Functions of primary cilia in cell growth and propagation

The primary cilium is an important organelle found in most eukaryotic cells. Unlike motile cilia, which aid in cell movement, the primary cilium acts as the main sensory organelle of the cell and is able to respond to physical and chemical stimuli. In order to effectively perform this role, primary cilia must contain certain molecules that take part in various signaling pathways. Deficiencies and defects in the structure or protein content of primary cilia can affect these pathways and cause severe disorders collectively known as ciliopathies, which include polycystic kidney disease, retinal degeneration and some types of cancer. The study of these pathways has been very difficult due to the small size of the organelle and to a lack of techniques that allow to visualize and induce specific protein dynamics. In particular, the involved proteins have other functions within the cell body, meaning that a complete removal of the corresponding genes would cause widespread effects outside the cilium.

Polycystic kidney disease (PKD) is the most common ciliopathy. It is characterized by the growth of numerous destructive cysts in the kidneys, which adversely affect the functions of the organ. Two kinds of PKD exist — autosomal dominant (ADPKD) and autosomal recessive (ARPKD), each characterized by mutations in different genes. As shown in figure 1, cells affected by PKD grow apart and form hollow cysts that fill with liquid. The genes whose mutations cause PKD all encode proteins that localize to the primary cilium (polycystin-1 and -2 for ADPKD and fibrocystin for ARPKD). Research has shown that the primary cilia of kidney cells sense urinary flow and direct cell proliferation. In fact, polycystin-1 and -2 are involved in the signaling pathway triggered by a physical bending of the cilium, precisely what happens when liquid is flowing by the surface of the cell. When any of the three aforementioned proteins are damaged, the result is unchecked cell proliferation and cyst formation.

Over the next three years, I hope to learn about and investigate primary cilia, namely their chemical content and physical structure. While laboratory cell cultures are not usually human cells and may not contain the same proteins as those involved in PKD, many of the pathways and structures are similar and can therefore be used as effective models. I would like to specifically focus on the proteins that regulate cell growth and proliferation, since PKD is caused by defects in precisely these functions. Ideally, this would lead to a greater understanding of the role of cilia in cell growth, which could then be applied to human cells affected by PKD. I have already begun training in the laboratory of Prof. Inoue, who studies primary cilia from a basic science perspective but maintains ties with the Johns...
Hopkins PKD Core Center, an organization focused on the clinical aspects of PKD. I will spend the summer of 2012 working with Prof. Inoue and will then hopefully continue work on this project while I study abroad during my sophomore year. I am currently making inquiries about what positions may be available at the University of Oxford. Upon my return to Baltimore, I will either continue this project in Prof. Inoue's lab or will find a position in another lab of the same field, depending on his availability.

In an effort to see PKD from both a laboratory and clinical perspective, I would like to shadow a doctor with experience in the field in parallel with the basic research that I will be performing. No effective treatments are currently available for PKD, though a number of chemical receptors inside kidney cells have been shown to decrease cyst formation when stimulated\(^2\). The variation of several epigenetic regulators could also help slow the progress of PKD\(^3\). However, current PKD patients are treated only with pain relievers and other medications that could curb complications of the disease. Once end-stage renal disease sets in and the kidneys begin to fail, they are replaced by transplants. A shadowing experience with a transplant surgeon would shed light not only on the clinical manifestation of PKD but also on other diseases that require organ transplantation, while work with a pharmacologist would give an idea of the efficacy of the PKD drugs currently in development.

I believe that the experience I have gained in the past year makes me qualified to pursue this project. Starting from the summer of 2011, I have been continuously involved in research. I took part in both clinical and basic science projects, in the process learning about the medical profession across its spectrum, from direct provider-patient interaction to far-removed experimentation on model organisms. My decision to do this specific project follows a lengthy period of exploration, and I am certain that this is the path I want to pursue. I have so far efficiently balanced class work with extracurricular research and see no reason why I would not be able to continue this in the future. A Woodrow Wilson scholarship would allow me to channel my research experiences into a more substantial project that could yield deeper insights into the pathogenesis and physiological impact of polycystic kidney disease.

References:
2. Polycystic kidney disease and therapeutic approaches, Park et. al, *BMB reports*, 44.6.359 (2011)