Hematology Journal Club

Title:

Selection of a novel DNA aptamer against oFA/iLRp for targeted delivery of doxorubicin to AML cells

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Selection of a novel DNA aptamer against OFA/iLRP for targeted delivery of doxorubicin to AML cells

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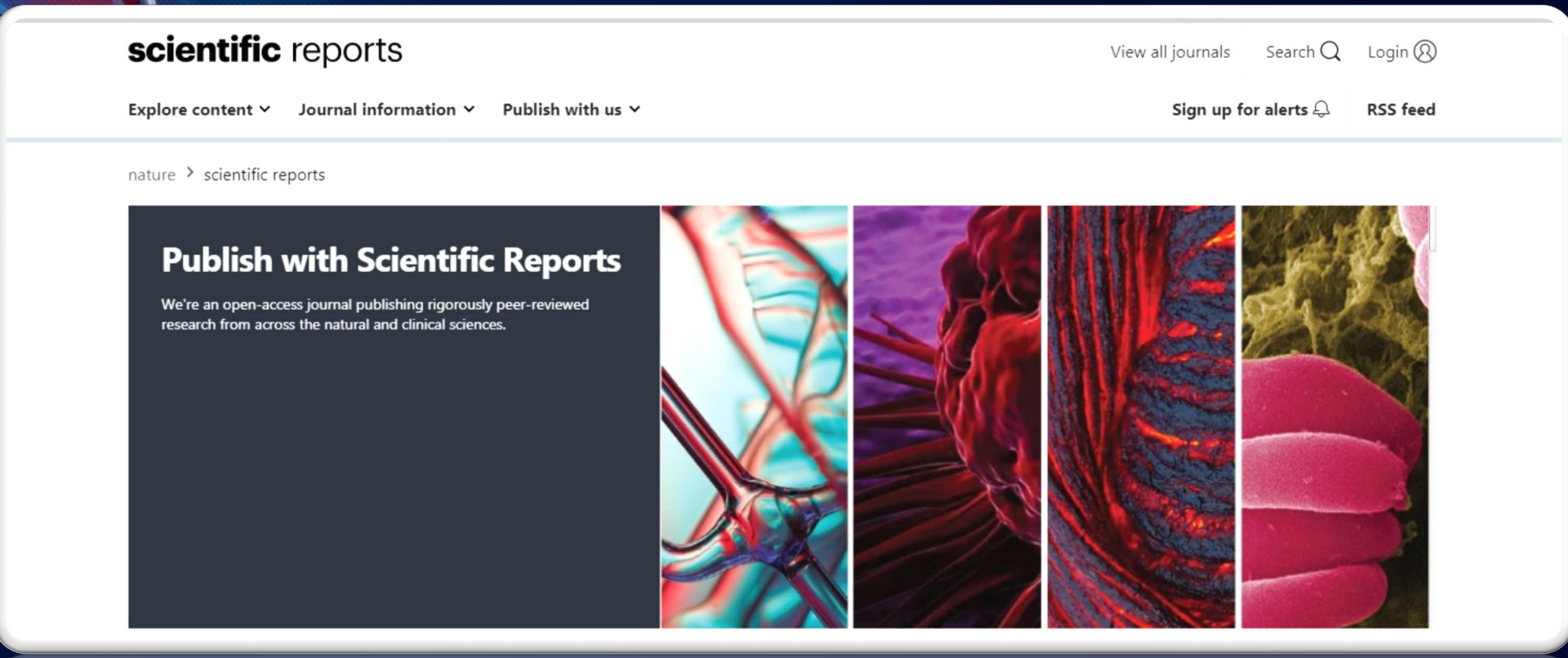


Article content:

- Introduction
- Material and methods
- Result
- Discussion

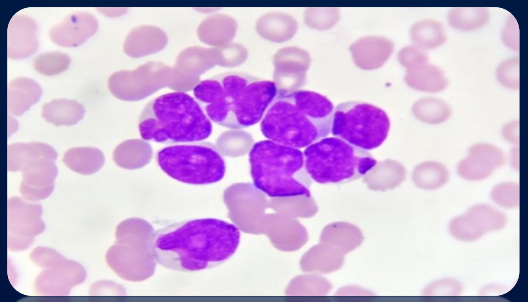
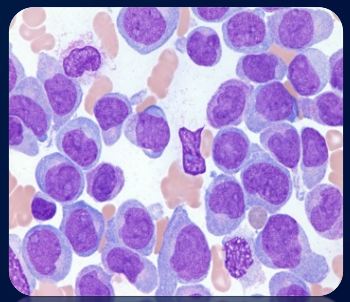
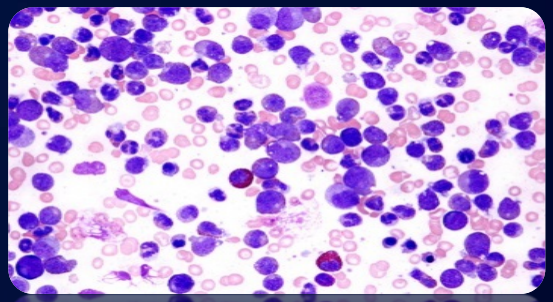
Introduction

Acute myeloid leukemia:

- Acute myeloid leukemia (AML) is one of the most common types of leukemia.

