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OBITUARY

In memoriam: John E. Folk (1925–2010)

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John Edward Folk (Jack Folk), one of the world's most distinguished biochemists and a dear friend of many colleagues around the world, died in Bethesda, MD, USA, on 22 December 2010, at the age of 85 years (Fig. 1). This, In memoriam, is an opportunity to present personal memories, hoping to provide more of a sense of the man, the colleague, and the friend of so many members of the global transglutaminase community.

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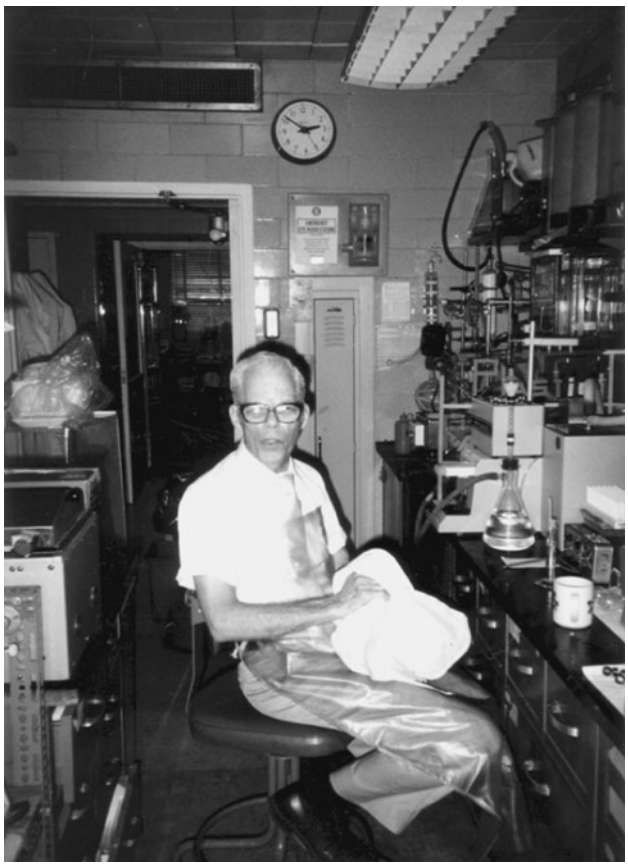

Fig. 1 Jack Folk at work with his apron in the laboratory of the Enzyme Chemistry Section of the former National Institute of Dental Research (present National Institute of Dental and Craniofacial Research)

Dr. Folk was born in Washington, D.C., USA, on 29 October 1925. He received a Bachelor of Science degree (1948), an M.S. in biochemistry and organic chemistry (1950), and a Ph.D. in biochemistry and organic chemistry

(1952) at the Georgetown University, Washington, D.C. He was married to Miss Ann Cooper and they have a daughter Miss Jacqueline Ann born in 1952. Initially, he worked as Fellow at the Georgetown University (1948–1952). Then he was assigned by ADA to the National Institute of Dental Research (NIDR) of the National Institutes of Health, Bethesda, MD, USA (1952–1959). In 1959, Jack was recruited to work as a chemist at NIDR and appointed chief of the Enzyme Chemistry Section in 1965. In 1986, he received the position of Acting Chief of the Laboratory of Oral Biology and Physiology, NIDR, NIH. After 44 years at NIDR, Folk retired as section chief, but continued his affiliation with NIDR as a scientist emeritus. He continued to work actively as a special volunteer/chemist in the laboratory of Dr. Kenner Rice (NIDDK and NIDA) from 2000 until his death. During his tenure at the NIH, he has been recognized for his accomplishments with many honors and awards and has served on several study sections, subcommittees (*Acting Chairman of Subcommittee on Enzymes, Division of Chemistry and Chemical Technology, National Academy of Sciences-National Research Council: 1970*), and editorial boards (*Journal of Biological Chemistry: 1973–1978; 1980–1985).*

