Histology-independent indications in Oncology Nonclinical Models – Proof of Concept

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Testing Therapeutic Potency of Anticancer Drugs in Animal Studies: A Commentary

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Considerations regarding the design of an in vivo experiment

- Animals
  - Immunocompetent animals
  - Cytotoxic drugs kill tumor cells directly
  - Dead cells will be phagocytosed and antigen presented, ultimately leading to immunity
- Tumor type
  - Transplantable counterparts for most human tumors are available (not for hairy cell leukemia and Hodgkin's lymphoma)
  - Chemically-induced tumors might be preferable (if available)
  - Tumor located in orthotopic position to ensure PK properties and physiological conditions
- Tumor load
  - Minimum tumor load in mice 200 mg or 2x 10^8 cells
  - Small tumor loads are a source of false-positive experiments
  - Duration of tumor free period should be approx 60 days

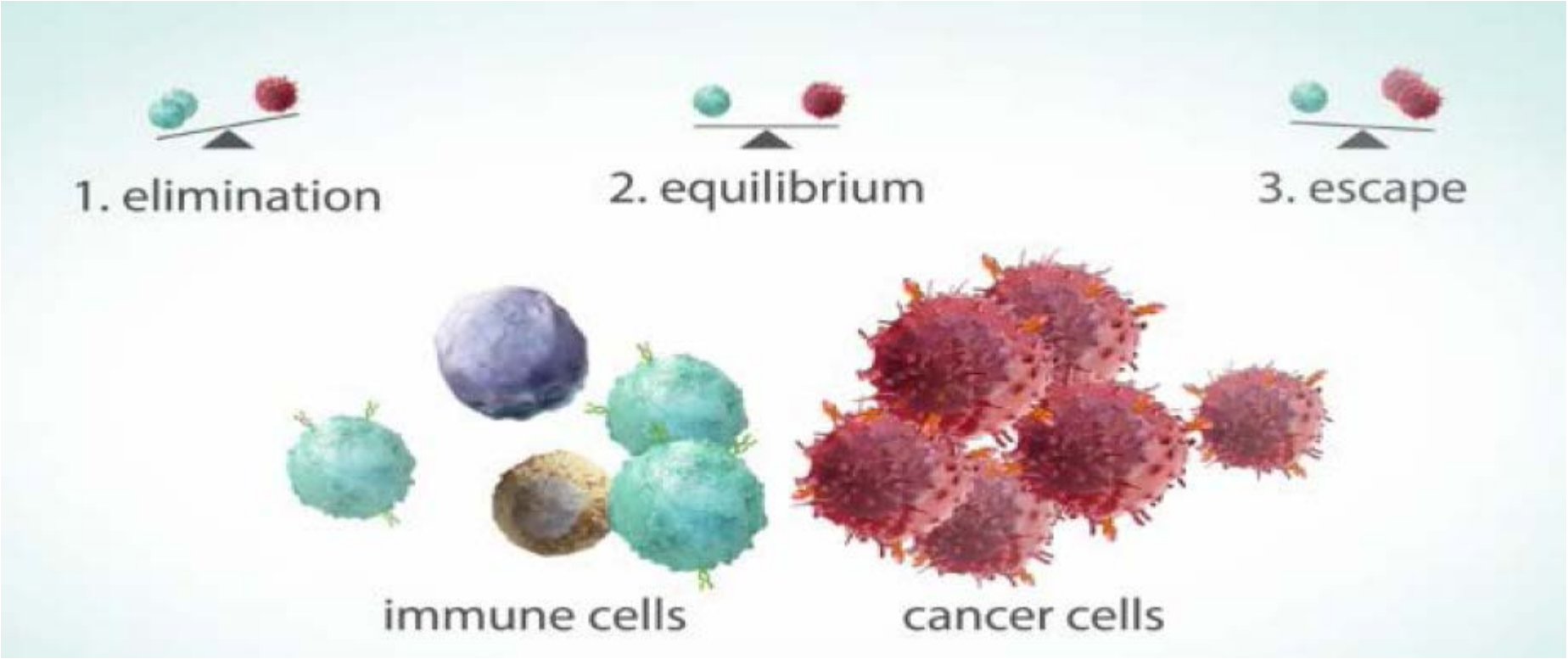
Den Otter et al. 2002

Choice of indication for cytostatic drugs

- PD-dossier contained screening of 50 cell-lines of different origin with respect to organs
- Choice of indication sought not always related to the sensitivity of cell lines

- Choice of indication dependent on (?):
  - Network of available oncologists and patients?
  - Niche for which there is a need for a new drug?

