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,

In this edition of the iCMLf Newsletter we bring you overviews of the keynote presentations from the 2018 iCMLf Prizewinners. Each of the three winners were awarded for their outstanding contributions to the field of CML. Professor Nick Cross, received the Rowley Prize in recognition of his scientific achievements to better understand the molecular pathogenesis of CML and the development, validation and standardisation of genetic tests. The 2018 Goldman Prize awarded to Professor Jorge Cortes, celebrates his globally recognised expertise and life-long commitment to the management of patients with CML and Professor Hemant Malhotra received the iCMLf prize in recognition of his tireless efforts and remarkable achievements to advance the treatment of CML patients in India and neighbouring countries.

"Nick Cross was involved, as principal figure in the harmonization of deep molecular responses definition criteria (MR4, MR4.5, MR5), an important step in the future of CML TFR studies."

The iCMLf prizes are awarded each year at the John Goldman Conference on CML. This year almost 300 people gathered in Miami for the 20th anniversary of this meeting. As always it was a meeting of friends and colleagues with great science presented and discussed. Summaries of the meeting from the meeting co chairs, Jorge Cortes and Daniela Krause can now be found on the *iCMLf website* and the presentations will soon be added so keep checking for updates.

The annual John Goldman fun run also took place in Miami and in spite of the humidity, over 40 people ran the beachside path before the Sunday sessions. The run is a fundraising event for the foundation and we raised over $1,500 going directly to the work of the Foundation in low and middle-income countries.

"The idea we can cure CML is one we should embrace and move forward with."
Tim Hughes, Chairman of the iCMLf

Despite the excellent progress we have made in managing patients with CML, major challenges remain. 15-20% of patients respond poorly to TKI therapy and half of these will die from CML-related causes. Among those who respond well, less than 25% are able to stop therapy and remain in remission with current approaches. By 2040 there are projected to be over 3 million people with CML worldwide so a concerted global effort working towards a cure is imperative. The iCMLf is uniquely positioned to drive this effort. In 2019, supporters, directors and advisors of the iCMLf are climbing Mount Kilimanjaro to raise funds for the Foundation. Every dollar raised through **Climb for a Cure 2019** will allow us to further drive the global effort working towards a cure.

"We wanted to do something a bit out of our comfort zone to celebrate 10 years of work by the iCMLf and to mark a new phase in our mission – working towards a cure. We have made great progress over the past two decades but we can't sit back and say the job is done when so many CML patients are still not receiving the best drug for them, and so few are achieving TFR." (Prof. Tim Hughes)

22 people are now registered for the **Climb for a Cure 2019**. Professors Tim Hughes and Jorge Cortes will be climbing along with Nicola Evans, the iCMLf chief executive and many other physicians, scientists and CML patients. In 2019 please join us on the mountain, support us with your donations, and work with us on our new global program.

For more information on how you can help the Foundation, or how we can work together, please email us at *info@cml-foundation.org.*

Your iCMLf team

John Goldman Conference on CML - 20th Anniversary Celebration

"This meeting, celebrating 20 years now, is an amazing evolution of our knowledge and progress treating CML."

Jorge Cortes

There are few hematological diseases that have progressed so much in science and management as CML has in recent years. The science is constantly evolving and the vision of cure is now within reach. At the annual John Goldman Conference on CML, co-sponsored by the iCMLf and the European School of Hematology (ESH), new and often unpublished data on CML is presented, discussed and put into perspective.

"Excellent meeting, with excellent science."

"Wonderful spirit – Great camaraderie"

Over 280 attendees from **over 30 countries** came together in Miami from September 13-16 to benefit from the excellent scientific program that related to:

1. **Biology of CML** including scientific workshops on imaging techniques and genomic editing, novel strategies with new pathways complementing existing TKI therapies, possible relationship between dopamine receptors and leukemic stem cell receptors, a debate on eradicating remaining stem cells and innovative new technologies for monitoring.
2. **Aspects of treatment** including updates on studies such as TIGER and SPIRIT, long-term outcomes from clinical studies on treatment discontinuation, various aspects on treatment-free remission such as predictors of success, biomarkers, gene analysis, the use of digital PCR, pregnancy and new modalities and tools of monitoring patients.

2018 'JOHN GOLDMAN FUN RUN' WAS A GREAT SUCCESS RAISING OVER $1,500

In good old tradition, a group of about 40 started the day very early at 7 am on Sunday morning running a 5 km track along Miami's beautiful South Beach to participate in the annual charity 'John Goldman Fun Run'.

By purchasing the annual run T-Shirt, participants raised over $1,500 that will go directly to programs supporting young physicians from the emerging regions in tribute to John Goldman.

