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Cancer and Entanglement Research Literatures

Dr. Mark Herbert

World Development Institute
39-06 Main Street, Flushing, Queens, New York 11354, USA, ma708090@gmail.com

Abstract: Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries. This article introduces recent research reports as references in the related studies.
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Key words: cancer; life; research; literature; cell

1. Introduction

Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries.

The following introduces recent reports as references in the related studies.

Abdusamad, K., et al. (2013). "Simultaneous bilateral torsion of the adnexae in an adult female without any history of ovarian stimulation." BMJ Case Rep **2013**.

Simultaneous bilateral adnexal torsion is very rare especially in adults. There have been few cases reported in children with only one previous case reported in adults since 1984, which was complicated by entanglement of both adnexae. In adults, the use of ovarian stimulation for treatment of infertility can increase the risk of ovarian torsion. We report the second case of simultaneous bilateral adnexal torsion in an adult female without follicular stimulation.

Al Mahmud, M. R., et al. (2020). "TDP2 suppresses genomic instability induced by androgens in the epithelial cells of prostate glands." Genes Cells **25**(7): 450-465.

Androgens stimulate the proliferation of epithelial cells in the prostate by activating topoisomerase 2 (TOP2) and regulating the transcription of target genes. TOP2 resolves the entanglement of genomic DNA by transiently generating double-strand breaks (DSBs), where TOP2 homodimers covalently bind to 5' DSB ends, called TOP2-DNA cleavage complexes (TOP2ccs). When TOP2 fails to rejoin TOP2ccs generating stalled TOP2ccs, tyrosyl DNA phosphodiesterase-2 (TDP2) removes 5' TOP2 adducts from stalled TOP2ccs prior to the ligation of the DSBs by nonhomologous end joining (NHEJ), the dominant DSB repair pathway in G0 /G1 phases. We previously showed that estrogens frequently generate stalled TOP2ccs in G0 /G1 phases. Here, we show that physiological concentrations of androgens induce several DSBs in individual human prostate cancer cells during G1 phase, and loss of TDP2 causes a five times higher number of androgen-induced chromosome breaks in mitotic chromosome spreads. Intraperitoneally injected androgens induce several DSBs in individual epithelial cells of the prostate in TDP2-deficient mice, even at 20 hr postinjection. In conclusion, physiological concentrations of androgens have very strong genotoxicity, most likely by generating stalled TOP2ccs.

Banerjee, D. (2019). "Cancer and Conjugality in Contemporary Delhi: Mediating Life between Violence and Care." Med Anthropol Q **33**(4): 579-594.

This article tracks the entanglement of cancer and patterns of conjugality in Delhi. Building on fieldwork with about 120 households in Delhi, it describes how the disease put pressure on already fraught marital biographies, revealing durable fissures in household relations. Often, these shifts in the distribution of conjugal vulnerability opened cracks

that allowed long histories of domestic violence to seep through. In subtle ways, women could accrue a delicate agency through their practices of care. But at the same time, they continued to inhabit the vulnerable space of affinal homes. This article describes how in these arrangements, care and violence followed each other closely in their tracks. Building on these insights, the article deepens and shifts how anthropologists have understood the social life of the cancer. Specifically, anthropologists writing about the disease have demonstrated the ubiquity of a biotechnical imaginary of hope and survivorship in the Global North. This article develops an anthropology of cancer from the Global South that takes seriously the work of palliation and reconciliation, in the process provincializing Global North imaginaries of hope and survivorship.

Blow, J. J. and P. J. Gillespie (2008). "Replication licensing and cancer--a fatal entanglement?" Nat Rev Cancer **8**(10): 799-806.

Correct regulation of the replication licensing system ensures that chromosomal DNA is precisely duplicated in each cell division cycle. Licensing proteins are inappropriately expressed at an early stage of tumorigenesis in a wide variety of cancers. Here we discuss evidence that misregulation of replication licensing is a consequence of oncogene-induced cell proliferation. This misregulation can cause either under- or over-replication of chromosomal DNA, and could explain the genetic instability commonly seen in cancer cells.

Booth-Butterfield, M. (2003). "Embedded health behaviors from adolescence to adulthood: the impact of tobacco." Health Commun **15**(2): 171-184.

Prevention of cancer risk behaviors before they become embedded in an individual's life is crucial. Health-related behaviors should be viewed for their embeddedness, critical aspects of which are (a) the complexity of the behavior itself; (.b) factors, both biological and psychological, within the individual communicator; (c) and external situational or sociocultural factors. The more extensively a behavior is embedded, the more difficult it will be to alter. Relative levels of embeddedness of the risk behavior and its entanglement with other nonrisky behaviors will evolve and change throughout one's life course. Smoking across the life span provides an excellent example of a thoroughly integrated, embedded behavior. How smoking is embedded with other behaviors changes from adolescence, where biological factors may be less salient and habit strength less pronounced, through adulthood, where habit strength is greater but health concerns are a more predictive factor. Researchers can produce more focused communication interventions by examining how health-endangering behaviors are embedded among benign behaviors or among other potentially dangerous behaviors. Ideally, the pattern of health behavior embeddedness should be analyzed prior to developing intervention communication strategies.

Brahmachari, S. and J. F. Marko (2018). "DNA Mechanics and Topology." Adv Exp Med Biol **1092**: 11-39.

We review the current understanding of the mechanics of DNA and DNA-protein complexes, from scales of base pairs up to whole chromosomes. Mechanics of the double helix as revealed by single-molecule experiments will be described, with an emphasis on the role of polymer statistical mechanics. We will then discuss how topological constraints-entanglement and supercoiling-impact physical and mechanical responses. Models for protein-DNA interactions, including effects on polymer properties of DNA of DNA-bending proteins will be described, relevant to behavior of protein-DNA complexes in vivo. We also discuss control of DNA entanglement topology by DNA-lengthwise-compaction machinery acting in concert with topoisomerases. Finally, the chapter will conclude with a discussion of relevance of several aspects of physical properties of DNA and chromatin to oncology.

Cantero, G., et al. (2006). "Topoisomerase II inhibition and high yield of endoreduplication induced by the flavonoids luteolin and quercetin." Mutagenesis **21**(5): 321-325.

Luteolin and quercetin are widely distributed plant flavonoids that possess a variety of chemical and biological activities, including free-radical scavenging and antioxidant activity. Recently, both flavonoids have been reported to inhibit DNA topoisomerases I and II (topo I and topo II), a property that, together with their ability to induce DNA and chromosome damage, has made them candidate anticancer compounds. In the present study, we confirmed that both compounds are topo II inhibitors by conducting a comparative study of their effect on topo II activity from Chinese hamster ovary AA8 cells. Because interference with the function of topo II to resolve DNA entanglement at the end of replication results in chromosome malsegregation at mitosis, we investigated whether luteolin and quercetin are effective in inducing endoreduplication in AA8 cells. Concentrations of luteolin and quercetin that inhibited topo II catalytic activity resulted in extraordinarily high yields of metaphases showing diplochromosomes. Given the established relationship of polyploidy with tumor development via aneuploidy and genetic instability, these results question the usefulness of luteolin and quercetin in cancer therapy.

Castro, M. A., et al. (2008). "Evolutionary origins of human apoptosis and genome-stability gene networks." Nucleic Acids Res **36**(19): 6269-6283.

Apoptosis is essential for complex multicellular organisms and its failure is associated with genome instability and cancer. Interactions between apoptosis and genome-maintenance mechanisms have been extensively documented and include transactivation-independent and -dependent functions, in which the tumor-suppressor protein p53 works as a 'molecular node' in the DNA-damage response. Although apoptosis and genome stability have been identified as ancient pathways in eukaryote phylogeny, the biological evolution underlying the emergence of an integrated system remains largely unknown. Here, using computational methods, we reconstruct the evolutionary scenario that linked apoptosis with genome stability pathways in a functional human gene/protein association network. We found that the entanglement of DNA repair, chromosome stability and apoptosis gene networks appears with the caspase gene family and the antiapoptotic gene BCL2. Also, several critical nodes that entangle apoptosis and genome stability are cancer genes (e.g. ATM, BRCA1, BRCA2, MLH1, MSH2, MSH6 and TP53), although their orthologs have arisen in different points of evolution. Our results demonstrate how genome stability and apoptosis were co-opted during evolution recruiting genes that merge both systems. We also provide several examples to exploit this evolutionary platform, where we have judiciously extended information on gene essentiality inferred from model organisms to human.

Castro, M. A., et al. (2007). "Impaired expression of NER gene network in sporadic solid tumors." Nucleic Acids Res **35**(6): 1859-1867.

Nucleotide repair genes are not generally altered in sporadic solid tumors. However, point mutations are found scattered throughout the genome of cancer cells indicating that the repair pathways are dysfunctional. To address this point, in this work we focus on the expression pathways rather than in the DNA structure of repair genes related to either genome stability or essential metabolic functions. We present here a novel statistical analysis comparing ten gene expression pathways in human normal and cancer cells using serial analysis of gene expression (SAGE) data. We find that in cancer cells nucleotide-excision repair (NER) and apoptosis are the most impaired pathways and have a highly altered diversity of gene expression profile when compared to normal cells. We propose that genome point mutations in sporadic tumors can be explained by a structurally conserved NER with a functional disorder generated from its entanglement with the apoptosis gene network.

Castro-Vazquez, G. (2022). "Cultural Scripts Underpinning Prostate Cancer-Literacy in Japan." Am J Mens Health **16**(1): 15579883221076658.

In a country where cancer has been dubbed a "national disease" (kokumin bio) that mostly affects Japanese men, this article presents a reading of the cultural scripts underneath prostate cancer-one of the "Western type of cancers" (obeigata no gan). The reading is grounded in an adaptation of the "sexual scripting theory," the construct of cancer-literacy, and the analysis of 3,092 newspaper reports published from 2005 to 2020, in three Japanese newspapers with the largest circulation in the country. The analysis is presented in line with three axes: cancer-self, cancer-biopedagogy, and cancer-economics to indicate that a cancer-self largely entails the subjectivity of a Westernized, married, heterosexual man who undergoes andropause, needs to understand what bladder somatics is, and depends on his family and the feminization of care to cope with cancer. The chances to prevent and/or survive the disease chiefly hinge on adopting a form of cancer-biopedagogy, which entails a composite entanglement of knowledge and health-related practices underpinned by the ethnicization of cancer through the consumption of "traditional food" (washoku) and the assumption that turning into a "healthy self" is determined by Japanese ethnic traits. Cancer-economics is concerned with costs of testing and treatments, health care insurance policies, and food and dietary supplements that serve to commodify a cancer-self who deals with prostate and urinary-related issues.

Chan, E. A., et al. (2019). "Nurses' perspectives on their communication with patients in busy oncology wards: A qualitative study." PLoS One **14**(10): e0224178.

BACKGROUND: Despite an increase in emphasis on psychosocial care in cancer nursing, time constraints and nurses' lack of knowledge in skilled communication continue to be challenges. AIMS: To examine how cancer care nurses view their communication with patients and how they deal with the psychosocial needs of patients in busy wards. DESIGN: A qualitative interview study. METHODS: Focus groups and individual interviews were conducted with eleven hospital-based cancer nurses in Hong Kong from July 2, 2017 to January 2, 2018. RESULTS: A qualitative thematic analysis of the data identified three themes: 1. Intentional and unintentional psychosocial care that is secondary in focus; 2. Managing an emotionally challenged environment; 3. Mentoring and learning. CONCLUSION: Oncology settings are time-

constrained, emotionally charged environments for nurses, and providing psychosocial care for patients is a secondary concern. While proactive strategies can be used to avert patient complaints, being open and attending to the individual needs of patients is equally important to avoid blocking in nurse-patient communication. Despite emotional entanglement and tensions, the positive follow-up strategies used by nurses to manage the patients' emotions and provide psychosocial care reflect good practices. Leadership and support are needed to deal with the nurses' perception that their communication training has been ineffective and their ability to manage strong emotions deficient. Communication skills, honed by making continuous opportunities to communicate available, as well as an understanding of emotional labour, need to be integrated with mindfulness in the nurses' care of themselves and their patients. Notwithstanding the importance of experience in oncology care for junior nurses, it is necessary for both junior and senior nurses to learn about and reflect upon the different forms of emotional labour if value-based care is to be provided. In addition, it is essential for junior nurses to receive continuous coaching and mentoring, and to engage in reflective learning from each clinical encounter with oncology patients.

Chen, B., et al. (2022). "The Love-Hate Relationship Between TGF-beta Signaling and the Immune System During Development and Tumorigenesis." Front Immunol **13**: 891268.

Since TGF-beta was recognized as an essential secreted cytokine in embryogenesis and adult tissue homeostasis a decade ago, our knowledge of the role of TGF-beta in mammalian development and disease, particularly cancer, has constantly been updated. Mounting evidence has confirmed that TGF-beta is the principal regulator of the immune system, as deprivation of TGF-beta signaling completely abrogates adaptive immunity. However, enhancing TGF-beta signaling constrains the immune response through multiple mechanisms, including boosting Treg cell differentiation and inducing CD8(+) T-cell apoptosis in the disease context. The love-hate relationship between TGF-beta signaling and the immune system makes it challenging to develop effective monotherapies targeting TGF-beta, especially for cancer treatment. Nonetheless, recent work on combination therapies of TGF-beta inhibition and immunotherapy have provide insights into the development of TGF-beta-targeted therapies, with favorable outcomes in patients with advanced cancer. Hence, we summarize the entanglement between TGF-beta and the immune system in the developmental and tumor contexts and recent progress on hijacking crucial TGF-beta signaling pathways as an emerging area of cancer therapy.

Chen, T. and Y. C. Cheng (2022). "Numerical computation of the equilibrium-reduced density matrix for strongly coupled open quantum systems." J Chem Phys **157**(6): 064106.

We describe a numerical algorithm for approximating the equilibrium-reduced density matrix and the effective (mean force) Hamiltonian for a set of system spins coupled strongly to a set of bath spins when the total system (system + bath) is held in canonical thermal equilibrium by weak coupling with a "super-bath". Our approach is a generalization of now standard typicality algorithms for computing the quantum expectation value of observables of bare quantum systems via trace estimators and Krylov subspace methods. In particular, our algorithm makes use of the fact that the reduced system density, when the bath is measured in a given random state, tends to concentrate about the corresponding thermodynamic averaged reduced system density. Theoretical error analysis and numerical experiments are given to validate the accuracy of our algorithm. Further numerical experiments demonstrate the potential of our approach for applications including the study of quantum phase transitions and entanglement entropy for long range interaction systems.

Collier, J. and H. Kienzler (2018). "Barriers to cardiovascular disease secondary prevention care in the West Bank, Palestine - a health professional perspective." Confl Health **12**: 27.

