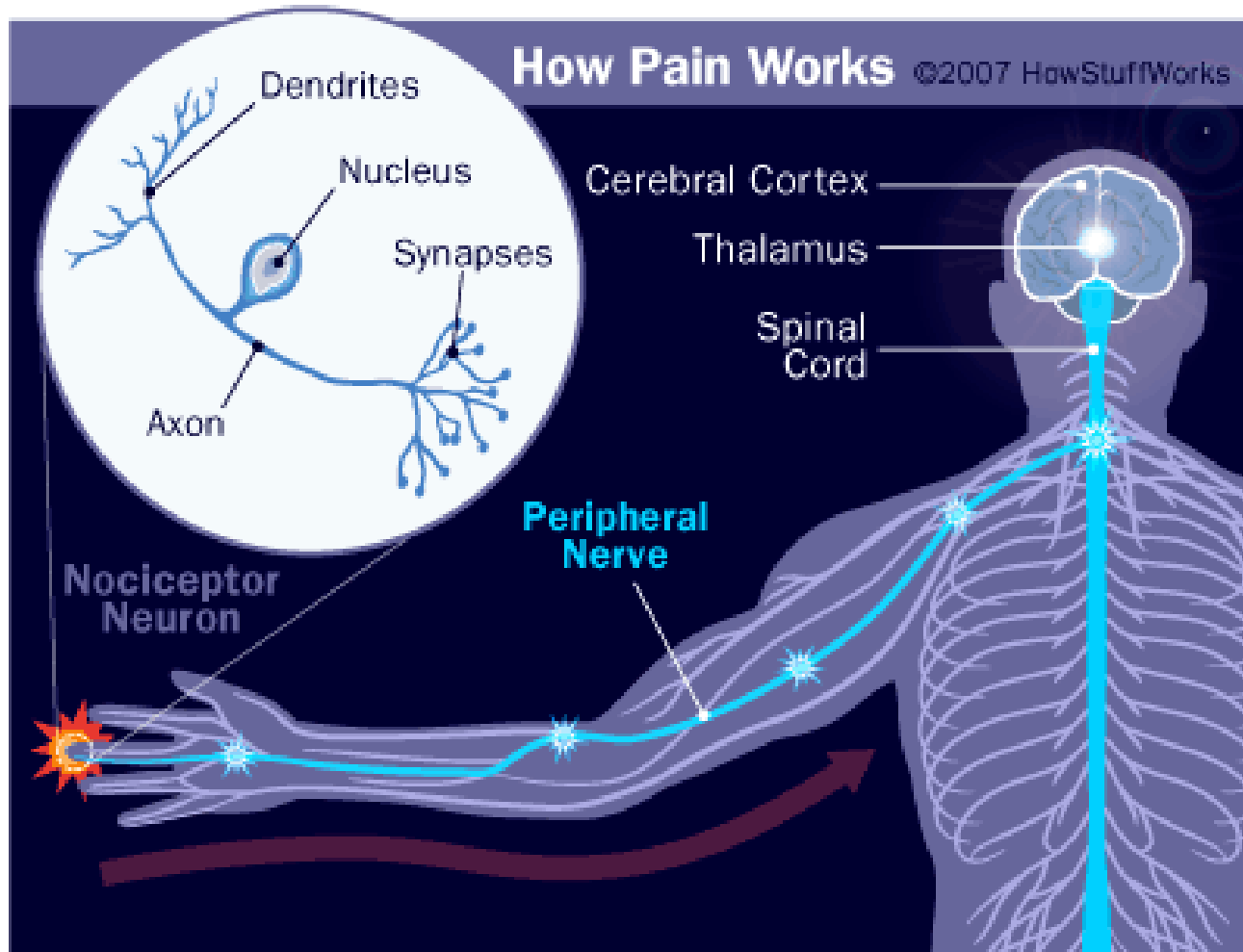
An anatomical illustration of a human body lying on its back, showing internal organs and muscles. Several circular callouts with red dots are placed over different parts of the body: the brain, the right shoulder joint, the spine, the right knee joint, and the right forearm. The text is overlaid on the center of the image.

