# Newsletter

iCMLf International Chronic Myeloid Leukemia Foundation

## May 2013

### *Dear Colleagues,*

The aim of the iCMLf is to optimise CML outcomes globally. While there is still a long way to go to fully achieve this we have begun to make significant inroads at the centres where we work. With a proactive approach, long term investment in development and education and by utilising expert partnerships the iCMLf is definitely part of the solution to improving CML management around the world.

*Speakers at the iCMLf Forum*

As part of the solution, the iCMLf is very focused on tangible projects. Our long running Preceptor-ship Program continues to host visitors from emerging economic regions, providing intensive one on one CML education and developing partnerships with CML centres of excellence. The iCMLf grants to increase access to CML diagnostics in low and middle-income countries have resulted in over 1780 tests to diagnose and monitor CML. As a direct result of this program patients have been able to access the therapy they could not before and learned the status of their disease where previously they were unaware. By building capacity, providing training, along with other immeasurable improvements in CML management capabilities, this program has had a significant impact for the centres involved. We are delighted to extend and expand this funding through further iCMLf Diagnosis and Testing grants this year.

Being part of the solution means taking part in the conversation and we hope to see you at the two international CML meetings supported by the iCMLf this year. The International CML Congress: Biology and Therapy (in partnership with ESH) and the iCMLf Forum for Physicians from Emerging Regions (in partnership with MAX) in December during ASH. Along with these face-to-face meetings the iCMLf continues to expand our online educational platform.

> "The iCMLf opening and encouraging CML centres of excellence in the countries should be a nucleus from which advanced science spreads."
>
> *Dr Hemant Malhotra, Jaipur, India*

20 presentations on best practice CML management are now available as part of the iCMLf Virtual Education Program. Our online Clinical Case Discussion Forum is an ideal place to post challenging cases for a second opinion from the iCMLf expert moderators, or just to share with colleagues.

*Dr Baccarani and Dr Schiffer commenting at the iCMLf Forum for Physicians from Emerging Regions*

Part of finding a solution to a problem is being able to identify the issues and conduct an open dialogue. Sometime these are the issues that trouble us most and in that regard the hardest to discuss. Cost of and access to medication is one of these issues. As part of this newsletter we look forward and think on these complex issues and how the iCMLf along with our colleagues and partners can begin to address these.

Curing CML would be the ultimate goal of the iCMLf. We recognise that this will take a multifaceted, multi-partnered approach and take the first step this year forming the iCMLf Consortium Understanding Residual diseasE (CURE) Program. We look forward to sharing more on this project over the years to come and in the meantime welcome any comments you have. Many groups are already working to understand minimal residual disease and in this newsletter the team from the Holyoake Laboratory in Glasgow, UK give an overview of their work investigating CML stem cells.

*Dr Benneh and her team in Ghana celebrating the arrival of the GeneXpert system for onsite PCR analysis*

So... join us as an iCMLf member, support the Foundation with a donation, or visit us at one of the international CML meetings. Get involved in whatever capacity and help the iCMLf continue to be part of the CML solution.

*Nicola Evans, John Goldman Tim Hughes, Jan Geissler, Melissa Davis-Bishop*

**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.

**Registered Address:**

International CML Foundation
33 Northumberland Place
London W2 5AS - UK

E-Mail: info@cml-foundation.org
Web: www.cml-foundation.org



**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.**

## Valuable education at CML centres of excellence

There's nothing more impactful than hearing direct feedback so below are just some of the statements from physicians taking part in the 2012 Emerging Regions Support and Partnership Preceptorship Program.

"My mentor Dr David Snyder is one of the best teachers I had the honor of working with in my time as a medical practitioner. He was very generous in sharing his patient experience and expertise especially on CML. He help me maximize my learning experience by not only including me in his patient consult, conferences but he spent time in discussing updates on CML, clinical dilemmas and any query that I have."

*Dr Alma Reyes-Calavera (Philippines)*

"On the whole the preceptorship was an enriching experience and will help me manage patients better. My understanding of the approach to diagnosis, choosing the right treatment, interpretation of lab results and managing side effects has transformed me into a better physician not only in managing CML but also the other aspects of hematology practice. I will share the knowledge I have gained with my colleagues at the hospital and also at various meetings. Most importantly, this visit has improved my understanding of the laboratory issues and this will help me interpret reports and interact with laboratory staff better. "

*Dr Rajappa (India)*

"This is a very useful learning to improve diagnosis and treatment in countries such as Kyrgyzstan. Of course, many of the technologies are not yet available for Kyrgyzstan, but direct communication with doctors, patients discuss with physicians patients is enormous clinical experience for each doctor."

*Dr Baizikova (Kyrgyzstan)*

"I was very interested in to know about the Stem cell transplantation (SCT), because here in Guatemala we do not have the program, and I think in countries like Guatemala SCT can be a great opportunity for our patients, specially because we do not have other marvelous but expensive drugs. I had an amazing time with the faculty in SCT department too, and had the opportunity to learn in which patients with CML the transplant is indicated and to know about the process and complications."

*Dr Chalapud (Guatemala)*

"In the short term CML patients will benefit from my improved morphology skills. This is the only diagnostic and monitoring modality we have available to us currently apart from routine full blood counts. In the long term, from what I learned during the preceptorship, it should be possible for us to work on introducing conventional cytogenetics."