BACKGROUND: Non-communicable diseases (NCDs) - including cardiovascular disease (CVD), cancer and diabetes - have become a significant global burden on health. Particularly concerning are CVD rates, causing approximately 18 million deaths worldwide every year. The statistics show that the disease is no longer a predominantly high-income country phenomenon, but affects, increasingly, countries in both developing regions and conflict-affected areas. In the occupied Palestinian territory (oPt), the focus of this article, CVD ranks top of ten NCD killers, accounting for approximately 37.6% of deaths. Key risk factors discerned in primary care settings have been related to both structural determinants (i.e. the Israeli occupation) and individual behavioural factors. Unfortunately, no data are available for secondary care settings in the region and, consequently, little is known about patients and their capacity for risk factor behaviour change to manage their CVD.To begin closing this gap in knowledge, our study provides insight into cardiovascular disease secondary prevention care with the overall aim to enhance the understanding of the complexities of

managing NCDs like CVD in conflict-affected settings. Specifically, research was carried out among Palestinian health professionals who specialise in coronary artery disease in the West Bank to elicit their views on (a) how socio-political, health system and individual behavioural factors might hinder patients to change their health behaviour and impact on the provision of healthcare and (b) possible solutions for overcoming identified barriers to behaviour change on societal as well as individual-patient levels within secondary care provision in a context of protracted conflict. METHODS: This study is based on a qualitative approach in order to provide more in-depth information about health beliefs and behaviours, experiences and views of health professionals with regards to CVD secondary care. In total, 12 semi-structured interviews were conducted among doctors providing treatment to patients with CVD in secondary care settings. Interviews focused on health professionals' perspectives on risk factors and perceived barriers to behaviour change among known CVD patients receiving secondary care. Interviewees were also asked to propose possible actions that could be taken to overcome the identified barriers at both societal and individual patient levels. All interviews were digitally recorded, transcribed and analysed using thematic analysis. RESULTS: Study results confirmed our prior theory of the complex entanglement of socio-political, health system and individual-level factors with regards to CVD experience, health-seeking and treatment. Also confirmed was our assumption that it is crucial to understand experts' definitions and approaches to treatment in order to grasp their visions for appropriate and improved prevention and treatment options. In particular, study participants highlighted how political determinants, notably the detrimental impact of the Israeli occupation, and social determinants, directly and indirectly influence behavioural determinants due to physical and bureaucratic barriers to accessing health facilities, economic hardship and chronic stress. These stressors, in turn, were perceived as having a negative effect on individual behavioural risk factors including smoking, unhealthy diet and an increasingly sedentary lifestyle. Proposed solutions included more focused interventions from the Ministry of Health as well as surveillance, primary prevention and health promotion, and management to positively effect behaviour change in order to address the growing burden of CVD in the region. CONCLUSIONS: The study has highlighted medical professionals' perceptions of how structural and individual behavioural determinants influence their own and individual patient's abilities to manage cardiovascular risk factors in a setting affected by chronic conflict. Consequently, we propose that medical and social intervention strategies generally used to address CVD risk, be strategically adapted in order to be useful and effective in contexts of armed conflict. Specifically, we call for a solid understanding of the socio-political context and existing health services as well as health providers' and patients' health beliefs and related behaviours when developing future health options aimed at addressing CVD in the region. Moreover, for health provision to be effective as well as sustainable, attention needs to be given above all towards a solution for political change.

Dai, M., et al. (2021). "Analysis of the Evolution of Pandemic Influenza A(H1N1) Virus Neuraminidase Reveals Entanglement of Different Phenotypic Characteristics." mBio **12**(3).

The influenza A virus (IAV) neuraminidase (NA) is essential for virion release from cells and decoy receptors and an important target of antiviral drugs and antibodies. Adaptation to a new host sialome and escape from the host immune system are forces driving the selection of mutations in the NA gene. Phylogenetic analysis shows that until 2015, 16 amino acid substitutions in NA became fixed in the virus population after introduction in the human population of the pandemic IAV H1N1 (H1N1pdm09) in 2009. The accumulative effect of these substitutions, in the order in which they appeared, was analyzed using recombinant proteins and viruses in combination with different functional assays. The results indicate that NA activity did not evolve to a single optimum but rather fluctuated within a certain bandwidth. Furthermore, antigenic and enzymatic properties of NA were intertwined, with several residues affecting multiple properties. For example, the substitution K432E in the second sialic acid binding site, next to the catalytic site, was shown to affect catalytic activity, substrate specificity, and the pH optimum for maximum activity. This substitution also altered antigenicity of NA, which may explain its selection. We propose that the entanglement of NA phenotypes may be an important determining factor in the evolution of NA.IMPORTANCE Since its emergence in 2009, the pandemic H1N1 influenza A virus (IAV) has caused significant disease and mortality in humans. IAVs contain two envelope glycoproteins, the receptor-binding hemagglutinin (HA) and the receptor-destroying neuraminidase (NA). NA is essential for virion release from cells and decoy receptors, is an important target of antiviral drugs, and is increasingly being recognized as an important vaccine antigen. Not much is known, however, about the evolution of this protein upon the emergence of the novel pandemic H1N1 virus, with respect to its enzymatic activity and antigenicity. By reconstructing the evolutionary path of NA, we show that antigenic and enzymatic properties of NA are intertwined, with several residues affecting

multiple properties. Understanding the entanglement of NA phenotypes will lead to better comprehension of IAV evolution and may help the development of NA-based vaccines.

Dimond, R., et al. (2022). "Genetic testing and family entanglements." Soc Sci Med **298**: 114857.

The development of the 'new genetics' in the early 1990's opened up a new space which required some patients and families to understand and navigate genetic testing. The social science literature that has grown alongside the 'new genetics', now spanning more than thirty years, has continued to explore and question assumptions about attitudes and responses towards genetic technologies. In this article we highlight how individual experience of genetic disease and personal responses towards genetic technologies can only be understood by considering their context. We focus on the rich literature on family within sociology, science and technology studies, anthropology, and family studies, to explore the myriad ways in which family is implicated in the patient experience of genetic testing. We explore these connections by drawing on a set of interviews held with individuals who have undergone a predictive test for a genetic condition, including Huntington's Disease and breast cancer. Five themes were developed: family disclosure, family gatekeeping, going for testing, individual and collective communication practices, and receiving a negative test result. To conclude, we highlight how these connections might be considered through the lens of entanglement, explaining the complex mechanisms through which family and genetics are intimately entwined.

Dorocka-Bobkowska, B., et al. (2017). "Recent advances in tissue conditioners for prosthetic treatment: A review." Adv Clin Exp Med **26**(4): 723-728.

Tissue conditioners (TCs) are short-term soft liners, formed in situ from a mixture of a polymer powder and a liquid plasticizer. This article reviews the recent advances in the composition, functions, clinical use, gelation process, and physical properties of TCs and their effects on denture bases and oral mucosa. TCs are used to improve the fit and function of an ill-fitting denture. They can also be used to treat abused mucosal tissues underlying ill-fitting acrylic dentures as temporary expedients. TCs are recommended as provisional liners to maintain the fit of removable dentures and to prevent mechanical irritation from the denture. TCs may also be used to rehabilitate cancer patients. The polymer powder, used in the formulation of TCs generally consists of polyethyl methacrylate (PEMA) and the liquid plasticizer is ester-based in ethyl alcohol solution without an acrylic monomer. The plasticizers are low molecular weight aromatic esters. Mixing of the powder and liquid results in polymer chain entanglement and the formation of a coherent gel characterized by viscoelastic behavior appropriate to its intended clinical use. The loss of surface integrity and surface roughness of TCs are regarded as the main problems in the denture bearing oral mucosa conditions resulting in inflammation of oral mucosa of the denture-bearing area - denture stomatitis. TCs provide an even distribution of masticatory force, accurately modeling itself to the changes which occur during the healing of lesion of substrate and can act therapeutically by incorporating antifungal or antibacterial agents.

dos Santos, R. G., et al. (2010). "Relationship between fibropapillomatosis and environmental quality: a case study with Chelonia mydas off Brazil." Dis Aquat Organ **89**(1): 87-95.

We documented the presence of fibropapillomatosis (FP), a debilitating tumor-forming disease, in marine turtles in Espirito Santo Bay (Brazil) from March 2007 to April 2008, and assessed the value of a specific environmental index for predicting the prevalence of FP. Turtles were captured monthly with entanglement nets and scored for presence and severity of FP. For the assessment of habitat quality, we used the ecological evaluation index (EEI) based on benthic macrophytes. The FP-free control area was classified as good quality (EEI = 8) and the study area, with high FP prevalence, was classified as bad quality (EEI= 2). Prevalence of FP in the study area was 58.3% with an average of 40 tumors per individual, and prevalence varied positively with curved carapace length (CCL). No FP was seen in the control area. The number of turtles heavily afflicted (tumor score category 3) was 10 times larger than those lightly affected (tumor score category 1). Most tumors were found on or near the front and rear flippers; no oral tumors or internal tumors were found. At recapture, 41% of formerly tumor-free turtles revealed FP, often increasing in severity with time, and very few turtles showed signs of disease regression. From the results of this study we concluded that FP is particularly severe in Espirito Santo Bay. Future studies should focus on evaluating how widespread FP is in Brazil, whether prevalence is increasing or decreasing, and elucidating the pathology and pathogenesis of FP in sea turtles in Brazil.

Dykhuizen, E. C., et al. (2013). "BAF complexes facilitate decatenation of DNA by topoisomerase IIalpha." Nature **497**(7451): 624-627.

Recent exon-sequencing studies of human tumours have revealed that subunits of BAF (mammalian SWI/SNF) complexes are mutated in more than 20% of all human malignancies, but the mechanisms involved in tumour suppression are

unclear. BAF chromatin-remodelling complexes are polymorphic assemblies that use energy provided by ATP hydrolysis to regulate transcription through the control of chromatin structure and the placement of Polycomb repressive complex 2 (PRC2) across the genome. Several proteins dedicated to this multisubunit complex, including BRG1 (also known as SMARCA4) and BAF250a (also known as ARID1A), are mutated at frequencies similar to those of recognized tumour suppressors. In particular, the core ATPase BRG1 is mutated in 5-10% of childhood medulloblastomas and more than 15% of Burkitt's lymphomas. Here we show a previously unknown function of BAF complexes in decatenating newly replicated sister chromatids, a requirement for proper chromosome segregation during mitosis. We find that deletion of Brg1 in mouse cells, as well as the expression of BRG1 point mutants identified in human tumours, leads to anaphase bridge formation (in which sister chromatids are linked by catenated strands of DNA) and a G2/M-phase block characteristic of the decatenation checkpoint. Endogenous BAF complexes interact directly with endogenous topoisomerase IIalpha (TOP2A) through BAF250a and are required for the binding of TOP2A to approximately 12,000 sites across the genome. Our results demonstrate that TOP2A chromatin binding is dependent on the ATPase activity of BRG1, which is compromised in oncogenic BRG1 mutants. These studies indicate that the ability of TOP2A to prevent DNA entanglement at mitosis requires BAF complexes and suggest that this activity contributes to the role of BAF subunits as tumour suppressors.

Even Chorev, N. (2019). "Data ambiguity and clinical decision making: A qualitative case study of the use of predictive information technologies in a personalized cancer clinical trial." Health Informatics J **25**(3): 500-510.

Personalized medicine aims to tailor the treatment to the specific characteristics of the individual patient. In the process, physicians engage with multiple sources of data and information to decide on a personalized treatment. This article draws on a qualitative case study of a clinical trial testing a method for matching treatments for advanced cancer patients. Specialists in the trial used data and information processed by a specifically developed drug-efficacy predictive algorithm and other information artifacts to make personalized clinical decisions. While using high-resolution data in the trial was expected to provide a more accurate basis for action, sociomaterial engagements of oncologists with data and its representation by artifacts paradoxically hindered personalized clinical decisions. I contend that the engagement between human discretion, ambiguous data, and malleable artifacts in this non-standardized trial produced moments of contradiction within entanglement. Sociomaterial approaches should acknowledge such conflicts in further analyses of medical practice transitions.

Felix, S., et al. (2016). "Rapid eye movement sleep behaviour disorder symptomatic of a brain stem cavernoma." J Sleep Res **25**(2): 211-215.

A 75-year-old man complained of excessive daytime sleepiness (EDS), difficulty falling asleep and nocturnal agitation during sleep. Restless legs syndrome (RLS) was diagnosed and treated. Because of persistent EDS, snoring and nycturia, a nocturnal polysomnography (PSG) was performed. PSG showed high sleep fragmentation related to a moderate to severe obstructive sleep apnea syndrome. Continuous positive airway pressure treatment (CPAP) was proposed. Because of the persistence of abnormal nocturnal behaviours, characterized by screaming, punching and falling out of bed, a video-PSG with CPAP treatment was performed. The recording showed typical chin electromyography (EMG) activity increase associated with violent movements during rapid eye movement (REM) sleep, suggesting REM sleep behaviour disorders (RBD). Clinical neurological examination found no parkinsonian syndrome, no dysautonomic sign and no neurological focal sign. Dopamine transporter imaging [123I-FP-CIT single photon emission computed tomography (SPECT)] did not find any presynaptic dopaminergic pathways degeneration. Brain magnetic resonance imaging showed a vascular lesion suggestive of cavernoma located in the pons. The present case illustrates the complexity of sleep disturbance diagnosis with a possible entanglement of aetiologies responsible for nocturnal agitation, and confirms that an isolated pons cavernoma should be considered among the rare causes of RBD.

Garland, J. (2017). "Unravelling the complexity of signalling networks in cancer: A review of the increasing role for computational modelling." Crit Rev Oncol Hematol **117**: 73-113.

Cancer induction is a highly complex process involving hundreds of different inducers but whose eventual outcome is the same. Clearly, it is essential to understand how signalling pathways and networks generated by these inducers interact to regulate cell behaviour and create the cancer phenotype. While enormous strides have been made in identifying key networking profiles, the amount of data generated far exceeds our ability to understand how it all "fits together". The number of potential interactions is astronomically large and requires novel approaches and extreme computation methods to dissect them out. However, such methodologies have high intrinsic

mathematical and conceptual content which is difficult to follow. This review explains how computation modelling is progressively finding solutions and also revealing unexpected and unpredictable nano-scale molecular behaviours extremely relevant to how signalling and networking are coherently integrated. It is divided into linked sections illustrated by numerous figures from the literature describing different approaches and offering visual portrayals of networking and major conceptual advances in the field. First, the problem of signalling complexity and data collection is illustrated for only a small selection of known oncogenes. Next, new concepts from biophysics, molecular behaviours, kinetics, organisation at the nano level and predictive models are presented. These areas include: visual representations of networking, Energy Landscapes and energy transfer/dissemination (entropy); diffusion, percolation; molecular crowding; protein allostery; quinary structure and fractal distributions; energy management, metabolism and re-examination of the Warburg effect. The importance of unravelling complex network interactions is then illustrated for some widely-used drugs in cancer therapy whose interactions are very extensive. Finally, use of computational modelling to develop micro- and nano- functional models ("bottom-up" research) is highlighted. The review concludes that computational modelling is an essential part of cancer research and is vital to understanding network formation and molecular behaviours that are associated with it. Its role is increasingly essential because it is unravelling the huge complexity of cancer induction otherwise unattainable by any other approach.

Gatenby, R. and B. R. Frieden (2016). "Investigating Information Dynamics in Living Systems through the Structure and Function of Enzymes." PLoS One **11**(5): e0154867.

