The Crafoord Prize 2004

The Royal Swedish Academy of Sciences has decided to award the Crafoord Prize in Polyarthritis 2004 to Professor ***EUGENE C. BUTCHER,*** *Stanford University, California, USA and Professor* ***TIMOTHY A. SPRINGER,*** *Harvard Medical School, Boston, Massachusetts, USA, "for their studies on the molecular mechanisms involved in migration of white blood cells in health and disease".*

Inflammation and immunity

EUGENE BUTCHER and **TIMOTHY SPRINGER** have elucidated the function of cell adhesion molecules that are expressed in white blood cells and direct their exodus across the blood vessel wall into tissue where they are crucial for the defence against disease.

Cell adhesion molecules (CAMs) are cell surface proteins expressed by many cells including white blood cells. The CAMs are activated by specific signals from peripheral tissues in response to injury or infection and their effector functions are important for processes of inflammation and immunity.

Examples of CAMs are *selectins* and *integrins*. The *selectins* are glycoproteins, consisting of a single chain. They enable the blood cells to bind to activated endothelium in the blood vessel wall. As a consequence, the blood cell can "roll" along the surface of the vessel and eventually adhere more firmly. The *integrins* consist of two sub-units – an alpha and a beta chain – and function as receptors on the white blood cells. The activity of the various molecules eventually allow the now flattened blood cell to migrate between the cells in the vessel wall to the site of the disease process (Fig. 1)

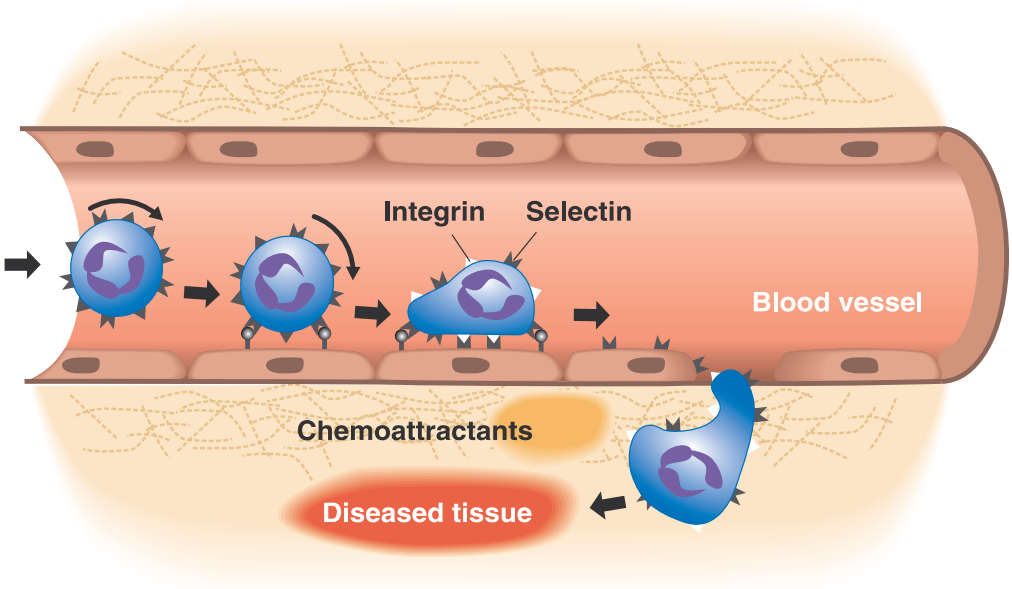

Fig 1. Selectins in the cellmembranes of white blood cells allow them to adhere to the blood vessel wall in the area around an injurious process. Aided by the integrins they leave the blood vessel and migrate to the damaged area where they act to eliminate the cause of injury.

Eugene Butcher has identified the selectins and their interaction with integrins that make them come to a halt, from high velocities along a stretch of some millimetres. Butcher has characterised the components of the process, including the ligands and receptors forming the bonds, and has formulated the now classical multi-step model to describe it.

Timothy Springer demonstrated the crucial role of the CAMs in cellular immunity. The integrins can rapidly increase in number when a blood cell has identified an antigen, and improve the defence. Springer showed that the integrins constitute a molecular family all consisting of an alpha chain and a beta chain. These exist in various configurations that can combine into a large number of defined variants with different specificities against highly variable targets. In recent years Springer has worked to determine the structures at high resolution and to define the functional domains. Like Butcher, he has produced multi-step models to reconcile the structure–function relationships. In recent years he has studied the molecular mechanisms that open and lock integrin in various conformations. If a disulphide binding (sulphur-based) is introduced, an integrin can be locked in an open position and its function is lost. The flow of white blood cells in inflammation can then be controlled.

New treatment strategies for inflammatory disease

Both Butcher and Springer have made successful attempts to apply their findings to the treatment of medical illness. In some cases advanced trials are in progress.

Butcher has shown that treatment with antibodies to the protein LFA-1 prevented or cured cerebral malaria in mice. The VCAM-1 protein plays an important part in the slow but progressive disease multiple sclerosis (MS), and Butcher's group have showed how antibodies to this protein has stopped the development of disease in some trials.

Springer's findings have inspired numerous companies working on new cures against rheumatism, psoriasis, asthma, intestinal disorders, haematological disorders and AIDS.

The Laureates:

Eugene C. Butcher, 54 years, (US citizen) Ph.D (medicine) at Washington University in St. Louis 1976; Professor of Pathology, Stanford University, California, USA.

www.stanford.edu/~ebutcher/

Timothy A. Springer, 56 years (US citizen), PhD in biochemistry and molecular biology 1976; Latham Family Professor of Pathology, Harvard Medical School, Boston, Massachusetts, USA.

http://cbr.med.harvard.edu/investigators/

Suggested reading:

Eugene Butcher's web site:
www.stanford.edu/~ebutcher/

Timothy Springer's web site:
http://cbr.med.harvard.edu/investigators/springer/lab/

Integrins:
http://integrins.hypermart.net/index.html

Adhesion molecules:
http://www.neuro.wustl.edu/neuromuscular/lab/adhesion.htm

The Crafoord Foundation:
www.crafoord.se

The Crafoord Prize

The Crafoord Fund was established in 1980 by a donation to the Royal Swedish Academy of Sciences from Anna-Greta and Holger Crafoord. The purpose of the Fund is to promote basic scientific research worldwide in the following disciplines: Mathematics, Astronomy, The Geosciences, the Biosciences (with particular emphasis on Ecology) and Polyarthritis. The prize was awarded for the first time in 1982 for Mathematics and has since been awarded annually to one discipline at a time, taking turns according to the list stated above. Both an international prize and research grants to Swedish scientists are awarded among the sciences mentioned. The prize amounts to USD 500 000.

KUNGL. VETENSKAPSAKADEMIEN
THE ROYAL SWEDISH ACADEMY OF SCIENCES

P.O. Box 50005, SE-104 05 Stockholm, Sweden
Phone: +46 8 673 95 00, Fax: +46 8 15 56 70
E-mail: info@kva.se, Web site: www.kva.se

Lilla Frescativägen 4A
Underground: Universitetet
Bus 40: Universitetet norra