Existing Conventional Treatments; Introduction to Alternative Approaches

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Introduction: Cancer - Neoplasia - DNA Damage / Mutations

Cancer is a word used to describe a wide range of disorders that result from the growth and spread of abnormal cells throughout many different parts of the body. Cancer was originally used to describe the 'spreading of blood vessels' around an abnormal tissue mass that resembled the limbs of a crab. Although 'cancer' is the most frequently used term for such disorders, the terms neoplasia and neoplasm are more descriptive.

Neoplasia (meaning, new growth) is a term that is used to define the development of a cell that has altered in such a way that its growth exceeds, and is not coordinated with, that of the normal tissues that it is surrounded by. Unchecked growth or multiplication of a neoplastic cell forms a mass of cells called a neoplasm. When a neoplasm reaches a clearly recognisable mass, it is usually referred to as a tumour. A cancer is in fact a malignant neoplasm or tumour. For simplicity, even though incorrect, cells at all stages of cancer are generally referred to as cancer cells.

There are many different types of cancer. They can be classified with regard to the biological identity of the tissue in which the primary tumour has developed. The word *sarcoma* is used to describe a number of uncommon malignant neoplasms that originate in soft tissues such as muscle, fat and cartilage for example that are derived from cells of mesenchymal origin. By contrast, the term *carcinoma* is used to describe a wide range of common malignant neoplasms that originate from cells of epithelial origin.

Molecular DNA

Even though there are many different types of cancer, many of them have a common underlying cause, damage to DNA. Such DNA damage is often referred to as a cancer causing genetic mutation. Cancer causing mutations can either be caused by genetic mutations that occur in a single cell at any stage of life. These genetic mutations are termed somatic mutations. By contrast, cancer predisposing genetic mutations can be included in DNA within either the egg or sperm, or both so that every cell in the resulting offspring contains the cancer predisposing cancer mutation. These mutations are referred to as *germline* mutations and are heritable. As might be expected, subjects who carry germline mutations are far more likely to develop cancer than those who carry a somatic mutation, and at an earlier age.

DNA damage may be caused by many factors such as inflammation, radiation, toxins, exposure to carcinogens, spontaneous deamination of methylated cytosine residues and more.

These DNA mutations can lead to loss of cell cycle control and lead to formation of a tumour, (referred to as*tumorigenesis*), the primary tumour. The most frequent mutations that cause cancer are found in the tumour suppressor gene, TP53 and the Ras oncogene family. Tumour suppressor genes control the cell cycle and oncogenes are responsible for loss of cell cycle control of cells and malignant transformation.

Loss of cell cycle control can also be caused by aberrations in the epigenetic gene expression controlling systems. It is now recognized that the DNA methylating machinery, as well as the interference RNA gene expression controlling system, also play an important role in activation of genes that initiate and permit progression of many types of cancer, especially *hypermethylation* of tumour suppressor genes or *hypomethylation* of oncogenes. Hypermethylation turns off gene expression whereas hypomethylation enhances gene expression.

Neoplastic Transformation

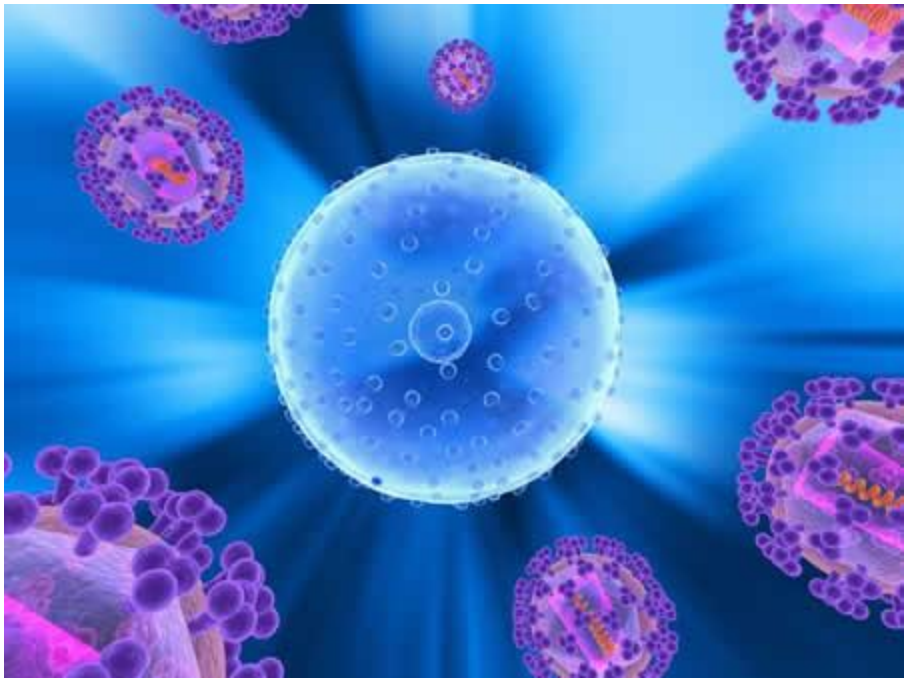
Generation of new tissues, as well as repair of damaged tissues relies on the activation of dormant stem cells that proliferate and differentiate into the mature cells of the tissue or organ when so