Enzymes are proteins that accelerate intracellular chemical reactions often by factors of 105-1012s-1. We propose the structure and function of enzymes represent the thermodynamic expression of heritable information encoded in DNA with post-translational modifications that reflect intra- and extra-cellular environmental inputs. The 3 dimensional shape of the protein, determined by the genetically-specified amino acid sequence and post translational modifications, permits geometric interactions with substrate molecules traditionally described by the key-lock best fit model. Here we apply Kullback-Leibler (K-L) divergence as metric of this geometric "fit" and the information content of the interactions. When the K-L 'distance' between interspersed substrate pn and enzyme rn positions is minimized, the information state, reaction probability, and reaction rate are maximized. The latter obeys the Arrhenius equation, which we show can be derived from the geometrical principle of minimum K-L distance. The derivation is first limited to optimum substrate positions for fixed sets of enzyme positions. However, maximally improving the key/lock fit, called 'induced fit,' requires both sets of positions to be varied optimally. We demonstrate this permits and is maximally efficient if the key and lock particles pn, rn are quantum entangled because the level of entanglement obeys the same minimized value of the Kullback-Leibler distance that occurs when all pn approximately rn. This implies interchanges pn right arrow over left arrow brn randomly taking place during a reaction successively improves key/lock fits, reducing the activation energy Ea and increasing the reaction rate k. Our results demonstrate the summation of heritable and environmental information that determines the enzyme spatial configuration, by decreasing the K-L divergence, is converted to thermodynamic work by reducing Ea and increasing k of intracellular reactions. Macroscopically, enzyme information increases the order in living systems, similar to the Maxwell demon gedanken, by selectively accelerating specific reaction thus generating both spatial and temporal concentration gradients.

Ge, S., et al. (2020). "Entanglement of biopsy needle with pre-existing breast marker clip-An unusual complication during ultrasound-guided breast rebiopsy." Breast J **26**(9): 1876-1878.

Geng, J., et al. (2013). "A general approach to prepare conjugated polymer dot embedded silica nanoparticles with a SiO2@CP@SiO2 structure for targeted HER2-positive cellular imaging." Nanoscale **5**(18): 8593-8601.

We report on a one-step synthesis of conjugated polymer (CP) embedded silica nanoparticles (NPs) with a SiO2@CP@SiO2 structure by combination of a precipitation method and a modified Stober approach. Four types of CPs are employed to demonstrate the versatility of the developed strategy, yielding fluorescent silica NPs with emission across the visible spectrum. Field emission transmission electron microscopy investigation reveals that the entanglement between hydrophobic CPs and the aminopropyl groups of 3-aminopropyl triethoxysilane contributes to the successful encapsulation of CPs into a silica matrix. The synthesized NPs exhibit excellent physical stability and good photostability. In addition, they have amine groups on surfaces, which benefit further conjugation for biological applications. Through reaction with a peptide (GGHAHFG) that is specific to the HER2 receptor, the synthesized NPs have been successfully applied for targeted cellular imaging of HER2-

overexpressed SKBR-3 breast cancer cells. Along with its high quantum yield and benign biocompatibility, the developed CP embedded silica NPs have great potential for applications in biological imaging.

Gheldof, A. and G. Berx (2013). "Cadherins and epithelial-to-mesenchymal transition." Prog Mol Biol Transl Sci **116**: 317-336.

Epithelial-mesenchymal transition (EMT) is a process whereby epithelial cells are transcriptionally reprogrammed, resulting in decreased adhesion and enhanced migration or invasion. EMT occurs during different stages of embryonic development, including gastrulation and neural crest cell delamination, and is induced by a panel of specific transcription factors. These factors comprise, among others, members of the Snail, ZEB, and Twist families, and are all known to modulate cadherin expression and, in particular, E-cadherin. By regulating expression of the cadherin family of proteins, EMT-inducing transcription factors dynamically modulate cell adhesion, allowing many developmental processes to take place. However, during cancer progression EMT can be utilized by cancer cells to contribute to malignancy. This is also reflected at the level of the cadherins, where the cadherin switch between E- and N-cadherins is a classical example seen in cancer-related EMT. In this chapter, we give a detailed overview of the entanglement between EMT-inducing transcription factors and cadherin modulation during embryonic development and cancer progression. We describe how classical cadherins such as E- and N-cadherins are regulated during EMT, as well as cadherin 7, -6B, and -11.

Golonka, R. M. and M. Vijay-Kumar (2021). "Atypical immunometabolism and metabolic reprogramming in liver cancer: Deciphering the role of gut microbiome." Adv Cancer Res **149**: 171-255.

Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer-related mortality worldwide. Much recent research has delved into understanding the underlying molecular mechanisms of HCC pathogenesis, which has revealed to be heterogenous and complex. Two major hallmarks of HCC include: (i) a hijacked immunometabolism and (ii) a reprogramming in metabolic processes. We posit that the gut microbiota is a third component in an entanglement triangle contributing to HCC progression. Besides metagenomic studies highlighting the diagnostic potential in the gut microbiota profile, recent research is pinpointing the gut microbiota as an instigator, not just a mere bystander, in HCC. In this chapter, we discuss mechanistic insights on atypical immunometabolism and metabolic reprogramming in HCC, including the examination of tumor-associated macrophages and neutrophils, tumor-infiltrating lymphocytes (e.g., T-cell exhaustion, regulatory T-cells, natural killer T-cells), the Warburg effect, rewiring of the tricarboxylic acid cycle, and glutamine addiction. We further discuss the potential involvement of the gut microbiota in these characteristics of hepatocarcinogenesis. An immediate highlight is that microbiota metabolites (e.g., short chain fatty acids, secondary bile acids) can impair anti-tumor responses, which aggravates HCC. Lastly, we describe the rising 'new era' of immunotherapies (e.g., immune checkpoint inhibitors, adoptive T-cell transfer) and discuss for the potential incorporation of gut microbiota targeted therapeutics (e.g., probiotics, fecal microbiota transplantation) to alleviate HCC. Altogether, this chapter invigorates for continuous research to decipher the role of gut microbiome in HCC from its influence on immunometabolism and metabolic reprogramming.

Gou, J., et al. (2017). "Improved tumor tissue penetration and tumor cell uptake achieved by delayed charge reversal nanoparticles." Acta Biomater **62**: 157-166.

The high affinity of positively charged nanoparticles to biological interfaces makes them easily taken up by tumor cells but limits their tumor permeation due to non-specific electrostatic interactions. In this study, polyion complex coated nanoparticles with different charge reversal profiles were developed to study the influence of charge reversal profile on tumor penetration. The system was constructed by polyion complex coating using micelles composed of poly (lysine)-b-polycaprolactone (PLys-b-PCL) as the cationic core and poly (glutamic acid)-g-methoxyl poly (ethylene glycol) (PGlu-g-mPEG) as the anionic coating material. Manipulation of charge reversal profile was achieved by controlling the polymer chain entanglement and electrostatic interaction in the polyion complex layer through glutaraldehyde-induced shell-crosslinking. The delayed charge reversal nanoparticles (CTCL30) could maintain negatively charged in pH 6.5 PBS for at least 2h and exhibit pH-responsive cytotoxicity and cellular uptake in an extended time scale. Compared with a faster charge reversal counterpart (CTCL70) with similar pharmacokinetic profile, CTCL30 showed deeper penetration, higher in vivo tumor cell uptake and stronger antitumor activity in vivo (tumor inhibition rate: 72.3% vs 60.2%, compared with CTCL70). These results indicate that the delayed charge reversal strategy could improve therapeutic effect via facilitating tumor penetration. STATEMENT OF SIGNIFICANCE: Here, the high tumor penetration capability of PEG-coated nanoparticles and the high cellular uptake of cationic nanoparticles were combined by a delayed charge reversal drug delivery

system. This drug delivery system was composed of a drug-loading cationic inner core and a polyion complex coating. Manipulation of charge reversal profile was realized by varying the crosslinking degree of the shell of the cationic inner core, through which changed the strength of the polyion complex layer. Nanoparticles with delayed charge reversal profile exhibited improved tumor penetration, in vivo tumor cell uptake and in vivo tumor growth inhibition effect although they have similar pharmacokinetic and biodistribution behaviors with their instant charge reversal counterpart.

Grignani, G., et al. (2020). "Delving into PARP inhibition from bench to bedside and back." Pharmacol Ther **206**: 107446.

With the ever-expanding therapeutic indications and ongoing clinical trials with Poly(adenosine diphosphate-ribose) Polymerase (PARP) inhibitors, it is of outmost importance to stop and rethink what we know and still do not know concerning one of the major revolutions in target therapies in the last decades. Indeed, many PARP inhibitors (PARPi) are able to bind multiple targets, with a plethora of potential interactions with cancer cell signaling, metabolism and the tumor microenvironment (TME). These interactions can mediate both response and resistance to PARPi, but also represent an opportunity for sequential and/or combinatorial therapies. Here we advocate a "look before you leap" approach in reviewing available clinical and preclinical evidence concerning PARPi, delving into this complex entanglement, trying to unravel the potential for innovative therapeutic strategies revolving on PARP inhibition.

Hamdy, S. and C. Nye (2019). "Comics and revolution as global public health intervention: The Case of Lissa." Glob Public Health: 1-21.

In this article, we discuss the inextricable entanglement of public health and political revolution, and why comics is a particularly amenable medium to explore how different people come to terms with illness and mortality against the backdrop of political, economic, and environmental crises. We discuss our process in creating a sequential comic narrative, Lissa, that portrays a working-class Egyptian family, informed by hundreds of interviews and ethnographic research in Egypt on the vulnerabilities that expose people to kidney and liver disease and the difficulties of accessing proper treatment. Lissa also draws on ethnographic research and interviews in the U.S. on a seemingly unrelated topic - the social and political calculus of managing genetic risk for breast and ovarian cancer within a commercial healthcare system. We draw out the similarities in bioethical dilemmas between these two disparate clinical realities by composing an unlikely friendship between two fictional characters: Anna, the daughter of an American oil company executive living in Cairo, who has a family history of breast cancer - and Layla, the daughter of the porter of Anna's apartment building, who grows to become a resolute physician struggling for better public health justice and rights in Egypt.

Hao, F. (2022). "Entanglement of methylation changes and cGAS-STING signaling in non-small-cell Lung Cancer." Comb Chem High Throughput Screen.

BACKGROUND: cGAS-STING signaling has been primarily discovered as an important DNA sensing machinery bridging between innate and adaptive immunity. Beyond its antiviral response, recent evidence expanded its complicated role to cancer therapy. METHODS: UALCAN, The TCGA Wander, GEPIA, SMART, TIMER, Kaplan-Meier plotter, TCGA Data and cBioPortal were utilized in the investigation. RESULTS: We evaluated the expression of four key molecules (MB21D1, TMEM173, TBK1, and IRF3) in cGAS-STING pathway and found that TMEM173 gene was significantly down-regulated in lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC). Not only immunostimulatory cells, but also regulatory T cells were triggered by the DNA sensing pathway. With gene enrichment analysis, we revealed that cell cycle and mechanotransduction/cytoskeleton signals were most closely connected with cGAS-STING signal alterations in non-small-cell lung cancer (NSCLC). cGAS-STING signaling was robustly correlated with methylation changes, especially histone H3K4 lysine demethylase KDM5s. Transient activation of cGAS-STING exerts tumor surveillance effect and inhibition of STING signaling co-opt elevated KDM5 demethylases may inadvertently worsen clinical outcomes. CONCLUSION: cGAS-STING signaling and KDM5 demethylases have the potential to be used as targets for evaluating an effective immune response in tumor microenvironment.

He, C., et al. (2022). "Histone demethylase IBM1-mediated meiocyte gene expression ensures meiotic chromosome synapsis and recombination." PLoS Genet **18**(2): e1010041.

Histone methylation and demethylation play important roles in plant growth and development, but the involvement of histone demethylation during meiosis is poorly understood. Here we show that disruption of Arabidopsis thaliana INCREASE IN BONSAI METHYLATION 1 (IBM1) causes incomplete synapsis, chromosome entanglement and reduction of recombination during meiosis, leading to sterility. Interestingly, these ibm1 meiotic defects are rescued by mutations in either SUVH4/KYP or CMT3.

Using transcriptomic analyses we show that mutation of IBM1 down-regulates thousands of genes expressed in meiocytes, and that expression of about 38% of these genes are restored to wild type levels in ibm1 cmt3 double mutants. Changes in the expression of 437 of these, including the ARABIDOPSIS MEI2-LIKE AML3-5 genes, are correlated with a significant reduction of gene body CHG methylation. Consistently, the aml3 aml4 aml5 triple have defects in synapsis and chromosome entanglement similar to ibm1. Genetic analysis shows that aml3 aml4 aml5 ibm1 quadruple mutants resembles the ibm1 single mutant. Strikingly, over expression of AML5 in ibm1 can partially rescue the ibm1 meiotic defects. Taken together, our results demonstrate that histone demethylase IBM1 is required for meiosis likely via coordinated regulation of meiocyte gene expression during meiosis.

Heung, M. and J. L. Koyner (2015). "Entanglement of sepsis, chronic kidney disease, and other comorbidities in patients who develop acute kidney injury." Semin Nephrol **35**(1): 23-37.

Acute kidney injury (AKI) is a common and severe complication for patients in the intensive care setting, often occurring in the setting of sepsis. Both sepsis and AKI are complex and heterogeneous syndromes with overlapping risk factors. Comorbidities - such as chronic kidney disease, diabetes mellitus, liver disease, cardiac disease and cancer - may contribute to the development of these syndromes and complicate their management. Recognition of the complex interplay between comorbid conditions, sepsis, and AKI is key to the successful management of these syndromes.

Hiesmayr, B. C. and P. Moskal (2019). "Witnessing Entanglement In Compton Scattering Processes Via Mutually Unbiased Bases." Sci Rep **9**(1): 8166.

We present a quantum information theoretic version of the Klein-Nishina formula. This formulation singles out the quantity, the a priori visibility, that quantifies the ability to deduce the polarisation property of single photons. The Kraus-type structure allows a straightforward generalisation to the multiphoton cases, relevant in the decay of positronium which is utilized e.g. for metabolic PET-imaging (Positron- Emission- Tomograph). Predicted by theory but never experimentally proven, the two- or three-photon states should be entangled. We provide an experimentally feasible method to witness entanglement for these processes via MUBs (Mutually Unbiased Bases), exploiting Bohr's complementarity. Last but not least we present explicit cases exemplifying the interrelation of geometry and entanglement including relations to its potentiality for teleportation schemes or Bell inequality violations or in future for detecting cancer in human beings.

Hubinont, C., et al. (2015). "Anomalies of the placenta and umbilical cord in twin gestations." Am J Obstet Gynecol **213**(4 Suppl): S91-S102.

The frequency of twin gestations has increased over the last few decades, mainly due to maternal age at childbearing, and the use of assisted reproductive technologies. Twins are at higher risk of aneuploidy, structural anomalies, and placental abnormalities. Some of the placental and umbilical cord abnormalities found in twin gestations are nonspecific and can be found in singleton gestations (ie, placenta previa, placental abruption, single umbilical artery, velamentous cord insertion, vasa previa, etc). However, other anomalies are unique to twin gestations, and are mainly associated with monochorionic twins-these include intraplacental anastomosis and cord entanglement. Most of these conditions can be diagnosed with ultrasound. An accurate and early diagnosis is important in the management of twin gestations. Determination of chorionicity, amnionicity, and the identification of placental anomalies are key issues for the adequate management of twin pregnancies. Pathologic placental examination after delivery can help in assessing the presence of placental and umbilical cord abnormalities, as well as providing information about chorionicity and gaining insight into the potential mechanisms of disease affecting twin gestations.

