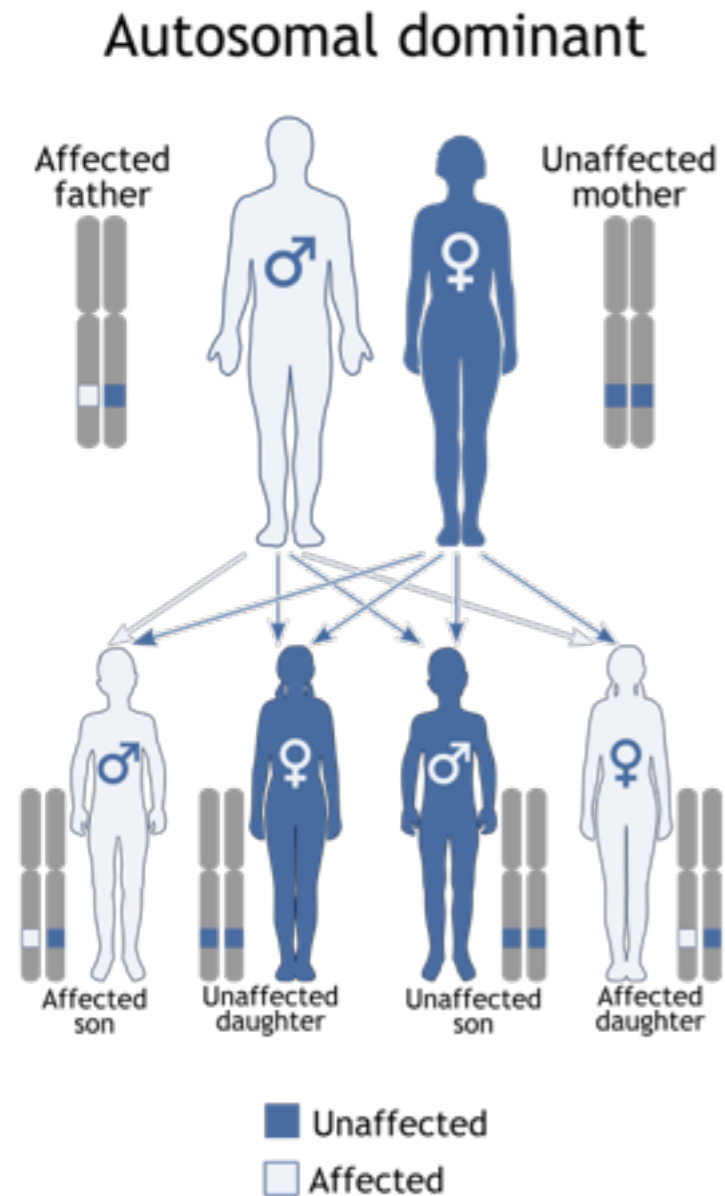


PTPN11 and Noonan syndrome

by Daniel Turner

What is Noonan syndrome and why is it important?



Short stature

Characteristic facial features³

Congenital heart defects³

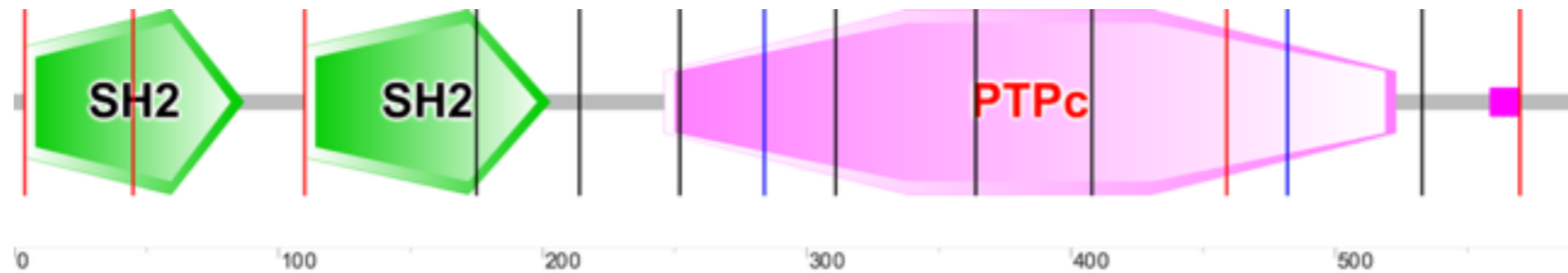


Affects 1 of 1000-2500

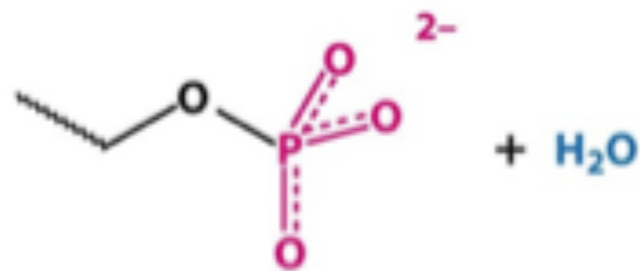
Reduces life expectancy by ~ 10 years

What causes Noonan syndrome and what does it do?

