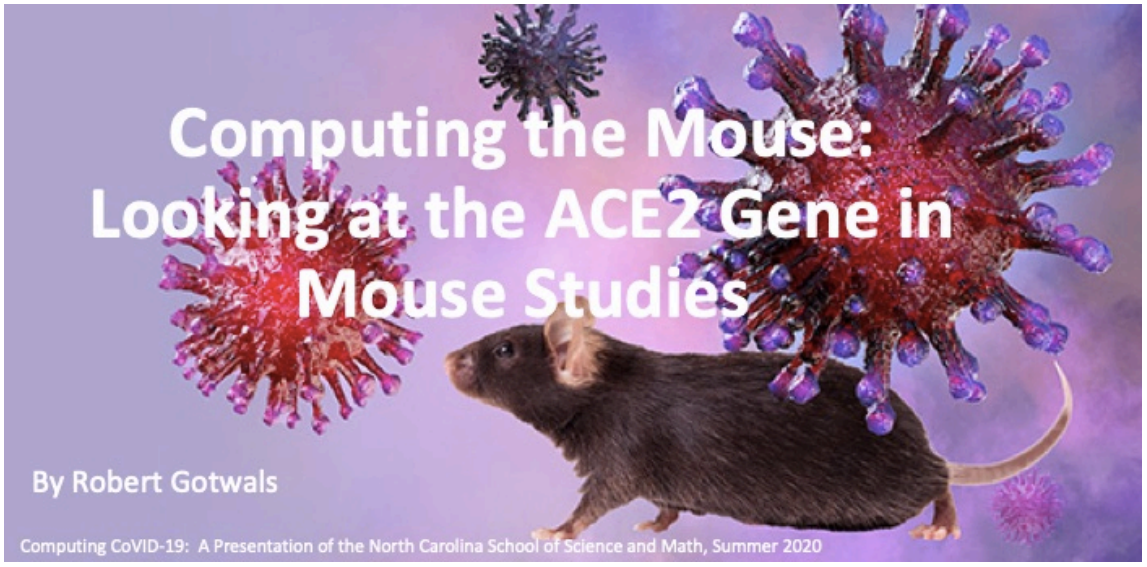

Computing CoVID-19: Summer 2020

Computing the Mouse:

Looking at the ACE2 Gene in Mouse Studies

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1

Introduction

The ability to develop a cure or a vaccine to the SARS-CoV-2 virus (or, as some call it, CoVID-19) depends upon having a good *animal model* on which to test new drugs or vaccines. Mice are the most commonly-used animal model. Why? Here are some reasons:

1. Mice are easy to care for in large numbers. Thousands of mice can be housed in climate-controlled clean rooms, protected from external contaminants
2. Mice breed quickly. To create a genetically-pure mouse, we need about 20 generations. The gestational time is about 22 days, so it is possible to create multiple generations in a relatively short period of time. [1]
3. Mice are very genetically similar to humans. A typical estimate for genetic similarity is between 85 and 99%, depending on which genes are under consideration. The genes that actually produce proteins are between 85 and 88% similar to humans.
4. Mice are really inexpensive
5. It is relatively easy to genetically alter a mouse. Whether it be removing a gene (a "knockout", or KO mouse), or to insert a gene from a different organism (a "transgenic", or TG mouse), mice are easy to manipulate and alter in the laboratory.

Figure 1 shows some of the more common strains of mice. The "normal" nouse is the C57Bl/6J mouse, otherwise known as the "Black 6" mouse. Many other genetically-altered mice are bred against the Black 6 mouse, which serves as something of a control on the breeding process.

