

CHEMISTRY AND BIOLOGY OF SERPINS

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CHEMISTRY AND BIOLOGY OF SERPINS

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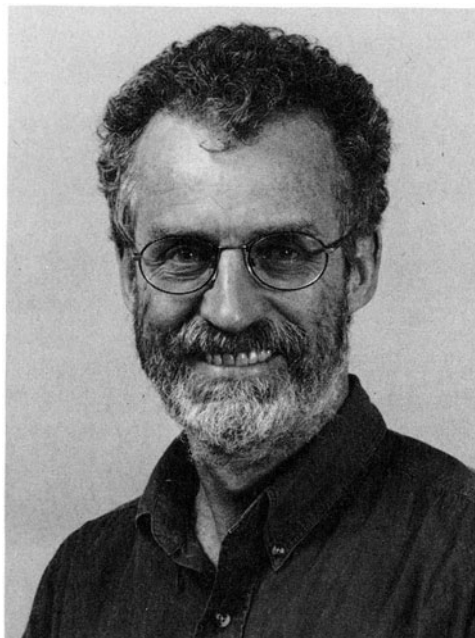
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STUART STONE 1951–1996

The inherent tragedy in the loss of a family man in the prime of life is such that it seems almost trivial to speak of the effect of the loss on his profession. Yet for Stuart Stone's colleagues there is a special sense of grief, not only for someone whose contributions helped establish the field we all work in, but also for someone whose career was just on the threshold of opening new understandings in our science.

Stuart Stone was born in Sydney on 1st November 1951 and he died, suddenly whilst swimming, on 16th December of 1996, shortly after his return to Australia to take up a senior Professorship at Monash University in Melbourne. His training had commenced as a student in Agricultural Science at the University of Sydney where he obtained his degree in 1973 with 1st class honours and won the University Medal for the outstanding graduate of the year. He stayed in Sydney to complete his PhD and was awarded a series of prizes and fellowships that took him to post-doctoral posts in Iowa State University from 1978–80 and as a Research Fellow to the John Curtin School of Medical Research in Canberra from 1980–83. During this time he carried out the studies that elucidated the catalytic mechanism of dihydrofolate reductase.

Stuart Stone's first substantive post, and the one in which he built the foundation for his career research, was in 1984 as a research scientist and then group leader in the Friedrich-Miescher Institut in Basel. Here over the next seven years, with Jan Hofsteenge, he carried out a series of key studies on the function of thrombin and the mechanism of its inhibition by hirudin. Their work, together with the structural group at Martinsried,

showed that hirudin interacts with regions of thrombin distinct from the active site. The conclusions from these studies provided the basis for the subsequent development of the recombinant analogues of hirudin.

In 1991 Stuart joined me in the Department of Haematology in the University of Cambridge as a University Lecturer. This tenured post provided him with the chance to undertake full-time independent research. He rapidly built up a strong team with a core of post-doctorals but with its main strength in a lively and ever-changing group of graduate students. All of his graduates were trained to meet the standards he expected of himself — there were no compromises. I would sometimes hear him shouting from the floor below, “This is just not good enough!” to be followed seconds later by an angry and flustered graduate student coming up the stairs and striding out of the door. Next day all would be well and Stuart would have grown in the respect and affection of his research students.

A reason for Stuart’s success was his approach to science. The alternative styles of research can be compared to that of artists, some fill their canvas with broad strokes and later add detail, others start with fine detail in one corner and work out from that to cover the canvas. The latter was Stuart’s style. His constant careful attention to detail made him an excellent research supervisor and a sought-after participant in Gordon Conferences and the like. Here he was at his best — equally able to exchange technical data and to debate broad concepts. His knowledge, his open manner, good humour and optimism all added together to inspire others and to provide motivation to the field as a whole.

