Websites:
http://www.sciencepub.net
http://www.cancerbio.net

Emails:
editor@sciencepub.net
sciencepub@gmail.com

Cancer Biology

MARSLAND PRESS
Multidisciplinary Academic Journal Publisher

Cancer Biology Research Literatures

Mark Herbert

Queens, NY 11418, USA, ma8080@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.
[Mark Herbert. **Cancer Biology Research Literatures.**Cancer Biology 2023;13(3):12-49]. ISSN: 2150-1041 (print); ISSN: 2150-105X (online). http://www.cancerbio.net 03.doi:10.7537/marscbj130323.03.

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.

Alberghina, L., et al. (2014). "A systems biology road map for the discovery of drugs targeting cancer cell metabolism." Curr Pharm Des **20**(15): 2648-2666.

Despite their different histological and molecular properties, different types of cancers share few essential functional alterations. Some of these cancer hallmarks may easily be studied in in vitro cultures, while others are related to the way in which tumors grow in vivo. According to the systems biology paradigm, complex cellular functions arise as system-level properties from the dynamic interaction of a large number of biomolecules. We previously newly defined four basic cancer cell properties derived from known cancer hallmarks amenable to system-level investigation in cell cultures: enhanced growth, altered response to apoptotic cues, genomic instability and inability to enter senescence following oncogenic signaling. Here we summarize the major properties of enhanced growth that is dependent on metabolism rewiring - in which glucose is mostly used by fermentation while glutamine provides nitrogen and carbon atoms for biosyntheses - and controlled by oncogene signaling. We then briefly review the major drugs used to target signaling pathways in preclinical and clinical studies, whose clinical efficacy is unfortunately severely limited by tumor resistance, substantially due to signaling cross-talk. We present a systems biology roadmap that integrates different types of mathematical models with conventional and post-genomic biomolecular analyses that will provide a deeper mechanistic understanding of the links between metabolism and uncontrolled cancer cell growth. This approach is taken to be instrumental both in unraveling cancer's first principles and in designing novel drugs able to target one or more control or execution steps of the cancer rewired metabolism, in order to achieve permanent arrest of tumor development.

Baker, V. V. (1994). "Molecular biology and genetics of epithelial ovarian cancer." Obstet Gynecol Clin North Am **21**(1): 25-40.

The majority of epithelial ovarian neoplasms occur in the absence of a familial or heritable component. Relatively little is known about the molecular genetic mechanisms that contribute to the development and progression of epithelial ovarian cancer. Although historically there have been difficulties encountered in basic science investigations, many key observations have been made during the past 5 years concerning the genetic alterations associated with this disease.

Beasley, N. J., et al. (2002). "Hypoxia-inducible factors HIF-1alpha and HIF-2alpha in head and neck cancer: relationship to tumor biology and treatment outcome in surgically resected patients." Cancer Res **62**(9): 2493-2497.

Hypoxia within head and neck squamous cell carcinoma (HNSCC) predicts a poor response to radiotherapy and poor prognosis. Hypoxia-inducible factor (HIF)-1 and HIF-2 are nuclear transcription factors that regulate the cellular response to hypoxia and are important for solid tumor growth and survival. Overexpression of HIF-1alpha and HIF-2alpha was demonstrated in three HNSCC cell lines under hypoxia and tumor tissue versus normal tissue (n = 20, HIF-1alpha, P = 0.023; HIF-2alpha, P = 0.013). On immunostaining, HIF-1alpha and HIF-2alpha expression were localized to tumor nuclei; HIF-2alpha expression was also seen in tumor-associated macrophages. Expression of HIF-1alpha in surgically treated patients with HNSCC (n = 79) was associated with improved disease-free survival (P = 0.016) and overall survival (P = 0.027).

Belani, C. P., et al. (2007). "Women and lung cancer: epidemiology, tumor biology, and emerging trends in clinical research." Lung Cancer **55**(1): 15-23.

Lung cancer is the leading cause of cancer-related death in both men and women. Environmental carcinogens, particularly tobacco smoke, play a dominant role in the development of lung cancer, although 10-15% of all patients diagnosed are non-smokers. In addition, emerging data demonstrate sex-specific differences in lung cancer susceptibility and prognosis. This implies that the development of lung cancer is modulated by complex interactions between genetic, hormonal, behavioral, and environmental factors. A better understanding of the differences between men and women and their impact on the prevention, diagnosis, and treatment of lung cancer requires continued basic and clinical research. Recent data on the epidemiological aspects of lung cancer in women, lung tumor biology, and emerging trends in clinical research were presented at a thought leaders' roundtable hosted by the Society for Women's Health Research. The panel concluded that as the patient population in lung cancer is changing from mostly male smokers to include women and non-smokers, an urgent need exists to increase awareness and research funding to improve lung cancer care, particularly in women. To further improve survival in this disease, both clinical characteristics and tumor biology should be considered in the development of new treatment options.

Belldegrun, A., et al. (2001). "Interleukin 2 gene therapy for prostate cancer: phase I clinical trial and basic biology." Hum Gene Ther **12**(8): 883-892.

Twenty-four patients with locally advanced prostate cancer (CaP) were enrolled in a phase I clinical trial using gene-based immunotherapy. A functional DNA-lipid complex encoding the interleukin 2 (IL-2) gene (Leuvectin; Vical, San Diego, CA) was administered intraprostatically into the hypoecogenic tumor lesion, using transrectal ultrasound guidance. Two groups of patients having locally advanced tumors were enrolled to receive a treatment regimen composed of two serial intraprostatic injections of the IL-2 gene agent administered 1 week apart. The first groups of patients included radical prostatectomy candidates who subsequently underwent surgery after the completion of the treatment regimen. The second group consisted of patients who had failed a prior therapy. Prostate specimens of the treated areas were attained after treatment and compared with the transrectal biopsies performed at baseline to assess for any responses. IL-2 gene therapy was well tolerated, with no grade 3 or 4 toxic reactions occurring. The most commonly reported symptoms were mild hematuria, transient rectal bleeding, and perineal discomfort that are likely attributable to the injection itself. During the entire course of treatment, there were no significant changes in American Urologic Association (AUA) symptom scores, in hematologic disturbances, electrolyte imbalances, or hepatic functions. Evidence of systemic immune activation was observed after IL-2 gene therapy, based on an increase in the intensity of T cell infiltration seen on immunohistochemical analysis of tissue samples from the injected tumor sites, and based on increased proliferation rates of peripheral blood lymphocytes that were cocultured with patient serum collected after treatment. Furthermore, transient decreases in serum prostate-specific antigen (PSA) (responders) were seen in 16 of 24 patients (67%) on day 1. Fourteen of the patients persisted in this decrease to day 8 (58%). In eight patients the PSA level rose (nonresponders). More patients (9 to 10) in the group that failed prior therapy responded to the IL-2 gene injections (chi-square test, p = 0.04), and 6 of the 9 also had lower than baseline PSA levels at week 10 after treatment. To the best of our knowledge, this is the first clinical study of its kind aimed at exploring the role of IL-2-based gene therapy in CaP patients. This phase I trial demonstrated the safety of intraprostatic Leuvectin injection, with transient PSA-based responses seen after therapy.

Bertram, J. S. (2000). "The molecular biology of cancer." Mol Aspects Med **21**(6): 167-223.

The process by which normal cells become progressively transformed to malignancy is now known

to require the sequential acquisition of mutations which arise as a consequence of damage to the genome. This damage can be the result of endogenous processes such as errors in replication of DNA, the intrinsic chemical instability of certain DNA bases or from attack by free radicals generated during metabolism. DNA damage can also result from interactions with exogenous agents such as ionizing radiation, UV radiation and chemical carcinogens. Cells have evolved means to repair such damage, but for various reasons errors occur and permanent changes in the genome, mutations, are introduced. Some inactivating mutations occur in genes responsible for maintaining genomic integrity facilitating the acquisition of additional mutations. This review seeks first to identify sources of mutational damage so as to identify the basic causes of human cancer. Through an understanding of cause, prevention may be possible. The evolution of the normal cell to a malignant one involves processes by which genes involved in normal homeostatic mechanisms that control proliferation and cell death suffer mutational damage which results in the activation of genes stimulating proliferation or protection against cell death, the oncogenes, and the inactivation of genes which would normally inhibit proliferation, the tumor suppressor genes. Finally, having overcome normal controls on cell birth and cell death, an aspiring cancer cell faces two new challenges: it must overcome replicative senescence and become immortal and it must obtain adequate supplies of nutrients and oxygen to maintain this high rate of proliferation. This review examines the process of the sequential acquisition of mutations from the prospective of Darwinian evolution. Here, the fittest cell is one that survives to form a new population of genetically distinct cells, the tumor. This review does not attempt to be comprehensive but identifies key genes directly involved in carcinogenesis and demonstrates how mutations in these genes allow cells to circumvent cellular controls. This detailed understanding of the process of carcinogenesis at the molecular level has only been possible because of the advent of modern molecular biology. This new discipline, by precisely identifying the molecular basis of the differences between normal and malignant cells, has created novel opportunities and provided the means to specifically target these modified genes. Whenever possible this review highlights these opportunities and the attempts being made to generate novel, molecular based therapies against cancer. Successful use of these new therapies will rely upon a detailed knowledge of the genetic defects in individual tumors. The review concludes with a discussion of how the use of high throughput molecular arrays will allow the molecular pathologist/therapist to identify these defects and direct specific therapies to specific mutations.

Bishop, M. R., et al. (2011). "National Cancer Institute's First International Workshop on the Biology, Prevention, and Treatment of Relapse after Allogeneic Hematopoietic Stem Cell Transplantation: summary and recommendations from the organizing committee." Biol Blood Marrow Transplant **17**(4): 443-454.

The National Cancer Institute's First International Workshop on the Biology, Prevention, and Treatment of Relapse after Allogeneic Hematopoietic Stem Cell Transplantation was organized and convened to identify, prioritize, and coordinate future research activities related to relapse after allogeneic hematopoietic stem cell transplantation (allo-HSCT). Each of the Workshop's 6 Working Committees has published individual reports of ongoing basic, translational, and clinical research and recommended areas for future research related to the areas of relapse biology, epidemiology, prevention, and treatment. This document summarizes each committee's recommendations and suggests 3 major initiatives for a coordinated research effort to address the problem of relapse after allo-HSCT: (1) to establish multicenter correlative and clinical trial networks for basic/translational, epidemiologic, and clinical research; (2) to establish a network of biorepositories for the collection of samples before and after allo-HSCT to aid in laboratory and clinical studies; and (3) to further refine, implement, and study the Workshop-proposed definitions for disease-specific response and relapse and recommendations for monitoring of minimal residual disease. These recommendations, in coordination with ongoing research initiatives and transplantation organizations, provide a research framework to rapidly and efficiently address the significant problem of relapse after allo-HSCT.

Brandi, M. L. (1992). "Parathyroid tumor biology in familial multiple endocrine neoplasia type 1: a model for cancer development." Henry Ford Hosp Med J **40**(3-4): 181-185.

Familial multiple endocrine neoplasia type 1 (FMEN 1) is an autosomal dominant disorder characterized by tumors of the parathyroid glands, pancreatic islets, and anterior pituitary. Hyperplasia appears to be the typical histopathological lesion in FMEN 1 endocrine tumors. A circulating mitogen related to basic fibroblast growth factor was active on proliferation of clonal bovine and human parathyroid endothelial cells. Moreover, the FMEN 1 mitogen modulated differentiation of human parathyroid endothelial cell in vitro. All these facts suggested that an extrinsic factor was active on parathyroid endothelial cell growth and differentiation. The FMEN 1 gene maps to chromosome 11q13, and allelic loss in this region has been shown in FMEN 1 parathyroid and pancreatic islet tumors and rarely in anterior pituitary tumors. Together

these results support the theory that FMEN 1 parathyroid clonal lesions can develop in the context of generalized hyperplasia. Similarly, in uremic hyperparathyroidism, where parathyroid hyperplasia is thought to be the primary lesion, loss of constitutional heterozygosity for chromosome 11 markers coexists in parathyroid tissue with a polyclonal pattern. Future efforts of scientists working on this genetic disorder will focus on the cloning of the FMEN 1 gene and the development of a suitable bioassay system to study its function.

Brown, K. A., et al. (2020). "Endocrine Therapy-related Endocrinopathies-Biology, Prevalence and Implications for the Management of Breast Cancer." Oncol Hematol Rev **16**(1): 17-22.

Nearly 270,000 new breast cancer cases are predicted to be diagnosed in the USA in 2019 with more than 70% being estrogen receptor positive and treated using endocrine therapy. The suppression of estrogen biosynthesis or action via the use of ovarian suppression, aromatase inhibitors and selective estrogen receptor modulators/degraders, respectively, is effective in approximately 70% of women. The systemic inhibition of estrogen during breast cancer treatment is also associated with side effects due to the important endocrine functions of this steroid hormone, including its role in the maintenance of energy homeostasis and bone health. The current work will present perspectives of the impact of endocrine therapy from the point of view of breast medical oncology, endocrinology, and basic science.

Cai, L., et al. (2022). "Lung Cancer Computational Biology and Resources." Cold Spring Harb Perspect Med **12**(2).

Comprehensive clinical, pathological, and molecular data, when appropriately integrated with advanced computational approaches, are transforming the way we characterize and study lung cancer. Clinically, cancer registry and publicly available historical clinical trial data enable retrospective analyses to examine how socioeconomic factors, patient demographics, and cancer characteristics affect treatment and outcome. Pathologically, digital pathology and artificial intelligence are revolutionizing histopathological image analyses, not only with improved efficiency and accuracy, but also by extracting additional information for prognostication and tumor microenvironment characterization. Genetically and molecularly, individual patient tumors and preclinical models of lung cancer are profiled by various high-throughput platforms to characterize the molecular properties and functional liabilities. The resulting multi-omics data sets and their interrogation facilitate both basic research mechanistic studies and translation of the findings into the clinic. In this review, we provide a list of resources and tools potentially valuable for lung cancer basic and translational research. Importantly, we point out pitfalls and caveats when performing computational analyses of these data sets and provide a vision of future computational biology developments that will aid lung cancer translational research.

Cairns, J. (2000). "The interface between molecular biology and cancer research." Mutat Res **462**(2-3): 423-428.

During the last thirty years, cancer research has been a remarkably fruitful resource for molecular biologists. Numerous fundamental discoveries in basic biology have come out of research into the properties of cancer cells; for example, the discovery of reverse transcriptase, RNA splicing and the protein kinases. Recently, information has started to flow in the other direction, and we are at last beginning to see molecular biology yielding discoveries of practical importance in the management and control of human cancer. Some of the past and possible future interactions of molecular biology and cancer research are discussed in this paper.

Calabrese, E. J. (2005). "Cancer biology and hormesis: human tumor cell lines commonly display hormetic (biphasic) dose responses." Crit Rev Toxicol **35**(6): 463-582.

This article assesses the nature of the dose-response relationship of human tumor cell lines with a wide range of agents including antineoplastics, toxic substances (i.e., environmental pollutants), nonneoplastic drugs, endogenous agonists, and phyto-compounds. Hormetic-like biphasic dose responses were commonly reported and demonstrated in 136 tumor cell lines from over 30 tissue types for over 120 different agents. Quantitative features of these hormetic dose responses were similar, regardless of tumor cell line or agent tested. That is, the magnitude of the responses was generally modest, with maximum stimulatory responses typically not greater than twice the control, while the width of the stimulatory concentration range was usually less than 100-fold. Particular attention was directed to possible molecular mechanisms of the biphasic nature of the dose response, as well as clinical implications in which a low concentration of chemotherapeutic agent may stimulate tumor cell proliferation. Finally, these findings further support the conclusion that hormetic dose responses are broadly generalizable, being independent of biological model, endpoint measured, and stressor agent, and represent a basic feature of biological responsiveness to chemical and physical stressors.

Carbone, P. P. (1981). "Cancer biology and cancer cures: reflections of a clinical investigator: presidential address." Cancer Res **41**(1): 1-6.

Basic biological principles in cancer biology can be learned from laboratory experiments as well as the clinic. The clinical investigator may be able to uncover cancer biology and clinical cures, an exciting possibility. Clinical trials can and should be designed to discover biological principles as well as to test one option of surgery or drug combination versus another. During the past 20 years, a variety of clinical research programs in patients with myeloma, chronic myelogenous leukemia, lymphoma, and breast cancer have led to the discovery of important biological principles. These include contributions leading to the origin of myeloid and lymphoid cells in the marrow, the discovery of immunoglobulin D myeloma, the development of effective combination chemotherapy in Hodgkin's disease, and the concept of adjuvant therapy in breast cancer. These studies also have led to improved or new therapy for these diseases. Future research and cancer cures will undoubtedly be facilitated by close collaboration between the clinical and the laboratory investigator.

Chakravarti, D., et al. (2016). "Synthetic biology approaches in cancer immunotherapy, genetic network engineering, and genome editing." Integr Biol (Camb) **8**(4): 504-517.

Investigations into cells and their contents have provided evolving insight into the emergence of complex biological behaviors. Capitalizing on this knowledge, synthetic biology seeks to manipulate the cellular machinery towards novel purposes, extending discoveries from basic science to new applications. While these developments have demonstrated the potential of building with biological parts, the complexity of cells can pose numerous challenges. In this review, we will highlight the broad and vital role that the synthetic biology approach has played in applying fundamental biological discoveries in receptors, genetic circuits, and genome-editing systems towards translation in the fields of immunotherapy, biosensors, disease models and gene therapy. These examples are evidence of the strength of synthetic approaches, while also illustrating considerations that must be addressed when developing systems around living cells.

Chambers, A. F., et al. (2000). "Molecular biology of breast cancer metastasis. Clinical implications of experimental studies on metastatic inefficiency." Breast Cancer Res **2**(6): 400-407.

Recent technological advances have led to an increasing ability to detect isolated tumour cells and groups of tumour cells in patients' blood, lymph nodes or bone marrow. However, the clinical significance of these cells is unclear. Should they be considered as evidence of metastasis, necessitating aggressive treatment, or are they in some cases unrelated to clinical outcome? Quantitative experimental studies on the basic biology of metastatic inefficiency are providing clues that may help in understanding the significance of these cells. This understanding will be of use in guiding clinical studies to assess the significance of isolated tumour cells and micrometastases in cancer patients.

Cherubini, C., et al. (2018). "Systems Biology Modeling of Nonlinear Cancer Dynamics." Methods Mol Biol **1702**: 203-213.

Systems Biology represents nowadays a promising standard framework for natural and human sciences to attack complicated problems involving Life. Here a particular application of such a program is discussed in the case of Cancer, by using a basic toy model for solid tumor spread for framing together two apparently different conceptual leading paradigms of Oncogenesis.

Chowdhury, U. R., et al. (2009). "Emerging role of nuclear protein 1 (NUPR1) in cancer biology." Cancer Metastasis Rev **28**(1-2): 225-232.

NUPR1, or p8 or com1, was first identified from rat pancreas during acute pancreatitis and later as a gene whose expression was upregulated in metastatic breast cancer cells. NUPR1 is a molecule whose expression is upregulated in response to stress and is hence influenced by the host microenvironment. While NUPR1 has been implicated in several diseases, there is no singular biochemical pathway that can be attributed to its role in cancer. NUPR1 has been found to aid the establishment of metastasis and to play a key role in the progression of several malignancies including those of breast, thyroid, brain and pancreas. NUPR1 has been implicated in inducing chemoresistance in pancreatic and breast cancer cells, protecting them from apoptosis and making tumor cells genetically unstable. In prostate cancer, however, NUPR1 appears to have tumor suppressive activity. Understanding the mechanism of action of the multifaceted functions of NUPR1 may open up new dimensions towards creating novel therapies against cancer as well as other pathologies. This review draws on several published studies on NUPR1, mainly in cancer biology, and assesses NUPR1 from the perspective of its functional role in making cancer cells resistant to the action of conventional chemotherapeutic drugs.

Coleman, C. N. (2002). "Radiation oncology--linking technology and biology in the treatment of cancer." Acta Oncol **41**(1): 6-13.

Technical advances in radiation oncology including CT-simulation, 3D- conformal and intensity-modulated radiation therapy (IMRT) delivery techniques, and brachytherapy have allowed greater

treatment precision and dose escalation. The ability to intensify treatment requires the identification of the critical targets within the treatment field, recognizing the unique biology of tumor, stroma and normal tissue. Precision is technology based while accuracy is biologically based. Therefore, the intensity of IMRT will undoubtedly mean an increase in both irradiation dose and the use of biological agents, the latter considered in the broadest sense. Radiation oncology has the potential and the opportunity to provide major contributions to the linkage between molecular and functional imaging, molecular profiling and novel therapeutics for the emerging molecular targets for cancer treatment. This process of 'credentialing' of molecular targets will require multi disciplinary imaging teams, clinicians and basic scientists. Future advances will depend on the appropriate integration of biology into the training of residents, continuing post graduate education, participation in innovative clinical research and commitment to the support of basic research as an essential component of the practice of radiation oncology.

