Scientific overview on CSCI-CITAC Annual General Meeting and 2017 Young Investigators’ Forum

Abstract

The 2017 Annual General Meeting of the Canadian Society of Clinician Investigators (CSCI) and Clinician Investigator Trainee Association of Canada/Association des Cliniciens-Chercheurs en Formation du Canada (CITAC/ACCFC) was a national Annual General Meeting (AGM) held in Toronto, Ontario November 20–22, 2017, in conjunction with the University of Toronto Clinician Investigator Program Research Day. The theme for this year’s meeting was “Roll up your sleeves—How to manage your physician scientist career”, emphasizing lectures and workshops that were designed to provide tools for being proactive and successful in career planning. The keynote speakers were Dr. Rod McInnes (McGill University and Canadian Institutes of Health Research Acting President), who was the Distinguished Scientist Award recipient, Dr. David Goltzman (McGill University), who was the 2017 Henry Friesen Award recipient, Dr. Gillian Hawker (University of Toronto), Dr. Mike Sapieha (Université de Montréal), who was the 2017 Joe Doupe Award recipient, and Dr. Alex MacKenzie (Children’s Hospital of Eastern Ontario Research Institute, University of Ottawa). The workshops, focusing on career development for clinician scientists, were hosted by Dr. Lisa Robinson, Dr. Nicola Jones, Kevin Vuong, Fran Brunelle, Dr. Jason Berman and Dr. Alan Underhill. Further to this, the Young Investigators’ Forum encompasses presentations from scientist-clinician trainees from across the country. All scientific abstracts are summarized in this review. There were over 100 abstracts showcased at this year’s meeting during the highlighted poster sessions, with six outstanding abstracts selected for oral presentations during the President’s Forum.

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Introduction to CITAC-CSCI AGM and its evolution

The Clinical Investigator’s Trainee Association of Canada (CITAC) was established in 2006 to address issues relevant to clinician-investigator trainees seeking dual training in medicine and research. CITAC fulfills this overall mission, in part, through shared initiatives with several partner organizations, including the Canadian Society for Clinical Investigation (CSCI). Importantly, our collective efforts come together yearly at the Annual General Meeting (AGM), a trainee-focused scientific meeting jointly planned with CSCI. The AGM provides a forum to discuss research and enhance the educational, and career prospects of CITAC members through workshops, mentorship opportunities, and scientific review. The AGM has grown from 53 abstracts in 2012 to 108 in 2017, with over 170 trainees in attendance. During this time, we have also published conference abstracts to facilitate long-term discussions (1-5). There has been some growth in number of abstract and attendees, but this has largely plateaued in recent years (Figures 1 and 2).

Over the years, the AGM has evolved to better meet trainee needs. For example, in response to feedback, the AGM now includes workshops on skill development (e.g., contract negotiations and creating individual development plan) and topical subjects (e.g., addressing underrepresentation within the clinician-investigator community). Growing relationships with the American Physician Scientist Association student group and the Canadian Federation of Medical Students bridges trainees with our American counterparts and the broader physician community in Canada, respectively. The AGM has also provided a platform for national and international collaborations, most recently demonstrated by a national survey of all MD-PhD alumni in Canada coordinated by CITAC members. This has resulted in at least three publications and the first ever data on MD/PhD program outcomes in producing clinician-investigators (6-8). Continued growth of the community from CITAC will only further improve training programs in Canada and demonstrate the importance of clinician-investigators within Canadian healthcare.