Cancer is a genetic disease AND an Immunological Disorder



From Haggerty, 2017

Approvals in Immune checkpoint inhibitors

Mechanism of action	Agent	Approval
Anti-CTLA4 (IgG1)	Ipilimumab (Yervoy)	2010 (EMA) 2010 (FDA)
Anti-PD1 (IgG4)	Nivolumab (Opdivo)	2015 (EMA) 2014-2017 (FDA)
Anti-PD1 (IgG4)	Pembrolizumab (Keytruda)	2015 (EMA) 2014-2017 (FDA)
Anti-PD-L1 (IgG1)	Atezolimumab (Tecentriq)	2016 (EMA) 2016 (FDA)
Anti-PD-L1 (IgG1)	Durvalumab (Imfinzi)	2017 (FDA)
Anti-PD-L1 (IgG1)	Avelumab (Bavencio)	2017 (EMA) 2017 (FDA)

Proof-of concept testing

- In vitro
  - Ipi binds to human CTLA-4
  - CDC no effect
  - ADCC activity in vitro, not in vivo
- In vivo
  - Humanized CTLA-4 transgenic mice with MC38 colon carcinoma cell line
  - Cynomolgous monkey studies for effect on T-cell dependent antigens: HBsAg, SK-Mel, KLH.

Proof-of concept testing

- In vitro
  - PD-1 blockade on human T-cells (with surface plasmon resonance)
  - ADCC – not stimulated
  - CDC no effect at low concentrations
- In vivo
  - Mouse: use of surrogate antimouse PD-1 (IgG1-isotype)
  - Use of murine cancer cells MC38 (Colon), SA1/N (fibrosarcoma), J558 (melanoma)

  With complete regressions

  Not for Renca (Kidney), 4T1 (breast), CT26 (Colon).

Proof-of concept testing

- In vitro
  - Downstream biological response with Jurkat T cells and monocytes, with an increase of IL-2 as endpoint
  - Binding to human and cynomolgus PD-1 receptor expressed in CHO cells
- In vivo
  - Mouse: use of surrogate antimouse PD-1 J43 in syngeneic mouse. Tumors reached a volume of 50-7- mm^3
  - Use of murine cancer cells MC38 (Colon), C1498 (acute myeloid leukemia), PDV6 (Squamous cell carcinoma), all of C57BL/6 origin
  - Also in combination with 5-FU or gemcitabine

  With complete regressions after 60 days.

Proof-of concept testing

- In vitro
  - In vitro binding and biological activity
  - Biomarker study in Paediatric tumor tissue
  - Atezolizumab does not bind to human Fcγ-receptors (by change in position 298, resulting in nonglycosylation)
- In vivo
  - Mouse: Use of chimeric mAB derivative (var.region of Atezolizumab in a mouse IgG2a)
  - Use of murine cancer cells MC38 and CT26 (both Colon) with complete remission
  - Cloudman S91 (melanoma) with partial remission
- Antiviral effect against mouse LCMV showing stimualtory action on T-cell mediated immunity

Proof-of concept testing

- In vitro
  - Kinetics of PD-L1 occupancy in non-tumor bearing C57BL/6 mice, FACS based assay with splenocytes and peripheral blood leukocytes
  - Complement-Dependent Cytotoxicity against human cancer cells (M21 cell line)
- In vivo
  - Mouse: use of avelumab against MC38 (colon cancer), antitumor effect associated with modulation of T-cell phenotypes ($CD8^+PD\text{-}1^+$ T cells). Increase of p15E (murine retroviral protei

NB.: Toxicity studies in Cynomolgus monkeys

Overall Proof of concept testing

- In vitro with human material
  - Receptor binding
  - Functional endpoints (e.g. IL-2 production)
  - Downstream pathway influence

- In vivo
  - with mice
    - Humanized, transgenic mice
    - Use of homologues with syngeneic tumors
  - With cynomolgus monkeys
    - Mechanistic data (if possible)

- **Technical remark:**
  Use of surrogate molecules during development requests again validation and qualification studies against the clinical candidate in order to being used in a proof-of-concept study

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Emphasis on pharmacodynamics and relation to intended application

Proof-of-concept testing in relation to agnostic indications

Principally not different from classical approach of anticancer drugs. Mode-of-action is driving the Proof-of-Concept

(Cytostatic drugs and) TK-inhibitors could also be handled in agnostic indications

However:

- Focus is the effect on the immune system
- Not on tumor cells

In vivo experiments contribute to the weight-of-evidence

- Use of humanized mice
- Homologous (surrogate) proteins

SAFETY:

First-in-Human should use the PD data to calculate the MABEL