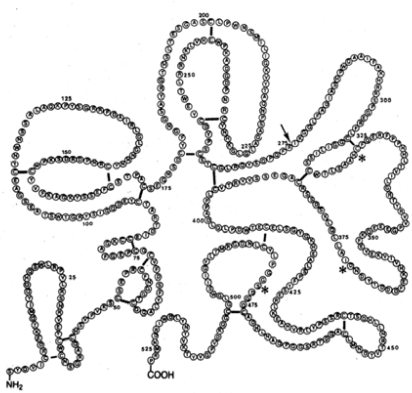
Désiré COLLEN



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An Anthology of Scientific Collaborations

Compiled at the occasion of his 65th birthday

Leuven, June 21, 2008

(*) structure of t-PA, adapted from Pennica et al., Nature 301, 214-221, 1983

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Foreword

Dear Colleagues and Friends,

Désiré Collen was born on June 21, 1943, and thus reached the official age of retirement this year. While a 65th birthday is a day for celebration and happiness, there is another – less pleasant – aspect to it. Our administration indeed requires that he resigns from all his official duties at the University at the end of this academic year. At this occasion, we have prepared this "Anthology of Scientific Collaborations" to recognize his research contributions on fibrinolysis, thrombosis and haemostasis. Many colleagues, as well from Belgium as from abroad, have collaborated with Désiré at a given moment in their scientific career. A list of all the non-Belgian collaborators of our laboratory at the University of Leuven in Belgium over the last 40 years is included in this booklet. As it was not possible to ask all of them for an account on their stay in Leuven, we have selected in total 40 past and present collaborators who published papers jointly with Désiré that received more than 100 literature citations. Of those colleagues 38 have kindly provided the present narratives and personal appreciations of their collaboration with Désiré. The picture that emerges speaks for itself: a great scientist, a visionary entrepreneur, a superb teacher, a delightful friend and above all a gentleman.

Having myself worked closely with Désiré for the past 30 years, it is my privilege to present a short historical perspective and personal account. In addition to his many other contributions to thrombosis, haemostasis and vascular biology, the landmark achievement has undoubtedly been the development of tissue-type plasminogen activator (t-PA) from a laboratory concept to a drug used worldwide for treatment of thromboembolic diseases.

Désiré's first experimental studies in the laboratory of blood coagulation, directed by Prof. Marc Verstraete and under the guidance of Guido Tytgat, in the early 1970's focused on prothrombin and plasminogen turnover. With the discovery (by our group and independently by two other groups) of α_2-antiplasmin, the fast-acting plasmin inhibitor, and the availability of highly purified proteins in the late 1970s, biochemical studies, mainly in collaboration with Bjorn Wiman, elucidated the molecular interactions between these proteins that regulate and control physiological fibrinolysis. A model was presented in a Plenary Lecture (Edward Kowalski Memorial Lecture) at the VIIth International Congress on Thrombosis and Haemostasis in 1979 in London. This model formed the basis of the concept of fibrin specificity of t-PA and stimulated great interest in its use for thrombolytic therapy.

A collaborative study with Alfons Billiau and Pieter De Somer in 1977 had revealed that malignant cells (sarcoma-virus transformed fibroblasts) secrete a plasminogen activator, which contributed to the malignant phenotype, but which remained unidentified at that time. Toward the end of 1978, Dan Rifkin from New York provided us with a cell line derived from a metastatic melanoma of a patient named Bowes, that subsequently turned out to be very efficient in secreting t-PA. We did, however, not succeed in purifying the t-PA

to full homogeneity. In October 1979, Dingeman ("Dick") Rijken joined us, and developed an efficient purification method. With this material, Dick Rijken, Marc Hoylaerts, Roger Lijnen, Irène Juhan-Vague and Christian Korninger clarified the mechanism and kinetics of plasminogen activation and developed quantitative assays. These data were present at the 5th Congress on Fibrinolysis in Malmo, Sweden, in 1980, where Diane Pennica from Genentech was present and proposed to clone and express the *t-PA* gene. This at that time major achievement was reported at the 6th Congress of Fibrinolysis in Lausanne, Switzerland, in 1982 and published in *Nature* in January 1983.

The thrombolytic effects of t-PA (melanoma) were first demonstrated in rabbits, in collaboration with Osamu Matsuo in 1980, and later in dogs with coronary thrombosis, in collaboration with Burton Sobel and with Frans Van de Werf. These studies in animal models were extended to recombinant t-PA, in collaboration with Herman ("Chip") Gold, Tsunehiro Yasuda, and Ik-Kyung Jang at Massachusetts General Hospital and with Willem Flameng at the University of Leuven.

In collaboration with Willem Weimar (Erasmus University, Rotterdam), and through the intermediary of Alfons Billiau, in 1981 the first patient with renal transplant vein thrombosis was successfully treated with melanoma t-PA. In 1983, in collaboration with Frans Van de Werf and Burton Sobel, melanoma t-PA was first given to patients with acute myocardial infarction. With the approval of the Food and Drug Administration, recombinant t-PA was first administered to a patient on February 11, 1984 by Eric Topol. The promising initial results with rt-PA have provided the foundation for the design of both the NIH Thrombolysis in Acute Myocardial Infarction (TIMI) trials led by Eugene Braunwald in the USA and the European Cooperative Study Group trials initiated and firmy led by Marc Verstraete. Numerous clinical trials have since studied the thrombolytic properties of recombinant t-PA. This culminated in the GUSTO trial lead by Eric Topol and Robert Califf and monitored by David Stump on behalf of Genentech, which conclusively established the potential of t-PA for treatment of AMI. Since, t-PA is established as a lifesaving drug for treatment of evolving myocardial infarction and other thromboembolic diseases.

Most of the colleagues mentioned in this brief historic overview have contributed to this booklet. Their brief narrative and personal appreciation does not only highlight their own contribution, but testifies of the impact that their collaboration with Désiré has had on their subsequent career.

While development of t-PA for thrombolytic therapy has undoubtedly been the main scientific achievement of Désiré, it is by far not the only one. Since the foundation of the Center for Transgene Technology and Gene Therapy (now Vesalius Research Center), together with Peter Carmeliet and colleagues, landmark contributions were made to the fields of vascular biology, tumour biology and neurobiology. Many of these achievements were only possible thanks to the vision of Désiré to invest early on in new technology and to attract top-level collaborators.

No doubt, Désiré has been the driving force to establish the Center for Molecular and Vascular Biology and the Vesalius Research Center as leading labs in their field. In addition, the successful creation of the spin-off company ThromboGenics testifies for his managerial and business talents. He has indeed been doing translational research before the term was coined.

For all these achievements, and for being a wonderful colleague and friend over so many years, thank you very much Désiré, on behalf of all of us. On a personal note, I would like to add that I have always very much enjoyed the generous hospitality of Louisa and Désiré in their charming house in Winksele. As most of us know, Désiré has not only realized many scientific breakthroughs, but he (that is to say primarily his wife) has also managed to raise a cohesive family of three children and (presently) three grand children.
We all wish you good health, happiness, success and exciting new experiences during the years to come.

Roger Lijnen
Leuven, June 21, 2008

Thank you!

Anthologies for a retirement are occasions were the contributors are presumed to say nice things about the person concerned. Thus I did not expect negative appreciations. However, on reading the present accounts, I was very touched by the fact that almost all of you clearly go “beyond the call of duty”. It is obvious that the contributors to this anthology have not only been talented collaborators, but that most of you also have become genuine friends.

I have always tried to be “a straight shooter without an hidden agenda” and I am very happy that many of you noticed this. Over the years I have developed somewhat of an allergy against hypocrisy, which proved to be a very expensive idiosyncrasy that at times made me wonder whether I had made the right career choices. However on reading your testimonials, such doubts have definitively disappeared and I now fully realize how lucky I have been to have had the privilege to work and play with all of you.

This anthology is the nicest farewell gift that I could have imagined. Thank you and thank you again for everything. My gratitude extends to all former and present, foreign and Belgian collaborators, listed at the beginning of this anthology, and especially to Prof. Marc Verstraete, who believed and strongly supported me for a NFWO fellowship (in 1968) at a time when I had very little track record.

Although I have had a somewhat ambivalent relationship with my main employer (K.U.Leuven) with respect to the priority assigned to competitive research, much of this was compensated by exceptional opportunities provided by The Flanders Institute for Biotechnology (VIB). On balance things could have been a lot worse and I therefore leave academia in peace and wish both institutions all the best.

Désiré Collen
21 June 2008

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Collaboration period

1980 - 1982

Collaboration topics

Production of t-PA from natural source
Informal reciprocal assistance

Selected joint publications

Collen D., Rijken D.C., Van Damme J., Billiau A. Purification of human tissue-type plasminogen activator in centigram quantities from human melanoma cell culture fluid and its conditioning for use in vivo. Thromb. Haemost. 48, 294-296,1982 (109 times cited).

Weimar W., Stibbe J., Vanseyen A.J., Billiau A., De Somer P., Collen D. Specific lysis of an iliofemoral thrombus by administration of extrinsic (tissue-type) plasminogen activator. Lancet 2, 1018-1020,1981 (174 times cited).

Brief narrative

A Brief Encounter
I vividly remember my first encounter with Désiré Collen in 1971. I had completed a one-year stay in the U.S., and had resumed working in the Rega Institute in Leuven. Encouraged by the Director, Pieter De Somer, I had begun on a project to elaborate a system for high-yield production of interferon from cultured human skin cells. My family and I were then living in Kessel-lo, one of Leuven's residential suburbs. Our senior next-door neighbours, René and Louisa Verbruggen, happened to be close and life-time friends of Désiré's family. One late evening in 1971, René solicited my assistance to drive him to his daughter's wedding party. On arrival at the site, he insisted on introducing me to Désiré who was present at the party. Thus happened my first very brief encounter with young Désiré: a stout and radiant appearance, of fair complexion and then still featuring a wealth of blond hair. The party was already well advanced, and Désiré, in high spirits, had disposed of his neck-tie and rolled up his shirt sleeves. When René introduced me as a scientist with the ambition to treat humanity with interferon, Désiré enthusiastically deployed his own plans to solve mankind's haemostasis problems. It was clear to me that here I had encountered an extremely creative, self-confident and decisive fellow scientist.

Chasing goats in the Winksele meadows.

In the second half of the 1970s my research had become focused on setting up a pilot plant for production and purification of interferon aimed at initiating clinical trials. What we then called 'fibroblast interferon' would later be named interferon-β, now in use to treat certain forms of multiple sclerosis. The project amounted to overcoming several major obstacles, such as the low production

yields (as little as a single microgram per culture bottle) and the major losses of material during purification (from 50 % upwards). My collaborators, in particular Jo Van Damme, then a PhD student, diligently passed all these hurdles. At one point we wished to prepare a potent and specific anti-interferon antiserum that we might need for characterization studies and for affinity chromatography. We wanted to immunize goats, so as to be able to obtain sizable quantities of serum. However, large animals were not available in our University's Experimental Animal Unit, and I recall that the Director advised us to contact Désiré Collen who, faced with a similar problem, was keeping a couple of goats in a meadow adjacent to his stately house in Winksele, another Leuven suburb. In fact, it appeared that Mrs. Louisa Collen had already become an expert and loving goat keeper, and we found her kind enough to keep two more animals for us, one to be immunized with partially pure interferon-β, the other with interferon-β that we believed was completely pure. Jo Van Damme still nostalgically remembers chasing the goats in the green and hilly landscape of Winksele. Both antisera would become critical reagents in the successful cloning, in 1980-1981, of interferon-β by a consortium of researchers from our Rega Institute, the Pasteur Institute of Brussels and the University of Ghent. More importantly, the difference between the two sera was to become a critical asset in the cloning of a protein (26K) co-produced with interferon and recognized by the first but not the second antiserum. This protein, also picked up by interferon workers in Rehovot and first considered by them as a variant interferon, would later turn out to be nothing less than interleukin-6.

A Leuven-Rotterdam return ticket.

It must have been winter time 1980-1981, when one day, out of the blue, Désiré stepped into my office, handing me a Falcon flask: 'Could I take care of keeping and culturing a melanoma cell line that he just brought along from a visit abroad?' He explained having information that the line, called 'Bowes', produced a protease with properties similar or identical to those of t-PA. He also gave me an initiation course on the plasmin fibrinolytic pathway, and noted that he had been studying with Dick Rijken t-PA isolated from uterus tissue. The enzyme appeared to become specifically activated by fibrin but not by fibrinogen and, therefore could initiate fibrinolysis without affecting fibrinogen levels. Thus, he also introduced me to the hypothesis that systemic administration of the t-PA might well dissolve intravascular clots without the disadvantages inherent to other plasminogen activators, in particular without the much feared complication of defibrination.

At the time, the haemostasis laboratory of K.U.Leuven, though extremely well equipped, possessed neither the hardware for, nor the expertise in cell culture. Of note, unlike today, cell culturing was not so common practice in biomedical laboratories of the time. So, Désiré needed a short-term solution for culturing his Bowes cells. Our pilot plant for production of interferon from cultured human skin fibroblasts was fully operational, and in no time did we produce sufficient fluid for Désiré's staff to confirm that the plasminogen activator released by the cell line was indeed identical to the t-PA from uterus. It also appeared that the cell line would be superior to uterus tissue as a source of t-PA in quantities sufficient to conduct animal experiments and, perhaps, initiating clinical trials. Désiré recruited a technician who set up semi-

mass culture in our pilot plant, and very soon he accumulated sufficient pure protein to deliver proof of principle in an animal model.

Meanwhile our own human interferon project at Rega was reaching a critical stage. We had used our material as intramuscular injections in several patients with cancer, multiple sclerosis or virus infections, including ones with chronic viral hepatitis or having received a renal transplant. Some of the trials had been conducted in Dijkzigt Hospital of Erasmus University of Rotterdam under the guidance of Willem Weimar, then in his early career as a nephrologist. The overall results were not negative, though not really convincing either. In fact, our enthusiasm and that of our mentor, Pieter De Somer, waned day after day. Moreover, recombinant DNA technology was booming and promised to become the method of choice for producing human interferons. Hence, we felt that we had reached the point were we would have to abandon our plans to develop commercial production of interferon from cultured human fibroblasts. The contrast between the ease of producing milligram amounts of t-PA versus the pains to obtain as little as microgram quantities of interferon, made our discouragement even greater. With these worries on my mind, on April 21st 1981, I traveled to Rotterdam in order to attend the Annual Interferon Conference. At the welcome reception, I met Willem Weimar and told him about our involvement with Désiré's t-PA project. Willem listened with growing attention and mentioned that, just that same day, he was being confronted with a renal transplant patient presenting in the Dijkzigt Hospital emergency ward, with a large life-threatening thrombus in the allograft vein, for which he saw no satisfactory therapeutic solution. If t-PA could at all be provided he would be eager to give it a try. On the morning of the first conference day, I returned to Leuven and called Désiré, who immediately agreed to provide a bolus quantity of t-PA to give to this patient. I returned to the meeting carrying the material, so that the patient could forthwith receive his first injection. The result was spectacular and convincing, as described in a report in Lancet (Weimar et al. 1981). The case was reminiscent of the first evidence for clinical effectiveness of penicillin, that also needed only a single patient's case.

Personal appreciation

I owe thanks to Roger Lijnen for inviting me to contribute to this *liber amicorum*. It gave me the opportunity to bring to mind an episode of my career during which I had the genuine feeling of being involved, be it sidewise, in an important discovery. Secondly, I valued the opportunity to pay tribute to Mrs. Louisa Collen, a great and most generous lady standing beside a great and generous gentleman.

Present co-ordinates

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Bounameaux, Henri

Collaboration period

October 1983 - September 1985

Collaboration topics

Fibrinolysis
Thrombolysis
Venous thromboembolism

Selected joint publications

Collen D., Bounameaux H., De Cock F., Lijnen H.R., Verstraete M. Analysis of coagulation and fibrinolysis during intravenous infusion of recombinant human tissue-type plasminogen activator in patients with acute myocardial infarction. Circulation 73, 511-517, 1986 (150 times cited).

Verstraete M., Bounameaux H., De Cock F., Van de Werf F., Collen D. Pharmacokinetics and systemic fibrinogenolytic effects of recombinant human tissue-type plasminogen activator (rt-PA) in humans. J. Pharmacol. Exper. Therap. 235, 506-512, 1985 (152 times cited).

Brief narrative

I obtained my M.D. at the University of Basle, Switzerland, in 1978, under the direction of Professor François Duckert (Ph.D.) with a thesis on the influence of oral contraceptives on antithrombin concentration, before training in internal and vascular medicine. From October 1983 to September 1985, I spent two years in the Center for Thrombosis and Vascular Research, as it was named at that time, under Professor Marc Verstraete's guidance, and under the supervision of Raymond Verhaeghe during the first year, which was mainly devoted to clinical research, and of Désiré Collen during the second year, which was more laboratory-oriented. In 1985, I was offered a position of Scientific Registrar in the Unit of Angiology at the University Hospital of Geneva, and I became Head of this unit three years later. In 1992, the Unit of Angiology was merged with the Unit of Hemostasis and I became the Director of the new division in 1993. I was then named associate professor and, in 2002, full professor. The same year, I was elected Chairman of the Department of Medicine. During these years, the Geneva group established itself as a strong contributor to the field of venous thromboembolism diagnosis, treatment, and prevention, with more than 250 publications in peer-reviewed journals, a recognition that culminated in my election as President of the 2007 Congress of the International Society on Thrombosis and Haemostasis (ISTH) that was held in Geneva.

Personal appreciation

Perhaps my first recollection of Désiré Collen was his State-of-the-Art lecture at the 1979 ISTH Congress in London. He spoke on fibrin-specific fibrinolysis with tissue-type plasminogen activator (t-PA) and I must confess that I have been deeply impressed. I joined the Leuven group at the time t-PA was becoming a therapeutic agent, a fascinating and exciting period, with people coming to Leuven from all over the world, speaking of recombinant DNA technology, pharmocokinetics in various species including humans, and use in acute myocardial infarction. I was among the few M.D.s in the group. Indeed, the work was done by biochemists and molecular biologists, and my modest contribution during that period has been to link the laboratory with the patient, either plasma samples or real patients. Thus, I remember a patient who suffered from a massive pulmonary embolism and who was lucky enough to be the first one in 1984 to receive recombinant t-PA for this condition and who recovered within minutes during the short infusion given in the emergency ward. Anecdotally, this patient has been the subject of a case report in the *Annals of Internal Medicine*.
I remember Désiré not only as a visionary scientist but also as a dedicated mentor to help me planning an experiment, writing a paper or answering a reviewer. For a young fellow like me, Désiré Collen has represented and still represents a model of a basic scientist who had an extraordinary sense of what could be useful in clinical practice. He was doing translational research before the term was coined. The two-year period in Leuven has been a unique personal and professional experience, which has strongly influenced my practice and my career.

Present co-ordinates

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Carmeliet, Peter

Collaboration period

1989 - now

Collaboration topics

Fibrinolysis
Coagulation
Angiogenesis
Neuro vascular disease

Selected joint publications

Carmeliet P., Kieckens L., Schoonjans L., Ream B., Van Nuffelen A., Prendergast G., Cole M., Bronson R., Collen D., Mulligan R.C. Plasminogen activator inhibitor-1 gene deficient mice.1. Generation by homologous recombination and characterization. J. Clin. Invest. 92, 2746-2755,1993 (204 times cited).

Carmeliet P., Stassen J.M., Schoonjans L., Ream B., Van den Oord J.J., De Mol M., Mulligan R.C., Collen D. Plasminogen activator inhibitor-1 gene deficient mice.2. Effects on hemostasis, thrombosis, and thrombolysis. J. Clin. Invest. 92, 2756-2760,1993 (245 times cited).

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Carmeliet P., Ferreira V., Breier G., Pollefeyt S., Kieckens L., Gertsenstein M., Fahrig M., Vandenhoeck A., Harpal K., Eberhardt C., De Clercq C., Pawling J., Moons L., Collen D., Risau W., Nagy A. Abnormal blood vessel development and lethality in embryos lacking a single VEGF allele. Nature 380, 435-439,1996 (1649 times cited).

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Carmeliet P., Moons L., Ploplis V., Plow E., Collen D. Impaired arterial neointima formation in mice with disruption of the plasminogen gene. J. Clin. Invest. 99, 200-208,1997 (133 times cited).

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Carmeliet P., Moons L., Herbert J.M., Crawley J., Lupu F., Lijnen H.R., Collen D. Urokinase but not tissue plasminogen activator mediates arterial neointima formation in mice. Circ. Res. 81, 829-839,1997 (151 times cited).

Carmeliet P., Moons L., Lijnen H.R., Baes M., Lemaitre V., Tipping P., Drew A., Eeckhout Y., Shapiro S., Lupu F., Collen D. Urokinase-generated plasmin activates matrix metalloproteinases during aneurysm formation. Nat. Genet. 17, 439-444,1997 (346 times cited).

Carmeliet P., Moons L., Lijnen H.R., Janssens S., Lupu F., Collen D., Gerard R.D. Inhibitory role of plasminogen activator inhibitor-1 in arterial wound healing and neointima formation - A gene targeting and gene transfer study in mice. Circulation 96, 3180-3191,1997 (160 times cited).