Ioannidou, E. (2017). "The Sex and Gender Intersection in Chronic Periodontitis." Front Public Health **5**: 189.

Periodontitis, a complex polymicrobial inflammatory disease, is a public health burden affecting more than 100 million people and being partially responsible for tooth loss. Interestingly, periodontitis has a documented higher prevalence in men as compared to women signifying a possible sex/gender entanglement in the disease pathogenesis. Although relevant evidence has treated sex/gender in a simplistic dichotomous manner, periodontitis may represent a complex inflammatory disease model, in which sex biology may interfere with gender social and behavioral constructs affecting disease clinical phenotype. Even when it became clear that experimental oral health research needed to incorporate gender (and/or sex) framework in the hypothesis, researchers overwhelmingly ignored it unless the research question was directly related to reproductive system or sex-specific cancer. With the recognition of gender medicine as an independent field of research, this study challenged the current notion regarding sex/gender roles in periodontal disease. We aimed to

develop the methodological and analytical framework with the recognition of sex/gender as important determinants of disease pathogenesis that require special attention. First, we aim to present relevant sex biologic evidence to understand the plausibility of the epidemiologic data. In periodontitis pathogenesis, sex dimorphism has been implicated in the disease etiology possibly affecting the bacterial component and the host immune response both in the innate and adaptive levels. With the clear distinction between sex and gender, gender oral health disparities have been explained by socioeconomic factors, cultural attitudes as well as access to preventive and regular care. Economic inequality and hardship for women have resulted in limited access to oral care. As a result, gender emerged as a complex socioeconomic and behavioral factor influencing oral health outcomes. Taken together, as disease phenotypic presentation is a multifactorial product of biology, behavior and the environment, sex dimorphism in immunity as well as gender socio-behavioral construct might play a role in the above model. Therefore, this paper will provide the conceptual framework and principles intergrading sex and gender within periodontal research in a complex biologic and socio-behavioral dimension.

Karpinska, A., et al. (2022). "Entanglement of polymer chains in hypertonic medium enhances the delivery of DNA and other biomacromolecules into cells." J Colloid Interface Sci **627**: 270-282.

HYPOTHESIS: Most experimental procedures applied in modern biology involve cargo delivering into cells. One of the ways to cargo introduction is osmotic-mediated intracellular vesicle swelling. However, its widespread use was hindered due to cargo size (<10 nm) and cell-type-related restrictions. We addressed the issue of the composition of colloidal loading solution to enhance the efficiency of cellular delivery. EXPERIMENTS: We examined the effectiveness of colloidal loading solutions of varied compositions, including various types and sizes of polymers building osmotic pressure. We used confocal imaging coupled with fluorescence correlation spectroscopy to evaluate the introduction of polymers, proteins, nanoparticles, and DNA plasmids (cargos of sizes 1-175 nm) to cells representing eight cell lines: cancer, normal, epithelial, and mesenchymal ones. FINDINGS: We found that cellular delivery effectiveness strongly correlates with the size and concentration of osmotic pressure building polymers and not with the high value of the osmotic pressure itself. We show that polymer solutions at the entangled regime of concentrations enhance the delivery of large biomacromolecules even of size 200 nm (DNA plasmids) into cells, including MDA-MB-231 cells - so far resistant to the osmotic procedure. We show that the colloid loading medium based on entangled polymer chains is a versatile cargo delivery tool for molecular biology.

Kim, H., et al. (2020). "BRC-mediated RNAi targeting of USE1 inhibits tumor growth in vitro and in vivo." Biomaterials **230**: 119630.

USE1 has been demonstrated to play crucial roles in the development and progression of human lung cancer. However, the antitumor efficacy of RNA interference (RNAi) targeting of USE1 has not yet been evaluated as a possible clinical application. We here synthesized USE1 targeting bubbled RNA-based cargo (BRC) composed of densely packed multimeric pre-siRNAs with specific Dicer cleavage sites to enable efficient siRNA release upon entry to target cells. The physical entanglement and continuous networking of RNAs via hybridization during enzymatic replication serve as a driving force for the self-assembly of BRCs. These molecules effectively suppressed the transcription of their target genes, leading to tumor growth suppression in vitro and in vivo. Moreover, their repeated intravenous administration efficiently inhibited the growth of A549 tumor xenografts. Based on these findings of a reduced cancer cell viability following a USE1 knockdown, we further explored cell cycle arrest and apoptosis pathways. The observed tumor cell growth suppression was found to be controlled by cell cycle arrest and apoptosis signals induced by the USE1 reduction. These results suggest that USE1 BRCs may have future clinical applications as an RNAi-based cancer therapy.

Kim, H. H., et al. (2010). "Stone extraction balloon-guided repeat self-expanding metal stent placement." World J Gastroenterol **16**(24): 3087-3090.

Self-expanding metal stent (SEMS) placement offers safe and effective palliation in patients with upper gastrointestinal obstruction due to a malignancy. Well described complications of SEMS placement include tumor growth, obstruction, and stent migration. SEMS occlusions are treated by SEMS redeployment, argon plasma coagulation application, balloon dilation, and surgical bypass. At our center, we usually place the second SEMS into the first SEMS if there is complete occlusion by the tumor. We discovered an unusual complication during SEMS redeployment. The guidewire passed through the mesh of the first SEMS and caused the second SEMS to become entangled with the first SEMS. This led to the distortion and malfunction of the second SEMS, which worsened the gastric outlet obstruction. For lowering the risk of entanglement, we studied stone extraction balloon-guided repeat SEMS placement. This is the first report of a SEMS entangled by the mesh of the first SEMS

and stone extraction balloon-guided repeat SEMS placement for lowering the risk of this complication.

Kim, H. S., et al. (2009). "An acetylated form of histone H2A.Z regulates chromosome architecture in Schizosaccharomyces pombe." Nat Struct Mol Biol **16**(12): 1286-1293.

Histone variant H2A.Z has a conserved role in genome stability, although it remains unclear how this is mediated. Here we demonstrate that the fission yeast Swr1 ATPase inserts H2A.Z (Pht1) into chromatin and Kat5 acetyltransferase (Mst1) acetylates it. Deletion or an unacetylatable mutation of Pht1 leads to genome instability, primarily caused by chromosome entanglement and breakage at anaphase. This leads to the loss of telomere-proximal markers, though telomere protection and repeat length are unaffected by the absence of Pht1. Strikingly, the chromosome entanglement in pht1Delta anaphase cells can be rescued by forcing chromosome condensation before anaphase onset. We show that the condensin complex, required for the maintenance of anaphase chromosome condensation, prematurely dissociates from chromatin in the absence of Pht1. This and other findings suggest an important role for H2A.Z in the architecture of anaphase chromosomes.

Kinney, N., et al. (2020). "Crossing complexity of space-filling curves reveals entanglement of S-phase DNA." PLoS One **15**(8): e0238322.

Space-filling curves have been used for decades to study the folding principles of globular proteins, compact polymers, and chromatin. Formally, space-filling curves trace a single circuit through a set of points (x,y,z); informally, they correspond to a polymer melt. Although not quite a melt, the folding principles of Human chromatin are likened to the Hilbert curve: a type of space-filling curve. Hilbert-like curves in general make biologically compelling models of chromatin; in particular, they lack knots which facilitates chromatin folding, unfolding, and easy access to genes. Knot complexity has been intensely studied with the aid of Alexander polynomials; however, the approach does not generalize well to cases of more than one chromosome. Crossing complexity is an understudied alternative better suited for quantifying entanglement between chromosomes. Do Hilbert-like configurations limit crossing complexity between chromosomes? How does crossing complexity for Hilbert-like configurations compare to equilibrium configurations? To address these questions, we extend the Mansfield algorithm to enable sampling of Hilbert-like space filling curves on a simple cubic lattice. We use the extended algorithm to generate equilibrium, intermediate, and Hilbert-like configurational ensembles and compute crossing complexity between curves (chromosomes) in each configurational snapshot. Our main results are twofold: (a) Hilbert-like configurations limit entanglement between chromosomes and (b) Hilbert-like configurations do not limit entanglement in a model of S-phase DNA. Our second result is particularly surprising yet easily rationalized with a geometric argument. We explore ergodicity of the extended algorithm and discuss our results in the context of more sophisticated models of chromatin.

Kirchberg, F. F., et al. (2017). "Metabolomics reveals an entanglement of fasting leptin concentrations with fatty acid oxidation and gluconeogenesis in healthy children." PLoS One **12**(8): e0183185.

BACKGROUND: Leptin and adiponectin communicate with organ systems in order to regulate energetic and metabolic homeostasis. Their different points of action have been well characterized; however, no study has investigated their interrelationship with the metabolism at the molecular level in vivo. OBJECTIVE: To examine the associations of leptin and adiponectin with the metabolic profile reflecting the intercellular and interorgan communication as well as activated metabolic pathways. PATIENTS/METHODS: We measured plasma concentrations of leptin, adiponectin, and insulin along with concentrations of 196 metabolites in 400 healthy, fasting 8-years old German children who participated in the German Ulm Birth Cohort Study (UBCS). Using multiple linear mixed models, we evaluated the associations between hormones and metabolites. RESULTS: Leptin levels increased exponentially with increasing BMI. Leptin was furthermore strongly associated with alanine and aspartate (Bonferroni corrected P[PBF] = 5.7x10-8 and 1.7x10-6, respectively), and negatively associated to the sum of the non-esterified fatty acids (NEFA) and the sum of the long-chain acylcarnitines C12-C18 (PBF = 0.009 and 0.0001, respectively). Insulin showed a similar association pattern, although the associations were less strong than for leptin. Adiponectin was neither related to BMI nor to any metabolite. CONCLUSION: Although children were presumably metabolically similar, we found strong associations of insulin and leptin with the metabolite profile. High alanine concentrations and the lower concentrations of NEFA in children with high fasting leptin concentrations might arise from an increased gluconeogenesis and from the disinhibiting effect of leptin on the carnitine-palmitoyltransferase-1, respectively. As insulin had the same trend towards these associations, both hormones seem to be related to processes that provide the body with energy in fasting state.

Kirmse, R., et al. (2011). "Interdependency of cell adhesion, force generation and extracellular proteolysis in matrix remodeling." J Cell Sci **124**(Pt 11): 1857-1866.

It is becoming increasingly evident that the micromechanics of cells and their environment determine cell fate and function as much as soluble molecular factors do. We hypothesized that extracellular matrix proteolysis by membrane type 1 matrix metalloproteinase (MT1-MMP) depends on adhesion, force generation and rigidity sensing of the cell. Melanoma cells (MV3 clone) stably transfected with MT1-MMP, or the empty vector as a control, served as the model system. alpha2beta1 integrins (cell adhesion), actin and myosin II (force generation and rigidity sensing) were blocked by their corresponding inhibitors (alpha2beta1 integrin antibodies, Cytochalasin D, blebbistatin). A novel, anisotropic matrix array of parallel, fluorescently labeled collagen-I fibrils was used. Cleavage and bundling of the collagen-I fibrils, and spreading and durotaxis of the cells on this matrix array could be readily discerned and quantified by a combined set-up for fluorescence and atomic force microscopy. In short, expression of the protease resulted in the generation of structural matrix defects, clearly indicated by gaps in the collagen lattice and loose fiber bundles. This key feature of matrix remodeling depended essentially on the functionality of alpha2beta1 integrin, the actin filament network and myosin II motor activity. Interference with any of these negatively impacted matrix cleavage and three-dimensional matrix entanglement of cells.

Kumar, S., et al. (2016). "Possible existence of optical communication channels in the brain." Sci Rep **6**: 36508.

Given that many fundamental questions in neuroscience are still open, it seems pertinent to explore whether the brain might use other physical modalities than the ones that have been discovered so far. In particular it is well established that neurons can emit photons, which prompts the question whether these biophotons could serve as signals between neurons, in addition to the well-known electro-chemical signals. For such communication to be targeted, the photons would need to travel in waveguides. Here we show, based on detailed theoretical modeling, that myelinated axons could serve as photonic waveguides, taking into account realistic optical imperfections. We propose experiments, both in vivo and in vitro, to test our hypothesis. We discuss the implications of our results, including the question whether photons could mediate long-range quantum entanglement in the brain.

Kumela, A. G., et al. (2022). "Noble classical and quantum approach to model the optical properties of metallic nanoparticles to enhance the sensitivity of optoplasmonic sensors." RSC Adv **12**(25): 16203-16214.

The bright light obtained from the quantum principle has a key role in the construction of optical sensors. Yet, theoretical and experimental work highlights the challenges of overcoming the high cost and low efficiency of such sensors. Therefore, we report a metallic nanoparticle-based metasurface plasmons polariton using quantum and classical models. We have investigated the material properties, absorption cross-section, scattering cross-section, and efficiency of the classical model. By quantizing light-matter interaction, the quantum features of light - degree of squeezing, correlation, and entanglement are quantified numerically and computationally. In addition, we note the penetration depth and propagation length from a hybrid model in order to enhance the optoplasmonic sensor performance for imaging, diagnosing, and early perception of cancer cells with label-free, direct, and real-time detection. Our study findings conclude that the frequency of incident light, size, shape, and type of nanoparticles has a significant impact on the optical properties of metallic nanoparticles and the nonlinear optical properties of metallic nanoparticles are dynamic, enhancing the sensitivity of the optoplasmonic sensor. Moreover, the resulting bright light shows the systematic potential for further medical image processing.

Kuzmin, E., et al. (2022). "Retention of duplicated genes in evolution." Trends Genet **38**(1): 59-72.

Gene duplication is a prevalent phenomenon across the tree of life. The processes that lead to the retention of duplicated genes are not well understood. Functional genomics approaches in model organisms, such as yeast, provide useful tools to test the mechanisms underlying retention with functional redundancy and divergence of duplicated genes, including fates associated with neofunctionalization, subfunctionalization, back-up compensation, and dosage amplification. Duplicated genes may also be retained as a consequence of structural and functional entanglement. Advances in human gene editing have enabled the interrogation of duplicated genes in the human genome, providing new tools to evaluate the relative contributions of each of these factors to duplicate gene retention and the evolution of genome structure.

Kuzmin, E., et al. (2020). "Exploring whole-genome duplicate gene retention with complex genetic interaction analysis." Science **368**(6498).

Whole-genome duplication has played a central role in the genome evolution of many organisms, including the human genome. Most duplicated genes are eliminated, and factors that influence the retention of persisting duplicates remain poorly understood. We describe a systematic complex genetic interaction analysis with yeast paralogs derived from the whole-genome duplication event. Mapping of digenic interactions for a deletion mutant of each paralog, and of trigenic interactions for the double mutant, provides insight into their roles and a quantitative measure of their functional redundancy. Trigenic interaction analysis distinguishes two classes of paralogs: a more functionally divergent subset and another that retained more functional overlap. Gene feature analysis and modeling suggest that evolutionary trajectories of duplicated genes are dictated by combined functional and structural entanglement factors.

La Torre, G. and A. Federici (2017). "How to not detonate the bomb: the case of the Italian National Health Service." Public Health **153**: 178-180.

