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PHARMACOKINETICS-PHARMACODYNAMICS OF ANTICANCER DRUGS: RESISTANCES AND SYNERGIES

PARIS, CORDELIERS RESEARCH CENTRE, DECEMBER 18-19, 2008

Organisers: Jean Clairambault, INRIA and Jean-Pierre-Marie, INSERM & Paris VI University
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Cell and tissue Pharmacokinetics-Pharmacodynamics (PK-PD) of anticancer drugs. Mathematical modelling, experimental and clinical studies of molecular mechanisms: targets, enzymes and transporters, tumour microenvironment, resistances, synergies, effects on cell proliferation, therapeutic optimisation.

This workshop on cell and tissue PK-PD of anticancer drugs, intended for mathematicians, biologists, pharmacologists and haemato-oncologists, comes after events organised on related themes in March 2008: http://www.inria.fr/actualites/colloques/cea-edf-inria/2008/models-cancer/index.en.html and http://www.math.u-bordeaux1.fr/~adimy/modlmc/detail3.html

We expect presentations dealing with molecular and physiologically based PK-PD, at the single cell level and at the level of cell populations, whole individuals and populations of patients, of mechanisms of action of anticancer drugs. Achievements encountered in haemato-oncology rely either on combinations of molecules with complementary effects, or on single drug therapies with multiple targets (e.g., tyrosine kinase inhibitors) or else on immuno-conjugated drugs; but the use of these treatments is always limited by toxicities on healthy tissues and/or by the emergence of resistance mechanisms to the drugs.

The mechanisms of these toxicities and resistances, either genetically determined or acquired, are many: cell drug processing enzymes, active efflux transporters, mutations of cancer cells protecting the targets, and they may vary from one subject to the other (genetic polymorphism) and from one hour to another within the 24 h span within a given subject (influence of circadian molecular clocks on PK-PD).

Mathematical models based on ordinary or partial differential equations, for drug action mechanisms and for the dynamics of cell populations, exist, and give a theoretical frame for the optimisation of synergies between drugs acting on different targets. The parameters of these equations, that describe the evolution dynamics of drug concentrations, proteins and their messenger RNAs, must be fit to within- and between-individual variations by experiments in cell cultures, on animal models, and by clinical data analysis.

The multi-scale aspect of molecular interactions (from molecular targets to therapeutic response), and the hidden nature of most parameters governing their dynamics, make necessary close exchanges between modellers, experimentalists and haemato-oncologists. **It is the aim of this workshop to foster such exchanges and interdisciplinary collaborations to optimise therapeutics in haemato-oncology.**

PK-PD workshop, Cordeliers Research Centre, Programme of the 1st day of the workshop: Thursday December 18, 2008

9:00-9:30 J. Clairambault & J.-P. Marie: Welcome, coffee and croissants
9:30-10:15 Annabelle Ballesta: *A Combined Biological and Mathematical Approach for Modeling PK-PD of the Anticancer Drug Irinotecan - Focus on Acquired Resistance and Circadian Rhythms at the Cell Population Scale*
10:15-11:15 Justine Bodin: *Multiscale modelling of 5-fluorouracil antitumour activity* Inès Paule: *Individual dose adaptation of capecitabine for reduction of severe hand and foot syndrome*
11:15-11:45 Coffee Break
11:45-12:30 Benjamin Ribba: *Mechanistic PK-PD models to reveal synergy between anti-angiogenesis drugs and chemotherapy*
12:30-13:15 Maciej Swat: *Modelling of PK-PD and drug-drug interaction (synergy / antagonism / additivity) with examples of anti-cancer and anti-inflammatory drug combinations*
13:15-14:30 Lunch Break
14:30-15:15 Vladimir Vainstein: *Physiologically-based PK/PD of targeted drug delivery by monoclonal antibodies*
15:15-16:00 Dinesh DeAlwis: *Exploring the potential of PK/PD in early phase oncology drug development*
16:00-16:30 Coffee Break
16:30-17:15 Jack Tuszynski: *Computational cancer chemotherapy drug design and laboratory validation*
17:15-18:00 Albert Goldbeter: *Using an automaton model for the cell cycle to probe temporal patterns of drug administration in cancer chronotherapy*

PK-PD workshop, Cordeliers Research Centre, Programme of the 2nd day of the workshop: Friday December 19, 2008

