

Bioactive Excipients in Cytomegalovirus Treatment

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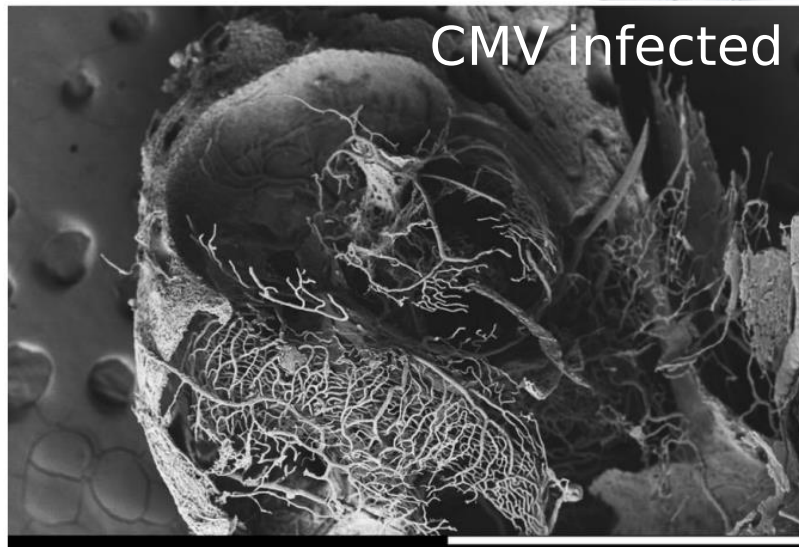
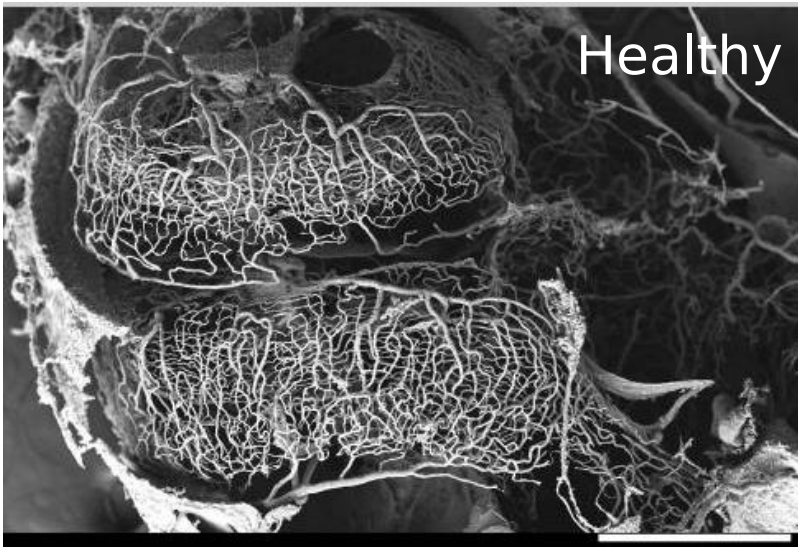
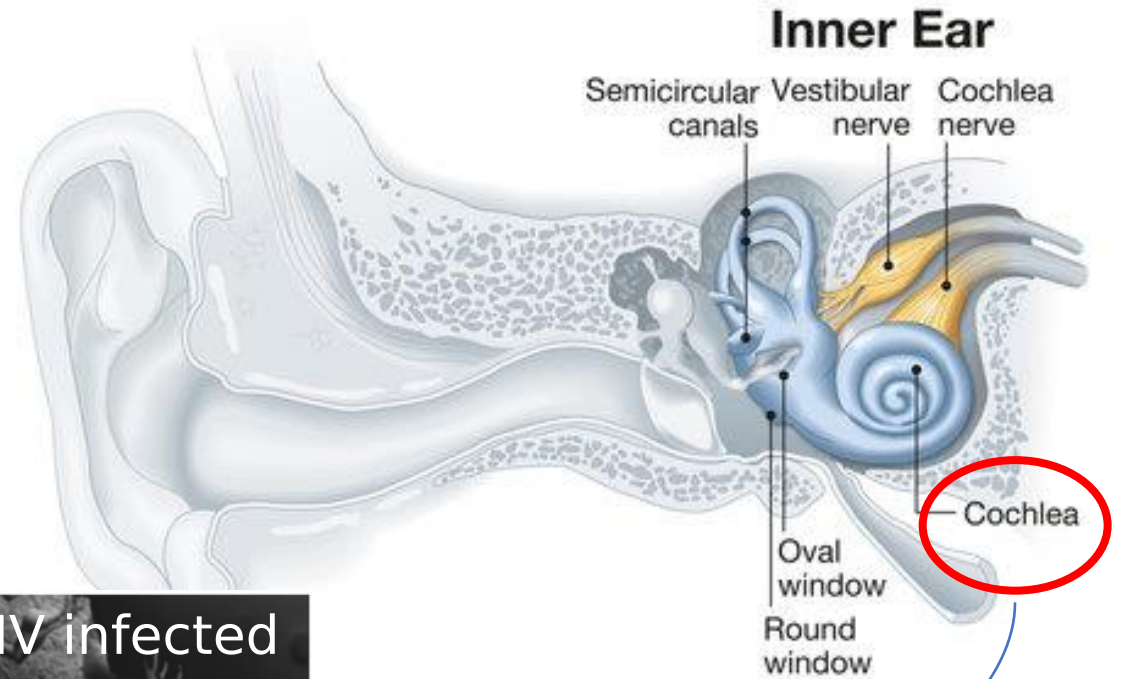
Albert Park MD

