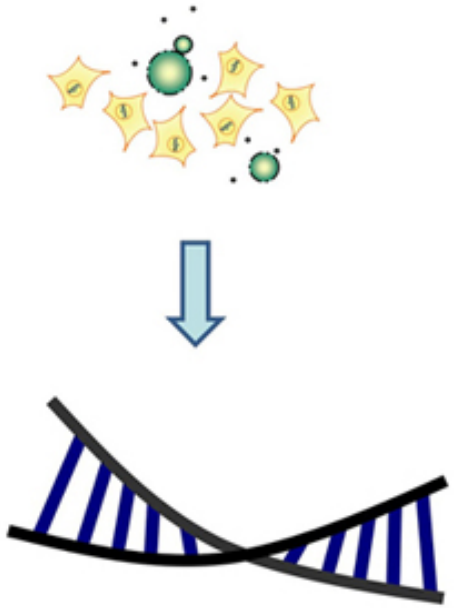
Chemical Genomics

Teja Mallela & Nikhil Desen

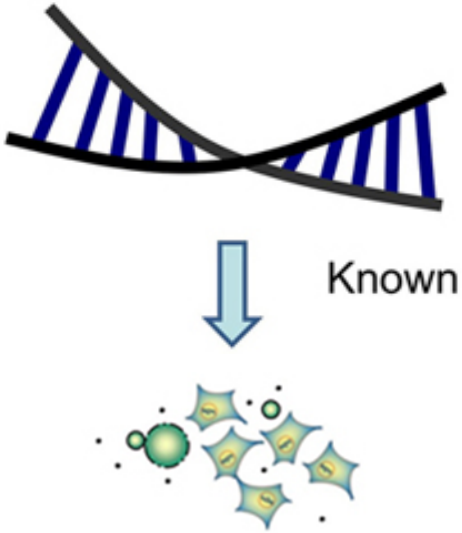
Traditional genetic approaches

Forward Genetic Screens



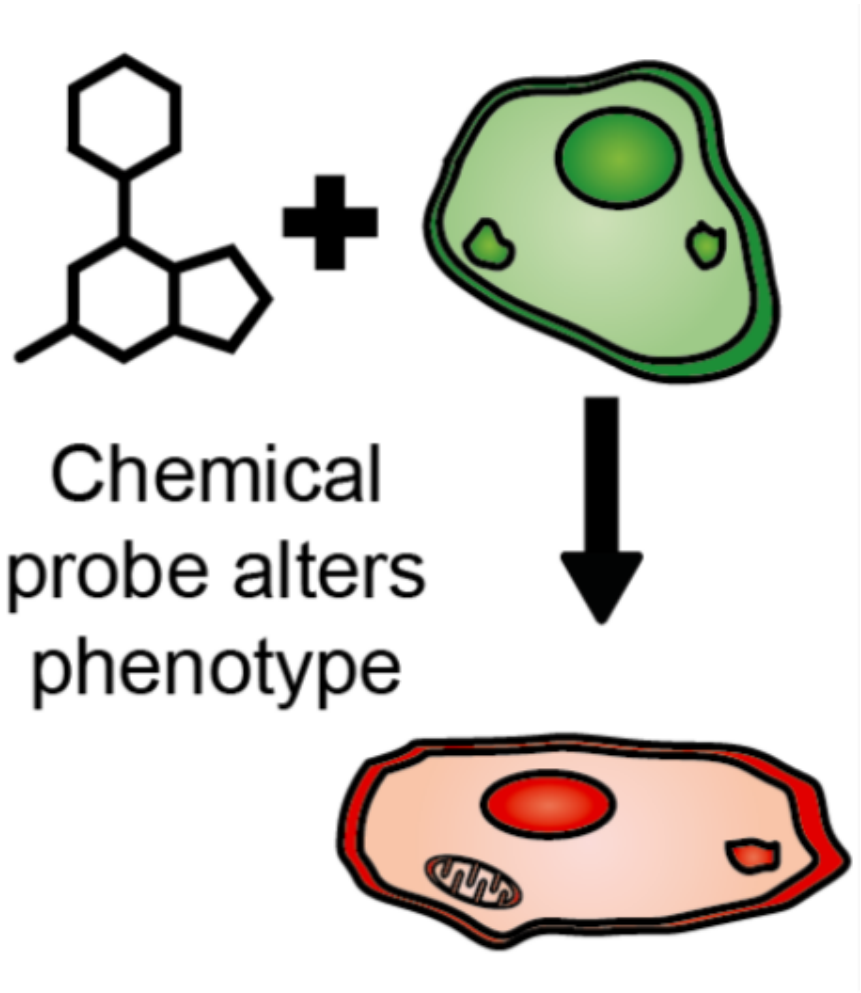
Discover Gene underlying Phenotype

Reverse Genetic Screens



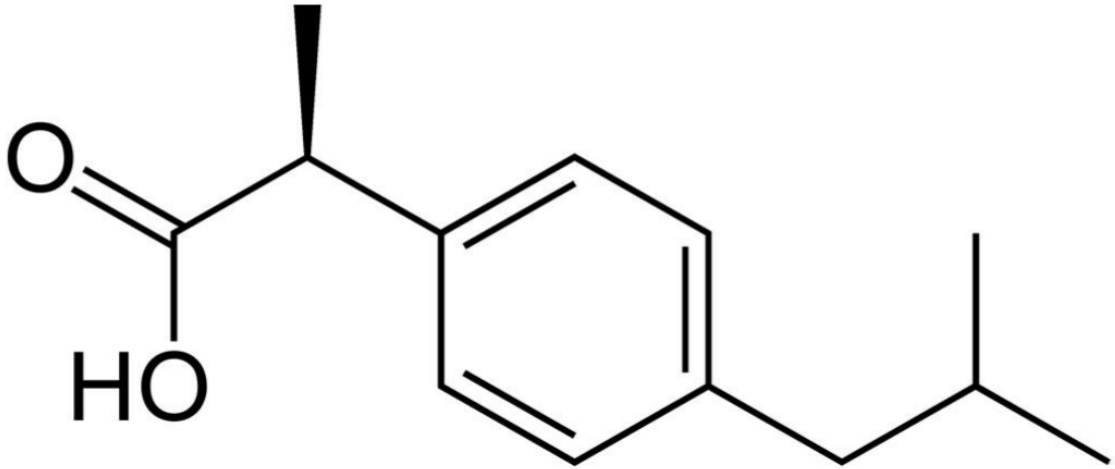
Phenotype Resulting from Alteration

What is Chemical Genetics?



The use of small molecules to perturb biological pathways

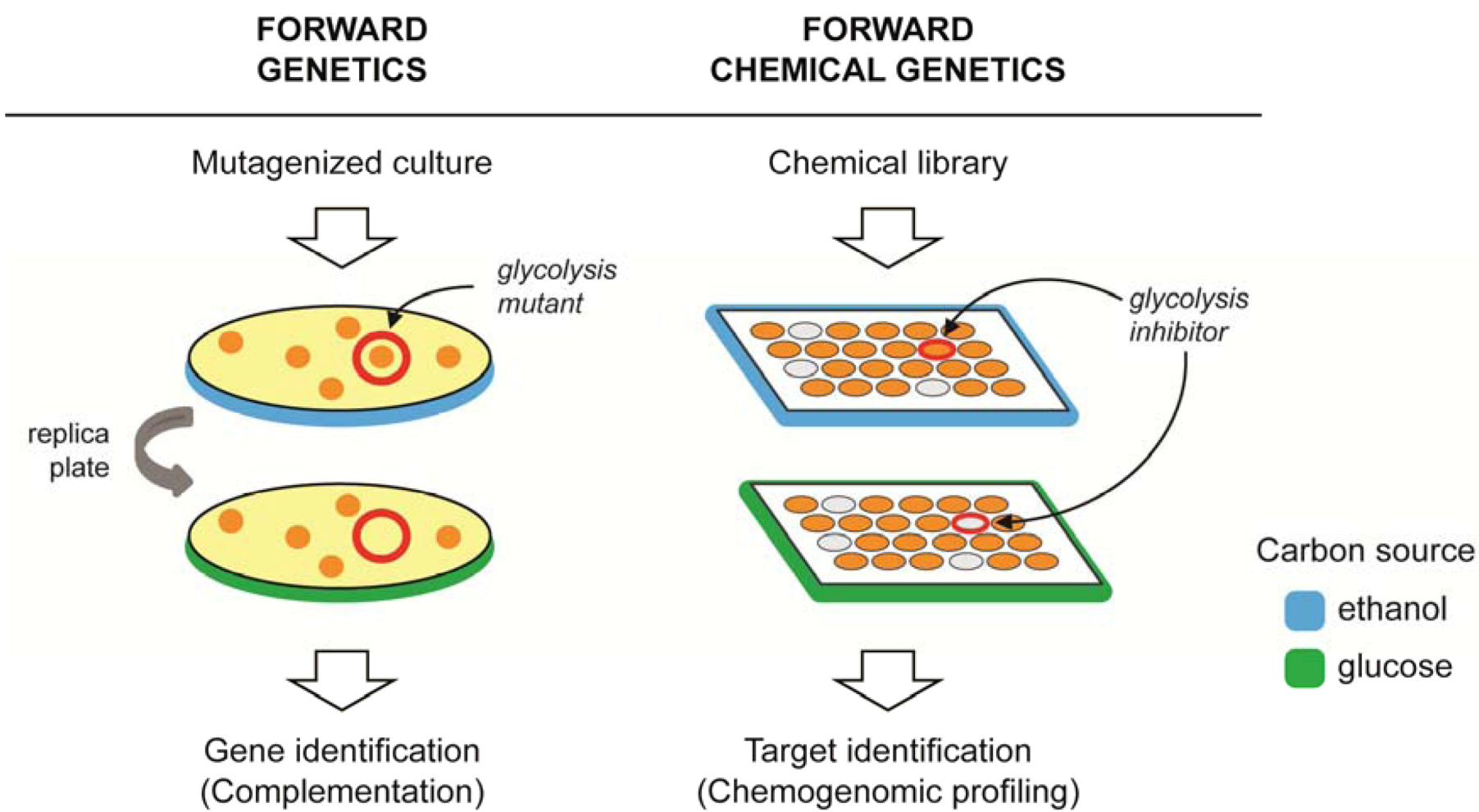
Why is chemical genetics useful?



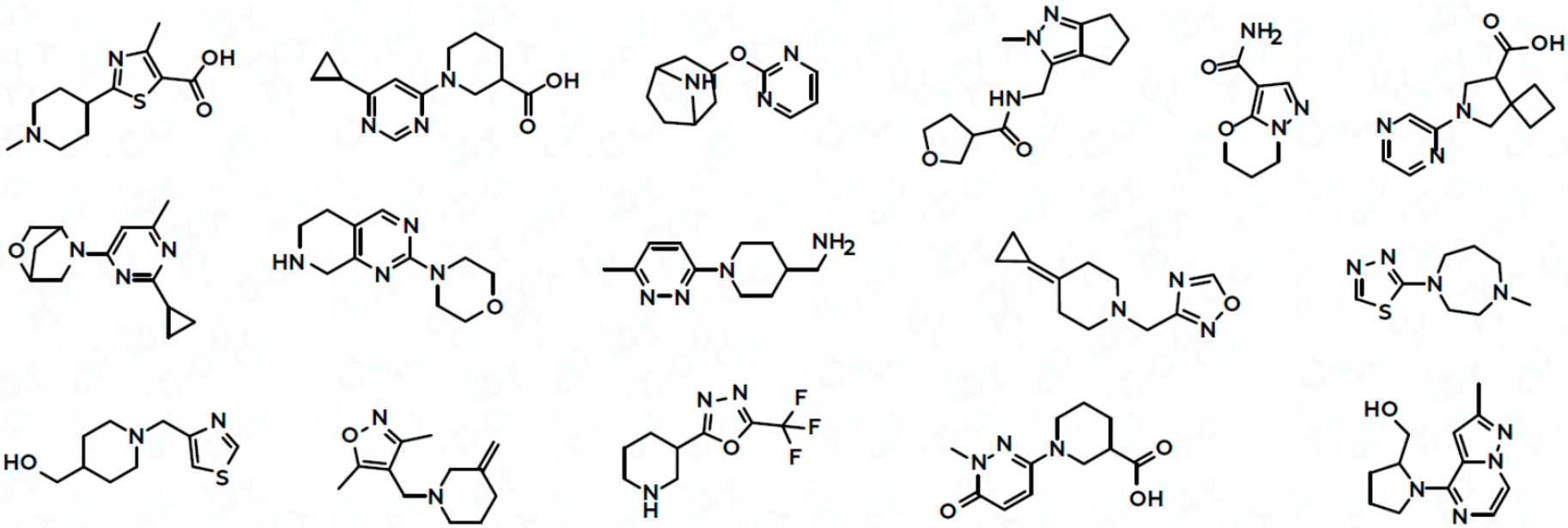
Can simultaneously:

- **identify target pathways**
- **identify novel therapeutic drugs**

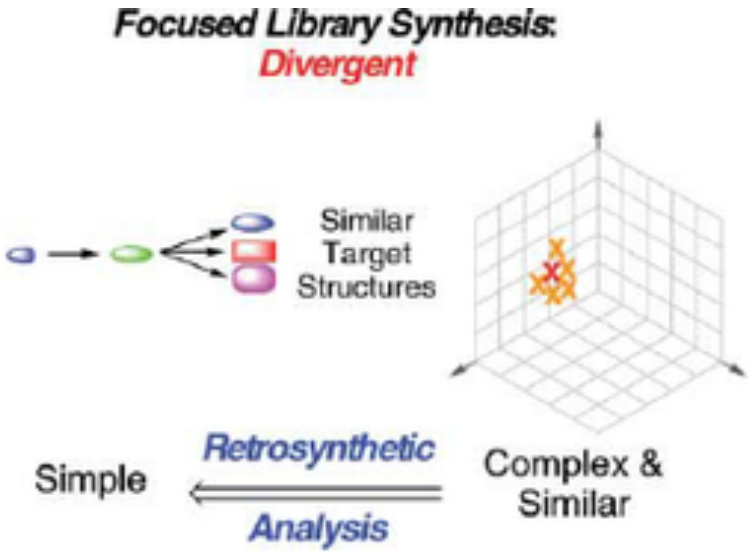
How can we use chemical genetics?

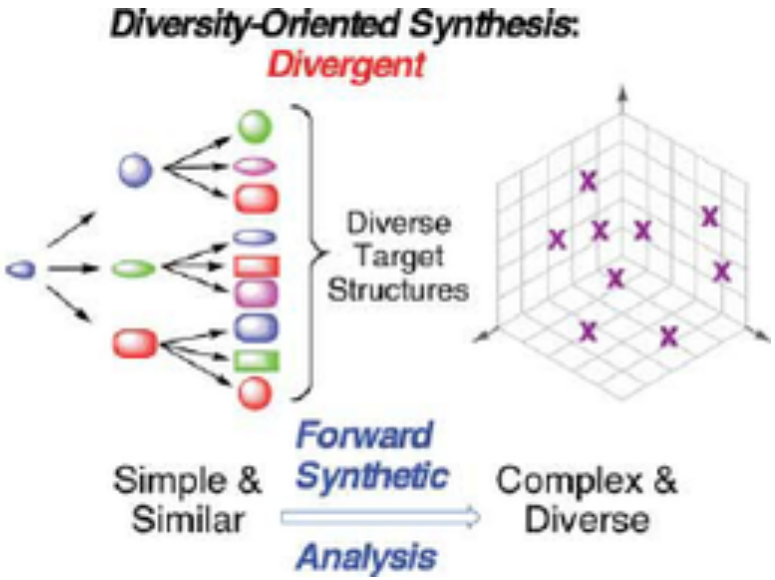


What is a chemical library?



What makes an ideal chemical library?

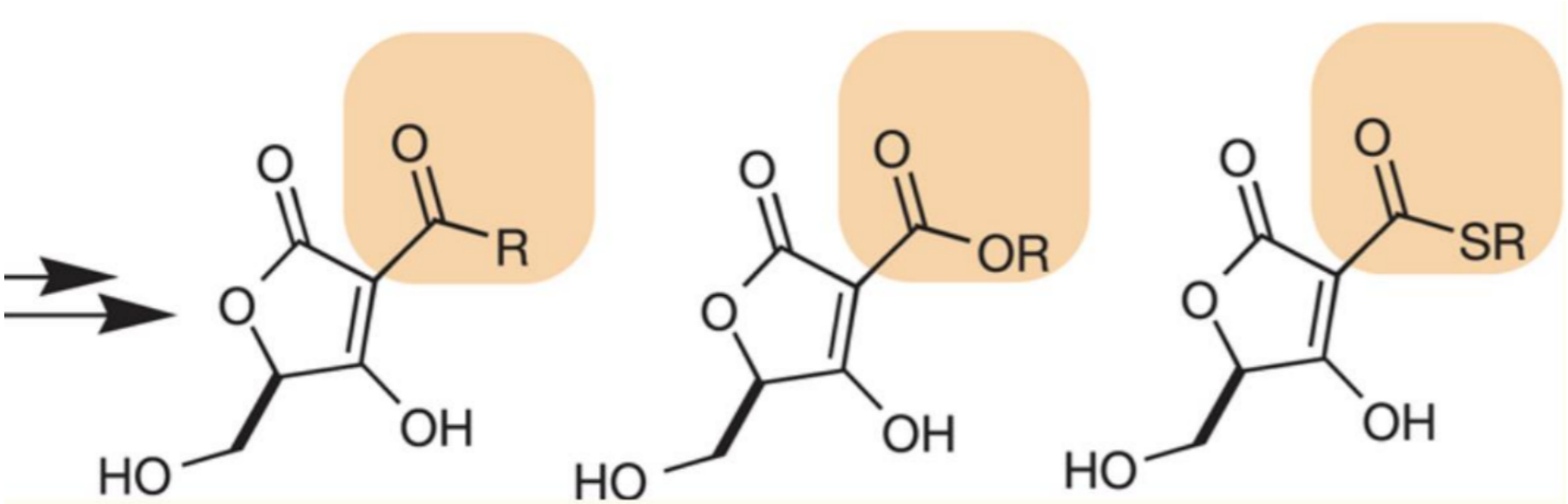




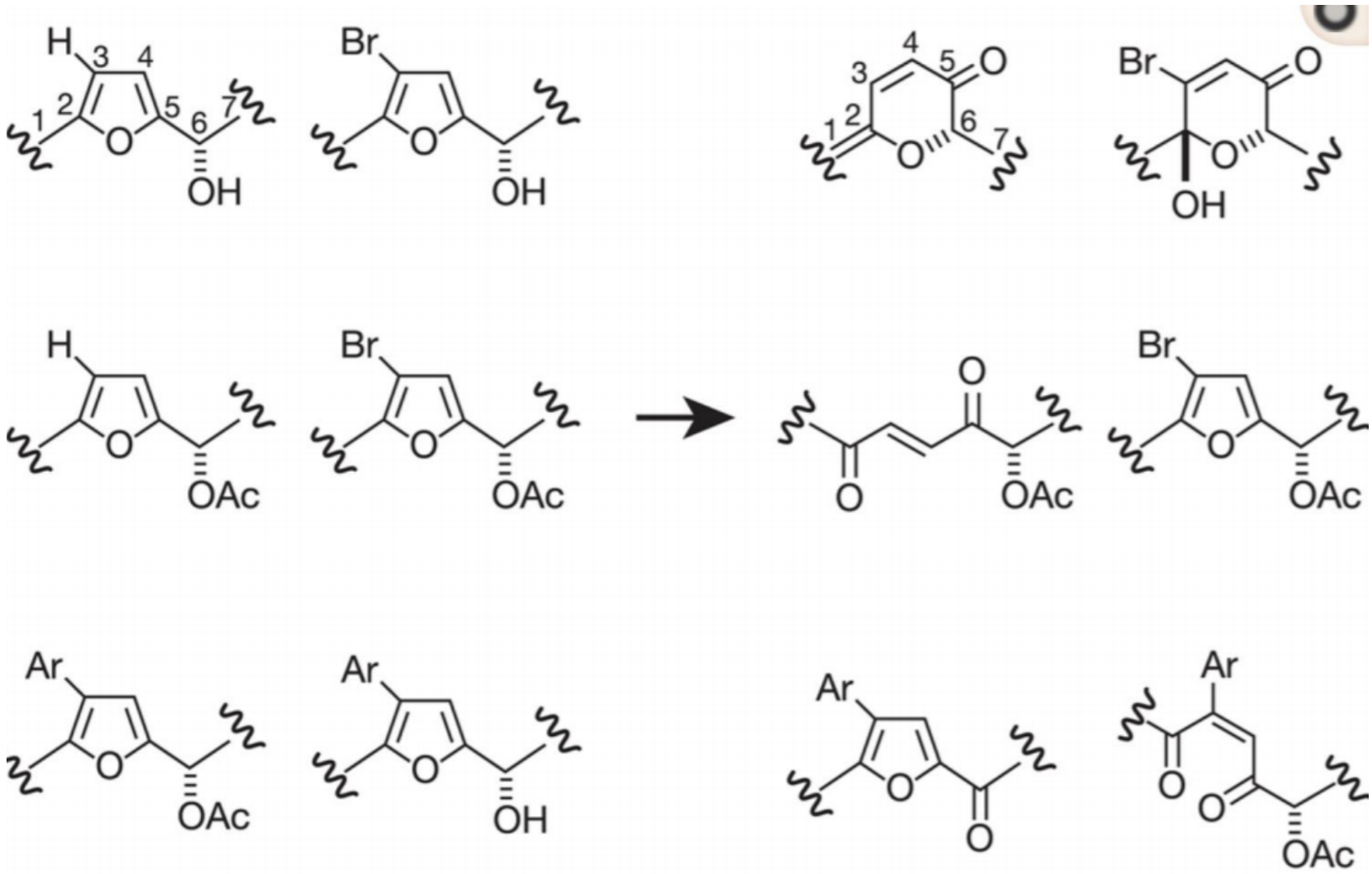
Focused library

Diversity-oriented library

What is a focused library?

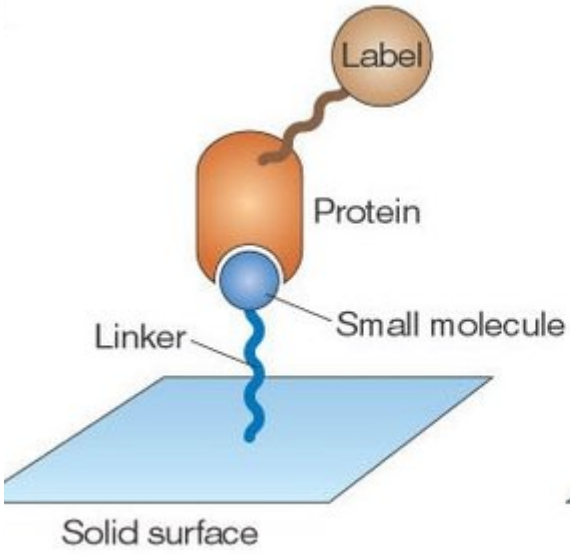


What is a diversity-oriented library?



