XVIII IWCLL

International Workshop on CLL
20-23 SEPTEMBER 2019 EDINBURGH

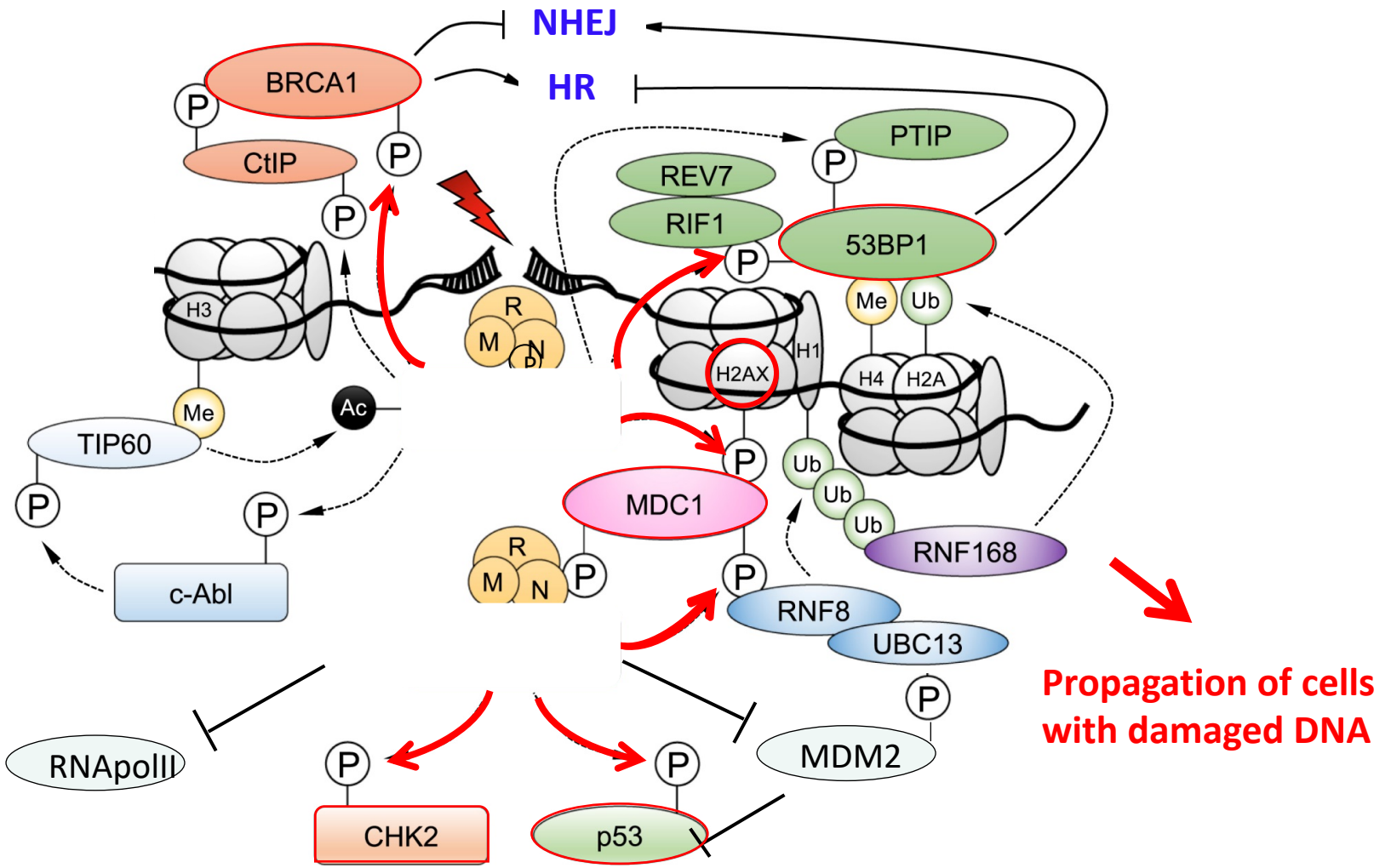
ATM: pathway, lesions, targeting

Tatjana Stankovic
Institute of Cancer and Genomic Sciences
University of Birmingham, UK

Disclosures

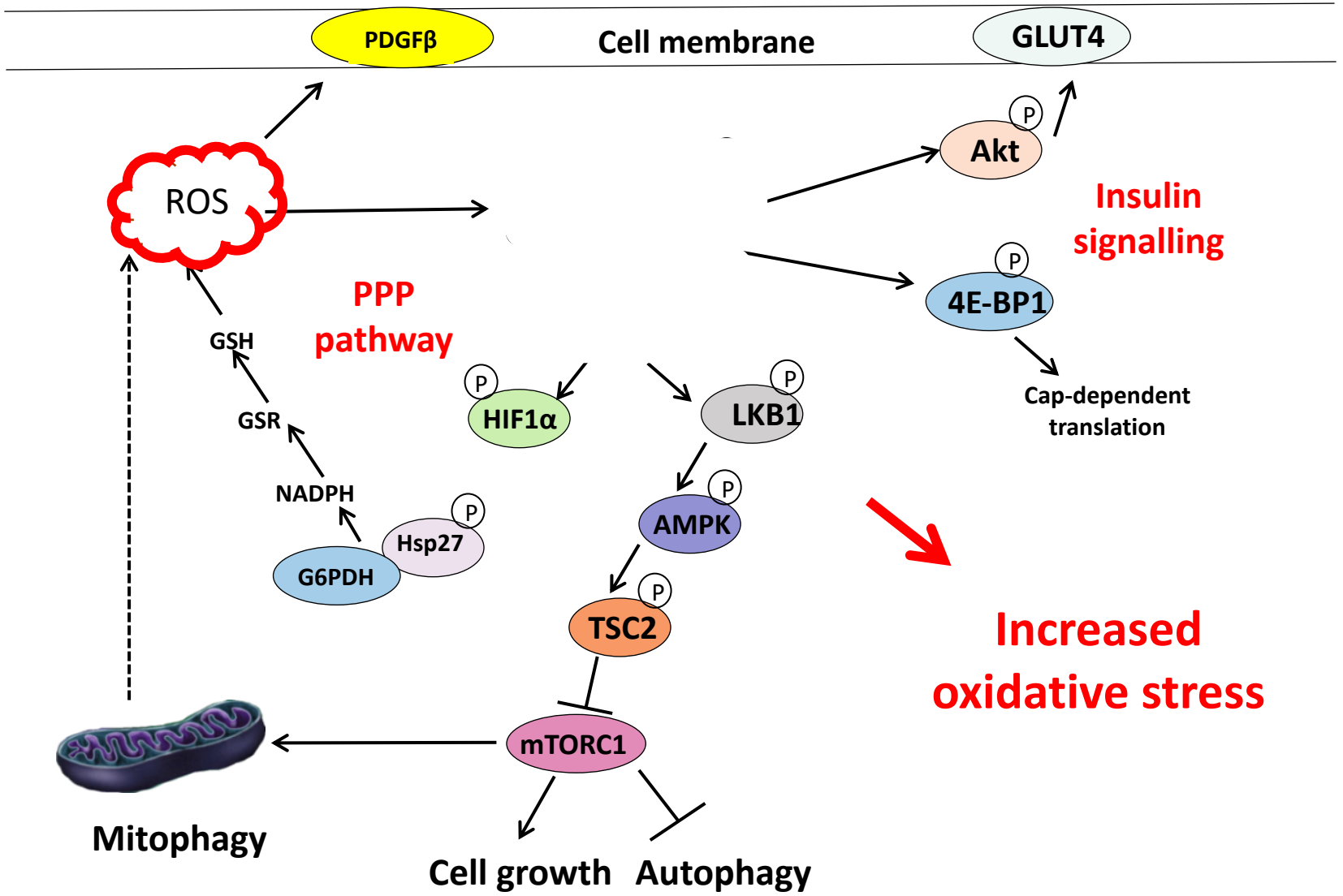
- None

ATM kinase as an active monomer: nuclear functions



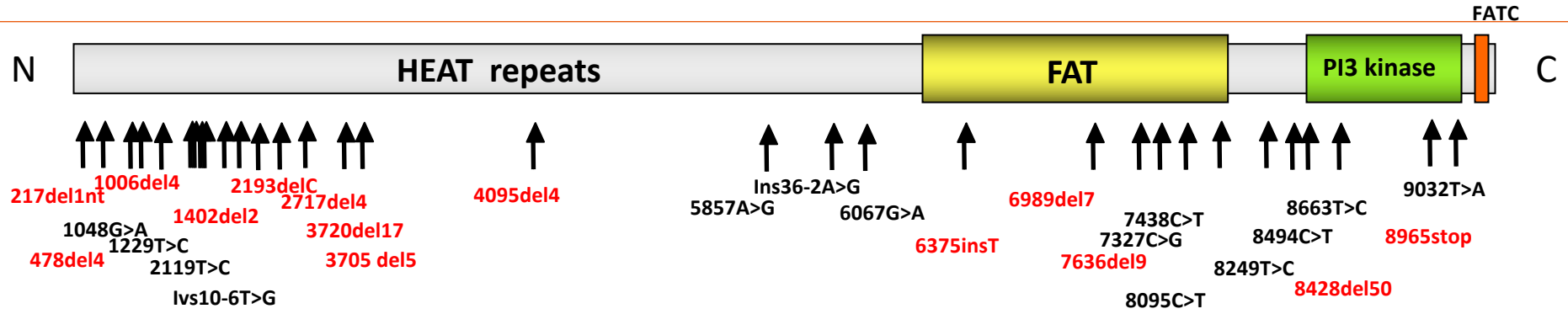
Adapted from Blackford, Jackson, Mol Cell 2017

ATM as an active dimer: cytoplasmic functions



Adapted from Ambrose, Gatti, Blood 2013

ATM gene, localised on 11q23, is frequently altered in CLL



EARLY REPORTS

Early reports THE LANCET • Vol 353 • January 2, 1999

Inactivation of ataxia telangiectasia mutated gene in B-cell chronic lymphocytic leukaemia

Tatjana Stankovic, Peter Weber, Grant Stewart, Tina Bedenham, Jim Murray, Phil J Byrd, Paul A H Moss, A Malcolm R Taylor

blood 2004 103: 291-300 doi:10.1182/blood-2003-04-1161 originally published online September 4, 2003

Microarray analysis reveals that *TP53*- and *ATM*-mutant B-CLLs share a defect in activating proapoptotic responses after DNA damage but are distinguished by major differences in activating prosurvival responses

Tatjana Stankovic, Mike Hubank, Debbie Cronin, Grant S. Stewart, Danielle Fletcher, Colin R. Bignell, Azra J. Alvi, Belinda Austen, Victoria J. Weston, Christopher Fegan, Philip J. Byrd, Paul A. H. Moss and A. Malcolm R. Taylor

blood 2001 98: 814-822 doi:10.1182/blood.V98.3.814

p53 dysfunction in B-cell chronic lymphocytic leukemia: inactivation of *ATM* as an alternative to *TP53* mutation

Andrew R. Pettitt, Paul D. Sherrington, Grant Stewart, John C. Cawley, A. Malcolm R. Taylor and Tatjana Stankovic

blood 2005 106: 3175-3182 doi:10.1182/blood-2004-11-4516 originally published online July 12, 2005

Mutations in the *ATM* gene lead to impaired overall and treatment-free survival that is independent of *IGVH* mutation status in patients with B-CLL

Belinda Austen, Judith E. Powell, Azra Alvi, Ian Edwards, Laura Hooper, Jane Starczynski, A. Malcolm R. Taylor, Christopher Fegan, Paul Moss and Tatjana Stankovic

blood 2002 99: 300-309 doi:10.1182/blood.V99.1.300

Ataxia telangiectasia mutated–deficient B-cell chronic lymphocytic leukemia occurs in pregerminal center cells and results in defective damage response and unrepaired chromosome damage

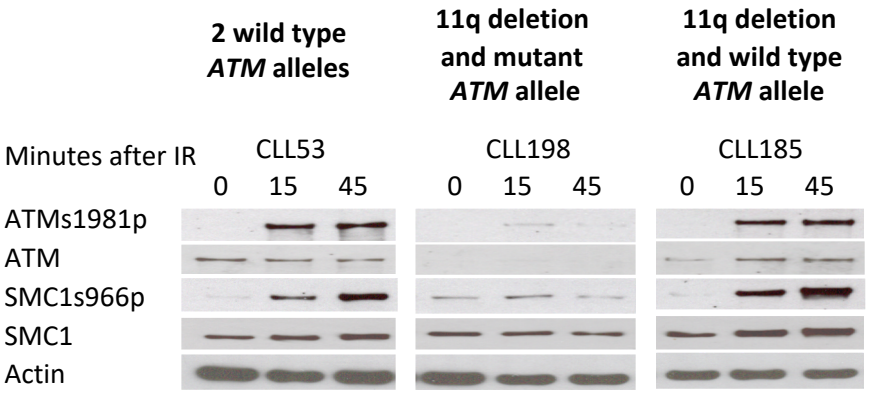
Tatjana Stankovic, Grant S. Stewart, Christopher Fegan, Paul Biggs, James Last, Philip J. Byrd, Russell D. Keenan, Paul A. H. Moss and Alexander M. R. Taylor

bjh research paper

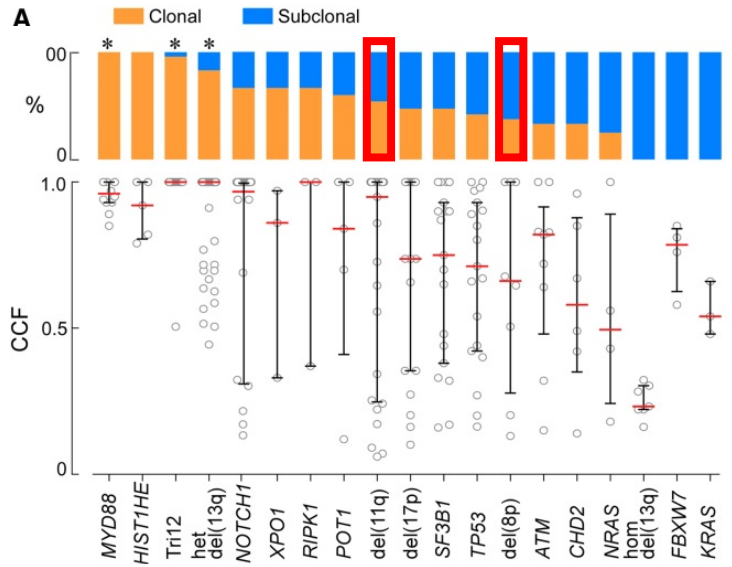
Association of gene mutations with time-to-first treatment in 384 treatment-naive chronic lymphocytic leukaemia patients

ATM gene alterations and ATM kinase deficiency

- ***ATM*** **mutations occur in up to 36% of patients with 11q deletion**
- **In majority of cases loss of both *ATM* alleles is required for the loss of ATM kinase activity**
- ***ATM*** **alterations are subclonal in a proportion of patients**



Austin et al, JCO, 2007



Landau et al, Cell 2013

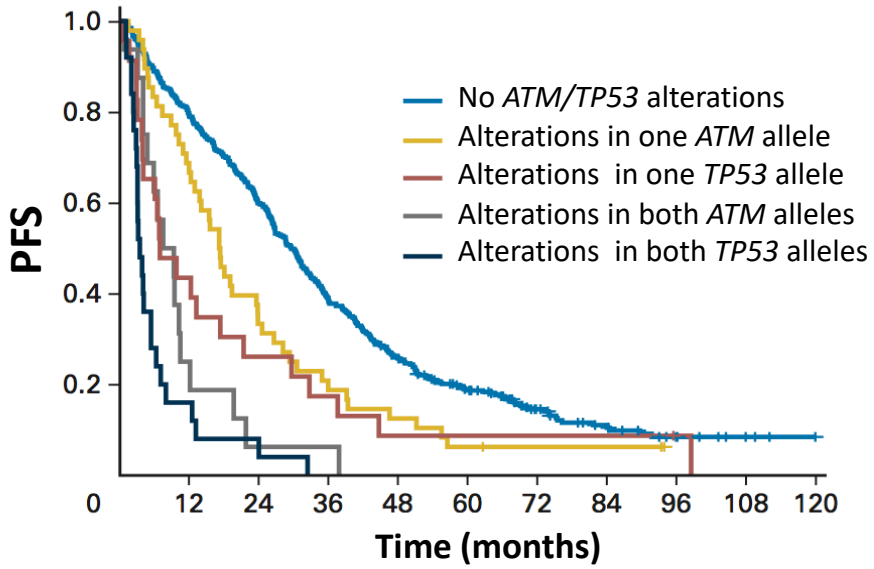
Clinical impact of *ATM* alterations

VOLUME 30 · NUMBER 36 · DECEMBER 20 2012
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Biallelic *ATM* Inactivation Significantly Reduces Survival in Patients Treated on the United Kingdom Leukemia Research Fund Chronic Lymphocytic Leukemia 4 Trial

Anna Skowronska, Anton Parker, Gulshanara Ahmed, Ceri Oldreive, Zadie Davis, Sue Richards, Martin Dyer, Estella Matutes, David Gonzalez, A. Malcolm R. Taylor, Paul Moss, Peter Thomas, David Oscier, and Tatjana Stankovic

CLL4 cohort (front-line Chl or F±C)

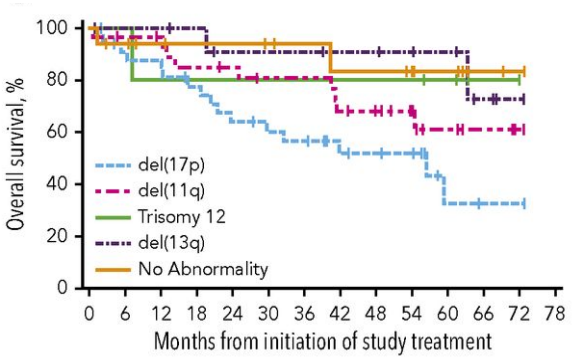


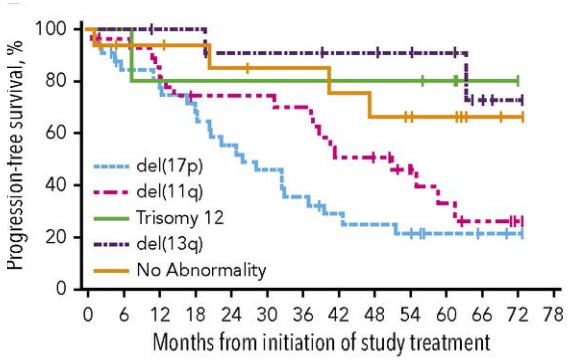
blood Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Single-agent ibrutinib in treatment-naïve and relapsed/refractory chronic lymphocytic leukemia: a 5-year experience

Susan O'Brien,[1,2] Richard R. Furman,[3] Steven Coutre,[4] Ian W. Flinn,[5] Jan A. Burger,[1] Kristie Blum,[6] Jeff Sharman,[7] William Wierda,[1] Jeffrey Jones,[6] Weiqiang Zhao,[4] Nyla A. Heerema,[6] Amy J. Johnson,[4] Ying Luan,[8] Danelle F. James,[8] Alvina D. Chu,[8] and John C. Byrd[6]



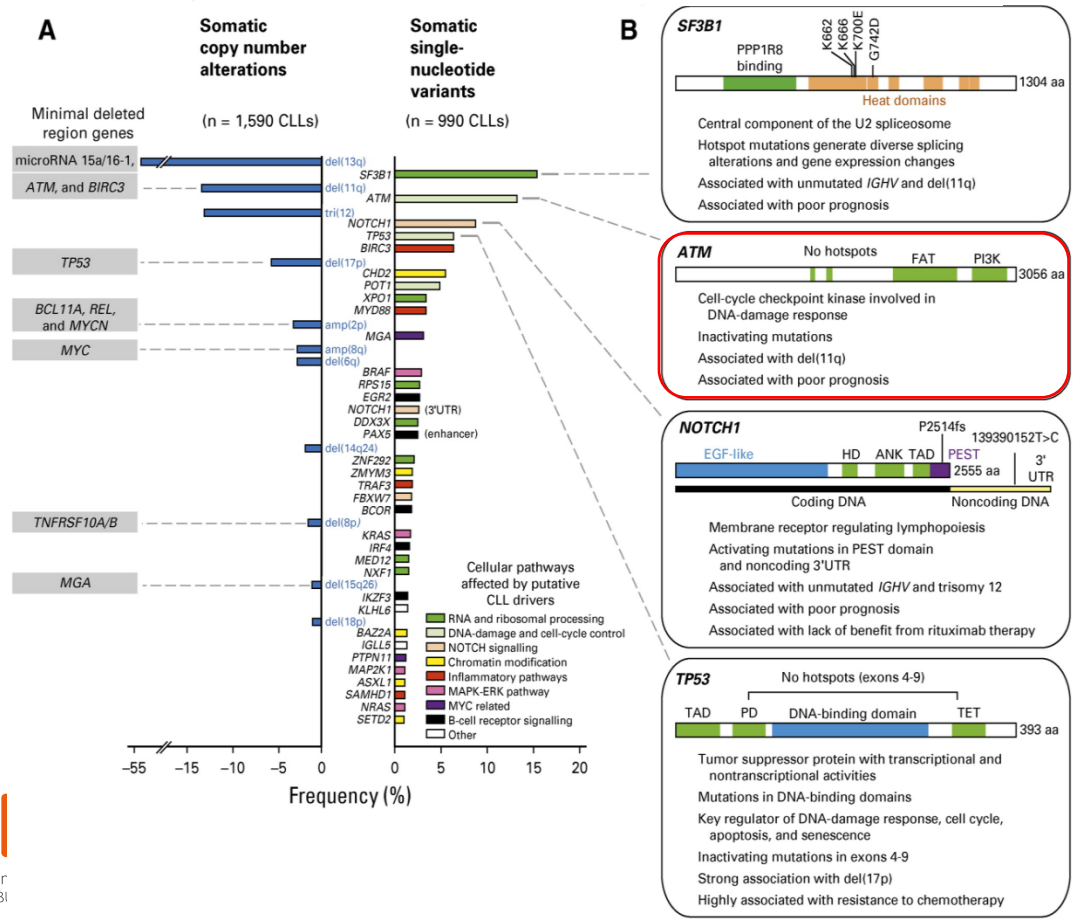


ATM alterations and genomic instability

VOLUME 35 · NUMBER 9 · MARCH 20, 2017
JOURNAL OF CLINICAL ONCOLOGY REVIEW ARTICLE

Clinical Implications of Novel Genomic Discoveries in Chronic Lymphocytic Leukemia

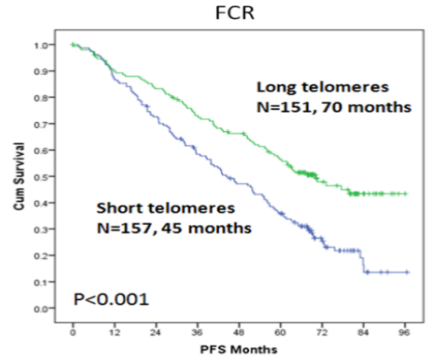
Gregory Lazarian, Romain Guièze, and Catherine J. Wu

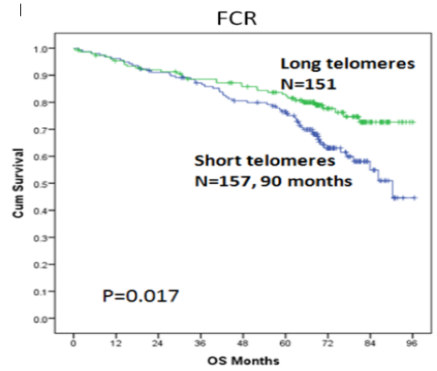


Leukemia
https://doi.org/10.1038/s41375-019-0446-4
ARTICLE
Chronic lymphocytic leukemia

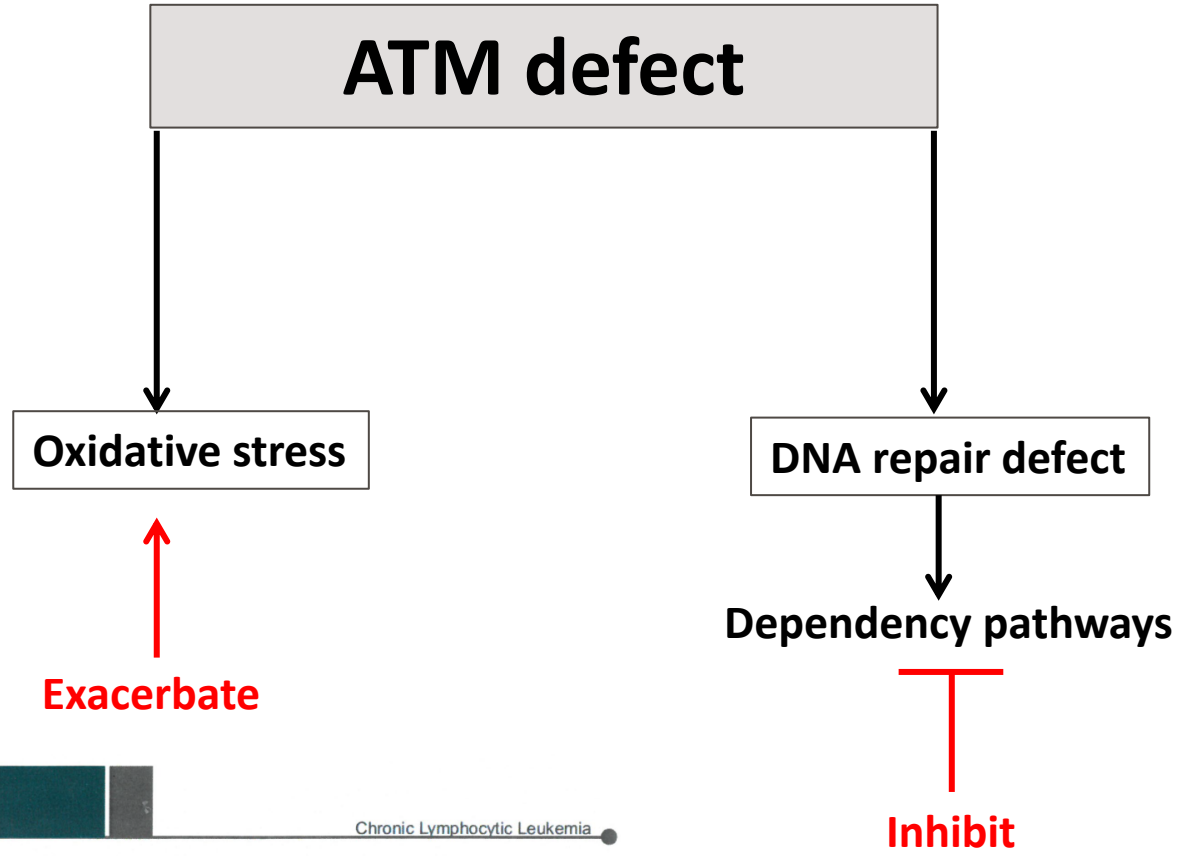
Short telomeres are associated with inferior outcome, genomic complexity, and clonal evolution in chronic lymphocytic leukemia

Billy Michael Chelliah Jebaraj[1] · Eugen Tausch[1] · Dan A. Landau[2,3,4] · Jasmin Bahlo[5] · Sandra Robrecht[5] · Amaro N. Taylor-Weiner[6] · Johannes Bloehdorn[1] · Annika Scheffold[1] · Daniel Mertens[1,7] · Sebastian Böttcher[8,12] · Michael Kneba[8] · Ulrich Jäger[9] · Thorsten Zenz[1,13] · Michael K. Wenger[10] · Guenter Fingerle-Rowson[10] · Clemens Wendtner[11] · Anna-Maria Fink[5] · Catherine J. Wu[6] · Barbara Eichhorst[5] · Kirsten Fischer[5] · Michael Hallek[5] · Hartmut Döhner[1] · Stephan Stilgenbauer[1]





Strategies to target ATM defect in CLL



MedChemComm

RESEARCH ARTICLE

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Cite this: *Med. Chem. Commun.*, 2019, **10**, 1379

Derivatisation of parthenolide to address chemoresistant chronic lymphocytic leukaemia†

Xingjian Li, ‡[a] Daniel T. Payne, ‡[a] Badarinath Ampolu,§[b] Nicholas Bland,¶[b] Jane T. Brown,[b] Mark J. Dutton,[a] Catherine A. Fitton, [c] Abigail Gulliver,[d] Lee Hale,[d] Daniel Hamza,[b] Geraint Jones,[b] Rebecca Lane,[b] Andrew G. Leach, [e] Louise Male,[f] Elena G. Merisor,[b] Michael J. Morton, [g] Alex S. Quy, [a] Ruth Roberts, [gh] Rosanna Scarll,[c] Timothy Schulz-Utermoehl,[b] Tatjana Stankovic,[c] Brett Stevenson,[b] John S. Fossey ‡*[a] and Angelo Agathanggelou ‡*[c]

ARTICLE

Chronic Lymphocytic Leukemia

Targeting the Ataxia Telangiectasia Mutated-null phenotype in chronic lymphocytic leukemia with pro-oxidants

Angelo Agathanggelou,[1] Victoria J. Weston,[1] Tracey Perry,[1] Nicholas J. Davies,[1] Anna Skowronska,[1] Daniel T. Payne,[2] John S. Fossey,[2] Ceri E. Oldreive,[1] Wenbin Wei,[1] Guy Pratt,[1,3] Helen Parry,[3] David Oscier,[4] Steve J. Coles,[5] Paul S. Hole,[5] Richard L. Darley,[5] Michael McMahon,[6] John D. Hayes,[6] Paul Moss,[1] Grant S. Stewart,[1] A. Malcolm R. Taylor,[1] and Tatjana Stankovic[1]

[1]School of Cancer Sciences, University of Birmingham; [2]School of Chemistry, University of Birmingham; [3]Haematology Department, Birmingham Heartlands Hospital; [4]Haematology Department, Royal Bournemouth Hospital, Dorset; [5]Department of Haematology, Institute of Cancer and Genetics, Cardiff University School of Medicine, Cardiff; [6]Medical Research Institute, University of Dundee, UK

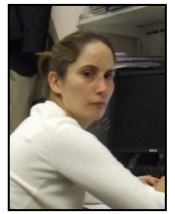
Dependency 1. ATM and single strand break repair- targeting PARP

Dr Weston

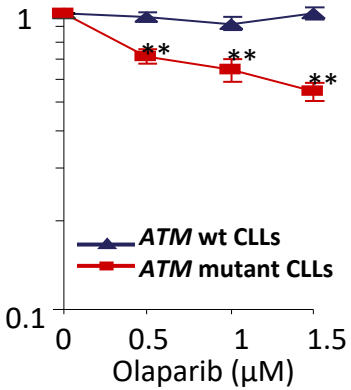
blood®
2010 116: 4578-4587
doi:10.1182/blood-2010-01-265769 originally published online August 25, 2010

The PARP inhibitor olaparib induces significant killing of *ATM*-deficient lymphoid tumor cells in vitro and in vivo

Victoria J. Weston, Ceri E. Oldreive, Anna Skowronska, David G. Oscier, Guy Pratt, Martin J. S. Dyer, Graeme Smith, Judy E. Powell, Zbigniew Rudzki, Pamela Kearns, Paul A. H. Moss, A. Malcolm R. Taylor and Tatjana Stankovic

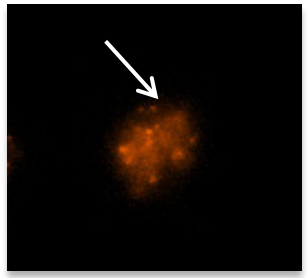


Dr Oldreive

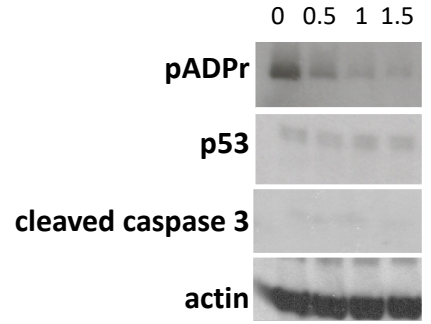


No treatment Olaparib

γH2AX



μM Olaparib



Significant cytotoxic effect *in vitro* and *in vivo*

Accumulation of damaged cells

Tumour killing without ATM/p53 apoptosis

PICLLE TRIAL

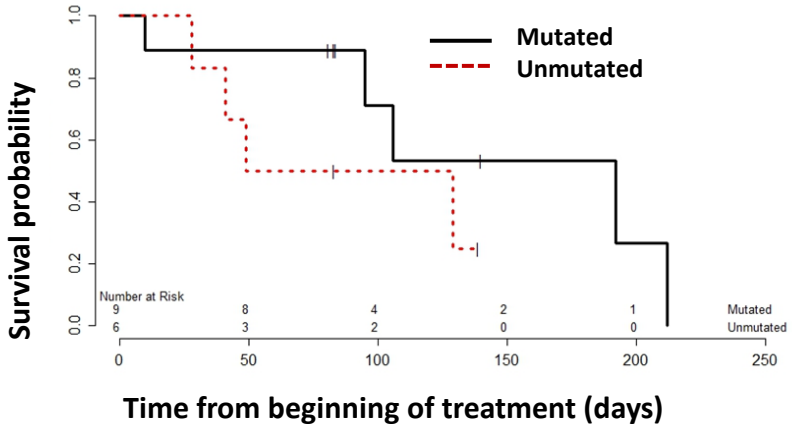
bjh correspondence

A multi-centre phase I trial of the PARP inhibitor olaparib in patients with relapsed chronic lymphocytic leukaemia, T-prolymphocytic leukaemia or mantle cell lymphoma

Dr Guy Pratt

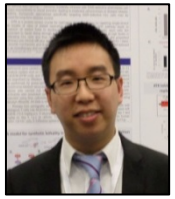
Nicola Fenwick

- **15 patients enrolled in the trial**
- **Olaparib generally well tolerated**



Therefore, aberrations in the ATM pathway may be associated with improved responses and OS with PARP inhibitor treatments even among heavily pre-treated and relapsed patients with CLL, MCL and T-PLL.

Dependency 2. ATM and replication stress –targeting ATR

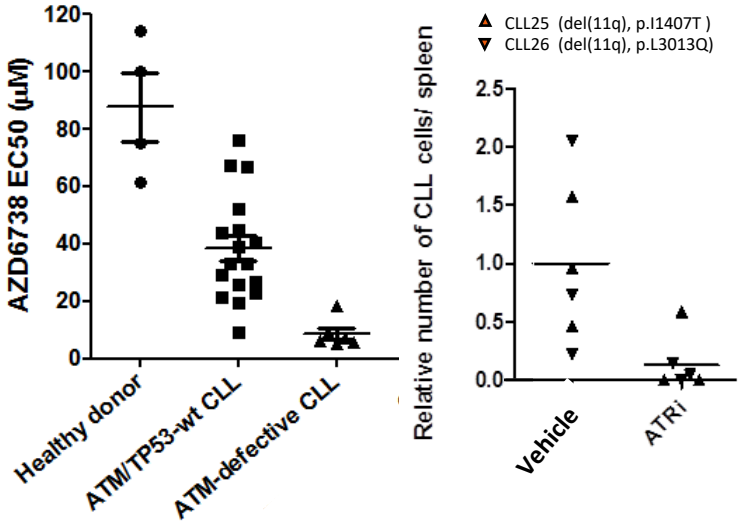


Dr Kwok

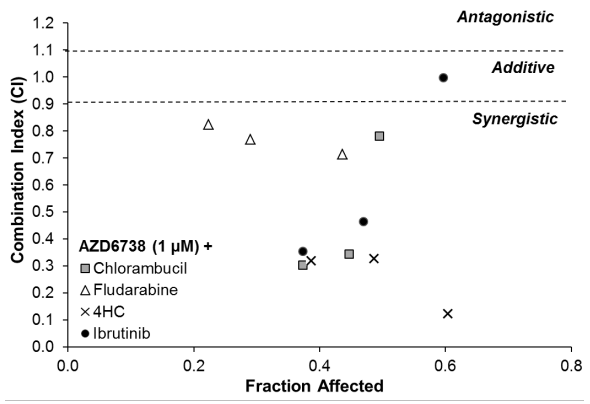
blood®
2016 127: 582-595
doi:10.1182/blood-2015-05-644872 originally published online November 12, 2015

ATR inhibition induces synthetic lethality and overcomes chemoresistance in *TP53*- or *ATM*-defective chronic lymphocytic leukemia cells

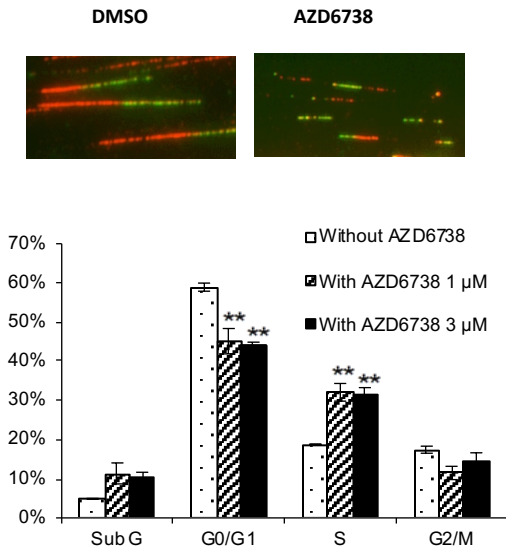
Marwan Kwok, Nicholas Davies, Angelo Agathanggelou, Edward Smith, Ceri Oldreive, Eva Petermann, Grant Stewart, Jeff Brown, Alan Lau, Guy Pratt, Helen Parry, Malcolm Taylor, Paul Moss, Peter Hillmen and Tatjana Stankovic



Selective killing of ATM deficient CLLs *in vitro* and *in vivo*



Synergy with Ibrutinib



Exacerbation of replication stress

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Dependency 3. ATM and HRR– targeting deubiquitinase USP7

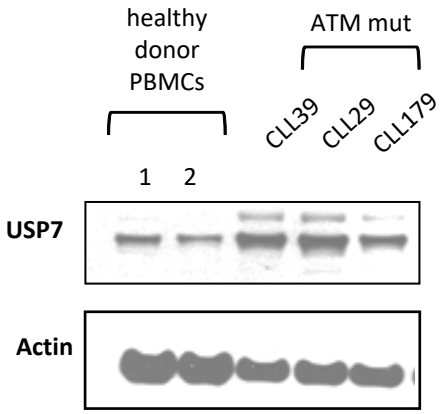
Dr Agathanggelou

Ed Smith

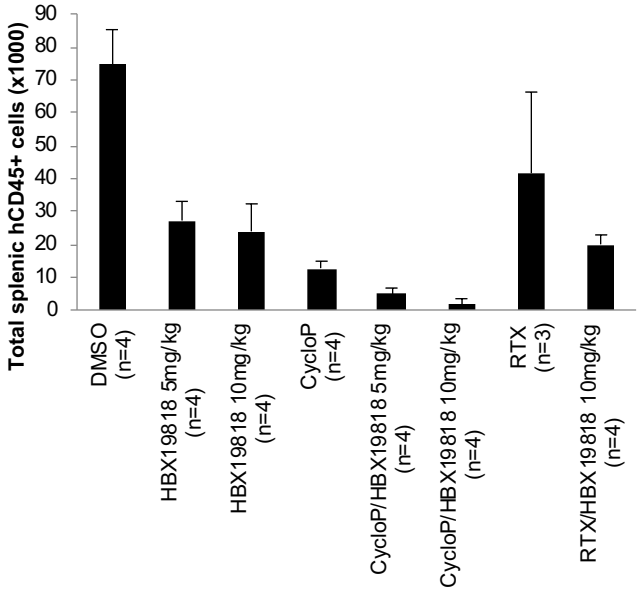
blood®
2017 130: 156-166
doi:10.1182/blood-2016-12-758219 originally published online May 11, 2017

