Newsletter

iCMLf International Chronic Myeloid Leukemia Foundation

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Edition 11

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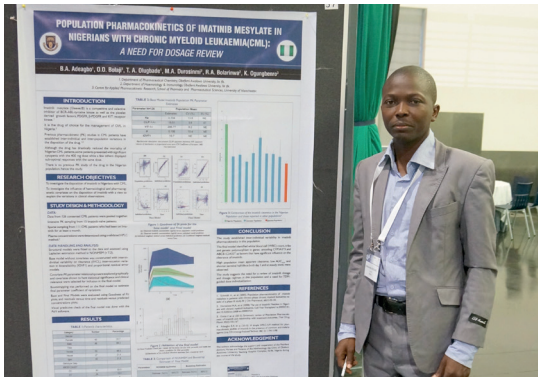
Please support the iCMLf! Your donations and unrestricted grants enable us to support the opportunity for all CML patients to have the best possible outcome no matter where they live.

Dear Colleagues,

The annual John Goldman Conference on CML: Biology and Therapy co-sponsored by the iCMLf and the European School of Haematology is well established as the premier CML meeting of the year. This year we returned again to Estoril, Portugal for a packed agenda dedicated to the latest CML information in both clinical management and basic science. With over 580 attendees, the 2015 meeting was the largest ever.

While the conference always provides the opportunity to update knowledge, it is also a chance to network and exchange ideas with colleagues from around the world and perhaps to have a little fun! For the second year attendees were able to participate in an early morning 5k 'fun' run. Although we started in the dark and watched the sun come up while jogging along the esplanade, the energy and enthusiasm was palpable. The run is also a fundraiser for the iCMLf Goldman fund and this year we raised over $1,300, so thank you to all those who donated and bought T-shirts.

The Goldman Fund, named in honour of John Goldman, is used to support one of John's passions, the education of young physicians from the emerging regions. This year the Goldman fund supported doctors from Ukraine and Nigeria to attend the John Goldman conference and present their work. Dr Adeagbo from Ile Ife presented his poster on population pharmacokinetics of imatinib in Nigerians with CML and Dr Kotlyarchuk from Liviv presented an analysis of pregnancy in CML in the Ukraine.



Dr Adeagbo presenting his poster

Professor Hughes speaking at the John Goldman Meeting

During the John Goldman meeting the iCMLf awards its annual prizes. In 2015 these were; Professor Rick Van Etten, the Rowley medal recognising lifetime contributions to our understanding of the biology of CML, Professor Michele Baccarani, the Goldman medal for lifetime contributions to clinical management and the inaugural Emerging Regions Support and Partnership (ERSAP) medal, Pat Garcia-Gonzalez from The Max Foundation. After each award the recipients spoke about their work and perspectives on CML over the years. It was inspiring to listen to the three different presentations to hear how far we have come and yet in some cases how far we have yet to go!

A synopsis of the Prize presentations can be found on pages 3-6 of this newsletter. We also offer an overview of the John Goldman meeting on page 2 and congratulate the winners of the 2015 iCMLf Diagnosis and Testing Program on page 7.

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

"Thank you very much for your help and support which enabled my participation in the 17th John Goldman Conference. It was an unforgettable experience from many points of view: a great chance to spend 4 days of CML education from the top lecturers; meeting some very nice people; presenting our own data; obtaining ground for new ideas as to how and which way we should move in terms of improving CML management at home; participating in a Fun Run which was a new experience for me!" Dr Kotlyarchuk, Ukraine

17th Annual John Goldman Conference on CML: Biology and Therapy

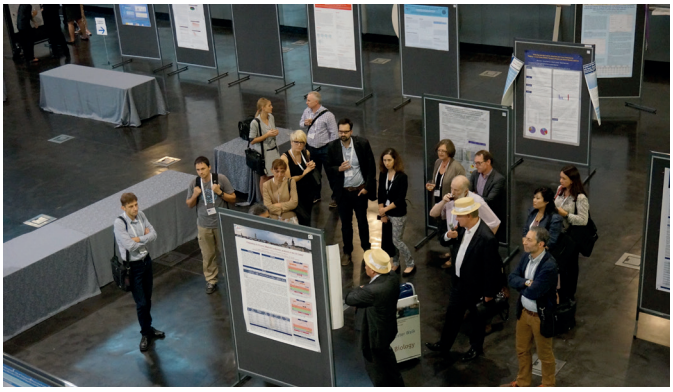
Every year the John Goldman Conference on CML, co-sponsored by the iCMLf and the European School of Haematology (ESH) is the premier CML-focused international meeting to mark on your calendar. From October 1-4, 2015 the international CML community again came to Estoril (Portugal) for this 4-day meeting to discuss latest findings in CML biology and management and to exchange experiences and perspectives.