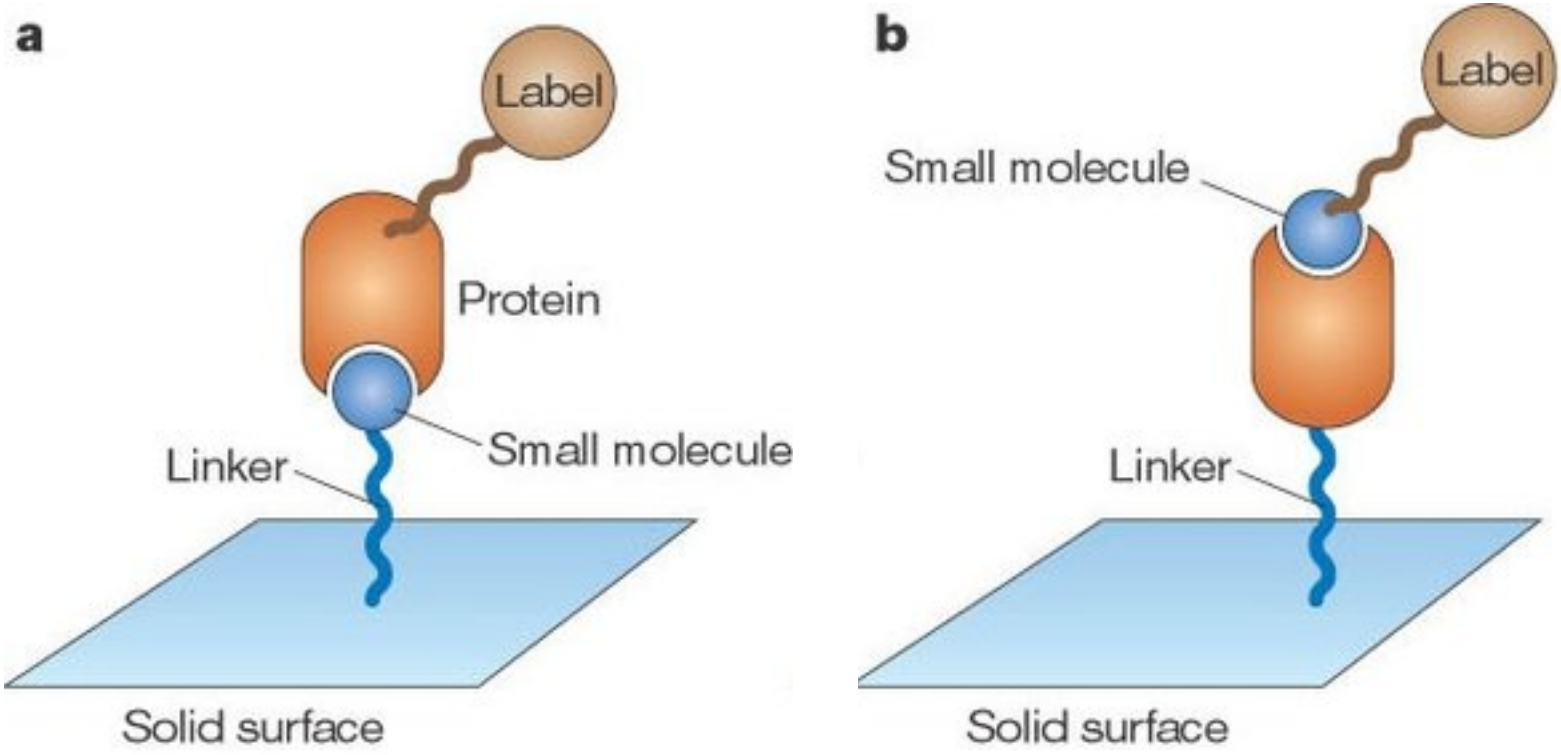
How do we utilize these libraries?

Protein-binding assays

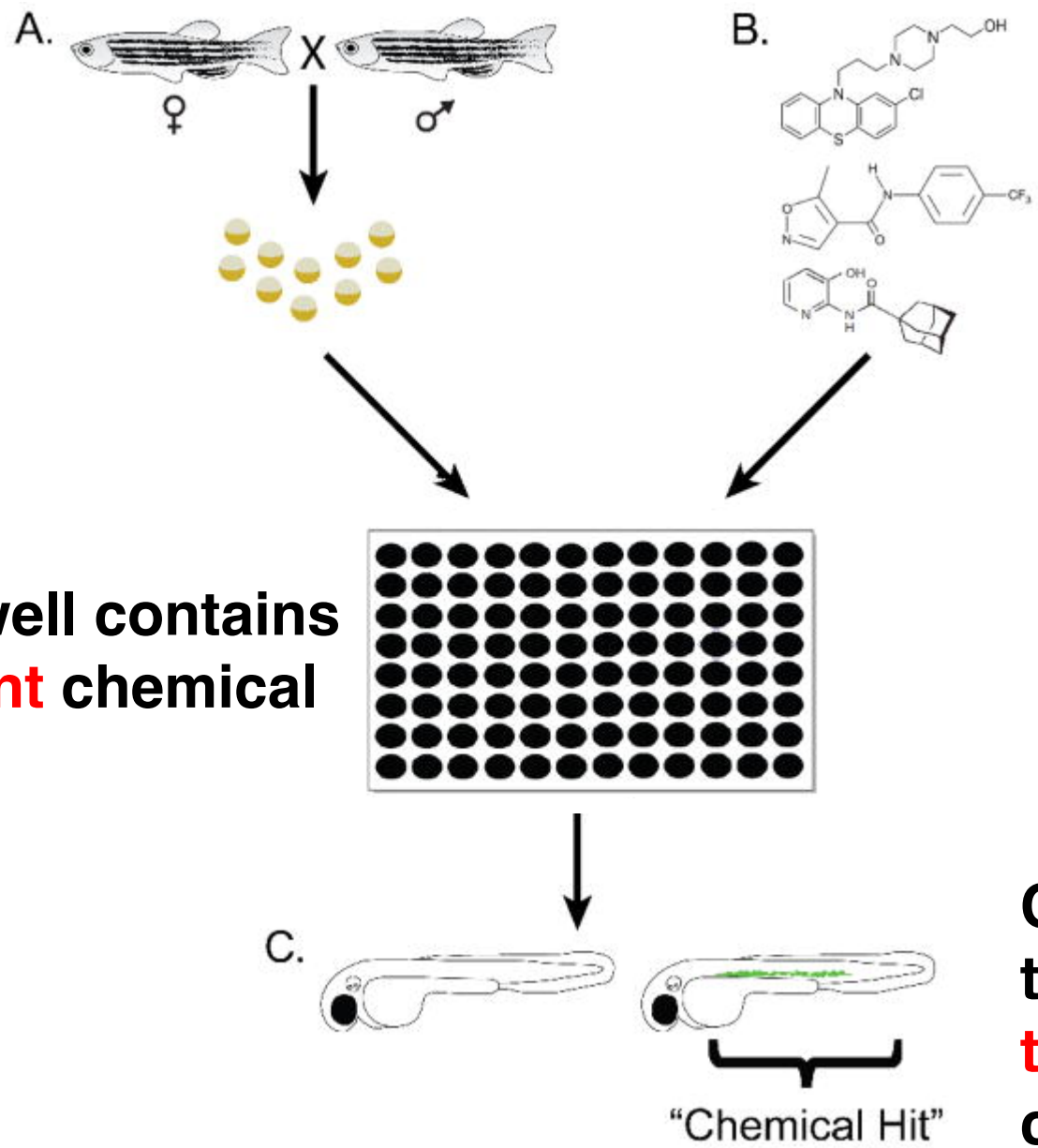


Phenotypic assays

What are protein-binding assays?



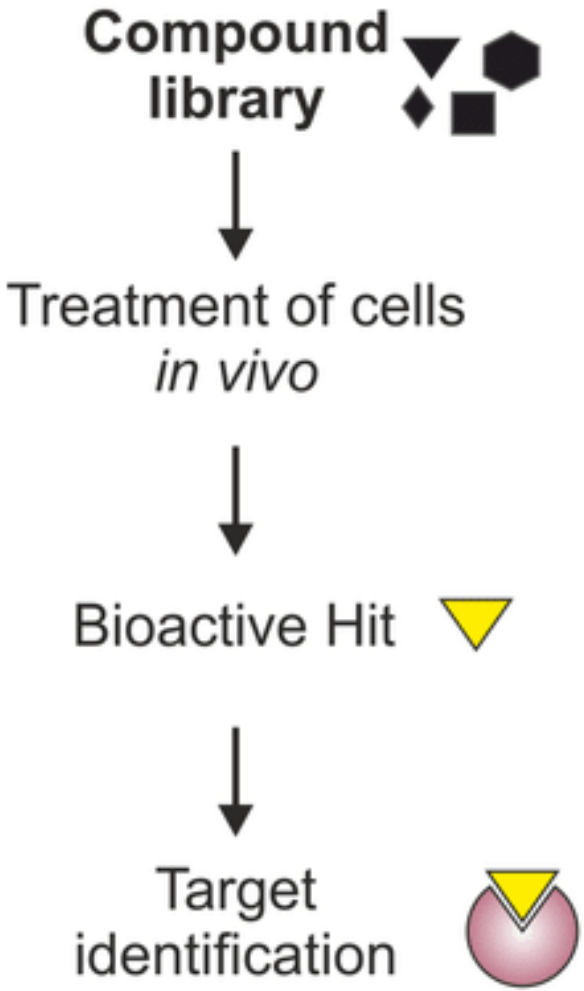
What are phenotypic assays?



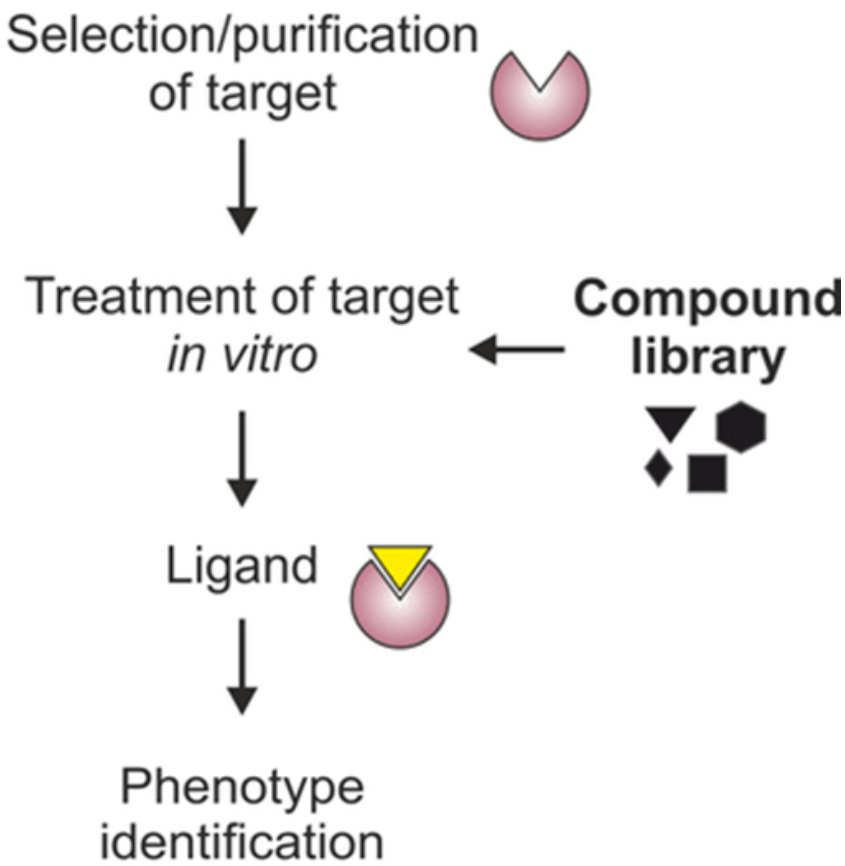
Each well contains different chemical

Can identify the protein target of the chemical

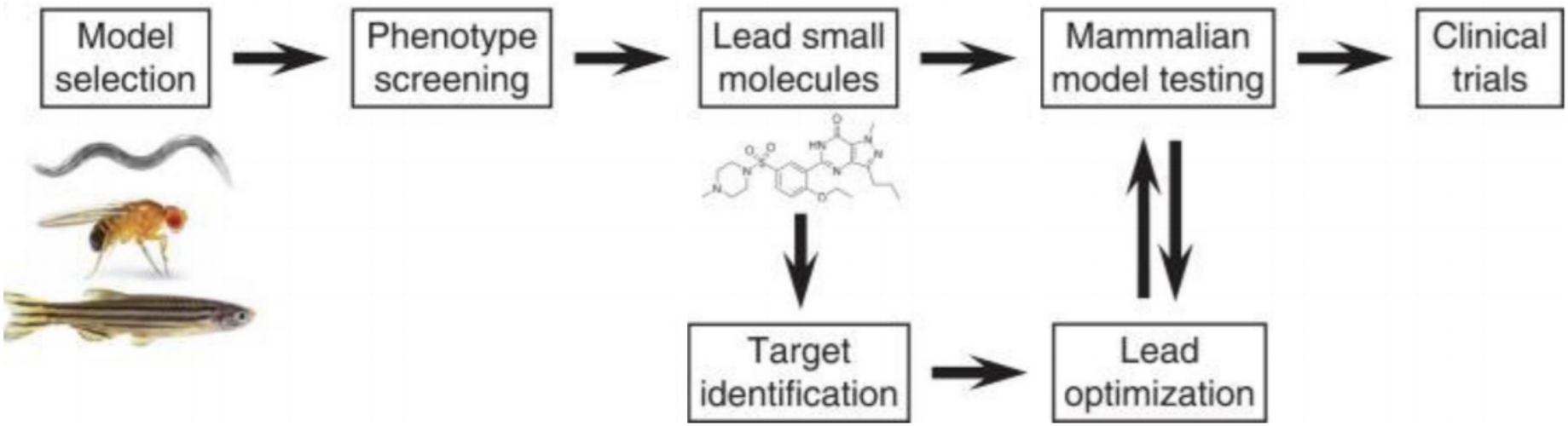
How do you conduct a forward chemical screen?