2018 Rowley Prize

Professor Nick Cross (Southampton, UK)

The 2018 Rowley Prize winner is Nick Cross, Professor of Human Genetics at the University of Southampton. Awarding the Rowley Prize the iCMLf recognises outstanding lifetime contributions to the understanding of the biology of CML. Professor Cross receives the prize in recognition of his scientific achievements to better understand the molecular pathogenesis of chronic myeloid leukemia and the development, validation and standardisation of genetic tests.

"I am extremely proud to be given the Rowley Prize. Janet was an extraordinary lady and an inspiration to myself and many others."

Professor Nick Cross during his acceptance of the Rowley Prize

MINIMAL, MEASURABLE, ATYPICAL

I was very fortunate to join John Goldman's group at the Hammersmith Hospital, London in the early 1990s as a post-doctoral scientist. At the time, the clinical focus of the group was very much on bone marrow transplantation (BMT), and Tim Hughes had established a sensitive RT-PCR test for BCR-ABL to try and distinguish those patients who would remain in remission from those who were destined to relapse. It was apparent that a qualitative test (detected/not-detected) was of limited value, and so my main task was to develop and apply a quantitative (competitive) PCR technique to monitor changes in the levels of minimal residual disease (MRD; now rebranded as measurable residual disease) over time. This was technically challenging but we were able to show that sequential, quantitative molecular monitoring could indeed identify early relapse after BMT, enabling early intervention with donor leucocyte infusions. Andreas Hochhaus joined the group and used competitive PCR to demonstrate the prognostic significance of MRD levels in patients undergoing interferon-alpha therapy. A few years later, the clinical landscape of CML was completely transformed by imatinib, and the development of real time quantitative PCR enabled molecular monitoring to become part of routine practice. International management recommendations for CML patients undergoing tyrosine kinase inhibitor therapy now emphasise the importance of frequent molecular monitoring to determine the degree of response. Achievement or non-achievement of time-dependent molecular milestones helps to identify individuals who may or may not benefit from a change in treatment. Sequential monitoring enables the timely detection of relapse and may help to highlight other issues influencing response such as compliance. From a laboratory perspective, we (in conjunction with many collaborators worldwide), have focused over the past 12 years on the international standardisation of molecular monitoring by the development of accredited reference reagents, guidelines and extensive performance evaluation, particularly throughout Europe as part of the EUTOS programme. These efforts are ongoing but we are now in a position whereby most testing laboratories worldwide report results on the International Scale for BCR-ABL1 measurement, and results between centres are generally much more comparable than they used to be. A recent focus has been to establish laboratory guidelines and processes for measuring deep molecular responses, which are important to realise the goal of routine treatment-free remission.

The other major line of investigation developed initially at the Hammersmith Hospital was aimed at understanding the pathogenesis of atypical, CML-like disorders. CML has been defined for many years as BCR-ABL positive disease only, but older publications refer to a poor prognosis, clinically heterogeneous entity termed 'Philadelphia chromosome negative or BCR-ABL negative CML' constituting about 5% of CML cases. We focused initially on BCR-ABL negative cases that presented with an aberrant karyotype and, in conjunction with Andreas Reiter, we have identified more than 30 tyrosine kinase fusion genes that structurally and functionally resemble BCR-ABL. Most of these cases are now classified as 'myeloid/lymphoid neoplasms associated with eosinophilia and rearrangement of PDGFRA, PDGFRB, or FGFR1 or with PCM1-JAK2' (MLN-eo) and are important to recognise because they are amenable to targeted therapy. Imatinib is now standard of care for patients with PDGFRA and PDGFRB fusions, and off label use of other inhibitors has shown clinically significant responses in many cases with FGFR1, JAK2 and FLT3 fusions. Recently we have identified activating STAT5B mutations in a subset of patients with myeloid neoplasia and eosinophilia, further strengthening the association between deregulated signalling and a myeloproliferative phenotype, as well as providing a potential new target for therapy in CML-like disorders.

Nick Cross
Professor of Human Genetics, University of Southampton, UK
Director, Wessex Regional Genetics Laboratory, Salisbury, UK

The keynote presentation will soon be available on the iCMLf website.

2018 Goldman Prize

Professor Jorge Cortes (Houston, USA)

The annual iCMLf Goldman Prize complements the Rowley Prize as a clinical equivalent acknowledging outstanding lifetime contributions to the management of patients of CML. Jorge Cortes, Professor of Medicine and Deputy Chair at the Department of Leukemia at the MD Anderson Cancer Center, has been awarded the 2018 Goldman Prize. The award celebrates his globally recognised expertise and life-long commitment to the management of patients with CML.

