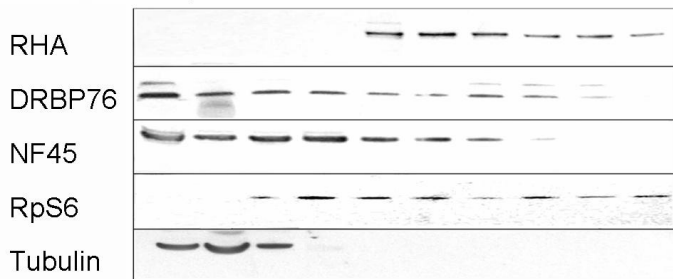
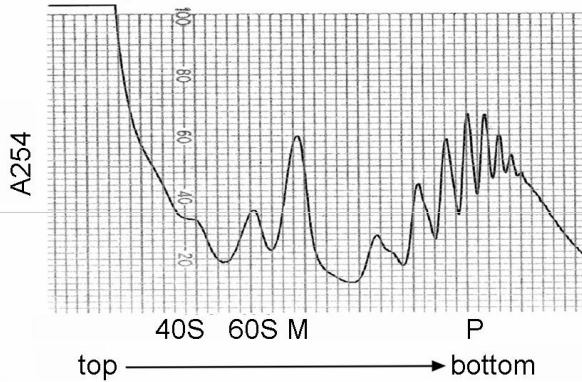
Cell type-specific distribution of the NFAR complex



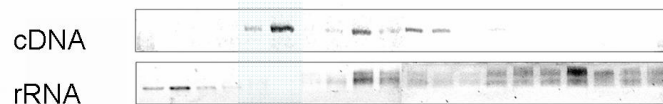
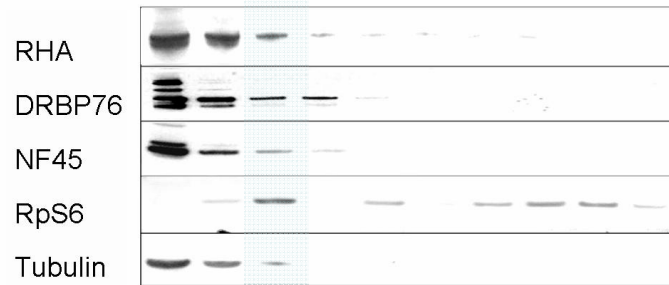
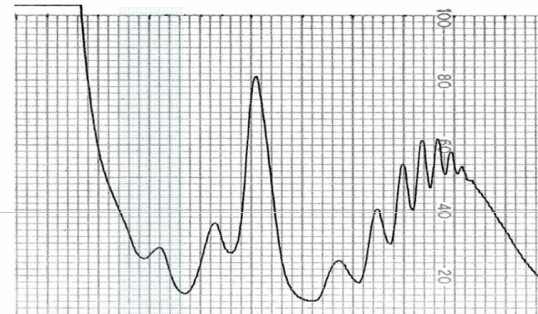
Ribosomal profiling of the NFAR complex



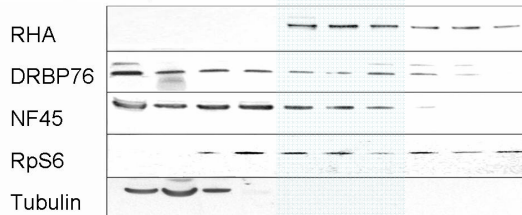
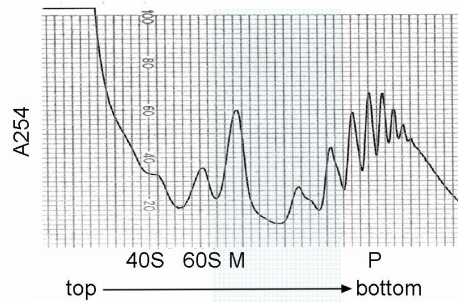
HEK-293, uninfected