PTPN11/SHP2

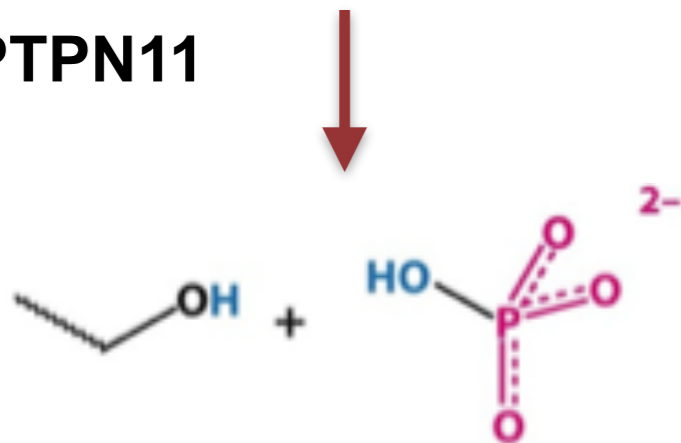


Molecular function



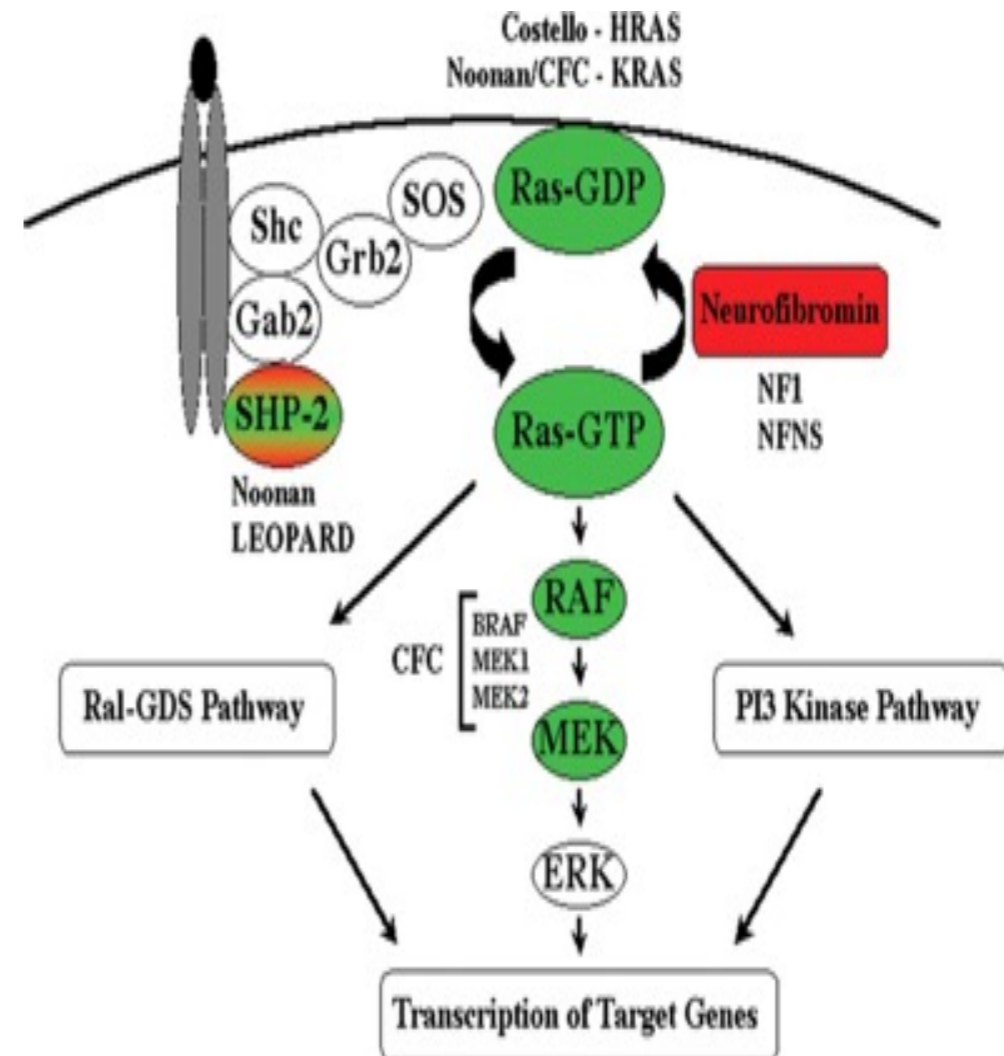
Phosphorylated protein

PTPN11



Dephosphorylated protein

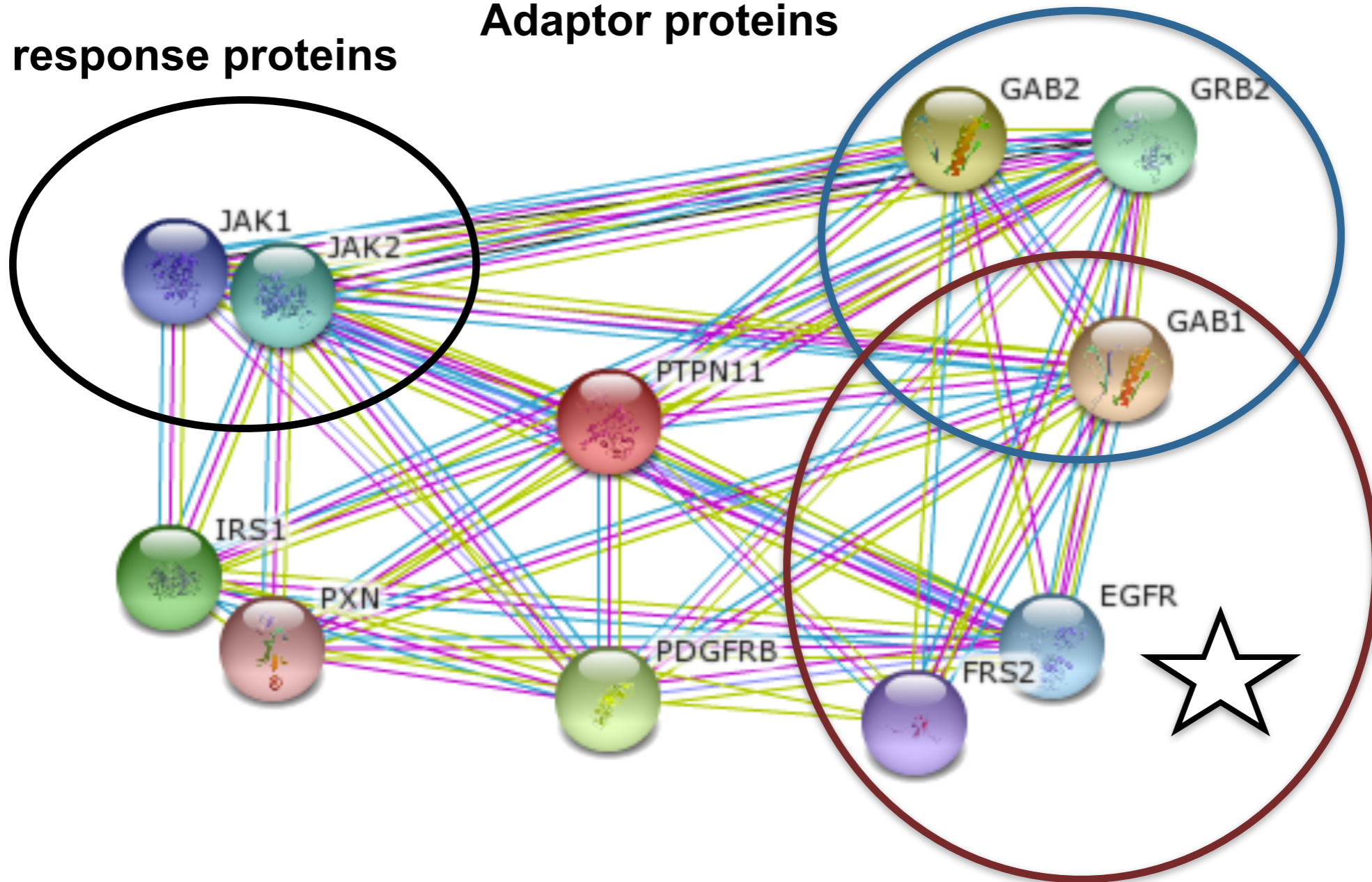
Biological processes and cellular component



What does PTPN11 interact with?

Immune response proteins

Adaptor proteins



Epidermal growth proteins

How conserved is PTPN11?