Why is Italy one of the world's highest ranked for ability and quality of healthcare in relationship to the resources invested? The last decade has been characterized by many Italian Regions with Recovery Plans, whose main focus was on short-term issues with a high impact on healthcare costs. Italy is now leaving this phase and at the regional level there will be an increase of new hirings in the healthcare sectors, as stated by the Ministry of Health. There is a large amount of scientific literature that supports the role of factors such as lifestyles, diet and genetics as the base of population health. The success of the Italian National Health Service (INHS) function is rooted in the ability of a system to adapt to evolving situations, but it is also important to ensure a mechanism of positive feedback correction. In the future, INHS will require a new set of reforms, like the redefinition of structures and mechanisms of governance, the implementation of strategic plans that conjugate better clinical and financial issues. In this context, Health Data Entanglement could be an option to improve the effectiveness of the health governance system in order to develop better quality of care. In Public Health several criticisms could detonate the bomb, and above all the decreasing levels of primary prevention in the fight to obesity (promoting the Mediterranean Diet and physical activity), to smoking and alcohol consumption, as well as to infectious diseases (promoting high vaccination rates). Secondary prevention is also key to this function as a practical experience of re-engineering of the public expense, giving much attention to what works in terms of cost effectiveness, and in particular to cancer screening.

Lancia, C., et al. (2019). "Marginal structural models with dose-delay joint-exposure for assessing variations to chemotherapy intensity." Stat Methods Med Res **28**(9): 2787-2801.

Marginal structural models are causal models designed to adjust for time-dependent confounders in observational studies with dynamically adjusted treatments. They are robust tools to assess causality in complex longitudinal data. In this paper, a marginal structural model is proposed with an innovative dose-delay joint-exposure model for Inverse-Probability-of-Treatment Weighted estimation of the causal effect of alterations to the therapy intensity. The model is motivated by a precise clinical question concerning the possibility of reducing dosages in a regimen. It is applied to data from a randomised trial of chemotherapy in osteosarcoma, an aggressive primary bone-tumour. Chemotherapy data are complex because their longitudinal nature encompasses many clinical details like composition and organisation of multi-drug regimens, or dynamical therapy adjustments. This manuscript focuses on the clinical dynamical process of adjusting the therapy according to the patient's toxicity history, and the causal effect on the outcome of interest of such therapy modifications. Depending on patients' toxicity levels, variations to therapy intensity may be achieved by physicians through the allocation of either a reduction or a delay of the next planned dose. Thus, a negative feedback is present between exposure to cytotoxic agents and toxicity levels, which acts as time-dependent confounders. The construction of the model is illustrated highlighting the high complexity and entanglement of chemotherapy data. Built to address dosage reductions, the model also shows that delays in therapy administration should be avoided. The last aspect makes sense from the cytological point of view, but it is seldom addressed in the literature.

Laryionava, K., et al. (2018). ""Rather one more chemo than one less...": Oncologists and Oncology Nurses' Reasons for Aggressive Treatment of Young Adults with Advanced Cancer." Oncologist **23**(2): 256-262.

BACKGROUND: Empirical research demonstrates that there is a tendency to administer tumor-directed therapy to patients with advanced cancer close to death, especially if they are young. The aim of this qualitative study was to understand oncologists' treatment decisions and oncology nurses' perception of these decisions in young adult patients and to investigate the extent to which young age was a factor in cancer treatment decisions. MATERIALS AND METHODS: We conducted 29 face-to-face interviews with oncologists and oncology nurses at the Department of Hematology and Oncology at the

University Hospital in Munich, Germany. The interviews were analyzed according to the grounded theory approach. RESULTS: Oncologists and nurses reported that decisions about limiting cancer treatment with young adult patients are the most challenging and stressful in clinical practice. Apart from using young age as a proxy for patient's medical fitness, oncologists' decisions in favor of more aggressive treatment of younger patients were mainly guided by ethical reasons such as patient preferences and the perceptions of injustice associated with dying at a young age, as well as by psychological reasons, such as identification and emotional entanglement. CONCLUSION: "Struggling" together with the patient against the injustice of dying young for a longer lifetime is an important factor driving aggressive treatment in young adult patients. However, oncologists might run a risk of neglecting other ethical aspects, such as a principle of nonmaleficence, that might even result in life-shortening adverse events. IMPLICATIONS FOR PRACTICE: This study identifies two ethical and one psychological reasons for patients' overtreatment: 1) patients' preference for further treatment; 2) oncologists' perception of un-fairness of dying young; and 3) identification and emotional entanglement with patient. These findings emphasize the need for oncologists' awareness of the reasons guiding their treatment decisions - a sole focus on patients' preferences and on the fighting against the unfairness of dying young might lead to neglecting obligations of non-maleficence. Self-reflection, the balance of empathy and professional distance as well as timely end of life discussions and involvement of psycho-oncologists are needed in the care of young cancer patients.

Lavergne De, H. and et al. (1949). "Complex clinical history; entanglement of a B. perfringens infection and a Krukenberg tumor." Rev Med Nancy **74**: 228-235.

Lee, C. M., et al. (2019). "Topoisomerase III Acts at the Replication Fork To Remove Precatenanes." J Bacteriol **201**(7).

The role of DNA topoisomerase III (Topo III) in bacterial cells has proven elusive. Whereas eukaryotic Top IIIalpha homologs are clearly involved with homologs of the bacterial DNA helicase RecQ in unraveling double Holliday junctions, preventing crossover exchange of genetic information at unscheduled recombination intermediates, and Top IIIbeta homologs have been shown to be involved in regulation of various mRNAs involved in neuronal function, there is little evidence for similar reactions in bacteria. Instead, most data point to Topo III playing a role supplemental to that of topoisomerase IV in unlinking daughter chromosomes during DNA replication. In support of this model, we show that Escherichia coli Topo III associates with the replication fork in vivo (likely via interactions with the single-stranded DNA-binding protein and the beta clamp-loading DnaX complex of the DNA polymerase III holoenzyme), that the DnaX complex stimulates the ability of Topo III to unlink both catenated and precatenated DNA rings, and that DeltatopB cells show delayed and disorganized nucleoid segregation compared to that of wild-type cells. These data argue that Topo III normally assists topoisomerase IV in chromosome decatenation by removing excess positive topological linkages at or near the replication fork as they are converted into precatenanes.IMPORTANCE Topological entanglement between daughter chromosomes has to be reduced to exactly zero every time an E. coli cell divides. The enzymatic agents that accomplish this task are the topoisomerases. E. coli possesses four topoisomerases. It has been thought that topoisomerase IV is primarily responsible for unlinking the daughter chromosomes during DNA replication. We show here that topoisomerase III also plays a role in this process and is specifically localized to the replisome, the multiprotein machine that duplicates the cell's genome, in order to do so.

Leonetti, J. P., et al. (1990). "Meningiomas of the lateral skull base: neurotologic manifestations and patterns of recurrence." Otolaryngol Head Neck Surg **103**(6): 972-980.

The eradication of basicranial meningiomas by traditional surgical techniques is often hindered by neoplastic entanglement with critical neurovascular structures. Apparent, complete tumor resection is frequently followed by extensive, yet clinically silent, recurrent disease with local infiltration of bone, cranial nerves, and brain. Fifty-five cases of sphenoid wing or parasellar meningioma were analyzed to identify clinical manifestations suggestive of early tumor recurrence. Regrowth patterns were then defined according to preoperative radiographic and intraoperative surgical findings. Medial tumor regrowth, involving the cavernous sinus, caused neurapraxia of cranial nerves III, IV, or VI, with associated diplopia or ophthalmoplegia. Inferior (caudal) regrowth of disease involved the infratemporal fossa, pterygomaxillary space, or paranasal sinuses by bony erosion of the middle cranial fossa floor or through natural anatomic foramina and fissures. Such inferior extension was manifested clinically by facial hypesthesia, trismus, and referred otalgia caused by trigeminal nerve involvement and by autophony or serous otitis media related to eustachian tube obstruction. Posterior tumor regrowth occurred along the petrous bone and horizontal carotid canal, resulting in internal auditory meatus erosion and

cerebellopontine angle extension with associated tinnitus, hearing loss, unsteadiness, and occasional facial twitching. While the clinical and radiographic evaluations of any patient with a suspected recurrent basicranial meningioma are critical in planning the method and magnitude of reoperation, an understanding of potential recurrence patterns can be used in devising more extensive, combined approaches that may allow complete tumor extirpation at the initial surgical intervention.

Liu, Y., et al. (2018). "Systemic siRNA delivery to tumors by cell-penetrating alpha-helical polypeptide-based metastable nanoparticles." Nanoscale **10**(32): 15339-15349.

Systemic, non-viral siRNA delivery for cancer treatment is mainly achieved via condensation by cationic materials (e.g., lipids and cationic polymers), which nevertheless, suffers from poor serum stability, non-specific tissue interaction, and unsatisfactory membrane activity against efficient in vivo gene knockdown. Here, we report the design of a metastable, cancer-targeting siRNA delivery system based on two functional polymers, PVBLG-8, a cationic, helical cell-penetrating polypeptide, and poly(l-glutamic acid) (PLG), an anionic random-coiled polypeptide. PVBLG-8 with rigid, linear structure showed weak siRNA condensation capability, and PLG with flexible chains was incorporated as a stabilizer which provided sufficient molecular entanglement with PVBLG-8 to encapsulate the siRNA within the polymeric network. The obtained PVBLG-8/siRNA/PLG nanoparticles (PSP NPs) with positive charges were sequentially coated with additional amount of PLG, which reversed the surface charge from positive to negative to yield the metastable PVBLG-8/siRNA/PLG@PLG (PSPP) NPs. The PSPP NPs featured desired serum stability during circulation to enhance tumor accumulation via the enhanced permeability and retention (EPR) effect. Upon acidification in the tumor extracellular microenvironment and intracellular endosomes, the partial protonation of PLG on PSPP NPs surface would lead to dissociation of PLG coating from NPs, exposure of the highly membrane-active PVBLG-8, and surface charge reversal from negative to positive, which subsequently promoted tumor penetration, selective cancer cell internalization, and efficient endolysosomal escape. When siRNA against epidermal growth factor receptor (EGFR) was encapsulated, the PSPP NPs showed excellent tumor penetration capability, tumor cell uptake level, EGFR silencing efficiency, and tumor growth inhibition efficacy in U-87 MG glioblastoma tumor spheroids in vitro and in xenograft tumor-bearing mice in vivo, outperforming the PSP NPs and several commercial reagents such as Lipofectamine 2000 and poly(l-lysine) (PLL). This study therefore demonstrates a facile and unique design approach of metastable and charge reversal NPs, which overcomes multiple biological barriers against systemic siRNA delivery toward anti-cancer treatment.

Maestre-Reyna, M., et al. (2022). "Serial crystallography captures dynamic control of sequential electron and proton transfer events in a flavoenzyme." Nat Chem **14**(6): 677-685.

Flavin coenzymes are universally found in biological redox reactions. DNA photolyases, with their flavin chromophore (FAD), utilize blue light for DNA repair and photoreduction. The latter process involves two single-electron transfers to FAD with an intermittent protonation step to prime the enzyme active for DNA repair. Here we use time-resolved serial femtosecond X-ray crystallography to describe how light-driven electron transfers trigger subsequent nanosecond-to-microsecond entanglement between FAD and its Asn/Arg-Asp redox sensor triad. We found that this key feature within the photolyase-cryptochrome family regulates FAD re-hybridization and protonation. After first electron transfer, the FAD(*-) isoalloxazine ring twists strongly when the arginine closes in to stabilize the negative charge. Subsequent breakage of the arginine-aspartate salt bridge allows proton transfer from arginine to FAD(*-). Our molecular videos demonstrate how the protein environment of redox cofactors organizes multiple electron/proton transfer events in an ordered fashion, which could be applicable to other redox systems such as photosynthesis.

Mahato, N. K. (2010). "Obliterated, fibrous omphalo-mesenteric duct in an adult without Meckel's diverticulum or vitelline cyst." Rom J Morphol Embryol **51**(1): 195-197.

Vitello-intestinal [omphalo-mesenteric duct (OMD)] connects the developing mid-gut to the primitive yolk sac, provides nutrition to the embryo and remains patent and connected to the intestines until the fifth to ninth week of gestational period. Varied remnants of the vitello-intestinal duct have been reported. The present case-report describes a completely obliterated fibrous remnant of the duct. The remnant presented as a thick cord extending from the umbilicus towards the terminal part of the ileum and beyond. The terminal part of the cord showed a few ramifications that ended in the mesentery. This embryological entity was not found to be associated with any other anomaly usually related to non-regression of the vitello-intestinal duct. Though very rare, the occurrence of such innocuous band of fibrous cord across the abdominal cavity may cause entanglement of intestinal loops around it. Possibility of such a situation should be suspected in an acute

abdominal condition. The structure reported in this study might not be detected by investigations used to uncover common anomalies of patent vitello-intestinal ducts.

Miller, K. M. and J. P. Cooper (2003). "The telomere protein Taz1 is required to prevent and repair genomic DNA breaks." Mol Cell **11**(2): 303-313.

One fundamental function of telomeres is to prevent the ends of chromosomes from being sensed and treated as DNA damage. Here we present evidence for additional roles of telomeres in promoting proper chromosome segregation and DNA repair. We find that the fission yeast telomere protein Taz1p is required for cell cycle progression at 20 degrees C, a temperature at which taz1Delta cells exhibit a G(2)/M DNA damage checkpoint delay, chromosome missegregation, and DNA double-strand breaks (DSBs). Spindle assembly checkpoint components and a checkpoint-independent function of Rad3p are required for taz1Delta cells to survive at 20 degrees C. Disruption of topoisomerase II activity suppresses the cold sensitivity of taz1Delta cells, suggesting a scenario in which telomeric entanglement is the primary defect. Furthermore, hypersensitivity to treatments that induce DSBs suggests that Taz1p is involved in DSB repair. Our observations imply roles for Taz1p-containing telomeres in preventing and repairing DNA breaks throughout the genome.

Mizuuchi, H. and E. Akashi (1980). "[Surface ultrastructure of the human uterine exfoliated endometrial cells--comparative studies of the same cell by light microscopy and scanning electron microscopy (author's transl)]." Nihon Sanka Fujinka Gakkai Zasshi **32**(10): 1557-1566.

The preparations for observations of the same cells by light microscopy (LM) and scanning electron microscopy (SEM) were examined and the exfoliated endometrial cells of the uterus obtained by the newly introduced brush and cannula was evaluated. 1) The degree of shrinkage of the area was not significant between the air drying method and critical point drying method. In the air drying group, adhesion, entanglement and disappearance of microvilli (mv) and the adhesion of cilia, and the collapse of cells were noted morphologically. 2) Papanicolaou stain had no effect on the degree of shrinkage of the area and the shape of cilia or mv. 3) When the samples were transferred from ethanol to critical point drying, without immersion in isoamyl acetate, artifacts appeared in small granulated form. 4) The menopausal phase was divided into two groups which showed a shift of the maturation Index (MI) to center and had a slender mv and the other group which showed a shift to the left and granular mv. The nether surface of the cells showed a wrinkled and irregular undulations and did not show cilia or mv. 5) In adenomatous hyperplasia, the ratio of ciliated cell to no ciliated cell was four to one. It was two to one in cystic glandular hyperplasia. 6) The dense and short mv were observed in well-differentiated adenocarcinoma and poorly-differentiated adenocarcinoma showed neither mv nor cilia. Morphologic changes of mv and cilia in carcinomatous change of uterine endometrium commenced with a decrease in cilia, shifted to the shortening and disappearance disappearance of mv.

