ΛΕΥΧΑΙΜΙΕΣ
Κλινική και Μεταφραστική Έρευνα
Διεθνή Ερευνητικά Δίκτυα
Ε. Μπριασούλης
Expression profiling of a panel of apoptosis-associated microRNAs in Acute Myeloid Leukemia identifies a number of differentially expressed microRNAs that target epigenetic modifiers

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1 Department of Hematology, University Hospital of Ioannina, St. Niarchou Av. 1, Ioannina 45500, Greece
2 Cancer Biobank Center, University of Ioannina, University Campus, Ioannina 45110, Greece
3 Computational Medicine Center, Sidney Kimmel Medical College, Thomas Jefferson University, 1020 Locust Street, Philadelphia, PA 19107, USA

INTRODUCTION

Identifying molecular aberrations that underlie Acute Myeloid Leukemia (AML) is still an unmet research target. Moreover few studies have implicated non-coding RNAs and especially microRNAs (miRNAs) in AML. We evaluated the expression of a panel of apoptosis-associated miRNAs in leukemic blasts isolated from AML patients and investigated their predicted targets.

METHODS

We used bone marrow or peripheral from 8 AML patients, donated at diagnosis for research purposes (5 male and 3 female, median age 67, range 31 – 83). Four cases had a normal karyotype and 4 had the following chromosomal abnormalities: +8, +21, inv(3) & del(7) and t(3,12)(q26;p13). Mononuclear cells were isolated by Ficoll-Histopaque (Sigma Aldrich) density gradient centrifugation and were cryopreserved in liquid nitrogen at the Cancer Biobank Center of the University of Ioannina. MicroBeads technology was used for magnetic cell sorting of CD34+ cells of patients' samples, while mononuclear blood cells from two healthy individuals were used as controls. Short RNA was extracted using the NucleoSpin® miRNA kit (Macherey Nagel). Simultaneous quantification of 84 apoptosis-associated miRNAs was performed using the miScript miRNA PCR Array Human Apoptosis (MIHS-114ZF, Qiagen) in a LightCycler® 480 instrument (Roche Instrument Center AG, Rotkreuz, Switzerland) and relative expression was determined by the 2^(-ΔΔCT) algorithm. We used RNA22 (http://cm.jefferson.edu/rna22v2) to identify genes that are predicted to be simultaneously targeted by all of the 10 top downregulated miRNAs and also the genes that are predicted to be simultaneously targeted by all of the 10 top upregulated miRNAs.

RESULTS

We found 51 downregulated and 12 upregulated miRNAs compared to control (Figure 1). Among the downregulated miRNAs the miR-29 family and among the upregulated was the miR-181 family, both of which have been previously implicated in AML. The top 10 downregulated miRNAs were miR-31-5p, miR-451a, miR-144-3p, miR-29b-3p, miR-204-5p, miR-9-5p, miR-409-3p, miR-542-3p, miR-29c-3p and miR-29a-3p (Table 1), whereas the top 10 upregulated miRNAs were miR-186-3p, miR-149-3p, let-7c-5p, miR-222-3p, miR-214-3p, miR-181c-5p, miR-181a-5p, miR-181b-5p, miR-34a-5p and miR-181d-5p (Table 2).

CONCLUSIONS

A variety of microRNAs are dysregulated in patients with AML. We confirm that the miR-29 family and the miR-181 family have altered expression in AML. The predicted targets of the miRNAs that were found to be down regulated are involved in chromatin remodelling, suggesting that altered function of epigenetic modifiers may be due to dysregulation of miRNAs in AML.

