Engineering the Future: Next Gen Platforms in Oncology

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Cancer Progress

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I am an employee of IGM Biosciences

The information presented is solely intended to foster the exchange of scientific and medical information.
What does a paradigm shift actually look like?
Innovation

- Surgery (1846)
- Radiotherapy (1903)
- Chemotherapy (1949)
- Targeted therapy (1998)
- Cancer Immunotherapy (2014)

Time

- 57 years
- 46 years
- 49 years
- 16 years

Wavelength (l)

Amplitude

Hegde and Chen, Immunity 2020

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Cancer Immunotherapy is a Breakthrough

**IMpower150 PFS**
Atezolizumab+Avastin+chemo
1L NSCLC

**HR, 0.617**
\[ P < 0.0001 \]

Reck, et al. ESMO IO 2017

**PACIFIC PFS**
(Durvalumab Stage III NSCLC)

**IMbrave150 OS**
Atezolizumab+Avastin
1L HCC

**HR, 0.58**
\[ P <0.001 \]

Finn, et al. NEJM 2020

**Keynote 189 OS**
(CarboPem+Pembrolizumab 1L NSCLC)

**HR, 0.70**
\[ P =0.0069 \]

Horn et. al. NEJM 2018

**IMpower133 OS**
Atezolizumab+chemo
1L Small Cell Lung

**HR, 0.62**
\[ (95\% CI 0.45-0.86) \]

Powles et al. Lancet 2018

**IMpassion130 OS**
Atezolizumab+chemo
1L TNBC PDL1≥1%

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Escudier, et al. ESMO 2017

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Escudier, et al. ESMO 2017
Cancer Immunotherapy is a Breakthrough

**Checkmate 214 OS**
(Ipi+Nivo 1L Int/Poor risk RCC)  
Escudier, et al. ESMO 2017

**Keynote 189 OS**
(CarboPem+Pembrolizumab 1L NSCLC)  
Gandhi et al. NEJM 2018

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**SO WHAT IS THE PROBLEM?**

**WHY CAN’T CANCER IMMUNOTHERAPY CURE CANCER MORE BROADLY?**

Reck, et al. ESMO IO 2017  
PACIFIC PFS  
(Durvalumab Stage IIIB NSCLC)

Gandhi et al. NEJM 2018


Finn, et al. NEJM 2020

Powles et. al. Lancet 2018

Chen DS Cancer Progress 2021
A complex set of tumour, host and environmental factors govern strength, and timing, of anti-cancer immune responses

\[ \int (F_{\text{stim}}) - \int (F_{\text{inhib}}) \geq \frac{1}{\sum_{n=1, y} (TCR_{\text{affinity}} \times \text{frequency})} \]

Chen and Mellman. Immunity 2013; Chen and Mellman. Nature 2017

Cancer immunity cycle

Cancer immune set point

Chen DS Cancer Progress 2021
Tumor immunity continuum

Adapted from Hegde et al., Clin Cancer Res, 2016.
Hegde and Chen, Immunity 2020
Chen DS Cancer Progress 2021
Problem Statement for Cancer Immunotherapy

- **Complex system:** *Immune system is highly complex with many positive and negative regulators comprising many cell types, circulating factors and compartments, all with spatial and temporal considerations*

- **Balance between anti-cancer immunity and autoimmunity:** *Simple systemic manipulation of immunity is often limited by stimulation of autoimmunity*

- **Cancer heterogeneity:** Human cancer can be broadly separated into three phenotypes that feature three distinct mechanisms of immune escape with each likely driven by specific dominant biology

...and learn and adjust to emerging data!
Cancer Immunotherapy Has Been a Breakthrough. How Do We Improve Upon It?

Many layers of immune regulation

Adapted from Hegde et al., Clin Cancer Res, 2016. Hegde and Chen, Immunity 2019 publication pending


https://cancer-immunity.nature.com/pages/map
How can Engineered Therapeutics help address these challenges in immunotherapy?
1. Alleviate immunosuppression

KILL CANCER CELLS
Inflamed

INFLAMED

CD8+ T cells infiltrated, but are inhibited

Community map of cancer immunity:
A multitude of suppressive factors in Inflamed Cancer

- How many of the suppressive factors are important?
- How will we target multiple suppressive factors at once?

https://cancer-immunity.nature.com/pages/map
A multitude of mechanisms to Immune Escape in Inflamed Cancers

Reported Mechanisms of Acquired Resistance to CPI

https://cancer-immunity.nature.com/pages/map
Chen and Mellman. Nature 2017

Schoenfeld and Hellmann, Cancer Cell 2020
Example: Enzymatic Glycomodulation

Glyco-Immune Checkpoints in Cancer: The Siglec/Sialoglycan Axis

Siglec binding to hypersialylated tumor glycans blocks innate and adaptive immune cell activation

Rodriguez et al 2018 Nature Reviews

Chen DS Cancer Progress 2021
2. Targeting immune exclusion

CD8+ T cells present but have not efficiently infiltrated

One of TGFβ’s functions is to trigger the formation of collagen fibers that can trap T cells: Will inhibiting TGFβ relieve this immune inhibition?