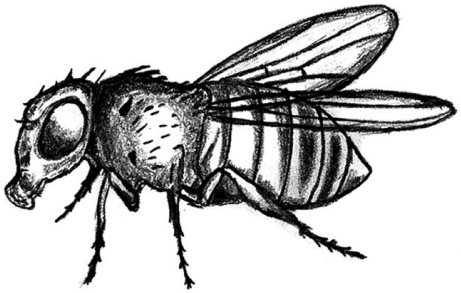
How do you conduct a reverse chemical screen?

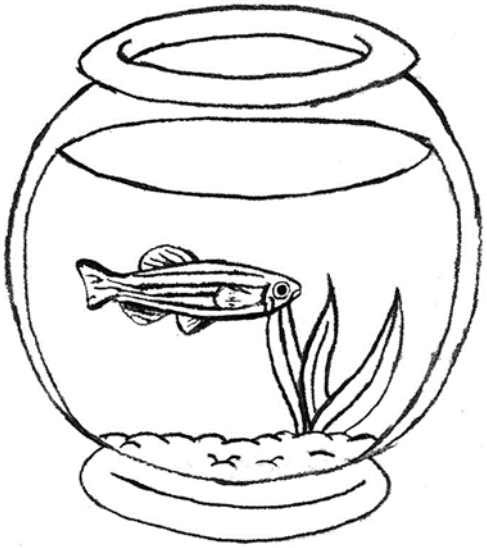


How would you use a model organism in a chemical screen?

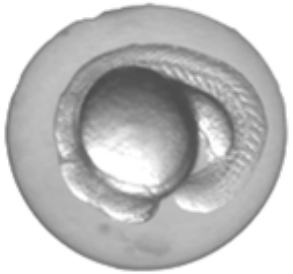


What are the best model organisms for chemical genetics?





What are the advantages of using zebrafish?

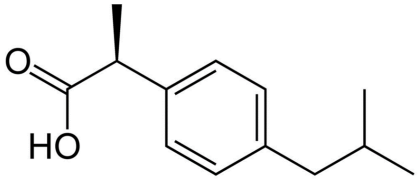


Chemical Genetics Summary

Used to study protein-molecule interactions

Utilizes chemical libraries to screen for either focused interactions, or a diverse set of interactions

Can point towards possible molecular therapeutic drugs

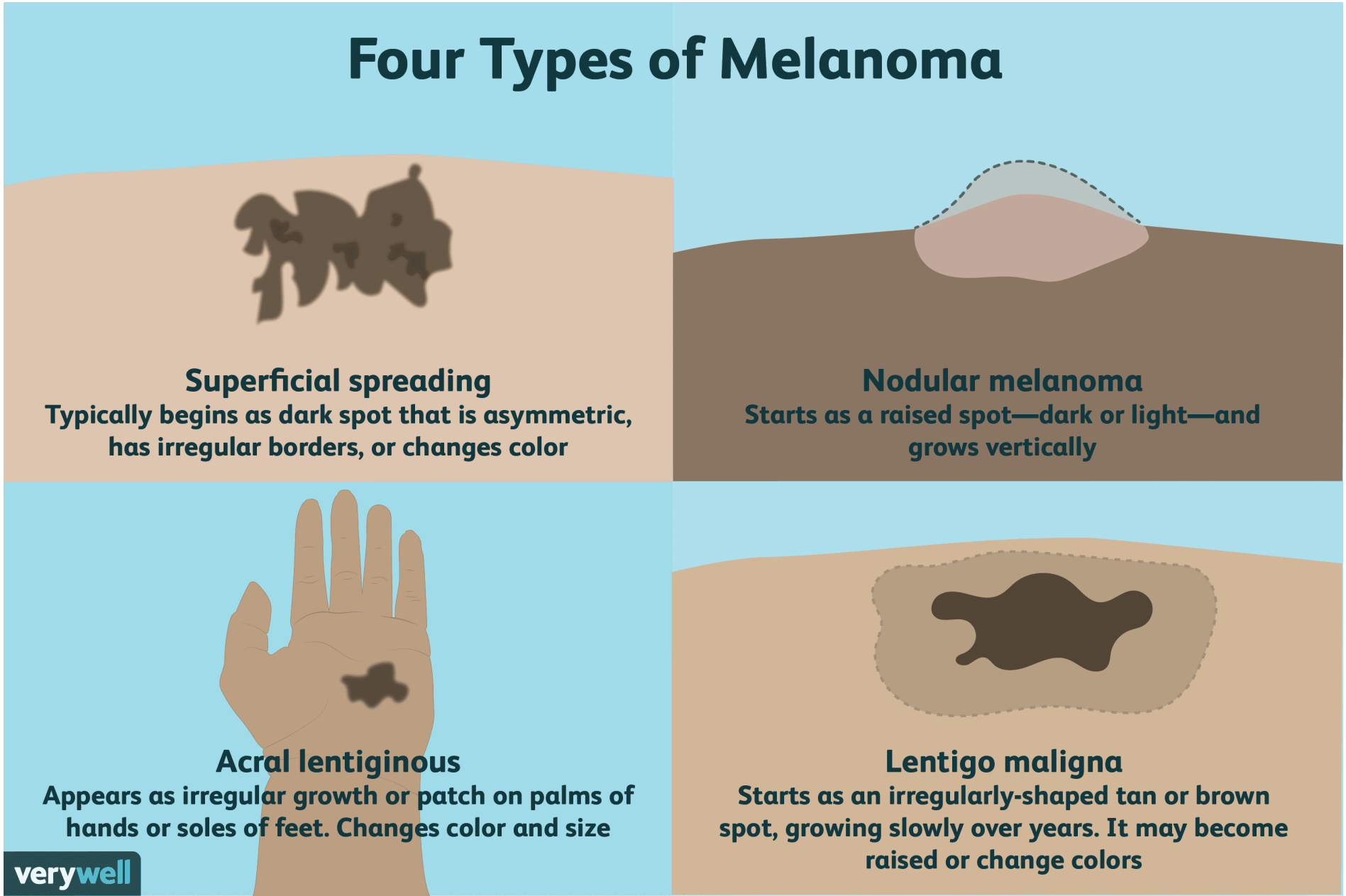


DHODH modulates transcriptional elongation in the Neural Crest and Melanoma

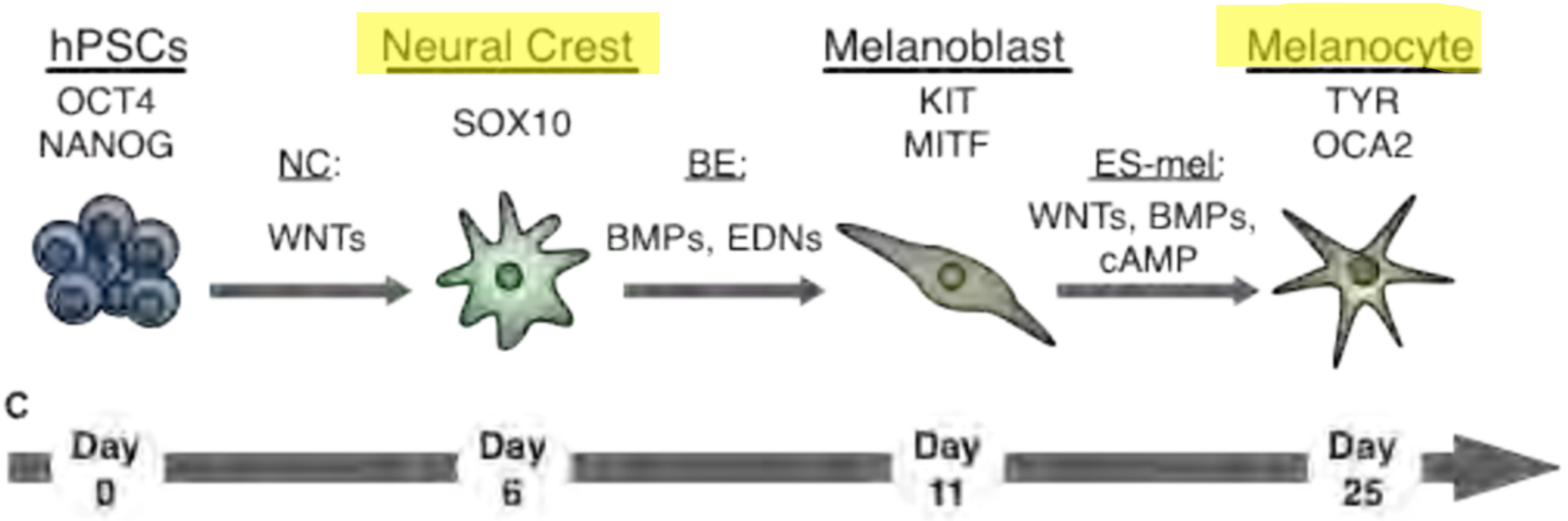
Letter, 2011

Richard Mark White[1,2], Jennifer Cech[1], Sutheera Ratanasirintrawoot[1], Charles Y. Lin[3,4], Peter B. Rahl[3], Christopher J. Burke[1], Erin Langdon[1], Matthew L. Tomlinson[5], Jack Mosher[6], Charles Kaufman[1,2], Frank Chen[7], Hannah K. Long[8], Martin Kramer[9], Sumon Datta[1], Donna Neuberg[10], Scott Granter[11], Richard A. Young[3,4], Sean Morrison[6], Grant N. Wheeler[5] & Leonard I. Zon[1]

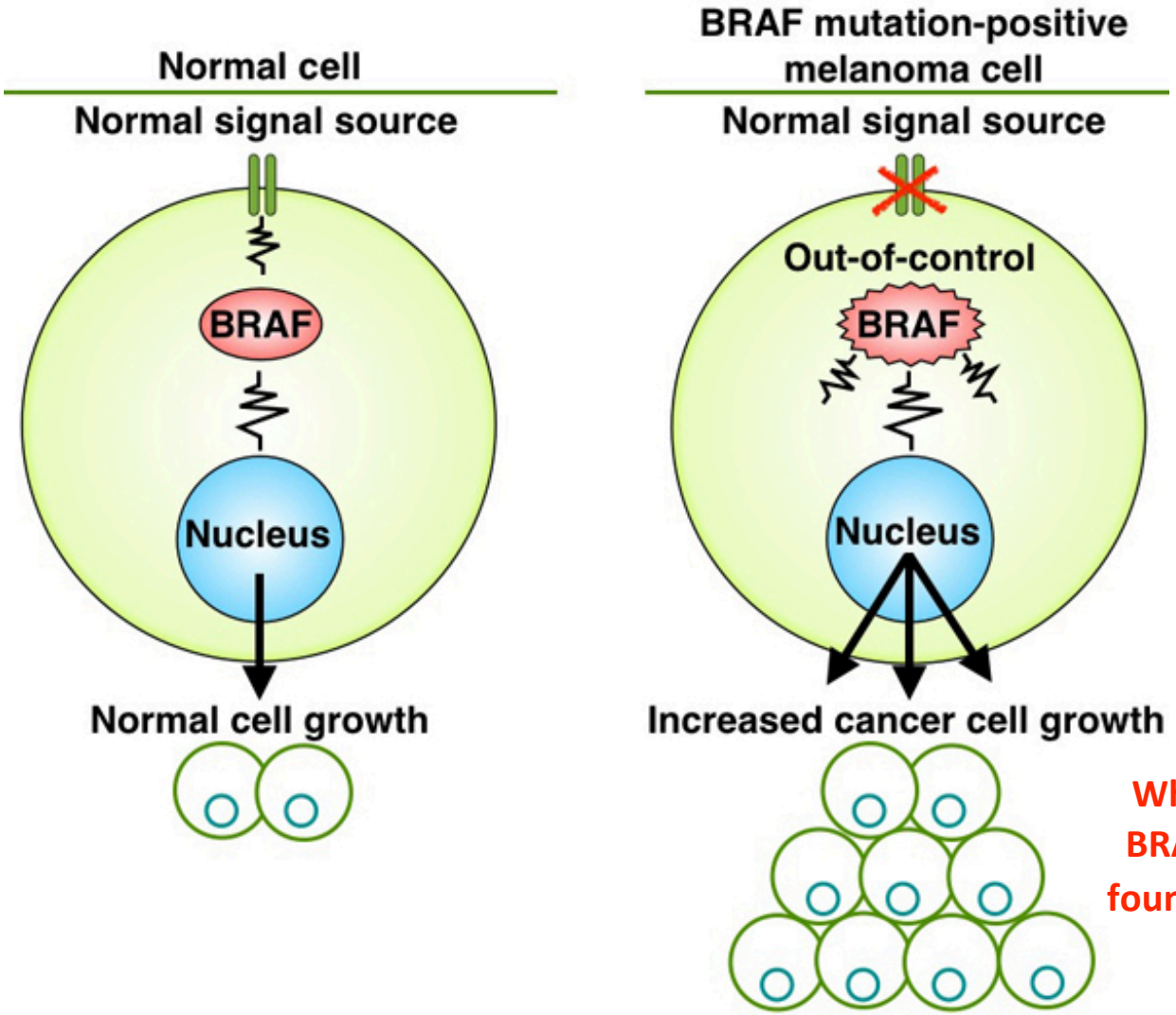
What is melanoma?