In Cambridge he commenced a series of kinetic studies on thrombin that, coupled with *in vivo* studies of inhibitors in animal models of thrombosis, have provided guidelines for the development of thrombin inhibitors as antithrombotic agents. In particular Stuart’s later work, on the detailed interactions of peptides, receptors and serpins with the active site of serine proteases, formed the basis for the planned work in his new post, as Professor of Biochemistry and Molecular Biology in Monash. It is a great sadness that his sudden death came at a time when he was just completing the organization of the research that he realistically believed would give international leadership in the field by the turn of the millennium.

For those who aspire to success in research and career it is worth noting that Stuart Stone achieved this by placing his family first. His children: Brangwen, Meredith and Simon, and his wife Eleanor (herself a scientist of distinction) were at the centre of his life and a constant support to him in his work. Stuart had a quiet but deep religious faith and the family came to be much loved in the village of Newnham in Cambridge where Stuart was a member of the vestry and the family were loyal supporters of the parish church. Newnham, Monash, Basel grieve for him, as do all his colleagues in our small but inter-dependent field of research.

Robin Carrell

REMEMBERING STUART R. STONE

(NOVEMBER 1, 1951–DECEMBER 16, 1996)

Dedication of the Serpin Symposium Proceedings

It seems like such a short time ago that I had the opportunity to be friends with Stuart Stone. He was very intelligent, hardworking, friendly, funny, personable, a family man who loved his wife and children very much, loyal to his lab, his University, true to his science, his family, and always available for advice, wisdom and words. He was a remarkable person. Susie Bauman, one of my graduate students, said that Stuart was her role model as a scientist, she admired his work very much. She had the opportunity, as we all did, to enjoy Stuart's company at the Serpin Symposium in Chapel Hill in April 1996. We then realized that all the things said about Stuart were true: he was a scholar, he was fun, he was caring, and he was an amazing person.

Recently, my wife, Gwyn Cutsforth, and I had dinner with Stuart and his wife, Eleanor Mackie, in London. My wife instantly liked both Stuart and Eleanor, and said that they were both so friendly, caring and very much in love.

Stuart touched everyone in his field of science. When I phoned, E-mailed or visited him he was always ready to talk science, to talk life experiences, or to talk about family and friends. I always wanted to have completed my best and most clever experiment when thinking about an upcoming chat with Stuart, I wanted to impress him and hoped that my science was as significant as his. But he was never disappointed in anyone's work, always supportive, always offering advice.

A saying by the great American football coach Vince Lombardi comes to mind when I think about the kind of person Stuart was: "The difference between men is in energy, in singleness of purpose, and in invincible determination. But the great difference between men is in sacrifice, in self-denial, in fearlessness and humility, in love and loyalty, and the perfectly disciplined will. This is not the only difference between men, but this is the difference between great men and little men." Stuart Stone was a giant among people, a leader among scientists. He has already been missed by all, he will continued to be missed by all. His legacy of excellence is established and his colleagues and friends will maintain and perpetuate his work as a scientist and as a person.

The Organizers of the Serpin Symposium unanimously agreed that it would be a fitting affirmation to dedicate this book in memory of Stuart R. Stone.

Frank C. Church, Ph. D.
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The University of North Carolina at Chapel Hill
March 1997

PREFACE

Serpins (*serine protease inhibitors*) are a superfamily of proteins whose physiological action is primarily targeted to inhibiting serine proteases. There are instances where serpins are not inhibitors (and can carry steroid hormones for instance), yet key structural and functional elements found in all serpins are maintained in these ‘non-inhibitor’ serpins. Many serpins have well-described biological properties which influence pathophysiological events, including: antithrombin (historically called antithrombin III), α_1 -protease inhibitor (historically called α_1 -antitrypsin), and plasminogen activator inhibitor-1, just to mention a few. A deficiency or defect in antithrombin leads to venous thromboembolic disease, while a deficiency or defect in α_1 -protease inhibitor is associated with chronic obstructive pulmonary emphysema. In contrast, it has been suggested that increased levels of plasminogen activator inhibitor-1 may be a predisposition to myocardial infarction. The list goes on for each of our own “favorite” serpin. The biological roles found for serpins are key participants in almost every physiological event. In other words, serine proteases are needed for many events in biology and the role of serpins to down regulate these proteases is essential. Thus, just using these three examples above for serpins and their pathophysiological roles reminds us that the medical costs to control such events is significant worldwide.

