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Changes in HLA class I antigen and NK cell-activating ligand expression have been identified in malignant lesions. These changes are believed to play a major role in the clinical course of the disease since both HLA class I antigens and NK cell-activating ligands are critical to the interaction between tumor cells and components of both innate and adaptive immune systems. In this study, novel molecular mechanisms underlying HLA class I antigen abnormalities have been identified in melanoma cells derived from malignant melanoma lesions. They include multiple hot-spot CT deletions in the & beta;2 m gene, selective HLA-A2 allospecificity loss, and antigen processing machinery component downregulation, which underlie a HLA class I antigen loss phenotype, as well as single amino acid substitution-carrying, loss-of-function? 2m and combined germline/somatic tapasin gene mutations along with selective epigenetic inactivation of HLA-A locus IFN- & gamma; responsiveness, which underlie a HLA class I antigen downregulaiton phenotype. The role of NK cell-activating ligand changes in melanoma immune escape is indicated by the markedly reduced sensitivity to NK cell-mediated lysis in vitro of two of four HLA class I & minus; melanoma cell lines because of their lack of expression of MICA, a ligand for the NKG2D activating receptor. These MHC defects have potential negative impact on both cytotoxic T lymphocyte- and NK cell-mediated anti-tumor responses and thus prompted the development of active specific cancer immunotherapy targeting non-MHC molecules. To this end, the three-dimensional structural basis of tumor antigen mimicry by an anti-idiotypic (id) antibody has been elucidated at the atomic level in the high molecular weight-melanoma associated antigen (HMW-MAA) system. A single complementarity-determining region loop of anti-id antibody MK2-23, which carries the internal image of the nominal HMW-MAA epitope, represents a useful system to investigate which extent of antigen mimicry would maximize the immunogenicity of an antigen mimic. Taken together, the results of my study advance our understanding of the mechanisms underlying the lack of immune control of clinically evident tumors and contribute to the development of alternative cancer immunotherapeutic strategies.

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Non-clinical safety assessment is essential during the drug development process in the pharmaceutical industry, and involves numerous, detailed in vitro and in vivo toxicology tests (general, reproductive and genetic), and safety pharmacology studies. The testis is a common organ for adverse drug effects leading to attrition of potential compounds. It would, therefore, be useful to detect testicular toxicity as early as possible in the drug development process. Histopathology is the standard method for assessing testis toxicity, but a biomarker for 'early warning' detection of testicular toxicity would be far more useful in non-clinical toxicology studies. The aim of this thesis was to evaluate the feasibility of this approach. It is thought that proteins can leak from seminiferous tubules into testicular interstitial fluid following testicular damage, due to either loss of integrity of the blood-testis barrier (BTB) or germ cell damage. A potential biomarker protein could, therefore, leak out of seminiferous tubules into interstitial fluid and then into blood following toxicological insult to the testis. A suitable biomarker protein must be testis specific, abundant,

and not normally be present in blood. It may also need to have a low molecular weight. To investigate if proteins do leak out of seminiferous tubules following testicular damage, three known testicular toxicants which affect different aspects of the testis were used; cadmium chloride causes disruption to the blood-testis barrier and spermatogenesis, methoxyacetic acid (MAA) specifically causes a loss of pachytene spermatocytes, and 1,3-dinitrobenzene (DNB) causes Sertoli cell vacuolation and subsequent germ cell disruption. Adult male Wistar rats were treated with various doses of these toxicants to give mild and moderate responses. Samples were collected 24 hours later. Testicular damage was investigated by immunohistochemistry for well-known germ cell markers (DAZL, VASA) and using a general antibody to seminiferous tubule proteins. The integrity of the BTB was evaluated using immunofluorescent co-localisation of occludin, ZO-1, claudin-11, N-cadherin and [beta]-catenin, and a biotin tracer. Protein leakage was investigated using analysis of interstitial fluid samples by 1D gel electrophoresis and staining with Coomassie-based dye or Western blotting for germ cell proteins and with the general antibody to seminiferous tubule proteins. Protein leakage from seminiferous tubules into interstitial fluid was observed with high dose cadmium chloride treatment. This was coincident with a loss of integrity of the BTB. No leakage was observed with MAA treatment which caused a specific loss of pachytene spermatocytes, or DNB which caused Sertoli cell vacuolation. With both treatments the BTB did not appear to be damaged suggesting that protein leakage occurs only following loss of integrity of the BTB. This was further investigated using treatments reported to specifically disrupt the BTB, namely intra-testicular administration of glycerol or transforming growth factor-[beta]3, with samples collected 48 hours later. The damage caused was very localised, although BTB disruption with glycerol treatment caused some protein leakage. The presence of germ cell proteins in interstitial fluid samples before and after the development of the BTB during normal development was also evaluated, although most proteins of interest were not expressed in germ cells of the immature testis before BTB formation. Finally, five potential biomarker candidate proteins (ADAM3, Calpastatin, DAZL, FABP9, VASA) were selected and investigated using samples from the testicular toxicant studies. Smaller molecular weight proteins were thought to be more likely to leak out of seminiferous tubules, however, VASA, a large molecular protein (76kDa) was shown to leak into interstitial fluid following high dose cadmium chloride treatment. However, FABP9 (low molecular weight) was found to be the most promising biomarker for loss of BTB integrity. The results suggest that a biomarker could only be detected if there is a loss of integrity of the BTB and severe disruption of spermatogenesis, thus conferring no real advantage over present histopathology-based toxicity evaluations. Therefore, an automated immunohistochemistry and image analysis method was investigated as a refined method for detection of testicular toxicity at the end of a toxicology study, and shown to have promise.

