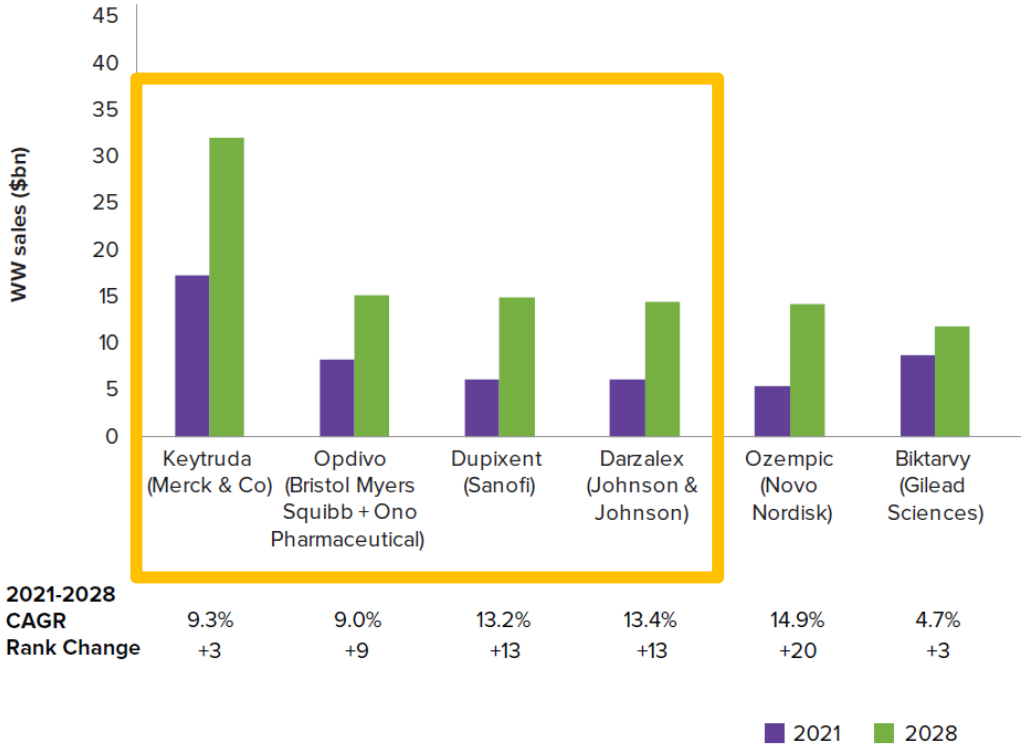
Disruptive biological approaches in immunotherapy, based on next generation BiXAb® bi- and multi-specific antibody platform for cancer treatment

Corporate deck for Galien start-up prize:
Deck2: Background Information & need for solution/product
May 2023

Antibodies will continue to lead the global sales race in the next 10-15 years, with the growth of bispecifics, especially with T Cell Engagers (TCE)

Top 6 selling products worldwide in 2028



Evaluate Pharma: WORLD PREVIEW 2022 Outlook to 2028

- **>60% of the top 100 molecules in global drug sales in 2028 from biotech**
- **First 4 molecules expected in 2028 in worldwide sales = antibodies (3 out of 4 in immunotherapy):**
  1. Keytruda (pembrolizumab) = $17 Bn in 2021, $32 Bn in 2028 (cancer)
  2. Opdivo (nivolumab) = $8 Bn in 2021, $14 Bn in 2028 (cancer)
  3. Dupixent (dumiplumab) = $6 Bn in 2021, $14 Bn in 2028 (asthma)
  4. Darzalex (daratumumab) = $7 Bn in 2021, $13.5 Bn in 2028 (cancer)
- **Complex antibodies (bi- and multi-specific; ADC) expected as the new generation of antibodies:**
  - ⇒ **Epcoritamab (Abbvie / Genmab): BsAb TCE anti CD3 x CD20 in Lymphoma: expected sales 2028: 1.7 Bn$**

A true momentum on IPO or M&A operations on CD3+ or non-conventional TCEs, demonstrating great potential for Biomunex

2021: Lava Therapeutics IPO: 100M$ levés
=> 380 m$ market cap at IPO raised

2021: Amunix acquisition by Sanofi pour $1Bn
For targeted, safer T cell engagers for cancer

2021: Maverick acquisition by Takeda
T-Cell Engager Therapies (gamma-delta) for Solid Tumors and Expand Novel IO Portfolio

2021: GammaDelta acquisition by Takeda
Accelerate Development of Allogeneic γδ T Cell Therapies (gamma-delta) for Solid Tumors

2022: Adaptate acquisition by Takeda
Develop Novel (gamma-delta) γδ T Cell Engager Therapies for Solid Tumors

2021: Teneobio acquisition by Amgen for $900M Upfront cash + future contingent milestone to Teneobio equity holders potentially worth up to an additional $1.6 Bn in cash

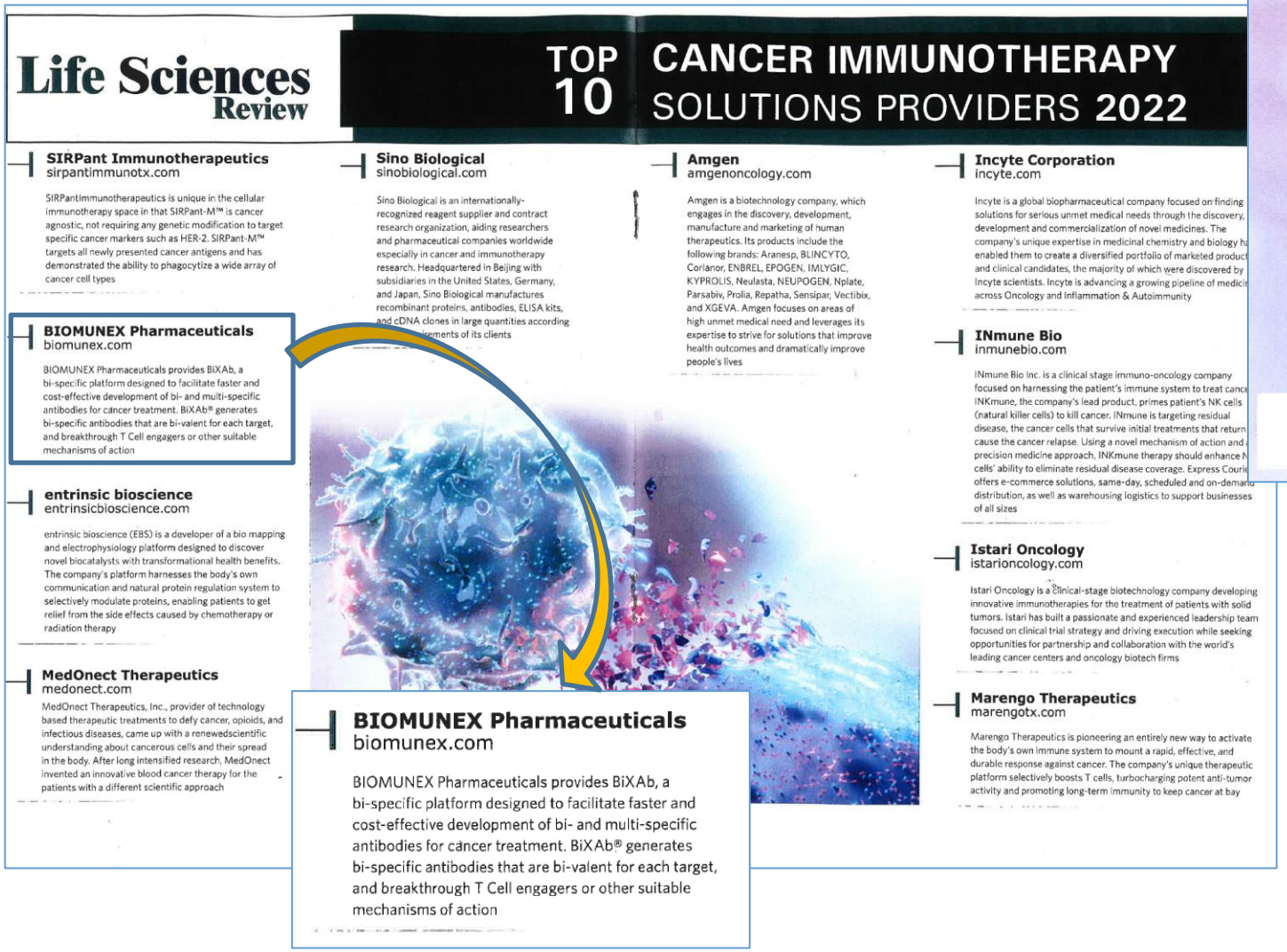
2022: TeneoTwo Acquisition by AstraZeneca CD19/CD3 TCE (Ph. 1 in RR B-cell non-Hodgkin lymphoma) **Upfront US$100M cash +** R&D milestones de **$805m** + commercial milestones **$360m**

With two unique and completely disruptive proprietary MAITs in Clinical Phases 1 and 2 and a sublicensed antibody in Phase 2-3 (Onward), the IPO or M&A potential for Biomunex is major in 2026-2027

Recent partnerships and transactions highlight the interest of Pharma & BioPharma companies in BsAb and CD3+ T cell engagers or γδ TCE