Where do melanocytes originate?



What gene is often mutated melanoma?



BRAF

What mutation in BRAF is commonly found in melanoma?

V600E

How did they use zebrafish to identify the transcriptional programs necessary for neural crest development?

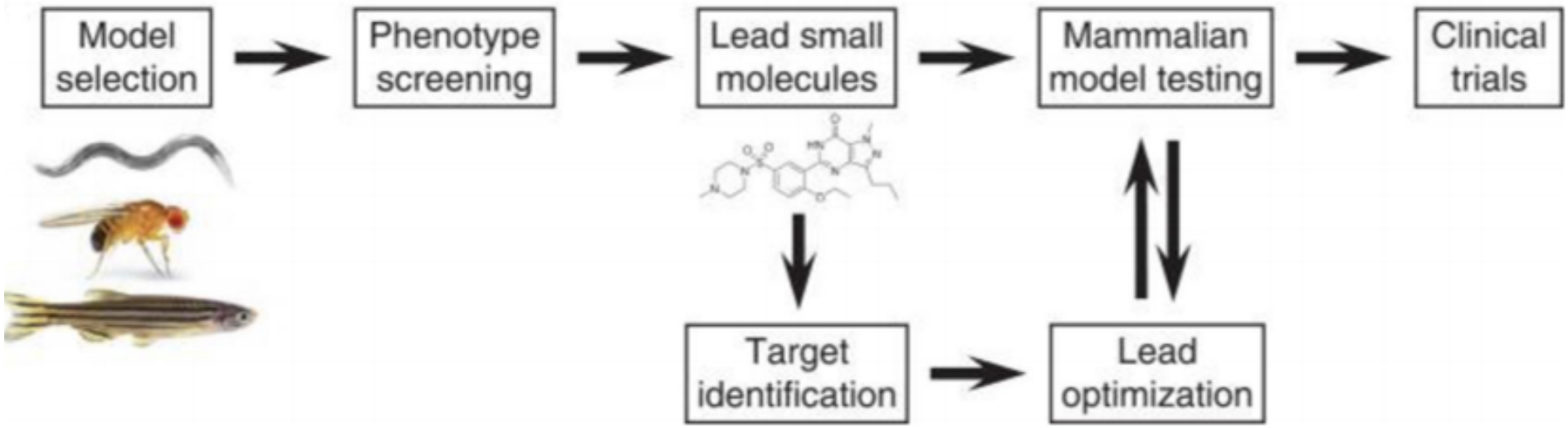


Fig 1a: What is the BRAF mutation in zebrafish?

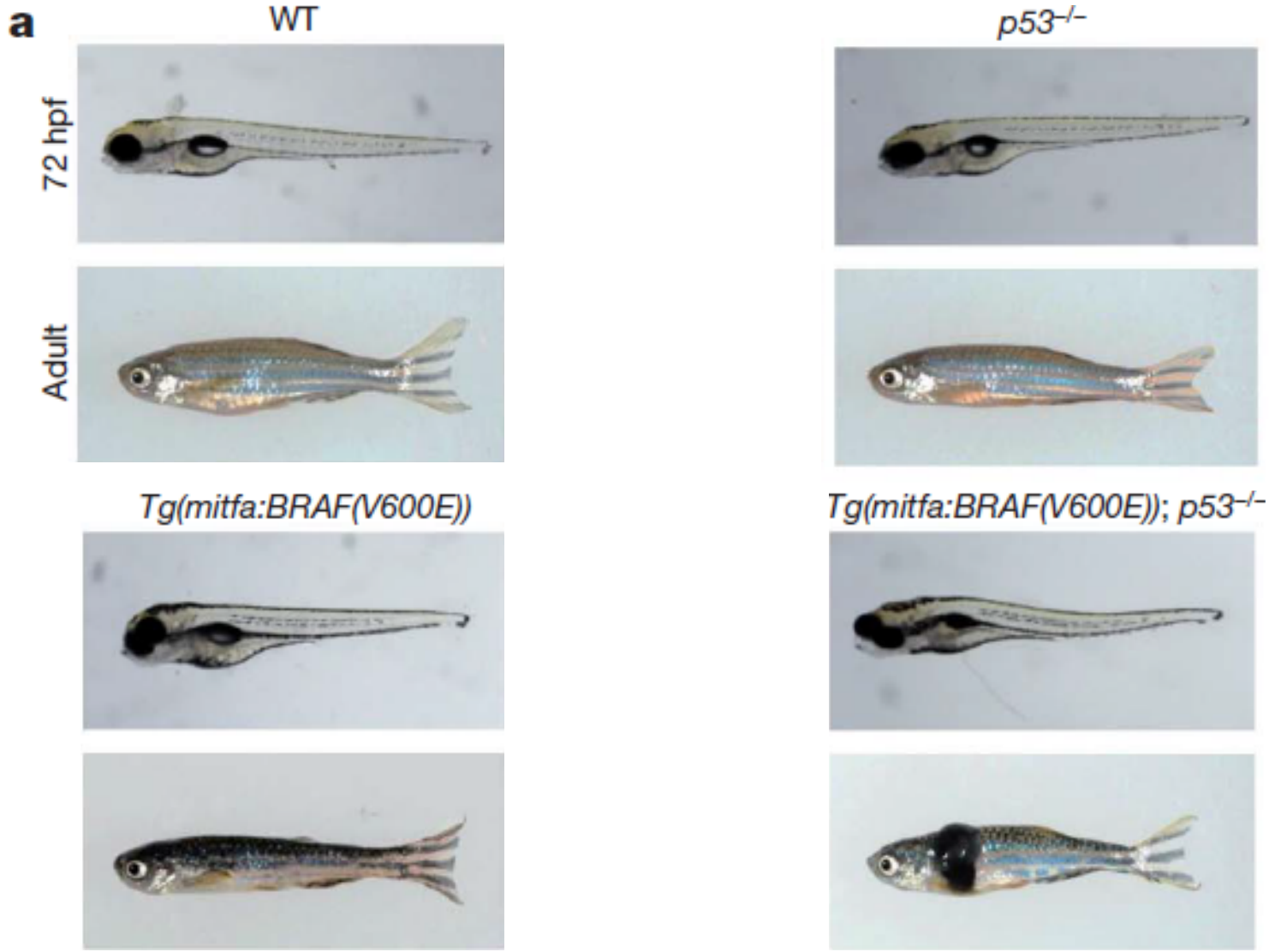


Fig 1b: What did the genetics screens tell us?

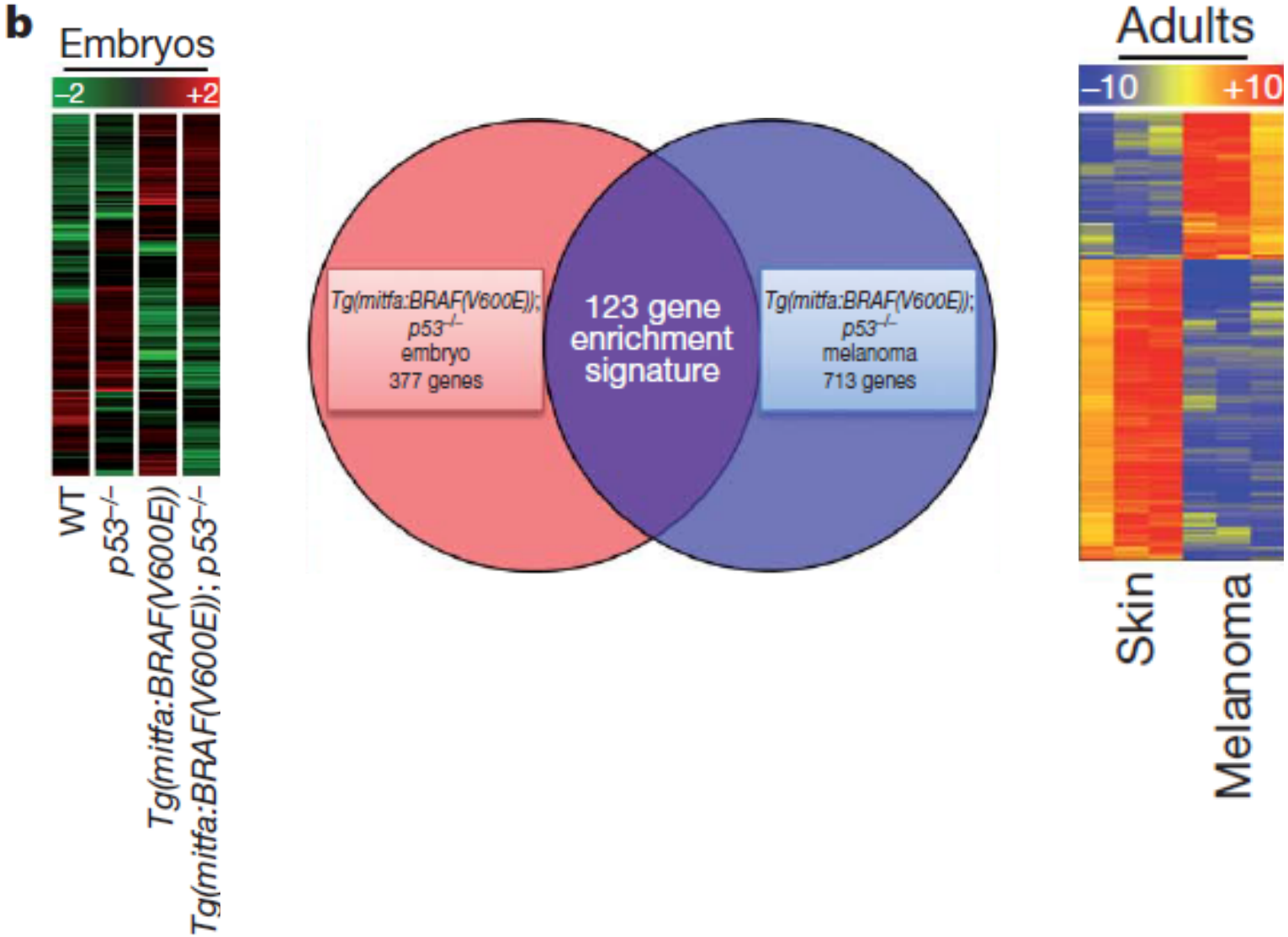
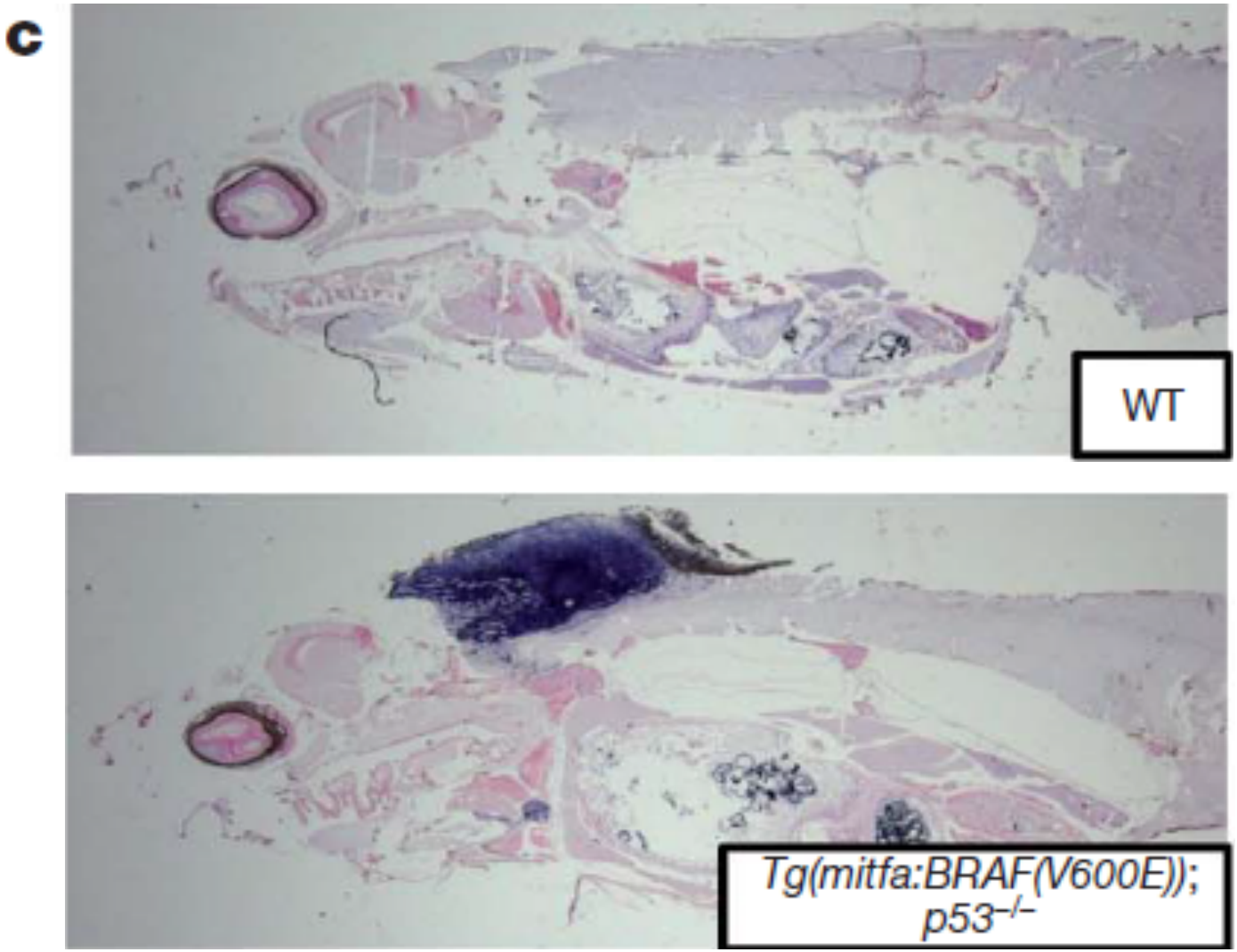