593 aa
100% identical



460 aa
100% identical



597 aa
99% identical



594 aa
91% identical

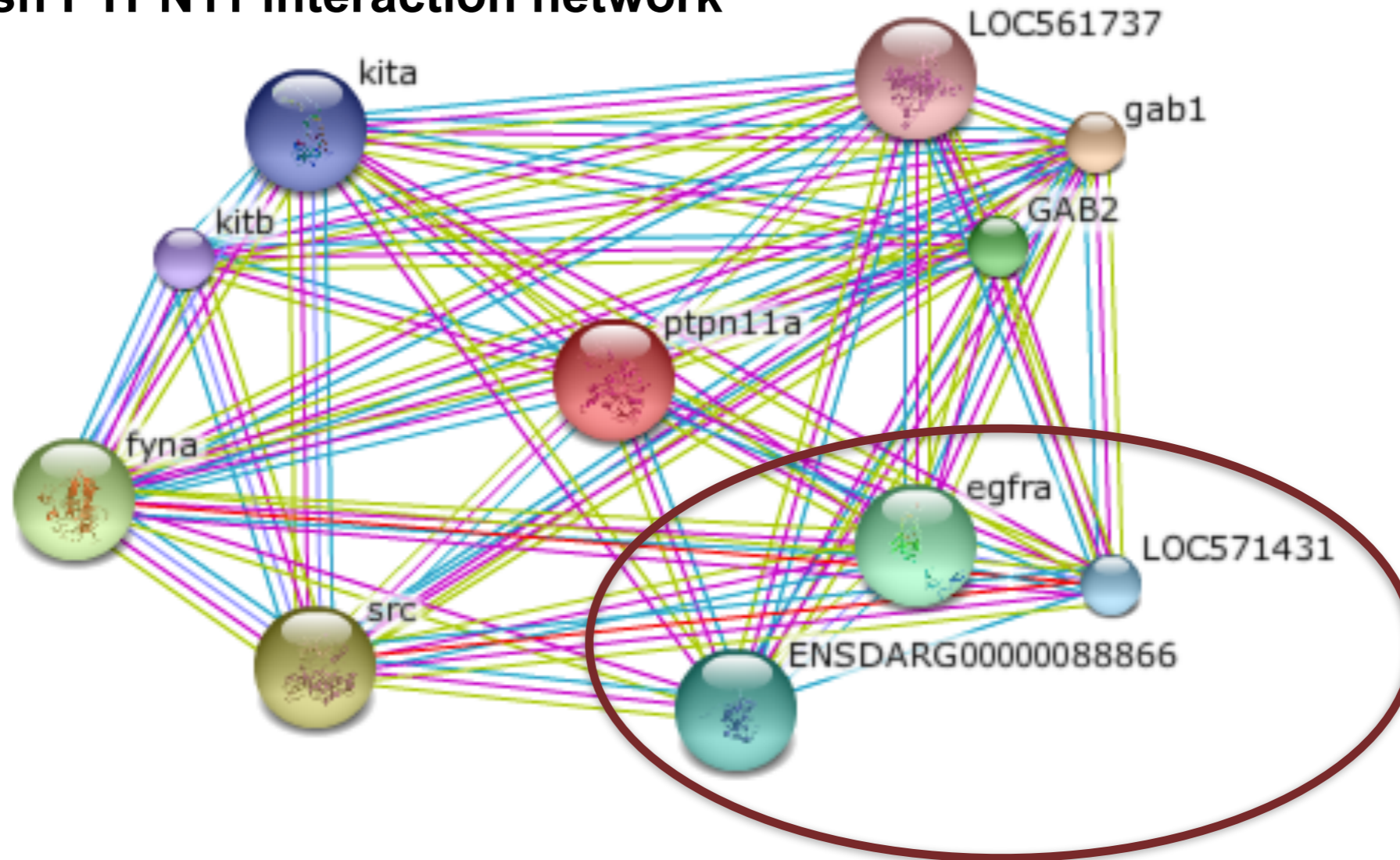


643 aa
66% identical

Why zebrafish?