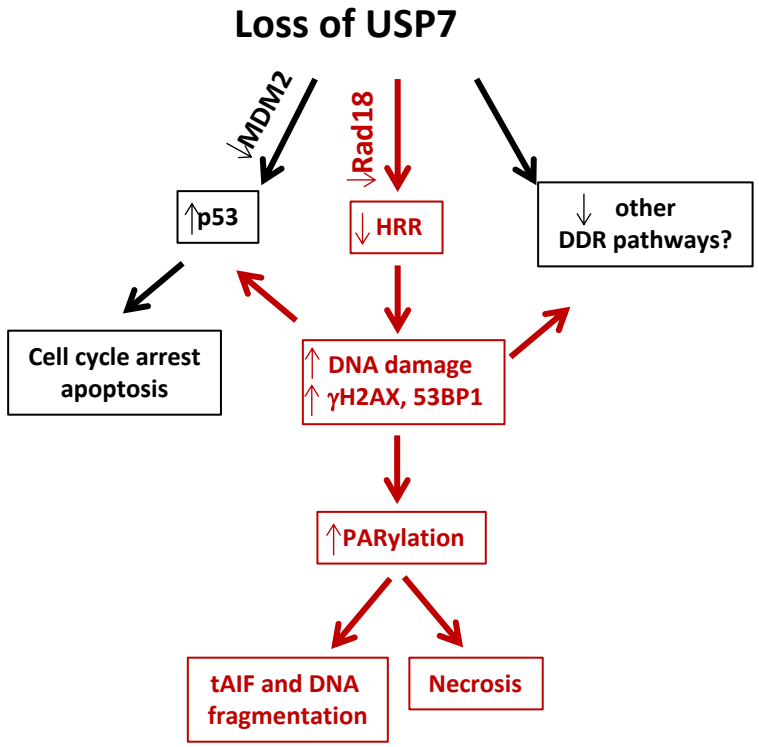
USP7 inhibition alters homologous recombination repair and targets CLL cells independently of ATM/p53 functional status

Angelo Agathanggelou, Edward Smith, Nicholas J. Davies, Marwan Kwok, Anastasia Zlatanou, Ceri E. Oldreive, Jingwen Mao, David Da Costa, Sina Yadollahi, Tracey Perry, Pamela Kearns, Anna Skowronska, Elliot Yates, Helen Parry, Peter Hillmen, Celine Reverdy, Remi Delansorne, Shankara Paneesha, Guy Pratt, Paul Moss, A. Malcolm R. Taylor, Grant S. Stewart and Tatjana Stankovic



USP7 inhibition sensitizes CLL to HRR inducing-therapy *in vivo*





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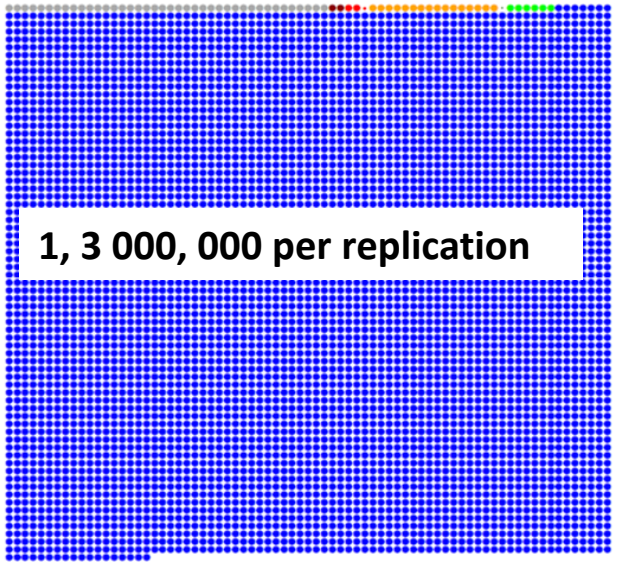
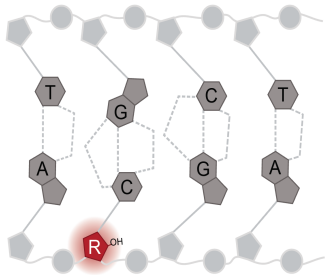
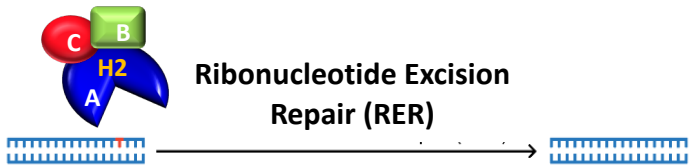
Dependency 4. ATM and Ribonucleotide excision repair RNaseH2 as a new target?





RNaseH2



LETTER NATURE | www.nature.com/nature

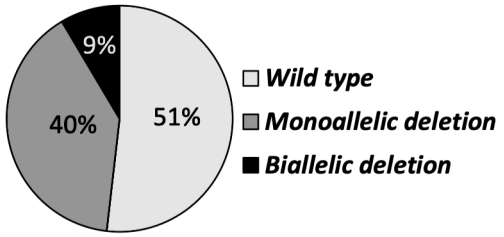
ps://doi.org/10.1038/s41586-018-0291-z

CRISPR screens identify genomic ribonucleotides as a source of PARP-trapping lesions

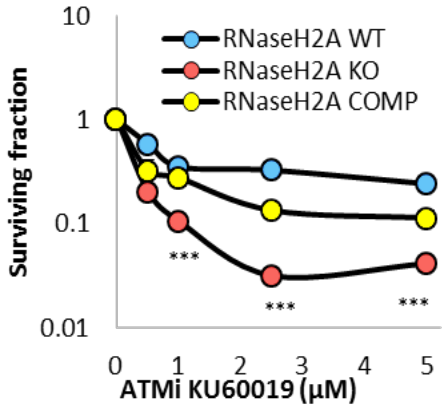
Michal Zimmermann[1,14], Olga Murina[2,14], Martin A. M. Reijns[2], Angelo Agathanggelou[3], Rachel Challis[2], Žygimantė Tarnauskaitė[2], Morwenna Muir[4], Adeline Fluteau[2], Michael Aregger[5], Andrea McEwan[1], Wei Yuan[6], Matthew Clarke[6], Maryou B. Lambros[6], Shankara Paneesha[7], Paul Moss[8], Megha Chandrashekhar[5,9], Stephane Angers[10], Jason Moffat[5,9,11], Valerie G. Brunton[4], Traver Hart[12], Johann de Bono[6,13], Tatjana Stankovic[3], Andrew P. Jackson[2]* & Daniel Durocher[1,9]*