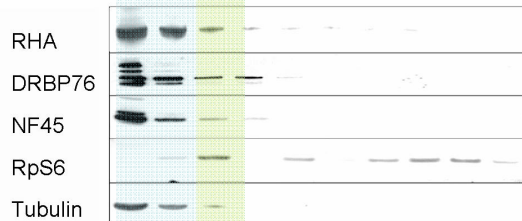
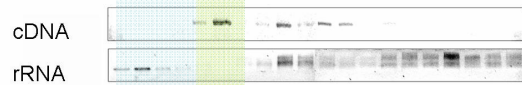
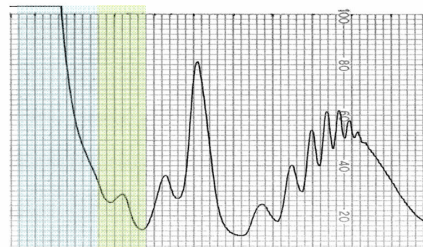
HEK-293, infected



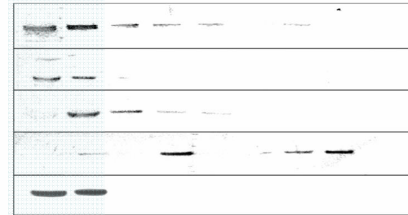
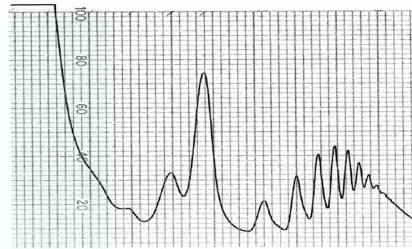
A HEK-293, uninfected



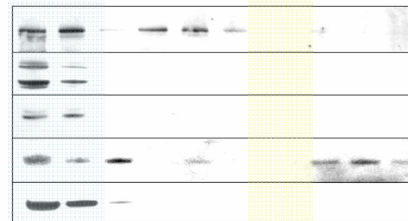
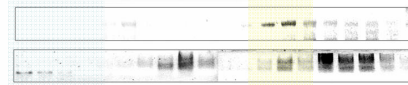
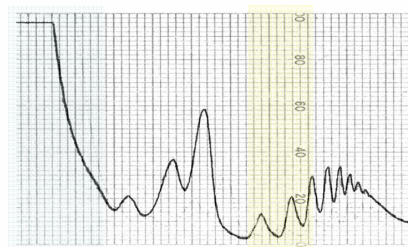
B HEK-293, infected



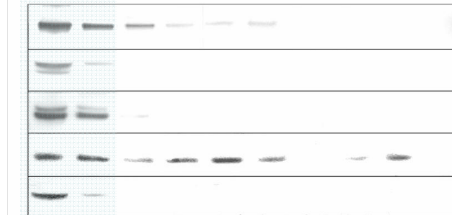
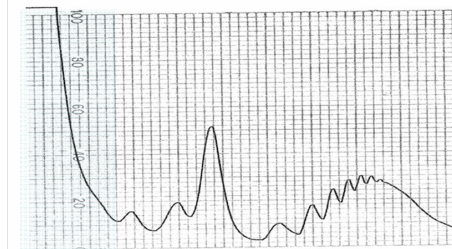
C HTB-14, uninfected



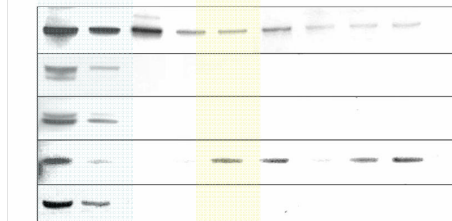
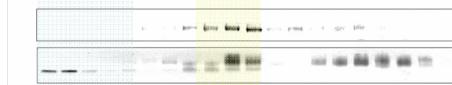
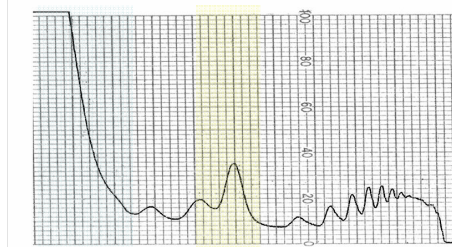
D HTB-14, infected