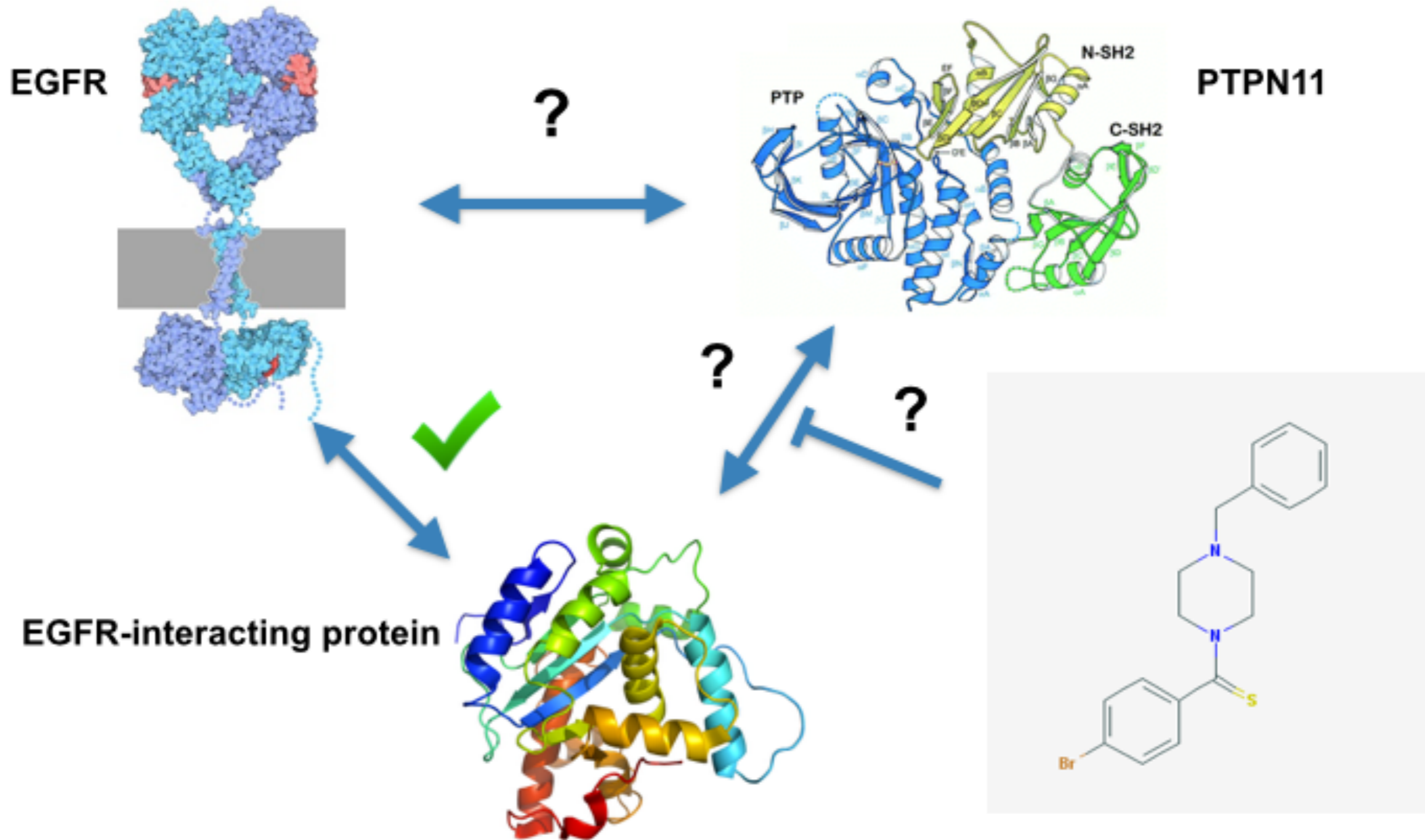


Zebrafish PTPN11 interaction network



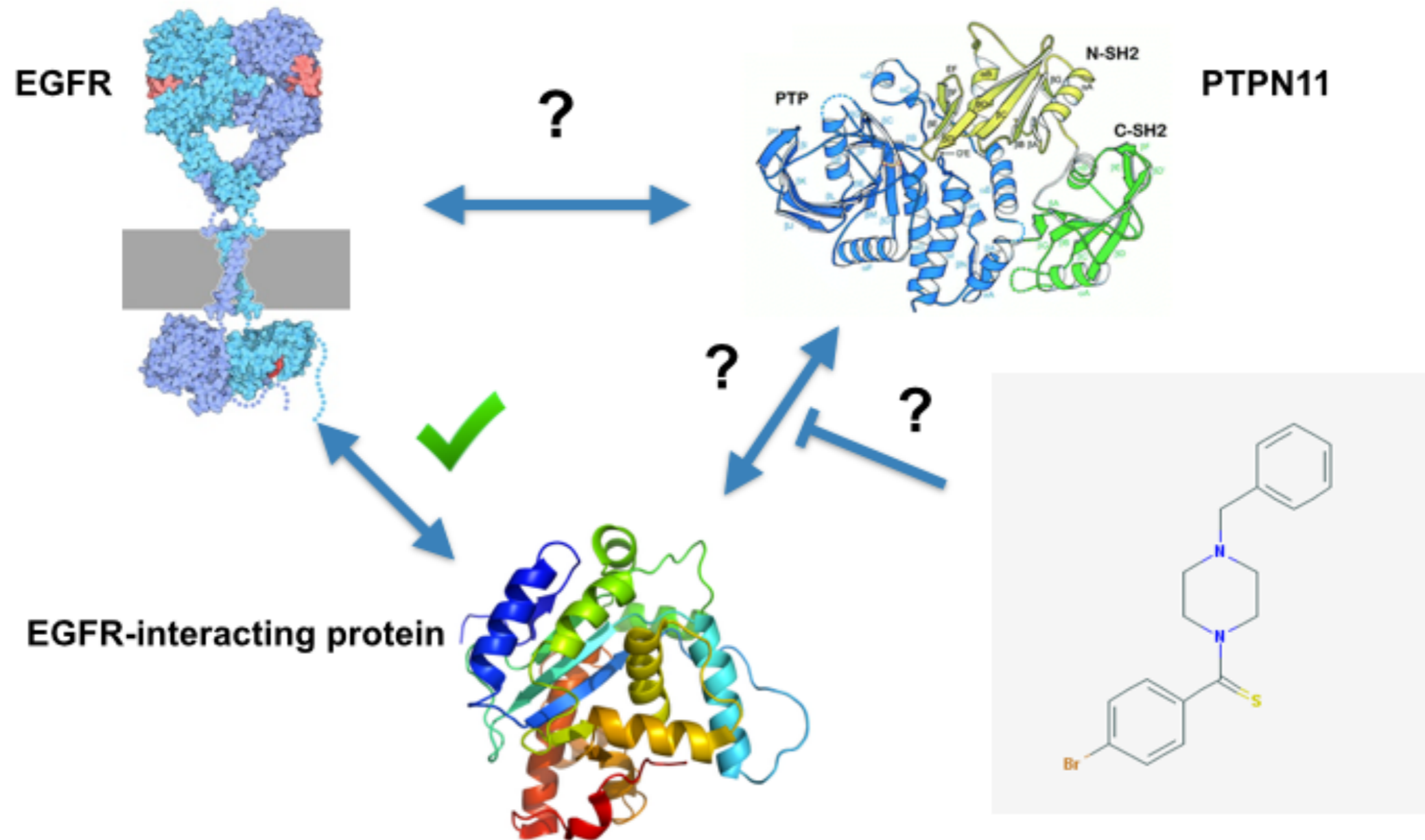
*
Epidermal growth proteins

What is unknown about PTPN11 in skin development?



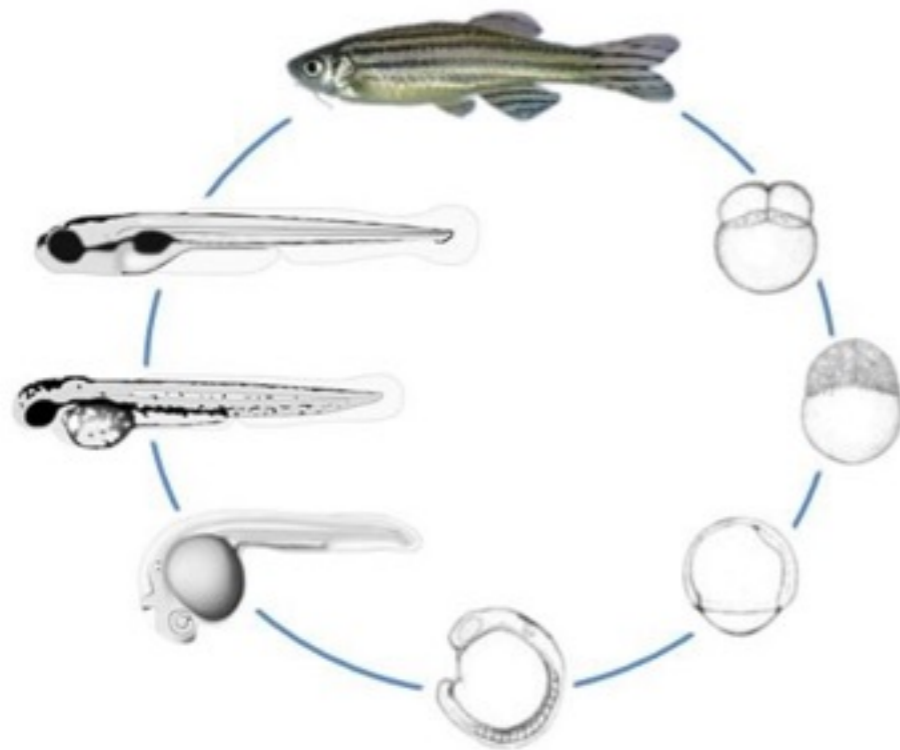
What is the goal of this experiment?