Scientific activity

Dr. Folk, made ground-breaking advances in three areas (Fig. 2). In his early years at NIH, he characterized proteolytic enzymes of the digestive system, including carboxypeptidases A, aminopeptidase A and chymotrypsin C and investigated how specific enzymes contributed to the biological activities of organs and tissues affected by degenerative diseases. In 1965, he started to investigate a new family of enzymes, "transglutaminases" which catalyze formation of protein–protein cross-links important in blood clotting and skin barrier formation and established the basic mechanism of the reaction. In 1980, he and his colleagues discovered a new enzymatic pathway that incorporates a portion of the polyamine spermidine into eukaryotic initiation factor 5A (eIF5A), which is essential for eukaryotic cell proliferation. In his lifetime, several new enzymes, including carboxypeptidase B, γ-glutamylamine cyclotransferase, deoxyhypusine hydroxylase and deoxyhypusine synthase, were discovered and characterized in his laboratory, laying the foundation for extensive further investigations. In these three areas, Dr. Folk was a pioneer and a leading scientist who established the basic mechanisms of these enzymes as well as the vital importance of these physiological reactions. In 1997, Dr. Folk was honored for his "*outstanding contributions and pioneering work on transglutaminase mechanisms*" by organizers of the "Fifth International Conference on Transglutaminases and Crosslinking Reactions", held in Cheju, Korea (Fig. 3). While with Dr. Rice, Dr. Folk contributed on projects that included crystal studies of a compound with high affinity and selectivity for the dopamine transporter, as well as with a large-scale synthesis of an important intermediate in the synthesis of delta- and opioid receptor ligands. Dr. Folk also worked on developing a nonselective ligand that would block the effects of methamphetamine-like stimulants at dopamine, serotonin, and norepinephrine transporters. Most recently, Dr. Folk synthesized several oxide-bridged phenylmorphans,

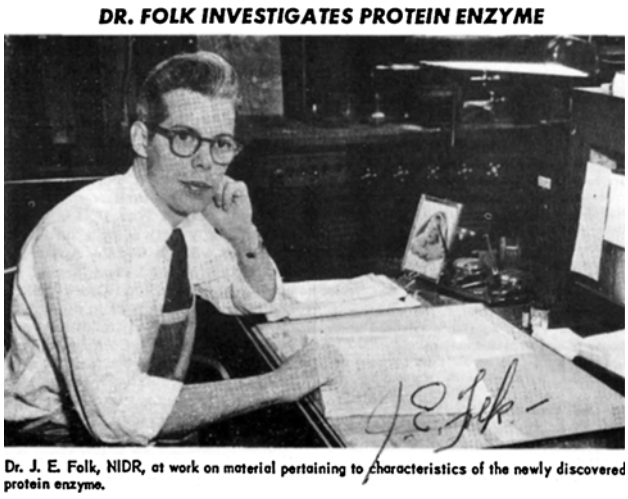

Fig. 2 Jack Folk at his desk in 1956. (10 December 1956, Vol. VIII, N. 23 NIH RECORD) with the permission of the NIH record Editor Richard McManus)

Fig. 3 Dr. Folk honored for his "*outstanding contributions and pioneering work on transglutaminase mechanisms*" by Soo Il Chung one of the organizers of the "Fifth International Conference on Transglutaminases and Crosslinking Reactions", held in Cheju, Korea 1996

pharmacological tools that could help scientists discern the recognition pattern needed by opioid receptors to produce analgesia or to block an overdose of heroin. He mentored numerous US and foreign scientists who were greatly influenced by his scientific insights and wisdom. Dr. Folk was highly respected in the international scientific community for his original and rigorous approach and was recognized with many awards for his superior service and contributions.

