

## Background for the Hematology-Conference in Kaliningrad 2018

### Bone Marrow and Stem Cell - History

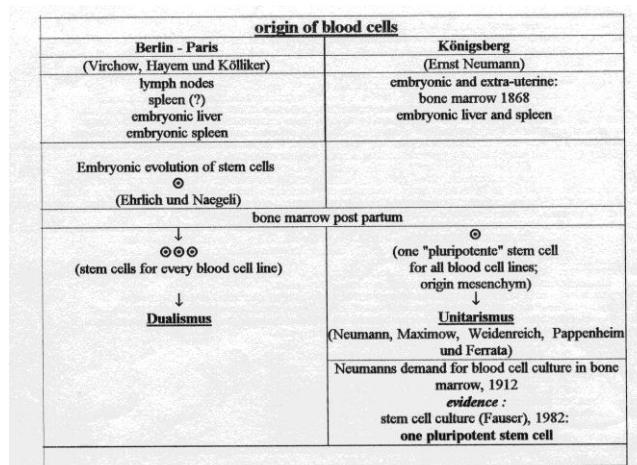
- I. Quotations
- II. History

#### I. Quotations 1980 - 2011:

**2011:** "At the same time, blood stem cells were conceptualized by histologists such as Ernst Neumann and Artur Pappenheim in studies of physiological haematopoiesis and various forms of leukaemia." "Ernst Neumann pointed to the first successes of Carrel in **tissue culturing** as a reason for his hope that blood cell cultures might in future be produced as well (1912, p.382)" (Maehle 2011).

**2007:** The beginning of Stem Cell research can be dated back to Ernst Neumann, who was appointed professor of pathology at the University of Koenigsberg in 1868. He described in a preliminary communication the presence of nucleated red blood cells in bone marrow (BM) saps. Neumann concluded in his subsequent papers, that during postembryonic life, erythropoiesis and leukopoiesis are taking place in the BM. On the basis of his observations, **Neumann was the first to postulate the BM as blood-forming organ with a common SC for all hematopoietic cells** (Zech NH, Shkumatov A. Koestenbauer S: The magic behind stem cells. Journal of Assisted Reproduction and Genetics Vo. 24, Nr. 6 (2007) 208 – 214

**2007** Although it was suggested in 1868 that most of hematopoieses occurred in the bone marrow (Neumann, 1868) the lymphatic system had historically been the first tissue believed to harbor hematopoietic activity (Müller, 1844). Ernst Neumann (1912) and others began to use the term stem cell to refer to the common precursor of the blood system after the turn of the century". Miguel Ramalho-Santor, Holger Willenbring: On the Origin of the Term "Stem Cell". Cell Stem Cell 1, July 2007, p.37



**1995** "Until the late nineteenth century blood cell formation was thought to be the prerogative of the lymph nodes or the liver and spleen. In 1868 Neumann and Bizzozero independently observed nucleated blood cells in material squeezed from the ribs of human cadavers and proposed that the marrow is the major source of blood cells (Abboud CN, Lichtman MA in Williams Hematology **1995**)

**1994:** "Es ist faszinierend, die scharfsinnige Argumentation Ernst Neumanns zu verfolgen, wie er ohne Polemik die komplexe Problematik darstellt („eine gemeinsame, auch im postembryonalen Leben stets vorkommende groß-lymphozytäre

Stammzelle", E.Neumann 1912) und gewissermaßen bis in den letzten Winkel hinein ausdiskutiert", in: Herbert A. Neumann, Yonne Klinger: Knochenmark und Stammzelle. Der Kampf um die Grundlagen der Hämatologie. Ex libris Roche, Bd.1, Blackwell Berlin 1994

**1992** „Neumann bringt 1880 wiederholt zum Ausdruck, daß sich die Vorstufen von kernhaltigen roten Blutkörperchen postembryonal über die lymphozytäre Stammzelle aus neugebildetem Knochenmark entwickeln“, in: Dissertation Yvonne Klinger: Ruhruniversität Bochum 1992, S.102 Über die Entdeckung der hämatopoetischen Funktion des Knochenmarks und das Postulat der Stammzelle. Von der Hypothese Ernst Neumanns (30.01.1834 - 06.03.1918) bis zum experimentellen Beweis.

