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AMGEN TRANSFER CIÈNCIA

Drosophila en investigació

Creat per **Lara Barrio**

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Drosophila en investigació: introducció

Què és la mosca del vinagre o la mosca de la fruita (*Drosophila melanogaster*)? Quina relació té amb malalties humanes complexes com el càncer i la metàstasi? Quina importància té i ha tingut en investigació?

Llegeix l'article de The Guardian "Six Novel prizes – what's the fascination with the fruit fly?" i dona resposta a aquestes preguntes i d'altres com quants dies creieu que dura el cicle vital de *Drosophila*? Quants parells de cromosomes té?

Les Lleis de Mendel: problemes amb *Drosophila melanogaster*

Com has vist a la presentació, l'observació i estudi de *Drosophila* melanogaster ens permet identificar marcadors d'aquesta espècie, observar diferències entre mascles i femelles i veure l'acció de les lleis de Mendel. A continuació, resoleu, en petits grups, els següents problemes.

1. La forma de les ales a *Drosophila* ve determinada per l'al·lel dominant curly (Cy), que dóna un fenotip d'ales corbades, i l'al·lel recessiuCy+, que dóna ales estirades. Si una mosca homozigòtica d'ales corbades es creua amb una mosca homozigòtica d'ales estirades, contesta:
    a. Com seran els genotips i fenotips de la descendència a la generació F1?
    b. I si creuem entre si dues mosques de la F1, com seran els genotips i fenotips de la descendència a la F2?
    c. Ara que has calculat les freqüències genotípiques i fenotípiques esperades, realitza el comptatge de les mosques tenint en compte el caràcter forma de les ales i comprova si les lleis de Mendel es compleixen.

F1: 15 ales corbes	F2: 5 ales normals 15 ales corbes

2. Si sabem que a *Drosophila* el color del cos negre ve determinat per l'al·lel recessiu ebony(e), i el color del cos marró pel seu al·lel dominant (e+). Quan creuem una femella amb el color de cos marró amb un mascle de color negre, observem a ladescendència (F1) mosques amb el cos de color negre.
    a. Quins són els genotips parentals?
    b. Quines serien les freqüències fenotípiques esperades que obtindríem a la F1?
    c. Comprova mitjançant el comptatge de les mosques les freqüències obtingudes en aquest experiment.

F1: 10 marrons 9 negres

3. El gen "yellow" (y) de *Drosophila* es troba el cromosoma X, per tant, parlem d'herència lligada al sexe.Si l'al·lel recessiu (y) determina color del cos groc i l'al·lel dominant (y+) color del cos marró,
    a. Si creuem una femella homozigota de color marró amb un mascle de color groc, quins genotips i fenotips ens trobarem a la F1? Es compleixen les lleis de Mendel?
    b. Que hauríem de fer per demostrar que el gen "yellow" te una herència lligada al sexe? Quina peculiaritat trobem a la F2?
    c. Calcula les freqüències obtingudes mitjançant el comptatge de les mosques de l'experiment.

F1: 14 marrons (8 femelles i 6 mascles)	F2:12 femelles marrons 6 mascles marrons 6 mascles grocs

    d. Que passaria si fem el creuament al inrevés? És a dir, femelles de color groc amb mascles de color marró. Quins genotips i fenotips esperem a la F1 i a la F2?

4. El gen "white" (w) de *Drosophila* també presenta herència lligada al sexe. En aquest cas, l'al·lel recessiu (w) determina ulls blancs i l'al·lel dominant (w+) ulls vermells. Vam realitzar un creuament amb mascles i femelles amb els colors dels ulls diferents.
    a. Compta les freqüències amb els descendents de la F1, i determina quin era el genotip dels parentals.

F1: 20 femelles vermelles 18 mascles blancs

5. Compta i calcula les proporcions de la F2 provinent d'aquest encreuament.

F1: 18 femelles vermelles 16 mascles vermells 21 femelles blanques 17 mascles blancs

a. En el cas d'obtenir totes les mosques de la F1 amb els ulls vermells, quines podrien ser les possibles combinacions genotípiques i fenotípiques dels parentals?
b. I quin hauria de ser el genotip dels parentals si obtenim les següents proporcions fenotípiques a la F1:

F1: 48 femelles vermelles 26 mascles vermells 24 mascles blancs

6. A *Drosophila* el marge de les ales pot ser sencer (fenotip salvatge) o bé serrat (fenotip mutant), i el color del cos pot ser marró (fenotip salvatge) o negre (fenotip mutant). En un encreuament entre individus heterozigots es van obtenir a la descendència: 580 mosques marrons amb ales serrades, 180 marrons amb el marge sencer, 60 mosques negres de marge sencer i 170 negres amb el marge serrat.
   a. Segons aquests valors, estableix la dominància dels al·lels mutants i els fenotips dels pares.
   b. Podem acceptar la tercera llei de Mendel?