Congenital Insensitivity to Pain with Anhidrosis (NTRK1)

By: Britainney Petrie

What is congenital insensitivity to pain with anhidrosis (CIPA)?



Autosomal recessive

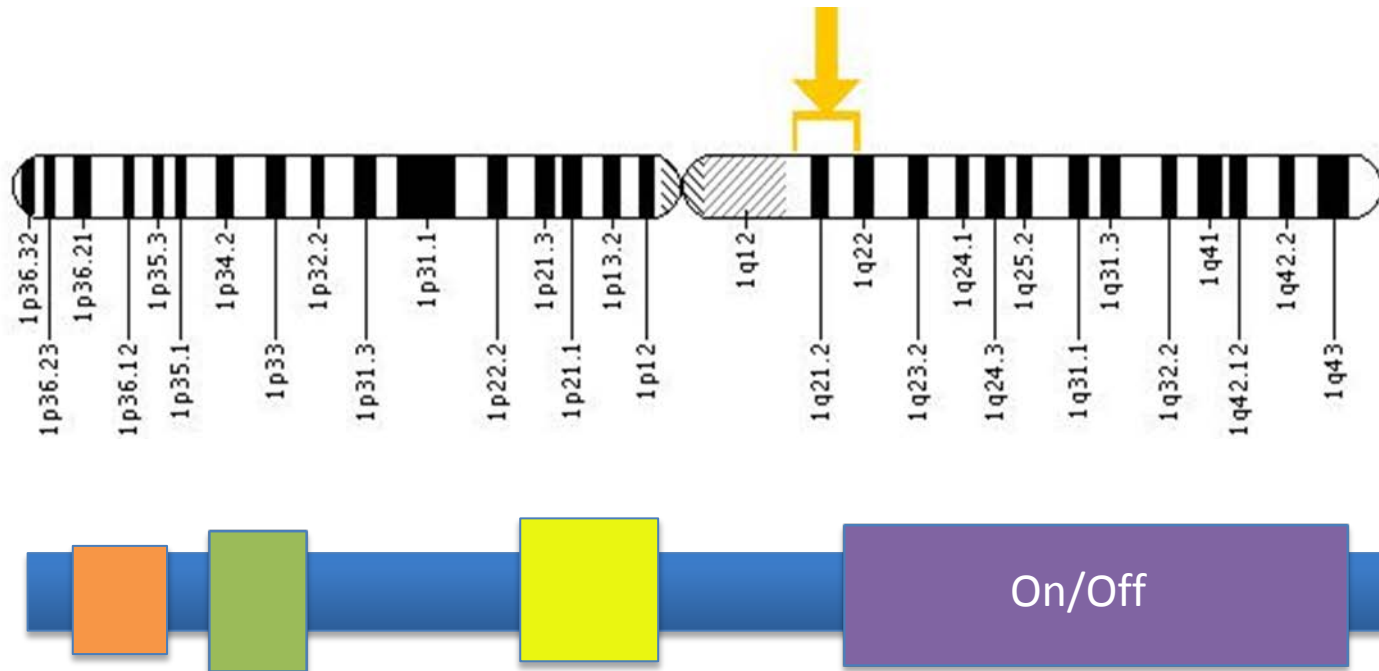
What are the symptoms and secondary consequences of CIPA?