Daniels, T. R., et al. (2006). "The transferrin receptor part I: Biology and targeting with cytotoxic antibodies for the treatment of cancer." Clin Immunol **121**(2): 144-158.

The transferrin receptor (TfR) is a cell membrane-associated glycoprotein involved in the cellular uptake of iron and in the regulation of cell growth. Iron uptake occurs via the internalization of iron-loaded transferrin (Tf) mediated by the interaction with the TfR. In addition, the TfR may also contain other growth regulatory properties in certain normal and malignant cells. The elevated levels of TfR in malignancies, its relevance in cancer, and the extracellular accessibility of this molecule make it an excellent antigen for the treatment of cancer using antibodies. The TfR can be targeted by monoclonal antibodies specific for the extracellular domain of the receptor. In this review, we summarize advancements in the basic physiology of the TfR including structure, function, and expression. We also discuss the efficacy of targeting the TfR using cytotoxic antibodies that inhibit cell growth and/or induce apoptosis in targeted malignant cells.

Dano, K., et al. (1989). "[Basic cancer biology]." Ugeskr Laeger **151**(1): 45-50.

Dembic, Z. (2014). "Pharmaco-therapeutic challenges in cancer biology with focus on the immune- system related risk factors." Curr Pharm Des **20**(42): 6652-6659.

Over the past, progress has always been achieved in therapy of various human diseases with the introduction of novel methodologies from basic to clinical research. Recent advances in techniques, especially DNA sequencing and methylation analyses, faster miniaturized proteomics and live cellular stainings, are opening a new era in cancer research. Perhaps the difference this time can be envisaged as the beginning of the long-sought individualization of forthcoming cancer therapies. Cancer has complex genetic susceptibility that is wider than previously thought. Apart from genes encoding six functional capabilities of cancer - independent growth, avoidance of apoptosis, immortalization, multi-drug resistance, neovascularization, and invasiveness - predisposition includes four more factors that promote genome instability, inflammation, deregulation of metabolism as well as evasion of destruction by the immune system. The underlying genetic events, i.e. base-pair DNA mutations, are not the sole factors in cancer development. Additional novel controls of gene expression have been found in the epigenetic machinery, which has been increasingly important in assessing cancer risk in recent years. The predisposing factors, including their regulatory elements, are bona fide potential new targets in prospective cancer pharmacotherapy.

Denduluri, N. and W. B. Ershler (2004). "Aging biology and cancer." Semin Oncol **31**(2): 137-148.

Epidemiologic analyses of current registries indicate that the majority of patients in the United States with cancer are 65 years old or older. Basic research in both gerontology and oncology has led to an understanding that these processes (normal aging and the development of cancer) have much in common. In this review we attempt to frame specific aspects of cancer biology in the context of normal aging.

Desai, P. B. (1994). "Understanding the biology of cancer: has this any impact on treatment?" J Cancer Res Clin Oncol **120**(4): 193-199.

Rapid advances in laboratory techniques in the last two decades and, what is more important, in the last 5-7 years have significantly increased our knowledge and understanding on many fronts. We have learned much about (a) the basic biological processes of growth control and its aberrations, (b) the possible mechanisms involved in genetic initiation, progression and suppression, (c) the complexity of the multistep carcinogenesis induced by viruses, chemicals, hormones and other iatrogenic factors, (d) the secrets of immunological defence mechanisms and a host of other fundamental processes, (e) the application of molecular biology techniques to clinical problems, etc. The list is unending and often leads the uninitiated clinician to believe that the resolution of the mystery of the cancer cell and its successful control and cure are almost at

hand. He or she often comes to believe that conventional principles in cancer treatment have radically changed from the 1960 and 1970 and that a new era in cancer treatment, based on our recent biological understanding, has already arrived. There is little doubt that the treatment scenario has changed significantly and that there is more hope for a cancer patient today than ever before-especially in certain types of paediatric and lymphoproliferative disorders; however, the unfortunate fact is that this cautiously optimistic therapeutic scenario has come about not because of any great understanding of the biological processes, which continue to confound us, but because of the intense interaction of various therapeutic disciplines and sophisticated technology now available for early diagnosis and more efficient therapeutic procedures in radiotherapy, chemotherapy and surgery. The author presents evidence and data here to show that, while treatment results have improved, we have a long way to go in understanding the biological processes before our knowledge can have a significant impact on the overall treatment methods in current use. The principles of cancer treatment, though modified have not changed. In fact, in the light of our current knowledge, they have been re-emphasized.

Dillon, D. A., et al. (1998). "The molecular biology of breast cancer: accelerating clinical applications." Crit Rev Oncog **9**(2): 125-140.

Recent advances in basic science have led to a better understanding of the molecular events important in the pathogenesis of breast cancer. Very little of this new knowledge, however, has had a significant impact on improving the diagnosis and therapy of breast cancer. We review many of the molecular events important in the pathogenesis of breast cancer, including inherited abnormalities in BRCA-1 and BRCA-2, p53, ATM, and PTEN and sporadic alterations in growth factors and their receptors, signal transduction, cell cycle control, DNA repair, cell death, angiogenesis, and invasion and metastasis. We suggest ways to speed up clinical applications of the new molecular knowledge base through the use of preclinical disease models, development of high throughput sample analysis and infrastructure programs to facilitate translational research, implementation of practice guidelines, and development of regional oncology networks. Only through the implementation of such a deliberate, multifaceted strategy will the gap between the research laboratory and the clinic be closed.

Dingjan, T., et al. (2015). "Structural biology of antibody recognition of carbohydrate epitopes and potential uses for targeted cancer immunotherapies." Mol Immunol **67**(2 Pt A): 75-88.

Monoclonal antibodies represent the most successful class of biopharmaceuticals for the treatment of cancer. Mechanisms of action of therapeutic antibodies are very diverse and reflect their ability to engage in antibody-dependent effector mechanisms, internalize to deliver cytotoxic payloads, and display direct effects on cells by lysis or by modulating the biological pathways of their target antigens. Importantly, one of the universal changes in cancer is glycosylation and carbohydrate-binding antibodies can be produced to selectively recognize tumor cells over normal tissues. A promising group of cell surface antibody targets consists of carbohydrates presented as glycolipids or glycoproteins. In this review, we outline the basic principles of antibody-based targeting of carbohydrate antigens in cancer. We also present a detailed structural view of antibody recognition and the conformational properties of a series of related tissue-blood group (Lewis) carbohydrates that are being pursued as potential targets of cancer immunotherapy.

Diori Karidio, I. and S. H. Sanlier (2021). "Reviewing cancer's biology: an eclectic approach." J Egypt Natl Canc Inst **33**(1): 32.

BACKGROUND: Cancer refers to a group of some of the worldwide most diagnosed and deadliest pathophysiological conditions that conquered researchers' attention for decades and yet begs for more questions for a full comprehension of its complex cellular and molecular pathology. MAIN BODY: The disease conditions are commonly characterized by unrestricted cell proliferation and dysfunctional replicative senescence pathways. In fact, the cell cycle operates under the rigorous control of complex signaling pathways involving cyclins and cyclin-dependent kinases assumed to be specific to each phase of the cycle. At each of these checkpoints, the cell is checked essentially for its DNA integrity. Genetic defects observed in these molecules (i.e., cyclins, cyclin-dependent kinases) are common features of cancer cells. Nevertheless, each cancer is different concerning its molecular and cellular etiology. These could range from the genetic defects mechanisms and/or the environmental conditions favoring epigenetically harbored homeostasis driving tumorigenesis alongside with the intratumoral heterogeneity with respect to the model that the tumor follows. CONCLUSIONS: This review is not meant to be an exhaustive interpretation of carcinogenesis but to summarize some basic features of the molecular etiology of cancer and the intratumoral heterogeneity models that eventually bolster anticancer drug resistance for a more efficient design of drug targeting the pitfalls of the models.

Domchek, S. M. and B. L. Weber (2002). "Recent advances in breast cancer biology." Curr Opin Oncol **14**(6): 589-593.

Developments in breast cancer biology over the last year have brought molecular medicine closer to the clinic. Within the past year, two major advances have taken place. First, microarray-based expression profiling has shown promise with the preliminary demonstration that clustering techniques can predict clinical outcome in lymphoma, pediatric leukemia, and breast cancer. Data in breast cancer have demonstrated the ability of microarray-based expression profiling to detect tumor cells in peripheral blood samples, to predict chemotherapy responses in fine-needle aspiration samples in neoadjuvant chemotherapy, and, most importantly, to predict disease-free survival and overall survival from profiles in breast cancer surgical specimens. Second, in breast cancer genetics, CHEK2 was identified as one of what are likely to be many low-penetrance breast cancer susceptibility genes. These studies demonstrate the transition of basic biologic research to clinical application.

Donaldson, T. D. and R. J. Duronio (2004). "Cancer cell biology: Myc wins the competition." Curr Biol **14**(11): R425-427.

During Drosophila development, cells with elevated levels of the Myc oncoprotein grow faster than, and induce cell death in, nearby wild-type cells, suggesting how inappropriate Myc over-expression provides cells with a competitive advantage that can lead to cancer.

Dzobo, K. (2020). "Taking a Full Snapshot of Cancer Biology: Deciphering the Tumor Microenvironment for Effective Cancer Therapy in the Oncology Clinic." OMICS **24**(4): 175-179.

A bottleneck that is hindering therapeutics innovation in cancers is the current lack of integration of what we have learned in tumor biology as well as the tumor microenvironment (TME). This is because tumors are complex tissues composed of cancer cells, stromal cells, and the extracellular matrix (ECM). Although genetic alterations might cause the initial uncontrolled growth, resistance to apoptosis in cancer cells and stromal cells play additional key roles within the TME and thus influence tumor initiation, progression, therapy resistance, and metastasis. Therapies targeting cancer cells are usually insufficient when the stromal component of the TME causes therapy resistance. For innovation in cancer treatment and to take a full snapshot of cancer biology, anticancer drug design must, therefore, target both cancer cells and the stromal component. This expert review critically examines the TME components such as cancer-associated fibroblasts and ECM that can be reprogrammed to create a tumor-suppressive environment, thereby aiding in tumor treatment. Better cancer experimental models that mimic the TME such as tumor spheroids, microfluidics, three dimensional (3D) bioprinted models, and organoids will allow deeper investigations of the TME complexity and can lead to the translation of basic tumor biology to effective cancer treatments. Ultimately, innovative cancer treatments and, by extension, improvement in cancer patients' outcomes will emerge from combinatorial drug development strategies targeting both cancer cells and stromal components of the TME. Combinatorial treatment strategies can take the form of chemotherapy and radiotherapy (targeting tumor cells and stromal components) and immunotherapy that is able to regulate immune responses against tumor cells. This expert review thus addresses a previously neglected knowledge gap in cancer drug design and development by broadening the focus in cancer biology to TME so as to empower disruptive health care innovations in the oncology clinic.

Effert, P. J. and T. G. Strohmeyer (1994). "Basic research in prostate cancer: molecular biology." Acta Urol Belg **62**(1): 15-21.

While a general appreciation for the importance of chromosomes in the development of cancer has existed for decades, molecular genetic analyses have gained considerable attention in recent years through identification of proto-oncogenes and tumor suppressor genes. Several different chromosomal aberrations, alterations of proto-oncogenes and suppressor genes have been described in prostate cancer. Loss of genetic material has been found to occur most frequently on chromosomes 7, 8, 10 and 16. The existence of tumor suppressor genes relevant to prostate carcinogenesis is suspected in these chromosomal locations. Several investigators are currently trying to identify these genes. Altered expression of several different oncogenes has been reported in prostate cancer. Among these, the ras- and myc-families of oncogenes have been studied most intensively. Structural oncogene alterations have been detected infrequently, most of the changes appear to occur transcriptionally. Despite an abundance of clinical material, knowledge about genetic lesions in prostate cancer is still very limited and sometimes conflicting results have been reported. With recent methodologic improvements and a growing interest in correlating genetic alterations with clinical disease progression, definition of prostate carcinogenesis at the molecular level will advance rapidly in the near future.

Errington, T. M., et al. (2021). "Challenges for assessing replicability in preclinical cancer biology." Elife **10**.

We conducted the Reproducibility Project: Cancer Biology to investigate the replicability of preclinical research in cancer biology. The initial aim of the project was to repeat 193 experiments from 53 high-impact papers, using an approach in which the

experimental protocols and plans for data analysis had to be peer reviewed and accepted for publication before experimental work could begin. However, the various barriers and challenges we encountered while designing and conducting the experiments meant that we were only able to repeat 50 experiments from 23 papers. Here we report these barriers and challenges. First, many original papers failed to report key descriptive and inferential statistics: the data needed to compute effect sizes and conduct power analyses was publicly accessible for just 4 of 193 experiments. Moreover, despite contacting the authors of the original papers, we were unable to obtain these data for 68% of the experiments. Second, none of the 193 experiments were described in sufficient detail in the original paper to enable us to design protocols to repeat the experiments, so we had to seek clarifications from the original authors. While authors were extremely or very helpful for 41% of experiments, they were minimally helpful for 9% of experiments, and not at all helpful (or did not respond to us) for 32% of experiments. Third, once experimental work started, 67% of the peer-reviewed protocols required modifications to complete the research and just 41% of those modifications could be implemented. Cumulatively, these three factors limited the number of experiments that could be repeated. This experience draws attention to a basic and fundamental concern about replication - it is hard to assess whether reported findings are credible.

Fiorentino, F. P., et al. (2011). "CTCF and BORIS regulate Rb2/p130 gene transcription: a novel mechanism and a new paradigm for understanding the biology of lung cancer." Mol Cancer Res **9**(2): 225-233.

Although innumerable investigations regarding the biology of lung cancer have been carried out, many aspects thereof remain to be addressed, including the role played by the retinoblastoma-related protein Rb2/p130 during the evolution of this disease. Here we report novel findings on the mechanisms that control Rb2/p130 gene expression in lung fibroblasts and characterize the effects of Rb2/p130 deregulation on the proliferative features of lung cancer cells. We revealed for the first time that in lung fibroblasts the expression of Rb2/p130 gene is directly controlled by the chromatin insulator CCCTC-binding factor, CTCF, which by binding to the Rb2/p130 gene promoter induces, and/or maintains, a specific local chromatin organization that in turn governs the transcriptional activity of Rb2/p130 gene. However, in lung cancer cells the activity of CTCF in controlling Rb2/p130 gene expression is impaired by BORIS, a CTCF-paralogue, which by binding to the Rb2/p130 gene could trigger changes in the chromatin asset established by CTCF, thereby affecting CTCF regulatory activity on Rb2/p130 transcription. These studies not only provide essential basic insights into the molecular mechanisms that control Rb2/p130 gene expression in lung cancer, but also offer a potential paradigm for the actions of other activators and/or corepressors, such as CTCF and BORIS, that could be crucial in explaining how alterations in the mechanism regulating Rb2/p130 gene expression may accelerate the progression of lung tumors, or favor the onset of recurrence after cancer treatment.

Friess, H., et al. (1994). "[Molecular biology of pancreatic cancer: overexpression of fibroblast growth factors]." Chirurg **65**(7): 604-610.

In the present study, the expression of a acidic fibroblast growth factor (aFGF), basic fibroblast growth factor (bFGF) and fibroblast growth factor receptor-1 were analyzed in 60 pancreatic cancer samples using Northern blot analysis, immunoblotting, in situ hybridization and immunohistochemical techniques. aFGF, bFGF and FGFR-1 were present in 63%, 55% and 52% of the tumor samples, respectively. Twenty-seven of the 60 pancreatic cancer tissue samples exhibited coexpression of aFGF and bFGF. In contrast, 14 of the tumor samples did not show immunoreactivity for aFGF or bFGF in the tumor cells. The expression of aFGF in the tumor cells had no influence on the postoperative survival period, whereas patients whose tumors were positive for bFGF and/or FGF-receptor-1 had significantly shorter postoperative survival periods. Our results suggest that bFGF and FGFR-1 may play a role in the growth behavior of pancreatic cancer and may contribute to tumor aggressiveness.

Fruhwald, M. C. and C. Plass (2002). "Global and gene-specific methylation patterns in cancer: aspects of tumor biology and clinical potential." Mol Genet Metab **75**(1): 1-16.

Heritable alterations of DNA that do not affect the base pair sequence itself but nevertheless regulate the predetermined activity of genes are referred to as epigenetic. Epigenetic mechanisms comprise diverse phenomena including stable feedback loops, nuclear compartmentalization, differential replication timing, heritable chromatin structures, and, foremost, DNA cytosine methylation (1-3). DNA cytosine methylation has recently gained major attention in the field of basic molecular biology as well as in studies of human diseases including cancer. Changes in DNA methylation patterns in human malignancies have been shown to contribute to carcinogenesis in multiple ways. Both hypo- and hypermethylation events have been described in various neoplasias leading to chromosomal instability and transcriptional gene silencing. DNA methylation research has entered the clinical arena and methylation patterns have become a major focus of clinicians seeking novel prognostic factors and therapeutic targets. The following minireview covers aspects of the basic

molecular biology of DNA methylation and summarizes its importance in human cancers.

Fujiwara, Y., et al. (2002). "[Molecular biology-based surgery for the future progress of cancer treatment]." Nihon Geka Gakkai Zasshi **103**(3): 278-283.

The basic surgical procedures for all diseases and organs were established by the end of the 20th century. However, the results of surgical treatment in cancer patients are still unsatisfactory. Despite radical resection based on the conventional diagnostic system for cancer metastases, disease recurrence and relapse are major problems in the clinical field of oncology. Standarized therapy without understanding the biology of tumors has not contributed significantly to cancer patients. Here, we propose that molecular biology-based surgery, or a strategy of surgical oncology based on information obtained from new molecular techniques should be urgently established to improve the management of cancer patients.

Giordano, G. G., et al. (2000). "New dimensions in cancer biology and therapy." J Cell Physiol **183**(2): 284-287.

The most successful and productive approach to defeat cancer relies on highly integrated and interchanging cooperation between basic research, diagnosis, and therapeutic innovation. Nevertheless, much remains to be done to achieve a consistent and continuous flow of theoretical and practical information among scientists actively involved in these equally relevant fields. The major objective of the International Conferences, "New Dimensions in Cancer Biology and Therapy," has been identified in gathering together basic scientists and clinicians who represent scientific leaders in their field, whose working efforts are focused on specific human malignancies. Thus, in pursuit of this well-defined goal, the third edition of the Conference has focused on human immunodeficiency virus (HIV) and cancer, cutaneous melanoma, and colorectal carcinoma, which are ideal clinical examples for innovative diagnostic and therapeutic intervention, as well as optimal models to unveil new mechanisms of tumor pathogenesis.

Green, A. S., et al. (2011). "LKB1/AMPK/mTOR signaling pathway in hematological malignancies: from metabolism to cancer cell biology." Cell Cycle **10**(13): 2115-2120.

The link between cancer and metabolism has been suggested for a long time but further evidence of this hypothesis came from the recent molecular characterization of the LKB1/AMPK signaling pathway as a tumor suppressor axis. Besides the discovery of somatic mutations in the LKB1 gene in certain type of cancers, a critical emerging point was that the LKB1/AMPK axis remains generally functional and could be stimulated by pharmacological molecules such as metformin in cancer cells. Notably, most of experimental evidence of the anti-tumor activity of AMPK agonists comes from the study of solid tumors such as breast or prostate cancers and only few data are available in hematological malignancies, although recent works emphasized the potential therapeutic value of AMPK agonists in this setting. Further basic research work should be conducted to elucidate the molecular targets of LKB1/AMPK responsible for its anti-tumor activity in parallel of conducting clinical trials using metformin, AICAR or new AMPK activating agents to explore the potential of the LKB1/AMPK signaling pathway as a new target for anticancer drug development.

Guller, A., et al. (2021). "Chick Embryo Experimental Platform for Micrometastases Research in a 3D Tissue Engineering Model: Cancer Biology, Drug Development, and Nanotechnology Applications." Biomedicines **9**(11).

Colonization of distant organs by tumor cells is a critical step of cancer progression. The initial avascular stage of this process (micrometastasis) remains almost inaccessible to study due to the lack of relevant experimental approaches. Herein, we introduce an in vitro/in vivo model of organ-specific micrometastases of triple-negative breast cancer (TNBC) that is fully implemented in a cost-efficient chick embryo (CE) experimental platform. The model was built as three-dimensional (3D) tissue engineering constructs (TECs) combining human MDA-MB-231 cells and decellularized CE organ-specific scaffolds. TNBC cells colonized CE organ-specific scaffolds in 2-3 weeks, forming tissue-like structures. The feasibility of this methodology for basic cancer research, drug development, and nanomedicine was demonstrated on a model of hepatic micrometastasis of TNBC. We revealed that MDA-MB-231 differentially colonize parenchymal and stromal compartments of the liver-specific extracellular matrix (LS-ECM) and become more resistant to the treatment with molecular doxorubicin (Dox) and Dox-loaded mesoporous silica nanoparticles than in monolayer cultures. When grafted on CE chorioallantoic membrane, LS-ECM-based TECs induced angiogenic switch. These findings may have important implications for the diagnosis and treatment of TNBC. The methodology established here is scalable and adaptable for pharmacological testing and cancer biology research of various metastatic and primary tumors.