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Carmeliet P., Lampugnani M.G., Moons L., Breviario F., Compernolle V., Bono F., Balconi G., Spagnuolo R., Oosthuyse B., Dewerchin M., Zanetti A., Angellilo A., Mattot V., Nuyens D., Lutgens E., Clotman F., de Ruiter M.C., Gittenberger-de Groot A., Poelmann R., Lupu F., Herbert J.-M., Collen D., Dejana E. Targeted deficiency or cytosolic truncation of the VE-cadherin gene in mice impairs VEGF-mediated endothelial survival and angiogenesis. Cell 98, 147-157,1999 (437 times cited).

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Brief narrative & personal appreciation

After graduating at the University of Leuven as M.D. (1984) and Ph.D. (1989), I was fortunate to meet Désiré, almost accidentally, at a seminar, he had organized for a top-class speaker from Harvard. This fortuitous meeting turned out to be the start of a long-lasting productive, inspiring and collegial collaboration, which has changed the face of my scientific and academic career. Even though I only knew Désiré then from his reputation, I could not know at that moment what a pioneer in molecular medicine he was, years ahead of his time.

Initially, Désiré offered me the opportunity and means to perform a postdoctoral training at Harvard Medical School as “D. Collen Research Foundation Fellow” (1989-1990). He thereafter had the vision to invest, at a very timely moment, in the gene-targeting technology, and offered me the unique opportunity to learn this technology during a second postdoctoral training at the Whitehead Institute (MIT; 1990-1991). To maximize and accelerate the learning process, Désiré also supported the salaries of two technicians, and, after my return to Belgium, that of Mieke Dewerchin, in addition to very substantial investments in equipment. This has allowed the entire team to acquire the gene-targeting technology at a very early time, shortly after its discovery. During this stay, t-PA, u-PA and PAI-1 knockout mice were generated. Anecdotally, Désiré carried the first t-PA knockout mouse home in his hand luggage on the airplane, and literally – and, justifiably, so – introduced the first knockout mouse into Belgium. I am extremely appreciative to Désiré for giving me the opportunity to perform this postdoctoral training, as this experience has been of unmeasurable value, allowed me to become an independent scientist and to acquire frontline technology, convinced me of asking important questions in science, taught me how to provide answers to difficult questions, and shaped my view on cutting-edge research in general.

After finishing this postdoc, Désiré offered me a position to work in his laboratory. This was a decision, that not many others in his position would have dared to take, when considering that substantial funding had been invested in a postdoc, who had generated three mutant mice, but not a single publication. It showed, however, that Désiré was not shy of investing in high-profile, high-risk projects – an important example to many of us.

Upon returning to Leuven, Désiré spared time, effort nor support to build a state-of-the-art SPF mouse facility, expand a phenotyping laboratory, and core group of excellent collaborators to establish, in a record time, a prime mouse knockout center in Europe – a tour de force, and evidence of his dynamic determination. During this period, several studies on the fibrinolytic and coagulation knockout mice were generated. Under his leading impulse, with his never-ending enthusiasm and vital energy, and with his motto “better to write than to read about your data”, lab meetings and other discussions were seeding grounds for papers and projects. His supreme writing skills and sharp critiques have undoubtedly contributed to the success of getting papers published in top journals. Désiré stressed the importance of focusing on important questions and publishing high-profile papers, and created a unique environment where young scientists had the chance of taking such risks, and persisting with determination until the goal was reached. He often provided important guidance in publication strategies, yet was not afraid of appealing peers and inform them that it was not feasible “to conduct the entire study once more at the backside of the moon”.

Some anecdotes (besides the many other more important cases) may, perhaps, illustrate his dedication to science. For instance, I vividly remember that both of us were sitting on May first’s holiday in the secretariat, waiting many hours for a fax from Nature with a final decision about the tissue factor knockout paper, as promised by the editor. Or, the days I slided a prefinal draft of a paper under the door of his home at 1AM in the morning, upon

which he would wake up at 5AM in the morning to revise the paper so that it could be submitted by noon the same day. Or, the times when we disturbed Désiré in holidays (even in the wake of Christmas) to ask advice or discuss strategies how to proceed with urgent scientific or publication matters – never did I get an answer that the time was not right. I therefore consider it a great honour to have received such an outstanding training and a true privilege to have been able to learn so much from his example of combining innovation, excellence, efficiency, entrepreneurship, perseverance, speed and leadership.

While still at the Whitehead Institute, the interest in angiogenesis and the plan to knockout out the VEGF gene grew. Though this endeavour differed from past projects in the laboratory, Désiré was generous and open-minded to support this new research avenue – as he has done ever so thereafter, for any of our new research directions. Again, Désiré supported us, in most challenging times, to generate the VEGF knockout mouse, and, in order to be competitive, he supported another (short-term) stay for myself and Lena Kieckens at the Lunenfeld Institute, Toronto. Thanks to enormous investments from Désiré, the VEGF knockout paper was finalized, and became a landmark paper in the field, from which the laboratory has greatly benefited. Around the same time, VIB was established, and Désiré offered me to become adjunct director of the Center for Transgene Technology and Gene Therapy at the VIB3 department (1996). Unique research and career opportunities became available, but, as Désiré warned, “there is no free lunch at VIB”.

With the growing interest in angiogenesis, we explored alternative animal model systems to accelerate angiogenesis research, including zebrafish. Once more, Désiré has been instrumental and key in establishing this state-of-the-art technology, at a record tempo, in VIB3, allowing the department to generate high-profile papers, and become recognized as a leading zebrafish angiogenesis laboratory. More recently, Désiré has invested once again in frontline technology, human genetics, thereby offering a junior staff member, Diether Lambrechts, promising career opportunities.

Besides science, I could not have imagined a better tutor to introduce me to the world of research valorization, technology transfer and intellectual property – an experience, very few scientists get a chance to become exposed to early during their career. His leading example to translate research into medicine has inspired all of us to combine fundamental research with a vision on translational medicine. Perhaps one of the best examples of such translational efforts is the work on PlGF. Because of an interest to study the role of other VEGF family members, we characterized the role of PlGF, an underappreciated gene in the angiogenesis field at that time. Genetic studies revealed that PlGF was a disease-specific angiogenic factor, leading us to suggest that this growth factor might be an attractive drug target. Through a productive collaboration with his newly founded company (ThromboGenics), we explored the therapeutic potential of anti-PlGF antibodies in preclinical animal models, which ThromboGenics is now further exploring in clinical trials. The depth and quality of the study could not have risen to its current level without the input and collaboration of Désiré.

From all the above, it is evident that the success of my personal career as well as that of many others in VIB3 would not have reached the current level without Désiré’s scientific excellence, pioneering vision, entrepeneurship,

dynamic leadership, managerial skills, financial support, understanding of important questions and goals, interest “avant la lettre” in translational medicine, and intuition and appreciation for top science. In name of all collaborators of VIB3, I therefore express my sincere gratitude and great appreciation, and wish Désiré the best of luck with his future ambitions.

Present co-ordinates

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Collen, Désiré

Collaboration period

1968 – 2008

Collaboration topics

cfr curriculum vitae at the back

Selected joint publications

Collen D. Identification and some properties of a new fast-reacting plasmin inhibitor in human-plasma. Eur. J. Biochem. 69, 209-216,1976 (315 times cited).

Collen D. On the regulation and control of fibrinolysis. Thromb. Haemost. 43, 77-89,1980 (1130 times cited).

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Collen D. The plasminogen (fibrinolytic) system. Thromb. Haemost. 82, 259-270,1999 (165 times cited).

Brief narrative

A few papers are listed here under my name because of some specific anecdotes.

1. The Eur. J. Biochem. paper of 1976 deals with the identification and indirect characterization of the fast acting inhibitor of plasmin in plasma, which is now called α_2-antiplasmin. This inhibitor was independently and almost simultaneously identified by the group of Aoki in Japan and Mullertz in Denmark.
2. The Circulation paper of 1984 represents the first study with recombinant t-PA in 50 patients with acute myocardial infarction. My first author position is strictly honorary as I was only involved in writing

of the manuscript. This somewhat questionable first author position is due to the fact that the participating Centers (Mass. Gen. Hosp. Boston, Barnes Hospital St. Louis and Johns Hopkins, Baltimore) could not agree amongst them on the first authorship.

3. The Circulation paper of 1993 is the first use of staphylokinase in patients with acute myocardial infarction. I remain convinced that staphylokinase would be an effective inexpensive life saving drug but economic obstacles have made its clinical development in the western world impossible.
4. The papers in Thrombosis and Haemostasis in 1980, in Blood in 1991 and in Thrombosis and Haemostasis of 1999 are three review papers. The first one summarizes the situation in 1980, when the field became sufficiently mature to engage in the development of thrombolytic therapy for acute myocardial infarction, the second one came at the height of the clinical use of thrombolysis and the last one at a time when the field had consolidated and the focus moved to other areas.

Personal appreciation

This initiative gives me the opportunity to most sincerely thank my many collaborators, some of whom have become amongst my best friends for the most gratifying time spent with them both within and alongside science.

Present co-ordinates

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Colucci, Mario

Collaboration period

February 1982 - May 1985

Collaboration topics

PAI-1 function and regulation
Protein C

Selected joint publications

Colucci M., Páramo J.A., Collen D. Generation in plasma of a fast-acting inhibitor of plasminogen activator in response to endotoxin stimulation. J. Clin. Invest. 75,818-824, 1985 (403 times cited).

Páramo J.A., Colucci M., Collen D., Van de Werf F. Plasminogen activator inhibitor in the blood of patients with coronary artery disease. Brit. Med. J. 291, 573-574, 1985 (272 times cited).

Brief narrative

I joined Désiré's group after a 4-year research experience at the "Mario Negri" Institute in Milan, during which I worked mainly on cell procoagulant activities and on the interaction between coagulation and malignancy. My first project in Leuven was centered on the identification of a novel t-PA-releasing hormone in the pituitary gland, whose existence had been hypothesized a few years earlier. The study ended with rather disappointing results (the only t-PA-releasing hormone we found was the well-known vasopressin) but still it was an exciting and fascinating experience thanks to which I learned a lot about the fibrinolytic system and the methods used to investigate it.
My next projects were focused on the profibrinolytic activity of protein C and on the function and regulation of PAI-1, and were carried out in collaboration with José Antonio Páramo and Jan Stassen. These studies yielded quite interesting results, clarifying some aspects of the role of PAI-1 in the regulation of fibrinolysis, and allowed us to publish several papers in top journals. Apart from this, working on these projects was fun and stimulating. On more than one occasion we came up with rather unexpected findings which cast in doubt our starting hypothesis and instigated new lines of research that we pursued with diversified and sometimes unconventional experimental approaches. It was the opportunity for long, and sometimes heated discussions that widened my views on fibrinolysis and experimental research in general. All this made me appreciate the outstanding level of Désiré's lab and the ease with which new accomplishments could be achieved, thanks to the know-how and skills of the staff, the expertise of my colleagues and the many laboratory facilities.

Personal appreciation

I first met Désiré in 1976, when I was a student. I went to Leuven to visit Nicola Semeraro who was completing his PhD thesis at the laboratory of Prof. Verstraete, in the St.-Rafaël Hospital. Rather unexpectedly, probably because of the rainy weather, my holidays turned into a working experience and I had the chance to take part in one of Désiré's projects on α_2-antiplasmin. At the time Désiré was a young investigator and I was very much impressed by his strong personality and self-confidence. When, six years later, I was given the opportunity for a research experience in a foreign country I had no hesitation in choosing Désiré's lab and moved to Leuven with great enthusiasm and great expectations. I spent three and half years there and I can say that beyond any doubt those expectations were totally fulfilled.

In the early 80s Désiré's group was already renowned world-wide but still not so large as to make it impracticable to have a lab meeting in a 5x4 m room with all the participants sitting around a medium-sized table, as we used to do every Friday morning at 9.00 a.m. on the dot, or to have a barbecue evening all together at Désiré's home, which happened many times, or even to organize a day out in the Ardennes with the whole group (an unforgettable experience with Whyte Owen providing a delightful musical background with his guitar, and Désiré lying on the grass after a good, rich meal on an unusually sunny day). This affable and relaxed environment made my stay in Leuven very enjoyable and gave me the opportunity to establish friendly relationships with all my colleagues, many of which still endure, and with the "boss". This has been the key to a rewarding experience from both the professional and personal standpoints.

As to my work, I am more than grateful to Désiré for having allowed me to test my ideas and to carry out my research projects under such exceptionally favorable conditions. He constantly supported my work with his clever advice and constructive criticisms and taught me to look beyond the obvious meaning of the experimental data. Working with Désiré was intellectually exciting and fun, and energized me to continue in the field of academic research.

Of course, like any new experience, it was not all smooth and easy. In my case the most difficult task was to get used to Belgian coffee, which differed in many aspects from Italian "espresso". But this was a fair price to pay.

Presently I am associate professor of General Pathology at the University of Bari and my main research interest is still in fibrinolysis.

Present co-ordinates

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Conway, Edward

Collaboration period

September 1995 – now

Collaboration topics

Inflammation
Coagulation
Endothelial cell survival
Angiogenesis

Selected joint publications

Conway E.M., Pollefeyt S., Cornelissen J., DeBaere I., Steiner-Mosonyi M., Ong K., Baens M., Collen D., Schuh A.C. Three differentially expressed *survivin* cDNA variants encode proteins with distinct antiapoptotic functions. Blood 95, 1435-1442, 2000 (98 times cited).

Conway E.M., Collen D., Carmeliet P. Molecular mechanisms of blood vessel growth. Cardiovasc. Res. 49, 507-521,2001 (233 times cited).

Brief narrative

I received my medical degree at the University of Toronto, my fellowship in Hematology-Oncology at Harvard University, and finally my introduction to "real" research at M.I.T. under the supervision of Bob Rosenberg and Ken Bauer. In 1988, I returned to Toronto to establish my own lab, with the main objective being to characterize the function of the vascular endothelial protein, thrombomodulin (TM). After 7 years of moderate progress, I was ready for a sabbatical, and searched for international labs with similar interests. Désiré's rapidly growing team at the K.U.Leuven and the emerging VIB, had already established a strong transgenic facility with a focus on utilizing mouse models to delineate the *in vivo* functions of coagulation-related proteins. Thus, thrombomodulin fit well into the scheme, and I was thrilled to have the opportunity to join an extraordinarily bright and resourceful group. We started by generating mice that lacked the cytoplasmic domain of thrombomodulin, expecting to find a spectacular vascular phenotype. Disappointingly, however, these mice were largely unaffected by the deletion. Nonetheless, with Désiré's encouragement, we then generated mice lacking the lectin-like domain of TM. These mice were considerably more impressive, and demonstrated that this structure has critically important anti-inflammatory properties, a novel finding that provided definitive evidence of molecular links between innate immunity and coagulation. Moreover, these studies form the

foundation for investigations into the role of the protein C mechanism in innate immunity, and are the basis for the development of safer therapies for numerous common clinically relevant disorders. With Désiré's scientific input and support, I have also been able to explore the role of endothelial cell apoptotic pathways, and in turn, gained insights into how the blood vessel system "talks" to the neural system, thereby co-ordinating critical developmental processes. These research endeavours are providing unique insights into our understanding of the pathogenesis of an array of devastating congenital disorders. Overall, through Désiré's consistent willingness to support well-conceived and occasionally "out-of-the-box" approaches to science, I have been privy to rare opportunities to make hopefully useful contributions.

Personal appreciation

In 1994, when I was seeking a stimulating and supportive environment to spend a sabbatical leave with my family, Désiré made all my other opportunities around the world seem inadequate. Not only did he wine and dine my wife and me at his home with the most exquisite cuisine, but he facilitated my entry into the lab by providing extraordinary resources and encouragement that I continue to appreciate. One year became 2 years, and 2 years became 12 years. Not once during this time, have I looked back with regret. With incredible foresight and rare entrepreneurial spirit, he has spearheaded and supported the development of new and exciting science and technologies that have placed the VIB and the Center for Transgene Technology and Gene Therapy solidly "on the international scientific map", and I have had the good fortune and honour to feel part of this exciting process. Beyond the science, Désiré's major "mark" on me has been his honesty, integrity, a genuine concern for the well-being and success of his staff, his strong decision-making skills, his notable forthright manner, and a creative view of the future. I cherish having been one of his many colleagues and friends, all of whom accord him the respect that comes with his many achievements. At a relatively later point in my career, I was doubly honoured that he was the promoter of my PhD in Biomedical Sciences. I wish Désiré continued success, health and happiness, and heartily thank him for all that he has given me.

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Declerck, Paul

Collaboration period

May 1986 – September 1992

Collaboration topics

Fibrinolysis

Selected joint publications

Declerck P.J., Mombaerts P., Holvoet P., De Mol M., Collen D. Fibrinolytic response and fibrin fragment D-dimer levels in patients with deep vein thrombosis. Thromb. Haemost. , 58, 1024-1029,1987 (100 times cited).

Declerck P.J., Alessi M.C., Verstreken M., Kruithof E.K.O., Juhan-Vague I., Collen D. Measurement of plasminogen activator inhibitor-1 in biologic fluids with a murine monoclonal antibody based enzyme-linked immunosorbent assay. Blood 71, 220-225,1988 (493 times cited).

Declerck P.J., De Mol M., Alessi M.C., Baudner S., Paques E.P., Preissner K.T., Müller-Berghaus G., Collen D. Purification and characterization of a plasminogen activator inhibitor-1 binding protein from human plasma - identification as a multimeric form of S-protein (vitronectin). J. Biol. Chem. 263, 15454-15461,1988 (363 times cited).

Declerck P.J., De Mol M., Vaughan D.E., Collen D. Identification of a conformationally distinct form of plasminogen activator inhibitor-1, acting as a noninhibitory substrate for tissue-type plasminogen activator. J. Biol. Chem. 267, 11693-11696,1992 (109 times cited).

Brief narrative

Even though the subject of my Ph.D. thesis (in Pharmaceutical Sciences, K.U.Leuven, 1984) was related to electrochemistry and my first postdoc (1984-1986, Dr. de Duve's lab, The Rockefeller University, NY) dealt with trichomonads and I had never 'seen' a monoclonal antibody, Désiré took the risk of hiring me as he was looking for an expert on monoclonal antibodies with a particular application in the field of fibrinolysis. My first project was on plasminogen activator inhibitor-1, the fast inhibitor of t-PA in plasma (please note the anecdote that there is an old paper of Désiré, published in 1981 together with Christian Korninger, a contributor to this booklet, describing the *absence of evidence for a specific inhibitor* !). In close collaboration with Bert Kruithof and the group of Marseille (Irène Juhan-Vague and Marie-Christine Alessi) I started the generation of a first set of monoclonal antibodies against PAI-1, laying the basis of my future research career dealing with various aspects of PAI-1 (assay methodology, *in vivo* distribution, structure-function

studies, mechanistic studies, design of inhibitory strategies, ….). Working in Désiré's lab was also a guarantee for excellent international contacts and collaborations. Many postdocs passed by. Our common and complementary interest in PAI-1 resulted in a longstanding collaboration with Doug Vaughan (postdoc in the late eighties, now at Vanderbilt University, Nashville). Even though initially I was not convinced of the existence of a binding protein for PAI-1, Désiré insisted we started looking for it. By doing so we ended up in competition with one of his former postdocs, Bjorn Wiman (University of Umea, Sweden). Eventually we both succeeded, virtually simultaneously, to identify vitronectin as the binding partner of PAI-1 in plasma and later found it to be important for the localization of PAI-1 in the extracellular matrix. The latter observation has led to many studies regarding the link between PAI-1 and cell migration and cancer. During my postdoc period in Désiré's lab I was also involved in some studies on urokinase and staphylokinase, closely collaborating with Roger Lijnen, a key co-worker of Désiré. Around 1991-1992, I got the opportunity to start up my own lab at the faculty of Pharmaceutical Sciences. Starting from scratch and with much (very much !) less financial resources this was very challenging and not easy. The extensive experience (scientifically as well as managerially) gathered in Désiré's lab under his firm guidance, and being enriched with the many collaborations established during that period made it possible for me to fully establish my independent academic career.
I also want to stress that the strong technical support available in the lab throughout my postdoc period (in particular by Maria De Mol, Huberte Moreau and Maria Verstreken) contributed significantly to our success.

Personal appreciation

It is beyond any doubt that Désiré has been a great mentor to me. His personal drive, his enthusiasm, his never ending push served as a model for all his co-workers. His famous device "*We want to write about it rather than to read about it*" was an unambiguous signal to hurry up with the experiments to complete a study. Notwithstanding this constant pressure he remained very critical in the analysis and interpretation of all results. Speed was important in this competitive world but quality always remained the most important. I am sure many other contributions in this booklet will also stress the fact that Désiré was extremely efficient. Never lose the focus was definitely another important motto and was often exemplified by his well known (and sometimes feared) statement "*Where is the meat ?*". Indeed his continuing inquiry, during the famous lab-meetings on Friday, about the added-value of particular projects learned us to (re-)evaluate our plans with sufficient self-criticism.

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Dewerchin, Mieke

Collaboration period

1988 - present

Collaboration topics

Fibrinolysis
Thrombolysis, coagulation, gene targeting
Angiogenesis, lymphangiogenesis

Selected joint publications

Dewerchin M., Van Nuffelen A., Wallays G., Bouche A., Moons L., Carmeliet P., Mulligan R.C., Collen D. Generation and characterization of urokinase receptor-deficient mice. J. Clin. Invest. 97, 870-878,1996 (131 times cited).

Carmeliet P., Moons L., Dewerchin M., Rosenberg S., Herbert J.M., Lupu F., Collen D. Receptor-independent role of urokinase-type plasminogen activator in pericellular plasmin and matrix metalloproteinase proteolysis during vascular wound healing in mice. J. Cell Biol. 140, 233-245, 1998 (87 times cited).