8:45-9:00 Coffee and croissants
9:00-9:45 Peter Hinow: *A mathematical model separates quantitatively the cytostatic and cytotoxic effects of a HER2 tyrosine kinase inhibitor*
9:45-10:30 Peter Kim: *Potential sources of drug resistance during Imatinib treatment*
10:30-11:00 Coffee Break
11:00-11:45 Pierre Magal: *Modelling P-gp transfer and acquired multi-drug resistance in tumour cells*
11:45-12:30 Jean-Pierre Marie: *Drug resistance induced by ABC-transporter proteins*
12:30-14:00 Lunch Break
14:00-14:45 Alissa Weaver: *Modulation of drug response and selection of clonal populations by microenvironment constraints*
14:45-15:30 Jeannette Soria: *Micro-environment and drug resistance in leukemia and ovarian cancer tumoral microenvironment and involvement of hospicells in drug resistance*
15:30-16:00 Coffee Break
16:00-16:45 Francis Lévi: *Circadian clock induction or disruption in cancer therapy*
16:45-17:30 Andrzej Swierniak: *Direct and indirect control of drug resistant cancer populations*
17:30-18:00 Jean Clairambault: *Towards optimisation of cancer therapeutics by taking into account patient-specific constraints: mathematical models for individualised medicine*
18:00-18:15 J. Clairambault & J.-P. Marie: *Conclusion of the workshop*

The speakers, and topics of their talks:

Annabelle Ballesta (INRIA, France) "A Combined Biological and Mathematical Approach for Modeling PK-PD of the Anticancer Drug Irinotecan - Focus on Acquired Resistance and Circadian Rhythms at the Cell Population Scale"

Justine Bodin (Lyon, France) "Multiscale modelling of 5-fluorouracil antitumour activity"

Jean Clairambault (INRIA, France) "Towards optimisation of cancer therapeutics by taking into account patient-specific constraints: mathematical models for individualised medicine"

Dinesh Dealwis (Eli Lilly, UK) "Exploring the Potential of PK/PD in Early Phase Oncology Drug Development"

Albert Goldbeter (Brussels, Belgium) "Using an automaton model for the cell cycle to probe temporal patterns of drug administration in cancer chronotherapy"

Peter Hinow (U. Minnesota, Minneapolis, MN) "A mathematical model separates quantitatively the cytostatic and cytotoxic effects of a HER2 tyrosine kinase inhibitor"

Peter Kim (U. Utah, Salt Lake City, UT) "Potential sources of drug resistance during Imatinib treatment of CML"

Francis Lévi (Villejuif, France) "Circadian clock induction or disruption in cancer therapy"

Pierre Magal (Le Havre, France) "Modelling P-gp transfer and acquired multi-drug resistance in tumour cells"

Jean-Pierre Marie (Paris, France) "Drug resistance induced by ABC-transporter proteins"

Inès Paule (Lyon, France) "Individual dose adaptation of capecitabine for reduction of severe hand-and-foot syndrome"

Benjamin Ribba (Lyon, France) "Mechanistic PK/PD models to reveal synergy between anti-angiogenesis drugs and chemotherapy"

Jeannette Soria (Paris, France): "Micro-environment and drug resistance in leukemia and ovarian cancer tumoral microenvironment and involvement of hospicells in drug resistance"

Maciej Swat (Simcyp, UK) "Modelling of PK-PD and drug-drug interaction (synergy /antagonism /additivity) with examples of anti-cancer and anti-inflammatory drug combinations"

Andrzej Swierniak (Gliwice, Poland) "Direct and indirect control of drug resistant cancer populations"

Jack Tuszynski (U. Alberta, Edmonton, Alberta, Canada) "Computational cancer chemotherapy drug design and laboratory validation"

Vladimir Vainstein (Jerusalem, Israel) "Physiologically-based PK/PD of targeted drug delivery by monoclonal antibodies"

Alissa Weaver (U. Vanderbilt, Nashville, TN) "Modulation of drug response and selection of clonal populations by microenvironment constraints"

Abstracts:

Annabelle Ballesta: "A Combined Biological and Mathematical Approach for Modeling PK-PD of the Anticancer Drug Irinotecan - Focus on Acquired Resistance and Circadian Rhythms at the Cell Population Scale"

Annabelle Ballesta, Jean Clairambault, Sandrine Dulong, Alper Okyar, Francis Levi
(email: annabelle.ballesta@inria.fr -presenting author)

Abstract- Irinotecan is an anticancer drug which is currently in use for chemotherapy against colorectal cancer. Here we are interested in the molecular mechanisms occuring within a cell population after Irinotecan exposure. We attempt to mechanistically model Irinotecan Pharmacokinetics (PK),which is what the cells do to the drug (e.g. metabolization, transport), and Pharmacodynamics (PD), which is what the drug does to the cells (e.g. DNA damage).

