Talking Science

January 9, 2016

Selected questions from the audience

Advice/Personal Questions for Dr. Sakmar

1. What tips would you give to a high school student hoping to go into medical research?

   Ans. It's never too early nowadays to get some practical experience in the laboratory and there are many organized programs offered by research institutes, colleges and universities. But be a bit careful not to specialize too quickly. There will be time once in college to choose a science major and to get both the course work and practical experience that you require based on individual preferences. And don't forget that research is a people-oriented endeavor, as supported by many examples in the lecture. Therefore, keep working on developing strong reading and writing skills along with the analytical work, including some solid math and computer training. Research is the type of career where perpetual learning pays off! So develop your study habits and routines now!

2. Do you believe that genetic engineering and cloning is ethical?

   Ans. There is nothing that is intrinsically unethical about genetic research and cloning. In some areas of research involving human subjects, or DNA from human subjects, review panels are established to insure that research meets ethical standards. These panels often include not only science experts, but members of the community as well. One recent example has been in the field of stem cell research where ESCRO (embryonic stem cell research oversight) committees review all research proposals for scientific validity and ethics considerations. Often technology advances faster than the legal and political systems, but scientists and public policy experts need to continually gauge and respond to public opinion and they have a responsibility to educate the public about science.

3. How do you feel about spending a lot of money on drugs to treat diseases that are preventable by lifestyle change, such as some Type II Diabetes or diseases caused by smoking?

   Ans. Drug development is just one part of the overall equation to improve public health. The fact that fewer and fewer young people smoke is tremendous good news. But it is often difficult to institute healthy lifestyle changes, including exercise/activity and healthy diet, into our daily routine. It takes personal commitment and dedication to develop a healthy lifestyle. But those who have difficulty making a commitment to healthy lifestyle choices should not be made to feel responsible for health problems that might have been ameliorated by earlier interventions. No one chooses to be less than healthy.

4. If someone (my student) has designed by computer 2 or 3 inhibitors for an enzyme specific to s. pneumonia, whom should she talk to about testing her inhibitors?

   Ans. Computer-aided design of drug candidates is a new and evolving field, but experimental work, but in vitro (in a test tube) and in animal models of disease is ultimately needed to prove the efficacy of any drug candidate even before clinical trials in human subjects. Anyone with a good idea should search for experts who might be able to help. And here, the internet is invaluable.

5. How do you keep track of what each well in a 384 well petri dish contains?

   Ans. Once an experiment moves from a single plate to a 384-well plate some instrumentation is required to monitor what is going on in each well. Most labs have automated microscopes or scanners that can read through each of the wells in a matter of minutes. Data can be collected on spread-sheets for analysis when needed.

6. What type of drug discovery application do you believe is most effective (e.g. gene therapy, gene engineering, etc.)? Why?

   Ans. As discussed in the afternoon lecture, a number of different approaches exist for developing new therapies to treat human diseases. However, despite many new and exciting technologies, including stem cell therapies, cell-based targeted therapies, and precision medicine, at present, looking for chemical or biological agents for known disease targets remains the most productive pathway to a new therapeutic agent.

7. Do you think that the sequencing of the human genome can eventually lead into issues with insurance or with privacy?

   Ans. Genetic information should be kept private and used only for legitimate medical reasons. In the U.S. it is illegal to use genetic information to discriminate against individuals or to deny insurance coverage for "pre-existing conditions." Your genome is yours and yours alone. We all have to consider the implications of sharing genetic information and we should stay well informed and make our views about genetic privacy known to policy makers and healthcare providers in the future.

8. What is the most important part of idea creation?

   Ans. Creative innovation is a new idea that addresses an existing problem in a new way – a new idea that adds value. Everyone has the potential for a creative spark! Everyone can think of something new given the right environment and some "quiet time." But be sure to write it down! Then develop your idea and share it with others.

9. Did you ever find medicine for any disease?

   Ans. Yes. My laboratory was involved in developing a "proof of concept" for a new type of drug to treat HIV-AIDS. A version of the drug was eventually approved for use in humans and its name is Selzentry (mozobil).

10. Why are you interested in science?

    Ans. I'm not sure that I can articulate an answer to that question. I am generally curious about many things, but science has been my passion for as long as I can remember.