President’s Forum oral presentations

Each year, six outstanding abstracts are selected for oral presentation during the President’s Forum session: Elina Cook (Queen’s University; Queen’s); Laura Mantella (Queen’s); Christopher Ahuja (University of Toronto; UofT); Nicholas Light (UofT); Nicole Burma (University of Calgary; UofC); and Rola Saleeb (UofT). Elina Cook et al. (Queen’s) presented her research investigating the connections between pre-neoplastic somatic mutations in white blood cells, systemic inflammation and age- and inflammation-associated disease.
Their research suggests that pre-cancerous neoplastic mutations in white blood cells are associated with elevated levels of pro-inflammatory cytokines and a higher risk of overall poor health in older patients. Laura Mantella et al. (Queen’s) presented her work on the relationship between atherosclerotic plaque neovascularization and severity of coronary artery disease. Their work suggests that plaque neovascularization, as detected by contrast-enhanced ultrasound, may be associated with more advanced coronary artery disease and higher risk of heart attack in patients. Christopher Ahuja et al. (UofT) presented research using engineered human neural stem cells for improved tissue regeneration following spinal cord injury. His data suggest that neural stem cells, engineered to express higher levels of a scar-degrading enzyme, show beneficial improvements in scar remodelling and axon extension following transplantation. Nicholas Light et al. (UofT) presented the results of the first comprehensive analysis of genomic hypermutation across a variety of cancers. Their work uncovered hypermutant phenotypes in cancers not previously associated with high mutation rates, and found that mutations in replication-repair-associated DNA polymerases are a major contributor to such tumours. Nicole Burma et al. (UofC) presented her work on using probenecid as a therapy to combat opioid withdrawal. Her research revealed that probenecid significantly attenuated withdrawal symptoms in rodent models, and provides a rationale to explore the impact of such a therapy in patients aiming to overcome opioid addictions and associated withdrawal symptoms. Rola Saleeb et al. (UofT) presented her work addressing the incomplete classification system currently applied to papillary renal cell carcinoma. Her integrated morphological, immunohistochemical and molecular analysis revealed the presence of a novel subtype with properties distinct from previously characterized subtypes. Her work has biological and potentially clinical ramifications for patients afflicted with this cancer.

Basic science

Biochemistry

Glenn Walpole et al. (UofT) presented their work investigating how certain bacteria utilize host cholesterol sources for growth and self-replication. They identified both a bacterial locus and protein, which may be implicated in the accumulation of cholesterol by Salmonella typhimurium; providing insight to the mechanism of bacterial cholesterol acquisition. Heather Leduc-Pessah (UofC) presented their work investigating the relationship between morphine analgesia and microglial reactivity using a mouse model. They concluded that male knock-out mice demonstrate altered...
microglial reactivity, which, in turn, decreases the analgesic effect of morphine.

Biomedical engineering

John Soleas et al. (UofT) presented their work investigating the role of mechanical cues to influence cell fate of lung epithelium. They demonstrated that mechanical cues significantly impact stem cell fate and suggest that this data may help guide future cell culture models.

Cancer

Laura Lee et al. (University of Alberta; UofA) presented their findings characterizing epigenetic (histone modifications and chromatin condensation) and transcriptional (gene expression) changes in cancer cell lines in response to hypoxic conditions. Their work suggests hypoxia may be a mechanism that induces cancer cell plasticity, affording an ability to metastasize and resist therapies. Audra Iness et al. (Virginia Commonwealth University) presented work investigating the effects of B-Myb levels on DREAM complex formation; B-Myb is an oncogene associated with a poor prognosis in many cancers. They determined that B-Myb sequesters and stabilizes LIN52, an essential MuvB protein, for DREAM disruption in cancer cells. Ayesh Seneviratne et al. (UofT) presented that tafazzin (TAZ) regulates the differentiation of acute myeloid leukemia (AML) cells by modulating levels of phosphatidylethanolamine, highlighting a mechanism by which phospholipids and mitochondrial enzymes regulate AML stemness and differentiation. Ben Ouyang et al. (UofT) presented that nanoparticle blood half-life and delivery to tumours are nonlinearly dependent on dose.

Cardiology and cardiovascular science

Tina Binesh Marvasti et al. (UofT) presented findings on the effect of aging on bone marrow stem cells (BMSC), which was proposed to have played a role in the limited efficacy seen in recent clinical trials of autologous BMSC therapy for heart failure. Analyzing BMSCs collected from patients with coronary artery disease, the authors found that the frequency and functional capacity of BMSCs in older patients was reduced. Mark Chandy et al. (Stanford University) presented his work on vascular dysfunction in an induced pluripotent stem cell model of insulin resistance. Through his work, they found that iPSC endothelial cells extracted from patients with diabetes model insulin resistance and endothelial dysfunction.

Endocrinology

Katarina Ondrusova et al. (UofA) presented work that demonstrated the effects of exposure to sunlight on metabolic processes. Specifically, they showed that visible blue light (470 nm) caused a reduction in the size and number of lipids and increased glycerol release.

