ESF PESC Exploratory Workshop:

MATHEMATICAL MODELLING AS A TOOL FOR BRIDGING THE GAP BETWEEN BIOLOGICAL OBSERVATIONS AND CLINICAL APPLICATIONS IN ONCOLOGY

Torino, 9-11 May 2002

EXECUTIVE SUMMARY

A. Workshop preliminary organization

Being the aim of the workshop to gather together leading scientists in different disciplines, a large effort was made during the period prior to the workshop to advertise the event in most of the leading scientific centers and labs in the field of oncology in Europe. This aim was achieved in a first stage by directly contacting leading scientists known to the workshop convenors. In a second phase the invitation was extended to researchers suggested by people who had already decideded to attend the workshop and to persons who were known to be working in the field. Finally, once the list of participants was almost complete, detailed information about the workshop organization was sent to several laboratory and oncology centers.

The workshop was welcomed by most of the people contacted. However, while a large participation was easily gathered in the mathematical and biological community, it was more difficult to obtain a direct involvement of participants in the medical community. While a general interest was found by all the speakers contacted, most of clinicians, in the end, rerouted the information to some of their collaborators in the same institution already dealing with mathematical problems.

One of the results of this approach of contacting the invited scientists was that the scientific extent of the meeting was further increased with respect to the original programme. In fact, topics more related to genomics and sub-cellular processes entered the topical sessions. However, this enlargement of the expertise in the scientific community attending the workshop turned out to be an enrichment, rather than an obstacle for fruitful discussions, as will be discussed later on.

Also, the effort of sending the information to as many scientists as possible led to a precious outcome. In fact, it was found that several scientists were extremely interested in the workshop, albeit it was not possible for them to attend the workshop due to other engagements in the same period. However, they asked to be kept posted about the outcome of the workshop and to be included in any further initiative. Among them the Netherlands Cancer Institute (Dr. Collard), the Ludwig Institute for Cancer Research in Sweden (Dr. Ivan Dikic) and the Oncologic Centre AZ-VUB in Brussels (Prof. Guy Storme). They have all been included in the proposals resulting from the workshop activity.

Before the workshop, all participants were invited to organize their presentation in order to keep the scientific level as simple as possible, in order to allow researchers without adequate background in the field to understand the potential cross-fertilization among the respective research topics. All the speakers made a large effort in this direction, which resulted to be strongly beneficial for the success of the workshop. Also, all participants were invited to be present at the round tables, following the scientific sessions, and to provide suggestions for possible collaboration and/or problems in which their interest could merge with the interest of people from other disciplines.

B. Scientific sessions

The first half of the workshop schedule was devoted to the three scientific sessions: biological, mathematical and clinical. As already indicated, presentations were kept at a very simple level, and the goal of the session to learn about each other's expertise was successfully achieved. Also the friendly atmosphere which was created from the very beginning helped to keep a lively level of discussion after each presentation. In this context, the contribution of several scientists with a very wide scientific experience, who helped in extracting, through stimulating questions, the essential key-points from each presentation, was particularly helpful.

The scientific content of the meeting covered diverse fields. In the biological session genomics, signal transduction and in vitro culture problems were presented. In the modelling session several approaches to modelling tumour growth were presented and were revealed to be complementary and integrative. Finally, the clinical session helped to understand which main issues should be addressed for therapeutic purposes, concerning both surgery and chemotherapy.

Although all presentations referred to specific problems, a general understanding from a global point of view was possible for all participants of the workshop.

C. Round Tables and discussion

The second part of the workshop was devoted to a round table, in order to discuss problematics that had arisen during the workshop and to investigate the opportunities of scientific collaboration among the various researchers.

The difficulty and importance of finding a common language among researchers in such different fields was stressed and represented, at the very beginning, a clear obstacle for the discussion. However, once a basic common language was found, it was pointed out that the only way for mathematical models to become an efficient tool in oncology, is to design together (mathematicians, biologists and clinicians) experiments and quantities to be measured. This was identified as a starting point for the discussion.