Memories in Jack Folk's laboratory

Simone Beninati

My deep respect for Dr. J.E.Folk arises from the fact that he was my mentor when I came to his laboratory in the middle of 1980s (Fig. 4). He guided me through the process, provided me discipline, and sharpened my research and writing skills. He was firm and strong, and yet friendly and supportive, always respectful and willing to listen. His critiques were phrases in the form of gentle suggestions. He was a real Master of Science. When I received a letter from Jack Folk, in 1984, I was a postdoc student at the University of Rome "La Sapienza", working on a project on polyamines, together with my supervisor Prof. Francesco Autuori. The letter from Jack was an invitation to his laboratory at NIH for a stage with the aim of collecting evidences about the possibility that polyamines were covalently linked to protein in mammalian cells. My arrival at NIH was exciting and scary at the same time. Once in Jack's laboratory, I was momentary confused about whom I should focus my attention on. Finally, Jack introduced himself with a brief sentence: "*Welcome in my lab. I hope you will enjoy your short stage at NIH*". Jack introduced me to his secretary Barbara Anne DeGraff to complete all the bureaucratic duties for a new fellow at NIH. I met Barbara in front of her office at the Enzyme Chemistry Section of NIDR. She was very interested and excited to talk to someone working with Jack Folk and she told me it was an honor to meet me. I said, "It's an honour to meet you." and our friendship lasted for several years, until her death due to breast cancer in 1992. Barbara was a unique person, always had a kind word, and made life a little nicer for everyone.

All these strong impressions hit me during those first few days at NIH and it was also nice to hear the experiences of other fellows like Alberto Abbruzzese, Enzo Cocuzzi, Franco Carmassi and many others, sharing the same impression and interest in science. Alberto Abbruzzese was the best person I have met in my life, a real friend. Alberto Abbruzzese passed away on the 26 October 2011. He was not just a colleague, but a cheerful, funny, and witty companion. Alberto, I thank you for being a part of my life and a part of my memory. I spent 6 years in Bethesda together with my wife Clara. In 1987, she gave

Fig. 4 From the left, S. Beninati, Jack Folk, and A. Abbruzzese (Alberto Abbruzzese, beloved friend and colleague, passed away on 26 October 2011)

me the joy of a son, Marco, who was born in Rockville, Maryland. On thinking about the work that I have done thanks to Jack, I noticed how many new things I learned and how I adapted my knowledge to my teaching career in the University of Rome "Tor Vergata".

Two decisive years in Jack Folk's lab

László Fésüs

From 1983, I had a period of 2 years as visiting scientist in the laboratory of Jack Folk at the National Institute of Dental Research in Bethesda. This was supported by the National Foundation for Cancer Research, a non-profit organization devoted to fund research activities related to the ideas of the Nobel Laureate Hungarian scientist Albert Szent-Györgyi, who at that time lived and worked in Woods Hole. My research on transglutaminases in Debrecen (Hungary) was already supported at that time by the above foundation through Koloman Laki, who originally discovered with Laszlo Lorand that clot insolubility is due to a Ca^{2+}-dependent enzyme, later termed FXIIIa.

Koloman also had a laboratory in another institute of the NIH and when he died after a brief illness in early 1983, it was my task to complete some of his ongoing experiments. For me, one of the most important benefits from working in Jack's laboratory was to learn how to investigate challenging issues of the field through systematic chemical approaches. As a medical doctor, my scientific thinking was more at the organ and tissue levels and, although I did cellular experiments before, I did not have the knowledge and techniques to prove my theories with hard biochemical data. This has been particularly important in the field of transglutaminases, since these enzymes catalyze post-translational protein modification, and the only way to prove their action is to detect and measure their products. So, I learned how to synthesize γ-glutamyl-amine standards and to determine their presence in protein digests obtained from biological samples. In later years, I could extend these works to find novel transglutaminase protein substrates, to demonstrate their modifications in apoptosis and various pathologic conditions, and to measure basal and pathologic level of the free $\varepsilon(\gamma$-glutamyl)lysine isodipeptide in blood plasma and cerebrospinal fluid. Mainly as a result of these 2 years, I have devoted during the following 25 years the major part of my research efforts to transglutaminases.