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University of Utah

Motivation - Cytomegalovirus

- Most common worldwide congenital infection
- Leads to progressive hearing loss
- Inner ear vasculature and cells are damaged

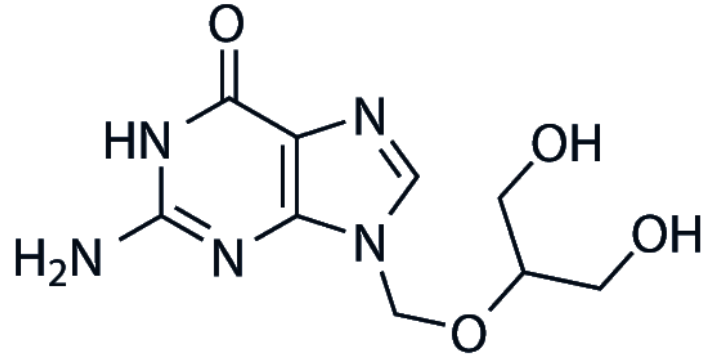


Axel Kock, "Inner ear anatomy, medical illustration with caption" *Adobe Stock Images*

Carraro, Mattia, et al. "Cytomegalovirus (CMV) infection causes degeneration of cochlear vasculature and hearing loss in a mouse model." *Journal of the Association for Research in Otolaryngology* 18.2 (2017): 263-273. 2

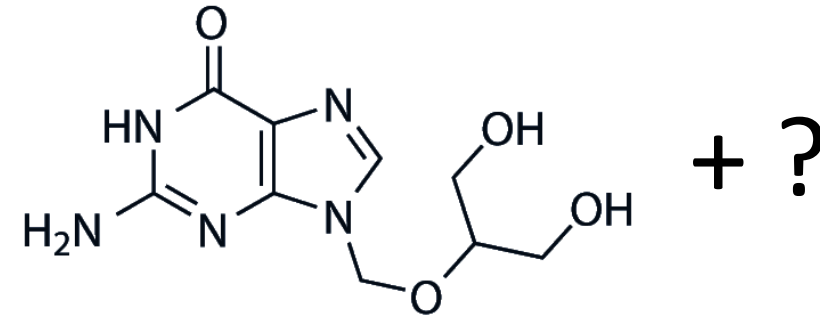
Ganciclovir treats CMV, but with consequences

Ganciclovir



- Blocks viral DNA replication in infected cells ✓
- clinical standard to treat CMV ✓
- Causes toxicity in over 30% of children treated ✗

Ganciclovir + Excipient



- An excipient increases the drug efficacy ✓
- Lower doses can be used, helping to avoid toxicity ✓

Goal: Identify an excipient for ganciclovir (GCV)