Stalmans I., Ng Y.S., Rohan R., Fruttiger M., Bouche A., Yuce A., Fujisawa H., Hermans B., Shani M., Jansen S., Hicklin D., Anderson D.J., Gardiner T., Hammes H.P., Moons L., Dewerchin M., Collen D., Carmeliet P., D'Amore P.A. Arteriolar and venular patterning in retinas of mice selectively expressing VEGF isoforms. J. Clin. Invest. 109, 327-336, 2002 (138 times cited).

Brief narrative

I studied biology at the University of Leuven and obtained my PhD in Science in July 1984. After a postdoctoral period at the laboratory of biochemistry of the Faculty of Medicine at the K.U.Leuven campus in Kortrijk, I joined the lab of Désiré in March 1988. In Kortrijk, I had been working on chemical conjugation of proteins, more particularly of anti-tumor antibodies with toxic proteins, in the framework of developing immunotoxins for tumor therapy. In Désiré's lab, this approach of chemical conjugation appeared to be directly applicable to the development of clot-targeted plasminogen activators for thrombolysis, and was explored using antibodies against D-dimer or against platelet receptors coupled to urokinase. Initially, chemical conjugation of the individual proteins was used; later, DNA technology was used to generate recombinant fusion proteins. In 1992, I was offered the unique opportunity to go to the Whitehead Institute in Cambridge in the US to train in mouse transgenesis. I spent about 1.5 years in the States, applying transgenesis to the generation of uPAR knockout mice. These studies were done in collaboration with Peter Carmeliet, who by that time had returned himself from

the states and started in Désiré's lab. After returning to Leuven, I continued working on transgenesis studies under the guidance of Désiré, together with Peter and other belgian and foreign PhD students and postdoctoral fellows. Applications included initially the fibrinolytic system, but soon also the coagulation system and the VEGF family of angiogenic and lymphangiogenic growth factors. In addition to the fundamental aspects of these studies, several studies were/are situated at the interface between biomedical and preclinical research. For instance, an anti-human factor VIII antibody was evaluated for its anti-thrombotic effects in our antithrombin mutant mice that develop spontaneous thrombosis (in collaboration with Marc Jacquemin and Thromb-X NV (now ThromboGenics)). Eventually, other powerful genetic animal models were also acquired and developed in the lab, including the zebrafish and Xenopus tadpoles, which are now being used as parallel or complementary models to the mouse to investigate gene functions in lymph/angiogenesis.

Personal appreciation

I still vividly remember the first time that I met Désiré. This was at the occasion of my interview with him when I applied for a position in his lab. The laboratory was then still on the 7th floor of O&N1, it's size was quite a bit smaller than that of the current lab and so was Désiré's office (but with a splendid view of Leuven). The interview did not last much longer than 10-15 minutes and ended with an 'OK, you can start next Monday'. I had not really expected that, so I was a bit surprised, but naturally very pleased and happy. I assume I came at the right time with the right expertise to the right place. The right place indeed it turned out to be. Compared to what I have learned here, I knew very little when I arrived. Scientifically, it was a totally different field of course, but it never stopped expanding to include the recent developments and the 'hot topics' in vascular biology; spot-on and from a leading position in the field. Technology-wise I also learned a lot here. I did not know anything about molecular biology before we started with the recombinant antibody/urokinase fusions. I was taught everything here. We were also very fortunate that all novel technological developments were available right away; the first PCR machine, the first automatic DNA sequencer, electroporation equipment, confocal microscopy, etc. The opportunities realized by Désiré, for me personally to train in mouse transgenesis, and for the lab to acquire the gene targeting and zygote injection expertise together with the SPF facility, and later the zebrafish and Xenopus functional genomic facilities, have been crucial to our own work as well as that of neighbouring labs and collaborating groups. I believe myself very fortunate to be able to work in this state-of-the-art environment -both scientifically and technologically- that was realized and supported by Désiré.

I benefited from Désiré's experience and support for numerous additional aspects. I greatly appreciate his support to obtain a tenure position at the K.U.Leuven and a position as staff scientist of the VIB institute, and his continuous support ever since. Furthermore, Désiré is a great teacher and example for matters related to writing (manuscripts, grant applications, etc), management, lecturing, organization. He is also always available for advice, in his office or even on the phone at home or abroad, which has helped

solving many smaller or bigger issues.
Many pleasant and funny memories also come from more casual situations or events: his whistling in the corridor announcing his arrival, the knee competition in the Ardennes, the shoemarks on the floor, and so many more.
During that first application interview, I was (somewhat intimidated and) greatly impressed by Désiré, and during the first months and years after joining the lab, I always thought there is nobody like Désiré. After twenty years, I am still impressed, and still believe there are no two Désiré's in the world. I wish him the very best and hope that we will still see and hear a lot of him.

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Gold, Herman

Collaboration period

1983 - 1994

Collaboration topics

Fibrinolysis
Thrombolytic therapy
Anticoagulant and antiplatelet agents

Selected joint publications

Gold H.K., Fallon J.T., Yasuda T., Leinbach R.C., Khaw B.A., Newell J.B., Guerrero J.L., Vislosky F.M., Hoyng C.F., Grossbard E., Collen D. Coronary thrombolysis with recombinant human tissue-type plasminogen activator. Circulation 70, 700-707,1984 (122 times cited).

Gold H.K., Leinbach R.C., Garabedian H.D., Yasuda T., Johns J.A., Grossbard E.B., Palacios I., Collen D. Acute coronary reocclusion after thrombolysis with recombinant human tissue-type plasminogen activator - prevention by a maintenance infusion. Circulation 73, 347-352,1986 (312 times cited).

Gold H.K., Johns J.A., Leinbach R.C., Yasuda T., Grossbard E., Zusman R., Collen D. A randomized, blinded, placebo-controlled trial of recombinant human tissue-type plasminogen activator in patients with unstable angina pectoris. Circulation 75, 1192-1199,1987 (145 times cited).

Garabedian H.D., Gold H.K., Leinbach R.C., Johns J.A., Yasuda T., Kanke M., Collen D. Comparative properties of 2 clinical preparations of recombinant human tissue-type plasminogen-activator in patients with acute myocardial infarction. J. Am. Coll. Cardiol. 9, 599-607,1987 (106 times cited).

Gold H.K., Coller B.S., Yasuda T., Saito T., Fallon J.T., Guerrero J.L., Leinbach R.C., Ziskind A.A., Collen D. Rapid and sustained coronary artery recanalization with combined bolus injection of recombinant tissue-type plasminogen activator and monoclonal antiplatelet FPIIb/IIIa antibody in a canine preparation. Circulation 77, 670-677,1988 (372 times cited).

Johns J.A., Gold H.K., Leinbach R.C., Yasuda T., Gimple L.W., Werner W., Finkelstein D., Newell J., Ziskind A.A., Collen D. Prevention of coronary-artery reocclusion and reduction in late coronary artery stenosis after thrombolytic therapy in patients with acute myocardial infarction - a randomized study of

maintenance infusion of recombinant human tissue-type plasminogen activator. Circulation 78, 546-556,1988 (113 times cited).

Gold H.K., Gimple L.W., Yasuda T., Leinbach R.C., Werner W., Holt R., Jordan R., Berger H., Collen D., Coller B.S. Pharmacodynamic study of f(ab')2 fragments of murine monoclonal antibody-7E3 directed against human platelet glycoprotein-IIb/IIIa in patients with unstable angina pectoris. J. Clin. Invest. 86, 651-659,1990 (159 times cited).

Gold H.K., Torres F.W., Garabedian H.D., Werner W., Jang I.K., Khan A., Hagstrom J.N., Yasuda T., Leinbach R.C., Newell J.B., Bovill E.G., Stump D.C., Collen D. Evidence for a rebound coagulation phenomenon after cessation of a 4-hour infusion of a specific thrombin inhibitor in patients with unstable angina pectoris. J. Am. Coll. Cardiol. 21, 1039-1047,1993 (151 times cited).

Brief narrative

During the compilation of this anthology, my very dear friend Herman (“Chip”) Gold unfortunately became very ill and passed away on March, 2 2008. The narrative of our collaboration has been covered by Dr. I.K. Jang and by Dr. T. Yasuda, who were active in Chip’s “MGH-team”.

Personal appreciation

As Dr. Yasuda recalls, I was very close to the Gold family and spent probably more nights in their home (on my “private” third floor) than in any specific hotel. Chip was one of my dearest friends and I believe this was reciprocal. Thank you for everything my friend.

Former co-ordinates

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Hanss, Michel

Collaboration period

October 1985 - September 1986

Collaboration topics

Production of fibrinolytic components by human endothelial cells

Selected joint publication

Hanss M., Collen D. Secretion of tissue-type plasminogen activator and plasminogen activator inhibitor by cultured human endothelial cells - modulation by thrombin, endotoxin, and histamine. J. Lab. Clin. Med. 109, 97-104, 1987 (186 times cited).

Brief narrative

In 1985, as a medical student, I asked Désiré to join his lab for a training period. The goal was to learn about fibrinolysis with one of the main actors of this field. The proposed model was not utilized in his lab but, despite everything, he did accept this project. After several months, a suitable human umbilical vessel endothelial cell culture model was set up, with a sufficiently established “cord supply”, and we were able to measure both t-PA and PAI-1 in the culture medium. Different stimuli known to affect cell metabolism were tested. The lipoxygenase-induced components carefully prepared in Lyon were totally ineffective (!), but the never tested histamine was found to be a potent activator of t-PA secretion, and dissociation of PAI-1 and t-PA cell secretions was shown. More than 300 cell culture experiments resulted in the above referenced paper. Other less successful projects were also started on my own or in collaboration with other students from this lab. Unfortunately, my position back in Lyon as a medical doctor specialized in haemostasis did not allow me to further study these interesting cells, neither new modulations, nor therapeutic interventions, nor determining immediate kinetic changes. But I started investigating diseases in relation with fibrinolysis thanks to Roger’s and Désiré’s help, a nice launching pad to study fibrinogen in pathology and to get a PhD degree. I always kept this team and lab somewhere in my mind.

Personal appreciation

This has been a hard time for me, but although results were not very conclusive initially, Désiré did respect the choice and gave me all the facilities to continue, as well as his pertinent advice. I remember:

how he made me feel welcome just arriving from a neighbouring but foreign country,
his understanding of personal implications,
his betting on someone's ideas,
his open-mindness,
his students' respect,
his efficacy,
his manager capacities, creating a very stimulating team spirit and a tremendous "research drive".

Thank you Désiré

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Hoylaerts, Marc

Collaboration period

February 1979 – February 1982

Collaboration topics

Fibrinolysis and coagulation

Selected joint publications

Hoylaerts M., Rijken D.C., Lijnen H.R., Collen D. Kinetics of the activation of plasminogen by human tissue plasminogen activator - role of fibrin. J. Biol. Chem. 257, 2912-2919,1982 (1036 times cited).

Collen D., Zamarron C., Lijnen H.R., Hoylaerts M. Activation of plasminogen by pro-urokinase. II. Kinetics. J Biol Chem. 261, 1259-1266, 1986 (138 times cited).

Brief narrative

My PhD training was in the same laboratory at the University of Leuven where Roger Lijnen graduated from. As a matter of fact, we presented our PhD thesis on the very same day in January 1978. In those days, some of us had to perform their military duties. I was one of them, joining the medical unit of our famous air force, for about 10 months. So, my first contact with the Center for Thrombosis and Vascular Research was indirect. When we would gather with friends, on the rare occasion during my duty, when such was possible, Roger would entertain us very enthusiastically about his research activities in the laboratory of Prof. Verstraete, where he was working with Désiré and with B. Wiman. Obviously, those activities not only sounded more useful than what I was doing at the time in the army, but the enthusiasm in this team and the fact that, seemingly, important new things were being studied there, were very appealing to me. When I got the opportunity, shortly after ending my military service to join this lab, which I already knew to some extent, I didn't hesitate for a second.

In the early days of fibrinolysis, not even all the players of the field were known – and even less so were the interactions between them. Désiré was too much an entrepreneur to leave it there. He attracted a series of competent people, several of whom contribute to this volume. This international environment of people, dealing with biochemical, cell biological, pharmacologic and animal therapeutic studies were moving the forefront of fibrinolysis. Désiré, in his own characteristic style, would stimulate everyone to do better and move faster. For a newbie, such as myself, this was an

environment to lift one up to a level, previously unknown. The availability of highly purified t-PA and other fibrinolytic enzymes – all produced in the laboratory, made it possible to study the molecular interplay between the components of the fibrinolytic system. Since the cascades to be studied consisted of enzymes, inhibitors and cofactors, it seemed logical to apply enzyme kinetic approaches to understand the molecular interactions controlling fibrinolysis.

To a large degree, the same reasoning holds up for the coagulation cascade and the mode of action of heparin, which was beginning to be studied in several labs, but was incompletely understood. After a few (published) introductory studies, describing the necessary tools to do so, under Désiré's stimulus, we could move these studies further to develop the ternary complex model, describing the mode of action of t-PA and the template model, describing the mode of action of heparin during inhibition of thrombin by antithrombin.

Personal appreciation

When I joined the Center for Thrombosis and Vascular Research, my baseline research training allowed me to do biochemically oriented research. That such is not enough to be successful in science, is something you quickly learned when working with Désiré. Under his continuous stimulus and inspiration, you learned that successful research relies on being critical and efficient. And you learned to repeat your observations, making them sufficiently trustworthy to withstand the criticism of the international scientific community. Internationally oriented papers in good journals…the importance of that, I learned very quickly from him.

Désiré had several oneliners, some of which I tend to repeat, now, 25 years later, to junior scientists, as part of their own formation. But, his extreme efficiency and managerial skills to make the team produce relevant new science, have been phenomenal. His critical eye, during data evaluation, lab meetings and paper discussions always impressed me. One glimpse…. And he knew where the problems were. So, by the time I had found my own niche in the laboratory, between the various specialists, by focusing on molecular interactions between proteins in fibrinolysis and coagulation via enzyme kinetics, I felt I could at least also contribute something myself.

I stayed in the laboratory for 3 years, as a postdoctoral scientist. Afterwards, I spent some time in a pharmaceutical company, but the sensation of being part of a team, working to advance scientific knowledge, and putting it into practise, had become too much a part of my nature. I therefore kept in close contact with the lab and with Désiré. Ultimately, I went back to Academia, in 1986 – and I came back to Leuven in 1993, where I joined the "Platelet" team, headed by Prof. J. Vermylen, after Hans Deckmyn moved to Kortrijk. Since then, I focus more on hemostasis and thrombosis, and on vascular biology. My contacts with Désiré, at the other end of the huge lab we moved into in 1993, have therefore become more organizational and more general. In some specific cases, I still had the pleasure of co-authoring papers with him, which every time reminded me of his firm and direct approach. His strong and

outspoken opinions have the advantage that he has no hidden agenda. He tells you things flat in the face and tries to solve whatever issue, on the spot, when possible, but, even when firm, he is straight and honest.

It would be presumptuous to even compare myself to him, but I learned a lot from him, during the years that I worked directly with him as a postdoctoral scientist. Also, now, in the continuous challenge to strive for quality and efficiency in our present research team, it makes you appreciate more his natural talent to do so…. I wish him a lot of success with his spin-off activities and a good health for many years, enabling him to be at the top of his company ThromboGenics, for a long time … and to enjoy some other aspects of life.

Present co-ordinates

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Jang, Ik-Kyung

Collaboration period

1985 - 1994

Collaboration topics

Fibrinolysis
Direct thrombin inhibitor
Antiplatelet agents

Selected joint publications

Jang I.K., Gold H.K., Ziskind A.A., Fallon J.T., Holt R.E., Leinbach R.C., May J.W., Collen D. Differential sensitivity of erythrocyte-rich and platelet-rich arterial thrombi to lysis with recombinant tissue-type plasminogen activator - a possible explanation for resistance to coronary thrombolysis. Circulation 79, 920-928,1989 (217 times cited).

Jang I.K., Gold H.K., Ziskind A.A., Leinbach R.C., Fallon J.T., Collen D. Prevention of platelet-rich arterial thrombosis by selective thrombin inhibition. Circulation 81, 219-225,1990 (194 times cited).

Brief narrative

Around the time that I started my clinical training at the University of Leuven in 1980, t-PA had just been purified by Désiré, and administered to a patient with acute myocardial infarction. In 1983, when I decided to do my PhD, I started working closely with Désiré. From this point on, his guidance would prove to be indispensable – not only during my thesis preparation, but even more so, four years later - when I would come to Boston. Working even more closely with Désiré in Boston, our focus was on the improvement of thrombolysis. A direct thrombin inhibitor and a glycoprotein IIb/IIIa inhibitor were tested as adjuncts to fibrinolytic therapy both in preclinical and clinical settings. Furthermore, the mechanism behind the resistance of thrombus to fibrinolytic therapy was identified through our collaboration.

Personal appreciation

Outside my family, Désiré has undoubtedly been the most influential figure in my life. Not only did he help shape my research career, but he also set me down the path to achieving my dreams as an academic cardiologist. Désiré has the distinctive ability - amongst his many talents - to make me feel like he has as much time as I need with him and more, although we all know what his schedule holds.

Désiré is truly like a member of my family. When my daughter was a freshman in college, she spent a summer in Désiré's lab. She still says that her birthday dinner at Désiré's house was one of the best. Désiré is also Godfather to my son, Peter – in whom, I have already begun to see some resembling patterns of passionate ambition.

During the twenty-five years I've known Désiré - I have only one regret. When he visited my home in Boston for the first time in this year, I was so excited and knowing Désiré to be a distinguished oenophile, I had prepared seven bottles of what I thought were good wines. He opened only two.

Present co-ordinates

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Janssens, Stefan

Collaboration period

March 1992 – present

Collaboration topics

Nitric oxide signaling
Gene transfer for myocardial dysfunction, restenosis and pulmonary hypertension
Growth factor therapy for myocardial ischemia

Selected joint publications

Janssens S., Flaherty D., Nong Z.X., Varenne O., van Pelt N., Haustermans C., Zoldhelyi P., Gerard R., Collen D. Human endothelial nitric oxide synthase gene transfer inhibits vascular smooth muscle cell proliferation and neointima formation after balloon injury in rats. Circulation 97, 1274-1281,1998 (134 times cited).

Varenne O., Pislaru S., Gillijns H., Van Pelt N., Gerard R.D., Zoldhelyi P., Van de Werf F., Collen D., Janssens S.P. Local adenovirus-mediated transfer of human endothelial nitric oxide synthase reduces luminal narrowing after coronary angioplasty in pigs. Circulation 98, 919-926,1998 (123 times cited).

Brief narrative

After obtaining my medical degree at the University of Leuven in 1984 and completing my cardiology fellowship at Gasthuisberg University Hospital in 1989, I left for additional cardiovascular research and clinical training at Massachusetts General Hospital, Harvard University in Boston. It is during my 3-year stay in Boston that I had the opportunity to frequently interact with Désiré. In those years, he was visiting on a regular basis (one of Sabena's most valuable frequent flyers) as part of his scientific collaboration with Dr. H. Gold of the cardiology division focusing on the new and exciting therapeutic possibilities offered by thrombolytic therapy. Désiré was keen on discussing science with the young Belgian "expats" in Boston as there were several of us. Although my research areas were not exactly related to thrombolytic therapy, but centered on the emerging role of Nitric Oxide in cardiovascular biology and disease, Désiré graciously offered me a position in his expanding laboratory in Leuven upon our return in 1992. He motivated us to help start and build a gene transfer research group within his laboratory and provided sufficient funding, logistical and scientific advise to make it work. His worldwide reputation and astute standing in the international scientific community proved invaluable in attracting many foreign pre- and postdoctoral

scientists, with whom I had the pleasure to collaborate. Moreover, his diplomatic skills were often crucial in securing sufficient protected research time for cardiologists with a US-infested desire to become clinician-scientists. Désiré had a special interest in the translational value of biomedical research and was absolutely essential in our dealings with foreign biotechnology companies, interested in investing in our gene therapy-based anti-restenosis program. The expertise we have gradually build over the years enabled us to expand the focus of these studies to include pulmonary hypertension and myocardial infarction and to translate many concepts first tested in gene-and cell-based preclinical models to phase 2 clinical testing in patients. When he became one of the key scientific directors of the newly formed Flemish Interuniversity Institute for Biotechnology (VIB) in 1994 a new success story took off with additional scientific opportunities, for which I am grateful to have been part of through my partim appointment as VIB group leader for the past 10 years. Most recently, as CEO of Thrombogenics, Désiré has maintained a close interest in our translational studies on the role of placental growth factor for ischemic myocardial dysfunction within the IWT and EU funding framework.

Personal appreciation

It is no understatement to describe Désiré as truly exceptional within the Belgian academic community, which for me personally relates to the unique combination of a superb intellect, relentless energy, and exceptional conviviality and kindness. As a junior medical student, I remember him as one of the few professors in medicine at our Alma Mater who stayed after courses to informally discuss scientific questions with interested students. He always impressed me with his “no-nonsense” approach, and infested many young colleagues with his adagio to always conduct proper control experiments and double checks, to excel in science through hard work and most importantly to always maintain scientific honesty. In addition to these scientific qualities, he is a wonderful human being and understands the art of warmly welcoming young people from all over the world within his research group. His advise surpassed merely scientific issues, and often became a lesson for life. He taught many of us how to deal with human resource problems, long before it became an obsession of modern management. But far and foremost, he also shared with many of us the pleasures in life offered by exquisite gastronomy and a carefully selected, fine glass of wine. Désiré stood by his loyal collaborators, no matter what. He offered wonderful dinners to many, but few made it to his “holy grail”. I am glad I saw his wine cellar and had the privilege to taste on many occasions.