Discover proteins involved in embryonic skin development and learn how to effectively manipulate them on a chemogenomic level

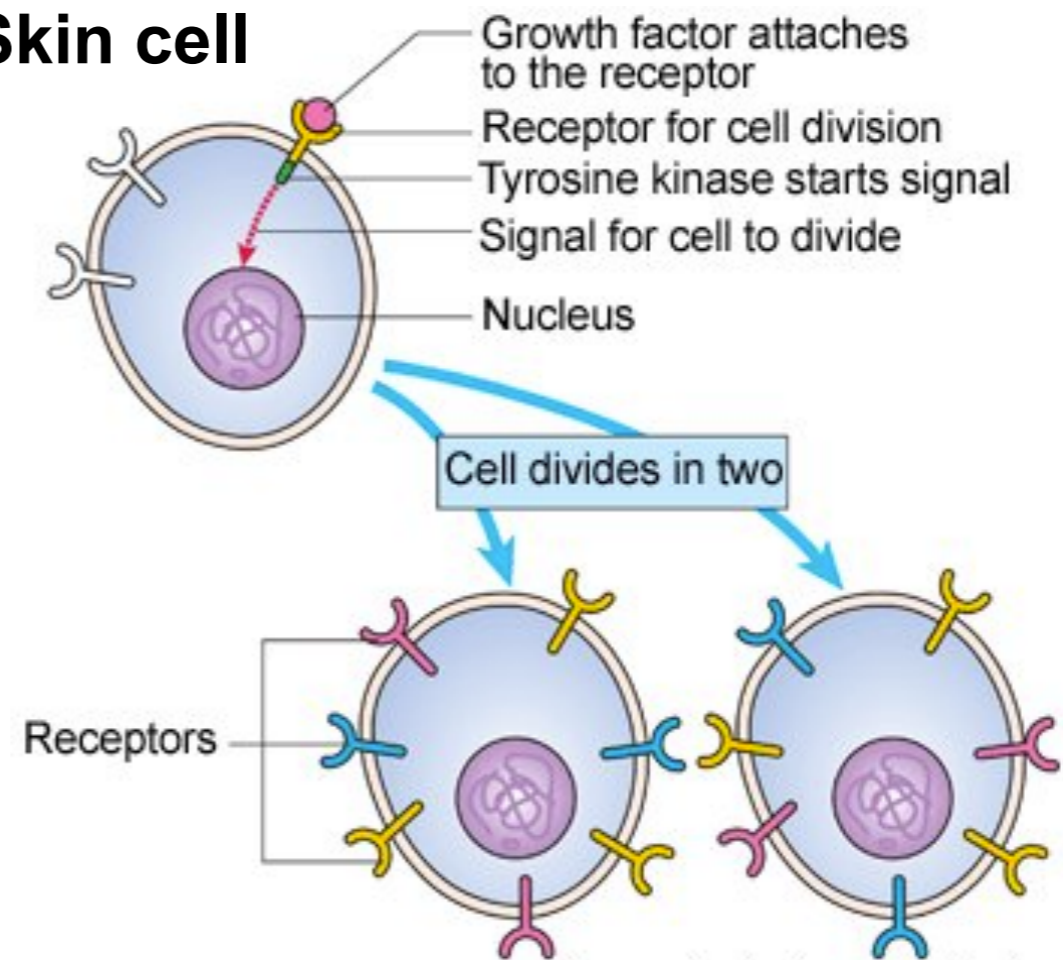


Based off what we know, how should we design an experiment to achieve this goal?

Hypothesis: PTPN11 regulates proteins involved with skin development during embryogenesis of zebrafish.



Skin cell



Experimental design:

Find protein interactions



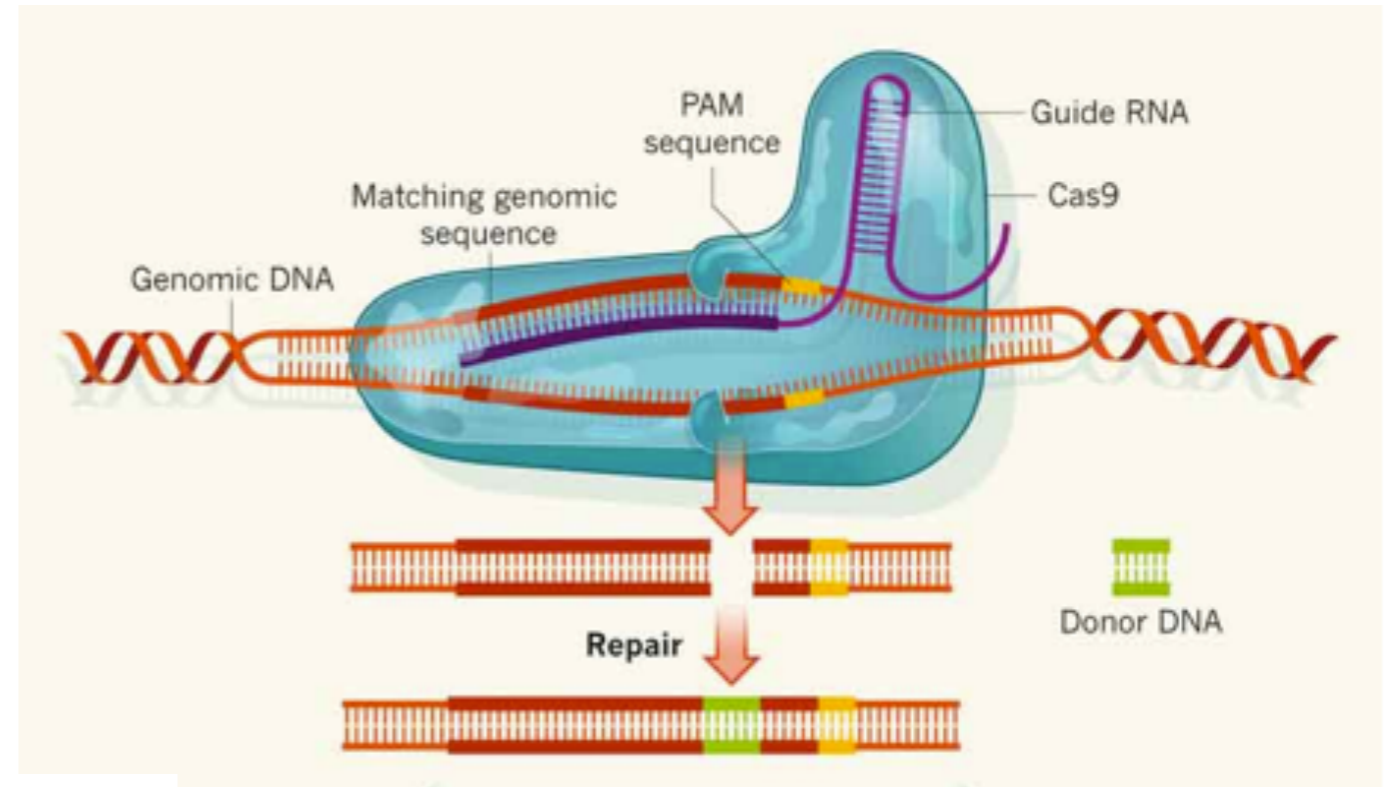
Find compounds that inhibit interacting proteins