Company	Partner	Platform/Stage	Year	Details
Janux	**Merck MSD**	2 programs BsAb TRACTr platform (T Cell engagers)	2020	Deal value (milestones) per program: **$500.5m** Total deal value: unknown upfront + **$1Bn for 2 programs**
Lava Therapeutics	**J&J Janssen**	BsAb to gamma-delta T cell engagers	2020	Upfront + development and commercial milestones + tiered royalties (not disclosed)
F-Star	**Astra & Zeneca**	Fcab platform / STING BsAb programs	2021	**Upfront $12 + $300m milestones + single digit % royalty** payments per program (nb of programs not disclosed)
Merus	**Loxo/Lilly**	Biclonic platform 3 BsAb programs	2021	**Upfront** $**40m upfront + $20m equity investment + $1.6Bn**
F-Star	**J&J Janssen**	Fcab platform 5 BsAb programs	2021	U**pfront 17.5 M + $1,35bn overall for 5 programs**
Immatics	**BMS**	Immatics' TCR bispecific program	2021	**Upfront $150 M + milestones to $770 m + tiered double-digit royalties**
Biomunex Pharma.	***Onward Ther.***	*BiXAb bispecific antibody development candidate*	*2021*	*Upfront + development and commercial milestones + tiered royalties + other payments (not disclosed)*
Dragonfly	**Roche**	Tri-specific NK Engager (TriNKET) platform + licence for DF7001	2022	**Upfront** $**300 M** with an option for **royalties up to 20%** on global net sales
Harbour Biomed	**AstraZeneca**	CLDN18.2xCD3 Bispecific Antibody	2022	**Upfront US$25 M + US$325 m** development, regulatory and commercial milestones + tiered royalties
Lava Therapeutics	**Seagen**	Gamma-delta T Cell engagers (LAVA-1223; preclinical)	2022	**Upfront US$50 M + up to $650m** development, regulatory and commercial milestones + tiered royalties
Macrogenics	**Gilead**	Phase 1-stage CD123 x CD3-directed + 2 programs (preclinical)	2022	**Upfront US$60 M + up to $1.7Bn** in target nomination, option fees, and development, regulatory, commercial milestones & double-digit royalties
Zymeworks	**Jazz Pharma.**	Zanidatamab, HER2 BsAb (biparato-pic); phase 2 in CEA (comb.° or mono)	2022	**Upfront $ 375M** (in 2 tranches: $50M + 325M) + potential milestones for total potential payments of up to $1.76 Bn, plus royalties on net sales
Akeso	**Summit Ther.**	ivonescimab, anti-PD1 VEGF BsAb in clinical (approved in China)	2022	**Upfront $500 M** + up to $4.5 Bn in milestones + low double-digit royalties on net sales

Biomunex: an international recognition, notably in the USA



Life Sciences Review

TOP 10 CANCER IMMUNOTHERAPY SOLUTIONS PROVIDERS 2022

SIRPant Immunotherapeutics
sirpantimmunotx.com

SIRPantImmunotherapeutics is unique in the cellular immunotherapy space in that SIRPant-M™ is cancer agnostic, not requiring any genetic modification to target specific cancer markers such as HER-2. SIRPant-M™ targets all newly presented cancer antigens and has demonstrated the ability to phagocytize a wide array of cancer cell types

BIOMUNEX Pharmaceuticals
biomunex.com

BIOMUNEX Pharmaceuticals provides BiXAb, a bi-specific platform designed to facilitate faster and cost-effective development of bi- and multi-specific antibodies for cancer treatment. BiXAb® generates bi-specific antibodies that are bi-valent for each target, and breakthrough T Cell engagers or other suitable mechanisms of action

entrinsic bioscience
entrinsicbioscience.com

entrinsic bioscience (EBS) is a developer of a bio mapping and electrophysiology platform designed to discover novel biocatalysts with transformational health benefits. The company's platform harnesses the body's own communication and natural protein regulation system to selectively modulate proteins, enabling patients to get relief from the side effects caused by chemotherapy or radiation therapy

MedOnect Therapeutics
medonect.com

MedOnect Therapeutics, Inc., provider of technology based therapeutic treatments to defy cancer, opioids, and infectious diseases, came up with a renewedscientific understanding about cancerous cells and their spread in the body. After long intensified research, MedOnect invented an innovative blood cancer therapy for the patients with a different scientific approach

Sino Biological
sinobiological.com

Sino Biological is an internationally-recognized reagent supplier and contract research organization, aiding researchers and pharmaceutical companies worldwide especially in cancer and immunotherapy research. Headquartered in Beijing with subsidiaries in the United States, Germany, and Japan, Sino Biological manufactures recombinant proteins, antibodies, ELISA kits, and cDNA clones in large quantities according to requirements of its clients

Amgen
amgenoncology.com

Amgen is a biotechnology company, which engages in the discovery, development, manufacture and marketing of human therapeutics. Its products include the following brands: Aranesp, BLINCYTO, Corlanor, ENBREL, EPOGEN, IMLYGIC, KYPROLIS, Neulasta, NEUPOGEN, Nplate, Parsabiv, Prolia, Repatha, Sensipar, Vectibix, and XGEVA. Amgen focuses on areas of high unmet medical need and leverages its expertise to strive for solutions that improve health outcomes and dramatically improve people's lives

Incyte Corporation
incyte.com

Incyte is a global biopharmaceutical company focused on finding solutions for serious unmet medical needs through the discovery, development and commercialization of novel medicines. The company's unique expertise in medicinal chemistry and biology has enabled them to create a diversified portfolio of marketed products and clinical candidates, the majority of which were discovered by Incyte scientists. Incyte is advancing a growing pipeline of medicines across Oncology and Inflammation & Autoimmunity

INmune Bio
inmunebio.com

INmune Bio Inc. is a clinical stage immuno-oncology company focused on harnessing the patient's immune system to treat cancer. INKmune, the company's lead product, primes patient's NK cells (natural killer cells) to kill cancer. INmune is targeting residual disease, the cancer cells that survive initial treatments that return and cause the cancer relapse. Using a novel mechanism of action and precision medicine approach, INKmune therapy should enhance NK cells' ability to eliminate residual disease coverage. Express Courier offers e-commerce solutions, same-day, scheduled and on-demand distribution, as well as warehousing logistics to support businesses of all sizes

Istari Oncology
istarioncology.com

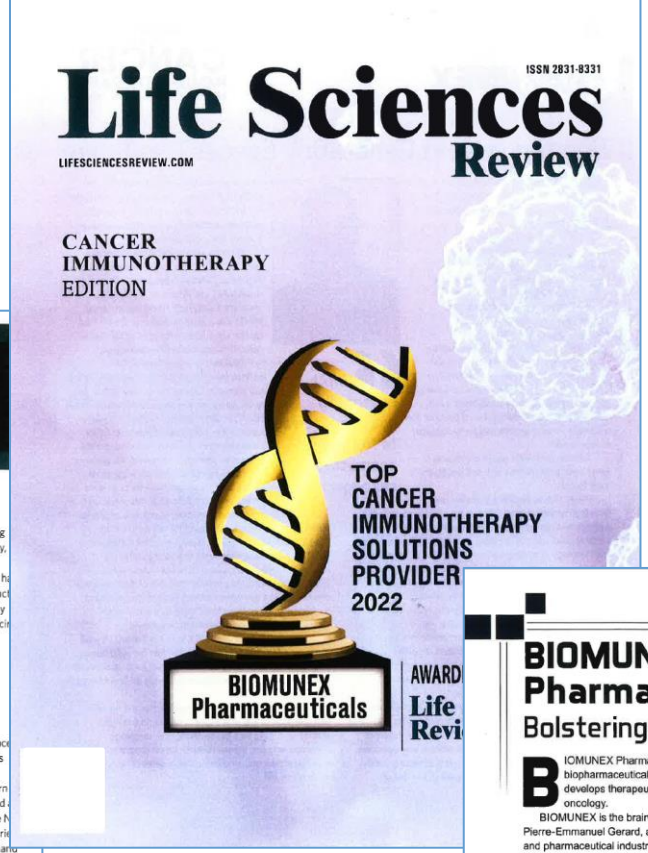
Istari Oncology is a clinical-stage biotechnology company developing innovative immunotherapies for the treatment of patients with solid tumors. Istari has built a passionate and experienced leadership team focused on clinical trial strategy and driving execution while seeking opportunities for partnership and collaboration with the world's leading cancer centers and oncology biotech firms

Marengo Therapeutics
marengotx.com

Marengo Therapeutics is pioneering an entirely new way to activate the body's own immune system to mount a rapid, effective, and durable response against cancer. The company's unique therapeutic platform selectively boosts T cells, turbocharging potent anti-tumor activity and promoting long-term immunity to keep cancer at bay

BIOMUNEX Pharmaceuticals
biomunex.com

BIOMUNEX Pharmaceuticals provides BiXAb, a bi-specific platform designed to facilitate faster and cost-effective development of bi- and multi-specific antibodies for cancer treatment. BiXAb® generates bi-specific antibodies that are bi-valent for each target, and breakthrough T Cell engagers or other suitable mechanisms of action



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CANCER IMMUNOTHERAPY EDITION

TOP CANCER IMMUNOTHERAPY SOLUTIONS PROVIDER 2022

BIOMUNEX Pharmaceuticals

AWARD

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Life Sciences Review TOP 10 CANCER IMMUNOTHERAPY SOLUTIONS PROVIDERS - 2022

BIOMUNEX Pharmaceuticals

Bolstering Next Generation Cancer Treatment

BIOMUNEX Pharmaceuticals is a biopharmaceutical company that develops therapeutics in immuno-oncology.