Present co-ordinates

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Juhan-Vague, Irène

Collaboration period

1982 - 1989
2000 - 2007

Collaboration topics

t-PA and PAI-1 in obesity and cardiometabolic risk.

Selected joint publications

Juhan-Vague I., Moerman B., De Cock F., Aillaud M.F., Collen D. Plasma levels of a specific inhibitor of tissue-type plasminogen activator (and urokinase) in normal and pathological conditions. Thromb. Res. 33, 523-530,1984 (270 times cited).

Vague P., Juhan-Vague I., Aillaud M.F., Badier C., Viard R., Alessi M.C., Collen D. Correlation between blood fibrinolytic activity, plasminogen activator inhibitor level, plasma insulin level, and relative body weight in normal and obese subjects. Metabolism 35, 250-253,1986 (387 times cited).

Juhan-Vague I., Valadier J., Alessi M.C., Aillaud M.F., Ansaldi J., Philip-Joet C., Holvoet P., Serradimigni A., Collen D. Deficient t-PA release and elevated PA inhibitor levels in patients with spontaneous or recurrent deep venous thrombosis. Thromb. Haemost. 57, 67-72,1987 (378 times cited).

Alessi M.C., Juhan-Vague I., Kooistra T., Declerck P.J., Collen D. Insulin stimulates the synthesis of plasminogen activator inhibitor-1 by the human hepatocellular cell-line Hep G2. Thromb. Haemost. 60, 491-494,1988 (285 times cited).

Juhan-Vague I., Alessi M.C., Joly P., Thirion X., Vague P., Declerck P.J., Serradimigni A., Collen D. Plasma plasminogen activator inhibitor-1 in angina pectoris - influence of plasma insulin and acute phase response. Arteriosclerosis 9, 362-367,1989 (202 times cited).

Brief narrative

I became MD in 1970 and then specialized in haematology with a special interest in haemostasis diseases. Having the responsibility of a clinical lab at the University Hospital LaTimone in Marseille, I became rapidly interested in thrombolytic therapy and the study of fibrinolytic factors circulating in plasma. In 1982, Désiré Collen accepted to be the mentor for my PhD thesis and I began to study plasma t-PA antigen variations in clinical situations. I used the radioimmunometric assay described by Dick Rijken. We were surprised to found markedly increased levels of t-PA related antigen in plasma of severely

ill patients. Most of the immunoreactive material occurred as high molecular weight form which could not be identified as complexes of t-PA with known plasma protease inhibitors. As several others in the mean time, we identified a rapidly acting inhibitor of t-PA and urokinase which could increase up to 50 fold in severely ill patients or after major surgery. It was PAI-1….
By screening several pathological conditions, we became particularly interested in the disregulation of PAI-1 in obese and diabetic subjects. We showed that the insulin resistance state with its marker, hyperinsulinaemia, was associated with increased PAI-1 levels and that, in vitro, insulin could have a direct stimulating effect on PAI-1 synthesis by cells of hepatic origin.
In the 90s with my group, especially Marie-Christine Alessi, we were particularly interested in the description of the molecular mechanisms responsible for the up-regulation of PAI-1 in patients with obesity and the metabolic syndrome. We showed that human adipose tissue and specially that from visceral origin was a good producer of PAI-1, with a special role for stroma cells and macrophages. These results could explain the link between PAI-1 and the cardiometabolic risk, as in the mean time we showed that PAI-1 was a risk marker for myocardial infarction in the context of insulin resistance.
In 2000 we became interested in a possible role of PAI-1 in the development of adipose tissue and metabolic disorders and we initiated a fruitful collaboration with Roger Lijnen in animal studies. PAI-1 deficient or transgenic mice were submitted to nutritionally induced obesity and we could demonstrate that PAI-1 had a direct effect on weight gain and metabolic disorders; the effect of an anti PAI-1 compound was subsequently evaluated. This project represented the second collaboration period with the Leuven group.

Personal appreciation

Link Leuven-Marseille with 4 participants : Collen, Lijnen, Juhan-Vague and Alessi…

I am extremely grateful to Désiré. He accepted at the beginning that I focussed my thesis on clinical research. Without his help it would have been extremely difficult for me to initiate a research team in Marseille. Despite that he was not specially interested by the fibrinolytic disorder described in the metabolic syndrome (this “rare disease” that nobody is interested in he said) he encouraged me to go ahead and I assume he has no regrets as now the cardiometabolic risk is a very active topic of research…. Thanks to Désiré for his help in the development , with Marie-Christine Alessi, who also performed her PhD thesis with Désiré Collen, of a research lab which was labelled by Inserm in 1993. The gratefulness of the Faculty of Medicine in Marseille led to the nomination of Désiré Collen as Doctor Honoris Causa of the University of Mediterranée.

Link Leuven-Marseille, with 4 participants : Désiré, Louisa, Irène and Claude…

This long-term scientific connection was accompanied by a permanent friendship relationship between Désiré, Louisa, Irène and Claude.

Among the good fun we had together, I can mention Désiré's intronisation in the Tastevin community in Bourgogne at the Clos Vougeot, the highly selected wines degusted in Désiré's house, the sale by auction in Amsterdam, the cruise in the Mediterranean sea…As I have decided to retire soon, I hope to continue to enjoy fruitful discussions on the Mediterranean coast…

Present co-ordinates

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Korninger, Christian

Collaboration period

September 1980 – June 1981

Collaboration topics

Fibrinolysis
Thrombolysis

Selected joint publications

Korninger C., Stassen J.M., Collen D. Turnover of human extrinsic (tissue-type) plasminogen activator in rabbits. Thromb. Haemost. 46, 658-661,1981 (195 times cited).

Korninger C., Collen D. Neutralization of human extrinsic (tissue-type) plasminogen activator in human plasma - no evidence for a specific inhibitor. Thromb. Haemost. 46, 662-665,1981 (111 times cited).

Korninger C., Collen D. Studies on the specific fibrinolytic effect of human extrinsic (tissue-type) plasminogen activator in human blood and in various animal species in vitro. Thromb. Haemost. 46, 561-565,1981 (148 times cited).

Korninger C., Matsuo O., Suy R., Stassen J.M., Collen D. Thrombolysis with human extrinsic (tissue-type) plasminogen activator in dogs with femoral vein thrombosis. J. Clin. Invest. 69, 573-580,1982 (174 times cited).

Brief narrative

I obtained my M.D. at the University of Vienna in December 1975 and started my training at the First Internal Department of the Allgemeines Krankenhaus in January 1976. During those first years, my main responsibility was bedside clinical work and I gained experience in the fields of toxicology, cardiology, gastroenterology and haematology. The haemostaseologists Professor Deutsch and Professor Lechner sparked my interest in research and at the end of the 1970s I published my first papers on thrombocytopenia, haemophilia, von Willebrand's disease and thromboembolism. Thanks to Professor Verstraete I was able to join the Center for Thrombosis and Vascular Research in September 1980. At that time, the coagulation unit was run by Désiré Collen and his team (Roger Lijnen, Marc Hoylaerts, Dick Rijken) with many co-workers from abroad. There was a general feeling of excitement

and anticipation, since tissue-type plasminogen activator had been purified in sufficient amounts to be tested as a thrombolytic agent. With little experience and abundant enthusiasm I plunged into work and within a year succeeded in publishing 4 papers under the guidance of Désiré. His vision to see tissue plasminogen activator as the future thrombolytic agent ultimately proved to be right and when I returned to Austria I was able to take part in the national clinical trials of Alteplase, as it was then called. Back home I was able to use my insights in a number of publications on haemorrhagic and thrombotic disorders. In 1982 I spent a month at the Department of Haematology in Cardiff (Professor Bloom) and in 1983 another month in Milano (Professor Manucci). After a period of mostly patient-oriented work I spent another year of research (Sept 1983 to June 1984) with Professor Binder at the Department of Physiology in Vienna. I received my professorship in July 1986. Two years later, however, my scientific career ended abruptly by my decision to join a Trauma Centre as its specialist for Internal Medicine. This is very rewarding work, but leaves little time for research.

Personal appreciation

I joined the lab without the slightest idea of how medical research was done. I will never forget the first day I was shown around Gasthuisberg; everyone explaining his projects and me understanding - nothing. But with the help of Désiré, Roger, Jean-Marie Stassen and many others I soon got into the work and enjoyed it immensely. After only a year, I published four good papers, which were additionally sweetened with many post-printing citations (that one paper was often quoted …*contrary to*…is something with which I have learned to live). My stay in Leuven proved to be truly enjoyable, as I was accepted not only as a co-worker, but as a guest and friend. My housing in the Begijnhof was especially pretty and comfortable, and the hospitality of my colleagues was memorable. I remember being invited to Désisé's house almost weekly, where I enjoyed delicious food (oysters!), stimulating discussions and the traditional Bell's whiskey. When Professor Verstraete offered me a job for another year, I found it hard to decline. I wish Désiré all the best for the future. I am sure he will continue to contribute greatly to scientific education and research.

Present co-ordinates

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Lijnen, Roger

Collaboration period

February 1978 – now

Collaboration topics

Fibrinolysis
Thrombolysis
Atherosclerosis
Obesity

Selected joint publications

Lijnen H.R., Hoylaerts M., Collen D. Isolation and characterization of a human plasma protein with affinity for the lysine binding-sites in plasminogen - role in the regulation of fibrinolysis and identification as histidine-rich glycoprotein. J. Biol. Chem. 255, 214-222,1980 (239 times cited).

Lijnen H.R., Hoylaerts M., Collen D. Heparin binding-properties of human histidine-rich glycoprotein - mechanism and role in the neutralization of heparin in plasma. J. Biol. Chem. 258, 3803-3808,1983 (179 times cited).

Zamarron C., Lijnen H.R., Van Hoef B., Collen D. Biological and thrombolytic properties of proenzyme and active forms of human urokinase.1. fibrinolytic and fibrinogenolytic properties in human plasma in vitro of urokinases obtained from human urine or by recombinant DNA technology. Thromb. Haemost. 52, 19-23,1984 (163 times cited).

Zamarron C., Lijnen H.R., Collen D. Kinetics of the activation of plasminogen by natural and recombinant tissue-type plasminogen activator. J. Biol. Chem. 259, 2080-2083,1984 (150 times cited).

Lijnen H.R., Zamarron C., Blaber M., Winkler M.E., Collen D. Activation of plasminogen by prourokinase.1. mechanism. J. Biol. Chem. 261, 1253-1258,1986 (209 times cited).

Lijnen H.R., Collen D. Strategies for the improvement of thrombolytic agents. Thromb. Haemost. 66, 88-110,1991 (127 times cited).

Lijnen H.R., Van Hoef B., De Cock F., Okada K., Ueshima S., Matsuo O., Collen D. On the mechanism of fibrin-specific plasminogen activation by staphylokinase. J. Biol. Chem. 266, 11826-11832,1991 (111 times cited).

Lijnen H.R., Ugwu F., Bini A., Collen D. Generation of an angiostatin-like

fragment from plasminogen by stromelysin-1 (MMP-3). Biochemistry 37, 4699-4702,1998 (134 times cited).

Lijnen H.R., Van Hoef B., Lupu F., Moons L., Carmeliet P., Collen D. Function of the plasminogen/plasmin and matrix metalloproteinase systems after vascular injury in mice with targeted inactivation of fibrinolytic system genes. Arterioscler. Thromb. Vasc. Biol. 18, 1035-1045,1998 (139 times cited).

Brief narrative

I obtained my Ph.D. in Biochemistry at the University of Leuven in January 1978, and was offered the opportunity - only a couple of days later - to join the Center for Thrombosis and Vascular Research (as it was called at that time), under the direction of Prof. M. Verstraete. I joined the team of Désiré with as main project the study of the mechanism of the interaction between plasmin and α2-antiplasmin. α2-Antiplasmin was then just discovered, by Désiré and a few others. Most of these studies were done in collaboration with B. Wiman (Umea, Sweden) who was visiting the lab for one year. With the purification of tissue-type plasminogen activator (t-PA) and the characterization of its fibrin-specificity and therapeutic potential, almost the whole lab became involved in in vitro and in vivo experiments with t-PA, culminating in the successful development for thrombolytic therapy. These studies were extended to single-chain urokinase (su-PA) and the characterization of its fibrin-specificity. Very significant efforts were devoted to improvement of the thrombolytic profile of t-PA and scu-PA, via the construction of mutants, variants and chimeric proteins. Later on, focus was on staphylokinase; understanding its unique mechanism of action paved the way for clinical application in pilot studies in patients with acute myocardial infarction. Again, numerous mutants and variants of staphylokinase were produced and characterizated in order to improve its pharmacokinetic profiles and reduce its immunogenicity in man. Thromb-X (now ThromboGenics) was founded by Désiré to develop it further for thrombolytic therapy. In addition to the fibrinolytic system, we started studies on matrix metalloproteinases and their role in vascular remodeling, atherosclerosis and, more recently, in development of adipose tissue and obesity. These studies have up to now resulted in over 250 joint publications. The solid international reputation that our lab acquired over the years has attracted many (over 100 by now) foreign post-docs to spend one or more years in Leuven. Not only has this allowed me to have successful collaborations with these colleagues, but it has also left me with many good friends all over the world.
On November 1, 2007, Désiré resigned as Director of the Center for Molecular and Vascular Biology (CMVB), and I became his successor. Obviously, he still keeps a keen interest in the ongoing research.

Personal appreciation

When I joined the lab of Désiré back in early 1978, I really still had to learn what biochemical research was all about. He taught me how to focus on a problem, come up with a hypothesis and test it experimentally. A major asset to the lab has always been his clear vision on what would become important

in the near future, and his focus on the relevant issues ("Where is the meat?"). As a consequence we were usually amongst the first in the field to introduce new technology, starting with hybridoma technology in the 1980's, recombinant DNA technology and genetic engineering in the 1990's, transgene technology and gene transfer in the 2000's, and more recently stem cell technology.
The focus was always on fundamental research, but with an open mind for applications. Thus, Désiré was the first to realize the potential of t-PA as a commercial drug. Part of the royalty income earned on t-PA was invested in the lab, which allowed us to continue our research under the best possible conditions. As a consequence, the CMVB has grown from about 15 collaborators when I joined to over 60 by now. In addition, the recognition as a department of the Flemish Institute for Biotechnology allowed the foundation of the Center for Transgene Technology and Gene Therapy (now the Vesalius Research Center). It is clear to all of us that Désiré has been the driving force behind all these achievements, thanks to his scientific capacities and his management skills.
I have had the privilege to collaborate with Désiré over the past 30 years, and have come to appreciate him not only as a scientist but also as a caring colleague.
At present I am full professor at the Faculty of Medicine, which I would not have achieved without the continuous support of Désiré Collen. I wish him all the luck and hope that we can continue to collaborate for many more years to come.

Present co-ordinates

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Mann, Kenneth

Collaboration period

1984 – 2000

Collaboration topics

Clinical laboratory thrombolysis

Selected joint publications

Bovill E.G., Terrin M.L., Stump D.C., Berke A.D., Frederick M., Collen D., Feit F., Gore J.M., Hillis L.D., Lambrew C.T., Leiboff R., Mann K.G., Markis J.E., Pratt C.M., Sharkey S.W., Sopko G., Tracy R.P., Chesebro J.H. Hemorrhagic events during therapy with recombinant tissue-type plasminogen activator, heparin, and aspirin for acute myocardial infarction - results of the thrombolysis in myocardial-infarction (TIMI), phase-II trial. Ann. Int. Med. 115, 256-265,1991 (170 times cited).

Braunwald E., Mccabe C.H., Cannon C.P., Muller J.E., Knatterud G., Thompson B., Prior M.J., Kufera J., Wilkins P., Giro R., Randall A., Frederick M., Canner M., Depkin J., Monroe L., Bell P., Desvignenickens P., Letendre C., Mann K.G., Bovill E. Effects of tissue-plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-q-wave myocardial infarction - results of the TIMI IIIb trial. Circulation 89, 1545-1556,1994 (500 times cited).

Brief narrative

I became aware of Désiré's rt-PA studies while I was at the Mayo Clinic in Rochester, Minnesota. At the time, I was advising the NIH with respect to new clinical trials of thrombolysis using streptokinase and recommended that if they were going to anticipate such a trial they should certainly involve tissue plasminogen activator. The result was the TIMI I trial, which showed advantages of rt-PA over streptokinase. Subsequently, I was asked to advise with respect to the design of TIMI II, which was being directed by Dr. Eugene Braunwald. TIMI II had been designed without incorporating laboratory studies of blood and I objected strongly to this omission. This led to my involvement with Ted Bovill and Russell Tracy in laboratory studies for TIMI II, which initially over-dosed the patients with rt-PA. The laboratory studies identified the need for a lower rt-PA dose and kept that trial from being terminated as a consequence of several cerebral hemorrhages. My involvement with the TIMI trials ended at #IV but my colleagues Bovill and Tracy continued in this enterprise which is now up to TIMI 40+. During this

interval, I came to know and regard Désiré as a close friend and invited him to a joint faculty position at the University of Vermont (which he still holds). Désiré spent a number of summers here in Vermont with his family and made significant intellectual contributions to the life of Biochemistry and Medicine at this institution. Subsequently, I had the opportunity to spend several months on sabbatical in Leuven, with Jeanette and I staying at the Begijnhof. This was a very memorable experience for both of us where we enjoyed the hospitality of the Collen family and the laboratory.

During the early days of rt-PA thrombolysis there was significant acrimony from the streptokinase devotees. Following the resolution in favour of rt-PA, I presented to Désiré, in the matador tradition, a pair of pig's ears.

With the success of thrombolysis in treating myocardial infarction, individuals in the cardiology and hematology community sought credit for Désiré's accomplishments. During a dinner at a Chinese restaurant in Washington with Désiré and Harold Roberts, we discussed the issue of scientific recognition. Remarkably, Désiré's fortune cookie read "you must advertise your accomplishments."

During my scientific career I have had the opportunity to develop many wonderful friendships frequently because of chance interactions. I have had the opportunity to develop one of my best friendships with Désiré Collen.

Personal appreciation

As I approach the end of my professional career, I realize that one of the most important privileges of the academic science occupation has been the continuous interaction with so many talented and interesting colleagues. Having remained in the same research field for 40 years, I have also had the privilege of retaining professional and social connections with many acquaintances, colleagues and competitors. During the duration of a professional career, one collects a small number of these individuals in the category of close friends. I am honoured to include Désiré and Louisa Collen (and family) in this category.

Present co-ordinates

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Matsuo, Osamu

Collaboration period

September 1979 - June 1980
1990 - 2000

Collaboration topics

Fibrinolysis
Thrombolysis

Selected joint publications

Matsuo O., Rijken D.C., Collen D. Thrombolysis by human tissue plasminogen activator and urokinase in rabbits with experimental pulmonary embolus. Nature 291, 590-591,1981 (227 times cited).

Matsuo O., Rijken D.C., Collen D. Comparison of the relative fibrinogenolytic, fibrinolytic and thrombolytic properties of tissue plasminogen activator and urokinase in vitro. Thromb. Haemost. 45, 225-229,1981 (176 times cited).

Brief narrative

I met Désiré and Roger at the Center for Thrombosis and Vascular Research, in April 1979. This was my first visit to Belgium. Désiré and I then went to the Schwarzwald (Germany) for an International Conference, driving his yellow car.
After joining Désiré's lab in September 1979, I stayed almost 1 year; I am convinced that the scientific activities and results in this short period are equivalent to those of 3-5 or more years in Japan. The organisation of the research in the Center for Thrombosis and Vascular Research was excellent with many well-trained and top-grade technicians. Because I received the funds for my travel expenses from our Government, I had to return to Japan on a fixed date (they check the passport record!). Therefore, I worked not only in the weekend but also on holidays in order to accomplish the experiments. Jan Stassen worked with me, preparing the animal experiments, and his technique improved markedly. One evening when I was working on a rabbit that was intravenously injected with t-PA, Désiré invited me for dinner. As I had to take blood samples until midnight, I brought the rabbit to his bathroom and continued the experiments at his house. The data including this rabbit were published in Nature (1981). Then, the experiments to confirm the efficacy of t-PA were upgraded to dogs (J Clin. Invest. 1982). After leaving Leuven, t-PA was administered to a lady with venous thrombosis. This was the first case where t-PA was injected to a human being, and a new thrombolytic strategy was developed.

