Module 3 Quiz

1. A Structure Activity Relationship (SAR) is the relationship between the chemical structure of a molecular and its biological activity. In Dr. Patnaik's presentation, he showed us how medicinal chemists can change specific residues and alter the following properties of a compound:
    a. Increased selectivity in target binding
    b. Increased efficacy in inhibiting the target
    c. More favorable pharmacokinetic profile (e.g. metabolism and clearance of the molecule in an in vivo model)
    d. All of the above
2. Successful medicinal chemistry projects rely on the following key components:
    a. Hypothesis-driven Structure Activity Relationships (SAR)
    b. Physiological disease models
    c. Robust chemistry to diversify structure
    d. All of the above
3. In this course, we have described medicinal chemistry as a pivot point between discovery and developing of a compound that can advance to clinical trials.
    a. True
    b. False
4. For the Metarrestin project, there were three key compounds evaluated in a range of assays, including looking at efficacy (e.g., PNC inhibition) and pharmacokinetic properties (e.g., cell permeability). The compound that went forward (now called Metarrestin) was not the most potent in inhibiting PNCs.
    a. True
    b. False
5. The "Dynamic Map for Therapeutic Development" shown early in Dr. Patnaik's first talk is an NCATS-developed resource and is now available in an interactive version you can explore.
    a. True
    b. False
6. Multi-agency partnerships are particularly effective in translational research because…
    a. Different agencies employ individuals of different areas of expertise
    b. Different agencies have different focus areas, for example, basic research, early drug discovery work, clinical trials, and engaging with the FDA
    c. Different agencies have different infrastructure and resources at their disposal, which may be harnessed for a particular drug discovery and development project
    d. All of the above

Answer Key

1. All of the above

   Using an IGF-1 receptor inhibitor as an example, Dr. Patnaik showed us selective inhibitors can be achieved by changing only one key residue. Making a change to one residue resulted in greater activity in inhibiting IGF-1R while decreasing the interaction of the compound with a different kinase (Aurora kinase). He also provided data on additional modifications that were needed to improve the pharmacokinetic profile.

   Even if a compound shows activity against the target in in vitro assays, if the compound does not have a favorable pharmacokinetic profile in vivo it will not move forward without additional modification. Pharmacokinetic profiles (ADME=Absorption, Distribution, Metabolism, and Excretion) will be addressed more in week 5.

2. All of the above
   Being able to draw on all of these components will increase the likelihood of a successful medicinal chemistry project.
   1) Hypothesis-driven SAR: The SAR is the relationship between the chemical structure of a molecular and its biological activity. Dr. Patnaik showed us how small changes can alter the properties of a compound. Using a hypothesis-driven approach allows one to make these modifications in a more systematic way.
   2) Physiological disease models: This was highlighted by Dr. Patnaik and also echoes comments from Dr. Ferrer. In order to have better predictability of the clinical efficacy and toxicity of a compound, these studies need to utilize disease-relevant models.
   3) Robust chemistry to diversify structure: All starting compounds will need to be optimized to refine efficacy in interacting with the target and to create a robust pharmacokinetic profile for in vivo evaluation. By employing a diverse array of chemical approaches, chemists can maximize their ability to achieve these attributes for a given compound.

3. True
   Medicinal chemists are evaluating the efficacy of their compounds in interacting with the target while also keeping an eye on the end goal of having a compound that can advance to clinical trials. The medicinal chemist must evaluate each compound for possible modifications that will increase efficacy and are likely to lead to a favorable pharmacokinetic profile when the compound moves from in vitro to in vivo testing. Therefore, medicinal chemists must make modifications anticipating the next steps for the project.
4. True
   Metarrestin inhibited PNC formation but was not the most potent in this assay. Metarrestin went forward based on the combination of its ability to inhibit PNC formation and having a more favorable profile with regard to cell permeability. This is addressed around minute 14 in Dr. Patnaik's second talk.
5. True
   Dr. Patnaik did not explicitly state this but we wanted you to know about this resource. This map showing different areas of expertise involved in drug development was developed by

NCATS can be found here (https://ncats.nih.gov/about/about-translational-science/resources). Two versions of the maps are available: one for small molecules, and another for biologics. We refer to these as the Drug Discovery, Development, and Deployment Maps (4DM). The maps have been adapted to provide a "dynamic map interface for enhanced usability and an interactive experience. Users can zoom into and out of areas of the process to view different levels of complexity, find information and best practices, and connect to relevant NCATS programs and resources." The interactive map can be found here (https://ncats.nih.gov/about/about-translational-science/resources) and is also available under Additional Resources at the bottom of the course website.

6. All of the above