**1985** "Neumann and Bizzozero reported observations and drew conclusions that were so revolutionary that they were not accepted". (M.WINTROBE1985).

**1980:** "Neumanns discovery was announced in the form of a preliminary report (LIT. 3). The promised thorough description appeared the next year in an extensive article (LIT. 1). In the interim, two communications appeared in *Italien* and were soon translated in the *Centralblatt*. They were both by G. Bizzozero, Turin. Of the two, Neumann was a more persistent student of the subject. He continued his work on the marrow, and toward the end of the century produced other classic contributions. Among his "firsts" were the identification of leukemia and of pernicious anemia as diseases of the marrow. He coined the term myelogenous leukemia. Like Immanuel Kant, Neumann preferred to remain a lifelong citizen of Königsberg, where he taught and worked almost all his life on blood production and blood pigments. His superb literary taste, reflected in his masterful German writings, provides the profile of a German scholar in the classical sense.

Despite the intensity of the search, Neumanns observations did not catch on easily. His ideas were received with the same skepticism with which Immanuel Kant's *Critique of Pure Reason* had been greeted almost a century before. Neumann was supported by Bizzozero and by Claude Bernard, but there were also Pouchet and Hayem to repudiate him. ..

and Robin to accuse him of adding to the confusion by postulating yet another theory. Georges

Hayem wrote an entire book in repudiation of Bizzozero. The preface of this book, despite a haughty tone, is but a -lamentoso- for plausible theories that were about to sink. Later, in reference to Hayem, Jolly deplored the "unfortunate" influence that did not permit Neumann's theory to be accepted universally for about 20 years.

Again, it was Neumann who provided us with the classic statement. In 1882, he enunciated the rule governing the development of yellow marrow.

In effect, he recognized a phenomenon that is sometimes referred to us as -Neumann's law. It states that at birth all bones that contain marrow contain red marrow. With age, the blood producing activity contracts toward the center of the body, leaving the more peripheral bones with only fatty marrow. For about 50 years, students of the marrow did not know what to make of this phenomenon. ... Despite all the opposition, however, within two decades, Neumann's discovery was a scientific axiom! The brilliance of the truth may first be blinding, but ultimately it supersedes all artificial illuminators" (TAVASSOLI 1980, p.62-72)

## II.

### 150<sup>th</sup> Anniversary of Modern Hematology

The role of the Universities of Königsberg/Kaliningrad, Berlin and St. Petersburg in stem-cell research 1868-1929 (death of A. Maximow)

#### 1868 Prussia Königsberg

E. Neumann Königsberg/ Prussia described in 1868 the original cell of the red blood corpuscles and called it the "Lymphoid marrow cell" (Neumann 1869; *Blut u. Pigmente*, S. 33) *"It is evident, that a continuing transformation of lymphoid cells into coloured blood cells" takes place in the bone marrow throughout life" 1869, BP.S. 19.*

This "**Lymphoid marrow cell**" forms not only the erythropoiesis but it is capable (in itself) of self-regeneration. 1869, BP. P. 30 - 34 . "Because of size differences in the lymphoid marrow-cells, we conclude that a permanent fluctuation will take place in the bone marrow" (1869, BP p. 30).

Neumann was supported by G. Bizzozero (who published the discovery some months later) and by Claude Bernard, Paris. R. Virchow refused to accept these new ideas concerning the function of bone marrow (*Cellular-pathologie* 1871, p.214).

