Cellular Therapy and Transplantation (CTT), Vol. 1, No. 3, 2009
doi: 10.3205/ctt-2009-en-000029.01

Submitted: 12 February 2009, accepted: 29 May 2009, published: 13 June 2009

A. J. Friedenstein, founder of the mesenchymal stem cell concept

Boris V. Afanasyev[1], Elena E. Elstner[2], Axel R. Zander[3]

[1]St. Petersburg State Pavlov Medical University, 197089, St. Petersburg, Lev Tolstoy street, 6/8, Russian Federation;
[2]Charité – Universitätsmedizin Berlin, Onkologie/Hämatologie, 10117 Berlin, Germany;
[3]Clinic for Stem Cell Transplantation, University Medical Center Hamburg-Eppendorf, Martinistr. 52, 20246 Hamburg, Germany

Correspondence: editors@ctt-journal.com

Summary

The outstanding scientists A. Maximow and A. Friedenstein consecrated their lives to the study of stem cells. A. Maximow created a theory of hematopoiesis and a concept of hematopoietic stem cells, A. Friedenstein discovered mesenchymal stem cells and the hematopoietic microenvironment. The achievement of both researchers inspired other scientists and doctors to develop hematopoietic stem cell transplantation and other methods of cellular therapy as a treatment for a variety of severe diseases.

Keywords: A.J. Friedenstein, A. Maximow, bone marrow, stroma mesenchymal stem cells

Maximow and Friedenstein

Two researchers, Alexander Maximow (1874–1928), and Alexander Friedenstein (1924–1998), are standing out in Russian experimental hematology and, today, their merits are recognized worldwide. They met a rather similar fate. Both of them started their medical carrier in the Military Medical Academy. Their theories on stem cells were far ahead of their time and were met with skepticism. Therefore, the merits of both were underestimated during their lifetime. Finally, the scientific concepts of Maximow and Friedenstein represent an experimental basis for the transplantation of hematopoietic stem cells and for the development of various approaches to cellular therapy and their implications. Cellular therapy is a promising research discipline which has rapidly developed since the last decade. For the history of this field, it is noteworthy today that Maximow postulated a unitary theory of hematopoiesis and a concept of hematopoietic stem cells (HSC), and Friedenstein discovered adult non-hematopoietic stem cells (mesenchymal stem cells, MSC) in bone marrow (BM).

A.J. Friedenstein pioneered the understanding and positive evaluation of Maximow's heritage: He restored the good name of Maximow in Russia where Maximow was discredited after the revolution of 1917 and his work unfairly forgotten. In the history of histology and hematology in the USSR, Maximow's name had been given a negative connotation when he was mentioned together with a group of other "reactionary" scientists, e.g., A. Weissman, L. Morgan, N. Vavilov et al., which was in fact a great honor for him. It was Friedenstein who studied in detail the main stages of Maximow's research in Russia, Germany, and the USA, together with Russian and foreign colleagues (M. Tavassoli, D. Rowley) and he can be credited today for having contributed to the restoration of Maximow's good name by

highlighting the great significance of Maximow's fundamental studies in hematology.

Friedenstein's scientific contributions

As a young researcher, A.J. Friedenstein performed studies on the regeneration of skin and bones in Amphibia, especially in vitro culturing of frog transitional epithelium. From 1950 onwards, A.J. Friedenstein worked at the N.F. Gamaleya Institute of Epidemiology and Microbiology (USSR Academy of Medical Sciences). During this period, he carried out various studies in morphology and microbiology, with a special interest on interactions between the bone and hematopoietic tissues. From 1963 onwards, A.J. Friedenstein was the head of the immunomorphological laboratory, which was run by him for 25 years [4]. He headed studies in cellular disturbances following irradiation, development of approaches to regeneration of hematopoiesis, as well as continuing research in bone tissues. (Please find a list of Friedenstein's publications after the references below.)

A.J. Friedenstein is generally credited with the discovery of MSC. He started his pioneering work about 40 years ago by stating the critical observation that BM in postnatal life is a reservoir of stem cells for mesenchymal tissues. From BM, Friedenstein isolated for the first time adherent, fibroblast-like, clonogenic cells (colony forming unit-fibroblast, CFU-F) with a high replicative capacity in vitro (Friedenstein et al. 1968, 1970, 1974), which was multipotential in that it was able to differentiate into osteoblasts, chondrocytes, adipocytes and hematopoietic supporting stroma when a single CFU-F was re-transplanted in vivo (Friedenstein et al. 1966, 1968, 1974, 1980, 1987).

