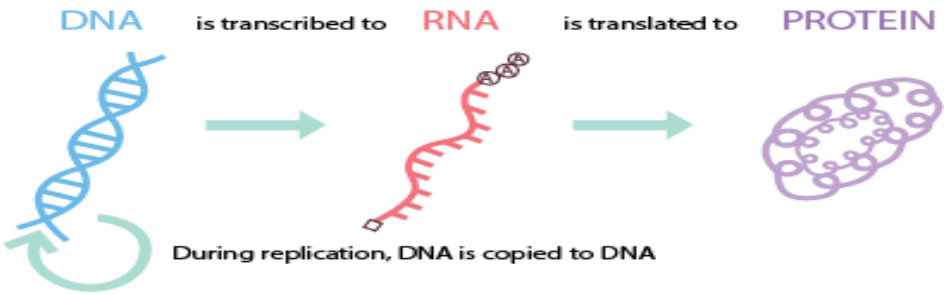
Learning for Life Week 8 Summary

Topic: Immunotherapy Approaches to Cancer Therapy

Speakers: Chad Mirkin, PhD and Andrew Lee, PhD

Today we were able to learn about the potential applications of nanotechnology and how Northwestern is a world leader in this field.

Chad started us off with a deep dive into how and why nanotechnology is going to play a huge role in drug development. Medicines are evolving from "small molecule drugs" which are chemically synthesized (examples are aspirin and Lipitor) to "biologics" which are antibodies and peptides isolated from living systems and used as drugs (examples are Rituxan and Humira). But the most promising new area of drug development is called "nucleic acid medicines." These are medications that are made with synthesized DNA and utilize nanotechnology for their delivery. He brought us back to the basics of biochemistry, reminding us of the ubiquitous pathway for protein production in the cell: double stranded DNA uses *transcription* to make single stranded messenger RNA which uses *translation* to make proteins.



In disease states like cancer, cells may produce too much of one type of protein and this may prevent the cell from dying, resulting in larger tumors and metastases. If we were able to target the production of those proteins by interfering with messenger RNA required to make the protein, we could stop the cancer from growing. You need three things to make nucleic acid drugs that can do this:

1. A nucleic acid synthesizing machine –we have these
2. A good understanding of the biologic pathways that the drugs should target--learning more and more about these every day.
3. A delivery mechanism for the drug to get to the cells and organs--this is where nanotechnology comes in.

Chad described the development of "spherical nucleic acids (SNAs)" (see image below). Cells do not allow linear DNA and RNA to enter their systems, but if the short strands of DNA (which are targeting the messenger RNA and therefore blocking the production of protein) are attached to nanoparticles, or "cores", the cells actively take them up.

spherical nucleic acid (SNA)

Dissolved gold has been used as the core because its size and density has many advantages including being able to cross the blood brain barrier. But gold is a foreign substance, and increasingly, spherical nucleic acids are being made with cores of liposomes, a naturally occurring nanosphere in the body.

Initially these nucleic acid drugs were injected systemically into the blood stream (Chad described the trials that are going on now at Northwestern for glioblastoma, the brain cancer that John McCain has) but now there are drugs that can be delivered straight to the tissues that are affected, like skin and eyes.

The next part of the presentation was delivered by Andrew, who built upon the foundation of what we learned about nucleic acid drugs to describe their promising role in cancer immunotherapy.

Our body's immune system uses our own immune cells to target and destroy foreign invaders like bacteria, viruses and even cancer. However, cancer cells are smart and develop resistance to the immune cells through "check points." Biologics like Keytruda have been developed that bind to the cancer cells and facilitate the body's immune system to target the cancer cells. What if we could also "hit the gas" and increase the number of immune cells that our body produces to fight the cancer? Just upregulating the entire system will have significant side effects as these cells can be toxic. We want to increase the number of immune cells that will specifically target cancer cells. Andrew described a therapeutic "cancer vaccine." The vaccine would include a "danger signal" composed of portions of viral or bacterial DNA, signaling to the immune system that it needs to respond by activating immune cells. The vaccine would also include tumor markers, or antigens, that would drive the immune cells to the tumor itself. All would be "packaged" on a nanoparticle core. Once injected, this Spherical nucleic acid vaccine would be injected into the patient resulting in engagement of the immune system to where it sends the activated immune cells to the cancer and results in destruction of the tumor. While these cancer vaccines have not been used in humans, they have been shown to improve survival in mice with lymphoma, a blood cell cancer. Their use in humans is certainly in the not too distant future.

Take home points:

1. Spherical Nucleic Acids(SNAs) are a class of nanomedicines that can effectively enter cells and tissues.
2. Nucleic acids can treat diseases not addressable with traditional therapies.
3. These novel drug delivery systems or SNAs, open up the possibilities of drug design-- shorter times from design and development of the drug to use in the patient.

Thank you to Shirley and to all of you for letting us be a part of this wonderful lecture series. It has been so fun to learn with all of you.