Newsletter

iCMLf International Chronic Myeloid Leukemia Foundation

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About the iCMLf

The International CML Foundation (iCMLf) is a Foundation established by a group of leading hematologists with a strong interest in CML. The mission of the iCMLf is to improve the outcomes for patients with CML globally. The Foundation is registered as a charitable organisation in England and Wales but its charter is global. Its aims are to foster and coordinate global clinical and research collaborations and to improve clinical practice and disease monitoring in CML, especially in emerging economic regions. Scientific advisors and national representatives spanning over 30 countries provide guidance and advice to further the aims of the iCMLf.

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Please support the iCMLf! Your donations and unrestricted grants enable us to support the opportunity for all CML patients to have the best possible outcome no matter where they live.

Dear Colleagues,

Two of the iCMLf programs that have the most immediate benefit for physicians and their CML patients are the iCMLf Clinical Preceptorship Program and the iCMLf Diagnosis and Testing Program. These look to enhance education for physicians in the emerging regions and improve access to CML diagnosis where resources can be limited.

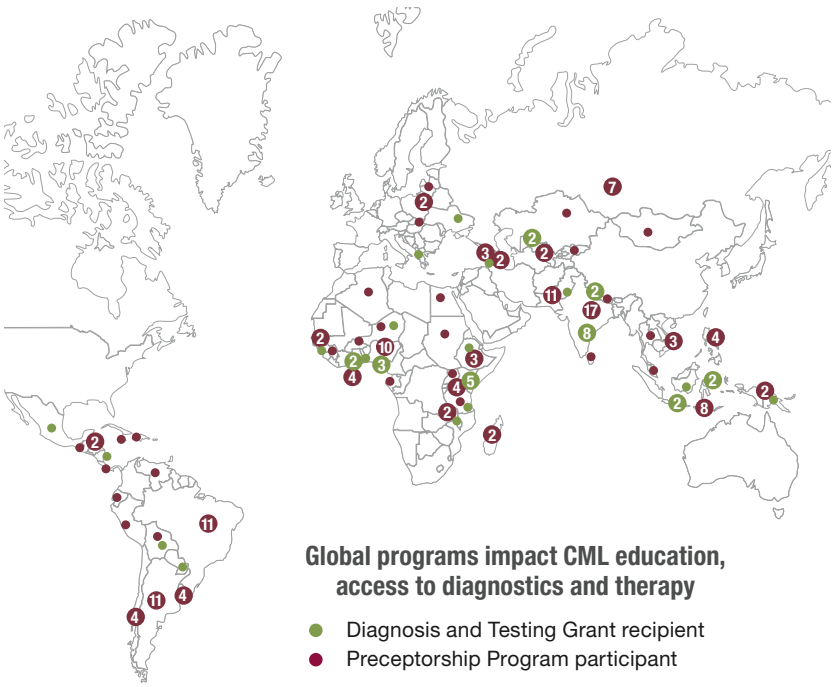
The clinical preceptorships can have a profound influence on the clinicians who attend. Augmenting current knowledge, learning new and different management skills and forming long lasting productive partnerships with international CML centres of excellence.

"In all, every part of the program was unique and rewarding. I am now confident and equipped with more vivid knowledge in CML management."

Dr Ezire Enifome Solomon, Benin-City, Nigeria.

With **146** preceptorships completed so far, we look forward to many more in 2017. Applications are open and to apply email *melissa@cml-foundation.org*, or go to *https://www.cml-foundation.org/index.php/emerging-regions/clinical-preceptorships*

The iCMLf Diagnosis and Testing Program, provides seed funding for centres in the emerging regions to improve access for CML diagnosis and monitoring. Thanks to the funding of this program and the work of the physicians and scientists behind the projects, many centres are able to offer local testing for BCR-ABL for the first time. With **42** sites funded to date, thousands of patients now have better access to CML diagnostics. For many this means improved access to therapies and for the first time the chance for the best possible outcome.



Global programs impact CML education, access to diagnostics and therapy

- Diagnosis and Testing Grant recipient
- Preceptorship Program participant

Another fixture on the iCMLf calendar is the annual John Goldman Conference on CML: Biology and Therapy. Co-sponsored by the iCMLf and the European School of Haematology this meeting is well established as the premier international CML meeting. In this edition of the iCMLf newsletter you can find more information on the meeting, the annual iCMLf prizes and keynote presentations and the Goldman fun run. The run is a fundraiser for the iCMLf Goldman fund. Over $1,600 was raised this year, our best yet! So thank you to all those who donated and received run T-shirts.