Gastroenterology and respirology

Jia Wan Lu et al. (University of Sherbrooke; USherbrooke) presented their work investigating the relationship between upper airway obstructions and gastroesophageal reflux in an ovine model. They concluded that moderate to severe upper airway obstruction resulted in an increased frequency of gastroesophageal reflux.

Hematology

Frank Lee et al. (UBC) demonstrated that plasmin-cleavage of coagulation cofactor, factor Va, activated its ability to accelerate plasminogen activation. This provides a possibility of a non-enzymatic cofactor-based approach for dissolving clots. Maria Georgescu et al. (Queen’s) presented her work on discovering the effect of dexamethasone during initial exposure to Factor VIII reducing inhibitor development in hemophilia A via thymic tolerance induction.

Immunology

Ali Zhang (McMaster University; McMaster) presented work by Stacey et al. investigating the interaction between broadly neutralizing antibodies (bNAbs) and neutrophils in order to characterize the protective mechanisms of bNAbs against infection. They demonstrated that IgA-mediated stimulation of neutrophil extracellular trap formation occurred via a novel pathway not requiring phagocytosis of immune complexes, and may play a significant role in bNAb-mediated protection against influenza virus infection. Alvin Qiu et al. (University of British Columbia; UBC) presented work profiling the epigenomic landscape of synovial sarcoma and how a fusion oncoprotein, SS18-SSX, dysregulates critical genes affecting differentiation and oncogenesis. They determined that synovial sarcoma possesses a unique epigenomic landscape.

Infectious disease

Madelaine Colden Leung et al. (McMaster) presented their work investigating potential mechanisms to combat antibiotic resistance by inhibiting resistance-conferring enzymes. They have conducted a preliminary screening identifying three
potential leads that inhibit resistance-conferring enzymes and are developing chemical libraries mimicking these scaffolds.

**Nephrology**

Robert D’Cruz *et al.* (UofT) presented work on the effect of constitutive stromal-specific activation of hedgehog signaling on kidney development. They reported that this led to late kidney malformation in the developing mouse embryo.

**Neurology and neurosurgery**

Ryden Armstrong *et al.* (UofC) presented work on the impairing effect of volatile anesthetics on synaptic network formation in an *in vitro* model using rat pup neurons. The work aims to investigate whether brief anesthetic exposures lead to long-standing synaptic impairments in children exposed to general anesthetics. Wissam Nassrallah *et al.* (UBC) discussed preliminary work to investigate the role of sigma-1 receptors (S1R) on homeostatic synaptic potential in a Huntington’s disease mouse model. They determined that S1R agonists can restore homeostatic synaptic potential as determined by imaging and behavioural models, and are investigating the role in calcium regulation as the underlying mechanism. Xiya Ma *et al.* (Université de Montréal; UMontreal) presented her work on developing a synthetic polymer coating for implantable intraneural electrodes. They found that the coated electrodes had increased synaptic markers compared with uncoated electrodes, suggesting a better biocompatible interface for neuronal plasticity after traumatic injury. Yining Chen *et al.* (Queen’s) presented her work using the zebra finch songbird to investigate the role of norepinephrine and dopamine on ethologically-relevant vocalizations. They found that social tutoring led to early gene expression in norepinephrine and dopamine neurons, and that norepinephrine manipulations in auditory processing areas affect the strength of sensory learning and vocal performance in adulthood. Debra Ann Dawson *et al.* (McGill University; McGill) presented her work on functional network modelling in unknown, densely connected network environments. They suggest the use of a lenient alpha with appropriate corrections, and regression of the local mean from data before computing network measures of small, densely connected networks. Matthew Carr *et al.* (UofT) presented his work on identifying the role of neural crest-derived mesenchymal precursors residing within adult peripheral nerves in adult mouse digit tip regeneration. Through this work, they discovered that peripheral nerves harbour a population of neural crest-derived mesenchymal precursors that contribute to tissue regeneration.