11. Modern or traditional medicine?

    Ans. Why not both? As we discussed in the afternoon lecture, the Nobel Prize in Medicine or Physiology this year was awarded to Dr. Tu You You, whose work was based on traditional Chinese medical remedies.

12. What was the most exciting thing you have learned from researching in the lab?

    Ans. The most exciting thing to me personally involved our work on vision, which was not discussed in the lecture. We discovered part of the puzzle about how color vision is possible. But more on that in another lecture!

13. To what do you attribute the success of Rockefeller University?

    Ans. Rockefeller University is a unique place and I am very lucky to be able to work here. The key factor in the success of Rockefeller over so many decades is that scientists here are given freedom to pursue their dreams! There are very few barriers, no walls, and few distractions. Everyone can work in a supportive environment with maximal encouragement and support – and the results speak for themselves.

14. Do you use genetic engineering to find cures for any illness?

    Ans. Yes, but indirectly. We use genetic engineering to study molecular targets for drugs that might treat diseases. For example, let's say that a certain membrane receptor, when activated, causes high blood pressure. It might be possible to use genetic engineering to clone the DNA for that receptor, study it in a test tube, and then develop a drug to block its action in the body.

15. Have you found the cure for any type of cancer? If yes, did you use some type of biotechnology?

    Ans. No, not yet. But we are working on some receptors that when mutated cause cancer in humans. One example is a receptor mutant that causes a very rare cancer of the eye called uveal melanoma.

16. Do you use selective breeding in plants so you get more desirable traits for the cure of a specific illness?

    Ans. Some labs are using genetically modified plants that might produce drugs or drug-related compounds. One example of note is that plant cells can be engineered to make the cancer drug paclitaxel, which previously had to be extracted from the bark of endangered Pacific yew trees.

17. What is the average number of times a scientist fails?

    Ans. I would say that some experiments work as predicted and some do not. The result of a well-designed experiment always provides useful information, so each experiment represents progress. Over time, results add up. A disappointment is not a failure, it's just a reason to do more experiments.

18. What is the process of an invention?

    Ans. Invention sometimes means innovation – a new idea – being present when the "light bulb" goes off in the cartoon drawing above the head of a scientist – the "Aha!" moment. Of course, the legal definition is a bit less glamorous. An invention is a practical solution to a concrete problem. It is a "claim" that something can be useful. It is a something that is novel and has utility, but is not obvious.

19. What difficulties did you encounter during your experiments/work?

    Ans. The main difficulty is the march of time. There is never enough time to carry out all of the experiments and work that might be interesting. Therefore, it's always important to prioritize. That's life.

20. If you could create any program written in R, what would it do and why would you create it?

    Ans. R is a computer language well suited for statistical analysis and I might want to use R to write code to analyze images to determine what is signal versus what might be noise.

History of Medicine

1. What were some of the innovations that led to DNA and RNA sequencing becoming cheaper?

   Ans. There have been about 15 or 20 specific innovations that have led to the DNA/RNA sequencing revolution. DNA sequencing became practical in about 1980, and by 2001 the human genome was sequenced. As discussed in the afternoon lecture, the speed of sequencing has increased dramatically while the cost has plummeted. Automation is a big factor, but advances in chemical probes and data analysis have also contributed.

2. On the 2001 DNA sequence, why are the peaks of each based on different heights?

   Ans. There are actually 4 "channels" of data, each corresponding to a different base: A, C, G or T. The peak heights allow a determination of which base predominates.

3. What is the original function of alkaloids in plants? Why do plants make alkaloids?

   Ans. Alkaloids are a part of the natural immune system of plants. Alkaloids help plants to adapt to their local environment and resist infections by fungi, bacteria or parasites.

4. How did the early people know to look in plants for medications?

   Ans. Were they actually looking for medications? I don't think so. They probably just noticed that when they ate certain things, there was an effect – sometimes negative, and sometimes positive. Over time, people could remember and select plants that caused some benefit. As discussed in the morning lecture, eventually people could write down and catalogue the positive effects of plant substances.

5. What was the name of the first medication to cure a serious bacterial illness (the illness that the little girl had and was cured of)?

   Ans. As discussed in the morning lecture, prontosil was invented by Gerhard Domagk, who used it to treat his daughter Hildegrad's infection.

6. Why did Ehrlich leave to start his own institute?

   Ans. I'm not sure; you would have to ask Dr. Ehrlich.