Gussack, G. S., et al. (1984). "Biology of tumors and head and neck cancer chemotherapy." Laryngoscope **94**(9): 1181-1187.

The management of advanced squamous cell carcinomas of the head and neck has shown disappointing results with surgery and radiation alone. Chemotherapy offers a third method of managing these patients. A background of basic tumor biology and cell cycle kinetics is essential in designing an effective head and neck chemotherapeutic protocol. The principles of the cell cycle, stem cell regulation, and doubling times are discussed. The kinetic classification of chemotherapeutic agents and experimental hypotheses of clinical relevance are reviewed.

Guttilla Reed, I. K. (2021). "CUREing cancer: Development and implementation of a molecular biology-focused course-based undergraduate research experience using a cancer cell culture model." Biochem Mol Biol Educ **49**(2): 287-297.

Many students in the sciences are interested in exploring research opportunities; however, the one-on-one faculty mentorship model often lacks the ability to supervise large numbers of students. An alternative mechanism for exposing undergraduate students to the research process is participation in a Course-based Undergraduate Research Experience (CURE). CUREs promote inclusivity in research, and provide structure for both students and faculty while engaging students in scientific discovery. This study describes a model for a CURE in cancer biology, and reports student outcomes. Students utilized bioinformatics to predict targets genes of miR-100, a microRNA that is differentially expressed in a cell culture model of breast cancer metastasis. Students were required to engage with primary literature to write a grant proposal for their target gene, and then were trained to perform basic molecular biology techniques to test their individual hypotheses. Additionally, the course integrated opportunities to troubleshoot experiments and present data to the group, and culminated in a publication style scientific report discussing the results of their individual research project. Students reported significantly increased confidence in executing various molecular biology techniques and research-related skills based on pre- and post-assessment surveys. Student feedback also indicated that they gained an understanding of primary literature, experimental design, and scientific writing as a result of the course. This study supports that CUREs can be an effective pedagogy for not only engaging larger groups of students in research, but also improving their confidence and skill set in the laboratory.

Haq, R. and D. E. Fisher (2011). "Biology and clinical relevance of the micropthalmia family of transcription factors in human cancer." J Clin Oncol **29**(25): 3474-3482.

Members of the micropthalmia (MiT) family of transcription factors (MITF, TFE3, TFEB, and TFEC) are physiologic regulators of cell growth, differentiation, and survival in several tissue types. Because their dysregulation can lead to melanoma, renal cell carcinoma, and some sarcomas, understanding why these genes are co-opted in carcinogenesis may be of general utility. Here we describe the structure of the MiT family of proteins, the ways in which they are aberrantly activated, and the molecular mechanisms by which they promote oncogenesis. We discuss how meaningful understanding of these mechanisms can be used to elucidate the oncogenic process. Because the expression of these proteins is essential for initiating and maintaining the oncogenic state in some cancer types, we propose ways that they can be exploited to prevent, diagnose, and rationally treat these malignancies.

Helder, M. N., et al. (2002). "Telomerase and telomeres: from basic biology to cancer treatment." Cancer Invest **20**(1): 82-101.

The limited capacity to divide is one of the major differences between normal somatic cells and cancerous cells. This 'finite life span' of somatic cells is closely linked to loss of telomeric DNA at telomeres, the 'chromosome caps' consisting of repeated (7TAGGG) sequences., In more than 85% of advanced cancers, this telomeric attrition is compensated by telomerase, 'the immortality enzyme', implying that telomerase inhibition may restore mortality in tumor cells. This review discusses the progress in research on the structure and function of telomeres and the telomerase holoenzyme. In addition, new developments in telomere/telomerase targeting compounds such as antisense oligonucleotides and G-quadruplex stabilizing substances, but also new telomerase expression-related strategies such as telomerase promoter-driven suicide gene therapy and telomerase immunotherapy will be presented. It will be discussed how these data can be implemented in telomerase-directed therapies.

Henze, A. T. and T. Acker (2010). "Feedback regulators of hypoxia-inducible factors and their role in cancer biology." Cell Cycle **9**(14): 2749-2763.

Malignant tumors are characterized by regions of low oxygen concentration (hypoxia). The hypoxic tumor microenvironment contributes to tumor progression by activating a set of adaptive responses via the key transcriptional regulators HIF-1alpha and HIF-2alpha. These factors have been traditionally linked to an aggressive tumor phenotype by promoting processes essential for tumor growth, such as angiogenesis, glycolysis, metastasis and invasion, as well as differentiation and self renewal. Notably, the complex HIF pathway also initiates anti-tumorigenic mechanisms that lead to cell cycle arrest or cell death, indicating the need for a stringent control of the extent and the direction of the hypoxia response. The importance of

this control for tumor cell survival is illustrated by the intricate regulation of HIF activity at the mRNA, protein and epigenetic level by a complex network of positive and negative feedback regulators. We propose that these feedback regulators help to flexibly adjust and adapt HIF activated responses to the fluctuating oxygen concentrations within tumors during acute and chronic hypoxia and to curtail the tumor-suppressing components of the HIF pathway. Moreover, feedback regulation of HIF induces a switch from HIF-1alpha to HIF-2alpha driven responses under chronic hypoxia which may have essential functions in the regulation of tumor cell differentiation and tumor stem cell maintenance. Given their central role in cancer biology, HIF feedback regulators may represent an attractive and novel anti-tumor therapy target to overcome cell death resistance in tumors.

Horwitz, K. B. (1992). "The molecular biology of RU486. Is there a role for antiprogestins in the treatment of breast cancer?" Endocr Rev **13**(2): 146-163.

Considerable animal research and clinical trials demonstrate that progesterone antagonists could treat hormone-dependent breast cancers. Since endogenous progesterone does include mitosis in epithelial cells of the breast, in theory, exogenous progesterone can cause breast cancer. Thus administration of progesterone antagonists could block endogenous progesterone. Yet we do not know the mitosis pattern in breast cancer cells during the menstrual cycle, so research obtaining such data is needed. Ethical problems arise, however, since researchers need multiple breast tumor samples to analyze proliferative activity at various times during the cycle. A possible solution is using an aspirated tumor sample for initial mitotic analysis immediately followed by RU-486 treatment then tumor removal 24 hours later for reanalysis. Ideally well controlled studies using organ-cultured human breast tumors, human breast cancer lines, and human tumors implanted into nude mice are needed to understand the mechanisms of the mitogenic actions of progestins and progestin antagonists. Progestin antagonist may be used to treat locally advanced or metastatic cancers either as an adjuvant endocrine therapy alone or with tamoxifen. An obstacle to longterm use of RU-486 as a treatment for breast cancer is its antiglucocorticoid side effects. But the molecules of newer progesterone antagonists appear to produce maximal antiprogestin activity and minimal antiglucocorticoid activity. In addition, if RU-486 is administered with drugs that prevent adrenal steroidogenesis or peripheral aromatization of adrenal steroids to estrogens, women may take it for longterm treatment. Researchers must have the opportunity to continue basic tumor biological and molecular research to gain an understanding of the exact molecular targets and mechanisms of antagonist action. The current political climate in the US hinders such research, however.
eng

Iacobuzio-Donahue, C. A., et al. (2019). "Cancer biology as revealed by the research autopsy." Nat Rev Cancer **19**(12): 686-697.

A research autopsy is a post-mortem medical procedure performed on a deceased individual with the primary goal of collecting tissue to support basic and translational research. This approach has increasingly been used to investigate the pathophysiological mechanisms of cancer evolution, metastasis and treatment resistance. In this Review, we discuss the rationale for the use of research autopsies in cancer research and provide an evidence-based discussion of the quality of post-mortem tissues compared with other types of biospecimens. We also discuss the advantages of using post-mortem tissues over other types of biospecimens, including the large amounts of tissue that can be obtained and the extent of multiregion sampling that is achievable, which is not otherwise possible in living patients. We highlight how the research autopsy has supported the identification of the clonal origins and modes of spread among metastases, the extent that selective pressures imposed by treatments cause bottlenecks leading to parallel and convergent tumour evolution, and the creation of rare tissue banks and patient-derived model systems. Finally, we comment on the future of the research autopsy as an integral component of precision medicine strategies.

Igarashi, K., et al. (2021). "The transcription factor BACH1 at the crossroads of cancer biology: From epithelial-mesenchymal transition to ferroptosis." J Biol Chem **297**(3): 101032.

The progression of cancer involves not only the gradual evolution of cells by mutations in DNA but also alterations in the gene expression induced by those mutations and input from the surrounding microenvironment. Such alterations contribute to cancer cells' abilities to reprogram metabolic pathways and undergo epithelial-to-mesenchymal transition (EMT), which facilitate the survival of cancer cells and their metastasis to other organs. Recently, BTB and CNC homology 1 (BACH1), a heme-regulated transcription factor that represses genes involved in iron and heme metabolism in normal cells, was shown to shape the metabolism and metastatic potential of cancer cells. The growing list of BACH1 target genes in cancer cells reveals that BACH1 promotes metastasis by regulating various sets of genes beyond iron metabolism. BACH1 represses the expression of genes that mediate cell-cell adhesion and oxidative phosphorylation but activates the expression of genes required for glycolysis, cell motility, and matrix protein degradation. Furthermore,

BACH1 represses FOXA1 gene encoding an activator of epithelial genes and activates SNAI2 encoding a repressor of epithelial genes, forming a feedforward loop of EMT. By synthesizing these observations, we propose a "two-faced BACH1 model", which accounts for the dynamic switching between metastasis and stress resistance along with cancer progression. We discuss here the possibility that BACH1-mediated promotion of cancer also brings increased sensitivity to iron-dependent cell death (ferroptosis) through crosstalk of BACH1 target genes, imposing programmed vulnerability upon cancer cells. We also discuss the future directions of this field, including the dynamics and plasticity of EMT.

Joiner, M. C., et al. (2017). "IBPRO - A Novel Short-Duration Teaching Course in Advanced Physics and Biology Underlying Cancer Radiotherapy." Radiat Res **187**(6): 637-640.

This article provides a summary and status report of the ongoing advanced education program IBPRO - Integrated course in Biology and Physics of Radiation Oncology. IBPRO is a five-year program funded by NCI. It addresses the recognized deficiency in the number of mentors available who have the required knowledge and skill to provide the teaching and training that is required for future radiation oncologists and researchers in radiation sciences. Each year, IBPRO brings together 50 attendees typically at assistant professor level and upwards, who are already qualified/certified radiation oncologists, medical physicists or biologists. These attendees receive keynote lectures and activities based on active learning strategies, merging together the clinical, biological and physics underpinnings of radiation oncology, at the forefront of the field. This experience is aimed at increasing collaborations, raising the level and amount of basic and applied research undertaken in radiation oncology, and enabling attendees to confidently become involved in the future teaching and training of researchers and radiation oncologists.

Jones, A. (2004). "The molecular cell biology of head and neck cancer with clinical applications. Section 1: Fundamental biology and the basis of cancer." Clin Otolaryngol Allied Sci **29**(5): 475-491.

This article addresses the subject of the fundamental workings of the cell. The essential mechanisms that underlie life are discussed and explained as succinctly as intelligibility will allow and the basic principles of molecular and cell biology detailed. In preparing this article I have made reference not only to standard works but also to the most recent research. In the article I attempt to provide both the surgical and medical head and neck oncologist with the basic insights into fundamental oncology necessary to understand and treat the clinical conditions that are head and neck cancer. In addition I hope it will facilitate the understanding of the various evolving novel treatment strategies.

Jones, J. and T. A. Libermann (2007). "Genomics of renal cell cancer: the biology behind and the therapy ahead." Clin Cancer Res **13**(2 Pt 2): 685s-692s.

Renal cell cancer (RCC) is the most lethal of the urological cancers and accounts for 3% of all adult malignancies. Despite numerous recent advances in diagnostic imaging, surgical therapy, and basic molecular understanding, many patients still experience metastatic disease. For metastatic disease patients, response rates to conventional therapies rarely exceed 15% to 25% and are associated with serious adverse effects. The recent development of novel targeted therapies based on the precise biological pathways deregulated in a particular patient has paved the way for individualized, targeted patient management. Nevertheless, to achieve this goal, it is important to delineate the molecular mechanisms underlying cancer development and progression. Genomic approaches have revolutionized the field of cancer research and have led to the rapid discovery of multiple, parallel disease hypotheses, which ultimately have to be validated in large cohorts of patients and in downstream biological experiments for translation into clinical applications. The variable course of RCC and, until recently, a paucity of therapeutic options in the event of metastasis have led to the search for diagnostic and prognostic markers. We and others have used transcriptional profiling to classify different subtypes of RCC and to identify subtype- and metastasis-specific gene signatures predictive for outcome. We discuss herein recent genomic approaches to RCC and the emerging biological pathways underlying RCC development and progression. We also speculate how genomics may affect drug development and the management of patients with RCC.

Jones, L., et al. (2018). "New Approaches in Cancer Biology Can Inform the Biology Curriculum." Am Biol Teach **80**(3): 168-174.

Students tend to be very interested in medical issues that affect them and their friends and family. Using cancer as a hook, the ART of Reproductive Medicine: Oncofertility curriculum (free, online, and NIH sponsored) has been developed to supplement the teaching of basic biological concepts and to connect biology and biomedical research. This approach allows integration of up-to-date information on cancer and cancer treatment, cell division, male and female reproductive anatomy and physiology, cryopreservation, fertility preservation, stem cells, ethics, and epigenetics into an existing biology curriculum. Many of the topics covered in the

curriculum relate to other scientific disciplines, such as the latest developments in stem cell research including tissue bioengineering and gene therapy for inherited mitochondrial disease, how epigenetics occurs chemically to affect gene expression or suppression and how it can be passed down through the generations, and the variety of biomedical careers students could pursue. The labs are designed to be open-ended and inquiry-based, and extensions to the experiments are provided so that students can explore questions further. Case studies and ethical dilemmas are provided to encourage thoughtful discussion. In addition, each chapter of the curriculum includes links to scientific papers, additional resources on each topic, and NGSS alignment.

Jordan, C. T. (2004). "Cancer stem cell biology: from leukemia to solid tumors." Curr Opin Cell Biol **16**(6): 708-712.

The biology of stem cells and their intrinsic properties are now recognized as integral to tumor pathogenesis in several types of cancer. This observation has broad ramifications in the cancer research field and is likely to impact our understanding of the basic mechanisms of tumor formation and the strategies we use to treat cancers. A role for stem cells has been demonstrated for cancers of the hematopoietic system, breast and brain. Going forward it is likely that stem cells will also be implicated in other malignancies. Hence, a detailed understanding of stem cells and how they mediate tumor pathogenesis will be critical in developing more effective cancer therapies.

Jullienne, A. and M. S. Moukhtar (1984). "[Current perspectives of basic biology in medullary cancer of the thyroid]." Bull Cancer **71**(2): 130-132.

Kalemkerian, G. P. (1994). "Biology of lung cancer." Curr Opin Oncol **6**(2): 147-155.

Recent advances in basic research have greatly increased our understanding of the biologic events involved in the pathogenesis and progression of lung cancer. A multitude of genetic aberrations have been detected in both small-cell and non-small-cell lung cancer, many of which affect the function of known oncogenes and tumor-suppressor genes, which may serve as molecular targets for interventional trials. Recently identified abnormalities in oncogene expression and signal transduction pathways in premalignant lesions will be useful in devising future early diagnosis and chemoprevention studies. Numerous growth factor pathways control the proliferation and invasiveness of lung cancer cells and offer relatively tumor-specific targets for novel therapeutic approaches. Recent studies have defined several drug resistant mechanisms in lung cancer and have suggested methods for preventing and reversing treatment resistance. Insight into the biology of lung cancer will allow the improvement of current approaches to the prevention, diagnosis, and treatment of this devastating disease.

Kane, P. B. and J. Kimmelman (2021). "Is preclinical research in cancer biology reproducible enough?" Elife **10**.

The Reproducibility Project: Cancer Biology (RPCB) was established to provide evidence about reproducibility in basic and preclinical cancer research, and to identify the factors that influence reproducibility more generally. In this commentary we address some of the scientific, ethical and policy implications of the project. We liken the basic and preclinical cancer research enterprise to a vast 'diagnostic machine' that is used to determine which clinical hypotheses should be advanced for further development, including clinical trials. The results of the RPCB suggest that this diagnostic machine currently recommends advancing many findings that are not reproducible. While concerning, we believe that more work needs to be done to evaluate the performance of the diagnostic machine. Specifically, we believe three questions remain unanswered: how often does the diagnostic machine correctly recommend against advancing real effects to clinical testing?; what are the relative costs to society of false positive and false negatives?; and how well do scientists and others interpret the outputs of the machine?

Karlstaedt, A., et al. (2021). "Cardio-Oncology: Understanding the Intersections Between Cardiac Metabolism and Cancer Biology." JACC Basic Transl Sci **6**(8): 705-718.

An important priority in the cardiovascular care of oncology patients is to reduce morbidity and mortality, and improve the quality of life in cancer survivors through cross-disciplinary efforts. The rate of survival in cancer patients has improved dramatically over the past decades. Nonetheless, survivors may be more likely to die from cardiovascular disease in the long term, secondary, not only to the potential toxicity of cancer therapeutics, but also to the biology of cancer. In this context, efforts from basic and translational studies are crucial to understanding the molecular mechanisms causal to cardiovascular disease in cancer patients and survivors, and identifying new therapeutic targets that may prevent and treat both diseases. This review aims to highlight our current understanding of the metabolic interaction between cancer and the heart, including potential therapeutic targets. An overview of imaging techniques that can support both research studies and clinical management is also provided. Finally, this review highlights opportunities and challenges that are necessary to advance our

understanding of metabolism in the context of cardio-oncology.

King, J., et al. (2021). "Testicular Cancer: Biology to Bedside." Cancer Res **81**(21): 5369-5376.

Testicular cancer is the first solid tumor with a remarkably high cure rate. This success was only made possible through collaborative efforts of basic and clinical research. Most patients with distant metastases can be cured. However, the majority of these patients are diagnosed at a young age, leaving many decades for the development of treatment-related complications. This has magnified the importance of research into survivorship issues after exposure to platinum-based chemotherapy. This research, along with research into newer biomarkers that will aid in the diagnosis and surveillance of patients and survivors of testicular cancer, will continue to advance the field and provide new opportunities for these patients. There also remains the need for further therapeutic options for patients who unfortunately do not respond to standard treatment regimens and ultimately die from this disease, including a cohort of patients with late relapses and platinum-refractory disease. Here we discuss the advancements in management that led to a highly curable malignancy, while highlighting difficult situations still left to solve as well as emerging research into novel biomarkers.

Kitamura, H., et al. (2009). "Cancer stem cell: implications in cancer biology and therapy with special reference to lung cancer." Lung Cancer **66**(3): 275-281.

The cancer stem cell (CSC) theory is currently central to the field of cancer research, because it is not only a matter of academic interest but also crucial in cancer therapy. CSCs share a variety of biological properties with normal somatic stem cells in terms of self-renewal, the propagation of differentiated progeny, the expression of specific cell markers and stem cell genes, and the utilization of common signaling pathways and the stem cell niche. However, CSCs differ from normal stem cells in their tumorigenic activity. Thus, CSCs are also termed cancer initiating cells. In this paper, we briefly review hitherto described study results and refer to some excellent review articles to understand the basic properties of CSCs. In addition, we focus upon CSCs of lung cancers, since lung cancer is still increasing in incidence worldwide and remains the leading cause of cancer deaths. Understanding the properties of, and exploring cell markers and signaling pathways specific to, CSCs of lung cancers, will lead to progress in therapy, intervention, and improvement of the prognosis of patients with lung cancer. In the near future, the evaluation of CSCs may be a routine part of practical diagnostic pathology.

Kitamura, H., et al. (2009). "Small cell lung cancer: significance of RB alterations and TTF-1 expression in its carcinogenesis, phenotype, and biology." Endocr Pathol **20**(2): 101-107.