Experiments on Caco-2 cells (human epithelial colorectal adenocarcinoma cells) have been performed in order to study the influence of acquired resistance and circadian rhythms on Irinotecan Pharmacokinetics-Pharmacodynamics. At the same time, we have built a deterministic ODE-based mathematical model, the parameters of which are fitted to the experimental data obtained on Caco-2 cells.

The experiments have shown evidence for a decrease in the intracellular accumulation of Irinotecan over time: the intracellular concentration increases until 12 hours of exposure and then decreases until 48 hours of exposure. We are currently investigating the hypothesis of an increased drug efflux due to the induction of ATP-Binding-Cassette(ABC) transporters (in particular P-gp).

The PK-PD of Irinotecan is also largely influenced by the circadian rhythms of proteins (in particular those of the drug target Topoisomerase I and of the deactivation enzyme UGT1A1), the mRNA levels of which (and probably also their protein amounts and activities) vary according to a 24-hour period both in vivo and in cultured cells.

Taking into account possible acquired resistance to the drug and the circadian control of relevant pharmacologic pathways, we use mathematical modeling to theoretically optimize the schedule of cell exposure to Irinotecan.

This study at the cell population scale may then be integrated into a whole-body approach leading to potential improvements in the administration of Irinotecan to patients.

Justine Bodin: "Multiscale modelling of 5-fluorouracil antitumour activity"

Justine Bodin, Benjamin Ribba, Emmanuel Grenier, François Gueyffier
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Abstract- 5-fluorouracil (5FU) is a key anticancer drug for the treatment of many types of solid tumours, including colorectal cancer liver metastases. This work is aimed at building a pharmacokinetic/pharmacodynamic model of 5FU. As a first step, we developed a multiscale mathematical model of 5FU activity on tumour growth which allows to i) simulate the effect of 5FU on liver metastastic colorectal cancer and ii) test hypotheses to help improve the clinical results observed in patients with this tumour.

Based on a review of 5FU mechanism of action, we modelled 5FU efficacy by taking into account two different observation levels. At the cell level, we focused on 5FU effect on DNA synthesis through two identified ways, a blockade of thymidylate synthase (TS) enzyme, resulting in an inhibition of DNA synthesis, and an incorrect incorporation of FdUTP to DNA leading to abnormal DNA production. At the tissue level, the model integrates the impact of normal and abnormal DNAs on tumour growth through cell cycle regulation. We studied the effect of continuous infusion 5FU, commonly used in advanced colorectal cancer, and tested the role of the TS level on the efficacy results as it is reported as a potential prognostic factor.

Simulation results may help comparing different 5FU-based protocols in terms of efficacy. This model may also provide relevant information about the optimal combination with other anticancer drugs such as oxaliplatin to improve clinical outcomes.

Jean Clairambault: "Towards optimisation of cancer therapeutics by taking into account patient-specific constraints: mathematical models for individualised medicine"

Jean Clairambault, Bang Project-team, INRIA Paris-Rocquencourt, France
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Abstract- In this talk, I will present some physiologically based dynamic mathematical methods that are currently being designed to help optimise multidrug, multitarget anticancer treatment. These methods include:
a) Modelling by ordinary differential equations (ODEs) drug kinetics and metabolism in blood and the liver, and at the intracellular level, account being taken of enzymatic genetic polymorphism, of toxic side effects on healthy cells, and on the possible occurrence of resistances to the treatment.
b) Modelling by age-structured partial differential equations (PDEs) the proliferation of cell populations represented by the evolution of these populations, healthy and tumoral, in the cell division cycle and the controlling effect of anticancer drugs on this evolution.
c) Using optimisation algorithms that aim at finding best drug delivery time schedules by maximising tumour cell kill under patient-linked constraints, that can be general state of health-linked treatment tolerability, genetic polymorphism of drug metabolising and DNA mismatch repair enzymes, and the expression of ABC transporters

Dinesh de Alwis: "Exploring the potential of PK-PD modelling in early phase oncology drug development"

Dinesh de Alwis, Eli Lilly & Company, Windlesham, Surrey, UK

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Abstract- If one considers the approach to the development of cytotoxics and targeted therapies, clear differences are apparent. Conventional cytotoxic chemotherapies followed a well worn empirical course; dose escalation followed a fixed or semi-fixed scheme from a starting dose based on some multiple of a preclinical toxicity dose. Escalation continued until the maximally tolerated dose (MTD) was defined and this single dose was carried forward into later phase clinical trials. Toxicity such as myelosuppression, was often used as a biomarker of the desired cytotoxic effect in the tumour.

