DOWNLOAD PDF MOLECULAR ASPECTS OF CHEMOTHERAPY

Chapter 1 : [Molecular aspects of chemotherapy].

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Chemotherapy may be given with a curative intent or it may aim to prolong life or to palliate symptoms. Induction chemotherapy is the first line treatment of cancer with a chemotherapeutic drug. This type of chemotherapy is used for curative intent. Consolidation chemotherapy is given after remission in order to prolong the overall disease-free time and improve overall survival. The drug that is administered is the same as the drug that achieved remission. The drugs differ in their mechanism and side-effects. The biggest advantage is minimising the chances of resistance developing to any one agent. Also, the drugs can often be used at lower doses, reducing toxicity. It can be used when there is little evidence of cancer present, but there is risk of recurrence. These micrometastases can be treated with adjuvant chemotherapy and can reduce relapse rates caused by these disseminated cells. For these regimens, in general, a better toxicity profile is expected. Performance status is often used as a measure to determine whether a person can receive chemotherapy, or whether dose reduction is required. Because only a fraction of the cells in a tumor die with each treatment fractional kill , repeated doses must be administered to continue to reduce the size of the tumor. The overall effectiveness ranges from being curative for some cancers, such as some leukemias , [9] [10] to being ineffective, such as in some brain tumors , [11] to being needless in others, like most non-melanoma skin cancers. At high doses the percentage of normal and cancer cells killed is very similar. For this reason, doses are chosen where anti-tumour activity exceeds normal cell death. If the dose is too low, it will be ineffective against the tumor, whereas, at excessive doses, the toxicity side-effects will be intolerable to the person receiving it. This formula was originally derived in a study and attempted to translate medicinal doses established with laboratory animals to equivalent doses for humans. Some people are overdosed while others are underdosed. Similar results were found in a study involving people with colorectal cancer who were treated with the popular FOLFOX regimen. Median progression free survival PFS and overall survival OS both improved by six months in the dose adjusted group. With an established target exposure for optimized treatment effectiveness with minimized toxicities, dosing can be personalized to achieve target exposure and optimal results for each person. Such an algorithm was used in the clinical trials cited above and resulted in significantly improved treatment outcomes. Oncologists are already individualizing dosing of some cancer drugs based on exposure. Simple blood tests are also available for dose optimization of methotrexate , [28] 5-FU, paclitaxel , and docetaxel. Different nitrogen mustards will have different chemical groups R. The nitrogen mustards most commonly alkylate the N7 nitrogen of guanine as shown here but other atoms can be alkylated. Alkylating antineoplastic agent Alkylating agents are the oldest group of chemotherapeutics in use today. Originally derived from mustard gas used in World War I , there are now many types of alkylating agents in use. This ability to bind covalently to DNA via their alkyl group is the primary cause for their anti-cancer effects. If the cell tries to replicate crosslinked DNA during cell division , or tries to repair it, the DNA strands can break. This leads to a form of programmed cell death called apoptosis. For this reason the effect on the cell is dose dependent; the fraction of cells that die is directly proportional to the dose of drug. The drugs are very similar but they have subtle differences in their chemical structure. The building blocks are nucleotides ; a molecule comprising a nucleobase , a sugar and a phosphate group. The nucleobases are divided into purines guanine and adenine and pyrimidines cytosine , thymine and uracil. Anti-metabolites resemble either nucleobases or nucleosides a nucleotide without the phosphate group , but have altered chemical groups. Also, after misincorporation of the molecules into DNA, DNA damage can occur and programmed cell death apoptosis is induced. Unlike alkylating agents, anti-metabolites are cell cycle dependent. This means that they only work during a specific part of the cell cycle, in this case S-phase the DNA synthesis phase. For this reason, at a certain dose, the effect plateaus and proportionally no more cell death occurs with increased doses. Subtypes of the anti-metabolites are the anti-folates , fluoropyrimidines, deoxynucleoside analogues and thiopurines. Methotrexate inhibits dihydrofolate reductase DHFR , an enzyme

