Immuno-Oncology: Cancer Therapies Powered by the Immune System

Dr. Marties Sproll, CSO
Power of the Immune System
Vaccination as Success Story

VACCINES WORK
These bubbles are sized according to the annual number of disease cases in the US during the 1900s versus 2010. We’ve come so far. It’s a reminder that while disease rates are low, most diseases haven’t disappeared. This is why we continue to vaccinate.

Source: http://sciencebasedpharmacy.wordpress.com/2013/05/12/vaccines-work-by-the-numbers/

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Milestones in Cancer Immunotherapy
From History to Future

W. Coley
Used live bacteria (Coley’s toxin) as anti-cancer vaccine

P. Ehrlich
Molecules within the body might have the ability to fight tumors

Burnet
Presence of antigens on the surface of tumor cells may induce an immune response leading to clinical manifestation

Interleukin-2 (IL-2) first discovered

Morton
Described marked tumor regression after injection of BCG vaccine (melanoma)

Köhler & Milstein
Nobel Price for development of monoclonal antibody technology

Approvals granted for use of interferons (IFNs) and IL-2 for treatment of neoplasias

FDA approval for use of rituximab as single agent in NHL

Phase I-III trials carried out using anti-CTLA-4 mAb

First monoclonal antibody approved by FDA

Human cytotoxic T-lymphocyte associated antigen-4 gene (CTLA4) cloned

Isolation and cloning of the first human tumor associated antigens (TAA) from melanoma patients

Provenge - 1st therapeutic cancer vaccine approved by FDA (prostate cancer)

Hunder et al infused autol. CD4+ T-cells (NY-ESO-1) into a patient with refract. met. melanoma. Patient showed complete tumor regression

Bristol-Myers Squibb
General Principles - YIN & YANG
Self/Non-Self versus Danger Model

- Constant integration of self vs. non-self and danger signals
- Decision between tolerance/ignorance and attack

Body cells/tissues

Pathogens, Allergens, Food components

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Immune System - A Capable Tumor Suppressor

Schreiber et al. Science 2011
Challenges - Mutational Burden / Heterogeneity of Tumors

Tumor Cells Use Immunosuppressive Strategies to Evade Immune Responses

B Recruitment of immunosuppressive cells
- Tregs
- MDSCs

A Ineffective presentation of tumor antigens to the immune system
- Downregulation of MHC expression
- Suppression of APC

C Release of immunosuppressive factors
- Factors/enzymes directly or indirectly suppress immune response

D T-cell checkpoint dysregulation
- CTLA-4
- OX40
- GITR
- CD137
- CD27
- HVEM
- TIM-3
- BTLA
- VISTA
- LAG-3

Tumor microenvironment

Marianne Davies, 2014
Cancer Immunotherapy Tool Box

**Active vs. Passive Immunization**

**“Active“**
- Antigen specific
- Antigen non-specific
- Cancer vaccines
  - Tumor cells/lysates
  - Dendritic cells
  - Antigens (peptides/proteins)
  - DNA/RNA
  - Anti-Idiotypes
  - Cytokines (IFN, TNF, IL2)
  - Adjuvants
    - Bacteria/Toxins (BCG, Coley’s Toxin)
    - TLR ligands (CpG, Poly I:C)

**“Passive“**
- Antibody Therapy
  - “Naked“ and Fc-engineered antibodies
  - Antibody drug/toxin/cytokine conjugates
  - Radioimmunoconjugates
  - Bi-specific antibody constructs
- Adoptive cell transfer (TILs, LAKs, CAR T cells)

**Immune checkpoints**
Immune Checkpoints

Proteins regulating the amplitude and the quality of an immune response

Co-stimulatory and co-inhibitory signaling molecules/receptors regulating T cell response

Crucial for the maintenance of self-tolerance (prevention of autoimmunity)

Protects tissue from damage when the immune system is responding to pathogenic infection

