



Paterson Institute
newsletter

The Newsletter for the Paterson Institute for Cancer Research

Cell cycle Group

replisome

Drug Discovery Unit

Clinical and Experimental
Pharmacology Group

Targeted Therapy Group

A word cloud visualization showing various biological terms. The most prominent words are "replication", "checkpoint", "stress", "kinase", "progression", "survive", "mechanisms", "cells", "resolution", "phosphorylated", "view", "direct", "across", "arrows", "within", "yeast", "cell", "bud", "erly", "trig", "Dna", "proliferation", "surprising", "cross", "arrows", "within", "yeast", "cell", "bud", "erly", "trig". The words are arranged in a circular pattern, with "replication" at the top and "checkpoint" at the bottom. Other words like "stress", "kinase", "progression", "survive", "mechanisms", "cells", "resolution", "phosphorylated", "view", "direct", "across", "arrows", "within", "yeast", "cell", "bud", "erly", "trig" are scattered around the perimeter. The colors range from light blue to dark blue.

Leukaemia Biology Group

Drug Discovery Unit
Applied Computational Biology
and Bioinformatics Group

Clinical and Experimental
Pharmacology Group

Immunology Group

Children's Cancer Group,
Medical Oncology

Carcinogenesis Group

Issue 25 - August 2012

[inside >>](#) [New Home for Cancer Research in Manchester >>](#) [Autoclave Installation >>](#) [Featured Publications](#)

MANCHESTER
1824

The University of Manchester

CANCER RESEARCH UK



Director's Introduction



This summer we bid farewell to Geoff Margison, leader of the Carcinogenesis group, who retired from the Institute after an association that extends back over forty years.

I would like to thank Geoff for

his exemplary service to the Institute and congratulate him on all that he has achieved during his tenure at the Paterson. We wish him well for his future endeavours which include an honorary position at the University of Manchester. We also wish Gail McGown and Mary Thorncroft all the best for their retirement after many years of service to the Institute.

After the successful start that we made to 2012, it is pleasing to see a continuation in high profile publications from the Institute's scientists. As always, the newsletter highlights some of our recent achievements including a major study published in Cancer Cell by the Leukaemia Biology group. Congratulations should go to Caroline Dive and her team for the successful renewal of the alliance between the Clinical Experimental Pharmacology Group and AstraZeneca. This collaboration will bring in substantial funds to the CEP Group which will facilitate the continuation of their vital Biomarker research.

A major focus going forward is to increase the amount of external funding that we bring into the Institute to supplement our grant from Cancer Research UK. This will allow us to carry out the full breadth of research that we need to undertake and so it is a pleasure to welcome Gill Campbell, our new Grants Advisor, to help us to do just that. As you know, the majority of our funding comes from the CR-UK core grant, which is a direct result of the generosity of the general public and fundraising for any charity is increasingly difficult in the current economic climate. It is therefore more important than ever that we take every possible opportunity to engage with the supporters whose

generosity underpins our research efforts. The coming months offer some excellent opportunities to do this including the Shine walking marathon on September 8th and the Institute Open Day on October 6th. I hope to see as many of you as possible taking part in these events in order to give something back to the people who make our research possible. Most importantly it is our chance to say thank you.

Also featured in this issue are the fundraising efforts made by members of the Institute themselves and I have been very impressed by the imaginative and innovative nature of these activities. Judging from the number of successful cake sales held in the last few months, the Institute is fostering a high degree of culinary expertise!

Finally, I am looking forward to the Institute Colloquium in September. Events such as this are an excellent opportunity for the Institute to come together and share ideas and develop collaborations. I hope to see many of you there.

Richard Marais
Director

SHINE
Manchester 2012

CANCER RESEARCH UK

Help make Shine a night to remember
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Manchester 2012
Old Trafford Football Stadium
8th and 9th September

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Together we will beat cancer

Registered charity nos 1089464 and SC041666

Front cover:
Word clouds constructed from the abstracts of recent publications produced by the Institute's scientists. These publications are featured in this issue. The words that appear most often in each publication are indicated with font size being proportional to frequency. The text has been filtered to remove the most common words.

CR-UK Research Travel Awards

By Giacomo de Piccoli



The focus of my research is on mechanisms developed by eukaryotic cells to safeguard genome stability following replication stress. Failure to preserve genome stability can drive the process of tumorigenic transformation. Moreover, many antineoplastic drugs target DNA replication, so a better understanding of how cells cope with replication stress is fundamental in the design of new strategies for more effective cancer drugs.

In the Cell Cycle Group, a combination of genetic and biochemical approaches are applied to characterise replication regulation. To understand how these processes then affect replication fork dynamics, we decided to use ChIP-sequencing, a powerful tool that can map the position of proteins within the chromosome with higher resolution and lower background noise than microarray analysis.

The Shirahige lab at the University of Tokyo has been at the forefront of the development of ChIP technology for many years. I have already enjoyed a productive collaboration with the Shirahige lab, but it is thanks to the Cancer Research UK Travel Grant that I had the opportunity to visit this lab for six weeks earlier this year. The aim of my visit was to learn the process of ChIP-sequencing so that I could undertake the analysis myself during future collaborations, as well as to explore the possibility of independently developing this technique here at the Paterson Institute.

While in Japan, I undertook several experiments which I hope will enable me to better understand replication fork regulation during nucleotide depletion. I also explored the function of new factors associated with replication machinery, which have been recently discovered in the Cell Cycle Group. If supported by ChIP-sequencing, these experiments will reveal new and exciting mechanisms regulating replication forks (the sequencing is still ongoing so I am keeping my fingers crossed!)

I had a great time in Japan. Everyone in the Shirahige lab was very welcoming and fun to be around. I learnt a lot and I would like to thank CR-UK for the great opportunity. Only one note of warning to anyone else thinking of going to Japan: make sure that the power adaptor of your electric razor works because, as I can testify, the half-bearded look is really hard to pull off, even in eclectic Tokyo.

Checkpoint Control of Replisome Function

During DNA replication, cells are extremely vulnerable to damage that impedes their ability to properly duplicate their genome. In response, cells activate survival mechanisms that slow down DNA replication and allow the damage to be repaired. Understanding how cells regulate replication stress is important as defects in chromosome replication are an early feature in the development of many human tumours.