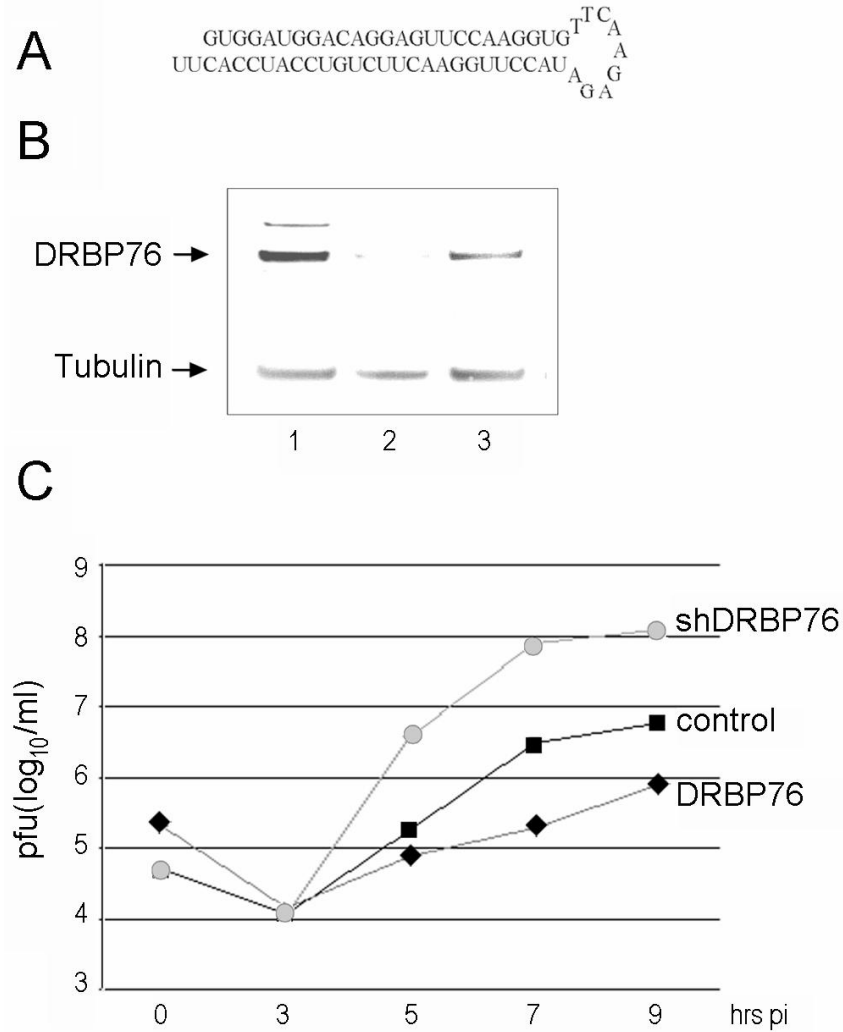
E shDRBP76, uninfected



F shDRBP76, infected



RNAi knock-down of DRBP76 restores neuronal IRES competence

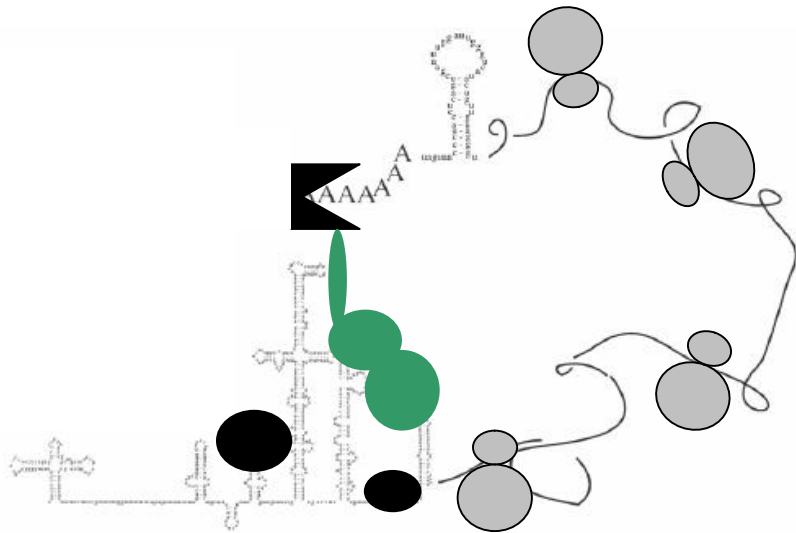


HRV2 IRES-mediated translation is repressed by the NFAR-1 complex

HTB-14: malignant glioma

