Summary of the 2014 International Consensus Conference from DBAF's Research Director, Steven Ellis, PhD:

The 13th Diamond Blackfan Anemia International Consensus Conference was held March 8th through the 10th at the Ritz-Carlton Hotel in downtown Atlanta, Georgia. This year's conference saw a record number of abstracts accepted for presentation as either short talks or posters. This increased number of abstracts submitted relative to previous years, in part, reflects an increasing number of investigators entering the DBA field. This, in turn, is a reflection of the interest in DBA generated on many fronts by the remarkable progress in the field over the past 10-15 years.

The desire to give as many investigators as possible the opportunity to present their work within a very short time frame made for a very jam-packed agenda. Fortunately, various session moderators and facilitators kept a tight reign over their different sessions and the meeting progressed without a hitch. While I may seem a bit obsessed with the meeting's logistical issues, efficiently packing all this content into a day and a half was a major factor the organizers had to contend with in setting up the meeting's agenda. As a way of limiting redundancies in meeting presentations, Jeff Lipton (New York) started the meeting off by giving an overview of DBA from both a clinical and scientific perspective.

Dr. Lipton's talk emphasized the limitations of current therapies for DBA (transfusions, steroids, and bone marrow transplants) and the need for improved therapies with fewer complications. This emphasis tied in nicely

with Dawn Baumgardner's (Buffalo) opening remarks stating that an overriding goal of this and past ICC meetings has been to identify therapies and strategies to improve the quality of life for patients and families with DBA.

Current Clinical Trials (New Mechanistic Insights)

In this light, it is worth mentioning the 3 different clinical trials (Leucine, Lenalidomide, and Sotatercept) currently underway in DBA patients. One of the more interesting aspects of this year's meeting concerns the drug Sotatercept. This drug was initially developed by Acceleron Pharma as a potential treatment for osteoporosis, but in clinical trials for this condition it was found that individuals receiving the drug showed a significant increase in red blood cell production. This increase could be considered an adverse side effect in individuals with osteoporosis, but as a consequence of this serendipitous finding, Sotatercept is now being tested as a treatment for different types of anemia, including DBA. A talk by Jingping Ge (Philadelphia) provided a potential mechanistic rationale for why this drug may be efficacious in DBA. Her work on induced pluripotent stem cells (IPSC) from DBA patients revealed that the same signaling pathway targeted by Sotatercept appears to be dysregulated in DBA patients. This observation provides a more solid scientific basis for the Sotatercept trail (in terms of full disclosure, I have no financial ties to either Acceleron Pharma or Celgene which is supporting the trial). The Sotatercept-DBA relationship was further reinforced by studies from Shuo Lin (Los Angeles) showing that the generic form of this drug rescues the DBA-like phenotype in zebrafish. While the Sotatercept clinical trial is still in early stages, these results certainly generated guarded optimism for a positive outcome.

The New Drug Pipeline (Turning the Spigot On)

In addition to the drugs currently in clinical trials for DBA, one of the most remarkable features of this year's meeting was the number of drugs entering the pipeline as potential therapies for DBA. Talks by Hsiang-Ying Lee and Harvey Lodish (working together in Boston) described screens for drugs that appear to work synergistically with steroids in enhancing red blood cell production. These results suggest that it may be possible to combine these drugs with steroids, and in doing so substantially reduce the amounts of steroids used in treating DBA and thereby cut back on their side

effects. These studies have been carried out in pre-clinical models so it is too soon to tell how well these treatments will work in DBA patients and whether these effects may be limited to patients responding to steroids. Nevertheless, some of these drugs are already being used in humans for other indications suggesting that their potential transition to trials for DBA patients could move relatively quickly.

Elizabeth Macari from Len Zon's laboratory (Boston) described a different class of drugs that ameliorate DBA-like phenotypes in zebrafish and also work in human cellular models of DBA indicating that there may be alternative routes for therapeutic interdiction in DBA patients. In this regard, there was also a report by TinChung Leung (Kannapolis) of a nutriceutical that appears to rescue DBA-like phenotypes in zebrafish. Two groups led by Ross Hannan (Victoria Australia) and Johan Flygare (Lund Sweden) have initiated large-scale screens for drugs that ameliorate DBA phenotypes in models systems distinct from those employed in the Lodish and Zon laboratories, raising the prospects that additional drugs will be flowing into the DBA pipeline in the not too distant future. Finally, Shubhranshu Debnath (Lund Sweden) presented ongoing work from Stefan Karlsson's laboratory developing gene therapeutic approaches for DBA. These are heady times for those awaiting new treatment options for DBA patients.

Mechanisms Underlying DBA Pathophysiology (Closing the Gap Between Ribosomes and GATA1 with a Little Heme Toxicity Thrown in the Mix)

The mechanisms underlying DBA pathophysiology continued to be a hot topic at the ICC. Several talks from the laboratories of George Thomas (Cincinnati), Stefan Karlsson (Lund Sweden), and Nick Watkins (Newcastle UK), illustrated the importance of ribosomal proteins L5 and L11 in signaling pathways leading to p53 activation and cell death in response to abortive ribosome assembly. Tempering this pathway presents another target for therapeutic development in DBA, but reducing p53 levels would seem to place young patients at an unacceptable risk for developing cancer thereby diminishing enthusiasm for targeting p53 directly. It is hoped that by learning more of the detailed mechanisms by which abortive ribosome assembly signals to p53 activation, it may be possible to intervene in this pathway upstream of p53 and thereby diminish cancer risks. Fabrizio Loreni (Rome)

reported on a different signaling pathway that may also contribute to DBA pathology by signaling to p53 activation. There was additional work on ribosome biology and protein synthesis presented by Pierre-Emmanuel Gleizes (Toulouse), Anthony Nguyen (Boston), and Marieke von Lindern (Leiden, Netherlands). On a different front, Janis Abkowitz (Seattle) showed that heme toxicity likely plays a role in cell death in DBA patients. She provided data that free heme is extremely toxic to erythroid progenitors where diminished protein synthesis rates reduce the production of globin chains. The most notable feature of Dr. Abkowitz's idea is that it provides a rationale for why red blood cell production appears to be selectively affected in DBA patients. Of course, it is possible that both the ribosome-based pathway and heme toxicity pathway both cooperate in promoting cell death in DBA patients.