*Dr Molombe (Malawi)*

*Dr Musteata from Moldova with Dr Cortes and colleagues from the MD Anderson*

## Thank you to all those who support us!

We thank our corporate partners for their ongoing generous contributions

**Premium Supporters:**

Novartis Oncology – The ERSAP Diagnosis and Testing Program
Bristol-Myers Squibb – Overall support for the iCMLf activities

**Major Supporters:**

Pfizer – The ERSAP Preceptorship Program

**Other Supporters:**

Ariad – Publication of the iCMLf Newsletters and Annual Report
MolecularMD –The ERSAP Preceptorship Program
Novartis Pharmaceuticals – The Virtual Education Program and iCMLf Forum
Cephied – Support and use of the GeneXpert System and Xpert BCR-ABL cartridges

**All of our projects, and the impact they have on treatment outcomes for CML patients, would not be possible with out the support of our sponsors, members and Friends of the Foundation.**
**From all of us that work at the iCMLf and the physicians and patients we help – Thank you.**

# Interactive, relevant and practical CML education

The online iCMLf educational platform is a critical part of the iCMLf's program to improve CML education. Our goal is to continue to improve the practical knowledge of CML treatment, strengthen networks within the CML community and build potential for future collaborations, both clinical and scientific to improve global outcomes for CML patients. At present there are two major projects within the iCMLf's online educational platform, the iCMLf Virtual Education Program and the iCMLf Clinical Case Discussion Forum.

## Best practice presentations from CML experts

Pregnancy in CML, safely stopping therapy and new drugs in CML treatment are just three of the current topics on the iCMLf Virtual Education Program (VEP). Developed in partnership with MAX and supported by unrestricted grants from Novartis the VEP is now in its 4th year. This program was designed to address a lack of easily accessible information on best practice CML management. This is especially relevant for clinicians in emerging economic regions with limited resources and potentially limited access to education at international hematology meetings.

Up to date, best practice CML management presentations from leading CML experts are available in English, French and Spanish. Many of these presentations consider the specific challenges that occur in the emerging economic regions. All modules are available on the iCMLf website, and USB flash drives are provided for physicians who may not have the capability for online viewing.

The iCMLf VEP has been well received. 3,000 USB drives have been distributed to physicians in more than 50 countries. With over 13,000 web streams delivered to date, the awareness and reach of the program increases exponentially each year spreading knowledge, sharing experience and globally enhancing CML management.


*Michele Baccarani*


*Jorge Cortes*


*Jane Apperley*


*Delphine Réa*


*François Mahon*


*Susan Branford*


*Jerry Radich*

## Discuss and share your challenging CML cases

The iCMLf website houses a discussion forum where clinicians can request advice, seek a second opinion, or simply share the interesting and challenging cases they come across. In this way we can spread knowledge and expertise through the CML community. So far topics have included pregnancy and pediatric CML cases, along with responses to and the side effects of, therapy.

The iCMLf Directors and advisory board members moderate the 'iCMLf Clinical Case Discussion Forum'. This year's moderators are:

- ★ Michele Baccarani (Italy)
- ★ Giuseppe Saglio (Italy)
- ★ Michael Mauro (USA)
- ★ Raghunadharao Digumarti (India)
- ★ Jorge Cortes (USA)
- ★ Charles Schiffer (USA)
- ★ Jeff Lipton (Canada)
- ★ John Goldman (UK)
- ★ Devendra Hiwase (Australia)
- ★ Giovanni Martinelli (Italy)
- ★ Tim Hughes (Australia)

If you have a case to ask the moderator about, or would just like to share an intriguing case you have treated, please submit it to the Forum.

1. Visit the Case discussion forum at www.cml-foundation.org/index.php/forumm/7-difficult-cases-in-cml
2. Submit your case by clicking on **+New Topic**.
3. Include a brief history of the patient along with the problem faced. Please add your name and hospital
4. The moderator will review your case and provide their opinion/comment in the Forum. You will be notified when this has occurred
5. Further comments, questions and discussion are then invited

As a full clinical history maybe necessary for accurate comment, cases are only accepted from clinicians. Interested individuals are welcome to view and make comments on the Forum provided their qualifications are included with any comment.

If you would like to receive notifications about the cases posted. Go to the iCMLf website and register. Registration is found on the bottom left corner of the home page.

The iCMLf Case Discussion Forum is a valuable resource to discuss and share your challenging CML cases.

To effectively engage physicians and those managing CML the iCMLf needs to provide ongoing and responsive means of interactive communication. In 2013 we plan to enhance the iCMLf educational platform to provide more interactive, up to date and practical information on best practice management of CML. By providing this effective interface we can augment physician networking through online discussion and education. In this way we will develop a truly global CML community.

# Overcoming challenges treating CML when resources are limited

## iCMLf Forum - Focused on solutions with practical expert discussion


*Nicola Evans Chief Executive of the iCMLf opens the Forum*

The annual 'iCMLf Forum for Physicians from emerging regions' is an ideal opportunity for physicians to meet and discus the challenges and opportunities treating CML when resources are limited. Held during the American Society of Hematology meeting (ASH), the Forum is a partnership project between the iCMLf and the Max Foundation (MAX) bring together a blend of CML expertise from around the globe.

In 2012 we wanted the iCMLf Forum delegates to leave the meeting with a tangible outcome. Therefore rather than just discussing the challenges faced, the forum focused on specific solutions that have been implemented to address these challenges. The specific goal was to share and discuss successful projects with the idea these could be adapted by other centres in similar situations and hopefully with similarly positive outcomes.

Over 100 forum attendees heard projects presented from India, Paraguay and Sri Lanka. After each presentation there was lengthy discussion with the iCMLf experts, questions asked and much learning, all specifically related to the practicality of treating CML with limitations in diagnostics, treatment and patient follow up. The full presentations and discussions are available on the iCMLf website for widespread viewing.

Focusing the iCMLf Forum on a solution-based discussion has been well received. The feedback from attendees has been exceedingly positive and we will repeat this same format in 2013.