"This conference is an excellent international scientific meeting that dedicates a full four-day scientific program to a single disease"
Meinolf Suttorp, Germany

Participants from all parts of the world - excellent opportunity to network

"This premier CML meeting usually offers an exciting CML focused scientific program of high-value, but the most important part of this conference are the discussions with other CML experts united in their effort to develop better treatment and care for patients with CML", said Jorge Cortes during his opening remarks of the congress.

584 key clinicians and scientists from 59 different countries attended the meeting. At 79%, the majority of attendees came from European countries, *"but the meeting also resonated well with participants from all parts of the world including the Middle East, Asia and Africa"* emphasised Professor Cortes.



Among the attendees were young scientists from the emerging regions who took the opportunity to present their research results during the mentored poster walks - a special feature of this CML conference. *"It was an honour for me to present my data here at this well-known conference and to discuss the results with the international CML community"*, said Dr Babatunde Adeagbo from Ile Ife in Nigeria. Dr Adeagbo's attendance was supported by the iCMLf Goldman fund and he presented his poster on population pharmacokinetics of imatinib in Nigerians with CML.

2015 Rowley Prize

Recipient: Professor Richard Van Etten

The iCMLf Rowley Prize is designed to honour persons who have made major contributions to the understanding of the biology of CML. In 2015 the iCMLf Rowley Prize is awarded to Professor Richard Van Etten to recognise his ground breaking research focusing on the development of new therapeutic strategies such as the tyrosine kinase inhibitors.

"Richard Van Etten is one of the pioneers of murine models in CML"

Dr Steffen Koschmieder introducing Dr Van Etten to accept his medal.

Tim Hughes presenting the Rowley Prize to Richard Van Etten

Mouse models of tyrosine kinase-driven hematologic neoplasms: historical perspectives and new insights

Models of chronic myeloid leukemia (CML) have proven invaluable for furthering our understanding of the molecular pathophysiology of this disease. Xenotransplantation of primary human CML cells into immunodeficient mice allows investigation into the nature of the most primitive repopulating cells in this leukemia, but the system is limited by variability and difficulty with experimental manipulation. Accordingly, much effort has been invested in developing models of CML through expression of the BCR-ABL1 oncogene in the hematopoietic system of laboratory mice. Two major approaches have been taken: i) retroviral or lentiviral transfer of the BCR-ABL1 gene into hematopoietic stem cells ex vivo, followed by transplantation into recipient mice, and ii) creation of BCR-ABL1 transgenic mice. The first approach was unsuccessful until the development in the late 1980s of retroviral vectors, based on myeloproliferative sarcoma virus, which allowed efficient proviral expression in stem cells, and has been subsequently facilitated by packaging systems based on the highly transfectable 293T cell line. This model system is now widely employed by molecular cancer researchers to express oncogenic driver genes in a variety of tissues. The second approach was initially stymied by issues of faithful transgene expression, toxicity, and silencing. Current models employ binary conditional transgenic mice to regulate the expression of BCR-ABL1 in hematopoietic stem/progenitor cells and avoid these problems.

Together, these two model systems have been employed in a complementary manner to address many fundamental questions in CML biology and as a preclinical platform to test new approaches to therapy. Important discoveries using these models include the understanding of the stem cell origin of CML, insight into the mechanism of leukemia cell killing with ABL1 tyrosine kinase inhibitor (TKI) drugs, and the elucidation of critical downstream pathways necessary for CML pathogenesis and for the survival and self-renewal of CML stem cells. The latter work, in turn, has spawned multiple clinical trials of small molecules targeting these pathways as approaches to eradicating CML stem cells and curing patients of their leukemia.

