Project BASTION „From Basic to Translational Research in Oncology”

Kick-off Meeting

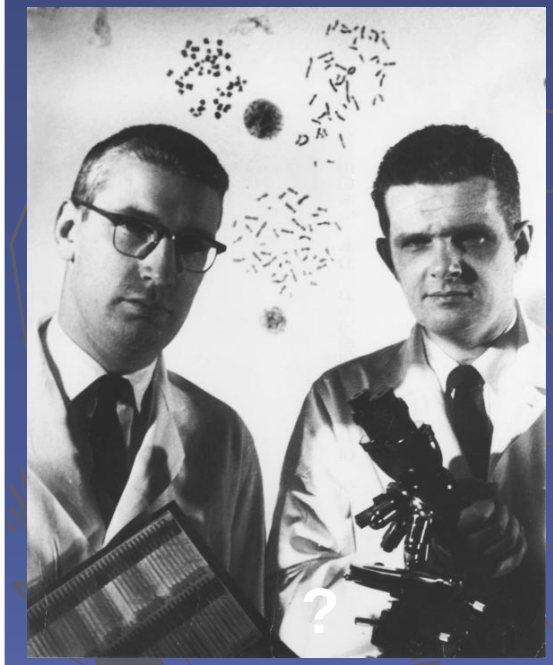
International Advisory Board Meeting

Warsaw

November 27th 2012

Tomasz Stokłosa

Philadelphia chromosome, chronic myelogenous leukemia and imatinib…

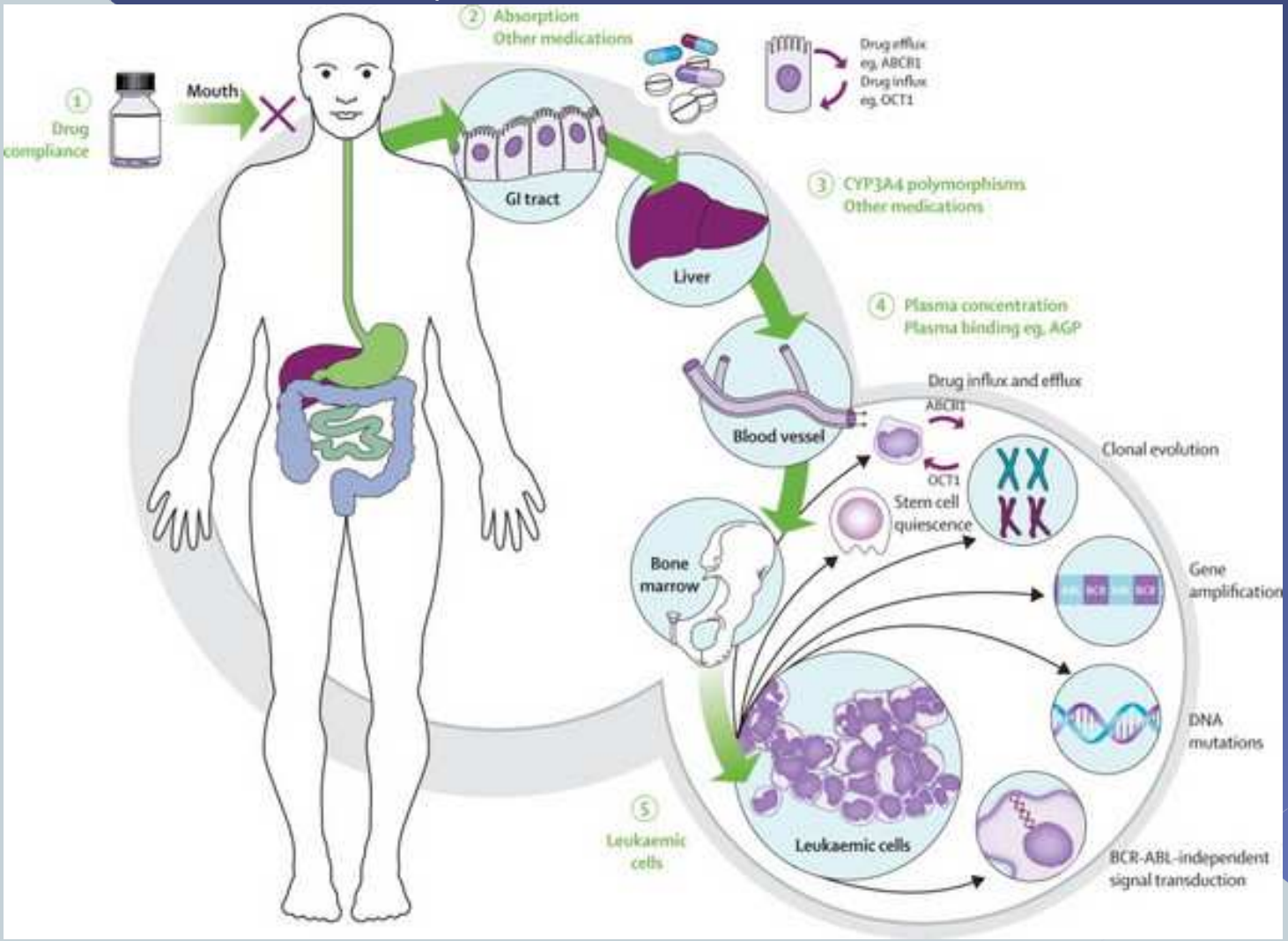


CD34+ → CD34+ Ph+ → 

Chronic phase

>10 years

Molecular mechanisms of drug resistance in chronic myeloid leukemia



Apperley J, Lancet Oncology 2007

Major DNA repair mechanisms

γ irradiation
Reactive oxygen species
Alkylating agents

UV light
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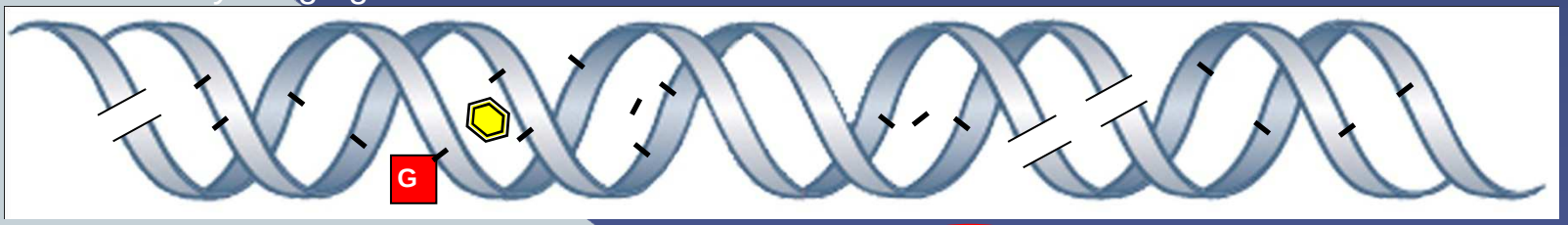
γ irradiation
Genotoxic agents
Replication error