In the meantime, further studies at the University of Königsberg pointed to the fact that even leukocytes are also formed in the bone marrow. The institute of pathology postulated a common stem cell for all hematopoietic cells. Unfortunately, outstanding contemporary investigators were reluctant to accept these new ideas. Besides R. Virchow, Pouchet

repudiated the Koenigsberg results. Charles Robin accused Neumann to add new confusion by "postulating yet another theory" (Tavassoli, p.62), and even George Hayem in 1884 rejected hematopoiesis in the bone marrow. "The preface to Hayem's book, despite a haughty tone, is but a *lamentoso* for theories that were about to sink. Later, in reference to Hayem, Jolly deplored the "unfortunate" influence that did not permit Neumann's theory to be accepted universally for some 20 years" (Tavassoli in Wintrobe p.62/63).

**1869 Italien:** Luigio Bizzozero confirmed the Prussian view of bone marrow as blood-forming organ and goes on to describe Thrombocytopoiesis

### **1870 Prussia (Koenigsberg)**

A further achievement by Ernst Neumann was the recognition that bone marrow is involved in Leukemia ("Myelogene Leukemia"). R. Virchow had proposed the classification of leukemia in "lineal" and "lymphatic" types.

### **1882 Prussia (Koenigsberg)**

Again, it was the Koenigsberg Institute that provided us with a classic statement. In 1882, Neumann enunciated the rule governing the development of yellow marrow. In effect, he recognized a phenomenon that is sometimes referred to as Neumann's Law.

### **1884-1898 Prussia (Berlin)**

Paul Ehrlich accepted bone marrow as a blood-forming organ. He showed wonderful coloured pictures of all cell-lines —erythropoiesis, leucopoiesis and lymphopoiesis. But a dispute broke out between P. Ehrlich as dualist and E. Neumann as unitarian. Neumann was an advocate of the **unitarian view**: All blood cells should be descended from this post embryonic stem cell. Even a compromise, to wait for a culture was not accepted by Ehrlich: *"Perhaps a final decision will only come, if it is possible, after isolating individual colourless cells and to study their life events in vitro for some time, as Robert Koch demonstrated with bacteria"* (Neumann, N 118, 1912, BP, p. 299).

Beside E. Neumann, other unitarians has been Theodor Boveri in München (1892), Artur Pappenheim in Berlin (Stammzelle 1896), and Alexander Maximow in St. Petersburg (1909).

### **1909-1922 Russia (St. Petersburg)**

Maximow proposed his (and Neumann's) "great Lymphozyt," as identical to the so called "Stammzelle" (Stem Cell). This term came 1868 originally from Ernst Haeckel, Jena (biologist, Darwins Theory), 1892 from Theodor Boveri (Willenbring) and 1896 A. Pappenheim.

### **1908-1918 Prussia (Berlin and Koenigsberg)**

Artur Pappenheim, a unitarian, used 1896 the term stem cell (Willenbring) and founded 1908 the Berlin Hematology Society. Other haematologists has been H. Hirschfeld and E. Grawitz. In Königsberg, E. Neumann and M. Askanazy since 1869 continued to postulate a common cell for all hematopoietic cells, and pronounced it 1912 "großlymphozytäre Stammzelle".

### **1922 - 1928 (Russia)**

Maximow emigrated in 1922 from St. Petersburg to Chicago, and took the unitarian point of view with him to the USA. (He died in 1928).

### **1945 - 2018 USA**

After the war, more and more of the history of hematology was displaced from Europe to the USA. Famous Hematologists had been: George Rosenow (a student of Ernst Neumann), M. Tavassoli, M. Wintrobe and Adolpho Ferrata. Germany: Axel A. Fauser:

In 1982 it was A.A. Fauser et al. who proved the unitarian point of view with stem cell-cultures.

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Zech, N.H., Shkumatov, A. Koestenbauer, S.: Die magic behind stem cells. Journal of Assisted Reproduction and Genetics Vo. 24, Nr. 6 (2007) 208 - 214 (Abstract: This review article summarizes historical development of stem cell research, presents current knowledge on the plasticity potential of both embryonic and adult stem cells and discusses on the future of stem cell based therapies.