Optimizing therapies of Chronic Myeloid Leukemia: One step closer to cure?

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Main Research Interests

1- Targeted Therapies of Leukemias
   - Focus on CML

2- Epigenetic modifications in Cancer
   - Focus on microRNAs in Breast and CRC Cancers

3- Studying MSC interaction with Cancer cells using a 3D silk model.

4- Impact of microbiome and Mediterranean diet on response therapy in cancer

5- Cancer Prevention and Awareness: AMALOUNA
As Nowell predicted in 1976:

« One may ultimately have to consider each advanced malignancy as an individual therapeutic problem »

Inter-tumor heterogeneity:
- Cell morphology
- Cell surface markers
- Genetic/Epigenetic lesions
- Niche/microenvironment
- Response to therapy
Cancer cells exhibit intra-tumor heterogeneity

How to explain this heterogeneity within a tumor?
A small subpopulation of cells capable of transferring human disease into immunodeficient murine hosts. Xenotransplantation, followed by serial transplantation, is regarded as an essential criterion in defining cancer stem cells.
Conventional Therapy

CSC-targeted Therapy

Complete Response

Combination Therapy
Chronic myeloid leukemia (CML)

Proliferative disorder of hematopoietic stem cells
Unique chromosome abnormality: Philadelphia Chromosome

The ABL gene encodes a non-receptor tyrosine kinase

The BCR gene encodes a serine-threonine kinase
BCR-ABL fusion gene → BCR-ABL fusion protein
(constitutively active tyrosine kinase)

Phosphate

BCR-ABL

ATP

substrate

Tyrosine

Phosphate

Effecter

Intracellular signals
BCR-ABL-induced proliferation reduced, apoptosis defected, adhesion to BM.
Tyrosine Kinase Inhibitors (TKIs): standard of care in CML treatment

- Imatinib
- Dasatinib
- Nilotinib
- Ponatinib
The cure of CML:
Is it possible with existing therapies?

CURE with TKI?
CURE with TKI?

Alive and Well

No detectable CSC

Off all treatment
CURE with TKI?

Alive and Well

No detectable CSC

Off all treatment
TKI are Excellent drugs but not Perfect

- Highly effective in the early stages but not in advanced stages
- Women of childbearing age who wish to conceive should discontinue TKI treatment during pregnancy and nursing
- Lack of sensitivity of CML CSC
- 2nd GTKI are active against some imatinib resistant Abl kinase mutants except T315I
Truly great drugs, but not a cure. Patients remain on treatment essentially for life with some resistance and disease progression.
For cure or long-term drug free survival

New therapeutic options

Eradicate CSC

Overcome resistance
Effects of arsenic trioxide (As) and interferon alpha (IFN) in CML preclinical models

As/IFN synergistically inhibits proliferation, induces apoptosis in CML cell lines, was preclinically superior to Imatinib in vivo
Does As/IFN combination work in TKI-resistant CML?
As/IFN inhibits proliferation and induces apoptosis in CML cell lines resistant to TKI.
- T315I accounts for 16% of kinase mutations in CML
- Resistant to primary and secondary TKI except ponatinib that causes life threatening side effects

Leukemic mice (T315I)

MSCV-BCR-ABL-T315I-IRES-GFP retrovirus

infection

BM cells collected from 5-FU treated mice

transfer

Primary recipients

Secondary recipients

treatment

time to relapse

Days

Survival

0 5 10 15 20 25 30

Untreated

Arsenic

IFN

Arsenic/IFN

Imatinib
Survival of primary TKI-resistant CML (T315I) mice
As/IFN decreases leukemic cell infiltration in liver and lungs.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Spleen</th>
<th>Liver</th>
<th>Lungs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>4 ± 0</td>
<td>2.8 ± 1.3</td>
<td>3.3 ± 1</td>
</tr>
<tr>
<td>Imatinib</td>
<td>3.4 ± 1.3</td>
<td>2.4 ± 1.7</td>
<td>2 ± 1.2</td>
</tr>
<tr>
<td>ATO</td>
<td>3.8 ± 0.4</td>
<td>2.5 ± 1</td>
<td>2.2 ± 0.8</td>
</tr>
<tr>
<td>IFN</td>
<td>4 ± 0</td>
<td>2.6 ± 1.1</td>
<td>2 ± 0.9</td>
</tr>
<tr>
<td>ATO + IFN</td>
<td>3 ± 1.4</td>
<td>1.8 ± 1.7</td>
<td>1.8 ± 0.5</td>
</tr>
</tbody>
</table>
This can also apply to CML harboring T315I
Ongoing work

• Investigate the mechanisms of action of the combination
As/IFN inhibits Hedgehog dependent genes
Who are we?
AUB-affiliated educational NGO that aims to fight cancer by focusing on 3 pillars:
- **Education**
- **Prevention**
- **Research**
Cures Come From Cancer Research

Cancer is limited. Research isn’t

Stand UP to Cancer Through RESEARCH

Make Cancer Research a Top National Priority

Let IMPOSSIBLE BE POSSIBLE: SUPPORT CANCER RESEARCH
Colorectal Cancer Awareness events: 600 FIT free tests were distributed
STUDENTS as RESEARCHERS Initiative

Deux élèves (un élève d’une école privée et l’autre d’une école publique)

Travailler sur un projet de recherche dans un labo à l'AUB

Produire des résultats expérimentaux

Présenter leur projet dans une mini conférence
Students as Researchers Initiative
1st Conference (SRI), Oct. 28, 2016
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**Core facilities at AUB:**
Animal Care Facility
Molecular and Protein core facility
CRSL
THANK YOU