Moloudizargari, M., et al. (2022). "Targeting Hippo signaling pathway by phytochemicals in cancer therapy." Semin Cancer Biol **80**: 183-194.

The current era of cancer research has been continuously advancing upon identifying novel aspects of tumorigenesis and the principal mechanisms behind the unleashed proliferation, invasion, drug resistance and immortality of cancer cells in hopes of exploiting these findings to achieve a more effective treatment for cancer. In pursuit of this goal, the identification of the first components of an extremely important regulatory pathway in Drosophila melanogaster that largely determines cell fate during the developmental stages, ended up in the discovery of the highly sophisticated Hippo signaling cascade. Soon after, it was revealed that deregulation of the components of this pathway either via mutations or through epigenetic alterations can be observed in a vast variety of tumors and these alterations greatly contribute to the neoplastic transformation of cells, their survival, growth and resistance to therapy. As more hidden aspects of this pathway such as its widespread entanglement with other major cellular signaling pathways are continuously being uncovered, many researchers have sought over the past decade to find ways of therapeutic interventions targeting the major components of the Hippo cascade. To date, various approaches such as the use of exogenous targeting miRNAs and different molecular inhibitors have been recruited herein, among which naturally occurring compounds have shown a great promise. On such a basis, in the present work we review the current understanding of Hippo pathway and the most recent evidence on targeting its components using natural plant-derived phytochemicals.

Mombach, J. C., et al. (2008). "On the absence of mutations in nucleotide excision repair genes in sporadic solid tumors." Genet Mol Res **7**(1): 152-160.

In general, stochastic tumors show genomic instability associated with the proliferation of DNA point mutations, that is, a mutator phenotype. This feature cannot be explained by a dysfunctional mismatch repair alone, and indicates that nucleotide

excision repair (NER) and/or base excision repair should be suppressed. However, mutations in NER genes are not causally implicated in the oncogenesis of sporadic solid tumors, according to the Cancer Gene Census at http://www.sanger.ac.uk/genetics/CGP/Census/. This brings up an apparent paradox: how to explain the recurrent non-existence in NER genes of somatic mutations causally related to cancer? In a recent study, we have shown that the origin of point mutations in cancer cell genomes can be explained by a structurally conserved NER with a functional disorder generated from its entanglement with a disabled apoptosis gene network. In the present study, we further characterize NER gene network properties and show that it has a highly connected architecture. This feature suggests that the absence of mutations in NER genes in sporadic solid tumors is a result of their participation in many essential cellular functions.

Mongiat-Artus, P., et al. (2019). "[Onco-urology of the aging patient: Epidemiological and biological aspects]." Prog Urol **29**(14): 797-806.

PURPOSE: First, to present the epidemiological data of aging and of cancers and to describe the respectives expected evolutions. Second, to present biological and genetic data on aging and on the relationships between aging and oncogenesis. METHOD: Bibliographic search from the Medline bibliographic database (NLM Pubmed tool) and Embase, as well as from the web sites of geriatric scientific societies, the United Nations, the World Bank, the World Health Organization, the Institut National du Cancer and the Ligue Contre le Cancer from the following keywords: aging, elderly, cancer, epidemiology, biology, genetics. RESULTS: The entire world population is aging very significantly and very rapidly. In France, new cases of cancer are diagnosed in 62.4% of cases in patients over 65 and in 11.5% of cases in patients over 80 years. Cancer mortality occurs in 75.3% of cases in patients over 65 years of age and in 24.8% of cases in patients over 80 years of age. Cancer-specific mortality is consistently higher in patients older than 75 years compared to younger patients; this reflects, among other things, an age discrimination which is called agism. It has been established that cellular aging is marked by 9 major families of biological and genomic abnormalities. Biological aging and oncogenesis are intertwined with increasingly well established relationships. They are both the product of natural selection and they are found in all species with both renewal tissues and a distinction between germinal tissue and somatic tissue. CONCLUSION: Epidemiological data predict that oncology, including urological oncology, is becoming very predominantly geriatric oncology; it is critical and urgent that society be prepared for it and that every care-giver be prepared, that is, be specifically trained. Biological and genetic data argue for a great entanglement between aging and oncogenesis; research in each of these areas should be reconciled for mutual benefit.

Muralikrishnan, G., et al. (2001). "Dual role of vitamin C on lipid profile and combined application of cyclophosphamide, methotrexate and 5-fluorouracil treatment in fibrosarcoma-bearing rats." Cancer Lett **169**(2): 115-120.

Combined application of cyclophosphamide, methotrexate, 5-fluorouracil (CMF) has been followed in the treatment of breast cancer. The combined effect of CMF and vitamin C on plasma lipid and lipoprotein is important, since vitamin C encumbers the lipid abnormalities instigated by CMF. Hence, the study was launched to appraise the salubrious role of vitamin C in CMF administered fibrosarcoma-bearing rats. Fibrosarcoma cell line-induced rats were treated with CMF (cyclophosphamide 10 mg/kg b.w., methotrexate 1 mg/kg b.w., 5-fluorouracil 10 mg/kg b.w. and vitamin C 200 mg/kg b.w.) individually and in combination for 120 days. The concentration of plasma lipids and lipoprotein was determined in control and experimental rats. The untreated as well as CMF administered fibrosarcoma-bearing rats divulged significantly in increased levels of plasma total cholesterol, triglycerides, phospholipids, very low density lipoprotein (VLDL) and low density lipoprotein (LDL) cholesterol, as compared with their respective control animals. Whereas ester and high density lipoprotein (HDL) cholesterol levels exhibited a marked decrease in these animals. However, these lipid abnormalities were found to be moderated by co-administration of vitamin C. These results suggested that some clinical entanglement of CMF was refrained by co-administration of vitamin C in tumor stress condition.

Nagashima, T., et al. (2018). "Thoracoscopic right S6 sleeve segmentectomy for squamous-cell carcinoma arising from the B6 central bronchus." J Thorac Dis **10**(2): 1077-1080.

We describe a patient with low respiratory function who underwent thoracoscopic sleeve segmentectomy to preserve lung function as much as possible. The patient had already used home oxygen therapy because of chronic obstructive lung disease. There was a squamous-cell carcinoma at inlet of right B6 bronchus, and cT1aN0M0 disease was diagnosed. Because respiratory function was poor, right S6 segmentectomy was scheduled. Moreover, to preserve the respiratory muscles as much as possible, a thoracoscopic approach was selected. We performed

S6 sleeve segmentectomy, and sutured the lower bronchus and basal bronchus. There were some limitations in handling needles during thoracoscopy. To resolve these difficulties, we devised two techniques. One was to suture the bronchus with continuous sutures on the mediastinal side and simple interrupted sutures on the other side. The other was to create a working space for handling the needles to avoid entanglement of the sutures. These techniques allowed us to suture the bronchi relatively easily.

Naim, V. and F. Rosselli (2009). "The FANC pathway and mitosis: a replication legacy." Cell Cycle **8**(18): 2907-2911.

Fanconi anemia (FA) is a chromosome instability syndrome characterized by progressive bone marrow failure and cancer proneness. The proteins mutated in FA constitute the so-called FANC/BRCA pathway, involved in DNA replication and damage response. However, it is not completely understood how the FANC proteins perform their functions and maintain chromosome stability. Two recently published works reported that FANCD2 localizes to discrete sites on mitotic chromosomes, as consequence of replication fork stalling. The FANC pathway proved to be required to promote BLM-mediated anaphase resolution of chromosome entanglements induced by replication stress. It has also been shown that chromosome entanglement derives from DNA intertwining at fragile sites and that FANCD2 specifically targets these sites. Collectively, our data highlight a new role for the FANC proteins in the prevention of chromosome instability and aneuploidy. These findings open new directions in understanding the mechanisms of chromosome fragility and the role of FANC proteins in preserving genome stability.

Narasimhan, G., et al. (2011). "A task-based analysis of machinery entanglement injuries among Western Canadian farmers." J Agromedicine **16**(4): 261-270.

Machinery entanglements are a leading cause of hospitalized injury on Canadian farms. This study evaluates the role farm tasks play in the occurrence of machinery entanglement events. A retrospective case series of 41 entanglement injuries involving 35 farm-machinery types was assembled. Only a few limited tasks were implicated in the majority of entanglements. These tasks were as follows: (1) field adjustments of machinery; (2) product handling and conveyance; and (3) driveline attachments and servicing. Hazards inherent and common to these tasks affected the behavior of farmers, leading to entanglements. This study establishes a need to identify hazards and assess risks associated with different tasks involving the use of farm machinery under actual field situations. Systemic changes are required to improve existing machinery safety practices through engineering, work methods, and work practice modifications. In addition to design solutions, occupational health and safety strategies should consider activities associated with hazardous situations to inform the content of injury prevention efforts.

Ogryzko, V. V. (2008). "Erwin Schroedinger, Francis Crick and epigenetic stability." Biol Direct **3**: 15.

Schroedinger's book 'What is Life?' is widely credited for having played a crucial role in development of molecular and cellular biology. My essay revisits the issues raised by this book from the modern perspective of epigenetics and systems biology. I contrast two classes of potential mechanisms of epigenetic stability: 'epigenetic templating' and 'systems biology' approaches, and consider them from the point of view expressed by Schroedinger. I also discuss how quantum entanglement, a nonclassical feature of quantum mechanics, can help to address the 'problem of small numbers' that led Schroedinger to promote the idea of a molecular code-script for explaining the stability of biological order.

Okamoto, S. Y., et al. (2012). "SCF ensures meiotic chromosome segregation through a resolution of meiotic recombination intermediates." PLoS One **7**(1): e30622.

The SCF (Skp1-Cul1-F-box) complex contributes to a variety of cellular events including meiotic cell cycle control, but its function during meiosis is not understood well. Here we describe a novel function of SCF/Skp1 in meiotic recombination and subsequent chromosome segregation. The skp1 temperature-sensitive mutant exhibited abnormal distribution of spindle microtubules in meiosis II, which turned out to originate from abnormal bending of the spindle in meiosis I. Bent spindles were reported in mitosis of this mutant, but it remained unknown how SCF could affect spindle morphology. We found that the meiotic bent spindle in skp1 cells was due to a hypertension generated by chromosome entanglement. The spindle bending was suppressed by inhibiting double strand break (DSB) formation, indicating that the entanglement was generated by the meiotic recombination machinery. Consistently, Rhp51/Rad51-Rad22/Rad52 foci persisted until meiosis I in skp1 cells, proving accumulation of recombination intermediates. Intriguingly bent spindles were also observed in the mutant of Fbh1, an F-box protein containing the DNA helicase domain, which is involved in meiotic recombination. Genetic evidence suggested its cooperation with SCF/Skp1. Thus, SCF/Skp1 together with Fbh1 is likely to function in the resolution of meiotic recombination intermediates, thereby ensuring proper chromosome segregation.

Ozimski, L. L., et al. (2021). "A fatal affair: Circulating tumor cell relationships that shape metastasis." iScience **24**(9): 103073.

Circulating tumor cells are metastatic precursors in several cancer types. Their biology and clinical utility are subject to numerous investigations, yet one aspect that is often neglected is their entanglement with the tumor microenvironment, namely the cross talk with stromal and immune cells and their relationships with other tumor-derived components such as circulating tumor DNA and extracellular vesicles in circulation. We will focus our short review specifically on these aspects, i.e., providing some examples of the liaison that circulating tumor cells have with stromal or immune cells and illustrating their relationship with other circulating tumor derivatives such as circulating tumor DNA and extracellular vesicles.

Pansky, M., et al. (2006). "Adnexal torsion involving hydatids of Morgagni: a rare cause of acute abdominal pain in adolescents." Obstet Gynecol **108**(1): 100-102.

OBJECTIVE: Hydatids of Morgagni are common embryonal remnants of the mullerian duct and among the infrequent causes of adnexal torsion. The purpose of this study was to investigate the occurrence of adnexal torsion involving hydatids of Morgagni, as well as its possible mechanisms. METHODS: A database search was conducted for cases of adnexal torsion treated in our institution from January 2002 to July 2005. These cases were analyzed, focusing on a subgroup of adolescents with adnexal torsion involving the hydatids of Morgagni. RESULTS: There were 76 patients with adnexal torsion. The rate of hydatid of Morgagni torsion was 26% (4 of 15 cases, 95% confidence interval [CI] 0.15-0.51) in the adolescent subgroup (10-19 years old), compared with 0% (0 of 61 cases, 95% CI 0-0.048) in the adult subgroup. The difference between the hydatid torsion rates in the two subgroups was statistically significant (P = .01, 95% CI 0.001-0.532). The four patients with hydatid torsion (postmenarchal girls, aged 13-18 years) were managed with laparoscopic adnexal detorsion and cystectomy of the affected hydatid of Morgagni. At surgery, we noted three different mechanisms of hydatid torsion: torsion of the adnexa together with torsion of the hydatid of Morgagni, torsion of the hydatid of Morgagni with intact adnexa (n = 2), and entanglement of the hydatid's pedicle around the distal fallopian tube. The hydatids of Morgagni were observed on the preoperative transabdominal ultrasonogram in only one patient and appeared as a simple cyst. CONCLUSION: Adnexal torsion involving the hydatids of Morgagni appears to be more common in adolescents than previously thought. LEVEL OF EVIDENCE: III.

Rakib Hasan Khan, M., et al. (2022). "Cellulose nanofibers as Scaffold-forming materials for thin film drug delivery systems." Int J Pharm **627**: 122189.

We explored the potential of cellulose nanofiber (CNF) for designing prolonged-release, thin-film drug delivery systems (TF-DDS). These delivery systems can be used as locally deployable drug-releasing scaffolds for achieving spatial and temporal control over therapeutic concentration in target tissues. Using doxorubicin (DOX) as a model anticancer drug, CNF-based TF-DDS were prepared using different film-formation processes, such as solvent casting and lyophilization. Formulations were prepared with or without the incorporation of additional macromolecular additives, such as gelatin, to include further biomechanical functionality. We studied the films for their mechanical properties, thermal stability, wettability, porosity and in vitro drug release properties. Our experimental results showed that CNF-based films, when prepared via solvent casting method, showed optimized performance in terms of DOX loading, and prolonged-release than those prepared via lyophilization-based fabrication processes. Scanning electron microscopy (SEM) analysis of the CNF-based films showed uniform distribution of fiber entanglement, which provided the scaffolds with sufficient porosity and tortuosity contributing to the sustained release of the drug from the delivery system. We also observed that surface layering of gelatin on CNF films via dip-coating significantly increased the mechanical strength and reduced the wettability of the films, and as such, affected drug release kinetics. The performance of the TF-DDS was evaluated in-vitro against two pancreatic cancer cell lines, i.e. MIA PaCa-2 and PANC-1. We observed that, along with the enhancement of mean dissolution time (MDT) of DOX, CNF-based TF-DDS were able to suppress the proliferation of pancreatic cancer cells in a time-dependent fashion, indicating that the drug liberated from the films were therapeutically active against cancer cells. Additionally, TF-DDS were also tested ex-vivo on patient-derived xenograft (PDX) model of pancreatic ductal adenocarcinoma (PDAC). We observed that DOX released from the TF-DDS was able to reduce Ki-67 positive, pancreatic cancer cells in these models.