Fig 1C: What alterations in neural crest development did they observe in BRAF/p53 double mutants?



DHODH Pathway

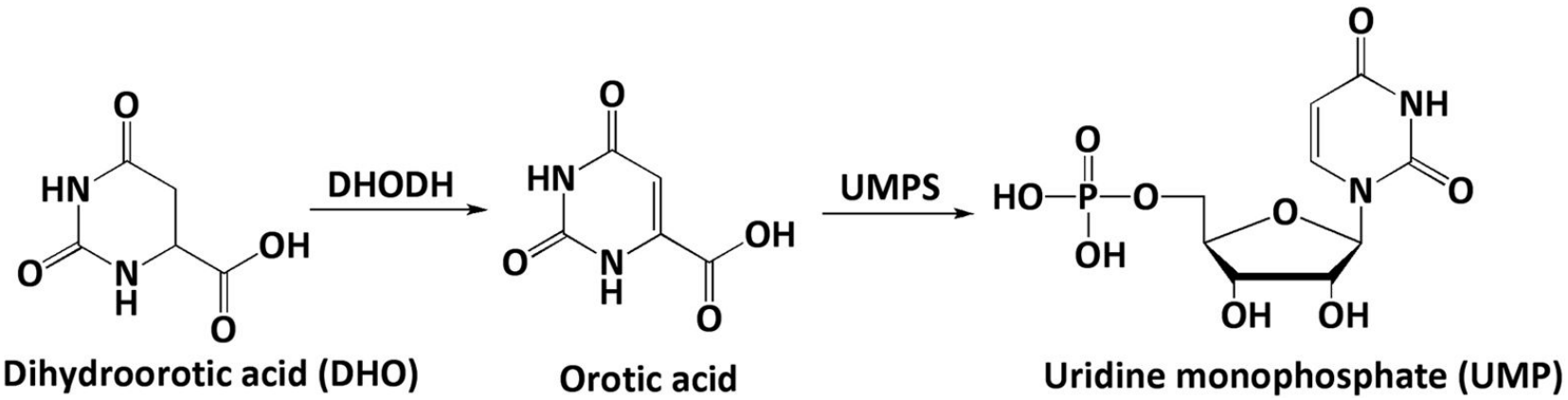
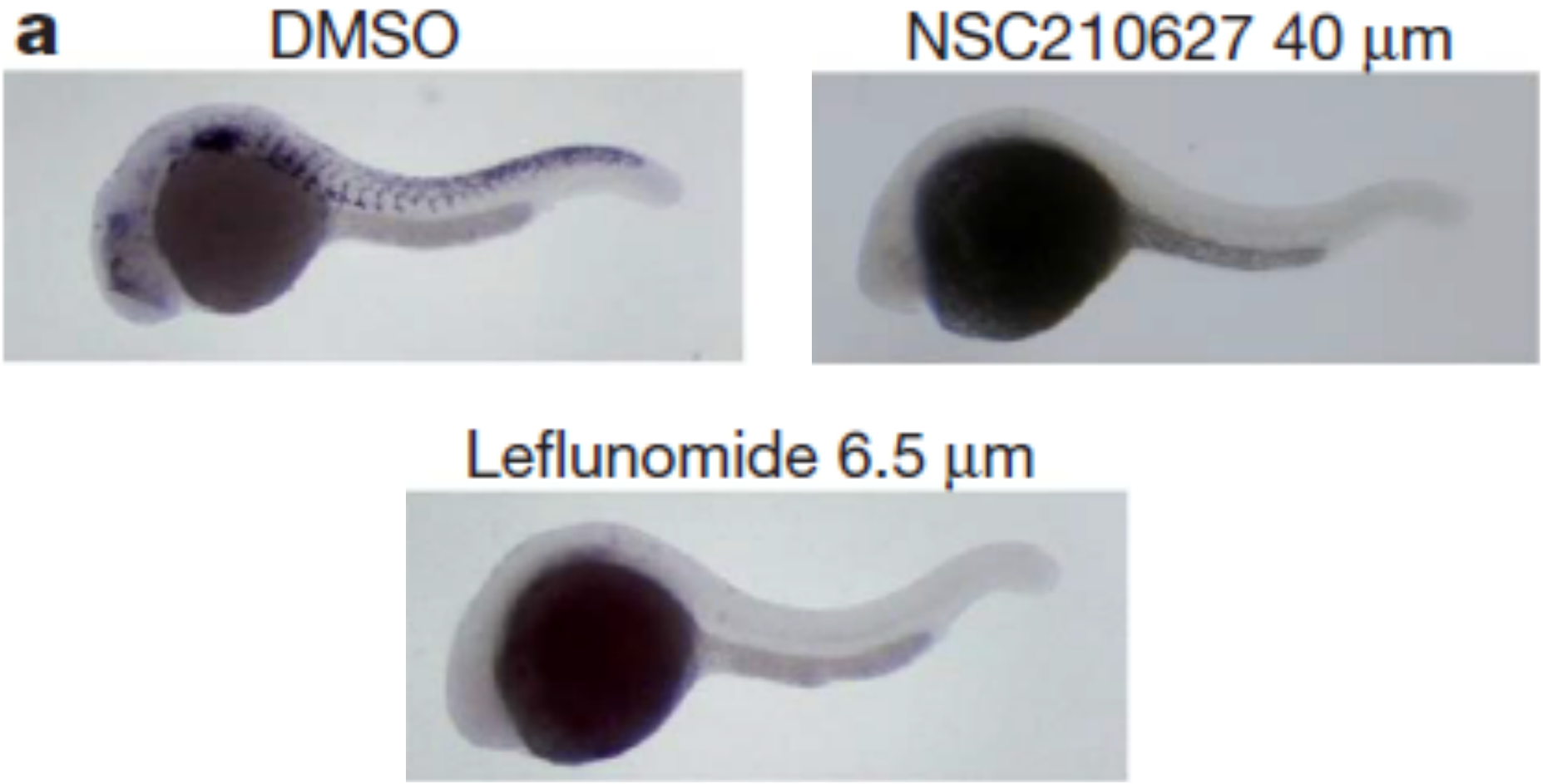


Fig. 2a: What suppresses neural crest development?



What is the impact of this treatment?

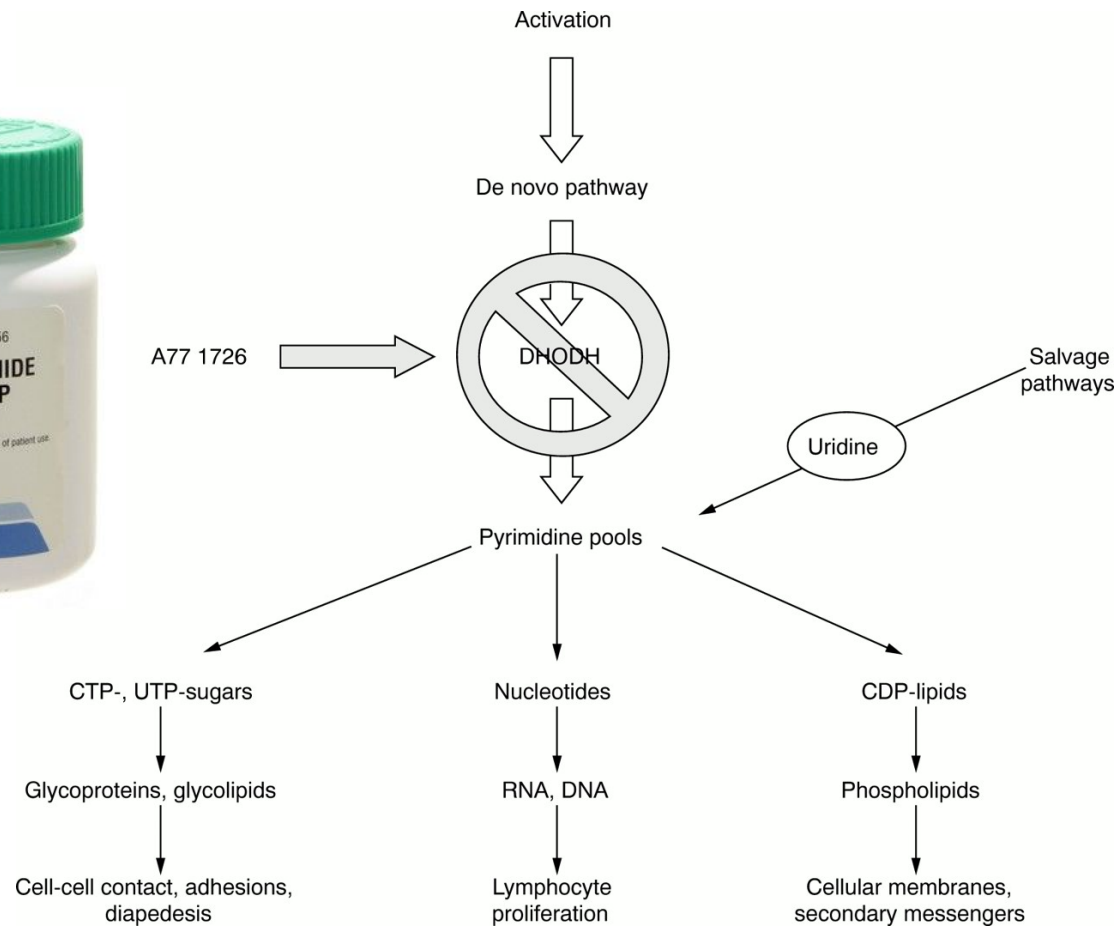


Fig. 2b,c,d: How does the drug effect neural crest derivatives?