Alexander Levit *et al.* (Western University; Western) presented work on behavioral dysfunction and white matter pathology in Alzheimer’s disease using a TgAPP21 rat model, which overexpresses a human variant of amyloid precursor protein. They found that TgAPP21 rats exhibited regressive behavioural inflexibility and accelerated age-dependent white matter inflammation. Sachin Kumar *et al.* (UofT) presented work on using a genome-wide lentiviral-based CRISPR knockout library in seven cell lines to identify novel genetic drivers of ependymoma. Siraj Zahr *et al.* (UofT) presented work on how the daughter neurons of neural precursor cells are specified. Using RIP-Chip, they found that a translational repression complex was involved in this process. Siddharth Nath *et al.* (McMaster) presented work on a novel genetic variant—Q35P in *ATXN7*—of spinocerebellar ataxia type 7 (SCA7). They found that the mutation altered the structure and localization of ATXN7 and the clinical presentation from the typical SCA7. Karamey Patel *et al.* (UofT) presented work that investigated the event-related potentials from the mesial temporal lobe in response to image presentation and eye movement. They found that image presentation produced a slow evoked neural response and eye movements produced a transient, phase-reset response.

**Obstetrics**

Vanessa Kay (Queen’s) presented her work on developing a neonatal murine retinal model to investigate decidual angiogenesis. They found that co-culture of these retinal models with non-pregnant uterine tissue or decidual leukocytes significantly decreased the number of sprouts in the vasculature.

**Pediatrics**

Kirill Zaslavksy *et al.* (UofT) presented work on investigating the human neuronal function of the SHANK2 gene, which is implicated in autism spectrum disorder. They demonstrated increased frequency of excitatory postsynaptic currents in neurons generated from stem cells of autism spectrum disorder patients.

**Reconstructive medicine**

Kevin Zuo *et al.* (UofT) proposed a study to establish the efficacy of acellular nerve allograft and local immunosuppression in the surgical repair of nerve transactions. Their objective is to investigate the application of acellular nerve allograft and FK506 (an immunosuppressant) to repair of nerve injuries resulting in large nerve gaps.
### Vasculopathy

Sivakami Mylvaganam et al. (UofT) presented investigations on loss-of-function mutations of diacylglycerol kinase epsilon, which has been found to cause atypical hemolytic uremic syndrome. Sivakumi used fluorescent biosensors and live-cell microscopy to characterize the lipid and platelet-binding dynamics of blood outgrowth endothelial cells derived from atypical hemolytic uremic syndrome patients. Tianwei Ellen Zhou et al. (McGill) presented investigations on the molecular mechanisms underlying impaired choroidal repair in ischemic retinopathy. They found that over-activation of the p53 tumor suppressor increased let-7b miRNA-mediated silencing of insulin-like growth factor 1 receptor mRNA; and that reversing this process promoted choroidal regeneration.

### Clinical research

#### Genetics

Casey Rosen et al. (UofT) presented a study that aimed to improve hypermobile Ehlers Danlos syndrome diagnostic accuracy. Rosen et al. reported a significant increase in the percent of patients to whom the diagnostic criteria were accurately applied with the revised form compared to the original form.

#### Population health and epidemiology

Mark Trinder et al. (UBC) presented his work on decreased HDL-C level as an early prognostic marker for organ dysfunction and death in suspected clinical sepsis. They found that HDL-C level was characterized by early decrease and high stability. Yunni Jeong et al. (UofT) discussed preliminary results from a retrospective cohort study investigating factors affecting treatment choice in patients with metastatic gastric cancer. Age, sex, comorbidities, tumour site, number of metastases, bleeding and malnutrition were significantly associated with treatment choice, whereas income, rurality, fatigue and number of symptoms were not. Lauren Mokry et al. (McGill) presented the results of their Mendelian randomization analysis to evaluate whether genetically increased body mass index (a measure of obesity) is associated with an increased risk of multiple sclerosis. They found that a genetically-increased body mass index significantly increased the risk of multiple sclerosis with an odds ratio of 1.41. Lev Bubis et al. (UofT) presented a retrospective review of symptom scores of gastric cancer patients in the final six months before death. They identified a high burden of moderate to severe symptom scores and increasing severity over time, suggesting that there is suboptimal symptom control for patients in the final months of life. Alanna Weisman et al. (UofT) presented work on the association between allopurinol and mortality in diabetic patients. They found that the time patients were exposed to allopurinol correlated with a reduction in mortality in both males and females, with no relationship found with cumulative dose.