Bladder “excluded” phenotype: CD8/Collagen

Mariathasan, et al. Nature 2018
Targeting the Excluded TME with Immune Stimulation and Modulation: Targeted Agonism or Synthetic Cell Circuits?

Targeted 4-1bb stimulation

Synthetic Cell Circuits

FAP x 41bb monotherapy PD

FAP x 41bb + Atezolizumab waterfall plot

Sanmamed et. al. Sci Trans Med 2019
Melero et. al. ESMO 2020, unpublished material
Trub et al. JITC 2020
Chen DS Cancer Progress 2021

Roybal Lab website https://www.roybal-lab.org/papers
3. Why do Immune Deserts even exist?

Immune Deserts: A Profound absence of T cells and other immune cells in the tumor Microenvironment

Possible MOAs?

Passive:
- Potential lack of immunogenic antigens
- Lack of Antigen Presentation
- Lack of appropriate co-stimulation
- Immune Hostile TME
- Lack of immune attractive chemokines

Active:
- Repulsive Chemokines

Adapted from Hegde et al., Clin Cancer Res, 2016.
Hegde and Chen, Immunity 2019 publication pending

Chen DS Cancer Progress 2021
Alternative: Bypass regulation of endogenous immunity

**IMMUNE DESERT**
- Immune cells are absent from tumor and its periphery

**EXCLUDED**
- CD8+ T cells present but have not efficiently infiltrated

**INFLAMED**
- CD8+ T cells infiltrated, but are inhibited

Synthetic Immunity and the Cancer Immunity Cycle

Adapted from Chen and Mellman, Immunity 2013
Hegde and Chen, Immunity 2020
Chen DS Cancer Progress 2021
New Data from American society of Hematology (ASH19): BCMA-targeted T cell Engagers and CAR-T

Costa, et. al. ASH 2019

CC-93269 2:1 BCMAxCD3 (BMS)

Measurable Disease

Change From Baseline (%)

Best Overall Response

6→10 mg and 10 mg

Patients treated at 10mg (n=9):
ORR 89%, 44% sCR/CR (MRD negative); CRS ~100%
1 patient with Gr3/Gr5 CRS

Berdeja, et. al. ASH 2019

bb21217 BCMA CAR-T (BlueBird/BMS)

Patients treated at 150x10^6 cells (n=12): ORR 83%, 33% sCR/CR (MRD negative); CRS ~67%, Neurotox 25%; 1 patient with Gr5 CRS at 450x10^6 cells

Costa, et. al Blood 2019; Berdeja, et. al Blood 2019

Chen DS Cancer Progress 2021
Challenges for Synthetic Immunity

• Safety and CRS
  
  How can these therapies be made easier to use?

• Low Levels of Target
  
  How can we overcome immune escape due to low levels of target?

• Immunotherapy:
  
  How can we recapture the advantages of endogenous immunity (antigen spread, immune memory, etc)?

• Solid Tumors
  
  How will we overcome issues related to T cell homing, hostile tumor microenvironments and sustaining anti-cancer immunity?
Safety and CRS
Cytotoxicity and cytokine hierarchy is a function of T cell receptor stimulation

Plate Bound T Cell Activation

Two different T cell activation thresholds

Cytokine release hierarchy

Plates coated with anti-CD3 antibodies

A highly artificial system to have based our understanding of underlying T cell biology on; Easy studies to perform, but likely does not represent actual physiologic conditions (eg TCR engagement density and level of cross linking are super physiologic)
T cell Engagers and Synthetic Immunity: Are we overstimulating T cells?

- Peak cytokine levels after 1st infusion (~EOI-4h);
- Reduced immune function and cytokine secretion following first dose
- Rationale and MOA for “step-up dosing”
- First dose leads to global “de-sensitization” of many T cell functions

EXAMPLE: STEP DOSING

Are synthetic immune approaches Cancer Immunotherapy
… or do they just use a T cell’s killing machinery to potently kill a cancer cell?
Engineered Platform Technology:

**Focus on Control of:**

- **Stoichiometry** (interaction strength vs two targets/cells)
  - Eg Stronger binding to cancer cells, more physiologic signaling to T cells
- **Spatial** (biophysical effects, signal strength)
  - Eg multimeric clustering, engagement density
- **Temporal** (prolonged vs pulsatile modulation)
  - Eg stability of signals, cellular context, limit overstimulation
How Do We Move T cell Engagers Forward?