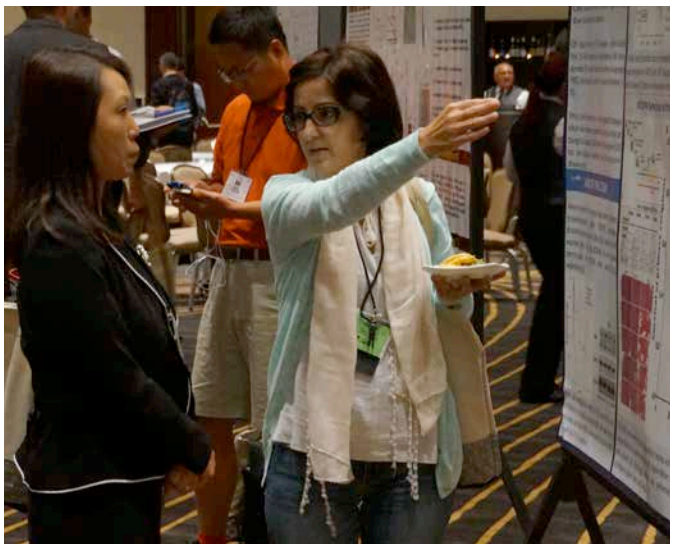
We hope you enjoy this edition of the iCMLf newsletter and remember, become a member of the iCMLf, join our community and together we will continue to work towards improving outcomes for CML patients worldwide.

Your iCMLf team

18th Annual John Goldman Conference on CML: Biology and Therapy

In September 2016 the international CML scientific community gathered in Houston for the annual John Goldman Conference. The latest and often unpublished data relating to the biology and clinical management of CML was presented. “John Goldman started this conference as a very small meeting a few years ago that has now evolved into one of the most important meetings for scientists and clinicians interested in CML who take each year a lot of new ideas and inspiration from this meeting”, said meeting Chair Professor Jorge Cortes during the opening session.

Comprehensive CML focused scientific program



“I appreciate that this meeting is dedicated to CML only”

“Packed agenda with a good mixed of science and clinical sessions”

The various scientific sessions included; special lectures, scientific debates, workshops, keynote lectures, symposia and brief oral communications. Meeting participants discussed topics such as; the origin of BCR-ABL1, basis of disease progression, therapeutic interventions, mechanisms of resistance, and aspects of treatment including predictors and modelling of responses and modern diagnostics and molecular monitoring, targeting residual stem cells and approaches to cure.

“Lots of experts and all the CML thought leaders are around here – a great opportunity to catch up”

Young scientist from Pakistan supported by the iCMLf Goldman Fund

More than 370 clinicians and scientists dedicated to CML from 33 different countries attended the meeting – among them many leaders in the field. Thanks to the Goldman Fund a young scientist from Pakistan also had the unique opportunity to attend this conference and meet with international experts. “It was a great chance for me to come to this meeting and to listen to all the international CML experts sharing their experience and knowledge, this would not have been possible without the support of the Foundation”, said Dr Uzma Zaidi from Karachi in Pakistan. Dr Zaidi also undertook a 4-week clinical preceptorship at the MD Anderson Cancer Center in Houston directly after the meeting.

Dr Zaidi with Nicola Evans, Chief Executive of the iCMLf

2016 Rowley Prize

Recipients:
Professor John Groffen
Professor Nora Heisterkamp

The iCMLf Rowley Prize is designed to celebrate persons who make outstanding contributions to the understanding of the biology of CML. In 2016 Professor Groffen and Professor Heisterkamp are recognised as co-discoverers of the genes that are directly involved in the t(9;22) Philadelphia (Ph) translocation found in CML.