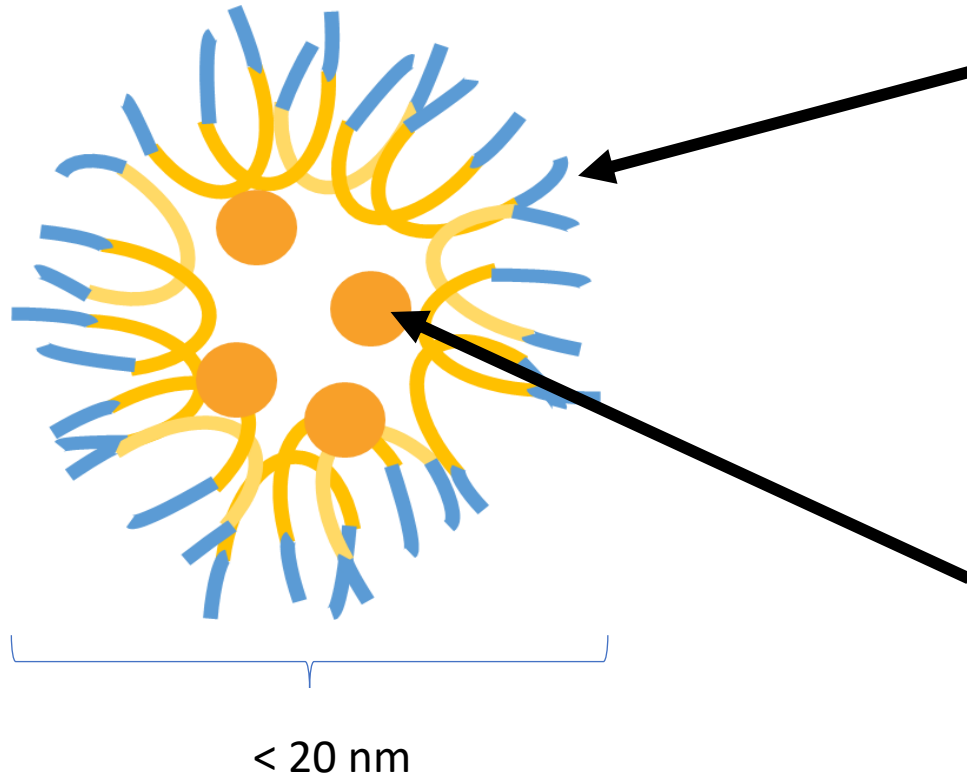
QF68 as a potential bioactive excipient

F68

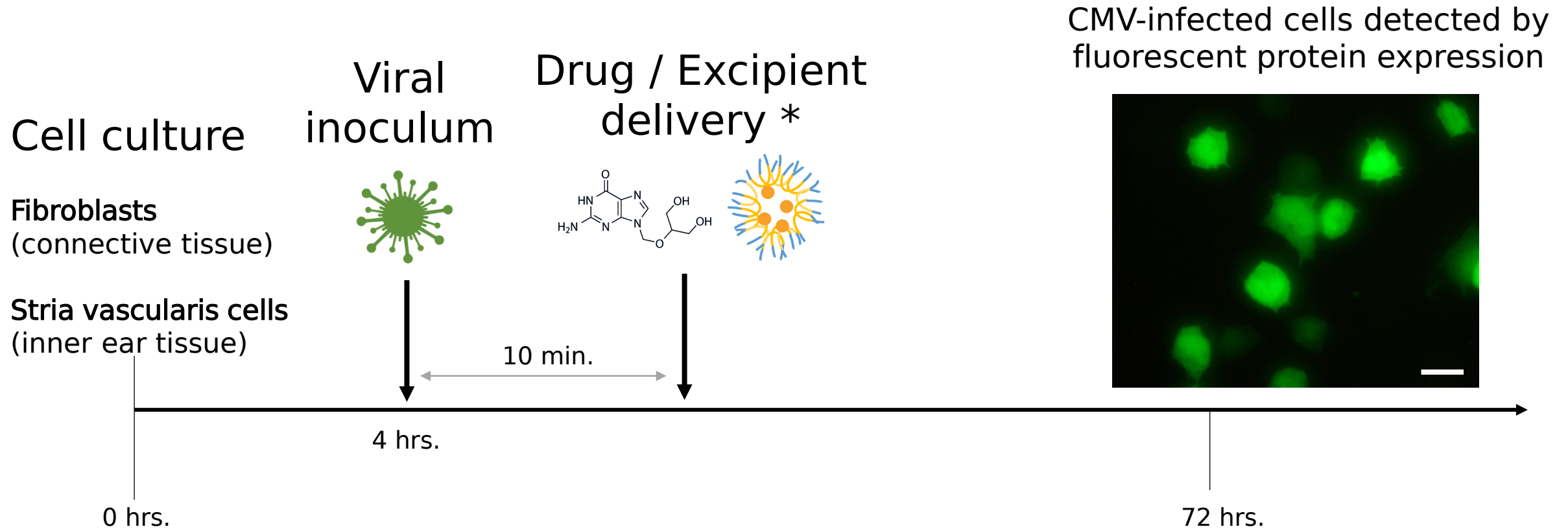
- FDA approved excipient
- Self-assembles into nanoparticle structures

Quercetin (Q)