required. To maintain the correct shape, size and function of the tissue or organ, proliferation and differentiation of stem cells, which involves activation of the cell cycle, must therefore be under strict control. If DNA mutations have occurred in a dormant stem cell's genes that control the cell cycle, such as a tumour suppressor gene, or direct differentiation, or in an oncogene, then when the stem cell's turn to proliferate and differentiate occurs, its cell cycle and differentiation pathway will continue in an uncontrolled way. This is how neoplasms or tumours begin. As indicated above, there are many different factors that inflict damage on DNA. Fortunately, DNA repair mechanisms have evolved that are continuously repairing damage to DNA.

Once a tumour has formed, some of the cells in the primary tumour may undergo further DNA changes which may involve epigenetic re-arrangements that enable them to break away from the primary tumour. They can then be deposited in other parts of the body, in vital organs such as the liver and lungs to form further tumours called 'secondaries' or *metastases*. It is usually the metastases that cause death.

Common Features of Neoplasia

Although there is a large number phenotypes and proteins involved in tumour formation, tumour progression and tumour invasion, as well as many different biological pathways, there are a number of critical steps or factors outlined below that are commonly by-passed or disabled in order for a damaged cell to form a tumour and then some of them metastasise.



1. Apoptosis

Apoptosis refers to a biological process that induces cells, in which DNA or other cell components have been irreparably damaged, to commit suicide. Apoptosis is also called programmed cell death. The decision regarding whether or not a damaged cell is to be instructed to kill itself is determined by a protein called p53, encoded by the gene TP53. Reduced p53 activity plays an important role in tumorigenesis[1] because if p53 is unable to deliver a strong enough message to a damaged cell to induce it to commit suicide, the damaged cell can readily grow into a tumour.

The expression or activity of p53 is controlled principally by a protein called Bcl-2. Over-expression of the gene BCL-2, which can be brought about by translocation of this gene in neoplastic cells, particularly of lymphoid origin, suppresses the function of p53 so that the neoplastic cells can continue abnormal growth by avoiding programmed cell death (reviewed in Ref 2).[2] Consequently, increasing the activity of p53 helps to overcome the negative influences of Bcl-2 and enable application of the apoptotic programme in neoplastic cells.

2. Loss of Cell Cycle Control, Tumour Suppression

As indicated above, many of the body's tissues are constantly being renewed and repaired by formation of new cells. For cells to proliferate they must undergo a series of well-controlled cell cycles. To retain the correct function and structure of the tissue, cellular proliferation is tightly controlled by a series of genes called tumour suppressor genes.

Many tumour suppressor genes have been identified. However, a recently discovered protein encoded by the gene KEAP1[3] plays an important master role in cell cycle control and tumour suppression. The KEAP1 gene product also helps to shut off a tumour's blood supply.

