gRED focus areas
Discovering new biologies and applying them broadly

**Oncology**
Discover and develop novel therapies and transformative combinations:
- Molecular oncology
- Cancer immunology

**Immunology**
Focus on high unmet need indications:
- Respiratory: asthma, COPD, IPF
- Rheumatology: RA, SLE, scleroderma
- Gastroenterology: UC, CD
- Opportunistic: wound healing, CSU

**Neuroscience**
Focus on:
- Alzheimer’s disease
- Parkinson’s disease
- Amyotrophic lateral sclerosis
- Moderate to severe pain

**Ophthalmology**
Focus on age-related macular degeneration

**Infectious disease**
Focus on difficult-to-treat bacterial and viral infections:
- Influenza
- Methicillin-resistant *Staph. aureus*
- ATB-resistant, gram-negative bacteria

**Today's highlights**
- Personalized cancer vaccine
- T-cell dependent bispecific antibody platform
- BTK inhibitor

COPD=Chronic obstructive pulmonary disease; IPF=Idiopathic pulmonary fibrosis; RA=Rheumatoid arthritis; SLE=Systemic lupus erythematosus; UC=Ulcerative colitis; CD=Crohn's disease; CSU=Chronic spontaneous urticaria; ATB=Antibiotic
gRED leads the industry in scientific publications
Sustained record of cutting-edge scientific discoveries

Past 7 Year Average
~400 Publications/yr
~16 in Cell, Nature and Science/yr

Key Benefits
- Progress science
- Recruit top talent
- External recognition for scientists
- Engage investigators’ interest to enhance collaboration

*As of Aug 2017, including articles, reviews, books and conference
The cancer immunity cycle

Oncology meets immunology

1. Cancer antigen release
2. Cancer antigen uptake and presentation
3. T cell priming and activation
4. T cell trafficking
5. T cell infiltration
6. Tumor antigen recognition by T cells
7. Killing of cancer cells

Personalized Cancer Vaccine (P1)

Source: Adapted from Chen & Mellman, Immunity 39(1):1-10
Personalized cancer vaccine
Overcoming potential priming defects in the tumor

- Fully individualized vaccine (mRNA-based approach)
- On demand-production (highly iterated and reproducible with low failure rate)
- Suitable for potentially all tumor indications, also with low incidences
- No negative thymic selection of high-affinity TCRs against mutated epitopes
- Induction of immune responses with high tumor specificity

TCR=T-cell receptor; PCV=Personalized cancer vaccine; PCV in collaboration with BioNTech
Sahin et al., Nature 547:222-229
Immunogenic responses against neoantigens

**Initial monitoring data from melanoma patients**

13 patients with stage III and IV melanoma

<table>
<thead>
<tr>
<th>TAA RNA vaccination</th>
<th>Days of vaccination, dose: 500 or 1,000 μg</th>
</tr>
</thead>
<tbody>
<tr>
<td>screening</td>
<td>1 4 8 11 15 22 29 43</td>
</tr>
<tr>
<td>Neo-epitope discovery and vaccine manufacturing</td>
<td>8 neo-epitope RNA vaccinations</td>
</tr>
<tr>
<td></td>
<td>Up to 12 vaccinations in continued treatment</td>
</tr>
</tbody>
</table>

**PCV induces T cell immunity**

Neoepitopes

- 32% de novo
- 68% pre-formed

T cells

- 26% CD4
- 17% CD8
- 57% CD4 & CD8

**Reduction of recurrent metastatic events post-vaccination**

- Pre neo-epitope RNA vaccination
- Post neo-epitope RNA vaccination

Cumulative sum of metastatic events

- **P < 0.0001**


PCV=Personalized cancer vaccine; PCV in collaboration with BioNTech
PCV may benefit all immunological phenotypes

*Inducing immunity in patients who have none*

**Immune Desert**

**Immune Excluded**

**Inflamed**

Vaccine well tolerated
Ongoing Phase 1b trial
Ph1 trial in combination with Tecentriq expected 2H 2017

PCV = Personalized cancer vaccine; PCV in collaboration with BioNTech
TDB Abs bypass cancer immunity cycle steps 1-3
Anti-CD3 arm activates T-cell killing of target cell

T-cell Dependent Bispecific Antibody

TDB=T-cell dependent bispecific antibody
TDBs for hematologic cancers

**CD20 TDB in Phase 1 in NHL and CLL ongoing**

- CD20 TDB for B cell lymphoma and leukemias
- Ongoing Phase 1b trial
- Combination with atezolizumab planned

**CD3**  **CD20**

- FcRH5 TDB for multiple myeloma

**CD3**  **FcRH5**

---

**Cyno splenic B cells (D7)**

- **Cyno plasma cells (D10)**

---

TDB=T-cell dependent bispecific antibody

TDBs for HER2-positive breast cancer

**Novel MOA for a HER2-directed therapy**

- Single agent activity in several models with durable complete responses (tumor regression observed at 0.05 mg/kg)
- Lack of killing HER-2 low expressing HT55 cells provides opportunity for therapeutic index
- Regression of T-DM1 insensitive tumors (*not shown here*)


TDB=T-cell dependent bispecific antibody; MOA=Mechanism of action

---

**Table:**

<table>
<thead>
<tr>
<th>Tumor Size (mm²)</th>
<th>HER2-TDB (0.05 mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPL4 + T cells</td>
<td>HT55 + T cells</td>
</tr>
<tr>
<td>HT55 cells alone</td>
<td>HT55 cells alone</td>
</tr>
<tr>
<td>KPL4 cells alone</td>
<td>KPL4 cells alone</td>
</tr>
<tr>
<td>KPL4 + T cells</td>
<td></td>
</tr>
</tbody>
</table>
gRED’s TDB pipeline targets

**Best in disease T-cell recruiting therapy**

**CD20**
- B-cell malignancies

**FcRH5**
- Multiple Myeloma

**HER2**
- Breast cancer

**Others to follow**
- Colorectal cancer, ovarian cancer, prostate cancer, small cell lung cancer

**Off-the-shelf therapeutic**
- Predictable PK/PD to aid drug development
- Predictable half-life

**TDB=T-cell dependent bispecific antibody**
BTK small molecule inhibitor for immunology

GDC-0853: highly potent, selective & reversible

**Rheumatoid arthritis (N=580)**
**Phase 2 (cohort 1):** GDC-0853 vs adalimumab in DMARD-IR patients (including dose ranging)
**Phase 2 (cohort 2):** GDC-0853 vs MTX in TNF-IR patients

**Systemic lupus erythematosus (N=240)**
**Phase 2:** GDC-0853 vs placebo in moderate to severe SLE patients

**Chronic spontaneous urticaria (N=45)**
**Phase 2:** GDC-0853 vs placebo

Data expected in 2018

BTK=Bruton’s tyrosine kinase; DMARD=Disease-modifying antirheumatic drug; TNF=Tumour necrosis factor; DMARD-/TNF-IR=Insufficient response to DMARD/TNF; SLE=Systemic lupus erythematosus
Questions & Discussion