

SYSBIOMED Workshop on Systems Biology and Cancer

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Despite their variety cancer diseases are systemic by nature. Accordingly, the participants expect SB to contribute valuable information required to elucidate pathological mechanisms thus providing key molecular targets and help to clinicians who have to decide on the targets (or combinations thereof) to be hit with maximum efficiency and minimal side effects. SB could possibly also shed light on fundamental problems like the notorious discrepancy between mouse and human 'model systems' with regard to therapeutic outcomes.

Defining and deciding upon experimental models in cancer systems biology projects

The discussion on which tumours to start studying by SB approaches with good prospects was guided by the following criteria:

- *High medical relevance.* (researchers have to rely on statistical data on frequency and mortality from the US National Cancer Institute since comprehensive, consistent data from Europe is not available.)
- *Well understood molecular pathology*
- *High quality experimental models available*
- *Variety of therapeutic options*

The following table, presented by Robert Jaster, gives a concise overview on the advantages and limitations of presently available tumour models:

Model	Strength	Weaknesses
Established tumour cell lines	<ul style="list-style-type: none"> • Unlimited availability • Useful to generate quantitative data for modelling 	<ul style="list-style-type: none"> • Very artificial • Inaccurate reflection of human diseases
Patient-derived tumour cells / cell lines	<ul style="list-style-type: none"> • reflect individual molecular pathology of individual patients/tumours 	<ul style="list-style-type: none"> • time consuming, lower throughput • availability
Tumour-bearing immunodeficient animals (e.g., nude or SCID mice)	<ul style="list-style-type: none"> • Relatively easy to establish • Generation of in vivo data 	<ul style="list-style-type: none"> • Still, quite far away from human reality
Immunocompetent animals with hetero- or orthotopic transplants	<ul style="list-style-type: none"> • Increased practical relevance 	<ul style="list-style-type: none"> • Often difficult to handle; low throughput
Genetic models	<ul style="list-style-type: none"> • Most accurate model of human disease 	<ul style="list-style-type: none"> • availability

The participants thoroughly discussed whether some comparatively rare cancer diseases (e.g. CML) could provide good opportunities for SB strategies. They concluded that such diseases, often lacking suitable model systems and a sound biomedical knowledge base, would not differ from diseases with higher incidence.

With regard to possible cancer stem cells they found that the yet not well understood nature and role of these cells does not suggest SB approaches into this special field at present.

A likely proof of principle case is **colorectal carcinoma** (CRC) which is considered a good choice since there is a high medical need, a good knowledge base from all stages of this multi-step disease and there is access to clinical material. A challenge for SB of much higher order, and probably not a good proof-of-principle case, is the difference/relationship between primary tumours and metastases, especially the investigation of the high flexibility of **metastatic cells** when evading chemotherapy (drug resistance). For example, given a limited set of 'anti-apoptotic signaling pathways', metastatic cells normally manage to activate/recombine alternative routes whose regulation can possibly be elucidated by SB. Insights into these mechanisms should translate into unprecedented leaps in therapy since it is the formation of metastases which makes tumour diseases hard to cure and eventually lethal.

The workshop participants were aware of the fact that the above recommendations for priorities in cancer research employing SB methods are sound but incomplete. Interdisciplinary SB projects involving experts from different fields generally face the problem on how to decide upon a suitable experimental system for which data can be shared allowing comparative studies and the integration of knowledge across scales from intracellular processes to structural models of tumours and a wide range of technologies employed.

It would therefore seem appropriate to organise a meeting that could guide consortia to decide upon common cell lines, suitable mouse models, tumor types, pathologies, technologies, pathways, methodologies employed. The group is to discuss which types of cancer would provide important challenges or would be suitable for proof-of-principle studies.

On modeling

The development of computational models from signalling to tumour growth (bottom-up and

top-down) shall be done on the intracellular, cellular, multicellular level. Discussing the scope and requirements of modeling of cancer diseases the participants agreed on the priority task of linking structural models with signaling and metabolic pathways and cell cycle. This would require the identification of functional units (signaling pathways: identify key targets within; metabolic networks: metabolic adaptation that support tumor proliferation; identify targets) and modeling across time scales from minutes in signalling to hours and days when studying growth. Model integration incorporating 'cross-talk' of signaling pathways is essential. Phenotypic information on cells and cell populations is required to identify possible signal transduction pathways. Clinical data from patients is considered valuable for applying SB models to translational research.

A bottleneck

Apart from the huge technological challenges, SB in biomedical research faces serious risks from insufficient (wo)manpower. Traditional career paths in the medical sciences still are incompatible with SB research: Researchers with a medical background and career ambitions are currently hard to recruit because systems biology projects are more time consuming, complex, interdisciplinary, and the bedside-benefits not around the corner.