Small cell lung cancer (SCLC) exhibits highly aggressive behavior and has a poor prognosis. While numerous investigations have been carried out, the exact mechanism of its carcinogenesis and aggressiveness is still unclear. SCLC is categorized as a neuroendocrine neoplasia and has a genetic profile characterized by universal alterations of the RB and TP53 genes. Epidemiological studies indicate the majority of SCLCs to be caused by smoking and the TP53 mutational pattern to be consistent with that evoked by smoke carcinogens; however, there is no direct evidence that such carcinogens induce alterations to RB in SCLC. While the importance of these alterations in the carcinogenesis of SCLC is strongly suggested, the exact molecular mechanism has been only little elucidated. SCLC cells almost always express mammalian achaete-scute homolog-1 (MASH1) and thyroid transcription factor-1 (TTF-1). MASH1 plays a critical role in neuroendocrine differentiation. TTF-1 is a characteristic marker of distal airway cells and pulmonary adenocarcinomas, but is also expressed in extrapulmonary neuroendocrine cancers. Thus, TTF-1 may well play a significant role in the development of neuroendocrine cancers. Recent studies indicate that the airway stem cell is committed to the neuroendocrine lineage through MASH1 and Notch signaling and that only RB-deleted neuroendocrine cells selectively proliferate in response to E2F3, eventually undergoing transformation to neuroendocrine cancer cells, probably in concert with TP53 gene aberrations. Thus, alterations of both the RB and TP53 genes are central to the carcinogenesis of SCLC, while many other factors including MASH1 and TTF-1 contribute to the development and biological behavior of SCLC.

Kobos, R., et al. (2013). "Combining integrated genomics and functional genomics to dissect the biology of a cancer-associated, aberrant transcription factor, the ASPSCR1-TFE3 fusion oncoprotein." J Pathol **229**(5): 743-754.

Oncogenic rearrangements of the TFE3 transcription factor gene are found in two distinct human cancers. These include ASPSCR1-TFE3 in all cases of alveolar soft part sarcoma (ASPS) and ASPSCR1-TFE3, PRCC-TFE3, SFPQ-TFE3 and others in a subset of paediatric and adult RCCs. Here we examined the functional properties of the ASPSCR1-TFE3 fusion oncoprotein, defined its target promoters on a genome-wide basis and performed a high-throughput RNA interference screen to identify which of its transcriptional targets contribute to cancer cell proliferation. We first confirmed that ASPSCR1-TFE3

has a predominantly nuclear localization and functions as a stronger transactivator than native TFE3. Genome-wide location analysis performed on the FU-UR-1 cell line, which expresses endogenous ASPSCR1-TFE3, identified 2193 genes bound by ASPSCR1-TFE3. Integration of these data with expression profiles of ASPS tumour samples and inducible cell lines expressing ASPSCR1-TFE3 defined a subset of 332 genes as putative up-regulated direct targets of ASPSCR1-TFE3, including MET (a previously known target gene) and 64 genes as down-regulated targets of ASPSCR1-TFE3. As validation of this approach to identify genuine ASPSCR1-TFE3 target genes, two up-regulated genes bound by ASPSCR1-TFE3, CYP17A1 and UPP1, were shown by multiple lines of evidence to be direct, endogenous targets of transactivation by ASPSCR1-TFE3. As the results indicated that ASPSCR1-TFE3 functions predominantly as a strong transcriptional activator, we hypothesized that a subset of its up-regulated direct targets mediate its oncogenic properties. We therefore chose 130 of these up-regulated direct target genes to study in high-throughput RNAi screens, using FU-UR-1 cells. In addition to MET, we provide evidence that 11 other ASPSCR1-TFE3 target genes contribute to the growth of ASPSCR1-TFE3-positive cells. Our data suggest new therapeutic possibilities for cancers driven by TFE3 fusions. More generally, this work establishes a combined integrated genomics/functional genomics strategy to dissect the biology of oncogenic, chimeric transcription factors.

Koeneman, K. S. (2006). "Prostate cancer stem cells, telomerase biology, epigenetic modifiers, and molecular systemic therapy for the androgen-independent lethal phenotype." Urol Oncol **24**(2): 119-121.

Numerous, relatively well-characterized androgen-independent osteotropic prostate cancer cell lines are now available to interrogate clinically relevant fundamental questions of prostate cancer metastasis and lethal progression systematically. Mounting basic and translational science efforts reveal that, very likely, the currently incurable form of androgen independent osseous prostate cancer originates from a more undifferentiated or "stem cell" like component, coexisting within a heterogeneous tumor mass containing more differentiated epithelial cancer subtypes. Current therapeutic preclinical investigations point toward the use of epigenetic modifiers, such as histone deacetylase inhibitors, to abrogate the continued survival of prostate cancer cells and likely can be used relatively chronically, with little morbidity. Telomere maintenance is critical in the immortalization of prostate cancer cells, and all known androgen independent cell line variants invariably express telomerase, and, thus, an argument can be made that these aggressive cells are likened to immature, progenitor variants. The arena of telomere biology has evolved enough to provide precise, nontoxic small molecule inhibitors of telomerase that limit viability of androgen-independent cell lines, yielding apoptosis. Both epigenetic modifiers and telomerase-directed small molecule inhibitors have enhanced efficacy when given in combination with conventional and novel cytotoxic drugs. Better knowledge of the "stem cell" nature of prostate cancer will help direct the molecularly targeted therapies of the near future.

Kohonen, P., et al. (2014). "Cancer biology, toxicology and alternative methods development go hand-in-hand." Basic Clin Pharmacol Toxicol **115**(1): 50-58.

Toxicological research faces the challenge of integrating knowledge from diverse fields and novel technological developments generally in the biological and medical sciences. We discuss herein the fact that the multiple facets of cancer research, including discovery related to mechanisms, treatment and diagnosis, overlap many up and coming interest areas in toxicology, including the need for improved methods and analysis tools. Common to both disciplines, in vitro and in silico methods serve as alternative investigation routes to animal studies. Knowledge on cancer development helps in understanding the relevance of chemical toxicity studies in cell models, and many bioinformatics-based cancer biomarker discovery tools are also applicable to computational toxicology. Robotics-aided, cell-based, high-throughput screening, microscale immunostaining techniques and gene expression profiling analyses are common tools in cancer research, and when sequentially combined, form a tiered approach to structured safety evaluation of thousands of environmental agents, novel chemicals or engineered nanomaterials. Comprehensive tumour data collections in databases have been translated into clinically useful data, and this concept serves as template for computer-driven evaluation of toxicity data into meaningful results. Future 'cancer research-inspired knowledge management' of toxicological data will aid the translation of basic discovery results and chemicals- and materials-testing data to information relevant to human health and environmental safety.

Kujawa, K. A. and K. M. Lisowska (2015). "[Ovarian cancer--from biology to clinic]." Postepy Hig Med Dosw (Online) **69**: 1275-1290.

Ovarian cancer is the most frequent cause of deaths from among gynecologic malignancies. Due to its asymptomatic development the disease is frequently diagnosed at an advanced, incurable stages. Although ovarian cancers usually respond well to the first line chemotherapy based on platinum compounds and taxanes, majority of patients develop recurrence and chemo-resistance. Despite many years of studies there is

still lack of reliable diagnostic markers as well as other diagnostic methods enabling early detection and suitable for screening. Thus, current studies are aimed on finding new biomarkers with diagnostic, prognostic and predictive potential as well as on the search for the new therapeutic targets. Interestingly, an understanding of ovarian cancer etiology has changed fundamentally within recent years. The classical theory, claiming that ovarian cancers originate from ovarian surface epithelial cells, was undermined. Currently, there is a lot of evidence that majority of serous ovarian cancers have its origin in malignant tubal epithelium, while endometrioid and clear cell ovarian cancers develop most likely from endometriosis. These new findings will have an impact on diagnostic approaches as well as on the prevention options for women with genetic predisposition to ovarian cancer. The new knowledge about an origin of different histological types of ovarian cancer may open new pathways in basic research and clinical studies. In this paper we report current knowledge about ovarian cancer risk factors, we also present the arguments for extraovarian origin of the majority of ovarian cancers and stress the mechanisms of action of new drugs for targeted therapies that show most promising results in the current clinical trials.

Ladanyi, M. and P. C. Hogendoorn (2011). "Cancer biology and genomics: translating discoveries, transforming pathology." J Pathol **223**(2): 99-101.

Advances in our understanding of cancer biology and discoveries emerging from cancer genomics are being translated into real clinical benefits for patients with cancer. The 2011 Journal of Pathology Annual Review Issue provides a snapshot of recent rapid progress on multiple fronts in the war on cancer or, more precisely, the wars on cancers. Indeed, perhaps the most notable recent shift is reflected by the sharp increase in understanding the biology of multiple specific cancers and using these new insights to inform rationally targeted therapies, with often striking successes. These recent developments, as reviewed in this issue, show how the long-term investments in basic cancer research are finally beginning to bear fruit.

Lamarre, N. S., et al. (2007). "Effect of obese and lean Zucker rat sera on human and rat prostate cancer cells: implications in obesity-related prostate tumor biology." Urology **69**(1): 191-195.

OBJECTIVES: Several reports have demonstrated the effects of obesity on prostate cancer. Also several reports have linked expression of vascular endothelial cell growth factor (VEGF) and basic fibroblast growth factor (FGF-2) to prostate cancer aggressiveness. The objective of this study was to determine whether a difference exists between lean and obese Zucker rat sera on proliferation prostate cancer cell lines, as well as to examine the differences in FGF-2 and VEGF concentrations. METHODS: Ten-week-old female obese and lean Zucker rat sera were subjected to charcoal stripping and tested for the proliferation of human LNCaP and rat AT3B-1 prostate cancer cells. An acetonitrile extract of the charcoal used to strip the sera was also tested for mitogenicity. VEGF and FGF-2 concentrations were determined by enzyme-linked immunosorbent assay. RESULTS: Both unstripped and charcoal-stripped obese rat sera had a greater mitogenic effect than did the lean sera on the LNCaP cell line. Charcoal stripping of both obese and lean sera reduced the mitogenic effect on the AT3B-1 cell line. The acetonitrile extract of the charcoal used to strip the sera was unable to recover this proliferative effect. The concentration of VEGF was greater in the obese serum than in the lean serum, and charcoal stripping reduced the concentrations of both FGF-2 and VEGF. CONCLUSIONS: The finding of greater VEGF in obese rat sera, as well as greater mitogenic responses on human prostate cancer cells in vitro, suggests this as one of the many possible mechanisms involved in obesity-related prostate cancer biology.

Larsen, J. E. and J. D. Minna (2011). "Molecular biology of lung cancer: clinical implications." Clin Chest Med **32**(4): 703-740.

Lung cancer is a heterogeneous disease clinically, biologically, histologically, and molecularly. Understanding the molecular causes of this heterogeneity, which might reflect changes occurring in different classes of epithelial cells or different molecular changes occurring in the same target lung epithelial cells, is the focus of current research. Identifying the genes and pathways involved, determining how they relate to the biological behavior of lung cancer, and their utility as diagnostic and therapeutic targets are important basic and translational research issues. This article reviews current information on the key molecular steps in lung cancer pathogenesis, their timing, and clinical implications.

Levi, F., et al. (2007). "Cross-talks between circadian timing system and cell division cycle determine cancer biology and therapeutics." Cold Spring Harb Symp Quant Biol **72**: 465-475.

The circadian clock orchestrates cellular functions over 24 hours, including cell divisions, a process that results from the cell cycle. The circadian clock and cell cycle interact at the level of genes, proteins, and biochemical signals. The disruption or the reinforcement of the host circadian timing system, respectively, accelerates or slows down cancer growth through modifications of host and tumor circadian clocks. Thus, cancer cells not only display mutations of cell cycle genes but also exhibit severe defects in clock

gene expression levels or 24-hour patterns, which can in turn favor abnormal proliferation. Most of the experimental research actively ongoing in this field has been driven by the original demonstration that cancer patients with poor circadian rhythms had poor quality of life and poor survival outcome independently of known prognostic factors. Further basic research on the gender dependencies in circadian properties is now warranted, because a large clinical trial has revealed that gender can largely affect the survival outcome of cancer patients on chronotherapeutic delivery. Mathematical models further show that the therapeutic index of chemotherapeutic drugs can be optimized through distinct delivery profiles, depending on the initial host/tumor status and variability in circadian entrainment and/or cell cycle length. Clinical trials and systems-biology approaches in cancer chronotherapeutics raise novel issues to be addressed experimentally in the field of biological clocks. The challenge ahead is to therapeutically harness the circadian timing system to concurrently improve quality of life and down-regulate malignant growth.

Lindblom, A. and M. Nordenskjold (2000). "The biology of inherited cancer." Semin Cancer Biol **10**(4): 251-254.

This issue of Cancer Biology is focused on inherited cancer. In this short introduction to the topic we give a brief overview and list genes and the corresponding inherited cancer syndromes. We discuss the basic mechanisms of inherited cancer and the clinical implication of predictive genetic testing for cancer.

Liu, K. E. (2018). "Rethinking Causation in Cancer with Evolutionary Developmental Biology." Biol Theory **13**(4): 228-242.

Despite the productivity of basic cancer research, cancer continues to be a health burden to society because this research has not yielded corresponding clinical applications. Many proposed solutions to this dilemma have revolved around implementing organizational and policy changes related to cancer research. Here I argue for a different solution: a new conceptualization of causation in cancer. Neither the standard molecular biomarker approaches nor evolutionary biology approaches to cancer fully capture its complex causal dynamics, even when considered jointly. These approaches map on to Ernst Mayr's proximate-ultimate distinction, which is an inadequate conceptualization of causation in biological systems and makes it difficult to connect developmental and evolutionary viewpoints. I propose looking to evolutionary developmental biology (EvoDevo) to overcome the distinction and integrate the proximate and ultimate causal frameworks. I use the concepts of modularity and evolvability to show how an EvoDevo perspective can be manifested in cancer translational research. This perspective on causation in cancer is better suited for integrating the complexity of current empirical results and can facilitate novel developments in the investigation and clinical treatment of cancer.

Logothetis, C. J., et al. (2008). "Understanding the biology of bone metastases: key to the effective treatment of prostate cancer." Clin Cancer Res **14**(6): 1599-1602.

Advanced prostate cancer is dominated by bone-forming osseous metastases. Understanding the biology behind this striking clinical manifestation is the key to its effective treatment. A clinical trial using a bone-targeting radiopharmaceutical agent, strontium 89, combined with chemotherapy showed increased survival time among patients with progression of prostate cancer in bone, suggesting that therapeutic strategies focused on treating the tumor in bone are effective. We and others thus hypothesize that interactions between prostate cancer cells and the bone microenvironment play a role in the progression of prostate cancer in bone. Clinical trials and basic science investigations aiming to understand such interactions have been carried out in parallel. In the laboratory studies, human bone marrow specimens have been collected for identification of proteins involved in the bidirectional interactions between prostate cancer cells and bone. In addition, specimens from bone biopsies of the cancer lesions have been used to generate xenografts in animals to establish animal models for testing therapeutic strategies. Clinical trials using agents to inhibit the stromal-prostate cancer interactions (e.g., docetaxel/imatinib or thalidomide) have been done. Analyses of the specimens from these trials provided support of our hypothesis and future development of diagnosis and therapy strategies.

Love, R. R. and S. M. Love (2016). "Peri-operative biology in primary breast cancer: a credible therapeutic target." Breast Cancer Res Treat **156**(3): 411-413.

Over the last 25 years, there has been a growing body of basic science, modeling, and clinical data suggesting that the peri-operative period in the treatment of primary breast cancer is dynamic and can be manipulated to improve long-term outcomes. Clinical data have demonstrated early peaks of hazards for recurrence and emphasized the relationship of these to peri-operative events. More recently, clinical trial data with surgical oophorectomy at different times in the menstrual cycle, peri-operative progesterone, and anti-inflammatory drugs suggest that interventional studies are particularly well justified, given the increasing recognition of the costs both financially and clinically of current systemic regimens.

Luker, G. D. (2002). "Special conference of the American Association for Cancer Research on molecular imaging in cancer: linking biology, function, and clinical applications in vivo." Cancer Res **62**(7): 2195-2198.

The AACR Special Conference on Molecular Imaging in Cancer: Linking Biology, Function, and Clinical Applications In Vivo, was held January 23-27, 2002, at the Contemporary Hotel, Walt Disney World, Orlando, FL. Co-Chairs David Piwnica-Worms, Patricia Price and Thomas Meade brought together researchers with diverse expertise in molecular biology, gene therapy, chemistry, engineering, pharmacology, and imaging to accelerate progress in developing and applying technologies for imaging specific cellular and molecular signals in living animals and humans. The format of the conference was the presentation of research that focused on basic and translational biology of cancer and current state-of-the-art techniques for molecular imaging in animal models and humans. This report summarizes the special conference on molecular imaging, highlighting the interfaces of molecular biology with animal models, instrumentation, chemistry, and pharmacology that are essential to convert the dreams and promise of molecular imaging into improved understanding, diagnosis, and management of cancer.

Machy, P., et al. (2023). "Biology of GD2 ganglioside: implications for cancer immunotherapy." Front Pharmacol **14**: 1249929.

Part of the broader glycosphingolipid family, gangliosides are composed of a ceramide bound to a sialic acid-containing glycan chain, and locate at the plasma membrane. Gangliosides are produced through sequential steps of glycosylation and sialylation. This diversity of composition is reflected in differences in expression patterns and functions of the various gangliosides. Ganglioside GD2 designates different subspecies following a basic structure containing three carbohydrate residues and two sialic acids. GD2 expression, usually restrained to limited tissues, is frequently altered in various neuroectoderm-derived cancers. While GD2 is of evident interest, its glycolipid nature has rendered research challenging. Physiological GD2 expression has been linked to developmental processes. Passing this stage, varying levels of GD2, physiologically expressed mainly in the central nervous system, affect composition and formation of membrane microdomains involved in surface receptor signaling. Overexpressed in cancer, GD2 has been shown to enhance cell survival and invasion. Furthermore, binding of antibodies leads to immune-independent cell death mechanisms. In addition, GD2 contributes to T-cell dysfunction, and functions as an immune checkpoint. Given the cancer-associated functions, GD2 has been a source of interest for immunotherapy. As a potential biomarker, methods are being developed to quantify GD2 from patients' samples. In addition, various therapeutic strategies are tested. Based on initial success with antibodies, derivates such as bispecific antibodies and immunocytokines have been developed, engaging patient immune system. Cytotoxic effectors or payloads may be redirected based on anti-GD2 antibodies. Finally, vaccines can be used to mount an immune response in patients. We review here the pertinent biological information on GD2 which may be of use for optimizing current immunotherapeutic strategies.

Mambetsariev, I., et al. (2023). "Clinical Network Systems Biology: Traversing the Cancer Multiverse." J Clin Med **12**(13).

In recent decades, cancer biology and medicine have ushered in a new age of precision medicine through high-throughput approaches that led to the development of novel targeted therapies and immunotherapies for different cancers. The availability of multifaceted high-throughput omics data has revealed that cancer, beyond its genomic heterogeneity, is a complex system of microenvironments, sub-clonal tumor populations, and a variety of other cell types that impinge on the genetic and non-genetic mechanisms underlying the disease. Thus, a systems approach to cancer biology has become instrumental in identifying the key components of tumor initiation, progression, and the eventual emergence of drug resistance. Through the union of clinical medicine and basic sciences, there has been a revolution in the development and approval of cancer therapeutic drug options including tyrosine kinase inhibitors, antibody-drug conjugates, and immunotherapy. This 'Team Medicine' approach within the cancer systems biology framework can be further improved upon through the development of high-throughput clinical trial models that utilize machine learning models, rapid sample processing to grow patient tumor cell cultures, test multiple therapeutic options and assign appropriate therapy to individual patients quickly and efficiently. The integration of systems biology into the clinical network would allow for rapid advances in personalized medicine that are often hindered by a lack of drug development and drug testing.

Mateo, J., et al. (2017). "DNA Repair in Prostate Cancer: Biology and Clinical Implications." Eur Urol **71**(3): 417-425.

CONTEXT: For more precise, personalized care in prostate cancer (PC), a new classification based on molecular features relevant for prognostication and treatment stratification is needed. Genomic aberrations in the DNA damage repair pathway are common in PC, particularly in late-stage disease, and may be relevant

for treatment stratification. OBJECTIVE: To review current knowledge on the prevalence and clinical significance of aberrations in DNA repair genes in PC, particularly in metastatic disease. EVIDENCE ACQUISITION: A literature search up to July 2016 was conducted, including clinical trials and preclinical basic research studies. Keywords included DNA repair, BRCA, ATM, CRPC, prostate cancer, PARP, platinum, predictive biomarkers, and hereditary cancer. EVIDENCE SYNTHESIS: We review how the DNA repair pathway is relevant to prostate carcinogenesis and progression. Data on how this may be relevant to hereditary cancer and genetic counseling are included, as well as data from clinical trials of PARP inhibitors and platinum therapeutics in PC. CONCLUSIONS: Relevant studies have identified genomic defects in DNA repair in PCs in 20-30% of advanced castration-resistant PC cases, a proportion of which are germline aberrations and heritable. Phase 1/2 clinical trial data, and other supporting clinical data, support the development of PARP inhibitors and DNA-damaging agents in this molecularly defined subgroup of PC following success in other cancer types. These studies may be an opportunity to improve patient care with personalized therapeutic strategies. PATIENT SUMMARY: Key literature on how genomic defects in the DNA damage repair pathway are relevant for prostate cancer biology and clinical management is reviewed. Potential implications for future changes in patient care are discussed.