*A full house at the 2012 iCMLf Forum*

## The iCMLf shares best practice abstracts from emerging economic regions

*Dr Wattegama receiving an iCMLf award for "Overcoming challenges treating CML"*

Three of the priority projects of the iCMLf are based in the emerging economic regions. Treating CML in situations or locations with limited resources can be challenging. Access to treatment, accurate diagnostics and to up to date knowledge is difficult to obtain at reasonable costs. Faced with these problems physicians, laboratory staff and others involved with patient care work tirelessly, to overcome these obstacles ensuring their patients get the best possible care.

In July 2012, to recognise and share the work and initiative of physicians faced with these challenges, the iCMLf invited the submission of abstracts outlining solutions implements to overcome challenges treating CML with limited resource. We were delighted to receive 26 abstracts outlining projects that enhanced patient care. Abstracts were submitted from 16 countries so were wide ranging in topic. They covered everything from facilitating access to therapy, forming a CML clinic, to creating an iPhone application to track CML treatment.

The iCMLf Advisory committee reviewed the abstracts and the three highest rated abstracts were presented at the 'iCMLf Forum for Physicians from Emerging economic Regions', in December 2012.

The overview of these presentations can be seen in the box overleaf and the full presentations can be viewed on the iCMLf website www.cml-foundation.org/index.php/meetings/196-icmlf-forum-streams.

We sincerely thank all the people who submitted their abstracts. We understand that the significant amount of effort and work it takes to write and compile this information. However, as we work towards improving the management of CML globally it is important to share these successful projects and ideas amongst the CML community, especially with colleagues encountering similar conditions.

All the abstracts can be viewed in full on the iCMLf website www.cml-foundation.org/index.php/abstracts. Have a look and see if any of the projects could be adapted for your centre. The iCMLf and the abstract authors welcome any further comments, or questions.

In June the iCMLf will invite submissions of projects to be presented and discussed at the 2013 Forum to be held in New Orleans during ASH.

*Pat Garcia Gonzalez from MAX, John Goldman, Tim Hughes and Nicola Evans of the iCMLf with Dr Kishore, Dr Ayala, and Dr Wattegama, the presenters at the 2012 iCMLf Forum*

## Award winning abstracts

### 1) Essential actions to improve CML management

*Dr Wattegama, Lakeside Adventist Hospital, Kandy, Sri Lanka*

**Aim of the project**

To explore minimum essential actions by a regional cancer centre in a country with limited resources to improve care, quality of life and possibly survival, of CML patients.

*"Clinic attendance increased threefold in one year and double the number of patients were able to access imatinib"*

**Key actions:**

- Raise finances through partnership with a charity. Introduce 'Foster Parents' to assist with accommodation, testing and incidental expenses
- Outsourcing the laboratory service led to fast and reliable results and more patients on treatment
- Streamline the CML clinic using CML counselling services and trained CML educators on clinic days

*"Sustainability of the project relies on financial stability, credibility and commitment"*

### 2) Implementation of molecular studies

*Dr Ayala, Health Research Institute National University of Asuncion, Paraguay*

**Aim of the project**

To implement molecular biology techniques to allow the diagnosis and follow up of myeloid chronic leukemia patients through the standardization of the BCR-ABL1 detection and measurement of the transcript levels in Paraguayan patients.

*"Even when you think there are no resources they are there. You just need to find them"*

**Key actions:**

- Financial - Begin as a research project with research grants, build on this with grants and scholarships from government, universities and pharma
- Human resources - Engage young motivated researchers who have defined time periods to complete research projects
- Partnerships – Internal, other departments may have resources to borrow. External for training
- Patient recruitment – Develop a referral system from other local centres

*"Radical change in treatment now that PCR is available. We can better manage changing from one TKI to another, leading to improved patient care" Dr Nizza, Paraguay*

### 3) Standardising care of CML

*Dr Kishore, Institute of Hematology and Transfusion Medicine, Kolkata, India*

**Aim of the project**

Develop a dedicated team consisting of both clinical and laboratory experts. Establish zero delay follow up OPD, with self-sufficient laboratory backup in a no loss-no gain principle. Ensure a tight compliance and follow up. Spread the truth about CML care in the imatinib era in peripheral health centers.

*"Someone is ready to help, find them"*

**Key actions:**

- By joining with other institutes cost of PCR reduced from $250 to $15 and 80% of patients could afford this
- MoU with National Institute of Hematology to provide free mutational analysis
- Decrease loss of patients to follow up by providing 'same day' service and implementing an efficient patient tracking service
- Utilise social workers to support patients and carers in conjunction with the clinical and laboratory practice

An honorary award was given to Dr Deepak Bansal and colleagues from Post Graduate Institute of Medical Education & Research, Chandigarh, India for their project Improving outcomes for pediatric patients with CML.

# *Investigating CML Stem Cells – Experiences from the Holyoake Laboratory, Glasgow, UK*

Chronic myeloid leukaemia is a haematological disorder defined by the presence of an abnormal chromosomal translocation, the Philadelphia chromosome that produces an abnormal fusion protein, Bcr-Abl. It is a clonal disorder characterised by an increased proliferative activity of the leukaemic progenitors that produce an elevated number of mature granulocytes. Cell cycle-active agents, even in very high doses, are alone unable to eradicate the leukaemic clone, suggesting the presence of a rare, drug refractory subset of leukaemic cells. The introduction of imatinib (IM), a tyrosine kinase inhibitor (TKI), represents the most successful example of targeted therapy in human cancer. However, this success has been tempered by problems of disease persistence, which we and others have shown arises from a population of quiescent leukaemic stem cells that survive despite complete inhibition of Bcr-Abl upon TKI treatment. The Holyoake laboratory has been influential in studying mechanisms of disease persistence and in developing novel approaches to combine TKI treatment with agents to effect eradication of this population of persistent, leukaemic stem cells.