that regenerates tetrahydrofolate from dihydrofolate. When the enzyme is inhibited by methotrexate, the cellular levels of folate coenzymes diminish. These are required for thymidylate and purine production, which are both essential for DNA synthesis and cell division. It primarily inhibits the enzyme thymidylate synthase , but also has effects on DHFR, aminoimidazole carboxamide ribonucleotide formyltransferase and glycinamide ribonucleotide formyltransferase. The thiopurines include thioguanine and mercaptopurine. Both mechanisms cause defective mitosis. Anti-microtubule agents are plant -derived chemicals that block cell division by preventing microtubule function. They are hollow rod shaped structures that are required for cell division, among other cellular functions. Vinca alkaloids and taxanes are the two main groups of anti-microtubule agents, and although both of these groups of drugs cause microtubule dysfunction, their mechanisms of action are completely opposite. The vinca alkaloids prevent the formation of the microtubules, whereas the taxanes prevent the microtubule disassembly. By doing so, they prevent the cancer cells from completing mitosis. Following this, cell cycle arrest occurs, which induces programmed cell death apoptosis. They bind to specific sites on tubulin, inhibiting the assembly of tubulin into microtubules. The original vinca alkaloids are natural products that include vincristine and vinblastine. They bind to the tubulin molecules in S-phase and prevent proper microtubule formation required for M-phase. The first drug of their class, paclitaxel , was originally extracted from the Pacific Yew tree, Taxus brevifolia. Now this drug and another in this class, docetaxel , are produced semi-synthetically from a chemical found in the bark of another Yew tree; Taxus baccata. These drugs promote microtubule stability, preventing their disassembly. Paclitaxel prevents the cell cycle at the boundary of G2-M, whereas docetaxel exerts its effect during S-phase. Taxanes present difficulties in formulation as medicines because they are poorly soluble in water. It has anti-microtubule activity, and its mechanism is similar to that of vinca alkaloids in that they bind to tubulin, inhibiting microtubule formation. Podophyllotoxin is used to produce two other drugs with different mechanisms of action: When the DNA double-strand helix is unwound, during DNA replication or transcription , for example, the adjacent unopened DNA winds tighter supercoils , like opening the middle of a twisted rope. The stress caused by this effect is in part aided by the topoisomerase enzymes. This allows the normal unwinding of DNA to occur during replication or transcription. Inhibition of topoisomerase I or II interferes with both of these processes. This prevents DNA replication and transcription , causes DNA strand breaks, and leads to programmed cell death apoptosis. These agents include etoposide , doxorubicin , mitoxantrone and teniposide. The second group, catalytic inhibitors, are drugs that block the activity of topoisomerase II, and therefore prevent DNA synthesis and translation because the DNA cannot unwind properly. This group includes novobiocin , merbarone, and aclarubicin , which also have other significant mechanisms of action. The common theme that they share in their chemotherapy indication is that they interrupt cell division. The most important subgroup is the anthracyclines and the bleomycins ; other prominent examples include mitomycin C , mitoxantrone , and actinomycin. Other clinically used drugs in the anthracyline group are pirarubicin , aclarubicin , and mitoxantrone. The mechanisms of anthracyclines include DNA intercalation molecules insert between the two strands of DNA , generation of highly reactive free radicals that damage intercellular molecules and topoisomerase inhibition. This occurs when bleomycin binds to a metal ion , becomes chemically reduced and reacts with oxygen. The girl at left has a central venous catheter inserted in her neck. The girl at right has a peripheral venous catheter. The arm board stabilizes the arm during needle insertion. Anti-cancer IV drip is seen at top right. Most chemotherapy is delivered intravenously , although a number of agents can be administered orally e. There are many intravenous methods of drug delivery, known as vascular access devices. These include the winged infusion device , peripheral venous catheter , midline catheter, peripherally inserted central catheter PICC , central venous catheter and implantable port. The devices have different applications regarding duration of chemotherapy treatment, method of delivery and types of chemotherapeutic agent. For continuous, frequent or prolonged intravenous chemotherapy administration, various systems may be surgically inserted into the vasculature to maintain access. These have a lower infection risk, are much less prone to phlebitis or extravasation , and eliminate the need for repeated insertion of peripheral cannulae. The main purpose of these approaches is to deliver a very high dose of chemotherapy to tumor sites without causing overwhelming systemic damage. Topical chemotherapies, such as 5-fluorouracil , are used to treat

