Cell. Mol. Life Sci.
DOI 10.1007/s00018-009-8789-z

Cellular and Molecular Life Sciences

Memories of a Senior Scientist

Self and non-self

Georg Wick

Section for Experimental Pathophysiology and Immunology, Laboratory for Autoimmunity, Biocenter, Medical University Innsbruck, Peter-Mayr-Straße 4a, 6020 Innsbruck (Austria), Fax: +43-512-9003-73960,
e-mail: georg.wick@i-med.ac.at

Received 11 December 2008; accepted 12 December 2008

The early years

Life has been good to me! This is true both looking back on my family, friends and private environment as well as reflecting on my professional career. The transition to Professor Emeritus on October 1st 2007, after having served as Chairman of the Institute of Pathophysiology at the University of Innsbruck, now Medical University of Innsbruck (MUI), since 1975, offered a unique opportunity to look back on my professional and personal life, and how each inform the other.

Despite being born in 1939 at the beginning of World War II, I nevertheless – at least in my perception – experienced a rather protected childhood. It only later became clear to me that I was privileged to have been born into an intellectual, liberal and cosmopolitan environment that was further extended when my father decided to send me to a College in the Engadin, a high-altitude Alpine valley in Switzerland. There I became integrated into a multicultural atmosphere and also fell in love with the fantastic natural habitat and its endless resources for all kinds of sports, one of my favorite daily past-times lifelong. As a matter of fact, during my scientific career, some of my best ideas for important experiments and new concepts seemed to arise during mountain biking, rowing or ski hiking. This period provided me with not only a solid educational background but also, more importantly, a sense of fairplay succinctly summarized by our cricket teacher, the Scotsman *Gordon Spencer: "winning without grimaces and losing without a wry face"*. I forged lifelong friendships there, and more importantly, was inspired by the outstanding natural sciences program, led by renowned entomologist and school headmaster Adolf Nadig (who had an amazing collection of beetles!), to make medicine my life's work. It is a direct reflection of the educational excellence of our college that I passed the Biology exam during my first year of Medical Studies in Vienna based only upon what I had learned in college without ever looking into a medical biology textbook. I initiated my medical studies in Vienna in 1958 and graduated 6 years later in 1964 after a most interesting medical school tenure – during which the signal event of my life occurred in meeting the woman who would become my wife, Traudi. This remarkable woman gave me five wonderful children (three boys and two girls), and a wonderfully supportive family that

encouraged me to pursue my hobby, i.e., medical research – a lifelong passion for which I even got paid. This period, when we were both students in Vienna, also laid the foundations for our joint interest in cultural activities, notably music, theater and other fine arts that, in addition to science and sports, has shaped our lives.

During my medical studies, I was very impressed by the textbook "Differential Diagnosis" by *Hegglin*, then Professor of Internal Medicine at the University of Zurich, Switzerland. After graduation, and on the occasion of a skiing trip to the Mont Blanc area with my new bride, Traudi, I passed through Zurich for a personal interview upon an invitation by Hegglin. He offered me a job, but only under the condition that I first spend 2 years as a postdoc in a theoretical medical research institute, preferably Experimental Pathology. Although as it turns out, this job never materialized, it was a decisive encounter in my professional life. Upon returning to Vienna, I first had to find out where the Institute of Experimental Pathology actually was, since it had not been mentioned as part of the regular medical curriculum. There I met *Adolf Lindner*, Professor and Chairmen of the Institute, who later became not only my boss, but also my fatherly friend. Starting in January 1965, I spent the next 2 years at this Institute, which I discovered to be very well equipped despite the difficult economic times. The first project assigned to me was an assessment of a newly developed diuretic, Furosemide, in young as compared to old rats. Unfortunately, my supervisor on this work turned out to be both incompetent and completely uninterested in my project, which might have discouraged some from further pursuing a scientific career. But life has its own rules, and both the decision to embark on Experimental Pathology as a general discipline and the good fortune of having started with a gerontologically orientated project turned out to be beneficial 25 years later when I became the founder and head of an Institute for Aging Research. In 1966, I decided to join the Immunology group within the Institute headed by *Carl Steffen*, a post-war pioneer in this discipline. In Steffen's laboratory, I met his laboratory chief, *Rupert Timpl*, who introduced me to the field of collagen immunology and was the first to show me how internationally competitive research really works. This fruitful collaboration lasted until Rupert's untimely death in 2005, interrupted only during my tenure in the United States from 1967 to 1970. It turned out that the basic immunological and biochemical expertise of Rupert and my own knowledge of general and experimental pathology were a perfect match. We developed the first antibodies against various types of collagens and the many different epitopes contained in/on these molecules. We demonstrated their physiological and pathological distribution and function and, with outside collaborators, discovered or co-discovered many new collagenous and non-collagenous connective tissue components, such as collagen type IV and its non-triple helically structured ("non collagenous") domain-1 (NC-1), which we (in collaboration with *George Martin* from the NIH) later identified as the relevant autoantigen in Goodpasture's syndrome. The non-collagenous molecules that we identified by immunological means included fibronectin (then cold insoluble globulin, CIG), laminin, nidogen and others [1–3].

My own experience in immunofluorescence and immunohistochemistry, acquired during my stay in Buffalo, NY (see below), gave us the opportunity to impressively visualize all these components in normal and pathologically altered tissues, such as dermatosparaxis (together with *Björn Olson*, now at Harvard University) and *Steffen Gay* (now in Zurich), together with his wife *Renate Gay*, who joined Rupert's group after an adventurous and dangerous escape from communist East Germany [4].

One of the pathological conditions that has always fascinated me is fibrosis. The foundation for this fascination was laid during my first forays in this area with Rupert. Its later ramifications were strengthened by communications with many other laboratories around the world, the leaders of which regularly met at Gordon Conferences on Collagen. The only adverse effect of my first 2 years with Rupert in Carl Steffen's Laboratory was a constant fishy smell, because he sent me to all Viennese fish stores to collect fish bladders as a rich source for type I collagen (then called "acid soluble collagen"). From 1966 to 1967, I also worked as an Intern at a peripheral Hospital for Internal Medicine in Vienna because I did not want to continue pure basic research without also having the invaluable perspective of some clinical experience. This was a most enlightening, interesting and humanly rewarding time, and I believe that I was a capable and compassionate practicing physician. I was especially fortunate that I had learned to inject and take blood in small experimental animals, which made the performance of these skills in human patients easy and painless. They respected my skills without realizing that giving painless injections was much less important than knowing what you actually injected. I later decided to return to basic research based on the perception that clinical medicine – at least at that time – was too empirical for a scientist who had been "spoiled" by first doing evidence-based research. However, I also learnt that clinical work required far less persistence and was more immediately gratifying than research in the inevitable moments of success, despite the tragic

failures that also occur. For a group leader in medicine, I have found that it is much easier to motivate colleagues working in a clinic than those engaged in basic research who have never enjoyed the experience of helping patients. To take advantage of these two complementary, but quite different, perspectives, I always found it helpful to assign two projects, or at least two facets of a given project, to each student or postdoc to minimize frustration: Since each high-risk project will encounter unforeseen obstacles or setbacks, it is encouraging to see sufficient progress in the other project. I have also avoided assigning more than one student and/or postdoc to the same project so that everybody has the feeling of intellectual responsibility for their "own baby".

