PBC RESEARCH UPDATE

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Allow me to provide the PBCers with an overview of research in PBC, including more recent events. My own work in PBC began in 1985, when new technology allowing gene cloning was developed for infectious diseases. I realized the potential for use in human autoimmune diseases and I successfully cloned the mitochondrial antigen that is used diagnostically to detect anti-mitochondrial antibodies. In fact, this was the first human autoantigen to be cloned for any autoimmune disease and it led to a prestigious paper in the New England Journal of Medicine. It was also the first recombinant DNA test to be approved by the Food and Drug Administration.

With this clone, my lab began to massively expand into PBC. Until that time (about 1986), there were but a handful of labs that were studying PBC and none, other than the group in Newcastle, United Kingdom, could really be coined as doing serious basic research. Our work began to look at the human immune response against the protein that was produced by this gene and ultimately, we found out there was an enzyme in mitochondria called pyruvate dehydrogenase. This enzyme, abbreviated as PDC or sometimes PDH, is the immune target that is “attacked” by sera and cells of people with PBC (and only PBC!)

This was really a major breakthrough and excited laboratories throughout the world. It began a major influx of postdoctoral fellows to visit UC Davis for periods of one to five years to study PBC and I like to think it was the catalyst for development of significant PBC research throughout the world. In fact, there are now nearly 20 former students who are professors and universities in China, Japan, France, England, Italy, Switzerland, Slovenia, Israel, Germany, and Australia, who are now involved in PBC work. Throughout all this time, which extends to the present, we have provided, at no charge, all of the reagents that we developed.

The PBCers became involved when Kathy Krivy was active in the organization. With her help, we launched the first major epidemiologic study of PBC in the United States and this was partially funded by donations from the PBCers. It led to the development of a standardized questionnaire, which was vetted and finally administered by more than 20 universities around the country and resulted in the first major breakthrough in the epidemiology of PBC in the U.S. It would not have happened without the PBCers donations and it has resulted in well over four million dollars in grants. This work is active and continues.

A major void in PBC has been the absence of an animal model. We tried initially to ask big pharmaceutical companies to support research in PBC and, in particular, to help us with the newer drugs they were developing in rheumatoid arthritis and other autoimmune diseases. The big pharmaceutical companies, with the exception of Bristol-Myers Squibb and Genentech, declined. In fact, some companies would not even provide us their drug at their own cost. The reason for this was an absence of an animal model and their concern that the
number of patients with PBC was too small for them to make a profit. My compliments go out to Bristol-Myers Squibb and Genentech for being willing to provide reagent, but actually to partially fund the projects. Both have led to a much better understanding of what targets are needed to treat patients with PBC. But, even more importantly, they help lead to the development of several mouse models.

Funds from the PBCers have been used to develop these mouse models and to constantly improve upon them so that we would have a lab model that resembled a human patient with PBC. We now have several models, but especially two models, the dnTGFbeta mouse and the AIRE-DEL mice, both of whom significantly recapitulate the clinical features that we see in patients in clinic. We have provided these mice without charge to investigators throughout the world and many are using them and they have resulted in more than 30 peer reviewed publications. This would not have been possible without funds from the PBCers. I might also say that it has ignited interest in smaller pharmaceutical companies and there are now so many clinical trials underway, that there is almost a competition for patients. In virtually every case, the drugs being tested are based on data from the mouse models, so this has been an enormous help.

Unfortunately, the majority of funding from NIH is going to either hepatitis C (especially in the past) and now to NASH. The Gershwin lab remains the best funded PBC lab in the country from NIH, but as with all laboratories, funding is diminishing and they continue to put more emphasis in areas where there are more patients. There is a tremendous need to raise money and awareness to fund PBC research. A cure may come from an absolutely serendipitous event that stimulates the final breakthrough. The PBCers are a major component of this.

Of interest is that although there are quite literally dozens of conferences on hepatitis virus and also on NASH, there were virtually none that were devoted entirely and exclusively to PBC. I organized a unique meeting approximately two years ago in which we invited scientists who work on PBC, clinicians who treat PBC, but also a number of basic scientists who do not work in PBC. We all met to discuss the road blocks and what is needed. We will hold a second such meeting next month, September 2018 in Switzerland, with representatives from the U.S., Canada, Japan, Holland, Australia, China, and multiple other European countries. The goal again is to identify gaps that need to be filled, including areas such as detection of disease before any symptoms appear, the treatment of fatigue, the treatment of itching, and which therapeutic venues are most likely to be of benefit.

We are all keenly aware that developing increased awareness to PBC is a major step towards developing funding so that funds can be used to explore high yield, but also high risk, research. It was this high yield, high risk research that led to our grants in genetics and mouse models, both of which again depended on initial donations from the PBCers.

It has been over 30 years since I personally began this venture and I hope it will be far less than 30 years before a cure appears.
Thank you,
Eric Gershwin, MD