A relevant example comprises the epidermal growth factor (EGF) and the respective receptor tyrosine kinases, namely ErbB-1/EGFR and HER2, which belong to a prototype signaling module that drives carcinoma development. The extended module includes two autonomous receptors, EGFR/ErbB-1 and ErbB-4, and two non-autonomous receptors, namely: a ligand-less oncogenic receptor, HER2/ErbB-2, and a kinase-dead receptor (ErbB-3). This signaling module is frequently involved in human cancer through autocrine loops involving co-expression of a receptor and one of the many EGF-like ligands, mutations and deletions within the *EGFR* gene (e.g., in lung and brain tumours), or amplification of either *HER2* (e.g., in breast cancer) or *EGFR* (e.g., in head and neck cancer). Moreover, both EGFR and HER2 serve as targets for several cancer drugs, such as monoclonal antibodies (e.g., Cetuximab and Trastuzumab) and tyrosine kinase inhibitors (e.g., Erlotinib and Lapatinib).

To explain the remarkable oncogenic potential of HER2/ErbB-2, a ligand-less receptor that forms heterodimers with the other three ErbB proteins, we proposed a network configuration: through a layered organization of ligands, receptor dimers, downstream pathways and transcription factors, the ErbB network tunes and diversifies signal transduction, with HER2 operating as a signal amplifier. The network achieves robustness by adopting universal features common to engineered and natural systems: a modular architecture, a common core process, and a dense web of feedback control circuitry. My presentation will concentrate on system controls, which can be divided into two categories: the immediate loops are the domain of post-translational protein modifications, such as receptor phosphorylation, ubiquitinylation and neddylation. One consequence of this phase comprises endocytosis of ligand-receptor complexes, a process evaded by several oncogenic mutants of EGFR. In my presentation I will describe our screens, which identified the DEP-1 tyrosine phosphatase, a putative tumour suppressor, as a regulator of EGFR. The late category of system control depends on newly transcribed messenger RNA and micro-RNA molecules. Through coordinated functions, inducible mRNAs and miRNAs terminate expression of the highly oncogenic, immediate early genes, such as *c-FOS* and *c-JUN*. My lecture will highlight examples of tumour evasion from system control. In addition, I will focus on the inevitable fragility of robust signaling networks, as well as propose that system level understanding may help identify Achilles heels amenable for therapeutic intervention.

11 From benchside to byteside: what we can learn from computational modelling

W. Kolch[1], M. Birtwistle[1], B. Kholodenko[1], J. Grindlay[2], O. Sturm[3], R. Orton[4], D. Gilbert[5], A. von Kriegsheim[1]. [1]*University College Dublin, Systems Biology Ireland, Dublin, Ireland,* [2]*The Beatson Institute for Cancer Research, Signalling and Proteomics Lab, Glasgow, United Kingdom,* [3]*St Jude Children's Research Hospital, Department of Immunology, Memphis TN, USA,* [4]*University of Glasgow, Institute of Comparative Medicine, Glasgow, United Kingdom,* [5]*Brunel University, School of Information Systems Computing and Mathematics, Uxbridge, United Kingdom*

Background: On the molecular level cancer can be perceived as a disease that deregulates signal transduction networks (STNs). This is reflected in the increasing number of anti-cancer drugs that are targeting signal transduction proteins. However, we have an insufficient understanding how the design properties of STNs can be exploited to gain insights into pathogenetic processes and improve drug therapies.

Materials and Methods: A combination of proteomics, biochemical measurements and mathematical modelling was used to generate computational models that can be used to analyse emergent network behaviour.

Results: Here, we show that the intrinsic design properties of STNs give rise to emergent functions that can specify the biochemical and biological behaviour of STNs. Thus, they are critical to determine the genuine behaviour of cancer cells as well as the response to drugs. We will discuss selected examples of STN design principles as revealed by computational modelling. They include the (i) modelling of drug responsiveness in the Ras-Raf-MEK-ERK pathway; (ii) switchlike changes between apoptosis and proliferation responses determined by the dynamics of the formation of competing protein complexes; and (ii) migration and invasion determined by the ERK pathway.

Conclusions: Emergent properties resulting of the design of STNs are crucial determinants of robustness, adaptation and dynamic response behaviour of STNs both in respect to physiological cues and drug therapies.

12 A systems approach to identification of therapy response subsets in breast cancer

No abstract received.

13 How genomics has reshaped our view of cancer

D. Botstein[1]. [1]*Princeton University, Lewis-Sigler Institute, Princeton NJ, USA*

The sequence of the human genome, the primary goal of the Human Genome Project, was achieved just a few years ago. The ability to obtain genomic sequences depended on revolutionary progress not just in DNA chemistry but also on the equally revolutionary advances in speed, capacity and versatility of digital computers. Among the many benefits to society provided by our knowledge of genomic sequences has been the identification, through their inheritance in families, of thousands of genes that cause inherited diseases. Among them are genes that cause inherited predispositions to breast cancer, colon cancer, and kidney cancer, among others. Study of how these genes cause relatively rare forms of cancer has informed our understanding cancer generally, because so many of these genes are homologs of genes better understood in model organisms, where experimental determination of their biological functions has been massively accelerated by genomic technology. More recent progress, driven by rapidly increasing productivity in sequence technology, has not only confirmed these relationships but also allowed the discovery of new mutations affecting previously unsuspected genes that contribute to cancer.

A quite different benefit of the genomic sequences is that they allow us to study the activities of all the genes simultaneously, using once again a combination of DNA chemistry and computational methods. With these methods it has become possible to study, at a comprehensive (genome-wide) level, the differences in gene activity that accompany the transformation of tissues from normal to cancerous, and to classify different subtypes of cancers by their "molecular signatures". We now can distinguish, for example, several kinds of breast cancer, some of which are more aggressive and lethal than others, and some of which are uniquely sensitive to new classes of unusually effective drugs directed specifically at these subtypes.