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The recent volume of *Annual Review of Medicine*, as in previous years contains articles which broadly survey progress in several fields of the speciality and provides a succinct overview of current research on the selected topics. Among the 35 reviews, 12 discuss novel diagnostic and management strategies for various types of cancers. Four articles deal with exciting advances in gene therapy; five articles are on therapy for infectious diseases. Cardiovascular diseases are the theme of the first five.

In the first article, C. A. James and H. Calkins from Johns Hopkins Medical Institutions at Baltimore present the progress in evidence-based personalized approaches in the management of patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) and their family members who are at risk for the disease. The new approaches combine insights from natural history studies, understanding of molecular mechanisms of pathogenesis of the disease and knowledge of genetic and environmental modifiers. The authors foresee that in the coming decade, research would target on how to predict, detect and manage right ventricular failure in patients with ARVC.

There are many advantages in integrating into drug development, knowledge regarding genetic variants that determine the risk for diseases. These include differentiating causal biomarkers from those that are only associated with the disease and the possibility of identifying alternatives when one target in a causal pathway is unsuitable as a drug target. A good example of translation of genetic knowledge into a therapy for coronary artery disease (CAD) is the use of proprotein convertase/subtilisin/kexin type 9 (PCSK 9) inhibitors to reduce low density lipoprotein cholesterol. A wide range of new drugs can be expected, as genetic studies enhance our knowledge of genetic risk factors and mechanisms of CAD. E. P. Young and N. O. Stitzie of Washington University School of Medicine at St. Louis, Missouri discuss the possible usefulness and important constraints in us-

ing a genetic approach to identify drug targets for CAD.

Another review is on the advances in technology of left ventricular assist devices (LVADs): optimizing treatment strategies such as anticoagulation, blood pressure control and use of a skin-silicone interface for drive lines and the refinements in making decisions on selection of patients for LVAD implantation. All these changes have improved the outcomes and reduced adverse events such as pump thrombosis, drive line infections and stroke in patients with end stage heart failure.

The new targets for treatment of pulmonary arterial hypertension include sex hormones, genetic, epigenetic and miR abnormalities of DNA damage, elastase inhibition, metabolic dysfunction, inflammatory and immune pathways, mitochondrial dysfunction, nervous system and renin-angiotensin-aldosterone system. Novel and repurposed drugs targeting these, which are in either preclinical studies or clinical trials are outlined by researchers from Stanford University School of Medicine and Perelman School of Medicine in the United States of America.

Another article provides the results of major clinical trials of non-vitamin K antagonist oral anticoagulants (NOACs) in patients with atrial fibrillation (AF). Clinical trials have demonstrated the safety and efficacy of NOACs in patients with AF. They are also non-inferior to warfarin with respect to incidence of stroke and systemic embolism. None of the NOACs needs routine monitoring. NOACs are not approved for use in patients with mechanical valves and rheumatic mitral valve disease. Recent data also indicate that NOACs are safe in patients with myocardial infarction and those undergoing percutaneous coronary intervention. Disadvantages of NOACs are their short half-life in the body and lack of a reversal agent.

Vaccine antigen designing has metamorphosed thanks to new possibilities in obtaining knowledge on viral surface proteins. Vaccine development is currently based on deliberate structure-based designing and a customized approach, hopefully leading to inducing specific antibody responses. B. S. Graham, M. S. A. Gilman and J. S. McLellan from Vaccine Research Centre of National Institutes of Infectious Diseases, Maryland explain the concepts of anti-

body neutralization and B-cell targeting and provide some examples of structure-based vaccines.

There are two articles related to tuberculosis (TB). J. A. Tornheim and K. E. Dooley from Johns Hopkins University School of Medicine at Baltimore recount the new drugs and regimens for treatment of TB and the ongoing clinical trials in TB treatment. Shorter, highly effective and safe regimens for latent TB infection are currently in phase III trials. Shorter duration and safe treatments effective for patients with drug susceptible TB and multidrug resistant TB infection are also on the horizon.

K. V. Dicks and J. E. Stout from Duke University Medical Centre at North Carolina survey probe-based and sequence based molecular diagnostics for *Mycobacterium tuberculosis* infection and the advances in molecular testing for drug resistance. They opine that increased knowledge on genotype-phenotype correlates could help in developing point-of-care assays and improving surveillance for resistance and treatment of drug resistant tuberculosis.