How can we make synthetic immunity cancer immunotherapy?

Example: Engineered IgM Antibody Framework:

Biophysics
Stoichiometry
Temporal Effects
IGM-2323 is a novel engineered high-affinity, high-avidity CD20xCD3 IgM bispecific T-cell engager

Bispecific antibodies that bridge lymphoma cells to T cells have shown promise in treating B-cell malignancies1–3

However, existing T-cell engaging antibodies that lead to dense clustering and supraphysiologic T-cell signaling are associated with toxicity (especially CRS) and have a limited therapeutic window that may be related to downregulation of T-cell function

IGM-2323 is a novel bispecific antibody, based on an engineered pentameric IgM framework, with a recombinant J-chain that is fused to an anti-CD3 scFv

In preclinical studies, IGM-2323 has been shown to bind irreversibly to CD20-expressing cells, including cancer cells expressing very low levels of CD20, and eliminate them through cell-dependent (TDCC) and cell-independent mechanisms (CDC)4,5


CD: cluster of differentiation; CDC: complement dependent cytotoxicity; CRS: cytokine release syndrome; IgG/M: immunoglobulin G/M; scFv: single-chain variable fragment; TDCC: T cell-dependent cytotoxicity

1. Anti-CD20
10 high affinity, high-specificity binding sites to CD20

2. Anti-CD3
Single high-specificity binding site to CD3

3. Complement
IgM mediates >100x greater complement mediated killing of bound cancer cells

Budde et al., Blood 2020
Synthetic Immunity: T Cell Signaling and Function Can Differ

~3-10 TCR-pMHC interactions required for CD8 T cell mediated killing of a cancer cell†

Purbhoo et al. Nature Immunology 2004

IGM-2323 may provide more physiologic T-cell activation compared with existing bispecific T-cell engaging antibodies
- T cells respond differently to different levels of TCR signaling
- Activation of T-cell cytotoxic mechanisms and IFNγ secretion require the lowest levels of TCR signal

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Treatment with IGM-2323 leads to repeatable IFNγ-dominant immune activity in R/R NHL

- Transient, repeatable cytokine elevations, with peak levels 6-12 hours post-infusion
- IFNγ detectable above baseline levels in 12/12 patients treated at ≥10mg
- IFNγ levels >> IL-6 and TNFα levels in vast majority of patients treated
- For patients dosed with ≥30 mg, 9/9 show repeatable IFNγ spikes; 4/9 show higher IFNγ spikes at later infusions

IFNγ levels pre/post-IGM-2323 treatment

Post-infusion peak cytokine levels

Cytokine levels in frozen plasma were assessed on a batched basis at a central lab. Plots are from n=14 patients and show the highest concentrations obtained during the sampling period: 2, 6, 12, 24, and 72 hours for Infusions 1 and 4, and only 24 hours for Infusions 2, 3, 5, 6. Box plots show 1st and 3rd quartile, blue line connects mean values. IFNγ: interferon-gamma; IL-6: interleukin-6; TNFα: tumor necrosis factor alpha

Data cut-off: October 30, 2020

Maximum levels of cytokines observed 6-12 hours post-infusion. Peak values at Infusions 2,3,5,6 likely missed due to sparse sampling.

Budde et al., Blood 2020
IGM-2323 in R/R NHL AE summary:
Treatment-emergent AEs occurring in ≥20% of patients

- Generally well tolerated
- No Grade 3 or higher CRS
- No neurotoxicity

<table>
<thead>
<tr>
<th>Preferred Term (N=16* patients)</th>
<th>Any grade n (%)</th>
<th>Grade 1 n (%)</th>
<th>Grade 2 n (%)</th>
<th>Grade ≥3 n (%)</th>
</tr>
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<tbody>
<tr>
<td>Fatigue</td>
<td>9 (56)</td>
<td>8 (50)</td>
<td>1 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>7 (44)</td>
<td>4 (25)</td>
<td>3 (19)</td>
<td>0</td>
</tr>
<tr>
<td>Chills</td>
<td>6 (38)</td>
<td>4 (25)</td>
<td>2 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>6 (38)</td>
<td>4 (25)</td>
<td>2 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Blood creatinine increasedb</td>
<td>5 (31)</td>
<td>4 (25)</td>
<td>1 (6)d</td>
<td>0</td>
</tr>
<tr>
<td>CRSb</td>
<td>4 (25)</td>
<td>3 (19)</td>
<td>1 (6)d</td>
<td>0</td>
</tr>
<tr>
<td>Infusion related reactionc</td>
<td>4 (25)</td>
<td>1 (6)</td>
<td>3 (19)</td>
<td>0</td>
</tr>
<tr>
<td>Anaemia</td>
<td>4 (25)</td>
<td>2 (13)</td>
<td>2 (13)</td>
<td>0</td>
</tr>
</tbody>
</table>