Pharmacokinetics was largely descriptive, body surface area dosing a substitute to individualized therapy, but without adequate understanding of the covariates (Gurney, 2002). In contrast, the early clinical development of targeted agents is driven by the need to assess the impact on the target which may occur in absence of clinically definable effect on the tumour or other tissues. Translation to clinical efficacy is more remote and hence more difficult to illicit in phase 1 studies. Dose escalation is more amenable to adaptive study design in which pharmacokinetics and pharmacodynamics play an increasingly important role. Biological effect rather than toxicity determines the subsequent range of doses which maybe taken into phase 2 studies.

New considerations have been introduced such as the degree and duration of target inhibition. Complete (100 %) inhibition indefinitely may adversely affect the margin of safety and may not be desirable for efficacy (Burgess and de Alwis, 2007). Two recent examples of developing a cytotoxic and a targeted agent within Eli Lilly & Company will be presented (Bueno et al., 2008). The cytotoxic agent exhibited a very high saturable protein binding, gender difference within a species and a species difference in toxicity. Total dose and total drug concentrations failed to explain a 30% mortality in male rats compared to a 3 % mortality in female rats given the same dose, however, incorporating protein binding and protein levels in a semi-mechanistic PK model explained these differences with predictions of unbound concentrations. This model also incorporated an in vitro bone marrow assay data to explain neutropenia differences between rat and dog. In another example, a preclinical model integrating PK, biomarkers, and tumour growth delay data described satisfactorily the mechanism of action of a TGF-β signal transduction inhibitor and provided a tool to investigate different experimental scenarios establishing levels of biomarker inhibition associated with efficacy, to assist in the design and description of the biologically effective dose range selection for the first in man study.

Albert Goldbeter: "Using an automaton model for the cell cycle to probe temporal patterns of drug administration in cancer chronotherapy"

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[d] Assistance Publique-Hôpitaux de Paris, Unité de Chronothérapie, Département de Cancérologie, Hôpital Paul Brousse, Villejuif, F-94807, France

Abstract- Determining optimal patterns of drug administration represents a central issue in chronopharmacology. Given that circadian rhythm profoundly affect the response to a variety of anticancer drugs, circadian chronotherapy is used clinically in cancer treatment. Assessing the relative cytotoxicity of various temporal patterns of administration of anticancer drugs requires a model for the cell cycle, since these drugs often target specific phases of this cycle. Here we use an automaton model to describe the transitions through the successive phases of the cell cycle. The model accounts for progressive desynchronization of cells due to the variability in duration of the cell cycle phases, and for entrainment of the cell cycle by the circadian clock. Focusing on the cytotoxic effect of 5-fluorouracil (5-FU), which kills cells exposed to this drug in S phase, we compare the effect of continuous infusion of 5-FU with various circadian patterns of 5-FU administration. The model indicates that the cytotoxic effect of 5-FU is minimum for a circadian delivery peaking at 4 a.m. —which is the profile used clinically for 5-FU— and maximum for the continuous infusion or a circadian pattern peaking at 4 p.m. These results are explained in terms of the relative temporal profiles of 5-FU and of the fraction of cells in S phase. The model further indicates that the optimal pattern of drug delivery depends on the characteristics of the cell cycle, such as its duration, variability, or entrainment by the circadian clock. Extension of this modeling approach to the case of another anticancer drug, oxaliplatin, will be discussed. The results throw light on possible mechanisms for the simultaneous improvement of chronoefficacy and chronotolerance in cancer chronotherapy.

References:

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Peter Hinow: "A mathematical model separates quantitatively the cytostatic and cytotoxic effects of a HER2 tyrosine kinase inhibitor"

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Abstract- Oncogene signaling is known to deregulate cell proliferation resulting in uncontrolled growth and cellular transformation. Gene amplification and/or somatic mutations of the HER2/Neu (ErbB2) proto-oncogene occur in approximately 20% of breast cancers. A therapeutic strategy that has been used to block HER2 function is the small molecule tyrosine kinase inhibitor lapatinib. Using human mammary epithelial cells that overexpress HER2, we determined the anti-proliferative effect of lapatinib through measuring the total cell number and analyzing the cell cycle distribution. A mathematical model was used to interpret the experimental data. The model suggests that lapatinib acts as expected by slowing the transition through G_1 phase. However, the experimental data indicated a previously unreported late cytotoxic effect, which was incorporated into the model. Both effects depend on the dosage of the drug, which shows saturation kinetics. The model separates quantitatively the cytostatic and cytotoxic effects of lapatinib and may have implications for preclinical studies with other anti-oncogene therapies.