some cases of non-melanoma skin cancer. The most common medications affect mainly the fast-dividing cells of the body, such as blood cells and the cells lining the mouth, stomach, and intestines. Chemotherapy-related toxicities can occur acutely after administration, within hours or days, or chronically, from weeks to years. Anemia and thrombocytopenia may require blood transfusion. Neutropenia a decrease of the neutrophil granulocyte count below 0. In very severe myelosuppression , which occurs in some regimens, almost all the bone marrow stem cells cells that produce white and red blood cells are destroyed, meaning allogenic or autologous bone marrow cell transplants are necessary. In autologous BMTs, cells are removed from the person before the treatment, multiplied and then re-injected afterward; in allogenic BMTs, the source is a donor. However, some people still develop diseases because of this interference with bone marrow. In Japan , the government has approved the use of some medicinal mushrooms like Trametes versicolor , to counteract depression of the immune system in people undergoing chemotherapy. Typhlitis is a medical emergency. It has a very poor prognosis and is often fatal unless promptly recognized and aggressively treated.

Chapter 2 : Molecular aspects of chemotherapy (edition) | Open Library

While serendipity and random screening continue to fulfil a significant role in the search for new drugs, current remarkable advances in molecular biology and genetics are dictating to a profound extent the approaches employed in their development.

The first such Symposium took place in The Organizing Committee, chaired by Prof. The Symposium was sponsored by 13 organizations and companies. The meeting gathered participants and 20 accompanying persons. Scientific contributions were authored and coauthored by authors. In the course of the Symposium 22 lectures were presented by invited speakers. Free communications included 14 oral presentations and 92 posters. Borowski, members of the Organizing Committee of the Symposium and comprising free communications in the journal Acta Biochimica Polonica Poland. Molecular approaches to immune defense modulating agents, control of gene expression, etc. While aimed primarily at problems of control in eukaryotic systems, prokaryotes were included. The meeting should contribute to better understanding of properties and action of chemotherapeutic agents, and to further development of a rational basis for new drug design. The following topics were covered: Gene and Antisense Therapies W. Szybalski USA , who was the first to perform, in , transformation of mammalian human cells, in a retrospective way showed how his fundamental discovery permitted the later development of: He also discussed problems and perspectives of gene therapy. Iyer USA, in the name of S. Agrawal evaluated the problems of antisense nucleotides in the therapy of cancer and of viral infections. The authors essentially contributed to an improvement of the potential of oligonuleotides as drugs by designing mixed backbone oligonucleotides. The advantages of these compounds over classical phosphorothioate oligodeoxynucleotides concerned the increase of in vivo stability, bioavailability, increase of biological potency in vivo and of safety profile. Another aspect concerning the improvement of therapeutic properties of antisense oligonucleotides was presented by W. His major achievement concerned new conjugates of phosphorothioate oligodeoxynucleotides obtained via a new oxathiaphospholane approach. These conjugates exhibited increased potency. Arcamone Italy pointed out that, since the discovery of Doxorubicin, many modifications have been performed, with only little results. He emphasized to the need of new approaches in designing modified products and presented his results based on the concept of expansion of the DNA sequence recognition options of the sugar portion of the antibiotic that lies in the minor groove of the DNA upon complexation. He described a new class of disaccharide analogues of Doxorubicin which exhibited strong, sequence specific induction of topoisomerase II mediated DNA cleavage. These compounds are now undergoing clinical trials. The same approach concerning the specific interaction of the drug with DNA, but with different types of chemical agents, was presented by C. His very promising contribution described bisimidazoacridinones. This new group of compounds, with a new mechanism of action, hopefully might be introduced to clinics as anticancer and anti-AIDS drugs. The interstrand crosslinking of DNA by bifunctional alkylating agents is an important effect of the action of many antitumor agents. A rational approach to the design of such drugs requires the recognition of the chemical structures of formed adducts. Novel and, perhaps, pregnant with consequences, proposals were presented by J. He was first to demonstrate that small molecules of a nonoligonuleotides type may be capable of inducing region-specific DNA lesions, provided their binding motif clusters in repetitive sequences. Several contributions dealt with non-DNA interacting agents. Showalter USA presented new class of small molecule bizelisin inhibitors of protein tyrosine kinases as potent agents for cancer chemotherapy. These are rationally designed pyrimidine derivatives. The author obtained good results in vitro and in vivo with tumor lines overexpressing tyrosine kinases of some growth factors and their receptors. These enzymes might be considered as interesting new targets for antitumor agents for some tumors overexpressing these enzymes. Very interesting data with promising perspectives in antitumor chemotherapy were presented by K. An important part of his contribution was the development of a new methodology for a large scale synthesis of methylenebis phosphonate -analogues of various NAD derivatives, now allowing for the biomedical utilization of NAD analogues. Thymidylate synthase is a long-standing target for chemotherapeutic agents due