Table 1

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Table 2

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<td>miR-126-5p</td>
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Figure 1. Scattergram that plots the log2 of normalized miRNA expression levels between the control group (x-axis) and the AML group (y-axis). MicroBeads technology was used for magnetic cell sorting of CD34+ cells of patients' samples, while mononuclear blood cells from two healthy individuals were used as controls. Short RNA was extracted using the NucleoSpin® miRNA kit (Macherey Nagel). Simultaneous quantification of 84 apoptosis-associated miRNAs was performed using the miScript miRNA PCR Array Human Apoptosis (MIHS-114ZF, Qiagen) in a LightCycler® 480 instrument (Roche Instrument Center AG, Rotkreuz, Switzerland) and relative expression was determined by the 2^(-ΔΔCT) algorithm. We used RNA22 (http://cm.jefferson.edu/rna22v2) to identify genes that are predicted to be simultaneously targeted by all of the 10 top downregulated miRNAs and also the genes that are predicted to be simultaneously targeted by all of the 10 top upregulated miRNAs.
Δομή μαθήματος

- Γιατί Επιστημονική Ιατρική Έρευνα;
- Evidence: διαβάθμιση & παραγωγή
- Αναζήτηση επιστημονικής πληροφορίας
- Είδη Έρευνας (προκλινική – μεταφραστική – κλινική)
- Δίκτυα Έρευνας (ELN, EORTC, EMN)
- Έρευνητής – Συνερευνητής - Προϋποθέσεις
- Γιατί Επιστημονική Ιατρική Έρευνα;
- Evidence: διαβάθμιση & παραγωγή
- Βιβλιογραφική αναζήτηση
- Είδη Έρευνας (προκλινική – μεταφραστική – κλινική)
- Δίκτυα Έρευνας (ELN, EORTC, EMN)
- Ερευνητής – Συνερευνητής - Προϋποθέσεις
Evidence Based Medicine

Data!

Δεδομένα!
Chronic Myeloid Leukemia: An Update of Concepts and Management Recommendations of European LeukemiaNet

Michele Baccarani, Jorge Cortes, Fabrizio Pane, Dietger Niederwieser, Giuseppe Saglio, Jane Apperley, Francisco Cervantes, Michael Deininger, Alois Gratwohl, François Guilhot, Andreas Hochhaus, Mary Horowitz, Timothy Hughes, Hagop Kantarjian, Richard Larson, Jerald Radich, Bengt Simonsson, Richard T. Silver, John Goldman, and Rudiger Hehlmann

Purpose
To review and update the European LeukemiaNet (ELN) recommendations for the management of chronic myeloid leukemia with imatinib and second-generation tyrosine kinase inhibitors (TKIs), including monitoring, response definition, and first- and second-line therapy.

Methods
These recommendations are based on a critical and comprehensive review of the relevant papers up to February 2009 and the results of four consensus conferences held by the panel of experts appointed by ELN in 2008.
European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013


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European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013


Advances in chronic myeloid leukemia treatment, particularly regarding tyrosine kinase inhibitors, mandate regular updating of concepts and management. A European LeukemiaNet expert panel reviewed prior and new studies to update recommendations made in 2009. We recommend as initial treatment imatinib, nilotinib, or dasatinib. Response is assessed with standardized real quantitative polymerase chain reaction and/or cytogenetics at 3, 6, and 12 months. BCR-ABL1 transcript levels ≤10% at 3 months, <1% at 6 months, and ≤0.1% from 12 months onward define optimal response, whereas >10% at 6 months and >1% from 12 months onward define failure, mandating a change in treatment. Similarly, partial cytogenetic response (PCyR) at 3 months and complete cytogenetic response (CCyR) from 6 months onward define optimal response, whereas no CyR (Philadelphia chromosome–positive [Ph+] >95%) at 3 months, less than PCyR at 6 months, and less than CCyR from 12 months onward define failure. Between optimal and failure, there is an intermediate warning zone requiring more frequent monitoring. Similar definitions are provided for response to second-line therapy. Specific recommendations are made for patients in the accelerated and blastic phases, and for allogeneic stem cell transplantation. Optimal responders should continue therapy indefinitely, with careful surveillance, or they can be enrolled in controlled studies of treatment discontinuation once a deeper molecular response is achieved. (Blood. 2013;122(6):872-884)
Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet


1Department of Internal Medicine III, University of Ulm, Ulm, Germany; 2Seattle Cancer Center Alliance, WA; 3Department of Hematology, Tor Vergata University Hospital, Rome, Italy; 4Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA; 5Department of Hematology/Oncology, University of Münster, Münster, Germany; 6Department of Haematology, University of Wales College of Medicine, Cardiff, United Kingdom; 7Institut Universitaire d'Hématologie Hôpital St. Louis, Assistance Publique-Hôpitaux de Paris, Paris, France; 8Service d'Hématologie Clinique, Hôpital Avicenne, Bobigny, France; 9Department of Medical and Molecular Genetics, Guy’s King’s and St. Thomas’ School of Medicine, London, United Kingdom; 10Department of Medicine and Cancer Research Center, University of Chicago, IL; 11Department of Biopathology, University Tor Vergata and Santa Lucia Foundation at Centro Europeo per la Ricerca sul Cervello, Rome, Italy; 12Department of Hematology, Nagoya University Hospital, Showa-ku, Japan; 13Department of Hematology, Oncology and Hemostasis, University of Leipzig, Leipzig, Germany; 14Department of Haematology, VU University Medical Center, Amsterdam, The Netherlands; 15Hematology and Bone Marrow Transplant Unit, University Hospital La Fe, Valencia, Spain; 16Clinical Hematology Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; 17Division of Hematology-Oncology, Northwestern University Feinberg School of Medicine, Chicago, IL; 18Department of Hematology, Erasmus University Medical Center, Rotterdam, The Netherlands; and 19The Ohio State University Comprehensive Cancer Center, Arthur G. James Cancer Hospital, Columbus

In 2003, an international working group last reported on recommendations for diagnosis, response assessment, and treatment outcomes in acute myeloid leukemia (AML). Since that time, considerable progress has been made in elucidating the molecular pathogenesis of the disease that has resulted in the identification of new diagnostic and prognostic markers. Furthermore, therapies are now being developed that target disease-associated molecular defects. Recent developments prompted an international expert panel to provide updated evidence- and expert opinion–based recommendations for the diagnosis and management of AML, that contain both minimal requirements for general practice as well as standards for clinical trials. A new standardized reporting system for correlation of cytogenetic and molecular genetic data with clinical data is proposed. (Blood. 2010;115:453-474)
Peripheral-Blood Stem Cells versus Bone Marrow from Unrelated Donors

Claudio Anasetti, M.D., Brent R. Logan, Ph.D., Stephanie J. Lee, M.D., M.P.H., Edmund K. Waller, M.D., Ph.D., Daniel J. Weisdorf, M.D., John R. Wingard, M.D., Corey S. Cutler, M.D., M.P.H., Peter Westervelt, M.D., Ph.D., Ann Woolfrey, M.D., Stephen Couban, M.D., Gerhard Ehninger, M.D., Laura Johnston, M.D., Richard T. Maziarz, M.D., Michael A. Pulsipher, M.D., David L. Porter, M.D., Shin Mineishi, M.D., John M. McCarty, M.D., Shakila P. Khan, M.D., Paolo Anderlini, M.D., William I. Bensinger, M.D., Susan F. Leitman, M.D., Scott D. Rowley, M.D., Christopher Bredeson, M.D., Shelly L. Carter, Sc.D., Mary M. Horowitz, M.D., and Dennis L. Confer, M.D., for the Blood and Marrow Transplant Clinical Trials Network*
Peripheral Blood Stem Cells vs. Bone Marrow

**A. Survival (%)**
- Peripheral blood
- Bone marrow
- $P = 0.33$

**B. Disease-free Survival (%)**
- Peripheral blood
- Bone marrow
- $P = 0.38$

**C. Cumulative Incidence of Death Unrelated to Relapse (%)**
- Peripheral blood
- Bone marrow
- $P = 0.99$

**D. Cumulative Incidence of Relapse (%)**
- Peripheral blood
- Bone marrow
- $P = 0.74$

**E. Cumulative Incidence of Chronic GVHD (%)**
- Peripheral blood
- Bone marrow

**F. Cumulative Incidence of Acute GVHD (%)**
- Peripheral blood
- Bone marrow

**G. Cumulative Incidence of Neutrophil Engraftment (%)**
- Peripheral blood
- Bone marrow

**H. Cumulative Incidence of Platelet Engraftment (%)**
- Peripheral blood
- Bone marrow

The New England Journal of Medicine

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Cytarabine Dose for Acute Myeloid Leukemia

