I would like to welcome all of you to this Novartis Foundation Symposium on Mast cells: development, activation and roles in allergic/autoimmune disease. We are fortunate to have assembled a tremendous group of investigators in the field and I am sure that this will result in an intense scientific meeting focusing on the latest basic (primarily molecular) research studies on the mast cell and basophil, and their relation to allergic and autoimmune diseases. The overall goal of this symposium is to advance our knowledge of the roles of these two granulocytes in varied disease settings such as those occurring in allergic inflammation and autoimmune disease.

With its focus on molecular aspects of mast cells and basophils, the meeting is part of a distinguished history of Novartis Foundation symposia in the area of hypersensitivity and autoimmunity. We all recall the first superb symposium chaired by Henry Metzger from the National Institutes of Health and the more recent one on anaphylaxis chaired by Steve Galli from Stanford. Importantly, this meeting will be quite distinct from the latter: while there is some overlap (since IgE signalling is key to anaphylaxis), the topics covered in that meeting were much broader, with a focus on the disease. This symposium, in contrast, focuses on mast cell development, activation and communications with other cells at the molecular level.

The three specific goals of the symposium are:

1. To present recent advances relating to the factors and mechanisms that regulate the growth, differentiation, and function of mast cells and basophils.
2. To discuss new technological advances that directly impact studies on mast cells and basophils.
3. To integrate the basic science findings on mast cells and basophils into the framework of therapeutic potential and treatment of diseases such as allergic inflammation and autoimmune disease which are mediated, in part, by these granulocytes.

The meeting will focus on contemporary issues of mast cell/basophil research as they relate to the pathogenesis of allergic and autoimmune diseases. The topics will include: (1) the development of mast cells and basophils; (2) early and late events in IgE/antigen activation of mast cells and basophils; (3) mechanisms of exocytosis; (4) non-IgE mediated activation of mast cells and basophils, as well as those
surface receptors that dampen activation responses; (5) protease, proteoglycan, lipid, and cytokine mediators released from activated mast cells and basophils; and (6) bilateral interactions of mast cells with other cell types.

The presentations in the area of mast cell development will examine some of the key intracellular factors that control mast cell development in humans and mice. Analysis of gene expression in mast cells that have been activated by different mechanisms is yielding important new information on genes and their products that are involved in mast cell development and activation. Additional information on embryonic stem cells that differentiate into mast cells is also emerging. Specifically, in vitro differentiated mast cells in adoptive transfer approaches address issues concerning mast cell development, signal transduction and function in vivo.

Presentations on early events in FcεRI-mediated activation of mast cells and basophils will focus on the molecular basis of activation of these cells. They will include models stemming from biophysical and crystallographic studies of the high-affinity IgE receptor FcεRI and its interactions with IgE. Other topics will include major molecules and their interactions that govern the signalling pathways stimulated by FcεRI in mast cells. The task ahead is to determine the critical factors that regulate the strength and persistence of signalling. Data on the relationship between ligand valency, affinity, and the kinetics of binding to a variety of cellular responses will be presented. The value of a quantitative model of the signalling cascades initiated by the aggregation of FcεRI, as well as some of the difficulties encountered in the development and use of such a model, should also be discussed. The interactions between multivalent antigens and sIgE give rise to a complex distribution of FcεRI aggregates on the surfaces of mast cells and basophils. Quantifying the clustering of FcεRI in ‘real time’ is yielding new insight into the biophysics of IgE-mediated mast cell activation. Other discussions might include the roles of detergent-insoluble membrane microdomains and lipid rafts. This will also include discussion on the facilitation of tyrosine phosphorylation of cross-linked receptors by Lyn in a process that is regulated, in part, by the actin cytoskeleton.

Presentations on signalling complexes and downstream signalling in FcεRI-mediated activation of mast cells and basophils will explore some of the downstream events that occur prior to exocytosis of the cell’s secretory granules. Discussions will likely focus on IgE receptor-activated macromolecular signalling complexes in mast cells, as well as the importance of the constituent molecules in mast cell degranulation and cytokine production.

There will also be presentations and discussion on the exocytosis of mediators from activated mast cells and basophils. They will include talks on cytoskeletal rearrangements required for degranulation of these effector cells, and the link between membrane activation events and these processes.

We also anticipate active debate on inhibition of FcεRI-mediated responses and non-IgE mechanisms of mast cell and basophil activation focusing on the signalling
pathways controlled by cytokines, chemokines and their receptors. It is now appar-
ent that FcεRI-mediated activation of mast cells and basophils can be either stim-
ulated or counteracted by other receptors on the surfaces of these cells. It is also
apparent that certain populations of mast cells and basophils can be activated by
surface receptors other than FcεRI. Of particular interest will be the role chemokine
receptors play in mast cell development, mast cell progenitor homing, and mast cell
activation.

The symposium will end with a discussion of the interaction of mast cells and
other cell types, and the role of the mast cells/basophils in disease. Some of the
discussions will naturally focus on the role of mast cells in allergic inflammation,
and the role of stabilization of these cells in novel therapies. There will also be dis-
cussions on mastocytosis and the mutations that give rise to this phenotype. In addi-
tion, significant attention will be placed on recent data suggesting a role for mast
cells in multiple sclerosis, diabetes and HIV-1 infection. Indeed recent studies have
implicated mast cells in processes that control the onset and severity of experi-
mental allergic encephalomyelitis and insulin-dependent diabetes (IDDM) in mice.
The strategic location of mast cells in the central nervous system (in multiple sclerosis)
and in the pancreas (in IDDM) as well as their ability to express a variety of
cytokines and other inflammatory mediators raises the possibility that mast cells
either directly initiate the inflammatory responses or act to modulate the character
of the T cell response in this disease.

In conclusion, I anticipate that this symposium (and the book that results from
the presentations and discussions) will take its place alongside the previous Novar-
tis Foundation symposia chronicling the study of mast cells and basophils in health
and disease. Let the work and the discussions help form the salient future ques-
tions, and draw in young scientists who will carry forward this field of research.