Can be dysregulated by tumors as an important immune resistance mechanism
T Cell Activation is Regulated by Co-Inhibitory and Co-Stimulatory Molecules

Cell cycle inhibition
Inhibition of effector functions
Tolerance
Exhaustion
Apoptosis

Proliferation
Cytokine production
Differentiation
Cytotoxic function
Memory formation
Survival

Modified from: Chen & Flies, 2013
Complex Intercellular Communication at Different Sites

Periphery / Lymphnodes

Activation (cytokines, lysis, proliferation, migration to tumor)

Tumor Microenvironment

CTLA-4 Blockade (ipilimumab)
AFFERENT

PD-1 Blockade (nivolumab)
EFFERENT

Yervoy - ipilimumab (anti-CTLA-4)

- Astonishing long-term survival data in melanoma patients elicits enthusiasm for immuno-oncology approaches

Hodi et al., NEJM, 2010
Wochok et al., Ann NYAS, 2013

- ongoing further development in e.g. NSCLC, SCLC, prostate cancer
CTLA-4
The Yin and Yang of T-Cell Regulation

CTLA-4 knock-out mice (Waterhouse et al., Science 1995)
- Normal at birth
- Death within few weeks: massive multi-organ T cell infiltration
- CTLA-4 acts as a negative regulator of T-cell activation and is vital for the control of lymphocyte homeostasis

CTLA-4 deficient mouse strains (Tivol et al., Immunity 1995)
- Positive and negative roles for CTLA-4 in T cell activation shown by blocking antibodies
- CTLA-4 deficient mice rapidly develop lymphoproliferative diseases with multiorgan lymphocytic infiltration and tissue destruction, with particularly severe myocarditis and pancreatitis
- CTLA-4 deficient mice die by 3-4 weeks of age

CTL-A4 blockade in cancer patients
- Impressive anti-tumor responses but at the price of significant side effects
- **anti-PD-1 antibodies**
  - believed to more “proximal” block immunosuppression compared to anti-CTLA-4; less serious side effects

  ➢ **Front running molecules:**
  - **Opdivo nivolumab** (human IgG4; BMS / Ono) - approved in Japan 07/14 for unresectable melanoma; treatment costs $ 181,921 p.a.  
    Under review EMA & FDA; PhIII interim data Non-small Cell Lung Cancer
  - **Keytruda pembrolizumab** (humanized IgG4; Merck & Co.) - FDA approval 09/14 for advanced melanoma; 24% of patients dosed at recommended dose of 2mg/kg every 3 weeks had tumor shrinkage; treatment costs $ 150,000 p.a.

- **anti-PD-L1 antibodies**
  - blocking PD-L1/PD-1 Interaction
  - additional blockade of PD-L1-B7.1 interaction

  ➢ **Front running molecules:**
  - **RG-7446/MPDL3280A** (hu IgG1; Roche/Genentech)
  - **MEDI-4736** (hu IgG1; MedImmune/AstraZeneca)

  - in mid stage clinical development, various cancer types
### Immunomodulatory Antibodies in Clinical Development

#### Table 3. Immunomodulatory antibodies in clinical development.

<table>
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<tr>
<th>Target</th>
<th>Antibody</th>
<th>Species</th>
<th>Isotype</th>
<th>Predicted ADCC</th>
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<td>Humanised, Humanised</td>
<td>IgG1, IgG2</td>
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<td>Bristol-Myers Squibb, AstraZeneca/Pfizer</td>
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<td>IgG2, IgG1, IgG1, IgG1</td>
<td>Yes, Yes, Yes, Yes</td>
<td>Pfizer, Novartis, Seattle Genetics, Univ. of Southampton</td>
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\(a\)Glycoengineered to abrogate Fc functionality.
\(b\)Glycoengineered to enhance ADCC.