BIOMUNEX is the brainchild of Pierre-Emmanuel Gerard, a biotech and pharmaceutical industry expert with extensive experience in developing innovative biopharmaceutical products. Under the strategic leadership of the industry stalwart, BIOMUNEX has architected its proprietary BiXAb technology to support the development of breakthrough immunotherapies. BiXAb® is a next-generation antibody technology platform based on computational modeling to effectively create bi-specific and multi-specific antibodies that are being used for the treatment of solid tumors and hematological malignancies.

"BiXAb essentially opens a gateway to forge novel approaches of T cell engagers," says Gerard.

The BiXAb bispecific antibodies are bi-valent for each target and can be used to specifically engage and redirect T Cells to kill cancer cells or other suitable mechanisms of action. BIOMUNEX's proprietary methodology of adding a second Fab with a proprietary linker to connect the domains has been patented. Since the solution depends on the natural pairing of light and heavy chains, point mutations in the constant region are introduced to prevent mispairing. It also holds the ability to produce tri- and tetra-specific formats.

"Our platform creates bi-specific antibody from any monoclonal antibody pair with excellent drug-like properties including high binding affinity, lack of aggregation, low risk of immunogenicity, high stability, and excellent manufacturability," Gerard explains.

BiXAb truly discerns itself in the bsAb field with its capacity to generate new compositions of matter, including design, production, purification, and characterization of antibodies in less than two months without any extensive engineering. This efficient platform has already grabbed the attention of large pharma companies like Sanofi.

Pierre-Emmanuel Gerard, CEO and Founder

> *"BiXAb essentially opens a gateway to forge novel approaches of T cell engagers*

They signed a licensing agreement with BIOMUNEX to access the BiXAb platform to produce bi-specific and multi-specific antibody therapeutics in a plug-and-play manner and optimize them.

To up its ante in the immunotherapy field, BIOMUNEX is undertaking various proprietary research programs. Take the novel MAIT cell (Mucosal Associated Invariant T cell) redirection, for instance. MAITs are a subpopulation of T cells that can be specifically engaged to kill cancer cells. This approach was developed by BIOMUNEX—using their BiXAb technology—in collaboration with the Cancer and Immunity Unit at the Curie Institute led by Dr. Amigorena, a key opinion leader in the field. This MAIT cell redirection outweighs some of the limitations of classical CD3+ T-cell engagers, such as cytokine release syndrome, which is detrimental for patients. This novel modality does not engage all T cells, and it's employable for both solid tumors and hematological malignancies.

BIOMUNEX has also developed a pipeline of BiXAb patented antibodies, including BMX-101 (anti CD38-PD-L1),BMX-003 (anti-RTK family) and BMX-500(anti-MAIT-TAA). One of which was licensed to a Swiss biopharmaceutical company, Onward Therapeutics, in 2021. Recognizing the potential benefits of their research endeavors, the company focused project was awarded a national grant of close to €3 million by the French Government—indeed a great feat to achieve.

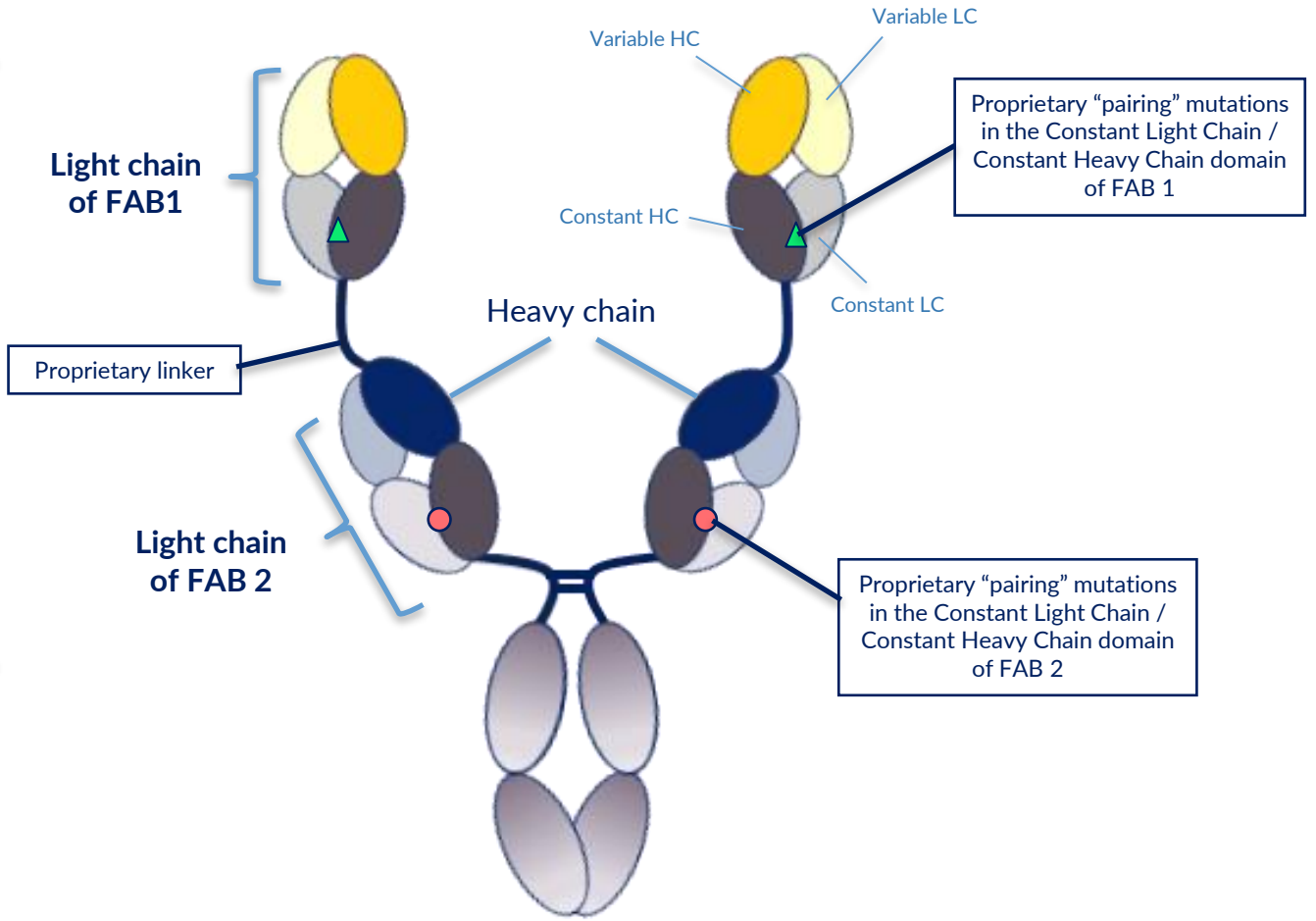
Looking ahead, BIOMUNEX is in the developmental stage for BMX-500 MAIT cell redirection for solid tumors. The company is gearing up to develop BiXAb platform for tri-specific antibodies and plans to launch its first tri-specific Ab program by 2024.

With all these plans in the pipeline, it won't be an exaggeration to say that BIOMUNEX is on the right path to emerging as a game changer in oncology immunotherapies, thanks to its focus on innovation, zeal to alter the status quo, and indomitable spirit of not yielding to adversities.

Biomunex Pharmaceuticals – May 2023

First level of disruptive innovation: Unique features of a BiXAb® antibody enabling the platform to be “Plug-and-Play” and easy to use

- **Plug and Play format.**
- **Swap any 2 FABs.**
- **Bispecific**
- **Bivalent (for each target).**
- **Fc effector function competent or null.**
- **IgG1 or other.**



The BiXAb® platform fulfills all key properties of a “best-in-class” bispecific technology; it generates genuine “drug-like” candidates

