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,

It was a bittersweet opening of the John Goldman conference on CML in October this year. While it was wonderful to see both familiar and new faces of this close knit CML community, the banner in remembrance of Professor Tessa Holyoake was a reminder that the community was missing a key member this year. Tessa's presence was still clearly felt through the meeting content and organisation and especially during the opening of the meeting where the iCMLf Rowley Prize was presented. The 2017 Rowley Prize was awarded to Professor Holyoake in recognition of her groundbreaking work understanding and targeting CML stem cells.

Connie Eaves introducing Dr Copland to give the Rowley keynote

"Tessa was the most energetic, the most stimulating, the most driven and the most wonderful and enthusiastic scientist and person. She gave us specific instructions to carry on the torch that she has been carrying. Derived from her energy we now go on and carry on with further investigating CML stem cells – a research that has given so much to the world, the science, the patients and the next generation of scientists." said Professor Connie Eaves as she presented the 2017 Rowley Prize.

Tessa was delighted to receive the award and at the time of her death had organized who would receive the medal on her behalf and who would present the acceptance keynote speech she had prepared. You can listen to Professor Mhairi Copland deliver Tessa's speech and view the slides on the *iCMLf website* along with those of the other winners Professor Tim Hughes (Goldman Prize) Professor Jerry Radich (iCMLf Prize).

"... having access to the CML international community, regular updates on practise is helping in doing what is best for the patients." Dr Durogbola, Nigeria

The iCMLf website has become a key CML education and information point for physicians. The clinical case discussions, expert presentations and monthly 'key publication' updates are widely viewed. In 2018 we are pleased to complement this with a more formal CML education learning resource. The iCMLf Knowledge centre will be an interactive online resource providing educational content on CML patient management, options for molecular monitoring, and practical considerations of BCR-ABL1 testing. This resource is intended to enhance knowledge of these areas through self-study, with two learning paths. One is tailored for clinicians and one specifically for molecular biologists and pathologists. Please register your interest for the program at *info@cml-foundation.org* and we will email you once it is available. While the content is developed independently by the iCMLf this resource would not have been possible without the support from Novartis and we thank them for this commitment.

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

19th Annual John Goldman Conference on CML: Biology and Therapy

Professor Jorge Cortes opening the conference.

The John Goldman Conference on CML, co-sponsored by the iCMLf and the European School of Hematology (ESH) has become an important event in the annual scientific calendar for the CML community. *"The fact that this meeting takes place for the 19th time this year tells a lot about the passion of the CML scientific community to constantly improving the management of patients with CML and to better understanding the biology of CML"*, said Jorge Cortes, chairman of the meeting, during the opening ceremony.

"It's so important to have clinical and scientific sessions on CML combined in one meeting"

"That's one of my favourite meetings of the year that always gives me a good overview of the latest scientific findings in CML"

Global scope of the conference – excellent opportunity to network

From 12-15 October 2017 more than **439** clinicians and scientists from **43** different countries came to Estoril, Portugal. In addition to the high-quality scientific program, participants always benefit from the opportunity to network with leading CML experts from around the world.

"This meetings always brings the perspectives from Europe, the US and other parts of the world together in one conference"

"The size of the meeting is perfect and you manage to get into conversation with all the important CML experts"

Comprehensive scientific program with interactive poster walks

The top-class scientific program included; scientific sessions, **3** workshops for non-clinical scientists on; metabolomics, cell fate tracking and bioinformatics and modelling, **5** satellite symposia, a symposium on myeloproliferative neoplasms, brief oral communications (biology and clinical) and various special lectures. Highlights of this conference are the biology and clinical interactive poster walks. The authors of **89** posters presented their key findings to the audience followed by moderated discussions.

"We had an excellent meeting. We came up with a lot of new questions and discussed how we can address these questions and how we can collaborate to further work on these questions. We now take all this with us home to further improving the care of our CML patients", said Dr Cortes as he closed the conference.