## The Holyoake laboratory aims:

- To understand CML stem cell quiescence
- To understand the activity of TKI within CML stem and progenitor cells
- To target therapy to the stem cell compartment
- To extinguish the clone early and remove the population in which resistance develops

In 1999, Tessa Holyoake, whilst working with Connie Eaves, identified and isolated a rare population of quiescent, highly primitive, leukaemic stem cells from patients with CML. These represented less than 2% of the stem and progenitor cell population and were present in all patients and expressed Bcr-Abl and the Philadelphia chromosome. These quiescent leukaemic stem cells were able to spontaneously exit this quiescent state and enter a continuously cycling state in vitro in the absence of growth factors and their quiescence was reversible as immunodeficient mice transplanted with these cells showed engraftment with primitive stem cells and their leukaemic progeny.

Following this, Dr Holyoake showed that few of these quiescent leukaemic stem cells expressed either interleukin-3 (IL-3) or granulocyte colony stimulating factor (G-CSF) transcripts, whereas both were present in most cycling leukaemic stem cells. However, in association with the entry of quiescent leukaemic stem cells into the cell cycle, IL-3 transcripts became detectable, suggesting that such autocrine cytokine production may drive cell cycle entry. This highlighted the potential physiologic relevance of quiescent CML progenitors, even in treated patients, in whom these cells would be predicted to have a proliferative advantage over their quiescent normal counterparts when cytokine concentrations are low.

We and others have since demonstrated that CML stem cells are not oncogene addicted for survival. In a transgenic mouse model, donor-derived CML stem cells, in which Bcr-Abl expression had been induced and subsequently shut off, were able to persist *in vivo* and re-initiate leukaemia in secondary recipients upon Bcr-Abl re-expression. *In vitro, TKI* treatment of human CML stem cells achieved complete inhibition of Bcr-Abl and downstream targets p-CrkL and p-STAT5, inhibition of proliferation and colony forming cells, and reduction of viable input cells to 10%, however the surviving fraction was enriched for primitive leukaemic cells capable of growth in long-term culture initiating cell (LTC-IC) assay and expansion upon removal of dasatinib and addition of growth factors. Together these data suggest that CML stem cell survival is Bcr-Abl kinase independent and that curative approaches in CML must focus on kinase independent mechanisms of resistance.

More recently we have shown that IM induces autophagy in CML blast crisis cell lines, CML primary cells, and TKI resistant $p210^{BCR/ABL}$-expressing myeloid precursor cells. IM-induced autophagy looks to be mechanistically different from IM-induced apoptosis. We further demonstrated that suppression of autophagy, using either pharmacological inhibitors or RNA interference of essential autophagy genes, enhanced cell death induced by IM in cell lines and primary CML cells. Critically, the combination of a TKI with inhibitors of autophagy resulted in near complete elimination of phenotypically and functionally defined CML stem cells.

Resistance to TKI treatment can be Bcr-Abl dependent or independent. The Holyoake laboratory has made advances in studying both these mechanisms. We demonstrated that ponatinib – a third generation TKI that inhibits almost all Bcr-Abl mutants and is being tested in the clinic for patients who are resistant to other TKIs - was effective in inhibiting proliferation and inducing apoptosis in chronic phase (CP) CML stem cells and in CP cells carrying the T315I mutation. Ponatinib, like 1st and 2nd generation TKIs, induced autophagy in CP stem and T315I expressing cells. Hydroxychloroquine (HCQ) mediated autophagy inhibition enhanced the effect of ponatinib in CML stem/progenitor cells with no significant effect on normal CD34+ cells and resulted in near complete elimination of CML stem cells with less that 1% surviving treatment in LTC-IC assay. Together, these findings suggest that autophagy inhibitors may enhance the therapeutic effects of TKIs in the treatment of CML.

The PI3K/Akt/mTOR pathway, downstream of Bcr-Abl, may provide an alternative drug target for CML patients with Bcr-Abl independent TKI-resistance. Treatment with a dual PI3K/mTOR inhibitor resulted in dose-dependent induction of apoptosis in CP CML CD34+ cells and in a ponatinib-resistant KCL22 cell line generated in the laboratory. We have also shown that inhibition of mTOR leads to induction of autophagy. Furthermore, autophagy inhibition, by Atg7 knockdown or HCQ treatment, augmented death induced by PI3K/mTOR inhibitors in CML cells, including ponatinib-resistant KCL22 cells. Taken together these data indicate that autophagy inhibition might not only potentiate

treatment for CML patients responsive to TKI treatment by enhancing elimination of CML stem cells, but may represent an improved treatment option for both Bcr-Abl dependent and independent mechanisms of TKI-resistance in CML patients.

Bcr-Abl signalling activates the PI3K/Akt pathway (amongst others), leading to inhibition of the transcriptional activity of the FOXO family proteins. TKI induce little apoptosis in CML stem/progenitor cells. However, rather than being inert, TKIs exert potent anti-proliferative effects in stem/progenitor cells through a poorly understood mechanism. FOXO transcription factors are known to transcriptionally modulate proteins that induce cell cycle arrest and apoptosis. Therefore, Bcr-Abl-mediated inhibition of FOXO transcription factors may contribute to CML cell proliferation and malignant transformation. We have demonstrated that TKI-induced G1 arrest in CML stem/progenitor cells is mediated by re-activation of FOXO transcription factors, whilst quiescence of CML stem cells is, at least in part, regulated by sustained FOXO activity. These data contribute to our understanding of CML stem cell quiescence and TKI activity, suggesting new strategies to target CML stem/progenitor cells by preventing or reversing this effect.

