

## In memory of Garry Abelev 1928–2013

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We thought that at least two authors were necessary to report on such a rich life and unique personality as that of Garry Abelev. Thus, the first author will be Natasha Engelhardt, who has worked for more than 50 years directly in collaboration with Garry and who will describe the stimulating and democratic atmosphere, which reigned in his research group, despite the pressure and the threat of the administration. She will also tell us about the seminal influence that Garry had, not only on every member of his group but also on numerous young Russian scientists who attended his very popular and modern courses Immunology at Moscow University.

The second author, Jean-Pierre Mach will try to communicate the great souvenirs and emotions he experienced during his numerous personal meetings with Garry, first at his laboratory and later at his datcha with his wife Galina Deichman, as well as in several scientific meetings organized by the International Society of Oncodevelopmental Biology and Medicine (ISOBM).

We start with the testimony from Natasha Engelhardt.

### The scientific career and numerous obstacles

Garry Israyelelevich Abelev graduated from the chair of plant biochemistry of Moscow University in 1950. His professor, Andrey Belosersky, was very fond of him since he was very capable and an outstanding student. But, as it was a time of state anti-Semitism in the USSR, Abelev was not permitted to enter the Lenin Mausoleum Laboratory, where he was invited after graduating. Thanks to the efforts of Prof. Belosersky, he was accepted, with difficulty and at first as a technician, in the Department of Biochemistry of the Gamaleya Institute for Epidemiology and Microbiology. Fortunately, 2 years later, he was able to move in the same institute to the Department of Virology headed by Prof. Lev Zilber, for whom he had a great admiration and where he developed his interests on research in

cancer immunology. There, he obtained his first scientific position and after several years could present his Ph.D. thesis. When I joined the department in 1957, he was scientific researcher and became senior scientific researcher approximately 2 years later. Soon he became head of a research laboratory. After the sudden death of the highly respected Prof. Zilber, in 1966, Abelev became his successor as head of the Department of Cancer Virology and Immunology.

At the end of the 1950s, his research group began to increase step by step. At the beginning, it included Drs. Zinaida Avenirova, Anatoly Goussev, Vladimir Tsvetkov, and myself. Two years later, Ninel Khramkova joined it, then came Svetlana Perova, Tatyana Beloshapkina, and Eleonora Karamova. There was no specialization in immunology at Moscow University or at the Moscow Medical Institute. The first course of Immunology was created by Abelev in the context of the chair of Virology of Moscow University in 1964. His course was modern and stimulating and soon became very popular and attractive for both biologists and medical doctors from different institutes all over Moscow. Abelev continued his teaching at Moscow University until 2005. To give an example of the impact of Abelev's teaching, one of his students, Ruslan Medzhitov, who became one of the best contemporary immunologists, now at Yale University, recently said that he became interested in immunology when he followed the teaching of Garry Abelev. The same interest was aroused for us, when we were exposed to new fields such as virology, cell biology, or leukemia research. Abelev always told us that we should be professional in the field of our work, and this was an obligatory rule of the group.

These rules were essential for his entire group, which was like his orchestra, where he was the conductor organizing and emphasizing the skillful initiatives of all its members. The atmosphere was very stimulating and encouraging. Our laboratory conferences were unforgettable. Abelev was never upset when experimental results did not confirm the proposed hypothesis, but was always ready to formulate a new one and to propose a way to verify it, including the elaboration of new methods. All the new experimental data were openly discussed there during the progression of the experimental work. All the objections were presented freely, as well as ways for verifying the results; everybody could give his or her opinion, express doubts, and voice a hypothesis, followed by how to prove the suggestion or how to overcome the difficulties. We trusted and respected each other independently of the official position, such as senior researcher or technician. Abelev used to say that his important gift was the ability to induce in people their best features and to make them communicate using their best sides. It was absolutely true, since despite different backgrounds, temperaments, and capabilities, his collaborators kept their friendship and confidence in complicated situations through their entire life. This very

free and open-minded attitude was not so common in the majority of Russian laboratories at the time.