As we all know, scientific activity is not only about research in the laboratory. It is done through interactions with colleagues, arguments, personal judgments, collaborations, and competition. Discussions with Jack, particularly the lunchtime ones when usually several of us got together in his room, gave me significant insights into this dimension of the scientific world and our field. Often, various other topics came up and his modest but firm opinions have provided solid anchors for thinking on politics, democracy, and society, particularly when later on I was elected to leadership positions at my university and at national level in Hungary. During the 2 years I also met new friends with whom I did many collaborations and joint activities. With Mauro Piacentini, I have published more than 20 papers together in subsequent years. Although he was not part of the team in Jack's laboratory, Peter Davies also worked at NIH and this was the time that the idea of organizing regular meetings on transglutaminase research was born. During the following years, nine such very successful international conferences were organized. Since 2010, this has continued in the form of a Gordon Conference series on Transglutaminases in Human Disease Processes (the first edition of the Gordon Conference on Transglutaminases: "*Transglutaminases in Human Diseases Processes*", chaired by Rickard L. Eckert and Kapil Mehta, was held at Davidson College, NC, USA, 18–23 July 2010).

Mauro Piacentini

It is a great honor for me to write a few words about my experience in Jack Folk's laboratory at NIH. In 1984, together with Simone Beninati, we had just started our career at the University of Rome "La Sapienza" working in the polyamines field and I got interested in this class of enzymes able to post-translationally modify proteins by covalently incorporating amines. I started some very preliminary studies in our laboratory in Rome, but very soon, together with Simone, we came to the conclusion that if we wanted to demonstrate that this biological reactions were indeed taking place in cells, we had to use a different approach involving technologies that were not available in our laboratory.

Thus, we convinced our mentor Francesco Autuori to try to send us for a short stage to Jack's laboratory to acquire the scientific background and the expertise required for these studies. So, we decided to phone Jack and were quite surprised to hear that he was ready to accept us for the summer in his "famous laboratory" at NIH in Bethesda, MD.

I still remember the emotion we had in meeting him on the first day discussing our naive ideas about the transglutaminase biology (Fig. 5). Jack's attitude with us was always very open and modest, but firm in his scientific rigor, one of the main message I learned from him. As a cell biologist, I always tried to speculate with him about the possible role of transglutaminase 2 in cells and I remember Jack saying one of his popular jokes "Cells are too complicated for a chemist like me". Between 1984 and 1988,

