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Introduction to Molecular Neurosurgery

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The term *molecular neurosurgery* has been applied to several different experimental strategies, including a variety of genetic manipulations. For the purposes of this book, the term is used to refer to the use of targeted cytotoxins to produce highly selective neural lesions. Used in this sense, the term is relevant to both experimental and potential clinical applications. The body of work addressed in this volume grew out of initial experiments in the laboratory of Donald J. Reis in 1980–1981. The initial experimental challenge was how to selectively destroy baroreceptor afferents that make up a small portion of the vagus and glossopharyngeal nerves. The strategy chosen was to develop a technique using toxin retrogradely transported from an application site on the peripheral baroreceptor nerves in the neck. First attempts used low-molecular-weight cytotoxic drugs, such as doxorubicin, and were unsuccessful. Reasoning that the initial lack of success reflected inadequate delivery of toxin to the cell bodies, a plan was developed to attach these drugs to a well-transported agent, such as wheat germ agglutinin, which at the time was introduced as a highly effective anatomical tracer *(1)*. However, a simpler option seemed attractive. If a lectin such as wheat germ agglutinin was well transported, then perhaps a toxic lectin such as ricin or abrin would work. In retrospect, Harper and colleagues *(2)* had previously shown evidence for retrograde axonal transport of ricin, but this publication was discovered only after the initial suicide transport experiments applied ricin to the vagus nerve *(3)*.

This suicide transport technique had obvious limitations, but drawing on work done in the cancer field, the toxic lectins eventually led to immunotoxins and most recently neuropeptide-toxin conjugates. Success in this transition to highly selective lesioning agents rests heavily on the work

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of Fiorenzo Stirpe. Stirpe did extensive work on ribosome-inactivating proteins, including saporin, the agent of choice for making antineuronal immunotoxins and neuropeptide-toxin conjugates. In Chapter 2, he reviews some of this extensive body of work.

Chapters 3–5 present three reviews of work using the immunotoxin 192 immunoglobulin G (IgG)-saporin (192 IgG-sap). This agent was the second antineuronal immunotoxin developed. The first, OX-7-saporin (OX-7-sap), was made by Stirpe and colleagues for studies in cancer research, and subsequently shown to be an effective suicide transport agent *(4)*. Based on success using OX-7-sap as a suicide transport agent, an antineuronal immunotoxin using a monoclonal antibody (192 IgG) to the low-affinity neurotrophin receptor ($p75^{NTR}$) was made next *(5)*. Widespread use has been made of 192 IgG-sap for selective lesions of the cholinergic basal forebrain (CBF) neurons in rats.

Chapters 3–5 present the accumulated experience of three of the most active groups using 192 IgG-sap to lesion the CBF, each for different experimental purposes. Chapter 3 covers the behavioral and neurochemical experiments of Waite and colleagues in rats with selective lesions of the CBF. Their experience illustrates some of the practical and theoretical challenges inherent in attempts to analyze behavior using selective neural lesions. Chapter 4 is a comprehensive review of the prolific contributions of Schliebs and colleagues that have focused on neurochemical issues in rats treated with intracerebroventricular (icv) 192 IgG-sap. Chapter 5 presents the use of 192 IgG-sap as a selective suicide transport agent to make anatomically restricted cortical cholinergic denervations rather than the typical strategy of destroying the entire CBF. In this application, 192 IgG-sap is used to retrogradely kill CBF neurons.

A limiting feature of 192 IgG-sap has been that it only works in rats. This drawback reflects the specificity of the 192 IgG monoclonal antibody for rat $p75^{NTR}$ *(6)*. Chapter 6 shows that substituting the ME20.4 monoclonal antibody made against human $p75^{NTR}$ results in an effective agent that has made possible a particularly revealing series of behavioral studies in primates. Chapter 7 describes use of ME20.4-saporin in rabbits, in which a provocative series of experiments suggests a relationship between cholinergic denervation and β-amyloid deposition in the cortex. Together, Chapters 3–7 provide an overview of past and present experiments using saporin-containing immunotoxins to lesion the CBF selectively. This line of investigation remains of interest in understanding Alzheimer's disease as well as the behavioral functions of the CBF.