In a recent paper published in Molecular Cell, Giacomo De Piccoli from the Cell Cycle Group investigated the role played by S-phase checkpoint kinases in regulating the replisome, which is the large multisubunit complex responsible for carrying out DNA replication. His results have shown that these kinases regulate the function of the replisome during replication stress, rather than its stability, as was suggested in previous work by others.

Chromosome replication requires a DNA helicase to unwind the parental DNA duplex. The helicase itself is inherently slow, but can move very rapidly through the chromosome as part of the replisome by being physically connected to DNA polymerase at the replication forks. Replication stress, induced by the genotoxic drug hydroxyurea, disrupts dNTP production, resulting in the slower movement of DNA helicase and an accumulation of single stranded DNA at each fork. This encourages the recruitment of a checkpoint kinase Mec1, ultimately triggering the activation of a downstream checkpoint kinase, Rad53. These kinases act in various ways to help cells survive replication stress.

In this study, the replisome was isolated intact from yeast cells lacking either Mec1 or Rad53, even after extended treatment with hydroxyurea and the use of harsh extraction conditions. The team also found that the replisome was still associated with DNA replication forks. The replisome spreads further away from forks in mec1 and rad53 mutants suggesting that these checkpoint kinases restrain replisome progression during times of replication stress. How might this happen? The team found that many components of the replisome are phosphorylated during activation of the checkpoint including at least one factor whose modification is dependent upon the Mec1 kinase. They hope to go on and characterise these substrates to unravel the mechanism by which Mec1 and Rad53 regulate replisome function.

Ref: de Piccoli et al., (2012). Replisome Stability at Defective DNA Replication Forks is Independent of S Phase Checkpoint Kinases. Molecular Cell 45, 696–704.

New Home for Cancer Research in Manchester



Work on the new Manchester Cancer Research Centre (MCRC) building started this spring with preparation of the development site prior to construction, marking an important new phase for cancer research in Manchester.

The new building will provide the vital space for expansion of research activity, enhancing the strong platform developed since the formation of the MCRC partnership in 2006. The arrival of Professor Richard Marais as Director of the Paterson Institute for Cancer Research, the appointment of Professor Ian Jacobs as the Dean of the Faculty of Medical and Human Sciences at The University of Manchester and the continued close interaction of the three MCRC partnership organisations highlights the ongoing commitment to cancer research in Manchester. Over the next three to four years there will be considerable investment in new research positions – an investment that is strategically important in order for the MCRC to achieve its goals.

The MCRC building will be situated close to existing facilities, including The Christie and the Paterson Institute, and will provide space for an additional 150 researchers on the site. Working alongside these researchers, The Christie will re-locate staff from its clinical trials coordination unit to the third floor of the building. As well as being a physical manifestation of the MCRC partnership, the new research building will strengthen key areas of research such as lung cancer, the development of personalised medicine, melanoma and radiation-related research. “We already have a good foundation in these areas – we aim to build and expand on these to become world-class. This is a very exciting time in Manchester; with the new research building we can provide our researchers with the environment

they need in order to take forward the personalised medicine agenda at a greater pace,” said Professor Nic Jones, Director of the MCRC.

Expansion of research relies on active recruitment of new research leaders and teams and an international search for promising and established researchers is taking place alongside the development. At a time when the economy is challenging and therefore securing investment in research is increasingly competitive it is very encouraging that Manchester is able to attract continued investment. “We have a rare opportunity in Manchester in terms of the MCRC partnership and the number of cancer patients in the region – developing the infrastructure and facilities that can support potentially ground-breaking research will ensure we make the most of this opportunity,” said Professor Jones.

MCRC Research Building Key Facts

- Located close to existing facilities
- Provides space for an additional 150 scientists on the site
- Provides over 6,000m² for expansion of research activity
- Due for completion in spring 2014



The Lab Services team alongside the new autoclave: From L to R: Christine Whitehurst, Fran Hockin, Mark Craven, Corine Hand and Andy Burns. Also part of the team are Tony Dawson and John Higgins.

Installation of New Autoclave in Laboratory Services

By Mark Craven

Over the last year a considerable amount of effort has gone in to improving the equipment available to the Lab Services team to allow them to provide sterile glassware and solutions to all the researchers in the Institute. With the greater demand for these services over the last few years it has become increasingly difficult for the team to process the volumes of glassware needed.

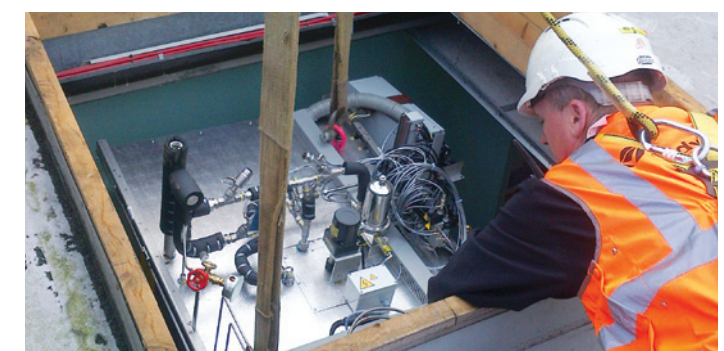
One aspect of this program has been the replacement of the older of our two autoclaves with a new one. This process is slightly complicated as Laboratory Services are on the top floor, and the autoclaves are too big to fit in any of our lifts. Both the new and old autoclaves had to enter and exit the building via the roof, a task that required steering a half ton piece of metal through a rather small opening, which the crane operator is not able to see from the ground. Hopefully the pictures will give you an impression of how little spare room there was when the units were being moved in and out of the access panel. It was a delicate job to position such a heavy piece of equipment into this small opening.



The operation required a series of people to make it happen; we needed an independent consultant and together with Estates' Manager Steve Alcock's help and guidance, we were able to carry out all the necessary steps to deliver the unit in the one day.

Once safely inside the building it required another couple of weeks for installation and testing before the Lab Services team were back to having two operational autoclaves. Around the same time we also added a new glass washer to help the team maintain a good turnaround time when demand is high.

During the next few months we will be carrying out a refurbishment of another space for Lab Services which will enable the team to provide a broader range of media and solutions. By the end of this year we will have completed all the necessary improvements to the workspace and equipment leaving us with a team well equipped to deal with the challenges of running a high quality central laboratory service.