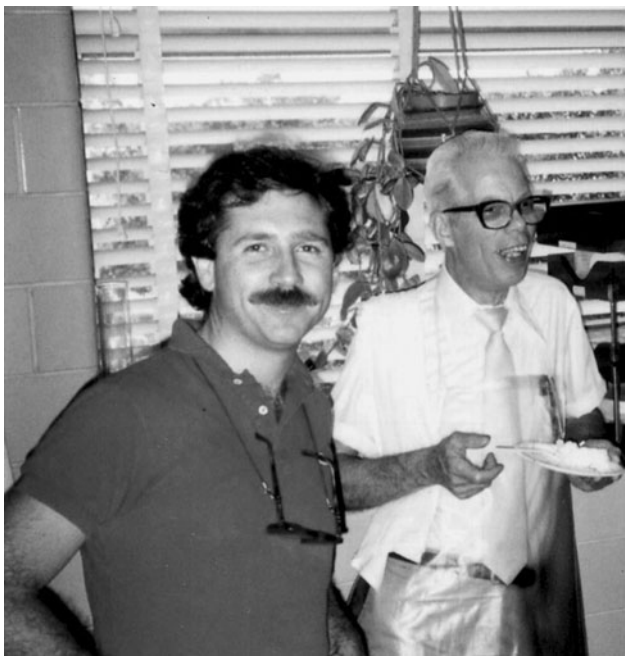

Fig. 5 M. Piacentini and Jack Folk at the Enzyme Chemistry Section of NIDR

I visited Jack's laboratory several times and I have to say that this has been a fundamental experience for my scientific career, giving me the opportunity to meet many great scientists who became good friends: Alberto Abbruzzese, Ron Chung, Enzo Cocuzzi, Laszlo Fesus, Myung Hee Park, and Scott Thacher. These personal interactions have been very productive, for example with Laszlo we started a long-lasting collaboration that has been very stimulating for us and has created the basis for many important developments in the transglutaminase 2 and cell death fields. I would like to remember our friend Alberto, who unfortunately recently passed away, for his great character and positive attitude to life. Thanks a lot, Jack.

Myung Hee Park

I worked for and with the well-known Dr. JE Folk for over 30 years at NIH. I would like to share my experience with Jack as the person, whom I know as a scientist, mentor, and friend. One word that comes to me of Jack's character is "genuine". He did not pretend and did not seek personal gain in his relationships or as a scientist. Jack was also a very private and unassuming man and did not seem to feel comfortable to be at the center of attention. In the past, near his retirement time, his long-time colleague Ron Chung, Edith Wolff and I wanted to organize a scientific symposium honoring him, but he adamantly refused.

In spite of his modesty and humility, I would like to say a few words on his scientific achievements. Dr. Folk obtained his Ph.D. in biochemistry and organic chemistry in Georgetown University and joined NIDR/NIH in 1952. He served as a research chemist for 44 years until his retirement in 1996. After retirement, he became an emeritus scientist and continued research activity at NIH until his bone fracture in early December. This shows how much he loved science and what a dedicated scientist he was. In his scientific career of over 50 years, he has made groundbreaking contribution in three major research areas. In his early career, he became the world's expert on proteolytic enzymes that degrades proteins in foods in the digestive system. Since the mid-1960s, he started a new project on an enzyme called transglutaminase. Jack again was a pioneer in solving the mechanism of this important enzyme. In 1980 when I joined his laboratory, we discovered a new cellular enzyme pathway and established its vital importance in cell growth. In these three areas of research, he was a pioneer and world's leading scientist. He is highly respected for his original and rigorous approach to the international scientific community and received several awards for his superior service and contribution.

He mentored a number of scientists from the USA and foreign countries and many of us regard him as a father of science. So, one may say that he has many international children and grandchildren in science. As a mentor, he has taught us not only science in the academic and technical sense, but also to be people of principles and integrity. He did this not by words, but by example. In science, there is fierce competition and high pressure to publish a lot by number, but he taught us not to compromise, not to follow the earthly trend, but to hold onto the ideals of finding the scientific truth and publishing high-quality papers.