From a biochemical perspective, serpins have become one of the model systems to study regarding protein structure and function relationships, and the docking of proteases to the reactive site loop of a serpin is also a model of protein:protein interactions. In fact, the “Holy Grail” of serpin protein biochemists must be the crystallization of a bimolecular complex between a serpin and its cognate protease. The general structural features of a serpin contain three β -sheets and nine α -helices. Serpins that are active as protease inhibitors have an exposed reactive site loop (to serve as a ‘pseudosubstrate’), which resides between the A- and C-sheets. Serpins that are not active protease inhibitors have variations on this theme. There are other structural elements of importance in serpins outside of the reactive site loop, one notable example is the “heparin-binding” serpins (with the A- and D-helices) such as antithrombin and heparin cofactor II whose inhibitory action is enhanced by glycosaminoglycans like heparin and dermatan sulfate. Again, for every one’s own “favorite” serpin there is a key structural element that points to an important biological function.

When I think about papers that have influenced me over the years in my research with serpins, I can think of many citations. I would like to mention just a few which were “milestone” papers to the serpin field, (I realize that each of us would have a different list of most important papers, so I apologize if your paper is not included or my list is too limited). Egeberg showed that a deficiency in antithrombin resulted in thrombophilia (1); Rosenberg and Damus described the mechanism of action of antithrombin in the presence

of heparin (2); Hunt and Dayhoff reported the existence of a new superfamily with a surprising group of proteins including antithrombin, α_1 -protease inhibitor and ovalbumin (3); Kurachi et al. cloned and sequenced α_1 -protease inhibitor (4); Owen et al. described α_1 -protease inhibitor Pittsburgh which occurred in a young boy that led to a fatal bleeding diathesis (5); Loebermann et al. presented the crystal structure of reactive site looped-cleaved α_1 -protease inhibitor (6); and Carrell and Travis coined the term 'serpin' and reviewed their general features (7).

This brief historical and personal introduction reminds us that serpins are intimately involved in regulating serine proteases important in most physiological processes ranging from blood coagulation to fibrinolysis to inflammation to reproduction to tumor cell invasion. Further, this is the "golden-age" of protein biochemistry and molecular medicine and those that work in the field of serpins are poised to contribute lasting information about biochemical processes, pathological functions, and medical treatment for many of these essential pathways and processes.

Considering the advances made in our understanding of the chemistry, biology and physiology of serpins over the past decade, it seemed timely and apropos to have a meeting focused on serpins. The genesis of this symposium started at another meeting, the "Heparin and Related Polysaccharides" symposium held in Uppsala, Sweden (September 1991). I can distinctly remember talking to Doug Tollefsen, Ingemar Björk, Steve Olson, Ulrich Abildgaard, and Dennis Cunningham during this magnificent symposium about whether anyone remembered a meeting focused on serpins, and whether someone should organize or was planning such a meeting. Over the next two years, at every meeting I attended I asked the very same questions, and to my excitement everyone said unanimously, "let's do it!" It is somewhat foggy about what happened next, but it seems that I starting organizing the event during 1994. For many different reasons, it was decided that mid-April 1996 would be the best time.

I got the Program Committee organized and it consisted of Dennis Cunningham, David Ginsburg, Stuart Stone, and Doug Tollefsen. Also, a local advisory panel consisting of Don Gabriel, Maureane Hoffman, and Harold Roberts was formed. The next event which solidified the time was a trip I took in September 1994, to visit Stuart Stone and Robin Carrell in Cambridge, England. I spent some time talking with Robin and I mentioned the idea for the serpin meeting and he immediately embraced the concept and his secretary reserved this time in April 1996. Upon returning to Chapel Hill, I immediately contacted Ingemar Björk and Jim Travis to check their availability to participate in the symposium. Once done, I had gotten the "Holy Triumvirate" of serpin scientists (in my opinion) scheduled for the meeting! It was all downhill from there. In selecting speakers for the six different sessions planned for the symposium, my School of Medicine colleagues asked that we have many extra names selected because it was their experience that you had to go three-deep sometimes just to get one speaker to commit. I am proud to say that everyone instantly accepted the invitation to speak at the serpin meeting except for two cases: one declination was for surgery scheduled immediately prior to the Symposium, and one speaker canceled at the last minute because of a clinical scheduling conflict. It was very gratifying that everyone was excited about the serpin meeting.