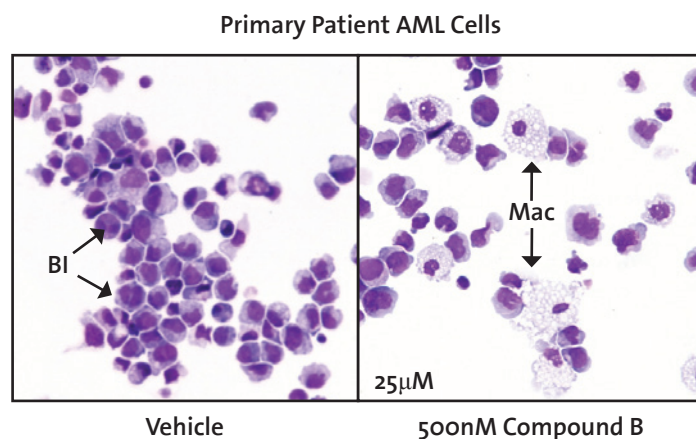


Featured Publications

Hitting the Epigenetic Target

Paterson scientists are continuing their successful start to 2012 with yet more publications in high profile journals. Of particular note is a recent study published by the Leukaemia Biology Group, led by Dr Tim Somervaille, in the prestigious journal *Cancer Cell*. The team have identified a gene, KDM1A, which plays an important role in sustaining the oncogenic potential of Acute Myeloid Leukaemic (AML) stem cells and as such, represents a potential therapeutic target for the treatment of AML.

Drugs targeting aberrant epigenetic mechanisms are a source of intensive investigation within the pharmaceutical industry due to their potential selectivity and reversibility. The Leukaemia Biology group have been assessing the potential of targeting deregulated epigenetic mechanisms in the treatment of AML as few targeted therapies currently exist for the treatment of this disease. Their study identified the histone demethylase KDM1A as an enzymatic target which, when inhibited, resulted in loss of engraftment and clonogenic potential coupled to induction of terminal myeloid differentiation. The finding that potent pharmacologic inhibitors of KDM1A abrogate clonogenic potential and induce differentiation of primary human patient leukaemia cells while sparing engraftment and multi-lineage differentiation in normal haematopoietic cells provides strong evidence for a possible therapeutic window. Specifically their data suggest that KDM1A is a candidate target for differentiation therapy in MLL-translocation AML, a common cause of both childhood and secondary, treatment-associated AML which tend to have a particularly poor clinical outcome.



Addition of compound B (a novel KDM1A inhibitor) to primary patient AML cells results in morphological differentiation from leukaemic blasts (BI) into macrophages (Mac), a cell type found in normal haematopoiesis.

This study also revealed intriguing preliminary evidence that KDM1A inhibition could be a therapeutic strategy in other molecular subtypes of myeloid malignancies. These results mandate further investigation into KDM1A as a therapeutic target in AML and reveal a necessity to further characterise its role in tumourigenesis. Further, the effect of KDM1A inhibition in the context of combination treatment requires further investigation.

Ref: Harris WJ, Huang X, Lynch JT, Spencer GJ, Hitchin JR, Li Y, Ciceri F, Blaser JG, Greystoke BF, Jordan AM, Miller CJ, Ogilvie DJ, Somervaille TC. (2012). The histone demethylase KDM1A sustains the oncogenic potential of MLL-AF9 leukemia stem cells. *Cancer Cell*. 17;21(4):473-87.

Circulating Tumour Cells Predict Survival for Patients with Small Cell Lung Cancer

In 1869 Thomas Ashworth observed microscopical circulating tumor cells in the blood of a man with metastatic cancer, and suggested that “.... cells identical with those of the cancer itself being seen in the blood may tend to throw some light upon the mode of origin of multiple tumours existing in the same person.” Given that these cells are rare when compared to the volume of cells in whole blood, analysis of these cells present a technical challenge.

In a recent paper published in the *Journal of Clinical Oncology*, Dr. Jian-mei Hou and colleagues from the Clinical & Experimental Pharmacology group reported on the findings from a prospective study that the number of circulating tumour cells (CTC) and the change in CTC number after one cycle of chemotherapy predict survival in patients with small cell lung cancer (SCLC). The researchers examined serial blood samples from 97 SCLC patients receiving chemotherapy for CTCs using EpCAM-based immunomagnetic detection and a filtration-based technique. They demonstrated that CTCs were prevalent (85%) and abundant (mean number: 1,589) in SCLC patients and that clusters of CTCs, Circulating Tumour Microemboli (CTM), were detected in 32% of patients.

The number of CTCs present before treatment predicts survival in SCLC patients, with 5.4 months of overall survival for patients with >50 CTC/7.5 mL of blood and 11.5 months for patients with less than 50 CTC/7.5 mL of blood. The failure of CTC numbers to decrease to less than 50 after one cycle of chemotherapy predicts shorter overall survival (4.1 months versus 10.4 months). Subpopulations of apoptotic and proliferating solitary CTCs were found but neither were seen within the Circulating Tumour Microemboli, implicating both protection from anoikis (programmed cell death) and relative resistance to cytotoxic drugs.

This study demonstrated the utility of CTC as prognostic, pharmacodynamic and predictive biomarkers in small cell lung cancer and reveals the potential of circulating tumour cells as a ‘virtual and real-time biopsy’.

Ref: Hou JM, Krebs MG, Lancashire L, Sloane R, Backen A, Swain RK, Priest LJC, Greystoke A, Zhou C, Morris K, Ward T, Blackhall FH and Dive C. (2012). Clinical Significance and Molecular Characteristics of Circulating Tumor Cells and Circulating Tumor Microemboli in Patients with Small-Cell Lung Cancer. *Journal of Clinical Oncology*, 30: 525-532

Ashworth TR (1869). "A case of cancer in which cells similar to those in the tumours were seen in the blood after death". *Australian Medical Journal* 14: 146–7.

Glycolysis as a target for drug development

The Paterson Drug Discovery group has recently published its work on the development of a novel drug in the *Journal of Medicinal Chemistry*. As tumours need far more energy for their growth than normal tissue they often utilise different methods to create this energy – an effect first noticed over 80 years ago and known as the Warburg effect. By targeting this difference between tumour and normal tissue it is hoped that effective drugs with minimal side effects can be developed.