- AML cells features:
  - A differentiation arrest
  - Abnormal clonal proliferation in bone marrow and blood

- AML has diverse outcomes and remains one of the most complex and challenging diseases in contemporary oncology.
- Among leukemic diseases that cause mortality in United States, AML is the most common type, with a 5-year survival of only 30–40%

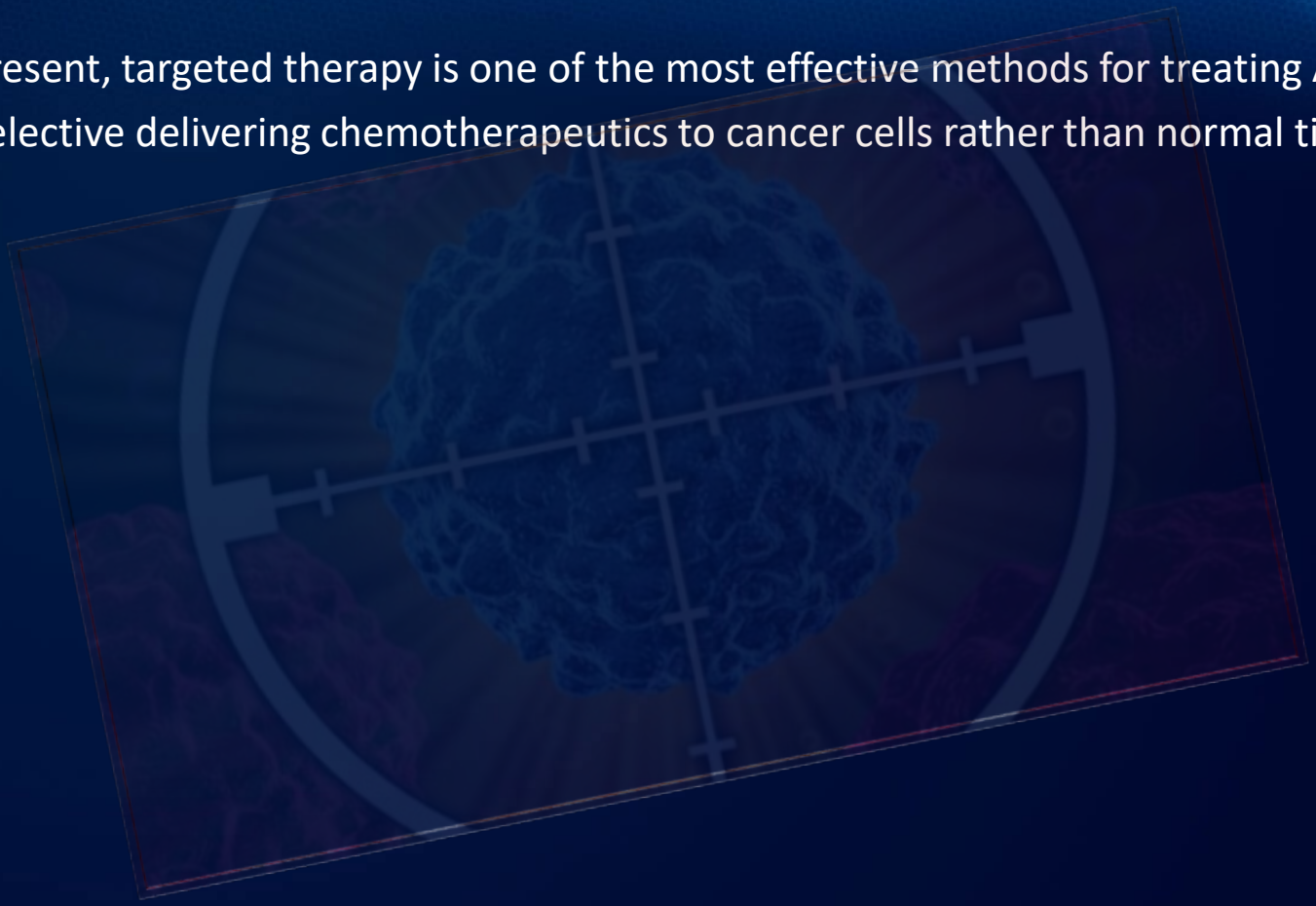
Treatment:

- After decades, chemotherapy remains the foremost therapeutic option for AML.

- Consequently, aged patients often have poor tolerance to cytotoxic drugs and survival of patients over 66 years is less than one year.

