



## Abstracts: Session III

downward approach; it has yielded only targets at low levels within the replication machinery, never at the level of proliferation control and signaling proteins. Drug-like molecules with molecular weights around 500 seem to work well as inhibitors of tyrosine kinases, docking in their ATP pocket; however, molecules of this kind are perhaps too compact for selective interference at the level of cross-talks between the domains of two signaling proteins. Rapid evolution has recently taken place in possibilities for internalizing amphipathic molecules of molecular weights of several thousand. Under these conditions it becomes possible to conceive peptidomimetic drugs of several dozen amino-acid-like units, and these are much better suited for such selective interference. Small, dedicated peptidomimetic combinatorial libraries, based on a natural protein motif involved in the cross-talk of interest and on computer modeling, are natural allies in this game. A recently developed peptidomimetic lead capable of interfering with Myc activity<sup>1,2</sup> will be discussed within the framework of this new strategy for developing antineoplastic drugs.

1. Pescarolo, M.P. *et al. Cancer Res.* **58**, 3654–3659 (1998).  
2. Pescarolo, M.P. *et al. FASEB J. Exp.* January 2001.

Paules, Richard S.

[1]

### ATM-dependent responses to DNA-damaging agents

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Ataxia telangiectasia is an autosomal recessive disorder characterized by neuronal degeneration, telangiectasias, acute cancer predisposition and hypersensitivity to ionizing radiation (IR). The gene defective in this disorder, *ATM* (for AT-mutated), encodes a protein, pATM, that has been found to have IR-inducible kinase activity. Cells from individuals with AT exhibit severely attenuated cell cycle checkpoint function in response to IR exposure and are hypersensitive to IR-induced killing. It has been suggested that pATM acts as part of a complex that senses DNA damage and in particular DNA double-strand breaks; it has also been speculated that pATM participates in response to oxidative damage. We have been studying pATM-dependent cellular responses to various DNA-damaging agents. As part of this effort, we are investigating global gene expression changes following exposures to IR in both lymphoblast and fibroblast cells from multiple individuals with either normal or defective pATM function. We are comparing gene expression changes in both normal and pATM-deficient cells from one cell type that is predisposed to undergo apoptosis (lymphoblasts) with those in cells predisposed to undergo a prolonged cell cycle arrest (fibroblasts) following IR exposure. In addition, we are comparing these responses to IR in normal and pATM-deficient fibroblasts with responses to exposure to ultraviolet light in the 000- to 000-nm range and reactive oxygen species. These analyses are being performed using National Institute of Environmental Health Sciences Human ToxCips, with approximately 2,000 known complementary DNA clones, as well as with Human Discovery Chips, a collection of approximately 12,000 known and anonymous cDNA

Pedersen, Tanja X.

[2]

### Profiling changes in keratinocyte gene expression during wound reepithelialization by laser capture microdissection combined with cDNA array analysis

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Incisional wounding of the skin triggers a series of dramatic events in the epidermal keratinocytes that are located immediately adjacent to the margins of the wound, ultimately leading to complete reepithelialization of the wound by these cells. These events include hyperproliferation of basal keratinocytes, dissolution of cell-cell adhesions, detachment from the basement membrane, lateral migration into the wounded area, invasion and proteolytic degradation of the provisional matrix of the wound bed. In many aspects, the healing response resembles the phenotypic events observed during squamous carcinoma progression, in which normal keratinocytes undergo a malignant conversion to acquire a proliferative, migratory and invasive phenotype. To elucidate the molecular mechanisms underlying the transformation of keratinocytes to a migratory and proteolytic phenotype, we initiated a study of global changes in keratinocyte gene expression during mouse incisional skin wound healing. We used laser capture microdissection, which allows the procurement of pure cell populations from heterogeneous histological samples, to isolate wound keratinocytes that actively migrate through and degrade the provisional matrix of full-thickness incisional mouse skin wounds. For comparison, we isolated nonmigrating keratinocytes distal to the wound edge, as well as keratinocytes from mock-wounded mice, in a similar manner. We isolated total RNA (11–18 ng) from approximately 5,000 keratinocytes and generated complementary DNA probes by reverse transcription of the messenger RNA fraction. We then screened cDNA expression arrays to identify the expression pattern of 1,176 mouse genes in the three populations of keratinocytes. Results of the expression studies will be presented and discussed.

Perry, Mary Ellen

[3]

### Conditional inactivation of *Mdm2*

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The *mdm2* oncogene encodes p90MDM2, a critical negative regulator of the p53 tumor suppressor protein. The early embryonic lethality of mice of *Mdm2* null genotype precludes an evaluation of MDM2's role in regulating p53 in adult tissues. It is critical to understand the mechanisms regulating levels and activities of p53, because loss of p53 function leads to tumorigenesis whereas high levels of active p53 can stimulate apoptosis. The ability of p53 to regulate the expression of its own inhibitor, p90MDM2, has led to the suggestion that p53 controls its own activity through a negative feedback loop with *Mdm2*. This feedback loop is con-