Management for CIPA Patients



NTRK1 is mutated in CIPA patients



Mutation-Off-No Phosphorylation-Sensory neuron death

LRRCT

IG

Transmembrane

TyrKc



NTRK1 Homologs

Humans:
796 aa



Cattle:
815aa



Chimpanzee:
822 aa



Mouse: 799 aa



Chicken: 790 aa



Zebra Fish: 619 aa



LRRCT

IG

Transmembrane

TyrKc

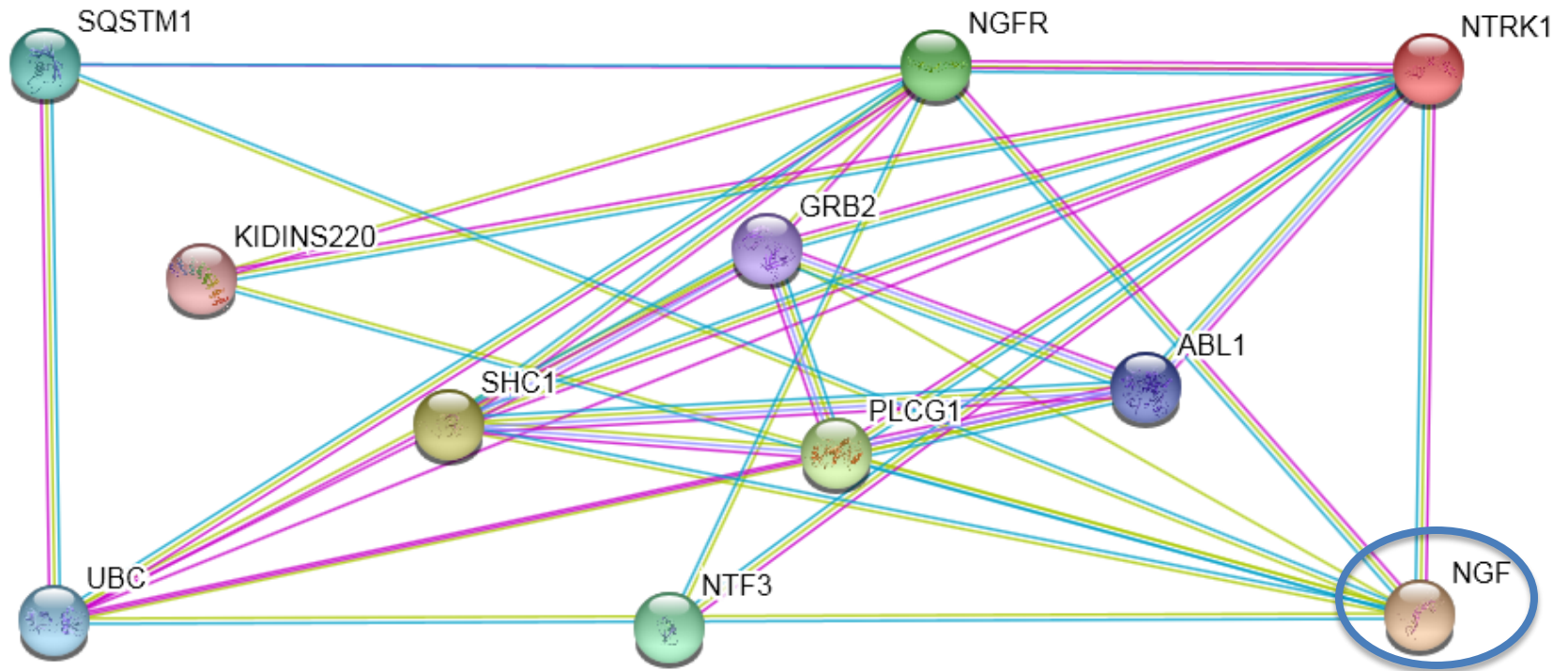
What are the NTRK1 mutation phenotypes in model organisms?



Homozygous mutants: premature death

Homozygotes with point mutation:
normal

What other proteins interact with NTRK1?





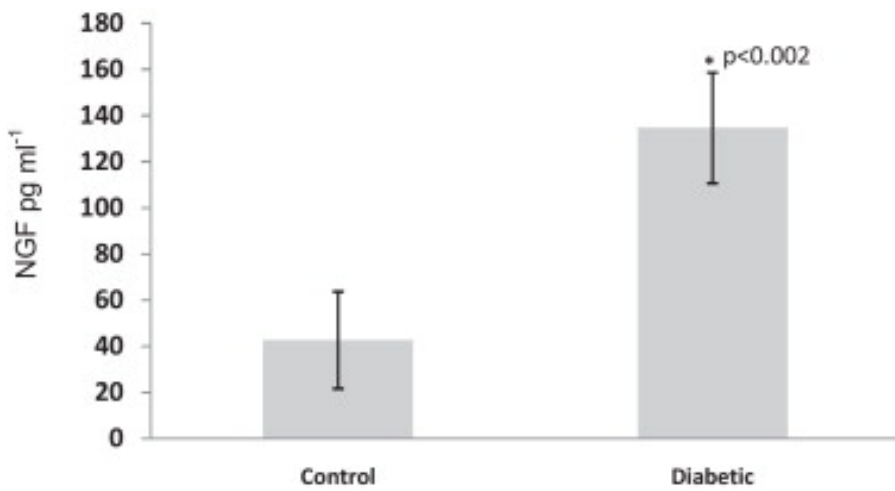
What is NGF?