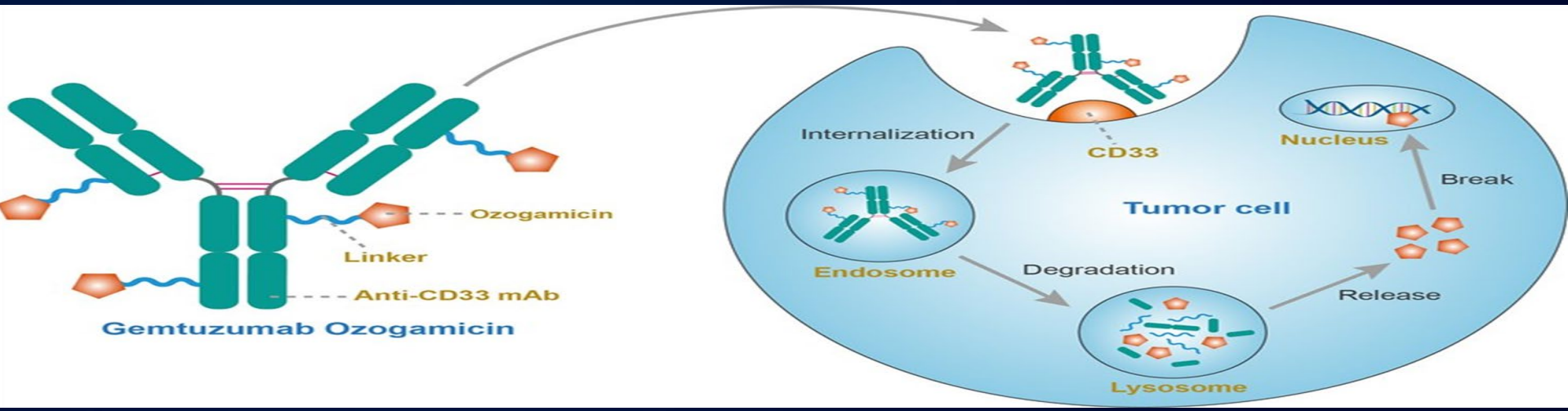
Targeted therapy:

- At present, targeted therapy is one of the most effective methods for treating AML.
- By selective delivering chemotherapeutics to cancer cells rather than normal tissues.



- Breast cancer treatment:
- trastuzumab emtansine (T-DM1): an antibody-drug conjugate ⇨ HER2

- For targeted AML treatment:
- gemtuzumab ozogamicin: a conjugation of anti-CD33 antibody and calicheamicin ⇨ CD33



Oncofetal antigen/immature laminin receptor protein:

- is expressed: in AML, colon cancer, Fibrosarcoma, lung cancer.
- but not on the surface of normal cells.

- is a potentially important molecular target for treatment of AML and other malignancies.

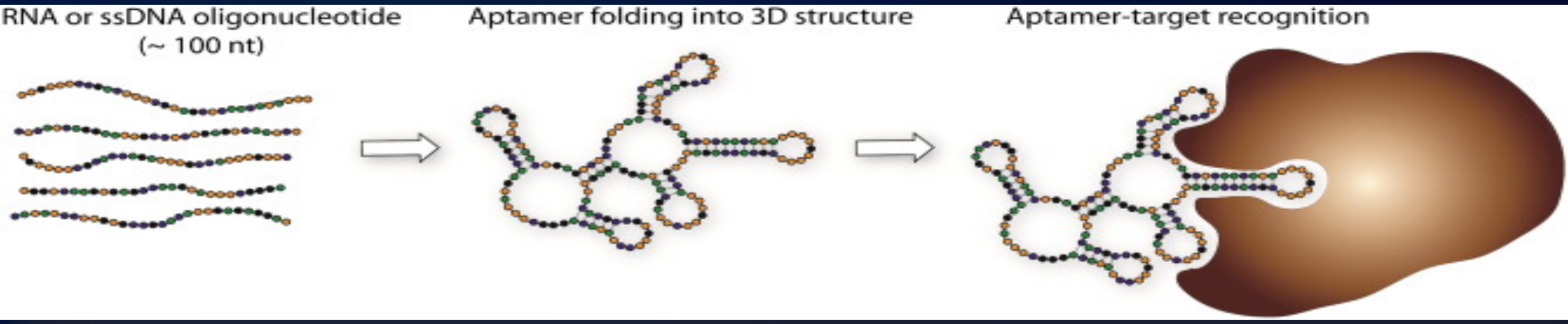
- Barsoum et al.
- OFA/iLRP could be employed as a tumor-associated antigen in immunotherapy.
- Scheiman *et al*.
- suggesting that OFA/iLRP may be a potential target for gene therapy

- OFA/iLRP expression is not only detected in many AML cell lines, but also in all clinical samples AML patient.

- Tumor-targeted therapy requires ligands that can bind specifically to tumor markers.

Aptamer:

- The aptamers are single stranded oligonucleotides of DNA or RNA type that have anti-cancer properties.
- Aptamers have a great advantages over antibodies.



- Aptamers can be used in diagnosis and treatment.
- After binding to the target, aptamers can inhibit or stimulate it.

