Professor Frank McCormick: K-Ras proteins offer new opportunities for therapeutic intervention against human cancers

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Frank McCormick, PhD, FRS (Figure 1), is Professor Emeritus of the UCSF Helen Diller Family Comprehensive Cancer Center. Prior to joining the UCSF faculty, Prof. McCormick pursued cancer-related work with several Bay Area biotechnology firms and held positions with Cetus Corporation (Director of Molecular Biology, 1981-1990; Vice President of Research, 1990-1991) and Chiron Corporation, where he was Vice President of Research from 1991 to 1992. In 1992 he founded Onyx Pharmaceuticals, a company dedicated to developing new cancer therapies, and served as its Chief Scientific Officer until 1996. At Onyx Pharmaceuticals, he initiated and led drug discovery efforts that led to the approval of Sorafenib in 2005 for treatment of renal cell cancer, and for liver cancer in 2007, and the approval of ONYX-015 in 2006 in China for treatment of nasopharyngeal cancer. Sorafenib is being tested in multiple indications worldwide. In addition, Prof. McCormick's group led to the identification of a CDK4 kinase inhibitor. Prof. McCormick's current research interests center on the fundamental differences between normal and cancer cells that can allow the discovery of novel therapeutic strategies.

Prof. McCormick holds the David A. Wood Chair of Tumor Biology and Cancer Research at UCSF. He recently held the position of director of the UCSF Diller Family Comprehensive Cancer Center. Prof. McCormick is the author of over 285 scientific publications and holds 20 issued patents. He also served as President, 2012-2013 for the American Association for Cancer Research (AACR). More recently, he has taken a leadership role at the Frederick National Lab for Cancer Research, overseeing an NCI supported national effort to develop therapies against Ras-driven cancers. These cancers include most pancreatic cancers, and many colorectal and lung cancers, and are amongst the most difficult cancers to treat.

At this year's ASTRO Annual Meeting held in San Francisco, Professor Frank McCormick gave a keynote address on "New Approaches to Targeting K-Ras", which addressed the promise of biology and targeting in oncology, especially as it relates to K-Ras proteins, which play a major role in many human cancers. After his excellent speech, Professor Frank McCormick has accepted the interview by ATM to share his latest discoveries of his lab's study on K-Ras, and his views about the development in biology (Figure 2).

Figure 1 Frank McCormick, PhD, FRS.

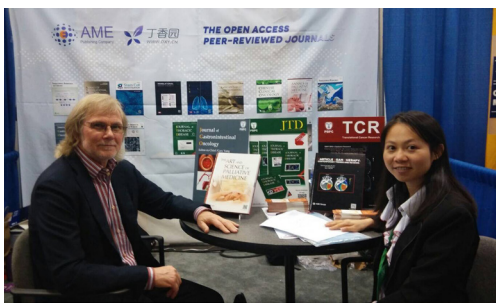

Figure 2 Professor Frank McCormick had a nice talk with *ATM* Science Editor during the 2014 ASTRO Annual Meeting.

ATM: As you have given an excellent speech about K-Ras proteins in this year's ASTRO meeting, would you like to share the latest advances of your lab's exploration in K-Ras?

Prof. McCormick: With regards to the latest advance

from my lab related to the discovery of K-Ras, K-Ras cancers have a stem-cell-like property, which is driven by K-Ras itself. So the cells expressing K-Ras resemble stem cells. In a sense, they are able to initiate tumors from a very small number of cells and also are very resistant to therapy. That is a big problem for clinic. The problems are both driven by K-Ras and the pathway that we identify the K-Ras uses, so that this discovery provides therapeutic opportunity. K-Ras, turns on a pathway that has several drug targets. In my presentation, I discuss a particular protein called leukemia inhibitory Factor, which K-Ras turns on and make K-Ras cancers more stem-like. Inhibiting LIF may be a new way of treating cancer, or maybe it can centralize typing cancer to radiation therapy or chemotherapy.

ATM: You started the study on K-Ras since 1984. At the beginning, what made you decide to launce such a study?

Prof. McCormick: That's a time when the *Ras* gene was first cloned, so *Ras* was identified as human onco-gene in 1981 or 1982. And then when the gene was sequenced, it was realized that the mutant protein was very similar to the wild type protein, just one or a minor *Ras* different. I was very struck by the fact that one minor change can make a normal protein into a cancer protein. Therefore, understanding that difference might be a way to develop drugs to distinguish between them, so that may be what interests me in the first way.

ATM: This year's ASTRO highlights science that showcases how technology and biology advance the field and improve patient outcomes and quality of life. What do you think are the most impressive advance in biology?

Prof. McCormick: In recent times, the most obvious big change in the fundamental biology of understanding cancer has been the understanding of the complexity of cancer. How many mutations are involved? How many genetic categories? How many different genes are involved? Particularly, next generation sequencing has greatly changed the way we think about cancer as a disease. So technology, fundamental knowledge based on deep sequencing has been most influential recently. But from the therapy point of view, the biggest influence in recent time has been the immunotherapy. Harnessing the immune system to attack the cancer has been an effective strategy in recent years. That is the field of a growing excitement in the future.

ATM: What would be the main trend in the future development of biology?

Prof. McCormick: The main trend that has been underlining the changes in cancers in the last five years has been tailoring specific therapies to particular diseases by using the genetics of the tumors to modify the treatment protocols, the most obvious example is in target therapy, but this must also be true in radiation oncology. Sometimes the tumor respond, but sometimes they don't. Deeper molecular understanding of why are these would be a huge impact, for sure.

ATM: Multidisciplinary treatment (MDT) has been increasingly getting attention in recent years. What do you think are the keys to effectively practice it in the near future?

Prof. McCormick: The logistical issues are quite complicated, but I think every medical center in the US has a tumor board in where people from radiation oncology, medical oncology, surgical oncology all come together to choose the best treatment protocol, so it is definitely true that the multidisciplinary approach is absolutely central to treatment in the US. In some big academic and medical centers, MDT is a common practice. In most hospitals in the regional cancer center, it is not possible, but in big medical center, like UCSF, MD Anderson, many doctors in different areas come together to make decisions. And I think everybody would agree this is the right approach. In the future, perhaps every patient can have the access to all those different disciplines via internet or virtually or in some other ways. Small centers may be able to get access to other people remotely from the internet.

ATM: As the 21st Century has become a big-data century, what do you think are important to be more innovative to make breakthrough in technology and biology?

Prof. McCormick: We understand that the molecular bases cancer is at the level which has never happened before. There is so much information available, big data, deep insight and so on. We need innovative people in the field to use that information in ways which haven't done before, i.e., thinking differently, maybe thinking a cross tumor type for pathway of tumor diseases, thinking the whole human not just the genetic of the tumor, but also the

genetic of the patients themselves, for example how they vary between the individuals. That is a lot of information to digest and accumulate simultaneously. But information technology is definitely a key part of medicine forward. So every patient in the clinical trial, everything they go through should become part of the dataset to help make thing better for future patients. So they only need to be iterated and analyzed by computer scientists and people who understand other crunched data. That is a huge room for innovation there. Now many people still diagnosis cancer base on the molecular information, but they need to have tumor cells, immune cells and blood sample, etc., a lot of information needs to be integrated. Every patient should become the data point to help others. People trying to do this, but there are many technical challenges for people to share information and useful knowledge together. It is tough, but that is what innovation does to take on the tough problems and solve them.

ATM: Thank you very much!

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