"The discovery of these genes is a historical milestone in CML research"

Professor Ravi Bhatia

Ravi Bhatia presenting the iCMLf Rowley Prize to Professors Groffen and Heisterkamp

Evolution in leukemia research: From identification of the BCR/ABL fusion to carbohydrate-mediated protection by the bone marrow microenvironment

As a biology student in Groningen, the Netherlands, John Groffen was given the opportunity to learn molecular cloning and Southern blotting in Richard Flavell's lab of Gene Structure and Function in Mill Hill, UK. After graduation, we were recruited to work in John Stephenson's lab at the Laboratory of Viral Carcinogenesis at the NCI Frederick, MD in the USA. Our projects included the molecular cloning of viral-transduced oncogenes. John Stephenson was studying type C RNA transforming viruses, and the lab had obtained a mouse v-Abl clone from David Baltimore. We made probes from it to investigate if human DNA contained homologous sequences. When we discovered that well-conserved sequences appeared to exist, John returned to Mill Hill to make a human cosmid library from which we then cloned out large segments of the human c-ABL gene. In collaboration with Nigel Spurr in Walter Bodmer's lab in the UK we were able to utilize a human DNA probe to localize the c-ABL gene to human chromosome 9.

Serendipity was responsible for the next development: when Frank Grosveld from Mill Hill visited us, he mentioned that his brother Gerard had just joined Dick Bootsma's lab in Rotterdam and was leading the effort to clone the breakpoint of the Ph-chromosome. Anne Hagemeijer and colleagues had generated somatic cell hybrids containing the Ph-chromosome and when Annelies de Klein used our c-ABL probe on a Southern blot, we all discovered that the part of c-ABL represented by the probe had been translocated to the Ph-chromosome. This significantly increased the chances that c-ABL was positioned near the translocation breakpoint, as the segment of DNA that had moved to chromosome 22 was too small to be visualized by cytogenetic techniques available at the time.

John and I subsequently started molecularly cloning DNA segments 5' to that contained in the cosmids which we had already isolated, and that encompassed what later was shown to be exons 2-11 of c-ABL. By combining cloning with Southern blotting of CML patient DNA, we discovered the first translocation breakpoint 5' in the c-ABL gene, cloned out a chimeric DNA fragment and by doing so obtained DNA probes from chromosome 22 which we then used to clone a large stretch of chromosome 22 DNA that contained this region. When we joined forces with Gerard to examine a large number of CML DNAs, we found that all contained breakpoints in a relatively small region of DNA, which we named the breakpoint cluster region (BCR) by lack of any idea regarding the function of this locus. We later isolated cDNA clones and showed it contains a gene which encodes a protein, and that transiently -in one publication- carried the name "Phl". Using Northern blotting we also showed that CML patients express chimeric BCR/ABL mRNAs.

In later studies we identified breakpoints in intron 1 of the BCR gene that, when fused to ABL, give rise to the P190 fusion protein found in Ph-positive ALL. I learned how to generate transgenic mice in Mill Hill, and our lab generated P190 Bcr/Abl transgenic mice to directly demonstrate that Bcr/Abl causes leukemias.

Gene targeting in mice was used to further examine the function of the BCR gene. We also identified Crkl as a direct substrate of the Bcr/Abl tyrosine kinase.

Without the advances in basic research and the technologies that emanated from them, such as Southern blotting, molecular cloning and transgenic mouse technology, our studies could not have happened. When we started our research in the early 1980s, chromosome 22 in terms of genes was almost entirely a terra incognita. The techniques we used were considered state-of-the-art at the time, but only 30 years later they have been entirely replaced by faster and more accurate methods which allow the sequencing of complete genomes. Yet, although genomics, transcriptomics and proteomics are able to provide us with a detailed inventory of the content of CML cells, it remains a challenge to relate these components to the way CML cells function and survive in the complex microenvironment of the bone marrow niche.

Our lab still focuses on leukemia but we have directed some of our effort to study it from the viewpoint of glycobiology, a path that is less well-travelled. We know that leukemia cells are protected when they reside in their microenvironmental niche in the bone marrow, and that contact is mediated by cell surface structures of which the carbohydrates are key components. In recent studies, we found that bone marrow stromal cells secrete a lectin that binds to poly-N-lactosamine modified glycoproteins, called Galectin-3, and which is endocytosed by B-cell precursor acute lymphoblastic leukemia (BCP ALL) cells. Stromal cells that can not produce Galectin-3 are defective in their ability to protect BCP ALL cells against chemotherapy. Thus our studies in BCP ALL, and those of Yamamoto-Sugitani et al in CML, suggest that there are still many possible approaches to eradicate leukemia cells other than to directly target them. Given the huge technological and conceptual advances in the past 30 years in CML research, it seems safe to predict that it will not take an additional 30 years to translate this type of approach into a therapy.