Research presentations

The participants briefly presented their research projects and views. *Robert Jaster* provided a concise introduction to tumour biology and discussed the requirements for successful SB approaches. *Andrea Ciliberto* showed that qualitative data was sufficient to build a comprehensive model for the cell cycle of yeast. Mammalian model systems, which are not well developed yet, are harder to study as genome duplication makes the situation complex and it is difficult to define the cell cycle engine. Current modeling attempts concentrate on key checkpoints. *Philippe Lenormand* supported this view and pleaded for choosing HeLa cells as model systems. Stem cells are probably not well suited, their G1/S transition being different from adult cells. *Jorrit Hornberg* reported on the impact SB is expected to have on pharmaceutical research and therapy. Tumours, sensitive to kinase inhibitors, should be destroyed by combinations of many drugs of this class, the therapies based on the analysis of biomarkers. SB is considered indispensable to generate the required multi-dimensional knowledge. *Marta Cascante* looked at the metabolome of tumour cells. The robustness of tumor metabolism often counteracts single hits of drugs. Unfortunately, multiple-hit strategies also fail due to unpredictable by-pass reactions of the tumour metabolism. SB is obviously urgently needed to increase the knowledge of the metabolic network and to rationally design drugs. *Christine Sers* focused on cell signaling. The time scale of signaling spans from seconds to days (e.g. secondary changes like DNA methylation associated with wound healing). She pointed to the lack of technical tools to quantitatively detect the components of pathways and to correlate signals and phenotypic output. *Dirk Drasdo* presented a 3D model of tumour growth controlled by contact inhibition of cells and nutrient supply. By varying parameters (cell cycle time, adhesion strength, migration speed, elastic modules) one can adjust the virtual tumour tissue to display a growth behaviour closely resembling the 'real thing'. It is noteworthy to say that APO-SYS, a FP7 project which grew out of FP6 'European Systems Biology Initiative for combating Complex Diseases', aims at applying 'Apoptosis Systems Biology' to cancer and AIDS.

Scientific challenges

The participants took the opportunity to concisely outline their favourite scientific goals/questions in cancer biology which they would like to see tackled by medical SB research. The following list provides brief profiles of the objectives of the proposals as communicated by the workshop members:

Proposal 1

Objective:

- Integrative spatial-temporal model of tumour growth and therapy in in-vitro setting, animal model and human.

Proposal 2

Objectives:

- Comprehensive pathophysiological understanding of the networks involved in colorectal carcinogens (e.g. oncogene/anti-oncogene, metabolic network)
- Generation of rational basis for therapeutic decisions: which drugs to choose in a given context to achieve maximum efficiency / strong therapeutic effect, low side effects
- Optimisation of therapeutic regimes (scheme, dosage, time course)

Proposal 3

Objectives:

- Build a multiscale model for normal ... dynamics and the early stages of cancer
- Couple fundamental pathways to cellular processes
- Provide a user-friendly tool which experimentalists and clinicians can use to study the system and generate new biological and testable hypotheses
- Carry out experiments in silico which provide new insight that complements and/or enforces the knowledge acquired by experimental methods

Proposal 4

Aims:

- Characterise metabolic adaptations that support colon cancer cell proliferation and metabolic changes accompanying oncogenic transformation and signal transduction activation/silencing

Objectives:

- Construct a model of dynamical metabolic fluxes in tumour cancer cell lines from tracer based metabolomics and metabolic profiling data obtained by GC/MS, LC/MS and NMRA platforms and software ...
- Quantify metabolic flux changes accompanying different oncogenic transformations using tracer metabolomics
- Quantify metabolic changes accompanying drugs targeting metabolic network, signal transduction networks or cell cycle machinery

Proposal 5

Objectives:

- Identify functional signalling pathways in colorectal cancer cells relevant for proliferation, survival, motility (MAPK, Wnt, PI3K, CDC42/Rac)
- Study the behaviour of these pathways in response to therapeutic interventions in vitro
- Identify underlying epigenetic modifications relevant for pathway function

- Identify epigenetic modifications caused by activated pathways relevant for proliferation, survival and motility

Proposal 6

Objectives:

- Role of MAPK signalling pathways to influence the balance between cell proliferation and apoptosis in colon cancer model cell line: Normal versus transformed cell
- Collaboration with modeller to understand cross-talks between MAPK pathways

Proposal 7

Objectives:

- Disease models data base which will be a collection of reference models
- Standardising of models
- Cancer and acute inflammations

Proposal 8

Objectives:

- Increase the success rates of drug development by
 - Identify better targets and
 - Identify combination of targets to increase efficacy and reduce toxicity
- For this we need models that include molecular targets such that combinations can be simulated. Please refer to the last slide of my presentation: That summarises what we need to have an impact in the near future

Proposal 9

Objectives:

- Building predictive mathematical models at appropriate molecular detail to a) integrate the measured data and b) be able to predict the outcome of interventions at signalling level
- Integrate changes of gene expression caused by signalling into the model to incorporate cross-talk (mainly through negative regulators such as DUSPs)
- Investigate targets and possible strategies to interfere at multiple points in the network.
- Simulate strategies of the cancer cells to circumvent treatment and find the best way to prevent that
- Make a statistical model that links signalling state to biophysical cell parameters to facilitate multi-scale modelling
- Make a link to the cell-cycle model