This is joint work with Shizhen Wang (Department of Cancer Biology, Vanderbilt University) and Glenn F. Webb (Department of Mathematics, Vanderbilt University).

Peter Kim: "Potential sources of drug resistance during Imatinib treatment of CML"

Peter Kim, Dept. of Mathematics, University of Utah, Salt Lake City (UT)
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Abstract- There are various models for the interaction between Imatinib, and chronic myelogenous leukaemia (CML). However, the role of the host immune response during Imatinib treatment remains unclear. Based on experimental data from the Lee Lab at Stanford Medical School, we hypothesize that Imatinib gives rise to a brief anti-leukaemia immune response as patients enter remission.

From this hypothesis, we propose that cancer vaccinations applied at appropriate times during Imatinib treatment can boost the existing immune response and lead to a sustained remission or a potential cure. To examine this hypothesis, we take a mathematical model by Michor et al. based on the analysis of 169 patients under Imatinib and incorporate an anti-leukaemia immune response.

Using this model, we study how the effects of Imatinib resistance and immune resistance mutations of leukaemia cells may affect the dynamics and duration of leukaemia remission during treatment. We propose that Imatinib resistance mutations may be partially compensated by a persistent, low-level anti-leukaemia immune response. Thus, we hypothesize that immune resistance is the primary cause of treatment failure.

Taking into account Imatinib resistance and immune resistance mutations, we show how properly timed cancer vaccines may optimally sustain the host immune response to lessen the effects of mutation and potentially reduce or eliminate residual leukaemia cells.

Francis Lévi: "Circadian clock induction or disruption in cancer therapy"

Francis Lévi, Xiao Mei Li, Ida Iurisci, Pasquale Innominato, Constance Ahowesso, Jacques Beau, Elisabeth Filipski, Jean Clairambault
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Abstract- **Background** Cellular metabolism and proliferation are rhythmically controlled by the Circadian Timing System (CTS). The CTS is constituted with molecular clocks in each cell, which are reset and coordinated by the supra-chiasmatic nuclei, a central hypothalamic pacemaker through the generation of circadian physiology. These molecular clocks give time to the cells through interwoven translation/transcription feedbacks loops involving a dozen of specific genes, among which *Rev-erbα, Per2* and *Bmal1* play an essential role. As a result, circadian changes characterize both tolerability and efficacy of more than 40 anticancer agents in experimental models.

Methods and results Using rest-activity and body temperature rhythms as non invasive biomarkers of the CTS in mice, anticancer drugs disrupted the Circadian Timing System (CTS), as a function of dose and circadian time of administration. The extent of drug-induced circadian disruption was associated with that of known drug-related toxicities for vinorelbine (a mitotic inhibitor), gemcitabine (an antimetabolite), irinotecan (a TOP1 inhibitor) or seliciclib (a CDK inhibitor), as well as with chemical carcinogen exposure (diethylnitrosamine). Furthermore, anticancer agents, including interferons, γ-radiations, or seliciclib could disrupt the rhythmic patterns in clock gene transcription in SCN and/or peripheral organs, including liver, thus contribute to circadian disruption. On the contrary, the circadian clocks of malignant tumors such as mouse Glasgow osteosarcoma, are usually disrupted. In this experimental model, seliciclib restored near normal circadian rhythms in core clock genes mRNA expression or had no effect on the clock, pending upon dosing time. The induction of the molecular clock was associated with a near doubling of antitumor efficacy of seliciclib. The clinical relevance is illustrated with the disruption or amplification of the rest-activity circadian rhythm in cancer patients on chemotherapy or gefitinib(an EGFR inhibitor) respectively.

Conclusions and perspectives The outcome of patients on chemotherapy can be influenced by disruption or induction of circadian clocks in host or tumor cells. Such novel effects of anticancer agents could play an important role in the optimal scheduling of chronotherapeutic delivery. Mapping the mechanistic relations between circadian clocks, cell cycle and pharmacologic pathways should enable the modelisation of optimal chronotherapeutic delivery schedules and their personalization.