Ramos-Perez, C., et al. (2017). "Genome-Scale Genetic Interactions and Cell Imaging Confirm Cytokinesis as Deleterious to Transient Topoisomerase II Deficiency in Saccharomyces cerevisiae." G3 (Bethesda) **7**(10): 3379-3391.

Topoisomerase II (Top2) is an essential protein that resolves DNA catenations. When Top2 is inactivated, mitotic catastrophe results from massive

entanglement of chromosomes. Top2 is also the target of many first-line anticancer drugs, the so-called Top2 poisons. Often, tumors become resistant to these drugs by acquiring hypomorphic mutations in the genes encoding Top2 Here, we have compared the cell cycle and nuclear segregation of two coisogenic Saccharomyces cerevisiae strains carrying top2 thermosensitive alleles that differ in their resistance to Top2 poisons: the broadly-used poison-sensitive top2-4 and the poison-resistant top2-5 Furthermore, we have performed genome-scale synthetic genetic array (SGA) analyses for both alleles under permissive conditions, chronic sublethal Top2 downregulation, and acute, yet transient, Top2 inactivation. We find that slowing down mitotic progression, especially at the time of execution of the mitotic exit network (MEN), protects against Top2 deficiency. In all conditions, genetic protection was stronger in top2-5; this correlated with cell biology experiments in this mutant, whereby we observed destabilization of both chromatin and ultrafine anaphase bridges by execution of MEN and cytokinesis. Interestingly, whereas transient inactivation of the critical MEN driver Cdc15 partly suppressed top2-5 lethality, this was not the case when earlier steps within anaphase were disrupted; i.e., top2-5 cdc14-1 We discuss the basis of this difference and suggest that accelerated progression through mitosis may be a therapeutic strategy to hypersensitize cancer cells carrying hypomorphic mutations in TOP2.

Reinholt, S. J. and H. G. Craighead (2018). "Microfluidic Device for Aptamer-Based Cancer Cell Capture and Genetic Mutation Detection." Anal Chem **90**(4): 2601-2608.

We present a microfluidic device for specifically capturing cancer cells and isolating their genomic DNA (gDNA) for specific amplification and sequence analysis. To capture cancer cells within the device, nucleic acid aptamers that specifically bind to cancer cells were immobilized within a channel containing micropillars designed to increase capture efficiency. The captured cells were lysed in situ, and their gDNA was isolated by physical entanglement within a second smaller-dimensioned micropillar array. This type of isolation allows the gDNA to be retained and purified within the channel and enables amplification and analysis to be performed on the gDNA without the loss of the original template. We developed a technique for selectively amplifying genes from whole gDNA using multiple displacement amplification. The amplified gene samples were sequenced, and the resulting sequence information was compared against the known wild-type gene to identify any mutations. We have tested cervical and ovarian cancer cells for mutations in the TP53 gene using this technology. This approach offers a way to monitor multiple genetic mutations in the same small population of cells, which is beneficial given the wide diversity in cancer cells, and therefore it requires very few cells to be extracted from a patient sample.

Rog, O., et al. (2009). "Sumoylation of RecQ helicase controls the fate of dysfunctional telomeres." Mol Cell **33**(5): 559-569.

Genome stability depends upon the RecQ helicases, which are conserved from bacteria to man, but little is known about how their myriad activities are regulated. Fission yeast lacking the telomere protein Taz1 (mammalian TRF1/TRF2 ortholog) lose many hallmarks of telomeres, including accurate replication and local protection from DNA repair reactions. Here we show that the RecQ homolog, Rqh1, is sumoylated. Surprisingly, Rqh1 acts on taz1Delta telomeres in a deleterious way, promoting telomere breakage and entanglement. Mutation of Rqh1 sumoylation sites rescues taz1Delta cells from these hazards without dramatically affecting nontelomeric Rqh1 functions. The prominence of Rqh1 in the etiology of several different telomere defects supports the idea that they originate from a common underlying lesion--aberrant processing of the stalled telomeric replication forks that accumulate in the absence of Taz1. Our work underscores the principle that RecQ helicases are "double-edged swords" whose activity, while necessary for maintaining genome-wide stability, must be vigilantly controlled.

Ronnlund, D., et al. (2013). "Spatial organization of proteins in metastasizing cells." Cytometry A **83**(9): 855-865.

The ability of tumor cells to invade into the surrounding tissue is linked to defective adhesive and mechanical properties of the cells, which are regulated by cell surface adhesions and the intracellular filamentous cytoskeleton, respectively. With the aim to further reveal the underlying mechanisms and provide new strategies for early cancer diagnostics, we have used ultrahigh resolution stimulated emission depletion (STED) microscopy as a means to identify metastasizing cells, based on their subcellular protein distribution patterns reflecting their specific adhesive and mechanical properties. We have compared the spatial distribution of cell-matrix adhesion sites and the vimentin filamentous systems in a matched pair of primary, normal, and metastatic human fibroblast cells. We found that the metastatic cells showed significantly increased densities and more homogenous distributions of nanoscale adhesion-related particles. Moreover, they showed an increase in the number but reduced sizes of the areas of cell-matrix adhesion complexes. The organization of the vimentin intermediate filaments was also found to be significantly different in the

metastasizing cells, showing an increased entanglement and loss of directionality. Image analysis procedures were established, allowing an objective detection and characterization of these features and distinction of metastatic cells from their normal counterparts. In conclusion, our results suggest that STED microscopy provides a novel tool to identify metastasizing cells from a very sparse number of cells, based on the altered spatial distribution of the cell-matrix adhesions and intermediate filaments.

Ruttala, H. B., et al. (2017). "Layer-by-layer assembly of hierarchical nanoarchitectures to enhance the systemic performance of nanoparticle albumin-bound paclitaxel." Int J Pharm **519**(1-2): 11-21.

Although protein-bound paclitaxel (PTX, Abraxane((R))) has been established as a standard PTX-based therapy against multiple cancers, its clinical success is limited by unfavorable pharmacokinetics, suboptimal biodistribution, and acute toxicities. In the present study, we aimed to apply the principles of a layer-by-layer (LbL) technique to improve the poor colloidal stability and pharmacokinetic pattern of nanoparticle albumin-bound paclitaxel (nab-PTX). LbL-based nab-PTX was successfully fabricated by the alternate deposition of polyarginine (pARG) and poly(ethylene glycol)-block-poly (L-aspartic acid) (PEG-b-PLD) onto an albumin conjugate. The presence of protective entanglement by polyamino acids prevented the dissociation of nab-PTX and improved its colloidal stability even at a 100-fold dilution. The combined effect of high nanoparticle internalization and controlled release of PTX from LbL-nab-PTX increased its cytotoxicity in MCF-7 and MDA-MB-231 breast cancer cells. LbL-nab-PTX consistently induced apoptosis in approximately 52% and 22% of MCF-7 and MDA-MB-231 cancer cells, respectively. LbL assembly of polypeptides effectively prevented exposure of PTX to the systemic environment and thereby inhibited drug-induced hemolysis. Most importantly, LbL assembly of polypeptides to nab-PTX effectively increased the blood circulation potential of PTX and improved therapeutic efficacy via a significantly higher area under the curve (AUC)0-infinity. We report for the first time the application of LbL functional architectures for improving the systemic performance of nab-PTX with a view toward its clinical translation for cancer therapy.

Samassekou, O., et al. (2010). "Sizing the ends: normal length of human telomeres." Ann Anat **192**(5): 284-291.

The ends of human chromosomes are constituted of telomeres, a nucleoprotein complex. They are mainly formed by the entanglement of repeat DNA and telomeric and non-telomeric proteins. Telomeric sequences are lost in each cell division and this loss happens in vitro as well as in vivo. The diminution of telomere length over the cell cycle has led to the consideration of telomeres as a 'mitotic clock'. Telomere lengths are heterogeneous because they differ among tissues, cells, and chromosome arms. Cell proliferation capacity, cellular environment, and epigenetic factors are some elements that affect this telomere heterogeneity. Also, genetic and environmental factors modulate the difference in telomere lengths between individuals. Telomere length is regulated by telomere structure, telomerase, the enzyme that elongates the 3'-end of telomeres, and alternative lengthening of telomeres (ALT) used exclusively in immortalized and cancer cells. The understanding of telomere length dynamic in the normal population is essential to develop a deeper insight into the role of telomere function in pathological settings.

Skoko, J. J., et al. (2019). "Signals Getting Crossed in the Entanglement of Redox and Phosphorylation Pathways: Phosphorylation of Peroxiredoxin Proteins Sparks Cell Signaling." Antioxidants (Basel) **8**(2).

Reactive oxygen and nitrogen species have cell signaling properties and are involved in a multitude of processes beyond redox homeostasis. The peroxiredoxin (Prdx) proteins are highly sensitive intracellular peroxidases that can coordinate cell signaling via direct reactive species scavenging or by acting as a redox sensor that enables control of binding partner activity. Oxidation of the peroxidatic cysteine residue of Prdx proteins are the classical post-translational modification that has been recognized to modulate downstream signaling cascades, but increasing evidence supports that dynamic changes to phosphorylation of Prdx proteins is also an important determinant in redox signaling. Phosphorylation of Prdx proteins affects three-dimensional structure and function to coordinate cell proliferation, wound healing, cell fate and lipid signaling. The advent of large proteomic datasets has shown that there are many opportunities to understand further how phosphorylation of Prdx proteins fit into intracellular signaling cascades in normal or malignant cells and that more research is necessary. This review summarizes the Prdx family of proteins and details how post-translational modification by kinases and phosphatases controls intracellular signaling.

Spyrou, N., et al. (2018). "Classic and Novel Adipocytokines at the Intersection of Obesity and Cancer: Diagnostic and Therapeutic Strategies." Curr Obes Rep **7**(4): 260-275.

PURPOSE OF REVIEW: In this review, we investigate the role of classic and novel adipocytokines in cancer pathogenesis synopsizing the mechanisms underlying the association between adipocytokines and

malignancy. Special emphasis is given on novel adipocytokines as new evidence is emerging regarding their entanglement in neoplastic development. RECENT FINDINGS: Recent data have emphasized the role of the triad of overweight/obesity, insulin resistance and adipocytokines in cancer. In the setting of obesity, classic and novel adipocytokines present independent and joint effects on activation of major intracellular signaling pathways implicated in cell proliferation, expansion, survival, adhesion, invasion, and metastasis. Until now, more than 15 adipocytokines have been associated with cancer, and this list continues to expand. While the plethora of circulating pro-inflammatory adipocytokines, such as leptin, resistin, extracellular nicotinamide phosphoribosyl transferase, and chemerin are elevated in malignancies, some adipocytokines such as adiponectin and omentin-1 are generally decreased in cancers and are considered protective against carcinogenesis. Elucidating the intertwining of inflammation, cellular bioenergetics, and adiposopathy is significant for the development of preventive, diagnostic, and therapeutic strategies against cancer. Novel more effective and safe adipocytokine-centered therapeutic interventions may pave the way for targeted oncotherapy.

Stohr, D., et al. (2020). "TRAIL receptor signaling: From the basics of canonical signal transduction toward its entanglement with ER stress and the unfolded protein response." Int Rev Cell Mol Biol **351**: 57-99.

The cytokine tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) is a member of the large TNF superfamily that can trigger apoptosis in transformed or infected cells by binding and activating two receptors, TRAIL receptor 1 (TRAILR1) and TRAIL receptor 2 (TRAILR2). Compared to other death ligands of the same family, TRAIL induces apoptosis preferentially in malignant cells while sparing normal tissue and has therefore been extensively investigated for its suitability as an anti-cancer agent. Recently, it was noticed that TRAIL receptor signaling is also linked to endoplasmic reticulum (ER) stress and the unfolded protein response (UPR). The role of TRAIL receptors in regulating cellular apoptosis susceptibility therefore is broader than previously thought. Here, we provide an overview of TRAIL-induced signaling, covering the core signal transduction during extrinsic apoptosis as well as its link to alternative outcomes, such as necroptosis or NF-kappaB activation. We discuss how environmental factors, transcriptional regulators, and genetic or epigenetic alterations regulate TRAIL receptors and thus alter cellular TRAIL susceptibility. Finally, we provide insight into the role of TRAIL receptors in signaling scenarios that engage the unfolded protein response and discuss how these findings might be translated into new combination therapies for cancer treatment.

Sun, W. N., et al. (2020). "Decision-Making Processes in Surrogates of Cancer Patients in a Taiwan Intensive Care Unit." Int J Environ Res Public Health **17**(12).

Background: Few studies in Asian countries have explored the emotional entanglements and conflicts that surrogates often experience during the medical decision-making process. This study was to explore decision-making processes in surrogates of cancer patients in a Taiwan intensive care unit (ICU). This qualitative study surveyed a purposive sample of surrogates (n = 8; average age, 48 years) of cancer patients in the ICU of a medical center in Taiwan. A phenomenological methodology was used, and a purposive sample of surrogates of cancer patients were recruited and interviewed during the first three days of the ICU stay. Results: Based on the interview results, four themes were generalized through text progression: (1) Use love to resist: internal angst. This theme was related to the reflexive self -blame, the feelings of inner conflict, and the reluctance to make healthcare decisions, which surrogates experienced when they perceived suffering by the patient. (2) Allow an angel to spread love among us: memories and emotional entanglements. Memories of the patient caused the surrogate to experience emotional entanglements ranging from happiness to sadness and from cheerfulness to anger. (3) Dilemmas of love: anxiety about ICU visitor restrictions. The confined space and restricted visiting hours of the ICU limited the ability of surrogates to provide emotional support and to share their emotions with the patient. (4) Suffocating love: entanglement in decision-making. Emotional entanglements among family members with different opinions on medical care and their struggles to influence decision-making often prevented surrogates from thinking logically. Conclusions: Expression of emotions by ICU surrogates is often restrained and implicit, particularly in Asian populations. These results can help health professionals understand the psychological shock and inner conflict experienced by surrogates and provide a useful reference for improving their communications with surrogates.

Tamulis, A. and M. Grigalavicius (2014). "Quantum entanglement in photoactive prebiotic systems." Syst Synth Biol **8**(2): 117-140.

This paper contains the review of quantum entanglement investigations in living systems, and in the quantum mechanically modelled photoactive prebiotic kernel systems. We define our modelled self-assembled supramolecular photoactive centres, composed of one or more sensitizer molecules,

precursors of fatty acids and a number of water molecules, as a photoactive prebiotic kernel systems. We propose that life first emerged in the form of such minimal photoactive prebiotic kernel systems and later in the process of evolution these photoactive prebiotic kernel systems would have produced fatty acids and covered themselves with fatty acid envelopes to become the minimal cells of the Fatty Acid World. Specifically, we model self-assembling of photoactive prebiotic systems with observed quantum entanglement phenomena. We address the idea that quantum entanglement was important in the first stages of origins of life and evolution of the biospheres because simultaneously excite two prebiotic kernels in the system by appearance of two additional quantum entangled excited states, leading to faster growth and self-replication of minimal living cells.