7. What were the major medical innovations in ancient civilizations (for example, the Incas, Aztecs, Egyptians, etc.)?

   Ans. There are some indications that early civilizations were concerned with treating diseases, but innovations, other that the limited uses of medicinal plants were limited.

8. Back then, when scientists would give medicine to the patient, how would they stand against side effects and giving the patient something worse?

   Ans. Well, in this case we certainly have to consider the old adage that the "cure is worse than the disease." It has only been in the past 50 years or so that controlled trials of drug efficacy and safety have been carried out systematically.

9. At what point in time do scientists treat fungal infections? How did they discover that fungi could cause infections like bacteria? What steps did they take to try and find treatments or cures?

   Ans. Nowadays, fungal infections are often related to immuno-compromised states or to treatment with antibiotics or chemotherapeutic agents. More common fungal infections, like skin infections, were always present, but I am not sure when specific treatments were developed. Please let me know if you find out any additional information. Thanks.

10. Was Koch related to the Koch brothers?

    Ans. No relation, as far as I know. But David Koch is a trustee of Rockefeller University and has been very generous in his philanthropic support of the university.

11. If people discovered the cinchona as the cure to malaria, why did so many people still die from malaria afterwards due to the lack of cure?

    Ans. A very good question, and many thousands of people still die from malaria today. The "cure" was not complete, many people did not have access to treatment, resistance to the drug developed and re-infection was possible. The same problems exist today!

12. Was it serendipity when the Nobel Prize winning drugs were discovered?

    Ans. Serendipity can be described as "finding something that you are not looking for." There are a few notable examples of serendipity in drug discovery that were discussed in the lectures, but finding a Nobel Prize winning drug is never an accident. Hard work and perseverance is always required.

13. Why does guanine appear with higher peaks than adenine, cytosine or thymine on 2001 DNA sequencing charts?

    Ans. Guanine usually appears as a higher peak because it has a higher "extinction coefficient," which means that that same amount of guanine gives a higher signal than the other bases. It's just the chemistry!

Current Medicine

1. What is a cause of penicillin allergies (molecular? Why does this drug elicit an immune response?)

   Ans. Penicillin happens to be a very good immunogen. It sometimes forms a "hapten," which means that it can attach to proteins in the body and can then elicit an immune response.

2. How would a medicine that blocks adrenaline from its receptors be helpful?

   Ans. So-called beta-blockers are medicines that block adrenaline from binding to its receptor. Such drugs would decrease heart rate and blood pressure and are especially useful to treat hypertension and heart failure.

3. Does changing the epigenetics of a human – therefore changing the genome – change and/or cause an evolution within the body during reproduction?

   Ans. Epigenetic changes don't really change the genome, but they do affect the expression of genes in the genome. The subject of epigenomics and the "code" of the epigenome are under active investigation at Rockefeller University by Prof. David Allis and other pioneers in the field.

4. In the video, it showed that the body can cure itself from cancer but how does this method work?

   Ans. Our immune system in principle has the capability for surveillance of cancer cells and it is quite likely that some cancers result from a failure of the immune system to remove aberrant cells from the body. Some scientists are working on methods to enhance the immune system to fight cancer. Stay tuned for more developments.

5. Do melanoma drugs lead to resistance of cancer cells?

   Ans. Yes, all cancer cells can develop resistance to drug treatments.

6. What barriers are present in synthesizing a new drug for a new gene, besides cost and ethics?

   Ans. In principle, any gene product can be targeted with a drug, either a small molecule or a biological agent. One barrier might be that the drug might be toxic to people and therefore not useful even though it might work in a test tube, or even in an animal.

7. How can a signal transduction pathway have two different responses? (In the STP, the STAYS led to Apoptosis and also gene regulation)

   Ans. One principle of signaling pathways is that there are almost always so-called counter-regulatory pathways that compete with each other. For every chemical that activates a given pathway, there is almost always another chemical that inhibits the same pathway. So it is with apoptotic and proliferative pathways.

8. What are the main boundaries of biology and chemistry? Where do they meet and at what point do they begin to differ and divert?

   Ans. This is certainly a complicated question, but the basic distinction is that biology deals with living systems, while chemistry deals with the properties of matter. Please take it from there, won't you?

9. Small molecules can block certain receptors but will they stay with the receptor forever? Will the cancer come back after the small molecules are degraded or new receptors were synthesized by the cells?