### Discovery of alpha-fetoprotein

In the beginning, most of the work was performed, using double diffusion in agar, which offered the possibility to study tissue extracts on the level of individual antigens. Abelev was excellent in the development of new technologies, and many methodological approaches were born during this period, forming an original analytical system. The immunofiltration technique, elaborated by Abelev and Tsvetkov, resulted in purification of the first specific tumor antigen from mouse hepatocarcinoma: hepatoma antigen (HA). Soon after, in January 1962, Ninel Khramkova began to study mouse liver organospecific antigens in early ontogenesis. Unexpectedly, an extremely high concentration of HA was observed in the extract of mouse fetal liver. G.I. Abelev together with Svetlana Perova immediately joined to study this phenomenon. In 4 months, they demonstrated that the HA antigen from hepatocarcinoma was identical to the main protein in fetal serum, produced by fetal liver. Thus, HA soon became  $\alpha$ fetal, the first oncofetal antigen. These results were presented by Abelev at the Oncological Congress in Moscow in 1962 and soon afterwards at the French-Soviet Symposium, invited by Prof. Pierre Grabar. The reports attracted a lot of interest. In August 1962, two full-length papers were submitted and soon accepted, one in Russian in *Biochimia* (USSR), 28, 625–634, and the other in English in *Transplantation* 1 N2, 174–180, 1963.

An important immunodiagnostic step was taken the following years by the biochemist Yuri S. Tatarinov from Astrakhan, who was aware of Abelev's results and described  $\alpha$ -globulin in the sera of four hepatoma-bearing patients. These findings were soon extended in a study performed by Prof. Natalia Perevodchikova and Nikolay Kraevsky, clinicians from the Institute of Experimental and Clinical Oncology together with Abelev and Svetlana Perova.  $\alpha$ -Globulin was found in sera of 17 out of 28 patients with primary liver cancer and moreover in several cases of patients bearing testicular teratocarcinomas. More than 200 sera from patients with various other types of tumors and 66 from patients with noncancerous diseases were negative. These results published by Abelev G.I. et al. "Embryonal serum alpha-globulin in cancer patients: diagnostic value" *Int. J. Cancer* (1967, 2, 551–558) attracted great attention and recognition.

Three other informative references about the work in Abelev's laboratory are as follows:

1. A monograph by L.A. Zilber and G.I. Abelev. *The Virology and Immunology of Cancer*, Medgiz, M. 1962 in Russian, with a second edition published in English

Pergamon Press, Oxford, 1968. Most of the immunological techniques developed in Abelev's laboratory, which were central to the alpha-fetoprotein discovery were described there.

2. A review, summarizing most of the data on alpha-fetoprotein, Abelev G.I. *Adv. Cancer Res.* 14, 295–358, 1971.
3. G.I. Abelev: An Autobiographical Sketch: 50 Years in Cancer Immunochemistry. G. Semenza (Ed.) *Stories of Success—Personal Recollections. X. (Comprehensive Biochemistry vol.45) C 2007.* pp 283–334.

### International recognition

At the end of the 1960s, our laboratory was functioning efficiently. Anatoly Goussev and Alla Yazova developed good antisera for human alpha-fetoprotein (AFP), and the Gamaleya Institute produced the first immunodiagnostic kit, for diagnosis of liver carcinoma and teratocarcinoma. Howard Goodman, chief of Immunology at WHO, organized an international trial for validation of the  $\alpha$ f-globulin test. Abelev was able to travel abroad and was invited with Tatarinov to visit several research centers from Africa involved in the study of primary liver cancer under the organization of IARC. Later, the serum samples from patients were centralized in three laboratories for independent examination: in Paris Jose Uriel, Moscow Abelev, and Astrakan Tatarinov. The results confirmed the validity of the test. In 1969, they were presented at a conference in IARC, Lyon, France, where  $\alpha$  feto was given its present name, alpha-fetoprotein (AFP). The results were published by O'Connor G.T., Tatarinov Y.S., Abelev G.I., and Uriel J. (*Cancer* 25, 1091–1098, 1970).

Thanks to a grant given to our laboratory by WHO, collaborators from Abelev's laboratory were able to travel abroad. With A. Goussev, I had personally the possibility to work for 3 months in the laboratory of Profs. René Masseyeff and René Camain at the University of Dakar in Senegal, where we made the first study of AFP by immunofluorescence in primary liver cancer (Goussev A.I., Engelhardt N.V. et al. *Int. J. Cancer* 7, 207–17, 1971).

