06 July 2008 08:00 - 08:50

EDUCATIONAL LECTURE

Drug design

17

Designing new cancer drugs: the science, the art and team sport

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Our understanding of the genetics and biochemistry of malignant cells, though still incomplete, has progressed sufficiently to form the basis for the development of a range of rationally designed, molecularly targeted drugs that have an impact on clinical outcome in cancer patients. Looking at the progress made in an objective fashion, the news so far has been mixed. On the one hand, we have spectacular successes with small molecules like imatinib and antibodies like trastuzumab. On the other hand, in many cases survival gains with approved agents have been modest; the approval rate for cancer drugs in the clinic remains low (10-20% at best) with attrition occurring late in development; and drug resistance is an enduring problem. Set against the background of a pharmaceutical and biotechnology industry that is under pressure on many fronts, there are important challenges ahead. Nevertheless, the figures show that the oncology therapeutic area has the highest rate of innovation in the sector, as measured by first-in-class drug approvals. Moreover, it is the area in which the benefits of the human genome sequence are most readily being harvested. In this presentation, I will describe the opportunities and challenges relating to the design of small molecule inhibitors acting on new cancer drug targets. I will emphasize the underlying science and technology breakthroughs, but also emphasize the art as well as the science of drug discovery. Above all, drug discovery is a team sport in which the various players, chemists and bioscientists, interact creatively in an attempt to combine all the best features – potency, selectivity, pharmacokinetics/metabolism and pharmacodynamic behaviour – within a single optimized drug molecule. The following critical aspects of the drug design and discovery process will be emphasized:

- Picking winners: Selecting the best drug targets
- Finding the needle in the haystack: Screening approaches to identify hit molecules
- Structure-based drug design: Improving potency and selectivity
- Multiparameter optimization: Building in robust pharmacokinetic and pharmacodynamic behaviour
- Rationalizing candidate selection and clinical trials: The importance of biomarkers

Examples will be provided from projects involving the design of inhibitors against exciting new targets like PI3 kinase, AKT, Aurora, CDK2 and the molecular chaperone HSP90.

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06 July 2008 09:00 - 09:45

PLENARY LECTURE

Microenvironment

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KISS1 induction of metastatic dormancy: A therapeutic opportunity?

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Since most cancer morbidity and mortality are associated with the development of metastases, effective strategies to control metastasis be a significant improvement. Since blockage of any step of the metastatic cascade can prevent development of metastasis, there are multiple targets. Unfortunately, many (perhaps most) of the steps have occurred prior to diagnosis. Patients can have disseminated cells present for years for which impact on organ function is negligible. As a result, the definition of a "metastasis" varies from a single disseminated cell to tumor cells that have seeded, but not yet proliferated (micrometastases) to macroscopic masses that grow discontinuous from the primary tumor. But merely seeding at ectopic sites does not guarantee growth. Thus, it is critical to distinguish between disseminated cells and overt metastases.

Functionally metastasis suppressors block metastasis without blocking primary tumor formation (fundamentally regulating cellular responses to a microenvironment). It follows that modulating the ability of cancer cells to respond to a microenvironment or modulating the secondary environment would be expected to alter metastasis development. Since one must assume that cancer cells disseminate, we need to focus therapeutic efforts on controlling their growth after they are away from the primary tumor.

The KISS1 metastasis suppressor functions in melanoma, breast and ovarian cancers. Nascent KISS1 is secreted and proteolytically cleaved to make kisspeptins (KP) which bind a G-protein coupled receptor, GPR54. Stable KISS1-expressing clones were isolated in the C8161 melanoma model, injected into athymic mice and metastases monitored. Macroscopic metastases in all organs was significantly suppressed, with corresponding increased survival. KISS1-expressing cells seeded lungs, but did not form macroscopic metastases. The cells were capable of completing antecedent steps of the metastatic cascade, but not able to colonize lungs.

Thus, the opportunity to control colonization may be close. If disseminated cells could be maintained in a permanently dormant state, cancer then becomes a controllable disease rather than simply something that requires acute elimination. Unfortunately, dormancy generally confers resistance to proliferation-dependent therapies such as radiation and chemotherapy. Once cells break dormancy and proliferate, patient survival drops precipitously. So, identification of molecular targets that selectively kill dormant cells or maintain them in a dormant state indefinitely, like KISS1, would have an immediate impact on patient survival.

06 July 2008 10:15 - 12:15

SYMPOSIUM

Cell death pathways

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Myc-induced apoptosis and tumour suppression: Lessons from mouse models

No abstract received.