Wandering in search of a scientific home
Clara Camaschella
San Raffaele Scientific Institute, Milano, Italy

My “story” with iron started while preparing my MD thesis on hemoglobinopathies. It was then that I “encountered” iron within the heme protoporphyrin ring, without realizing it would eventually become central in my medical and scientific life! In those days university courses provided only vague information about iron physiology, mostly related to iron deficiency anemia. About the clinical consequences of iron excess, I learnt in the Hemoglobinopathy Center of the University of Torino while taking care of a handful of thalassemia patients who in the 70’s-early 80’s lived in miserable conditions (the majority died at young age). To my surprise, those patients were iron overloaded despite of occasionally (if at all) been transfused. At that time the clinical side of thalassemia made progress with the advent of novel iron chelation protocols that ameliorated the iron burden and increased survival of thalassemic patients. However, the reason for iron overload in non-transfusion-dependent patients remained a mystery.

In the 80 ´s the road opened up for the identification of molecular defects of various diseases and establishment of correlations between genotype and phenotype. Research on Hemoglobinopathies swiftly moved from protein to DNA studies as the human globin gene got cloned and the use of PCR protocols were successfully applied to globin genes research. I found Hemoglobinopathies to be a compelling biological model that led me to Genetics, Biology and Biochemistry. In the exciting classes given by Mario Cazzola in Pavia to hematologists I became aware of the seminal ferrokinetic studies of Clement Finch that explained the iron trafficking in vivo in the different body compartments. I learnt that iron absorption was inversely related to the store repletion and directly related to the erythropoietic drive. I realized that thalassemic patients absorbed too much iron in response to their expanded erythropoiesis being the “erythroid regulator” of iron more powerful than the “store regulator”. The problem was how to identify the nature of these regulators?

I opted to move to hemochromatosis as it was also characterized by deregulated iron hyper-absorption and was still one of the last relatively common genetic diseases with unidentified genes. In collaboration with a group of Italian colleagues (Alberto Piperno, Domenico Girelli, Paolo Gasparini) we started the ambitious project of identifying the diseased gene by positional cloning using a genomic collection from Italian families. That time coincided with my move to San Luigi Hospital at Torino University and with the enrolment of Antonella Roetto, a geneticist, in my research group. As hemochromatosis was a disease diagnosed and treated by hepatologists, I attended Italian and European Hepatology Meetings where I learnt how to diagnose hemochromatosis and that proved essential for selecting the appropriate probands/families for linkage analysis. Cloning the hemochromatosis gene was in theory simple because of the strong linkage disequilibrium with HLA A3 that located the gene on the short arm of chromosome 6. However, the extended region of linkage disequilibrium in the HLA region made the cloning process rather complex and probably over-ambitious for our group. The HFE gene (at that time HLA-H) was in fact cloned by the Californian company Mercator
Genetics already in 1996. Those were exciting news, but obviously also frustrating for us, since we were close to the correct chromosome region. However, from that experience we learnt that another chance existed. That was when we realized that Italian patients were in fact not as homogeneous a group as those reported in the seminal Nature Genetics paper since many in our group lacked the classic HFE C282Y homozygosity. This out of the box insight was my debut into the Genetic phase of my scientific life.

The competence we acquired in cloning strategies was immediately applied to the identification of hemochromatosis genes other than HFE C282Y. Here the strategy was the homozygosity mapping in consanguineous families, a powerful approach applied to rare disorders that led us to to define the genetic heterogeneity of hemochromatosis such as: the identification of the the locus of type 2 juvenile hemochromatosis (whose gene, hemjuvelin, was later cloned by the Canadian company Xenon Genetics) on 1q and of TFR2 as the gene of type 3 hemochromatosis. The TFR2 paper in Nature Genetics had a major impact on the Bioiron community as I started to receive invitations to lecture at Iron Meetings, as that organized by Lawrie Powell in Cairns Australia in 2001. The use of the Italian heterogeneity of hemochromatosis favored the establishment of new contacts with various European researchers, such as those involved in hemochromatosis projects coordinated by Marie-Paule Roth, a multiunit European grant that was later followed by others coordinated first by Kathryn Robson and next by Pierre Brissot. Within these groups I got in close contact with well known scientists and clinicians active in Bioiron, most of them great friends/competitors till present days!