Bob Löwenberg, M.D., Thomas Pabst, M.D., Edo Vellenga, M.D., Wim van Putten, M.Sc., Harry C. Schouten, M.D., Carlos Graux, M.D., Augustin Ferrant, M.D., Pieter Sonneveld, M.D., Bart J. Biemond, M.D., Alois Gratwohl, M.D., Georgine E. de Gref, M.D., Leo F. Verdonck, M.D., Martijn R. Schaafsma, M.D., Michael Gregor, M.D., Matthias Theobald, M.D., Urs Schanz, M.D., Johan Maertens, M.D., and Gert J. Ossenkoppele, M.D., for the Dutch–Belgian Cooperative Trial Group for Hemato-Oncology (HOVON) and Swiss Group for Clinical Cancer Research (SAKK) Collaborative Group*

CONCLUSIONS

Induction therapy with cytarabine at the lower dose already produced maximal antileukemic effects for all response end points, suggesting a plateau in the dose–response relationship above this dose level. High-dose cytarabine results in excessive toxic effects without therapeutic benefit. (Netherlands Trial Register number, NTR230.)
• Γιατί Επιστημονική Ιατρική Έρευνα;

• Evidence: διαβάθμιση & παραγωγή

• Βιβλιογραφική αναζήτηση

• Είδη Έρευνας (προκλινική – μεταφραστική – κλινική)

• Δίκτυα Έρευνας (ELN, EORTC, EMN)

• Ερευνητής – Συνερευνητής - Προϋποθέσεις
Levels of Evidence for Adult and Pediatric Cancer Treatment Studies (PDQ®)

**Strength of Study Design**

1. Randomized controlled clinical trials
   - I. Double-blinded.
   - II. Nonblinded treatment delivery
     ~ meta-analyses of quality randomized trials without heterogeneity

2. Nonrandomized controlled clinical trials
   ~ Subset analyses within randomized trials

3. Case series.
   - I. Population-based, consecutive series.
   - II. Consecutive cases (not population-based).
   - III. Nonconsecutive cases.
Strength of Endpoints

A. Total mortality (or overall survival from a defined time)
B. Cause-specific mortality (or cause-specific mortality from a defined time).
C. Carefully assessed quality of life
D. Indirect surrogates.
   I. Event-free survival.
   II. Disease-free survival.
   III. Progression-free survival.
   IV. Tumor response rate.
Clinical Trial Protocol

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<td>Volasertib (BI 6727)</td>
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<td>Title:</td>
<td>A phase III randomized, double-blind, controlled, parallel group study of the combination of intravenous volasertib + subcutaneous low dose cytarabine (LDAC) vs. intravenous volasertib placebo + subcutaneous LDAC in patients ≥ 65 years with previously untreated AML and considered ineligible for intensive remission induction therapy.</td>
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<td>Clinical Phase:</td>
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Dear Colleagues,

The EORTC Leukemia Group is investigating the possibility of running a phase III double blind placebo-controlled study for newly diagnosed FLT3+ AML patients<60 yrs, which will combine a promising FLT3 inhibitor to conventional induction-consolidation treatment. The trial would be planned to open in the course of Q1 2016.

Therefore we are contacting you to assess preliminary interest and feasibility of such trial in your center.

Please find here the link to the questionnaire:

https://eortc.wufoo.com/forms/zrkyffm-w8aknb/

Looking forward to receiving your feedback!