Recent developments in molecular genetic technology promise to increase the value and versatility of these models. Unbiased forward screens using transposon mutagenesis or siRNA libraries allows identification of novel pathways involved in CML disease progression, stem cell maintenance, and TKI resistance. Next-generation sequencing, including RNASeq and ChIPSeq, permits the rapid elucidation of genetic and epigenetic variations in leukemia cells from these models. Cas9/CRISPR genome editing technology has accelerated the development of mutant mouse strains for study, and will soon be incorporated directly into BCR-ABL1-expressing mouse models for efficient interrogation of the role of specific genes in leukemogenesis. Looking forward, we can anticipate mouse models of CML to contribute directly to answering some of the major burning questions in the field, including mechanisms of primary resistance to TKIs, pathways of disease progression to blast crisis, and the identification of biomarkers and strategies to predict and enhance treatment-free remissions when TKI therapy is discontinued.

Richard A. Van Etten, MD PhD
Professor of Medicine and Director, Chao Family Comprehensive Cancer Center
University of California, Irvine

2015 Emerging Regions Support and Partnership Prize

Recipient: Patricia Garcia-Gonzalez

The Emerging Regions Support and Partnership (ERSAP) Prize will be awarded each year to an individual, or organisation that has made outstanding contributions to the treatment of CML in the emerging economic regions. The iCMLf Directors and Scientific Advisors has awarded the inaugural ERSAP prize to Pat Garcia-Gonzalez not only for her role in leading The Max Foundation, but also to recognise the personal passion and motivation that she brings into her work aiming for dignity and hope for all in the face of cancer.

"Pat well deserved this inaugural ERSAP prize for her tremendous work in granting access to diagnosis and treatment for so many people in the emerging regions"

Jorge Cortes during the ERSAP prize award ceremony

iCMLf Directors; J. Cortes, J. Radich and T. Hughes awarding the ERSAP prize medal to Pat Garcia-Gonzalez

Access to treatment for CML in low and middle income countries.

In the world of oncology, it is not too often that we see an event, let alone two converging events, that would change the course of history. But this is the case for the treatment of chronic myeloid leukemia (CML). The approval of imatinib as the first tyrosine kinase inhibitor in 2001, and its accessibility to patients in low and middle income countries almost simultaneously with patients in the Western world, changed not only the nature of the disease, but also shifted our accepted paradigm about global access to innovative oncology treatments.

In late 2001 shortly after the approval of Gleevec by FDA and EMA, Novartis launched The Glivec International Patient Assistance Program (GIPAP) in partnership with The Max Foundation to provide access to imatinib to patients in 80 low and middle-income countries who did not have access to reimbursement or insurance, and who were not able to otherwise afford the treatment. GIPAP represented a new model in international humanitarian programs, making the drug available specifically to each individual patient confirmed by The Max Foundation to be properly diagnosed with an indication as per the approved label, who met program criteria. To be able to continue re-supply to each patient The Max Foundation developed the Patient Assistance Tracking System (PATS®), a smart web-engine that tracks and propels the treatment life-cycle of each patient. In the past 14 years the treatment of over 59,000 CML patients has been tracked with PATS; The Max Foundation and Novartis have worked in partnership with 1,500 hematologists, and more than 3 million monthly doses of Glivec have been approved and delivered.

A look at the CML patient profile in the PATS database shows a younger patient population with an average age at diagnosis in the 30's including a cohort of 6,000 patients diagnosed under the age of 20 (Figure 1). A look at disease phase at entry into the system reveals a positive trend over time towards capturing patients with earlier diagnosis as the program matured (Figure 2).

Figure 1.

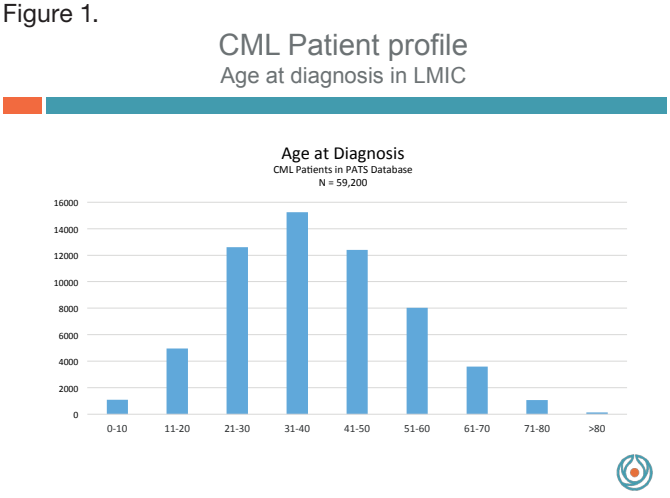
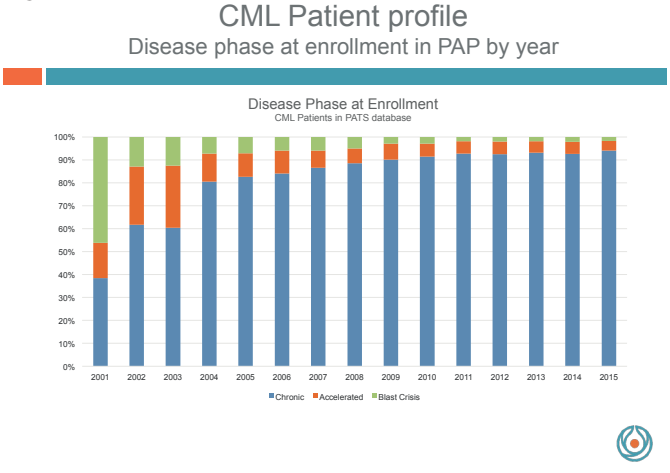