to its central role in DNA synthesis. It is still an excellent target for antitumor and antiviral agents. X-ray crystallographic studies presented by W. Montfort USA with the E. Poo USA has thrown a different light on thymidine in connection with antitumor chemotherapy. Thymidine is a biomodulator of alkylating agents. It protects the cellular immune response and organ function from alkylating agents through modulating DNA repair enzymes. Thus it protects from toxicities and potentiates treatment efficacy. Many research centers are active in search for tumor-specific antigenes as a promising route, not only to immunotherapy, but also for tumor chemotherapy. An important contribution in this respect was presented by B. Woynarowska USA concerning some specific prostate gland tumor antigens, as targets for chemotherapy. China presented interesting results with a differentiation inducer, all-trans retinoic acid, in the treatment of acute promyleocytic leukemia and proposed a mechanism for the observed effects. Gdansk scientists Poland also presented several important results. There were communications presenting molecular mechanisms of action of a novel group of potent antitumor agents, imidazoacridines, crosslinking DNA and inhibiting topoisomerases I and II. They also developed a new theory concerning the molecular mechanisms of the mediation by anthraquinone antitumor agents of one electron transfer, inducing peroxidation effects and cardiotoxicity. Also very important results on molecular aspects of rational design of anthraquinone antitumor agents overcoming MDR were shown. One contribution of essential importance, presented by an invited speaker, G. Marshall USA , should be mentioned. The author discussed the role of molecular modelling in therapeutic approaches to AIDS. Modelling influenced greatly the design of inhibitors of HIV proteases, but because of the mutational rate of viral replication, resistance with viral - encoded targets makes these achievements problematic. Recently, a co-receptor, a G-protein coupled receptor, for viral entry into the cell has been described. This receptor offers a novel mammalian target for therapeutic intervention. Modelling of 3-dimentional structure of this receptor may play an important role in the development of an effective drug. Progress in these studies was presented by the author. Multidrug Resistance in Tumors and Microorganisms The appearance of multidrug resistance MDR in tumors, and recently in microorganisms, is a new and dramatic challenge facing mankind. To this problem a topic group was devoted in the program of the meeting. Three presentations given by invited speakers should be mentioned. Borst The Netherlands reviewed current knowledge on molecular mechanisms of multidrug resistance in cancer cells. The speaker evaluated methodology and perspectives for the design of new agents overcoming MDR. The emerging problem of multidrug resistance in fungi was presented by A. He discussed the family of fungal ABC transporters, comprising 28 proteins subdivided into 5 subfamilies. Of importance for the development of research in this area was the presentation of a fluorescence-based assay allowing rapid determination of structure-activity relationships among inhibitors of yeast multidrug transporters. Molecular mechanisms of drug resistance in fungi and perspectives for overcoming these problems were reviewed by P. The ideas and concepts presented were very inspiring. A novel look at the problem of resistance of tumor cells to cytotoxic agents was presented by F. He discussed the apoptotic response in cellular resistance to these agents. The preclinical observations that tumor response to effective drug treatment is associated with induction of apoptosis support the possibility that a decrease of susceptibility to apoptosis induction is relevant to clinical resistance. Antimicrobial and Antiparasitic Chemotherapy L. Hardy USA presented promising perspectives concerning pteridine reductase 1, an enzyme absent from mammalian cells, as a new target in chemotherapy of infections caused by Leishmania spp. Deletion of the gene coding for this enzyme is lethal for the microorganisms and the selective inhibitors of the enzyme could be effective chemotherapeutics. Lombardi Italy designed and synthesized a series of oligopyrrolamidine analogues of Distamycin showing much lower toxicity than the parent antibiotic and high in vitro and in vivo activity against chloroquine-resistant strains of Plasmodium falciparum. New derivatives of antibiotic the Eremomycin exhibiting high activity against Vancomycin-resistant bacteria strains were described by M. Rast Switzerland proposed b-N-acetylglucosaminidase as a new target in antifungal chemotherapy. Successful targeting of this enzyme involved in cell wall biosynthesis and breakdown seems to be a very promising approach, taking into account its extracellular location, especially as far as resistance problems are concerned. Dabrowska Poland demonstrated that muscle larvae of Trychinella spiralis show unexpectidyly high expression of enzymes involved in thymidylate biosynthesis, including thymidylate