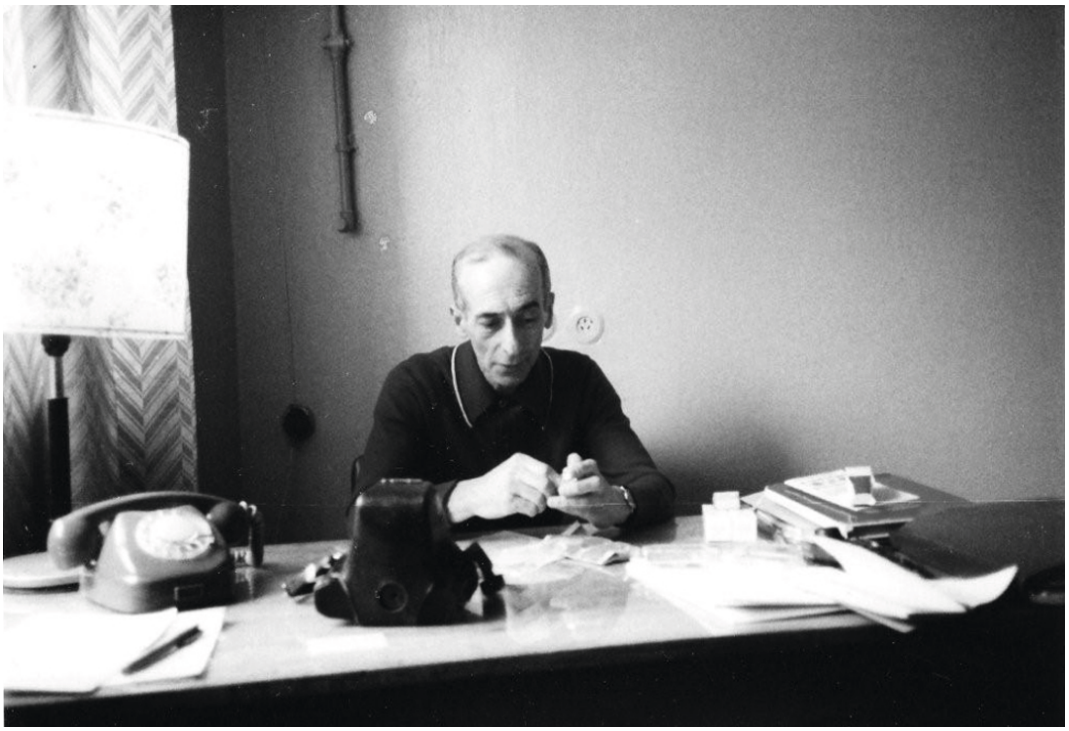

Image 1. A.J. Friedenstein (1924-1998), © Elena Elstner

Collectively, these pioneer studies demonstrated that BM contains a cell population, distinct from HSC that is clonogenic, capable of protracted self-maintenance and differentiation into multiple mesenchymal cell lineages. Accordingly, these cells fulfill the criteria of stem cells [5].

Several generations of scientists, in particular biologists and medical doctors now working both in Russia and abroad got their basic knowledge from the books of A J. Friedenstein and continue his studies in mesenchymal stem cells for various goals. A lot of scientists belong to A.J. Friedenstein's scientific school: R.K. Chailakhyan, N.V. Latsinik, Yu.V. Gerasimov, A.I. Kuralesova, A.G. Konoplannikov and others. In the West, Friedenstein's findings were important for research undertaken by, e.g., T.M. Dexter [6]. Those who remember the personal contacts and discussions with Friedenstein appreciate today that the real depth of his mind lay in his predictions on the role of mesenchymal cells. In his detailed studies he cooperated with leading Russian traumatologists, including G.A. Ilisarov, a professor at the Academy of Medical Sciences of the USSR (RAMN). Together they made a pioneering proposal on applications of mesenchymal cells in clinical settings.

The life of A.J. Friedenstein was full of research endeavours, which he acted on without any compromise. His devotedness in defending his scientific viewpoints and ideas today may serve as a good example for young researchers and scientists.

References

1. Friedenstein AJ, Lalykina KS. Bone tissue induction and osteogenic presursor cells. Moscow: Izd-vo "Medizina Publ."; 1973. Russian.

2. Friedenstein AJ, Deriglazova UF, Kulagina NN, et al. Precursors for fibroblasts in different populations of hematopoietic cells as detected by the in vitro colony assay method. Exp Hematol. 1974;2:83-92.

3. Friedenstein AJ, Luria EA. Cellular basis of hematopoietic microenvironment. Moscow: Izd-vo "Medizina Publ."; 1980. Russian.