Matherly, L. H., et al. (2014). "The major facilitative folate transporters solute carrier 19A1 and solute carrier 46A1: biology and role in antifolate chemotherapy of cancer." Drug Metab Dispos **42**(4): 632-649.

This review summarizes the biology of the major facilitative membrane transporters, the reduced folate carrier (RFC) (Solute Carrier 19A1) and the proton-coupled folate transporter (PCFT) (Solute Carrier 46A1). Folates are essential vitamins, and folate deficiency contributes to a variety of health disorders. RFC is ubiquitously expressed and is the major folate transporter in mammalian cells and tissues. PCFT mediates the intestinal absorption of dietary folates and appears to be important for transport of folates into the central nervous system. Clinically relevant antifolates for cancer, such as methotrexate and pralatrexate, are transported by RFC, and loss of RFC transport is an important mechanism of methotrexate resistance in cancer cell lines and in patients. PCFT is expressed in human tumors, and is active at pH conditions associated with the tumor microenvironment. Pemetrexed is an excellent substrate for both RFC and PCFT. Novel tumor-targeted antifolates related to pemetrexed with selective membrane transport by PCFT over RFC are being developed. In recent years, there have been major advances in understanding the structural and functional properties and the regulation of RFC and PCFT. The molecular bases for methotrexate resistance associated with loss of RFC transport and for hereditary folate malabsorption, attributable to mutant PCFT, were determined. Future studies should continue to translate molecular insights from basic studies of RFC and PCFT biology into new therapeutic strategies for cancer and other diseases.

Mattes, M. D., et al. (2017). "Methods of Academic Course Planning for Cancer Biology PhD Students to Enhance Knowledge of Clinical Oncology." Cancer Res **77**(18): 4741-4744.

Little is known about how clinical oncology concepts are taught to PhD students or the most effective methods of doing so. In this study, electronic surveys were sent to faculty and students at PhD training programs, assessing their institution's methods of clinical oncology education and their perspective on optimal approaches to clinical oncology education. Only 40.0% of students reported any clinical oncology component to their institution's training, and only 26.5% had a clinician on their graduate advisory committee. Forty-three percent of students believed that they had a good understanding for translating basic science research into clinical practice, and 77.2% of all participants believed dual degree MD/PhD students were superior to PhD students in this regard. Lectures on clinical oncology research topics were the most valuable type of experience for all participants and were also the most common type of experience utilized. Working with a clinician to develop a clinical trial with correlative endpoints was also highly valued, but was only utilized by approximately 10% of programs. Faculty rated the value of nearly all types of clinical oncology exposure significantly lower than did students. Inclusion of the approaches identified in this study is likely to enhance PhD training in oncology-related disciplines. Cancer Res; 77(18); 4741-4. (c)2017 AACR.

McKaig, R. G., et al. (1998). "Human papillomavirus and head and neck cancer: epidemiology and molecular biology." Head Neck **20**(3): 250-265.

BACKGROUND: Human papillomaviruses (HPV) are known to cause cancers of the cervix and other anogenital tract sites. Molecular biology has provided some evidence as to the specific mechanisms involved in the HPV-related carcinogenesis. Epidemiologic and molecular biology studies have also suggested that HPV infection may be associated with cancers of the head and neck. METHODS: This review summarizes the biology of HPV and its potential etiologic role in head and neck cancer. Published reports were used to determine the prevalence of HPV in benign, precancerous, and neoplastic lesions of the oral

cavity, pharynx, and larynx. The prevalence was also examined by head and neck site, HPV type, and method of HPV detection. In addition, the occurrence of HPV in normal head and neck tissue, epidemiologic factors related to HPV infection, and clinical implications are discussed. RESULTS: Overall, the frequency of HPV in benign and precancerous lesions ranged from 18.5% to 35.9%, depending upon the detection methodology. Based upon the most sensitive method of detection, polymerase chain reaction (PCR), the overall prevalence of HPV in head and neck tumors was 34.5% (416 of 1205 tumors). The majority of HPV-positive tumors contained the "high risk" HPV types 16 (40.0%) and 18 (11.9%). Among head and neck sites, HPV was most often detected in tumors of the oral cavity (59%), followed by the pharynx (43%), and larynx (33%). The frequency of HPV positivity in oral samples from healthy individuals ranged from 1% to 60%. A limited number of descriptive and analytic epidemiologic studies have indicated that age (<60 years) and sex (male) were associated with the presence of HPV in the tumor, whereas tobacco and alcohol use were not. The relationship between HPV and survival is unclear, with few comprehensive studies currently available. CONCLUSIONS: The prevalence of HPV, particularly the high-risk types, suggests a potential etiologic role for the virus in head and neck cancer. Molecular biology has provided important data on the interaction of the HPV oncoproteins with genes important in cell cycle control. Nonetheless, more basic research is needed to describe the physical state of the virus in a variety of cell types and the interaction with other genes. In addition, epidemiologic research is required to further understand the association between HPV and demographic and other risk factors as well as possible routes of transmission. Finally, much work is warranted to provide a definitive assessment of the prognostic significance of HPV in head and neck cancer.

Meeker, A. K. and A. M. De Marzo (2004). "Recent advances in telomere biology: implications for human cancer." Curr Opin Oncol **16**(1): 32-38.

PURPOSE OF REVIEW: Research into the basic biology of telomeres continues to reveal details relevant to fundamental aspects of human cancer. The goal of this review is to highlight discoveries made within the last year, with emphasis on their relevance to cancer prevention, diagnosis, prognostics, and treatment. RECENT FINDINGS: Increasing evidence indicates that dysfunctional telomeres likely play a causal role in the process of malignant transformation, in at least a fraction of human cancers, by initiating chromosomal instability. Telomeres form protective capping structures composed of telomeric DNA complexed with a multitude of associated proteins, the loss of which can have profound effects on telomeric stability. Critical telomeric shortening can lead to telomere "uncapping" and may occur at the earliest recognizable stages of malignant transformation in epithelial tissues. The widespread activation of the telomere synthesizing enzyme telomerase in human cancers not only confers unlimited replicative potential but also prevents intolerable levels of chromosomal instability. Several details regarding telomere structure and telomerase regulation have recently been elucidated, providing new targets for therapeutic exploitation. Various therapeutic strategies aimed at either telomerase or its telomeric substrate are showing promise and may synergize with established anti-cancer agents. Further support for anti-telomerase approaches comes from recent studies indicating that telomerase may possess additional functions, beyond telomere maintenance, that support the growth and survival of tumor cells. SUMMARY: Substantial progress has been made in understanding the complex relationships that exist between telomeres and cancer. However, important issues, such as transient activation of telomerase in normal cells and the potential for tumor cell immortalization via telomerase independent means, remain to be clarified.

Miller, W. R. (1996). "Steroid hormones and cancer: (I) basic biology and endocrinology." Eur J Surg Oncol **22**(6): 627-633.

Mimeault, M., et al. (2007). "Stem cells: a revolution in therapeutics-recent advances in stem cell biology and their therapeutic applications in regenerative medicine and cancer therapies." Clin Pharmacol Ther **82**(3): 252-264.

Basic and clinical research accomplished during the last few years on embryonic, fetal, amniotic, umbilical cord blood, and adult stem cells has constituted a revolution in regenerative medicine and cancer therapies by providing the possibility of generating multiple therapeutically useful cell types. These new cells could be used for treating numerous genetic and degenerative disorders. Among them, age-related functional defects, hematopoietic and immune system disorders, heart failures, chronic liver injuries, diabetes, Parkinson's and Alzheimer's diseases, arthritis, and muscular, skin, lung, eye, and digestive disorders as well as aggressive and recurrent cancers could be successfully treated by stem cell-based therapies. This review focuses on the recent advancements in adult stem cell biology in normal and pathological conditions. We describe how these results have improved our understanding on critical and unique functions of these rare sub-populations of multipotent and undifferentiated cells with an unlimited self-renewal capacity and high plasticity. Finally, we discuss some major advances to translate the experimental models on ex vivo and in vivo

expanded and/or differentiated stem cells into clinical applications for the development of novel cellular therapies aimed at repairing genetically altered or damaged tissues/organs in humans. A particular emphasis is made on the therapeutic potential of different tissue-resident adult stem cell types and their in vivo modulation for treating and curing specific pathological disorders.

Mishra, A., et al. (2007). "Head and neck squamous cell cancer: Biology (1)." Indian J Otolaryngol Head Neck Surg **59**(1): 28-32.

This review is the first section of tumor biology pertaining to head and neck squamous cell carcinoma (SCCHN). It is intended to introduce the basic concepts of cancer biology to enhance the translational research. The basic tumour biology relates to the aberrations in the normal cell cycle. cell growth and cell death. The genetic aspects of cancer focus upon the roles of oncogenes, tumor suppressor genes and stability genes. The epigenetic mechanisms of the cancer relates to DNA methylation and histone acetylation. This review, discusses the basics of these concepts.

Moller Sorensen, N., et al. (2008). "Biology and potential clinical implications of tissue inhibitor of metalloproteinases-1 in colorectal cancer treatment." Scand J Gastroenterol **43**(7): 774-786.

Colorectal cancer (CRC) is the second leading cause of cancer-related death in the industrialized world. About half of "curatively" resected patients develop recurrent disease within the next 3-5 years despite the lack of clinical, histological and biochemical evidence of remaining overt disease after resection of the primary tumour. Availability of validated biological markers for early detection, selection for adjuvant therapy, prediction of treatment efficacy and monitoring of treatment efficacy would most probably increase survival. Tissue inhibitor of metalloproteinases-1 (TIMP-1) may be such a marker. TIMP-1 inhibits the proteolytic activity of metalloproteinases, which are centrally involved in tumour invasion and metastases. However, in clinical investigations high tumour tissue or plasma levels of TIMP-1 have shown a strong and independent association with a shorter survival time in CRC patients, suggesting that TIMP-1 could have a tumour-promoting function. Furthermore, measurement of plasma TIMP-1 has been shown to be useful for disease detection, with a high sensitivity and high specificity for early-stage colon cancer. This review describes some basic information on the current knowledge of the biology of TIMP-1 as well as the potential use of TIMP-1 as a biological marker in the management of CRC patients.

Muc-Wierzgon, M., et al. (2004). "On the holistic approach in cancer biology: tumor necrosis factor, colon cancer cells, chaos theory and complexity." J Biol Regul Homeost Agents **18**(3-4): 261-267.

TNFalpha plays a role in the pathogenesis of septic shock, inflammatory diseases, autoimmune diseases, graft rejection reaction, acute, and chronic respiratory inefficiency among others. Its activity depends on the type of target cells and different regulating factors, but the effect of biological activity is conditioned by specific receptors such as p55 (type I, TNF R55) and p75 (type II, TNF R75). The aim of the study was to answer the following questions: 1) Is it possible to apply elements of non-linear dynamics to assess the level of expression of TNF, TNFRI, TNFRII genes in tumor cells, pathologically unchanged tissue and metastatically changed lymph nodes? 2) Is theoretically anticipated variability of cytokine and its receptors in colorectal carcinoma cells and the immediate vicinity justified in the developed mathematical model? The research material--specimens taken from tumor, unchanged tissue and metastatic lymph nodes--were histopathologically and molecularly analysed. Results of the molecular research were used to develop a mathematical model using the basic studies on the theory of chaos and biological system modelling.

Naitoh, J., et al. (1998). "The University of California, Los Angeles/Jennifer Jones Simon Foundation symposium on prostate cancer and epithelial cell biology: bringing together basic scientists and clinicians in the fight against advanced prostate cancer." Cancer Res **58**(13): 2895-2900.

Prostate cancer is the most common solid tumor in American men and is the second most common cause of cancer deaths. Although surgery and radiation therapy are effective for the treatment of organ-confined cancer, there is no effective treatment that is currently available for patients who have metastatic disease. Antiandrogen therapy is only palliative, and chemotherapy has largely been ineffective. However, recent advances in the understanding of the molecular biology of prostate cancer have lead to the development of new treatment strategies for metastatic cancer, including gene-based therapies, immunotherapies, and antiangiogenesis-based therapy. In association with the Jonsson Comprehensive Cancer Center and the University of California, Los Angeles Department of Urology, the Jennifer Jones Simon Foundation assembled 30 of the world's experts in prostate cancer research to review the most recent advances in the study of prostate cancer, with the hope that the resulting discussions would facilitate the rapid translation of new discoveries from the laboratory bench to the clinic.

Navaratnam, R. M., et al. (1999). "The molecular biology of colorectal cancer development and the associated genetic events." Ann R Coll Surg Engl **81**(5): 312-319.

Colorectal carcinoma remains the second most common malignancy in the western world. Mortality has remained stable despite advances in surgical and adjuvant radio- and chemotherapy regimens. This has renewed interest in the understanding of the basic principles of the molecular biology of colorectal carcinogenesis. The condition is characterised by multiple mutations in common oncogenes and tumour suppressor genes encompassing the inherited conditions familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer. The latter is characterised by genomic instability due to mismatch repair gene defects. These conditions and the role of the tumour protease systems, e.g. the plasminogen activation system and the matrix metalloproteinases, involved in the degradation of the extracellular matrix, provide an ideal role model for the study of carcinogenesis. The understanding and future application of these basic mechanisms, combined with the recent innovative work on the potential prophylactic role of COX2 inhibition, may provide further insight in the ultimate quest for a 'cure'. In the long-term, this concept may have to be achieved at the molecular level.

Nawaz, M., et al. (2016). "Extracellular vesicles in ovarian cancer: applications to tumor biology, immunotherapy and biomarker discovery." Expert Rev Proteomics **13**(4): 395-409.

In recent years there has been tremendous interest in both the basic biology and applications of extracellular vesicles (EVs) in translational cancer research. This includes a better understanding of their biogenesis and mechanisms of selective cargo packaging, their precise roles in horizontal communication, and their application as non-invasive biomarkers. The rapid advances in next-generation omics technologies are the driving forces for these discoveries. In this review, the authors focus on recent results of EV research in ovarian cancer. A deeper understanding of ovarian cancer-derived EVs, the types of cargo molecules and their biological roles in cancer growth, metastases and drug resistance, could have significant impact on the discovery of novel biomarkers and innovative therapeutics. Insights into the role of EVs in immune regulation could lead to novel approaches built on EV-based immunotherapy.

Neesse, A., et al. (2019). "Stromal biology and therapy in pancreatic cancer: ready for clinical translation?" Gut **68**(1): 159-171.

Pancreatic ductal adenocarcinoma (PDA) is notoriously aggressive and hard to treat. The tumour microenvironment (TME) in PDA is highly dynamic and has been found to promote tumour progression, metastasis niche formation and therapeutic resistance. Intensive research of recent years has revealed an incredible heterogeneity and complexity of the different components of the TME, including cancer-associated fibroblasts, immune cells, extracellular matrix components, tumour vessels and nerves. It has been hypothesised that paracrine interactions between neoplastic epithelial cells and TME compartments may result in either tumour-promoting or tumour-restraining consequences. A better preclinical understanding of such complex and dynamic network systems is required to develop more powerful treatment strategies for patients. Scientific activity and the number of compelling findings has virtually exploded during recent years. Here, we provide an update of the most recent findings in this area and discuss their translational and clinical implications for basic scientists and clinicians alike.

Negendank, W. G., et al. (1992). "Proceedings of a National Cancer Institute workshop: MR spectroscopy and tumor cell biology." Radiology **185**(3): 875-883.

In December 1991, the National Cancer Institute held a workshop to evaluate the role of magnetic resonance (MR) spectroscopy in human cancer biology. The clinical and basic cancer research issues requiring use of MR spectroscopy, the advantages and limitations of MR spectroscopy, and future directions in MR spectroscopy of cancer were discussed. Consensus-building panels were formed on the following four topics: cell membrane biochemistry, tumor therapeutic response or drug resistance, appropriate model systems, and potential clinical applications of MR spectroscopy. The workshop members concluded that large prospective clinical studies as well as in vivo animal and human studies to define prognostic variables should be performed, with correlation between MR spectroscopic results and biochemical and physiologic features. Studies of phospholipid metabolism, the pharmacokinetics of anticancer agents, and effects of new cancer treatments on the tumor vasculature and normal tissues are needed.

Nickerson, M. L., et al. (2017). "Molecular analysis of urothelial cancer cell lines for modeling tumor biology and drug response." Oncogene **36**(1): 35-46.

The utility of tumor-derived cell lines is dependent on their ability to recapitulate underlying genomic aberrations and primary tumor biology. Here, we sequenced the exomes of 25 bladder cancer (BCa) cell lines and compared mutations, copy number alterations (CNAs), gene expression and drug response to BCa patient profiles in The Cancer Genome Atlas (TCGA). We observed a mutation pattern associated

with altered CpGs and APOBEC-family cytosine deaminases similar to mutation signatures derived from somatic alterations in muscle-invasive (MI) primary tumors, highlighting a major mechanism(s) contributing to cancer-associated alterations in the BCa cell line exomes. Non-silent sequence alterations were confirmed in 76 cancer-associated genes, including mutations that likely activate oncogenes TERT and PIK3CA, and alter chromatin-associated proteins (MLL3, ARID1A, CHD6 and KDM6A) and established BCa genes (TP53, RB1, CDKN2A and TSC1). We identified alterations in signaling pathways and proteins with related functions, including the PI3K/mTOR pathway, altered in 60% of lines; BRCA DNA repair, 44%; and SYNE1-SYNE2, 60%. Homozygous deletions of chromosome 9p21 are known to target the cell cycle regulators CDKN2A and CDKN2B. This loci was commonly lost in BCa cell lines and we show the deletions extended to the polyamine enzyme methylthioadenosine (MTA) phosphorylase (MTAP) in 36% of lines, transcription factor DMRTA1 (27%) and antiviral interferon epsilon (IFNE, 19%). Overall, the BCa cell line genomic aberrations were concordant with those found in BCa patient tumors. We used gene expression and copy number data to infer pathway activities for cell lines, then used the inferred pathway activities to build a predictive model of cisplatin response. When applied to platinum-treated patients gathered from TCGA, the model predicted treatment-specific response. Together, these data and analysis represent a valuable community resource to model basic tumor biology and to study the pharmacogenomics of BCa.

Ochoa, S., et al. (2019). "Comutation and exclusion analysis in human tumors: A tool for cancer biology studies and for rational selection of multitargeted therapeutic approaches." Hum Mutat **40**(4): 413-425.

Malignant tumors originate from somatic mutations and other genomic and epigenomic alterations, which lead to loss of control of the cellular circuitry. These alterations present patterns of co-occurrence and mutual exclusivity that can influence prognosis and modify response to drugs, highlighting the need for multitargeted therapies. Studies in this area have generally focused in particular malignancies and considered whole genes instead of specific mutations, ignoring the fact that different alterations in the same gene can have widely different effects. Here, we present a comprehensive analysis of co-dependencies of individual somatic mutations in the whole spectrum of human tumors. Combining multitesting with conditional and expected mutational probabilities, we have discovered rules governing the codependencies of driver and nondriver mutations. We also uncovered pairs and networks of comutations and exclusions, some of them restricted to certain cancer types and others widespread. These pairs and networks are not only of basic but also of clinical interest, and can be of help in the selection of multitargeted antitumor therapies. In this respect, recurrent driver comutations suggest combinations of drugs that might be effective in the clinical setting, while recurrent exclusions indicate combinations unlikely to be useful.

Onn, A., et al. (2003). "Development of an orthotopic model to study the biology and therapy of primary human lung cancer in nude mice." Clin Cancer Res **9**(15): 5532-5539.

PURPOSE: This study was conducted to develop biologically relevant animal models of human lung cancer that are reproducible, inexpensive, and easy to perform. EXPERIMENTAL DESIGN: Human lung adenocarcinoma (PC14PE6), bronchioloalveolar carcinoma (NCI-H358), squamous cell carcinoma (NCI-H226), poorly differentiated non-small cell lung cancer (NCI-H1299 and A549), or small cell lung cancer (NCI-H69) cells in Matrigel were injected percutaneously into the left lungs of nude mice. The growth pattern of the different lung cancer tumors was studied. For PC14PE6 and NCI-H358, the growth pattern in the subcutis and the response to paclitaxel were also studied. RESULTS: As is observed for human primary lung cancer, tumors formed from a single focus of disease and progressed to a widespread and fatal thoracic process characterized by diffuse dissemination of lung cancer in both lungs and metastasis to intra- and extrathoracic lymph nodes. When the lung cancer cell lines were implanted s.c., systemic therapy with paclitaxel induced tumor regression. However, only a limited therapeutic response to paclitaxel was observed when the same cells were implanted orthotopically into the lung. Immunohistochemical analysis of tumor tissue revealed increased expression of the proangiogenic factors interleukin 8, basic fibroblast growth factor, and vascular endothelial growth factor/vascular permeability factor. CONCLUSIONS: Our orthotopic models of human lung cancer confirm the "seed and soil" concept and likely provide more clinically relevant systems for the study of both non-small cell lung cancer and small cell lung cancer biology, and for characterizing novel therapeutic strategies.