synthase, pointing to the latter as an interesting target in chemotherapy of the muscle larvae phase of trychinellosis. Gdansk scientists Poland presented novel data for the rational design of Amphotericin B derivatives of low toxicity and data confirming the potential utility of glucosaminephosphate synthase as a new target in antifungal chemotherapy, including results of studies on interaction of the enzyme with transition state analogue inhibitors and active site directed glutamine analogues. Bergan Norway described the essential role of mechanisms governing tissue penetration of antibiotics in therapeutic efficacy of drugs. Bodor USA presented new interesting concepts of drug targeting, based on retrometabolic drug design approaches. Omura Japan in an extensive overview presented and discussed new strategies for the screening of new chemotherapeutics comprising inhibitors of cell to cell adhesion, inhibitors of cytokines activity and of antimalarial agents. Regardless of intensive development of a rational approach to drug design, the role of rational screening for new agents is still of importance. It offers chances for the discovery of new drugs, but above all, is still a major source of new drug prototypes lead compounds. The meeting will be held in Gdansk, Poland, at the beginning of September,

Chapter 3 : 6th International Symposium on MOLECULAR ASPECTS OF CHEMOTHERAPY

Molecular aspects of chemotherapy by International Symposium on Molecular Aspects of Chemotherapy. (3rd GdaÅ„sk, Poland), , Springer-Verlag, Polish Scientific Publishers edition, in English.

