fcri
Fundació Catalana per a la Recerca i la Innovació

AMGEN TRANSFER CIENCIA

Drosophila en investigación

Creado por **Lara Barrio Guerrero**

Programa **Amgen TransferCiencia 2019-2020**

Drosophila en investigación: introducción

¿Qué es la mosca del vinagre o la mosca de la fruta (*Drosophila melanogaster*)? ¿Qué relación tiene con enfermedades humanas complejas como el cáncer y la metástasis? ¿Qué importancia tiene y ha tenido en investigación?

Lee el artículo de The Guardian "Six Novel prizes – what's the fascination with the fruit fly?" y contesta a estas preguntas y a otras como ¿cuántos días crees que dura el ciclo vital de *Drosophila*? ¿Cuántos pares de cromosomas tiene?

Las Leyes de Mendel: problemas con *Drosophila melanogaster*

Como has visto en la presentación, la observación y estudio de *Drosophila melanogaster* nos permite identificar marcadores de esta especie, observar diferencias entre machos y hembras y ver la acción de las leyes de Mendel. A continuación, resolved, en pequeños grupos, los siguientes problemas.

1. La forma de las alas en *Drosophila* viene determinada por el alelo dominante curly (Cy), que da un fenotipo de alas curvadas, y el alelo recesivoCy+, que da alas estiradas. Si una mosca homocigótica de alas curvadas se cruza con una mosca homocigòtica de alas estiradas, contesta:
    a. ¿Cómo serán los genotipos y fenotipos de la descendencia a la generación F1?
    b. Y si cruzamos entre sí dos moscas de la F1, ¿cómo serán los genotipos y fenotipos de la descendencia en la F2?
    c. Ahora que has calculado las frecuencias genotípicas y fenotípicas esperadas, realiza el conteo de las moscas teniendo en cuenta el carácter forma de las alas y comprueba si las leyes de Mendel se cumplen.

F1: 15 alas curvas	F2: 5 alas normales 15 alas curvas

2. Si sabemos que en *Drosophila* el color del cuerpo negro viene determinado por el alelo recesivo ebony(e), y el color del cuerpo marrón por su alelo dominante (e+). Cuando cruzamos una hembra con el color de cuerpo marrón con un macho de color negro, observamos en la descendència (F1) moscas con el cuerpo de color negro.
    a. ¿Cuáles son los genotipos parentales?
    b. ¿Cuáles serían las frecuencias fenotípicas esperadas que obtendríamos en la F1?
    c. Comprueba mediante el conteo de las moscas las frecuencias obtenidas en este experimento.

F1: 10 marrones 9 negras

3. El gen “yellow” (y) de *Drosophila* se encuentra el cromosoma X, por tanto, hablamos de herencia ligada al sexe si el alelo recesivo (y) determina color del cuerpo amarillo y el alelo dominante (y+), el color del cuerpo marrón,
    a. Si cruzamos una hembra homocigota de color marrón con un macho de color amarillo, ¿qué genotipos y fenotipos nos encontraremos en la F1? ¿Se cumplen las leyes de Mendel?
    b. ¿Qué tendríamos que hacer para demostrar que el gen “yellow” tiene una herencia ligada al sexo? ¿Qué peculiaridad encontramos en la F2?
    c. Calcula las frecuencias obtenidas mediante el conteo de las moscas del experimento.

F1: 14 marrones (8 hembras y 6 machos)	F2:12 hembras marrones 6 machos marrones 6 machos amarillos

    d. ¿Qué pasaría si hacemos el cruzamiento al revés? Es decir, hembras de color amarillo con machos de color marrón. ¿Qué genotipos y fenotipos esperamos en la F1 y en la F2?

4. El gen “white” (w) de Drosophila también presenta herencia ligada al sexo. En este caso, el alelo recesivo (w) determina ojos blancos y el alelo dominante (w +) ojos rojos. Realizamos un cruzamiento con machos y hembras con los colores de los ojos diferentes.
    a. Cuenta las frecuencias con los descendentes de la F1, y determina cuál era el genotipo de los parentales.