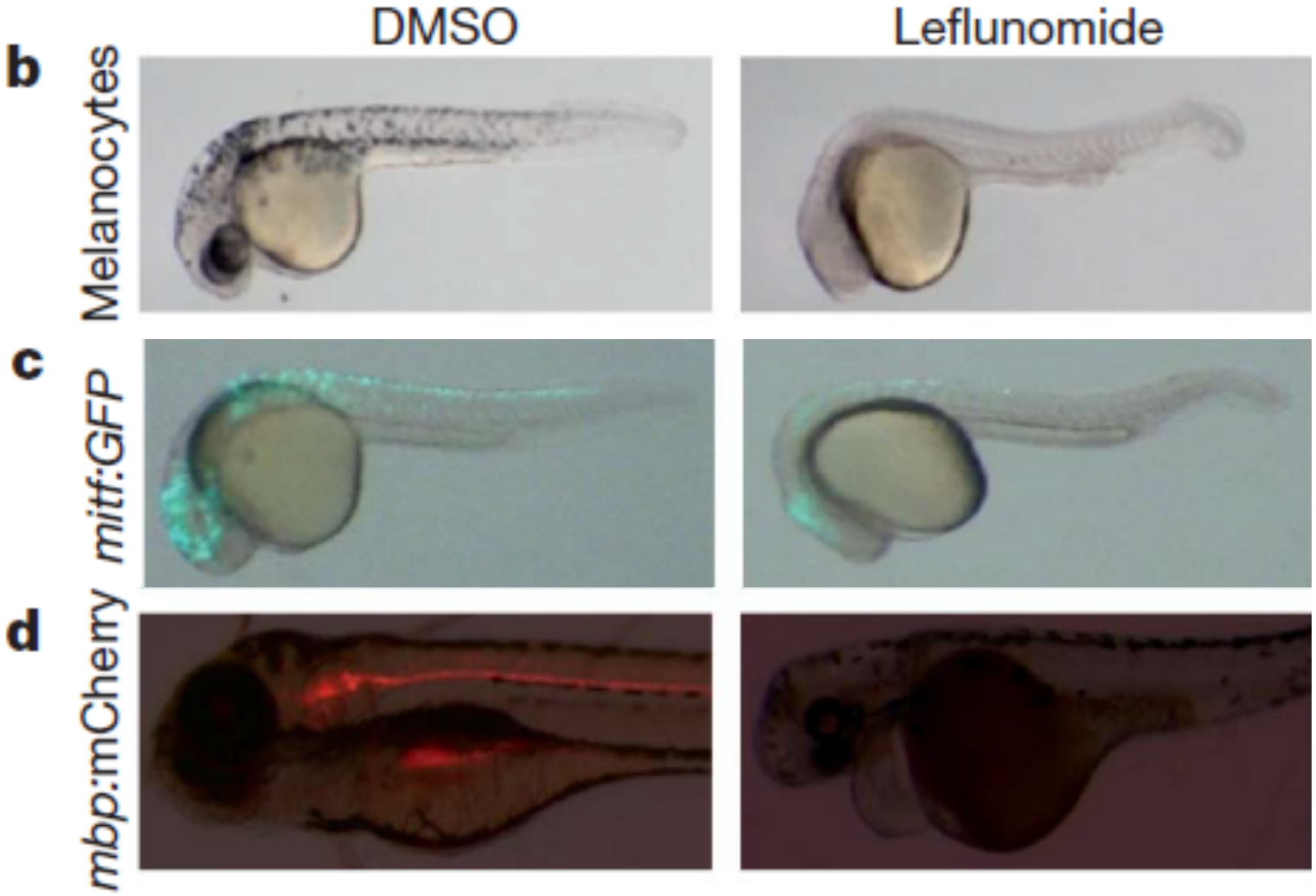


Fig. 2e: Does the amount of drug have an impact on multipotent daughter cell count?

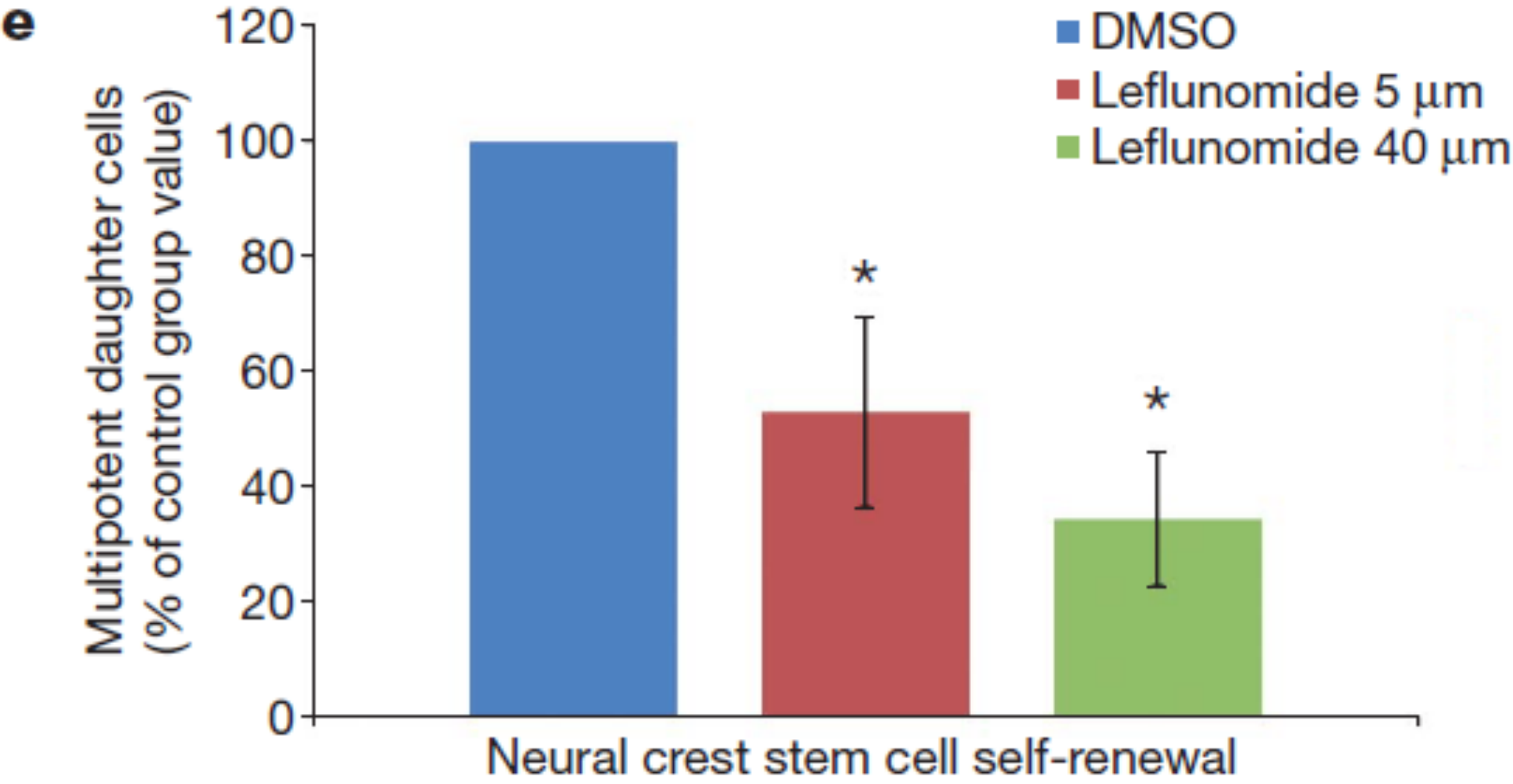
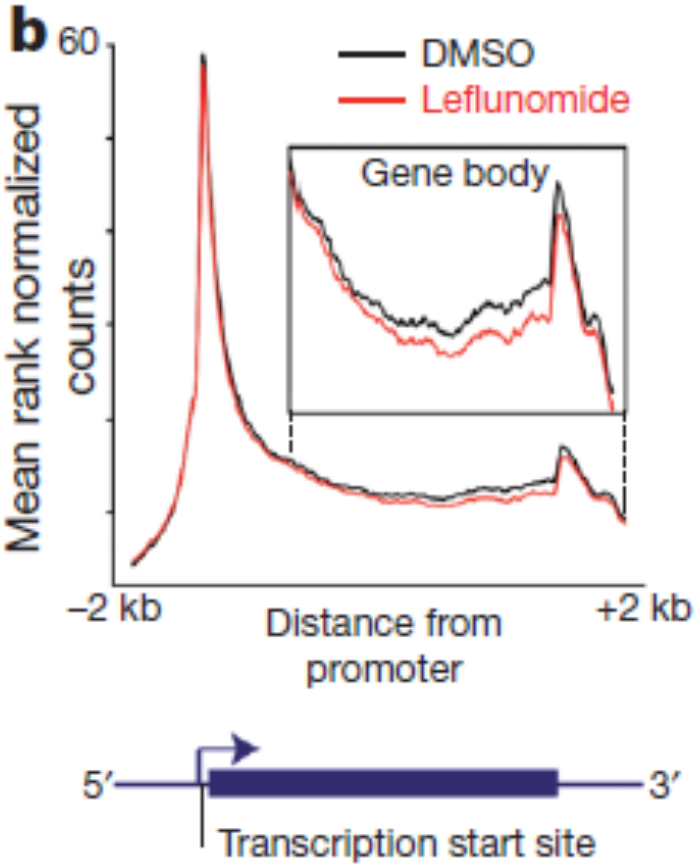
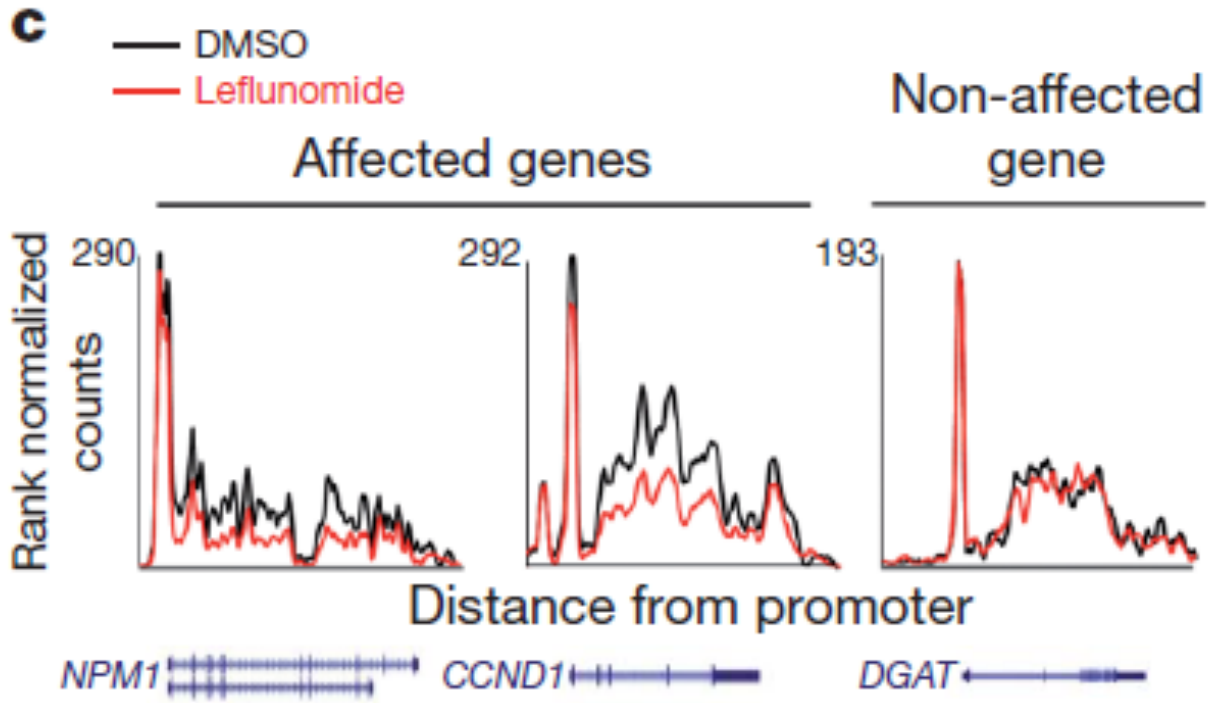


Fig. 3a: Does the drug have an impact on transcriptional elongation?





How do DHODH and BRAF interact?