A postdoc abroad

In the fall of 1967, I obtained a postdoctoral fellowship that allowed me to take Traudi and my first two children, Gregor and Veronika, to the Center for Immunology in Buffalo, a Center of Excellence founded by Ernest Witebsky at the Department of Microbiology and Immunology, State University of New York at Buffalo (SUNYAB). Ernest Witebsky, a German Jewish scientist who, with great foresight, emigrated to the US already in 1933, had established a large imperium of Microbiology and Immunology at SUNYAB that, at the time, represented the leading force in autoimmunity research worldwide. Although Witebsky had just retired as the Chairman of the Department when I arrived, he still had ample financial support to continue his work with a small group of three dedicated young postdocs, i.e., *Lasse Nielsson*, a Swedish colleague from the laboratory of Ochterlouny in Gothenburg, *Ole Werdelin*, from Copenhagen, Denmark, and myself. Together with administrative and technical personnel, we formed the core of the Center of Immunology that was meant to bring together scientists from the outstanding immunological community in Buffalo. The biannual Convocations on Immunology organized by the Center of Immunology always brought the worldwide leaders in our discipline to Buffalo. For me as the youngest postdoc, this was an invaluable and critical opportunity to start networking, which later proved to be so important not only for myself, but also for the members for my group. I was honored to be in the company of such pioneering scientists who were making seminal contributions to the field. I met *Milan Hašek*, the discoverer of immunological tolerance in the chicken system (who personally showed me his ingenious parabiosis technique), who barely missed receiving the Nobel Prize for this work. The man who was awarded the Nobel Prize for this immunological topic, *Sir Peter Medarwar*, was also a speaker at a Convocation and simultaneously demonstrated allotransplant immunity and tolerance in mice. My time in Buffalo was obviously the most decisive period in my early scientific life, especially since Ernest Witebsky graciously abandoned his understandable reservations against everything that came from the German-speaking world: I was apparently the first postdoc with whom he started to speak German again! We developed a very close personal relationship and I enjoyed many evenings in his home and long discussions of our common scientific projects on autoimmunity, particularly the failure of the immune system to distinguish "self" from "non-self". This is a path I have deviated from only occasionally. Upon my arrival in Buffalo, he assigned a project to me that dealt with the elucidation of a Hashimoto-like autoimmune thyroiditis in chickens that had been observed by *Randy Cole*, a geneticist at the Veterinary College in Ithaca, NY. Randy first brought these birds to Witebsky, the "king of autoimmunity", because he rightly felt that he might have developed a new animal model for thyroid autoimmunity. I was initially disappointed that I would be working with chickens instead of soaring within eagles and saving human lives, but within 2 weeks I was fascinated by this model, the so-called Obese Strain (OS) of chickens, and these birds determined the next 15 years of my scientific career in two ways: I became a fairly good expert in autoimmune disease in general, and autoimmune thyroiditis in particular, and I acquired considerable knowledge of developmental and comparative immunology with a focus on avian immunology.

These were the times when *Robert Good*, then still at Minneapolis, Minnesota, developed the B-T cell concept based on his unique gift of incorporating experimental and clinical data into the formulation of new theories. Since *Max Cooper* and other members of Bob's Group regularly performed *in ovo* bursectomies and thymectomies in chicks on the day of hatching, Witebsky sent me to Minneapolis to improve my techniques in this area. Working on the OS chicken project in the bustling scientific atmosphere in Buffalo resulted in what I consider to be two of my most important scientific achievements: (a) We were the first to show that neonatal thymectomy of OS chickens surprisingly resulted in the development of the most severe form of thyroiditis [5]. More detailed analyses of this phenomenon, which continued until well after I returned to Austria, suggested that there were two types of T cells, i.e., the effector cells that contributed to the autoimmune destruction of the thyroid, and "controlling T cells" that were able to suppress the

former. We hypothesized that these "controlling T cells", now designated as regulatory T cells, were destined to leave the thymus during ontogeny later than the effector cells, and were therefore removed by early thymectory, leaving the effector T cells in the periphery unsuppressed and thus able to deploy their destructive potential. This work was cited by subsequent authors, e. g., *Shimon Sakaguchi*, who repeated the thymectomy experiments in rodents. However, due to the fact that we made our discovery in the chicken system, which is not so widely used as an animal model of human disorders, this finding did not receive the recognition we humbly believe it deserved. (b) We also produced the first anti-B and anti-T cell sera by immunizing turkeys with chicken thymocytes or bursa lymphoid cells, respectively, and using extensive cross-absorption procedures [6]. These polyclonal sera not only proved to be specific *in vitro* [7, 8], but could also selectively suppress T and B cell reactivity *in vivo* and consequently prevent spontaneous autoimmune thyroiditis in OS chickens [9].

Coming from a country with rather old fashioned traditions of academic structures, the lack of hierarchy in seminars and scientific meetings (notably at the annual FASEB Meetings in Atlantic City) and the openness of the American group leaders and chairpersons towards their postdocs were perhaps the most significant facet of the culture shock that I experienced in the US. This was even more evident since we spent the irrational revolutionary late sixties in the States with all the unrest on university soils that later spilled to the rest of the world. The foreign postdocs in our Department were, however, too conscious of the fact that our stay in the US was only temporary to participate in the turmoil that took place at SUNYAB and that we were responsible for the good use of our fellowships by getting the maximum intellectual harvest from our unique association with a truly world-class scientific community.

Finally, our stay in the US also forged an everlasting love for this country and its way of life that was further augmented by the birth of our third child, Natalie, adding an American citizen to our family.

The unexpected premature death of Ernest Witebsky in the fall of 1969 was not only a blow to the Center of Immunology in general, but also to his small group of collaborators in particular. His young postdoctoral fellows were deprived of a truly stellar mentor and we all had to stand alone after returning to our home countries. I therefore never had the good fortune of relying on an outstanding scientist or teacher as my mentor, a fact that has made me appreciate the critical service a good mentor provides and I wanted to provide that to my own students. In addition to trying to convey the message that good science relies on the three pillars of "innovation, diligence and passion", I always also tried to teach my students "the art of losing", in Gordon Spencer's spirit, and to be tolerant of other scientist, defining tolerance as the often uncomfortable feeling that the other person may be right after all.