F1: 20 hembras rojas 18 machos blancos

5. Cuenta y calcula las proporciones de la F2 proveniente de este cruce.

F1: 18 hembras 16 machos rojos 21 hembras blancas 17 machos blancos

a. En el caso de obtener todas las moscas de la F1 con los ojos rojos, ¿cuáles podrían ser las posibles combinaciones genotípicas y fenotípicas de los parentales?
b. ¿Y qué tendría que ser el genotipo de los parentales si obtenemos las siguientes proporciones fenotípicas a la F1?:

F1: 48 hembras rojas 26 machos rojos 24 machos blancos

6. En *Drosophila* el margen de las alas puede ser entero (fenotipo salvaje) o bien serrado (fenotipo mutante), y el color del cuerpo puede ser marrón (fenotipo salvaje) o negro (fenotipo mutante). En un cruce entre individuos heterocigotos se obtuvieron en la descendencia: 580 moscas marrones con alas serradas, 180 marrones con el margen entero, 60 moscas negras de margen entero y 170 negros con el margen serrado.
   a. Según estos valores, establece la dominancia de los alelos mutantes y los fenotipos de los padres.
   b. ¿Podemos aceptar la tercera ley de Mendel?

El método científico: casos prácticos

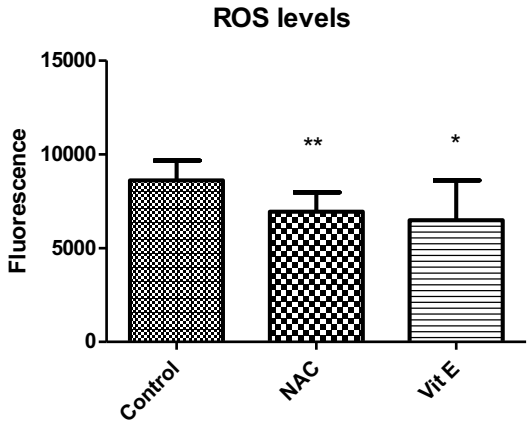
Por parejas o grupos de tres, escoged un caso práctico para trabajar, discutir, elaborad una hipótesis y extraed las conclusiones según los resultados.

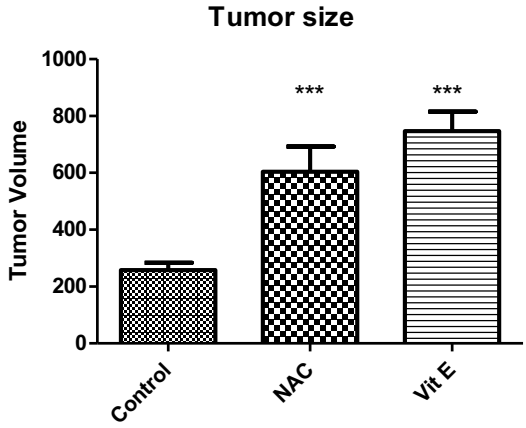
Biological question: Are antioxidants important in the context of tumor development?

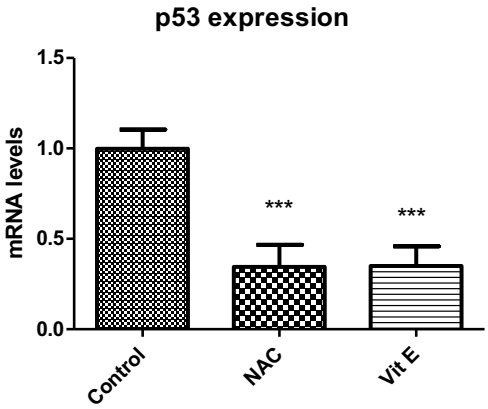
In the recent year many researchers have been hypothesizing that **antioxidants** might be able to protect against cancer. This hypothesis is based on their ability to **neutralize** **reactive oxygen species** (ROS) that can **damage DNA**. However, multiple placebo-controlled prevention clinical trials 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

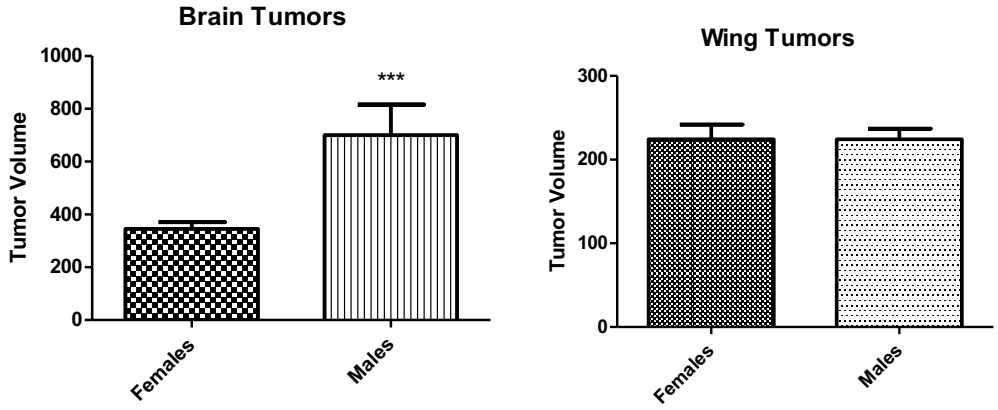
Biological question: Is sexual dimorphism relevant for tumor growth?