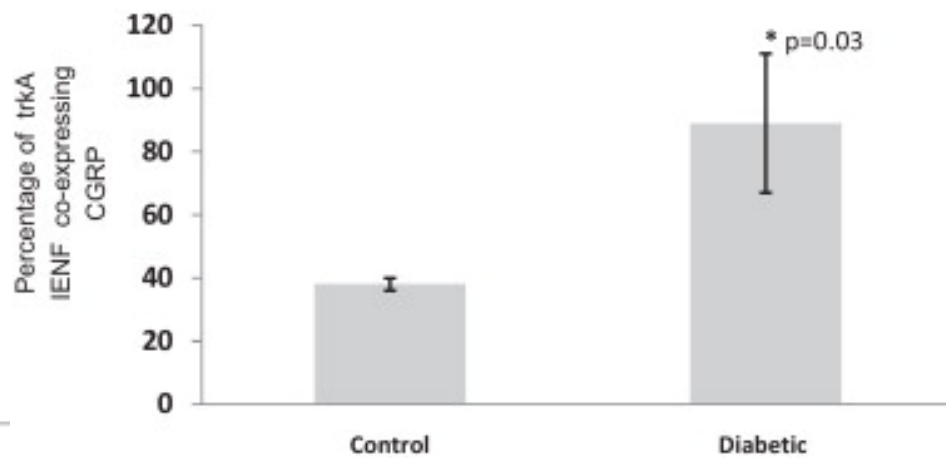
Growth Factor

Growth, maintenance and survival of neurons

NGF & NTRK1 are overexpressed in diabetic patients



NGF



NTRK1

Evans, Laura. "Increased Cutaneous NGF and CGRP-labelled TrkA-positive Intra-epidermal Nerve Fibres in Rat Diabetic Skin." *Neuroscience Letters* 506.1 (2012): 59-63. Print.

What is the connection between CIPA and diabetic patients?



Pain

vs

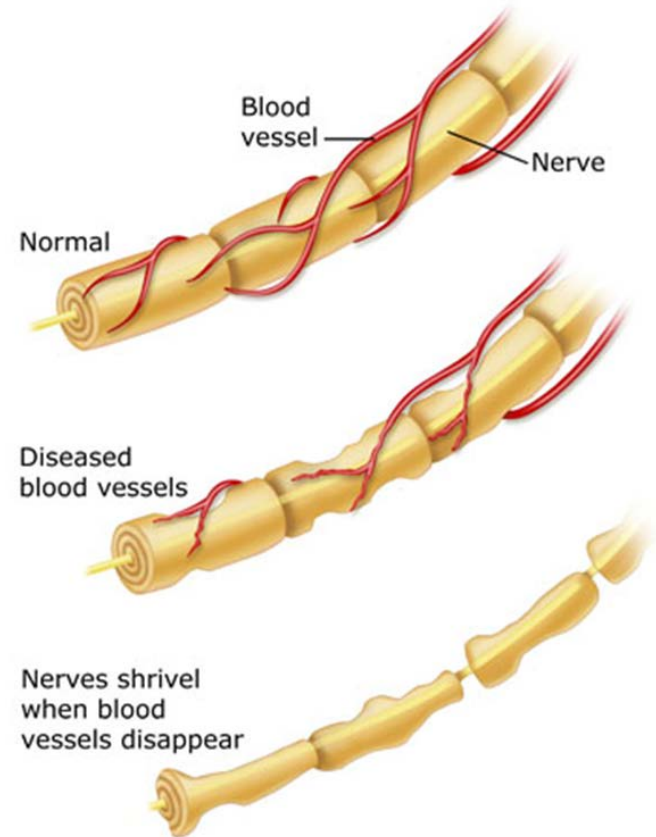


No Pain

	Wild Type	CIPA	Diabetes
NTRK1	Normal	Decreased	Increased
Phenotype	Normal	No Pain	Lots of Pain