The atmosphere between students and mentors should be one of mutual respect and acceptance. For the mentor it is, of course, the ultimate reward to have the student surpass the teacher in their given field. In science, as in other professional fields, it is always important to ask "why do we not finish this project" rather than "why do we carry on with this project"? In other words, the determination of appropriate and logical break-off points, in my view is one of the most important and difficult tasks of a group leader. As the head of a group of competent people, I often considered it my task not to tell them what to do (they usually may know better than I) but rather what not to do.

The years in Vienna

Returning to Austria in 1970 was not easy. I had several offers to join the Departments of Internal Medicine, Pediatrics, or Immunology and General Experimental Pathology (Pathophysiology) at various Austrian Universities, but decided to return to my former home, the Institute for General and Experimental Pathology at the Medical Faculty of the University of Vienna. With written permission of Ernest Witebsky, I had organized the shipment of hatching OS chicken eggs to Vienna, and Adolf Lindner, with all his good connections, was able to provide space to raise a new colony at the Viennese Veterinary School. Originally, the veterinarians assigned a box in the horse stable to my project, so my chickens were kept between the stalls of two impressive white Lipizzan stallions. This situation later improved and we ended up having our own chicken room in the center of Vienna right next to the institute.

In 1969, the Austrian Research Fund (Österreichischer Fonds zur wissenschaftlichen Forschung – FWF) was founded as a very modest source of competitive grants for all fields of research. I filed my first successful grant application already from the US, and this was the beginning of a continuous succession of grants from this organization that has been the most important single factor for the establishment of scientific excellence in Austria after World War II. The FWF was not only decisive for my own scientific career, but for those of many young members of my group who were recruited on the basis of FWF-funded

grants. Their consistent support of science allowed me to establish a proper scientific school, and former members of my laboratory are now spread all over the world. Some will be mentioned in more detail below. From 1970 to 1975, I went through the academic ranks of University Dozent (Assistant Professor) and Full Professor in Vienna while building up my own Immunopathology Group focusing on autoimmunity and avian immunology. This was perhaps the most informal period of my scientific life, surrounded by a group of bright and dedicated collaborators with good senses of humor. The group consisted of my first technician, *Renate Steiner*, who not only played a central role in establishing the OS colony and continuing to produce the first anti-B and anti-T cell sera worldwide, as mentioned above, but also technically trained further postdocs, notably *Boris Albini*, *Konrad Schauenstein* from Austria as well as a former Buffalo acquaintance, *Roy Sundick*, from the US. Boris and Konrad were among the most intelligent and educated people I have ever met and their scientific brilliance combined with the fact that they were both semiprofessional musicians created a unique laboratory atmosphere. In spite of all the hard work, there was enough leisure time for all of us. However, I personally never met a student or postdoc later enjoying an outstanding career who did not also show up in the lab on weekends. Boris was the first to differentiate lymphocyte subpopulations by means of the above-mentioned anti-T and anti-B cell antibodies using the newly developed membrane immunofluorescence technique [7, 8]. Konrad and Boris also soon discovered their interest in the methodological aspects of immunofluorescence, and the three of us started to organize Annual International Immunofluorescence Courses partly supported by the World Health Organization (WHO). These courses attracted a large crowd of young immunologists whom we often later met again as prominent leaders in the field. We were supported in these activities by a physicist, *Fritz Herzog*, from the scientific department of what then was the Viennese Reichert Microscope Company. Roy Sundick was the first to draw our attention to the fact that the target cell for an autoimmune disease, in this case the thyroid epithelial cell, deserved special attention and, from a genetic viewpoint, play an equally important role as the autoreactive immune system attacking this cell, as detailed below. He also showed that the extent of iodination of thyroglobulin determined its autoantigenic potential [10, 11]. This is also the reason why autoimmune thyroiditis is the most important thyroid disease in the US (*vs* thyroid cancer in Europe): In the US, iodine is added to salt, bread and water, thus people are ingesting three times as much iodine as Europeans, where it is only added to salt. The importance of the susceptibility of the target cell to the autoimmune attack was later proven in detail in genetic experiments conducted together with *Karel Hala.*

In 1975, I became Professor and Chairman of the Institute for General and Experimental Pathology (later renamed Pathophysiology) and Immunology at the Medical Faculty of the University of Innsbruck in the mountains of Tyrol. Konrad Schauenstein was my deputy chairman, while Boris left for the US to continue his career in Buffalo and join his family. Just before moving to Innsbruck, our last two children, the twin boys Nikolaus and Marius, were born. Both are now both MDs specializing in pathology and radiology, respectively. It gives me great pleasure to now collaborate on joint research projects with each of them.

The years in Innsbruck

The Institute for General and Experimental Pathology in Innsbruck turned out to be attractive for young postdocs and students from all over the world. I recently counted all the master and doctoral theses performed during the 33 years of my chairmanship and came up with the amazing number of 190. We were also able to recruit a large number of very gifted postdocs, many of whom went on to successful scientific, clinical or business careers either in Austria or abroad. My greatest professional pleasure from the time moving from Vienna to Innsbruck until today is the optimal mentoring of my scientific collaborators as well as the members of the administrative and technical staff. Members who joined the institute as students or postdocs and later became internationally renowned figures in science include *Beatrix Grubeck-Loebenstein* (Innsbruck), *Guido Krömer* (Paris), *Josef Penninger* (Vienna), *Quing Bo Xu* (London*), Richard Boyd* (Melbourne), *Reinhard Fässler* (Munich), *Georg Schett* (Erlangen), *Stefan Dirnhofer* (Basel), *Yping Zou* (Shanghai), *Lukas Huber*, *Reinhard Kofler*, *Peter Berger*, *Pidder Jansen-Dürr*, *Andreas Villunger* and *David Bernhard*, all currently in Innsbruck, and many more. The achievements of these and other former members of our group are easily evident upon an internet literature search.

The only academic member of the former Institute in Innsbruck who stayed on after my appointment was *Siegfried Schwarz*, perhaps the most knowledgeable endocrinologist in Austria and with whom we edited two highly successful Pathophysiology textbooks. Together with Siegi, we not only performed excellent endocrinological research but also built a highly specialized diagnostic laboratory for clinical immu-

nology, allergology and endocrinology that not only provided a crucial link to clinical medical practice, but also served as financial support for the institute.

The years in Innsbruck were characterized by a tremendous drive in research and teaching, and also by exuberant personal friendships between the members of the group. Scientifically, we concentrated on autoimmunity, developmental and comparative immunology and immunoendocrinology. We were lucky to be able to rely on a perfect infrastructure of highly motivated and competent technical personnel as well as administrative expertise. Most importantly, *Hermann Dietrich*, a veterinarian who specialized in experimental animal medicine, took perfect care of our precious chicken lines.