The Holyoake laboratory is largely divided into two teams

### 1) Systems biology/discovery team - identify and follow up on novel targets of potential therapeutic importance.

When we compared CML with normal stem cells across multiple screens for gene expression, microRNA levels and proteomics, aiming to find differences between the two and to identify early and late factors/pathways that mediate survival of CML stem cells when exposed to TKI, we found that:

- The cell cycle is deregulated in leukaemic stem cells. We are currently investigating the role of the protein E2F1 in the function of normal and leukaemic stem cells. Screening also revealed deregulation of two important proteins - c-myc and p53 - that are well known to be involved in oncogenesis.
- Transcriptional analysis identified that a group of chemokines (CXCLs) is highly up-regulated in quiescent compared to proliferating stem cells. To investigate the role of these proteins in stem cell properties, we have modulated the expression of a chemokine ligand (CXCL1) and used an inhibitor against the CXCR2 receptor to examine effects on human stem cells. We have identified both CXCL chemokines and their receptors as a group of key genes involved in normal stem cell survival.
- CML stem cells were shown to express low levels of HLA Class 2 and we are currently investigating if this enables them to evade immune control in patients. We are investigating this downregulation, its mechanism and its meaning and whether modulation of HLA Class 2 expression can sensitise CML stem cells to killing by the immune system.
- We found the rho kinase pathway to be upregulated in CML versus normal stem cells and demonstrated that this did not normalise with TKI treatment. The rho kinase (ROCK) pathway is a central regulator of the actomyosin cytoskeleton and is critical for the maintenance of cellular structure and effective cell division. This suggests a potential role for this pathway in treating resistant and persistent disease and we are investigating whether targeting this pathway alone, or in combination with current treatment, will cause additional kill of CML cells. This will help us to identify new potentially curative treatment options for CML patients on long-term TKI treatment and may identify new pathways that can be targeted in patients with resistant disease.

### 2) Autophagy team

The autophagy team works to investigate the effects of inhibition of autophagy, alone and in combination with TKI and other inhibitors of survival pathways in the treatment of Bcr-Abl dependent and independent resistant CML. The overall aim of our project is to identify the best autophagy drug target in CML cells and to test newly developed autophagy inhibitors in order to determine the optimal treatment for CML cell eradication. In terms of Bcr-Abl dependent resistant disease, we have been testing autophagy inhibitors in combination with TKI to see if this helps eliminate resistant disease. Treatment of ponatinib resistant cells with mTOR inhibitors inhibits their survival providing hope for another treatment for Bcr-Abl independent resistant disease.

## Clinical Trials

Our work has led to several clinical trials and we are currently responsible for the CHOICES trial. This randomised phase II trial is comparing the safety and efficacy of giving IM with or without HCQ in treating patients with CML with major cytogenetic response (McyR) to IM who remain PCR positive for Bcr-Abl transcripts. CML CP patients who are in MCyR after >1 year of IM treatment and tolerating IM well are randomised between IM alone and IM and HCQ 800mg/day. All trial samples are analysed to investigate the effect of adding an autophagy inhibitor on their stem cell population. This trial is currently recruiting in the UK, France and Germany.

In the fifteen years since Tessa Holyoake and colleagues first isolated CML stem cells major strides have been taken within our group to understand this population in an attempt to eradicate it and find a cure for CML and alternative treatments for patients with resistant disease. We currently have many exciting projects ongoing to investigate the survival of leukaemic stem cells and we are hopeful that we can keep up this pace of scientific endeavour to one day achieve this goal!

*The Holyoake laboratory team*

# The ERSAP Diagnosis and Testing Program - working towards equal access to CML diagnostics around the world

**1785 tests and counting...**

*Dr Benneh training colleagues on the newly arrived GeneXpert System*

The ERSAP Diagnosis and Testing Program assists clinicians in emerging regions use objective testing to confirm CML diagnosis via FISH, cytogenetics, or PCR to detect the BCR-ABL1 gene, or transcripts. Solutions differ according to the local situation, however the long-term goal for this program is to allow centres to become self-sufficient in monitoring their own CML patients and potentially patients from other local centres.

> The component of CML diagnostics can be greatly improved in the developing countries, through the support from iCMLf. Teams from rest of the country can be trained at a nodal centre like our department, so as to benefit more number of CML patients.
>
> *Dr Varma, India*

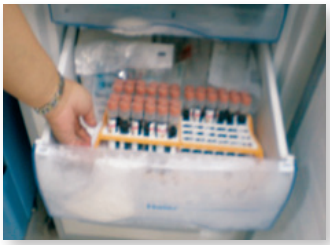
The lack of diagnostic capabilities for CML is a major barrier to optimising clinical outcomes in many low and middle income countries, but by the end of 2012 the iCMLf's ERSAP Diagnosis and Testing Program had supported 1785 diagnostic tests that would otherwise not have occurred.

There are three critical components in each Diagnosis and Testing project:

- Clinician training – it is vital that the clinicians involved in patient care and decision making have access to the most up date CML knowledge
- Long term partnerships – each centre in emerging regions has a partner CML centre of excellence to ensure ongoing clinical and laboratory support and advice
- Every centre taking part in the iCMLf programs establishes a tailored, flexible solution according to the local needs, making use of existing resources

The ERSAP Diagnosis and Testing Program provides a multifaceted approach to build sustainable local capacity for CML diagnosis and testing while ensuring adequate on going support from clinical and laboratory mentors.