Processive translation

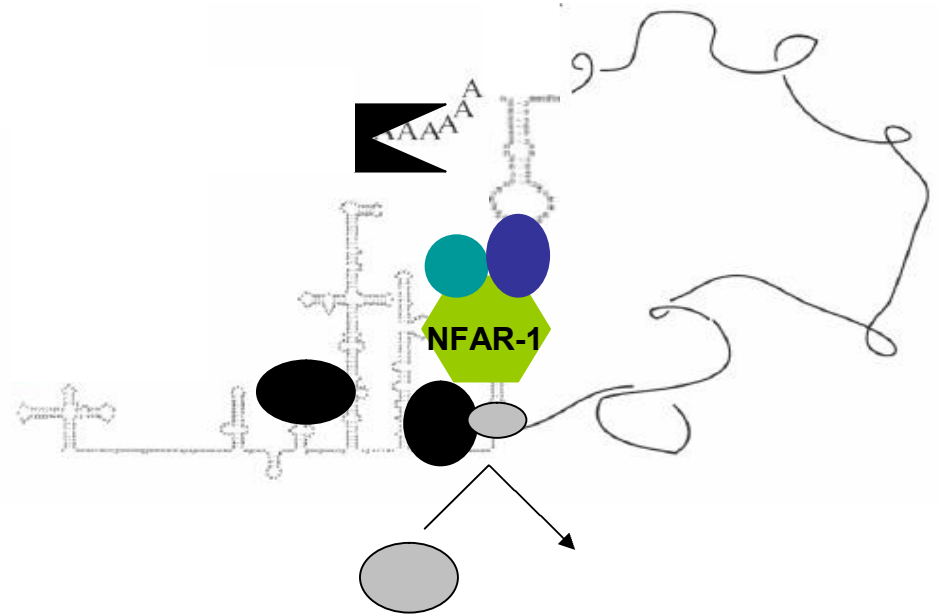
NFAR-1 does not associate with ribosomes, viral RNA sediments with polysomes



HEK-293: neuron-like

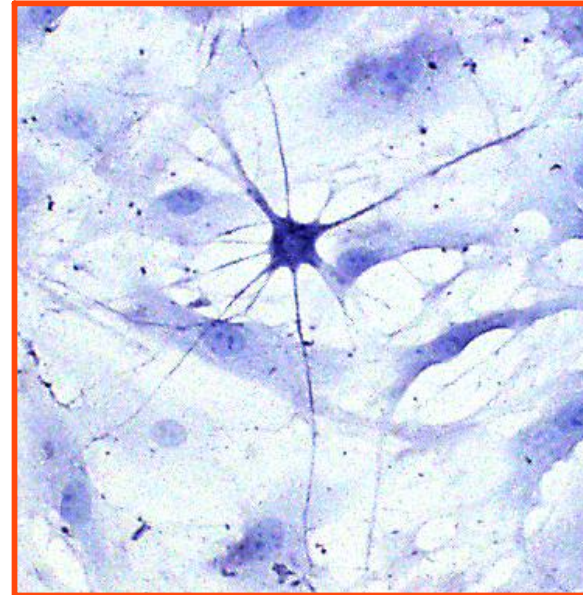
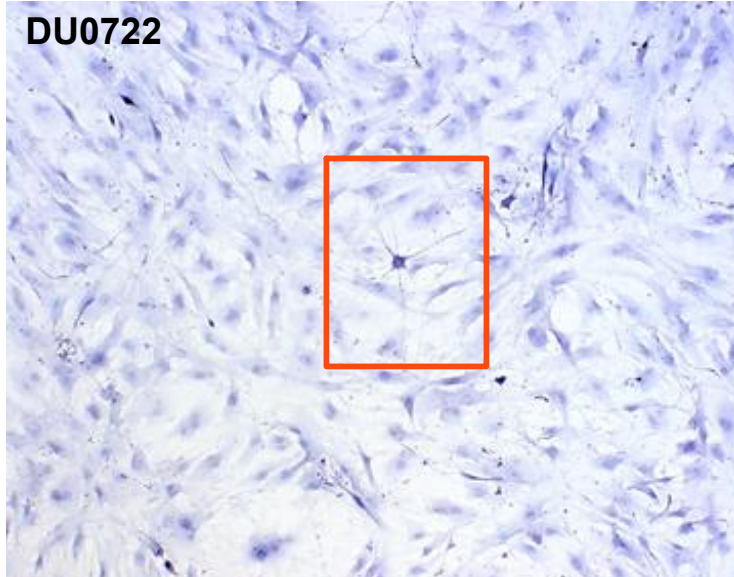
NFAR-1 blocks translation by remodeling the RNP