The work described in the paper is based on targeting the pentose phosphate pathway, and describes the synthesis and testing of an inhibitor of the enzyme, glucose 6-phosphate dehydrogenase (G6PD) which is a rate limiting step in this NADPH regenerative pathway. The steroid dehydroepiandrosterone 1 (DHEA 1) is known to inhibit G6PD and has been shown to have chemopreventative and antiproliferative effects but is not as specific or as metabolically stable as would be hoped for in a chemotherapy.

The work described uses DHEA 1 as a starting point and details the synthesis of several derivatives and their efficacy as inhibitors of G6PD in both enzyme and cell based assays. In order to do this, over 40 compounds were synthesised and enzyme and cellular assays were developed. The work described led to the development of inhibitors with an approximately ten fold increase in potency which retain good solubility and will hopefully aid in the design of future synthetic inhibitors of G6PD for use in the clinic.

Ref: Hamilton NM, Dawson M, Fairweather EE, Hamilton NS, Hitchin JR, James DI, Jones SD, Jordan AM, Lyons AJ, Small HF, et al. (2012). Novel Steroid Inhibitors of Glucose 6-Phosphate Dehydrogenase. *Journal of Medicinal Chemistry* 55, 4431-4445.

Marker for invasive ALL

A collaboration between the Immunology and Children's Cancer groups has resulted in a recent publication in “*Leukemia*”. By focussing on the cases where childhood lymphoblastic leukaemia (ALL) reoccurs, the two groups were able to identify a marker (5T4) of a small population of the leukaemic cells which were more resistant to treatment. This population of cells is thought to migrate to specific sites within the body from which it can spread following treatment. Consistent with this, 5T4 has previously been shown to be involved in cancer cell migration and, as therapies targeting 5T4 are already under development, it is hoped these will help play a role in the treatment of childhood ALL in the future.

Although the overall prognosis in childhood acute lymphoblastic leukaemia (ALL) is good, outcome after relapse is poor. Recurrence is frequently characterised by the occurrence of disease at extramedullary sites such as the central nervous system and gonads. Subpopulations of blasts able to migrate to such areas may have a survival advantage and give rise to disease recurrence. Gene expression profiling of diagnostic pre-B-ALL bone marrow samples revealed higher 5T4 oncofoetal antigen transcript levels in cytogenetic high-risk subgroups of patients. Flow cytometric analysis determined that bone marrow from relapse patients have a significantly higher percentage of 5T4 positive leukaemic blasts than healthy donors. 5T4 has also been shown to regulate CXCL12 chemokine and Wnt signalling pathways which are important in leukaemia growth and spread. For example, CXCL12 is naturally produced by various tissues of the body and controls the distribution of different types of immune cells but can also act as a “magnet” for leukaemia cells. Only 5T4+ve B-ALL cells show CXCL12 specific chemotaxis in vitro and this can be blocked by a monoclonal antibody (mAb) to 5T4 but not HLA.

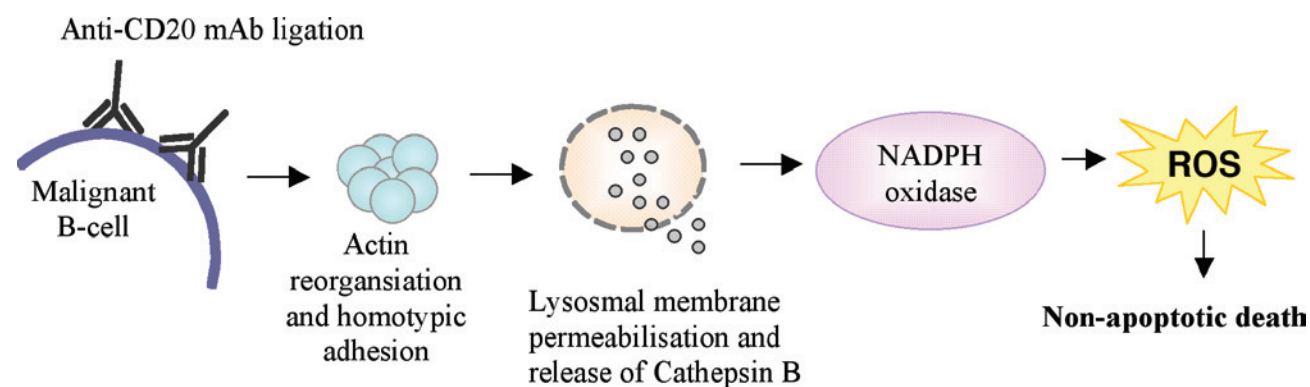
Further, in a xenograft model 5T4+ve compared to 5T4-ve B-ALL cells showed differential spread to the omentum and ovaries following intraperitoneal inoculation; this could also be blocked by mAb5T4. Consistent with this, the 5T4+ve B-ALL cells show increased invasion *in vitro* concordant with increased LFA-1 and VLA-4 integrin expression, adhesion to extracellular matrix and secretion of matrix metalloproteases (MMP-2/-9) compared with their negative counterparts. The xenograft model system was used to show that 5T4+ve B-ALL are susceptible to 5T4 specific superantigen antibody-dependent cellular toxicity providing support for targeted immunotherapy in high risk pre-B-ALL patients. The results of this study are consistent with the hypothesis that 5T4 is a marker of leukaemic cells which are relatively resistant to chemotherapy including through increased ability to migrate to tissue sites which provide for disease relapse following treatment. If 5T4 marks the most drug resistant B-ALL then 5T4 directed therapies provide a rational and effective way to treat such patients.

Castro FV*, McGinn OJ*, Krishnan S, Marinov G, Li J, Rutkowski AJ, Elkord E, Burt D, Holland M, Vaghjiani R, Gallego A, Saha V and Stern PL. (2012) 5T4 oncofoetal antigen is expressed in high risk of relapse childhood pre-B acute lymphoblastic leukemia and is associated with a more invasive and chemotactic phenotype. Leukemia 26(7):1487-98.

Killer ROS

Recently the Targeted Therapy Group identified a role for reactive oxygen species (ROS) in the novel cell death pathway triggered by type II anti-CD20 monoclonal antibodies in human B-lymphoma and leukaemia cells.

The anti-CD20 monoclonal antibody (mAb) rituximab has substantially improved outcome for patients with a range of B-cell malignancies however, responses are often not curative, prompting investigations into the development of “next generation” CD20 mAb with improved clinical activity.



Proposed mechanism of cell death induced by type II anti-CD20 mAb

Identifying the effector mechanisms by which anti-CD20 mAb kill cancer cells is central to the design of mAb with improved therapeutic efficacy.