- Several aptamers are being investigated in clinical trials:

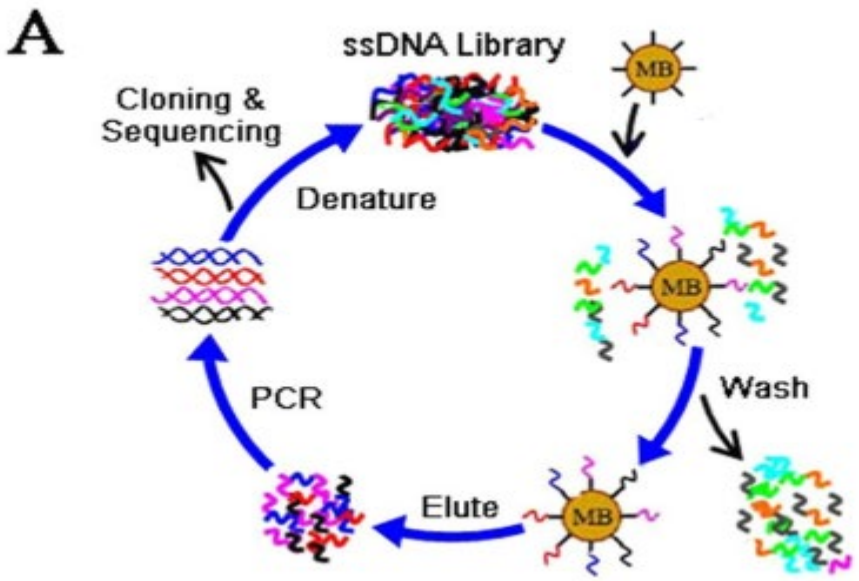
- E1003042
- NOX-A1243
- Pegpleranib

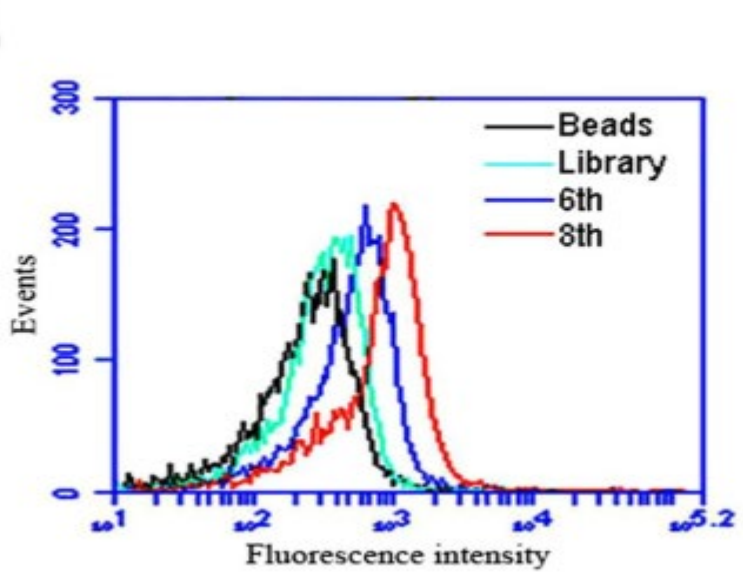
In this article, we want to evaluate the new aptamer against OFA / iLRP

Results

Selection of aptamer against OFA/iLRP:

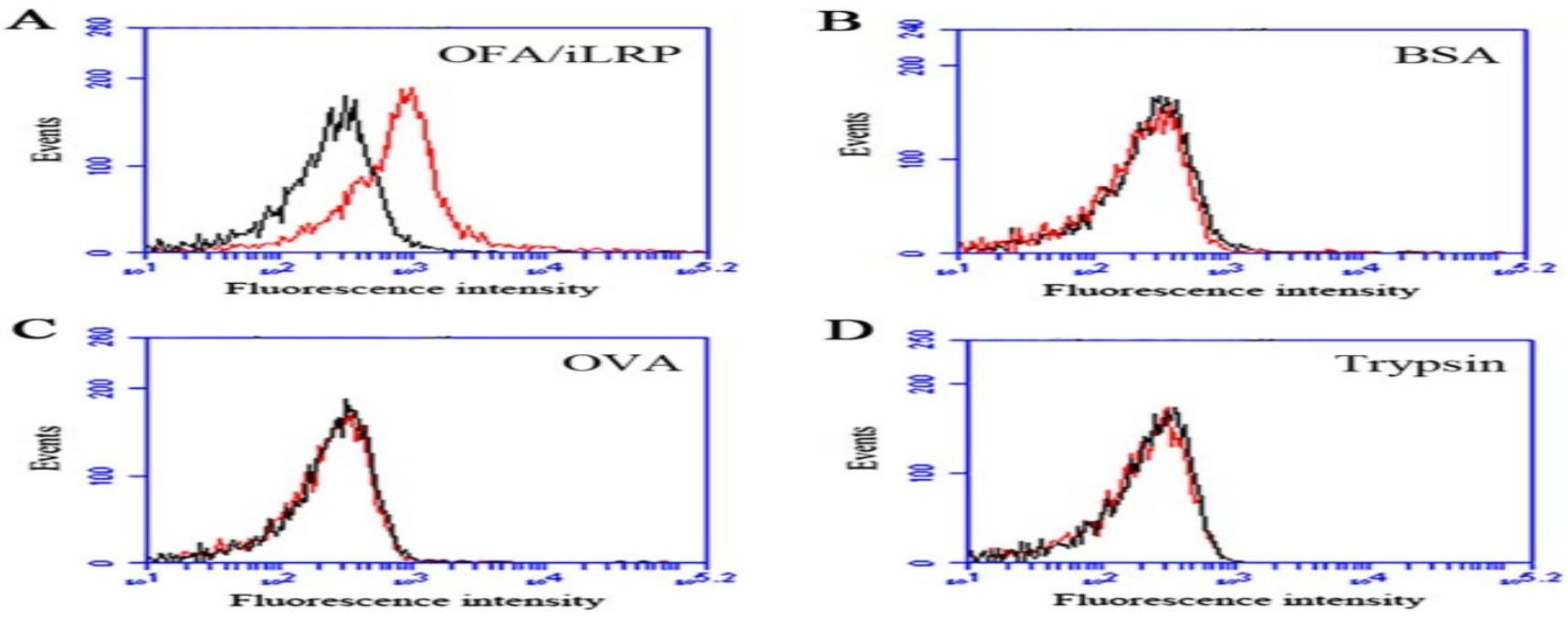
- extracellular domain of OFA/iLRP with the sequence of NQIQAAFREPR.