NFAR-1 complex and viral RNA sediment with 40S.

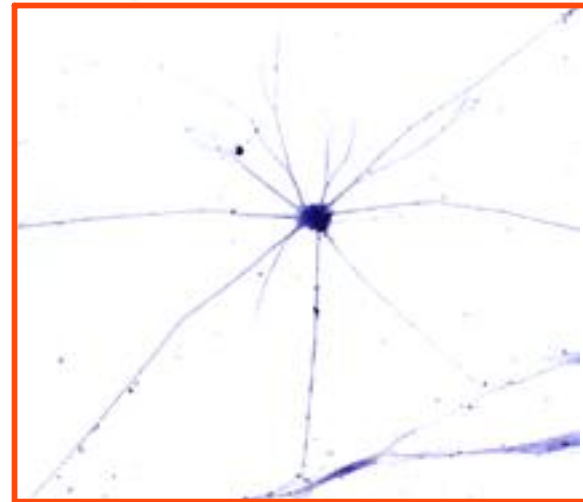
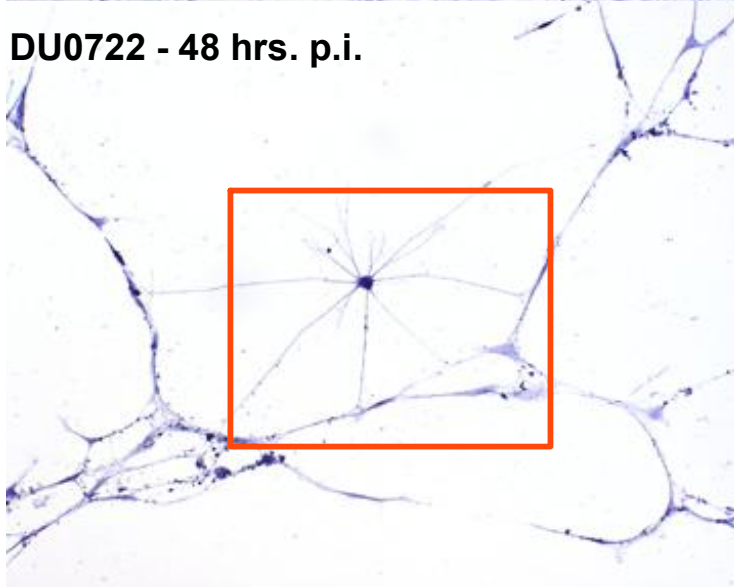


Tumor-specific cytopathogenicity of PVS-RIPO *in vitro*

DU0722



DU0722 - 48 hrs. p.i.



Tropism

CD155 mediates selective motor neuron tropism; Ectopic expression in cancer confers natural target tropism for neoplastic cells

Virulence

Depends on compatibility of protein:(viral) RNA interactions; Genetic features of PV, but not HRV, permit replication within motor neurons

Condition of the host/Circumstance

N/A



Elena Dobrikova
Shelton Bradrick
Melinda Merrill
Paola Florez
Andrew Dufresne
Stephanie Moore
Jennifer Lin
Constanze Kaiser
Robert Walters
Rachel Grisham
Lee Selznick

Darrell Bigner
John Sampson
Henry Friedman
Allan Friedman
Duke University
Brain Tumor Center

New York Brain Bank
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