In the field of autoimmunity, the intuitive work of *Richard Boyd* and *Guido Krömer* gave credence to the fact (mentioned above) that certain thymocyte subpopulations had an immunosuppressive effect [12, 13]. In cooperation with the group of *Ivan Roitt* (London) and a joint graduate Student from Brazil, *Lain Pontes de Carvalho*, we provided experimental proof for the original idea mentioned above that T effector cells leave the thymus earlier than the regulatory cells, thus explaining the thyroiditis-enhancing effect of neonatal thymectomy [9].

In continuation of Roy Sundick's work, the genetic experiments of *Karel Hala*, a refugee from communist Czechoslovakia, opened a new outlook on the development of autoimmune diseases in general: in contrast to most other groups worldwide, we not only emphasized the autoreactivity of the immune system, but discovered that a genetically encoded target cell susceptibility to the autoimmune attack is most important for the development of both organ-specific and systemic autoimmune diseases, a concept that has governed all our research in this field to this day [14].

In the fields of endocrinology and immunoendocrinology, respectively, the interaction of highly competent immunologists and endocrinologists bore fruit: Reinhard Kofler was the first to introduce the production of monoclonal antibodies to Austria. He established hybridomas that produced antibodies specific for human glycoprotein hormones [luteinizing hormone (LH), follicle-stimulating hormone (FSH) thyroid-stimulating hormone (TSH) and human chorionic gonadotropin (hCG)] and used this new tool to visualize the production site of these hormones [15]. Later, Siegfried Schwarz, together with Peter Berger, extended this line of research and gained international recognition by monoclonal antibody-based epitope mapping of glycoportein hormones [16]. These maps also formed the basis of the development of highly specific, sensitive and practically applicable immunoassays. An interesting sideline of these studies was the critical proof by Peter Berger and *Stefan Dirnhofer* that the hCG-based anti-fertility vaccine sported by the WHO could not work [17]. These results finally led to the decision by the WHO to abandon this project. A most important discovery during this area was made by Konrad Schauenstein, together with *Reinhard Fässler*, showing that the immunoendocrine communication *via* the hypothalamo-pituitary-adrenal (HPA) axis was malfunctioning in the OS model for autoimmune thyroiditis [18], an observation later corroborated by many other authors and ourselves, also in experimental rodent models in cooperation with *France Haour* (Institut Pasteur, Paris) and *Alberto Panerai* (Milano).

These data nicely complemented our new, above-mentioned concept for the development of autoimmune diseases, i.e., their dependence on the presence of two sets of essential genes coding for autoreactivity of immune system on one hand and target organ susceptibility on the other. This genetic constellation leads to a baseline expression of the disease that can then be further modulated by other factors, such as endogenous steroid hormones (influencing the immune system) and iodine (determining the autoantigenicity of thyroglobulin in the target cell). Together with Karel Hala and one of his students, *Nikolaus Neu*, we were able to show that in the OS, in contrast to, say, lupus, only a relatively small number of genes is involved in the development of thyroiditis; three to four dominant genes coding for autoreactivity of the immune system and one recessive gene being responsible for target organ susceptibility [19]. Since the chicken genome is now sequenced, the exact identity of all of these genes will be unveiled in the course of an ongoing cooperative study with the groups of *Olli Kämpe* and *Olof Ekwall* from Uppsala, Sweden.

In subsequent experiments combining our knowledge in developmental and comparative immunology with the endocrinological expertise, *Oskar Lechner* and the Brazilian postdoc *Antonio Oliviera dos Santos* demonstrated the extra-adrenal synthesis of glucocorticoid hormones in the thymus [20], an unexpected discovery that formed the basis for extensive future investigations by *Jan G. Wiegers* on the effect of these hormones on thymocyte maturation, differentiation and selection in mice.

In technically demanding experiments, *Josef Penninger* [21, 22] showed that positive selection in the thymus takes place within so-called thymic nurse cells, i.e., thymic epithelial cells harboring immature T cells. Among the many methodological inventions developed in the course of our scientific projects was the discovery of a low bleaching immunofluorescence excitation device by Konrad Schauenstein and the

biophysicist *Günther Böck* using short laser flashes [23] instead of continuous excitation. This constituted a significant technical improvement that complemented our earlier invention of the multichannel micropipette [24].

In the late 1980 s and early 1990 s, our interest in developmental and comparative immunology turned from investigations of T cell development to the other end of the chronological spectrum, i. e., age-related changes of immune reactivity. Again applying a multidisciplinary approach, we successfully combined the known facts on age-related alterations of the lipid metabolism with our immunological expertise. This work was begun by *Karin Traill*, an experienced senior postdoc from the UK, who worked with me and supervised a promising medical student, *Lukas Huber.* Lukas is one of the success stories from our institute mentioned above. Upon finishing his thesis, he went to Germany and Switzerland before returning to Vienna. He is now Professor and Chairman of Cell Biology at the Medical University of Innsbruck, and also acts as the Managing Director of the Biocenter of which I am still a member. This is a perfect example of the closing of a circle. Karin and Lukas together with Günther Böck and *Hugo Wolf*, who contributed their expertise in Physics and Biochemistry, respectively, were instrumental in laying the foundations for our later large group in aging research. They clearly showed that age-dependent alterations of cholesterol metabolism entailed a high plasma membrane viscosity of white blood cells, including lymphoid cells, that correlated with a decreased mitogenic and antigenic response. Fluidizing plasma membranes again by removing free cholesterol and decreasing the molar ratio of cholesterol to phospholipids led to a "rejuvenation" of immune reactivity [25].

Again, several important, and in this case also clinically relevant, methodological innovations emanated from this period of our research. These included the first demonstration of lipoprotein receptors on living (lymphoid) cells by the use of fluorescently labeled lipoproteins, and the first measurements of plasma membrane viscosity on a single cell level, both applying flow cytometry [26]. As a matter of fact, we had a long controversial discussion with the editors of the Journal of Biological Chemistry until they understood that, in contrast to the Nobel Prize winning radiolabeling technique of Goldstein and Brown using purified membrane preparations, we were performing our experiments on *living* cells. It is, of course, rewarding to see that this approach is now the standard worldwide over earlier methods [27].

In the late 80 s, during one of my visits to China, I met and recruited *Qingbo Xu,* a promising young PhD working on an atherosclerosis project at the Beijing Medical College. Qingbo, with his charming wife *Yanhua Hu*, became my closest collaborator for the next 12 years. During this period, he not only obtained his medical degree at the University of Innsbruck and was promoted to the position of an Associate Professor but, surprisingly and although not being a Ping-Pong player, was granted Austrian citizenship, which later allowed him to settle down freely within the European Union. Qingbo is now a Professor of Vascular Biology at Kings College, London, where he successfully leads his large own research group.