   Ans. It is true that some drugs might block receptors indefinitely, and that new cells or new receptors might appear with time. However, one principle of pharmacology deals with the measurement of such occurrences, and tries to predict what dose of a drug is needed to overcome the effects of new synthesis of targets. This field is called pharmaco-dynamics and is relevant to understanding proper drug dosing.

10. Is drug discovery only used by plants (herbals) in order to cure diseases?

    Ans. Some drugs, although not many, are totally synthetic and not related to any known structure previously discovered in plant extracts.

11. At which point in the malaria life cycle does quinine have its effect? What does it inhibit?

    Ans. I once asked the same question to a famous Rockefeller professor named Dr. Trager, who was the first person to culture the malaria parasite in a test tube. Even he was not quite sure, but he thought that the drug prevented the parasite from entering the interior of the red blood cell.

12. In regard to HIV, how much of an understanding do we have of it and how to stop it completely (remove it from one's system)?

    Ans. The issue of "latent" infection is one of the key challenges in treating, and curing, HIV infection. Currently HIV is a "chronic" condition, but in the future it might be possible to target the HIV genome directly.

13. Are there any other more advanced research being done with recombinant DNA technology besides insulin?

    Ans. Yes. Many genes have now been "expressed" in the laboratory and approximately 20 biological drugs are now available for clinical use.

14. Are ancient medicines from the early ages overlooked because of how much we have progressed? For example, a treatment for an infection similar to staph was overlooked from Bald's Leechbook until very recently and it treated staph effectively.

    Ans. A potential remedy from the old English text Bald's Leechbook made the news last year when a remedy described in the book made from garlic and bile salts was tested for activity against Staph infections. I have not heard about any progress but please let me know if you hear any news.

15. What types of specializations does pharmacy have?

    Ans. Some pharmacists specialize in hospital work, others in research and still others in outpatient services. Pharmacist school is a great career pathway.

16. Are there dyes that are used commonly/casually (in clothes, etc.) that was found to help in an illness or disease?

    Ans. In the lecture, we talked about why some dyes that might be useful as textile dyes might also be useful to stain the proteins of cells. Very few dyes nowadays are used as drugs, but nevertheless the origins of the pharmaceutical industry lie in the dye chemistry industry.

17. Is it difficult/less beneficial to pharmaceutical companies like Merck & Co. to invest in developing drugs for developing countries if you know most will not be able to afford these medicines? And along with that is there a sort of social responsibility these companies feel in this?

    Ans. Merck is a great example, among others, that have devoted resources to providing drugs to underserved developing countries. The entire story of the development of Ivermectin, a drug to treat many parasitic infections, is a testament to the generosity and foresight of Merck to develop a drug for which there was not a clear profit motive. A part of this year's Nobel Prize in Medicine or Physiology was given for the discovery of Ivermectin.

18. What is river blindness? Is there a treatment/cure? When was it discovered?

    Ans. River blindness is the result of a fluke worm infestation and can be cured if treated early enough using Ivermectin.

19. Earlier in the video, I heard something about humans having a natural ability to cure cancer. How is that possible?

    Ans. Cancer is a complex disease with many components that can arise in many tissues. As outlined in earlier answers, the human immune system probably has the ability to detect and clear early cancer cells, before they might become established as tumors. This phenomenon is sometimes called cancer surveillance.

20. The extract from YouYou Tu is interesting. Is it a derivative of quinine? Does it target a different pathway?

    Ans. The extract discovered by Tu You You, also known as Artemisinin, is not really a derivative of quinine, and it most likely targets a unique pathway.

21. If bacteria are gram stained, isn't it done to separate them into two categories and identify them?

    Ans. Gram staining of bacteria is commonly used to distinguish between two classes of bacteria, gram-positive and gram-negative. By the way, the method was developed by Dr. Hans Christian Gram, a Danish physician, in 1884, which fits nicely into our story of the use of dyes in medical practice.

22. How is drug discovery related to immunity?

    Ans. Humm? Well, one answer might be that about 20 or so "drugs" are actually engineered monoclonal antibodies that target specific proteins or complex carbohydrates. These types of "drugs" in that sense mimic the function of the immune system.

23. Is there a difference between natural and synthetic medicine that treat the same disease?

Ans. Not really. A drug is defined by its chemical structure, be it synthetic or natural product.