### Crisis and philosophy

The situation seemed favorable for our laboratory despite painful events in our country, such as savage treatment of dissidents and intervention in Czechoslovakia in 1968. Abelev remained optimistic and always told us “You must simply work; all the people, all the scientists believe us and all are ready for cooperation.”

However, in summer 1971, Abelev refused to collaborate with KGB and everything changed. He could not travel abroad anymore, namely, at a conference in Kampala where he was expected, a proposal of nomination at the Academy of Medical Sciences was cancelled. Later, Abelev refused to attend a Scientific Board of the Institute, where he was supposed to blame one collaborator who made a demand to emigrate to Israel. The reaction of the director was very hard; he reorganized the Department and wanted to dismiss Abelev and the whole staff. But all the coworkers refused to betray Abelev. After a long and difficult struggle, the director's order was partially repealed, but these events were followed by a new period of confrontation with the administration, which lasted until May 1977.

Fortunately, Abelev was morally supported by his international recognition. In 1975, the Cancer Research Institute (CRI), directed by Lloyd Old, bestowed the first William B. Coley Award on a group of 16 men and women dubbed the “founders of tumor immunology.” Garry Abelev was among this elite group of scientists, whose work on tumor antigens opened up a whole new vista in the diagnosis and treatment of cancer. He was elected at the New York Academy of Science, as well as at the Scientific Advisory Council of the (CRI). He had to wait until 1987 to be elected corresponding member of the Russian Academy of Science. In 1977, the president of the Medical Academy of Science Vladimir Timakov ordered to transfer Abelev's laboratory to the Russian Oncological Center where the working conditions were much more favorable.

I am pleased to give a brief portrait of Abelev, as it is alive in the memory of those who had the chance to deal with him. He was an authentic researcher; with age, he became also a philosopher interested in general life problems. He was a real patriot and citizen, very anxious about the contemporary fate of science in our country.

We follow with the experience of Jean-Pierre Mach.

### A difficult visit

I first met Garry Abelev in 1974, in very particular conditions. I was about to leave for Japan to attend one of the first ISOBM meetings organized by Hidematsu Hirai in Tokyo, when Howard Goodman, chief of Immunology at WHO in Geneva, told me that he was very worried about the situation of Garry Abelev in Moscow with whom he had lost all contact. Thus, Howard asked me to stop by in Moscow on my way to Japan to investigate what was going on with Abelev at the Gamaleya Institute. Despite having all the official papers, prepared by WHO, when I arrived at the Institute, I was told by administrators that Prof. Abelev was absent. After an hour of waiting, following my stubborn insistence, an official from the foreign visitor staff, Dr. E. escorted me to an office, where Garry was indeed present with Natasha Engelhardt. He welcomed me

very warmly, as if I were coming from another planet. We spent the whole day talking about his scientific results on the induction of expression of alpha-fetoprotein during carcinogenesis, as well as his development of new immunofiltration methods for antigen purification. He was also interested by my results on in vivo tumor localization of radiolabeled anti-carcinoembryonic antigen (CEA) antibodies (Mach J.P. et al., *Nature* 1974), but at no time was it possible to discuss his current administrative problems, since the official Dr. E. was constantly present during the whole day, including lunch, to prevent such discussion.

I learned later that Garry, who was already well known internationally (with his picture and that of his respected former chief, the late Prof. Zilber, on the front page of the August 1974 issue of *Cancer Research*) was under strict official surveillance, because he refused to collaborate with the KGB and was in severe conflict with Prof. Baroyan, director of the Gamaleya Institute. Thus, Abelev was not able to travel abroad, as he did before, and to accept the invitation of Prof. Hidematsu Hirai to attend the Tokyo Congress, where most of the founders of the future ISOBM, such as Sabine von Kleist, Jose Uriel, René Masseyeff, Pierre Burtin, Phil Gold, Eliot Alpert, Shinzo Nishi, and others, were meeting. Two years later, in 1976, at the San Diego ISOBM meeting, the organizers, Bill Fishman and Stewart Sell, two central members of our Society, delivered an ISOBM prize to Abelev in absentia.

Fortunately, 1 year later, Gary was able to move from the Gamaleya Institute to the Russian Oncological Center, where the conditions of his laboratory and research group were improved, but he was not yet allowed to travel outside the USSR.

### The ISOBM meetings

In 1980, Garry was able to organize an ISOBM meeting in Tallinn in collaboration with Prof. Riatsep. Unfortunately, many members from the USA did not attend the meeting because of the first Afghanistan war and the boycott of the Olympic Games by the USA. The meeting was of excellent scientific quality; Sten Hammarström and Torgny Stigbrand came from Stockholm, as close neighbors, but Garry was obviously still very nervous and did not attend the social events.

In 1983, Garry was allowed for the first time to attend an ISOBM meeting outside the USSR, which was organized by Sten Hammarström in Stockholm, but we were never sure if he would obtain permission to go abroad for the next meeting. In 1989, he attended the Freiburg ISOBM meeting in Germany, organized by Sabine von Kleist, who was also a great friend and supporter of Garry.

In 1987, Garry Abelev was finally elected a corresponding member of the Russian Academy of Science, which meant a late but essential recognition of his scientific merits. Interestingly, this election coincided with the policy of glasnost (transparency), initiated by Mikhail Gorbachev. In 1990, Garry took the responsibility of organizing the ISOBM meeting at the Russian Oncological Center in Moscow. It was the beginning of freedom in Russia, and Garry with his friends, Yuri Vassiliev, Galina Deichman, and Natasha Engelhardt, was all hopeful of a new era of democracy in their country. In 1991, Garry attended the ISOBM meeting from Sienna, Italy, organized by Gian Carlo Torre, where he received the Abbott Award attributed by a special commission from ISOBM. Next year, he attended the Sapporo meeting organized by Akira Yachi, and in 1993, he had the pleasure to participate in the Jerusalem meeting in Israel, organized in 1993 by Haim Biran, where he could meet with several excellent scientists from the Weizmann Institute. In 1996, he was finally able to attend the second San Diego ISOBM meeting, organized by Jose Milan and Bill Fishman. In 1997, I had the pleasure of welcoming Garry with a strong delegation of Russian scientists at the Montreux Palace, where we held the 25th ISOBM meeting. He also attended the next ISOBM meeting, held in Umea, Sweden, and organized by Stigbrand and Hammarström, as well as the Kyoto meeting in 1999, organized by Khozoh Imai and Shinzo Nishi. In 2000, he participated in the Munich meeting organized by Petra Stieber and Rolf Lamerz and, in 2001, in the meeting in Barcelona organized by Rafael Molina and Antonio Ballesta. Garry enjoyed visiting the Picasso Museum, but had a little more difficult time to appreciate the art of Miro, to which he was not accustomed. To my knowledge, the last ISOBM meeting Garry was able to attend was in Boston, in 2002, where the organizer, Herb Kupchik, was able to include several prestigious speakers from Harvard and MIT.

It was evident that Garry enjoyed these yearly ISOBM meetings, each with its own unique scientific qualities and social events. However, he discretely expressed his regrets that the emphasis of the meetings was progressively shifting towards simple application of repetitive and multiple marker analyses, proposed by commercial companies, rather than on original experimental cancer research. In his own laboratory, while also trying to improve AFP diagnosis potential, by dissecting its different epitopes with monoclonal antibodies and sophisticated electrophoresis/immunoblotting technologies (Karamova ER et al. *Tumour Biology* 2003), his main interest, in recent years, was focused on the role of microenvironment in the partial dedifferentiation of epithelial cells during tumor progression (Abelev G.I. and Lazarevich N.L., *Adv Cancer Res.* 2006).

## An exceptional personality

In addition to being a pioneer in the field of oncofetal proteins and a central figure of our Society ISOBM, Abelev was also a model for many of us for several genuine human qualities.

First, I should mention his deep scientific honesty. For instance, he never claimed that alpha-fetoprotein was absolutely oncofetal specific; instead, he was interested in its expression during particular stages of hepatic cell differentiation as well as during liver regeneration. He never denied the merits of those who contributed to the field, like the Russian scientist Youri S. Tatarinov, who, after visiting Abelev's laboratory in 1962, was the first to demonstrate the presence of alpha-fetoprotein in serum from patients with liver carcinoma, or the contribution in the field of Jose Uriel from Paris. Alpha-fetoprotein happened to be the first oncofetal protein described, but soon afterwards, in 1965, the carcinoembryonic antigen (CEA) was discovered by Gold and Freedman and Abelev acknowledged the essential contribution of Phil Gold in designing the first radioimmunoassay for detecting CEA and monitoring the evolution of several types of carcinomas. Despite his unique biological discovery, Garry was against "flashy research." He was also deeply interested in the invention of laboratory methods such as the counterflow immunoelectrophoresis on porous membranes that he developed in collaboration with another faithful collaborator of more than 30 years, Eleonora Karamova. This method was original and allowed the purification of minute amounts of antigens from a mixture of abundant proteins, but it was relatively complex and did not lead to industrial development.

The second typical facet of Garry's character was his independence. At the end of the 1970s, after all his difficulties with the administration, he wrote with his first wife, the late Elfrida A. Abelev, a very respected geneticist, his only polemic article on the role of ethics in science. The paper was submitted to the Russian journal *Nature (Priroda)*. Despite positive reviews and support from two great academicians, including Vladimir Engelhardt, the pioneer of molecular biology in Russia (and father of our first author today), the paper was first rejected, but finally appeared much later in 1985, in another Russian journal called *Chemistry and Life*. Garry also wrote, around 1990, a philosophical essay entitled "On dignity in life and in science" in which, in relation with his struggle in life, he insisted that human dignity should be based on respect rather than on power.

Several years after the death of his first wife, who suffered for many years from rheumatoid arthritis, Garry remarried with Galina Deichman, a well-known tumor immunologist, who also had a very independent character. For instance, she was forbidden to accept an invitation for a sabbatical year

from Eva Klein in Stockholm, because, just before her departure, she refused to report to KGB on her planned stage abroad. Galina was a great support to Garry in the later part of his life. They lived together in a dacha that Galina had built in large wooden logs, at the periphery of Moscow.

The third among the many charming traits of Abelev's personality was his admiration of art and his spirituality. He was of Jewish background but shared with all his visitors his admiration for Christian art. For instance, he made us visit, with my wife Marie-Louise, the most beautiful orthodox churches in Moscow. He wanted, during the Moscow ISOBM meeting, to have a special day off to visit the Golden Ring of the towns of Vladimir and Suzdal and in particular the little church of the Intercession at Bogolyubovo, which he considered as the jewel of Russian art (and is classified as a UNESCO world heritage site). Another example, during one of his visits to Switzerland, we visited together a temporary exhibition of early Chagall paintings that he had never seen in Russian museum. He was moved by the expression of humble Russian peoples, who meant so much to his culture. I also remember that, in his office, there was always, in a central place, an impressive small van Gogh painting representing a peasant joining his hands praying. For me, this was the image of Garry fighting against isolation from the world and hoping for a better future.

## The international testimonies and souvenirs

For all these qualities, Gary Abelev will be remembered as a great scientist and a great humanist. This is immediately confirmed when one speaks about Abelev with some very successful Russian scientists, who emigrated to the USA, such as the most well-known immunologist, Ruslan Medzhitov, or Igor Roninson or Andrey Gudkov; they all have moving memories of their time in Moscow, where Garry was a scientific personality of reference. Also, internationally recognized scientists, such as Lloyd Old and Edward Boyse from New York, always referred to Abelev as the father of tumor immunology in Russia. Among numerous important scientific personalities, who were invited to teach in Moscow by Sergei Nedospassov, one of the successors of Garry Abelev in the teaching of Immunology at Moscow University, many, such as Robert Weinberg, as well as George and Eva Klein, asked to visit Garry Abelev at his laboratory or at his dacha. They still had wonderful scientific exchanges on tumor micro-environment and tumor immunology. These visits gave a great joy and satisfaction to both Garry and Galina in their period of semiretirement.