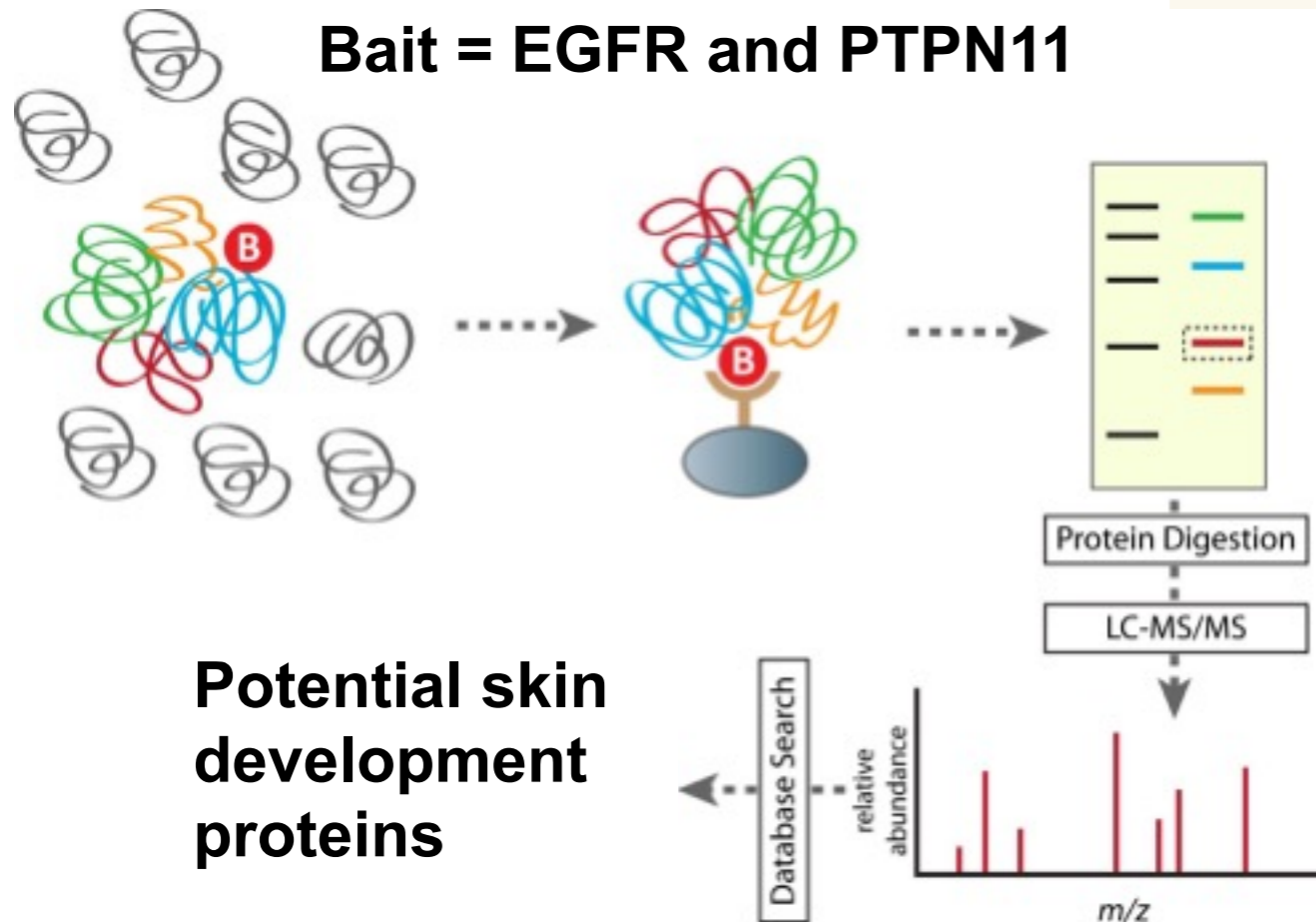
Test compounds for efficacy

Aim 1: Determine mutant and WT protein interactions controlling skin development

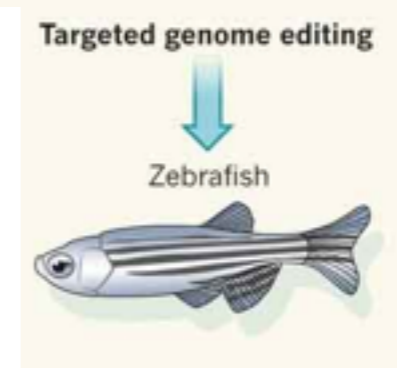
A. Generate mutant zebrafish



Bait = EGFR and PTPN11



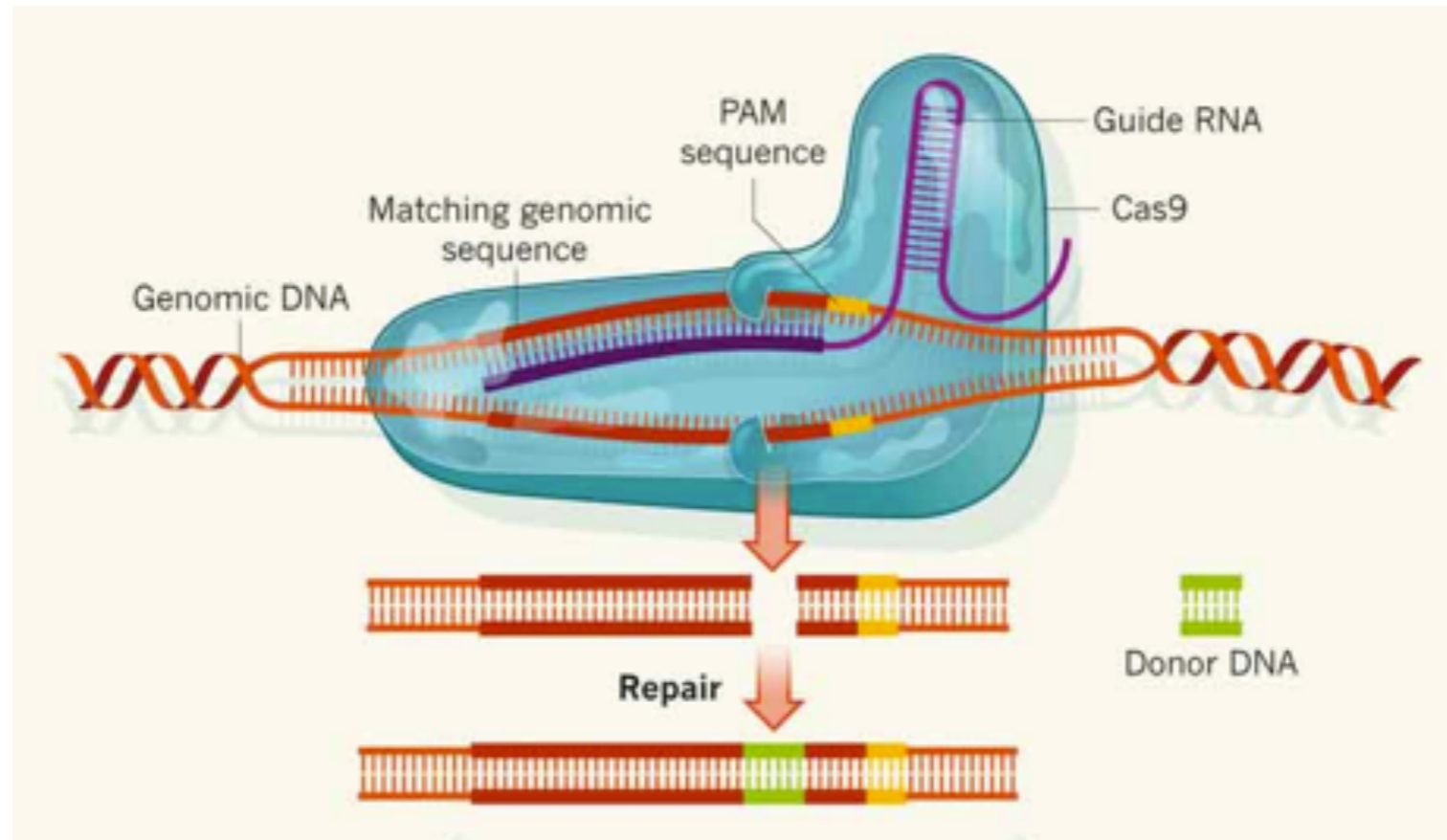
Potential skin development proteins



B. Identify protein interactions within Mutant and WT zebrafish

Aim 1: Determine mutant and WT protein interactions controlling skin development

C. Knockout potential skin development proteins found via TAP



Aim 2: Identify compounds that inhibit WT and/or mutant PTPN11 interacting proteins