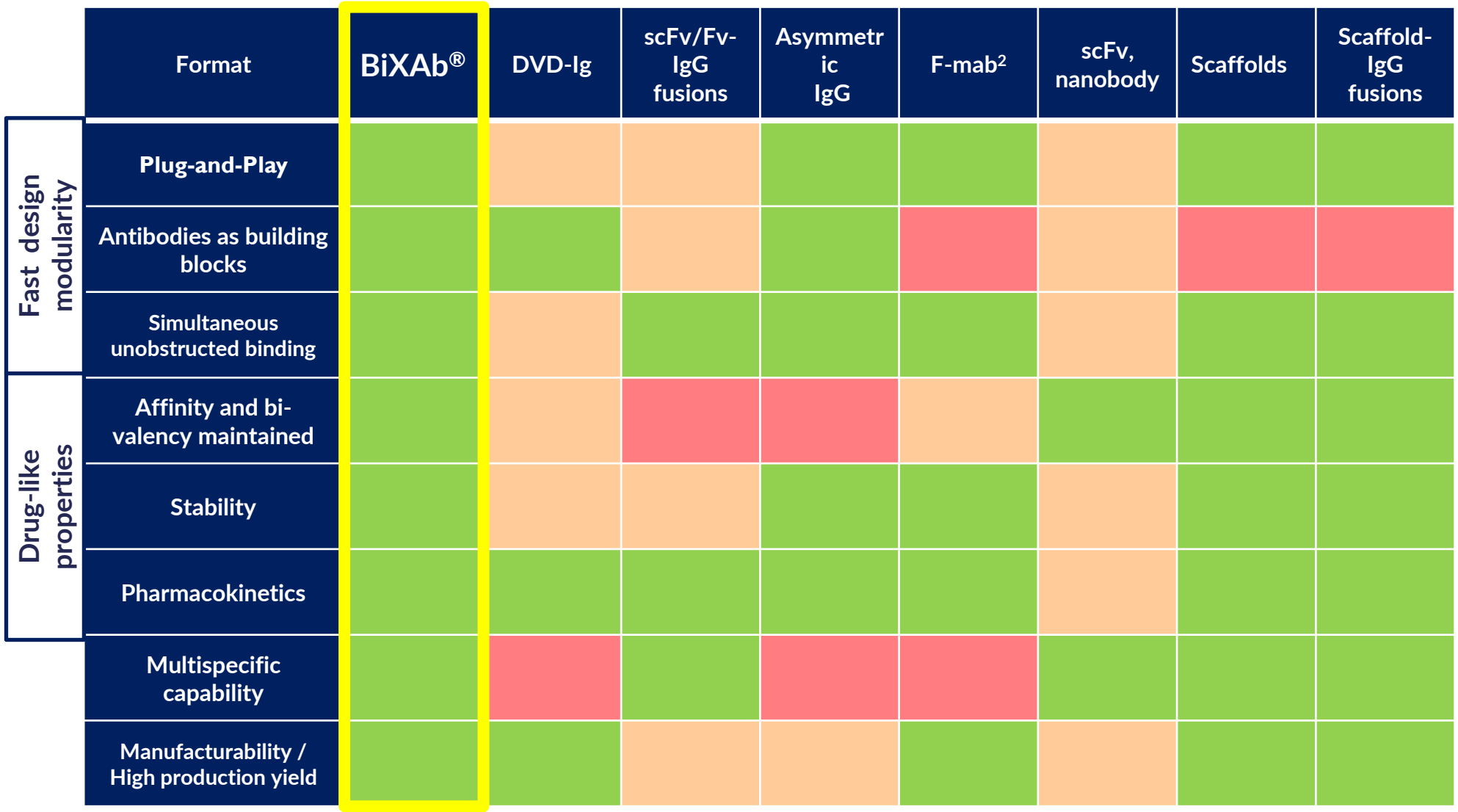
Main properties	Bispecific development with BiXAb®
Rapid generation and modularity	• “Plug-and-Play” • Proprietary computational modelling approach • Rapid generation, selection & purification (< 2 months) • Bivalency for each target • Fast IP generation of new composition of matter
Excellent drug-like properties	• IgG1 format • Excellent pairing • No steric hindrance • Low aggregation & immunogenicity risk • High stability
Excellent manufacturability	• High titer • High production yield = parental mAbs • Competitive COGS
Versatility & Multi-specific capability	• Versatile platform • Supports tri- and tetra-specific formats • Fab-Fab, IgG and Fab-Fab-plus formats

BiXAb® Technology

Tetravalent BiXAb

Bivalent Fab-Fab

BiXAb® is the unique platform overcoming challenges and limitations of other bispecific antibody technologies



An article recently showed the high value of the BiXAb platform to generate many druggable efficacious BsAb in a very short period of time

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Design and selection of optimal ErbB-targeting bispecific antibodies in pancreatic cancer

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The ErbB family of receptor tyrosine kinases is a primary target for small molecules and antibodies for pancreatic cancer treatment. Nonetheless, the current treatments for this tumor are not optimal due to lack of efficacy, resistance, or toxicity. Here, using the novel BiXAb™ tetravalent format platform, we generated bispecific antibodies against EGFR, HER2, or HER3 by considering rational epitope combinations. We then screened these bispecific antibodies and compared them with the parental single antibodies and antibody pair combinations. The screen readouts included measuring binding to the cognate receptors (mono and bispecificity), intracellular phosphorylation signaling, cell proliferation, apoptosis and receptor expression, and also immune system engagement assays (antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity). Among the 30 BiXAbs™ tested, we selected 3Patri-1Cetu-Fc, 3Patri-1Matu-Fc and 3Patri-2Trastu-Fc as lead candidates. The in vivo testing of these three highly efficient bispecific antibodies against EGFR and HER2 or HER3 in pre-clinical mouse models of pancreatic cancer showed deep antibody penetration in these dense tumors and robust tumor growth reduction. Application of such semi-rational/semi-empirical approach, which includes various immunological assays to compare pre-selected antibodies and their combinations with bispecific antibodies, represents the first attempt to identify potent bispecific antibodies against ErbB family members in pancreatic cancer.

KEYWORDS
ErbB, systems biology, antibody, bispecific, pancreatic cancer, ADCC, signaling, phosphoproteome

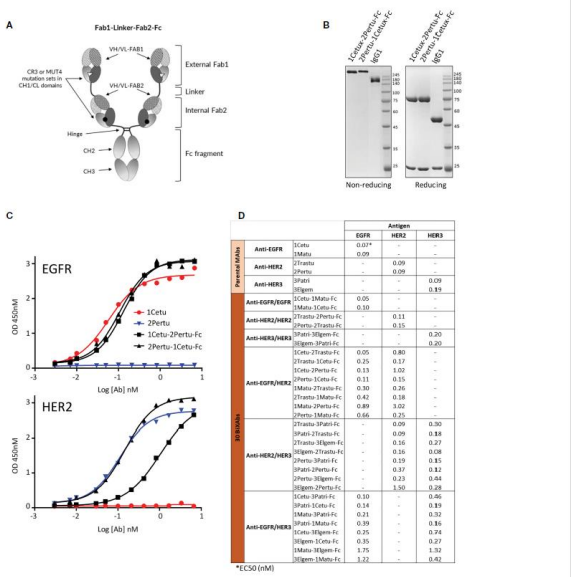


FIGURE 1
Biochemical characterization of ErbB-specific BiXAb™. **(A)** Schematic illustration of the BiXAb™ platform. **(B)** Representative SDS-PAGE analysis of the BiXAb™ 1Cetu-2Pertu-Fc and 2Pertu-1Cetu-Fc in non-reducing and reducing conditions. Proteins were stained with Coomassie brilliant blue. IgG1 was used as control and molecular weight markers are indicated. Other BiXAb™ are in Supplementary Figure 1. **(C)** Representative results of ELISA to assess binding of 1Cetu-2Pertu-Fc, 2Pertu-1Cetu-Fc, 1Cetu, and 2Pertu to immobilized EGFR (top panel) and HER2 (bottom panel). See Supplementary Figure 2 for all antibodies used in this study. **(D)** EC50 values extracted from ELISA binding curves.

original set of mutations have been introduced at the interface of the CH1 and CL domains of the two Fabs to facilitate cognate pairing of heavy/light chains and prevent their mispairing (described in WO2018178101). The two tandem Fabs are constructed on an Fc fragment to endow the obtained BiXAb™ with immune-related mechanisms and adopt the full bispecific, bivalent antibody architecture to permit efficient binding to the two targeted epitopes. The variable regions of six mAbs were cloned in separate vectors resulting in 30 heavy chain cassettes that comprised all possible combinations of the six antibodies in both orientations, and the six light chains. The BiXAb™ synthesis required the production of one continuous fused heavy chain with two separate light chains (submitted patent; application number EP22305242.4). The BiXAb™ antibodies were produced by transient co-transfection of three genes coded on separate pQMCF vectors in a 2:1:1 (heavy chain1:light chain1:light chain2) molecular ratio.