- Naturally-derived plant flavonoid
- Antioxidant
- Antimicrobial / *antiviral*

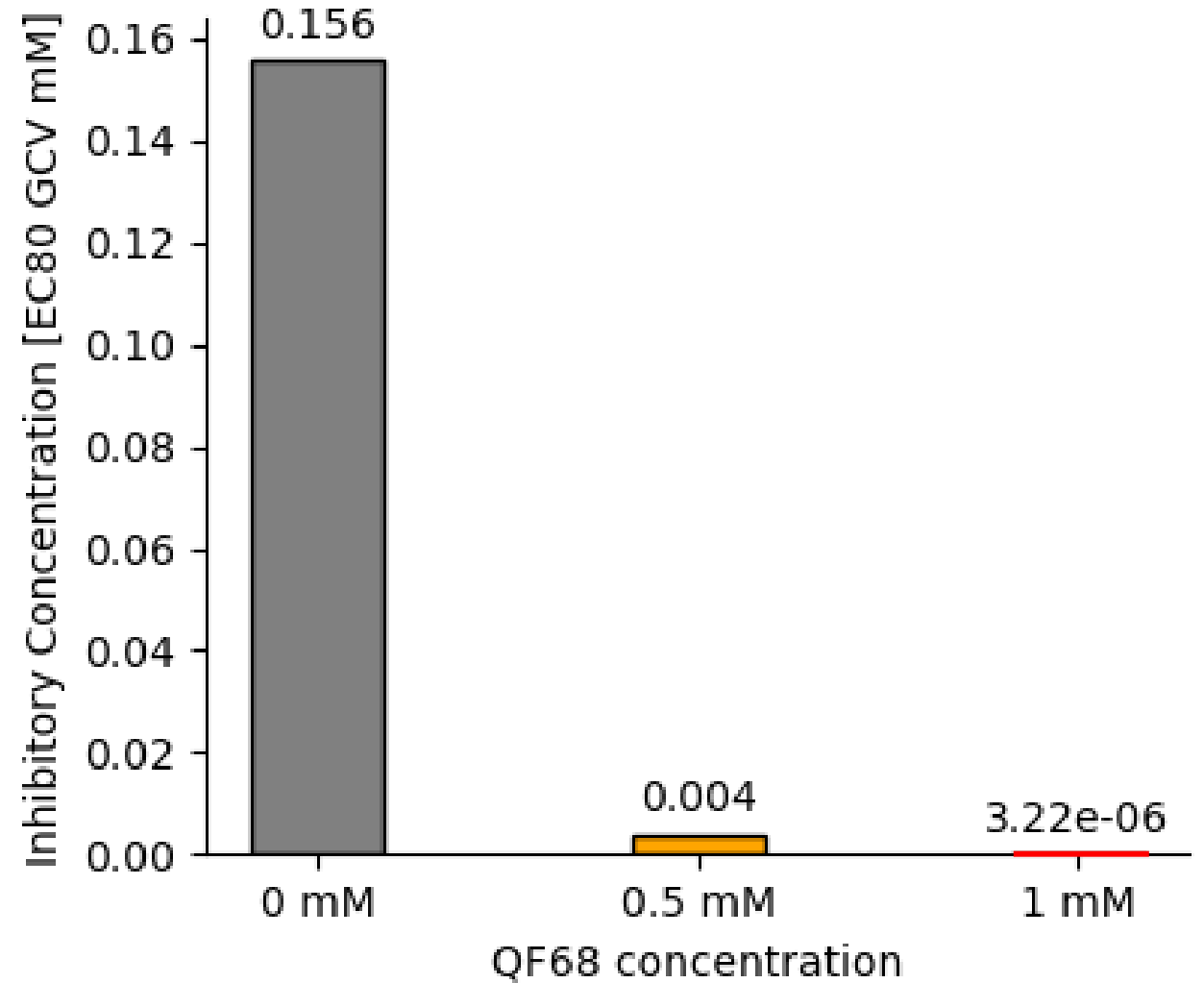
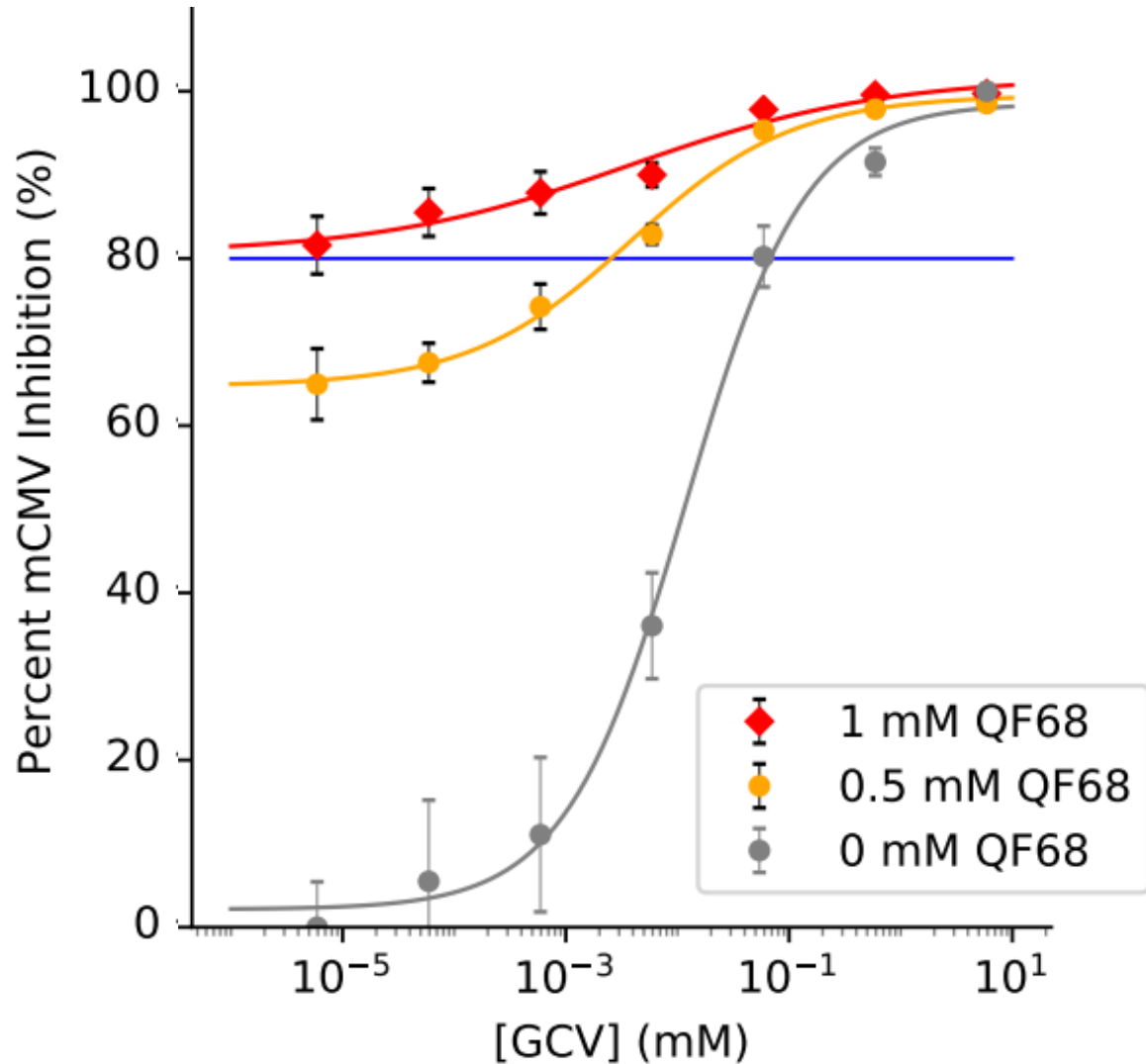


