7. Differentiated CD38-CD3 bionic to treat AML

(City of Hope)

5TH KDDF GLOBAL C&D TECH FAIR

Asset Overview

Product Type	Antibody
Disease Area	Oncology
Indication	Acute Myeloid Leukemia (AML)
Current Stage	Lead Optimization
Target	CD38-overexpressing cancers as AML
MoA	• In an in vivo human AML BM-like scaffold (huBMsc) patient-derived xenograft (PDX) model, targeting CD38 on the surface of AML cells with daratumumab was shown to reduce tumor burden in both high and low CD38 expressing cells • AML cells resistant to therapeutic intervention can become CD34 negative but maintain CD38 expression on their surface
Brief Description	• Inventors have developed bispecific molecules ("bionics") directed against CD38 and CD3 to target CD38-overexpressing cancers such as AML. • The molecules show significant advantages over conventional daratumumab therapy including that – they kill AML cells w/o affecting human peripheral blood viability – they specifically kill CD38+ cancer cells – They engage with CD4 positive cells, leading to high levels of IFN-g production – Local IFN-g induced CD38 on leukemic stem cells and their subsequent destruction – They do not kill human NK or T cells in co-culture assays – They exhibit favorable therapeutic/manufacturing properties extensive biochemical, in vitro and in vivo data (multiple animal models) are available under confidentiality • The bionic technology is a platform that can be expanded to other antigens/bispecifics.
Intellectual Property	WO2022094147A1
Publication	-
Inventors	Guido Marcucci, Mariam MURTADHA, John C. Williams, Miso Park, Flavia Pichiorri

Highlights

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- CD38-CD3 BIONICS show favorable therapeutic properties in vitro
- CD38-CD3 BIONICS activates both CD4+ and CD8+ cells inducing high level of IFN-gamma release
- CD38-CD3 BIONICS kills total AML cells but not non-CD38+ immune cells
- CD38-CD3 BIONICS has strong preclinical activity in AML models
- CD38-CD3 BIONICS eradicated AML in PDx mouse models

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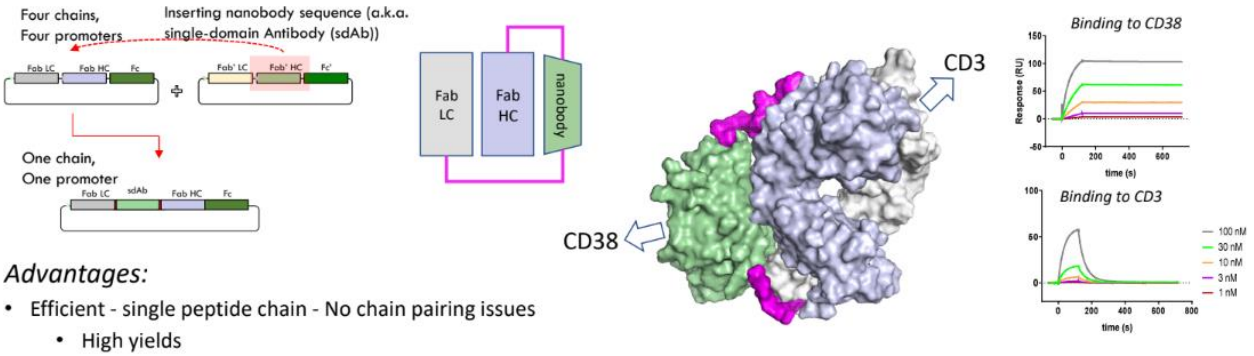
Key Data

BIONIC™ Technology

Biologics Nested Inside Chains or BIONICs™ involves the insertion of a second targeting domain ("nanobody") between the light and heavy chains of a Fab – in the example below, a Fab encoding CD3 and a nanobody encoding CD38.



Advantages:

- Efficient - single peptide chain - No chain pairing issues
  - High yields
  - High stability
- Compact - potential to strengthen the immunological synapse, leading to improved killing efficiency
- High monovalent affinity to CD38 antigen
- Low affinity to CD3 for improved biodistribution (e.g., T cells don't act as a sink).

CD38-CD3 BIONIC has strong preclinical activity in AML models