Relication errors
Alkylating agents



Abasic sites,
Uracil,
Oxidative nucleotide modifications,
Single strand brakes

Photoadducts,
Purine dimers

Double strand brakes

Mismatches,
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Deletion

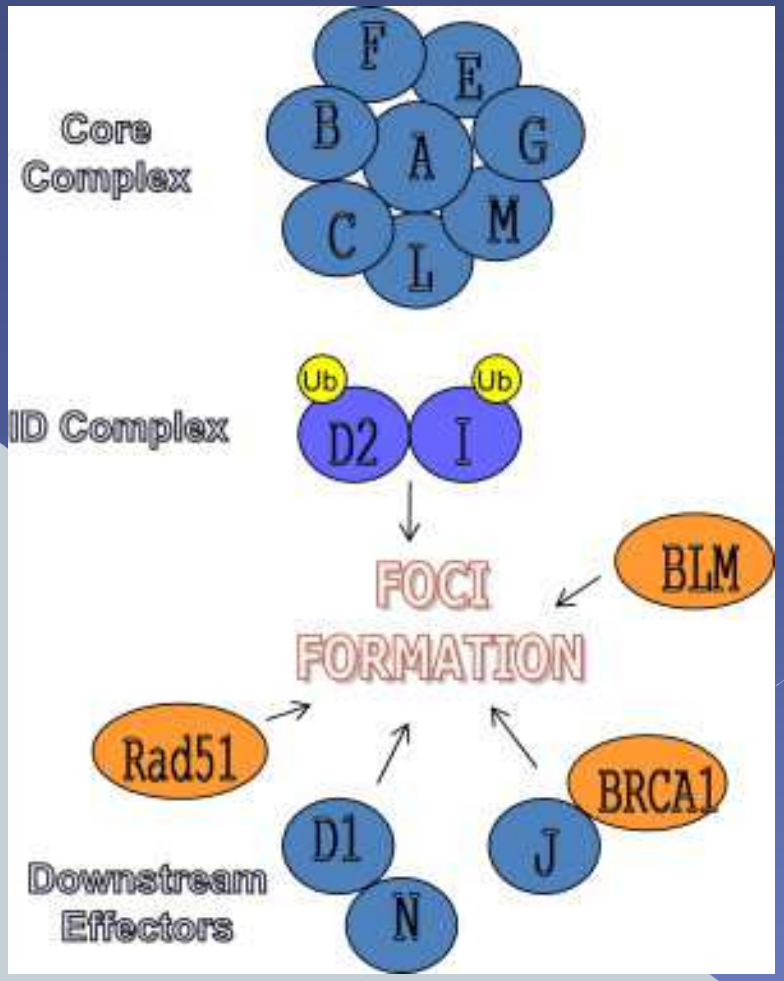
BER

NER

HRR
NHEJ