The cloning, production and purification of mAbs and BiXAb™ was performed at Icosagen (Tartu, Estonia). The thirty 250-kDa BiXAb™, derived from 1Cetu (EGF-competitive, specific for EGFR domain 3), 1Matu (EGF-non-competitive, specific for EGFR domain 3), 2Pertu (HER2 domain 2-specific; no ligand identified), 2Trastu (HER2 domain 4-specific; no ligand identified), 3Patri (NRG1-competitive and specific for HER3 domain 2) and 3Elgem (NRG1-non-competitive and specific for HER3 domains 2/4), were produced in CHO cells and purified by Protein A affinity chromatography. The control BiXAb™ HLA-DR/CD5 was described elsewhere (61) and the control CD3/CD19

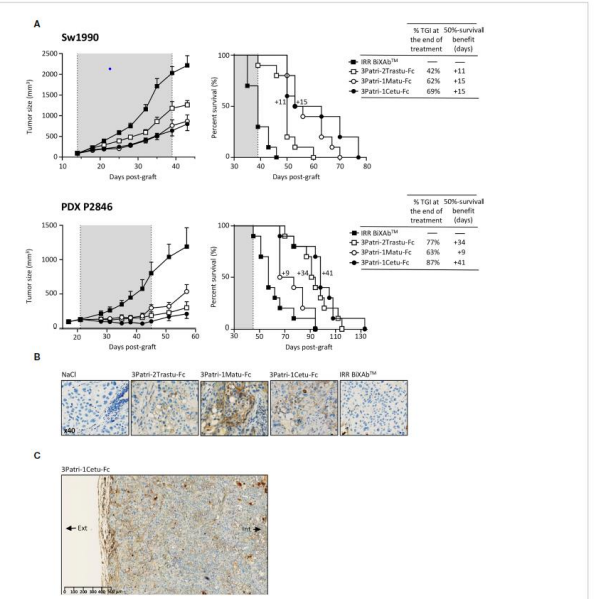


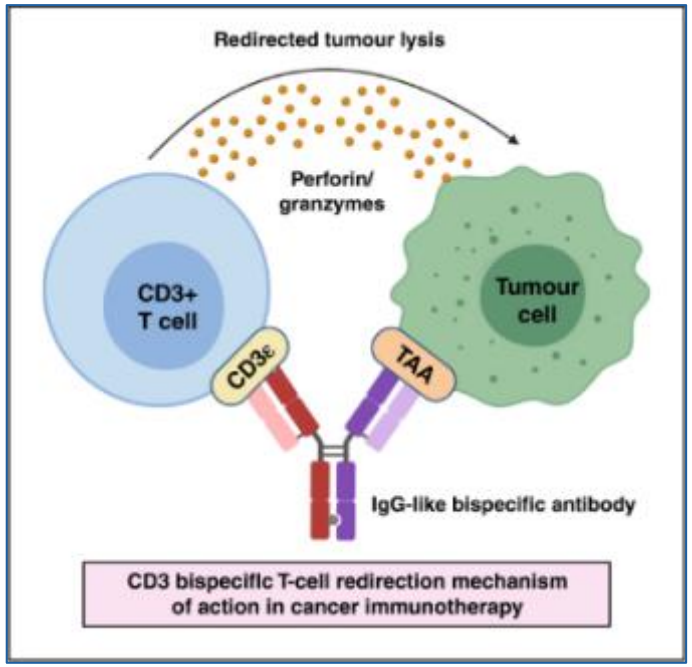
FIGURE 5
Pre-clinical evaluation of the three selected lead BiXAb™ 3Patri-2Trastu-Fc, 3Patri-1Matu-Fc, and 3Patri-1Cetu-Fc. **(A)** Tumor growth (left) and survival (middle) of BiXAb™-treated mice xenografted with Sw1990 and PDX P2846 PDAC cells. The percentage of tumor growth inhibition (TGI) at treatment end, and the 50% survival benefit (days) are indicated in the right panel. **(B)** Immunohistochemistry analysis of BiXAb™ penetration in Sw1990 cell xenografts. BiXAb™ were detected using peroxidase-conjugated anti-human Fc. IRR BiXAb™, BiXAb™ targeting HLA-DR and CD5 (negative control). NaCl was used as negative control. **(C)** Tumor penetration of 3Patri-1Cetu-Fc evaluated in whole tumor slices at lower magnification. The external (Ext) and internal (Int) parts of the tumor slice are indicated.

Pre-clinical evaluation of 3Patri-1Cetu-Fc, the best-in-class BiXAb™

We selected the BiXAb™ 3Patri-1Cetu-Fc as best-in-class because it induced the strongest tumor growth inhibition and longest median survival in xenografted mice. We compared the effect on tumor growth of 3Patri-1Cetu-Fc (at equimolar doses of Fc: 17 mg/kg; or at equimolar doses of Fab: 8.5 mg/kg), of the 2MAb 3Patri+1Cetu (5 + 5 mg/kg), and of the parental 1MAbs 3Patri and 1Cetu (10 mg/kg). At day 38 post-Sw1990 cell xenograft (Figure 7, upper panel), tumor growth was reduced by 77% in mice treated with Fc equimolar doses of 3Patri-1Cetu-Fc (p <0.001 *vs* IRR BiXAb™), by 65% in mice treated with 1Cetu+3Patri (p <0.001), by 54% in mice treated with Fab equimolar doses of 3Patri-1Cetu-Fc (p <0.001), by 50% in mice treated with 1Cetu (p <0.001) and by 43% in mice treated with 3Patri (p <0.001). The median survival was increased by 18 days (p <0.001) in mice treated with 17 mg/kg of 3Patri-1Cetu-Fc and with 3Patri+1Cetu, by 11 days in mice treated with 8.5 mg/kg of 3Patri-1Cetu-Fc and with 3Patri, and by 7 days in mice treated with 1Cetu (Figure 7, upper panel). We obtained similar results in mice xenografted with the PDX P2846 (Figure 7, lower panel). At day 60 post-graft (treatment end), tumor growth was reduced by 63%, 61%, 43%, 41%, and 19% in mice treated with Fc equimolar doses of 3Patri-1Cetu-Fc (p <0.001

T Cell engagers have brought substantial promise to the immunotherapy field

- **T Cell CD3-targeted redirection approach => immunotherapy promise**
- **> 60 clinical trials evaluating CD3+ T Cell redirection => high interest of pharma companies**
  - > 20 TAAs evaluated by > 20 different pharma companies
  - Therapeutic areas: mainly hematological malignancies
- **1 BsAb T cell engager on the market (Blincyto), 2 recently approved (Tecvayli, Lunsumio) and several BsAb/TCE in Phase 3**



Problems associated with CD3+ T Cell redirection approaches:

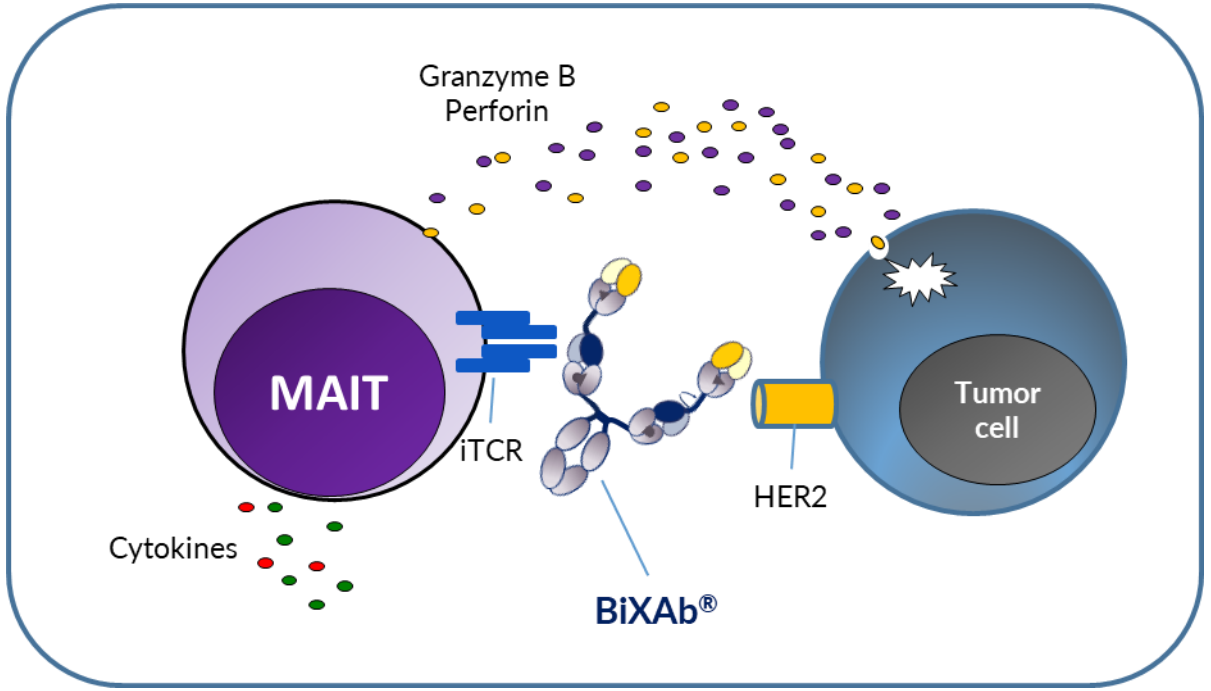
- Pan-T cell activation including Th and Treg subsets
- Cytokine release syndrome
- Other dose-limiting toxicities
- Limited anticancer efficacy in solid-tumors

BsAb: bispecific antibody; TCE: T cell engagers

BiXAb® approach for MAIT-cell redirection conceived together with the Curie Institute

- **Together with Institut Curie (Dr. Amigorena, Dr. Lantz), Biomunex has co-invented and is co-owner** of the unique approach of MAIT engagers (first globally)
- Biomunex has developed a **BiXAb® that targets specifically the MAIT iTCR** and does not bind other T-cell populations
- A BiXAb® targeting the iTCR on MAIT cells and a TAA on a cancer cell will permit the **formation of an effective immunological synapse** =>Activation / degranulation / proliferation / cytotoxicity

- Multiple Mechanisms would contribute to final tumor control (**Spark effect**)
- **A series of BiXAb®s against several TAAs** in initial proof-of-principle studies with Curie Institute
- A first DC targeting **HER2+ cancers** ready for CMC in Q2 2023
- Another program targeting **another TAA** (from 3 novel TAAs) is ongoing
- **Strong patent position** for the redirection of MAIT