The Organizing Committee 9 members was chaired by Prof. The meeting gathered ca 2OO participants coming from 18 countries. The Symposium program included 22 invited lectures and communications. All contributions were authored and coauthored by persons. The Symposium proceedings comprising invited lectures and communications will be published as special issues of journals Pharmacology and Therapeutics and Acta Biochimica Polonica respectively. The financial aid to the Symposium was given by 11 sponsors. The official language of the meeting was English. The Symposium was of multidisciplinary character with the intention to bring together scientists representing different disciplines related to molecular chemotherapy of neoplastic and infectious diseases: Molecular approaches to immune defense modulating genes and control of gene expression were also discussed. The meeting contributed to better understanding of properties and action of chemotherapeutic agents and to further development of a rational basis for new drug design. Main topics discussed during the Symposium were following: Contributors have concentrated mostly on several topics essential for antitumor, antiviral, antibacterial and antifungal chemotherapy. Selected problems were discussed by the invited speakers. Inhibitors of telomerase activity were discussed by S. Neidle UK and L. Targeting of defined DNA sequences by the cytostatic agents was presented by W. Novel developments in cis-platin drugs were subject of the lecture presented by M. Antifolate agents were discussed by A. Rosowsky USA , A. Kisliuk USA , and J. A number of lectures were devoted to the antisense strategy approach by M. Manoharan USA , R. Kole USA , J. Bolard France , M. Caruthers USA , and C. Nucleosides and nucleotides as chemotherapeutics agents were discussed by J. Zemlicka USA and P. Miller USA and L. Alexandrova who substituted passed away A. Important problems concerning the multidrug resistance were presented by A. Larsen France and W. Other resistance problems were discussed by S. Special session moderated by B. Lesyng was devoted to current problems of molecular modelling in a rational drug design. Invited lectures were given by E. Meyer USA , J. Briggs USA , U. The Symposium program included also some recreation activities. All interested are also invited to actively participate in the preparation of the next meeting by contacting the organizers with suggestions concerning the Symposium program, including the proposals for the topics and names of potential speakers for the next meeting. The contact e-mail address: The meeting will be held in Gdansk, Poland, at the beginning of September,

Chapter 4 : Chemotherapy | American Cancer Society

The foregoing comprised the subject matter of the 3rd InterÂ- national Symposium on "Molecular Aspects of Chemotherapy", under the auspices of the International Society of Chemotherapy, and organized by the Committee on Drug Research, Polish Academy of Sciences, and the Department of Biotechnology and Biochemistry, Technical University of Gdansk.