Palma, S., et al. (2016). "From Molecular Biology to Clinical Trials: Toward Personalized Colorectal Cancer Therapy." Clin Colorectal Cancer **15**(2): 104-115.

During the past years, molecular studies through high-throughput technologies have led to the confirmation of critical alterations in colorectal cancer (CRC) and the discovery of some new ones, including mutations, DNA methylations, and structural chromosomal changes. These genomic alterations might

act in concert to dysregulate specific signaling pathways that normally exert their functions on critical cell phenotypes, including the regulation of cellular metabolism, proliferation, differentiation, and survival. Targeted therapy against key components of altered signaling pathways has allowed an improvement in CRC treatment. However, a significant percentage of patients with CRC and metastatic CRC will not benefit from these targeted therapies and will be restricted to systemic chemotherapy. Mechanisms of resistance have been associated with specific gene alterations. To fully understand the nature and significance of the genetic and epigenetic defects in CRC that might favor a tumor evading a given therapy, much work remains. Therefore, a dynamic link between basic molecular research and preclinical studies, which ultimately constitute the prelude to standardized therapies, is very important to provide better and more effective treatments against CRC. We present an updated revision of the main molecular features of CRC and their associated therapies currently under study in clinical trials. Moreover, we performed an unsupervised classification of CRC clinical trials with the aim of obtaining an overview of the future perspectives of preclinical studies.

Park, J. G. and A. F. Gazdar (1996). "Biology of colorectal and gastric cancer cell lines." J Cell Biochem Suppl **24**: 131-141.

Cell lines established from the human colorectal and gastric cancers may provide very useful tools to the study of the disease and to develop and test new therapeutic approaches, and a large bank of well-characterized cell lines should reflect the diversity of tumor phenotypes and provide adequate models for the study of tumor heterogeneity. Colorectal lines are relatively easy to establish, while gastric cancer cell lines remain extremely difficult to propagate in long-term culture, and the number of cell lines is very limited. In this paper, we describe the up-to-date results of the characteristics of our nine colorectal cancer cell lines and four gastric cancer cell lines. Based on culture, xenograft, and ultrastructural morphologies, these cell lines could be subtyped into well-differentiated, moderately differentiated, poorly differentiated, and mucinous carcinomas. Basic properties concerning expression and secretion of antigens, neuroendocrine features, receptor binding of various gastrointestinal hormones and neurotransmitters, cytogenetic studies, gene amplification and expression, and chemosensitivity profiles are described. In particular, a greater number of receptors for hormones and neurotransmitters are expressed on human colorectal cancer cell lines compared to gastric cancer cell lines, raising the possibility that gastrointestinal hormones may have a greater autocrine effect on colon cancer cell growth. Despite major differences in the biology of colorectal cancer and gastric cancer as indicated by clinical studies, the multiple properties that we examined reveals marked similarities between the colorectal and gastric cancer cell lines. However, in vitro chemosensitivity patterns to cytotoxic drugs are very different in colorectal and gastric cell lines. Some of these observations may be due to the relatively low expression of the multidrug-resistance-associated (MDR1) gene in gastric cancer cell lines. In addition, colorectal cancer cell lines express receptors for peptide hormones more frequently.

Patel, S. A., et al. (2008). "Breast cancer biology: the multifaceted roles of mesenchymal stem cells." J Oncol **2008**: 425895.

Recent upsurge in the interest of breast cancer metastasis is partly attributed to the discovery of novel, yet unclear, mechanisms of breast cancer interaction with sites of distant metastasis such as the bone marrow microenvironment. In this review, we discuss the significance of the interactions between breast cancer cells and cells of the bone marrow. This is a subject of intense research studies aim to provide new methods of treatments and perhaps the identification of new drug targets. This review also discusses the role of inflammation and the bimodal function of the transforming growth factor-beta signaling pathway in the process of tumorigenesis. We bring attention to future prospects in breast cancer research, including the role of microRNAs in cancer quiescence in the bone marrow and the application of microRNAs to basic science discoveries in oncology. Finally, we discuss the cancer stem cell hypothesis, which is not a new idea, but has resurged with investigative questions.

Perou, C. M. and A. L. Borresen-Dale (2011). "Systems biology and genomics of breast cancer." Cold Spring Harb Perspect Biol **3**(2).

It is now accepted that breast cancer is not a single disease, but instead it is composed of a spectrum of tumor subtypes with distinct cellular origins, somatic changes, and etiologies. Gene expression profiling using DNA microarrays has contributed significantly to our understanding of the molecular heterogeneity of breast tumor formation, progression, and recurrence. For example, at least two clinical diagnostic assays exist (i.e., OncotypeDX RS and Mammaprint(R)) that are able to predict outcome in patients using patterns of gene expression and predetermined mathematical algorithms. In addition, a new molecular taxonomy based upon the inherent, or "intrinsic," biology of breast tumors has been developed; this taxonomy is called the "intrinsic subtypes of breast cancer," which now identifies five distinct tumor types and a normal breast-like group. Importantly, the intrinsic subtypes of breast cancer predict patient relapse, overall survival, and response to

endocrine and chemotherapy regimens. Thus, most of the clinical behavior of a breast tumor is already written in its subtype profile. Here, we describe the discovery and basic biology of the intrinsic subtypes of breast cancer, and detail how this interacts with underlying genetic alternations, response to therapy, and the metastatic process.

Petruzzelli, G. J. (2001). "The biology of distant metastases in head and neck cancer." ORL J Otorhinolaryngol Relat Spec **63**(4): 192-201.

The detection and treatment of metastatic cancer continues to be a challenge for the head and neck oncologist. Unfortunately, head and neck cancer patients who develop distant metastases commonly present late in their course and rapidly succumb to their disease, despite advances in imaging technologies and increased sophistication of biochemical analyses. The development of a rational approach to detection and treatment of metastatic head and neck cancers should begin with an understanding of how these tumors occur and which patients are at greatest risk for developing them. This article presents an overview of the biological processes resulting in the speed of a malignancy from one site to another, with particular attention to head and neck carcinomas. The basic histopathologic, immunology and biochemical abnormalities associated with the development of these secondary tumors are also discussed.

Phillips, K. G., et al. (2014). "Physical biology in cancer. 2. The physical biology of circulating tumor cells." Am J Physiol Cell Physiol **306**(2): C80-88.

The identification, isolation, and characterization of circulating tumor cells (CTCs) promises to enhance our understanding of the evolution of cancer in humans. CTCs provide a window into the hematogenous, or "fluid phase," of cancer, underlying the metastatic transition in which a locally contained tumor spreads to other locations in the body through the bloodstream. With the development of sensitive and specific CTC identification and isolation methodologies, the role of CTCs in clinical diagnostics, disease surveillance, and the physical basis of metastasis continues to be established. This review focuses on the quantification of the basic biophysical properties of CTCs and the use of these metrics to understand the hematogenous dissemination of these enigmatic cells.

Pocard, M., et al. (2012). "[Cancer research program performed by surgeons invade the biology field - from dormancy to metastasis]." Bull Cancer **99**(12): 1193-1196.

Cancer research program was analyzed. This research was identified using the "master of science in surgery" performed by the majority of surgical resident and fellow. It was analyzed as three axes studying: (i) how to improve the technical practice; (ii) the contribution of surgical skills in basic research, in particular via orthotopic animal models as microenvironment; and (iii) the research in basic biology, testing hypotheses and strategies not confined to surgery but totally multidisciplinary. This research is active with more than half of the fellowships grant in urology sponsored via the French Urologist Association, for projects studying cancer and more than a third of subjects pertaining to the master oncology.

Poche, R. A. and B. E. Reese (2009). "Retinal horizontal cells: challenging paradigms of neural development and cancer biology." Development **136**(13): 2141-2151.

A group of retinal interneurons known as horizontal cells has recently been shown to exhibit a variety of unique biological properties, as compared with other nerve cells, that challenge many long-standing assumptions in the fields of neural development and cancer biology. These features include their unusual migratory behavior, their unique morphological plasticity, and their propensity to divide at a relatively late stage during development. Here, we review these novel features, discuss their relevance for other cell types, outline open questions in our understanding of horizontal cell development and consider their implications.

Porcaro, A. B., et al. (2010). "Investigative clinical study on prostate cancer: on the role of the pretreatment total PSA to free testosterone ratio in selecting different biology groups of prostate cancer patients." Int Urol Nephrol **42**(3): 673-681.

OBJECTIVES: To show that prostate cancer biology is related to serum levels of both free testosterone (FT) and prostate-specific antigen (PSA), that PSA level is linearly related to FT and that the PSA to FT ratio may be considered as the growth rate parameter expressing cancer phenotype biology. MATERIALS AND METHODS: The study includes 135 consecutive patients diagnosed with prostate cancer. Pretreatment simultaneous serum samples for analyzing total testosterone (TT), FT and total PSA levels were obtained. The study was assessed according to a multidimensional approach of the five continuous variables including TT, FT, PSA, AGE and percentage of positive biopsies (=P+). The all sets of data were considered as one--sample with no groupings among the observations. Multivariate analysis included factor analysis (FA) and principal component analysis (PCA). Multivariate inferential statistics for comparing different groups of patients according to the PSA to free testosterone ratio (PSA/FT) included Hotteling's multivariate two-sample T(2)-Test for comparing two mean vectors as well as Box's M-Test with the chi-

square approximation for comparing multiple covariance matrices when patients were sampled in more than two groups. RESULTS: Factor analysis showed the two natural grouping of variables, FT-TT and PSA-P+. PCA assessed FT and PSA as the two variables with large variances having a notable influence on the first two principal components. Multiple linear regression analysis showed that all the income variables, except age, significantly predicted the PSA/FT ratio. Patients were first sampled according to the PSA/FT ratio in group 1 (PSA/FT </= 0.20) and group 2 (PSA/FT > 0.20), and Hotteling's multivariate two sample T(2)-Test was significant (P < 0.01). Patients were then sampled according to the PSA/FT ratio in group 1 (PSA/FT </= 0.20), group 2 (PSA/FT > 0.20 and </= 0.40), and group 3 (PSA/FT > 0.40), and Box's M-Test comparing the covariance matrices of the 3 groups differed significantly (P < 0.001). Finally, patients were sampled according to the PSA/FT ratio in 6 groups, and Box's M-Test was again significant (P < 0.001). CONCLUSIONS: The PSA to FT ratio is the growing rate parameter expressing different biology patterns and assessing different groups of prostate cancer patients. In our opinion, the results of the present study might have wide applications in understanding, assessing and planning prostate cancer studies including basic science, screening, assessing risk of the disease, predicting disease stage as well natural history after a planned treatment involving biochemical recurrence, progression, hormone refractory prostate cancer and disease-specific survival.

Price, D., et al. (2003). "Methods for the study of protein-protein interactions in cancer cell biology." Methods Mol Biol **218**: 255-267.

Development of sensitive methods to monitor and quantitatively assess the expression levels of endogenous genes and the association-interaction of proteins in living cells and whole organisms is a complex and challenging problem. In this chapter, we have described basic methods for investigating protein-protein interactions which include immunoprecipitation, GST pull-down assays, peptide bead pull-down assays, chemical crosslinking and photoaffinity labeling. These methods should provide important tools to dissect crosstalk between proteins and the direct implications of this crosstalk in signaling pathways and cancer biology.

Prokop, A. (2021). "Towards the First Principles in Biology and Cancer: New Vistas in Computational Systems Biology of Cancer." Life (Basel) **12**(1).

These days many leading scientists argue for a new paradigm for cancer research and propose a complex systems-view of cancer supported by empirical evidence. As an example, Thea Newman (2021) has applied "the lessons learned from physical systems to a critique of reductionism in medical research, with an emphasis on cancer". It is the understanding of this author that the mesoscale constructs that combine the bottom-up as well as top-down approaches, are very close to the concept of emergence. The mesoscale constructs can be said to be those effective components through which the system allows itself to be understood. A short list of basic concepts related to life/biology fundamentals are first introduced to demonstrate a lack of emphasis on these matters in literature. It is imperative that physical and chemical approaches are introduced and incorporated in biology to make it more conceptually sound, quantitative, and based on the first principles. Non-equilibrium thermodynamics is the only tool currently available for making progress in this direction. A brief outline of systems biology, the discovery of emergent properties, and metabolic modeling are introduced in the second part. Then, different cancer initiation concepts are reviewed, followed by application of non-equilibrium thermodynamics in the metabolic and genomic analysis of initiation and development of cancer, stressing the endogenous network hypothesis (ENH). Finally, extension of the ENH is suggested to include a cancer niche (exogenous network hypothesis). It is expected that this will lead to a unifying systems-biology approach for a future combination of the analytical and synthetic arms of two major hypotheses of cancer models (SMT and TOFT).

Ptitsyn, A. A., et al. (2008). "Systems biology approach to identification of biomarkers for metastatic progression in cancer." BMC Bioinformatics **9 Suppl 9**(Suppl 9): S8.

BACKGROUND: Metastases are responsible for the majority of cancer fatalities. The molecular mechanisms governing metastasis are poorly understood, hindering early diagnosis and treatment. Previous studies of gene expression patterns in metastasis have concentrated on selection of a small number of "signature" biomarkers. RESULTS: We propose an alternative approach that puts into focus gene interaction networks and molecular pathways rather than separate genes. We have reanalyzed expression data from a large set of primary solid and metastatic tumors originating from different tissues using the latest available tools for normalization, identification of differentially expressed genes and pathway analysis. Our studies indicate that regardless of the tissue of origin, all metastatic tumors share a number of common features related to changes in basic energy metabolism, cell adhesion/cytoskeleton remodeling, antigen presentation and cell cycle regulation. Analysis of multiple independent datasets indicates significantly reduced oxidative phosphorylation in metastases compared to primary solid tumors. CONCLUSION: Our

methods allow identification of robust, although not necessarily highly expressed biomarkers. A systems approach relying on groups of interacting genes rather than single markers is also essential for understanding the cellular processes leading to metastatic progression. We have identified metabolic pathways associated with metastasis that may serve as novel targets for therapeutic intervention.

Ramisetty, S., et al. (2023). "A Systems Biology Approach for Addressing Cisplatin Resistance in Non-Small Cell Lung Cancer." J Clin Med **12**(2).

Translational research in medicine, defined as the transfer of knowledge and discovery from the basic sciences to the clinic, is typically achieved through interactions between members across scientific disciplines to overcome the traditional silos within the community. Thus, translational medicine underscores 'Team Medicine', the partnership between basic science researchers and clinicians focused on addressing a specific goal in medicine. Here, we highlight this concept from a City of Hope perspective. Using cisplatin resistance in non-small cell lung cancer (NSCLC) as a paradigm, we describe how basic research scientists, clinical research scientists, and medical oncologists, in true 'Team Science' spirit, addressed cisplatin resistance in NSCLC and identified a previously approved compound that is able to alleviate cisplatin resistance in NSCLC. Furthermore, we discuss how a 'Team Medicine' approach can help to elucidate the mechanisms of innate and acquired resistance in NSCLC and develop alternative strategies to overcome drug resistance.

Real, A. M., et al. (2023). "The TCI Clinical Encounter Program for PhD Students in Cancer Biology: a Feasibility Pilot." J Cancer Educ **38**(1): 134-140.

Clinical rotations are often not included in graduate-level cancer biology curricula; however, basic insight into clinical oncology is often crucial for developing translational research that addresses unmet needs with the potential to benefit cancer patients. We describe a needs assessment, design, implementation, and descriptive evaluation of an oncology-specific pilot clinical encounter program developed for PhD students in the Cancer Biology Training Area (CAB) in the Graduate School of Biomedical Sciences (GSBS) and Tisch Cancer Institute (TCI) at the Icahn School of Medicine at Mount Sinai (ISMMS). Prior to the development of this pilot program, CAB students, in years 2-5 + , were surveyed to determine their interest in a structured clinical experience. Seventeen out of thirty-one students responded (55%) to the survey. Of those seventeen respondents, fifteen (88.2%) expressed that exposure to cancer patients in the clinical setting would be useful for their pre-doctoral biomedical science and cancer biology training and indicated an interest in participating in the clinical encounter program. Based on these responses, a three-session clinical encounter pilot program was designed. Two separate cohorts of 5 students participated in this pilot program. During a formal debrief, following the clinical experience, students commented on the resilience of patients and the importance of research on clinical decision making, and reported that they found the experience motivational. Five out of 10 students responded (50%) to a post-program assessment survey; all five respondents answered that they would recommend the clinical encounter program to their peers. While limited in size and scope, this pilot TCI Clinical Encounter Program proved feasible and has the potential to enrich and inform the experience of PhD students pursing advanced degrees in a cancer biology.

Rieger, P. T. (2004). "The biology of cancer genetics." Semin Oncol Nurs **20**(3): 145-154.

OBJECTIVES: To review cancer biology and associated genetic change. DATA SOURCES: Professional journals, texts, monographs, and Internet websites. CONCLUSION: Several types of genetic damage occur in cancer cells: activation of protooncogenes into oncogenes that give cells an abnormal growth advantage; inactivation of tumor suppressor genes that would normally slow or stop abnormal cell growth; the bypass of genes that cause aberrant cells to die by apoptosis; the ability to establish vasculature, and the ability to override genes that regulate cell senescence. The end result of accumulated genetic errors is cells that can reproduce without restriction, invade local tissues, and ultimately, establish distant metastases. IMPLICATIONS FOR NURSING PRACTICE: Identification of the genetic changes in cancer cells and of the proteins that these changes affect promises to provide diagnostic and prognostic markers as well as molecular targets for therapeutic intervention. It is critical that nurses have a basic understanding of cell biology and genetics so they may better comprehend the unfolding changes in medicine to best serve patients and families.

Roberts, D. D., et al. (2017). "Regulation of Cellular Redox Signaling by Matricellular Proteins in Vascular Biology, Immunology, and Cancer." Antioxid Redox Signal **27**(12): 874-911.

SIGNIFICANCE: In contrast to structural elements of the extracellular matrix, matricellular proteins appear transiently during development and injury responses, but their sustained expression can contribute to chronic disease. Through interactions with other matrix components and specific cell surface receptors, matricellular proteins regulate multiple signaling pathways, including those mediated by

reactive oxygen and nitrogen species and H(2)S. Dysregulation of matricellular proteins contributes to the pathogenesis of vascular diseases and cancer. Defining the molecular mechanisms and receptors involved is revealing new therapeutic opportunities. Recent Advances: Thrombospondin-1 (TSP1) regulates NO, H(2)S, and superoxide production and signaling in several cell types. The TSP1 receptor CD47 plays a central role in inhibition of NO signaling, but other TSP1 receptors also modulate redox signaling. The matricellular protein CCN1 engages some of the same receptors to regulate redox signaling, and ADAMTS1 regulates NO signaling in Marfan syndrome. In addition to mediating matricellular protein signaling, redox signaling is emerging as an important pathway that controls the expression of several matricellular proteins. CRITICAL ISSUES: Redox signaling remains unexplored for many matricellular proteins. Their interactions with multiple cellular receptors remains an obstacle to defining signaling mechanisms, but improved transgenic models could overcome this barrier. FUTURE DIRECTIONS: Therapeutics targeting the TSP1 receptor CD47 may have beneficial effects for treating cardiovascular disease and cancer and have recently entered clinical trials. Biomarkers are needed to assess their effects on redox signaling in patients and to evaluate how these contribute to their therapeutic efficacy and potential side effects. Antioxid. Redox Signal. 27, 874-911.

Robertson, M. J. and J. Ritz (1996). "Interleukin 12: Basic Biology and Potential Applications in Cancer Treatment." Oncologist **1**(1 & 2): 88-97.

Interleukin 12 is a heterodimeric cytokine that has potent effects on innate and adaptive immunity. Interleukin 12 induces interferon g secretion by T cells and natural killer cells, enhances the proliferation of activated T cells and natural killer cells, augments the cytolytic activity of cytotoxic T lymphocytes and natural killer cells, and supports the differentiation of Th1 helper effector cells. Interleukin 12 stimulates in vitro antitumor activity of lymphocytes from patients with cancer and in vivo antitumor activity in many murine tumor models. Current data indicate that CD4 T cells, CD8 T cells, natural killer cells and interferon g may contribute to the antitumor effects of interleukin 12 therapy. However, further investigation is required to elucidate the precise mechanisms involved in the antitumor activity of interleukin 12.

Rubio Briones, J., et al. (2000). "[Molecular biology in testicular cancer]." Arch Esp Urol **53**(6): 565-570.