Anti-CD20 mAb are defined as type I (rituximab-like) and type II (tositumomab-like) according to their ability to elicit complement deposition and programmed cell death respectively. Recent characterisation of the mode of cell death elicited by type II anti-CD20 mAb has revealed that the pathway involves homotypic adhesion (HA), lysosome membrane permeabilisation (LMP) and release of cathepsins. Importantly, cell death is independent of caspase activity suggesting that mAb may be able to circumvent apoptosis-resistance.

In this study, the Targeted Therapy Group have demonstrated that reactive oxygen species (ROS) are critical to mAb-induced cell death in a range of human lymphoma cell lines and primary leukaemia samples. Type II anti-CD20 mAb and anti-HLA-DR mAb trigger the production of ROS that occurs down-stream of HA, LMP and cathepsin release. ROS scavengers such as tiron protect against cell death demonstrating the critical requirement for ROS in evoking cell death. mAb-induced ROS is independent of mitochondria and instead appears to be derived from an NADPH oxidase.

Notably, ROS production is unaffected by over-expression of the anti-apoptotic protein BCL-2 confirming that this mechanism of cell death can potentially overcome apoptotic resistance mechanisms thus this cell death pathway may be able to eradicate malignant cells refractory to conventional chemotherapy. It is hoped that further definition of the mechanism of action of clinically relevant mAb may lead to the generation of novel therapeutics with enhanced clinical efficacy.

Ref: Honeychurch J, Alduaij W, Azizyan M, Cheadle EJ, Pelicano H, Ivanov A, Huang P, Cragg MS, Illidge TM. (2012). Antibody induced non-apoptotic cell death in human lymphoma and leukaemia cells is mediated through a novel reactive oxygen species-dependent pathway. Blood, 119(15):3523-33.

Recent Awards and Events

Contract Renewal for CEP Group

[Congratulations to Caroline Dive and the Clinical and Experimental Pharmacology Group for the successful renewal of their contract with AstraZeneca worth £3.1million over the next three years. This will enable them to continue their alliance covering blood borne biomarker assays.](#)

A biomarker is a signal that gives doctors a clue about what is happening in a patient's body. It's like a molecular flag that can indicate if someone has a certain type of cancer or even whether a treatment for cancer is working. Normally a sample of a tumour would be required to obtain this sort of information but if the biomarkers can be detected in blood, this allows cancer treatment to be followed much more easily. The alliance between CEP and AstraZeneca has been in place since 2006 and has grown to cover a number of biomarkers including indicators of whether cells are dying in response to cancer treatment as well as identifying cancer cells circulating in the blood. Their ever-increasing portfolio of biomarkers is allowing the CEP group to analyse thousands of samples from clinical trials that are taking place all over the world which will help shape the use of many future cancer therapies.

Fellowship Success



[part of the selection process for the fellowship, she visited Erasmus University in Rotterdam to present a seminar on](#)

[Congratulations to Alexia Eliades who has been awarded an EMBO Post-Doctoral Fellowship. Alexia, who is part of the Stem Cell Haematopoiesis Group headed by Valerie Kouskoff, will be carrying out research into the molecular mechanisms of haematopoietic specification. As](#)

[“Mechanisms of regulation: from megakaryopoiesis to the origins of haematopoiesis”. She joined the Paterson Institute in September 2011 having completed her PhD in Biochemistry at Boston University School of Medicine in the US.](#)

Avinash Patel from Cell Division was awarded a Scholarship to attend the Keystone meeting on Proteomics, Interactomes in Stockholm in May. He has also just been awarded a short term EMBO fellowship to work in the lab of Boris Macek of the Proteome centre in Tuebingen, to complete the analysis of the polo kinase phosphoproteome of fission yeast that he began there last summer.

Chemistry Meeting at the Paterson

[By Ali Raoof](#)



[As an additional responsibility to working as a Drug Discovery Unit chemist I am a member of the "Young" Chemist Panel \(YCP\), Society of Chemical Industry. This is a charity run conference organising committee made up of chemists from academia](#)

[and industry throughout the UK. A couple of years ago I had a novel idea for a one day meeting, which was to my delight, soon after approved by the committee. It was decided that Paterson would be the perfect venue for holding the meeting. The conference, titled Candidate to Market, successfully went ahead on 16th May 2012.](#)

This meeting was aimed at a wide audience of chemists and biological scientists in both academia and industry. The focus of the meeting was two fold: firstly to gain an understanding of the key processes involved in drug development from the stage when a compound is identified as a potential drug candidate up to its FDA approval as a drug on the market. The second reason for running this event was to familiarise researchers with the

multitude of support roles involved in the development of a drug to market - for example toxicology, formulation, clinical research (CRA), regulatory, medical writing, quality assurance (QA).

It was hoped that a broad knowledge of the drug development process would allow scientists embarking on a career in drug discovery/development to make an informed choice of where their skills and interests lie. Scientists already working within the pharmaceutical industry may have found this advantageous as they consider future career moves during this turbulent time. The feedback received from delegates and speakers has been very positive and holding the meeting at The Paterson has most definitely further raised the profile of the Institute to the broader pharmaceutical and academic world. A big thank you to our very own Allan Jordan and Chris Morrow for the opening remarks and chairing the morning and afternoon sessions respectively. Finally I am not really sure what defines young anymore as I am now officially one of the oldest members on the committee and will step down eventually if my YCP SCI colleagues allow me to - apparently they value me.....or maybe my humour too much!"

Distinguished Achievement

Tim Illidge, Group Leader of the Targeted Therapy Group, has been named "a Researcher of the Year" at the University of Manchester's Distinguished Achievement Awards.

These awards are held each year to recognise outstanding achievements from across the University. Professor Illidge is a clinician scientist who has increased our understanding of the mechanisms underpinning the successful use of radioimmunotherapy to treat lymphoma. His practice-changing trials have increased treatment options for the disease and improved outcomes both within and outside the UK.



The 2012 Distinguished Achievement Awards winners with the President and Vice-Chancellor, the presenters and guests

A Fine Fellow



Congratulations to Allan Jordan, who heads up the Chemistry team in the Drug Discovery Unit, on his recent admission as a Fellow of the Royal Society of Chemistry (FRSC).