Besides t-PA, I worked on a thrombin inhibitor when I came to Leuven (J. Lab. Clin. Med. 1982). During the research on t-PA, I have done several other experiments including studies on urokinase (Thromb. Haemost. 1981 and 1982), and on APSAC (anisoylated plasminogen streptokinase activator complex) (Thromb. Res. 1981).
Désiré invited me for dinner many times, and every time I found that the road from his place to the Begijnhof is not straight; it became an S-type snake road due to Smuggler!
The time I spent in Leuven was very short, but it is was very impressive and I vividly remember it. During my stay in Leuven, we published 5 papers, confirming that it was very productive. After coming back to Japan, I visited Leuven many times, and noticed major changes not only in KUL but also in Leuven city itself. A new highway was opened and it became very easy to access Leuven, but inside the city, new one-way streets or newly closed streets appeared at many places.
As my interest has been in Fibrinolysis, Thrombolysis, and related areas, I kept performing research in these fields, and started on a new exciting protein, staphylokinase (BBRC 1989, Blood 1900). In order to confirm the mode of its action in animal experiments, Désiré and me started a new collaboration on staphylokinase. This collaboration was the 2nd stage for us and opened a new era for thrombolytic agents (JBC 1991, Thromb. Haemost. 1991, BBA 1992). Ueshima Shigeru from my lab joined Désiré's lab and also worked on staphylokinase (Thromb. Haemost. 1993) and urokinase (Thromb. Haemost. 1994).
In 1997, Okada Kiyotaka from my lab joined Désiré's lab, and succeeded to clone the murine alpha2-antiplasmin gene with Roger, which led to produce alpha2-antiplasmin knock-out mice (Thromb. Haemost. 1997, Blood 1999). I can say this is the 3rd stage of the collaborations between Désiré and me. Since then, we are now on the 4th stage of the collaboration, which focuses on new functions of fibrinolytic factors in vascular biology (Thromb. Haemost. 1999), neuroscience (Neuroscience Lett. 1997), or thrombogenesis (Br. J. Pharmacol 2000, J. Cardiovasc. Pharmacol. 2000).
In 2007, Nagai Nobuo joined my lab from Désiré's lab. Thus, my staff (Ueshima, Okada and Nagai) are all "pro-Leuven"!!

Personal appreciation

When I first found Désiré's name in the literature, I was a student in Kobe Graduate School of Medicine. Since then, I found him always at the front edge of new fields in science. He is an excellent leader in the field of not only Fibrinolysis and Thrombolysis, but also Genetic Biology and Stem Cell Biology.
He manages a very big lab with a large number of researchers, which is, I believe, No. 1 in the world. This is due to Désiré's powerful and superhuman activity in science as well as society. I have learned something very helpful to manage an organization when I obtained a position as professor at Kinki University.
I greatly appreciate Désiré Collen for his excellent leadership in KUL as well as academic society and also for supporting me at various occasions. I wish

him and his family good health and good luck, and hope to continue our collaboration further (it may become 5th stage).

Present co-ordinates

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Nagai, Nobuo

Collaboration period

September 1997 - February 2007

Collaboration topics

Ischemic stroke
Fibrinolysis
Thrombolysis
Microplasmin development

Selected joint publications

Nagai N., De Mol M., Lijnen H.R., Carmeliet P., Collen D. Role of plasminogen system components in focal cerebral ischemic infarction - A gene targeting and gene transfer study in mice. Circulation 99, 2440-2444, 1999 (102 times cited).

Brief narrative

I started to do research at the University of Leuven as a postdoctoral fellow with Peter Carmeliet in September 1997. First, I introduced a mouse ischemic stroke model for studying the roles of plasmin system components in cerebral ischemic stroke, and found the neurotoxic role of t-PA. This gave me an opportunity to work with Désiré. He proposed to study the effects of other plasminogen activators, streptokinase and staphylokinase. This was difficult because staphylokinase did not work in mice. Thus, I had to establish a stroke model in the hamster. This was very difficult because no hamster stroke model existed. Finally I succeeded to make the model, which took about half a year, and found that these activators also had neurotoxic effects on ischemic stroke. Furthermore, I found a protective role of plasmin and neurotoxic role of α_2-antiplasmin on ischemic stroke. These data suggested that microplasmin, which neutralizes α_2-antiplasmin, might be used as an anti-stroke agent. In 1998, I went back to Japan, and then came back to Leuven in July 2000 as a staff scientist. I started to evaluate the effect of microplasmin treatment on ischemic stroke in mice and other species. This project was strongly supported by Ms. Ingrid Vanlinthout, a senior technician of Thromb-X, and Dr. Yasuhiro Suzuki, a post doctoral fellow from Hamamatsu University School of Medicine in Japan. In April 2006, I started to work as a postdoctoral fellow with Roger Lijnen on a project of obesity and thrombosis. In February 2007, I left Leuven to move to a new position in Kinki University School of Medicine, Osaka Japan.

Personal appreciation

My Belgium life was quite comfortable and busy. I could concentrate on research and enjoy life with my family. This was thanks to the support of Désiré both in public and private matters. In research, he supervised me very closely, but never commanded oppressively. I always discussed with him and then went ahead with satisfaction.
I learnt form him to express my opinion. Usually, Japanese do not show their opinion clearly. But he always pointed out and told me “Answer clearly. Say YES or No”. He also told me “Keep your position like a SUMO wrestler”. This advice was very persuasive because he has a strong physique. Thanks to his advice, I am able to express my opinion and communicate smoothly with colleagues. This attitude has brought me a lot of advantages even after coming back to Japan.

I am very happy that I had the opportunity to work with him for almost 10 years.

Present co-ordinates

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Nelles, Luc

Collaboration period

1985 - 1993

Collaboration topics

Tissue-plasminogen activator and urokinase protein engineering.
Regulation of expression of plasminogen activators and their inhibitors.

Selected joint publications

Nelles L., Lijnen H.R. Collen D., Holmes W.E. Characterization of a fusion protein consisting of amino-acids 1 to 263 of tissue-type plasminogen activator and amino-acids 144 to 411 of urokinase-type plasminogen activator. J. Biol. Chem. 262, 10855-10862, 1987 (105 times cited).

Nelles L., Lijnen H.R., Collen D., Holmes W.E. Characterization of recombinant human single chain urokinase-type plasminogen activator mutants produced by site-specific mutagenesis of lysine 158. J. Biol. Chem. 262, 5682-5689, 1987 (121 times cited).

Brief narrative

I was finishing my PhD at the Antwerp University when I got a call from a colleague in Leuven, saying that a certain Professor Collen was looking for someone with experience in DNA cloning. At that moment in history we were few with that ability (lucky me), and I was almost instantly hired. I spent the next nine years trying to improve on Nature, making improved plasminogen activators with properties more suited for thrombolytic therapy, which turned out to be extremely difficult, (Nature of course has had the advantage of a few million years time). Later on we also engaged in figuring out how the different players in the field of plasminogen activation are regulated.

Personal appreciation

When I now think back at that period, I have visions of Désiré presiding the lab meeting with some 20-odd people, and he knew of all of them what they were doing, critically going through every experiment, giving detailed advice on how to proceed, telling which lead to take and what to focus on.
What I learned from him is to do sound statistical analysis of results, differentiate important from unimportant observations (although somehow I never got the touch of that), and to get from time to time a decent beard cut (no comments).

Present co-ordinates

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Owen, Whyte

Collaboration period

July 1981 – June 1983

Collaboration topics

Mechanism of heparin
Assay of protein C

Selected joint publications

Hoylaerts M., Owen W.G., Collen D. Involvement of heparin chain length in the heparin-catalyzed inhibition of thrombin by antithrombin III. J. Biol. Chem. 259, 5670-567, 1984 (96 times cited).

Sala N., Owen W.G., Collen D. A functional assay of protein-C in human plasma. Blood 63, 671-675, 1984 (137 times cited).

Brief narrative

I came to Brussels in July of 1981 for a sabbatical with Pierre DeMeyts at UCL-St. Luc. I studied insulin metabolism, but because I was acquainted with Désiré I visited for a seminar on thrombomodulin, then a fresh topic. We struck up a collaboration to develop an approach to assay protein C in plasma, spearheaded by Nuria Sala, then a graduate student in his program. I began visiting his lab on Fridays to review her progress and advise. As the year developed, conversations with Marc Hoylaerts led to a second collaboration, made possible by a covalent adduct of antithrombin to heparin. By year's end, we had made enough progress that papers from both collaborations were soon to be submitted. The paper on Nuria's work was accepted after some revisions. The one with Marc, however, had an issue that could only be addressed with further, and substantial, work. So, I returned to Leuven for three months in the Spring of 1983 to tidy up. During that second visit I was full time in the lab and was able to appreciate the wonderful community of people he had gathered around him.

Personal appreciation

The two papers arising from our brief collaboration rank among the best in my regard among those in my bibliography. However, what makes those two papers memorable is the process through which they arose. I was in Désiré's lab during the time he was commuting to Genentech to develop t-PA as a pharmaceutical, so he was away much of the time, and often subject to jet lag

when not. Sometimes he may have come from the airport to the lab. In spite of these demands, when we met on Fridays for review, he knew every detail of every measurement in Nuria's notebooks, and during my second visit he would have the same insight into that of mine and Marc's. It seemed that he had (has?) turbocharged adrenal glands. As I spent more time in the lab it became clear that, in spite of a daunting number of personnel, maybe twenty five or so? (Roger was a start-up staff member then), and diversity of projects, Désiré was mentoring each person in the lab with the same intensity, commitment and insight that he showed with Nuria and Marc. This was true for visiting faculty such as I, post-docs, graduate and undergraduate students, technicians, and colleagues on the KUL faculty. I can also see in retrospect that each person he mentored held him in highest regard and respect, and proved it with a level of focus and effort I still find grand. It is no surprise that Nuria and Marc, like so many he has mentored, went on to their own successful research careers.

Present co-ordinates

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Páramo, José

Collaboration period

September 1983 - December 1984

Collaboration topics

Fibrinolysis
Thrombosis
Atherosclerosis

Selected joint publications

Colluci M., Páramo J.A., Collen D. Generation in plasma of a fast-acting inhibitor of plasminogen activator in response to endotoxin stimulation. J. Clin. Invest. 75,818-824, 1985 (403 times cited).

Páramo J.A., Colucci M., Collen D., Van de Werf F. Plasminogen activator inhibitor in the blood of patients with coronary artery disease. Brit. Med. J. 291, 573-574, 1985 (272 times cited).

Brief narrative

I obtained my degree of Medicine at the University of Salamanca (Spain) in 1979, and the title of Hematology as well as the PhD in Medicine in 1982 at the University of Navarra with a project on hypercoagulable states in orthopaedic surgery. After my postdoctoral stay in Leuven, I became consultant in Hematology since 1990, and Professor of Hematology at the University of Navarra since 2002. At present, I am the Director of Hematology Service at the University Clinic of Navarra.
After joining the team of Désiré as postdoctoral fellow I continued doing clinical research in fibrinolysis and venous thrombosis, to further move to the atherosclerosis field, in which I continue developing clinical and basic research, mainly in the areas of inflammation and proteolysis. We have performed a series of studies showing the expression of different metalloproteinases (e.g. MMP-10) by human endothelial cells in response to either inflammatory or thrombotic stimuli and we are currently developing a model of atherosclerosis in MMP-10 knockout mice. At the clinical level, we are interested in measuring biomarkers of inflammation, proteolysis and thrombosis both in subjects free from clinical atherosclerosis and in patients with established atherothrombosis.

Personal appreciation

I had the pleasure of working in Désiré's lab from September 1983 to December 1984. I met him for the first time during a congress early 1983 and, quite shyly, asked him to develop a project in his lab, which he immediately approved. It was really a lucky day for me and my first experience abroad which, I should confess, was unique and definitely marked my future as both physician and scientist. I learned from him how important a rigorous and solid project can be. I specially remember the lab meetings and realize how clever and firm Désiré was regarding the results obtained and conclusions to be drawn. I was always impressed by his charismatic leadership, his scientific and pedagogic level, his enthusiasm and humanity.
I appreciate very much his support while at Leuven and at different occasions afterwards, and I consider the time I spent as a research fellow in his lab as a real privilege.

Present co-ordinates

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Pennica, Diane

Collaboration period

June 1980 – November 1987

Collaboration topics

Cloning of t-PA

Selected joint publications

Pennica D., Holmes W.E., Kohr W.J., Harkins R.N., Vehar G.A., Ward C.A., Bennett W.F., Yelverton E., Seeburg P.H., Heyneker H.L., Goeddel D.V., Collen D. Cloning and expression of human tissue-type plasminogen activator cDNA in escherichia coli. Nature 301, 214-221,1983 (1107 times cited).

Collen D., Stassen J.M., Marafino B.J., Builder S., De Cock F., Ogez J., Tajiri D., Pennica D., Bennett, W.F., Salwa J., Hoyng C.F. Biological properties of human tissue-type plasminogen activator obtained by expression of recombinant DNA in mammalian-cells. J. Pharmacol. Exper. Therap. 231, 146-152, 1984 (138 times cited).

Brief narrative

Back in 1980, less than two months after my first day on the job, Genentech sent me to a conference in Malmo, Sweden. There, Désiré Collen would be presenting his research results on the tissue plasminogen activator (t-PA) protein. We thought at the time that this protein held great potential for dissolving blood clots in heart attack and stroke victims.
The story of how I actually got to spend time with Désiré face-to-face is nothing short of fate, and my penchant for punctuality. I arrived at the hotel a day early and decided to go ahead and locate the conference room so that I would know exactly where to go the next morning. When I asked for directions, the hotel receptionist told me that the "meeting of the doctors" was already in progress.
Thinking that I'd mixed up the dates due to the time change, I stashed my bags in my room and, wearing my same travel clothes of pants and a hot-pink sweater, ran to the meeting where Désiré was just beginning his talk. I sat in the back, busily scribbling notes. About 30 men were sitting around the table in suits and ties, and they all kept looking back at me.
It was only during a break that, after introducing myself to several of the participants including Désiré, I realized that I'd stumbled into a very exclusive pre-conference meeting restricted to a small elite group of researchers. The actual conference was, indeed, scheduled for the next day. With more than

300 attendees, the chance was slim that I would have met any of these leading scientists, let alone Désiré.
One of the men told me that they just assumed I was one of the speakers' daughters, otherwise I would have been asked to leave that small pre-conference meeting. Instead, the scientists invited me to join them for dinner, where I struck up a conversation with Désiré, and explained my desire to clone t-PA.
He told me that it would be very difficult because it was such a huge protein. To be honest, I didn't know much about cloning at that time. I knew Genentech scientists had cloned human insulin and growth hormone, so I didn't see any reason why we couldn't clone t-PA, as well. I told him, “Sure, we can do it!” Désiré agreed to share some of his reagents and work with us as a consultant.
I returned to Genentech and began what would become two years' worth of work. For at least nine months of that time, I worked 18-hour days, seven days a week with no time off. We'd heard that other drug companies were attempting to clone t-PA. I knew that to beat the competition, we needed to work harder than anyone else.
There were many months of disappointing results and false leads in the attempt to find the t-PA clone. Finally, in October of 1981, after being given the sequence of one of the clones, I recognized a stretch of five amino acids that I knew was a portion of the t-PA protein.
I started shaking because I realized that we had finally succeeded in determining it’s structure. We'd worked so long and so hard to get the t-PA clone. It was incredibly exciting and we could not have succeeded without Désiré’s help and expert advice. I still have the empty bottle of Dom Perignon that we drank to celebrate that day. I only wish Désiré could have been there to share it with us. I called him immediately to share the exciting news. After the FDA approved Activase on November 13, 1987 for treating heart attacks, Genentech held a huge celebration, complete with fireworks over the bay.
Hospitals and drug wholesalers scooped up $58 million worth of Activase within the product's first seven weeks on the market. Bob Swanson called Activase "the most successful new drug ever launched," during a speech to analysts in early 1988.
In 1996 t-PA was approved for the treatment of strokes. But it's not the celebrations that I remember most. It's the Christmas card that I have framed in my office, and the many notes like it that I’ve received over the years.
I'll never forget receiving a Christmas card from Mike Blum, a heart attack patient who received t-PA. He wrote, “Dear Dr. Pennica, Thank you for helping to save my life.”

Personal appreciation

Thank you Désiré for making my first project at Genentech the most exciting time of my life. You have become a personal friend during our collaboration. Thank you for your vision, your encouragement and excitement during this project. You made our dream of developing a drug for heart attack and stroke

victims come true.
I wish you good health, happiness and exciting new adventures during your retirement.
Best wishes my dear friend!

Diane

Present co-ordinates

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Plow, Edward

Collaboration period

1978 - now

Collaboration topics

Plasmin-antiplasmin complex
Plasminogen-deficient mice
Plasminogen and inflammation
Fibrinolytic receptors
Appreciation of fine wines

Selected joint publications

Miles L.A., Levin E.G., Plescia J., Collen D., Plow E.F. Plasminogen receptors, urokinase receptors, and their modulation on human endothelial cells. Blood 72, 628-635,1988 (123 times cited).

Ploplis V.A., Carmeliet P., Vazirzadeh S., Van Vlaenderen I., Moons L., Plow E.F., Collen D. Effects of disruption of the plasminogen gene on thrombosis, growth, and health in mice. Circulation 92, 2585-2593,1995 (196 times cited).

Ploplis V.A. French E.L., Carmeliet P., Collen D., Plow E.F. Plasminogen deficiency differentially affects recruitment of inflammatory cell populations in mice. Blood 91, 2005-2009, 1998 (91 times cited).

Brief narrative

I have known Désiré for more than 30 years as a colleague, a collaborator and as a friend. Over time, some of my recollections may have faded but are hopefully not entirely inaccurate. One of my first memories of meeting Désiré was in the early 1970s when Tom Edgington and I visited Leuven. We met in Désiré's office, still at the hospital, where he told us of his data indicating the existence of a new and fast acting inhibitor of plasmin. To suggest that there was an inhibitor of plasmin other than α2-macroglobulin was certainly iconoclastic, but Désiré had already assembled considerable evidence and was passionate in his presentation and his believe in α2-antiplasmin. In fact, over the next 2-4 years, he not only convinced me but also the entire scientific community that α2-antiplasmin was the primary inhibitor of plasmin. By 1978, Désiré was in the midst of developing immunoassays specific for the complex with plasmin (PAP). I had developed considerable experience in immunochemistry and I spent a 3-month sabbatical working on a latex agglutination assay specific for PAP and for other aspects of the

immunochemistry of the plasminogen system. At this time, Roger Lijnen was just joining the lab and Bjorn Wiman was in Leuven. It was a great pleasure to work with them and Désiré and I learned a lot. I note that the papers we published from our studies during this period are not on our “best seller” list, but the assays were robust and the experience and friendships made have lasted a long, long time. I note with some comfort that PAP assays are still in use and may enjoy revitalization as a predictor of risk in CAD in association with genetic markers.

Désiré and I continued to collaborate occasionally and to meet when we could throughout the 1980s and early 1990s. His passion, drive and tenacity, coupled with his keen sense of observation and grasp of scientific significance, led to his many landmark discoveries during this period. It is not my place to enumerate them here and leave it to his direct collaborators during this time to note the significance of his many accomplishments. In 1994, I relocated to the Cleveland Clinic and took advantage of my new environment and Désiré’s generosity to initiate a new collaboration. Vicky Ploplis was joining our Center at the Clinic and relocated via Leuven. She spent a year with Désiré and Peter Carmeliet creating the plasminogen knock-out mouse. Vicky will comment on her memories of this time. My recollection is the keen competition to get the mouse. Yet, more than 14 years after their creation, we continue to use these mice in my own research program, and the collaborative papers with Désiré on the plasminogen deficient mice did make our best seller list.

Personal appreciation

I begin by gratefully acknowledging Désiré for his scientific contributions. They have had an enormous impact and have changed the face of fibrinolysis. He has not only defined our understanding of the most fundamental aspects of fibrinolysis but has impacted on its most practical aspects, patient care. In short, his findings have saved lives. This bench to bedside translation is a goal that we all give lip service to but only very few in our profession achieve. Désiré has accomplished this and continues to be driven by this most admirable goal of our profession.

But to dwell on Désiré’s scientific accomplishments is not begin to give the full picture of my appreciation. Rather I want to acknowledge and thank him for his friendship. Désiré is such an open and generous individual. He has always been willing to help, always willing to share. He has helped my scientific career and most importantly has given me perspective. He has opened his home to me on numerous occasions, Even when we have not seen each other for long periods of time, I always feel glad to see him; I always feel that he and Louisa welcome me back into their home and their lives. Thank you.

Of course, it is hard to imagine Désiré as “retired.” I know that this is just the next phase of his career, of his life. I wish him health and I have no doubt that he will be successful.

Best wishes,

Ed

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Rakoczi, Istvan

Collaboration period

January 1977 - October 1977

Collaboration topics

Fibrinolysis
Postoperative deep vein thrombosis

Selected joint publications

Rakoczi I., Wiman B., Collen D. Biological significance of specific interactions between fibrin, plasminogen and antiplasmin. Biochim. Biophys. Acta 540, 295-300, 1978 (112 times cited).

Brief narrative

I was a young Hungarian OB/GYN, when I could get a fellowship in the frame of a Belgian-Hungarian Cultural Exchange Programme. The date was 1977. The iron curtain still existed! I was the first east-european guest – researcher in the blood coagulation laboratory who came from behind the iron curtain. It was an exciting time for me and an unbelievable opportunity to participate in the work of the blood coagulation research laboratory led by Prof. Verstraete. Being an obstetrician-gynaecologist I worked among other things on the prediction of postoperative leg-vein thrombosis in gynaecological patients: the paper of which I was the first author was published in the Lancet (1978). Another first author paper was published in Surgery, Gynaecology, Obstetrics (1980). This work was done in collaboration with the Department of Obstetrics and Gynecology, University Hospital Gasthuisberg (Prof. Van Assche, Prof. Spitz). Besides this main topic, during my stay in Leuven I worked with Désiré's team as well, mainly to study the mechanism of interaction between plasmin and α2-antiplasmin. I worked with Björn Wiman and Désiré, and we studied the specific interaction between fibrin, plasminogen and α2-antiplasmin. These results were published in Biochim.Biophys.Acta (see above).