OBJECTIVE: To review the advancements in basic molecular biology and current insight into the pathogenesis of germ cell tumors of the testis, as well as the utility of the different genetic and molecular markers in the management of these tumors. METHODS: The literature on this subject was reviewed. The epidemiological data related to the pathogenesis of this tumor type, the cytogenetic and molecular alterations that could serve as a prognostic factor in these tumors were analyzed. RESULTS/CONCLUSIONS: The prenatal estrogenic effect together with the pubertal hypergonadotrophism could be responsible for the pathogenesis of germ cell testicular tumors. The cytogenetic changes of chromosome 12, although typical of the phenotype of these tumors, do not appear to be useful as a prognostic factor. However, cell proliferation, particularly of Ki-67, appears to be useful as a prognostic factor, although further studies are warranted.

Shi, H., et al. (2016). "Process of hepatic metastasis from pancreatic cancer: biology with clinical significance." J Cancer Res Clin Oncol **142**(6): 1137-1161.

PURPOSE: Pancreatic cancer shows a remarkable preference for the liver to establish secondary tumors. Selective metastasis to the liver is attributed to the development of potential microenvironment for the survival of pancreatic cancer cells. This review aims to provide a full understanding of the hepatic metastatic process from circulating pancreatic cancer cells to their settlement in the liver, serving as a basic theory for efficient prediction and treatment of metastatic diseases. METHODS: A systematic search of relevant original articles and reviews was performed on PubMed, EMBASE and Cochrane Library for the purpose of this review. RESULTS: Three interrelated phases are delineated as the contributions of the interaction between pancreatic cancer cells and the liver to hepatic metastasis process. Chemotaxis of disseminated pancreatic cancer cells and simultaneous defensive formation of platelets or neutrophils facilitate specific metastasis toward the liver. Remodeling of extracellular matrix and stromal cells in hepatic lobules and angiogenesis induced by proangiogenic factors support the survival and growth of clinical micrometastasis colonizing the liver. The bimodal role of the immune system or prevalence of cancer cells over the immune system makes metastatic progression successfully proceed from micrometastasis to macrometastasis. CONCLUSIONS: Pancreatic cancer is an appropriate research object of cancer metastasis representing more than a straight cascade. If any of the successive or simultaneous phases, especially tumor-induced immunosuppression, is totally disrupted, hepatic metastasis will be temporarily under control or even cancelled forever. To shrink cancers on multiple fronts and prolong survival for patients, novel oral or intravenous anti-cancer agents covering one or different phases of metastatic pancreatic cancer are expected to be

integrated into innovative strategies on the premise of safety and efficacious biostability.

Shih, R. M. and Y. Y. Chen (2022). "Engineering Principles for Synthetic Biology Circuits in Cancer Immunotherapy." Cancer Immunol Res **10**(1): 6-11.

Recent advances in biomolecular engineering have led to novel cancer immunotherapies with sophisticated programmed functions, including chimeric antigen receptor (CAR) T cells that bind tumor-associated antigens (TAA) to direct coordinated immune responses. Extensive engineering efforts have been made to program not only CAR specificity, but also downstream pathways that activate molecular responses. Collectively, these efforts can be conceptualized as an immunotherapy circuit: TAAs bind the CAR as input signals; intracellular signaling cascades process the binding interactions into transcriptional and translational events; and those events program effector output functions. More simply, this sequence may be abstracted as input, processing, and output. In this review, we discuss the increasingly complex scene of synthetic-biology solutions in cancer immunotherapy and summarize recent work within the framework of immunotherapy circuits. In doing so, a toolbox of basic modular circuits may be established as a foundation upon which sophisticated solutions can be constructed to meet more complex problems.See related article on p. 5.

Shimosato, Y. (1989). "[Recent advances in pathology and biology of small cell lung cancer]." Gan To Kagaku Ryoho **16**(8 Pt 1): 2513-2521.

Small cell lung cancer (SCLC) is histologically simple and looks undifferentiated, but possesses cytoplasmic dense-cored granules resembling neuroendocrine granules, and frequently produces amine and peptide hormones, occasionally presenting related symptoms. Among these bioactive substances, gastrin releasing peptide (GRP) is most important, which is known as autocrine growth factor and one of the useful monitoring markers for SCLC together with neuron-specific enolase. Aromatic L-amino acid decarboxylase is another important enzyme in SCLC. Abnormality of myc family oncogenes is occasionally noted in SCLC, which appears related to proliferative activity of the tumor rather than development. Deletion of chromosomes 3p, 13q and 17p is noted in almost every SCLC, where antioncogene is suspected to be present, and inactivation of antioncogene may play an important role in development of SCLC. Nucleolar size is the important parameter for proliferative potential of SCLC. The larger the nucleoli, the faster is the growth of SCLC. Phenotypes of SCLC in vitro may be altered by change of microenvironment, although it may be due to the selective growth of a certain clone. SCLC and nervous tissue specific membrane antigen is named cluster 1 SCLC antigen, the monoclonal antibody to which will be utilized for immunohistological diagnosis, imaging and treatment of SCLC. Accumulation of basic knowledge is now leading to reconsideration of histological subtyping of SCLC.

Simion, V., et al. (2021). "LentiRILES, a miRNA-ON sensor system for monitoring the functionality of miRNA in cancer biology and therapy." RNA Biol **18**(sup1): 198-214.

A major unresolved challenge in miRNA biology is the capacity to monitor the spatiotemporal activity of miRNAs expressed in animal disease models. We recently reported that the miRNA-ON monitoring system called RILES (RNAi-inducible expression Luciferase system) implanted in lentivirus expression system (LentiRILES) offers unique opportunity to decipher the kinetics of miRNA activity in vitro, in relation with their intracellular trafficking in glioblastoma cells. In this study, we describe in detail the method for the production of LentiRILES stable cell lines and employed it in several applications in the field of miRNA biology and therapy. We show that LentiRILES is a robust, highly specific and sensitive miRNA sensor system that can be used in vitro as a single-cell miRNA monitoring method, cell-based screening platform for miRNA therapeutics and as a tool to analyse the structure-function relationship of the miRNA duplex. Furthermore, we report the kinetics of miRNA activity upon the intracranial delivery of miRNA mimics in an orthotopic animal model of glioblastoma. This information is exploited to evaluate the tumour suppressive function of miRNA-200c as locoregional therapeutic modality to treat glioblastoma. Our data provide evidence that LentiRILES is a robust system, well suited to resolve the activity of endogenous and exogenously expressed miRNAs from basic research to gene and cell therapy.

Slaby, O., et al. (2008). "[Involvement of microRNAs in cancer biology and possibilities of their application to diagnostic and predictive oncology]." Cas Lek Cesk **147**(1): 25-31.

MicroRNAs (miRNAs) are large class of non-coding RNAs that post-transcriptionally regulate gene expression. Their ability of translational repression applied for example on oncogenes or tumor-suppressor genes indicates involvement of miRNAs in multi-step carcinogenesis. Evidences of miRNAs linkage to biological processes like apoptosis, proliferation, differentiation and cell survival are rapidly accumulating. Approximately 50% of miRNAs are located at fragile sites of chromosomes or regions known to be amplified or deleted in human cancer. That is why, non-coding miRNAs seem to be another level of

genetic information which regulation is altered or lost during neoplastic growth. Expression profiles of miRNAs are successfully used for molecular classification, more exact diagnosis and prognosis of human cancers and reached analogical analytical characteristics like studies based on DNA micro-arrays technology and profiling of coding transcripts. In this review we attempt to introduce basic knowledge of miRNAs biogenesis and biological functions and in particular summarise reports focused on miRNAs in oncology research area.

Sloane, B. F., et al. (2006). "I2 imaging: cancer biology and the tumor microenvironment." Cancer Res **66**(23): 11097-11099.

The use of imaging techniques to understand the role of the tumor microenvironment in cancer progression was the topic of a National Cancer Institute (NCI)-sponsored think tank entitled "I2 Imaging: Cancer Biology and the Tumor Microenvironment," held in Alexandria, Virginia on June 8 to 10, 2006. Participants discussed both recent progress in the use of imaging to dissect cellular and molecular interactions within the tumor microenvironment and the challenges that remain. Recommendations made to the NCI included (a) holding an annual meeting at which biologists, clinicians, and imaging scientists could exchange data, facilitating new collaborations within this multidisciplinary field; (b) funding both research and training specifically designed to foster a cross-disciplinary focus; (c) creating and making available a variety of resources to interested investigators, such as a repository of stromal cells and extracellular matrix molecules; and (d) taking steps to encourage translation of the basic research findings into the clinic.

Spill, F., et al. (2018). "Mechanical and Systems Biology of Cancer." Comput Struct Biotechnol J **16**: 237-245.

Mechanics and biochemical signaling are both often deregulated in cancer, leading toincreased cell invasiveness, proliferation, and survival. The dynamics and interactions of cytoskeletal components control basic mechanical properties, such as cell tension, stiffness, and engagement with the extracellular environment, which can lead to extracellular matrix remodeling. Intracellular mechanics can alter signaling and transcription factors, impacting cell decision making. Additionally, signaling from soluble and mechanical factors in the extracellular environment, such as substrate stiffness and ligand density, can modulate cytoskeletal dynamics. Computational models closely integrated with experimental support, incorporating cancer-specific parameters, can provide quantitative assessments and serve as predictive tools toward dissecting the feedback between signaling and mechanics and across multiple scales and domains in tumor progression.

Srivastava, S., et al. (2016). "Research Needs for Understanding the Biology of Overdiagnosis in Cancer Screening." J Cell Physiol **231**(9): 1870-1875.

Many cancers offer an extended window of opportunity for early detection and therapeutic intervention that could lead to a reduction in cause-specific mortality. The pursuit of early detection in screening settings has resulted in decreased incidence and mortality for some cancers (e.g., colon and cervical cancers), and increased incidence with only modest or no effect on cause-specific mortality in others (e.g., breast and prostate). Whereas highly sensitive screening technologies are better at detecting a number of suspected "cancers" that are indolent and likely to remain clinically unimportant in the lifetime of a patient, defined as overdiagnosis, they often miss cancers that are aggressive and tend to present clinically between screenings, known as interval cancers. Unrecognized overdiagnosis leads to overtreatment with its attendant (often long-lasting) side effects, anxiety, and substantial financial harm. Existing methods often cannot differentiate indolent lesions from aggressive ones or understand the dynamics of neoplastic progression. To correctly identify the population that would benefit the most from screening and identify the lesions that would benefit most from treatment, the evolving genomic and molecular profiles of individual cancers during the clinical course of progression or indolence must be investigated, while taking into account an individual's genetic susceptibility, clinical and environmental risk factors, and the tumor microenvironment. Practical challenges lie not only in the lack of access to tissue specimens that are appropriate for the study of natural history, but also in the absence of targeted research strategies. This commentary summarizes the recommendations from a diverse group of scientists with expertise in basic biology, translational research, clinical research, statistics, and epidemiology and public health professionals convened to discuss research directions. J. Cell. Physiol. 231: 1870-1875, 2016. (c) 2015 Wiley Periodicals, Inc.

Steele, G., Jr. (1994). "SSO Clinical Award Lecture. The surgical oncologist as a key translator of basic biology to patients with gastrointestinal cancer: asking the right questions." Ann Surg Oncol **1**(3): 262-269.

Steinert, G., et al. (2012). "Biology and significance of circulating and disseminated tumour cells in colorectal cancer." Langenbecks Arch Surg **397**(4): 535-542.

PURPOSE: More than 130 years ago, circulating tumour cells (CTCs) and disseminated tumour cells (DTCs) have been linked to metastasis.

Since then, a myriad of studies attempted to characterise and elucidate the clinical impact of CTCs/DTCs, amongst others in colorectal cancer (CRC). Due to a flood of heterogeneous findings regarding CTCs/DTCs in CRC, this review aims to describe the known facts about CTC/DTC biology and clinical impact. METHODS: To identify the basic scientific literature regarding the biology and clinical impact of CTCs/DTCs in CRC, we reviewed the literature in the PubMed database. We focused on publications written in English and published until January 2012. As search terms, we used "colorectal cancer (CRC)", "colon cancer (CC)", "CTC", "DTC", "bone marrow (BM)", "lymph node (LN)", "peripheral blood (PB)", "significance" and "prognosis". RESULTS: CTC detection and quantification under standardised conditions is feasible. Several studies in large patient settings have revealed prognostic impact of CTCs in CRC. CRC-derived DTC detection and analysis in BM exhibits a more heterogeneous picture but also shows clinical value. Furthermore, the presence of DTCs in LN has a strong prognostic impact in CRC. CONCLUSIONS: Clinical relevance and prognostic significance of CTCs/DTCs in CRC have been clearly demonstrated in many experimental studies. The major challenge in CTC/DTC research is now to harmonise the various identification and detection approaches and consequently to conduct large prospective multi-institutional trials to verify the use of CTCs/DTCs as a valid prognostic and predictive biomarker for clinical routine.

Stock, C. and S. F. Pedersen (2017). "Roles of pH and the Na(+)/H(+) exchanger NHE1 in cancer: From cell biology and animal models to an emerging translational perspective?" Semin Cancer Biol **43**: 5-16.

Acidosis is characteristic of the solid tumor microenvironment. Tumor cells, because they are highly proliferative and anabolic, have greatly elevated metabolic acid production. To sustain a normal cytosolic pH homeostasis they therefore need to either extrude excess protons or to neutralize them by importing HCO(3)(-), in both cases causing extracellular acidification in the poorly perfused tissue microenvironment. The Na(+)/H(+) exchanger isoform 1 (NHE1) is a ubiquitously expressed acid-extruding membrane transport protein, and upregulation of its expression and/or activity is commonly correlated with tumor malignancy. The present review discusses current evidence on how altered pH homeostasis, and in particular NHE1, contributes to tumor cell motility, invasion, proliferation, and growth and facilitates evasion of chemotherapeutic cell death. We summarize data from in vitro studies, 2D-, 3D- and organotypic cell culture, animal models and human tissue, which collectively point to pH-regulation in general, and NHE1 in particular, as potential targets in combination chemotherapy. Finally, we discuss the possible pitfalls, side effects and cellular escape mechanisms that need to be considered in the process of translating the plethora of basic research data into a clinical setting.

Stone, H. B., et al. (1998). "Molecular Biology to Radiation Oncology: A Model for Translational Research? Opportunities in basic and translational research. From a workshop sponsored by the National Cancer Institute, Radiation Research Program, January 26-28, 1997, Bethesda, Maryland." Radiat Res **150**(2): 134-147.

Many exciting discoveries are being made that are providing new insights into how molecules, cells and tissues respond to ionizing radiation. There remains a need, however, to translate these findings into more effective treatments for cancer patients, including those treated with radiation therapy. This complex task will require the collaboration of scientists studying molecular, cellular and tissue responses, and those performing clinical trials of emerging therapies. The Radiation Research Program of the National Cancer Institute sponsored a workshop entitled "Molecular Biology to Radiation Oncology: A Model for Translational Research?" to bring together basic scientists and clinicians to exchange ideas and fundamental concepts and to identify opportunities for future research and collaboration. Four broad topics were addressed: signal transduction and apoptosis, the cell cycle, repair of radiation damage, and the microenvironment. The development, selection and use of appropriate experimental models is crucial to finding and developing new therapies, and opportunities exist in this area as well. This paper and the accompanying paper by Coleman and Harris that provides the viewpoint of radiation oncologists (Radiat. Res. 150, 134-147, 1998) summarize the background concepts and opportunities for translational research identified by the workshop participants.

Subramanian, A., et al. (2015). "Development of nanotheranostics against metastatic breast cancer--A focus on the biology & mechanistic approaches." Biotechnol Adv **33**(8): 1897-1911.

Treatment for metastatic breast cancer still remains to be a challenge since the currently available diagnostic and treatment strategies fail to detect the micro-metastasis resulting in higher mortality rate. Moreover, the lack of specificity to target circulating tumor cells is also a factor. In addition, currently available imaging modalities to identify the secondaries vary with respect to various metastatic anatomic areas and size of the tumor. The drawbacks associated with the existing clinical management of the metastatic breast cancer demands the requirement of multifunctional nanotheranostics, which could diagnose at macro- and

microscopic level, target the solid as well as circulating tumor cells and control further progression with the simultaneous evaluation of treatment response in a single platform. However, without the understanding of the biology as well as preferential homing ability of circulating tumor cells at distant organs, it is quite impossible to address the existing challenges in the present diagnostics and therapeutics against the breast cancer metastasis. Hence this review outlines the severity of the problem, basic biology and organ specificity with the sequential steps for the secondary progression of disease followed by the various mechanistic approaches in diagnosis and therapy at different stages.

Tamaddon, M., et al. (2023). "Single-cell transcriptome analysis for cancer and biology of the pancreas: A review on recent progress." Front Genet **14**: 1029758.

Single-cell sequencing has become one of the most used techniques across the wide field of biology. It has enabled researchers to investigate the whole transcriptome at the cellular level across tissues, which unlocks numerous potentials for basic and applied studies in future diagnosis and therapy. Here, we review the impact of single-cell RNA sequencing, as the prominent single-cell technique, in pancreatic biology and cancer. We discuss the most recent findings about pancreatic physiology and pathophysiology owing to this technological advancement in the past few years. Using single-cell RNA sequencing, researchers have been able to discover cellular heterogeneity across healthy cell types, as well as cancer tissues of the pancreas. We will discuss the new immunological targets and new molecular mechanisms of progression in the microenvironment of pancreatic cancer studied using single-cell RNA sequencing. The scope is not limited to cancer tissues, and we cover novel developmental, evolutionary, physiological, and heterogenic insights that have also been achieved recently for pancreatic tissues. We cover all biological insights derived from the single-cell RNA sequencing data, discuss the corresponding pros and cons, and finally, conclude how future research can move better by utilizing single-cell analysis for pancreatic biology.

Taylor, M. R., et al. (2021). "The biology of stress in cancer: Applying the biobehavioral framework to adolescent and young adult oncology research." Brain Behav Immun Health **17**: 100321.

The stress response influences the development and trajectory of cancer through a host of complex neuroimmune mechanisms. Basic, translational, and clinical research has elucidated these biobehavioral connections and offers a new paradigm for scientific investigation and patient care. Using a biobehavioral approach could offer new diagnostic and therapeutic opportunities in oncology, and this approach will be particularly impactful for adolescent and young adult (AYA) patients with cancer. To date, nearly all biobehavioral oncology research has been done in the adult population. And yet, AYAs have traditionally poorer mental health and cancer-related outcomes, and thus represent a population that could benefit from parallel psychosocial and biomedical intervention. Future biobehavioral work in oncology should focus on the AYA population, integrating new cancer therapies and technology into the next generation of research.

Teng, M. W., et al. (2011). "Biology and clinical observations of regulatory T cells in cancer immunology." Curr Top Microbiol Immunol **344**: 61-95.

This review specifically examines the role of regulatory T cells (Tregs) in cancer in both mice and the clinic. Due to the rapid refinement of the definition of Tregs and their heterogeneity, emphasis is given to research findings over the past three years. For clarity, this review is broadly divided into three short sections that outline the basic biology of Tregs - (1) Treg lineage and development, (2) Treg subsets, and (3) mechanisms of Treg-mediated immune suppression; followed by two more comprehensive sections that cover; (4) clinical observations of Tregs and cancer, and (5) modifications of Treg biology as cancer immunotherapies. The latter two sections discuss the measurement of function and frequency of Treg in model systems and clinical trials and possible ways to interfere with Treg-mediated immune suppression with the focus on recent pre-clinical and clinical findings.

Tenjin, Y., et al. (2019). "Ascl1-induced Wnt11 regulates neuroendocrine differentiation, cell proliferation, and E-cadherin expression in small-cell lung cancer and Wnt11 regulates small-cell lung cancer biology." Lab Invest **99**(11): 1622-1635.

The involvement of Wnt signaling in human lung cancer remains unclear. This study investigated the role of Wnt11 in neuroendocrine (NE) differentiation, cell proliferation, and epithelial-to-mesenchymal transition (EMT) in human small-cell lung cancer (SCLC). Immunohistochemical staining of resected specimens showed that Wnt11 was expressed at higher levels in SCLCs than in non-SCLCs; 58.8% of SCLC, 5.2% of adenocarcinoma (ADC), and 23.5% of squamous cell carcinoma tissues stained positive for Wnt11. A positive relationship was observed between Achaete-scute complex homolog 1 (Ascl1) and Wnt11 expression in SCLC cell lines, and this was supported by transcriptome data from SCLC tissue. The expression of Wnt11 and some NE markers increased after the transfection of ASCL1 into the A549 ADC cell line. Knockdown of Ascl1 downregulated Wnt11 expression

in SCLC cell lines. Ascl1 regulated Wnt11 expression via lysine H3K27 acetylation at the enhancer region of the WNT11 gene. Wnt11 controlled NE differentiation, cell proliferation, and E-cadherin expression under the regulation of Ascl1 in SCLC cell lines. The phosphorylation of AKT and p38 mitogen-activated protein kinase markedly increased after transfection of WNT11 into the SBC3 SCLC cell line, which suggests that Wnt11 promotes cell proliferation in SCLC cell lines. Ascl1 plays an important role in regulating the Wnt signaling pathway and is one of the driver molecules of Wnt11 in human SCLC. Ascl1 and Wnt11 may employ a cooperative mechanism to control the biology of SCLC. The present results indicate the therapeutic potential of targeting the Ascl1-Wnt11 signaling axis and support the clinical utility of Wnt11 as a biological marker in SCLC.