Progress in the development of long acting and extended release anti-retroviral (LA/ER) drugs for the prevention and treatment of human immune deficiency virus infection is evaluated in one of the articles. The anti-retroviral agents under trial include nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, integrase inhibitors, entry inhibitors and capsid inhibitors. Only one long acting anti-retroviral drug is currently approved. The challenges are to control the side effects, drug-drug interactions, drug resistance and use in pregnant women. An interesting facet is that experience in the development of LA/ER drugs could be beneficial in developing long acting antimicrobial preparations to treat or prevent other infectious diseases such as tuberculosis, malaria and chronic hepatitis and also long acting agents to treat non-communicable diseases such as diabetes, hyperlipidemia and asthma.

The increasing prevalence of autism spectrum disorders (ASD) in recent decades has spurred the debate on the role of epigenetics and environmental factors in the causation of ASD. M. W. Tremblay and Y-hui Jiang from Duke University, Durham discuss the genetic and epigenetic dysfunction in ASD. In patients with ASD, evidences of epigenetic

dysregulation of DNA methylation include genetic mutations in DNA methylation writers, readers and erasers and gene specific, genome wide as well as DNA methylation changes. Tremblay and Jiang also examine what could result in abnormal DNA methylation and how epimutations contribute to the pathogenesis of ASD. They indicate that 'understanding the significance of DNA methylation in ASD pathophysiology can shed light on other neuropsychiatric disorders in which DNA methylation may also play a causal role'.

Ilse Gantois and colleagues from McGill University at Montreal describe the molecular basis of the pathogenesis of fragile X syndrome (FXS) and the therapeutic potential of metformin, a well-known anti diabetic drug in the treatment of FXS. Behavioural improvement has been reported in six patients with FXS after many months of treatment with metformin. Metformin has beneficial effects in Parkinson's disease, epilepsy and Alzheimer's disease as well. The precise mechanism of action of metformin is not clear at present.

Advances in the knowledge about pathophysiology of postpartum depression (PPD) have led to new treatments, drugs and evidence-based psychotherapy. D. E. Stewart and S. N. Vigod from University of Toronto summarize the emerging management strategies for PPD. A large randomized clinical trial, the results of which are looked forward to, is of brexanolone, a formulation of allopregnanolone, which is a modulator of the gamma amino butyric acid receptor. A somatic therapy in the wings is focal brain stimulation.

Current understanding of the genetic and cellular mechanisms, pathophysiology and emerging targeted treatment of pulmonary and non-pulmonary manifestations of cystic fibrosis (CF) are detailed by M. M. Rey, M. P. Bonk and D. Hadjiliadis from Perelman School of Medicine at Philadelphia. Novel therapies targeted to specific gene and protein defects have led to improvement in survival of patients with CF. Be that as it may, co-morbidities such as gastrointestinal cancers and CF related diabetes are being recognized.

Progress in understanding the genetic predisposition and improvements in the diagnosis and treatment of idiopathic pulmonary fibrosis are highlighted in another article. The novel mechanisms

involving epithelial, mesenchymal and inflammatory cell responses and interactions which regulate capacity for cellular differentiation and repair are being elucidated and it is expected that disease relevant pathways would soon be identified for targeted therapy.

X. M. Anguela and K. A. High from Spark Therapeutics at Philadelphia have compiled the wide range of applications of augmentation gene therapy, potential and versatility of gene transfer approaches, current clinical trials as well as some examples of clinical success with various gene therapy approaches. They also indicate the potential complications of gene therapy.

In the context of the ethical concerns about editing the human genome, a multidisciplinary international committee constituted by the National Academy of Sciences and National Academy of Medicine in USA has made recommendations on policies and procedures for human genome editing. Barry S. Collier of Rockefeller University at New York, a member of that Committee, in his illuminating article provides the highlights of the report of the Committee. The report focuses on the regulatory standards for somatic (non-heritable) human genome editing and for experimental germ line genome editing. The author states that the public reaction to the report which was published two years ago has generally been favourable. As per the Committee recommendations, clinical trials using heritable genome editing are to be restricted to prevent a serious disease when there are no reasonable alternative options and when reliable preclinical data on risks and potential health benefits are available. Long term and multigenerational follow up plans are to be included for continued assessment of both health and societal benefit and risks as well as to prevent uses for undesirable purposes such as enhancement of certain traits.