Personal appreciation

I arrived in Belgium in January 1977. Docent Collen was waiting for me at Zaventem Airport. That was my very first „western trip", so I was deeply impressed and excited. During the trip to Leuven I felt instantly his special personality and hospitality. During my ten months stay in Leuven I always had kind help from all members of the blood coagulation laboratory. I made a lot of friends. It was my privilege to work with Désiré; Désiré was not only a brilliant

scientist but also a caring friend. I was invited several times by Désiré's family into their house. We had nice red wine in the summer time in their garden, and I helped to care for the goats raising antibodies against several factors of blood coagulation. When I returned home to Budapest, I continued to study aspects of blood coagulation related to obstetrics and gynaecology. I wrote a book entitled „Perinatal blood coagulation disorders" and several chapters on hemostasis in other books. Our results have resulted in several publications in Hungarian and foreign journals. I obtained my PhD in 1980 and became Doctor of Sciences in 1991 (Both scientific degrees related to blood coagulation in obstetrics and gynaecology.) In 1995 I was appointed head of the OB/GYN Department in one of the largest hospitals in Budapest. At present I am full professor of OB/GYN. I vividly remember the time spent in Leuven in 1977. It was a great time. Thanks to all members of the laboratory.

Present co-ordinates

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Rijken, Dingeman

Collaboration period

October 1979 – April 1982

Collaboration topics

Fibrinolysis
Thrombolysis

Selected joint publications

Rijken D.C., Collen, D. Purification and characterization of the plasminogen activator secreted by human melanoma cells in culture. J. Biol. Chem. 256, 7035-7041,1981 (767 times cited).

Rijken D.C., Hoylaerts M., Collen D. Fibrinolytic properties of one-chain and two-chain human extrinsic (tissue-type) plasminogen activator. J. Biol. Chem. 257, 2920-2925,1982 (352 times cited).

Rijken D.C., Juhan-Vague I., De Cock F., Collen D. Measurement of human tissue-type plasminogen activator by a two-site immunoradiometric assay. J. Lab. Clin. Med. 101, 274-284,1983 (155 times cited).

Brief narrative

In 1974 I obtained my master's degree in biochemistry at the University of Utrecht, the Netherlands, and started as a PhD-student at the Gaubius Institute TNO in Leiden. The topic of my research was the purification of tissue plasminogen activator from human uterine tissue. In that time the director of our Institute, Dr. Pieter Brakman, organized small meetings of the Fibrinolysis Working Party of the European Thrombosis Research Organization (ETRO) in our laboratory. During one of these meetings, it was on plasminogen in 1975, I saw Désiré for the first time. I was not allowed to attend the meeting, although I was highly interested in the topic. Plasminogen was the substrate of my favourite enzyme. Two years later the topic of the meetings moved to t-PA and I was invited to tell my story to t-PA experts such as Fedor Bachmann and Per Wallén. Désiré was not present this time. He was probably not (yet) interested in t-PA, because α_2-antiplasmin was much more important at that moment.
The first time that I really spoke with Désiré was during the International Fibrinolysis Conference in Karlovy Vary, in September 1978. Pieter Brakman and Professor Marc Verstraete had arranged that I could possibly spend some time in Leuven as a post-doc. Initially I hesitated somewhat to continue

with research on t-PA, because I had the idea that we already knew most properties of t-PA. I did not realize that thousands of papers would still be published on this particular enzyme. Désiré was the big star of the Karlovy Vary meeting, where he received, together with Björn Wiman, the "Prix Servier" for the excellent work on α_2-antiplasmin. Accordingly I was excited that I could work with this famous researcher, in spite of the fact that I noticed that he did not attend my presentation on the biochemical and immunological characterization of t-PA during this conference.
In October 1978 I visited the laboratory in Leuven, I presented my work and we arranged that I would come after completion of my PhD thesis. The plan was to study the kinetics of the activation of plasminogen by t-PA in the presence of fibrin. In the summer of 1979 I met Désiré again during the ISTH Congress in London. Désiré presented here the plenary Edward Kowalski Memorial Lecture. The publication of this lecture in Thrombosis and Haemostatsis would prove to be the standard reference in fibrinolysis papers for many years. Désiré told me in London that he had obtained a human melanoma cell line, which could be a better source for t-PA than uterine tissue. And so I started in October in Leuven with the purification of the plasminogen activator secreted by the melanoma cells, together with Eddy Demarsin.
I spent 2.5 years in Leuven and had a beautiful time. We isolated and characterized t-PA from both melanoma cell cultures and uterine tissue, I collaborated with Ksenia Bykowska who discovered that bovine aortic endothelial cells in culture did not produce t-PA but u-PA, with Osamu Matsuo who performed the first thrombolysis experiments with t-PA both in vitro and in vivo, and with Marc Hoylaerts and Roger Lijnen who disclosed the complicated kinetics of plasminogen activation. Together with Frans De Cock we developed the first immunoassay for t-PA and found that t-PA in plasma was largely bound to proteinase inhibitors. I had the chance to spend some time in London with David Blow trying to crystallize t-PA (which did not succeed) and in La Jolla with Edward Plow trying to characterize the interaction between t-PA and fibrin with specific antibodies against fibrin. Although Désiré was sometimes more absent than present in the laboratory, he was the central motor of all these studies.
In 1982 I returned to the Gaubius Institute in Leiden and continued with fibrinolysis research. Now and then we had a collaboration with Désiré's group, such as on α_2-antiplasmin Enschede (Holmes et al. Science 1987) and on staphylokinase (Sakharov et al. J Biol Chem 1996). We had frequent contacts about t-PA-patent issues and very funny, in the second half a the nineties, I met Désiré sometimes in our institute in Leiden, because his daughter Annemie performed her PhD study in our laboratory. It was always a nice experience to hear Annemie speaking in the laboratory, because it felt as if I was back in Leuven. I even have a joint publication not with D. Collen, but with A. Collen.
In October 2003 I moved to my present place in the Erasmus University Medical Center in Rotterdam, the Netherlands. At the Department of Hematology I continue working on issues in hemostasis. This is the hospital where the first two patients were treated with t-PA (Weimar et al. Lancet 1981). I still remember that I transported purified t-PA for the second of these patients from Leuven to Rotterdam on a Saturday morning. In this way I could combine a scientific trip with a visit to my relatives in Holland. The Erasmus

University is also the university where Désiré was awarded for the first time as doctor honoris causa (1988).

Personal appreciation

Looking back to my scientific career, I realize that this would have been completely different if I had never met Désiré. His guidance, view and support have been critical for my research activities. Above all I appreciate his sincere personality and our friendly contacts. I spent just 2.5 years in Leuven, but I can not remember how many times Désiré and Louisa made us feel cordially welcome in the Schoonzichtlaan!

Present co-ordinates

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Sala, Nuria

Collaboration period

September 1981 - September 1983

Collaboration topics

Anticoagulant protein C
Bioassay
Thrombophilia

Selected joint publication

Sala N., Owen W.G., Collen D. A functional assay of protein C in human plasma. Blood 63, 671-675, 1984 (137 times cited).

Brief narrative

I obtained my degree in Biological Sciences at the *Universitat Autònoma de Barcelona*, in Catalunya (Spain), in June 1976. In 1980 I started my scientific activity by joining the group of Dr Jordi Félez, at the Hematology Service in Hospital de Sant Pau, Barcelona. Jordi Félez, who had previously been working with Désiré Collen's team at the Center for Thrombosis and Vascular Research of the K.U.Leuven, introduced me to the field of thrombosis research and encouraged me to perform a stage at Dr. Collen's laboratory in order to improve my knowledge and scientific experience. With a grant from Caixa de Barcelona, in September 1981, I had the great opportunity to join the group at the Center for Thrombosis and Vascular Research, at that time lead by another great person and scientist, Dr. Marc Verstraete. I will never forget the two years I spent there, how much Désiré and all his colleagues (scientists as well as technicians and administrative staff) helped me. Though my initial purpose was to work in the field of fibrinolysis, the fact that Whyte Owen from Iowa University (USA), had just arrived in Brussels for a sabbatical year and was interested in collaborating with Désiré on the development of a functional assay for activated PC activity, made that I was proposed to work under the supervision of Désiré and White. A proposal that I accepted with pleasure because I knew I was having a great opportunity. Under their supervision, excellent advise and the help of other scientists of the Center (I must mention Roger Lijnen, Marc Hoylaerts and Hans Deckmyn) as well as technicians (Berthe, Maria, Frans, Jan, An and many others), after two years I succeeded in publishing the assay and, once back to Hospital de Sant Pau, in Barcelona, I used it to study inherited causes of thrombophilia in Spanish patients with familial thrombosis of unknown origin. All this work was used in my PhD thesis, defended at the *Universitat Autònoma de Barcelona*. Furthermore, all the experience I got in Dr. Collen's laboratory was essential

for my future scientific career in Barcelona, where I initially continued my work at the Hematology Service of Hospital de Sant Pau, studying the PC and PS pathways in inherited thrombophilia. From 1991 to 2006, I got a position as investigator at the Oncology Research Institute of Barcelona (IRO), where I continued my research on the genetics of thrombophilia, focusing essentially on the study of *PROC* and *PROS* genes and the molecular pathology of PC and PS deficiencies. In May 2006 I moved to the Catalan Institute of Oncology in Barcelona, where I am now working as an investigator of the Translational Research Laboratory, leading the group of molecular and genetic epidemiology of cancer. At present my main research is on the genetic susceptibility to cancer, particularly gastric cancer.

Personal appreciation

I will never forget the two years I spent in the laboratory of Désiré at the Center forThrombosis and Vascular Research; how much Désiré Collen and all his colleagues (scientists as well as technicians and administrative staff) helped me in the beginning and the friendship they offered me all the time. I still remember my first day: I was expected at 9 a.m., and the shuttle that had to take me from the old hospital in the Center of Leuven to Gasthuisberg was never leaving. The driver didn't speak anything else than Flemish and I was the only passenger. No way to understand each other! But he finally left me at Gasthuisberg and I arrived in the lab in the middle of the weekly lab meeting. Everybody was explaining his/her work, how it had progressed, the problems they had….Oh my God, how nervous I was! I was in the lab of one of the greatest scientists in the world in the field of thrombosis and fibrinolysis. Everything was new to me and I had to learn so many things! Was I going to succeed? Yes, I managed and I thank it to Désiré's support, enthusiasm and humanity which I must also extend to all his team, with particular mention to Roger and Ingrid Lijnen, Marc Hoylaerts, Hans and Liesbeth Deckmyn, Maria, Berthe, An, Jan and Frans, to mention the ones I had most contact with. Ah! And Jaqueline, the secretary! Everybody was friendly and doing everything possible to make my life there easy and pleasant. They also guided me in the laboratory and thought me all the techniques I was going to use and, which is essential, most of the tricks that make a technique work well. With their help and the extraordinary supervision, excellent advice and continuous encouraging support of Désiré, after some time I started to loose my fears and begun to move, work and think by myself and started to do something positive (at least that was my purpose). Désiré taught me what scientific research is and what is needed to become a good scientist. I am convinced that the two years I spent with Désiré's team and all I learned from him, have positively marked my scientific career for ever. He has not only been one of the greatest scientists I have ever met, but also a great person and one of the best teachers I have ever had. I wish him and his family the best for all his life that, I am convinced, will continue as productive as it has been for many, many years on.

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Sobel, Burton

Collaboration period
January 1980 - Now

Collaboration topics

Fibrinolysis
t-PA
Myocardial infarction
Thrombolysis
Pharmacology

Selected joint publications

Bergmann S.R., Fox K.A.A., Ter Pogossian M.M., Sobel B.E., Collen D. Clot-selective coronary thrombolysis with tissue-type plasminogen activator. Science 4602, 1181-1183, 1983 (216 times cited).

Sobel B.E., Geltman E.M., Tiefenbrunn A.J., Jaffe A.S., Spadaro J.J., Ter Pogossian M.M., Collen D. Ludbrook P.A. Improvement of regional myocardial metabolism after coronary thrombolysis induced with tissue-type plasminogen activator or streptokinase. Circulation 69, 983-990,1984 (123 times cited).

Brief narrative

After graduating from Cornell University and Harvard Medical School, magna cum laude, I completed clinical training at the Peter Bent Brigham Hospital and fellowship in cardiology and biochemistry at the National Heart, Lung, and Blood Institute. Subsequently, I was fortunate enough to hold leadership positions at the University of California, San Diego (Director, Myocardial Infarction Research Unit), Washington University and Barnes Hospital (Lewin Professor and Director, Cardiovascular Division), and the University of Vermont (Amidon Professor and Chair, Department of Medicine and more recently, Director of the Cardiovascular Research Institute). Largely as a result of the collaborative work with Désiré and the ultimate successful development of t-PA and demonstration of its efficacy in reducing infarct size and mortality I was the recipient of honours including: the Heart Research Foundation's International Recognition Award (1981); the AHA Scientific Council's Distinguished Achievement Award (1984); the ACC's Distinguished Scientist Award (1987); the Pasarow Foundation Award (1988); the AHA James B. Herrick Award (1992) and Special Recognition Award in Thrombosis, Atherosclerosis, and Vascular Biology (1999); and recognition as Master, ACP (2000). My research has been supported by the NIH, the ADA, and the AHA as a Program Director, Specialized Center of Research (SCOR)

in Ischemic Heart Disease; Program Director, Collaborative Clinical Trial of Therapy to Protect Ischemic Myocardium; Program Director, Principles in Cardiovascular Research, National Institutes of Health Training Grant; Co-Investigator, Hemostasis & Thrombosis Program for Trainees, National Institutes of Health; Co-Investigator, Postdoctoral Cardiovascular Research Training Program, National Institutes of Health; Principal Investigator, BARI 2D Fibrinolysis and Coagulation Core R01HL63804, National Institutes of Health, 2000-2007; and Principal Investigator, Inflammation, Procoagulation, and Plaque Vulnerability R01HL71305, National Institutes of Health, 2000-2007.

The work with Désiré exploded when he was kind enough to collaborate with Steve Bergmann and me in demonstrating that Bowes melanoma cell derived t-PA given intravenously to dogs and subsequently to patients, lysed coronary thrombi with alacrity and without inducing a systemic lytic state. We subsequently worked on numerous small scale and massive clinical trials utilizing the techniques employed in those early studies including positron emission tomography and enzymatic estimation of infarct size. My work has led to publication of more than 850 manuscripts and enabled me to serve major cardiovascular and medical scientific journals including: *Circulation*, editor; *Journal of Clinical Investigation*, associate editor; *American Journal of Physiology*, associate editor; *Coronary Artery Disease*, editor; *Current Opinion in Cardiology*, editor; *Fibrinolysis*, associate editor; and *Circulation Research*, *Annals of Internal Medicine*, *American Journal of Cardiology*, *American Journal of Medicine*, *Diabetes Care*, editorial board member.

The work with Désiré led to many major research accomplishments including: quantification of infarct size with the use of biomarkers and positron emission tomography; favourable modification of infarct size with clot selective fibrinolytic agents; elucidation of molecular mechanisms related to fibrinolysis underlying evolution of vulnerable atherosclerotic plaques associated with insulin resistance and type 2 diabetes mellitus; and, most recently, delineation of mechanisms potentiating heart failure in diabetes.

Personal appreciation

During the course of a career and a life time one is blessed to have the benefit of a few stellar relationships with remarkably fine human beings. For me, friendship with Désiré exemplifies such relationships. No one has meant more to me professionally than he. No one has aided and abetted my development as an investigator more than he. No one has stood shoulder to shoulder with me when we were the targets of calumny, as unjustified as it was, more than he. No one was more altruistic in sharing ideas, information, reagents, methods, and time more than he.

Désiré's intellect is legendary. It is always inspirational. His humility and graciousness complement that intellect superbly. He is the penultimate teacher of teachers, and he taught me much that I could not have learned without his guidance, ranging from enzyme kinetics to experimental design and implementation.

The work that I was privileged to do as a collaborator was made possible only because of Désiré's graciousness. His work contributed to the saving of tens if not hundreds of thousands of lives and constitutes a critical milestone on the

path to reduction of the toll from heart disease. Whether characterizing molecular interactions in vitro, modulating gene expression to achieve required experimental conditions in isolated systems, or performing clinical investigations, Désiré's contributions have always addressed elucidation of pathophysiology as well as characterization of phenomena. I remember well when he took a sabbatical at Genentech in order to become expert in gene cloning and modulation of gene expression, an expertise he acquired in a remarkably short time from his base in an apartment in south San Francisco rather than his elegant home in Leuven.

For more than 25 years I have had the privilege of knowing, working with, and collaborating with a delightful friend and colleague whose skills as a wine taster are rivaled only by his luminosity as a scientist. Perhaps the best statement of what his relationship with me has meant is the following: "Strange is our situation here on Earth. Each of us comes for a short visit, not knowing why, yet sometimes seeming to divine a purpose. From the standpoint of daily life, however, there is one thing we do know, that man is here for the sake of other men – above all those upon whose smiles and well-being our own happiness depends." -- Albert Einstein

Present co-ordinates

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Stassen, Jean-Marie

Collaboration period

July 1975 – October 1995
March 2001 – now

Collaboration topics

Cardiovascular Research
Cardiovascular Drug Development

Selected joint publications

Collen D., Stassen J.M., Verstraete M. Thrombolysis with human extrinsic (tissue-type) plasminogen activator in rabbits with experimental jugular vein thrombosis - effect of molecular form and dose of activator, age of the thrombus, and route of administration. J. Clin. Invest. 71, 368-376,1983 (276 times cited).

Collen D., Stassen J.M., Marafino B.J., Builder S., De Cock F., Ogez J., Tajiri D., Pennica D., Bennett W.F., Salwa J., Hoyng C.F. Biological properties of human tissue-type plasminogen activator obtained by expression of recombinant DNA in mammalian cells. J. Pharmacol. Exper. Therap. 231, 146-152,1984 (138 times cited).

Collen D., Stassen J.M., Blaber M., Winkler M., Verstraete M. Biological and thrombolytic properties of proenzyme and active forms of human urokinase.3. Thrombolytic properties of natural and recombinant urokinase in rabbits with experimental jugular vein thrombosis. Thromb. Haemost. 52, 27-30,1984 (115 times cited).

Brief narrative

I met Désiré in May 1975 during an internship at the Department of Gastroenterology under the direction of Prof. G. Vantrappen. After my graduation as B.Sc. I joined the team of Désiré as a technician in July 1975. As a technician I was involved and assigned to numerous projects including clinical and pre-clinical research in the areas of vascular diseases, coagulation and fibrinolysis.
This included the generation of antibodies and assay development together with Frans De Cock and many other team members and visiting scientists. As most of the team members I became involved in t-PA research around 1980, and together with O. Matsuo (Osaka, Japan) we started the in vivo characterization of t-PA. As of then I was predominantly focused on in vivo pharmacology of a wide range of potentially new thrombolytic agents as well

as their combination with antithrombotic agents.
In the early 1990's the generation of gene-inactivated small animals and their phenotyping required a downscaling of the existing models (together with P. Carmeliet).
These activities resulted in approximately 80 joint publications. After a break of almost 6 years I joined Désiré's group again in 2001 albeit in a different function. As managing director of Thromb-X NV we closely collaborated on cardiovascular drug development.

Personal appreciation

Joining the research group of Désiré in 1975 as a junior technician was a great opportunity to learn all about medical and biochemical research. The exposure to clinical and pre-clinical activities allowed me to understand basic mechanisms behind pathologies and what could be done to diagnose, prevent and/or treat these disease states.
Beside his focus on research Désiré always was, and still is, very eager to investigate/explore the potential use of research observations. Based on this attitude Désiré was able to expand and develop research institutes and bring the company, which today employs more than 50 employees and of which I am proud to be part of, to the stock exchange.

Present co-ordinates

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Stump, David

Collaboration period

August 1984 – May 1989

Collaboration topics

Fibrinolysis
Thrombolysis

Selected joint publications

Stump D.C., Thienpont M., Collen D. Purification and characterization of a novel inhibitor of urokinase from human urine - quantitation and preliminary characterization in plasma. J. Biol. Chem. 261, 2759-2766,1986 (114 times cited).

Stump D.C., Lijnen H.R., Collen D. Purification and characterization of single-chain urokinase-type plasminogen activator from human cell cultures. J. Biol. Chem. 261, 1274-1278,1986 (105 times cited).

Stump D.C., Lijnen H.R., Collen D. Purification and characterization of a novel low-molecular-weight form of single-chain urokinase-type plasminogen activator. J. Biol. Chem. 261, 7120-7126,1986 (119 times cited).

Stump D.C., Thienpont M., Collen D. Urokinase-related proteins in human-urine - isolation and characterization of single-chain urokinase (prourokinase) and urokinase inhibitor complex. J. Biol. Chem. 261, 1267-1273,1986 (143 times cited).

Stump D.C., Califf R.M., Topol E.J., Sigmon K., Thornton D., Masek R., Anderson L., Collen D. Pharmacodynamics of thrombolysis with recombinant tissue-type plasminogen activator - correlation with characteristics of and clinical outcomes in patients with acute myocardial infarction. Circulation 80, 1222-1230,1989 (120 times cited).