El mètode científic: casos pràctics

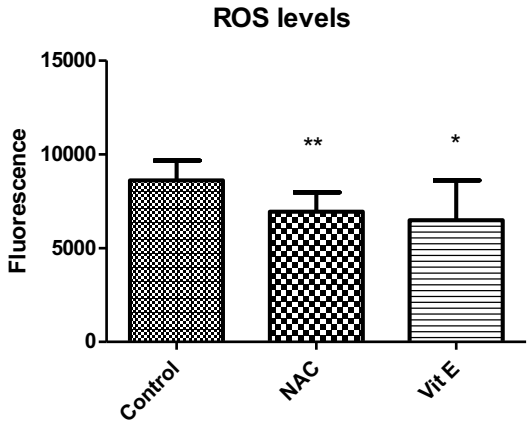
Per parelles o grups de tres, escolliu un cas pràctic per treballar, discutir, elaboreu una hipòtesis i extraieu les conclusions segons els resultats.

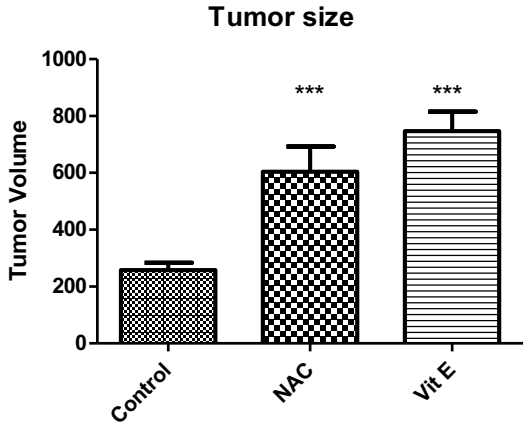
Biological question: Are antioxidants important in the context of tumor development?

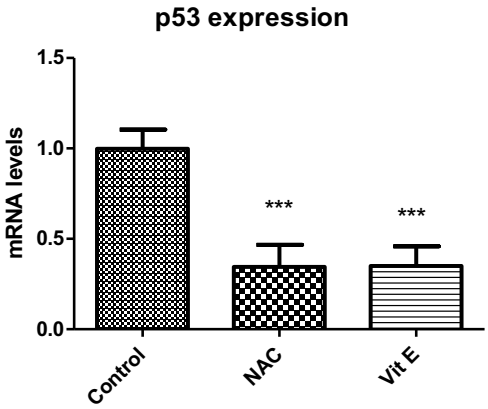
In the recent year many researchers have been hypothesizing that **antioxidants** might be able to protect against cancer. This hypothesis is based on their ability to **neutralize** **reactive oxygen species** (ROS) that can **damage DNA**. However, multiple placebo-controlled prevention clinical trials failed to prove this idea. Some of the largest clinical trials, in fact, were aborted because the patients receiving antioxidants had a higher incidence of cancer than patients who did not receive them. But why did that happen?

You are part of a team at the IRB that is studying the impact of antioxidants, particularly NAC and vitamin E, on tumor development and progression. You realized that a good way to start attacking this problem was by performing a small experiment with *Drosophila* flies. You generated a tumor in their wing imaginal disc and then fed them with antioxidants. You are evaluating the tumors **ability to produce ROS**, but also looking at the expression of **p53(a tumor suppressor gene)** and **tumor size** due to the results of the clinical trials.

These are your results:


ROS levels
Fluorescence
15000
10000
5000
0
**
*
Control
NAC
Vit E


Tumor size
Tumor Volume
1000
800
600
400
200
0
***
***
Control
NAC
Vit E


p53 expression
mRNA levels
1.5
1.0
0.5
0.0
***
***
Control
NAC
Vit E

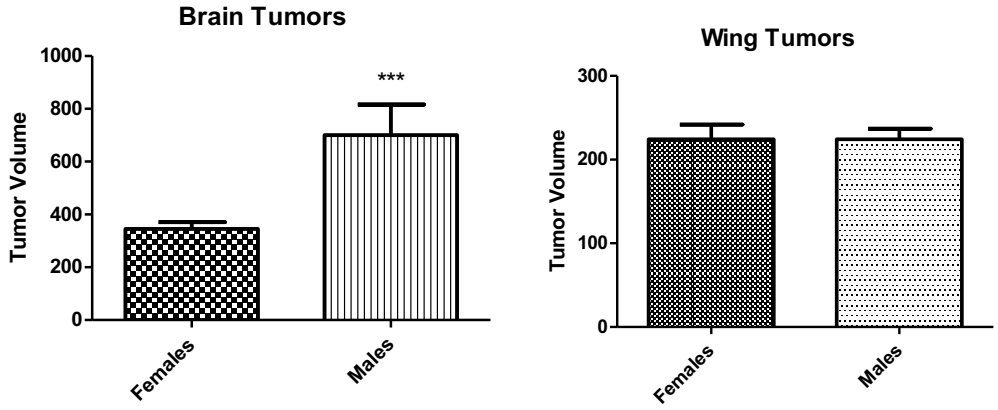
Biological question: Is sexual dimorphism relevant for tumor growth?

Sex differences in human development, aging, and disease are so common that they are often ignored as a relevant feature. Yet, the ways in which males and females consistently differ have significant importance for disease risk and prognoses, and cancer is no exception. There are measureable differences between men and women in cancer prevalence, mortality, and progression. But is this a common feature for all cancer types?

You are part of a team of researchers from the IRB and you want to study sexual dimorphism in carcinomas, solid tumors that have an epithelial origin.

To do so, you analyze the tumor size of both male and female *Drosophila* flies in two different carcinoma like tumors: a wing tumor (highly proliferatory cells) and a brain tumor (low proliferatory cells).

These are the results you got from your measurements:



Biological question: Is the X gene involved in tissue regeneration?

It is known that gene X is able to travel into the brain and stop the production of the steroidal hormone ecdysone, responsible for life cycle transitions in the *Drosophila* fly. Recently it has been noticed that the X gene is produced by the epithelial tissue when there is some type of damage, such as abnormal growth or a mechanical injury.

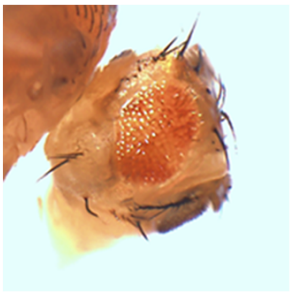
You are studying the connection of the X gene with tissue regeneration. For that purpose you have been given a team and a lab from the IRB. The aim of this team is to understand if the production of X is essential for reestablishing the tissue after an injury and why.

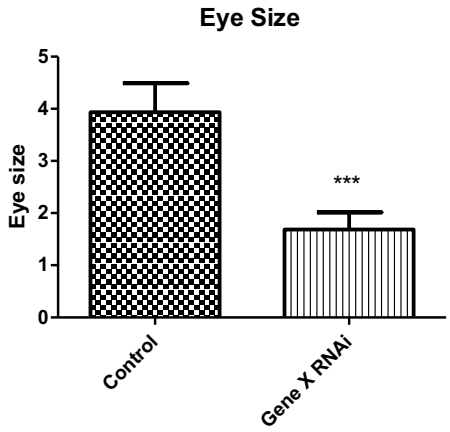
You start by preforming an eye screening in your lab. You will analyze the eyes of control flies versus flies without the X gene 3 days after irradiation in order to evaluate if the tissue was able to regenerate or not.

Here are your results:

Control flies with X

Mutant flies without X





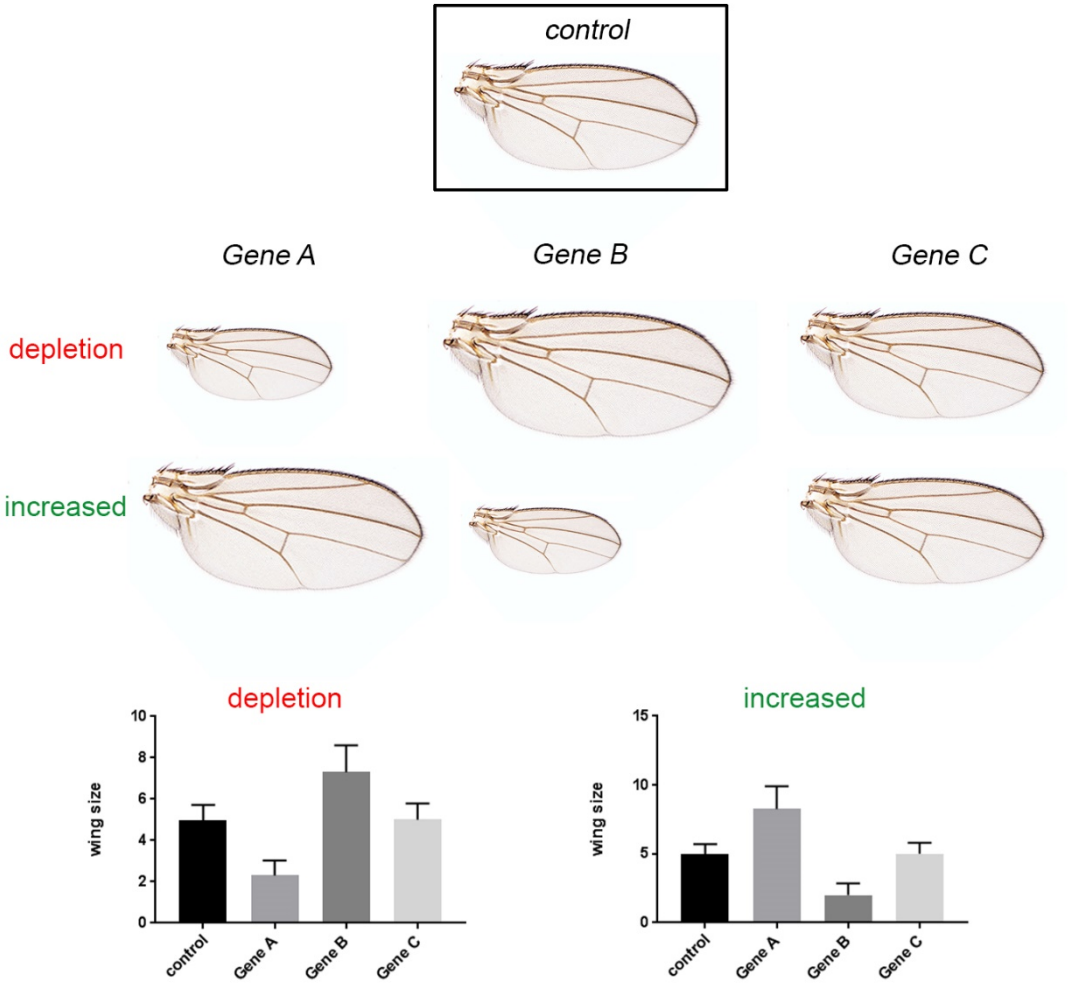
Biological question: Are the genes A, B and C involved in tissue growth?

During the development of all organism many cellular processes, such as cell proliferation and cell death, are coordinated to give rise to the final adult structures in a proportional manner. These two processes are regulated by different signaling pathways and genes. Some of them are already known, but there are still many more to test.

You are studying the connection of the three new genes (A, B, and C) with tissue growth during normal development. For that purpose, in your lab at the IRB you will use the wing imaginal of *Drosophila*, an epithelium that grows from a group of 50 cells to thousands during this development.

You start your experiments using the Gal4/UAS system to either, deplete the genes A, B and C, or to increase the expression of the genes A, B and C, and you quantify the size of the resulting adult wing.

Here are your results:


control
Gene A
Gene B
Gene C
depletion
increased
depletion
wing size
10
8
6
4
2
0
control
Gene A
Gene B
Gene C
increased
wing size
15
10
5
0
control
Gene A
Gene B
Gene C