Nora Heisterkamp, Ph.D. and John Groffen, Ph.D.
Division of Hematology, Oncology and Bone Marrow Transplantation, Children's Hospital Los Angeles

Professor Heisterkamp's full keynote lecture when accepting the Rowley prize can be found at *https://www.cml-foundation.org/index.php/science-education/scientific-news-cml-3*

2016 Goldman Prize

Recipient: Professor Hagop M. Kantarjian

The iCMLf awards the 2016 Goldman Prize to Professor Kantarjian in recognition of his groundbreaking discoveries, including new targeted-therapies, which improved prognosis and survival in patients with CML. The annual Goldman Prize, awarded in honour of Professor John Goldman, acknowledges outstanding lifetime contributions to the management of patients with CML.

"It was very easy to choose Hagop Kantarjian from all the nominations this year because so many CML patients in the world have benefited from his research"

Jorge Cortes, iCMLf Director

Jorge Cortes awarding the iCMLf Goldman Prize to Professor Kantarjian

Professor Kantarjian's full keynote lecture when accepting the Goldman prize can be found at *https://www.cml-foundation.org/index.php/science-education/scientific-news-cml-3*

Chronic Myeloid Leukemia Beyond 2016 – Some important Questions

Imatinib mesylate and other BCR-ABL selective tyrosine kinase inhibitors (TKIs) have dramatically changed the treatment algorithm and prognosis of Philadelphia chromosome-positive chronic myeloid leukemia (CML) [1-8]. With these therapies, the annual mortality in CML has been reduced from a historical rate of 10% in the first 2 years and 15 to 20% subsequently to a CML-causal annual mortality rate of 1%. When treated appropriately and compliantly, and monitored for early signs of resistance, patients with CML have an expected 15-year survival rate of 85%, not different with imatinib and second generation TKIs, because of the availability of highly effective salvage therapies among patients identified early to have cytogenetic relapse and treated appropriately. Today, imatinib, nilotinib and dasatinib are approved for frontline therapy [4, 5]. Among patients with CML resistance or treatment intolerance, nilotinib, dasatinib and bosutinib are potential salvage therapies depending on prior exposure, co-morbid conditions, and identification of CML resistant mutations. Ponatinib, a third generation TKI selectively effective against T315 I mutations, and highly effective generally across other mutations, is also useful as subsequent salvage therapy [9, 10]. Long-term side effects are emerging with TKIs that require proper management. These include renal dysfunction; rare neuro-toxicities misdiagnosed as Alzheimer's disease, dementia or Parkinsonism, and which can be reversible with treatment interruption; vaso-spastic conditions including myocardial insufficiency and infarct, transient cerebral ischemic attacks or cerebrovascular accidents, peripheral arterial disease; systemic and pulmonary hypertension; worsening of diabetes; rare pancreatitis, etc.

Multiple questions remain as to optimal treatment and monitoring of CML. These include:

1. The role of frontline therapy with generic imatinib versus second TKIs. Perhaps second TKIs could be reserved as first-year of therapy to reduce the incidence of transformation in general, followed by imatinib therapy once patients achieve cytogenetic CR. Alternatively should second TKIs be used in high-risk CML and in younger patients (e.g. age younger than 50 to 60 years) to induce higher rates of durable complete molecular responses (CMR) which may help improve the rates of TKI treatment discontinuation (a more important consideration among younger patients)? This raises the question of the cost-benefit of second TKIs: how much should we pay for TKIs for the treatment of the total population in order to allow for a differential treatment discontinuation and differential molecular cure rates of 5 to 10%?
2. Can we improve the rates of durable CMRs and potential molecular cures and what are potential optimal strategies (e.g. pegylated interferon, checkpoint inhibitors, BCL-2 inhibitors, JAK-2 inhibitors, etc.)?
3. What is the optimal management of CML in transformation? Can we develop better definitions of CML accelerated phase (e.g. high percent of blasts and basophils, selective cytogenetic abnormalities including isochromosome 17 and 3q26.2 rearrangements)?
4. What is an optimal treatment monitoring and timing interventions? Is the aim of therapy achievement of complete cytogenetic response or deeper molecular responses? Should we consider a change of TKI therapy based on BCR-ABL transcript levels (International Standard) of >10% at 3 or 6 months into frontline therapy? Is cytogenetic CR necessary for older patients who become resistant to multiple TKIs or can they maintain durable chronic phase disease with lesser degrees of cytogenetic response? Should BCR-ABL mutations detection be performed with more sensitive next generation sequencing (versus the current Sanger sequencing) as the new standard of care?
5. What is the optimal role and timing of allogeneic stem cell transplant (SCT) in advanced nations (where the cost of long-term TKI therapy is less relevant) versus emerging nations (where SCT could be a one-time curative treatment with a cost of less than $20,000)?
6. Treatment interruption of TKIs among patients with durable CMR.
7. Management of women with CML on TKIs in relation to pregnancy.
8. What are the dose-schedule ranges of each of the TKIs that allow continued benefit from equal efficacy and reduce toxicities? For example, is the approved dose of ponatinib 45 mg daily the best dose, or are daily doses of 30 mg or 15 mg appropriate depending on response status and side effects or co-morbid conditions?