Brief narrative

I obtained my M.D. from Indiana University in 1976 and completed my training in internal medicine at the University of Iowa in 1979. Thereafter I undertook specialty training in clinical and laboratory hematology and oncology, during which I developed a specific scientific interest in hemostasis and thrombosis. At the end of three years of laboratory training in general hemostasis and biochemistry, I became aware of the excellent work ongoing in the area of fibrinolysis at Leuven University. After a brief exploratory visit in 1983 I

decided to join Désiré's group in the Center for Thrombosis and Vascular Research headed by Professor Marc Verstraete. In August 1984 my wife Carolyn, our 5 year old daughter Shana and I moved to Leuven and took residence in the Groot Begijnhof for the next two years. Since t-PA had already been purified and characterized as well as cloned and expressed by scientists at Genentech, we agreed that the next interesting area of research would be to study the fibrinolytic and thrombolytic properties of single chain urokinase (scu-PA). Over the next year we developed methods for purification of scu-PA from human urine and conditioned cell culture media. By serendipity we also purified a serpin-like inhibitor of urokinase in urine which we also identified in plasma and later learned its identity to be the inhibitor of protein C. During my second year in Leuven Désiré, Roger Lijnen, and I characterized the biochemical properties and fibrin-specific thrombolytic potential of scu-PA and a novel low molecular weight variant of it both alone as well as synergistically in combination with t-PA. In mid 1986 I returned to the U.S. to join the faculty of medicine and biochemistry at the University of Vermont. My collaboration with Désiré continued for three more years as he accepted an adjunct appointment at that institution. Together we established a laboratory there performing specialized fibrinolytic assays in support of the large TIMI and TAMI cardiology clinical research groups.
In 1989 I accepted a position at Genentech to lead the clinical development of rt-PA. In subsequent years we completed the GUSTO trial which established rt-PA as the thrombolytic agent of choice for acute myocardial infarction. We also demonstrated the efficacy of rt-PA in the treatment of acute ischemic stroke. In the late 1990's I completed my work on thrombolysis with the development of tenecteplase, a long half-life more fibrin-specific variant of rt-PA which is now approved worldwide for clinical use.

Personal appreciation

There is no doubt that my decision to join Désiré as a visiting investigator in Leuven was pivotal in my scientific career. Not only did he motivate me to learn the basics of biochemical fibrinolysis (when I volunteered to learn Flemish, his response was that if I had that much excess energy I should focus it on biochemistry!), he inspired me to always be looking toward the creative application of biochemistry and biology to the treatment of human disease. The truth was always to be found in data obtained from focused and rigorous experimentation. The brand of having successfully worked with Désiré opened many doors and created many opportunities for me in ensuing years. More importantly, remembering the lessons of Leuven has served me well as I continued to pursue a career in biotechnology through development of new recombinant human therapeutic proteins and monoclonal antibodies as well as even more novel genomic derived products in my later years at Genentech and now at Human Genome Sciences. It was indeed a privilege to work with Désiré and a pleasure to know him as a colleague and friend. Carolyn and I wish him the very best as he transitions to the next stage of his professional life. But above all, on behalf of patients with life-threatening thrombotic disease I thank him for the lives saved and improved as a result of his life work.

Present co-ordinates

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Topol, Eric

Collaboration period

1984 - 2000

Collaboration topics

Myocardial Reperfusion

Selected joint publications

Topol E.J., Morris D.C., Smalling R.W., Schumacher R.R., Taylor C.R., Nishikawa A., Liberman H.A., Collen D., Tufte M.E., Grossbard E.B., O'Neill W.W. A multicenter, randomized, placebo-controlled trial of a new form of intravenous recombinant tissue-type plasminogen activator (activase) in acute myocardial infarction. J. Am. Coll. Cardiol. 9, 1205-1213,1987 (165 times cited).

Topol E.J., Califf R.M., George B.S., Kereiakes D.J., Rothbaum D., Candela R.J., Abbotsmith C.W., Pinkerton C.A., Stump D.C., Collen D., Lee K.L., Pitt B., Kline E.M., Boswick J.M., O'Neill W.W., Stack R.S. Coronary arterial thrombolysis with combined infusion of recombinant tissue-type plasminogen activator and urokinase in patients with acute myocardial infarction. Circulation 77, 1100-1107,1988 (204 times cited).

Brief narrative

I have had the remarkable pleasure and opportunity to collaborate with Désiré Collen from the early days of tissue-type plasminogen activator which he pioneered. In February 1984 building upon years of his prior efforts, we treated the first patient with the recombinant form of t-PA and later did multicenter trials together, culminating in the largest heart attack clinical trial ever performed—GUSTO-1 of 41,021 patients—showing definitively that t-PA saves more lives than the streptokinase reference standard.

Personal appreciation

Désiré was responsible for helping to get my career started. The opportunity to achieve rapid myocardial reperfusion with a recombinant fibrinolytic agent was, at the time, revolutionary. His infectious enthusiasm and scientific brilliance ignited the whole initiative and the prior work that he did to pave the way completely revamped the field of heart attack therapy. Dr. Collen has been a fantastic supporter throughout my career, and was the first speaker at our Jacobs Center for Vascular Biology and Thrombosis when we opened the

Center in Cleveland in the late 1990s. His work has been so impressive and he is surely deserving to be a Nobel Laureate. I am forever grateful to all the impact he had not only for me, at a very impressionable and young time in my career, but for millions of patients who have benefited from his discovery and perseverance.

Present co-ordinates

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Vanderschueren, Steven

Collaboration period

1992 - 1996

Collaboration topics

Thrombolysis
Staphylokinase

Selected joint publications

Vanderschueren S., Barrios L., Kerdsinchai P., Vandenheuvel P., Hermans L., Vrolix M., Deman F., Benit E., Muyldermans L., Collen D., Van de Werf F.V. A randomized trial of recombinant staphylokinase versus alteplase for coronary artery patency in acute myocardial infarction. Circulation 92, 2044-2049,1995 (120 times cited).

Brief narrative

During my training in Internal Medicine, I have spent 4 happy years preparing my thesis in the Center for Thrombosis and Vascular Research, which then became the Center for Molecular and Vascular Biology, reflecting the expanding scope of research. My work focused on preclinical and clinical studies of the fibrinolytic agent staphylokinase. Roger Lijnen and co-workers had just revealed its mechanism of action and of fibrin specificity. Recombinant DNA-technology enabled production of large quantities of wild-type staphylokinase and its mutants. With the collaboration of Jan Stassen and co-workers, I studied the immunogenicity of staphylokinase and its variants in baboon and rabbit models, the differential hemorrhagenic effects of staphylokinase and non-fibrin specific fibrinolytic agents in a rabbit bleeding time model, and the thrombolytic potential of staphylokinase in a newly established rabbit embolic stroke model. Meanwhile, I coordinated clinical studies of staphylokinase and mutants in patients with acute myocardial infarction and peripheral arterial occlusion, in close collaboration with the teams of Frans Van de Werf and Jos Vermylen. This parallel deployment of experimental animal and clinical studies allowed for a permanent cross-talk between the bench and the bedside and the delineation of the potential of staphylokinase as a thrombolytic agent.

Personal appreciation

I have learned that three criteria have to be met for a valuable thesis: a catching topic, a strong promoter and a supportive lab. For me, Désiré proved

to be the guarantee for all three. In 1992, when I decided to add a research dimension to my clinical training, Jos Vermylen introduced me to Désiré who became my promoter. Désiré understood that patient-centered internal medicine was my true vocation and suggested to take up the preclinical and clinical study of recombinant staphylokinase, that just had been used for the first time in man. This choice was fortunate and the topic proved to be both challenging and rewarding. Saying that Désiré was a dynamic promoter is an understatement. Although the Center was ever expanding, with growing numbers of scientists and lab personnel from around the country and abroad, Désiré followed and directed all lines of research, with concern, focus and intellect. The lab meetings were legendary. Once one could get away by explaining why an experiment did not quite work out, but 2 weeks later one had to be back on track. No thesis can be accomplished without the input and support from many co-workers. I always will be grateful to the Center's dedicated and skilful laboratory personnel, especially of the 'animal lab'. Scientific writing is among the many skills I have learned from Désiré. When I got the first version of my first manuscript back, I found that Désiré had preserved almost none of my original sentences. At that time, I was disappointed but now I understand that fruitful scientific reading requires concise and focused writing. Désiré also taught me that an entire article could be written at the very start of an experiment. Only the actual figures, to be entered in the results and the tables, had to follow. While I first considered this a prejudiced and unscientific starting point, I learned that the contrary is true. An experiment always starts with a scientific hypothesis to be confirmed or rejected. Clearly explaining at the very start why and how a study is conducted and what one tries to find, guarantees focused research. As others, I have come to appreciate Désiré as a true intellectual, an unequalled scientist, a far-seeing manager, and a man who enjoys what life has to offer. The four years that I had the privilege of collaborating with him and his team, have an ever-lasting impact on the way I conduct medicine and research. Désiré, I thank you for your major contributions to my career and wish you all the best, enjoying what you value most.

Present co-ordinates

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Van de Werf, Frans

Collaboration period

1982 - now

Collaboration topics

Fibrinolysis
Acute myocardial infarction

Selected joint publications

Van de Werf F., Bergmann S.R., Fox K.A.A., De Geest H., Hoyng C.F., Sobel B.E., Collen D. Coronary thrombolysis with intravenously administered human tissue-type plasminogen activator produced by recombinant DNA technology. Circulation 69, 605-610,1984 (185 times cited).

Van de Werf F., Ludbrook P.A., Bergmann S.R., Tiefenbrunn A.J., Fox K.A.A., De Geest H., Verstraete M., Collen D., Sobel B.E. Coronary thrombolysis with tissue-type plasminogen activator in patients with evolving myocardial infarction. New Engl. J. Med. 310, 609-613,1984 (349 times cited).

Van de Werf F., Vanhaecke J., De Geest H., Verstraete M., Collen D. Coronary thrombolysis with recombinant single-chain urokinase-type plasminogen activator in patients with acute myocardial infarction. Circulation 74, 1066-1070,1986 (133 times cited).

Van de Werf F., Nobuhara M., Collen D. Coronary thrombolysis with human single-chain urokinase-type plasminogen activator (prourokinase) in patients with acute myocardial infarction. Ann. Int. Med. 104, 345-348,1986 (119 times cited).

Brief narrative

I first met Desiré when I was a junior staff member at the department of Cardiology.
In the laboratory of Experimental Cardiology I was working on an animal model for coronary artery thrombosis. I started this experimental work after attending a symposium in Hannover at which Dr. K.P. Rentrop presented his first results with the intracoronary infusion of streptokinase in patients with an ST-elevation acute myocardial infarction. The introduction of a copper coil into the left anterior descending coronary artery of a dog induced an occlusive thrombus within a few minutes. The complete occlusion and clot lysis could be easily checked by repeated angiography.

I still remember very well the first conversation I had with Désiré in 1982 on the parking lot of the St.-Rafaël hospital site. Désiré came back from lunch and just by coincidence saw me entering the hospital. He said: “I’ve heard that you have an animal model with a coronary artery thrombus. Well, I have a new agent that is better than streptokinase. Let’s study it in your animal model”. Obviously I agreed and Désiré went to his lab. The whole discussion lasted less than 2 minutes, I guess, but it was the start of a long-standing collaboration which had a major impact on my academic career.
The first (intracoronary) administration of tissue-type plasminogen activator (made in Desiré’s lab from the melanoma cell line) to a patient with an ST-elevation acute anterior myocardial infarction (still alive today!) in our cath lab was witnessed by at least 20 people including, of course, Désiré. Although the initial results were not that encouraging -because we did not have a good idea of the right dose- Désiré’s enthusiasm convinced us to continue our work both in the experimental lab and in patients. When recombinant tissue plasminogen activator finally became available I became involved in major international studies such as GISSI-2/International, the GUSTO and ASSENT trials, etc.
Désiré has been the driving force of the implementation of the experimental work in his lab. Without his insights (and impatience!) fibrinolysis with tissue plasminogen activator and fibrin-specific agents in general, might have never become” the gold standard “ for pharmacological reperfusion.
The work of Désiré Collen has had a great impact on the research activities of the department of Cardiology of the K.U.Leuven. It has put us in the forefront of the treatment of acute myocardial infarction and enabled us to coordinate several worldwide multicentre studies in the field of coronary reperfusion and later in the field of new antithrombotic treatments for acute coronary syndromes.

Personal appreciation

Désiré Collen has a creative, investigative and analytical mind. In addition to his research achievements he has a unique capacity for combining science and business acumen, both in the search of commercial sponsors and collaborators. In the selection of his collaborators he was very critical and intellectual capacities came always first. He was able to unite physicians and researchers from all over the world in a common cause.
Apart from being ambitious, Désiré has a high interest in art and an extensive knowledge (and appreciation) of good wines. His wine cellar is one of the best in Belgium!

Present co-ordinates

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Vaughan, Douglas

Collaboration period

1988-1992

Collaboration topics

Fibrinolysis
Plasminogen activator inhibitor-1
Plasminogen activators and platelets

Selected joint publications

Declerck P.J., De Mol M., Vaughan D.E., Collen D. Identification of a conformationally distinct form of plasminogen activator inhibitor-1, acting as a noninhibitory substrate for tissue-type plasminogen-activator. J. Biol. Chem. 267, 11693-11696, 1992 (109 times cited).

Vaughan D.E., Declerck P.J., Vanhoutte E., De Mol M., Collen D. Reactivated recombinant plasminogen activator inhibitor-1 (rPAI-1) effectively prevents thrombolysis in vivo. Thromb. Haemost. 68, 60-63, 1992 (56 times cited).

Brief narrative

I was doing my fellowship in cardiology at a Brigham and Women's Hospital in Boston when I was first exposed to recombinant t-PA. I was asked to join a research team led by Dr. Sam Goldhaber to investigate the efficacy and safety of rt-PA in the treatment of acute pulmonary embolism in humans. At the time, I was also working in the laboratory of Dr. Joseph Loscalzo. One day, I brought some unused rt-PA back to the lab, and we asked the question "what does this do to platelets?" I began investigating this interaction, and learned that Désiré and his laboratory had been instrumental in the development of t-PA as a drug. I really became fascinated by the concept and the physiological regulation of the fibrinolytic system. I decided to write an application for a Physician Scientist career development award from the American Heart Association to study the interaction of plasminogen activators and platelets. On the advice of Dr. Braunwald, I solicited Désiré to serve as my mentor for the project. He agreed, the grant was funded, and I went to Leuven to work in the Center for Thrombosis and Vascular Research in August of 1988.
Soon after arriving in Leuven, I met with Désiré to discuss my plans and interests. He brought up some other possibilities of projects to work on, including looking at the effects of PAI-1 on thrombolysis and on bleeding associated with administration of t-PA. I said that sounded interesting. Soon

thereafter, I started a project with Jan Stassen investigating the effects of PAI-1 on bleeding in rabbits following the combined use of t-PA and aspirin. Later that year, I worked with Paul Declerck to explore the reactivation of latent PAI-1 in vivo. After leaving Leuven, my own research laboratory developed a focus on PAI-1. I spent four more years at the Brigham as a junior faculty member before moving to Vanderbilt in 1993. I was named Chief of the Division of Cardiovascular Medicine at Vanderbilt in 1999. I currently serve as Principal Investigator on a National Heart, Lung and Blood Institute (NHLBI) Specialized Center of Clinically Oriented Research (SCCOR) in Hemostatic and Thrombotic Disease, one of three such programs in the United States. I was recently named Chair of the Department of Medicine at the Northwestern University Feinberg School of Medicine in Chicago, a position that I will assume in June of 2008.

Over the last several years, my laboratory has been involved in a number of studies designed to investigate the molecular regulation of PAI-1 expression and the role this fascinating SERPIN plays in cardiovascular disease and tissue remodeling. We have also been extensively involved in translational and clinical studies exploring the regulation of fibrinolytic balance and t-PA release in humans. So, that brief conversation with Désiré back in 1988, as we discussed potential projects, ended up defining the investigative focus of my career. Even now, PAI-1 is the protein that I dream about at night!

Personal appreciation

There are several things that I appreciate about Désiré. I noticed right away when I arrived in Leuven that much of his research, while basic in orientation, was directed towards developing new insights and treatments for human disease. The laboratory incorporated molecular biology, biochemistry, pharmacology, physiology, and a keen interest in drug development and clinical trials. This “bench to bedside” approach captured my imagination, and has been the driving principle (albeit on a smaller scale) behind my own laboratory. I also appreciated Désiré’s generosity, as a mentor and a scientist. He gave freely of his time and his resources and reagents from the Center were distributed all over the world. I have tried to pattern my own behavior in this regard based on the generous example set forth by Désiré. Finally, much to my own delight and unfortunate financial chagrin, I gained a sincere appreciation for the merits of white Burgundies from visiting his house and enjoying some of the stock held in his remarkable cellar. Nothing else quite compares!

Present co-ordinates

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2220 Pierce Avenue
Nashville
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USA
E:mail: douglas.e.vaughan@vanderbilt.edu

Verstraete, Marc

Collaboration period

1965 - 1991

Collaboration topics

Coagulation
Fibrinolysis
Thrombolysis

Selected joint publications

Verstraete M., Vermylen J., Collen D. Intravascular coagulation in liver disease. Ann. Rev. Med. 25, 447-455,1974 (102 times cited).

Verstraete M., Bory M., Collen D., Erbel R., Lennane R.J., Mathey D., Michels H.R., Schartl M., Uebis R., Bernard R., Brower R.W., Debono D.P., Huhmann W., Lubsen J., Meyer J., Rutsch W., Schmidt W., Von Essen R. Randomized trial of intravenous recombinant tissue-type plasminogen activator versus intravenous streptokinase in acute myocardial infarction. Lancet 1, 842-847,1985 (746 times cited).

Verstraete M., Brower R.W., Collen D., Dunning A.J., Lubsen J., Michel P.L., Schofer J., Vanhaecke J., Van de Werf F., Bleifeld W., Charbonnier B., Debono D.P., Lennane R.J., Mathey D.G., Raynaud P., Vahanian A., Vandekley G.A. Double-blind randomized trial of intravenous tissue-type plasminogen activator versus placebo in acute myocardial infarction. Lancet 2, 965-969,1985 (252 times cited).

Verstraete M., Bounameaux H., De Cock F., Van de Werf F., Collen D. Pharmacokinetics and systemic fibrinogenolytic effects of recombinant human tissue-type plasminogen activator (rt-PA) in humans. J. Pharmacol. Exper. Therap. 235, 506-512,1985 (152 times cited).

Verstraete M., Collen D. Thrombolytic therapy in the eighties. Blood 67, 1529-1541,1986 (169 times cited).

Verstraete M., Arnold A.E.R., Brower R.W., Collen D., Debono D.P., Dezwaan C., Erbel R., Hillis W.S., Lennane R.J., Lubsen J., Mathey D., Reid D.S., Rutsch W., Schartl M., Schofer J., Serruys P.W., Simoons M.L., Uebis R., Vahanian A., Verheugt F.W.A., von Essen R. Acute coronary thrombolysis with recombinant human tissue-type plasminogen activator - initial patency and influence of maintained infusion on reocclusion rate. Am. J. Cardiol. 60, 231-237,1987 (121 times cited).

Brief narrative

My interest in blood coagulation was aroused by three unrelated events. My father, a gynecologist-obstetrician, had witnessed in his practice a few cases of intravascular coagulation, also known as defibrination syndrome, a severe complication of delivery. The second influencing fact was that three of the five children of an uncle died from, at that time, a mysterious bleeding disorder, which I later could diagnose as von Willebrand disease. The third circumstance was that Professor P. Nolf, a physiologist at the University of Liege (Belgium) and a distant cousin, had demonstrated at a time that I was still a medical student that an intravenous injection of peptone in dogs was associated with massive fibrinolysis. P. Nolf invited me to join his laboratory, a proposal which I declined preferring to remain family independent. These three events had also a bearing on my selection of research topics once I started my own one-man laboratory. My first publication (1951) was on the defibrinating effect of an intravenous injection of amniotic fluid in dogs and its prevention by pretreatment with heparin. Being later on in charge of the diagnosis and treatment of bleeding patients in the university hospital, I did set up tests to properly diagnose patients with congenital or acquired single or combined coagulation defects, inhibitors to coagulation, quantitative or qualitative platelet disorders, all research domains which were perspicuously pursued by my previous co-worker and friend Jos Vermylen. My interest in therapeutic thrombolysis, induced by synthetic drugs, streptokinase and later on tissue-type plasminogen activator, was aroused by my coworker Antony Amery, an astute coworker of the first years.

Désiré Collen joined as a research student my laboratory, which was, that time, a modest enterprise of about 15 persons. Each day we had to find normal blood to calibrate our prothrombin times performed on the blood samples of patients treated with coumarin drugs. At the end of an ex cathedra lecture for medical students I had called on volunteers to donate the next day some blood. Désiré was challenged by some friends and it came to a betting that he would never dare to volunteer for this innocent blood letting. The next day he presented himself at the laboratory, had blood taken and won the bet. More important was his instantaneous keen interest in the prevailing research topics of the laboratory. He wanted to come back and get acquainted with members of the group. He was soon attracted by the research line and personality of Guido Tytgat, who was, at that time, preparing his PhD thesis on intravascular coagulation. Fibrinogen, labeled with radioactive iodine, was injected in healthy dogs and in dogs with CCl4 induced liver damage, in healthy individuals and in patients with cirrhosis of the liver. A mathematical computer analysis for accurate determination of the metabolic parameters was developed by Guido Tytgat and Désiré. Using the same mathematical model the turnover of radiolabeled plasminogen, antithrombin III, plasmin-antiplasmin complex and prothrombin were assessed in experimental animals, healthy volunteers and patients with cirrhosis of the liver.