GATA1 was also a hot topic at this year's ICC. Vijay Sankaran (Boston), who discovered GATA1 as a DBA gene, presented a unified theory that ties together the ribosome and GATA1 sides of DBA by showing that perturbation of ribosome synthesis interferes with GATA1 production. John Crispino (Chicago), Mitch Weiss (Philadelphia), Leif Ludwig (Boston) and Shai Izraeli (Tel Aviv Israel) presented their work on the role of GATA1 in erythropoiesis exploring the role of this transcription factor in the pathogenesis of DBA. One concern regarding DBA patients with GATA1 mutations is whether they have an increased risk of leukemia relative to other DBA patients. Irma Dianzani (Novara Italy) reported on the identification of a GATA1 patient in the Italian DBA registry who had progressed to MDS prior to having received a bone marrow transplant. While it is difficult to reach a definitive conclusion on leukemic risks in GATA1 patients based on one patient, this is clearly an area of concern.

DBA in the Clinic (DBA Registries, Gene Discovery, DBA Beyond the Anemia, and New Tools for Diagnosis)

Gene discovery continues to be an active area of research. Kelly O'Brien and Lisa Mirabello (both Bethesda) reported on patients in US Registries, whereas Josu de la Fuente (London), Yigal Dror (Toronto), and Hannah Tamary (Tel Aviv) reported on patients in the UK, Canada, and Israel, respectively. There were also several talks on aspects of DBA beyond the classical anemia

presentation. A presentation from Deena Iskander (London) suggested that immunity appears to be affected in DBA patients while Neelam Giri (Bethesda) explored potential audiologic and otological manifestations of DBA. Dagmar Pospisilova (Olomouc Czech Republic) suggested that there may be defects in iron metabolism and Blanche Alter (Bethesda) explored the incidence of MDS in DBA, comparing it with other bone marrow failure syndromes. It is also becoming clear based on work presented from Adrianna Vlachos (New York) that DBA is likely under diagnosed. Patients without anemia but having certain of the congenital anomalies observed in DBA, for example, congenital heart defects, may have nonclassical forms of DBA.

There were also a number of presentations on outcomes related to current therapies for DBA. Posters from Ina Hainmann (Freiburg) reported on outcomes for bone marrow transplantation in European patient cohorts and Theirry LeBlanc (Paris) reported on chelation therapy in French DBA patients.

New tools for DBA diagnosis are also on the horizon as a direct result of research advancements in the past few years. Jason Farrar (Little Rock) and Anirban Chakraborty (Toulouse, France) presented work on using pre-rRNA processing as a tool for DBA diagnosis, which appears very close to reaching the clinic. Philip Mason (Philadelphia) reported on a protein found in red cell membranes from DBA patients, which may also be developed as a diagnostic tool. Sioban Keel (Seattle) and Irma Dianzani (Novara Italy) presented tools and diagnostic algorithms, which could aide physicians in making a DBA diagnosis. These tools are necessary as evidenced by results reported by Sunjeet Agarwal who described another bone marrow failure syndrome that can be confused with DBA.

Investigators are also making inroads developing additional models for DBA research including new mouse models from Sharon Singh (New York), Yan Liu (Indianapolis), Colin Sieff (Boston), and Hanna Gazda (Boston). There was also a cautionary presentation relating to model systems, regarding differences in erythropoiesis between mice and humans by Novalia Pishesha (Boston). Zebrafish also continue to be a popular system for modeling aspects of DBA including presentations by Alyson MacInnes (Utrecht, Netherlands), Arati Khanna-Gupta (Boston) and Tamayo Uechi (Tokyo,

Japan). Finally, this year's ICC saw an increased number of IPSC models for DBA presented by Marisol Betensky (Philadelphia) and Frederick Goldman (Birmingham).

News from Washington

I wish I could say all the news at this year's ICC was positive and encouraging, but alas, this was not the case. Terry Bishop and Pankaj Qasba from the National Institute of Diabetes and Digestive and Kidney Diseases and the National Heart, Lung, and Blood Institute, respectively, provide rather depressing news on funding for DBA research by the Federal Government in the near future. This news continues to shift the onus of funding DBA research to private foundations.

Concluding Statements

I hope you can tell from this brief overview that substantial inroads are being made in DBA research on both the clinical and basic science fronts. Moreover, these inroads are translating into a better understanding of the natural history of this disease and its various incarnations, which together with great strides in therapeutic development, promise to translate into significant improvements in the care of DBA patients in the near future.

I wish to thank the other conference organizers; Jeff Lipton and Adrianna Vlachos (New York), David Bodine (Bethesda), David Nathan (Boston), Mitch Weiss (Philadelphia), Johan Flygare (Lund) and Josu de la Fuente (London) for their efforts in putting on an outstanding meeting. A very special thanks goes out to Dawn Baumgardner who ultimately pulled it all together and made it happen. I would also like to thank the Diamond Blackfan Anemia Foundation for their role in hosting this year's meeting and Diamond Blackfan Anemia Canada, the Daniella Maria Arturi Foundation, Captain Courageous and DBA-UK for major sponsorship roles in supporting the meeting. Finally, I thank the many individuals and families who made donations to support specific events and components of the 13th DBA Consensus Conference.