Kind regards

Katrien Baus
EORTC, Clinical Trial Assistant
Tel: +32 2 774 10 53 Fax: +32 2 774 10 92
Avenue E. Mounier 83/11 • 1200 Brussels • Belgium
katrien.baus@eortc.be • www.eortc.org
EORTC Leukemia Group - FLT3+ AML Questionnaire

Country

Institution Name

Institution number (for EORTC sites)

Name of the Principal Investigator

First

Last

Email address

In principle are you interested to participate in this proposal?

- Yes
- No
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Δεκέμβριος 2010
Ε. Μπριασούλης, Ιατρική Σχολή Ιωαννίνων
Το σημερινό πλήρες ανάληψης της κλινικής δοκιμής περιλαμβάνει την επικεφαλής και την επικεφαλής του εργαστηρίου.

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• Γιατί Επιστημονική Ιατρική Έρευνα;
• Evidence: διαβάθμιση & παραγωγή
• Αναζήτηση
• Είδη Έρευνας (προκλινική – μεταφραστική – κλινική)
• Δίκτυα Έρευνας (ELN, EORTC, EMN)
• Έρευνητής – Συνερευνητής - Προϋποθέσεις
search - research

On the web

- https://www.clinicaltrialsregister.eu
- http://clinicaltrials.gov/

Tools

- http://www.refman.com
- http://endnote.com

~ citations of a recent article

Δομή μαθήματος

- Γιατί Επιστημονική Ιατρική Έρευνα;
- Evidence: διαβάθμιση & παραγωγή
- Αναζήτηση
- Είδη Έρευνας (προκλινική – μεταφραστική – κλινική)
- Δίκτυα Έρευνας (ELN, EORTC, EMN)
- Ερευνητής – Συνερευνητής - Προϋποθέσεις
preclinical research

- In silico
- In vitro
- In vivo

εύκολα επαναλαμβανόμενη
eπαναλαμβανώμενα και τα σφάλματα
eπιρρεπής σε bias ... μη ελεγχόμενη
συχνά “out of context ..”
CROSSING THE VALLEY OF DEATH

A chasm has opened up between biomedical researchers and the patients who need their discoveries. Declan Butler asks how the ground shifted and whether the US National Institutes of Health can bridge the gap.
Cell-Based Therapeutics: The Next Pillar of Medicine

Microbial and human cell-based therapies form the next pharmaceutical frontier.
χρειάζεται

- Ερευνητές με γνώσεις κλινικής ιατρικής & βασικής επιστήμης
- Διεπιστημονική συνεργασία
- Καλή γνώση των κύριων κλινικών ερωτημάτων
The collagen prolyl hydroxylases are novel transcriptionally silenced genes in lymphoma

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ORIGINAL ARTICLE: CLINICAL

Bcl2-interacting killer CpG methylation in multiple myeloma: a potential predictor of relapsed/refractory disease with therapeutic implications

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Dose-Ranging Study of Metronomic Oral Vinorelbine in Patients with Advanced Refractory Cancer

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Abstract  Aim: To determine the safe dose range and scheduling of oral vinorelbine and obtain preliminary data on biomarker expression associated with tumour and tumour microenvironment in patients with advanced refractory cancer.

Translational Relevance

Metronomic chemotherapy is a novel dosing strategy that refers to dense, nonbreak administration of subtoxic doses of chemotherapy over protracted periods of time, even years, with the aim to primarily target tumor endothelial cells. Metronomic chemotherapy moved fast to clinical investigation on the basis of robust preclinical data, but early clinical development has been empirical. This is the first-in-man dose-investigating study of metronomic chemotherapy with an antimicrotubule agent. In addition, this study provides clinical proofs supporting the concept of antiangiogenic basis of metronomic chemotherapy. The demonstrated sustainable antitumor activity and negligible toxicity of this therapy, taken together with the pharmacokinetic and biomarker data, suggest that this is a novel therapeutic approach, which opens new horizons in cancer anti-vascular therapy beyond vascular endothelial growth factor blockade.
the evidence provider