As a second result, it was agreed that a "universal" approach, although optimal, is not yet affordable. So, it was decided to start the scientific and programmatic discussion from the problems outlined by clinicians, i.e. identification of the optimal therapeutic approaches for surgery (i.e. the margin problem) and chemiotherapy (i.e. design of patient oriented approaches).

The discussion stimulated the presentation of three proposals for collaborations, which were presented and discussed during the final round table. Most of the participants found a role in one of the proposals which will be pursued. The possibility of a future collaboration was found in the focusing on a multi-scale analysis (from subcellular, to cellular, to macroscopic behaviors) in Head and Neck and colorectal tumors.

SCIENTIFIC CONTENT

The design of a strategy for bridging the gap between basic research and applications has been the main scientific content of the workshop. To this purpose, it has been identified that at least three features must distinguish a new approach to the problem from other more traditional procedures and make it complementary to them.

The first feature is the point of view adopted. Besides the usual bottom-up approach (transfer knowledge gained from lab experiments on the cell behaviour to clinics), a complementary procedure may be extremely innovative: to design specifically oriented experimental models, starting from a well defined clinical problem. In other words, from a top-down point of view, the clinical problem will dictate which are at a molecular and cellular level the relevant processes to be investigated and quantities to be measured.

A second distinguishing feature for a multidisciplinary research is the development of mathematical models (on various scales) to be used as tools for virtual experiments in order to reduce the need of "in vivo" animal experiments, either by optimizing the design of models or by gaining a sufficient predictive capability. In fact, mathematical models represent the most suitable path for obtaining a quantitative description of the mechanisms involved in the molecular, cellular and extracellular processes. Also, the ease to apply models in different conditions and with controlled environment makes them an optimal tool for suggesting optimal protocols for medical treatment.

One of the major drawbacks in the translation of knowledge in the field of oncology is the lack of compatibility among different experimental models on different space scale. The "multi-scale" approach will guarantee a sufficient uniformity and integration of experimental and mathematical approaches at different levels. Translation from one scale to the nearest one should than be easier, with consequent benefits on the predictive power of the models developed. Essential is indeed a continuous collaboration in designing and interpreting experiments among researchers with strong expertise and large experimental facilities in the fields of genomics, signal transduction, cell mechanisms, development of in vitro and in vivo models, mathematicians, physicists, clinicians and pharmacologists.

To achieve this scientific goal, however, the research needs to focus on some specific clinical problems which were presented during the scientific communications (in particular for what concerns colorectal and Head & Neck tumours):

a) Metastasis: prediction of the invasive properties of an in vivo neoplasm has a strong relevance in surgery, since it may enable to optimize the determination of surgical margins, which are often one of the major causes of tumour recurrence;
b) Drug resistance: prediction of the conditions in which tumour cells develop resistance to drugs used in chemotherapy. Prevention of such resistance is a big issue in optimizing chemotherapy and developing a patient-oriented strategy.
c) Side-effects: prediction of radiosensitivity and drug-sensitivity of normal tissues in patients treated with ionizing radiation and chemotherapy on a basis of an in vitro DNA repair tests. Prevention or minimizing of an acute and late reaction is a major issue in optimizing therapy.
d) Efficiency of therapeutic protocols: estimation of effects of different protocols of radio- and chemotherapy on proliferation of cancer cells and tumor growth, prediction based on clinical data and statistic models.

Several steps have been identified as lacking in the current scientific "panorama" and need to be addressed:

a) Data collection from existing clinical and experimental data bases, followed by design and performance of pivoting experiments to obtain complementary information.
b) Mathematical model identification including design of qualitative models, parameter estimation and data validation.
c) Comparison of mathematical model results and experimental data (both in vitro and in vivo), and model verification in experimental practice.
d) Design of predictive tests for clinical applications.