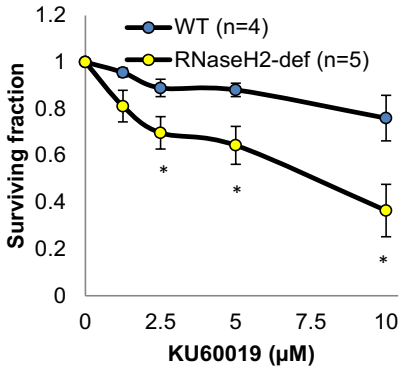
Dr Agathanggelou

***RNASEH2B* loss (13q del)**



n=164





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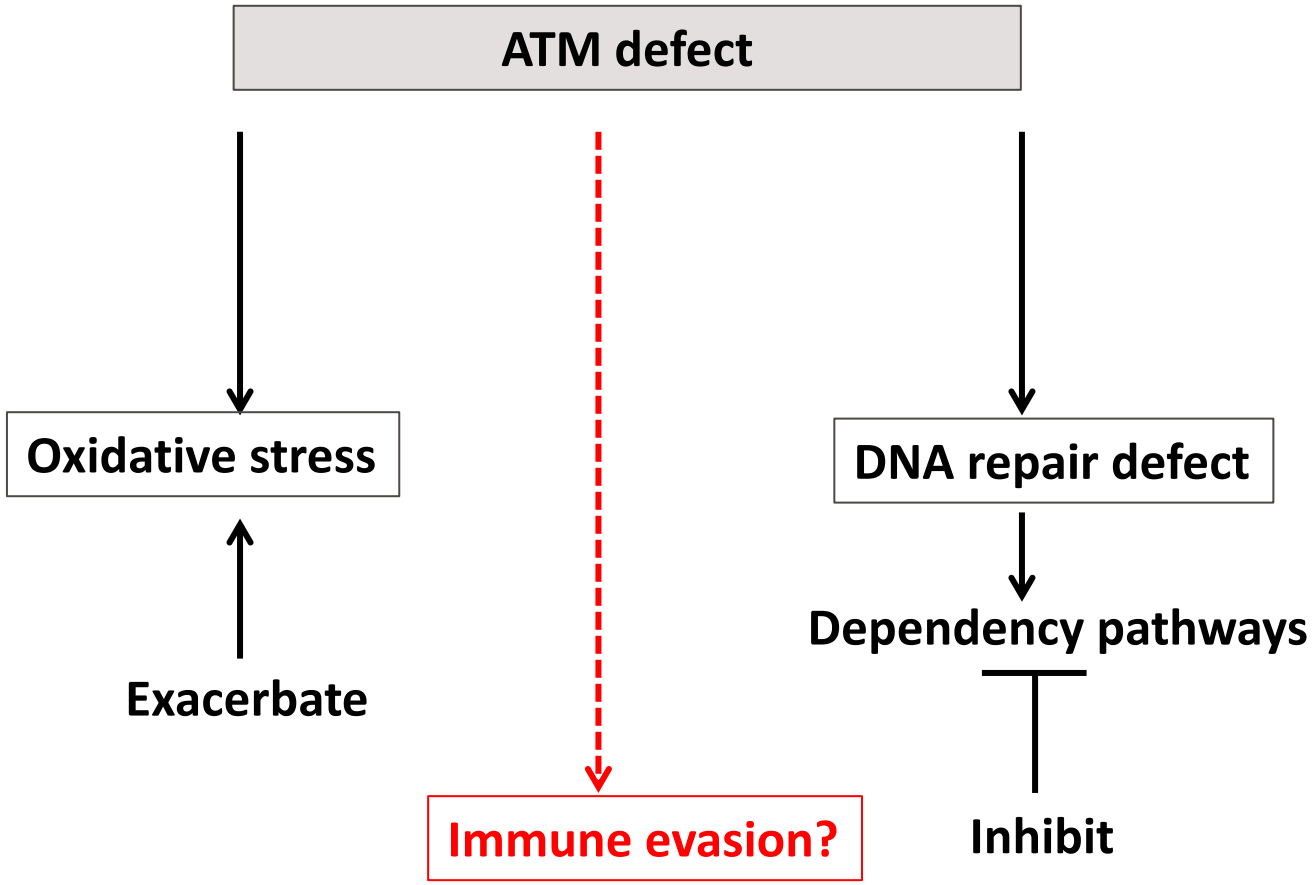
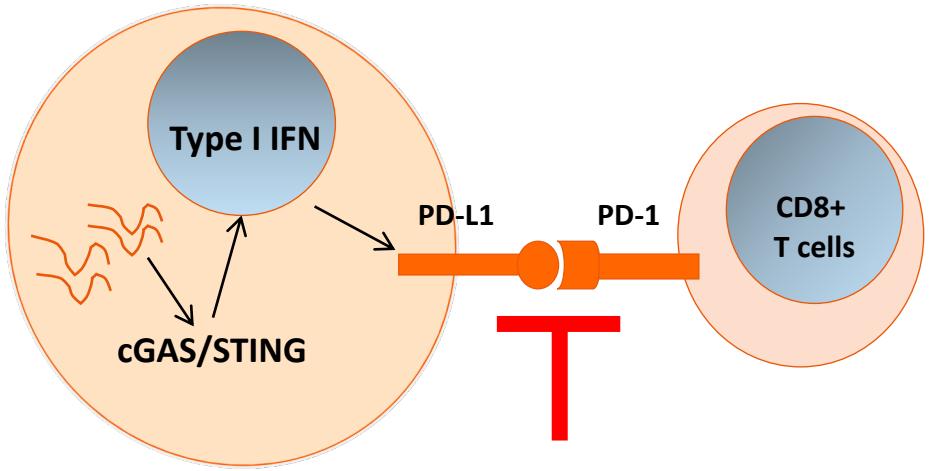
Strategies to target ATM defect in CLL





Conclusions

- ATM-defective phenotype in CLL has functional and clinical consequences.
- Due to genomic instability ATM-defective CLL subclones may drive disease progression even in an era of new targeted treatments.
- ATM-deficient phenotype provides an opportunity for targeting oxidative stress, DNA repair dependency pathways and potentially immune checkpoints.

Acknowledgements

Marwan Kwok
Angelo Agathanggelou
Nicholas Davies
Ceri Oldreive
Edward Smith
Victoria Weston
Anna Skowronska
Belinda Austen

Paul Moss
Guy Pratt
Malcolm Taylor
Grant Stewart
Peter Hillmen

Daniel Durocher
Michal Zimmermann
Andrew Jackson
Olga Murina