4. Chailakhian RK, Latsinik NV, Gerasimov YuV, et al. Life in Research. In memory of AJ Friedenstein. The Scientist and The Teacher. Cellular Transplantology and Tissue Engineering. 2006;4(6):9-12. Russian.

5. Till JE, McCulloch EA. A direct measurement of the radiation sensitivity of normal mouse bone marrow cells. Radiat.Res. 1961; 14: 213-222.

6. Dexter TM, Allen TD, Lajtha LG. Conditions controlling the proliferation of haemopoietic stem cells in vitro. J Cell. Physiol. 1977;91:335-344.

A.J. Friedenstein's publications

1. Kuznetsov SA, Friedenstein AJ, Robey PG. Factors required for bone marrow stromal fibroblast colony formation in vitro. Br J Haematol. 1997;97:561-70.

2. Friedenstein AJ. Marrow stromal fibroblasts. Calcif Tissue Int. 1995;56 Suppl 1:S17.

3. Friedenstein AJ, Latzinik NV, Gorskaya YuF, Luria EA, Moskvina IL. Bone marrow stromal colony formation requires stimulation by haemopoietic cells. Bone Miner. 1992;18:199-213.

4. Friedenstein AJ. Osteogenic stem cells in bone marrow. In: Heersche J.N.M., Kanis J.A., eds. Bone and mineral research. The Netherlands: Elsevier Science Publishers; 1990. p. 243-272.

5. Friedenstein AJ. Stromal-hematopoietic interrelationships: Maximov's ideas and modern models. Haematol. Blood Transfus. 1989;32:159-167.

6. Owen M., Friedenstein AJ. Stromal stem cells: marrow-derived osteogenic precursors. Ciba Found Symp. 1988;136:42-60.

7. Friedenstein AJ, Chailakhyan RK, Gerasimov UV. Bone marrow osteogenic stem cells: in vitro cultivation and transplantation in diffusion chambers. Cell Tissue Kinet. 1987;20:263-272.

8. Luria EA, Owen ME, Friedenstein AJ, Morris JF, Kuznetsow SA. Bone formation in organ cultures of bone marrow. Cell Tissue Res. 1987;248:449-454.

9. Friedenstein AJ, Latzinik NW, Grosheva AG, Gorskaya UF. Marrow microenvironment transfer by heterotopic transplantation of freshly isolated and cultured cells in porous sponges. Exp Hematol. 1982;10:217-227.

10. Friedenstein AJ, Latzinik NV, Gorskaya UF, Sidorovich SY. Radiosensitivity and postirradiation changes of bone marrow clonogenic stromal mechanocytes. Int J Radiat Biol Relat Stud Phys Chem Med. 1981;39:537-546.

11. Friedenstein AJ. Stromal mechanisms of bone marrow: cloning in vitro and retransplantation in vivo. Haematol Blood Transfus. 1980;25:19-29.

12. Friedenshtein AJ, Lurija E.A. Kletochnye osnovy krovetvornogo mikrookruzhenija [Cell basis of hematopoietic microenvironment]. Moscow: Izd-vo "Medizina Publ."; 1980. 216 p. Russian.

13. Friedenstein AJ, Ivanov-Smolenski AA, Chajlakjan RK, Gorskaya UF, Kuralesova AI, Latzinik NW, Gerasimow UW. Origin of bone marrow stromal mechanocytes in radiochimeras and heterotopic transplants. Exp Hematol. 1978;6:440-444.

14. Chertkov IL, Friedenstein AJ. Kletochnye osnovy krovetvorenija [Cell basis of hematopoiesis]. Moscow: Izd-vo "Medizina Publ."; 1977. 274 p. Russian.

15. Friedenstein AJ, Gorskaja JF, Kulagina NN. Fibroblast precursors in normal and irradiated mouse hematopoietic organs. Exp Hematol. 1976;4:267-674.

16. Friedenstein AJ. Precursor cells of mechanocytes. Int Rev Cytol. 1976;47:327-359.

17. Friedenstein AJ, Chailakhyan RK, Latsinik NV, Panasyuk AF, Keiliss-Borok IV. Stromal cells responsible for transferring the microenvironment of the hemopoietic tissues. Cloning in vitro and retransplantation in vivo. Transplantation. 1974;17:331-40.

18. Friedenstein AJ, Deriglasova UF, Kulagina NN, Panasuk AF, Rudakowa SF, Luriá EA, Rudakow IA. Precursors for fibroblasts in different populations of hematopoietic cells as detected by the in vitro colony assay method. Exp Hematol. 1974;2:83-92.

19. Friedenstein AJ, Lalykina KS. Indukcija kostnoj tkani i osteogennye kletki-predshestvenniki [Induction of bone tissue and osteogenic cell-precursors]. Moscow: Izd-vo "Medizina Publ."; 1973. 216 p. Russian.

20. Friedenstein AJ, Chailakhjan RK, Latsinik NV. Kletki, otvetstvennie za perenos mikrookrujenia v krovetvorniy I limphoidtoy tkani. (Stromal cell responsible for transfer of microenvironment of hematopoietic and lymphoid tissue). Probl Hematol Blood Transf. 1973;10:14-23.

21. Friedenstein AJ, Lalykina KS. Thymus cells are inducible to osteogenesis. Eur J Immunol. 1972;2:602-603.

22. Friedenstein AJ, Kurolesova AI. Osteogenic precursor cells of bone marrow in radiation chimeras. Transplant.1971;12:99-108.

23. Friedenstein AJ, Chailakhjan RK, Lalykina KS. The development of fibroblast colonies in monolayer cultures of guinea-pig bone marrow and spleen cells. Cell Tissue Kinet. 1970;3:393-403.

24. Friedenstein AJ, Chailakhjan RK, Vasiliev AV. Clonoobrasovanie v monosloinich kulturach kostnogo mozga (Formation of clone in monolayer of bone marrow cultures). Bull Exp Biolog Med. 1970;2:94-96.

25. Latsinik NV, Luria EA, Friedenstein AJ, Samoylina NL, Chertkov IL. Colony-forming cells in organ cultures of embryonal liver. J Cell Physiol. 1970;75:163-165.

26. Friedenstein AJ, Petrakova KV, Kurolesova AI, Frolova GP. Heterotopic of bone marrow. Analysis of precursor cells for osteogenic and hematopoietic tissues. Transplantation. 1968;6:230-247

27. Friedenstein AJ, Piatetzky-Shapiro II, Petrakova KV. Osteogenesis in transplants of bone marrow cells. J Embryol Exp Morphol. 1966;16:381-90.

28. Friedenstein AJ. Humoral nature of osteogenic activity of transitional epithelium. Nature. 1962;19:698-699.

29. Friedenstein AJ. Osteogenetic activity of transplanted transitional epithelium. Acta Anat (Basel). 1961;45:31-59.

А.Я. Фриденштейн, основатель концепции мезенхимальной стволовой клетки

Борис В. Афанасьев, Елена Эльстнер, Аксель Р. Цандер

Резюме

Два выдающихся ученых – А.А. Максимов и А.Я. Фриденштейн – сделали огромный вклад в теоретические и экспериментальные исследования стволовых клеток. Выдающийся гистолог А.А. Максимов, работая в Санкт-Петербурге (в Военно-Медицинской Академии), предложил унитарную теорию кроветворения и обосновал концепцию гематопоэтических стволовых клеток на различных животных моделях. Примерно 50 лет спустя, А.Я. Фриденштейн проводил свои первые исследования с регенерацией костей и переходного эпителия лягушек. Начиная с 1950 г., А.Я. Фриденштейн работал в Институте эпидемиологии и микробиологии им. Н.Ф. Гамалея (Москва). В своей лаборатории иммуноморфологии он осуществлял исследования клеточных повреждений после облучения, разрабатывал подходы к восстановлению гемопоэза, а также продолжал исследования костных тканей. При изучении взаимодействий между костной тканью и системой крови, он открыл мезенхимные стволовые клетки и предложил идею гемопоэтического микроокружения, образуемого популяциями негемопоэтических клеток. Из костного мозга он впервые выделил адгезивные, фибробластоподобные клоногенные клетки (КОЕ-Ф) с высокой репликативной способностью и мультипотентностью, состоящей в возможности их дифференцировки в остеобласты, хондроциты, адипоциты и стромальные клетки, поддерживающие гемопоэз. Кроме того, Фриденштейн был первым, кто понял и позитивно оценил наследие А. Максимова. Несколько поколений ученых, особенно биологов и клиницистов, теперь работают в России и за ее пределами, получают базовые знания из книг Фриденштейна и продолжают его исследования в области мезенхимных стволовых клеток для различных целей, в том числе – для улучшения регенерации костей в клинических условиях. Таким образом, вклад обоих выдающихся русских исследователей привел к возникновению основы для развития трансплантации гемопоэтических стволовых клеток и других методов клеточной терапии в качестве метода лечения разнообразных тяжелых заболеваний.

Ключевые слова: Фриденштейн А.Я., Максимов А.А., костный мозг, мезенхимные стволовые клетки, клоногенность, мультипотентная дифференцировка