A. Perform pubchem database search



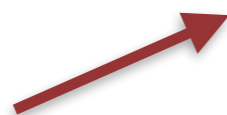
B. Perform chemogenomic assay on interacting proteins to identify additional inhibitors

WT and mutant interacting proteins



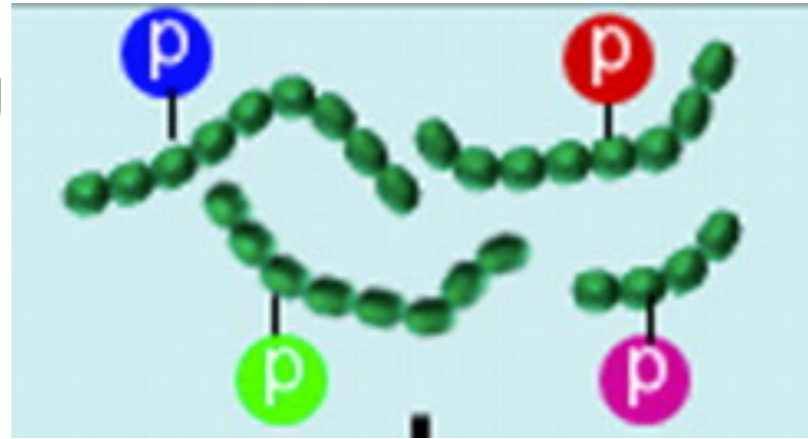
Active compounds

Potential inhibitors



Aim 3: Test active compound efficacy using phosphoproteomics

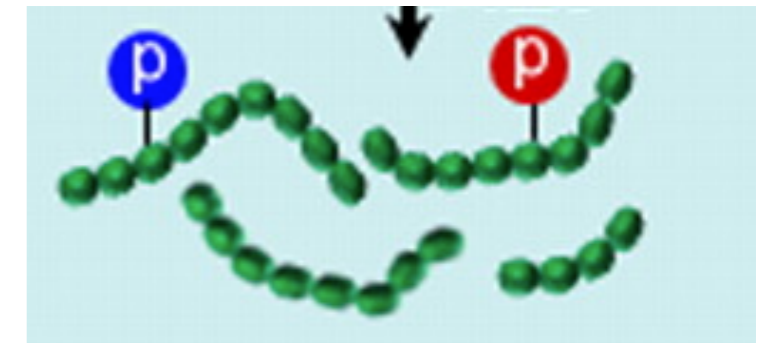
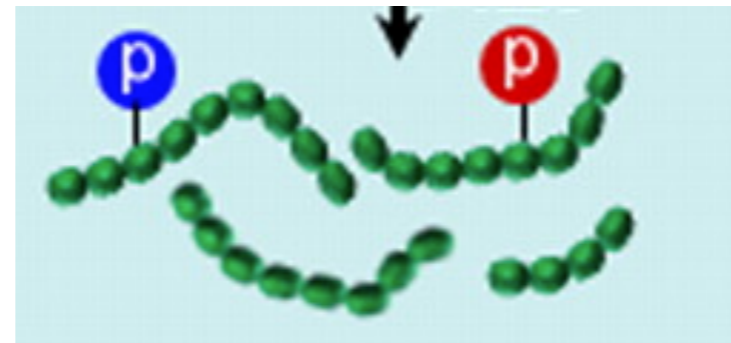
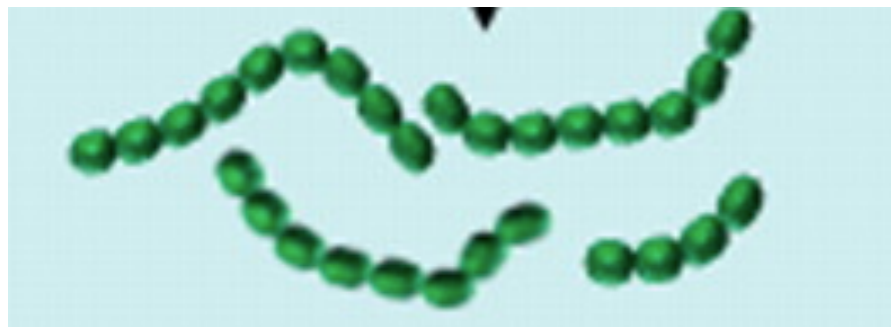
EGFR and PTPN11 interacting protein peptides



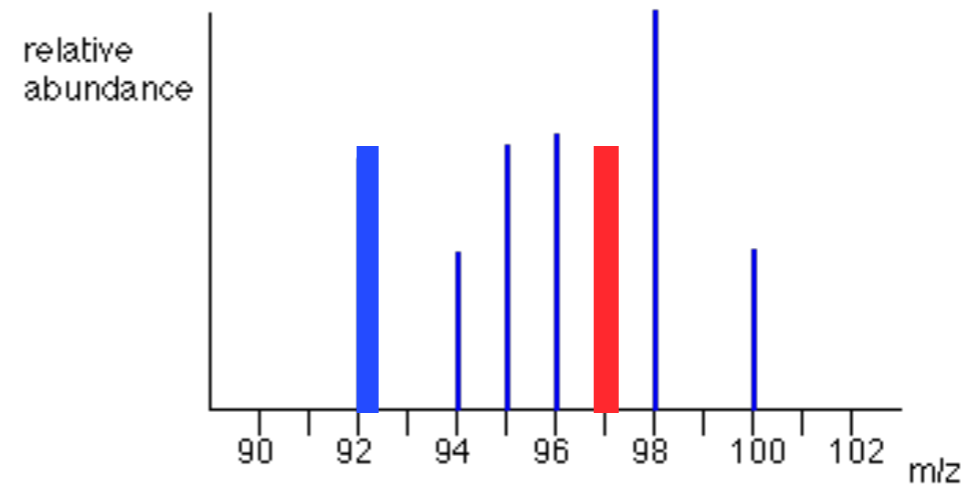
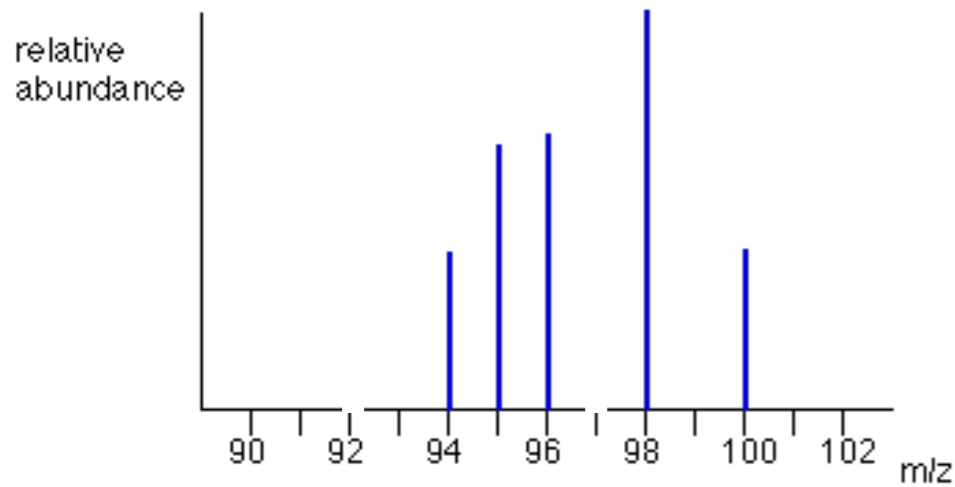
Mutant PTPN11

