Trend – a general direction in which something is developing or changing

Before bidding adieu to the year past and benvenuto to the year ahead, I thought I would use this end-of-year article to mention what I have perceived as trends in the DBA-related sciences in 2014.

1) Increased globalization – Last spring many clinical and basic science researchers met in Atlanta for the 13th Diamond Blackfan International Consensus Conference. This conference has been a forum for clinicians and researchers (predominantly, but not exclusively) from the US, Canada, and Europe to get together to discuss their latest findings and build collaborations that have led to significant advances in the DBA field over the years. The DBA community increased its global reach with the EuroDBA conference held in Freiburg, Germany in September where representatives from 26 countries (including many countries from the Middle and Far East) came together to share challenges and successes in dealing with DBA in different cultures. It is clear from these meetings that there is much to learn from one another and that by pooling resources as the DBA global community continues to grow, further advances can be made to improve the lives of individuals affected by DBA.

2) Focus on iron – While iron overload has always been a major cause of morbidity and mortality in DBA and other transfusion dependent patients, the past couple of years have marked a watershed in terms of the number of studies that have been published comparing and contrasting iron overload in DBA relative to other transfusion dependent patient populations. ***Considerable evidence is mounting that DBA patients load iron in ways that are distinct from, and more deadly, than other patient populations receiving similar transfusion burdens.*** **This increased awareness has led to calls for more forceful efforts to strengthen patient compliance with chelation therapy.** Further, as more and more is learned about the molecular basis for the differences in iron loading in DBA patients, more effective disease-specific strategies may be devised to address this critical problem.

3) From gene to genome – From 1999 when the first DBA gene was identified to 2014 when several additional genes were added to the still growing list of DBA genes, we've gone from sequencing individual genes to sequencing the expressed regions for virtually all genes in the human genome (termed whole exome) in DBA patients. This approach has led to the discovery of additional ribosomal protein genes affected in DBA and to the first non-ribosomal protein gene, *GATA1* (published in 2012).

A recent manuscript using this approach in the Japanese DBA population illustrates the benefits and pitfalls of this approach to gene discovery [1]. The group performed whole exome sequencing on 48 patients that lacked mutations in known DBA genes. They identified ten patients with mutations in different ribosomal protein genes that had not previously been identified in DBA patients. Of these mutations, 8 were considered variants of unknown significance because the mutations identified change one amino acid for another in an expressed ribosomal protein or caused the deletion of a single amino acid. In these cases, as I've mentioned in previous articles, it is difficult to predict *a priori* whether such a subtle change is pathogenic or not. Two other genes contained mutations that would cause more global changes in the amount and/or function of protein encoded by the gene. These genes, RPS27 and RPL37, were characterized further and although they have only been identified in single DBA patients to date, appear to be *bona fide* DBA genes. Thus, filtering data for changes in the coding regions of ribosomal protein genes allowed the authors to come up with two new DBA genes and 8 maybes.

Thirty-six of the patients studied in this report did not have identifiable changes in ribosomal protein coding regions. These patients may have pathogenic mutations in any of the tens of thousands of non-ribosomal protein genes in the human genome. The identification of a pathogenic mutation in a sea of sequence polymorphisms found when analyzing all genes within the human genome presents a huge challenge.

It also remains a distinct possibility that the remaining 36 patients in this population could have mutations in ribosomal protein genes outside of their coding sequences in regulatory sequences needed for the expression of the ribosomal proteins. To address this issue, the next trend in gene discovery will involve whole genome, rather than whole exome sequencing (including sequencing over 98% of the human genome's 3.5 billion bases that do not encode proteins). The challenges here become even greater as the number of sequence polymorphisms in non-coding sequences in the human genome is enormous and our understanding of allowable variations in sequences found within regulatory loci limited. As with other challenges we have faced throughout the years of DBA research, these challenges too shall be overcome.

4) A trend towards unity – With the discovery of *GATA1* as the first non-ribosomal protein DBA gene there were suggestions that DBA caused by mutations in GATA1 may be distinct from DBA caused by mutations in ribosomal proteins genes. While this is most certainly true in terms of modes of inheritance, recent work from Sankaran and colleagues have suggested a unifying model for the molecular basis of DBA by showing that mutations in ribosomal protein genes influence the expression of GATA1 [2].

5) A trend below the surface in 2014 – Bubbling below the published surface in 2014 has been a trend towards improved therapeutics for DBA. Results from clinical trials for leucine and sotatercept in DBA populations should be available soon providing critical data on whether either of these two potential treatments for DBA will be efficacious for any, all, or perhaps only a subset of DBA patients. Further, these trials may also identify uses for these drugs for disease manifestations apart from the bone marrow failure. There are also several drugs screens that have been initiated at a more basic science level that should come to fruition within the next year that will likely lead to new drugs entering the DBA pipeline.

The trends outlined here represent a somewhat limited view of all the different areas under investigation relevant to DBA patients and their families, but I hope they give you all a sense for the concerted worldwide efforts that are making significant inroads on a number of fronts that will have positive impacts on the lives of individuals affected by DBA.

I wish you all the best in 2015!

[1] Loss of function mutations in RPL27 and RPS27 identified by whole-exome sequencing in Diamond Blackfan Anemia (2014) Wang, R., Yoshida, K., Toki, T., Sawada, T., Uechi, T., Okuno, Y., Sato-Otsubo, A., Kudo, K., Kamimaki, I., Kanezaki, R., Shiraishi, Y., Chiba, K., Tanaka, H., Terui, K., Sato, T., Iribe, Y., Ohga, S., Kuramitsu, M., Hamaguchi, I., Ohara, A., Hara, J., Goi, K., Matsubara, K., Koike, K., Ishiguro, A., Okamoto, Y., Watanabe, K., Kanno, H., Kojima, S., Miyano, S., Kenmochi, N., Ogawa, S., and Ito, E. *Br. J. Hematol.* doi: 10.1111/bjh.13229. [Epub ahead of print]

[2] Altered translation of GATA1 in Diamond Blackfan anemia (2014) Ludwig, L.S., Gazda, H.T., Eng, J.C., Eichhorn, S.W., Thiru, P., Ghazvinian, R., George, T.I., Gotlib, J.R., Beggs, A.H., Sieff, C.A., Lodish, H.F., Lander, E.S., Sankaran, VG. *Nat. Med.* **20:** 748-753