#### Internal medicine

Shelly Luu et al. (UofT) presented a retrospective review of a multi-institutional database to determine predictive factors for cancer recurrence after curative resection for gastric adenocarcinoma. Luu et al. found that recurrence at any site was predicted by age≤60 years, male sex and AJCC stage>II. Alexandra Legge (Dalhousie University; Dalhousie) presented work investigating habitual moderate-vigorous physical activity (MVPA) performance, a lack of which is a known cardiovascular disease risk factor, among systemic lupus erythematosus (SLE) patients. They determined that SLE patients demonstrated suboptimal MVPA, with results highlighting the negative impact of SLE disease activity and associated functional disability on MVPA. Amanda Ricciuto (UofT) presented work hypothesizing that symptoms underestimate endoscopic activity in primary sclerosing cholangitis-associated inflammatory bowel disease and that fecal calprotectin more accurately reflects mucosal inflammation. They determined that symptoms do not reliably indicate whether mucosal healing has been achieved and that calprotectin was superior in its ability to identify mucosal healing. Michael Verret et al. (Laval University) presented their work on the impact of red blood cell transfusion in severe traumatic brain injury.

#### Neurology

Allen Champagne et al. (Queen’s) presented work assessing cerebral blood flow, functional-connectivity and behavioral measures in collegiate football athletes. It was determined that while college football players exhibited intact functional-connectivity and behavioural outcomes at pre-season baseline, they displayed significantly lower regional cerebral blood flow in the frontoparietal network. Elizabeth Kouzmitcheva et al. (UofT) investigated the safety of antithrombotic therapy in paediatric cardioembolic stroke. They discussed their plans to study newborns and children with cardioembolic arterial ischemic stroke to evaluate the frequency and predictors of anticoagulant-associated cerebral hemorrhaging. Abdullah Ishaque et al. (UofA) presented work...
on the use of an *ex vivo* post-mortem protocol to understand the pathological basis of MRI-based biomarkers for amyotrophic lateral sclerosis.

**Neonatology**

Kamini Raghuram (UofT) presented an initial framework to validate the General Movements Assessment (GMA) and will perform correlations between GMA and motor impairment scores.

**Psychiatry**

The role of diet and gut microbiota in obsessive compulsive disorder in youth was presented by Emily Macphail *et al.* (UofC). Their work outlined the importance of exploring the connections between zinc deficiency, cognitive flexibility and the gut microbiota in situations of youth obsessive compulsive disorder.

**Surgery**

Konrad Salata *et al.* (UofT) presented work evaluating the accuracy of the Ontario administrative data codes in identifying open and endovascular repairs of elective and ruptured abdominal aortic aneurysms. They found high overall accuracy, except for identifying endovascular repairs of ruptured abdominal aortic aneurysms in a retrospective chart review. Irene Harmsen *et al.* (UofT) presented their prospective research investigating the use of magnetoencephalography in patients undergoing deep brain stimulation. Christopher Hewison *et al.* (UofC) investigated the role of the augmentation of single bundle anatomic anterior cruciate ligament reconstruction with or without lateral extra-articular tenodesis in individuals at high risk of graft failure. No significant differences were found between the two groups at designated time points.

**Urology**

Alaina Garbens *et al.* (UofT) presented work on the feasibility of the Generic Error Rating Tool to quantify errors in open and robotic partial nephrectomy. They found that bleeding was the most common consequence of an error in both surgical methods.

**Medical education**

Michael Goldenberg *et al.* (UofT) presented his work on surgeon performance predicting early continence after robotic-assisted radical prostatectomy. This was a retrospective analysis that identified a potential link between surgeon technical performance and functional outcomes in robotic-assisted radical prostatectomy.

**Applied sciences: biomedical engineering, surgery and translational research**

**Applied sciences—Biomedical engineering**

Paraish Misra *et al.* (UofT) proposed a study to investigate whether functional human stem cell-derived β-like cells (hβLCs) can be maintained in immunocompetent hosts and improve the progression of diabetic nephropathy. Maneesa Rajora *et al.* (UofT) presented their work optimizing the development of ApoE porphyrin lipid nanoparticles to treat glioblastoma. The unique photophysical properties of porphyrin and tailoring of particles to tumour cells demonstrated promising capacity for this nanoparticle in cancer theranostics. Mustafa Ege Babadagli *et al.* (Dalhousie) discussed the clinical assessment of “center-specific” automated treatment plans for low dose rate prostate brachytherapy. They used a novel mixed-integer linear programming model for interstitial low-dose rate prostate brachytherapy that demonstrated solution times from less than a minute to roughly five minutes, for small to large prostates, and verified clinically acceptable results in a cohort of patients.