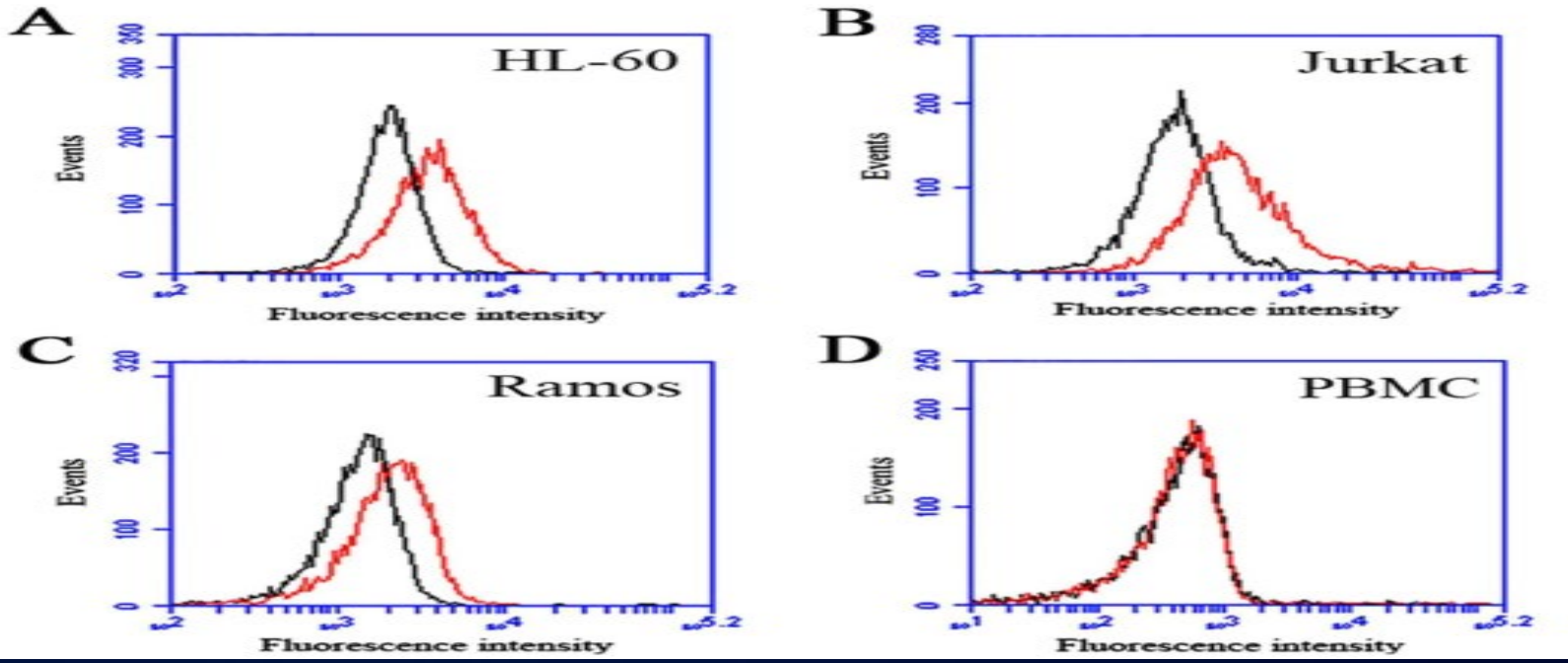


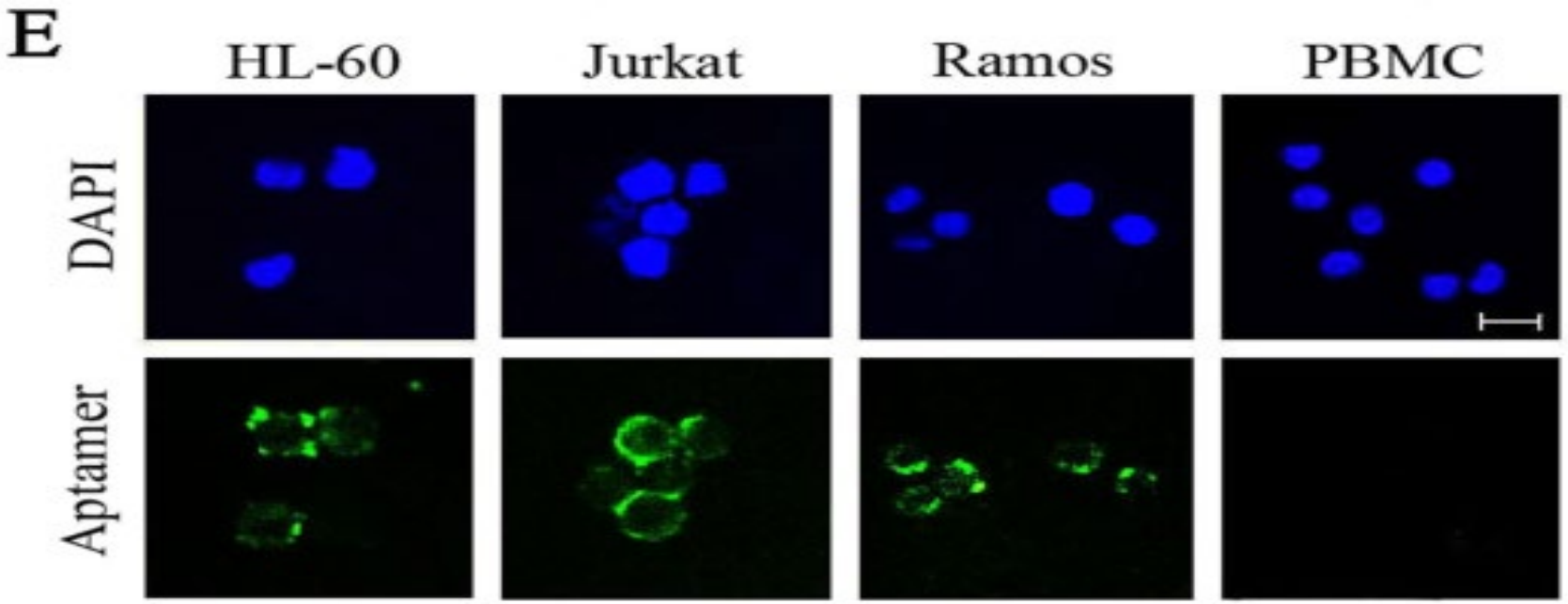
5′-TGCGTGTGTAGTGTGTCTGTTGTTTGTATTGTTGTCTATCCTCTTAGGGATTTGGGCGG-3′

Characteristics of the aptamer:

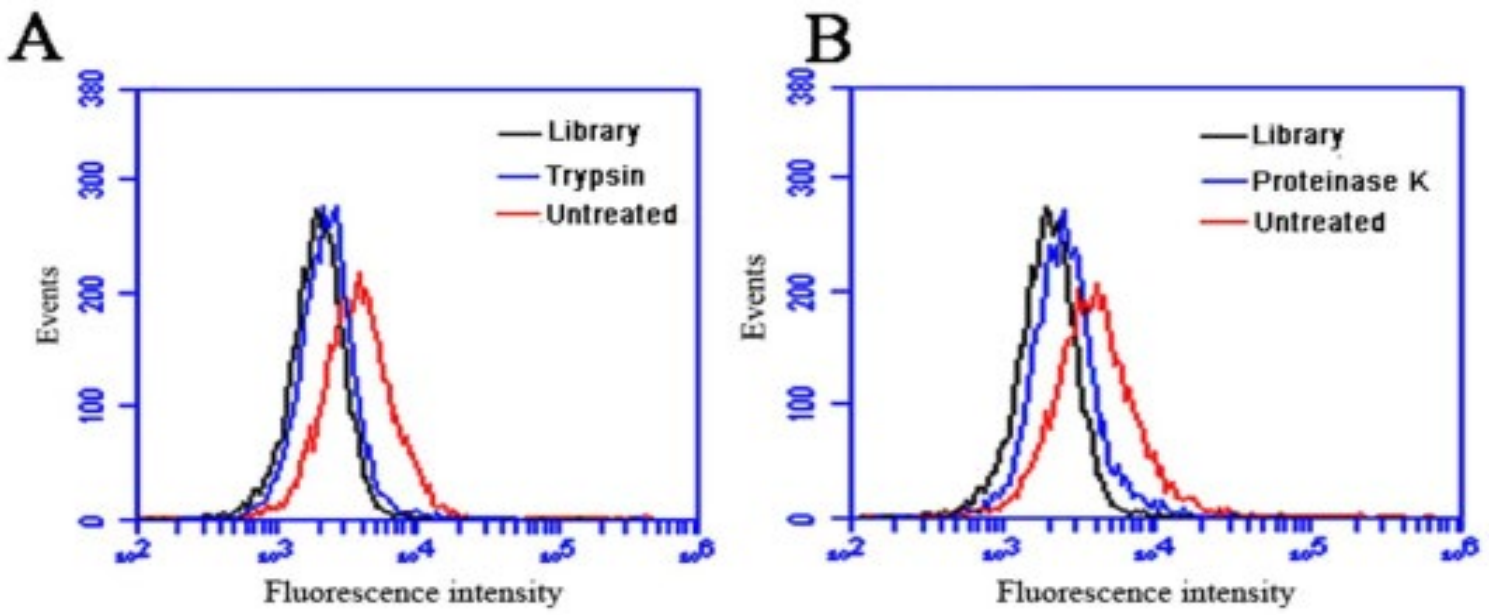


Aptamer AB3 selectively bound to OFA/iLRP-expressing tumor cells:

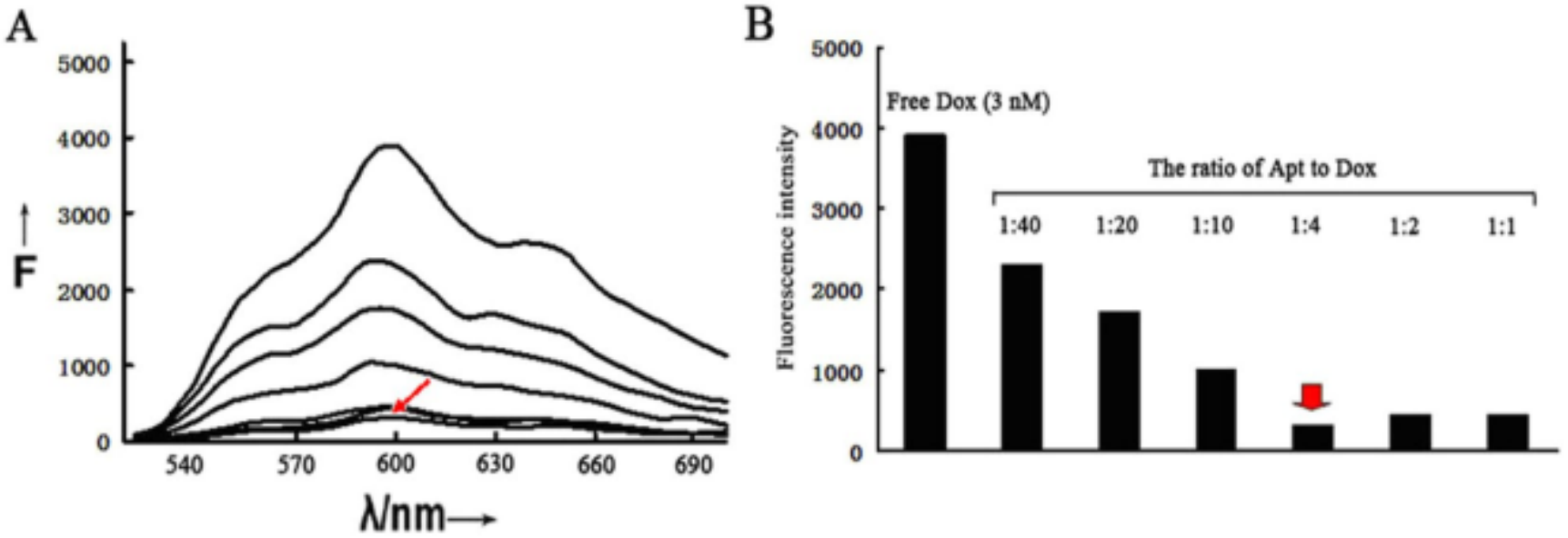