For those of you who were able to attend the Serpin Symposium, the meeting was almost "magical": the science significant, the weather perfect, the Carolina Inn accommodations outstanding, and the social events were a great way to end a day of "serpin-oriented" science (many science and life stories were exchanged during the evening spectacles). The keynote address at the banquet by Jim Travis was one for the memories; I am sorry that it was not videotaped for posterity purposes. It was especially noteworthy to

view the posters (which numbered close to 100 total) each day and to see such wonderful science and that every poster was dedicated to serpins. Finally, it is important to state that there were over 200 scientists, clinicians and students (graduate, medical and undergraduate) in attendance who represented 13 different countries (photo page 339).

I wish to thank my fellow Program Committee Members who took the time to develop and plan the agenda for the symposium and who enthusiastically endorsed the purpose of this meeting: Dennis Cunningham, Ph.D.; Don Gabriel, M.D./Ph.D.; David Ginsburg, M.D.; Maureane Hoffman, M.D./Ph.D.; Harold Roberts, M.D.; Stuart Stone, Ph.D.; and Doug Tollefsen, M.D./Ph.D. The collective input from each member contributed directly to the foundation on which this meeting was based, and their contributions insured for a successful meeting. It was an absolute delight to work with this group.

I also wish to thank the numerous financial grants and contributions by federal, state and by numerous industries that allowed us to have this symposium, this volume, and a permanent memory and record of the symposium. Without these generous contributions, the symposium would have been mediocre instead of the reality, a significant event. A list of contributors is included in this volume. I encourage all readers of this book to note each contributor on the list.

This meeting could not have been planned or even existed without the help of the Office of Continuing Medical Education at The University of North Carolina at Chapel Hill School of Medicine. This office provided constant guidance and logistical support for each phase of the meeting. In particular, two individuals should be acknowledged, Ms. Jane Radford and Dr. William Easterling. Jane was instrumental in making many of the arrangements for the meeting and she provided a constant source of encouragement during all of the planning stages and she was present during the symposium 'working tirelessly' and 'putting out fires.'

My most profound thanks go to Ms. Jaime Welch-Donahue of the Center for Thrombosis and Hemostasis of The University of North Carolina at Chapel Hill School of Medicine. Jaime was the mainstay of the entire mission for this meeting. Without her constant efforts to organize the symposium, to stay in contact with speakers, to keep us informed on fund raising, to serve as the liaison with CME, and to keep me focused on the calendar for when things "had to get done," this meeting would have never happened, it would have been a disaster. Her persistent efforts resulted in the success that became the Serpin Symposium. And her job did not end there, it is her vigilance that has gotten this volume to the publishers within a year of the actual meeting.

Finally, I would like to acknowledge my wife, Gwyn Cutsforth, Ph.D., and my laboratory group. Without their constant support and encouragement to organize this meeting, and their tolerance of my absence during its planning stages, this meeting would have never materialized. Their collective enthusiasm for the Serpin Symposium fueled my fire to go through with the necessary steps to host and plan this symposium. Without the help and support of everyone mentioned here (and many others not even noted), there would have been no symposium and no proceedings!

Frank C. Church, Ph.D.
School of Medicine
The University of North Carolina at Chapel Hill

Note Added in Proof: I am sorry to note that we learned of the death of Professor Ruth Sager, a contributor to this volume (and speaker at the Symposium) and a senior figure in the field, as this book entered production. Ruth was a wonderful person and a very successful scientist who late in her scientific career got involved in serpin science by discovering maspin. Her research in this area provided new emphasis and importance to both the basic and clinical sciences regarding the role of serpins in tumor cell biology.

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