In 1975, I was the youngest Chairman of a Department at a Medical Faculty in the whole of Austria. Negotiating the conditions of my appointment with the Federal Ministry of Science and Research as a scientist inexperienced in academic management turned out to be difficult and, in hindsight, I was much too modest in my understanding of what would be required, and subsequently in my demands. I was, however, able to introduce a short paragraph into my contract that allowed me – to my knowledge the only professor in Austria so allowed – to go on a one semester sabbatical every fourth year. I regularly took advantage of this privilege by going to what was then considered the Mecca of Immunology, the Basel Institute for Immunology (BII) founded and supported by Hoffman-La Roche. My first of three sabbaticals at the BII took place under the directorship of the Nobel Laureate *Niels Jerne*, the next two under the auspices of its new director and now my long-term friend, *Fritz Melchers.* I took these sabbaticals as an opportunity not only to broaden my scientific horizons, but also to stay abreast of new techniques in demand for our ongoing research projects. I spent my first sabbatical in the group of *Auli* and *Paavo Toivanen*, two eminent avian immunologists from Finland who had invited me to test our specific anti-chicken B and T sera using the newly available fluorescence-activated cell sorting (FACS) technique. Back in Innsbruck, we then got the first such machine in Austria that was, and still is, successfully run by Günther Böck. During my second sabbatical at the BII, I was invited by *Ivan Levkovits* (who earlier had developed the limiting dilution technique) to make use of his fantastic multistage 2D-gel electrophoresis setup to study possible differences between lysates of OS and normal chicken thyroid glands as a basis for the target organ susceptibility that we had observed in earlier experiments. This was my introduction to proteomics, a field of research that had increasingly come into the center of interest in our lab, especially regarding our investigations on the immunology of fibrosis, mentioned below. During my third and last stay in Basel, I joined the laboratory of *Louis du Pasquier*, an expert in amphibian immunology. There, I completed my morpholog-

ical assessment of thymic nurse cells by showing that they also existed in frogs, but that there was a clear-cut decrease of the number of intrathymic nurse cell lymphocytes from mice over humans and chickens to amphibians. In addition to the scientific harvest of these sojourns in Basel, it also became very clear that excellence in research can be achieved in small groups in an institution with flat hierarchies provided that one could recruit the brightest people from all over the world who could then exclusively concentrate on their research projects, supported by an efficient infrastructure and without having to continually divert attention, time and resources to preparing applications for competitive grants. I have never again experienced an atmosphere that paralleled the intellectual stimulation encountered at the BII. During the first 10 years of its existence, three Nobel prizes emanated from this outstanding institution, i.e., *Niels Jerne*, *Georges Köhler* and *Susumu Tonegawa.* Fritz Melchers was the optimal choice to succeed Niels Jerne as the head of the institute, and former members of the BII are now spread all over the world in important research positions. It is difficult to understand why Hoffmann-La Roche decided to close down this jewel in 2000.

After successfully completing my first 15 years as the Chairman of Pathophysiology and Immunology at the University of Innsbruck, the Austrian Academy of Sciences approached me to establish an Institute for Biomedical Aging Research under its auspices, also in Innsbruck. This was not only a distinctive honor, but also a very timely proposal, since gerontological research was consistently gaining momentum internationally in general and in our own group in particular. The Institute for Biomedical Aging Research (IBA) is housed in a beautiful building that was adapted for research purposes.

After an intensive recruiting phase, it was opened in 1991 and remained under my directorship until 2003. Surprisingly, the IBA remains the only Institute of this kind in the German-speaking world. It was organized into four sections: Immunology (led by *Beatrix Grubeck-Loebenstein*), Endocrinology (led by *Peter Berger* from the previous Immunoendocrinology Group at the University), Molecular and Cell Biology (led by *Pidder Jansen-Dürr*) and Pathology (led by myself). The IBA continues to be completely independent from the Medical School of the University of Innsbruck, but enjoyed close academic ties through my joint appointment as its director, and by extensive collaborative efforts at both the scientific and teaching levels. In my group, Qingbo Xu became the leading figure, and attracted many compatriots from China. After a short period continuing our research on the role of an altered lipid metabolism in the age-

depended decline of immune responsiveness, we decided to switch all our personnel and financial recourses to a new project, i.e., the Immunology of Atherosclerosis, which became a central theme for the next 15 years. Based on *in vitro* work, animal experiments and longitudinal as well as cross-sectional studies in humans, we developed our new "autoimmune hypothesis" of atherosclerosis [28]. In essence, this hypothesis was developed based on the known fact that inflammatory processes occur in atherosclerotic lesions. Our interest, however, was exclusively focused on the *very first, clinically inapparent stage* of the disease and our discoveries in this area were based on our broad knowledge of pathophysiology and cardiovascular diseases in general, and our background in immunology and autoimmunity in particular. We showed that classical atherosclerotic risk factors, the well-proven atherogenic role of which we, of course, did not deny, first act as endothelial stressors that induce the expression of a stress protein, heat shock protein 60 (HSP60), that is transported to the endothelial cell surface and there acts as a "danger signal" for preexisting adaptive and innate anti-HSP60 immunity. HSP60 is a phylogenetically highly conserved molecule. Thus, an over 97 % homology exists between HSP60 of different bacterial species and there is still an over 50 % homology between bacterial and eukaryotic HSP60, which at certain domains of the molecule even exceeds 70 %. Every healthy person has protective adaptive and innate immunity against microbial HSP60 as well as *bona fide* autoimmunity against biochemically altered autologous HSP60. When this molecule appears on the surface of endothelial cells injured by classical atherosclerotic risk factors, this danger signal triggers an

attack of preexisting anti-HSP60 immune mechanisms on endothelial cells, subsequently leading to the first, still reversible, inflammatory stage of the disease [29]. An interesting byproduct of this period of research was the discovery of the vascular-associated lymphoid tissue (VALT), i.e., mononuclear cell infiltrations at arterial branching points that can be found in babies and young children as well as adults, and are accompanied by a dense Langerhans cell-like network of vascular-associated dendritic cells [30]. The VALT seems to fulfill similar functions as the mucosa-associated lymphoid tissue (MALT), i.e., protecting bodily surfaces, in this case the inner vascular surface, from potentially harmful exogenous and endogenous agents.

The many invitations to prestigious meetings, such as Gordon Conferences, Keystone Symposia, etc, reflect the impact of our research in this field.