The iCMLf Goldman Fund supports the training of young physicians from the emerging regions

During the John Goldman Conference on CML the Goldman Fund plays a major role. The iCMLf has established this special fund in honour of Professor John Goldman for people wanting to give a donation to the foundation in his memory. The 'Goldman Fund' will be used specifically for the training of young CML clinicians and scientists from the emerging regions. This was something that John was passionate about.

Physicians from Macedonia and Pakistan supported by the iCMLf Goldman Fund

Each year the fund supports physicians from the emerging regions to attend the conference, providing a comprehensive overview of the latest scientific findings on the biology and the management of CML to those who would not otherwise be able to attend.

In the previous years the fund has assisted young physicians from Nigeria, Ukraine, Pakistan and India to attend the conference.

Among the participants of the 2017 meeting were physicians from Macedonia and Pakistan whose attendance was supported by the Goldman Fund. At a ceremony shortly after the opening of the conference, both received a certificate from the iCMLf chairman, Professor Tim Hughes.

Dr Marica Pavkovic, a hematologist working at the University Clinic for Hematology, in Skopje (Macedonia) also undertook a 3-week clinical preceptorship at the

Hammersmith Hospital in London just before she attended the conference.

Dr Syed Owais Ali is currently completing his fellowship in hematology at the Haematology Department of the Armed Forces Institute for Pathology in Rawalpindi (Pakistan) presented a poster on 'Frequency of TET2 gene mutation in MPNs patients' during the biology poster walks at the conference.

The 2017 'John Goldman Fun Run' was a great success raising over $3,400

The 'John Goldman Fun Run', which takes place at the end during the conference, is an annual fundraiser for the iCMLf Goldman Fund. Over $3,400 was raised this year including monthly pledges – our best year ever!

By purchasing a T-Shirt participants of the run supported the Goldman Fund. This year the T-Shirts were in striking bright green! We thank everyone for your generous contributions to support the work of the iCMLf in this way.

The 2017 run was held in memory of Jean Khoury, who passed away this year. Jean was always a part of this group of colleagues and friends supporting of the iCMLf and he was very much missed.

If you would like to donate got to *www.cml-foundation.org*

'It's so much fun running together with colleagues and friends and at the same time a good opportunity to support the work of the Foundation"

2017 Rowley Prize

Recipient: Professor Tessa Holyoake

The iCMLf Rowley Prize recognizes persons for their outstanding lifetime contributions to the understanding of the biology of CML. In 2017 the iCMLf Rowley Prize was awarded to Tessa Holyoake for her groundbreaking work understanding and targeting CML stem cells.

Tessa was very touched when she heard about the award and had already completed her presentation when she died in August. At Tessa's request, her iCMLf medal was accepted by Professor Tim Brümmendorf, from the Universitätsklinikum Aachen, Germany and her keynote on 'CML stem cells: from discovering to targeting' was presented by Mhairi Copland, Professor of Translational Haematology at the Paul O' Gorman Leukemia Research Center at the University of Glasgow.

The keynote presentation is available on the *iCMLf website*.

Connie Eaves presenting Tessa Holyoake's Rowley Prize to Professor Brümmendorf

2017 Goldman Prize

Recipient: Professor Timothy P. Hughes

The annual iCMLf Goldman Prize complements the Rowley Prize as a clinical equivalent acknowledging outstanding lifetime contributions to the management of patients of CML. The iCMLf awarded the 2017 Goldman Prize to Timothy Hughes for his contributions to the clinical research and the management of CML. These include; demonstrating the importance of molecular monitoring in CML patients receiving kinase inhibitor therapy, showing the clinical relevance of mutation monitoring in the resistance setting and promoting treatment-free remission as the new goal of CML management.

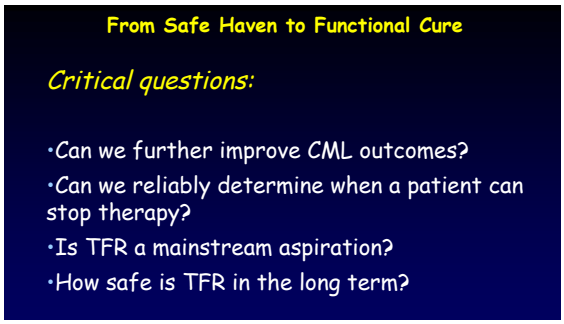
"There is no one who deserves this prize in honour of John Goldman more than Tim Hughes. He has contributed significantly to clinical research in CML and helped us to understand how to better manage our CML patients. He is also a great teacher always keen to share his knowledge."

(Professor Jorge Cortes)

Jorge Cortes awarding the Goldman Prize to Professor Hughes

From Safe Haven to Cure

Over the past 2 decades CML clinicians have become increasingly ambitious when setting treatment goals for our CML patients. When imatinib data was just emerging, the hope was that we could significantly delay the "inevitable" progression to blast crisis that had always characterised the CML disease course. When we demonstrated that the achievement of a major molecular remission (MMR) was associated with a near zero risk of progressing to blast crisis, the new goal of therapy became the "safe haven" of MMR. With longer follow up many patients treated with imatinib achieved a steady improvement in molecular response to the point where the leukemic transcript was undetectable. This was initially termed a "complete" molecular response but now the more cautious term "deep" molecular response is favoured. This observation led to the question as to whether patients could maintain their deep molecular responses off-therapy. The pioneering French studies and subsequent studies from our group and many others have demonstrated that a majority of patients who achieve stable deep molecular responses will maintain those responses without further therapy – now termed treatment free remission (TFR). In the current era it is very clear that under the appropriate monitoring regimen and in the eligible patient group, attempts at TFR are safe. For the CML clinician who has many patients on long term TKI therapy, an increasing number of patients are now potentially eligible for a trial of cessation. The difficult decision for the clinician is to determine if and when to recommend a TFR attempt and how to counsel the patient about the risks involved. In terms of timing, the Euroski study has provided very helpful modelling suggesting that the probability of TFR success increases by around 13% (relative, not absolute) for every year of TKI therapy or every year of deep molecular response. This suggests that these patients are reaching a "point of no return" with prolonged therapy, and that this becomes progressively more likely over time. This can help to frame the discussion with the patient – at least in providing an approximation of the prospects of achieving TFR. For instance, in a patient with a relatively short duration of therapy, would they be comfortable attempting TFR if the chances of success were considerably less than 50%? When discussing the risks involved, the withdrawal syndrome, and the possibility of losing molecular response and having to restart therapy,



are the known risks. Having to go back onto TKI therapy, possibly for life, can be very distressing for patients, but the additional concern for these patients is that an unsuccessful attempt may delay the achievement of the "point of no return", and thus successful TFR, significantly. For patients who do achieve TFR, the long-term risk of relapse or progression are unknown. This justifies ongoing frequent and regular RQ-PCR monitoring, possibly indefinitely. At this stage there is no emerging evidence that late relapse or progression are significant issues.

As we work towards making TFR a mainstream goal of therapy and focus of clinical practice, it is interesting to speculate about how many CML patients will eventually be able to achieve TFR. This will largely depend on the impact of the more potent TKIs – used either front-line, or second-line in patients who do not achieve optimal responses on imatinib. The emerging data from the nilotinib and dasatinib stopping studies look very promising here. It raises the hope and expectation that TFR may be achievable for the majority of CML patients. The implications from this are that CML is no longer a simple disease to treat where a safe haven is the endgame of therapy. Maximising the achievement of TFR will require a much more proactive and engaged approach to management. In centres with eligible patients where the facilities are not available to enable TFR to be safely attempted, the institutional requirements for mainstream TFR practice need to be established with some urgency, or alternatively, these potentially eligible patients could be referred to centres that are already "TFR enabled".

Professor Tim Hughes
SAHMRI / University of Adelaide / Royal Adelaide Hospital
Adelaide, Australia

The keynote presentation is be available on the *iCMLf website*.

2017 iCMLf Prize

Recipient: Professor Jerald Radich

The iCMLf Prize is awarded by the Foundation to recognise outstanding contributions to the improvement of CML treatment in the emerging economic regions.

The iCMLf awarded the 2017 prize to Professor Jerald Radich recognising his dedication to overcome the challenges of access and expense of CML testing around the world. He has consistently worked to develop new methods to make molecular monitoring less expensive, giving both his personal and professional time to increase access to CML diagnosis and monitoring for those who need it most.

"Jerry is a worthy winner of this award because his work makes a real impact on the life of CML patients in less developed countries by improving access to diagnostics. He is a true friend and important advisor to me and a real champion to CML patients around the world."

(Pat Garcia-Gonzalez, CEO of The Max Foundation and winner of the inaugural iCMLf Prize)

Pat Garcia-Gonzalez awarding the iCMLf Prize to Professor Radich

Weird Solutions to Real World Problems

Our lab has spent roughly three decades studying the genetics of luck. Why do some patients with leukemia relapse, while others are cured? How do we predict resistance, response, and relapse? Much of our emphasis has been in CML, which has become the poster child of the well-worn paradigm (at least, in grant applications) of "bench to bedside." We have spent a good deal of creative energy, and hard work, devising better mousetraps to diagnose and monitor disease.

Our lab being honoured with the iCMLf prize is about luck as well. For CML patients, the biggest facet of luck is where he or she was born, as most of the world's CML patients have no ready access to TKIs treat CML, or diagnostics to even prove they have the disease. It has been our great fortune to be able to make a dent in this dilemma, albeit mainly through an unlikely series of coincidence and collaborations.

Twenty years ago, the remarkable Pat Garcia-Gonzalez (a previous iCMLf Award winner), started the Max Foundation, dedicated to delivering TKIs to needy CML patients in areas that could not afford TKI and diagnostics. Early in the building of Max, Pat lamented to a software volunteer that she needed a way to diagnose CML cases, as pharma would only dole out drug to proven cases of

CML. As it happens, that volunteer happened to have been a CML patient that I transplanted years ago, who had been in frequent contact with our lab regarding his BCR-ABL PCR results over the years. Soon the Max Foundation was sending us peripheral blood from patients around the world for diagnostic testing, starting principally from Central and South America.

Then we were using a "home brew" BCR-ABL assay that had been standardized with other major Centers involved with CML testing. Cepheid, who had a strong footing in automated molecular testing in infectious diseases, approached our lab about collaborating to develop an automated BCR-ABL assay. In another remarkable circumstance, one of Cepheid's top technician's (Bret Helton) wife had just been accepted to the University of Washington to pursue her doctoral work, so we were able to jump start the process by being able to do assay development in house. The creation of the Cepheid system allowed us to consider establishing local diagnostic centers in the developing world. Cepheid was (and still is) fantastically supportive of this effort and there are now >20 testing sites in the developing world. Our lab has subsequently offered technical help, traveling around the world to train and troubleshoot, essentially becoming roving PCR ambassadors. The sum of this activity is that this novel alliance of philanthropy, academia, and industry has been remarkably successful, with free TKIs now going to roughly 50,000 patients worldwide.

Still, testing is limited since many sites have not yet been able to acquire the Cepheid technology and blood samples must still be rushed to diagnostic centers overseas. This is logistically challenging and very expensive. For example, a tube of peripheral blood air shipped from Africa to Seattle can cost around $500. Moreover, peripheral bloods cannot easily be batched to reduce the shipping cost. Thus, shipping peripheral bloods to specialized centers is not a scalable or affordable solution. We wondered if you could do testing using samples of dried blood spots, a tricky proposition since BCR-ABL testing is done on RNA, not DNA, and the common wisdom was that the rapid degradation of mRNAs would make accurate testing (or, testing at all) impossible.

Fortunately, conventional wisdom is sometimes wrong. RNA is indeed degraded while drying on the spot, but with some work methods to accurate quantify BCR-ABL were established. We teamed with long-time friends and colleagues Sue Branford and Tim Hughes in Adelaide to compare fresh BCR-ABL testing with spotted aliquots of the same sample, dried and sent by "snail mail" to the U.S. (mysteriously, this took from 8-71 days). A simple X-Y plot of fresh versus spotted sample was remarkably similar. From this work, in a fantastic collaboration that includes the Fred Hutch, the Max Foundation, the iCMLf, and Cepheid, we started "Spot on CML," and effort to diagnose ~500 cases this year (roughly, a "cure," a day).

The needs of diagnostics in low resource settings are still large, and there are several other avenues that our lab is pursuing to pitch in. First, we are collaborating with a local medical device start-up (Tasso) to develop a one-step device that can draw and spot blood without syringes and needles, making sample acquisition possible by untrained or patients in any almost any environment. In addition, thermocycling machines for PCR require electricity, which is a big problem in much of the world. We are working on isothermal amplification reactions that do not require machines (or electricity) that can allow "point of care" testing. We envision essentially a "pregnancy test" for CML (and other types of leukemia). And lastly, can we envision a future where the patient does not come to the lab for testing, but the lab comes to the patient? Why not drones? Why can't patients use their cell phone to summon a drone to their home, grab a device from a cargo bay (please avoid the blades), collect their own blood, and send it back to the lab?

Our lab's involvement in helping out CML patients in need has had a huge impact in how we value ourselves and our work. We have done many wild and weird (as in strange, not the acronym) things over the years (my team is remarkably patient and tolerant of my tendency to dive into rabbit holes). We spent a whole year in the early 1990s trying to do RT-PCR in a cell (bad choice). We work on elaborate microfluidic systems to perform single cell genotyping (probably a good choice). We do massive parallel genetic studies to understand the pathways that define treatment response and leukemia biology (verdict still out). This is fun, creative, and exciting work, and may lead to improving patient outcomes. But nothing has come close to the sense of accomplishment and satisfaction as figuring out ways to help CML patients get the therapy they need and deserve. It is our lab's infinite luck to have found this mission, with the help of our generous friends and collaborators.

Professor Jerald Radich
Fred Hutchinson Cancer Resarch Center, Seattle, USA

The keynote presentation is available on the *iCMLf website*.

COMING IN 2018

Register your interest at
info@cml-foundation.org

Join us at these 2018 international meetings

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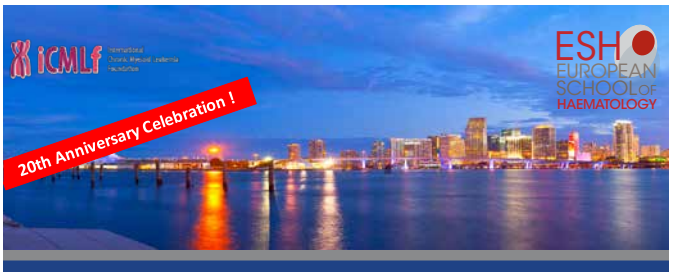

20th Annual John Goldman Conference on
CHRONIC MYELOID LEUKEMIA: BIOLOGY AND THERAPY

MIAMI, FL, USA
September 13-16, 2018

Chairs: J. Cortes, T. P. Hughes, D. S. Krause
Organizers: R. Bhatia, M. Copland, M. Deininger, P. Hari, D. Perrotti, J. Radich, D. Réa
Advisory Committee: J. Apperley, S. Branford, C. Gambacorti-Passerini, F. Guilhot, R. Hehlmann, P. Laneuville, F-X. Mahon, G. Saglio, C. Schiffer, S. Soverini, P. Valent, R. Van Etten

DEADLINE FOR ABSTRACTS: MAY 8, 2018