20 YEARS OF CML RESEARCH: A FEW THINGS I HAVE LEARNED (AND MANY I HAVE NOT)

Many of us have been witnesses of an unprecedented change in the management, and with that the outcome, of patients with CML. When I started my career in Mexico, we were treating patients with busulfan (yes, that is how old I am!), in part because of the lack of resources but also because treatments were otherwise not widely effective (eg, interferon which induced cytogenetic responses, but at a generally low rate) or not applicable to most patients (e.g., stem cell transplant). The transformation we have witnessed with the use of tyrosine kinase inhibitors (TKIs) has been a model in cancer therapy. The life expectancy of patients diagnosed with CML today is nearly the same as that of the general population. I have learned many things during my very fortunate time conducting clinical research in CML, I have many questions that I have not been able to answer, perhaps more than I did 20 years ago. This is perhaps a reflection of the greater knowledge that we have generated that opens the door to areas we never imagined. I know all TKIs are generally effective and safe, but I still do not know if there are real differences in choosing one versus the other on a given patient. Second generation TKIs give us more, faster, and deeper responses, but most patients treated with imatinib can have an excellent outcome, particularly if we are alert to identifying patients who may be falling behind on their response. I also do not know what the right dose is for each TKI. It appears that we have gotten the dose wrong on all TKIs as we initially developed them. For second generation TKIs, the initial dose approved for salvage therapy, seems to be unnecessarily high, at least for the frontline setting. But for imatinib, the standard dose appears to be less than optimal to produce the best possible response. Although controversial for many years, in my opinion studies using higher initial doses of imatinib (such as TIDEL II and the MDACC studies) have resulted in similar rates of early and deep molecular responses as studies with second generation TKIs.

In regards to the molecular response endpoints, it is still unclear to me what the optimal endpoint should be for clinical trials and, more important, for patient management. We know that deeper and earlier responses are associated with a better long-term outcome. Yet, most patients treated with TKI have a good long-term outcome. In addition, despite our recognition in multiple analyses that patients with BCR-ABL/ABL >10% have a worse outcome, we have failed to show that intervention at that time changes outcome. Some studies have attempted a change or intensification of therapy, but the measured endpoints are only changes in transcript levels after a few months, typically not more than 12 months. This is clearly insufficient to convince me that we have truly changed the long-term outcome of patients, particularly their overall survival, progression free survival, or their ability to undergo successful treatment discontinuation. Unfortunately our patience for measuring long-term outcomes in clinical trials has run out. Most trials are designed for 2-5 years of follow up, clearly insufficient follow-up for assessing the type of outcomes we are most interested in assessing now.

One curious development that is emerging, is the suggestion that deeper molecular responses may actually be associated with improved survival, but as expected, this cannot be measured in 2-5 years. This requires much longer follow-up but despite my conviction to the contrary in earlier years, I am becoming increasingly convinced that an improved survival is

"Jorge has led many of the most important CML trials over the past decade and is now regarded as the pre-eminent world expert in CML management. He has also tirelessly disseminated his unique expertise to colleagues at his own centre and around the world."

Timothy Hughes, Chairman of the iCMLf

possible, even likely. And of course these responses have the potential benefit of considering treatment discontinuation, something that has become of increasing value to patients and to most investigators.

The safety of these agents also needs to be reassessed, or rather further studied. I still believe TKIs are a model of favorable balance of risk and benefit in cancer therapy. But they are not perfect. It took us long to recognize the potential of some events such as arterio-occlusive events. Only when it became obvious with ponatinib that these events were more than just things that happen to patients in the age group we were treating, did we recognize that this is a class effect, perhaps with a gradient of risk intensity, but certainly affecting more than just ponatinib. The analysis of the risk of these events has been unacceptably inadequate.

The reports from different series are incomplete and heterogeneous in what events are investigated, how they are assessed and other elements that sometimes give erroneous impressions of the risk or safety of a given drug. There has also been precious little interest in the assessment of the reason for the increased risk of these events with TKIs. Other adverse events have gained little attention, such as the risk of renal dysfunction and the possible neurologic effects of some of these drugs. We have been too consumed with the minimal changes in transcript levels to focus on the integral management of our patients.

We need to pay attention to every aspect of patient's health, in research and in practice.

Many other aspects of the management (and the biology) of CML have still many mysteries to me. The proper management of CML during pregnancy, better treatments for blast phase CML, understanding the mechanisms of resistance beyond mutations, understanding the whole spectrum and significance of molecular heterogeneity of the disease, and the incorporation of patient reported outcomes in our standard assessment are among the many things I still do not know about CML after 20 years of research. I see this as a result of our progress. Before we had the great treatments and assessment tools we have today, these questions were of lesser significance or even irrelevant. Therefore, I am thankful for my ignorance and hope that we as a scientific community do not lose our interest in continue addressing these questions and coming up with new ones.

