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Complex behaviours—new targets against cancer

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We enjoyed reading the Perspectives article by Funda Meric–Bernstam and Gordon B. Mills (Overcoming implementation challenges of personalized cancer therapy. *Nat. Rev. Clin. Oncol.* **9**, 542–548; 2012)[1] on the challenges of personalized cancer therapy. In their high-quality paper, the authors focus on the biological and technical challenges that must be surmounted before personalized cancer therapy can be realized. We agree with their viewpoints and appreciate their sharp insights on personalized cancer therapy. We are especially interested in tumour heterogeneity, molecular evolution and resistance in biological challenges. In particular, the fundamental mechanisms that cause tumour heterogeneity must be addressed before any new approach to personalized cancer therapy can be developed.

Tumour heterogeneity is associated with the growth and development of cancer at different stages, which is regulated by a series of complex behaviours that include self-organization, dissipative structures, the biological clock, fractals and chaos. In recent years, complexity theory, which encompasses these behaviours, has increasingly entered fundamental studies of the growth and development of cancer.

Disrupted self-organization has been revealed in complex 3D-space models of cancer formation. Greaves and Maley[2] elaborated that cellular evolution and selection can occur in cancer systems, and suggested the use of self-organization models to interpret the dynamic formation of cancer. Indeed, self-organization is a dynamic and lineage-intrinsic property of mammary epithelial cells—loss of E-cadherin, which governs self-organization, promotes breast cancinogenesis.[3] Additionally, tumour microenvironment complexity has emerged as having important roles in cancer. For example, the microenvironment is involved in the dynamic evolution of cancer, acts as a pathway of communication between stromal and tumour cells and has immunomodulatory roles in the lymphatic system.[4]

According to Sahar and Sassone-Corsi,[5] the disruption of circadian rhythms might be directly linked to carcinogenesis and might lead to abnormal metabolism by controlling the circadian oscillations of NAD^+ and SIRT1 activity. Fractal analysis with nonlinear dynamics also provides new approaches to cancer therapy by describing quantitative fractal parameters used to induce dramatic cell-shape changes to reverse malignant cancer cells to non-malignant.[6] These reports encompass the multidisciplinary study of complex behaviours in cancer.

Importantly, complex behaviours can provide new therapeutic targets against cancer. We believe that the future direction of personalized cancer therapy will not only focus on traditional chemotherapy, but will combine chemotherapy with interventions that disrupt the formation of complex behaviours. These combined therapies will be implemented by mathematically and computationally systematic analyses. Several recent studies of this kind have been used in animal models by modifying the tumour microenvironment. For example, the experimental Hedgehog inhibitor IPI-926[7] and a pegylated variant of hyaluronidase (PEGPH20)[8] were developed using this rational approach. In terms of clinical application, the complexity of molecular signalling networks in cancer is also correlated with the 5-year survivability of patients. Specifically, a correlation between degree-entropy of the cancer and 5-year survival was found, which suggests that cancers with complex molecular pathways are more refractory to treatment than those with simpler pathways.[9] Analyses of this kind could provide new molecular targets for drugs and provide useful platforms from which to evaluate prognosis. Accordingly, we believe that future treatments will be increasingly varied and informative than those of today because of these complexity-based advances.

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Competing interests
The authors declare no competing interests.

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