Another protein, Nrf 2 has been recognized to promote tumour growth and resistance to chemotherapeutic drugs because cancer cells hijack Nrf2 activity to support their malignant growth. KEAP1 controls the action of Nrf 2, therefore increasing the activity of KEAP1 also has other important advantages by controlling tumour progression and increasing the sensitivity of malignant cells to chemotherapeutic drugs.[4]

3. Abnormal Angiogenesis

Angiogenesis refers to the formation of new blood vessels. When a tumour has formed, it can only continue to grow if it has an adequate supply of nutrients as well as oxygen from the blood. To do this, it must develop an extensive new network of blood vessels. Angiogenesis is controlled by many factors. However, the apoptotic protein p53 also plays an important role in inhibition of the formation of undesirable blood vessels such as those that form in tumours because of a lack of available oxygen, or a state of hypoxia, within the tumour.[1] Consequently, impaired activity of p53 leads to tumour survival because the growth of new blood vessels within the tumour is unrestricted. Increased activity of p53 therefore plays an important role in many aspects of tumorigenesis and tumour progression.

4. Immune Evasion

Immune mechanisms play an important role in suppression of tumour growth. It is now known that the adaptive immune system is able to produce tumour specific cytotoxic T cells that have the capacity to kill tumour cells. However, a link has been identified between hypoxia induced angiogenesis and generation of immune tolerance to neoplastic cells. Recent studies have shown that a protein encoded by the gene OX40 is able to interact directly with tumour specific cytotoxic T cells to help them break this tolerance and begin to kill tumour cells more effectively.[5] The application of OX40 as a potential anti-cancer treatment has already been initiated.[6]

5. Chemotherapy Induced Immune Suppression

Many chemotherapy drugs work by helping to kill cells that are rapidly proliferating such as tumour cells. Immune cells are also continually proliferating rapidly in the bone marrow in order to make new immuno-competent cells. Consequently, many chemotherapy drugs also stop the production of new immune cells which are required to help attack the tumour cells. The bone marrow can be

stimulated to produce more immuno-competent cells by a cytokine called IL-7. The value of reconstitution of immuno-competency by administration of IL-7 has been confirmed with regard to its significance in front line anti-cancer therapy.[7] Increasing the production of IL-7 plays an important role in resolution of cancer.

6. Tumour Spread, Metastasis

Some of the rapidly dividing cells within a tumour may undergo further changes that permit them to leave the primary tumour and come to rest in other organs to form lethal metastatic lesions. A recently discovered protein encoded by a gene TIP30 plays an important role in inhibiting tumour cells from escaping from the primary tumour.[8] Therefore, increasing TIP30 activity has the capacity to slow down and arrest the spread of neoplastic cells.

7. Impaired DNA Repair

DNA is continuously being damaged by exposure to many environmental factors such as radiation and toxic substances as well as inflammation and other factors outlined above. There are many genes that encode proteins that repair this damage. One of them is BRCA1. If BRCA1 does not produce an effective gene product or too little of the gene product, DNA is not repaired satisfactorily. As indicated above, if DNA damage is inflicted upon tumour suppressor genes, then control of the cell cycle is lost, resulting in tumorigenesis and rapid tumour progression. Scientists have clearly demonstrated that reduced activity of BRCA1 by whatever means, results in increased susceptibility to development of cancer and disease progression.[9, 10] Therefore up-regulation of BRCA1 plays an important role in protecting against development and progression of many cancers.

How is Cancer Diagnosed and Treated?

Diagnostic Methods

There are many ways of diagnosing cancer. The diagnostic method largely depends on the site of the neoplasm.

Location of Neoplasm/s

Magnetic resonance imaging (MRI) can be used to develop whole body images which can identify abnormal cell growths or tumours;

A computerized tomographic (CT) scan is an X-ray procedure that uses a computer to take detailed, three-dimensional pictures of abnormal tissue in the body. Tumour detection is very effective by use of such technologies. However, exposure to excessive X-rays can damage DNA in radiation sensitive people;

Other non-invasive procedures such as X-ray and ultrasound investigations can also be used to identify suspicious tissue masses;

Once an abnormal tissue mass is identified, a biopsy can be taken for more precise characterization of the tumour mass.

Histopathology

Thin sections of the biopsy can then be prepared and examined microscopically by a pathologist. Sections of the tissue can be treated with a range of different reagents (usually immunohistochemicals) that can help the pathologist to comment on the source of, and many other features of the neoplasm;

There is a wide range of reagents and immunohistochemicals that the tissue sections can be treated or stained with that can be used to identify important features of the neoplasm and whether they have or have not started to spread. Many such reagents are used to determine clonality of cells (that is, has the neoplasm been derived from a single neoplastic cell) in a biopsy specimen. Confirmation of clonality is an important step for diagnosis of cancer. Once clonality is established, other markers can be used as prognostic indicators, such as the use of a reagent that identifies cells containing a protein called Ki-67. Ki-67 is a marker of cellular proliferation, therefore, the number of neoplastic cells that are positive for Ki-67 gives an indication of the rate of proliferation of cells within the tumour;

Properties such as oestrogen receptor status and HER2 status can be used to determine whether anti-oestrogen therapy or other would be helpful in cases of breast cancer for example with regard to treatment selection. The significance of these properties will be discussed further below along with treatment considerations.