Iron Meetings were essential in my scientific career. I had attended Hematology, Genetics, Hepatology, Internal Medicine Meetings but when I met members of the societies that later merged into IBIS I finally realized which was my scientific home. I have attended all Bioiron Meetings from Saint Malo to Cairns from Sorrento to Bethesda from Kyoto to Vancouver just to mention a few, always impressed by the science that was presented, coming back with exciting news and stimulating ideas. I like reminding that in a simultaneous session in Cairn a bizarre mouse model was presented with iron overload due to deficiency of a peptide with obscure function called hepcidin. Several groups worldwide started sequencing the hepcidin gene in patients lacking the HFE C282Y mutations, a great but unproductive effort. We reasoned that since iron overload of hepcidin deficient mice was severe, the gene was an excellent candidate for the very rare cases of juvenile hemochromatosis unlinked to 1q (human hepcidin maps to chromosome 19). The finding of Hamp gene mutations in these patients linked the hepcidin function to iron homeostasis in humans. However, the molecular mechanism was clarified only in 2004 in the seminal Science paper by Ella Nemeth and coworkers. Unexpectedly I received the Marcel Simon award in 2003: the plate on my desk reports as a motivation my studies of disorders negatively defined as “non-HFE hemochromatosis”.

At the end of 2004 I moved to San Raffaele University and Scientific Institute in Milano. With my novel research group (Laura Silvestri, Alessia Pagani, Antonella Nai and later Alessandro Campanella) we started functional genetics studies to unravel the role of the hemochromatosis proteins. From the analysis of HJV mutations we moved to proteins of the BMP/SMAD hepcidin regulatory pathway. Thanks to a direct contact with the late Ernie Beutler, who, few months before passing away, had identified the transmembrane protease TMPRSS6 as the first hepcidin inhibitor in mice, we showed that the protease
inhibits hepcidin expression by cleaving the BMP coreceptor hemojuvelin from the membrane. After encountering Carlos Lopez Otin who, within his broad interest in proteases, had developed the Tmprss6 KO mouse, we imported the mouse and started working on murine models of iron disorders, an effort that was quite rewarding. We were the first to show the positive effect of deleting Tmprss6 on anemia and iron overload of beta-thalassemia mice, a finding confirmed by pharmacological approaches of Tmprss6 inhibition, that are now in clinical trial in thalassemic patients.

The discovery of erythroferrone by the group of Tom Ganz clarified the crosstalk between erythropoiesis and iron and explained why the thalassemic patients I was taking care more than 30 years before were iron loaded! Within erythropoiesis/iron crosstalk we discovered that the hemochromatosis gene TFR2, a partner of erythropoietin (EPO) receptor in erythroid cells, is another essential link, connecting the most important growth factor of erythroid cells with hepcidin and iron availability. Selective inactivation of TFR2 in mouse bone marrow led to erythrocytosis indicating that TFR2 is a kind of brake of EPO signaling and disclosed the potential therapeutic value of TFR2 inactivation in different types of anemia, an issue our lab is actively pursuing.

In the last years I retired from my clinical activity to funnel my energies to research. As a representative of the benign hematology, I was involved in several international Committees and editorial activities, all new and important experiences. However, the most exciting was to be elected as IBIS President and the led the organization of the 2013 Meeting in London. That Meeting was a training school to develop novel ideas and events with the essential help of the board of directors, local organizers and especially of Ioav Cabantchik. Thanks to an unrestricted support from Pharma we had in London the first educational course, the first meet the expert breakfasts, an ad hoc committee to assign fellowship for trainees based on merits, all initiatives developed in the effort of placing young researchers in the center of the BioIron life.

The advances in the iron field raised a novel interest in the Hematology community: at the 2013 ASH Meeting in New Orleans, organized under the Presidency of Jane Abkowitz, I was awarded the Ham Wasserman lecture reserved to non-US scientists. In 2016 at the EHA Kopenhagen Meeting I received the Jean Bernard life time achievement by the President Tony Green while Martina Muckenthaler was an EHA Board influential member. As I said after the latter award: “Now the only consequent and reasonable thing I can do is to retire!”

I know I have been lucky to be active during years that have been globally called “The golden age of iron research”. The story is not yet finished. However, soon I will leave to my collaborators, all IBIS active members, the task of further travelling the iron journey. I only hope that their research may be as interesting, stimulating and at the same time pleasant and full of surprises as mine has been. Doing research is the most exciting and rewarding job that only requires being able to enjoy few successes (as I described) and endure multiple failures (as I did not)!

Legend to Figure:
I apologize to the many others I was unable to show for space constraints. They are all in my mind. Adapted from Photo Gallery, IBIS, at https://bioiron.org/meetings/photo-gallery.aspx?