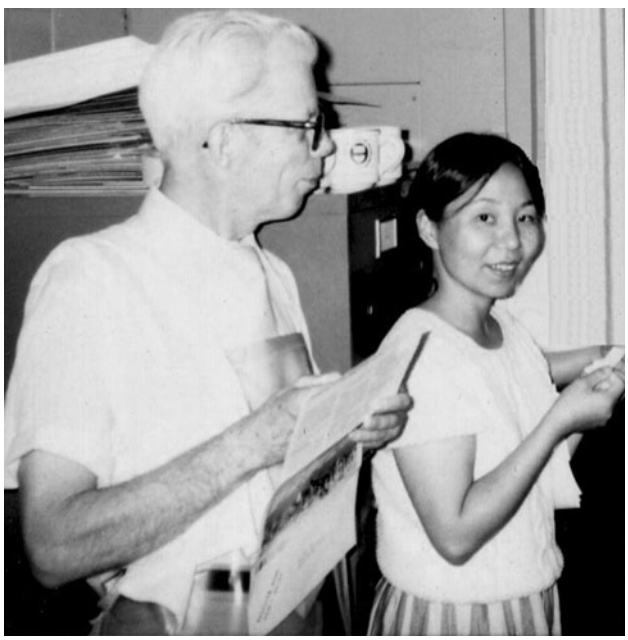

Fig. 6 Jack Folk and Myung Hee Park

Finally, I would like to add my personal gratitude to Jack. When I came to attend an interview for a postdoc position in his laboratory in 1979, Ron Chung told me that Jack was the nicest boss. Other than anything, I decided to work for the nicest boss without knowing that it would lead to a lifelong relationship. He was much more than a nice boss. He was a great mentor and a father of science to me. He and Mrs. Folk embraced me and treated me as their other child. He supported me for my tenure and promotion at NIH and constantly provided me with moral and emotional support to stand firm in our belief of basic science (Fig. 6).

I would have not come this far without his support, encouragement, and friendship, for which I am infinitely grateful. He has been one of the greatest blessings in my life and I thank God for him and pray that he rests in peace.

Edith Wolff

In the late 1970s, when transglutaminase activity had been shown in tissues, Jack became interested in exploring whether transglutaminase might be responsible for new cross-linking reactions in cells, especially in situations where an increase in transglutaminase activity had been observed, such as lymphocytogenesis. He and Jim Schrode reported that polyamines, putrescine, spermidine or spermine, could act as acyl acceptors in vitro, at either one or both terminal amino groups, with guinea pig liver transglutaminase or clotting factor XIII to produce intermolecular cross-linking. In collaboration with Herbert Cooper, in the National Cancer Institute, he incubated mitogen-activated lymphocytes with radioactive putrescine and spermidine. A proteolytic digest of the total cell protein did show a single major peak of radioactivity of a radioactive compound that, upon ion-exchange chromatography, eluted at a time very close to that of γ-glutamylspermidine. Radiolabeling of this basic compound was clearly related to activation of lymphocyte cell growth, as it was very low in resting lymphocytes. They wrote this up and it was accepted by the J. Biol. Chem. However, a new postdoctoral fellow in the laboratory, Myung Hee Park, noticed that the elution time of the new peak did not exactly match that of γ-glutamylspermidine in the ion-exchange chromatographic pattern. Furthermore, its elution time did not change after acid hydrolysis, indicating that it was an acid hydrolysis-resistant amino acid, contrary to what would be expected for a γ-glutamyl spermidine derivative. They added a statement on the unknown identity of this new polyamine-derived compound to the paper before publication. In this same paper, they also reported about a radioactive protein of $\sim$18,000 Da and pI of 5.3 upon 2-D-electrophoresis analysis of the lymphocyte proteins. In following up on these observations, Myung Hee found a report by Tetsuo Shiba and T. Nakajima in Japan that described and chemically characterized a new basic amino acid in urine and brain digests, N^{ε}-(4-amino-2-hydroxybutyl)lysine, which T. Shiba called "*hypusine*"—the name was derived from **hy**droxy**pu**trescinely**sine**—assuming that it was a lysine modified by hydroxyputrescine. Myung Hee and Jack proved that the labeled compound in the lymphocyte protein was, in fact, hypusine, it was derived from spermidine, but not by a transglutaminase-catalyzed reaction, and that hypusine occurred only in one cellular protein. Later, with the collaboration of Herbert Cooper and others, they identified the hypusine-containing protein as a eukaryotic initiation factor, eIF4D, (now termed eIF5A). Jack and Myung Hee, and others to come in the laboratory, proceeded to work out the details of the two enzymatic reactions (catalyzed by deoxyhypusine synthase and deoxyhypusine hydroxylase) that form hypusine posttranslationally, and thus the whole field revolving around this unique and essential polyamine-derived basic amino acid was begun. Although Jack continued to be primarily involved in the study of transglutaminase-related projects, he also participated actively in the exploration of the details of hypusine synthesis and, especially, the mechanisms of the two enzymes involved, until, and after, his formal retirement in 1997. Jack's immediate laboratory was never very large, generally consisting of four to five fellows, often transients from other countries, and also involved collaborations with other laboratories at the NIH and elsewhere. For example, in addition to Myung Hee Park, who has been and still is the primary investigator in the hypusine studies, Alberto Abbruzzese did the early characterization of deoxyhypusine hydroxylase and Simone Beninati contributed to both the transglutaminase and hypusine areas showing that hypusine can be added to a protein by transglutaminases during the same time (1985–1995). Edith Wolff joined the laboratory in 1986 and characterized both deoxyhypusine synthase, in particular the role of NAD, and later the hydroxylase. Judith Jakus and Young Bok Lee synthesized numerous inhibitors of the synthase and determined the effects of these inhibitors on the enzyme and in cells. Young Ae Joe also contributed importantly by cloning the synthase and investigating the structural features of the eIF5A precursor. Meanwhile, collaboration with other laboratories, notably those of John Hershey at the University of California at Davis and Herbert Tabor at NIDDK, NIH, helped to establish that hypusine was essential for eIF5A activity and cell proliferation, and explored features of the hydroxylase reaction with Hartmut Hanauske-Abel at Cornell (later UMDNJ). In addition to his insights into enzyme kinetics and mechanism, Jack was an accomplished chemist. He synthesized many of the compounds that were studied, from deoxyhypusine and hypusine, to inhibitors for the