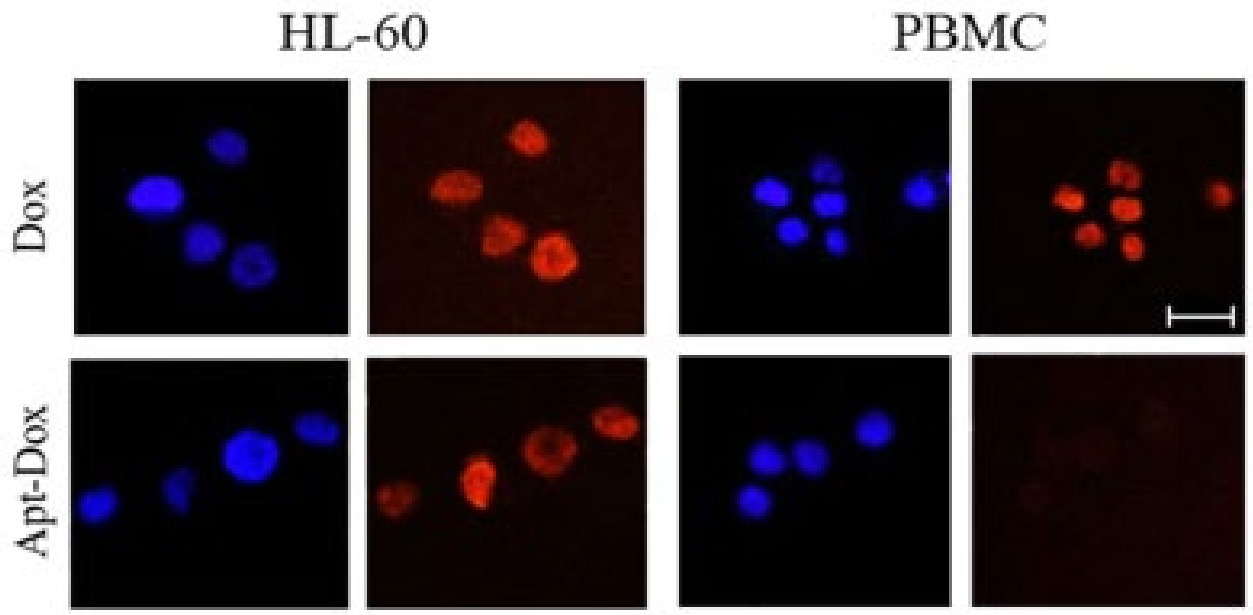
Aptamer AB3 targeted membrane proteins on the surface of OFA/iLRP-expressing cells:



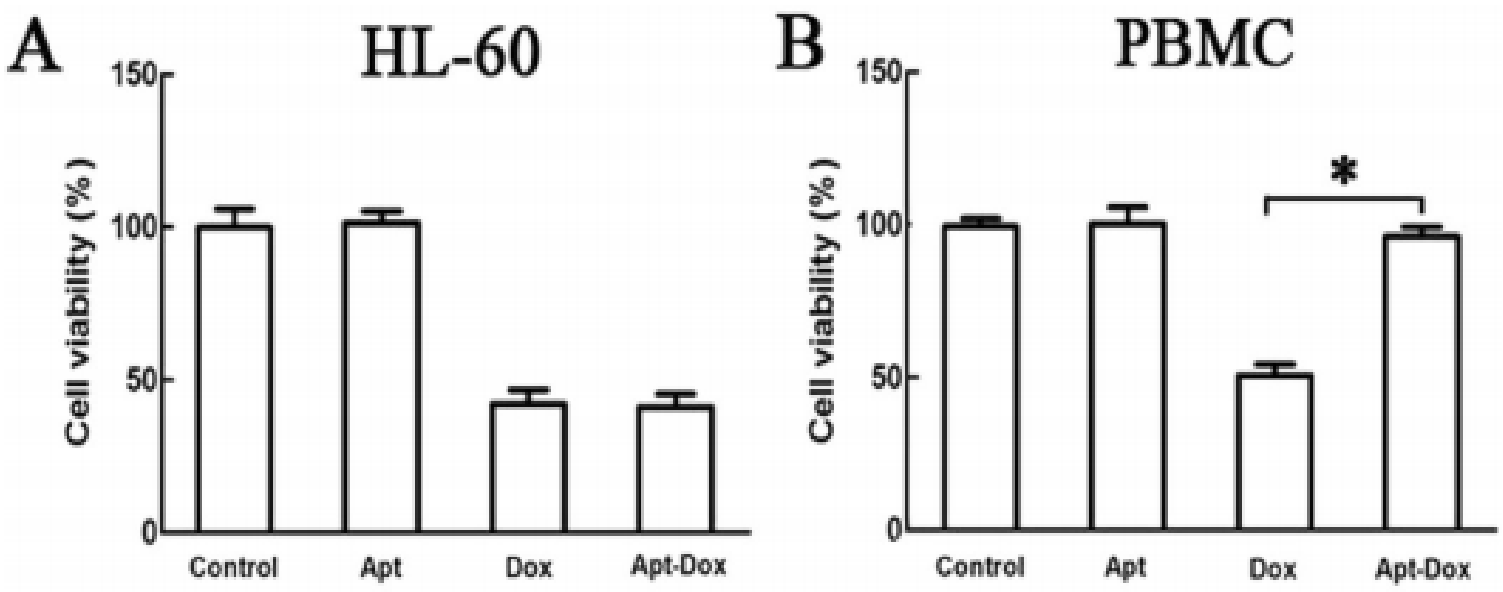
Formation of the aptamer-doxorubicin complex:



Aptamer AB3 selectively delivered doxorubicin to OFA/iLRP-positive AML cells:



Apt-Dox generated a targeted cytotoxicity against the OFA/iLRP-positive AML cells:



Discussion

- the first aptamer for recognizing OFA/iLRP.
- Moreover, the aptamer bound strongly to OFA/iLRP-positive AML/lymphoma cells, but weakly to OFA/iLRP-negative control cells.
- Confocal microscopy revealed that Apt-Dox could selectively deliver doxorubicin into AML cells, while significantly reduced the drug intake by OFA/iLRP-negative control cells *in vitro*

These results indicate that the OFA/iLRP aptamer may potentially serve as a tumor-homing ligand in targeted therapy against AML.

Thanks for your attention

HEMATOLOGY