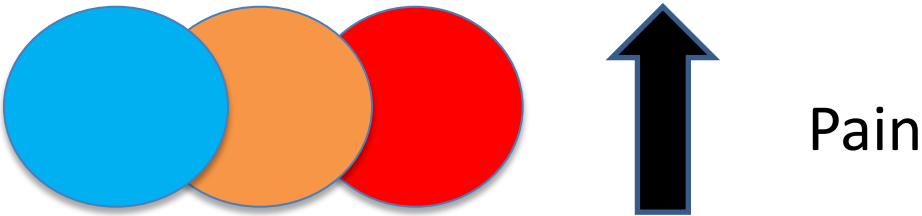
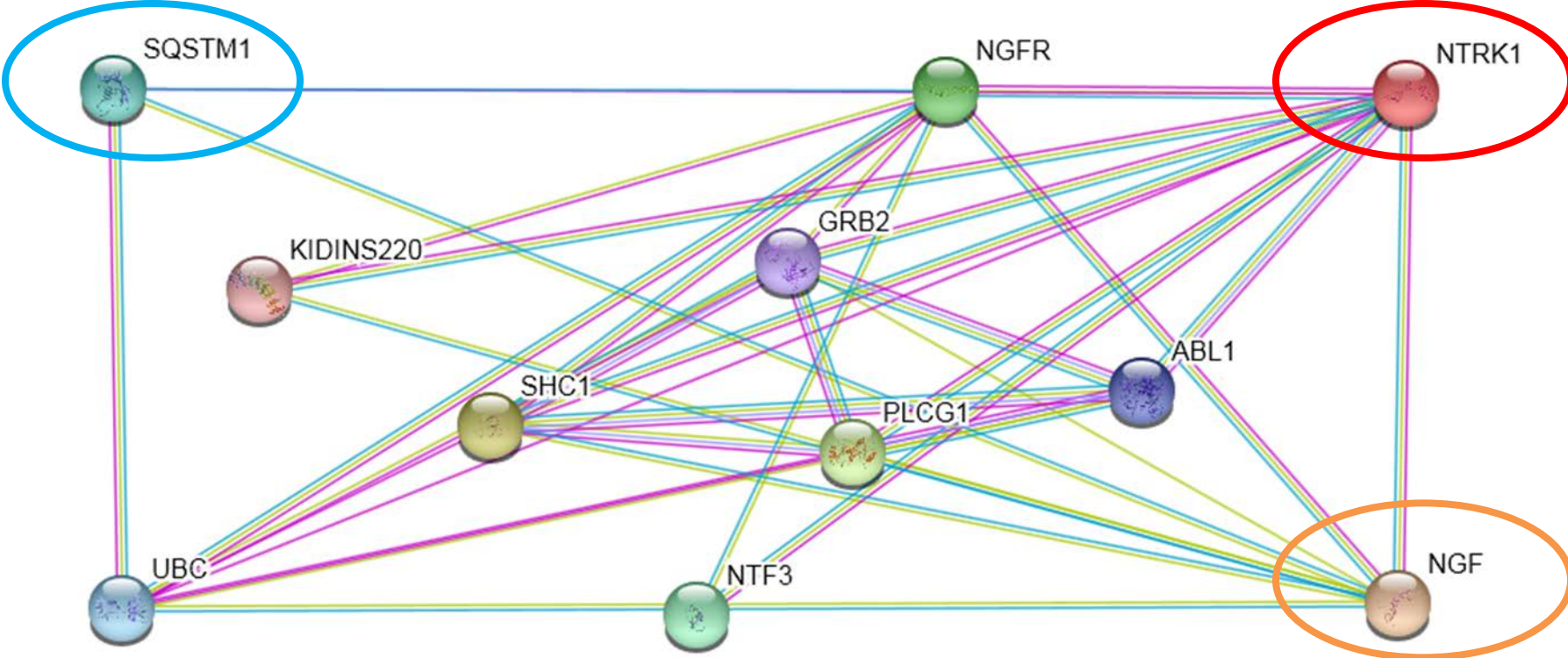
Diabetic Neuropathy