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Pierre Magal: "P-gp transfer and acquired multi-drug resistance in tumour cells"

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Co-Authors: Frank Le Foll, LEMA, Le Havre University, France; Jennifer Pasquier, LEMA, Le Havre University, France; Glenn Webb, Vanderbilt University, USA; Peter Hinow, University of Minnesota, USA

Abstract- Multi-Drug resistance for cancer cells has been a serious issue since several decades. In the past, many models have been proposed to describe this problem. These models use a discrete structure for the cancer cell population, and they may include various classes of resistant, non-resistant, and acquired resistant cells. Recently, this problem has received a more detailed biological description, and it turns out that the resistance to treatments is due in 40% of cancers to a protein called P-glycoprotein (P-gp). Moreover it has been proved that P-gp can be transferred from cell to cell by an osmotic phenomenon. This transfer turns to be responsible for the acquired resistance of sensitive cells. The goal of this talk is to introduce this problem, and to present a cell population dynamic model with continuous P-gp structure.

Jean-Pierre Marie: "Drug resistance induced by ABC-transporter proteins"

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Abstract- Three ATP-binding cassette (ABC)-superfamily multidrug efflux pumps are known to be responsible for chemoresistance; P-glycoprotein (ABCB1), MRP1/3 (ABCC1/3) and ABCG2 (BCRP). These transporters play an important role in normal physiology by protecting tissues from toxic xenobiotics and endogenous metabolites. Hydrophobic amphipathic compounds, including many cytotoxic drugs (anthracyclines, vinca-alkaloids, taxanes…), are expelled out of the cell by these pumps. These efflux pumps are expressed in many human tumors, where they likely contribute to resistance to chemotherapy treatment, as it was demonstrated in acute myelogenous leukemia. However, the use of efflux-pump modulators in clinical cancer treatment has proved disappointing. Today we know that the family of ATP-binding cassette transporters (ABC transporters) comprises 48 different proteins. When Heracles fought the ancient Hydra, he had to fight all the heads at once but only one head was vital for the beast. Can we block all the relevant ABC transporters at once? Is there one transporter more important than the others?

Inès Paule: "Individual dose adaptation of capecitabine for reduction of severe hand-and-foot syndrome"
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Individual dose adaptation of capecitabine for reduction of severe hand-and-foot syndrome

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Introduction:
Capecitabine, an oral prodrug of 5-fluorouracil (5FU), used to treat metastatic or advanced colorectal cancer, is equivalently effective and better tolerated than reference intravenous treatment by an association of 5FU and leucovorin (5FU/LV), except for the hand-and-foot syndrome (HFS), which occurs in 54% patients taking capecitabine, compared to 6% of those taking 5FU/LV. This dermatotoxicity affects the palms and soles as redness, numbness and even desquamation, pain and loss of function in severe cases. Standard dose adaptation consists in dose reduction by 25% or by 50 % according to the frequency and severity of previous toxicity. This crude adaptation might by suboptimal and an individualized dose adaptation, based on all available and pertinent patient's information, combined in an appropriate longitudinal model, might allow a better control of toxicity and thus improve the therapeutic benefit.

Objectives:
To set up the methodology for individual dose adaptation on the basis of ordinal observations and evaluate its feasibility and performances, as compared to the standard approach, by randomized *in silico* clinical trials.

Methods:
Individual prediction-based dose adjustment schemes for capecitabine were derived on the basis of a longitudinal HFS toxicity model previously developed in [1]. This mixed effects transitional and proportional odds model for longitudinal ordinal data links taken doses, basal creatinine clearance and previous toxicity to the risk of (the highest) HFS grade of the week. The population model is reajusted for the particular patient before each new cycle by estimating the random (individual) effects of the model, on the basis of pertinent patient's data (taken doses, toxicity and renal function), using Bayesian techniques. The individualized model is then used to predict the risk of severe toxicity in 2 weeks and calculate the dose for the next cycle.
Proof-of-concept is given by an *in silico* clinical trial, comparing the standard and model-based adaptations in 2 x 10,000 virtual patients during 30 weeks of treatment.

Results:
The proof-of-concept simulation showed that model-based adaptation would result in reduction of severe toxicity incidence by 13% and of its average duration by 1.6 weeks (12 days), as compared to the routine adaptation. Continuous monitoring of individual toxicity risk showed to be especially beneficial for allowing earlier detection of the patients at high risk of severe toxicity and suggesting another therapy for them.

Conclusion:
Individualized dose adaptation on the basis of ordinal observations, using the developed methodology, showed to be feasible and beneficial. *In silico* results indicate that in the case of hand-and-foot syndrome induced by capecitabine, severe toxicity incidence may be reduced by 13% and its mean duration by 12 days. Moreover, estimation of individual toxicity risk showed to be especially beneficial for allowing early detection of patients intolerant to capecitabine and therefore better determination of the optimal moment to switch to another treatment.
There are several limitations to this work. Firstly, judgement of adaptation strategies is limited because impact on anti-cancer efficacy and other toxicities could not be evaluated. It should be considered that individual adaptation leads to 18% reduction of drug exposure as compared to the standard adaptation. The second restriction of this dose adaptation is related to the model which seems to assume inertia of HFS toxicity. This may be due to cumulative nature of the drug or model producing some bias for toxicity recovery. Nevertheless, this work shows that individual dose adaptation of oral anticancer drugs, performed on the basis of ordered categorical data, should be beneficial and feasible in clinical routine.