The designation FRSC is given to a group of elected Fellows who have made major contributions to chemistry and

represents the highest category of membership of the Society which normally requires a minimum of five years' experience in a senior position. The award to Allan, after just three years in post, is based upon the fantastic progress made by the Drug Discovery team in their short time within the Institute.

Cancer Research UK Research Travel Awards

Could your research benefit from a short stay in another lab? If you are a post-doctoral researcher whose funding comes from CR-UK, the Research Travel Award will allow you to visit groups elsewhere in the UK, or overseas, to carry out a specific piece of work.

CR-UK are looking for proposals that will allow you to introduce new skills or techniques to your current research group and to establish or develop collaborations. They also welcome proposals that allow researchers to develop their own independent careers. The awards cover travel, accommodation and research expenses to visit another group for a period between two weeks and three months. Applications should be made by the post-doctoral researchers themselves and details of how to apply can be found here:

www.cancerresearchuk.org/research-travel-award

These awards are competitive. Criteria considered by the selection panel include the quality of the proposed research and the benefits to both the applicant and their research group. The deadline for the next round of awards is December 7th 2012. Further information can be obtained from Dr Matthew Kaiser:

Matthew.Kaiser@cancer.org.uk

Staff News

The past couple of months have been full of great personal and sporting achievements for Paterson staff.

Andrew Lloyd from the Logistics Department has two things to celebrate; he won the Institute's Fantasy Football league for the second year running and is hoping to go for the hat trick this year; but more importantly he and Claire have welcomed their third child, a beautiful baby girl Abbey Tracey Sarah Lloyd who was born on 28/04/2012 weighing 7lbs 13oz.



Natalie Mack also has several pieces of news; she would like to announce the birth of her beautiful baby boy Fraser William Hepburn Mack who was born on 22nd April 2012 weighing 10lbs. Natalie said "He is very happy and healthy and I am loving being a mummy". After almost 6 years at the Paterson, Natalie shall be moving in the autumn to begin a postdoc with Marios Georgiou at the University of Nottingham. She will be working on cancer models in Drosophila, a project which is again being funded by CR-UK. "I have really enjoyed my time at the Paterson working in Angeliki's Cell Signalling group and am now looking forward to some new challenges. I would like to give a big thank-you to everyone at the Paterson who has helped me with my work over the years". We wish Natalie the best of luck in the future. The Operations department have celebrated two weddings this spring. Human Resources Advisor Laura Humes married Phil

Jones on 11th May at the Wordsworth Hotel at Grasmere in the Lake District, 'The loveliest spot that man hath ever known'. Laura and Phil stayed in their favourite place in the Lakes for their honeymoon. Meanwhile Finance Officer Debbie Southern married John Trunkfield at the Riu Palace Hotel, Cancun, Mexico on the 4th May 2012.

Kath Spence and Kate Williams from Breast Biology, along with Kath's brother and a friend completed a sponsored bike ride from London to Paris in May. They completed the 300 mile ride in 4 days encountering some awful weather along the way and they managed to raise over £7500 for the Breast Cancer Campaign!



Kath Spence reaches the finish line.

Date for your diary

Paterson Institute Open Day to be held on Saturday 6th October

We are hoping to welcome around 100 members of the public and Cancer Research UK supporters to this year's open day at the Institute.

The purpose of the day is to showcase our research and thank those that work tirelessly to raise money for the charities that fund our work.

We require groups/areas that are willing to give 4 x 25 minute demos from 11:00 – 13:00 for up to 10 visitors at a time.

We also require guides who will take the visitors around the Institute from demo to demo.

On conclusion of the tours, lunch will be provided for all involved.

If you would like to help out or require more information please contact James Dunphy.



Farewell to Geoff Margison and the Carcinogenesis Group



The Institute has recently bid farewell to three of its longest serving members including Dr Geoff Margison who is retiring from the Institute after a lengthy association that began in 1966 and which culminated in his position as a Senior Group Leader.

For the last fifteen years, Geoff has led the Carcinogenesis Group where his research has focused on the biological effects

of alkylating agents and in particular, on the carcinogenic and chemotherapeutic nature of these compounds. Rather than leaving science completely, Geoff will be taking up an honorary post in the University of Manchester's Centre for Occupational and Environmental Health where he will continue his research in the laboratory of Dr Andy Povey, himself a former member of the Paterson Institute. Gail McGown and Mary Thorncroft have also served the Institute for many years, including the last twelve in the carcinogenesis group and Geoff, along with Jenny Varley (former head of the Cancer Genetics Group), reflects on their contributions below. First we feature a recent publication by the group in the prestigious journal Molecular Cell describing their work on the At1 DNA repair pathway.

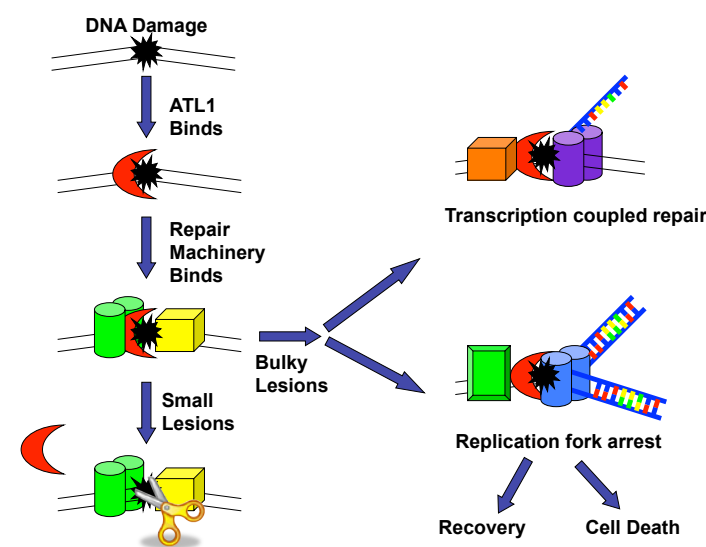
Decoding DNA Damage

Understanding DNA damage and how it is repaired is crucial in our understanding of cancer and how to treat it. DNA damage, if not correctly repaired, can lead to genetic mutations which cause cancer and allow it to adapt and grow. However the majority of cancer therapies (both chemotherapy and radiotherapy) work by causing enough DNA damage that the cancerous cells are forced to commit suicide in a process known as apoptosis. The Carcinogenesis group has recently published in Molecular Cell work on a key player in DNA damage repair, the protein alkyltransferase-like 1 (At1). The group has shown that At1 is responsible for regulating which of the nucleotide excision repair (NER) repair pathways (a process where the damaged DNA is chopped out and replaced with undamaged DNA) is used by the cell following exposure to chemotherapeutic drugs.