These above questions and other important ones related to optimal CML management and monitoring will be discussed.

Hagop M. Kantarjian, MD
MD Anderson Cancer Center
University of Texas, Houston

** References can be found with the online article at https://www.cml-foundation.org/index.php/about-us/prizes/631-goldman-prize-2016*

2016 iCMLf Prize

Recipient: Associate Professor Susan Branford

The iCMLf has awarded the 2016 iCMLf prize to Associate Professor Branford. This award recognises the critically important work she has performed to improve the quality and availability of reliable molecular testing for CML in the emerging regions. Her efforts have significantly impacted and improved the management of so many CML patients in these regions.

"Sue is an incredibly worthy winner because of her beautiful science, her mastery in communication skills and her sincere humanity and generosity"

Tim Hughes, iCMLf Chairman

Tim Hughes awarding the iCMLf prize to Dr Branford

Challenges for monitoring patients in emerging economic regions

Monitoring response to tyrosine kinase inhibitor therapy is now an important component of patient management and BCR-ABL1 transcript levels can dictate a change of treatment. The test is performed on peripheral blood at a relatively small cost compared with the overall cost of drug therapy. Most patients have a successful outcome and their response can be tracked as an initial rapid decline in BCR-ABL1 transcripts followed by a very slow decline over many years that culminates in a deep molecular response, which is associated with long term optimal outcome. A rise in BCR-ABL1 can signal the onset of resistance and loss of response, in which case BCR-ABL1 mutation analysis is warranted. A rise can also accompany non-adherence to the prescribed dose of tyrosine kinase inhibitor, which is a warning that long-term response may be less than optimal.

Molecular monitoring in some countries would be considered optimal: standardised to the international reporting scale, available to all patients through government subsidy or at a low cost, and available at the appropriate frequency. The frequency of testing changes over the course of therapy and according to treatment response. More frequent monitoring in the initial months is important to assess the trend of response and the response level. BCR-ABL1 values that remain >10% on the international scale at 3 and 6 months are associated with poorer long term outcomes and signal treatment failure, which mandates a change of therapy to reduce the risk of disease progression. Reaching a major molecular response (≤ 0.1%) at 12 months is considered optimal and continuation of the current therapy is advised. More frequent molecular monitoring is required in case of less than optimal response or if drug resistance is suspected. More frequent monitoring may also be required many years after commencing therapy to track a deep molecular response, which is a prerequisite for a trial of drug cessation. Patients with a sustained deep response may be candidates for treatment free remission. The most critical time for molecular recurrence after drug cessation is within the first 6 months of stopping, and monthly monitoring is important to allow rapid drug restart upon molecular recurrence.