Molecular mechanisms regulating the G1-S transition. Cyclins are unstable proteins and their levels vary throughout the cell cycle. This process relies on the sequential action of the ubiquitin-activating enzyme E1, the ubiquitin-conjugating enzyme E2, and the ubiquitin-ligase E3 [23]. Distinct ubiquitination pathways operate on the G1 cyclins D1, D2, D3, and E depending on whether or not the cyclin is bound to Cdk. Degradation of Cyclin D is dependent on phosphorylation when bound to Cdk4 and independent of phosphorylation when unbound Fig. Cdk activity is inhibited by phosphorylation on specific tyrosine residues, and phosphatase treatment leads to a hyperactive kinase Fig. Three different mammalian phosphatases are known, Cdc25 A, B, and C. In G1-arrested cells, Cdk4 is phosphorylated at tyrosine 17, and UV irradiation prevents dephosphorylation and re-entry into the cell cycle, suggesting that Cdk4 is a target for Cdc25A [26]. E2F triggers expression of proteins like dihydrofolate reductase, thymidine kinase, different DNA polymerases and the late-G1 cyclin E Fig. Expression of Cyclin E establishes a positive feedback loop of Rb phosphorylation, since Cyclin E in complex with Cdk2 will continue to phosphorylate Rb Fig. Similar to Cdk4, Cdk2 is also a target for Cdc25 phosphatase Fig. The biochemical events are primarily phosphorylation, dephosphorylation, and ubiquitination, with the overall mission to either prevent or induce a new cell cycle via the Rb pathway. Disruption in the G1-S Transition and Cancer Rb Pathway Disruption The cell cycle regulatory genes most often altered in tumors are those involved in controlling the G1-S transition through the regulation of the Rb pathway described above. The overall mechanism of tumor formation seems to consist of inhibitory effects on the Rb pathway, resulting in a growth advantage [2]. Rb is mutated in several human tumors [17 , 18]. Mutated or deleted Rb is no longer able to repress the function of E2F Fig. Rb normally protects against cancer development in its dominant phenotype. Therefore, both alleles must be mutant for the disease to develop homozygous. Loss of heterozygosity is a classic feature of tumor suppressor genes. The Rb gene is implicated most often in adult cancers, particularly small cell carcinomas, and inherited allelic loss of Rb confers increased susceptibility to cancer formation [2]. An inactivation of the Rb pathway is also accomplished by mutations in other regulatory components. Loss-of-function mutations in the INK4a family members, particularly p16INK4a, occur frequently in human cancers [2 , 31]. In familial melanomas, for instance, one copy of mutated p16INK4a is inherited and the second is lost in the tumor cell loss of heterozygosity. Homozygous deletions of the INK4a locus are a common feature in gliomas, mesotheliomas, carcinomas, acute lymphocytic leukemias, sarcomas, ovarian cancer, and probably also others. Reciprocally, mutations in Cdk4 resulting in lost ability to bind p16INK4a, have been found in some melanomas [2]. Gain-of-function mutations are also involved in disrupting the Rb pathway by overexpression of cyclins. For instance, the accumulation of Cyclin D1 is found to be implicated in most human colon cancers. In addition, there is evidence for the participation of the G1 cyclins D and E in breast cancer. Overexpression of Cyclin D1 has been reported in ductal carcinoma in situ, and similar overexpression of Cyclin E has been suggested [32]. Recently, it has been shown that there is an absolute requirement for Cyclin D1 overexpression in malignancy transformation that cannot be complemented by other, closely related cyclins like D2 and D3. This supports putative anti-Cyclin D therapy highly specific for breast cancer [14]. Taken together, the overall mechanisms of disturbing the Rb pathway converge into one common scheme: The loss of function in INK4a mimics Cdk hyperactivity and overexpression of cyclin, which all lead to Rb hyperphosphorylation and disruption of the G1-S restriction point. This supports the observation that inactivation of one of these components in the RB pathway results in decreased tumor suppression [34]. Hence, its role is to break the cycle only when the cell is damaged, by either G1 arrest or by inducing cell suicide apoptosis [35]. Due to the fact that p53 is the most frequently mutated gene in human cancers, it is a crucial target for therapy in