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.

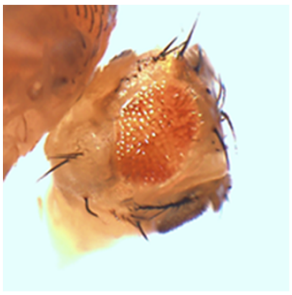
You are studying the connection of the X gene with tissue regeneration. For that purpose you have been given a team and a lab from the IRB. The aim of this team is to understand if the production of X is essential for reestablishing the tissue after an injury and why.

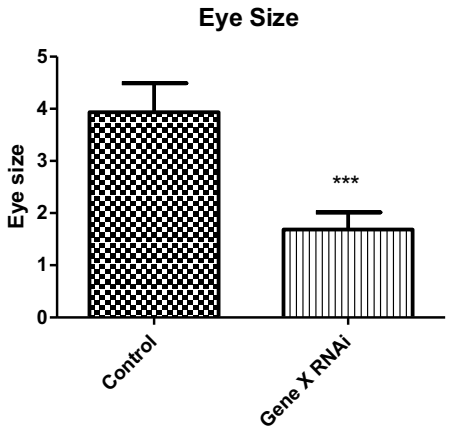
You start by preforming an eye screening in your lab. You will analyze the eyes of control flies versus flies without the X gene 3 days after irradiation in order to evaluate if the tissue was able to regenerate or not.

Here are your results:

Control flies with X

Mutant flies without X





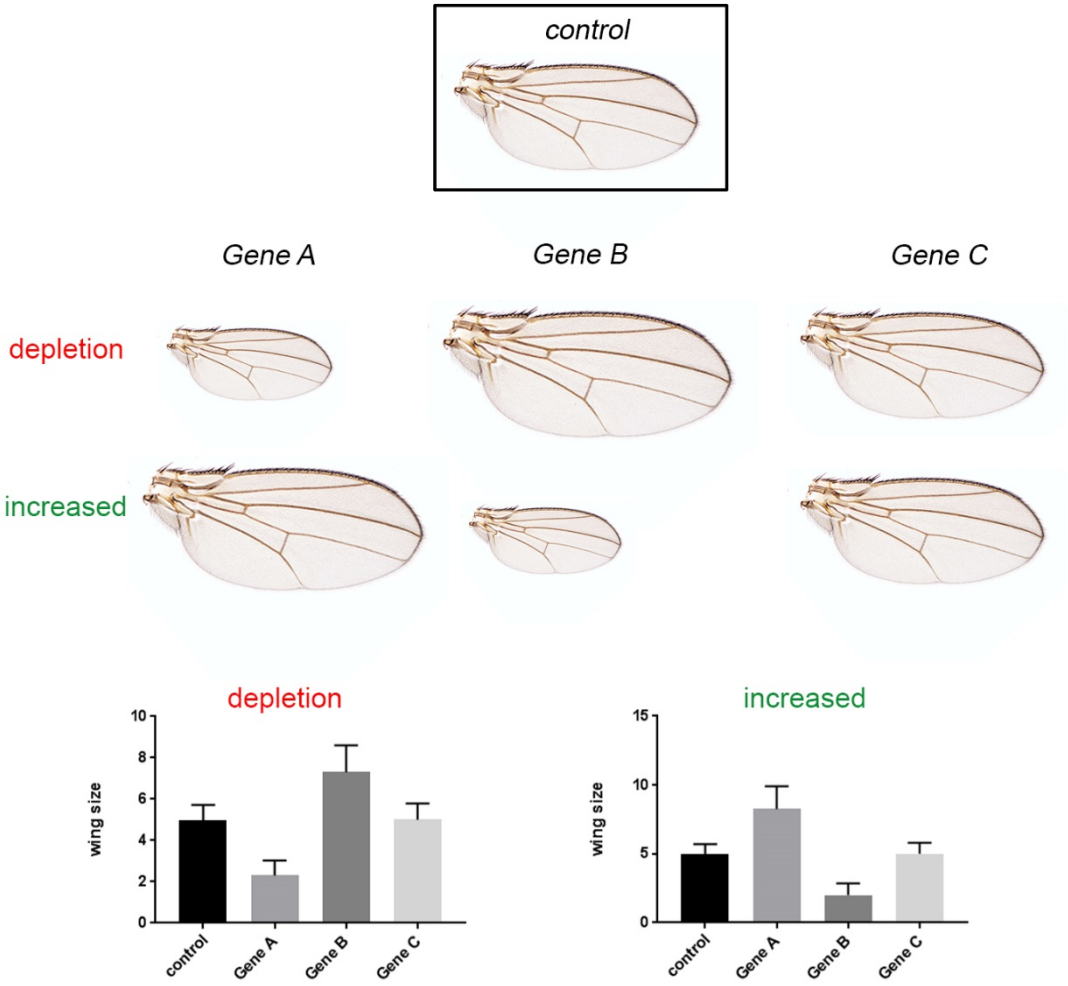
Biological question: Are the genes A, B and C involved in tissue growth?

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

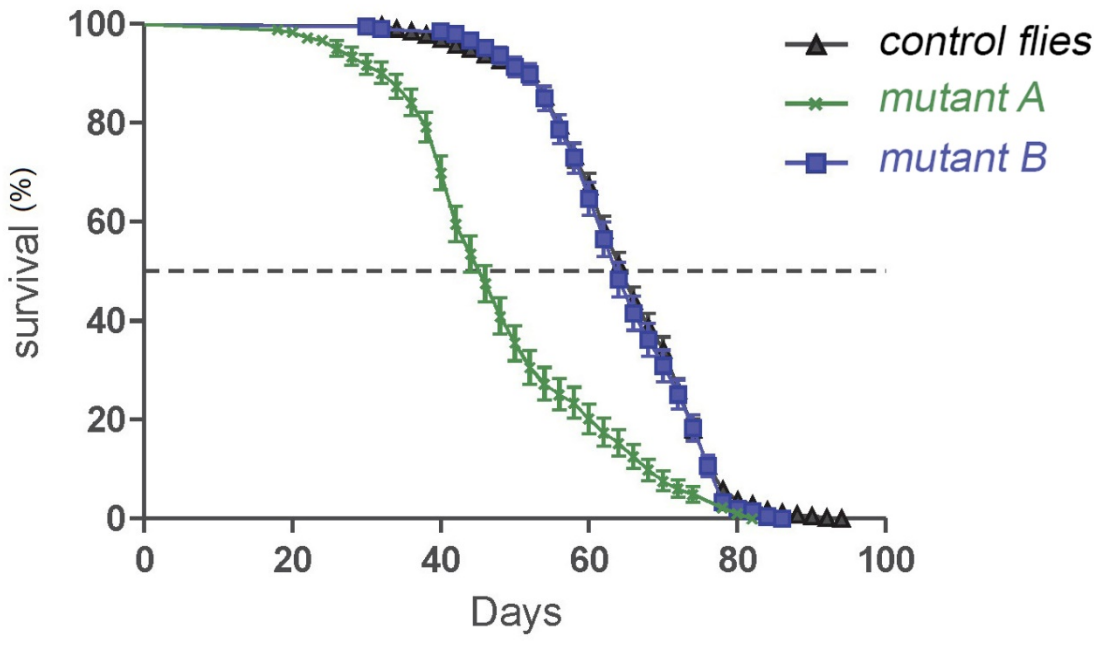
Biological question: Does the size of the wings affect survival of the adult fly?

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?

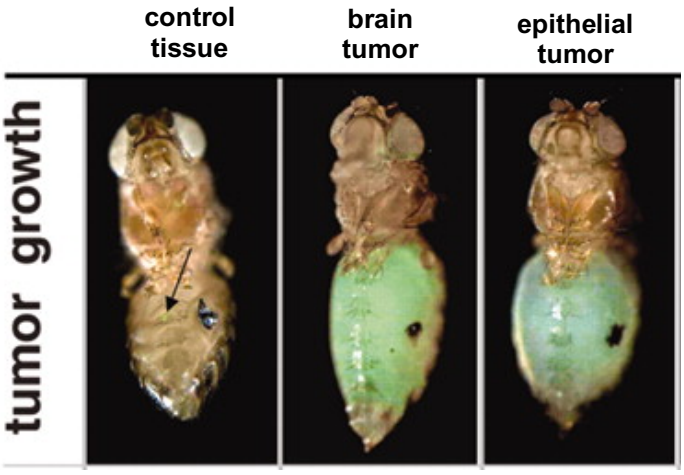
Tumor cells can transit from the primary tumor via the blood circulation to form metastases in distant organs. It has been shown that this secondary metastasis are indeed the cause of about 90% of cancer-associated deaths.

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