***Deliberations on Treating/Curing APBD with Guaiacol, November 2016***

First discovered in 1826, Guaiacol is yellowish aromatic oil usually obtained from wood resin. It is an FDA-approved food supplement that is available over the counter. And it has been used for treating reflux, lung abscesses, and other ailments.

In a series of E-mail exchanges during September and October 2016, scientists deliberated on the prospects, uncertainties, and costs of using Guaiacol to treat or cure APBD. The Foundation facilitated these deliberations to give the APBD community a realistic view of clinical trials.

These E-mail exchanges involved five scientists: The Foundation’s Scientific Advisory Board members Edwin Kolodny, MD; Or Kakhlon, Ph.D; H. Orham Akman, Ph.D.; and Alexander Lossos, MD. As well as Yoseph Caraco, MD, Head of the Clinical Pharmacology Unit, Hadassah Medical Center.

We quote each of their key remarks under the following three umbrella questions.

***Q1***- What did we learn about Guaiacol from the APBD mouse model?

***Akman***: APBD mice can live 12 to 14 months; with normal GBE1 up to 28 months. I did finish the [Guaiacol] experiment [on the APBD mice and extended their life through] 24 months; [only went this far] to obtain tissue and test the amount of glycogen and polyglucosan.

***Kakhlon***: ….even if the improvement in life span is only up to two years, it is still a significant improvement as compared to the affected mice which don't survive more than a year. In addition, reducing polyglucosans in the liver is a significant improvement as well.

***Caraco:***  I don't expect Guaiacol to completely cure APBD… polyglucosans were NOT reduced in the brain and …a significant improvement of neurological symptoms in the APBD mice have not been observed.

***Q-2*** *Should we undertake a Guaiacol APBDF clinical trial?*

***Kolodny***: I am still interested in documenting the effects of Guaiacol on various tissues in the mouse model; neurophysiology, general and neuropathology of various organs, body chemistry, effects on residual GBE1 activity, etc. This is what the FDA will want to know before approval of a human protocol. Jumping the gun might assuage anxious patients but the age-old adage in medicine of “do no harm” is especially important in dealing with human trials of a new therapeutic agent.

Guaiacol is available as a conjugate in many different forms. Which form was employed in the animal trials? Have other conjugates of Guaiacol been tried in the animal model? Until this “simple” question can be answered, I think it is unethical to proceed to a human trial.

A multicenter multiyear trial with the entire known patient population will cost an enormous amount, using up resources that could otherwise be utilized to continue the search for additional perhaps more effective treatments.

***Kakhlon***: Perhaps it is possible (only suggesting) to initiate clinical trials while doing in parallel all the important mouse experiments (nerve conduction velocity etc.) …..which will require time and resources and thus might postpone clinical trials even more. …..the dilemma we have between a musculoskeletal and neurological etiology in the APBD mice stems from their poor performance in the grip test.

….the lifespan of the mice has been completely restored ….with no side effects, justifying clinical trials. This is not only my opinion; other clinicians…. said that such a complete restoration of life span without side effects, can on its own justify clinical trials

Gene therapy will take years if not a decade to bring to clinical trials. The chaperones stabilizing GBE Y329S still have to demonstrate specificity (as opposed to LTKE, by the way, which has already demonstrated specificity in a published work). So if I were the APBDRF I would work with what we have for now because time is running out for our patients. Guaiacol is on the verge of clinical trials so it has to be given higher priority simply because it is at the most advanced stage.

***Q3***- *What is the approach for a Guaiacol APBD clinical trial?*

***Lossos and Kakhlon***: It took us, the basic researchers, much time and many efforts to reach a point where we are ready to start clinical trials for APBD. Let's collaborate with Prof. Caraco and make this happen.

***Caraco***: It is my understanding that the best approach at present would be to invest a substantial effort in putting together the study protocol along with all other regulatory documents including Investigator Brochure, informed consent form etc. ….for the submission to the IRB [(Institutional Review Board)]…. The cost of preparing all the necessary documents for submission to the IRB is approximately 35,000 US $.

It is clear that the study should be designed as a multi-center study with one center in Jerusalem and at least two additional centers in the USA.  However there are still many unresolved issues concerning the most appropriate protocol.

Some of the questions that need our consideration are:

1. The dose and the formulation of Guaiacol to be used in the study.

2. The duration of the study.

3.  The study format – double-blind, randomized vs. an open study. Another option could be a combination of initial double-blind randomized study for 12-24 months …., [and] an open study for the remaining duration of the study. The decision which is the right design could be heavily influenced by the number of available patients that may consider taking part in the study.

4.  The study procedures aimed to evaluate efficacy.

**Kolodny**: Without the mechanism by which Guaiacol is prolonging the life of the animal model and absence of any other marker of efficacy, how can we choose effective study endpoints and markers of efficacy?

If a double-blind trial is proposed, desperate patients may resort to taking Guaiacol on their own. One can obtain it from many sources including, for example, eBay.

***Kakhlon***: Prof. Lossos' clear instruction to all patients is not to take any drug (even if available over the counter) unless within the framework of clinical trials. Beyond that I don't think there is anything we can do. The patients are independent adults and we can't make them do anything they don't want to do.

**Kolodny**: If a patient trial is undertaken, it should start with a small group of patients (perhaps as few as 4 - 6) at a single site to assess tolerability and safety. …it is not often possible to directly scale up dosing from the mouse to human.

***Kakhlon***: …. we will prepare an image based fingerprint for APBD, differentiating it from other disorders…. will be used for testing possible side effects of drugs. All this will be done at Prof. Weil's lab in Tel Aviv University. We have already recruited 10 Israeli patients to give us skin biopsies which will be cultured for that purpose. We need as many patients as possible so that statistically the fingerprint will be unique to APBD.