 doctors (only) privilege & responsibility
• Γιατί Επιστημονική Ιατρική Έρευνα;
• Evidence: διαβάθμιση & παραγωγή
• Αναζήτηση
• Είδη Έρευνας (προκλινική – μεταφραστική – κλινική)
• Δίκτυα Έρευνας (ELN, EORTC, EMN)
• Ερευνητής – Συνερευνητής - Προϋποθέσεις
194 centers in 39 countries
- 114 national leukemia study groups
- 109 interdisciplinary partner groups
- 1000 physicians and scientists
- Caring for ten thousands of patients
The European LeukemiaNet is an EU-funded organisation of physicians, scientists and patients with interest in leukemia. It aims to improve the treatment and knowledge about Leukemia in Europe and spread excellence. The website delivers information for physicians, patients (e.g. patient organisations in Europe), ongoing clinical trials and further information about the disease. You can get information about the European LeukemiaNet in various european languages. The European LeukemiaNet is funded by the 6th Framework Program of the European Community.

**News**

- [Regulation on clinical trials - Comments and points of interest for academic clinical trials](#)
- In July 2012, the European Commission prepared a proposal for the European Parliament, which is not a directive but a regulation. Questions and comments are welcome.

**Events**

- **Fr 2013/04/05 - Su 2013/04/07**
  - [2013 European Focus on Myeloproliferative Neoplasms and Myelodysplastic Syndromes](#)
- **Th 2013/04/25 - Sa 2013/04/27**
Structure of the group

FRÉDÉRIC BARON
Chair
C.H.U. Sart-Tilman
Liège, Belgium

RADOVAN VRHOVAC
Secretary
University Hospital Centre
Zagreb, Croatia

PETRA MUUS
Treasurer
Radboud University Nijmegen Medical Centre
Nijmegen, The Netherlands
Welcome to European Myeloma Network (EMN)

All EMN members with login to the members only part of the homepage site should be able to access.

If you are unable to do so please do not hesitate to contact EMN Sponsor Office secretary assistant Louise Vistisen at lv@emn.dk.

The EMN Sponsor Office

In 2011 the European Myeloma Network established The EMN Sponsor Office.

The EMN Sponsor Office is located at Aalborg Hospital – Aarhus University Hospital, Aalborg, Denmark and provides professional support in clinical trial studies at the administrative level.

The European Myeloma Network was established in 2003 by integrating 27 research institutions and 14 trial groups with the intent to support development of novel diagnostics and therapies for multiple myeloma. Now, EMN is legalised and ready to initiate and support co-operative clinical trials and laboratory research.

The Myeloma Stem Cell Network (MSCNET) is part of EMN.

It is supported by EU’s Sixth Framework Programme.
BBMRI during the transition phase

BBMRI (Biobanking and Biomolecular Resources Research Infrastructure) was one of the first projects entering the European Research Infrastructure preparatory phase of the ESFRI roadmap funded by the European Commission (EC). The preparatory phase of BBMRI came to its end in January 2011. Over the past 3 years BBMRI has grown into a 54-member consortium with more than 225 associated organisations (largely biobanks) from over 30 countries, making it one of the largest research infrastructure projects in Europe.

BBMRI will form an interface between biological specimens and data (from patients and European populations) and top-level biological and medical research. This can only be achieved through a distributed research infrastructure with operational units in most if not all participating Member States. BBMRI will be implemented under the ERIC (European Research Infrastructure Consortium) legal entity with headquarters (central coordination) in Graz, Austria, responsible for coordination of the activities of National Nodes established in participating countries. By December 2012, 14 countries (Austria, Bulgaria, Czech Republic, Estonia, Finland, France, Greece, Italy, Latvia, Malta, the Netherlands, Norway, Spain, and Sweden) have signed the Memorandum of Understanding (MoU) where they express their aim to establish BBMRI as an ERIC and become Members of BBMRI-ERIC. The application to the European Commission has been submitted (Business Plan, BBMRI Statutes) and BBMRI is seeking to recruit the Director General of BBMRI. The expected start date of BBMRI-ERIC operations is the second half of 2013.
Your Turn!