24. What is it about nitrogen ions in chemicals that give these chemicals such curative properties?

Ans. In the morning lecture we talked about the chemical properties of alkaloids and that one key element was the presence of nitrogens and ring structures.

25. What is the significance of nitrogen in an alkaloid?

Ans. Most ring, or cyclic, structures in organic compounds are made up of both carbon and nitrogen atoms because of the unit chemical bonding properties of both atoms.

26. Are these alkaloids only found in herbs/plants? Is it possible to synthesize a complex similar to it in a laboratory? If so, how?

Ans. It is certainly possible to synthesize alkaloids in the laboratory, but it is often difficult and challenging and might require multiple steps and years of effort.

27. Are the same concepts as chemical affinity in dyes used in the modern surgical field for dyeing tumors and organs?

Ans. Yes. In fact, there are new initiatives to develop fluorescent dyes and dyes that can be used in conjunction with imaging techniques such MRI to detect the presence of tumor cells.

28. Were the pathogenic microbes extracted from humans? If not, were the dyes harmful to humans if they were just injected into them?

Ans. Pathogenic microbes by definition cause disease. Most dyes will have some degree of toxicity, which is in part why dyes are rarely used nowadays as therapeutic agents.

29. How many bacteria can make living things sick?

Ans. Of course, it depends. But some types of bacteria are very pathogenic even at very low levels of "inoculation." As few as 300 Shigella bacteria, for example, can cause food poisoning.

30. Can you discuss the use of bacteria in synthesizing medicine?

Ans. Some bacteria, notably certain strains of E. coli, are used in basic methods of molecular biology and DNA cloning to produce recombinant DNA and to express recombinant proteins. The example of Humulin, the recombinant version of insulin was presented in the lecture.

31. How does the molecular shape of alkaloids affect the medicinal changes and effects within our bodies? Is it due to their organic properties?

Ans. Shape is just one factor, but certainly and important one. Another factor is charge.

32. Do all synthetic drugs have alkaloid structures?

Ans. No, not at all, but many drugs share ring structures and are of a similar size to common alkaloids.

33. Is there one medicine that is still used today but no background story to it?

    Ans. There are probably many sad drugs without interesting stories, but I know mainly about their more interesting relatives.

34. Why do people with sickle cell anemia have a resistance to malaria?

    Ans. There is a detailed explanation to the association between malaria and sickle cell disease that is beyond the scope of this Q & A session.

35. How can antibiotics differentiate between healthy body cells and their target bacteria?

    Ans. Most antibiotics target either molecular structures or enzymes that are unique to the bacteria and are essential for its survival. The evolutionary distance between humans and bacteria is such that this targeting strategy is feasible.

36. What research is being done on intracellular receptors?

    Ans. This question is quite broad. Please look it up.

37. Is Prontosil the first of antibiotics known as "Sulfa Drugs?" It does have sulfur in its molecular composition.

    Ans. Technically, prontosil is a "pro-drug" in which enzyme action releases a sulfa-drug-like constituent. So, yes, there is a sulfa component, which does contain a sulfur atom.

38. You said only 1% of genes are for protein coding. What is the other 99% for then?

    Ans. Actually, I said that 1% of DNA is for genes that encode proteins. The rest of the DNA is for everything else.

39. How is the genetic code of t-cells modified?

    Ans. The genetic sequences of the T-cells are modified for C-ART therapy. However, the genetic code itself in universal and is not altered.

40. Is the cancer therapy medicine available to the public?

    Ans. Yes. In practice, everyone should have access to cancer treatments.

41. Whose DNA is used for the Human Genome Project? Why/what is the purpose of using just one person's DNA when there are billions of humans in the world?

    Ans. Only one genome can be sequenced at a time and in the original human genome project several genomes were chosen for consideration. It is now widely known that the first genome to be sequenced was that of J. Craig Venter, a genome pioneer and the founder of Human Genome Sciences.

42. The Vertex drug helps 4% of patients in America with cystic fibrosis, but what percentage does it help of the world?

    Ans. Right now the drug is only approved for use in the U.S.

43. What breakthroughs, if any, have been made in the field of stem cells and regeneration?

Ans. One key breakthrough was the observation that pluripotent stem cells could be produced not only from embryonic cells, but also from mature differentiated cells like fibroblasts. These cells are called induced pluripotent stem cells.