Our overall project on the "Immunology of Atherosclerosis" was again the basis of numerous medical and PhD theses, postdoctoral projects, academic appointments and successful grant applications, including several very large recent grants that allow me as Professor Emeritus to continue my research with a strong group of young, international, eager collaborators. "The immunology of Atherosclerosis" also was the springboard for many successful academic careers of former collaborators of my group in addition to Qingbo Xu, such as Georg Schett, now Professor and Chairman of Rheumatology at the University of Erlangen, Germany. An especially close cooperation in this area developed with the groups of *Josef Willeit* and *Stefan Kiechl* from the Neurological University Clinic in Innsbruck within the framework of their prospective atherosclerosis prevention study conducted in the little town of Bruneck in Southern Tyrol (Italy), just across the border from Austria. Becoming part of this so-called "Bruneck Study" not only allowed us to show that our concept translated from animal models to human patients, but also provided the gateway to its successful application to the prevention of atherosclerotic disease in both an elderly population and in young cohorts [31]. In recent years, we also put great emphasis on the role of cigarette smoke as a most important stressor of endothelial cells making them a target for an autoimmune attack [32]. From our side, a dedicated group of young scientists, *Bernhard Metzler*, *Gunda Millong*, *Michael Knoflach*, *Blair Henderson* and *David Bernhard*, were instrumental in the great success of this project. For the many national and international cooperation partners, coauthors and friends engaged in our atherosclerosis project, *Yehuda Shoenfeld* at Tel Hashomer from Israel, is an excellent representative examples.

During the planning, establishment and running of the IBA, I was confronted with serving two scientific management cultures, i.e., a Medical Faculty from a Federal University and the Austrian Academy of Sciences as an independent, non-profit organization. In contrast to the university, where good professional management was often hindered by science administrators and academic members who, due to a lack of individual scientific success, chose to become influential *via* participation in various Committees, the Academy supported lean management, short decision pathways, gentlemanly interactions with the directors and employees of its Institutes combined with a good sense of intellectual competition. The spiritus rector of the IBA and the Chairman of its Scientific Board was *Hans Tuppy* who somehow, and at first unconsciously, influenced my entire professional life from being my teacher in Biochemistry in Medical School to acting as the Dean of the Vienna Medical school and then the Rector of the University of Vienna, President of the Austrian Academy of Sciences, President of the FWF and even Federal Minster of Science and Research. This is perhaps a good occasion to thank him for his personal and scientific advice during many stages of my life. I would also like to thank the former President of the Austrian Academy of Sciences, *Werner Welzig* and as well as its successive Secretaries General *Karl Schlögl* and *Herbert Mang*, for their continuous interest in, and support of, the IBA, despite their not representing the natural sciences in general and medicine in particular.

Back in Vienna as a research manager

In 2003, a high caliber search committee, again headed by Hans Tuppy, proposed me as a candidate for the presidency of the FWF, and I made a principal decision that in some ways conflicted with my overall plan for the rest of my academic life. I would now spend part or all of this time as a scientific manager, albeit of the most prestigious organization in Austria that supported all basic research in all disciplines of the humanities, from natural and technical sciences to biology and medicine. In principle, the position of the president of the FWF is an honorary job considered to require a 50% time commitment. In my case, an additional complication was the commute from Innsbruck to Vienna and staying there at least 3 days per week. I finally decided to accept the position after consulting with my wife and my children, the members of my Department and my own research group. As a first action after my election, I stepped down as the Director of the IBA and as the head of the Experimental Animal Unit at the Innsbruck Medical School.

In addition, the Dean of our Medical School and Rector of the University of Innsbruck granted me exemption from my heavy teaching obligations. It was, however, again *Hans Tuppy* who advised me not to completely abandon research, and so I started working 7 days a week for the next 3 years, dividing my time between research and science management.

This was perhaps the most interesting time of my academic life since I was confronted with all different scientific fields and their excellent proponents on a National and European level. The most surprising experience, however, was the completely un-Austrian efficiency, strict impartiality and professionalism of all members of this organization, ranging from the telephone operators to the Section Leaders and the Secretary General, *Gerhard Kratky*. The latter I was lucky enough to recruit for this important job, and he assisted me both with the internal reorganization of the FWF administration and the external representation, including financial negotiations with the relevant ministries. I was gratified to have the excellent qualifications of the Austrian civil servants confirmed in their dealing with matters of basic and applied research, but I was surprised and disappointed by the scientific incompetence of the ministers involved in these issues. They had never heard of the recipe of *Vandever Bush*, the science advisor of President *Franklin D. Roosevelt* who set the stage in the US by stating that "support of basic research will entail economic success". In contrast, during my term as president of the FWF, I had the impression that in Austria "building a successful industry was considered the basis for being able to afford the luxury of funding basic research". Another, unexpected experience during my term as the FWF President was the pressure exerted by politicians and their staffs, ranging from attempts to influence decisions about scientific projects to bluntly connecting funding of the FWF with political issues. However, after a few months of scrutiny and meticulous note-keeping about such interference, it became clear to everybody that these interventions were counterproductive and I was not bothered further.

A special upshot of the term of my presidency was the increased representation of Austrian science in general and the FWF in particular on the European platform. These contacts were most effective *via* an organization called European Heads of Research Councils (EUROHORCS), in which general research strategies with a focus on funding policies were discussed on a European level. For me, these encounters were both interesting and enlightening, the latter because I recognized that the FWF had a very privileged position in this European concert; although our budget was much too small in relation to Austria's ranking as among the most affluent countries in the world, we were the most politically independent organization. The FWF can spend its low budget in a completely autonomous way without considering political interference (in spite of the frustrating attempts mentioned above). Furthermore, we are the only European organization of its kind that sends out all research projects for expert review abroad rather than having the majority of the reviewing process take place within the national research community and unavoidable attendant bias. I have always summarized these specific characteristics of the FWF as its "five jewels", which are:

- full autonomy
- a bottom-up approach of research projects only
- an international peer review system
- quality as the only selection criterion for grant approval
- all disciplines treated equally

My most important achievement as a president of the FWF at this very difficult period was perhaps keeping it autonomous in the face of enormous political pressure to fuse the FWF with a second organization in our country that funds applied research. Incidentally, besides the ministries themselves, the Austrian Council for Research and Technology (Rat für Forschung und Technologie – RFT), an organization established to advise the government in matters of research policy, was the most ardent advocate of such a fusion, which reflected the unfortunate inclination of the RFT towards applied *versus* basic science. I am gratified that this position has changed and take some small pride in believing my resistance contributed to this development. In hindsight, I also seem to have been successful in propagating the idea that "culture" does not equal "art", but rather also comprises "science" and many other facets of human life. For this purpose I created a formula that, in a nutshell, encompasses the differences and similarities of art and science, notably the fact that both are driven by curiosity and thus have a common "surprise factor (SF)"

$[\text{culture} = (\text{art} + \text{science})^{\text{SF}}]$.

This and all other achievements were only possible because the scientific community gave me enthusiastic and constant support for which I am grateful.

Spending time in Austria's Capital also permitted me to enjoy all its cultural and social treasures again that I sometimes miss in the provincial town of Innsbruck, such as daily musical performances by top artists, abundant exciting theater premieres and exhibitions, not to mention the culinary treasures, such as a good

glass of wine at the famous Heurigen, where we often met our friends old and new.