Data cut off: 30 October 2020

*4 out of 5 patients with creatinine increase were assessed as unrelated to study treatment, per investigator
*CRS grading by ASTCT criteria; all CRS patients are also captured under pyrexia and/or chills.
*3 of 4 IRR patients are also captured under CRS

Some patients experience post-infusion chills and/or fever:
- Transient (≤3 hours), low grade; majority limited to first cycle; acetaminophen is most common treatment;
- No ICANS symptoms (Immune Cell Associated Neurotoxicity)
- Associated with CRP elevation at 24 hours
- Easily prevented with low dose dexamethasone premedication on subsequent infusions if desired

No CRS observed in the 3 patients treated in 50/100 cohort

Example: patient treated with IGM-2323 30 mg dosing

Chills/fever

10 mg dexamethasone pre-treatment
C1D1 per protocol
6-10 mg dexamethasone pre-treatment

Budde et al., Blood 2020
IGM-2323 in R/R NHL best overall response (PET-CT scans): 9 of 14 patients showing evidence of tumor size reduction

- B-cell depletion/reduction observed in 6/6 patients with circulating B cells at baseline

Data cut-off: October 30, 2020. Assigned dose level noted. \(^4\)PR cut-off, Lugano 2014 criteria, local reads. \(^5\)100 mg indicates 50/100 mg dose level; \(^6\)PR lymph node size decreased to below normal size with marked decrease in PET activity; CAR-T: chimeric antigen receptor T-cell; FL: follicular lymphoma; IHC: immunohistochemistry; Mantle: mantle cell lymphoma; MZL: marginal zone lymphoma; PET-CT: positron emission tomography-computerized tomography; PR: partial response; SPD: sum of the products of diameters.
Post-CART DLBCL
Example of pseudoprogression following IGM-2323 monotherapy

^PR cut-off, Lugano 2014 criteria, local reads.  
^100 mg indicates 50/100 mg dose level;  
^PR lymph node size decreased to below normal size with marked decrease in PET activity;  
CAR-T: chimeric antigen receptor T-cell;  
FL: follicular lymphoma;  
IHC: immunohistochemistry;  
Mantle: mantle cell lymphoma;  
MZL: marginal zone lymphoma;  
PET-CT: positron emission tomography-computerized tomography;  
PR: partial response;  
SPD: sum of the products of diameters,  

Immunity, pseudoprogression, and response
Example: 63 year old Post-CAR-T patient with R/R DLBCL treated with IGM-2323 (30 mg)

- Biopsy of new PET-avid lesion at 8 weeks shows intense T-cell infiltration with only scant lymphoma cells, >95% CD3+ T-cell infiltrates by flow cytometry post-treatment
- Lesion completely resolved by PET-CT at 12 weeks

Pathology Images courtesy of MD Anderson Pathology

Budde et al., Blood 2020

Pre-treatment (CD3 IHC)  
8 weeks post-treatment (CD3 IHC)
Pseudoprogression Has Been Observed When Strong Endogenous Anti-cancer Immune Responses are Induced: Anti-CTLA4 and Anti-PD(L)1

Metastatic Melanoma treated with Anti-CTLA4

Metastatic Melanoma treated with Anti-PDL1

Dana Farber Cancer Institute (Ibrahim/Hodi)

Wolchok et al. CCR 2009

Chen DS Nature Webcast 2021
Conclusions

• Cancer Immunity is highly complex, with many layers of regulation and multiple immune escape mechanisms

• Synthetic immunity such as CAR-T and bispecific T cell engagers may help bypass immune escape posed by appropriate immunogenic target expression, MHC loss and multiple layers of T cell regulation- by generating potent T cell based killing of cancer cells

• Challenges for synthetic immune approaches include overstimulation of T cells, leading to safety events (eg CRS, neurotox), limiting T cell function and potential for negative impact on endogenous anti-cancer immunity

• One next generation approach to overcoming these challenges involves engineered IgM based T cell engagers that can bind irreversibly to cancer cells, limit overstimulation of T cells and provide T cell dependent killing of cancer cells, complement dependent killing of cancer cells and lead to repeatable IFN\(_\gamma\) dominant immune activation
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