Heidelberger Symposium: Introduction

Heidelberger symposium on the 50th anniversary of fluoropyrimidines

Franco M. Muggia

NYU Langone Medical Center, New York, New York

“Targeted” therapies are dominating new cancer therapeutics during the past decade. However, the term is not precise because drugs referred to as “cytotoxics” are often targeted, and drugs developed as targeted often exert many of their antitumor actions by “off-target” effects; that is, results may bear little relationship to the drug reaching the presumed target. Examples abound in both directions: topoisomerase I poisons are among the most precisely targeted drugs. Conversely, farnesyl transferase inhibitors reproducibly affect ras farnesylation but the relationship to antitumor activity and inhibition of ras has not been established in any study where some clinical usefulness of these agents has been documented. Target expression and therapeutic effects have perhaps been most extensively studied for epidermal growth factor receptor inhibitors, and any such relationship has varied greatly among tumor types.

The struggle for precision in the term “targeted” leads one to explore several possible alternative definitions. Perhaps not subject to as many exceptions is one in which a drug designed with a target in mind becomes “targeted”, to be contrasted with those drugs that are empirically selected in an antitumor screen. We are now in an era when “targeted therapy” discovery is flourishing, but one should not assume that future advances will only come through introduction of such new drugs. Knowing more about our empirically introduced drugs can also lead to improved therapeutic results.

The contributions to this Heidelberger symposium commemorating the 50th year of the introduction of 5-fluorouracil best exemplify the intricacies of drug development. 5-Fluorouracil was rationally synthesized and targeted to solid tumors by Charles Heidelberger in 1957. After decades of clinical experience and mechanistic studies, two targets of 5-fluorouracil have emerged most prominently: incorporation into RNA (at very high and short drug exposures) and DNA synthesis inhibition (following protracted drug exposure) via its nucleotide forming a ternary complex with the enzyme thymidylate synthase and the folate cofactor that donates a methyl to uracil in its enzymatic conversion to thymidine. Pharmacology and metabolism have led to improvements in its therapeutic index through “biochemical modulation” of pyrimidine or folate pools or through the development of oral drugs not activated as readily in the bone marrow. The drug continues to be an essential backbone of regimens for the treatment of gastrointestinal cancers and to a lesser extent of breast cancer. Rather than predicting (as others have done in the past) that the drug would soon be replaced, it behooves us to continue to focus on how to attack the neoplastic process on all fronts, and that includes learning more about a drug such as 5-fluorouracil. Contributions to the symposium also relate to other areas of drug development; they further illustrate the need for continuing a multiprong search for drugs useful in fighting cancers: whether introduced via “rational” design, via “modifiers” of known agents, or via “empiric” discovery.
Molecular Cancer Therapeutics

Heidelberger symposium on the 50th anniversary of fluoropyrimidines

Franco M. Muggia

*Mol Cancer Ther* 2009;8:991. Published OnlineFirst April 21, 2009.

Updated version

Access the most recent version of this article at:
doi:10.1158/1535-7163.MCT-08-0732

E-mail alerts

Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions

To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions

To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.