Methods: Viral Infection Cell Culture Model

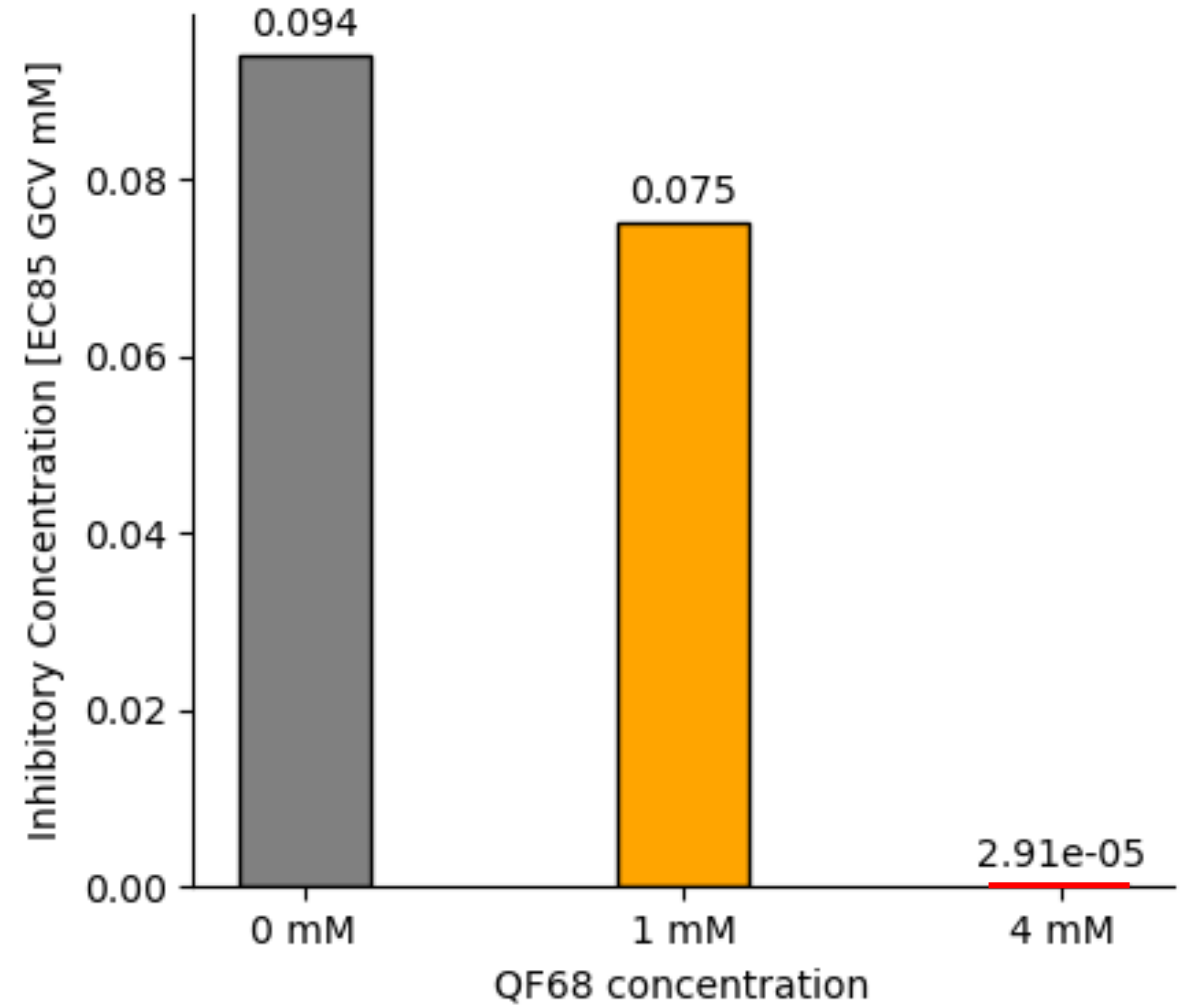
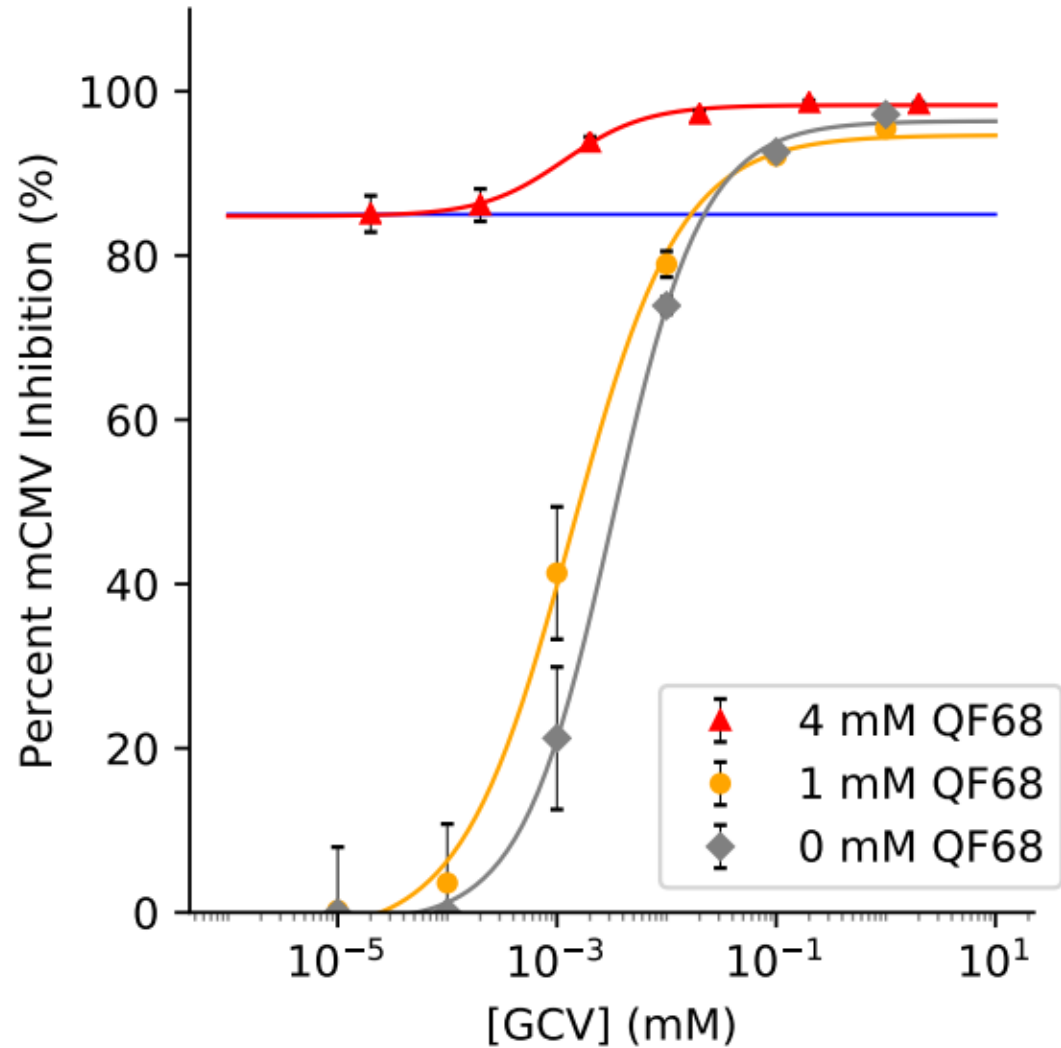


* Ganciclovir (GCV) + excipient (QF68) combinatorial activity assessed for multiple GCV/QF68 concentrations

