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## Editorial

# Guest Editor's introduction

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Transitional cell carcinoma of the bladder is a common malignancy which is increasing in incidence. In the USA it represents the fourth most prevalent human non-cutaneous malignancy. Bladder cancer is, along with testicular cancer, one of a very few cancers that has responded with significant reduced mortality in the past two decades. Two advances, improved cisplatin and methotrexate-based combination chemotherapy and intravesical therapy, most notably *Bacillus Calmette-Guérin* (BCG) immunotherapy, may explain the improvement in patient survival.

Bladder cancer is an ideal malignancy for the development of improved immunotherapy. Unlike most human malignancies, about 75% of patients with bladder cancer present with superficial disease amenable to surgical resection. These patients are typically adequately nourished and, for the most part, immunocompetent. The high recurrence rate, which is a consequence of incomplete resection, diffuse malignant transformation of urothelial cells or continued carcinogenesis, allows the introduction of treatment at the earliest of stages in tumor development. As evidenced by dramatic responses to BCG immunotherapy, transitional cell carcinoma is sensitive to immunotherapy. The anatomy of the bladder permits direct application of therapeutic agents at the site of tumor formation and meticulous patient follow-up by direct observation of the site of tumor. It is therefore most appropriate that bladder cancer be among the first tumors to demonstrate a consistent response to interferon (IFN-α2b).

IFNs, initially identified as proteins which inhibit viral growth, have extensive biologic activity as noted by Dr Alvarez de Mon and associates. Although important modulation of the immune system, including activation and proliferation of macrophages, natural killer (NK) cells, and T and B lymphocytes occur in response to IFN-α administration, direct inhibition of cell growth and neoplastic transformation can also occur. The observation of recurrence of grade I papillary transitional cell carcinoma in patients with carcinoma *in situ* treated with intravesical IFN suggests that important mechanisms of action not present in other therapies may exist. The current studies suggest that, unlike intravesical BCG which produces only marginal effects on peripheral blood NK and cytotoxic activity, intravesical IFN-α can significantly increase NK activity and T cell activity (Carballido). As shown by Alvarez de Mon, intravesical IFN-α induces infiltration of NK cells and T lymphocytes within the bladder wall. Serretta and associates also demonstrate that intravesical IFN-α results in heightened urinary interleukin 2 and interleukin 4.

The pilot studies reviewed in this issue make important contributions to the knowledge of the immune mechanism of action of intravesical interferon and further confirm the safety of intravesical IFN treatment. The efficacy of intron A in bladder cancer is best demonstrated by the phase III randomized prospective multicenter trial of high and low dose therapy reported in this issue by Sarosdy. The complete response rate reported (47% in evaluable patients) compares very favorably with the best of intravesical chemotherapies. Importantly, responses were seen in six of nine patients that had previously failed BCG immunotherapy. Responses have now lasted, in my experience, over 4 years. The confirmed efficacy of Intron A in the treatment of carcinoma *in situ* suggests that it should be effective in the prophylaxis of bladder cancer as well, since many recurrences are due to progression of occult *in situ* disease. Confirmation of benefit in prophylaxis, however, requires comparison with a randomized control group. Studies presented in this issue suggest that IFN is effective in the prophylaxis of recurrent transitional cell carcinoma, but further confirmation with randomized phase III trials is needed. Similarly, while pilot studies suggest IFN may increase the efficacy of intravesical chemo-

therapy, large phase III trials will be needed to confirm this impression.

Intron A is a highly effective immunotherapy in the treatment of carcinoma *in situ* of the bladder. It has the advantage over similarly effective chemotherapies in that it is essentially non-toxic. Additional studies will be needed to confirm its efficacy in the prophylaxis of recurrent superficial bladder cancer and its role in the prevention of tumor progression and mortality.