- Increasing number of molecular targets on various cell types
- Various mechanisms of action: depleting, killing, agonistic, antagonistic
- Different antibody isotype formats: +/- immune effector functions, different FcR affinities
- Growing number of cancer types
- Multiple pharma and biotech players
- Multiple combinations


..and more to come!
Cross Tumor Potential Shown with PD-1/PD-L1 Agents

Mutational Burden/ Heterogeneity By Tumor

Source: Lawrence et al., Nature 2013; Leerink Partners LLC
Cancer Immunotherapy
Active vs. Passive Immunization

„Active“
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Immune checkpoints

Combinations
Combinations as Next Logical Step & More To Come

- Many combinations and schedules in testing, including combination of modalities (e.g. chemotherapeutics, vaccines, radiotherapy, other targeted therapies)
- Ipilimumab and Nivolumab combined with impressive response rates of
  - 41% complete (10%) and near complete (31%) response-rate
  - yet comes at a cost of 53% of pts with grade 3 and 4 adverse events

- Various agents in phase I or lined-up for entry into human:
  - LAG3, CD70, TIM3, B7-H3, 4-1BB ("classical" T-Cell Immunological Synapse)
  - KIR, NKG, MICA (NK-Cell Immune Modulation)
  - CSF-1R (Modulation/Attenuation of Tumor Promoting Macrophages)

- Outlook into immune modulation by addressing further cell types
  - CXCR2 (MDSC suppression - myeloid derived suppressor cells)
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<th>Companies</th>
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<td>Novartis</td>
<td>CoStim Acquisition: PD1, PD-L1 assets, IP</td>
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<td>AstraZeneca</td>
<td>Amplimmune Acquisition: AMP-224, AMP-514, IP</td>
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<td>CytomX Collaboration agreement</td>
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<td>Bayer</td>
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<td>Pierre Fabre</td>
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<td>Pfizer</td>
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<td>Jounce Therapeutics</td>
<td>Third Rock Venture 47 Mill US$ Series A funding</td>
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Outlook & Challenges

- Immune intervention to fight cancer can be successful!
- Immuno-oncology aims to swing the immune system back into action by either „releasing the brakes“ or „pushing on the accelerator“ and requires multiple steps
- Interactions between various immune cells, components of the tumor microenvironment and tumor cells are complex and take place at different sites
- There is no one immune checkpoint but rather a bunch of them
- Major differences between immune systems of rodents, non-human primates and humans result in poor predictivity of non-clinical models
- Immunotherapies targeting checkpoints can take a long time to first clinical response (weeks to months!)
- Checkpoint inhibitors do not necessarily show classical dose-response curves
- Expression of checkpoint inhibitors is dynamic and does not necessarily predict response; biomarkers?
- Approaches need to be adapted to tumor type/immune status of patients (immunoscoing)
- Combination therapies are imminent, however, selection of suitable combination partners, timing & sequence of application and complexity of clinical trial design will be challenging; treatment costs?
- YIN & YANG: Balance between tumor immunity and autoimmunity is delicate, thus side-effect profiles need to be watched carefully
The main driver of growth is an exciting new class of cancer products targeting the programmed death-1 (PD-1) pathway with a collective value of $63bn' (Evaluate Pharma World Preview 2014-2020).

Source: ASCO2014
## The MorphoSys Pipeline
20 Clinical Programs, 93 Total

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Thank You!
MorphoSys is a Leader in the Discovery & Development of Therapeutic Antibodies

- MorphoSys...
  - Founded 1992
  - Located close to Munich, Germany
  - Listed on the Frankfurt Stock Exchange
  - Around 300 employees

- Most successful antibody library technology in the industry based on number of MorphoSys antibodies in clinical trials

- Proven antibody development expertise

- Highly successful track-record of partnering with pharmaceutical companies world-wide
  - Next generation technologies
  - Proprietary innovative compounds

- Financially strong
  - 2013 profitable with revenues of EUR 78 million
  - Cash position of around EUR 375 million

- Deep pipeline of proprietary and partnered therapeutic programs