enzymes, and related peptides and intermediates. In fact, just before his untimely death he completed the synthesis of compounds critical for current studies on the modification of eIF5A and its bacterial ortholog, EF-P.

Enzo Cocuzzi

It has been a great honor and a privilege to have known and worked with Jack, a humble man of science who made important contributions to the field of biochemistry (Fig. 7). It was because of him that I was granted a postdoctoral visiting fellowship at NIH, for which I will always be grateful. Although I will never forget his total commitment and dedication to science, his affection and concern for all those who were given the opportunity to do research with him, and the unselfish sharing of his knowledge and experience with all of us, I will absolutely miss his wonderful sense of humor. He was and continues to be a true inspiration to me. So, I give you many thanks Jack, but most of all I thank you for the three-and-a-half years of professional relationship that I had with you and for allowing me to be myself in your laboratory.

Mary Lynn Trawick (*formerly Mary Lynn Fink*)

Jack Folk represented science at its best in terms of generous collaboration with other investigators. Many international researchers rotated through Jack's laboratory and he took special pleasure in promoting the careers of young scientists. Jack Folk was a scientist who accomplished a great deal by his steady productivity and diligence in experimental benchwork. Dr. Folk is irreplaceable and will be greatly missed.

I first came to Jack Folk's laboratory as a peptide chemist with limited experience with enzymes. My first actual laboratory experience was somewhat alarming, as I looked all over the crowded laboratory for the source of an electrical fire that turned out to be a cup of the laboratory's trademark tea—lapsang soochong with its characteristic smoky aroma (an acquired taste, and one that we all picked up). My initial project was a continuation of Jack's previous work to design and synthesize peptides to unravel the substrate specificity of tissue transglutaminase to shed some light on the requirements for physiological transglutaminase substrates—still a burning question. Jeff Gorman who arrived later made a major contribution in this area. My project changed direction as a result of a lunchtime discussion. Laboratory members often had lunch together in Jack's office. It soon became clear to me that beyond the pleasant small talk and interesting shoptalk, Jack was always thinking far ahead of the challenges of ongoing experiments. In one lunch session, Jack posed the question—What happens to glutamyL-lysine crosslinks formed by transglutaminases since they do not