Professor Jorge Cortes

Professor of Medicine and Deputy Chair at the Department of Leukemia at the MD Anderson Cancer Center

Houston, USA

The keynote presentation from Professor Cortes will soon be available on the iCMLf website

2018 iCMLf Prize

Professor Hemant Malhotra (Jaipur, India)

The iCMLf Prize is awarded for outstanding contributions to the improvement of CML treatment under the challenging conditions of emerging economic countries with unequal access to monitoring and treatment. The iCMLf has selected Hemant Malhotra, Senior Professor at the SMS Medical College Hospital and Head of the Division of Medical Oncology at the RK Birla Cancer Centre in Jaipur as the 2018 iCMLf Prize winner. Dr Malhotra receives the prize in recognition of his tireless efforts and remarkable achievements to advance the treatment of CML patients in India and neighbouring countries.

CHRONIC MYELOID LEUKEMIA IN EMERGING REGIONS: SOME PERSPECTIVES AND PROBLEMS

Various hematological cancers in developing countries, CML included, have significant differences in incidence, age of onset, stage at presentation, phenotype and stage-for-stage response rates and prognosis as compared to their western counterparts. Several reasons have been postulated for this and include socio-economic status, genetic differences, environmental factors (infections, particularly, viral infections, exposure to pesticides e.g.) and nutritional factors.

CML is the most common adult leukemia in India. Figures from various Indian cancer registries show a CML incidence of 0.8 to 2.2 per 100,000 population for men and 0.6 to 1.6 per 100,000 population for women. The disease is seen in a younger population, the median age at onset being between 30 to 40 years. Complete hematological responses to imatinib are seen in more than 90% of patients but complete cytogenetic and molecular responses are documented in less than 60% of patients after one year of treatment.

Approximately 70-80% of patients of CML in India are on the GIPAP (Glivec International Assistance Program) despite the fact that several low-cost Indian generic versions of imatinib are freely available in the Indian market. Most patients who did not qualify for the GIPAP program are on Indian generic imatinib as are patients diagnosed after the program has stopped enrolling new patients. Questions regarding quality of the generic imatinib have been addressed in several Indian studies, we have also looked at the trough imatinib blood levels post Glivec versus generic imatinib, and there is no significant difference in response rates, hematological, cytogenetic and molecular as well as blood level between the two.

Second generation TKIs are approved and available for first as well as second line use in India but are accessible to a much smaller number of eligible patients because of economic reasons. As suboptimal responders do not have the option of 2nd generation TKI (due to economic reasons) several innovative approaches have been tried. We have had good responses to the addition of pioglitazone to imatinib with a significant number of patients achieving a major molecular response with the combination. We also have some data on the synergistic effect of the combination of imatinib with curcumin, a traditional Indian herb used in ayeurvedic medicine for centuries, both in cell line in-vitro model as well as a small clinical study.

In the past few years, there have been several studies suggesting that earlier and deeper molecular responses to TKIs predict for better progression-free and over-all survival (PFS and OS) and the importance of getting an accuracy RQ-PCR for bcr/abl has become even more curtail for treatment decisions. Cytogenetic and molecular testing is not freely available, other that at large cancer centres and big private labs in the metros, and there is lack of standardization of the methodology. High quality RQ-PCR testing has several quality control issues one of which is transportation of the specimen without the loss of RNA. Extraction of RNA from dried blood spots (DBT) on filter paper and then testing for bcr/abl gene expression is a low cost option, which we are exploring at our centre.

In India, where most patients are not candidate for up front more expensive 2nd generation TKIs, the early assessment of molecular response, at three months and/or six months, may be even more important.

"The award recognises Hemant's remarkable achievements in CML management in a challenging environment and his work to improve outcomes for CML patients."

Professor Tim Hughes, Chairman of the iCMLf

One approach could be to administer 1st line imatinib to all patients of CML-CP and only those who have a suboptimal response at 3 and/or 6 months may then be considered for a change to the 2nd line agents.