Results: QF68 potentiates GCV in fibroblast cells

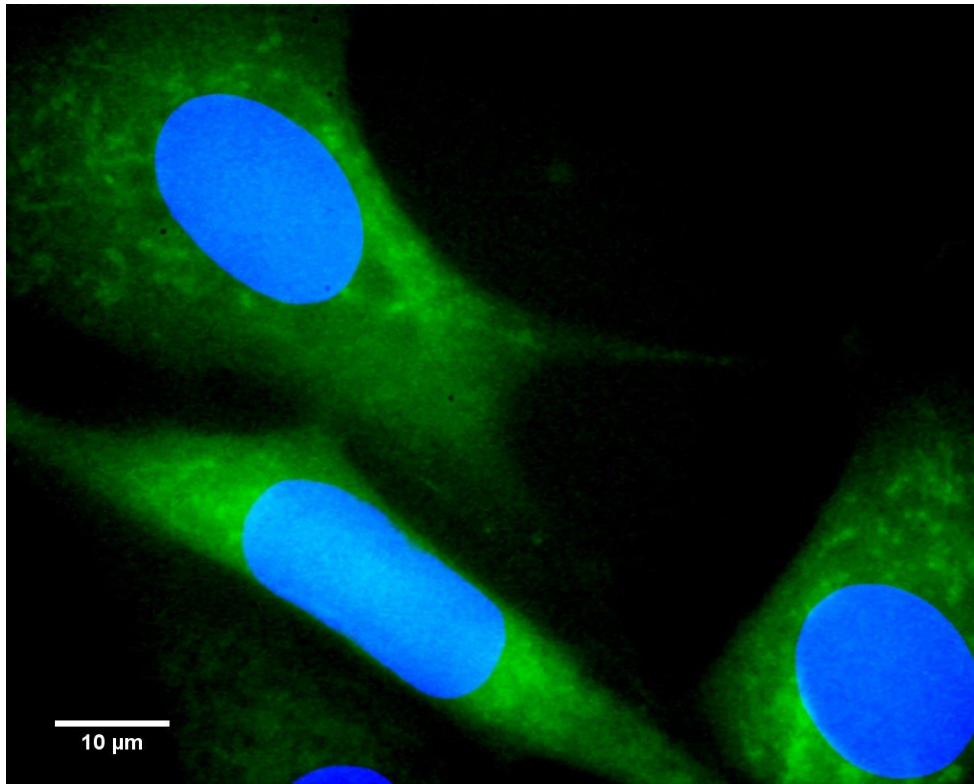


Results: QF68 potentiates GCV in stria vascularis cells

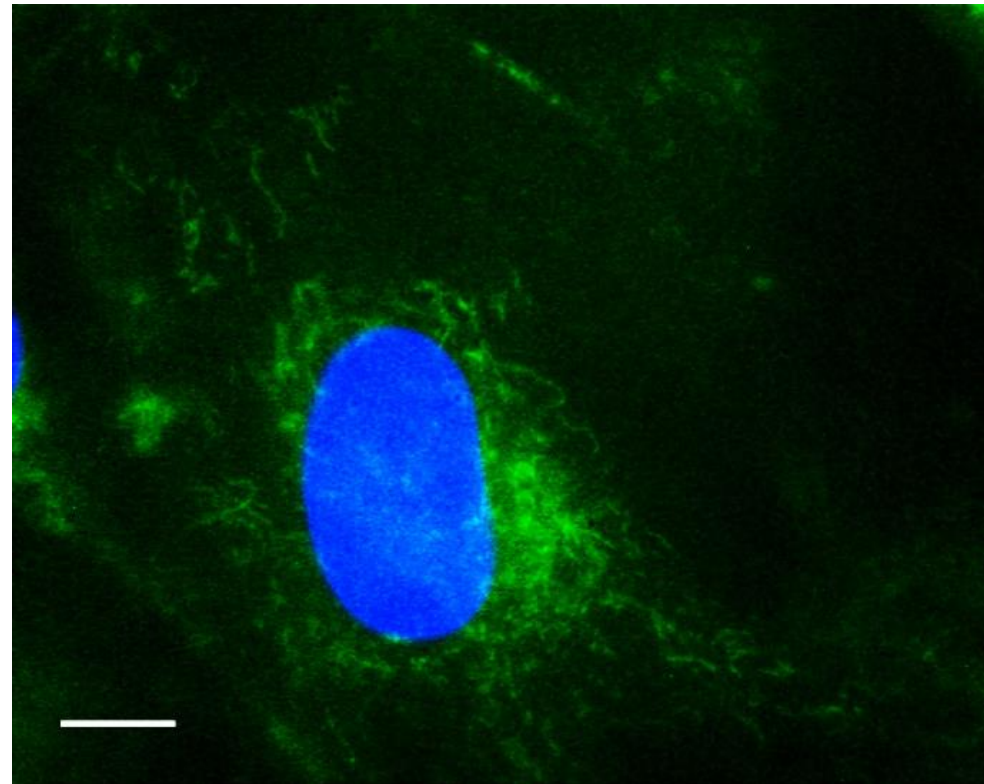


QF68 Mode of Action: External or Internal?

- Both cell lines were incubated with fluorescent **QF68** and **nuclear dye**
- Fluorescence patterning indicates excipient uptake (i.e. not restricted to external cell membrane) – appears concentrated in organelles (which ones?)