Reference:
[1] Hénin E et al. PAGE 2006; abstract No 929. http://www.page-meeting.org/?abstract=929

Benjamin Ribba: "Mechanistic PK/PD models to reveal synergy between anti-angiogenesis drugs and chemotherapy"

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Mechanistic model of tumor growth in mice to optimize anti-angiogenesis drug delivery in combination with chemotherapy

Benjamin Ribba

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Et
Ciblage Thérapeutique en Oncologie (EA3738), Faculté de Médecine Lyon-Sud, Université Lyon 1

To primary evaluate drug efficacy, simplistic animal models such as athymic mice bearing subcutaneous xenograft of human tumor cells are often used. In many published work, it has been proposed that a simple Gompertz model could describe the time-course evolution of tumor volume. Based on mice experiments, we first evaluate the validity of this simple model by means of mixed-effect modeling techniques. We then propose a new model that integrates the process of tumor angiogenesis. Parameter estimations of this new model are shown to be consistent to biological literature. Developing a mechanistic version of this model is shown to be potentially useful to optimize anti-angiogenic drug in combination with chemotherapy.

Maciej Swat: "Modelling of PK-PD and drug-drug interaction (synergy /antagonism /additivity) with examples of anti-cancer and anti-inflammatory drug combinations"

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Abstract- Different aspects of combination therapies will be discussed, among others, the compartmental and physiologically based pharmacokinetics, pharmacodynamics, drug-drug interactions with the emphasis on drug synergy/antagonism and experimental design. The most popular mathematical approaches to drug synergy will be presented in more detail. Examples of their application in the anti-cancer and anti-inflammatory drug development will be given.

Andrzej Swierniak: "Direct and indirect control of drug resistant cancer populations"

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Abstract- This paper presents brief survey of our research in which we have used control theoretic methods in modelling and control of cancer populations. We focus our attention on two classes of problems: optimization of anticancer chemotherapy taking into account both phase specificity and drug resistance, and modelling and optimization of antiangiogenic therapy. In the case of chemotherapy the control action is directly aimed against the cancer cells while in the case of antiangiogenic therapy it is directed against normal cells building blood vessels and only indirectly it controls cancer growth. We discuss models (both finite and infinite dimensional) which are used to find conditions for tumour eradication and to optimize chemotherapy protocols treating cell cycle as an object of control. Two major obstacles in successful chemotherapy are phase dependence of cytotoxic drugs and drug resistance. Cell-cycle-phase specificity is important since it makes sense to apply anticancer drugs when cells gather in sensitive phases of the cell cycle. It can be approached by considering dissection of the cell cycle into an increasing number of disjoint compartments, with drug action limited to only some of them. In many papers we have provided a classification of several models of this kind and analyzed a problem of protocol optimization basing on them. In our research we have developed a model of chemotherapy based on a stochastic approach to evolution of cancer cells. Our works dealt with models with tridiagonal system matrix. They led to development of a methodology for investigating such systems and formed a basis for further generalisation. More recently the research has been pushed a step further, studying properties of a model, in which significantly less simplification has been made and less additional assumptions are required. Moreover, it has combined models that so far have been studied separately, taking into account both the phenomenon of gene amplification and multidrug chemotherapy, in their different aspects. As far as phase-specificity of chemotherapy is concerned it was usually considered without any regard to problems stemming from increasing drug resistance. Combining infinite dimensional model of drug resistance with the phase-specific model of chemotherapy should move mathematical modelling much closer to its clinical application.

The important factor which should be taken into account is that while drug resistance is acquired by cancer cells the normal tissues retain sensitive to the drugs. This negative feature of chemotherapy may be used as an advantage in the antiangiogenic therapy which is directed towards special part of normal tissues and only indirectly destroys tumor cells and it is why it has been called by Kerbel a therapy resistant to drug resistance. We consider a class of models proposed by Hahnfeldt et al. who proposed to use classical models of self-limiting tumour growth with variable carrying capacity defined by the dynamics of the vascular network induced by the tumour in the process of angiogenesis and we find conditions for tumour eradication in asymptotic sense and we optimize protocols of antiangiogenic therapy. In contrast to the control problems arising in phase-specific and drug resistant chemotherapy, modeling antiangiogenic therapy leads to indirect control problems in the sense that the control action is directed against normal tissues and only indirectly enables formation of dynamics of cancer populations.