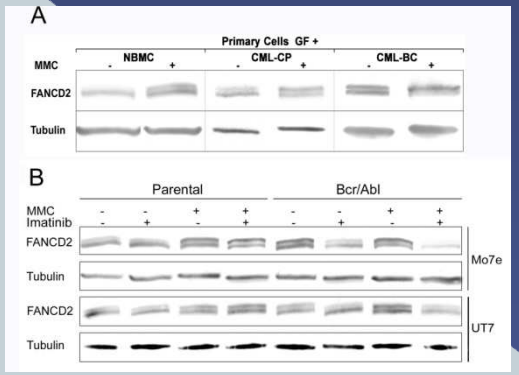
MMR

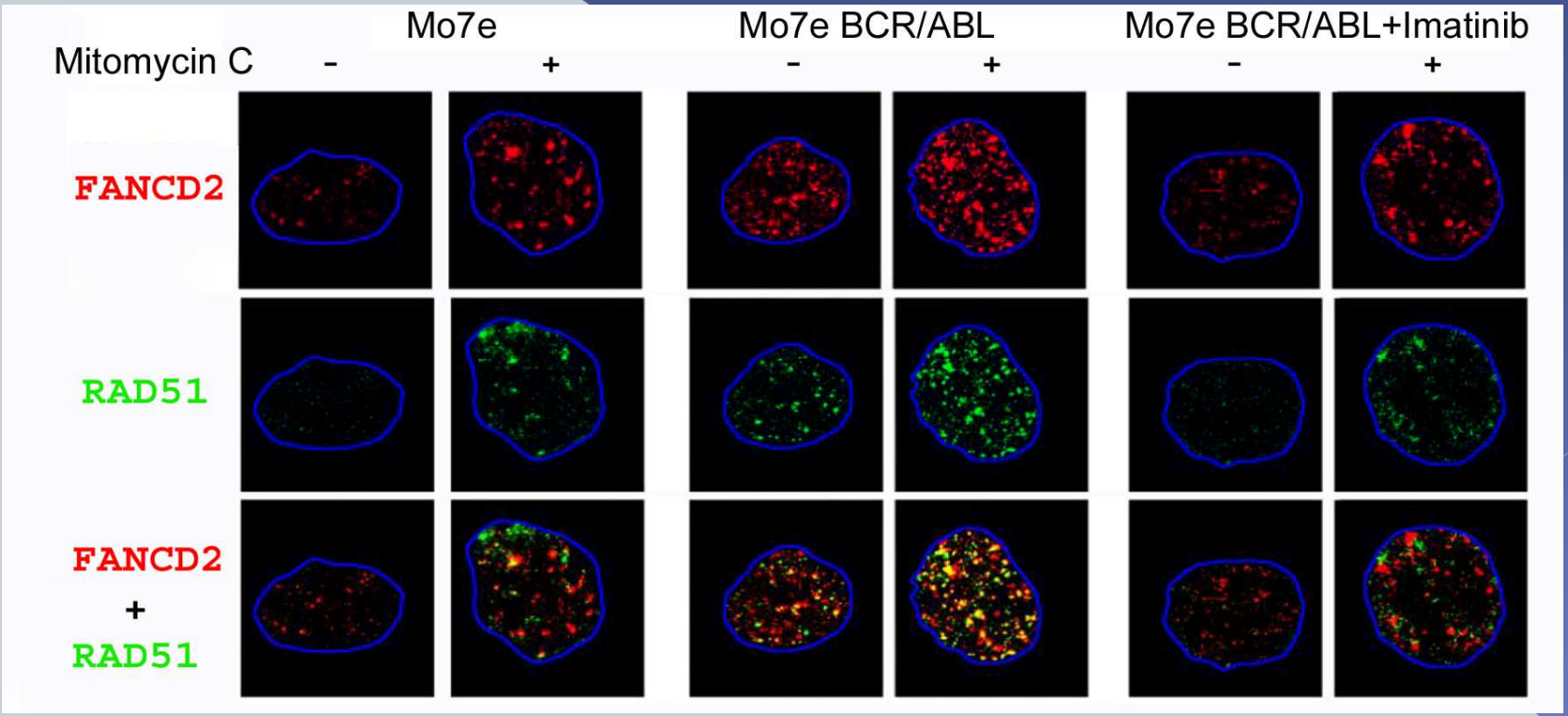
Role of Fanconi Anemia proteins in DNA damage response



Green and Kupfer, 2009 Hematol Oncol Clin N Am

FANCD2 pathway is hyperactived in CML cells





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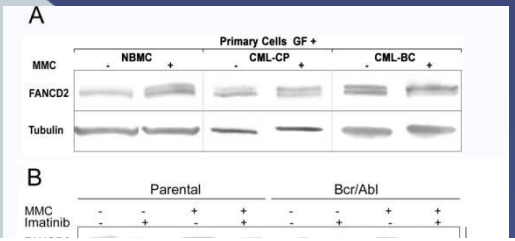