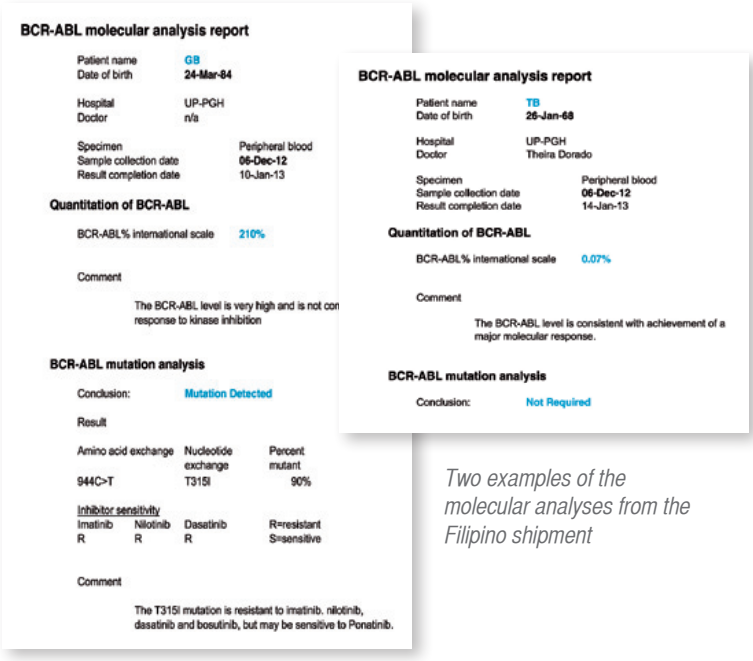
Current projects underway shipment of samples for free testing, providing access to the Cepheid GeneXpert system for onsite, convienient, low cost PCR analysis, and direct iCMLf funds for local projects.



*Filipino samples ready to be shipped to Adelaide for testing*

## 1) Short term solutions while long term resolutions are found

The iCMLf has supported three shipments of over 180 samples from the Philippines to Australia for free PCR and mutation testing. This has provided both physicians and their patients with much needed guidance on their disease status. The Philippines will soon have the capacity for reliable PCR locally and so these shipments are no longer needed and the iCMLf resource can move to another centre in need.



**BCR-ABL molecular analysis report**

Patient name GB
Date of birth 24-Mar-84
Hospital UP-PGH
Doctor n/a
Specimen Peripheral blood
Sample collection date 06-Dec-12
Result completion date 10-Jan-13

**Quantitation of BCR-ABL**

BCR-ABL% international scale 210%
Comment
The BCR-ABL level is very high and is not con
response to kinase inhibition

**BCR-ABL mutation analysis**

Conclusion: Mutation Detected
Result

| Amino acid exchange | Nucleotide exchange | Percent mutant |
|---|---|---|
| 944C>T | T315I | 90% |

Inhibitor sensitivity

| Imatinib | Nilotinib | Dasatinib | R=resistant S=sensitive |
|---|---|---|---|
| R | R | R | |

Comment
The T315I mutation is resistant to imatinib, nilotinib, dasatinib and bosutinib, but may be sensitive to Ponatinib.

**BCR-ABL molecular analysis report**

Patient name TB
Date of birth 26-Jan-68
Hospital UP-PGH
Doctor Theira Dorado
Specimen Peripheral blood
Sample collection date 06-Dec-12
Result completion date 14-Jan-13

**Quantitation of BCR-ABL**

BCR-ABL% international scale 0.07%
Comment
The BCR-ABL level is consistent with achievement of a major molecular response.

**BCR-ABL mutation analysis**

Conclusion: Not Required

*Two examples of the molecular analyses from the Filipino shipment*

## 2) Accessing diagnostic equipment

The iCMLf, Cepheid and MAX have facilitated access to GeneXpert machines in Honduras and Ghana. As a result for the first time these centres have access to onsite PCR testing to diagnose and monitor their CML patients. This has and will continue to revolutionise these CML clinics and transform the physician's management of CML. We sincerely thank Cepheid for the donation of the machines and Xpert BCR-ABL cartridges and MAX for the onsite logistics. It was truly a team effort to bring PCR to these centres.

First of all THANK YOU on behalf of all our patients from Honduras! In just a short period of time they have received lots of Benefits regarding the management of CML that were not available for any part of our country. We used to rely the therapeutic conduct and management of our patients basically on the CBC (complete blood count) and clinical manifestations, which we know are criteria that can manifest late in the course of resistance to CML treatment. Before we received the donation of the Cepheid GeneXpert, there was No way in our country that we could use molecular diagnostics and take molecular responses as a way of following our patients. We also hope, and are more than glad, that this GeneXpert can also benefit the lives of patients with CML not just in Honduras, but in the whole Central America Region.

The support we have received from the iCMLf and the Max Foundation has been great. Just a couple of weeks ago we were honored by the visit of Ines Garcia Gonzalez which came on behalf of The Max Foundation, certifying that the donations of the treatment (imatinib) that our patients receive are adequately managed. And at the same time, Jordan Smith, a biochemist from the Fred Hutchinson Cancer Research Center, came and gave us training and feedback on the adequate management and troubleshooting of the GeneXpert equipment. Jordan's visit meant a lot to us, because the failing rate of the results of the GeneXpert have been none since he came; and he was kind enough to tell us that he would be more than glad to help if any problems happened in the future.

All of the support we have received has been a real honor for us in the "Centro de Cancer -Emma Romero de Callejas" and gives us a huge responsibility to basically serve in a better way all of our patients in our country.

Once again, thank you on behalf of all of our patients.

*Dra. Flora Duarte, Director and Chief Physician, Centro de Cancer Emma Romero de Callejas*

"Have Science, Will Travel!"

My name is Jordan Smith. I am a researcher in Dr. Jerry Radich's lab, at the Fred Hutchinson Cancer Research Center in Seattle, WA. I think that to work in scientific research is to pursue the wonder of the unknown--to be inspired by questions and mystery and the unfathomable complexity of life. Honestly, I think it is rather adventurous. I'm into adventure…even if that adventure is limited to cell culture and DNA sequence analysis.