Diabetes Affects the Nerves



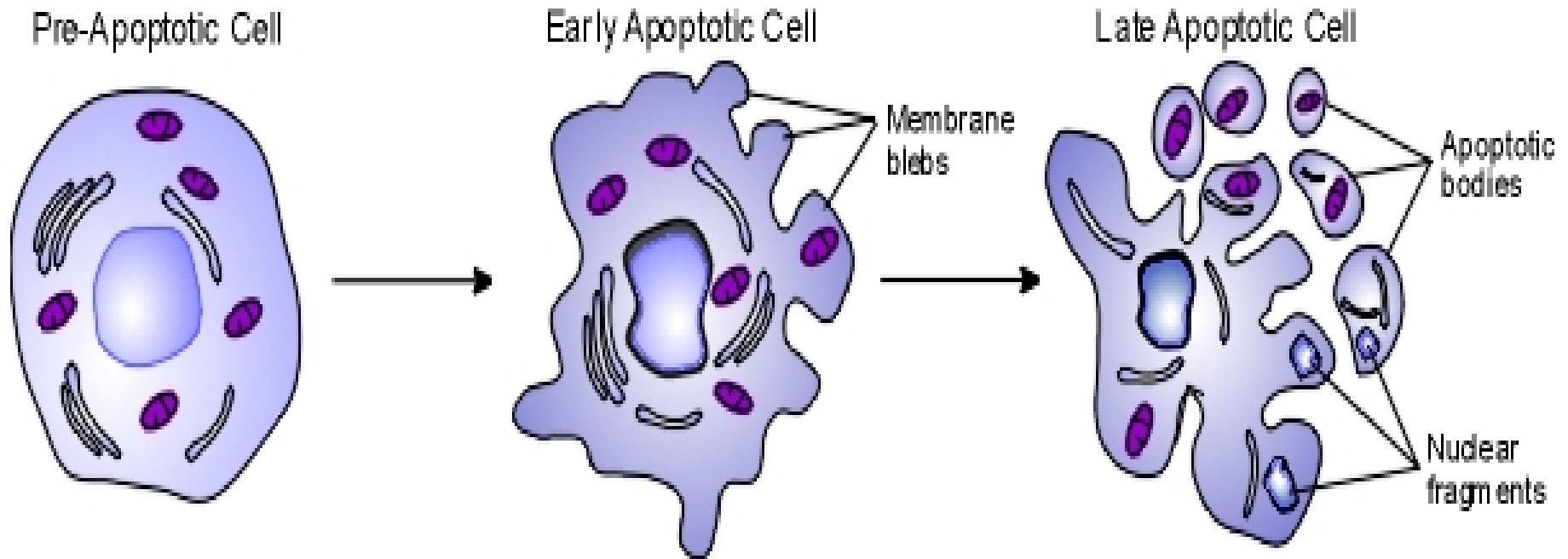
Why do nerves degenerate in diabetic patients?

What other NTRK1 interactors are upregulated in diabetic patients?