Wallner, P. E., et al. (2014). "Current status and recommendations for the future of research, teaching, and testing in the biological sciences of radiation oncology: report of the American Society for Radiation Oncology Cancer Biology/Radiation Biology Task Force, executive summary." Int J Radiat Oncol Biol Phys **88**(1): 11-17.

In early 2011, a dialogue was initiated within the Board of Directors (BOD) of the American Society for Radiation Oncology (ASTRO) regarding the future of the basic sciences of the specialty, primarily focused on the current state and potential future direction of basic research within radiation oncology. After consideration of the complexity of the issues involved and the precise nature of the undertaking, in August 2011, the BOD empanelled a Cancer Biology/Radiation Biology Task Force (TF). The TF was charged with developing an accurate snapshot of the current state of basic (preclinical) research in radiation oncology from the perspective of relevance to the modern clinical practice of radiation oncology as well as the education of our trainees and attending physicians in the biological sciences. The TF was further charged with making suggestions as to critical areas of biological basic research investigation that might be most likely to maintain and build further the scientific foundation and vitality of radiation oncology as an independent and vibrant medical specialty. It was not within the scope of service of the TF to consider the quality of ongoing research efforts within the broader radiation oncology space, to presume to consider their future potential, or to discourage in any way the investigators committed to areas of interest other than those targeted. The TF charge specifically precluded consideration of research issues related to technology, physics, or clinical investigations. This document represents an Executive Summary of the Task Force report.

Wang, K., et al. (2018). "p21-activated kinase signalling in pancreatic cancer: New insights into tumour biology and immune modulation." World J Gastroenterol **24**(33): 3709-3723.

Pancreatic cancer is one of the most aggressive and lethal malignancies worldwide, with a very poor prognosis and a five-year survival rate less than 8%. This dismal outcome is largely due to delayed diagnosis, early distant dissemination and resistance to conventional chemo-therapies. Kras mutation is a well-defined hallmark of pancreatic cancer, with over 95% of cases harbouring Kras mutations that give rise to constitutively active forms of Kras. As important down-stream effectors of Kras, p21-activated kinases (PAKs) are involved in regulating cell proliferation, apoptosis, invasion/migration and chemo-resistance. Immunotherapy is now emerging as a promising treatment modality in the era of personalized anti-cancer therapeutics. In this review, basic knowledge of PAK structure and regulation is briefly summarised and the pivotal role of PAKs in Kras-driven pancreatic cancer is highlighted in terms of tumour biology and chemo-resistance. Finally, the involvement of PAKs in immune modulation in the tumour microenvironment is discussed and the potential advantages of targeting PAKs are explored.

Wang, Z., et al. (2023). "Circular RNAs: biology and clinical significance of breast cancer." RNA Biol **20**(1): 859-874.

Circular RNAs (circRNAs) are novel noncoding RNAs with covalently closed-loop structures that can regulate eukaryotic gene expression. Due to their stable structure, circRNAs are widely distributed in the cytoplasm and have important biological functions, including as microRNA sponges, RNA-binding protein conjugates, transcription regulators, and translation templates. Breast cancer is among the most common malignant cancers diagnosed in women worldwide. Despite the development of comprehensive treatments, breast cancer still has high mortality rates. Recent studies have unmasked critical roles for circRNAs in breast cancer as regulators of tumour initiation, progression, and metastasis. Further, research has revealed that some circRNAs have the potential for use as diagnostic and prognostic biomarkers in clinical practice. Herein, we review the biogenesis and biological functions of circRNAs, as well as their roles in different breast cancer subtypes. Moreover, we provide a comprehensive summary of the clinical significance of circRNAs in breast cancer. CircRNAs are believed to be a hot focus in basic and clinical research of breast cancer, and innovative future research directions of circRNAs could be used as biomarkers, therapeutic targets, or novel drugs.Abbreviations: CeRNA: Competitive endogenous RNA; ciRNA:

Circular intronic RNA; circRNA: Circular RNA; EIciRNA: Exon-intron circRNA; EMT: Epithelial-mesenchymal transition; IRES: Internal ribosome entry site; lncRNA: Long non-coding RNA; miRNA: MicroRNA; MRE: MiRNA response element; ncRNA: Non-coding RNA; RBP: RNA-binding protein; RNA-seq: RNA sequencing; RT-PCR: Reverse transcription-polymerase chain reaction.

Wayne, A. S., et al. (2013). "Proceedings from the National Cancer Institute's Second International Workshop on the Biology, Prevention, and Treatment of Relapse after Hematopoietic Stem Cell Transplantation: introduction." Biol Blood Marrow Transplant **19**(11): 1534-1536.

Despite advances in hematopoietic stem cell transplantation (HSCT) for the treatment of hematologic malignancies, relapse remains the leading cause of death after transplant. Biologic and clinical investigations are needed to combat this primary cause of death after transplantation. The National Cancer Institute held international workshops in 2009 and 2012 to help address this problem. Three major initiatives for coordinated research were proposed: 1) To establish multicenter networks for basic, translational, epidemiologic and clinical research; 2) To establish a network of biorepositories for the collection of samples before and after HSCT to aid in laboratory and clinical studies; and 3) To refine, implement and study proposed definitions for disease-specific response and relapse and for monitoring of minimal residual disease. The workshop in 2012 also featured nine presentations, summaries of which follow in three manuscripts.

Welm, A. L. (2004). "AACR Special Conference: Advances in Breast Cancer Research--Genetics, Biology, and Clinical Implications, Huntington Beach, California, USA, 8-12 October 2003." Breast Cancer Res **6**(1): E6.

The recent meeting 'Advances in Breast Cancer Research--Genetics, Biology, and Clinical Implications' was an American Association for Cancer Research (AACR) Special Conference in Cancer Research, for which the underwriting sponsor was the Avon Foundation. Presentations were made from prominent scientists on several relevant basic science and clinic-oriented topics, including mammary stem cells and development, steroid receptors, matrix and stromal-epithelial interactions, oncogene signaling and imaging, genetics and prevention, and molecular therapeutics. A summary of recent findings is presented here, with a particular emphasis on unpublished work.

Willingham, M. C. (1989). "Use of colloidal gold cytochemistry in the study of the basic cell biology of cancer." Am J Anat **185**(2-3): 109-127.

We are currently investigating the morphologic aspects of two areas of the basic cell biology of cancer: tumor-specific surface antigens as targets for immunotoxins, and the phenomenon of multidrug resistance in chemotherapy of human tumors. Colloidal gold cytochemistry has provided a useful method for the electron-microscopic cytochemical detection of materials endocytosed by cells in culture. This technique has been used to study the internalization pathway of ligands bound to the surface of cancer cells, particularly antibodies for use as immunologic targeting reagents for the construction of immunotoxins. These colloidal gold conjugates with monoclonal antibodies have demonstrated the internalization of these immunologic reagents through coated pits and receptosomes, which is a necessary step in the delivery of immunotoxins into the cell where they can mediate their cell-killing functions. Morphologic methods have been employed for the screening and selection of monoclonal antibodies reactive with the surface of human ovarian cancer cells for use as immunotoxins and have demonstrated the in vivo activity of immunotoxins made with these antibodies and Pseudomonas exotoxin in a nude mouse model system. In other studies, we have employed such reagents for the immunocytochemical detection of the surface expression of P170, the cell-surface efflux pump protein responsible for the phenotype of multidrug resistance in tumor cells, and to investigate the distribution of this protein by using immunocytochemistry in normal human tissues. These results have suggested a role for P170 in normal cell membrane transport of metabolites in various organ systems.

Workman, P. and P. Clarke (2012). "PI3 Kinase in Cancer: From Biology to Clinic." Am Soc Clin Oncol Educ Book: e93-98.

The discovery and clinical development of small-molecule inhibitors of the phosphatidylinositide 3-kinase (PI3 kinase) family of lipid kinases have marked a remarkable 20-year journey that follows the progressive developments in cancer biology over the last few decades: from hypothesis-driven, basic cancer research that began with viral oncogenesis and developed in the 1960s and 70s, through the discovery of individual mutated oncogenes and tumor suppressor genes in 1970 and 80s and the linkage of these cancer genes to signal transduction pathways in the 1990s, to all large-scale genome-wide sequencing, functional screening, and network biology efforts today. Thus, PI3 kinase research began with the discovery in 1985 of a new type of enzyme activity associated with viral oncogenesis. It benefited greatly from the discovery of wortmannin and LY294002 as PI3 kinase inhibitors and chemical tools in late 1980s to mid-90s. Alongside these tools, genetic validation of PI3 kinase as a target initially

involved activation by upstream oncogenic receptor tyrosine kinases and RAS mutation, together with overexpression and amplification of the p110alpha catalytic isoform of PI3 kinase and frequent loss of the tumor suppressor and negative regulator of PI3 kinase activity, PTEN. As PI3 kinase drug development began, further stimulus came from the discovery through genome sequencing of mutations in PIK3CA, which encodes p110alpha and is the most frequently mutated kinase in the human genome. From these beginnings, there are now many PI3 kinase inhibitors in clinical trials and more in preclinical development. We review progress, current challenges, and future opportunities in this article.

Yang, I. and L. M. Liau (2010). "American Association for Cancer Research Genetics and Biology of Brain Cancers 2009, December 13-15, 2009, San Diego, CA." J Neurooncol **99**(2): 297-306.

Molecularly targeted therapies promise to transform the treatment of cancer patients, including those with brain tumors. A deeper understanding of the biology of brain tumors has led to a palpable excitement that new and more effective treatments are on the horizon for these deadly diseases. This conference brought basic, genomic, and translational scientists together with clinicians to discuss how to develop more effective molecularly targeted therapies for brain tumor patients based on a mechanistic understanding of the molecular circuitry and biology of the disease.

Yang, X., et al. (2013). "Bridging cancer biology with the clinic: relative expression of a GRHL2-mediated gene-set pair predicts breast cancer metastasis." PLoS One **8**(2): e56195.

Identification and characterization of crucial gene target(s) that will allow focused therapeutics development remains a challenge. We have interrogated the putative therapeutic targets associated with the transcription factor Grainy head-like 2 (GRHL2), a critical epithelial regulatory factor. We demonstrate the possibility to define the molecular functions of critical genes in terms of their personalized expression profiles, allowing appropriate functional conclusions to be derived. A novel methodology, relative expression analysis with gene-set pairs (RXA-GSP), is designed to explore the potential clinical utility of cancer-biology discovery. Observing that Grhl2-overexpression leads to increased metastatic potential in vitro, we established a model assuming Grhl2-induced or -inhibited genes confer poor or favorable prognosis respectively for cancer metastasis. Training on public gene expression profiles of 995 breast cancer patients, this method prioritized one gene-set pair (GRHL2, CDH2, FN1, CITED2, MKI67 versus CTNNB1 and CTNNA3) from all 2717 possible gene-set pairs (GSPs). The identified GSP significantly dichotomized 295 independent patients for metastasis-free survival (log-rank tested p = 0.002; severe empirical p = 0.035). It also showed evidence of clinical prognostication in another independent 388 patients collected from three studies (log-rank tested p = 3.3e-6). This GSP is independent of most traditional prognostic indicators, and is only significantly associated with the histological grade of breast cancer (p = 0.0017), a GRHL2-associated clinical character (p = 6.8e-6, Spearman correlation), suggesting that this GSP is reflective of GRHL2-mediated events. Furthermore, a literature review indicates the therapeutic potential of the identified genes. This research demonstrates a novel strategy to integrate both biological experiments and clinical gene expression profiles for extracting and elucidating the genomic impact of a novel factor, GRHL2, and its associated gene-sets on the breast cancer prognosis. Importantly, the RXA-GSP method helps to individualize breast cancer treatment. It also has the potential to contribute considerably to basic biological investigation, clinical tools, and potential therapeutic targets.

Yarden, Y. and G. Pines (2012). "The ERBB network: at last, cancer therapy meets systems biology." Nat Rev Cancer **12**(8): 553-563.

Although it is broadly agreed that the improved treatment of patients with cancer will depend on a deeper molecular understanding of the underlying pathogenesis, only a few examples are already available. This Timeline article focuses on the ERBB (also known as HER) network of receptor tyrosine kinases (RTKs), which exemplifies how a constant dialogue between basic research and medical oncology can translate into both a sustained pipeline of novel drugs and ways to overcome acquired treatment resistance in patients. We track the key early discoveries that linked this RTK family to oncogenesis, the course of pioneering clinical research and their merger into a systems-biology framework that is likely to inspire further generations of effective therapeutic strategies.

Yoshida, Y. and T. Nakano (2014). "[Topics of radiation biology for cancer treatment]." Igaku Butsuri **34**(2): 48-56.

Recent advances in the field of radiation therapy (RT) have considerably improved treatment outcomes of various cancers. It is related to not only the technological progress in medical physics but also the analytical progress in radiation biological effectiveness. However, the treatment results of RT, especially in advanced cancer, are still insufficient, therefore it is necessary to establish a safety and more effective method for treating cancer. Understanding the radiation biology is essential to appreciate the effect of RT. Hence, we review the controversial point of RT for

radiation biology and introduce the results of basic research.

Yu, K. D., et al. (2021). "Estrogen receptor-low breast cancer: Biology chaos and treatment paradox." Cancer Commun (Lond) **41**(10): 968-980.

Hormone receptor testing mainly serves the purpose of guiding treatment choices for breast cancer patients. Patients with estrogen receptor (ER)-positive breast cancers show significant response to endocrine therapy. However, the methods to define ER status and eligibility for treatment remain controversial. Despite recent guidelines considering staining >/=1% of tumor nuclei by immunohistology as ER-positive, it has raised concerns on the benefit of endocrine therapy for tumors with ER 1%-10% expression, termed "ER-low positive". This subgroup accounts for 3% to 9% of all patients and is likely to have unique molecular features, and therefore distinct therapeutic response to endocrine therapy compared with ER-high positive tumors. The latest guidelines did not provide detailed descriptions for those patients, resulting in inconsistent treatment strategies. Consequently, we aimed to resolve this dilemma comprehensively. This review discusses molecular traits and recent ER-low positive breast cancer innovations, highlighting molecular-targeted treatment rather than traditional unified endocrine therapy for future basic and clinical research.

Zhang, X., et al. (2017). "The Biology of Aging and Cancer: Frailty, Inflammation, and Immunity." Cancer J **23**(4): 201-205.

The majority of patients with common malignancies are older adults. Intrinsic complex biological changes of aging along with inflammation, immunosenescence, age-associated chronic diseases, and extrinsic environmental and psychosocial factors have significant impact on not only development and behavior of individual malignancies, but also physiologic reserve and vulnerability of older patients who suffer from them. As a result, clinical practice of geriatric oncology demands integration of careful geriatric assessment and management. This article provides an overview of basic biology of aging and its relationship with cancer. After a brief introduction about the definition and mechanisms of aging, as well as age-related biological and physiological changes, the discussion mainly focuses on recent development and insights into the relationship of frailty, inflammation, and immunity with cancer, highlighting how the new knowledge can help further improve assessment and treatment of older patients with malignancies and promote cancer research.

Zhang, Y., et al. (2023). "Innate Immunity in Cancer Biology and Therapy." Int J Mol Sci **24**(14).

Immunotherapies including adaptive immune checkpoint inhibitors (ICIs) and chimeric antigen receptor (CAR) T cells, have developed the treatment of cancer in clinic, and most of them focus on activating T cell immunity. Although these strategies have obtained unprecedented clinical responses, only limited subsets of cancer patients could receive long-term benefits, highlighting the demand for identifying novel targets for the new era of tumor immunotherapy. Innate immunity has been demonstrated to play a determinative role in the tumor microenvironment (TME) and influence the clinical outcomes of tumor patients. A thorough comprehension of the innate immune cells that infiltrate tumors would allow for the development of new therapeutics. In this review, we outline the role and mechanism of innate immunity in TME. Moreover, we discuss innate immunity-based cancer immunotherapy in basic and clinical studies. Finally, we summarize the challenges in sufficiently motivating innate immune responses and the corresponding strategies and measures to improve anti-tumor efficacy. This review could aid the comprehension of innate immunity and inspire the creation of brand-new immunotherapies for the treatment of cancer.

Zhang, Z., et al. (2023). "Molecular Biology Mechanisms and Emerging Therapeutics of Triple-Negative Breast Cancer." Biologics **17**: 113-128.

Triple-negative breast cancer (TNBC) is an aggressive subtype of breast cancer that is conventionally characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2), accounting for approximately 15-20% of all breast cancers. Compared to other molecular phenotypes, TNBC is typically associated with high malignancy and poor prognosis. Cytotoxic agents have been the mainstay of treatment for the past few decades due to the lack of definitive targets and limited therapeutic interventions. However, recent developments have demonstrated that TNBC has peculiar molecular classifications and biomarkers, which provide the possibility of evolving treatment from basic cytotoxic chemotherapy to an expanding domain of targeted therapies. This review presents a framework for understanding the current clinical experience surrounding molecular biology mechanisms in TNBC (Figure 1). Including immunotherapy, polymerase (PARP) and PI3K/AKT pathway inhibitors, antibody-drug conjugates, and androgen receptor (AR) blockade. Additionally, the role of miRNA therapeutics targeting TNBC and potential strategies targeting cancer stem cells (CSCs) are discussed and highlighted. As more and more treatments arise on the horizon, we believe that patients with TNBC will have a new sense of hope.

Zupancic, D., et al. (2020). "Combined lectin- and immuno-histochemistry (CLIH) for applications in cell biology and cancer diagnosis: Analysis of human urothelial carcinomas." Eur J Histochem **64**(3).

Lectin histochemistry (LHC) and immunohistochemistry (IHC), which demonstrate the composition and localisation of sugar residues and proteins in cell membranes, respectively, are generally used separately. Using these two methods, we previously demonstrated that malignant transformation of urothelial cells results in the alterations of protein glycosylation and reduced expression of urothelium-specific integral membrane proteins uroplakins (UPs). However, the correlation between these changes was not studied yet. To evaluate this correlation, we developed innovative method, which we named combined lectin- and immuno- histochemistry (CLIH). We used human biopsies of 6 normal urothelia and 9 papillary urothelial carcinomas, i.e. 3 papillary urothelial neoplasms of low malignant potential (PUNLMP), 3 non-invasive papillary urothelial carcinomas of low grade (pTa, l.g.), and 3 invasive papillary urothelial carcinomas of high grade (pT1, h.g.). We tested five different protocols (numbered 1-5) of CLIH on paraffin and cryo-semithin sections and compared them with LHC and IHC performed separately. Additionally, we carried out western and lectin blotting with antibodies against UPs and lectins Amaranthus caudatus agglutinin (ACA), Datura stramonium agglutinin (DSA), and jacalin, respectively. We showed that incubation with primary antibodies first, followed by the mixture of secondary antibodies and lectins is the most efficient CLIH method (protocol number 5). Additionally, 300 nm thick cryo-semithin sections enabled better resolution of co-localisation between sugar residues and proteins than 5 microm thick paraffin sections. In the normal urothelium, CLIH showed co-localisation of lectins ACA and jacalin with UPs in the apical plasma membrane (PM) of superficial umbrella cells. In papillary urothelial carcinomas, all three lectins (ACA, DSA and jacalin) labelled regions of apical PM, where they occasionally co-localised with UPs. Western and lectin blotting confirmed the differences between normal urothelium and papillary urothelial carcinomas. Our results show that CLIH, when used with various sets of lectins and antigens, is a useful, quick, and reliable method that could be applied for basic cell biology research as well as detailed subtyping of human urothelial carcinomas.

The above contents are the collected information from Internet and public resources to offer to the people for the convenient reading and information disseminating and sharing.

References

[1]. Baidu. http://www.baidu.com. 2019.
[2]. Google. http://www.google.com. 2019.
[3]. Ma H, Chen G. Stem cell. The Journal of American Science 2005;1(2):90-92.
[4]. Ma H, Cherng S. Eternal Life and Stem Cell. Nature and Science. 2007;5(1):81-96.
[5]. Ma H, Cherng S. Nature of Life. Life Science Journal 2005;2(1):7-15.
[6]. Ma H, Yang Y. Turritopsis nutricula. Nature and Science 2010;8(2):15-20. http://www.sciencepub.net/nature/ns0802/03_1279_hongbao_turritopsis_ns0802_15_20.pdf.
[7]. Ma H. The Nature of Time and Space. Nature and science 2003;1(1):1-11. Nature and science 2007;5(1):81-96.
[8]. National Center for Biotechnology Information, U.S. National Library of Medicine. http://www.ncbi.nlm.nih.gov/pubmed. 2019.
[9]. Wikipedia. The free encyclopedia. http://en.wikipedia.org. 2019.
[10]. Marsland Press. http://www.sciencepub.net. 2019.

9/21/2023