Everybody has a love story; some are mutual and some are one-sided. Most of them start budding during school life, when we are not matured enough to understand the new emotions and sensations for the very first time. Some stories are everlasting while some ends with school life. This is one such story that started during school life, when Anand fell in love with his junior, Swati. He made uncountable efforts to get the same love back that he always had for her. When all his efforts went into vain, he was stuck with a question - " How can he prove his love for her?". Dive-in the story to find out, how he proved his love. Relive your school life

with the teenage love story, loaded with craziness, purity, endless hope and love.
We all have got our journeys in life; some lead to destinations; others lead to a new beginning again, but everything ends up teaching something. Love is indeed very precious. In the walk of our lives, we come across many strangers with whom we share many moments. These are undoubtedly the one whom we love, and it becomes so arduous to understand when love happens by chance..... It feels so good to talk about a school love story, a story without a relation, where the two strangers, strangers even when they were well known to each other and continued to be a stranger, loved each other but believed in their Destiny. Shaurya, a nerd boy who just opposed his name's meaning, lacked the courage and courage to speak his heart. Time is his deadliest fear. Abhilasha, a lovely girl who was synonymous with the meaning of her name, was loved by all; happiness is her shadow... Both of them are busy accepting whatever is going on in their life, and their Destiny is still unjustified, which is desperate with many surprises. Waiting for years, the story is all about the unexpected that happened in their life. And finally, one question which strikes corner to corner in their heart and mind, "WHAT MATTERS"....
No Marketing Blurb
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Popular Science gives our readers the information and tools to improve their technology and their world. The core belief that Popular Science and our readers share: The future is going to be better, and science and technology are the driving forces that will help make it better.
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Using step-by-step screen captures, this in-depth manual provides self-paced learning in an easy-to-use format. It shows learners how to use the Multisim 7 circuit simulation program from Electronics Workbench. The book focuses on a wide range of circuits, and features a collection of examples that show how to create a circuit, how to run different analyses, and how to obtain the results from those analyses. Chapter topics cover editing a basic schematic, the postprocessor and the grapher, DC measurements, DC sweep, magnitude and phase simulations, tine domain analyses, and digital simulations. For electrical engineers, electronics engineers, circuit simulation specialists, computer engineers, power electronics, analog electronics, and project managers.
It is significant that the only character in Hindu mythology, a king at that, to be given the title of ekam-patni-vrata, devoted to a single wife, is associated with the most unjust act of abandoning her in the forest to protect family reputation. This seems a deliberate souring of an uplifting narrative. Ram's refusal to remarry to produce a royal heir adds to the complexity. The intention seems to be to provoke thought on notions of fidelity, property and self-image. And so the mythologist and illustrator Devdutt Pattanaik retells the Ramayana, drawing attention to the many oral, visual and written retellings composed in different times, in different places, by different poets, each one trying to solve the puzzle in its own unique way. This book approaches Ram by speculating on Sita: her childhood with her father, Janaka, who hosted sages mentioned in the Upanishads; her stay in the forest with her husband, who had to be a celibate ascetic while she was in the prime of her youth; her interactions with the women of Lanka, recipes she exchanged, emotions they shared; her connection with the earth, her mother, and with the trees, her sisters; her role as the Goddess, the untamed Kali as well as the demure Gauri, in transforming the stoic prince of Ayodhya into God.
Vols. for 1964- have guides and journal lists.

Proofs without words (PWWs) are figures or diagrams that help the reader see why a particular mathematical statement is true, and how one might begin to formally prove it true. PWWs are not new, many date back to classical Greece, ancient China, and medieval Europe and the Middle East. PWWs have been regular features of the MAA journals Mathematics Magazine and The College Mathematics Journal for many years, and the MAA published the collections of PWWs Proofs Without Words: Exercises in Visual Thinking in 1993 and Proofs Without Words II: More Exercises in Visual Thinking in 2000. This book is the third such collection of PWWs.

Inequalities permeate mathematics, from the Elements of Euclid to operations research and financial mathematics. Yet too often the emphasis is on things equal to one another rather than unequal. While equalities and identities are without doubt important, they don't possess the richness and variety that one finds with inequalities. The objective of this book is to illustrate how use of visualization can be a powerful tool for better understanding some basic mathematical inequalities. Drawing pictures is a well-known method for problem solving, and we would like to convince you that the same is true when working with inequalities. We show how to produce figures in a systematic way for the illustration of inequalities; and open new avenues to creative ways of thinking and teaching. In addition, a geometric argument can not only show two things unequal, but also help the observer see just how unequal they are.

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Ever since Regulatory T cells (T-Regs) were first defined as peripheral CD4+ T cells that express the interleukin-2 (IL-2) receptor alpha chain (IL-2Ra), there have been intensive efforts to determine the molecular mechanisms whereby this minor subset of CD4+ T cells (~ 5-10%) nonspecifically suppresses all potential effector T cells, whether reactive to self or non-self antigens. Multiple possible molecular mechanisms have been implicated, including the scavenging of IL-2 via the expression of high densities of IL-2Rs, the inhibition of antigen presentation via CTLA-4 molecules leading to decreased IL-2 production, the activation of intracellular cAMP thereby suppressing both IL-2 production and action, and the production of suppressive cytokines such as IL-10 and Tumor Growth Factor-beta, to list a few. However, the field has thus far failed to come to a consensus, such that some investigators have now asserted that many molecular mechanisms may be operative, in fact that perhaps all of the described mechanisms may account for the suppressive effects of these cells, acting either simultaneously or sequentially. Thus, this Research Topic is focused on articles that can shed some new light on the molecular mechanisms responsible for T-Reg immunosuppression.