Current knowledge on mechanisms, protocols and present-day as well as potential future indications on the clinical use of fecal microbiota transplantation (FMT) are reviewed by R. E. Ooijselaar and colleagues from the Netherlands. FMT is presently indicated in recurrent *Clostridioides difficile* infection. Clinical evidence indicates the potential use of FMT for a wide range of diseases, which include irritable bowel syndrome, inflammatory bowel disease, Crohn's disease, metabolic syndrome,

autism, graft versus host disease and hepatic encephalopathy. In several instances however, protocol optimization, randomized control trials and identification of methods to select suitable donors as well as patients who are likely to respond are important issues to be resolved.

Y. Ito and A. Miyauchi from Kuma Hospital at Kobe in Japan in a persuasive presentation advocate active surveillance as the first line in the management of low risk papillary thyroid micro carcinoma (PMC). PMC without aggressive features such as metastasis and vocal cord paralysis are low risk, indolent and slow growing. Active surveillance for patients with low risk PMCs was initiated in 1993 in their hospital and the authors have found in their analysis that active surveillance is more beneficial than immediate surgery. The strategy the authors follow for active surveillance is included in the article.

Clinical experience of seven single centre and five multicentre studies on T cell depleted (TCD) allogeneic haematopoietic cell transplantation in the treatment of haematologic malignancies and emerging approaches for refinement of allografts are summed up by C. Cho and M. A. Perales from Memorial Sloan Kettering Cancer Centre at New York. The two challenges that are to be met are management of relapse and transplant related complications sans associated toxicities. TCD transplantation has reduced graft versus host disease. Targeted grafts seem to reduce the risk of off target effects.

Preclinical and clinical state of individual cancer vaccine development based on knowledge of a person's cancer mutanome (complete cancer mutations) form the subject of another article. Temporo-spatial heterogeneity is considered as a basis for the failure of conventional cancer treatment. This problem is expected to be overcome by the use of neoepitope vaccines which simultaneously target genetic aberrations of the heterogeneous clones of malignant cells.

Checkpoint blockade or costimulatory agonists are used for antibody modulation of T cell function and thus revive survival, proliferation and effector function of tumour infiltrating T cells. Antibodies which modulate cytotoxic T lymphocyte associated protein-4 (CTLA-4), programmed death ligand-1 (PD-L1) are the important check point inhibitors in clinical practice. Clinical experiences with combining cancer vaccines and check point modulation in the treatment

of human papilloma virus related cancers, prostate cancer and pancreatic cancer are compiled by M. A. Curran and B. S. Glisson from the University of Texas MD Anderson Cancer Centre at Houston.

There are several on-going clinical trials to evaluate the safety, feasibility and efficacy of immunotherapy using neoadjuvant checkpoint inhibitors for early stage non-small cell lung cancer. S. Rosner, J. E. Reuss and P. M. Forde from Johns Hopkins University School of Medicine at Baltimore summarize these studies and provide the rationale for neoadjuvant immunotherapy. Early results from clinical trials with neoadjuvant PD-1 blockade are promising for provisionally including the strategy in standard clinical care.

CD3 bispecifics are those drugs which recruit and redirect T cells to kill tumour cells. They cross link a CD3 component of the T cell receptor with a tumour associated antigen and bypass the human leucocyte antigen. Their action is also independent of tumour mutational load. They are useful in combination with check point blockers. A large number of CD3 bispecific antibodies are in clinical development. Among them, blinatumomab has been approved for treatment of relapsed or refractory B cell acute lymphocytic leukemia. Several others are being investigated for both solid and haematologic malignancies. In their article on CD3 bispecifics, R. A. Clynes and J. R. Desjarlais from Xencor Inc. at California also explain the management of cytokine release syndrome and neurotoxicity associated with the use of CD3 bispecifics.