Leukemia (2011), 1–9

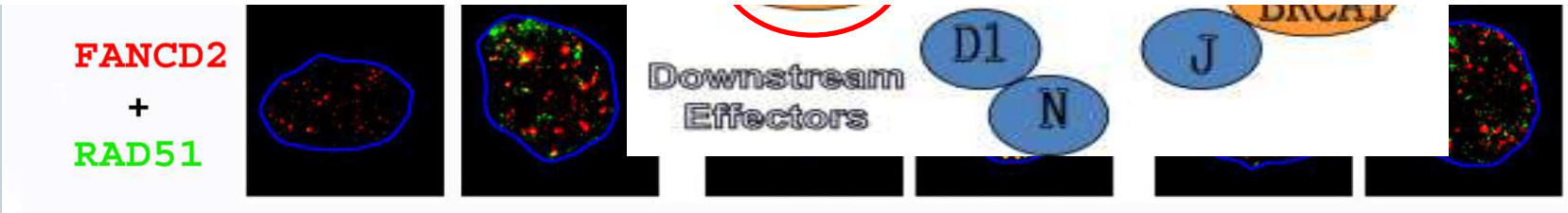
www.nature.com/leu

ORIGINAL ARTICLE

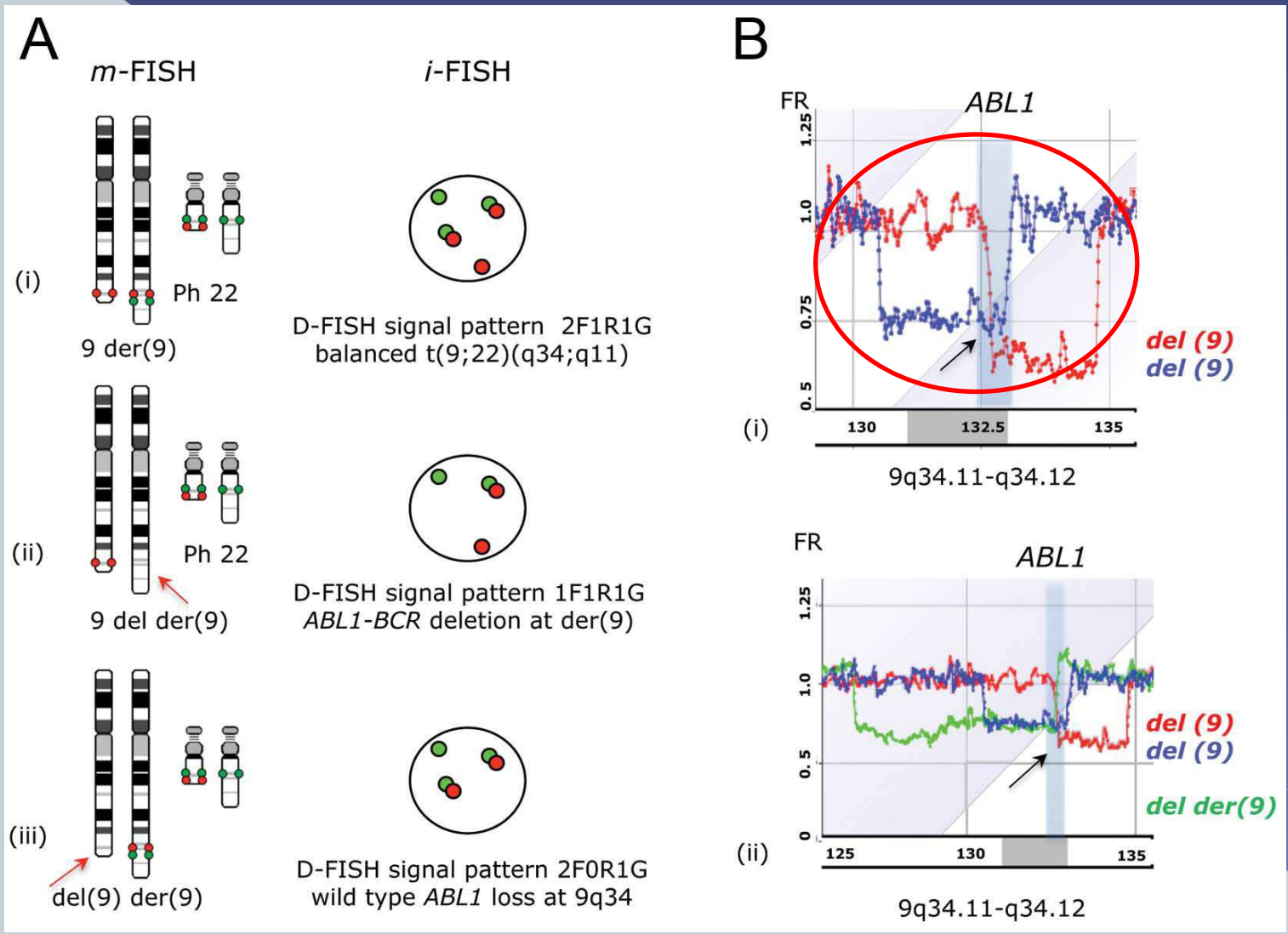
Monoubiquitinated Fanconi anemia D2 (FANCD2-Ub) is required for BCR-ABL1 kinase-induced leukemogenesis

M Koptyra[1,5], T Stoklosa[2], G Hoser[3], E Glodkowska-Mrowka[2], I Seferynska[4], A Klejman[5], J Blasiak[6] and T Skorski[1,5]

[1]Department of Microbiology and Immunology, Temple University School of Medicine, Philadelphia, PA, USA; [2]Department of Immunology, Medical University of Warsaw, Warsaw, Poland; [3]Department of Clinical Cytology, Medical Center for Postgraduate Education, Warsaw, Poland; [4]Department of Hematology, Institute of Hematology and Blood Transfusion, Warsaw, Poland; [5]Center of Biotechnology, College of Science and Technology, Temple University, Philadelphia, PA, USA and [6]Department of Molecular Genetics, University of Lodz, Lodz, Poland



Microdeletions in normal *ABL* allele who didn't respond to TKI (lack of CCyR in 12 m).



Virgili et al., Cancer Res, 2011, 71(16): 5381-6

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Published OnlineFirst June 21, 2011; DOI:10.1158/0008-5472.CAN-11-0068

Cancer Research

Priority Report

Imatinib Sensitivity in BCR-ABL1–Positive Chronic Myeloid Leukemia Cells Is Regulated by the Remaining Normal *ABL1* Allele

Anna Virgili[1], Mateusz Koptyra[2], Yashodhara Dasgupta[2], Eliza Glodkowska-Mrowka[3], Tomasz Stoklosa[3], Elisabeth P. Nacheva[1], and Tomasz Skorski[2]

Abstract

Chronic myeloid leukemia in chronic phase (CML-CP) cells that harbor oncogenic *BCR-ABL1* and normal *ABL1* allele often become resistant to the ABL1 kinase inhibitor imatinib. Here, we report that loss of the remaining normal *ABL1* allele in these tumors, which results from cryptic interstitial deletion in 9q34 in patients who did not achieve a complete cytogenetic remission (CCyR) during treatment, engenders a novel unexpected mechanism of imatinib resistance. BCR-ABL1–positive *Abl1*$^{-/-}$ leukemia cells were refractory to imatinib as indicated by persistent BCR-ABL1–mediated tyrosine phosphorylation, lack of BCR-ABL1 protein degradation, increased cell survival, and clonogenic activity. Expression of ABL1 kinase, but not a kinase-dead mutant, restored the antileukemic effects of imatinib in ABL1-negative chronic myelogenous leukemia (CML) cells and in BCR-ABL1–positive *Abl1*$^{-/-}$ murine leukemia cells. The intracellular concentration of imatinib and expression of its transporters were not affected, although proteins involved in BCR-ABL1 degradation were downregulated in *Abl1*$^{-/-}$ cells. Furthermore, 12 genes associated with imatinib resistance were favorably deregulated in *Abl1*$^{-/-}$ leukemia. Taken together, our results indicate that loss of the normal ABL1 kinase may serve as a key prognostic factor that exerts major impact on CML treatment outcomes. *Cancer Res; 71(16); 5381–6. ©2011 AACR.*

Virgili et al., Cancer Res, 2011, 71(16): 5381-6

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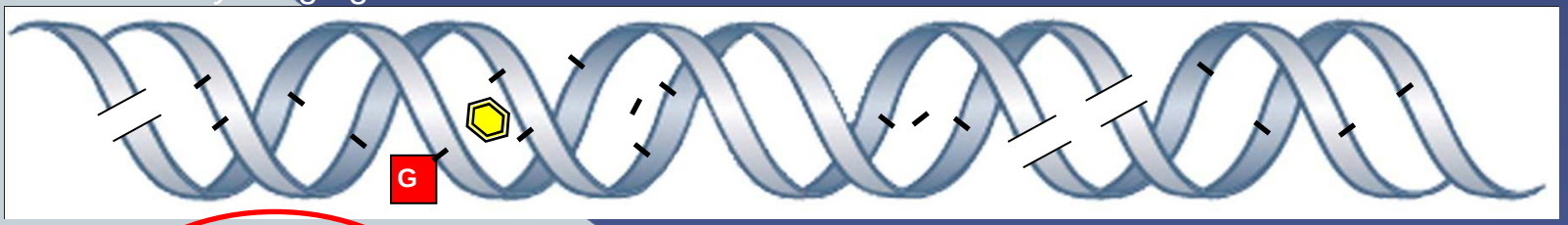

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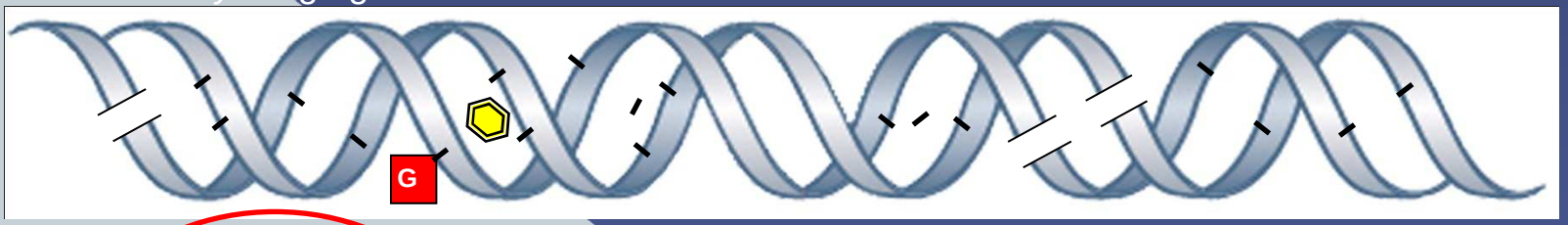

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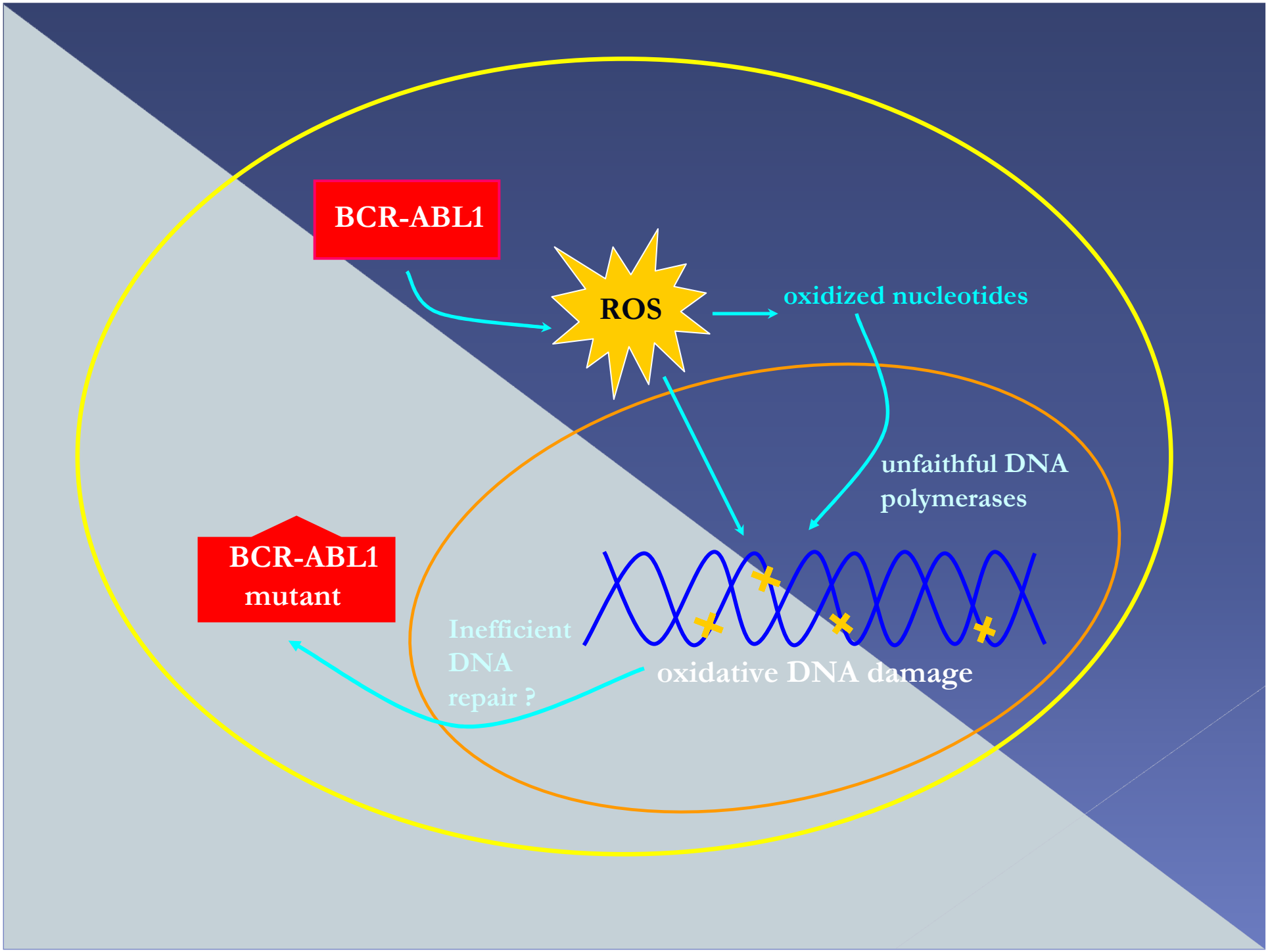
Leukemia (2012), 1–6

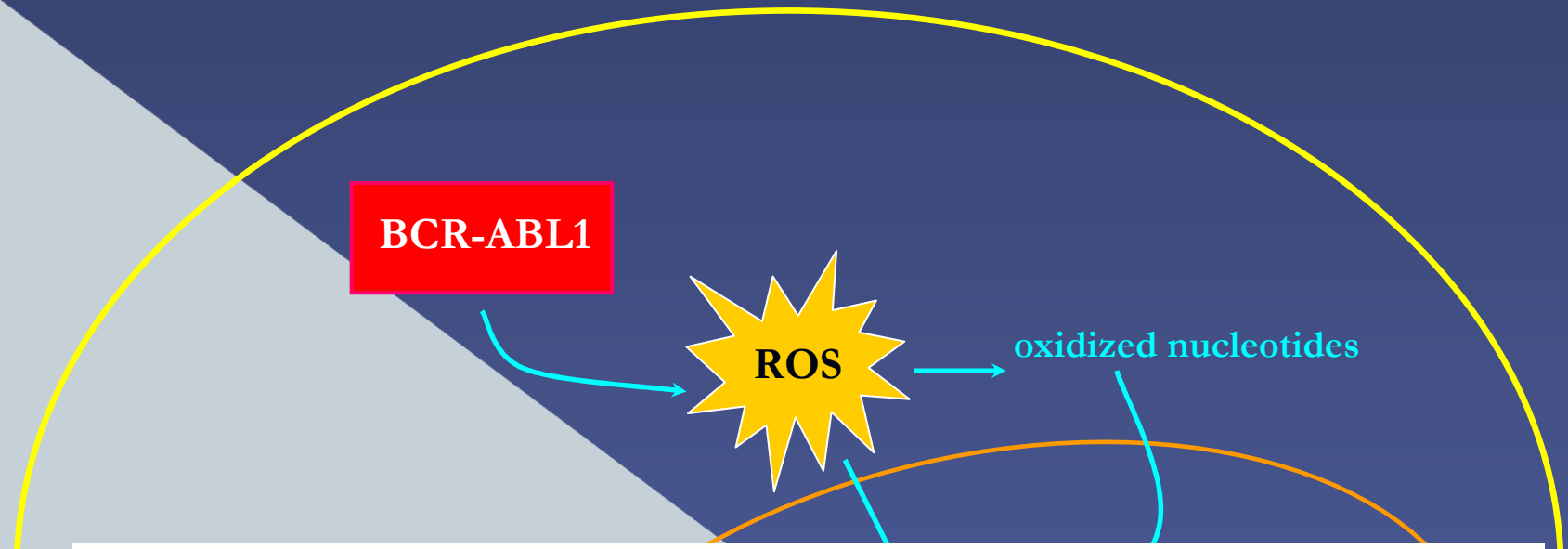
www.nature.com/leu

ORIGINAL ARTICLE

BCR-ABL1 kinase inhibits uracil DNA glycosylase UNG2 to enhance oxidative DNA damage and stimulate genomic instability

A Slupianek[1], R Falinski[1], P Znojek[1], T Stoklosa[1,2], S Flis[1], V Doneddu[3], D Pytel[1,5], E Synowiec[4], J Blasiak[4], A Bellacosa[3] and T Skorski[1]


BCR-ABL1
ROS
oxidized nucleotides
unfaithful DNA polymerases
BCR-ABL1 mutant
Inefficient DNA repair ?
oxidative DNA damage



MYELOID NEOPLASIA

Rac2-MRC-cIII–generated ROS cause genomic instability in chronic myeloid leukemia stem cells and primitive progenitors

Margaret Nieborowska-Skorska,[1] Piotr K. Kopinski,[1] Regina Ray,[1] Grazyna Hoser,[2] Danielle Ngaba,[1] Sylwia Flis,[1] Kimberly Cramer,[1] Mamatha M. Reddy,[3] Mateusz Koptyra,[1] Tyrone Penserga,[1] Eliza Glodkowska-Mrowka,[4] Elisabeth Bolton,[1] Tessa L. Holyoake,[5] Connie J. Eaves,[6] Sabine Cerny-Reiterer,[7] Peter Valent,[7] Andreas Hochhaus,[8] Timothy P. Hughes,[9] Heiko van der Kuip,[10] Martin Sattler,[3] Wieslaw Wiktor-Jedrzejczak,[11] Christine Richardson,[12] Adrienne Dorrance,[13] Tomasz Stoklosa,[4] David A. Williams,[13] and Tomasz Skorski[1]

[1]Department of Microbiology and Immunology, Temple University School of Medicine, Philadelphia, PA; [2]Department of Clinical Cytology, Medical Center for Postgraduate Education, Warsaw, Poland; [3]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA; [4]Department of Immunology, Medical University of Warsaw, Warsaw, Poland; [5]Paul O'Gorman Leukemia Research Centre, University of Glasgow, Glasgow, United Kingdom; [6]Terry Fox Laboratory, British Columbia Cancer Agency, Vancouver, BC; [7]Department of Internal Medicine I, Division of Hematology and Hemostaseology, Medical University of Vienna and Ludwig-Boltzmann Oncology Cluster, Vienna, Austria; [8]Department of Hematology/Oncology, Jena University Hospital, Jena, Germany; [9]Department of Hematology and Centre for Cancer Biology, University of Adelaide School of Medicine, Adelaide, Australia; [10]Dr Margarete Fischer-Bosch Institute of Clinical Pharmacology and University of Tuebingen, Stuttgart, Germany; [11]Department of Hematology, Oncology and Internal Diseases, Medical University of Warsaw, Warsaw, Poland; [12]Department of Biology and Center of Bioinformatics, University of North Carolina at Charlotte, Charlotte, NC; and [13]Division of Hematology/Oncology, Children's Hospital Boston, Dana-Farber Cancer Institute, Harvard Medical School, Harvard Stem Cell Institute, Boston, MA

- Molecular mechanisms of drug resistance in chronic myeloid leukemia
- *Investigation of the potential targets and markers of sensitivity to tyrosine kinase inhibitors in chronic lymphocytic leukaemia*

Chronic lymphocytic leukemia (CLL)

Chronic lymphocytic leukemia remains most often diagnosed leukemia in adults and there is no curative treatment for this disease.

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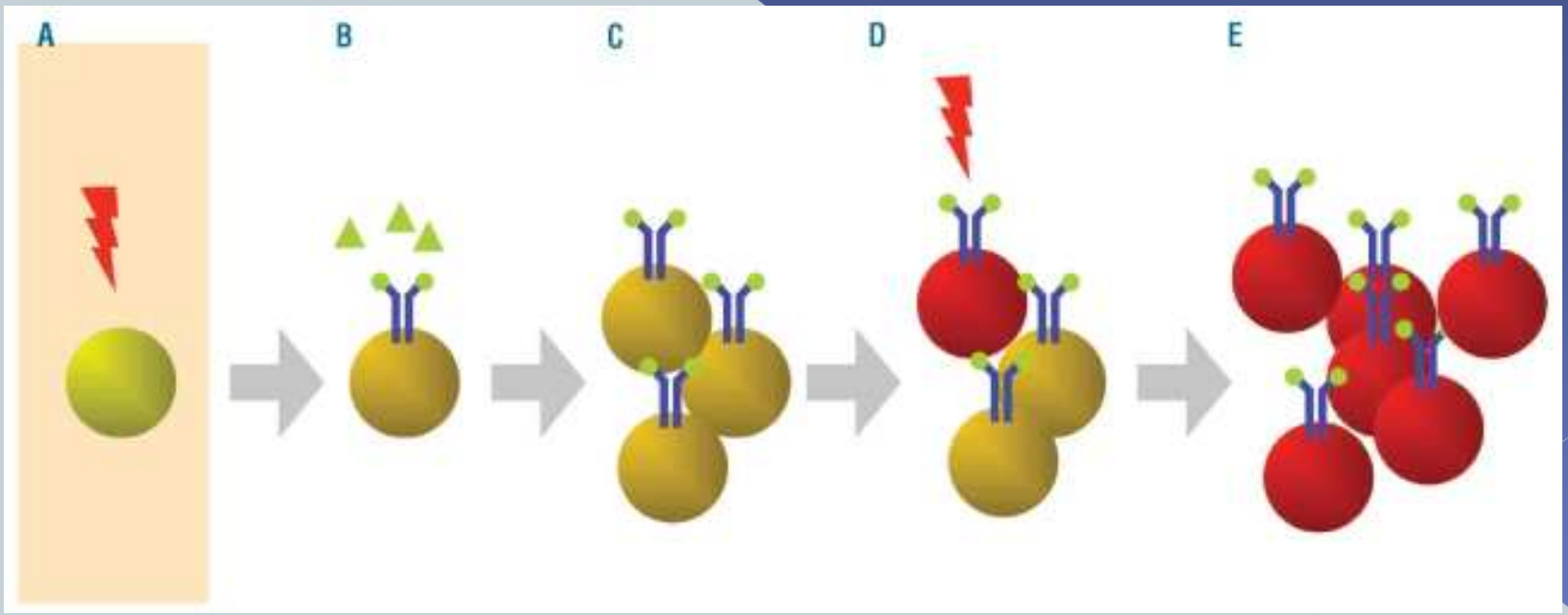
Putative model for the mechanism of leukemogenesis of CLL.



Mertens D, Bullinger L, Stilgenbauer S, Haematologica. 2011; 96(10):1402-5..

Chronic lymphocytic leukemia (CLL)

- We plan to investigate potential pathways and targets for TKIs in CLL cells, employing gene expression profiling (GEP) analysis.

- We aim to characterize genes involved in response to these promising novel drugs for CLL and we will try to define group of patients who will mostly benefit from such treatments (based also on cytogenetic as well as molecular characterization of prognostic markers).

BASTION

Thank you!