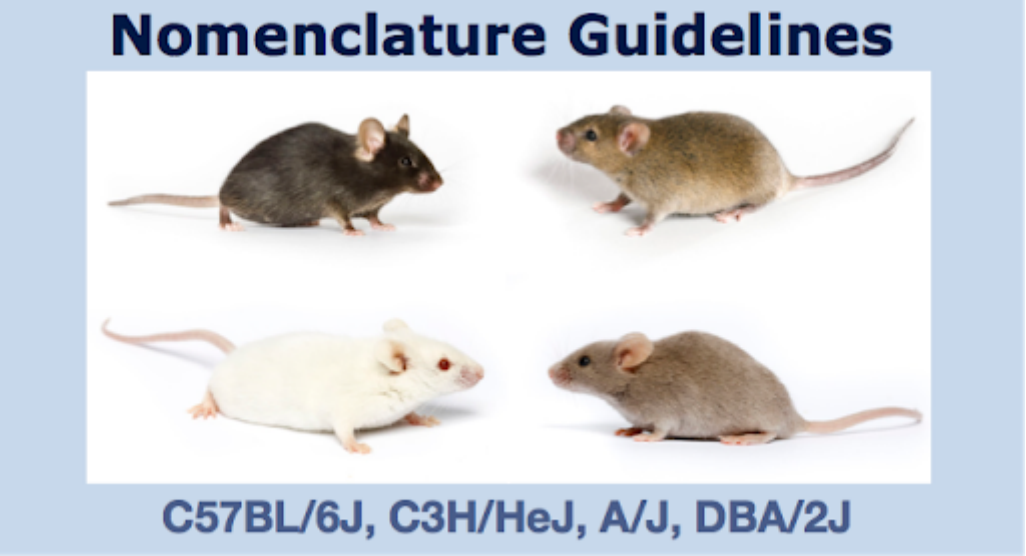

Figure 1: Common strains of mice

Figure 2 shows one increasingly popular strain, the "BTBR" mouse from Alan Attie's lab at the University of Wisconsin-Madison. This mouse was bred primarily for studies of inflammatory diseases, such as obesity and diabetes. Notice the reference to cytokines – these are signaling proteins that play a role in infection and inflammation. You will read about a "cytokine storm", a condition in which the body releases an overabundance of cytokines into the bloodstream. There are strong indications that this dumping of cytokines has significantly harmful effects, including deaths.

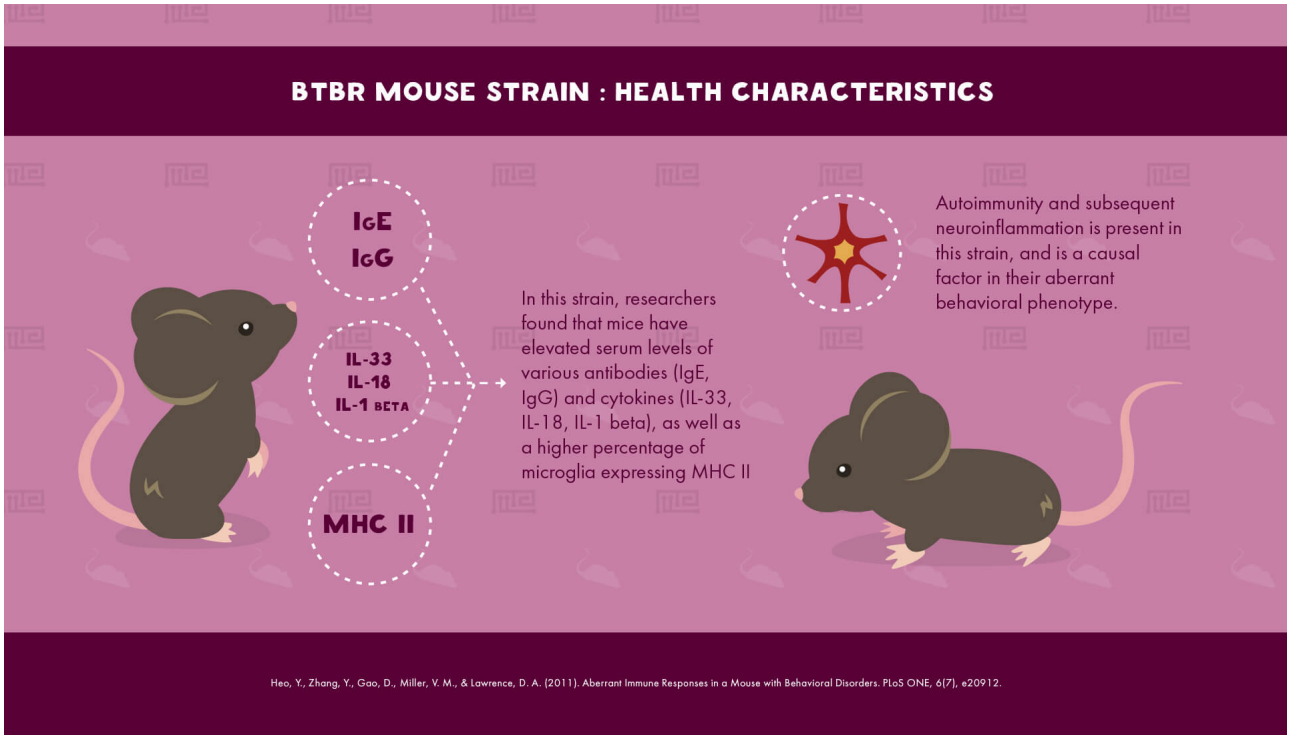

Figure 2: Characteristics of the BTBR strain of mouse

So where do mice come from? The primary scientific organization that produces research-grade, genetically-engineered mice is the Jackson Lab, located in Bar Harbor, Maine, just outside the entrance to Acadia National Forests. The "Jax Lab,as it is typically called, is shown in Figure 3. It is the nation's foremost mouse genomics research organization. NCSSM had a 10-year, National Institutes of Health (NIH)-funded grant to teach high school students the advanced tools of bioinformatics as related to mouse studies. That grant led to the development of NCSSM'S course in bioinformatics, open to NCSSM students in the spring semester. The Jax Lab also runs a highly prestigious summer research program, one where the students receive a large stipend and live in a mansion on the eastern side of the island!

Figure 3: The Jackson Lab, the nation's premiere mouse lab

Mice genes are identified using the notation "Gene", where the first letter of the gene is capitalized, and the others are lowercase. This differentiates mouse genes from human genes, which are all uppercase. As such, the gene "Ace2" is a mouse gene, and "ACE2" is the human version of that gene.

