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Editorial

Reinhard Ebner and Thomas Ried

Methods for high-throughput analysis of genomes and transcriptomes are now offering unprecedented insights into genetic alterations of cancer cells. The systematic and unbiased exploration of such changes offers opportunities for the development of new, targeted therapeutics and carries remarkable promise for the identification of agents that modulate aberrant pathways in diseased cells with greatly improved specificity. This, in turn, will hopefully expand the clinical choices by revealing novel avenues for drug development, in addition to the conventional targets used in cancer therapy today, such as cell cycle, cell proliferation and avoidance of apoptosis.

This issue of *Drug Development Today: Disease Mechanisms*, begins with an overview by Edgren and colleagues of state-of-the-art genome profiling approaches. The paper gives an example on how these approaches revealed a, so far, entirely underappreciated mechanism for oncogene activation in prostate cancer, *i.e.*, the generation of oncogenic fusion genes, a process hitherto observed predominantly in the hematological malignancies. The subsequent three articles all deal with encouraging observations for novel cancer therapeutic concepts; they discuss recently emerging trends for three such promising pathways: Epithelial-to-mesenchymal transition, biochemical modification of the histone family of proteins and efforts to target so-called oncofetal gene products, such as the components of the hedgehog, notch and Wnt signaling pathways.

In the last few years, the process of epithelial-mesenchymal transition (EMT) has gained increased attention from the cancer research community, due to its possible involvement in the development of metastasis disease, which, for cancer patients, often defines the threshold from treatment with curative attempt to mere palliation. EMT is a transdifferentiation process that allows epithelial cells to assume many of the typical characteristics of stromal, mesenchymal cell types. The EMT of primary epithelial cancer cells is strikingly similar to the EMT long known to occur during normal embryogenesis and tissue repair. EMT is also involved in tumor angiogenesis, another critical feature of cancer cells. It is still unclear whether EMT is a required step in the malignant dissemination of cells of all carcinoma types, or whether metastatic spread can be triggered by a multitude of other programs as well. The article in this issue by Chua and colleagues, however, makes a compelling case for how many of the more recently developed targeted anti-proliferative or anti-angiogenic therapeutics may have additional – and in some cases predominant – roles in the prevention of metastatic disease by affecting EMT.

Histone modifications play a central role in the control of gene expression patterns. Among the histone modifications most relevant in terms of drug development, *i.e.*, histone methylation and histone deacetylation, the enzymes regulating the levels of acetylation of histones have been most actively pursued as critical targets, and several first-generation histone deacetylase

inhibitors (HDACi), alone or in combination, are now in phase I and II clinical trials. The article by Heinzel and Krämer provides a representative overview and status report on strategies to affect these modification reactions with small molecule inhibitors.

There is considerable and justified hope that targeting signaling pathways that go beyond the classical targets in cancer therapy will offer more specific treatments, with greatly reduced treatment associated toxicity. Oncofetal proteins are components of pathways that were initially explored because of their roles in early development and tissue homeostasis. There is now ample evidence that they are frequently over-expressed, re-expressed or aberrantly activated in tumors. Therefore, they hold considerable promise to be much more specific intervention targets, suitable for the modulation of oncogenic and metastatic processes in novel ways. The article by Muller *et al.* provides a comprehensive summary of therapeutic targeting initiatives, both using biotherapeutics as well as synthetic small molecules, for three of the most intensively studied such pathways, *i.e.*, Hedgehog, Notch, and Wnt.

We hope that the reader perceives this issue as a stimulating overview of novel genomic tools and their use, and of recent trends in targeting some prominent cancer specific pathways, that will ultimately allow the development of novel generations of cancer drugs that are more efficient and associated with lower general toxicity.

Biographies

REINHARD EBNER is Principal Scientist at Avalon Pharmaceuticals, Inc., in Germantown, Maryland. Having joined the company as one of the earliest investigators, he is working in the fields of chemical genomics, cancer research, genomic data mining and HTS assay development. He also coordinated the company's therapeutic antibody target discovery alliances and has a long-standing interest in alternative and novel drug discovery paradigms and development strategies.

Prior to that, Dr. Ebner was at Human Genome Sciences from 1995–2000 where he discovered several of the proteins around which HGS established pre-clinical and clinical development programs, including the molecules LIGHT, DR4, IL-17B and its receptor, BlyS and TR6.

In 1989, Dr. Ebner was awarded a research fellowship to serve as a visiting scientific specialist at Genentech, Inc. in San Francisco. Working in the fields of cytokine biology, receptor-ligand interactions and intracellular trafficking, he cloned the long elusive first type I TGF- β receptor. He was first to show TGF β -induced epithelial-mesenchymal-transitions (EMTs) in cells in culture and has made other contributions to cell differentiation, early development and tissue repair, first at Genentech and then at the University of California, San Francisco and at Stanford University Medical School.

He has authored more than 50 original research publications and has been invited to present numerous plenary lectures; he is a recipient of grant and manuscript peer review service awards and society memberships, an *ad hoc* reviewer and editor for scientific journals, and the inventor on several hundred patent applications world wide, with 40 issued US patents. Dr. Ebner received his undergraduate degree in Biology at the University of Regensburg and his doctorate in Microbiology and Genetics at the University of Osnabrück, Germany, where he then served on the faculty of the Genetics department.

Thomas Ried serves as Chief of the Cancer Genomics Section at the Center for Cancer Research, NCI/NIH. His research is focused on understanding genome dynamics in cancer cells and on learning how genome mutations and nuclear architecture affect the cancer transcriptome. His laboratory has a strong interest in applying genetic information for the improvement of cancer diagnosis, prognosis, and therapeutic stratifications.

Dr. Ried conducted his thesis research at the Max-Planck Institute for Medical Research in Heidelberg, and received his M.D. from Heidelberg University in 1989.

Before joining the NCI in 1998, Dr. Ried was on the faculty of the National Human Genome Research Institute, a position he assumed after postdoctoral training at the Universities of Heidelberg, Leiden and Yale. At the Genome Institute his laboratory developed spectral karyotyping (SKY), a method that greatly facilitates the identification of complex chromosomal aberrations in human cancers and murine models. Dr. Ried's group also identified specific genetic changes that predict the progression of dysplastic lesions of the uterine cervix to invasive carcinomas in individual patients, and, in collaboration with colleagues in Göttingen, Germany, now elucidates how gene expression patterns in rectal carcinomas can help to predict response to preoperative radiochemotherapy.

From 1994 until 2000, Dr. Ried taught and organized advanced courses at Cold Spring Harbor Laboratories.

Dr. Ried has authored more than 200 original publications. He serves on the editorial board and as a reviewer for numerous scientific journals, as a reviewer for national and international funding agencies, and he was a member of the scientific advisory board of several biotech companies.

In 2000, Dr. Ried received the ASBMB-Amgen award from the American Society of Biochemistry and Molecular Biology