In resource limited countries like India with a population of more than 1.2 billion, where 85% of expenditure on health happens from non-insured, out-of-pocket spending, it is important to keep economic in the forefront of all research initiatives. Priorities pertaining to CML treatment and research in India include availability of free/subsidized, standardized and reliable testing for bcr/abl at all premier state medical college institutions and cancer centres at diagnosis and for monitoring during therapy for all patients, kinase domain mutational testing at few referral centres and regional cancer centres and GIPAP-like support program for second line drugs (dasatinib and nilotinib). Can bcr/abl testing be done on RNA obtained from a dried blood spot on a piece of filter paper? This would eliminate to a large extent the issued of transporting samples from patient bedside to reference testing laboratory. Clinical trials involving stopping of imatinib after prolonged complete molecular remission in the Indian setting would also be important and relevant. The lower response rates to imatinib seen in India, in addition to other factors, could also be due to sub-optimal absorption of the drug with lower serum levels because of India-specific dietary and/or genetic factors. This needs to be studied. Interventions to improve molecular response rates like drug combinations of imatinib with interferon, use of new leukemia stem-cell targeting agents like the mTOR inhibitors, hedge-hog pathway inhibitors and JAK2 inhibitors need to be studied in the laboratory and in the clinic.

Pioglitazone, a PARP- agonist, in combination with a bcr/abl TKI may be a cost effective way to eliminate residual stem cells and convert a suboptimal response into a deep molecular response. Can one of the traditional Indian medicinal plants/herbs in combination with a TKI have an additive effect on CML control? There is some preliminary evidence of synergy with curcumin and imatinib. These are the trials which need to be done in India.

There is also a need to get together a group of clinicians, haematologists and oncologists interested in CML who could address India-specific problems, suggest and implement solutions, and direct India-specific research in the field.

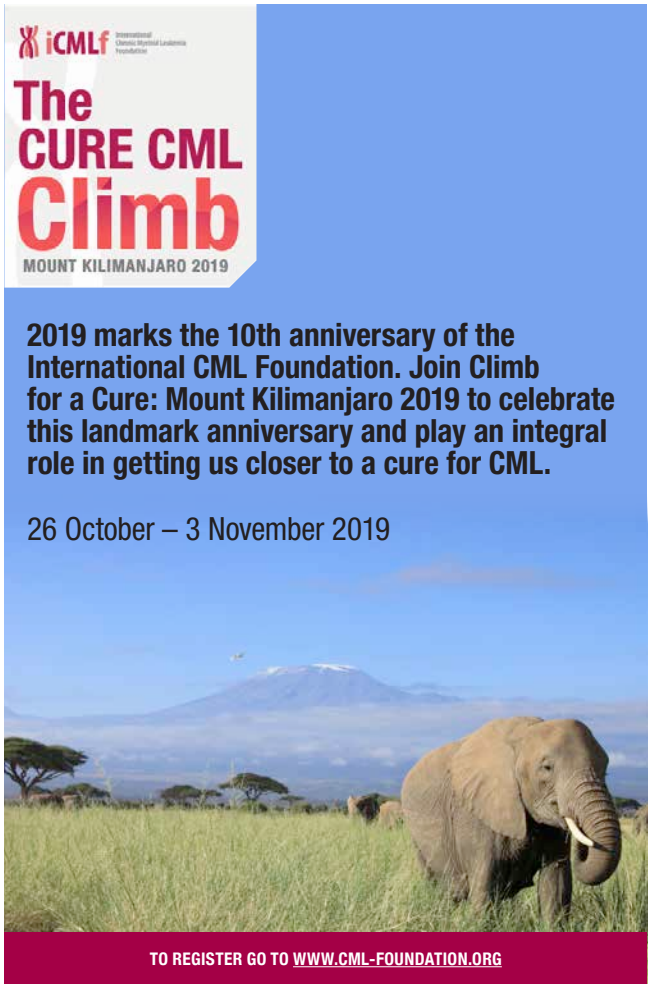
Professor Hemant Malhotra

Senior Professor of Medicine & Head, Division of Medical Oncology

RK Birla Cancer Center, SMS Medical College Hospital, Jaipur, India

The keynote presentation will soon be available on the iCMLf website.

Join us in 2019



21th Annual John Goldman Conference on
CHRONIC MYELOID LEUKEMIA: BIOLOGY AND THERAPY

Chairs: J. Cortes, T. P. Hughes, D. S. Krause
Organizers: R. Bhatia, M. Copland, M. Deininger, P. Hari, D. Perrotti, J. Radich, D. Réa

BORDEAUX, FRANCE | SEPTEMBER 12-15, 2019

Program will include:

- John Goldman Prize
- Janet Rowley Prize
- iCMLf Prize
- Keynote lectures
- Special lectures and oral presentations selected from submitted abstracts
- Workshops for non-clinical scientists
- Clinical and biology manned poster walks
- 2018 Symposium on Ph+/PH- like ALL
- Concurrent 'Meet the Expert' sessions