Back to the lab and Professor emeritus

As mentioned, during this period of my life I was running both my own research laboratory in Innsbruck and the FWF in Vienna, and thus had the opportunity to experience both sides of academic activities, bench work and discussions with students and postdocs on one hand and science management on the other. When the time came to decide whether I should run for a second 3-year term and later possibly for a third period, this dual viewpoint played a critical role. It was quite clear to me that the part of my work at the FWF that I enjoyed most was that most directly relating to the research itself, e.g., evaluations of projects encompassing all disciplines with highly qualified experts in the Scientific Committee (Board), laboratory visits, discussions with presidents of Universities and the Academy of Sciences, meetings with the EUROHORCS and conferences on broader issues on the European level. In long and lonesome reflections, I came to the conclusion that, despite my fascination with science management, the day to day life in the laboratory is my real passion, and where I want to devote the rest of my active life as a scientist. I am grateful for the unique experience of having been part of the inner circle of national and European research management, and would not have wanted to miss becoming aware of the broader social and economic forces that can impact the conduct of science in significant ways. However, discussing new data with members of my group, sitting at the microscope, interpreting and photographing interesting immunohistological slides, writing scientific papers and engaging in lively critiques and discussions with my colleagues in the lab and at scientific meetings were closer to my heart. This life seems to be my true destiny, and thus I decided to not to run for a second term, but rather fully concentrate on the two topics of research that I am currently pursuing, "The Immunology of Atherosclerosis" and "The Immunology of Fibrosis".

Now in 2008, I can say that I did not regret my decision. An additional incentive for returning to Innsbruck was the fact that I was ripe for retirement at the end of 2007, so, in order to be able to continue doing research, I had to sit down and start writing grants again, which I did – keeping in mind the old principle "win a few, lose a few". Surprisingly, these endeavors turned out to be unexpectedly successful and I enjoy sufficient support for a group of about 8–9 people for the next 3–4 years, two thirds focusing on atherosclerosis research and the remainder on the immunology of fibrosis. With respect to atherosclerosis, my most successful grant application was one in which my role would be coordinator for an EU-funded project (10 million €) in Gerontology aimed at developing vaccines against atherosclerosis and rheumatoid arthritis based on the induction of immune tolerance against HSP60, i.e., the antigen that seems to be instrumental in both of these diseases, albeit *via* sensitization against different arthritogenic and atherogenic epitopes, respectively. *Blair Henderson*, a very bright long-term colleague in the lab from New Zealand specializing in genomic analysis of pro- and anti-inflammatory factors involved in atherogenesis, is instrumental in this large project together with nine other European groups.

In the field of fibrosis research, together with *Aleksandar Backovic*, a student and now postdoc from Serbia, we have developed and patented a test based on the "signature" of serum proteins deposited on the surface of silicone breast implants and other silicone-coated implants, which identifies patients prone to develop severe fibrotic peri-implant complications [33].

Also, as part of our research on the immunological basis of fibrosis, *Roswitha Sgonc*, a long-term member of my group, in cooperation with *Eric Gershwin*, University of California at Davis (UCD) is successfully continuing comparative studies in an avian model with a spontaneous disease resembling human scleroderma, the UCD-200 line of chickens [34]. First in this model, and then corroborated in human patients, we made the important discoveries that (a) autoantibody-induced endothelial apoptosis rather than perivascular mononuclear cell infiltration is the first pathogenetic process in this crippling disease, and (b) post-inflammatory fibrosis is due to a lack of the anti-fibrotic cytokine transforming growth factor β2 (TGFβ2).

In all our projects, the close proximity of our institute to the major medical clinics has proven to be an invaluable advantage, particularly in those concerning atherosclerosis and fibrosis. In addition to the neurologists mentioned above, *Raimund Margreiter*, a pioneer in transplantation medicine, and his group were perfect partners for our atherosclerosis project, and *Hildegunde Piza-Kratzer*, head of the Clinic for Plastic and Reconstructive Surgery of our university, and her crew proved to be an optimal complementation for our research on the immunology of fibrosis.

I now have a group of four postdocs, two graduate students, two technicians and a secretary, easy to oversee and enjoyable characters to spend time with. The lab is rather crowded, but crowding notoriously promotes interaction between scientists. As in the

past, we do basic research without losing sight of the inherent medical problems. I also run a diagnostic laboratory specializing in clinical immunology, allergology and endocrinology that provides a very effective tool for clinical problem solving. Teaching, writing and lectures about our scientific results to scientific and well as lay audiences have always been a passion of mine that I will continue to exercise in the future. Reviewing this essay, I wonder if I should have accepted the Editor's invitation. There is so much, and so many colleagues, friends and other important persons who have contributed to my scientific and personal life that I could not mention due to space limitations. I am especially fond of my technicians, the administrative manager of the Institute for Pathophysiology, *Pia-Ulrike Müller*, my competent loyal and efficient secretaries throughout the years, *Margit Kirchebner*, *Andrea Hohenauer*, *Anita Ender*, *Barbara Gschirr* and *Claudia Ram*. There are so many crucial people and seminal events that go unacknowledged in this article. On the other hand, I thought it was interesting that I completely forgot about memberships, official positions, awards, *etc.* – apparently not so important in a broader perspective. I also could not mention all the guest scientists who visited our lab over the years, and did not emphasize failures of my own or others despite the fact that we learn as much from our failures as our successes.

In the present stage of my life, the fact that I have been, and still am, involved in aging research and "successful aging" has turned out to be quite useful for the planning and performance of my own aging strategy. It gives me continuous pleasure to see my former collaborators thrive and become highly successful group leaders and professors in Austria and abroad. Finally, Traudi and I now enjoy our more independent and relaxed life, both with each other and with our ever enlarging family.

1 R. Timpl, I. Wolff, G. Wick, H. Furthmayr and C. Steffen, (1968) Immunogenicity and specificity of collagen VII. Differences between various collagens demonstrated by cross-reaction studies. J. Immunol. 101, 725–729

2 G. Wick, H. Nowack, E. Hahn, R. Timpl and E. J. Miller, (1976) Visualization of type I and II collagens in tissue sections by immunohistologic techniques. J. Immunol. 117, 298–303

3 G. Wick, H. von der Mark, H. Dietrich, and R. Timpl, (1986) Globular domain of basement membrane collagen induces autoimmune pulmonary lesions in mice resembling human Goodpasture disease. Lab. Invest. 55, 308–317

4 R. Timpl, G. Wick and S. Gay, (1977) Antibodies to distinct types of collagens and procollagens and their application in immunohistology. J. Immunol. Methods 18, 165–182

5 G. Wick, J. H. Kite, Jr. and E. Witebsky, (1970) Spontaneous thyroiditis in the Obese strain of chickens. IV. The effect of thymectomy and thymobursectomy on the development of the disease. J. Immunol. 104, 54–62

6 G. Wick, B. Albini and F. Milgrom, (1973) Antigenic surface determinants of chicken lymphoid cells. I. Serologic properties of anti-bursa and anti-thymus sera. Clin. Exp. Immunol. 15, 237–249