**Applied sciences—Surgery**

Sydney McQueen *et al.* (UofT) presented an exploratory mixed-methods study on how surgeon stress in the operating room impacts quality of care. They found that acute stress in the operating room is a variable phenomenon. Hasan Abdullah *et al.* (UofC) presented their work assessing predictors of post-surgical infections in pediatric patients following spine surgery. They found that fluid resuscitation on post-surgical days one and two led to increased rate of infection. Nader S. Aboelnazar *et al.* (UofA) compared the effects of acellular, red blood cell and whole blood perfusates in *ex vivo* lung perfusion. They found that cellular perfusates improved lung compliance and decreased molecular markers of lung injury in both positive pressure and negative pressure ventilated lungs. Nirmeen Zagzoog *et al.* (UofT) proposed a study to investigate the accuracy of an Optical Topographical Imaging (OTI)-based neuro-navigation system for skull base procedures guided by both human and robotic drill operators. They hypothesize that an OTI-based navigation system can allow better visualization of anatomical landmarks during a procedure.
Applied sciences—Translational research

Charles Yin et al. (Western) demonstrated that lesion-resident macrophages can be successfully isolated by LCM from human aortic wall. Their gene expression profiling results showed defects in phagosome maturation and antigen processing in the pathogenesis of atherosclerosis in humans. Christopher McFaul et al. (UofT) described a platform for high-content, in vivo drug screening using a spinning disk confocal microscope coupled to an automated embryo injection system. This novel tool allows identification of pathways critical for cardiac precursor migration, polarization and cell-cell adhesion. Na’ama Avitzur et al. (UofC) investigated the relationship between T1 mapping and strain-based analyses values in patients with confirmed cardiac amyloidosis (CA). Avitzur et al. found that in patients with CA, T1 mapping was associated with a decrease in segmental deformation when measured by 3D strain analysis. Sze Wah Samuel Chan et al. (UofT) presented on procedural preferences for corneal transplants in Toronto. They found that the majority of transplants were partial-thickness, for which Descemet’s membrane endothelial keratoplasty has emerged as the procedure of choice. Vadim Iablokov et al. (UofC) presented a novel protocol using matrix-assisted laser desorption/ionization-mass spectrometry for analyzing kidney biopsies from patients with chronic kidney disease. The biomarkers identified in Vadim’s research can differentiate between diabetic nephropathy and hypertensive nephrosclerosis robustly and with high sensitivity. Christopher Newell et al. (UofC) presented his work on mesenchymal stem cells (MSC) shifting mitochondrial dynamics and enhancing oxidative phosphorylation. They found that MSC treatment rescued fibroblasts from a mitochondrial diseased state by improving mitochondrial network formation. The clinical translation of genomic scars in advanced breast cancer was discussed by Eric Zhao et al. (UBC). The provide evidence that showed an association of platinum-based chemotherapy response with deficiencies in homologous recombination in advanced breast cancer.

Other topics

Medical technology and data science

Orly Bogler (UofT) presented work by Appel et al. on whether exposure to natural settings through virtual reality in patients with dementia/cognitive impairment decreases symptoms of depression and anxiety. They found that participants felt more relaxed and less anxious after virtual reality therapy. Paul Kudlow et al. (UofT) investigated whether promoting article links in a novel online distribution channel (TrendMD) affects article saves on an online reference manager (Mendeley). They found that TrendMD enhanced saves on Mendeley, suggesting that TrendMD may increase citations of scholarly articles.

Quality improvement

Leedan Cohen et al. (UofT) presented their preliminary findings on the efficacy of a new Hospital Handbook developed by OpenLab and incorporating patient feedback. Participants recruited from a pre-surgery clinic found that the new Hospital Handbook was effective and an improvement over current resources.

Concluding remarks

The national 2017 CITAC-CSCI AGM once again highlighted the research avenues pursued by clinician investigator trainees, and the event will continue to showcase and adapt to the landscape and needs of this rigorous training program in Canada. Thus, the AGM continues to represent a critical conduit through which CITAC’s overall objective is met.

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References