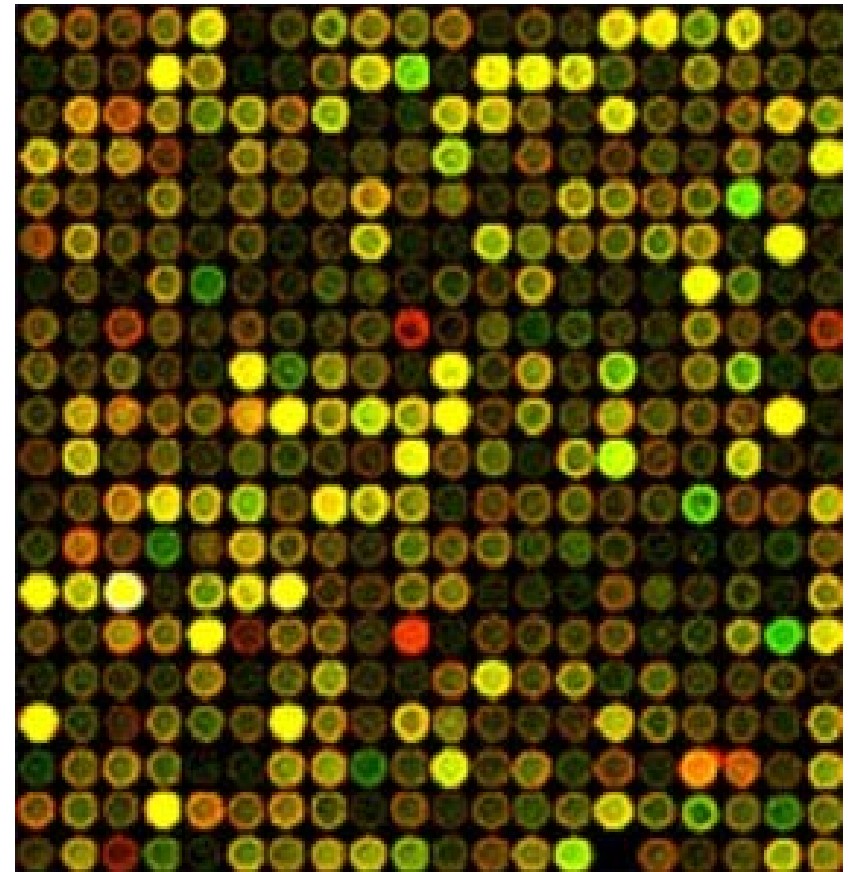
What is SQSTM1?

Binds ubiquitin



Is SQSTM1 highly expressed in diabetic patients?

	Wild Type	Diabetes
NTRK1	Normal	Increased
NGF	Normal	Increased
SQSTM1	Normal	?????????



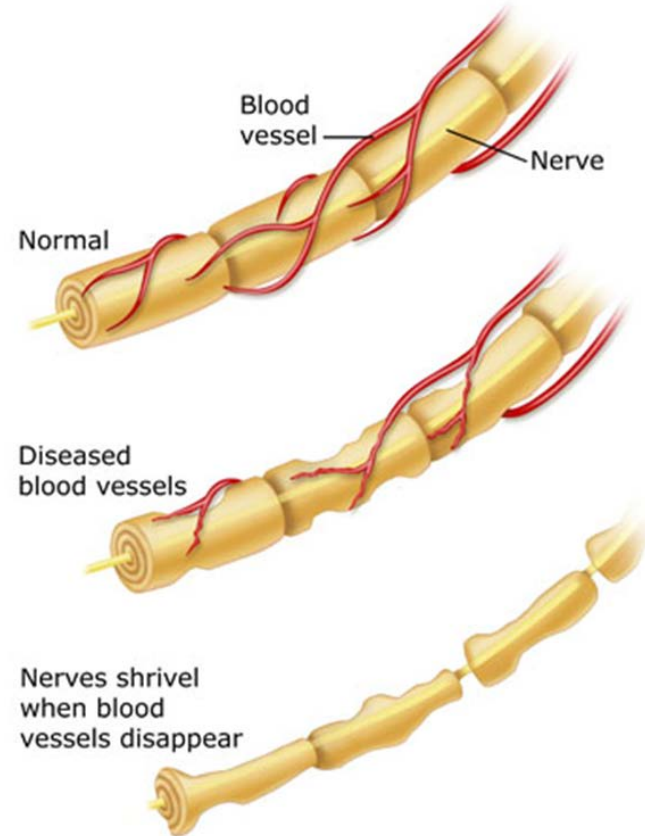
SQSTM1 is involved in nerve degeneration in diabetic patients