respect to tumor formation and elimination of damaged cells. With the loss of Rb pathway function, the cell is, therefore, able to bypass the G1 arrest mediated by p Thus, loss-of-function mutations in p53 mimic the loss of the Rb pathway in respect to deregulated G1-S transition, and the cell becomes tumorigenic. ARF p19ARF is yet another tumor suppressor gene recently identified in mice to be involved in cell cycle arrest and tumor formation [36]. It is encoded on the INK4a gene and transcribed by an alternative reading frame, using alternative splicing. It is evident that ARF and p53 are acting in the same pathway due to the fact that ARF interferes with all the known functions of Mdm2 [8]. There are reasons to believe that ARF reduces the ability of p53 to be a tumor suppressor. Recently, it has been shown that both p16INK4a and p19ARF are acting as strong tumor suppressors in mice models, and that double-acting mutations knockout mice of p16INK4a and p19ARF are required for severe cancer formation [37]. Previous Section Next Section Prognostic and Therapeutic Aspects The enormous progress in understanding the molecular mechanisms of the mammalian cell cycle and its involvement in cancer development in the last decades has shown that cell cycle regulators have a huge potential both as prognostic and therapeutic markers of cancer. Genetic alterations, implicated in disturbed regulation of the G1-S transition discussed above , provide relevant information to assess the risk or prognosis of the disease and target therapy [38]. Recently, it has been shown that p16INK4a-status has an important prognostic relevance for patients with pancreatic cancer, where alterations in p16INK4a are connected with a bad prognosis [39]. The molecular defects in G1-S regulators in a given cancer affect the outcome of radiotherapy or chemotherapy treatment. For instance, the efficiency of radiotherapy-induced p53 apoptosis or cell cycle arrest will not be optimal in tumors with deleted or mutated p Increased knowledge of the molecular mechanisms of G1-S transition involved in tumor formation suggests that modulators of Cdks and cyclins are potent therapeutic targets in cancer therapy [41 , 42]. There are currently extensive efforts being made to develop new therapeutic anticancer agents specifically targeting these modulators, and several agents are currently in clinical trials [43 , 44]. The specific Cdk inhibitor flavopiridol, for instance, is the first Cdk modulator tested in clinical trials already in phase II. Flavopiridol most effectively inhibits Cdk1, Cdk2, and Cdk4. Treatment with flavopiridol has resulted in blocking cell cycle progression, promoting differentiation, and inducing apoptosis in various types of cancerous cells. Another Cdk modulator currently being tested is UCN This modulator has been shown to block the cell cycle and induce apoptosis in hematopoietic models [43] with promising results. Several other chemical Cdk inhibitors have been developed, like paullones and induribines, showing a potential for anticancer treatment in vitro [45 , 46]. However, the inability to target the drugs or genes to specific cancer cells makes therapy difficult. This is indeed the case in a recent study, utilizing adenovirus-associated virus which selectively infects and kills cells lacking p53 [47]. Another recent approach is the use of antisense oligonucletides to specifically target cell cycle regulators. A recent study using Cyclin D1 antisense oligonucleotide showed cell death induction specifically induced in colon cancer cells [48]. Although great progress in understanding the molecular aspects of cancer has been made and several therapeutic agents have been developed, it is still difficult to cure cancer. Tumor formation is a multistep process, and the components of the different cell cycle phases crosstalk with each other and other components. The inactivation of Cyclin D1 for instance, resulting in a block in the Rb pathway, may have far-reaching consequences, and the Rb pathway block might be bypassed by other crosstalking components. Combined treatment using conventional chemotherapy together with new specific therapeutic agents might be a compromise. It still remains to find the correct combination for each and every incidence of cancer. Previous Section Next Section Summary A subset of proto-oncogenes and tumor suppressor genes has been identified to be involved in the uncoupling of the cell cycle from its normal regulation. Their signaling pathways seem to converge on the machinery involved in passing from the G1 phase into the S phase and allowing the cell to exit the cycle the Rb and the p53 pathways Fig. Disabling the Rb and p53 pathways is clearly a hallmark of human cancer. The ability to restore these functions is likely to be a very efficient way to treat cancer. In this respect, there have been major advances in understanding the mechanisms of cell cycle regulation, in particular the G1-S phase. From this point of view, it is obvious that the full potential of cancer therapy as small molecule inhibitors has yet to be reached. As a final comment, to emphasize the importance of an increased understanding of the molecular events of the cell cycle, the action of

the cell cycle most likely is involved in other noncancerous diseases as well, which also need to be explained and treated.

Chapter 5 : Chemotherapy - Wikipedia

Cancer cell resistance to chemotherapy is still a heavy burden that impairs treatment of cancer patients. Both intrinsic and acquired resistance results from the numerous genetic and epigenetic changes occurring in cancer cells.

Chapter 6 : Molecular Aspects of the Mammalian Cell Cycle and Cancer

national Symposium on "Molecular Aspects of Chemotherapy", under the auspices of the International Society of Chemotherapy, and organized by the Committee on Drug Research, Polish.

Chapter 7 : 7th International Symposium on MOLECULAR ASPECTS OF CHEMOTHERAPY

1. Verh Dtsch Ges Inn Med. ; [Molecular aspects of chemotherapy]. [Article in German] Drews J, Eich F, HÃ¶genauer G. PMID: