SPRING 2022 NEWSLETTER

International Replication Repair Deficiency Consortium

Welcome

Dear readers,

Here at the International Replication Repair Deficiency Consortium (IRRDC), our patients and our research are always our top priority. For over a decade, the IRRDC has been dedicated to making sure that every patient and physician with a suspected case of Replication Repair Deficiency (RRD) can find the care that is right for them. Our initiative to capture these rare diagnoses in a global registry has led us to personally collaborate with hospitals in over 45 countries, building a network of relationships that reaches every corner of the world - and we've loved every second of it.

We are now pleased to bring you the second edition of the IRRDC's bi-annual virtual newsletter. These newsletters in conjunction with our bi-annual educational seminar series, aim to bring awareness to syndromes of DNA Replication Repair Deficiency through engaging content from our own team as well as our collaborators and families globally.

The following edition features articles and research updates written by IRRDC's internal and external collaborators, who are leveraging precision approaches the diagnose and treat RRD in novel ways. We hope you enjoy it!

Want to learn more about the IRRDC? Visit us at replicationrepair.ca or email us at replication.repair@sickkids.ca

Our Team - The Consortium Leadership Committee

Members of The Consortium Leadership Committee

Uri Tabori, MD
Consortium Lead

Anirban Das, MD
Paediatric Oncologist and Cancer Geneticist

Melissa Edwards, PhD
Clinical Research Project Manager

Vanessa Bianchi, PhD
Clinical Research Project Coordinator

Sheradan Doherty, MESc
Clinical Research Project Coordinator

Lucie Stengs, BSc
Research Technologist and Biobanker

Research Updates - Advancements in Immunotherapy

Written by Dr. Vanessa Bianchi (Clinical Research Project Coordinator, The IRRDC)

In this edition of the IRRDC newsletter, we want to highlight recent work that has advanced our understanding of immune-based therapies for patients with CMMRD. These therapies work by activating the body's immune response which allows the patient's own T-cells to identify and attack cancer cells.

Discovering Biomarkers that Predict Tumour Response to Immunotherapy.

Utilizing the vast amount of clinical information collected as part of our IRRDC registry, Dr. Das and Dr. Sudhaman were able to pioneer the first study of its size assessing the use of immune checkpoint inhibitors (a type of immunotherapy) to treat patients with mismatch repair deficient (MMRD) cancers (Das et al. Nat Med 2022). This study assessed 45 immunotherapy treated cancers from 38 patients and demonstrated favourable responses and improved overall survival for patients, including those with cancer types not previously known to respond to immunotherapy. This paper also identified a number of new molecular characteristics (known as "biomarkers") which predict how likely a tumour will be to respond to treatment.

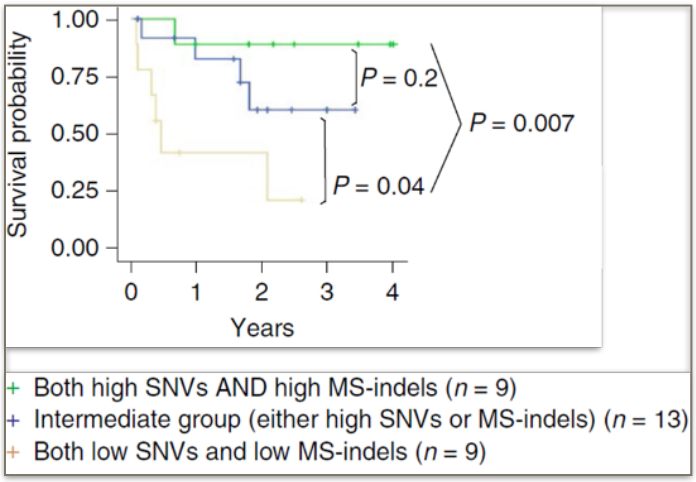
Dr. Anirban Das

Dr. Sumedha Sudhaman

This article is open access and can be found here
DOI: https://doi.org/10.1038/s41591-021-01581-6

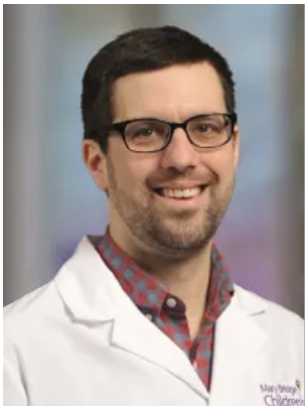
Impact for patients: This paper is the first of its kind to show in a large number of patients that CMMRD cancers will respond well to immunotherapy if the tumour has specific molecular characteristics or "biomarkers". This personalized medicine approach will allow physicians all over the world to provide patients with the best care upfront. We now have over 100 CMMRD patients in the IRRDC being treated with immunotherapy globally.

Furthermore, understanding that some cancers which do not have favourable biomarkers will not respond as well to immunotherapy allows for further research to be done to assess what treatments or combination therapies will work best for this group of cancers. This will be the focus of our next stages of research and will guide our future clinical trials



Survival Probability Predictions by Biomarker Profile. Cancers with both high SNVs (single nucleotide variants) and high MS-indels (microsatellite indels) responded significantly better to immune checkpoint inhibitor therapy than cancers with low SNVs and low MS-indels. Kaplan-Meier (KM) estimates using combined SNVs/Mb and MS-indel in all replication repair-deficiency cancers.

Using Immunotherapy to Treat Patients with More Than One Cancer



Dr. Jacob Henderson
Paediatric Hematology & Oncology
Mary Bridge Children's Hospital
Tacoma

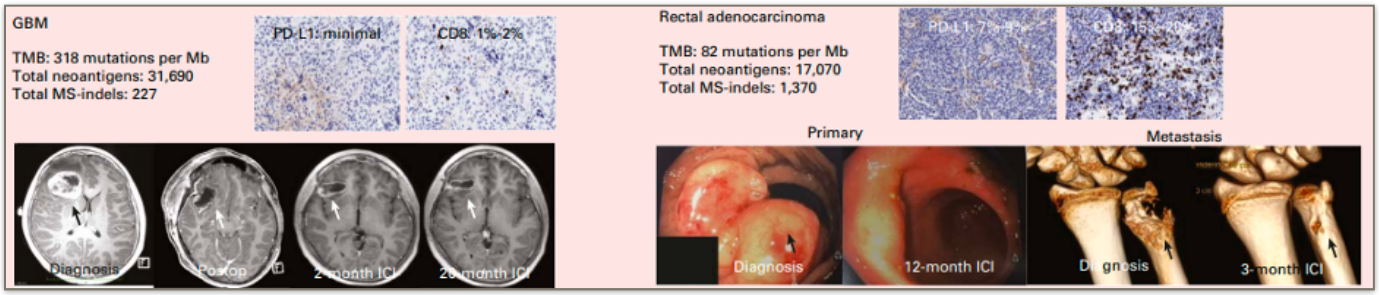
Most cancer patients will only develop one cancer in their lifetime. However, we know that individuals with CMMRD are predisposed to developing a number of different cancer types, and patients may develop more than one cancer at the same time. This poses a difficult challenge for physicians as treatment often differs for different cancers, and therapy with two regimes at the same time can pose significant toxicity to the individual.

For CMMRD patients, their cancers are unique and share one important similarity; they are hypermutant. Hypermutant cancers respond well to immunotherapy and so we investigated whether we could use this one therapy to treat patients with more than one cancer.

In a recent study by Dr. Henderson and Dr. Das (*Henderson et al. JCO Precis Oncol 2022*), we showed for the first time that patients with hypermutant synchronous cancers (more than 1 at the same time) could benefit from a single immune-based therapy. This approach is unlike classic approaches to cancer therapy which differ depending on the cancers tissue of origin.

This article is open-access and can be found here: DOI https://doi.org/10.1200/PO.21.00286

Impact for Patients: For patients with more than one cancer, the use of combined therapies can pose a significant toxcicity concern, and treating one cancer at a time is sometimes not an option. Knowing that hypermutant cancers in different tissues or areas of the body can be treated together with 1 single therapy will help provide these individuals with the best care while reducing the negative side effects of combined or subsequent therapies.



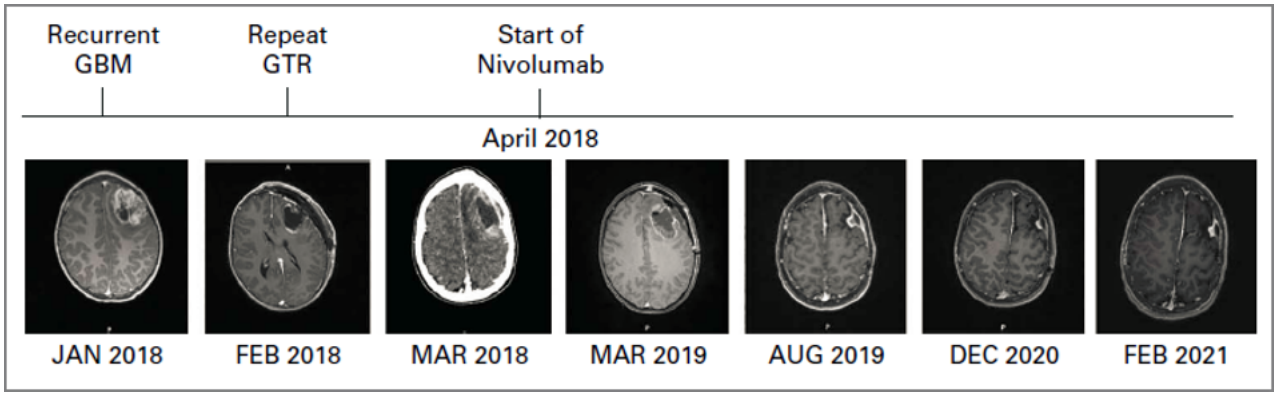
Immunotherapy Treatment in a Patient with Synchronous Brain and Colon Cancer. Brain cancer, classified as a glioblastoma (left) decreases in size over the course of treatment with immunotherapy. Similarly in the same patient with synchronous colon cancer (rectal adenocarcinoma) and metastasis to the bone (right), both cancers decrease in size over the course of therapy. Both cancers are hypermutant.

Treating MMRD Brain Cancer with Immunotherapy Alone; A Chemoradiation-Sparing Approach

Dr. Trisha Larkin
Paediatric Hematology & Oncology
St. Joeseph's Children's Hospital
BayCare Medical Group

Radiation and chemotherapy are often part of a standard treatment protocol for patients with brain cancer, however they come with potential morbidity and damage to the developing brain. Therefore, improved therapies and protocols need to be established. In a recent case report in collaboration with Dr. Larkin, we describe a positive treatment outcome for a patient treated using immunotherapy alone for a rapid recurring/relapsed MMRD glioblastoma (*Larkin et al. JCO Precis Oncol. 2021*). To date the patient remains in complete remission (>40 months) with no functional regression or challenges with academic performance.

This article is open access and can be found here:
DOI https://doi.org/10.1200/PO.21.00153



MRI Imaging at Relapse Pre- and Post-Immunotherapy (Nivolumab). MRI imaging of a patient who received immunotherapy only for a recurrent brain cancer (GBM, left) with no tumour recurrence after 2 years of immunotherapy (right).

CONGRATULATIONS: Stand Up To Cancer Maverick Award Recipient

Dr. Anirban Das

To conclude this segment of the IRRDC newsletter we wanted to take a moment to congratulate Dr. Anirban Das who was the recent recipient of the Stand Up To Cancer Maverick Award. This award was based on a proposal to initiate a new immunotherapy clinical trial for patients with hypermutant and MMRD cancers. This new proposed clinical trial builds on the recent findings highlighted above. Congratulations!

CMMRD in Low- and Middle-Income Countries

Written by Dr. Vanessa Bianchi (Clinical Research Project Coordinator, The IRRDC)

Dr. Vanessa Bianchi, PhD

In this edition of the IRRDC newsletter we wanted to highlight an important issue; the health disparity between cancer patients in western and other high-income countries (HIC) compared to cancer patients in low- and middle-income countries (LMIC). The CDC defines “health disparity” as “*preventable differences in the burden of disease, injury, violence, or in opportunities to achieve optimal health experienced by socially disadvantaged racial, ethnic, and other population groups, and communities*”. Health disparities may also be termed health inequalities or health inequities, but for the purpose of this article, this means that cancer patients in LMIC may not receive the same standard of care that cancer patients in HIC receive, significantly affecting the survival of these individuals. There are a number of factors including limited infrastructure (lack of or limited machinery such as radiotherapy machines and laboratory equipment for specialized/molecular testing), a lack of trained specialists (surgeons, pathologists, etc..), a lack of standard treatment protocols, limited drug availability in these regions and treatment abandonment, all of which contribute to this disparity. More than 80% of the world’s children live in developing countries and the vast majority of the new cases of pediatric cancer each year are diagnosed in a LMIC. When looking at patient survival in these regions, this disparity is shocking.

Dr. Naureen Mushtaq, who you will hear from in her own words shortly, is a Pediatric Neuro-Oncologist at Aga Khan University, in Karachi, Pakistan. In 2019, Dr. Mushtaq published an article summarizing the clinical outcome of patients who presented with brain cancers over a 10-year period. Notably, of the patients for which they were able to re-contact for up-to-date information, only 20% were still alive (*Riaz, Q. et al. Child's Nervous System (2019) 35:2347–2353*). This number is strikingly different when compared to 82% reported for Americans aged 0-14 years (*data from the National Brain Tumour Society*).

So why is this important for CMMRD? Well, as you will hear from Dr. Mushtaq shortly, CMMRD is suspected to be more prevalent in LMIC due to an increased rate of marriage between individuals with similar ancestry and it is estimated that the number of brain cancers in LMIC that result because of MMR deficiencies could be as high as 40%. Standard approaches to therapy are not as effective in these individuals which means that in order for patients in LMIC to get the right treatment, these centers need to be able to have the tools to identify these patients and the opportunity to provide them with the care they need. With the help of Dr. Eric Bouffet, Director, Paediatric Neuro-Oncology Program at the Hospital for Sick Children, physicians like Dr. Mushtaq. have been able to come to Toronto for observer-ship training programs and have been able to establish “Twinning” programs in their regions. These programs offer a collaborative learning relationship between cancer programs in HIC and LMIC. Through the hard work of Dr. Mushtaq, Pakistan now has protocols that mimic ours for treating brain tumour patients. In addition, the IRRDC works collaboratively with these centers in Pakistan to identify patients with CMMRD and ensure they get the best therapy. We hope you enjoy this next article written by our dear colleague abroad Dr. Naureen Mushtaq.

Constitutional Biallelic Mismatched Deficiency in Pakistan

Written by Naureen Mushtaq (Karachi. Pakistan)

Dear Colleagues and friends ,

My name is Naureen Mushtaq, I have completed my fellowship from The Hospital for Sick Children in 2014 and now working as an Associate Professor and Pediatric Neuro-oncologist at Aga Khan University Hospital (AKU) Karachi. Pakistan.

Since my return from Toronto we have developed very intensive collaboration for our children with the International Consortium of CMMRD and I must say they helped us immensely in diagnosing and managing better in the context of cancer predisposition syndrome.

As you know that individuals with CMMRD are affected with multiple tumours arising from multiple organs during childhood. The most common tumours observed are central nervous system, hematological, and gastrointestinal malignancies, these tumours exhibit a hyper mutation phenotype with some of the greatest mutational burdens in all human cancer.

From left to right: Dr Bilal Mazhar Qureshi (Radiation Oncologist), Ms Anum Mistry (Neuro-Oncology Nurse Navigator), Dr Shahzadi Resham (Paediatric Palliative Care Physician), Myself, Dr Salman Kirmani (Endocrinologist and Geneticist), Dr Khurram Minhas (Pathologist), and Dr Gohar Javed (Neurosurgeon)

2nd Pakistan Pediatric Neuro-oncology symposium held November 2021, hybrid meeting attended by more than 900 participants across the globe virtually and 100 physically. Dr Eric also visited Karachi.

The incidence of CMMRD is expected to be high in low middle-income countries due to a high rate of consanguinity in these regions, and it is thought to be under recognized and consequently under-diagnosed. In Pakistan more than 70% marriages are consanguine therefore we expect many cases of CMMRD in our population. A country with limited resources and essentially no multidisciplinary team to deal such disorders we have started twinning program with the Hospital for Sick Children, Toronto in 2014 and till date we have managed more than 500 patients across Pakistan.

This twinning initiative not only helped us in establishing multidisciplinary teams at AKU but also served as a conduit in capacity building of Pediatric Neuro-oncology and CMMRD surveillance services across 10 public/private hospitals of Pakistan. With three (per month) National Pediatric

Brain tumour boards covering most of the big cities of Pakistan our strong network of health care professionals are working really hard to treat their children well. Many of my colleagues are now also collaborating with International consortium of CMMRD and improving the quality of lives of their children. Dedicated multidisciplinary teams and constant collaboration with international colleagues helped us to establish a strong network of health care professionals who are now working hard to improve the outcomes of children with CMMRD.

Making the Impossible Possible: Caring for Children with Brain Tumours in Low and Middle Income Countries

An Interview with Dr. Vanessa Bianchi (The IRRDC's Clinical Research Coordinator) and Dr. Eric Bouffet (Director of Paediatric Neuro-Oncology at the Hospital for Sick Children)

For this edition, we were very lucky to sit down with one of the IRRDC's founders, Dr. Eric Bouffet, Director of Paediatric Neuro-Oncology at the Hospital for Sick Children. We took this opportunity to ask him some questions on how we can mitigate international healthcare disparities for patients with CMMRD.

Dr. Eric Bouffet

Hi Eric! What do you see as the greatest barrier right now between equitable health care in high income versus low- and middle-income countries? *Well firstly thank you for asking about this topic, as it is absolutely one of the greatest challenges in children's healthcare right now, and actually one of the present aims of the GICC (The Global Initiative for Childhood Cancer), is to identify what those specific barriers are. First and foremost the greatest barrier is essential drug access. As of now, the UICC (Union for International Cancer Control), has approved immune checkpoint inhibitors in the list of essential drugs for adults, but not for children. So clearly there is a need for education as well, not only in the medical community but in the mindset of the policy makers. We know are specific needs for specific populations, for example, in Africa we know that Burkitt's lymphoma and retinoblastoma are much more common than here in Canada. Similarly in populations with high rates of consanguinity, mismatch repair is a specific issue. Those regions see increased rates of colon cancer in teenagers and greater incidence of high-grade gliomas, 40% of which are mismatch repair deficient. In this context, you can imagine that if you bring immune checkpoint inhibition to those countries, it's like you bring a magic pill that integrates prevention and early detection into practice.*

What insight can you offer for physicians and healthcare providers in low- and middle-income countries who are seeking compassionate care? *Compassionate access seems to work well in certain countries, for example, we have had a great partnership with compassionate access over in Jordan. There's this critical moment that you initially put your foot in the door, establish a relationship, and from there things can really take off quickly. However, it is also incredibly important that you streamline by some indication of what is a good fitting population to access this drug. Because most of our knowledge is about patients with CMMRD in high income countries, it is important to know whether there are key differences at the root of these populations, which may affect the efficacy of the drug. We must put in place foundations that ensure the same success story elsewhere. As far as I can say right now, we have been able to provide the medication in Jordan, but we are not necessarily seeing the same results in their patient cohort. It is still early, and there can be bad luck because we may have good responders, poor responders, and some in between, but the percentages in things like this are critical to our understanding, and we don't have all the data from these patients that we may need to call this case a success. So in short, any changes in care need to be made with caution and education, but absolutely, compassionate access can be incredibly powerful.*

Dr Eric Bouffet visiting Pakistan for the first time in 2018, for their Brain Tumour Rounds with Sickkids.

We know that individuals with hyper-mutated cancers, commonly in CMMRD, respond to ICI. What work still needs to be done to get these drugs approved and more accessible?
So actually, the policy and approval is not as much of a barrier here - there are many examples of drugs that are FDA approved but that are still not available in low- and middle-income countries. But what we need to do is look at providing access in countries that simply do not have the resources to afford the price of the drugs that are being discussed in high income countries. It has been done successfully in some conditions, for example HIV, that with very strict control and slow roll out to the economic market, you can effectively introduce the drug at a more affordable cost. But right now, if a child is diagnosed with CMMRD and needs immunotherapy, there are only two choices. The first is to claim refugee status and go to a country that has access, or alternatively, to have money. The issue of cost is very important, but it is tricky because when you look at the cost of treating childhood cancer, even in low-income countries, it is a big drop in the ocean. My wish really is to have a clinical trial in these counties where CMMRD is most common.

What do you see as the future for clinical trials for patients with CMMRD? *The response we have seen in trials from high income countries, where there is relatively easy access to immune checkpoint inhibitors, has been so promising. Dr. Tabori and Dr. Das are right now proposing a clinical trial design that should focus on when is the appropriate time to give the medication (since this really should be an up-front therapy) and promoting radiation-free survival where we are limiting the possibly harmful effects associated with radiation. Certainly, there are many other clinical trial opportunities for hypermutant tumours, such as identifying the most effective combinations of immune-checkpoint drugs or even identifying the most appropriate antigen that we can explore for a tumour vaccine. To bypass the issue of the cost of medication by providing a more cost effective tumour-vaccine - that's a wonderful opportunity!*

In your long career, how have you personally seen the management of CMMRD change and what do you feel has made the biggest impact? *At the start of my career, I didn't know anything about CMMRD. When I did start to learn about it, it was primarily thanks to the people I met who were working in countries that had very limited resources. For many of us, this success story is accredited to those early ambassadors, and it has been a huge privilege to work with them. From them, absolutely the most important thing that I have learned has been a message of hope. This disease when first identified was just awful and had no cure at the time. Children were developing multiple cancers, with very concerning histology, and there were such terrible patterns of relapse. With standard treatments, the median survival after relapse was but three months, and now thanks to the progress we've made we are seeing children with CMMRD alive and well even 4 to 5 years after relapse. This is a huge message of hope. What we now know is that, for the whole concept of brain tumours, and other diseases that have nothing to do with mismatch repair deficiency, nothing is impossible.*

" This is a huge message of hope … We now know that nothing is impossible."

- DR. ERIC BOUFFET

IRRDC Patient Corner "A life worth hoping for; a life lived."

Written by Ryan Hoshaw

Ryan Hoshaw

Hello everyone, I'm Ryan. I'm 27 and from Michigan in the US. I am a 2-time colon cancer survivor and a whole human who happens to also have the lovely 1-in-a-million CMMRD. To finish up my credentials I have dealt with recurrent colon cancer since 2017, and have one super sneaky low grade glioma hanging out in my brain. Genetically, I have MSH6 mutations from each of my parents, and no problems occurred until I had already reached adulthood. All things considered I have been disease free for over 2 years now, and I have done everything in my power to lead a normal life within the seesaw that is chronic illness.

2021 was one of the years where I was on the healthy side of the seesaw. Because of this, I was feeling the pull to do something different. So I went on a 2-month solo road trip across the United States. I'll stop there by saying I was inspired by several different things to do this, but I want to give a shout-out to one of my favourite authors and cancer survivors Suleika Jaouad for her book "Between Two Kingdoms" as one of the largest inspirations.

I went west from home all the way up to Denali, Alaska, then south as far as Death Valley, California, before heading back home. After 50 days on the road I had seen, done, and experienced things I never imagined possible just a few years ago.

During the worst times within my own cancer diagnosis, I thought to myself that there was no way out. That nothing better laid on the other side of the physical and emotional pain. But deep down I still had hope that things would turn the other way in my favour, and on that trip it really felt like they did. I think the reason I'm saying all of this is that CMMRD really puts us all up against a wall. An impossible wall that feels hard to beat, and with that wall comes an unbelievable amount of uncertainty, and I think that's what hurts the most. "What's next?" - we ask ourselves and our loved ones. Well I hope for all of us it's good things, or peace, or both.

"To learn to swim in the ocean of not knowing, this is my constant work."

Here are a few of my favourite photos from my journey. Oh and a picture of my girlfriend Carly and I!

Peace y'all,
Ryan Hoshaw

Ways to Give

Thank you for considering making a donation towards the International Replication Repair Deficiency Consortium.

Thanks to your donations, we are able to continue funding the most promising cancer research, look for better treatments for this devastating condition, educate parents and families throughout the world about RRD and provide trusted information, resources and support for every patient and family who are on a journey to beat an RRD cancer.

If you are interested in making a donation, please reach out to us directly at replication.repair@sickkids.ca.

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