Tamulis, A., et al. (2013). "Phenomenon of quantum entanglement in a system composed of two minimal protocells." Orig Life Evol Biosph **43**(1): 49-66.

The quantum mechanical self-assembly of two separate photoactive supramolecular systems with different photosynthetic centers was investigated by means of density functional theory methods. Quantum entangled energy transitions from one subsystem to the other and the assembly of logically controlled artificial minimal protocells were modeled. The systems studied were based on different photoactive sensitizer molecules covalently bonded to a non-canonical oxo-guanine::cytosine supramolecule with the precursor of a fatty acid (pFA) molecule attached via Van der Waals forces, all surrounded by water molecules. The electron correlation interactions responsible for the weak hydrogen and Van der Waals chemical bonds increased due to the addition of polar water solvent molecules. The distances between the separated sensitizer, nucleotide, pFA, and water molecules are comparable to Van der Waals and hydrogen bonding radii. As a result, the overall system becomes compressed, resulting in photo-excited electron tunneling from the sensitizer (bis(4-diphenylamine-2-phenyl)-squarine or 1,4-bis(N,N-dimethylamino)naphthalene) to the pFA molecules. Absorption spectra as well as electron transfer trajectories associated with the different excited states were calculated using time dependent density functional theory methods. The results allow separation of the quantum entangled photosynthetic transitions within the same minimal protocell and with the neighboring minimal protocell. The transferred electron is used to cleave a "waste" organic molecule resulting in the formation of the desired product. A two variable, quantum entangled AND logic gate was proposed, consisting of two input photoactive sensitizer molecules and one output (pFA molecule). It is proposed that a similar process might be applied for the destruction of tumor cancer cells or to yield building blocks in artificial cells.

Trapecar, M., et al. (2020). "Gut-Liver Physiomimetics Reveal Paradoxical Modulation of IBD-Related Inflammation by Short-Chain Fatty Acids." Cell Syst **10**(3): 223-239 e229.

Although the association between the microbiome and IBD and liver diseases is known, the cause and effect remain elusive. By connecting human microphysiological systems of the gut, liver, and circulating Treg and Th17 cells, we created a multi-organ model of ulcerative colitis (UC) ex vivo. The approach shows microbiome-derived short-chain fatty acids (SCFAs) to either improve or worsen UC severity, depending on the involvement of effector CD4 T cells. Using multiomics, we found SCFAs increased production of ketone bodies, glycolysis, and lipogenesis, while markedly reducing innate immune activation of the UC gut. However, during acute T cell-mediated inflammation, SCFAs exacerbated CD4(+) T cell-effector function, partially through metabolic reprograming, leading to gut barrier disruption and hepatic injury. These paradoxical findings underscore the emerging utility of human physiomimetic technology in combination with systems immunology to study causality and the fundamental entanglement of immunity, metabolism, and tissue homeostasis.

Vanaja, A., et al. (2021). "Symphony of the DNA flexibility and sequence environment orchestrates p53 binding to its responsive elements." Gene **803**: 145892.

The p53 tumor suppressor protein maintains the genome fidelity and integrity by modulating several cellular activities. It regulates these events by interacting with a heterogeneous set of response elements (REs) of regulatory genes in the background of chromatin configuration. At the p53-RE interface, both the base readout and torsional-flexibility of DNA account for high-affinity binding. However, DNA structure is an entanglement of a multitude of physicochemical features, both local and global structure should be considered for dealing with DNA-protein interactions. The goal of current research work is to conceptualize and abstract basic principles of p53-RE binding affinity as a function of structural alterations in DNA such as bending, twisting, and stretching flexibility and shape. For this purpose, we have exploited high throughput in-vitro relative affinity information of responsive elements and genome binding events of p53 from HT-Selex and ChIP-Seq experiments respectively. Our results confirm the role of torsional flexibility in p53 binding, and further, we reveal that DNA axial bending, stretching stiffness, propeller twist, and wedge angles are intimately linked to p53 binding affinity when compared to homeodomain, bZIP, and bHLH proteins. Besides, a similar DNA structural environment is observed in the

distal sequences encompassing the actual binding sites of p53 cistrome genes. Additionally, we revealed that p53 cistrome target genes have unique promoter architecture, and the DNA flexibility of genomic sequences around REs in cancer and normal cell types display major differences. Altogether, our work provides a keynote on DNA structural features of REs that shape up the in-vitro and in-vivo high-affinity binding of the p53 transcription factor.

Vasavi, H., et al. (1998). "The salubrious effects of ascorbic acid on cyclophosphamide instigated lipid abnormalities in fibrosarcoma bearing rats." Cancer Biochem Biophys **16**(1-2): 71-83.

The combined effect of cyclophosphamide and ascorbic acid on plasma lipids and lipoprotein profiles are important since, ascorbic acid encumbered the lipid abnormalities initiated by cyclophosphamide during cancer chemotherapy. Hence, the study was launched to appraise the salutary role of ascorbic acid in cyclophosphamide administered fibrosarcoma bearing rats. Fibrosarcoma cell line induced rats were treated with cyclophosphamide (10 mg/kg body weight) and ascorbic acid (200 mg/kg body weight) individually and in combination for 28 days. The concentration of plasma lipids and lipoprotein profiles were determined in control and experimental animals. The untreated, as well as cyclophosphamide administered fibrosarcoma bearing rats, divulged significantly increased levels of plasma total cholesterol, triglycerides, phospholipids, VLDL- and LDL-cholesterol, as compared with their respective control animals. In contrast, ester and HDL-cholesterol levels exhibited a marked decrease in these animals. Similar observations were also noticed in liver lipid values, as well. However, these lipid abnormalities were corrected by the co-administration of ascorbic acid. These results suggested, that some clinical entanglement of cyclophosphamide was refrained by co-administration of ascorbic acid in tumor stress condition.

Wang, D., et al. (2017). "Bioresponsive DNA Hydrogels: Beyond the Conventional Stimuli Responsiveness." Acc Chem Res **50**(4): 733-739.

Bioresponsive hydrogels can respond to various biological stimuli by a macroscopic change of physical state or by converting biochemical inputs into biological or mechanical outputs. These materials are playing an increasingly important role in a wide variety of applications, especially in the biological and biomedical fields. However, the design and engineering of intriguing bioresponsive materials with adequate biocompatibility and biodegradability have proven to be a great challenge. DNA, on the other hand, possesses many unique and fascinating properties, including its indispensable genetic function, broad biocompatibility, precise molecular recognition capability, tunable multifunctionality, and convenient programmability. Therefore, DNA has provided crucial prerequisites for the exploration of novel bioresponsive hydrogels and has since become an ideal building block for the construction of novel materials. In this Account, we describe our efforts over more than a decade to develop DNA-based materials including bioresponsive hydrogels. These DNA hydrogels were created through either chemical cross-linking or physical entanglement among DNA chains. We further divided them into two categories: pure DNA-based and hybrid DNA-based hydrogels. For the pure DNA-based hydrogels, we developed the first bulk DNA hydrogel entirely from branched DNA by using enzymatic ligation. Certain drugs were encapsulated in such hydrogels in situ and released in a controllable manner under the stimulation of environmental factors such as nucleases and/or changes in ionic strength. Furthermore, we prepared a protein-producing hydrogel (termed a "P-gel") by ligating X-shaped DNA (X-DNA) and linear plasmids. Following the central dogma of molecular biology, this hydrogel responded to enzymes and substrate and converted them into proteins. This was the first example showing that a hydrogel could be employed to produce proteins without the involvement of live cells. This might also be the first attempt to create cell-like hydrogels that will be ultimately bioresponsive. In addition, we also constructed a DNA physical hydrogel via entanglement of DNA chains elongated by a special polymerase: Phi29. This hydrogel (termed a "meta-hydrogel") exhibited a "meta" property: freely reversible change between liquidlike and solidlike states through stimulation by water molecules. Besides these pure DNA-based hydrogels, we also created a hybrid DNA-based hydrogel: a DNA-clay hybrid hydrogel utilizing electrostatic interactions between DNA and clay nanocrystals. We discovered a synergistic responsiveness in biochemical reaction in this hydrogel, suggesting that a DNA-clay hydrogel might be the environment for the origination of life and that DNA and clay might have been coevolving during early evolution. In summary, DNA links the nonbiological world with biological processes by virtue of its bioresponsiveness. We envision that bioresponsive DNA hydrogels will play an irreplaceable part in the development of future evolvable materials such as soft robots and artificial cells.

Wang, S., et al. (2022). "Reversible and Highly Ordered Biointerfaces for Efficient Capture and Nondestructive Release of Circulating Tumor Cells." Anal Chem **94**(26): 9450-9458.

The engineering strategy of artificial biointerfaces is vital for governing their performances in bioanalysis and diagnosis. Highly ordered

arrangement of affinity ligands on the interface surface facilitates efficient interaction with target molecules, whereas biointerfaces aimed at drug delivery or rare cell isolation require sophisticated stimuli-response mechanisms. However, it is still challenging to facilely fabricate biointerfaces possessing the two features. Herein, we endow a biointerface with both reversibility and capability to orderly assemble affinity ligands by introducing boronic acid moieties alone. By boronate conjugation via glycosylation sites, avidin was well arranged at the surface of boronic acid-decorated carbon nitride nanosheets for the assembly of biotinylated aptamers. The ordered orientation of aptamers largely relieved their inactivation caused by inter-strand entanglement, facilitating significant increase in cell affinity for the isolation of circulating tumor cells (CTCs). The reversible boronate conjugation also facilitated mild release of CTCs by acid fructose with high cell viability.

Wang, X., et al. (2016). "Affinity-controlled protein encapsulation into sub-30 nm telodendrimer nanocarriers by multivalent and synergistic interactions." Biomaterials **101**: 258-271.

Novel nanocarriers are highly demanded for the delivery of heterogeneous protein therapeutics for disease treatments. Conventional nanoparticles for protein delivery are mostly based on the diffusion-limiting mechanisms, e.g., physical trapping and entanglement. We develop herein a novel linear-dendritic copolymer (named telodendrimer) nanocarrier for efficient protein delivery by affinitive coating. This affinity-controlled encapsulation strategy provides nanoformulations with a small particle size (<30 nm), superior loading capacity (>50% w/w) and maintained protein bioactivity. We integrate multivalent electrostatic and hydrophobic functionalities synergistically into the well-defined telodendrimer scaffold to fine-tune protein binding affinity and delivery properties. The ion strength and density of the charged groups as well as the structure of the hydrophobic segments are important and their combinations in telodendrimers are crucial for efficient protein encapsulation. We have conducted a series of studies to understand the mechanism and kinetic process of the protein loading and release, utilizing electrophoresis, isothermal titration calorimetry, Forster resonance energy transfer spectroscopy, bio-layer interferometry and computational methods. The optimized nanocarriers are able to deliver cell-impermeable therapeutic protein intracellularly to kill cancer cells efficiently. In vivo imaging studies revealed cargo proteins preferentially accumulate in subcutaneous tumors and retention of peptide therapeutics is improved in an orthotopic brain tumor, these properties are evidence of the improved pharmacokinetics and biodistributions of protein therapeutics delivered by telodendrimer nanoparticles. This study presents a bottom-up strategy to rationally design and fabricate versatile nanocarriers for encapsulation and delivery of proteins for numerous applications.

White, S. M., et al. (2019). "The complex entanglement of Hippo-Yap/Taz signaling in tumor immunity." Oncogene **38**(16): 2899-2909.

The Hippo-Yap/Taz pathway, originally identified as a central developmental regulator of organ size, has been found perturbed in many types of human tumors, and linked to tumor growth, survival, evasion, metastasis, stemness, and drug resistance. Beside these tumor-cell-intrinsic functions, Hippo signaling also plays important immune-regulatory roles. In this review, we will summarize and discuss recent breakthroughs in our understanding of how various components of the Hippo-Yap/Taz pathway influence the tumor immune microenvironment, including their effects on the tumor secretome and immune infiltrates, their roles in regulating crosstalk between tumor cells and T cells, and finally their intrinsic functions in various types of innate and adaptive immune cells. While further research is needed to integrate and reconcile existing findings and to discern the overall effects of Hippo signaling on tumor immunity, it is clear that Hippo signaling functions as a key bridge connecting tumor cells with both the adaptive and innate immune systems. Thus, all future therapeutic development against the Hippo-Yap/Taz pathway should take into account their multi-faceted roles in regulating tumor immunity in addition to their growth-regulatory functions. Given that immune therapies have become the mainstay of cancer treatment, it is also important to pursue how to manipulate Hippo signaling to boost response or overcome resistance to existing immune therapies.

Wu, Q., et al. (2022). "The Entanglement between Mitochondrial DNA and Tumor Metastasis." Cancers (Basel) **14**(8).

Mitochondrial DNA, the genetic material in mitochondria, encodes essential oxidative phosphorylation proteins and plays an important role in mitochondrial respiration and energy transfer. With the development of genome sequencing and the emergence of novel in vivo modeling techniques, the role of mtDNA in cancer biology is gaining more attention. Abnormalities of mtDNA result in not only mitochondrial dysfunction of the the cancer cells and malignant behaviors, but regulation of the tumor microenvironment, which becomes more aggressive. Here, we review the recent progress in the regulation of cancer metastasis using mtDNA and the underlying

mechanisms, which may identify opportunities for finding novel cancer prediction and therapeutic targets.

Yang, M. J., et al. (2018). "Prospective Multicenter Study of the Challenges Inherent in Using Large Cell-Type Stents for Bilateral Stent-in-Stent Placement in Patients with Inoperable Malignant Hilar Biliary Obstruction." Gut Liver **12**(6): 722-727.

Background/Aims: Although endoscopic bilateral stent-in-stent placement is challenging, many recent studies have reported promising outcomes regarding technical success and endoscopic re-intervention. This study aimed to evaluate the technical accessibility of stent-in-stent placement using large cell-type stents in patients with inoperable malignant hilar biliary obstruction. Methods: Forty-three patients with inoperable malignant hilar biliary obstruction from four academic centers were prospectively enrolled from March 2013 to June 2015. Results: Bilateral stent-in-stent placement using two large cell-type stents was successfully performed in 88.4% of the patients (38/43). In four of the five cases with technical failure, the delivery sheath of the second stent became caught in the hook-cross-type vertex of the large cell of the first stent, and subsequent attempts to pass a guidewire and stent assembly through the mesh failed. Functional success was achieved in all cases of technical success. Stent occlusion occurred in 63.2% of the patients (24/38), with a median patient survival of 300 days. The median stent patency was 198 days. The stent patency rate was 82.9%, 63.1%, and 32.1% at 3, 6, and 12 months postoperatively, respectively. Endoscopic re-intervention was performed in 14 patients, whereas 10 underwent percutaneous drainage. Conclusions: Large cell-type stents for endoscopic bilateral stent-in-stent placement had acceptable functional success and stent patency when technically successful. However, the technical difficulty associated with the entanglement of the second stent delivery sheath in the hook-cross-type vertex of the first stent may preclude large cell-type stents from being considered as a dedicated standard tool for stent-in-stent placement.

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