WT PTPN11

Mutant PTPN11 with inhibitor



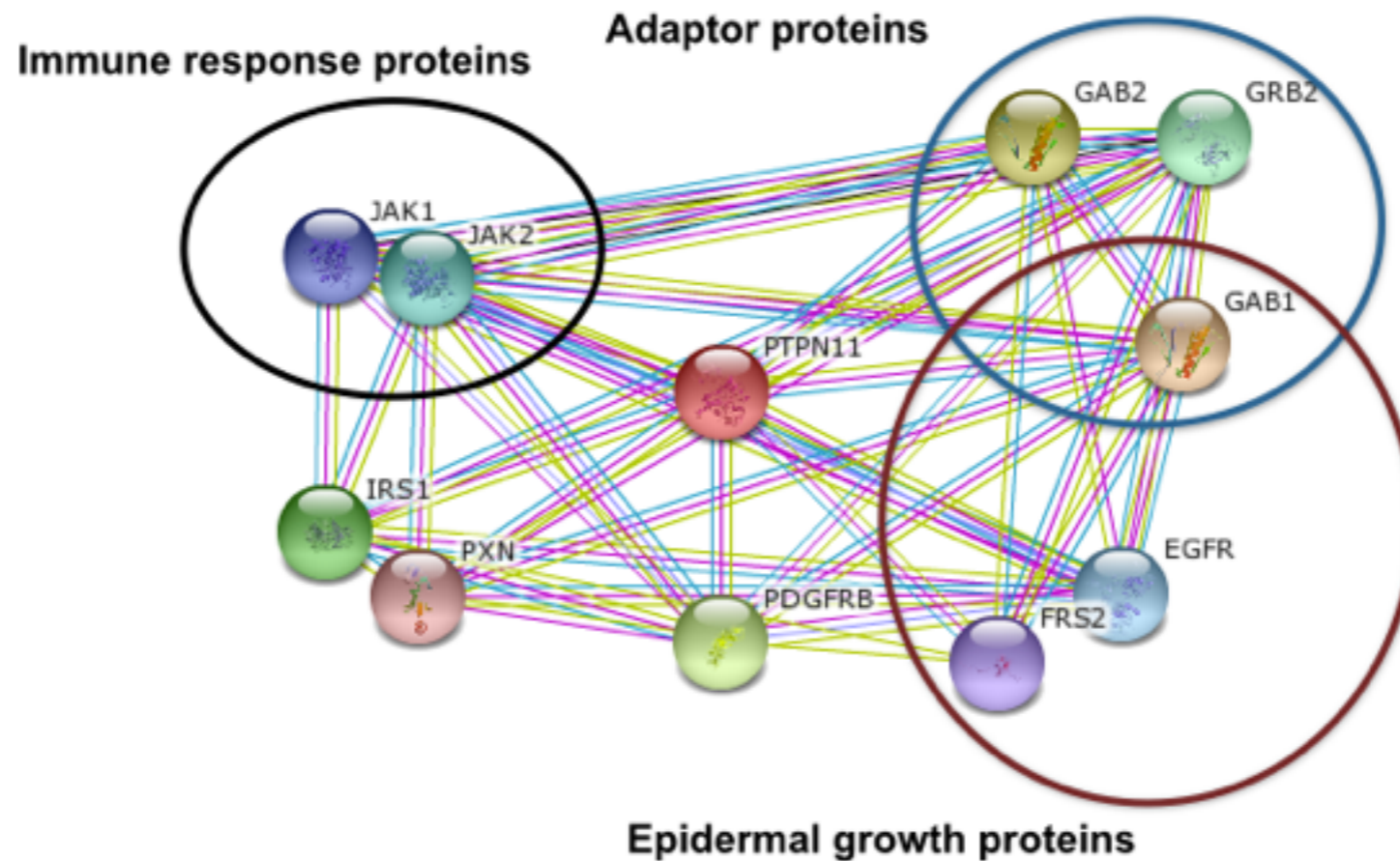
Tandem MS



Future directions



©Witna Photographic





References

Literature

"Noonan Syndrome." Genetics Home Reference. U.S National Library of Medicine, 4 May 2015. Web. 06 May 2015.

"PTPN11 Gene." Genetics Home Reference. U.S National Library of Medicine, 4 May 2015. Web. 06 May 2015.

"STRING: Functional Protein Association Networks." STRING: Functional Protein Association Networks. SIB, n.d. Web. 06 May 2015.

Images

<http://www.clipartbest.com/check-mark-png>

<http://boston.cbslocal.com/2015/04/05/red-cross-marking-marathon-bombings-with-blood-drives/>

<http://www.cancerresearchuk.org/about-cancer/cancers-in-general/treatment/biological/types/cancer-growth-blockers>

http://red.dfc.harvard.edu/eck_structures.html

http://hmg.oxfordjournals.org/content/15/suppl_2/R220/F1.expansion

<http://turnergen564s15.weebly.com/gene.html>

http://web.science.uu.nl/developmentalbiology/boxem/interaction_mapping.html

<http://www.origene.com/CRISPR-CAS9/>

<http://www.chemguide.co.uk/analysis/masspec/howitworks.html>

<http://www.nature.com/scientificamerican/journal/v301/n2/full/scientificamerican0809-70.html>

http://www.nature.com/cr/journal/v17/n1/fig_tab/7310140f1.html

<http://crenshawcomm.com/clients-ask-pr-agencies-wrong-questions/>

<https://www.edgebio.com/products/96-well-treated-microplates-u-bottom-50063>

<https://pubchem.ncbi.nlm.nih.gov/search/#collection=bioassays>

<http://www.heliosderm.com/zebra-fish-ipilimumab-las-vegas-dermatology.html>