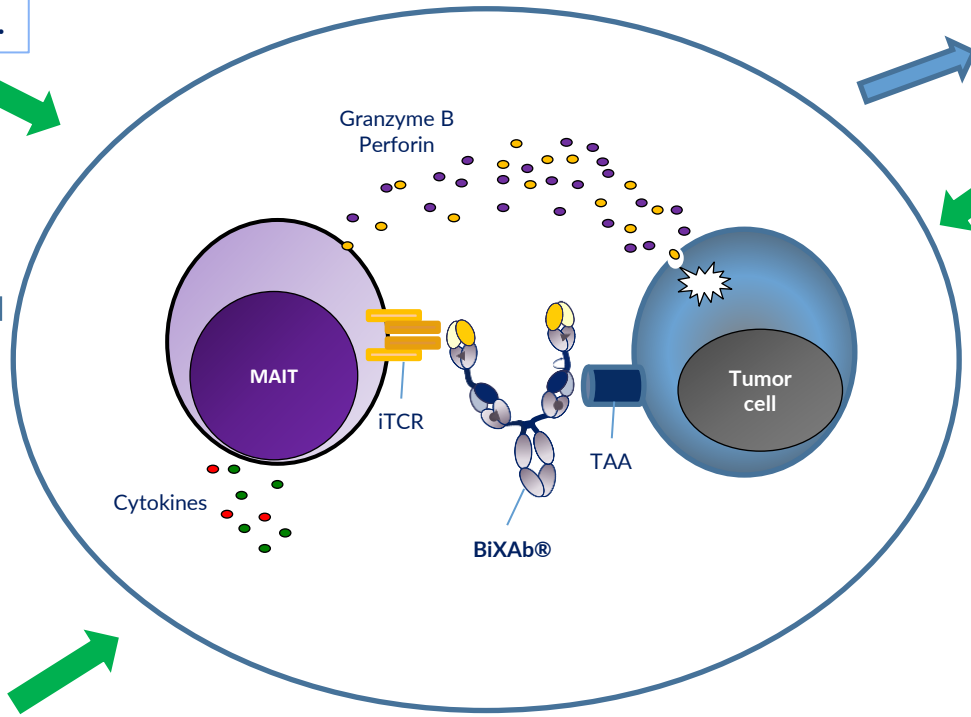


What we expect from BiXAb®-mediated MAIT cell redirection: Multiple mechanisms

- **MAIT cell-directed tumor killing**

- Activation and recruitment of NK cells.
- **NK-mediated tumor killing.**

- Immunological cell death
- Neoantigen presentation .
- **New adaptive immune response.**
- Influx of primed CTLs.
- **CTL-directed tumor killing.**



- **MAIT-cell activation** and proliferation and cytokine release

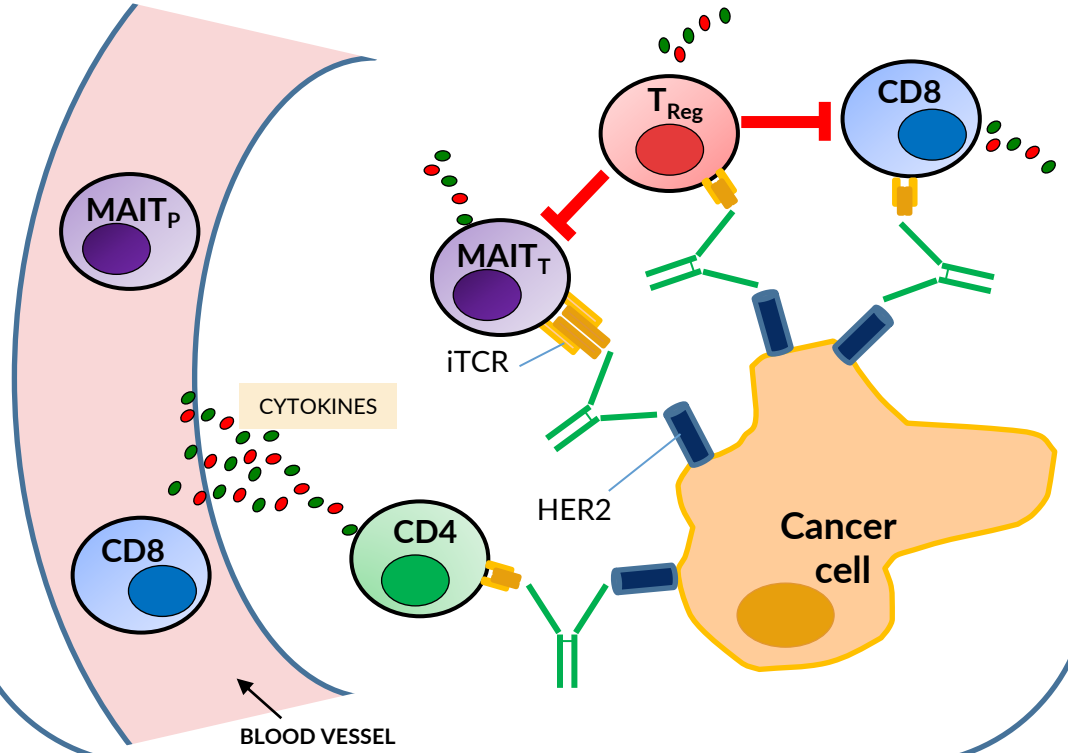
- MAIT-induced **activation of macrophages.**

- Influx of effector memory MAITs from the periphery.
- **BiXAb®-mediated tumor killing**

Advantages of MAIT engagers compared to classical TCEs in solid tumors

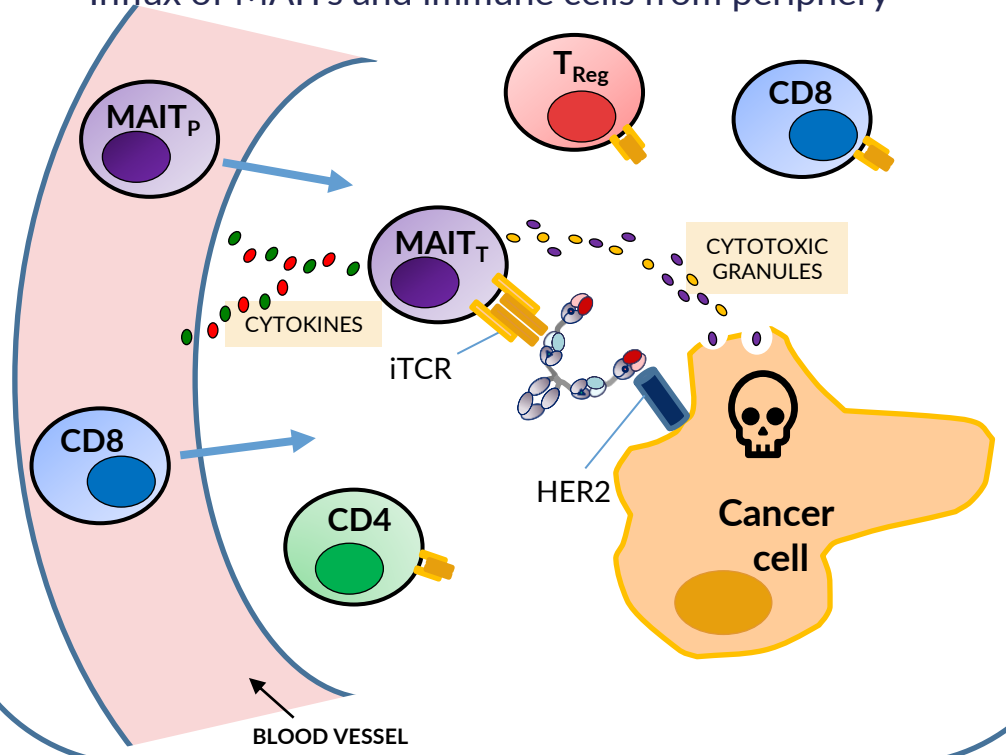
Classical TCE

- Classical TCE activate all T-cell subsets
- Activated Tregs can supress activity of other T cells in TME
- Activated CD4 (and others) release significant cytokines



BiXAb MAIT engager

- BiXAb-mediated MAIT activation and direct cytotoxicity
- Limited cytokine release to initiate secondary immune response.
- No Treg activation
- Influx of MAITs and immune cells from periphery



Comparison of T-cell redirection modalities: the MAIT engager approach could provide a clear superiority to other T cell engagers