ASSESSMENT OF RESULTS

In order to establish the basis for the realization of the scientific goals outlined during the workshop, several possible ways forward have been identified and some of them have been scheduled for the month following the workshop. Among these, the following practical lines have been detailed:

a) the submission of an Expression of Interest (deadline 7 June) for the 6FP, coordinated either by the Catalan Institute of Oncology, or by the German Cancer Research Center in Heidelberg. A preliminary EOI has been circulated among participants and other scientists eventually interested. As a result, an EOI including about 14 research institutions (almost all the participants to the workshop are included in the EOI) has been submitted;
b) the proposal for a ESF network to address the more basic aspects of the research, such as the individuation and description of the basic biological processes (feeding, growth, competition, etc.) involved in tumor growth. Some difficulties has been found in selecting the coordinator for the ESF Programme proposal. In fact, the chosen coordinator (Prof. Pescarmona) was not able to write the proposal for the deadline of the 31 May. So it has been decided to postpone the submission for the next deadline.
c) The creation of a mailing list (by the German Cancer Research Center in Heidelberg) including all participants to the workshop and open to the addition of other interested scientists. The mailing list (for information contact Dr. Ute Platzer) is now active and is intended as a forum to suggest applications, problems, etc.
d) Bilateral or multilateral collaboration on specific problems have also been discussed among single researchers and hopefully some of them will start in September.

WORKSHOP SCHEDULE

Thursday 9 May 2002

14.45: Meeting of the participants
15.00 - 15.15: Presentation of the ESF activities - *Mats Gyllemberg*
15.15 - 15.30: Welcome and workshop introduction – *Pier Paolo Delsanto*

Scientific communications: Biological aspects of tumor growth

15.40 - 16.00: The life context: cells, nutrients and signals – *GianPiero Pescarmona*
16.00 - 16.20: Interaction between signaling pathways in tumor cells – *Chris Marshall*
16.20 – 16.40: Simulation of signal transduction pathways – *Marco Weismueller*

16.40 – 17.20: Coffee break

17.20 – 17.40: Low density cell growth and death kinetics: comparison of two cell systems and their relevance or irrelevance to in vivo cell kinetics – *Denys Wheatley*
17.40 - 18.00: Three-dimensional cell culture as an in vitro model to study angiogenesis and cancer – *Olivier Oudar*
18.00 – 18.20: Common genetic evolutionary pathways in FAP tumors – *Gabriel Capella*
18.20 – 18.40: Analysis of DNA-microarray data in studies of genome structure – K*rzystof Fujarewicz*

Social dinner

Friday 10 May 2002

Scientific communications: Modeling

9.00 - 9.20: Mathematical modeling of aspects of solid tumor growth – *Mark Chaplain*
9.20 - 9.40: Modeling brain tumors as dynamic bio-systems – *Thomas Deisboeck*
9.40 – 10.00: Modeling the formation of vascular networks – *Luigi Preziosi*
10.00 – 10.20: A local approach to the simulation of tumor growth and angiogenesis – *Marco Scalerandi*

10.20 – 10.50: Coffee break

Scientific communications: Clinics

10.50 - 11.10: Mathematical modeling in Head and Neck Oncology: clinical implications - *Mauro Magnano*
11.10 - 11.30: Genetics of tumor response to cytotoxic nucleoside analogs in humans - *Romano Danesi*
11.30 - 11.50: – Studies of DNA damage and repair in prediction of side effects of radiotherapy – *Joanna Rzeszowska*
11.50 – 12.10: Simulation of genetic networks regulating cell differentiation – *Ute Platzer*

Lunch

Round Tables

15.00 – 15.15: Presentation of funding opportunities
15.30 – 16.30: Round Table

16.30 - 17.00 Coffee Break
17.00 - 18.30 Round Table

Dinner

Saturday, 11 May 2002

9.00 – 12.00 Round Table and discussion of grant proposals
12.00 - 12.10 Closing of the workshop – *Pier Paolo Delsanto*

Lunch

Afternoon: free for scientific and programmatic discussions

LIST OF PARTECIPANTS

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