In April, I had the humbling opportunity to combine my love of adventurous science with adventurous travel. I was invited by Dr. Flora Duarte to visit El Centro del Cancer - Emma Romero de Callejas (CCERC), in Tegucigalpa, Honduras. The CCERC had recently received a Cepheid GeneXpert machine to assist them in monitoring BCR-ABL expression in their CML patients, but were having some issues running problematic samples. It was an honor to assist the lab staff in those two most harrowing scientific tasks: troubleshooting and data interpretation. Together, we solved their GeneXpert problems and established an exciting collaboration for further knowledge exchange in the future.

It really is a testament to the efforts of the MAX foundation and the iCMLf that collaborations like this one can occur. I know that it requires a substantial infrastructure to facilitate connections between leukemia researchers and clinicians around the world. I want to thank both the iCMLf and the MAX foundation for all of their help in this endeavor.

New job description: Scientist/Adventurer? Perhaps!

*Jordan Smith, FHCRC, Seattle, USA*

"The presentation of the Cepheid GeneXpert machine at our centre; Department of Haematology, Korle- Bu Teaching Hospital Accra, Ghana was definitely a dream come true. Gone are the days when patients had to 'cough up ' $500 to have their blood samples for PCR to be done abroad in order to determine whether they had Ph positive CML. For them the possibility of benefiting from a tyrosine kinase inhibitor was not an option. Monitoring of patients on tyrosine kinase was virtually non-existent. These difficulties are now a thing of the past? Patients who have waited for years to have their PCR done can now afford to do so 'in house' with a short turn around time. As a haematologist looking after patients with CML, effective monitoring and management of my patients is no longer a mirage but a reality. On behalf of my patients and on my own behalf I will like to say a big thank you to iCMLf, Max Foundation, Cepheid and everyone who has worked behind the scenes to make this possible."

*Dr. Amma Benneh, Korle-Bu Teaching Hospital, Korle-bu, Accra, Ghana*

## 3) iCMLf funding to enhance local capacity for CML diagnostics

In late 2011, the iCMLf launched the ERSAP Diagnosis and Testing Grants Program. The program offered small seeding grants to hematology institutions in emerging economic regions to facilitate the diagnosis and long term monitoring of CML patients. Grants provide funding of up to US $10,000 as well as additional support from a partnering centre of excellence to ensure the successful implementation of the proposal and ongoing mentoring and support at a clinical and laboratory level.

### Grant criteria:

- The primary focus of the iCMLf funding will improve or introduce facilities for CML diagnosis and monitoring in an existing area of need
- The iCMLf grant will underpin the development of onsite facilities
- The project utilises both the partnership with the CML centre of excellence, and the iCMLf funding

"The partnering CML centre of excellence has been very supportive. I am able to discuss and seek advice on cases and issues. They are also with me every step of the way to help me achieve the aims and objectives of the project."

*Dr Benneh, Ghana*

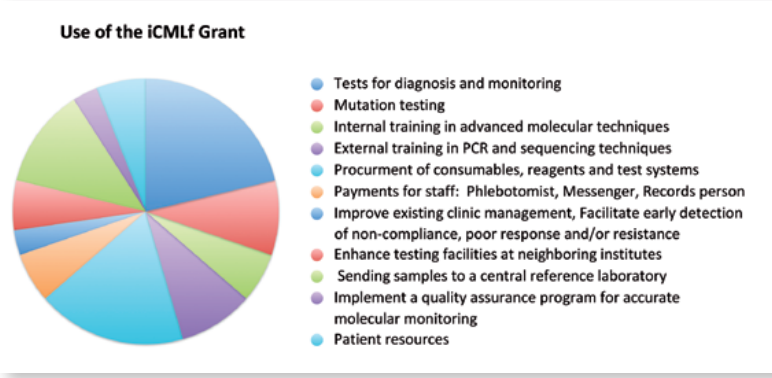
### Awarded Grants

Nine projects were awarded iCMLf grants. Countries involved are Ghana, Indonesia, India, Nepal, Nigeria, Kenya and Uzbekistan.

The majority of the iCMLf funding was directed to purchasing reagents and consumables (18%) and performing PCR analysis (21%). However a wide variety of needs were addressed.

### Success:

- The program has achieved its aim, providing seeding grants to initiate change in local capacity and practice of CML diagnostics. This will lead to long term benefits for CML patients




- For many of the centres awarded iCMLf grants the partnership with the centre of excellence has been instrumental in the successful implementation of the project
- The response to this program has been overwhelming and there is a clear need for ongoing support of funding and education in a similar manner to this structured iCMLf program

"This project has helped patients to monitor their disease on a regular basis. So far the response to the treatment is satisfactory. Preliminary analysis shows that ninety nine percent of the patients have CHR (Complete hematologic response) within 3 months and more than 75% of the patients have CCR (Complete cytogenetic response) within 6 months. New patients continued to be enrolled in GIPAP. Additional funding is necessary to support the new patients."

*Dr Kayastha, Nepal*

### 2013

The 2013 ERSAP Diagnostic and Testing Program will be open in June. Please contact Melissa@cml-foundation.org to register your interest.

# *Looking to the future*

Access to all treatment for all people with CML, ultimately leading to a cure is the utopian vision of the iCMLf. We have a way to go…

## Sustainable Global Healthcare

Improving access to treatment means different things to different people according to where they live and the resources available. For some therapies are out of reach because the diagnostic tools aren't available, for some the cost is too high, for others it is a regulatory issue.

A recent article published in Blood looks at the cost of CML therapies and questions whether the current situation is sustainable. The article 'Price of drugs for chronic myeloid leukemia (CML), reflection of the unsustainable cancer drug prices: perspective of CML experts' was co authored by many of the iCMLf Directors and advisors. The aim of the article is to highlight the cost of drugs for CML and open the discussion for a long term sustainable health care model in the USA and around the world.