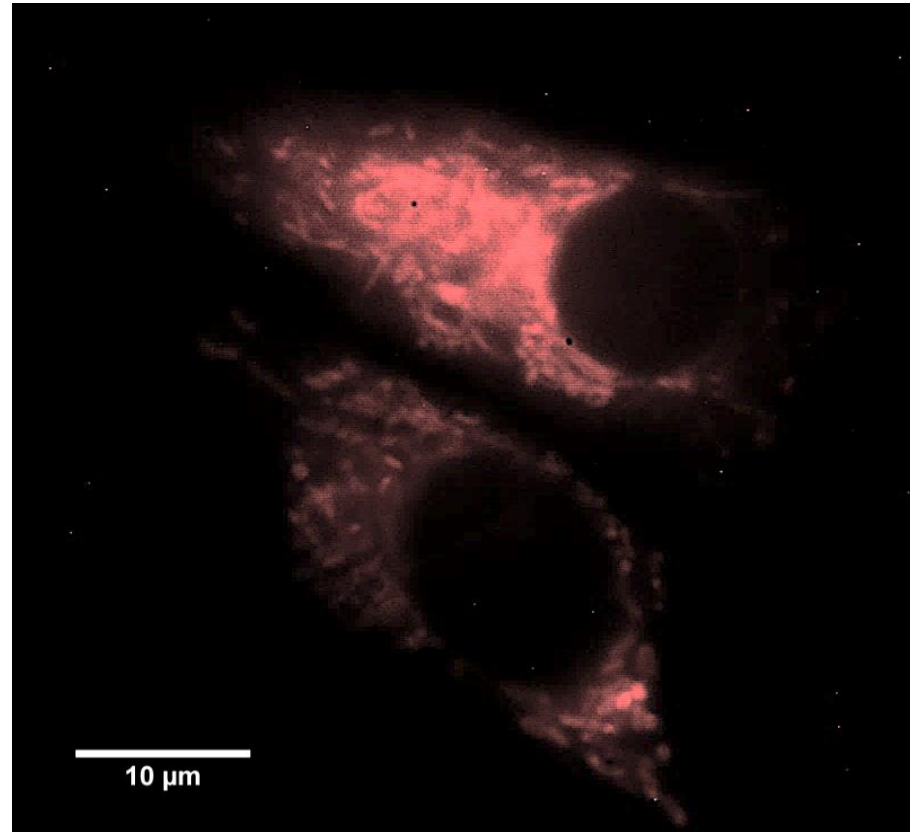
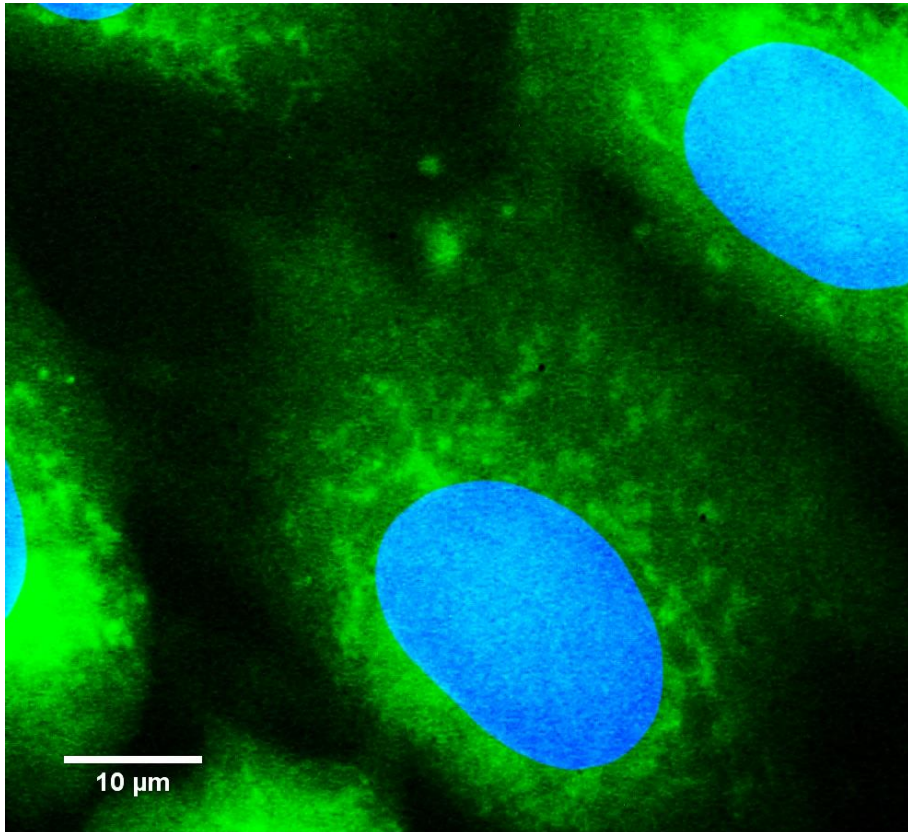
Fibroblast cells



Stria vascularis cells

Does QF68 concentrate in mitochondria?

- Fibroblasts were incubated with fluorescent QF68, nuclear dye, and mitochondrial dye
- QF68 and mitochondrial dye have the same pattern = same location



Conclusions

- Coadministration with QF68 **significantly decreases** the amount of GCV necessary in fibroblasts and stria vascularis cells
- Mitochondrial uptake of QF68 was observed in both cell lines
 - CMV infection requires enhanced cellular metabolism to produce viral progeny
 - Mitochondria are the “powerhouses” of the cell - providing energy in the form of ATP
- Positive outcomes in connective tissue and inner ear cell lines support **transition to small animal models**
- Clinically, this would mean lower dose GCV treatments to prevent CMV infection and hearing loss

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