7 B. Albini and G. Wick, (1974) Delineation of B and T lymphoid cells in the chicken. J. Immunol. 112, 444–450

8 B. Albini and G. Wick, (1974) Proportional increase of bursa-derived cells in chickens of the Obese strain. Nature 249, 653–654

9 L. de Carvalho, G. Wick and I. M. Roitt, (1981) Requirement of T cells for the development of spontaneous autoimmune thyroiditis in Obese strain (OS) chickens. J. Immunol. 126,750–753

10 R. S. Sundick and G. Wick, (1976) Increased iodine uptake by Obese strain thyroid glands transplanted to normal chick embryos. J. Immunol. 116, 1319–1323

11 L. C. P. de Carvalho, J. Templeman, G. Wick and I. M. Roitt, (1982) The role of self-antigen in the development of autoimmunity in Obese strain (OS) chickens with spontaneous autoallergic thyroiditis. J. Exp. Med. 155, 1255–1266

12 R. L. Boyd, K. Hala and G. Wick, (1985) Interactions and quantitative analysis of immunoregulatory cells in the chicken thymus. J. Immunol. 135, 3039–3045

13 G. Krömer, K. Schauenstein, N. Neu, K. Stricker and G. Wick, (1985) *In vitro* T cell hyperactivity in obese strain (OS) chickens is due to a defect in non-specific suppressor mechanisms. J. Immunol. 135,2458–2463

14 G. Wick, K. Hala, H. Wolf, A. Ziemiecki, R. S. Sundick, M. Stöffler-Meilicke, M., DeBaets, (1986) The role of genetically-determined primary alterations of the target organ in the development of spontaneous autoimmune thyroiditis in Obese strain (OS) chickens. Immunol. Rev. 94, 113–136

15 R. Kofler, P. Berger and G. Wick, (1982) Monoclonal antibodies against human chorionic gonadotropin (hCG): Production, specificity, and intramolecular binding sites. Am. J. Reprod. Immunol. 2, 212–216

16 S. Schwarz, P. Berger and G. Wick, (1986) The antigenic surface of human chorionic gonadotropin as mapped by murine monoclonal antibodies. Endocrinology 118, 189–197

17 S. Dirnhofer, R. Klieber, R. De Leeuw, J. -M. Bidart, W. E. Merz, G. Wick and P., Berger, (1993) Functional and immunological relevance of the COOH-terminal extension of human chorionic gonadotropin β: implications for the WHO birth control vaccine. FASEB J. 7, 1381–1385

18 K. Schauenstein, R. Fässler, H. Dietrich, S. Schwarz, G. Krömer and G. Wick, (1987) Disturbed immune-endocrine communication in autoimmune disease. Lack of corticosterone response to immune signals in obese strain chickens with spontaneous autoimmune thyroiditis. J. Immunol. 139, 1830–1833

19 G. Wick, G. Krömer, N. Neu, R. Fässler, A. Ziemiecki, R. G. Müller, M. Ginzel, I., Beladi, T. Kühr and K. Hala, (1987) The multi-factorial pathogenesis of autoimmune disease. Immunol. Lett. 16, 249–257

20 O. Lechner, G. J. Wiegers, A. Oliveira-Dos-Santos, H. Dietrich, H. Recheis, M., Waterman, R. Boyd and G. Wick, (2000) Glucocorticoid production in the murine thymus. Eur. J. Immunol. 30, 337–346

21 J. Penninger, K. Hala and G. Wick, (1990) Intra-thymic nurse cell lymphocytes can induce a specific graft-*versus* host reaction. J. Exp. Med. 172, 521–529

22 J. Penninger and G. Wick, (1992) Thymic nurse cell lymphocytes react against self major histocompatibility complex. Eur. J. Immunol. 22, 79–83

23 K. Schauenstein, G. Böck and G. Wick, (1980) Short time bleaching of fluorescein isothiocyanate. A possible parameter for the specific binding of conjugates in immunofluorescence. J. Histochem. Cytochem. 28, 1029–1031

24 K. Schauenstein, G. Wick and H. Kink, (1976) The micro-membrane-immunofluorescence test: A new semiautomated technique based on the microtiter system. J. Immunol. Methods 10, 143–150

25 K. N. Traill, L. A. Huber, G. Wick and G. Jürgens, (1990) Lipoprotein interactions with T cells: an update. Immunol. Today 11, 411–417
26 L. A. Huber, Q. Xu, G. Jürgens, G. Böck, E. Bühler, K. F. Gey, D. Schönitzer, K. N., Traill and G. Wick, (1991) Correlation of lymphocyte lipid composition membrane microviscosity and mitogen response in the aged. Eur. J. Immunol. 21, 2761–2765
27 G. Jürgens, Q. Xu, L.A. Huber, G. Böck, H. Howanietz, G. Wick and K. N. Traill, (1989) Promotion of lymphocyte growth by the high density lipoproteins (HDL): physiological significance of the HDL binding site. J. Biol. Chem: 264: 8549–8556
28 G. Wick, M. Knoflach and Q. Xu, (2004) Autoimmune and inflammatory mechanisms in atherosclerosis. Annu. Rev. Immunol. 22, 361–403
29 Q. Xu, J. Willeit, M. Marosi, R. Kleindienst, F. Oberhollenzer, S. Kiechl, T. Stulnig, G. Luef and G. Wick, (1993) Association of serum antibodies to heat-shock protein 65 with carotid atherosclerosis. Lancet 341, 255–259
30 G. Millonig, C. Schwentner, P. Müller, C. Mayerl and G. Wick, (2001) The vascular-associated lymphoid tissue: a new site of local immunity. Curr. Opin. Lipidol. 12, 547–553
31 M. Knoflach, S. Kiechl, M. Kind, M. Said, R. Sief, M. Gisinger, R. van der Zee, H. Gaston, E. Jarosch, J. Willeit and G. Wick, (2003) Cardiovascular risk factors and atherosclerosis in young males ARMY study (atherosclerosis risk factors in male youngsters). *Circulation* 108, 1064–1069
32 D. Bernhard, A. Rossmann, B. Henderson, M. Kind, A. Seubert and G. Wick, (2006) Increased serum cadmium and strontium levels in young smokers: Effects on arterial endothelial cell gene transcription. Arterioscler. Thromb. Vasc. Biol. 26, 833–838
33 Backovic, H. L. Huang, B. Del Frari, H. Piza, L. A. Huber and G. Wick, (2007) Identification and dynamics of proteins adhering to the surface of medical silicones *in vivo* and *in vitro*. J. Proteome Res. 6, 376–381
34 G. Wick, L. Andersson, K. Hala, M. E. Gershwin, C. Selmi, G. F. Erf, S. J. Lamont and R. Sgonc, (2006) Avian models with spontaneous autoimmune diseases. Adv. Immunol. 92, 71–117