"The problem is less acute in Europe where government agencies play a role in determining the prices of individual drugs. It seems to apply particularly to the US where there is less regulatory control and also to poorer countries where many patients cannot afford any treatment at all. These issues do need to be addressed in the 21st century and sooner rather than later."

*John Goldman*

Recognising the innovation and experience required in the development of novel therapies these experts will look at ways and

*next page ...*

means to work towards lower cost of drugs and therefore increased access. Mechanisms will include:

- Consultation with the manufacturers to guarantee sustainable pricing
- Enhanced diagnostic tools for patient identification to lower development costs
- Improved insurance funding models
- Working with regulators to ensure cost:benefit

Patent life is also pertinent to greater access to medicines and this in itself is a highly complex issue. On April 1st 2013 the Supreme Court of India rejected Novartis' application to patent an updated version of its cancer drug Glivec (imatinib). The decision means generic drugmakers can continue to sell copies of the drug at a lower price in India, one of the fastest growing pharmaceutical markets.

"There is a huge ecosystem that needs to be considered. There are drug companies that need profits to stay in business so that they can invest in the discovery of new medications and they are the most skilled entities at drug discovery and development. There are patients who need access to life-saving drugs at affordable prices, but also with access to appropriate monitoring of therapies. I have consistently spoken out about what I view as the high price of drugs, but if we too severely restrict the price of medications, we may lose the ability to invest in new drugs. The HIV model is a good example of providing access to drugs and monitoring, which can be replicated for other diseases. Novartis has actually begun a similar effort with their Glivec patient assistance program. At issue, however, is when does a country move from needing assistance to make drugs affordable to being able to contribute more to this cycle of drug discovery and innovation. This patent decision clearly makes more affordable drugs available immediately and this is good for patients in the short-term. Whether patients will be adequately monitored is another issue and for the long-term, whether this patent decision damages the drug discovery cycle remains to be seen."

*Dr Brian Druker*

There are many parties that can contribute to the solution and here at the iCMLf we support the dialogue leading to increased access to therapies, be that improved science, lower cost, or refining regulatory structure.

## Seeking the Holy Grail

If the availability of optimal medication for every CML patient is an unrealistic vision then maybe, just maybe, CML cure could be a viable alternative.

With this in mind the iCMLf will form an international consortium focused on all aspects of understanding, measuring and managing minimal residual disease, with the ultimate goal of working towards a cure for CML. Through this consortium of leaders in the science and clinical management of CML the iCMLf will identify, develop and oversee global projects focused on establishing a cure for patients with CML.

Great advances have been made in the management of patients with CML, with improving results with currently available frontline therapy, and salvage therapy that is effective for many patients who experience resistance or intolerance to their initial therapy. However, a majority of patients with excellent response to therapy remain with detectable (and some with undetectable) residual disease that presents the potential for eventual recurrence of the disease and underlines the need for continued indefinite therapy in most patients. Perhaps the most important challenge remaining in CML is a better understanding of the mechanisms that govern the persistence of the disease, developing better tools that allow us to identify residual disease and the ever-elusive leukemic stem cell, and identifying treatment modalities that will allow total eradication of the disease.

Cure may mean different things to different people, but the aim of the consortium is to invite interested parties to work together on specific projects under the banner of 'cure'. This iCMLf program will be known as the " iCMLf Consortium Understanding Residual disEase (CURE) Program".

CML leaders in science and clinical management working together should attract larger funding pools and create greater momentum than individual centres, or smaller national groups.

Projects within the iCMLf CURE Program would include: developing tools to measure residual disease, discussing and assessing hypotheses of 'cure' versus therapy cessation or lack of relapse and generate the science to explain why CML persists.

1) Establish an international tissue bank and mechanism for exchange of patient samples to study minimal residual disease
2) Explore mechanisms of persistence of CML and the variability among different patient populations (eg, based on Sokal score, treatment modality, etc.)
3) Develop tools to better identify residual disease beyond what is now offered by standard PCR
4) Design and conduct clinical trials aimed at eradicating residual disease

### Proposed aims

CURE and GLOBAL ACCESS TO TREATMENT, these are lofty goals for a Foundation in its forth year, however we firmly believe we must aim high because with that direction there is no limit to what is possible.

We welcome your comments, expressions of interest and any questions at info@cml-foundation.org

*The iCMLf Directors and Advisers meet annually to discuss how the iCMLf can address current challenges in CML management.*

# Please mark your diary for the upcoming CML meetings

## 1) European Hematology Association Meeting – June 2013


### CML- Scientific Working Group

The CML Scientific Working Group session will take place in conjunction with the 18th Congress of EHA in Stockholm on Thursday 13th June (18.30-20.00, Hall A7).

**Agenda:**

1. A murine model of CML blastic crisis - Brian Huntly (Cambridge, UK)
2. The role of the pTEN/PML/HAUSP network in CML - Alessandro Morotti (Boston, USA & Torino, Italy)
3. A PPAR-gamma agonist in CML - Philippe Rousselot (Paris, France)
4. Topical questions addressable in clinical trials - Stephen O'Brien (Newcastle, UK)

## 2) International Conference of CML – September 2013


## 3) The Second CML Africa Workshop for Healthcare Professionals and Patient Leaders – 20th November 2013

The iCMLf is pleased to support this meeting to be held in conjunction with AORTIC in Durban, South Africa. The meeting is organised by MAX and sponsored by Novartis. To register your interest contact info@themaxfoundation.org

## 4) The Forth iCMLf Forum for Physicians from Emerging Regions – December 2013

The iCMLf Forum will be held during the annual American Society of Hematology meeting in New Orleans. To register your interest contact info@cml-foundation.org

**Also make a note:**
**The 16th International CML Conference is in Philadelphia 4-7 September 2014**

**We look forward to seeing you there!**