

## Albert S. Baldwin

### Cancer Cell Biology

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### RESEARCH INTERESTS

Dr. Baldwin's laboratory is broadly interested in how differential gene expression is controlled. One major effort in the laboratory is the study of the transcription factor known as NF- $\kappa$ B. NF- $\kappa$ B serves as the prototype of the inducible transcription factor since it is found in the cytoplasm of most cells in association with an inhibitor known as I- $\kappa$ B and since its movement into the nucleus can be induced by various physiological stimuli. Once in the nucleus, NF- $\kappa$ B regulates a wide range of critical genes including those involved in cell

growth control and in immune and inflammatory responses. In addition, NF- $\kappa$ B is a critical regulator of HIV gene expression. Present studies in the laboratory are focused on identifying the signal transduction pathways involved in activation of NF- $\kappa$ B, and the role of this transcription factor in mediating diseases such as cancer and in controlling apoptosis. New directions are aimed at improving the effectiveness of chemotherapy via the inhibition of NF- $\kappa$ B and understanding the molecular mechanisms associated with muscle dysfunction and cachexia.

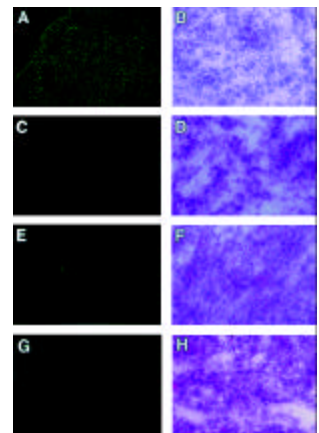
Results from Dr. Baldwin's group show:

- that NF- $\kappa$ B activation suppresses apoptosis induced by TNF, chemotherapy or radiation (Wang et al., 1996, *Science* 274:784-787).
- that the transcription factor NF- $\kappa$ B is required for oncogenic transformation controlled by Ras (Finco et al., 1997, *J Biol Chem* 272:24113-24116) and by BCR-ABL (Reuther et al., 1998, *Genes and Dev* 12:968-981).
- that the role of NF- $\kappa$ B in cellular transformation is to suppress a transformation-associated apoptosis (Mayo et al., 1997, *Science* 278:1812-1815).
- that NF- $\kappa$ B may play a direct role in oncogenesis through the transcriptional upregulation of the cyclin D1 gene (D. Guttridge et al., 1999, *Mol. Cell Biol.* 19:5785-5799).
- that NF- $\kappa$ B is activated in human breast cancer and that it is the NF- $\kappa$  B2/p52 and c-Rel subunits (not the classic p50/p65 form) that are activated. Additionally, we detect significant upregulation of the I $\kappa$ B homolog Bcl-3 in breast cancer. This is important because Bcl-3 can function with p52 to stimulate transcription. (P. Cogswell et al., 2000, *Oncogene* 19:1123-1131).
- the mechanism whereby NF- $\kappa$ B suppresses apoptosis. We have identified c-IAP1 and c-IAP2 and TRAF1 and 2 as NF- $\kappa$ B regulated genes which function together to suppress apoptosis induced by TNF. c-IAP1 and 2 can suppress apoptosis induced by the chemotherapeutic compound etoposide. (Wang et al., 1998 *Science*, 281, 1680-1683).
- that inhibition of NF- $\kappa$ B in parallel with chemotherapy can elicit a dramatic anti-tumor response in animal models. This is based on the concepts developed in Wang et al. (1996). We have taken two experimental approaches to inhibit NF- $\kappa$ B: (1) use of adenoviral delivery of a modified form of I $\kappa$ Ba and (2) use of a systemic NF- $\kappa$ B inhibitor (PS341). Using adenoviral delivery of I $\kappa$ Ba, we have obtained complete regression of experimental tumors in mice with systemic CPT-11 (camptothecin derivative) (*Nature Medicine* 5, 412-417). The response is based on the induction of apoptosis in the tumor cells. Using PS341 (a proteasome inhibitor) and CPT-11 we have obtained dramatic tumor responses where either drug alone gives a negligible response (Cusack et al., *J. Nat. Cancer Inst.*, in review).

A patent is pending for the use of NF- $\kappa$ B inhibitors to augment chemotherapeutic responses in human cancer. A clinical trial has been initiated based on the use of PS341 (proteasome inhibitor and inhibitor of NF- $\kappa$ B activation) alone and in combination with chemotherapy for the treatment of solid and hematological cancers.

### SELECTED PUBLICATIONS

- J. Reuther, G. Reuther, A.M. Pendergast and A. Baldwin. 1998. NF- $\kappa$ B is required for BCR-ABL Induced Transformation. *Genes and Dev.*, 12, 968-981.
- C. -Y. Wang, M. Mayo, R. Korneluk, D. Goeddel and A. Baldwin. 1998. NF- $\kappa$ B anti-apoptosis: Induction of TRAF1 and 2 and c-IAP1 and 2 to suppress caspase-8 activation. *Science* 281,1680-1683.
- Cheshire, J. and A. Baldwin. 1999. Involvement of double-stranded MA activated kinase (PKR) in the synergetic activation of NF- $\kappa$ B by TNF and interferon. *J. Biol. Chem.* 274, 4801-4806.
- Wang, C.-Y., J. Cusack, R. Liu, and A. Baldwin. 1999. Control of inducible chemoresistance: enhanced anti-tumor therapy via increased apoptosis through inhibition of NF- $\kappa$ B. *Nature Medicine* 5, 412-417.
- D. Guttridge, C. Albanese, J. Reuther, R. Pestell and A. Baldwin. 1999. NF- $\kappa$ B controls cell growth and differentiation through transcriptional regulation of cyclin D1. *Mol. Cell Biol.* 19, 5785-5799.
- J. Cusack, R. Liu, and A. Baldwin. 2000. Inducible chemoresistance to CPT-11 in colorectal cancer cells and a xenograft model is overcome by inhibition of NF- $\kappa$ B. *Cancer Res.* 60: 2323-2330.
- D. Guttridge, M. Mayo, L. Madrid, C.Y. Wang and A. Baldwin. 2000. Activation of NF $\kappa$ B inhibits MyoD mRNA: Implications for muscle dysfunction and cachexia. *Science*, in press.



Induction of tumor cell apoptosis following combined chemotherapy and NF- $\kappa$ B inhibition.

TUNEL assays for apoptosis (A,C,D,E) or tumor cell staining (B,D,F,H). Combined chemotherapy and gene therapy delivery of I $\kappa$ B, the inhibitor of NF- $\kappa$ B (A,B). Chemotherapy treatment alone (C,D). Adenoviral delivery of I $\kappa$ B alone (E,F). Control tumor (G,H). Thus, induction of NF- $\kappa$ B by chemotherapy blocks the efficacy of cancer therapy. Inhibition of NF- $\kappa$ B leads to dramatic tumor regression in combination with chemotherapy (A).