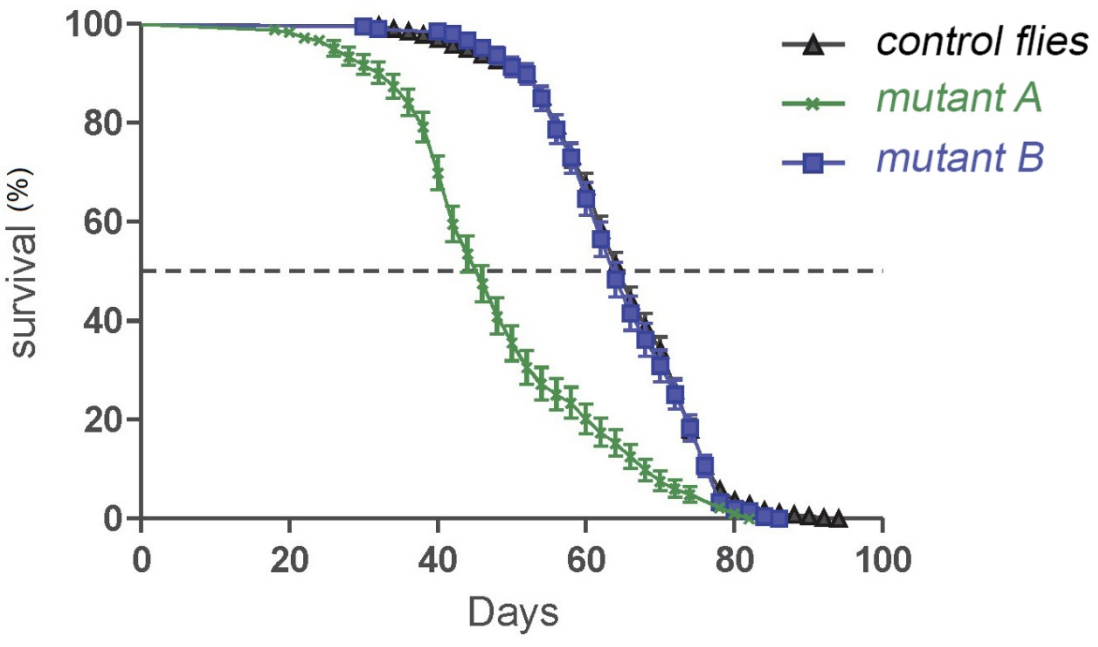
Biological question: Does the size of the wings affect survival of the adult fly?

It is known that the gene A is required for normal growth of the adult wing in *Drosophila melanogaster*. Flies that are mutant for the gene A have smaller wings than control and normal flies. On the contrary, the gene B inhibits growth of the adult wing. Flies that are mutant for the gene B have bigger wings than control and normal flies.

In your laboratory at the IRB you have previously showed that this anatomic defects affect the locomotor capacity of the adult animal, flies with bigger wings move faster while flies with smaller wings move slowly than control flies. However nothing is known about their role in aging and longevity. Due to the fact that flies have a shorter lifespan than mouse, *Drosophila* has emerged as an excellent genetic model to study the aging process.

The aim of this project is to study the connection between the size of the adult wing and the lifespan of the adult. For that purpose you start by preforming a longevity assay in your lab. You will compare the survival rates of control flies versus flies without the gene A, and as a consequence, with smaller wings.

Here are your results:



Biological question: Are *Drosophila* tumors able to produce metastasis?

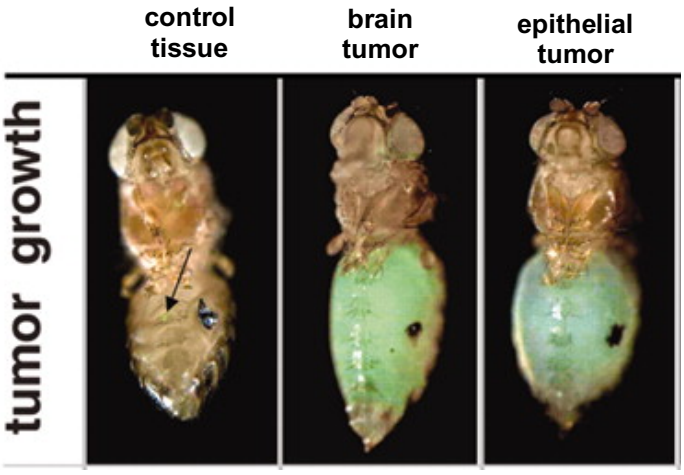
Tumor cells can transit from the primary tumor via the blood circulation to form metastases in distant organs. It has been shown that this secondary metastasis are indeed the cause of about 90% of cancer-associated deaths.

As part of the IRB community and in collaboration with "The Metastasis Challenge" the institute is asking you to set-up a model of metastasis using the fruit fly *Drosophila*.

For that, your lab have developed a transplantation assay that allow to test the invasive capacity of tumors. Tumor tissues will be positively marked by GFP (green fluorescent protein), and a piece of this tissue generated in the larvae is implant in the host of the abdomen of an adult fly to later on, address its tumorigenic capacity in terms of growth and to metastatic ability to other part of the body.

For your experiment you have tested two different types of tumors, brain and epithelial tumors.

Here are your results:



(Janic et al., Science, 2010)

Tumor growth in abdomens	0/156	94/117	95/115
No growth in abdomens	156/156	23/117	20/115
Metastasis in eyes	0/156	85/117	5/115