Questions week 12

Which residues in the molecule are critical to designing potent inhibitors?

RAS catalytic pocket is small, and they could not find improvements in small molecule inhibitors, but His95 groove can host an aromatic ring, and this has allowed them to improve potency.

Why measure p-ERK to determine AMG510 activity?

Because is one of the main downstream targets of Ras, and if RAS signaling is inhibited it needs to block the effect on ERK phosphorylation.

Why did they check a cysteine proteome profile?

To understand specificity, because a covalent inhibitor reacting with cysteines could bind no-specifically to other proteins *in vivo* and cause side effects.

What are the main differences between the experiments done *in vivo* using human and mouse cells?

Human cells were engrafted in immunocompromised animals, while mouse cells were engrafted in immunocompetent animals, starting to reveal that the effect of RAS inhibition can depend on the activity of the immune system.

Was a RAS inhibitor used as a first line of treatment in lung cancer patients?

No, they already received chemotherapy, indicating that these are relapsed tumors.

What is the effect of carboplatin?

It is an alkylating agent that binds to the DNA and induces DNA damage and cell death.

Note: In Figure 5, there is a test of RAS inhibitor in combination with anti-PD1. We will describe the mode of action of anti-PD1 and why it is considered an immunomodulatory agent in the next lecture.

Can the combination of a RAS inhibitor and immunotherapies be tested in xenografted mouse models using human cells?

No, because to assess the activity of the immune therapies we need immunocompetent animals and human cells cannot be engrafted in immune-competent mice.

Groups for discussion

Figure 1
Figure 2
Figure 3-4
Figure 5