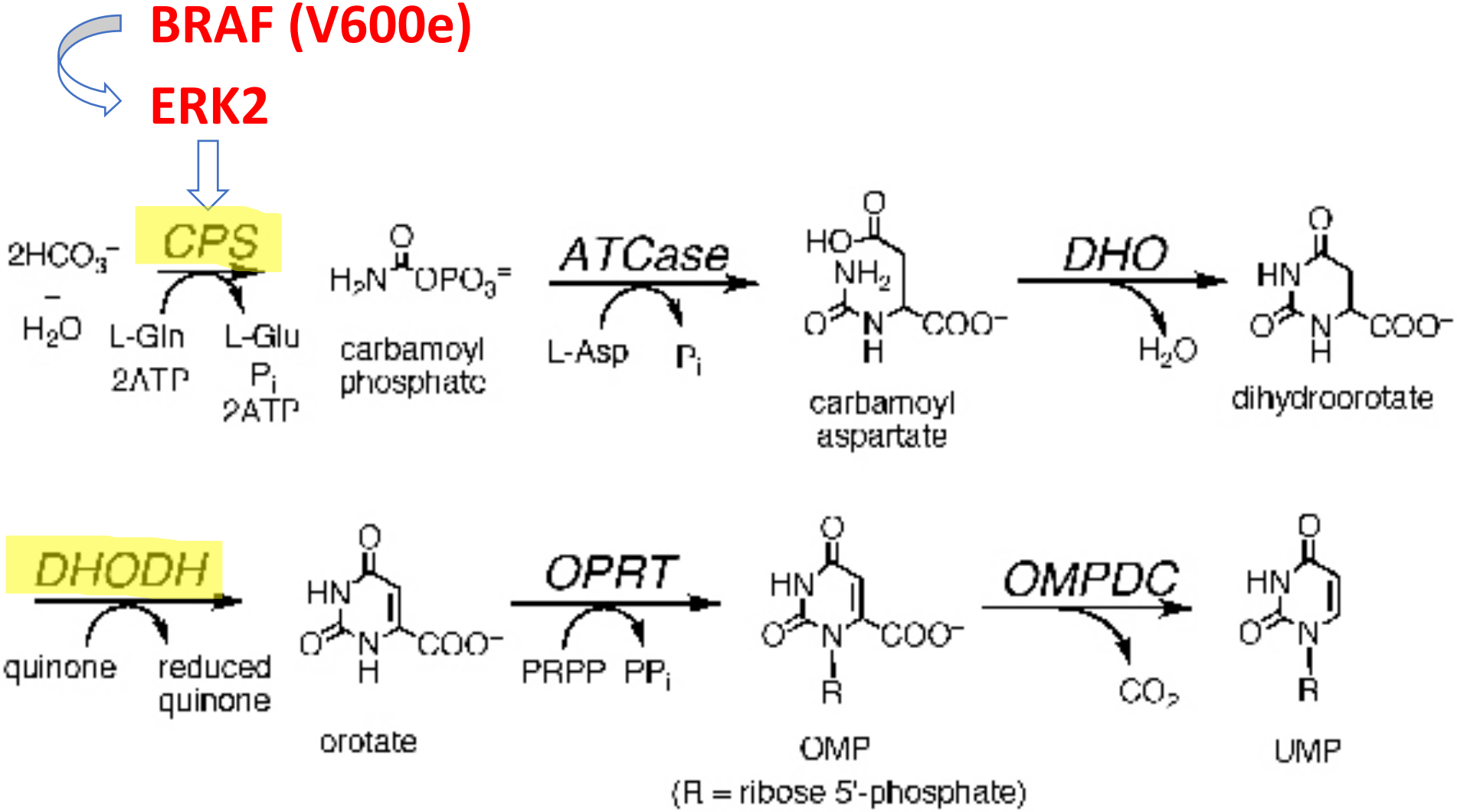
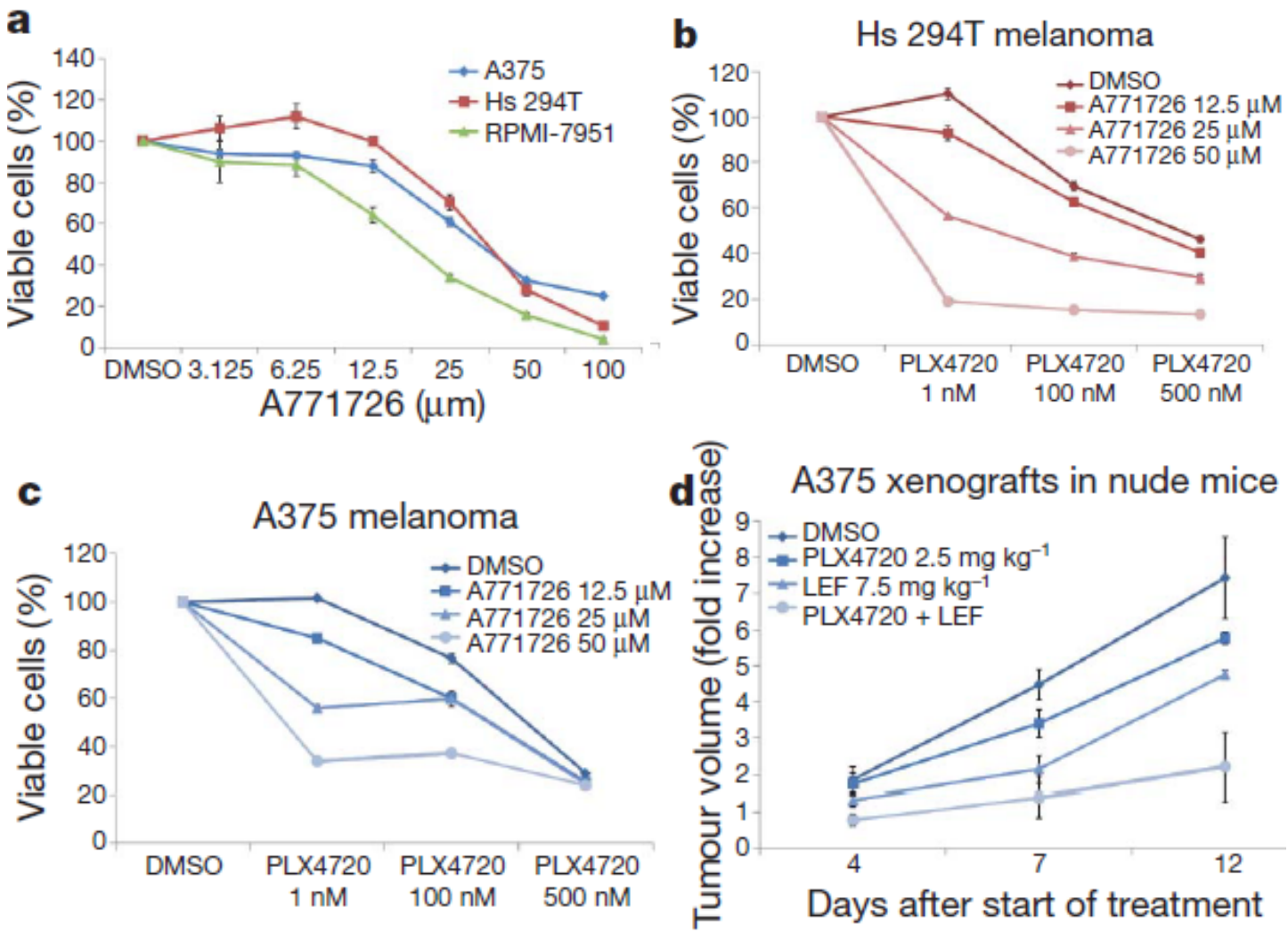
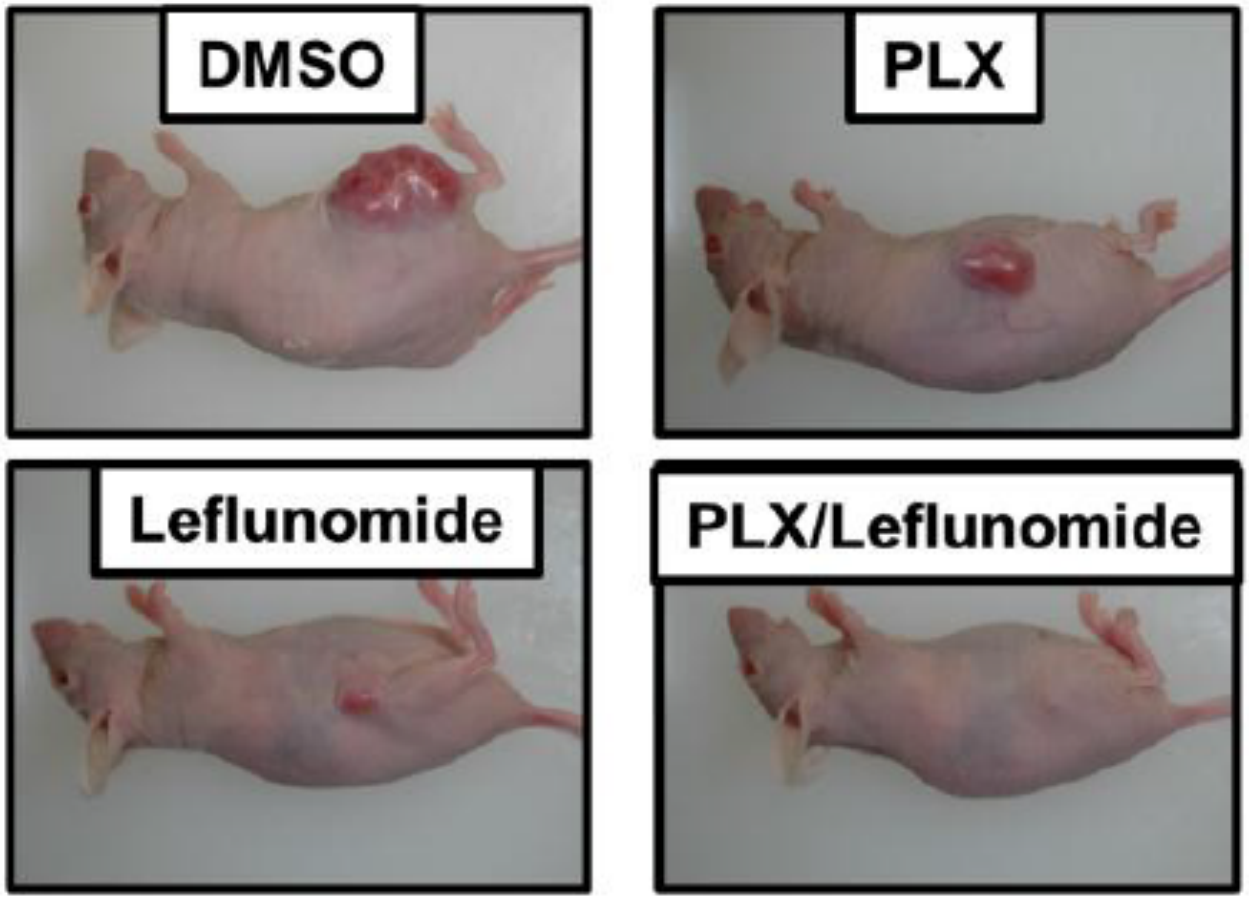


Fig. 4: Can the combination of drugs be more effective than used alone?

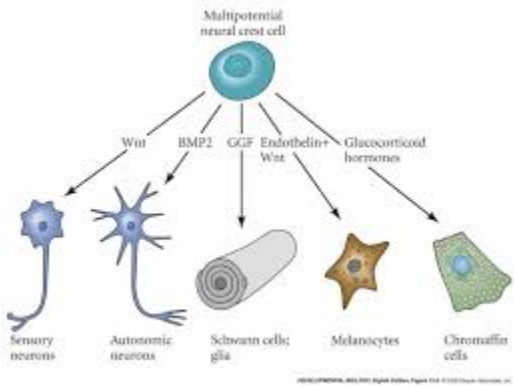


Treatment in Mice

A375 xenografts at day 12 post treatment



Summary



- Zebrafish is a good model organism to use in the study of human disease.
- DHODH inhibitor acts on all neural crest derivatives and not just melanocytes.
- The drug leflunomide acts as versatile chemical in tandem with a BRAF inhibitor to slow down melanoma growth.

- Human Trials: side effects, effectiveness.

Future Directions

References

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Image References

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