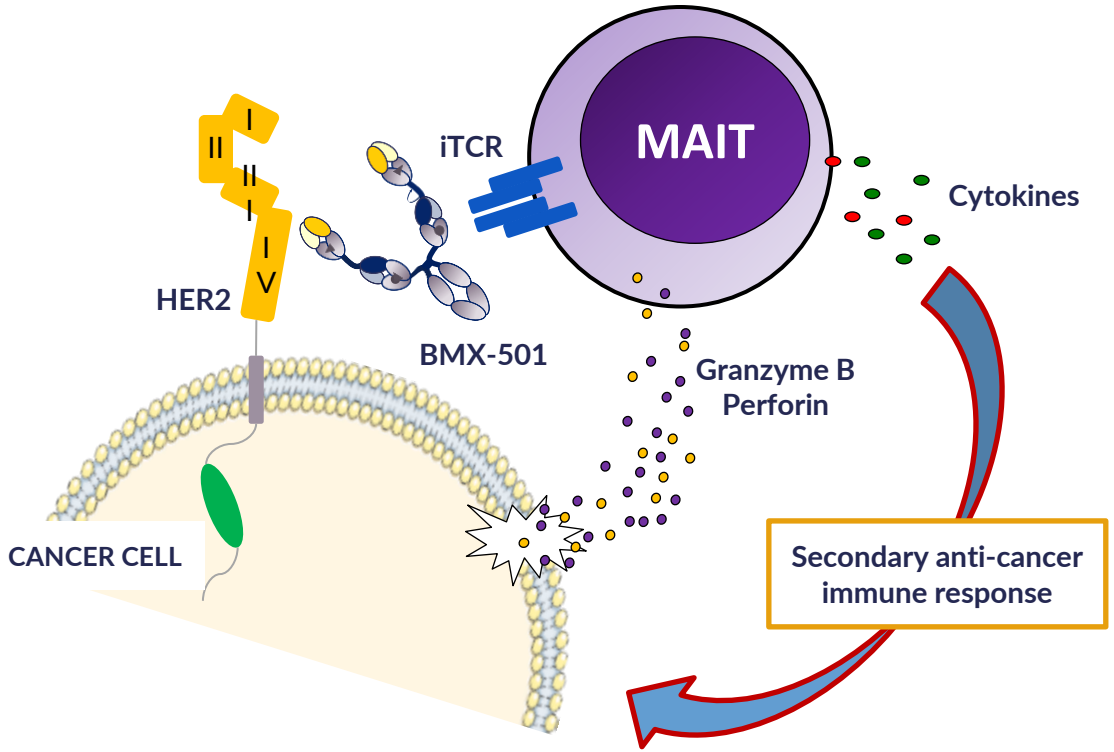
Feature	MAITs	α/β T-cells	γ/9δ2 T cells
Treg activation	No	Activate Tregs	γ9δ2 can potentially differentiate into Tregs (in response to TGFβ and IL-15).
Cytokine release	Limited	Widespread	Limited
Resistant to chemo-therapy (MDR gene)	Resistant	Not resistant	Not resistant
TCE activation	Restricted to MAITs	Activate all T cells	Restricted to γ/δ T cells
Subsets	Very limited subsets	Variety of subsets	limited subsets (but could be Treg)
Tissue resident	Naturally resident in barrier tissues (and others)	Traffic through tissues and resident	γ9δ2 are not naturally tissue resident
Abundance	Up to 20% of circulating T cells	Majority of T cells	<3% of circulating T cells
Cytotoxic function	Strong cytotoxic activity	Strong cytotoxic activity	Strong cytotoxic activity
TCR repertoire	Very limited: semi-invariant	Vast	Limited
Global Landscape	First-of-its-kind BsAb to MAIT cell engagers BIOMUNEX pharmaceuticals	Crowded space, with unsolved problems	Several examples: Lava Therapeutics, (Nasdaq), Adaptate, Maverick Ther., Gamma-Delta Ther. (acquired by Takeda)

Growing evidence strongly suggests that MAIT cell redirection would significantly impact solid tumors

First BiXAb-MAIT engager development candidate: BMX-501 has an extrinsic MOA, HER2 is a cancer anchor

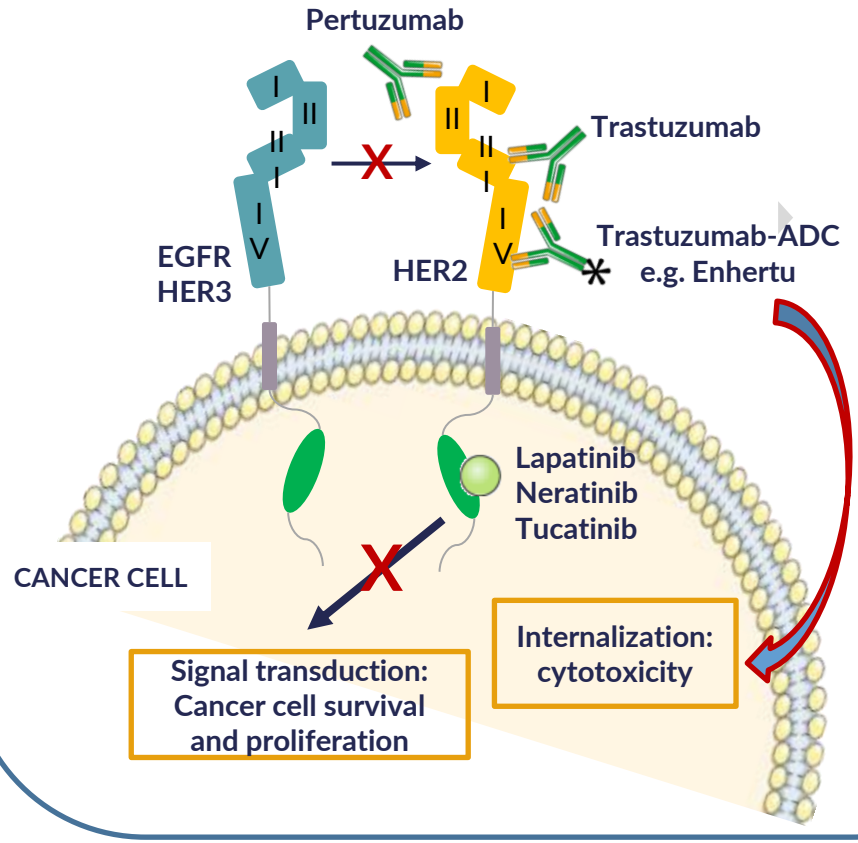
Extrinsic mechanism

(Recruits external effector cells (MAITs))



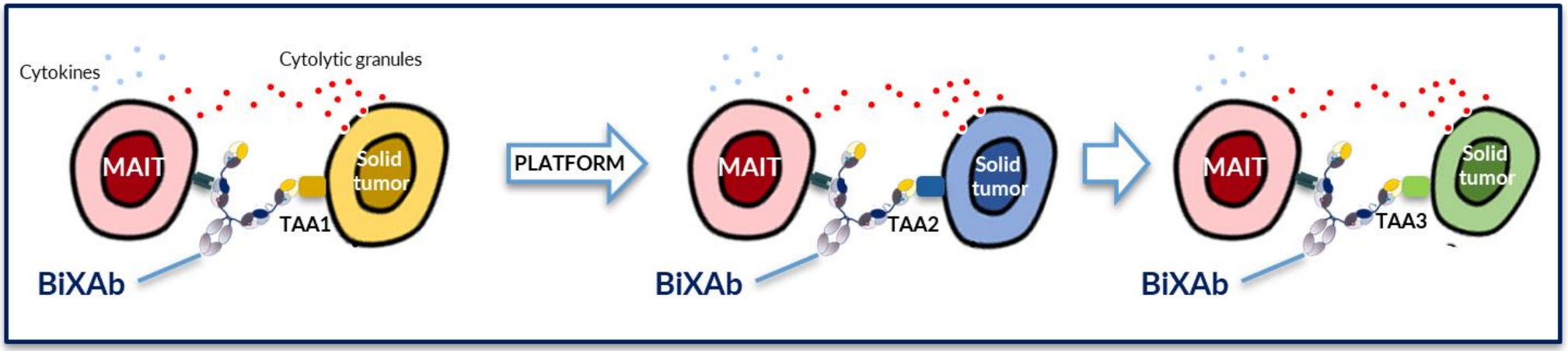
Instrinsic mechanisms

(Work via HER2 pathway to inhibit cancer cell)



The Biomunex MAIT-cell redirection platform is able to rapidly generate new MAIT engagers targeting new TAAs

- **First candidate nomination**
  - BMX-501: Evaluating **HER2 (as an anchor for MAIT redirection) for an initial indication in solid tumors** (i.e. for HER2+ lung or colorectal or small intestine or pancreatic or bladder cancers, etc)
- **Platform approach development**
  - Generating a **large proprietary panel of antibodies** (diverse epitopes and affinities) **towards the MAIT iTCR**
  - BMX-50X: **3 different TAAs evaluated** to define the best BiXAb targeting MAIT + a specific TAA
  - **Additional TAAs in the pipeline** being evaluated
  - **Potential for several programs in solid tumors**



A Poster at AACR 2023 presenting BiXAb-MAIT engagers

MAIT Engagers: an efficacious novel modality in the field of T-cell engagers for the treatment of solid tumors.

Simon Plyte[1], Marie Fraudeau[1], Jonathan Grivel[1], Paloma Hougron[1], Katja Klausz[3], Dorothee Winterberg[3], Britta von Below[3], Alexandre Ivagnes[1], Claire Germain[1], Sebastian Amigorena[2], Eugene Zhukovsky[1], Matthias Peipp[3], Pierre-Emmanuel Gerard[1], Olivier Lantz[2] and Julie Prigent[1]

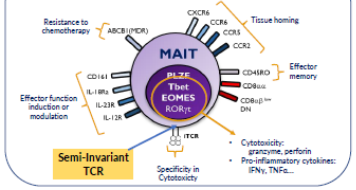
[1] Biomunex Pharmaceuticals, Bioincubateur Paris Biotech Santé, Paris, France; [2] Institut Curie, Rue D'Ulm, Paris France; [3] UNIVERSITÄTSKLINIKUM SCHLESWIG-HOLSTEIN Kiel, Germany

Poster No. 2954

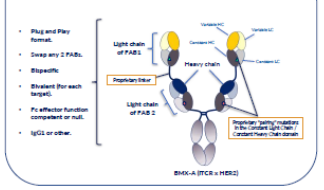
Introduction

Mucosal-Associated Invariant T cells (MAITs) are an abundant subset of non-conventional T-cells with potent cytotoxic capacity (up to 20% of circulating T-cells) that are naturally resident in many tissues and solid tumors. They can be activated by a TCR-dependent and independent manner and exhibit a rapid, innate-like response to bacterial and viral infections. MAITs express a semi-invariant TCR and respond to microbial metabolites presented in the context of the MHC-like protein, MR1. They have potent cytotoxic potential and readily infiltrate inflamed tissues where their cytotoxic activity can be induced by TCR engagement or by IL-12/IL-18.

Mucosal Associated Invariant T cells.

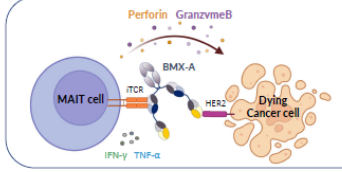


Features of the BiXAb® platform.



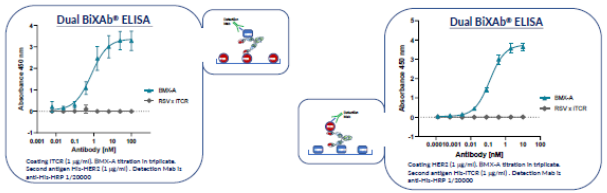
T-cell redirection is a clinically validated approach to treating haematological cancers but has had limited success so far in solid tumors. Classical T-cell engagers (TCE) bind the epsilon chain of the TCR leading to activation of all T-cells (Cytotoxic CD8s and all CD4 subsets including Tregs) which can lead to Cytokine Release Syndrome (CRS) and associated dose limiting toxicities. Activation of the Treg population in the tumor microenvironment by classical TCEs may also contribute to the reduced activity of this modality in solid tumors.

Biomunex Pharmaceuticals, using their proprietary BiXAb® technology, has developed a bispecific antibody to uniquely engage MAIT cells and redirect them to kill cancer cells by binding the invariant TCR (iTCR) expressed on MAIT cells and a tumor associated antigen (HER2). Given the significant abundance of MAIT cells and their propensity to infiltrate tissues and cancers, MAIT cell redirection is expected to significantly increase efficacy in solid tumors where there will be no activation of tumor resident Tregs with increased immunosuppression and no overt activation of all T-cell subsets leading to CRS.



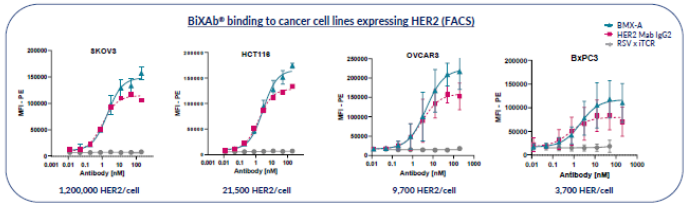
- The BiXAb® binds "in trans" to form an immunological synapse
- Activated/bridged MAIT cells directly kill the cancer cell.
- Local release of cytokines to induce secondary immune cell recruitment.

The BiXAb® MAIT Engager can bind both targets simultaneously (ELISA)



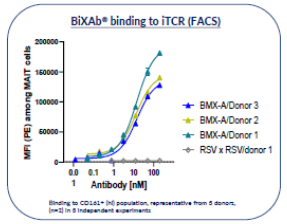
The BiXAb® BMX-A, targeting the MAIT iTCR and HER2 is able to bind both proteins simultaneously, as judged by dual ELISA (performed in both orientations).

The BiXAb® binds to HER2 on cancer cells lines as effectively as the parental Mab



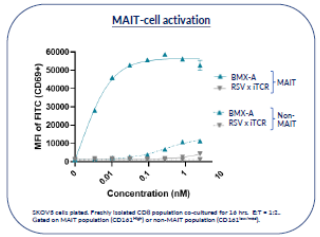
The iTCR x HER2 BiXAb® (BMX-A) is able to effectively bind HER2 expressed on cells over a wide range of receptor density. Note, at low receptor density (BxPC3) BMX-A binds with a higher "Y-max", compared to the parental Mab, due to the architecture of the BiXAb® format.

The BiXAb® MAIT Engager is able to bind the iTCR on MAIT cells



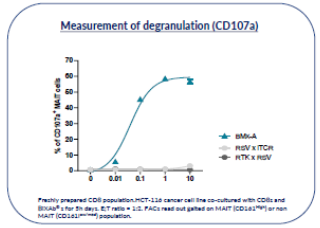
The BiXAb® (BMX-A) is able to bind to the iTCR on freshly isolated human MAIT cells .

Upon engagement with HER2-expressing cells, the BiXAb® binds and activates MAIT cells



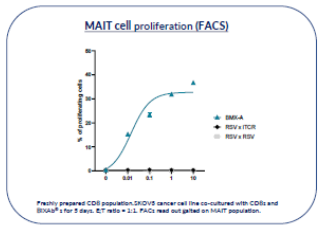
The BiXAb® (BMX-A) induces MAIT cell activation in the context of binding HER2+ cells. It does not activate the other CD8 cells present.

The BiXAb® can induce MAIT cell degranulation in co-culture with cancer cells expressing HER2



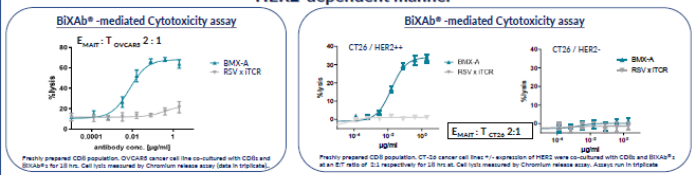
The BiXAb® (BMX-A) induces MAIT cell degranulation in the context of binding HER2+ cells. It does not impact other CD8 cells (data not shown).

The BiXAb® can induce MAIT cell proliferation when co-cultured with cancer cells expressing HER2



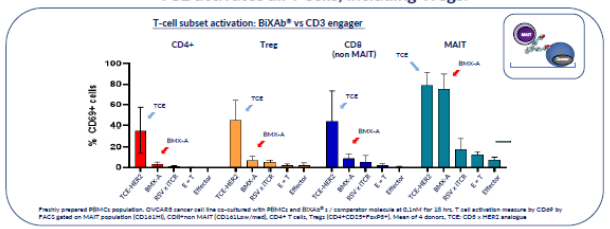
The BiXAb® (BMX-A) induces MAIT cell proliferation in the context of binding HER2+ cells. It does not impact other CD8 cells (data not shown).

The BiXAb® MAIT Engager can redirect MAIT cells to directly kill cancer cells in a HER2-dependent manner



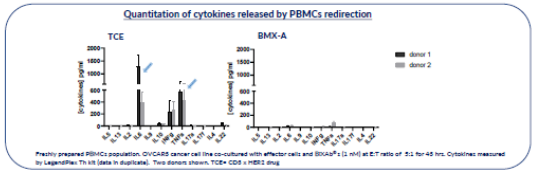
Even at low E:T ratio, the MAIT engager demonstrates potent cytotoxicity towards OVCAR3 cells expressing HER2 (ca 70% cytotoxicity in 18 hrs). Using an isogenic cell line CT26, depletion of HER2 prevents MAIT engager cytotoxicity and confirms the HER2 specificity of the BiXAb®-mediated MAIT cell redirection.

The BiXAb® MAIT Engager only activates MAIT cells whilst a classical HER2-directed TCE activates all T cells, including Tregs.



The MAIT engager only activates MAIT cells whilst the classical TCE activates all T cells. Treg activation could lead to increased immuno-suppression in the TME.

Minimal cytokines are released by a MAIT engager compared to a classical TCE when incubated with HER2 target cells and PBMCs.



In a PBMC mixture, the classical TCE induced the production of significant quantities of IL-6 and TNFα. The MAIT engager induced minimal cytokines, as expected

Discussion

- Biomunex Pharmaceuticals has developed a bispecific antibody platform (BiXAb®) that can effectively redirect MAIT cells to specifically kill cancer cells. The BiXAb® can:
  - Bind both the iTCR and HER2 simultaneously and bind HER2 on cancer cells over a wide [HER2] range
  - Activate MAIT cells, leading to degranulation, proliferation and direct cancer cell cytotoxicity.
- MAIT engagers have great therapeutic potential for the treatment of solid tumors:
  - Efficiently and specifically redirect MAIT cells to kill cancer cells (e.g. expressing the HER2).
  - Reduced cytokine storm due to the activation of a limited subset of T-cells.
  - Do not activate Tregs and therefore do not increase local immunosuppression in the TME.
  - From the above attributes, BiXAb® MAIT engagers should be efficacious in solid tumors
  - Can be designed to target any Tumor Associated Antigen.