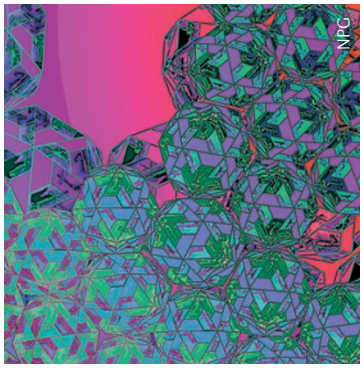
IN THIS ISSUE

Validating therapeutic targets through human genetics p581



Novel therapies for hepatitis C p595

The high failure rate of compounds in clinical trials is largely responsible for the high costs of drug development. These failures reflect the limited predictive capacity of standard preclinical disease models, and in our first Review Plenge and colleagues propose that greater use of knowledge from human genetics — in particular on naturally occurring mutations that affect the activity of specific proteins — could help to address this problem. They present examples supporting the use of genetics in target validation, propose objective criteria for prioritizing drug targets and consider the limitations of this approach.

In the second Review, Manns and von Hahn discuss the recent acceleration in the development of therapies for hepatitis C virus (HCV). They summarize the molecular targets of antiviral therapy and assess the various classes of compounds currently under development while considering the key challenges faced in HCV treatment. Next, Turkson and colleagues review the abnormal activation of STAT (signal transducer and activator of transcription) signalling pathways in various disorders, including cancer, autoimmune diseases, asthma and diabetes. Various strategies and agents that are currently under investigation for the modulation of individual STAT protein activity, as well as future directions for the field, are highlighted. Finally, Sexton and colleagues focus on the growing interest in allosteric ligands of G protein-coupled receptors, which influence receptor activity by binding to a site distinct to that of endogenous ligands. They discuss recent advances in understanding the complex actions of allosteric modulators, such as the induction of biased signaling, and consider how this knowledge may be therapeutically exploited.

EDITORIAL & PRODUCTION OFFICE
The Macmillan Building, 4 Crinan Street, London N1 9XW, UK
Tel: +44 (0)20 7843 3620; Email: NatureReviews@nature.com
www.nature.com/reviews/drugdisc
CHIEF EDITOR Peter Kirkpatrick
SENIOR EDITORS Alexandra Flemming, Charlotte Harrison, Sarah Crunkhorn, Monica Hoyos Flight
SENIOR NEWS EDITOR Asher Mullard
ASSISTANT EDITOR Man Tsuey Tse
SENIOR COPY EDITOR (NRD) Mariam Faruqi
ART CONTROLLER Susanne Harris
COPY EDITING MANAGER Catriona Rodwell
SENIOR COPY EDITORS Matthew Smyllie, Isabel Woodman, Lucie Wootton
SENIOR EDITORIAL ASSISTANTS Laura Corns, Ella Lines
MANAGING PRODUCTION EDITOR Judith Shadwell
SENIOR PRODUCTION EDITOR Simon Fenwick
SENIOR ART EDITORS Kirsten Lee, Patrick Morgan, Vicky Summersby
PRODUCTION CONTROLLER Natalie Smith
PUBLISHER (BIOPHARMA) Melanie Brazil
PUBLISHING DIRECTOR Peter Collins

CUSTOMER SERVICES www.nature.com/help
PERSONAL SUBSCRIPTIONS subscriptions@nature.com
REPRINTS www.nature.com/reprints
ADVERTISING & SPONSORSHIP www.nature.com/advertising
SITE LICENCES www.nature.com/libraries/site_licenses/index.html
PRESS OFFICE press@nature.com
MARKETING marketing@nature.com

MANAGEMENT OFFICES
NPG LONDON The Macmillan Building, 4 Crinan Street, London N1 9XW, UK. Tel: +44 (0)20 7833 4000
NPG NEW YORK 75 Varick Street, 9th floor, New York, NY 10013-1917, USA. Tel: +1 212 726 9200
NPG ASIA-PACIFIC Chiyoda Building 2-37 Ichigayatamachi, Shinjuku-Ku, Tokyo 16200843, Japan. Tel: +1 212 726 9200
A list of other offices can be found at www.nature.com/npg_/contact/offices.html

Printed in Wales by Cambrian Printers on acid-free paper.