The main Jax Lab resource is the Mouse Genome Informatics (MGI) (http://www.informatics.jax.org/. From this page, researchers can obtain everything one could possibly want to know about mouse genomics.

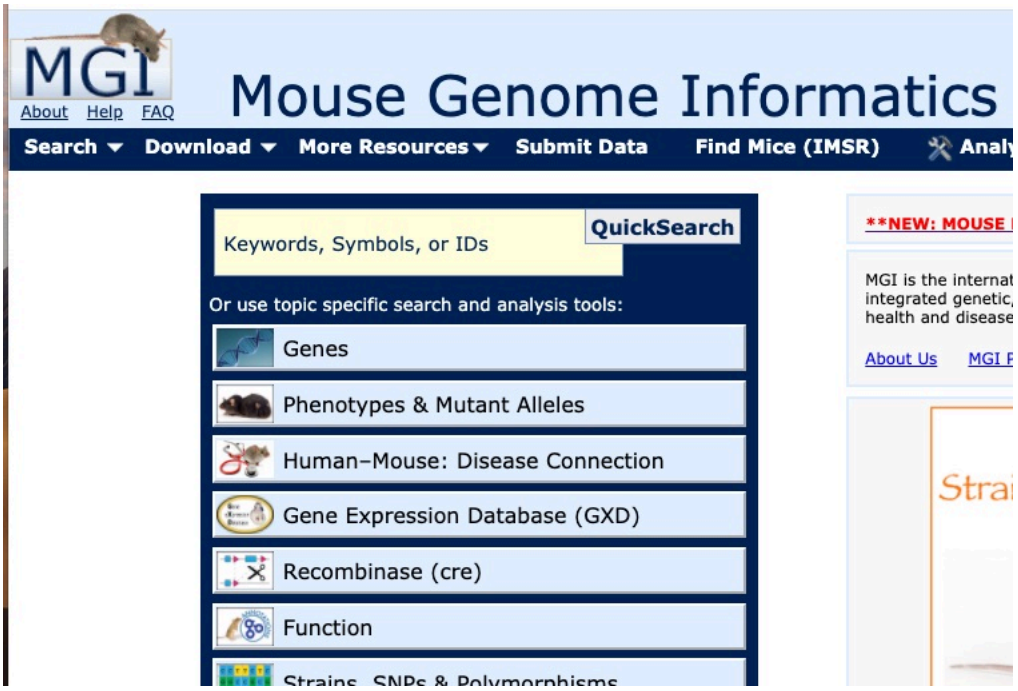

Figure 4: The Mouse Genome Informatics database

Like virtually every other genetics/genomics database these days, a special collection of resources related to CoVID-19 has been created. At the Jax Lab, this site is at `http://www.informatics.jax.org/mgihome/other/coronavirus.shtml`. As Figure 5 suggests, this page is updated every day:

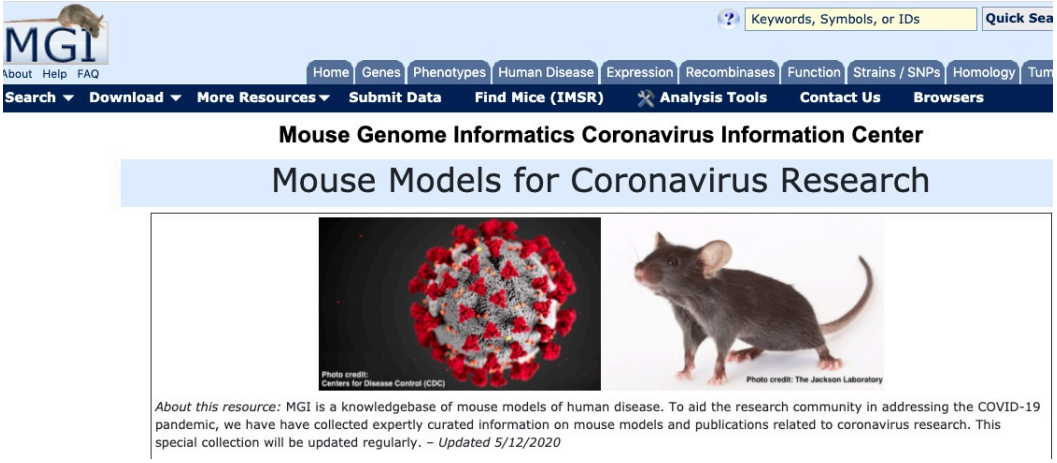

Figure 5: The CoVID-19 Mouse Genome Informatics resource page

For this morning's labs, you will be using this resource to find information about some of the mice being used for CoVID-2 studies and the genes that are current targets.

2

Student Activity: Using MGI to explore the Ace2 Gene

NOTE! The majority of the steps for the activity will be demonstrated in the webinar. These instructions are meant only as short reminders of the steps you need to take to effectively modify the lead drug and test the new compounds!

For this activity, you will use MGI (http://www.informatics.jax.org/ as demonstrated in the webinar to explore the Ace2 gene/protein in mice. A series of questions, both from the lab reading and the use of MGI, are found on Canvas.

References

[1] Silver, Lee M. Mouse genetics: concepts and applications. Oxford University Press, 1995.