Cancer is the second most prevalent cause of death in developed countries. Some 2.9 million cases are diagnosed annually in Europe, with over 1.7 million deaths attributed to cancer each year. Chemotherapy regimes currently used show limited effectiveness, with chemoresistance a major therapeutic shortcoming. SYNLET’s novel approach to this key drawback will not only improve our understanding of cancer cell chemoresistance but propose combination drug treatment regimes for fighting cancer.

As the statistics clearly indicate, there is a vital need to improve cancer survival rates as well as the quality of life for those affected, while also reducing the overall social and economic consequences of cancer-related illnesses. Yet, despite decades of cancer research, only limited fundamental knowledge has been gained about the central aspects of cellular malignancy at different stages of the disease. Cancer treatment regimes tend to be designed for obtaining a specific effect in a particular stage of the disease. The consequence of this lack of understanding is rapid resistance to chemotherapeutics, in the worst case leaving only palliative care.

SYNLET aims at obtaining a greater understanding of the complex processes involved in malignant transformation by combining theoretical, computational and experimental approaches. An interdisciplinary consortium involving theoretical biologists, complex systems scientists and experimental oncologists will integrate this knowledge towards improving the effectiveness of cancer drugs.

Killing cancerous and healthy cells
Current chemotherapy treatment regimes apply drugs to kill rapidly dividing cancer cells. However, such drugs can also be lethal to normal cells, which restrict the types of drugs that can be used and the treatment duration. Chemotherapy resistance is particularly complex, as robustness and viability of drug-resistant cancer cells depends on a variety of molecular changes that are difficult to interpret.

Survival and malignancy of chemotherapy-resistant cancer cells appears to depend on gene expression and protein-interaction networks that differ markedly from those of chemotherapy-sensitive cells. Furthermore, the acquisition of chemotherapy resistance is commonly associated with a more malignant phenotype, indicating increased robustness of chemoresistant cancer cells.

Genes, their expression and the cellular function of encoded proteins, can be seen as a complex interaction network defining the phenotype of a cell – being ‘healthy’ or malignant and, as a consequence, being chemosensitive or chemoresistant.
SYNLET is developing a complex systems analysis approach for identifying the key proteins that enable cells to overcome drug toxicity resulting in chemoresistance. Blocking these proteins in their functional context may result in synthetic lethality, leading to re-sensitising chemotherapy-resistant cancer cells to conventional drug treatment. However, simultaneous inhibition of two or more genes/proteins rather than any single gene/protein may be needed to realise synthetic lethality on this level.

While this general concept has been discussed in scientific literature, the practical implementation has been limited due to a lack of understanding of key cellular mechanisms involved. Availability of broad experimental data sets from chemoresistant cancer cells, combined with mathematical modelling of the cellular dynamic system on the level of interaction networks, now allows for qualitative and quantitative analyses. This provides novel hypotheses for overcoming chemoresistance mechanisms. Such hypotheses can now also be directly tested in an experimental setting.

Systems analysis and biology

Complex systems science has provided pivotal concepts, theories and insight towards an understanding of dynamic systems both at a general level and in the practical context of cellular processes.

SYNLET unites leading European experts in complex systems science and computational biology with clinical oncologists to create an alternative procedure towards solving the phenomenon of chemoresistance. This work is focused on a unique collection of drug-resistant cancer cell lines.

A broad experimental profile characterising chemoresistant cancer cells will trigger computational analysis procedures using complex systems science methodologies. These results will feed into experimental verification. Small interfering RNA (siRNA) molecules directed against synthetically lethal hubs in the cellular control network will be tested for overcoming chemoresistance in conjunction with current cancer drugs.

Merging algorithmic approaches in complex systems analysis with state-of-the-art computational simulation of biological processes is one of the major innovative procedures involved in this project. SYNLET will also focus on deepening our understanding of cellular interaction network dynamics in terms of stability, robustness and the prevalence of escape routes used by cancer cells towards overcoming external selection pressure actuated by cancer drugs.

Once functional protein hubs enabling cellular drug resistance escape routes have been identified, experimental efforts will be applied towards blocking these processes, followed by in vitro analysis of effects on chemoresistance. As a result, novel strategies for improving the effectiveness of cancer drug treatment may emerge.

SYNLET will strengthen Europe’s position on the broader scale of the global research community. The research organisations and small and medium-size enterprises involved will ensure that the results are clinically tested and that the subsequent commercial avenues for the new combinational cancer drug treatment regimes are explored.

“Towards solving the phenomenon of chemoresistance.”