

EXAMPLE OF A SIGNIFICANCE SUBSECTION

Significance. The γ subunit of the receptor complex for IFN- γ is the means by which this important cytokine binds to cells and initiates transmembrane signaling (Yang, 1977; Telfer and Gomez, 1988; Homer et al., 1995). Through it, IFN- γ exerts a wide range of immunoregulatory activities (Klein & Klein, 1995). Serious infectious disease problems are experienced by those who become deficient in the cells that produce this cytokine, either because they are lost as part of a disease process (e.g., AIDS; Galbreath, 2002; Toliver, 2003), during chemotherapy (Aikens and Osada, 2000), or as a natural consequence of the aging process (James and Kary, 1997; Zeleny et al., 2004). In addition to its homeostatic and defensive roles, in such diseases as Hashimoto's thyroiditis and asthma, IFN- γ appears to have a pathogenetic role, either because there is an overabundance of the cytokine (Alcott and Cochrane, 1998; Jones et al., 2000) or because cells become hyper-reactive to normal, physiologic concentrations (Sandoval, 1999). Responsiveness to IFN- γ can be modulated, either up or down, by altering the number of its receptors that are present on a cell's surface (Carlson et al., 2003). Such findings suggest that cellular functions that are attributable to the effects of IFN- γ could be modulated by altering the number of γ subunits that are available to bind it. Our contribution here is expected to be detailed understanding of how production of the receptor is regulated transcriptionally. *This contribution is significant because it is expected to provide the knowledge needed to develop pharmacologic strategies that will allow the number of γ subunits on the surface of targeted cells to be regulated, either up or down.* Once such strategies become available, there is the promise that in diseases that are associated with hyper-responsiveness to IFN- γ , cellular responsiveness could be down-regulated by reducing the number of γ chains that are available to bind the cytokine. Conversely, when greater responsiveness is needed – for example, to ward off pathogenic microorganisms or, in the case of immunocompromised patients, opportunistic invaders – responsiveness of host-defensive cells to IFN- γ , could be increased. Thus, important advances in the therapy of diseases and complications that are associated with cellular immune dysfunction could be expected. It is also expected that what is learned will be equally applicable to the prevention/treatment of diseases of agriculturally relevant animals. In addition, the research will be of significance, because what is learned is expected to contribute to broader understanding of how components of other receptor complexes can be modulated as an approach to therapy. Furthermore, better fundamental understanding of how receptor proteins are transcribed can be anticipated.

DEVELOPMENTAL STEPS FOR CHAPTER NINE:

1. Appreciate that, of the five mandatory review criteria used to evaluate NIH grants, "Significance" is the most important. This subsection is where that criterion is primarily addressed.
2. Understand that this section should be written to help justify the need for what you are proposing.
3. Begin citing the literature here using author/year, rather than numerals.
4. Understand and use the three-part approach that is recommended for the development of this critically important subsection.
5. File this 'Significance' subsection as the first part of the Background and Significance section, to which you will add 'Review of Relevant Literature' subsection later.
6. Seek constructive criticism of your *Specific Aims* section and significance paragraph from members of your pre-submission review committee (see chapter 22 for details regarding its composition and use).