Finally we propose probably the simplest model of combined antiangiogenic and chemo-therapy.

Keywords: Biomedical models, optimal control, nonlinear control systems, anticancer therapy

Jack Tuszynski: "Computational cancer chemotherapy drug design and laboratory validation"

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Abstract- The structural protein, β-tubulin is the target for a number of anti-mitotic compounds that bind to and inhibit microtubule dynamics, leading to apoptosis in all dividing cells. The existence of several isotypes of β-tubulin, coupled with their varied distribution in normal and cancerous tissues provides us with a platform upon which to construct novel chemotherapeutic agents that are able to differentiate between normal and cancerous cells. A drug that targets those tubulin isotypes specifically expressed in tumor cells would maintain its cytotoxic activity on these cancerous cells, yet have a reduced effect on dividing cells in normal tissue, resulting in a reduction of side effects. We have performed homology modeling of approximately 500 α- and β-tubulin sequences and identified an expected global, structural similarity of tubulin monomers. We have been able to calculate discernable differences in several properties, including their net electric charge, volume, surface area, dipole moment and dipole vector orientation. These are properties that may influence the functional characteristics of individual tubulin monomers, thereby resulting in a global effect on microtubule stability and assembly kinetics. Using these homology models, we have obtained a consensus set of nine human β-tubulin isotypes and analyzed them for differences within the previously characterized paclitaxel, colchicine and vinblastine binding sites. Several colchicine and paclitaxel derivatives were then computationally designed and their binding to the isotypes tested Quantum Mechanics and Molecular Mechanics modeling experiments. Using these techniques, a clear differentiation between the tubulin isotype being considered and relative binding affinities for each of these derivatives was observed. These computationally based experiments have provided us with a small virtual library of drug structures that have increased binding affinity towards specific tubulin isotypes. This library is now being used to direct the synthesis and testing of these drugs, both in vitro and in vivo, to determine their effect on different tubulin isotypes. Small scale testing of these compounds on a number of primary tumour cell cultures has produced promising results for their ability to selectively target specific cancer cells. In this presentation, the preliminary results of our computational and experimental studies will be summarized. The achieved correlation between theoretical prediction and laboratory assay outcomes is very encouraging.

Acknowledgements:
Funding for this work was provided by ACB, the Allard Foundation, NSERC and MITACS and the US Army. Oncovista of San Antonio, Texas, provided samples of colchicine derivatives for our tests. Collaboration on the project with Dr. R.F. Luduena is gratefully acknowledged.

Vladimir Vainstein: "Physiologically-based PK/PD of targeted drug delivery by monoclonal antibodies"

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Abstract- For the last few decades, modern pharmacology, in general, and hematological cancers, in particular, largely benefited from the development of molecular targeted drugs on the basis of monoclonal antibodies (MA). Cancer cells can develop resistance to the conjugated antibodies by several mechanisms such as low expression of the target membrane antigen, rapid metabolism, rapid excretion from the cell, or resistance to the conjugate toxin. All the aforementioned resistance mechanisms contribute to the high response variability already seen in MA-based drugs (MA-BD). We present a physiologically-based MA-BD PK/PD mathematical model that includes blood PK and detailed model of MA-BD interactions with its target receptor. It can be coupled with various indirect response mechanism-based PD. We applied our model to experimental data of Gemtuzumab Ozogamycin interaction with leukemic blasts in vitro and in vivo in order to evaluate individual model parameter values in the patient population. Mathematical analysis of model behavior under physiological parameter value ranges allowed for formulation of general principles of treatment by targeted drug delivery, including identification of parameters with highest influence on drug efficacy and optimization of treatment schedule.

Alissa Weaver: "Microenvironmental resource constraints in tumor progression and drug response"

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Abstract- Tumor-microenvironment interactions are increasingly recognized to influence the course of tumor progression. To understand the role of the microenvironment in tumor progression, we experimentally parameterized a model of tumor evolution with phenotypic trait data gathered from a set of related mammary cell lines with normal, transformed, or tumorigenic properties. We find an important role of resource limitation in both progression and response to idealized cytotoxic therapy of our experimentally defined cell phenotypes. Implications for the process of tumor formation and aggressiveness will be discussed.

PHARMACOKINETICS-PHARMACODYNAMICS OF ANTICANCER DRUGS: RESISTANCES AND SYNERGIES

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