Fig. 7 From the left, S. Beninati, E. Cocuzzi (*down*), and M. Piacentini (*up*) in Jack Folk's laboratory at NIDR, NIH (1984)

accumulate? My limited enzyme experience had included working with a kidney lysine deacetylase investigating lysine protection in peptide synthesis (with the late Professor Miklos Bodanszky), and I suggested that perhaps a kidney lysine deacylase would do the job. The next thing I knew, Jack had synthesized the isolated cross-link, *N*ε-(γ-glutamyl)-L-lysine, Ron (Soo Il) Chung had secured some rabbit kidney, and we were trying to quantify lysine release with dansylated reaction products with the new technique of HPLC. It was clear that lysine was released from the kidney homogenates, but difficult to quantify because we were limited in the buffers we could use on those early and very expensive columns and pumps for the HPLC. Life became much easier when Jack purchased an amino acid analyzer with a short column that was especially well suited for basic amino acid and polyamine analysis. The amines were reacted automatically post-column, on-stream with *o*-phthalaldehyde, and were very easy to quantitate. Edith Wolff, a longtime associate of Jack, was especially helpful with the analyzer and everything else in the laboratory. With Ron Chung's expertise, we were able to purify the enzyme to a point where it was stable frozen for long periods of time, and to separate it from an enzyme that catalyzed a closely related reaction, gamma-glutamyl cyclotransferase. Jack who diligently read the literature knew that we had to determine not only if the activity we had found was a lysine deacetylase, but we had to prove that the enzyme was not gamma-glutamyl cyclotransferase, an enzyme that is part of the glutathione metabolism and acted on gamma-glutamylamino acids. Jack methodically and efficiently synthesized a series of gamma-glutamylamines including ones that could probe the specificity of the enzyme activity. We demonstrated that this new enzyme, which Jack called gamma-glutamylamine cyclotransferase, was indeed a separate enzyme from gamma-glutamyl cyclotransferase, and that its specificity was complementary to downstream metabolism of transglutaminase-catalyzed products (after protein digestion). This included gamma-glutamylpolyamines since a number of researchers, including Simone Beninati who I met when he rotated through Jack's laboratory, had demonstrated the importance of polyamine incorporation into proteins. It was an exciting time in the Folk laboratory, Myung Hee Park, a new staff fellow, started out investigating glutamyl-lysine cross-links in proteins with radiolabeled lysine and ended by discovering with Jack the role of hypusine in eIF-4D. It was a privilege to work in the Folk laboratory—for the science and the scientists I met during this time.

A tribute to Jack Folk

Franco Carmassi

I met Jack Folk first at the NIH when I joined the Enzyme Chemistry Laboratory on 8 August 1980, under the Fogarty International Program.

Sponsored by Dr. Soo Il (Ron) Chung, I had planned some studies on factor XIII metabolism and the influence which lipoproteins might have on its catalytic properties. Unfortunately, few experiments made it clear that such a project did not promise anything good and then, together with Ron, I addressed a different program.

Ron and I had to work hard to purify alpha 2 plasmin inhibitor (the primary, fast inhibitor of plasmin) and to establish its kinetic properties. Alpha 2 plasmin inhibitor showed to be the best among the known protein substrates of factor XIIIa, which, at the moment of coagulation, catalyzes its covalent binding into fibrin according to a kinetic "burst and halt pattern", which confers fibrin with early stabilization against plasmin degradation. Following the end of my appointment at the NIH, I kept cooperating with Dr. Chung and visiting Jack's laboratory frequently. Ron and I described the "cooperative binding of fibrinogen with Glu-plasminogen" and investigated the mechanism of fibrin and fibrinogen degradation by leukocyte elastase in rheumatoid arthritis as model of "extravascular fibrinolysis".

I used to talk with Jack about my experiments and other matters of discussion, always finding the rigorous, competent and ironic teacher who impressed me since I had the privilege to know him. Concerning his career, I do not think Jack received the appreciation he deserved; maybe, he used to be too sincere, rigorous, unsuitable to play politics? In relation to this subject, I noticed that sometimes, talking with him, he could not conceal a sort of disappointment.

To pay a tribute to Jack I do not need to emphasize how bright a scientist he was, as his work first, and Dr. Chung, Dr. Park, Dr. Wolff and all his *alumnus* bore the witness of Jack Folk's greatness, rather I would like to remark how his honesty and talent mixed up to generate such an outstanding, irreplaceable scientist.