Molecular Pathology

There is a wide range of molecular pathological tests that can be performed on DNA or mRNA isolated from neoplastic tissues. As there are very many tests, only a few are referred to here. Many of these tests are also used to determine clonality of a neoplasm. Importantly, molecular pathological tests can also identify precise genetic lesions that are responsible for neoplastic transformation of the original aberrant cell. Knowledge of the genetic re-arrangement that is present in neoplastic cells is useful for prognostication as well as diagnosis. For example, chronic myelogenous leukaemia can be identified by testing for aberrant DNA re-arrangements such as the Philadelphia chromosome, a translocation event involving fusion of part of chromosome 9 with chromosome 22, or B-cell and T-cell IgH and TcR gene rearrangements respectively for diagnosis and classification of lymphomas and leukaemias.

Circulating Tumour Cells

A few years ago, a technology was developed which permits recognition of metastatic cells that have escaped from the primary tumour and are circulating in the blood[11] This test is able to identify neoplastic cells of epithelial origin such as those derived from breast, colon or prostate cancer that have escaped into the blood. In breast cancer patients, studies[11] have shown that the presence of more than about 6 epithelial cells per 10 millilitres of blood is associated with a worse outcome. This test can be used to monitor the efficacy of treatment. Evaluation of epithelial cells at any time during the course of therapy allows assessment of patient prognosis and is predictive of progression-free survival and overall survival. As shown in Ref. 11, the validity of the use of counting epithelial cells in peripheral blood has been confirmed by well-planned investigations.[11] This test, however, cannot be used as a screening test because a small number of healthy people do have epithelial cells in their blood.

As this test identifies cells in the blood that have epithelial cell markers, it cannot detect cells that have been derived from sarcomas, neoplastic cells of mesenchymal origin.

There have been other tests developed by various laboratories based of the isolation of epithelial cells, presumed to reflect metastatic cells, from peripheral blood, such as the testing system outlined in www.thegalkinalab.co.uk . Results of such tests, which are aimed at quantitation of expression of various genes in a small number of cells are claimed to have significant prognostic benefits. In contrast to the rigorous validations shown in Ref. 11, insufficient data could be found in prestigious scientific publication outlets to support the validity of such tests. In these testing systems, it is suggested that expression of genes such as TP53 and BCL-2 can be measured in individual epithelial cells in the blood of cancer patients. Technically, this is a very difficult assay system.

In conclusion, with regard to diagnostic and prognostic tests for cancer, there is a wide range of tests available. Each of the different tests provides information that can be used in a diagnostic and prognostic setting. Many tests can provide information that can help in treatment choice. It is recommended that well tried and tested technologies and tests are used that have been included and validated in first class scientific articles.

Treatments

There are many treatments now available for different types of cancer. The advantages and disadvantages of some of them are now discussed. This section is included to enable both patient and practitioner to become more aware of some of the problematic features associated with different treatment options.

Other than surgery, it is considered by many that there are only two options, chemotherapy and/or radiotherapy with regard to cancer treatment. However, there are many other options that deserve consideration.

Immunological Considerations

Some cancers simply disappear or regress without any treatment. This is a well-known phenomenon.[12] The problem is that the mechanism/s that underpin spontaneous remissions are not clearly understood. However, an immunological mechanism has been recognized as a strong candidate because many spontaneous remissions have been associated with the previous onset of fever, perhaps reflecting some type of viral or pyogenic bacterial infection.