Novel therapeutic agents for multiple myeloma are mitogen activated protein kinase inhibitors, protease inhibitors, drugs that target anti apoptotic pathways and adoptive cellular immunotherapy. C. Kunacheewa and R. Z. Orlowski of University of Texas MD Anderson Cancer Centre at Houston apprise on recent regulatory approvals for small molecules and monoclonal antibodies and outcomes of recent trials of novel agents for multiple myeloma.

C. K. Kuhl of RWTH Aachen University in Germany deliberates on the current controversies on breast cancer screening, drawbacks of mammographic screening and describes the rationale and concept of abbreviated breast magnetic resonance imaging (MRI). He suggests that abbreviated MRI has a broad range of clinical applications which include

screening for liver metastases in patients with cirrhosis, to rule out musculoskeletal injuries in the emergency room and to avoid sedation for MRI in children. Abbreviated MRI protocols are designed to answer specific clinical questions resulting in reduction in the time for image acquisition and interpretation.

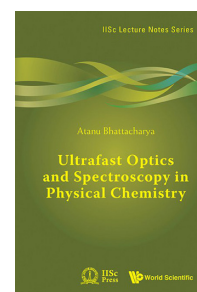
Three reviews relate to prostate cancer. One of them is an update on prostate magnetic resonance imaging for lesion detection and local staging. Another considers preclinical development of small molecule radiotracers for positron emission tomography imaging to target prostate specific membrane antigen (PSMA) and the clinical utility of these agents for imaging patients with prostate cancer. The authors also remark on the potential role of PSMA targeted agents for imaging non-prostate malignancies. The third review on prostate cancer examines the broad landscape of therapy for metastatic castration resistant prostate cancer and metastatic hormone sensitive prostate cancer. Better knowledge of the different genomic pathways of these cancers and advanced functional imaging tools have aided the development of biomarkers and better treatment options in the management of patients with advanced prostate cancer.

Other reviews in the book relate to (i) progress in the development of Zika virus vaccines; (ii) recent advancements and current status of living donor liver transplantations in the USA; (iii) mechanisms of action, metabolic effects, risk reduction in renal and cardiovascular outcomes, results of safety trials and safety concerns of sodium glucose cotransporter 2 inhibitors; (iv) opportunities and challenges in mutation repair in patients with Duchenne muscular dystrophy (DMD) by CRISPR/CAS-9 mediated genome editing and the lessons learnt from studies on gene editing strategies in DMD; (v) the novel approaches that employ globin gene addition and gene editing to correct sickle cell disease mutation and enhance production of foetal haemoglobin through genetic control; (vi) the state of the anti-sense oligonucleotide technology for treatment of genetic diseases, and (vii) the differences between Asia and the Western countries in the causes, screening programmes, diagnostic methods and treatment strategies such as the use of minimally invasive techniques and peri-operative adjuvant therapies for gastric adenocarcinoma.

In summary, the latest volume of *Annual Reviews of Medicine* has concise yet comprehensive reviews which provide recent insights on pathogenesis and evolving strategies to improve diagnosis and treatment of several diseases. All articles have prefatory synopsis of the prior knowledge on the topics reviewed. There are clear illustrations of concepts and pertinent references. The book is thus illuminating and valuable for both physicians as well as biomedical scientists.

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Ultrafast Optics and Spectroscopy in Physical Chemistry. Atanu Bhattacharya. World Scientific Publishing Co. Pte. Ltd, 5 Toh Tuck Link, Singapore 596224. 2018. 292 pages. Price: US\$ 58 (soft cover)/US\$ 118 (hard cover).

The new arrival on the Indian and global scene of education in ultrafast science is a refreshing take on the subject from a relatively young author. Atanu Bhattacharya's book on ultrafast science is a welcome contribution to the existing body of instructional literature. There can be no better time than now to emphasize the dynamics and nature of femtosecond science which is heralded by the Nobel prize 2018 given in part to the inventors of the chirped pulse amplification technique, the most essential amplification scheme in vogue in most modern day ultrafast lasers producing such pulses.

In spite of excellent texts by Akhmanov, Ruliere *et al.*, Diels and Rudolph, A Weiner and the ongoing one by R. Trebinno, Atanu's fresh take on the subject is relevant for several reasons. This book presents femtosecond laser pulses with chemical physics, or molecular science, as the key application. This may misleadingly sound like a limited take on this