With the discovery of $\alpha_2$antiplasmin by Désiré his interest shifted to the fibrinolytic system. As mentioned in the contribution of Roger Lijnen the purification and characterization of tissue-type plasminogen activator (t-PA) were the start of an extraordinary research period.

Personal appreciation

The arrival of Désiré at the Center for Molecular and Vascular Biology has been the start of an almost explosive development from a middle-sized laboratory of 30 persons to a multi-disciplinary and international group close to 150 persons. There has also been a remarkable qualitative progress as evidenced by the list of top medical journals in which articles of Désiré and his group were and continue to be published. Being passionate in his commitments he remained restrained in his demeanour. Désiré set his high standards for himself but also for anyone who works for him. He commands a lot of respect from the people who work with him at all levels.
My long acquaintance with Désiré over almost 3 decades allows me to judge his agile intellect as well as his moral qualities. He feels deeply about many issues and does not hesitate to express his convictions, but always in terms acceptable to supporters and opponents alike, his writing never sounds the strident note. He established himself a reputation for credibility, integrity, probity, loyalty and liberal tendencies.
Under Désiré's determined leadership, the research center became world wide one of the 10 highest-ranking laboratories active in the field of thrombosis, haemostasis and fibrinolysis. Désiré, with his pioneering spirit, has played a major role in this development. Generous in advice, never overbearing, he continues to offer intellectual and material support to many successful investigators, both in Belgium and abroad. His remarkable achievements have made him a highly respected scientist at world-class level.
Désiré has a broad scope of interests. In addition to medical sciences he can talk intelligently about wine, finances, pictural art, music and aviation (he pilots his own plane). Several co-workers decline nowadays to join him on an airtrip; this is one way to consolidate and sustain friendship.

Present co-ordinates

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Belgium
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Weimar, Willem

Collaboration period

1981

Collaboration topics

Thrombolysis
t-PA

Selected joint publications

Weimar W., Stibbe J., Vanseyen A.J., Billiau A., De Somer P., Collen D. Specific lysis of an iliofemoral thrombus by administration of extrinsic (tissue-type) plasminogen activator. Lancet 2, 1018-1020,1981 (174 times cited).

Brief narrative and personal appreciation

Nostalgia, Trust end Serendipity

These days I was sitting behind a huge pile of forms needed to embark on a new clinical trial. I counted 32 documents deemed necessary for approval by my local medical ethical committee. There were 18 pages of patient information and 3 questionnaires from the financial department. I had corresponded with the lawyers of our hospital on one main and two subcontracts. Our national central committee for medical research on humans needed an application form as well. We had to appoint an independent study monitor, a research nurse and a safety committee consisting of pharmacologists and statisticians. Moreover, our IT people had to build a protected study database. No wonder my thoughts drifted away in nostalgia to those happy late 1970-ies, early 1980-ies when life was simple and clinical research was purely based on mutual trust between basic scientists, clinicians, and patients. We were not confronted yet with loads of counterproductive paperwork and lengthy procedures based on mistrust. In this happy pre- committee era we investigated with Fons Billiau and Piet de Somer of the Rega Institute in Leuven the clinical potential of interferons as antiviral agents against Hepatitis B and against the life threatening viruses that emerged after organ transplantation. During an international interferon meeting that we organized in Rotterdam from April 21-24,1981,I arrived late for the opening reception at the Town Hall, where I met Fons Billiau. I explained to him the sad reason for my being-late. It was a clinical problem with a renal transplant recipient that at that same day was developing an ascending thrombosis from her iliac vein to her renal transplant. Graft function was already deteriorating and graft loss was expected within a day.

“Ever heard of t-PA, tissue plasminogen activator?”, Fons asked me, “Désiré Collen is working on it. Yes, he is also from Leuven. It seems to induce fibrinolysis without affecting fibrinogen levels. Therefore, in theory, this compound should not lead to defibrination and massive bleeding. In the Rega we just produced a first batch for clinical application”. “ Why not give it a try in my patient”, I proposed. “We have no other therapeutic options!” The rest of the story is simple: Fons returned by car to Leuven, contacted Désiré, fetched the t-PA, drove back to Rotterdam where I immediately administered the t-PA to the patient resulting in a dramatic effect. The clot completely dissolved, as we proved radiologically. There were indeed no side-effects, kidney graft function rapidly improved, we wrote a Lancet paper and Désiré became famous. Now, 27 years later, the patient is still alive with a perfectly functioning renal allograft.

I told you in those days clinical research was purely based on trust between basic scientists, clinicians and patients. But certainly, the serendipity factor played a role too: My renal transplant unit happened to cooperate with the Rega Institute in Leuven. One of my patients was developing an ascending thrombosis exactly during an Interferon meeting in Rotterdam, which was attended by De Somer and Billiau. Désiré Collen had just produced his first t-PA batch and Fons Billiau had a car.

The spectacular success of t-PA in this first patient reminds us of the success of the first shot of penicillin. These so-called parachute single patient experiments have been instrumental for the development of new medical therapies. Désiré Collen is to be congratulated for being the Godfather of t-PA therapy which has saved so many lifes.

Present co-ordinates

Erasmus MC
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Wiman, Bjorn

Collaboration period

August 1977 – September 1978

Collaboration topics

Antiplasmin
Regulation of fibrinolysis

Selected joint publications

Wiman B., Collen D. Purification and characterization of human antiplasmin, fast-acting plasmin inhibitor in plasma. Eur. J. Biochem. 78, 19-26,1977 (201 times cited).

Wiman B., Collen D. Molecular mechanism of physiological fibrinolysis. Nature 272, 549-550,1978 (349 times cited).

Wiman B., Collen D. Kinetics of reaction between human antiplasmin and plasmin. Eur. J. Biochem. 84, 573-578,1978 (285 times cited).

Wiman B., Boman L., Collen D. Kinetics of reaction between human antiplasmin and a low-molecular-weight form of plasmin. Eur. J. Biochem. 87, 143-146,1978 (103 times cited).

Wiman B., Lijnen H.R., Collen D. Specific interaction between the lysine-binding sites in plasmin and complementary sites in alpha-2-antiplasmin and in fibrinogen. Biochim. Biophys. Acta 579, 142-154,1979 (234 times cited).

Wiman B., Collen D. Mechanism of the reaction between human alpha-2-antiplasmin and plasmin. J. Biol. Chem. 254, 9291-9297,1979 (147 times cited).

Brief narrative

Our main collaboration was within antiplasmin biochemistry, including purification of active antiplasmin and its reaction with plasmin. This turned out to be important also for regulatory aspects of fibrinolysis. Another very important aspect was that the action of t-PA mainly occurs at the surface of fibrin. This was a discovery I made in Umeå, in collaboration with Per Wallén, prior to my visit in Leuven. I believe, however, that the transfer of this knowledge to Désiré Collen played an important part in his career.
I was lucky to get a post doc position in the center for Thrombosis and

Vascular Research at K.U.Leuven, at professor Verstraete's department. The meaning was to join Désiré Collen, working on problems with antiplasmin, a project that had already started. When I arrived the department had just moved to a new building at campus Gasthuisberg. The laboratory was almost empty from equipment, but with a lot of available resources, it was operational within only a short period of time. It was like a dream working with Désiré. His dynamic mind and positive attitude made an unforgettable impression. It resulted in a dramatic increase in our knowledge about in particular antiplasmin biochemistry, but also in important knowledge about how the fibrinolytic system was regulated. Of course, our studies resulted in a great number of publications, which had a reasonable impact within the field of fibrinolysis research at that time. It was also important for me to meet a number of kind and intelligent people working at Désiré's laboratory, such as Roger Lijnen, Ed Plow, Eliana Monteiro and others.

Personal appreciation

My stay in Leuven became a very memorable time. This was of course due to the fact that work was going so well in a friendly, but efficient atmosphere. However, this is not the complete story, since Désiré and his wife Louisa took very good care of me also in my spare time. I cannot count all the exceptionally good dinners that I experienced at Désiré's and Louisa's home, including visits to the wine cellar. Eventually, this led to that I nowadays have my own wine cellar, which I cannot compare to that of Désiré, of course, but it is nice anyhow.

Present co-ordinates

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SE-17176 Stockholm
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E-mail: tor-bjorn.wiman@karolinska.se or bjorn@wimania.com

Yasuda, Tsunehiro

Collaboration period

1983-1994

Collaboration topics

Clinical application of rt-PA for thrombolysis in patients with acute myocardial infarction
Reperfusion with antiplatelet agents, Glycoprotein IIb/IIIa receptor

Selected joint publications

Yasuda T., Gold H.K., Fallon J.T., Leinbach R.C., Guerrero J.L., Scudder L.E., Kanke M., Shealy D., Ross M.J., Collen D., Coller B.S. Monoclonal antibody against the platelet glycoprotein (GP) IIb/IIIa receptor prevents coronary artery reocclusion after reperfusion with recombinant tissue-type plasminogen-activator in dogs. J. Clin. Invest. 81, 1284-1291,1988 (225 times cited).

Yasuda T., Gold H.K., Yaoita H., Leinbach R.C., Guerrero J.L., Jang I.K., Holt R., Fallon J.T., Collen D. Comparative effects of aspirin, a synthetic thrombin inhibitor and a monoclonal antiplatelet glycoprotein-IIb/IIIa antibody on coronary artery reperfusion, reocclusion and bleeding with recombinant tissue-type plasminogen activator in a can. J. Am. Coll. Cardiol. 16, 714-722,1990 (148 times cited).

Yasuda T., Gold H.K., Leinbach R.C., Yaoita H., Fallon J.T., Rijken D.C., Napier M.A., Bunting S., Collen D. Kistrin, a polypeptide platelet GP IIb/IIIa receptor antagonist, enhances and sustains coronary arterial thrombolysis with recombinant tissue-type plasminogen activator in a canine preparation. Circulation 83, 1038-1047, 1991 (98 times cited).

Brief narrative

I was first introduced to Désiré Collen in 1983 when the t-PA dog model was first used. I was a junior faculty in cardiology and nuclear medicine. I am a cardiologist but I did nuclear cardiac imaging and human clinical trials funded by NIH with Drs. Gold, Leinbach, and Strauss prior to this t-PA research.
One day, I found out that we were going to do a thrombolysis study in humans. I did not know anything about rt-PA or what "recombinant" meant. Important things were apparently to move fast and yield results fast. The Genentec t-PA research director was here often and we discussed and made

the research protocol. We hired a dog technician Mr. Louis Guerrero who has worked with us as competent technician.
We also used angiograms to document the occlusion and reperfusion and even videotaped to record the success. It was hard to make a stable, consistent obstructive clot in the healthy dog's LAD. We learned to damage the endothelium by pinching the LAD by forceps, then made a " sausage like clot" where a tiny side branch goes to the right ventricular side. That small branch was used to inject the blood and then thrombin to form the clot in the LAD by a TB syringe. When we were ready to give rt-PA, we were not certain what dose would be the best. It was known for in vitro experiments, but we had to extrapolate the dose for a dog. It was decided to use a dose of 0.5 mg/kg/min by "complicated computation " and it did work. After establishing the dose, we decided to randomize the rt-PA treatment, meaning that nobody knows what each dog received, except for one technician, named Bob Holt. He was smart and much better organized than Dr. Gold or I. We started the experiments in March, 1983, doing 2-3 dogs a week. Désiré came in the morning at 7 am and stayed all day to see the progress. He did not have a clinical responsibility. After the day's work, he had a Scotch at Dr. Gold's home. He said that Scotch refreshed his mind, and he could work with vigor the next day.
As the experiments progressed day after day, week after week, he asked me all the data to be tabulated in an accountant table. Fortunately at that time, the famous small hand carrying computer from Macintosh was introduced. I used it to the full extent and kept the records. When December of 1983 arrived, the company was anxious to know and so were all of us. The work intensified in the first weeks of December. Finally after the second week, the randomized dog experiments were over, and decoding was completed with the greatest care. Then the data were analyzed in the late evening about 2 weeks before Christmas. To our amazement, t-PA dogs had 100% reperfusion rate and control saline dogs had none. We were just stunned. I was impressed with the incredible poker face and tight lips of Bob Holt. He was smart and he knew the importance of blinded research. This completely blinded study gave me a tremendous confidence in rt-PA.
The dog model provided the foundation for the subsequent human multicenter trial to determine the dose. Later it was modified with a new single chain rt-PA . Years later, an additional dog model with an inverted segment in the circumflex artery was developed to test Glycoprotein IIb/IIIa antiplatelet agents to enhance the reperfusion time and patency after the initial reperfusion.
Every time, when we completed a project, Désiré sat in Dr. Gold's office and wrote by hand all day till 6 pm. Dr. Gold's typist, Ms. Missy Stanton was called in even in the weekend when Dr. Collen was writing. The stamina and concentration of writing are beyond belief. Neither Chip nor I can sit that long writing a manuscript. That distinguishes extraordinarily successful people from successful people in academic society. I learned to sit and write from Désiré but Chip and I have an "itchy buttock" and could not sit too long.
His knowledge of thrombosis and thrombolysis changed the understanding of arterial obstruction and reperfusion in human. Cardiologists must learn about coagulation and the thrombolysis cascade. Even hematologists would not know much about it at that time. We recognized quickly that platelet participation is unavoidable in thrombolysis and keeping the artery open.

Promptly, the antiplatelet agent study began in our later collaboration with addition of Dr. Coller's Glycoprotein IIb/IIIa antibody.
Désiré other important contribution is that Dr. Gold purchased a house. His residence was a small 2-bedroom apartment in the Prudential Center when we started to work together. Mrs. Gold/Dr. Nath was very anxious to move to a normal American house since she had a small girl, Lisa. She was 5-6 years old and needed a play ground and friends to play. The Prudential Center is an office business district and no children lived there. So Mrs. Gold asked Désiré and me to persuade Dr. Gold to say "Yes" to a house in Brookline, west of Boston. Mrs. Gold liked the house very much but Dr. Gold did not like it. After seeing the house with Dr. Gold, Désiré said, "It is a perfect house. You should buy it." Dr. Gold said "It's too big. There are six bedrooms." Désiré said " That's nonsense. You will fill it up with junk quickly." Finally, Dr. Gold agreed to purchase it and secured his peaceful place in the suburbs. Then Dr. Gold invited Désiré to stay at the third floor of the house whenever he visited Boston. The floor was arranged for professor Collen with TV and bathroom. The house of course has been filled with various goodies in the following years and then a second child, Jonathan Gold was born. Now it just looks like a perfect house. Professor Collen did great scientific work, but also helped human life with unusual common sense.
I remember vividly the work we did together. It was the busiest but most fulfilled time of my research carrier.

Personal appreciation

A persuasive, bright, well-organized and powerful man, Désiré has changed the treatment of acute myocardial infarction. We do many things for patients suffering from acute myocardial infarction today, such as thrombolysis, stenting, and more. But t-PA thrombolysis created the concept that early reperfusion saves lives and function of the patient. The GUSTO trial documented the details.
I am honoured to have know him, worked with him and shared the fantastic research that changed human life.

Present co-ordinates

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Désiré COLLEN

Curriculum vitae, June 2008 (*)

Personal Data

Gender:	male
Place and date of birth:	Sint Truiden, Belgium, June 21, 1943
Married to:	Reniers Louisa, July 14, 1966
Children:	An, born February 2, 1968 Peter, born May 10, 1971 Christine, born November 14, 1972
Home Address:	Schoonzichtlaan 20, B-3020 Herent, Belgium
Office addresses:	• Center for Molecular and Vascular Biology Department of Molecular and Cellular Medicine Faculty of Medicine Katholieke Universiteit Leuven (K.U.Leuven) Herestraat 49, box 911 B-3000 Leuven, Belgium (Tel 016/345775; Telefax 016/345990) • Vesalius Research Center Vlaams Instituut voor Biotechnologie Herestraat 49, box 912 B-3000 Leuven, Belgium (Tel 016/345772; Telefax 016/346001) • ThromboGenics N.V. Leuven Bioincubator 1 Gaston Geenslaan 1 B-3001 Heverlee, Belgium

Education

1968:	Doctor in Medicine (MD), K.U.Leuven, Belgium
1969:	Licentiaat (MSc) in Medical Sciences, K.U.Leuven, Belgium
1974:	PhD in Chemistry, K.U.Leuven, Belgium
1974:	Geaggregeerde "Higher Education in Medicine", K.U.Leuven, Belgium

(*) foto: © <http://www.bartvanleuven.com>www.bartvanleuven.com.

Residencies and Research Fellowships

1968-1971: Resident Internal Medicine,
University Hospitals K.U.Leuven, Belgium

1971-1972: Associate Research Scientist,
New York University Medical Center, New York, N.Y.

1972-1973: NATO Research Fellow,
Karolinska Institutet, Stockholm, Sweden

Academic Appointments within the University of Leuven

1973-1976: Aangesteld Navorser NFWO

1975-1976: Extraordinary ("Buitengewoon") docent, Faculty of Medicine, K.U.Leuven

1976-1981: Docent, Faculty of Medicine, K.U.Leuven, Belgium

1981-1998: Professor, ("Gewoon hoogleraar") Faculty of Medicine, K.U.Leuven, Belgium

1990-2007: Director of the Center for Molecular and Vascular Biology (previously Center for Thrombosis and Vascular Research) Faculty of Medicine, K.U.Leuven, Belgium

1998-2002: Extraordinary Professor ("Buitengewoon hoogleraar"), Faculty of Medicine, K.U.Leuven, Belgium

2002-2008: Professor, ("Gewoon hoogleraar") Faculty of Medicine, K.U.Leuven, Belgium

Academic Appointments outside the University of Leuven

1984-2005: Professor of Biochemistry and Medicine,
University of Vermont College of Medicine, Burlington, VT, USA

1986-1989: Visiting Professor, Faculty of Medicine and Pharmacy,
Free University Brussels, Belgium

1987-1994: Visiting Professor of Medicine, Harvard Medical School, Boston, USA

1994-2008: Director of the Center for Transgene Technology and Gene Therapy (presently Vesalius Research Center)
Vlaams Instituut voor Biotechnology
Leuven, Belgium

Appointments in University Hospitals

1975-1976: Consultant (Consulent), University Hospitals, K.U.Leuven, Belgium

1976-1998: Adjunct Head of Clinic, University Hospitals, K.U.Leuven, Belgium

1987-2005: Consultant in Medicine, Massachusetts General Hospital, Boston, MA, USA

1998-2008: Consultant (Consulent), University Hospitals, K.U.Leuven, Belgium

1999-2002: Visiting Professor in the Division of Surgery and Anaesthesia, Guy's King's and St. Thomas' School of Medicine, London, UK

Other Appointments

1976-2001:	Division Head, Protein Research Division, Leuven Research and Development VZW, K.U.Leuven, Belgium
1988-2007:	Statutory Chairman of the D. Collen Research Foundation V.Z.W.
1991-2007:	Chairman of the Board of Thromb-X NV (Spin-off company of Leuven Research and Development, K.U.Leuven, Belgium)
1998-2006:	Chief Executive Officer and Chairman, ThromboGenics, Ltd., Ireland
2006- :	Chief Executive Officer, ThromboGenics, Ltd., Ireland
2006- :	Chief Executive Officer and Chairman, ThromboGenics, NV, Belgium
2007- :	Statutory Chairman of Life Sciences Research Partners, VZW (previously D. Collen Research Foundation, VZW)

Awards and Honors

1984:	Francqui Prize (University Foundation), Belgium
1985:	Member of the Royal Academy of Medicine of Belgium
1986:	Prix Louis Jeantet de Médecine (Fondation L. Jeantet), Geneva, Switzerland
1988:	Doctor honoris causa, Erasmus University, Rotterdam, the Netherlands
1990:	Five-yearly Prize of Fundamental Medical Sciences of the Belgian Government (Royal Academy of Medicine of Belgium)
1994:	Bristol-Myers-Squibb Award for Cardiovascular Research, New York, N.Y. (jointly with M. Verstraete)
1994:	Doctor honoris causa, Free University of Brussels (VUB), Brussels, Belgium
1995:	Doctor honoris causa, University of Notre Dame, Notre Dame, IN
1999:	Doctor honoris causa, Université de la Méditerranée, Marseille, France
2005:	Health Prize of the Interbrew-Baillet Latour Fund, Belgium (jointly with P. Carmeliet)
2006:	Member of the European Molecular Biology Organization (EMBO)
2007:	2007 Leadership Prize by the Harvard Club of Belgium

Research Areas

Molecular biology and pathophysiology of haemostasis and thrombosis
Development of new thrombolytic and antithrombotic agents
Transgenesis, gene targeting and gene transfer studies of the cardiovascular system
Translational research on cardiovascular drug development

Research Output

The scientific output of D. Collen between 1968 and 2008 consists of approximately 650 research papers (in peer-reviewed international journals), 170 survey articles and 28 issued US patents. He ranked among the 100 most cited scientific authors of the 1980's (Current Contents August 31, 1992, p3) and is listed with the highly cited authors of the 1980 and 1990's (http: //www.highlycited.com).

Relevant Links

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http://www.kuleuven.ac.be/mcm/
http://www.vib.be/Research/EN/Research+Departments/Vesalius+Research+Center/
http://www.isihighlycited.com/ (click: “Search by name”, enter last name: “Collen”)
http://www.thrombogenics.com
http://opa.faseb.org/pages/Publications/breakthroughs.htm (click: “Clot Busters! – Discovery of Thrombolytic Therapy for Heart Attack and Stroke”)