Interestingly, in this context, reovirus was noted to be a potential cancer therapeutic agent when early studies on reovirus suggested it reproduces well in certain cancer cell lines. Reovirus has since

been shown to replicate specifically in cells that have an activated Ras oncogene. Reovirus replicates in and eventually kills Ras-activated tumour cells and as cell death occurs, progeny virus particles are free to infect surrounding cancer cells. This cycle of infection, replication and cell death is believed to be repeated until all tumour cells carrying an activated Ras pathway are destroyed. Virus anti-cancer therapy shows great promise for the future and clinical trials are well underway.[13] Unfortunately, the use of reovirus anti-cancer treatment is only applicable in cases where activation of the Ras oncogene family is involved.

It has been suggested that some viruses can infect neoplastic cells more readily making them more accessible to T cell cytotoxicity and natural killer cell targets.[14] Of course, the problem with this exciting mode of anti-cancer therapy is that it is preferable that the sufferer has not been exposed to the virus previously and developed immunity against that particular virus. In such a situation, the infectivity of neoplastic cells by the virus may be impaired.

Based on immunological considerations, it is also possible to extract antigenic substances from neoplastic cells that can be recognised as immunologically foreign and use them to prepare vaccines that can be used to boost the immune response to specific tumour cells. This approach holds great promise.[15]

Prior to chemotherapy or radiotherapy, it is actually possible to withdraw healthy immune cells from a patient, grow them up in culture, stimulate them with components of the patient's neoplastic cells such as found in melanoma and then return the primed immune cells to the patient. Melanoma cells have a protein called PD-L1 on their surface that helps them avoid being recognized and destroyed by the body's immune system. New drugs that block the PD-L1 protein, or the corresponding PD-1 protein on immune cells, can help the immune system recognize melanoma cells and attack them. Again, the patient must have a sound immune system in order to take advantage of such types of immunologically based anti-cancer treatments.

In situations in which the patient's immune system is compromised, it is also possible to resolve some cancers by reconstitution of the patient's failing immune system with someone else's bone marrow stem cells. Basically, bone marrow transplants are another approach to resolving many cancers such as leukaemia. It is important to stress once again, that immunologically based therapeutic approaches cannot be considered once a patient has started chemotherapy or radiotherapy as these treatments suppress immune responsiveness.

Chemotherapy - Pharmacogenetic Considerations

There are many important factors to consider when choosing treatment options. Chemotherapy is a well-recognised treatment modality. However, not many are aware of some important limitations in the use of chemotherapy. To understand some of the limitations of chemotherapy, it is necessary to understand how some drugs actually work. As there are a large number of different chemotherapeutic drugs, I will generalize and use tamoxifen as an example.

Many chemotherapeutic drugs are designed to arrest the cell cycle in some way by causing damage to the DNA of cells that are rapidly dividing. Chemotherapeutic drugs are very often administered orally in an inactive form. This minimizes drug inflicted damage to the oral tissues and beyond. The inactive drug is then absorbed into the bloodstream. The body has its own detoxifying system which, in the first part, comprises a family of detoxifying enzymes encoded by the cytochrome P450 gene family. One or more members of the cytochrome P450 system recognize the inactive drug as an invading toxin and begin to chemically alter or metabolize the drug. One family member, called CYP2D6 plays an important role in metabolizing many drugs including tamoxifen.

Once CYP2D6 metabolises the inactive drug, it is chemically converted into an active form. This is when it can actually do its job. Eventually, another anti-toxin system reacts with the active drug so that it can be expelled from the body. Then another dose is required.

For optimum drug action, it is very important to have the right amount of active drug in the bloodstream for the right amount of time. The problem is that it is very difficult to achieve this.

The reasons why. The gene that encodes the drug metaboliser, CYP2D6 (as well as many other members of the cytochromeP450 family) is highly polymorphic. That means that there are many different genetically controlled functional variants of CYP2D6. Some inherited variants metabolize drugs very effectively. When the inactive drug is administered to people who have a fast metabolising CYP2D6 genetic variant, a large amount of active drug can build up in their bloodstream very quickly. This can manifest as a drug overdose with serious complications. By contrast, around 10% of people have a genetic form of CYP2D6 that is a very slow metaboliser. In these people, drugs that need activating by CYP2D6 just do not work. Thus, with many chemotherapeutic drugs, for the most desirable results of the treatment, it is important to consider the genetic make-up of the patient.