By working in the yeast *Schizosaccharomyces pombe* the group were able to show that if the DNA damage contained small O6-alkylguanines At1 could easily dissociate allowing global genome repair (GGR) to be completed accurately. In contrast if the DNA damage contained bulky O6-alkylguanines then At1 bound strongly and blocked GGR. This blockage of GGR stalls gene transcription and diverts the damage to the transcription-coupled repair pathway which results in cell cycle arrest followed either by repair of the damage or death of the cell. Should this process exist in humans it has the potential to be of great clinical significance with implications in both cancer prevention

(by improving DNA repair) and treatment (either by increasing the efficacy of current drugs or allowing the development of novel targeted therapies).

Ref: Latypov, Vitaly F., Tubbs, Julie L., Watson, Amanda J., Marriott, Andrew S., McGown, G., Thorncroft, M., Wilkinson, Oliver J., Senthong, P., Butt, A., Arvai, Andrew S., et al. (2012). At1 Regulates Choice between Global Genome and Transcription-Coupled Repair of O6-Alkylguanines. Molecular Cell. 13;47(1):50-60.



Reflections on Gail and Mary

By Geoff Margison



Gail McGown and Mary Thorncroft

June 29th 2012 will go down in history as the last day at the Paterson Institute for Gail McGown and Mary Thorncroft. Gail came to the Paterson as Gail Smart in 1980 to work with John Boyle in Brian Fox's Experimental Chemotherapy Group. There she was swept off her feet by a dashing young scot by the name of Alan McGown and they were married soon after. Mary joined David Scott and Margaret Fox's Cancer Genetics group at the Paterson in 1992 to work with John Boyle in a job share with Gail who having had her first child wanted to work part time and a famous partnership was born. When Margaret and then David retired, Jenny Varley took over that group and then when Jenny became Assistant Director, they joined the Carcinogenesis Group.

Gail and Mary's time at the PICR has been a metaphorical marriage of minds and souls, and like Simon and Garfunkel, Lennon and McCartney, the music that they made both to support the Paterson's research productivity and to colour our lives has been really amazing. In their scientific input, which has ranged from single nucleotide polymorphisms to surface plasmon resonance, and so very much more in between, their meticulous analytical approach to methodology has generated huge amounts of outstanding and high impact data. And as far as bringing colour to our lives is concerned, if lately the Carcinogenesis group had a personality, it was theirs, non-stop gassing and gossip, celebrating birthdays, organising social events, mothering students, smothering post docs. It really is impossible to adequately convey Gail and Mary's combined 55-year devotion to the spirit and objectives of the Paterson, but I can try. In terms of their scientific contribution, I think a most appropriate quotation is from Isaac Newton:

"If I have seen further, it is by standing on the shoulders of giants" And thinking back over the years; the good things and the bad things, the happy times and the sad times, the many good friends they made and the legions of colleagues they worked with; all of this and more might be summed up in:

"We few, we happy few, we band of brothers" [William Shakespeare] And finally a rather apt quote attributed to Theodor Geisel: "Don't cry because it's over, smile, because it happened".

By Jenny Varley

Gail and Mary worked with me for many years in the Cancer Genetics Group. They were engaged on a project identifying and characterising germline TP53 mutations in DNA from members of families with so-called Li-Fraumeni Syndrome.

As such their work had to be of the highest quality, reproducible and communicated with sensitivity to both me and to clinical colleagues managing these patients and families. They did a superb job and they were totally committed to their work. They job-shared in a fantastically efficient way, and I know they spent many hours speaking on the phone to each other to make sure the project proceeded seamlessly, which it always did. Geoff was very fortunate when they joined his group when I took over as Assistant Director, and I know that they continued to work at the highest level. When I first arrived in the Paterson, like many people, I confused Gail and Mary, but not as much as they baffled another (nameless) colleague who spent many years thinking they were a single person! Not only were they great scientific colleagues, but also they were great fun to work with. They wrote kind words about me when I left the Institute, including mentioning the infamous Bar Rallies we jointly participated in. Maybe my most vivid memory of these times was when our Department chose to go as multiple Margaret Thatchers (with poor Martin Greaves as the sole and uncannily realistic Dennis). Happy Days! I wish them both the very best for the future, and thank them for their professionalism, help, friendship and laughter when we worked together.

Fundraising

A Cut Above The Rest

As well as the usual Relay for Life activities, Paterson scientists also decided to do something a little different to help raise money as part of this year's event. One of the Paterson Scientists' team, Danielle Potter, was a hair stylist for twelve years before starting her PhD last autumn in the Clinical and Experimental Pharmacology Group.

The team decided to make good use of Danielle's extensive experience as a senior stylist at Toni and Guy and set up a 'pop up' hair salon in the Institute for a day. Here staff from both the Institute as well as The Christie had their hair cut and styled at discounted prices with all the proceeds adding to the overall total raised by the Relay for Life event. The salon was in one of the Institute's meeting rooms and created a few strange looks but a great response. Toni and Guy on Deansgate, Manchester supported the event by donating styling products, gowns and mirrors and Danielle invited her old Toni and Guy work colleagues, Charlotte Farrell, Clare Hall and Kylie Jones to join her. They were more than happy to help and dedicate their time for such a worthwhile cause. The success of the event has even



Danielle Potter from the CEP Group styles Hannah Harrison from Molecular Pathology



The four stylists: Clare Hall, Danielle Potter, Charlotte Farrell and Kylie Jones.

led to ideas for a repeat session sometime in the future. The four stylists cut and styled forty clients from 10am till 6.30pm resulting in a fantastic £886 raised for the Relay for Life event.

Many thanks to Danielle, Charlotte, Clare and Kylie for their fantastic work, to the Relay for Life team for organising the event and tidying up and finally to everyone who came along for a new look!

Relay for Life

By Emily Holmes



Some of the members of the Relay for Life Team

For the past four years Paterson Scientists have taken part in the Stockport Relay for Life. This event provides us with the opportunity to not only raise money for Cancer Research UK, but also to say thank you to the hard working fundraisers in Manchester.

The relay is a 24 hour event where at least one member of the team has to walk around an athletics track at any time. On the day we set up a stall from which we were able to demonstrate DNA extraction from cheek cells and strawberries. Thanks to the entertainment put on throughout the event, including Zumba, space hopper races and the "Relay's Got Talent" competition, the 24 hours passed quickly! Despite the weather, which at one point blew over our stall, the event was great fun. We would like to thank everyone who supported the Paterson Scientists team, including those who bought cakes, entered the football sweepstake, bought raffle tickets and had their hair cut, as so far we have raised over £2300 for CR-UK.

Making Great Strides for Cancer Research UK

By Helen Whalley

The coast to coast walk was devised by Alfred Wainwright, whose famous book describes the route; beginning in St. Bees on the west coast, it crosses three national parks to finally reach Robin Hood's bay on the east coast. What better way to spend our holiday than a lovely walk across the English countryside, and raise money for Cancer Research UK at the same time? Great idea!

With over £1000 sponsorship money promised and accommodation booked, we set off keenly with our rucksacks carrying everything we would need for the 2-week trek. The first few days promised to be the most spectacular, from the coast to the first hills and across the Lake District. But wait, we didn't realise we would have to climb hundreds of metres up these hills & mountains every day! Apparently the vertical distance over the whole walk is equivalent to climbing Mount Everest (why did no-one tell me this before I set off?) And what's this, surely not RAIN for days on end during the British summer-time? A few days in, up to our knees in water on top of the Yorkshire Dales (or Giant Marsh as it would more appropriately be called), we're thinking maybe this wasn't such a good idea after all. However, we continued regardless, and it was all worth it when on day 13 (now with very unhappy legs) we caught the first glimpse of Robin Hood's Bay. We'd made it!



Helen and her husband Mike making their way through the Lake District

It was certainly an adventure we'll never forget, and would recommend it, but my advice to anyone mad enough to attempt the coast to coast is to buy waterproof everything & take plenty of spare socks!

Drug Discovery On The Run

By Kate Smith

Not all scientists wear white coats, but those from Drug Discovery did whilst running the Bupa Great Manchester Run on Sunday 20th May.

Thirteen researchers ran or walked the 10K distance through the streets of Manchester to raise both money for Cancer Research UK, and awareness of the work funded by the charity at the Paterson Institute. They formed part of the 1,400-strong team who took part in the Bupa Great Manchester Run on behalf of Cancer Research UK, raising an estimated £180,000 for the charity.

A number of the group run regularly on a Tuesday evening, and the idea to run the Bupa Great Manchester Run as a department came from this informal gathering. Somewhere along the line wearing lab coats was mentioned, and the idea grew to involve the whole group in our fundraising efforts, which aimed to raise £1500. As a team we hoped the impact of running in our lab coats would raise awareness of the scientists at the Paterson Institute.

We all felt we should do something to raise money for Cancer Research UK as we know only too well just how vital fundraising is to the charity. It was also our way of getting out and thanking all the fundraisers who work so hard for us and allow our team to carry out such fantastic work here in Manchester. If the cheers and clapping from the many spectators lining the route were anything to go by, we certainly made an impression. We were even tweeted about by our fellow runners, including those from Manchester United!

Although running the 10K in lab coats was rather warm and tough in places, the support the team received in our fundraising spurred us on; thank you to everyone who sponsored us or thought of us whilst tucking into cakes from our cake sale! The cake sale and raffle held at the Institute was a major boost to our fundraising. The many bakers of the Drug Discovery team set to work making cakes, muffins and biscuits, resulting in a fantastic display of sweet treats. In addition, several local businesses donated a variety of goods for the raffle, with top prizes including Afternoon Tea for two from Silver Apples of West Didsbury and a hamper of goodies and £20 voucher from Didsbury Farm shop.

Thank you to everyone on the team and in Drug Discovery for their enthusiasm and participation. Thank you again to everyone who has helped and supported us in our fundraising efforts; the total raised so far is a fantastic £3200 (including Gift Aid). We all thoroughly enjoyed the run and taking our lab coats out of the lab and onto the streets of Manchester!

For anyone interested in joining our weekly running group, Tuesday 5.10 pm, please email ksmith@picr.man.ac.uk

The team included: Allan Jordan, Ali Raoof, Alison McGonagle, Alex Boakes, Bohdan Waszkowycz, Dave Stowell, Donald Ogilvie, Gemma Hopkins, Helen Small, Ian Waddell, Kate Smith, Kiran Batta, Mark Cockerill.



The Chemists looking keen – well most of them.....

In the spotlight with Jodie Whitaker

From the Molecular Biology Core Facility

Jodie has been at the Institute for three years having joined us directly from studying Biology at the University of York. She started work on the sequencing and genotyping services and now runs the Cancer Research UK microarray service which processes samples from across the country. She is currently studying for an MSc in Molecular Pathology and Genomics at Barts and the London School of Medicine and Dentistry via distance learning.

1. What is your favourite part of the UK?

The Yorkshire Dales

2. What was your best ever holiday and why?

India-it's amazing.

3. Which website do you always check, and why?

Ebay-I'm addicted.

4. What is your favourite film?

O Brother, Where art Thou?

5. What is your favourite band/singer?

Pulp

6. If you had to change careers tomorrow, what would you do?

In reality? Probably a waitress.

Ideally? Book Critic.

7. What is the most important lesson that you have learnt from life?

Don't take it seriously.

8. Name three things you would take with you to a desert island?

Swiss army knife, rope, beginners guide to raft making.

9. What is your greatest fear?

Madness.

10. How would you like to be remembered?

Fondly.

11. If you could change one thing in your past what would it be?

Bad decisions make you who you are.

12. What is your signature dish to cook?

Lentil and vegetable soup.



13. You've just won the lottery and have £5 million pounds to spend.

What do you buy first?

A round of drinks and a round the world ticket.

14. What is your idea of perfect happiness?

Pink gin -bath -book.

15. What keeps you awake at night?

I'm very good at sleeping.

Editorial Team:

Steve Bagley
Gillian Campbell
James Dunphy
Ruth Perkins
Siana Peters
Darren Roberts
Steve Royle
Caroline Wilkinson

Paterson Institute for Cancer Research

The University of Manchester
Wilmslow Road
Manchester
M20 4BX

t: 0161 446 3156

www.paterson.man.ac.uk

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www.cornerstonedm.co.uk

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