Figure 2.



GIPAP and subsequent similar access programs for Glivec have greatly contributed to removing the affordability barrier for patients from these countries, yet other barriers exist that prevent optimization of clinical outcomes for CML patients: poverty and stigma, supply chain challenges, and access to diagnostics being the most pervasive barriers. For the past 14 years, The Max Foundation has worked with local and international stakeholders to decrease the impact of these barriers.

In 2009, eight years after the launch of GIPAP, access to diagnostics was scarce to non-existent in more than 40 countries, and some patients who otherwise could have access to imatinib were unable to be treated. In the past three years, the situation has significantly improved through the collaboration of The Max Foundation with Cepheid and with the International CML Foundation among others, as well as with patient associations. Combining education and awareness through the What is My PCR campaign with preferential pricing for BCR-ABL assays has resulted in 17 countries now able to perform molecular BCR-ABL tests for the first time.

Social challenges, especially poverty and pervasive social stigma greatly contribute to sub-optimal compliance. Often patients are simply not able to freely disclose their diagnosis to their family or employers, making it difficult to keep regular doctor appointments. To overcome this challenge, in the past decade The Max Foundation has partnered with patient leaders to form 35 patient associations, and provided social support and education to patients through more than 200 patient education workshops.

Further, the organization today supports and partners with 68 organizations from 56 countries through the Max Global Network and works closely with key opinion leaders, industry partners and other stakeholders to continuously provide education and support services to patients.

The efforts of the past 14 years have taught us important lessons. Of significance, we have learned that it is possible to safely treat CML in low and middle-income countries. We have also learned that providing access to treatment requires long-term vision; it represents an investment in a community and a partnership with each patient. Availability of treatment proved to be a catalyst for strengthening of healthcare systems, improved healthcare providers' capacity, and increased access to diagnostics.

The surge of CML specific organizations both local and international has greatly contributed to the wellbeing of patients worldwide; of note, the leadership of the international CML Foundation in the training and capacity building of providers from emerging regions. Efforts should continue to seek opportunities for collaboration among all stakeholders.

Much has been achieved in the past 14 years, yet many challenges remain; access to second generation TKIs is still ad-hoc and limited, and a lot more can and should be done to support access to diagnostics. But perhaps the biggest challenge for patients in LMIC is the current nature of TKI treatment. It is just not sustainable for patients to remain on treatment for several decades, especially considering their young age at diagnosis. We urge researchers to continue to look for a cure for CML and thank them for their relentless efforts on behalf of patients.

Pat Garcia-Gonzalez,
Chief Executive Officer, The Max Foundation

2015 Goldman Prize

Recipient: Professor Michele Baccarani

The annual Goldman Prize awarded by the iCMLf in honour of Professor John Goldman recognises outstanding lifetime contributions to the management of patients with CML. The iCMLf awards the 2015 Goldman Prize to Professor Michele Baccarani in acknowledgment of his over forty years of dedication to clinical excellence in the management of CML.

"This decision was made due to his contributions to CML clinical practice through the leadership of both clinical research and the development of internationally recognised guidelines and recommendations".

