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

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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.

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Abstract not received.

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

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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.

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START programme

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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.

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Guidelines and clinical databases: The role of scientific societies

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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.

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The Future of CME!

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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

individuals who have finished their formal training and entered into independent or consultant practice need to maintain their knowledge by embracing the concept of CME. An already very busy set of individuals now find themselves in a position of having to divert more time to keep abreast of changes in their fields. Some Countries have responded by making CME mandatory via national legislation whilst others have strongly urged the professional institutions to take the lead on setting the standards and solving the problem of reassuring a concerned and questioning general public. Europe is reflecting its concerns by the tide of activity produced as the various professional bodies strive to create accreditation systems to demonstrate the efforts of their members. Currently the systems are not equivalent and some health professionals are experiencing difficulties having credit points gained in one country translated within their home country. Other concerns include health professionals being told by employers that they will only support attendance at events which carry an accreditation stamp recognised within their home country. The directives of the EC require freedom of movement of the workforce between the component European Countries and reciprocal recognition of these systems throughout Europe is an important and as yet not well considered prerequisite for a harmonious Europe. It is in the interest of everyone, that as Europe shifts from a voluntary perspective of CME towards a compulsory standpoint, freedom of mobility and freedom of choice to access CME is maintained. Present day Information technology allows educational activities or events to be transmitted around the world and this will impact on the need for individuals to travel to access CME. The European Commission has expressed its feelings on the future of CME that it is rightly the business of the health professionals and the institutions to which they belong.

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In pursuit of evidence-based cancer nursing

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Whilst evidence for the effectiveness of cancer nursing can be difficult to obtain, not to search for it might be considered a little risky. The nature of the difficulties cuurently confronting cancer nursing will be explored in this presentation. The first concerns the philosophical basis for evidence based medicine (EBM), evidence based nursing (EBN) and clinical effectiveness, and the second concerns the cancer nursing agenda for research. EBM and EBN depend on a series of arguments. Most importantly, they depend on the notion that there is a hierarchy of evidence, at the apex of which are experimental studies and, at the base the every day experience of the individual practitioner (1). As it is currently described it is of limited use to cancer nursing. This is in part due to its emphasis on particular types of empirical evidence and partly because of the scarcity of this type of evidence in nursing. The similarities between the issues currently connfronting cancer nurses and physicians in general practice will be drawn out. Cancer nursing is beginning to address the need for a research agenda at both national and international level in order to fill the gaps in our current knowledge base. Essential elements of a cancer nursing research and development strategy will be outlined. Of prime importance is the fact that any agenda must start by addressing the real problems faced by patients and must, therefore, start by asking them what questions should be addressed. Second, since it will be clinical nurses who will be asked to implement the findings of any research, they should be for guidance on ways to answer patients' questions, ways which have meaning in the clinical environment. Ongoing dialogue is critical to ensure any resulting research agenda remains relevant to practice.

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Epstein-Barr virus and lymphomagenesis

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Epstein-Barr virus (EBV) is a human gamma herpesvirus with cell growth transforming ability which efficiently colonises the B lymphoid system. The growth transforming infection is normally controlled by cytotoxic T lymphocyte (CTL) surveillance directed against virus latent cycle antigens. Virus persistence depends upon the establishment of a pool of non-cycling memory B cells which carry the virus genome but express few if any.

EBV is linked to three distinct lymphomas of B cell origin, each exhibiting a different form of latent infection. These are;- (i) *Post-transplant lymphoproliferative disease* which at least in its initial stages is directly EBV-driven, expresses the full spectrum of latent proteins and remains susceptible to a restoration of CTL surveillance. (ii) *Burkitt's lymphoma,* a tumour of germinal centre cell origin where virus antigen expression is restricted to EBNA1 and where defects in antigen processing function allow efficient tumour cell escape from CTL detection. (iii) *Hodgkin's Disease,* a post-germinal centre tumour, where expression of the latent membrane proteins LMPs 1 and 2 (in addition to EBNA1) renders the malignant cells potentially immunogenic to the CTL response.

EBV is also strongly implicated in the pathogenesis of certain non-B-cell tumours, reflecting the fact that the virus is not exclusively B cell tropic. The best known tumours of this type are nasopharyngeal carcinoma and nasal T/NK cell lymphoma, both consistently EBV genome-positive and displaying patterns of latent protein expression intermediate between Burkitt's lymphoma and Hodgkin's Disease. The prospects far successful immunotherapy of EBV-associated malignancies, in particular nasopharyngeal carcinoma, are discussed.

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Present understanding of HBV associated carcinogenesis

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Hepatitis B virus (HBV) causes a spectrum of liver diseases ranging from fulminant hepatitis to inapparent infection that frequently lead to liver cirrhosis and hepatocellular carcinoma (HCC). With about 350 million chronic HBV carriers worldwide, and one million deaths attributed to HBV-related liver disease each year, this virus remains a major public health problem. Despite significant advances in understanding the HBV genome structure and function and the viral replication strategy, the pathogenesis of HBV-induced liver disease and the molecular basis of liver cell transformation remain largely unknown. Evidence for a direct role of HBV DNA integration into the host genome in the cis-activation of cellular genes has been provided only in a minor proportion of HCC cases. Liver injury can be mediated by the host immune response against cells expressing the HBV antigens, and by host-virus interactions, implicating notably persistent expression of the regulatory protein HBx and abnormal overload with non secretable large envelope protein. By inducing liver cell necrosis and compensatory regeneration, HBV replication and associated inflammatory activity might result in the accumulation of genetic defects that ultimately lead to malignant transformation.

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Molecular mechanisms of HIV-associated Kaposi's sarcoma

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Kaposi's sarcoma (KS) is the most common AIDS-associated malignancy. Several observations closely relate the etiology of epidemic KS to both KSHV/HHV-8 and HIV-1 infection.

In early stage KS appears as an hyperplastic, non-tumoral, highly angiogenic lesion, characterized by the infiltration of spindle shaped cells, macrophages, lymphocytes and neutrophils: this stage is probably characterized by an emerging KSHV infection in the immunosuppressed host. KSHV encodes numerous cellular homologues that might be involved in the insurgence of KS, these include proteins linked to cell cycling (vCyclin-D, vBcl-2), angiogenesis (vMIPs, vIL-6, and a chemokine receptor) and antiviral immunity (CD21, vIRF). Some of the proteins encoded by KSHV have been linked to a neoplastic phenotype in transduced cells. The role of KSHV as a true "transforming virus" are still disputed, although late stage KS closely approaches a "true" sarcoma.

The association with HIV clearly plays an important role in KS occurrence among AIDS patients. AIDS KS is often found in an unusually aggressive form. An important contribution of HIV-1 to KS progression is probably linked to the expression of the Tat protein. We have shown that Tat is able to act as a chemokine, recruiting and activating monocytes and PMN through chemokine receptors, and as an angiogenic growth factor activating the VEGF receptor KDR on endothelial and KS cells. Tat also acts as an integrin ligand interacting with alpha5beta1, alphaVbeta3 and alphaVbeta5.

The complex network of viral activators involved in KS etiology and progression is not yet completely elucidated, both HIV-1 Tat and several KSHV proteins are a strong pro-angiogenic, pro-inflammatory stimuli supporting the development of this neoplasm.