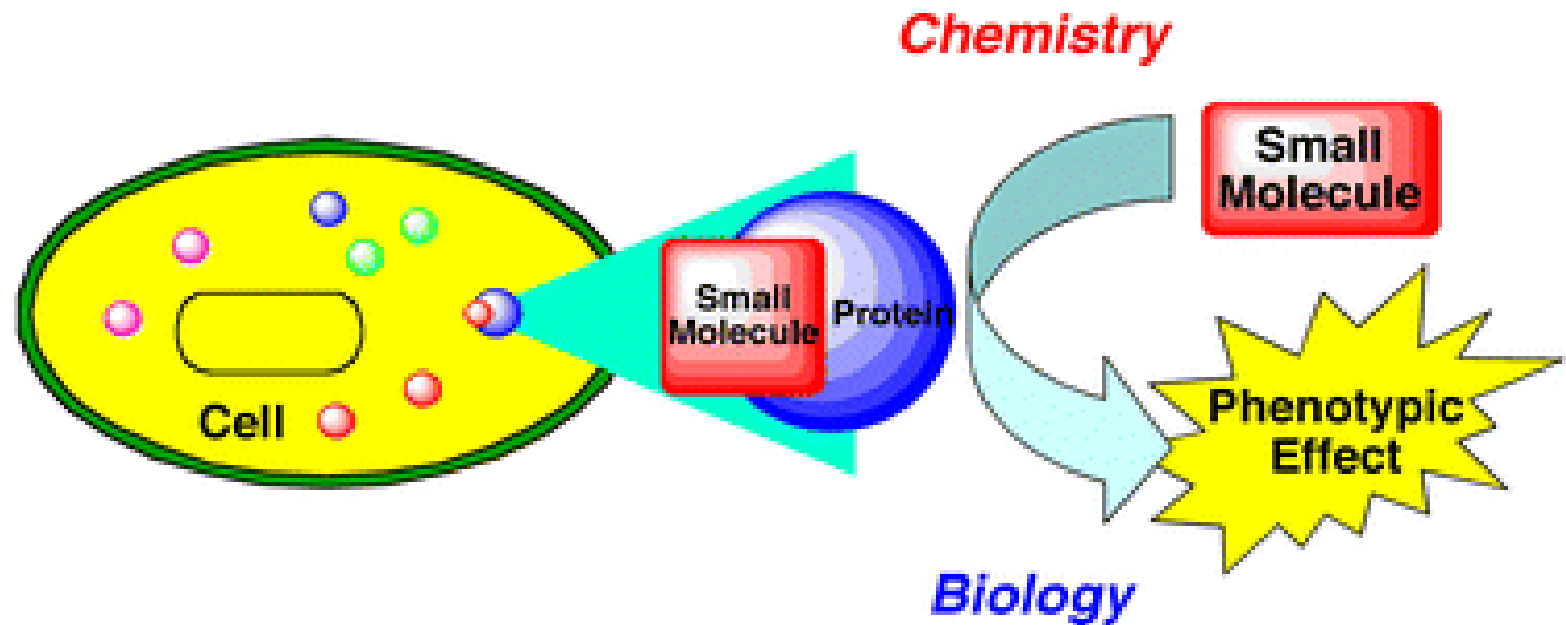
apoptosis



Diabetes Affects the Nerves



Can I modulate these genes in diabetic patients so the pain goes away?



Hypothesis: Genes that are upregulated in diabetics cause pain, regulation of these genes using a small molecule would alleviate pain.

How do I find a new compound that binds SQSTM1?

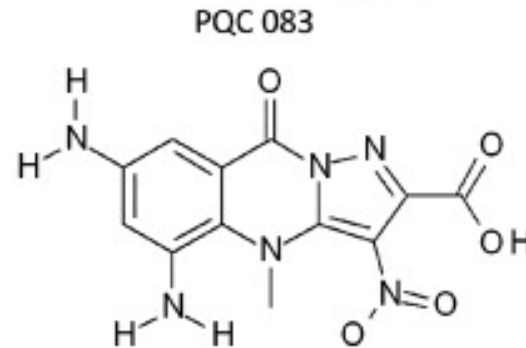
Chemical Genetics Screen

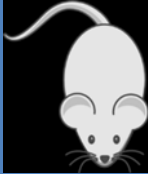


New
Compound



Can a drug that binds NGF affects the expression of SQSTM1 and NTRK1?



	Wildtype (Control)	Wildtype +Drug (Control)	Diabetic	Diabetic + Drug
NGF	Black	Green	Red	Green
SQSTM1	Black	Green	Red	Green
NTRK1	Black	Green	Red	Green

Upregulated
Downregulated
Constitutive
Expression

Conclusions



Potential drug therapy implications for diabetic neuropathy