Tim Hughes, iCMLf Chairman

Jorge Cortes awarding the iCMLf Goldman Prize to Professor Baccarani

Discussing chronic myeloid leukemia: The known and the unknown

Chronic myeloid leukemia (CML) is a rare disease, is no longer a fatal disease, and is becoming a curable disease. Current treatment is based on the inhibition of the leukemogenic proteins that are coded by the bcr-abl1 gene on the Philadelphia chromosome. Today, six tyrosine kinase inhibitors (TKIs) are available (imatinib, dasatinib, nilotinib, bosutinib, ponatinib, and radotinib), but not worldwide, and at different prices, and with different indications. Where and when imatinib is available in first-line, and the other TKIs are available in second- and third-line, the survival of CML patients is very close to the survival of the general population. The success of treatment is so big, and the knowledge of the disease is so advanced, that it is difficult to improve further on. However, some patients still die from leukemia or from treatment, the quality of life is not always optimal, only few patients achieve a treatment-free remission, that is the anteroom of cure, the cost of treatment is a heavy burden, and monitoring facilities are limited. Any improvement will be laborious, requiring on one hand a fair distribution of the resources (drugs and laboratory facilities), and on another hand a deeper understanding of the biology of the disease.

Many questions are still unanswered. Some questions date from the past century, like the prognostic value of eosinophils and basophils, the meaning of low leukocyte phosphatase acitivity, the biologic relevance and the meaning of the splenic microenvironment, and the detection of BCR-ABL1 transcripts in healthy subjects, (although at a very low level, and transiently). Some questions are growing today, concerning two main issues; What causes resistance to TKIs, that is the anteroom of progression? What causes the persistence of minimal residual disease that limits the possibility of achieving a treatment-free remission and of moving to cure?

Today, the focus of research is on genetic instability and on the development of additional genomic abnormalities. It may be also hypothetized that the number of Ph+, BCR-ABL1+ cells, a different amount of BCR-ABL1 transcripts in the cells (depending on gene transcription and on mRNA turnover), and a different amount of BCR-ABL1 coded proteins in the cells (depending on translation and on protein turnover), may be important, likely more important, than the total amount of BCR-ABL1 transcripts, as it is currently assessed by quantitative, real time, polymerase chain reaction. Answering these questions will help to improve the treatment and care of patients with CML.

Michele Baccarani

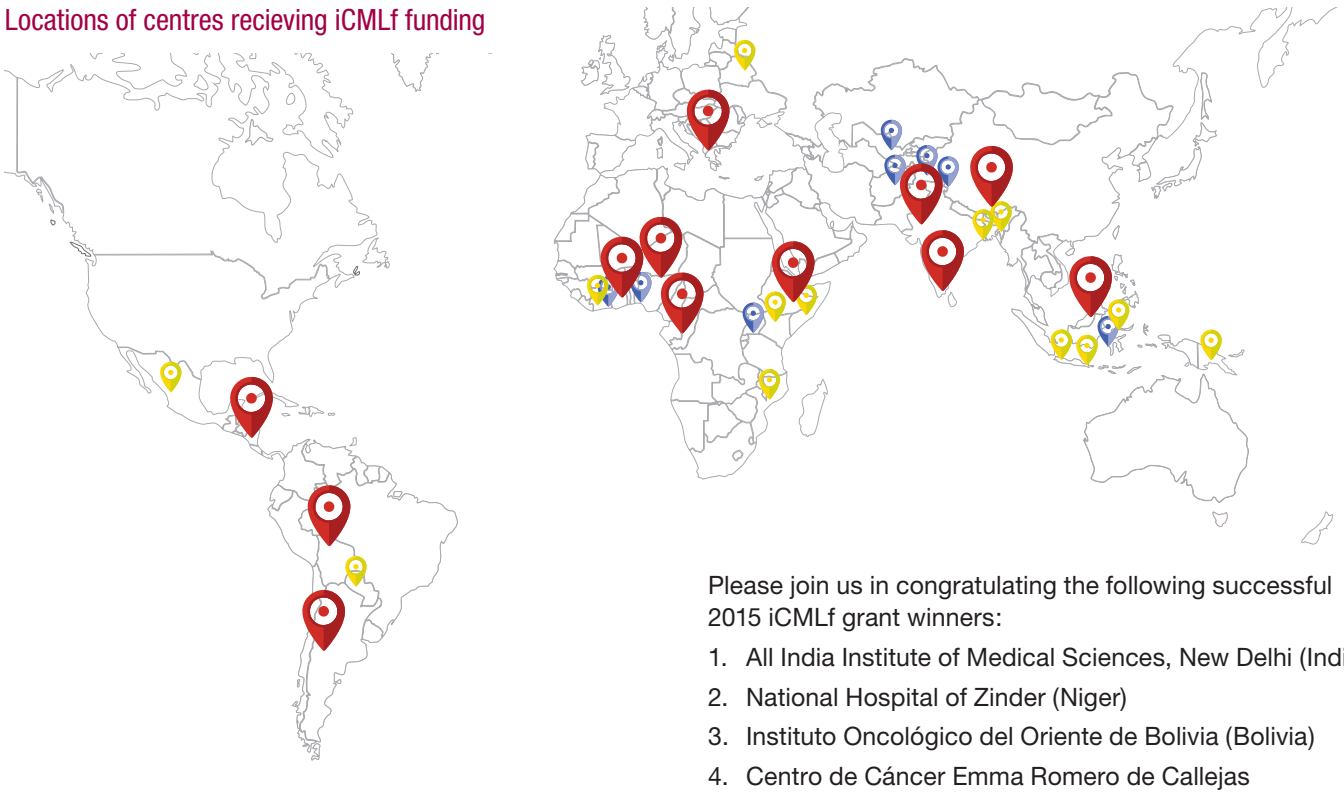
Professor of Hematology at the Universities of Trieste, Udine, and Bologna Chairman, CML Working Party of the Italian Group for Hematologic Malignancies in Adults, and of the European LeukemiaNet CML Working Package, European CML Registry and CML recommendations.

