1574

The search for and potential therapeutic applications of chemical inhibitors of cyclin-dependant protein kinases

L. Meijer[1], M. Leost[1], M. Garnier[1], S. Leclerc[1]. *CNRS, Station Biologique, Roscoff, France*

Cyclin-dependent kinases (CDK1, 2, 3, 4, 6, 7) trigger and coordinate the cell division cycle phases. They also play a role in neuronal cells (CDK5) and in the control of transcription (CDK 7, 8, 9). Intensive screening has lead in a few years to the identification of a series of chemical inhibitors of CDKs: olomoucine, roscovitine, purvalanol, CVT-313, indirubin-3′-monoxime, paullones, CGP60474, flavopiridol, butyrolactone, toyocamycin. Some of these compounds display remarkable selectivities and efficiencies (IC50 < 25 nM). Many have been co-cristallised with CDK2 and their atomic interactions with the kinase have been analysed in detail: all are located in the ATP-binding pocket of the enzyme. These inhibitors are antimitotic, they arrest cells in G1 and, at higher doses, in G2/M.

Furthermore they facilitate or even trigger apoptosis in proliferating cells. In contrast, they protect neuronal cells from apoptosis. The potential use of these inhibitors is being extensively evaluated in cancer chemotherapy (clinical trials, phase I and II). Possible clinical applications are being investigated in other fields: cardiovascular (restenosis, tumoral anglogenesis, atherosclerosis), dermatology (psoriasis), nephrology (glomerulonephritis), parasitology (unicellular parasites such as Plasmodium, Trypanosomes, Toxoplasm,...etc.), neurology (Alzheimer's disease), viral infections (cytomegalovirus, H.I.V., herpes). We anticipate the discovery of novel selective and powerful inhibitors in the near future and hope for their efficient applications in various human pathologies.

1575

Abstract not received.

1576

New players in separating sister chromatids during mitosis. Potential new drug targets?

K. Nasmyth[1], F. Uhlmann[1], F. Lottspeich[2]. [1]*Institute of Molecular Pathology, IMP, Vienna, Austria;* [2]*Max Planck Institute of Biochemistry, D-82152 Martinsried, Germany*

A multi subunit complex, called cohesin, tethers sister chromatids together after their synthesis during DNA replication. In yeast, cohesin holds sister chromatids together until metaphase when cohesion opposes the pulling force of the mitotic spindle. A sudden loss of cohesion between sister chromatids is then thought to initiate anaphase. Loss of cohesion depends on Esp1p function in the yeast S. cerevisiae. Scc1p, a cohesin subunit required to maintain cohesion in metaphase, dissociates from chromosomes at the time of sister chromatid separation. We address here the mechanism by which Esp1p acts to initiate sister separation. We show that Esp1p directly causes Scc1p's dissociation from chromosomes by inducing its proteolytic cleavage at a specific and conserved site. Cleavage resistant Scc1p no longer dissociates from chromosomes, which prevents sister chromatid separation. Esp1p is conserved through evolution, thus proteolytic cleavage of cohesion proteins might be the general mechanism to separate sister chromatids at the onset of anaphase.

1577

START programme

A. Costa[1], P. Casali[2], L. Licitra[2], C. Tondini[2], F. De Braud[3], P. Bruzzi[4]. [1]*European Institute of Oncology, Breast Division, Milan;* [2]*Istituto Nazionale Tumori, State-of-the-Art Cancer Medicine Research Unit, Milan;* [3]*European Institute of Oncology, Medical Oncology Division, Milan;* [4]*Istituto Ricerca Cancro, Epidemiology and Trials Unit, Genova, Italy*

START ("State-of-the-Art Oncology in Europe") is an "information base" on current clinical approach to human tumours, as perceived by the European community of oncologists. It is freely accessible through the Internet at the following Web address: http://www.cancereurope.org/start. This state-of-the-art instrument tailored to oncologists and physicians is a collaborative effort of the European School of Oncology, pursued in collaboration with the Istituto Nazionale Tumori, Milan, Italy, involving all over Europe more than 150 experts in the various fields of oncology.

START is an evidence-based instrument to serve as a decision support tool for the clinician. Main clinical recommendations are codified: therapeutic or diagnostic options may be "standard", "investigational", or "suitable for individual clinical use". Also their "basis" is codified, reflecting their strength in terms of evidence/consensus on a five-level scale ("consensus", "randomised, strong", "randomised, weak", "uncontrolled", "rational"). Likewise, clinical information is provided in details, in an effort to fit the needs of clinical oncologists in their daily practice.

START is an effort still under development. As of today, more than 15 chapters are online. A pilot validation feedback project has been already carried out on the first chapters. Feedback on START contents was solicited from the whole European oncology community. This feedback project was granted by the European Commission and was mainly carried out in collaboration with ESMO, ESSO and ESTRO, as well as with EONS and EORTC. The agreement rate proved high. From now on, formal collaboration with these societies will be ongoing, in order to establish a wider consensus development process on each chapter. This continuous process of "internal" filtering of the chapters through multi-step reviews is aimed at rendering START a true European state-of-the-art instrument over the next few years. An "external" feedback mechanism will be operating as well, adding to the validation process.

START joins the movement towards evidence-based medicine. START is focusing on filling the gap between evidence provided by clinical research and current practice. This leaves room for methodological research, to which START wishes to contribute through its concrete work in the field of clinical oncology.

1578

Abstract not received.

1579

Guidelines and clinical databases: The role of scientific societies

M. Baumann[1]. [1]*Universitätsklinikum Carl Gustav Carus, Klinik und Poliklinik Strahlentherapie, Dresden, Germany*

Evidence based oncology (EBO) databases play an increasingly important role in promotion of state-of-the-art treatment. Some databases were developed in-house by high profile institutions or small working parties with or without interdisciplinary input whereas more stringent EBO-instruments such as START have developed elaborated scientific mechanisms of data accumulation and review. In theory, only one best scientific solution should exist at a given time for a given medical problem, therefore different approaches generating EBO-databases should theoreti-cally yield the same result. However, in real life the situation is much more complex, with different well supported views of different medical specialties, with strong heterogeneity of regional and national treatment policies and resources, with a substantial lack of solid scientific information in many fields, and with conflicting results of clini-cal trials in other fields. International scientific societies have established over decades well functioning mechanisms to cope with many of these problems. Therefore the scientific societies have a key role in the development of valid and useful clinical databases: identification of experts who generate databases in an interdisciplinary and multinational setting, continuous peer-review mechanisms by expert referees from countries with different treatment ap-proaches, feed-back-mechanisms by members, integration of EBO-databases in training and CME programs, etc. The scientific societies also have a key role in making sure that resources are not diluted by parallel efforts but rather are concentrated to generate and sustain one or a small number of well functioning systems that cover all needs e.g. on the European level. With help of international, national and regional societies such EBO-databases can be used as an effective source for the development of guidelines that are both, state-of-the-art and at the same time compatible with regional resources.

1580

The Future of CME!

J. Geraghty. *City Hospital, United Kingdom*

The concept of education as a lifelong learning process was first proposed formally at the beginning of the twentieth century. In the last decade there has been an increasing public interest in how the medical and allied health professions govern and regulate themselves. Rapid advances in medical science, research and technology, have focused interest on the field of Continuing Medical Education (CME). There is widespread acceptance that