There is a further complication when considering the use of chemotherapy. When the inactive drug enters the bloodstream, a large proportion of it, sometimes around 90% will bind to plasma proteins such as albumin. When the drug is slowly released from the albumin in a controlled way, it is activated. Unfortunately, some other drugs, when administered simultaneously, can displace most of the inactive anti-cancer drug from the albumin which when activated, can have serious overdose effects.

With regard to breast cancer, the biopsy investigations that are usually carried out by the pathologist will determine whether the neoplasic cells are oestrogen receptor (ER) positive or negative (ER+ or ER-). ER+ breast cancer cell growth is promoted by the presence of oestrogen. Therefore the drug tamoxifen, which binds to the ER, is used to block the union of oestrogen to the ER on ER+ breast cancer cells and slow down their growth. Tamoxifen needs to be converted to hydroxytamoxifen to bind effectively and block the ER on ER+ breast cancer cells. Conversion of tamoxifen to hydroxytamoxifen is brought about by CYP2D6, therefore tamoxifen is far less effective in patients who have a slow metabolising form of CYP2D6.

Quite different chemotherapeutic approaches are required for breast cancers that are ER-. Some breast cancer cells are positive for a protein called HER2. HER2 positive breast cancer cells require treatment with a drug called Herceptin rather than tamoxifen.

There is yet a further hurdle to be overcome sometimes with use of chemotherapeutic drugs - multi-drug resistance. It is a natural process that has evolved to expel toxic substances from cell. Multi-drug resistance, the principal mechanism by which many cancers develop resistance to chemotherapy drugs, is a major factor in the failure of many forms of chemotherapy. It affects patients with a variety of blood cancers and other neoplastic disorders including breast, ovarian and lung cancers. Resistance to therapy is caused by induction of the gene multi-drug resistance 1 (MDR1) and the gene that encodes the multidrug resistance-associated protein (MRP).

Radiation Therapy

It has long been known that the sensitivity to ionizing radiation differs from one subject to another, with respect to the amount of damage caused to healthy cells. In those with increased sensitivity

to radiation damage, exposure to ionizing radiation therapy can cause sufficient DNA damage to initiate the development of further neoplasms.

In recent years, much work has been carried out to identify genetic markers which will permit identification of those individuals with heightened radiation sensitivity so that more appropriate doses of radiation therapy can be applied. To date, some relevant genes have been identified;[17] however, it remains difficult to predict the outcome of radiation therapy in cancer patients.

Surgery

Surgical removal of a tumour is an important first line of defence against cancer, particularly if the tumour is well defined. Surgery is not without problems. Surgery has been shown to greatly increase the risk of death by metastasis in certain cancer patients by simple mechanical disruption of tumour integrity. Surgical trauma may lead to facilitation of metastasis by seeding the tumour, inducing local angiogenesis, immune suppression and enhancement of tumour growth. Surgical stress also greatly enhances metastasis by increasing the expression of proteinases in the target organ of metastasis.[12]

Concluding Remarks

As outlined above, there are many different approaches to treatment of cancer. Standard treatments such as chemotherapy, radiation and surgery do have inherent difficulties that need to be addressed in order to achieve the most favourable outcome. It is very important to take many factors into account when helping a cancer patient to choose the most appropriate course of action. In fact, because everyone is genetically different, it is important to take genetic considerations into account on an individual basis.

I have also discussed the pros and cons of different treatments. In some cases, a 'do nothing' approach may be the best option; however, it is often difficult for a patient to accept this approach. The importance of reference to laboratory and other diagnostic information with regard to treatment selection cannot be over-emphasized. For example, the use of reovirus infection would only be suitable for patients who had neoplasms in which the Ras gene was over-active. From a diagnostic standpoint, it is important to realize that cellular monoclonality of an unusual tissue mass must be confirmed before cancer can be unambiguously diagnosed.

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Further Information

Dr Peter Kay has a clinic - the Homeovitality Natural Super Health Clinic wherein as a geneticist, cancer biologist, immunologist and molecular pathologist, he offers consultations, guidance and a cancer support service to cancer patients to help them understand their condition and choose an appropriate treatment approach. To do that, he takes all the above considerations, and more, into account. Dr Kay has referred to some genes, KEAP1, TP53, IL-7, OX40, TIP30 and BRCA1 which play a pivotal role in all cancers. In the consultation process, the utility of these genes is discussed. Peter Kay is also available for public lectures and consultation by Skype, phone or email.

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