michele.baccarani@unibo.it

2015 Diagnosis & Testing Grants
Building capacity for CML diagnostics

Each year the iCMLf provides seed funding to centres to build local capacity for CML diagnostics. This year 10 new grants were awarded. The initial patient impact through PCR testing and on-going molecular monitoring is expected to be over 4000 patients. The long-term impact of these projects establishing local PCR capabilities and enhanced laboratory functions has enormous potential.

Locations of centres recieving iCMLf funding



2015 2014 2013

Expected outcomes:

Patient impact in 12 months	4059
Provide molecular monitoring	8 centres
Enhanced laboratory capacity	8 centres
Establish local PCR	3 centres
Established as a referral centre	3 centres
Physician training	2 centres
Patient education	1 centre

Please join us in congratulating the following successful 2015 iCMLf grant winners:

1. All India Institute of Medical Sciences, New Delhi (India)
2. National Hospital of Zinder (Niger)
3. Instituto Oncológico del Oriente de Bolivia (Bolivia)
4. Centro de Cáncer Emma Romero de Callejas (Honduras)
5. Ulin General Hospital, Banjarsamin, South Kalimantan (Indonesia)
6. University of Nairobi/Kenyatta National Hospital, Nairobi (Kenya)
7. University Clinic for Hematology, Faculty of Medicine, Skopje (Macedonia)
8. National Hospital Abuja, Abuja (Nigeria)
9. Prince Aly Khan Hospital, Mumbai (India)
10. Obafemi Awolowo University, Ile Ife (Nigeria)

Each centre awarded iCMLf funding will partner with a CML centre of excellence for on-going mentoring and support at a clinical and laboratory level. This will ensure the successful implementation of each project.

John Goldman Fun Run

52 participants of the 17th John Goldman Meeting on CML in Estoril had an early start to the day running with colleagues and friends at the 5 km 'John Goldman Fun Run' along the Estoril promenade. What a start to the day – and all for a good cause!

"To run and laugh together brings the CML community even closer together"

A special thank you to those you donated to the iCMLf and received a John Goldman Run T-Shirt. The Foundation raised **$1,300** that will go directly to the iCMLf Goldman Fund to improve CML treatment in the emerging regions.

The iCMLf Goldman fund was established in honor of Professor John Goldman.

John had a particular passion to educate young physicians. The Goldman Fund supports young physicians to attend and present their work at the annual John Goldman CML meeting. In 2015 physicians from Nigeria and Ukraine came to the meeting in Estoril and presented their work to the CML community. Thank you to those who donated to the Goldman Fund to make this possible.

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

Join us at these 2016 international meetings

18th Annual John Goldman Conference on
CHRONIC MYELOID LEUKEMIA: BIOLOGY AND THERAPY

HOUSTON, TX USA
SEPTEMBER 15-18, 2016

Chairs: J. Cortes, T. Holyoake, T. P. Hughes
Organizers: M. Copland, M. Deininger, P. Hari, F.X. Mahon, D. Perrotti, J. Radich, R. Van Etten
Advisory Committee: A.M. Carella, G.Q. Daley, C. Gambacorti-Passerini, F. Guilhot, R. Hehlmann, P. Laneuville, J.V. Melo, G. Saglio, C. Schiffer, P. Valent