Although an increasingly integral factor for optimal outcomes, molecular monitoring is not available to all patients at the required frequency, or indeed may not be available at all due to lack of testing capacity or prohibitive cost to the patient. The iCMLf and the Max Foundation aim to improve access to molecular monitoring in low resource regions, such as the Philippines where in 2010 no molecular testing was available and patients had never been monitored despite having had CML for years. To this end, some high resource countries through the iCMLf and Max Foundation were able to offer molecular testing to a few patients who were otherwise denied monitoring, many of whom were suspected of having drug resistance. In the Philippines a concerned father of a young boy with CML coordinated the first monitoring for 30 patients from

Manilla where frozen blood samples were sent to Adelaide, Australia for testing. Approximately 40% of patients had BCR-ABL1 resistant mutations and advice was offered for the appropriate TKI for rescue of response based on the mutation resistance profile. Frozen blood shipment is very expensive, but recent studies performed in Seattle have demonstrated that blood spotted onto a paper template and posted via standard mail generates reliable BCR-ABL1 values at a substantially reduced cost.

For improved outcomes for patients in low resource countries, point of care molecular monitoring is needed and efforts towards standardised protocols have improved the reliability of results, although most methods require expensive machinery and high technical skill and training. An alternative is the Cepheid GeneXpert analyser where all of the processes required to generate a quantitative BCR-ABL1 value is contained within a microfluidic cartridge and requires low technical skill. Many centres have acquired the instrument through agreements with the Max Foundation and can now offer patient monitoring.

An unmet need for all patients is appropriate prediction and effective intervention for those with primary drug resistance or early disease transformation. The next generation of sequencing technology is starting to identify genomic lesions in addition to BCR-ABL1 that may impact treatment outcome. A greater understanding of the mechanisms driving poor outcome will lead to improved treatment options and outcomes. Our understanding of CML is far from complete and although tremendous advances have been made for the majority of patients, future research and greater access to fundamental monitoring should lead to improved outcomes for more patients and potentially increase the number of patients able to achieve treatment free remission.

A/Prof Susan Branford, PhD, FFSc (RCPA)
Head, Leukaemia Unit
Genetics and Molecular Pathology
SA Pathology, Adelaide, Australia

Dr Branford's full keynote lecture when accepting the iCMLf prize can be found at *https://www.cml-foundation.org/index.php/science-education/scientific-news-cml-3*

2016 Grants to improve access to CML diagnosis and testing

We are delighted to congratulate the winners of the 2016 iCMLf Diagnosis and Testing grants. These centres will receive up to $10,000 to improve access to local CML diagnostics.

1) Hematology Center after Prof. Yeolyan, Yerevan, Armenia
2) Medical research laboratory Inova LLC, Tbilisi, Georgia
3) Sancheti Hospital & Cancer Institute, Jodhpur, India
4) The Nairobi Hospital, Nairobi, Kenya
5) Aga Khan Hospital, Kisumu, Kenya
6) BP Koirala Memorial Cancer Hospital, Chitwan, Nepal
7) Khyber Medical University, Peshawar, Pakistan
8) Cheikh Anta Diop University, Dakar, Senegal
9) Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania
10) APSBES / Diligence group, Lomé, Togo

The grants allow access to equipment, consumables, along with staff resources and training and patient education. Many thousands of patients will receive improved care as a direct result of the projects supported by this iCMLf funding.

"Firstly I would like to express my gratitude for selecting our institution as one of the 2016 the iCMLf grant recipients. Am confident this grant will go a long way in improving access to BCR-ABL transcripts testing to our patients." Dr Boniface Kairu Githaiga, Kenya

John Goldman Fun Run

The sky was still dark and the moon overhead when 43 John Goldman conference participants had an early start to the Sunday morning, running a 5km loop round through Houston's beautiful Memorial Park. Whether for recreation, or sporting excellence, it was great fun running together with colleagues and friends all while supporting the work of the iCMLf.

"Nice opportunity to talk to colleagues and to enjoy some time together"

A special thank you to those you donated to the iCMLf and received a 2016 John Goldman Fun Run T-Shirt.

The Foundation raised over $1,600 that will go directly to programs supporting young physicians from the emerging regions.

Funds from the annual John Goldman fun run are directed to the 'Goldman Fund'. This fund, created in memory of the work of Professor Goldman, has already supported young physicians from Nigeria, Ukraine, Pakistan and India to attend the John Goldman Conference on CML.

If you would like to donate go to *www.cml-foundation.org* and click

Donate

Join us at these 2017 international meetings

19th Annual John Goldman Conference on
CHRONIC MYELOID LEUKEMIA: BIOLOGY AND THERAPY

ESTORIL, PORTUGAL
OCTOBER 12-15, 2017

Chairs: J. Cortes, T. Holyoake, T. P. Hughes
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