Immunotoxicity Testing of Drugs and Chemicals

CITT-28: A **C**omprehensive **I**mmunotoxicity **T**ier-1 **T**esting protocol integrated into a **28**-days repeated dose toxicity test

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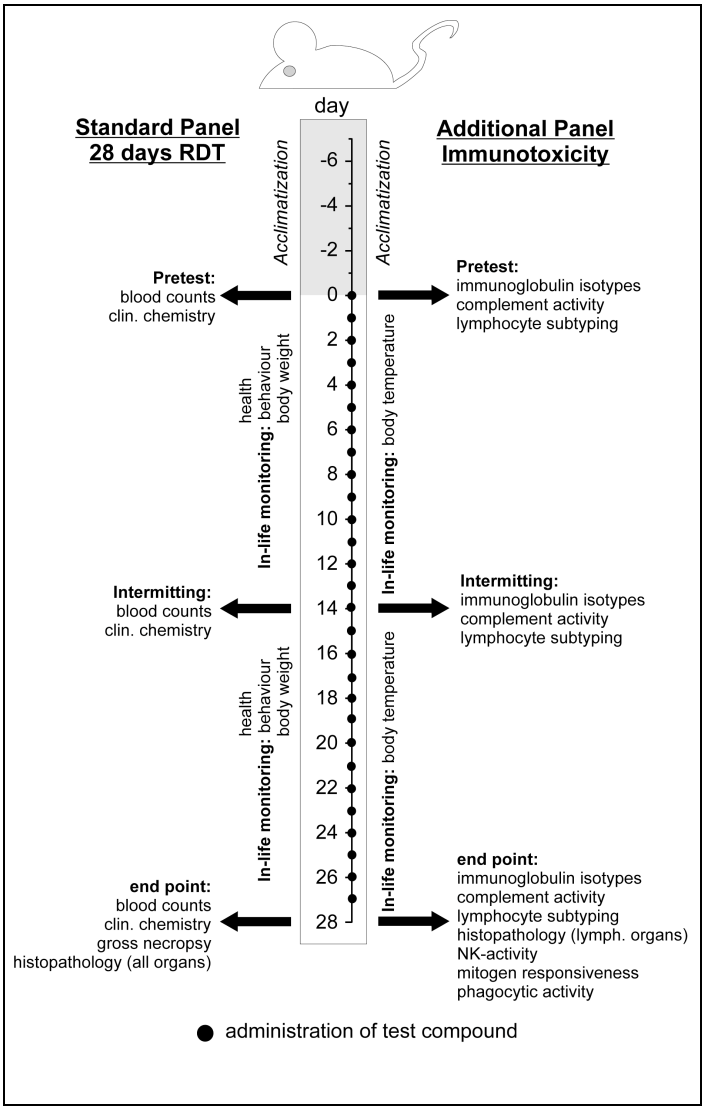
Background:

The assessment of immunotoxicity is an important component of safety assessment within preclinical toxicology studies. Recent guidelines from the EMEA (1) and FDA/CDER (2) emphasize the need to assess immunotoxic effects during the preclinical phase of drug development, and recommend specific tests to measure immunotoxicity.
Comparable guidelines have been issued by regulatory agencies like the OECD or EPA regarding the safety assessment of e.g. chemicals or food additives (3,4).

(1) EMEA: Note for Guidance on Repeated Dose Toxicity, CPMP/SWP/1042/99
(2) FDA: Guidance for Industry: Immunotoxicology Evaluation of Investigational New Drugs, October 2002.
(3) OECD: Guidelines for Testing Chemicals: Repeated Dose Oral Toxicity-Rodent: 28 Day or 14 Day Study (Guideline 407)
(4) EPA: Health Effects Test Guidelines, Immunotoxicity, OPPTS 870.7800



Principle of the protocol:

A comprehensive immunotoxicity tier-1 testing, as required by the actual guidelines, includes most parameters already assessed during a standard 28-days repeated dose toxicity testing (RDT).

The CITT-28 protocol has been optimised to assess RDT and immunotoxicity parameters within the same animal (mouse), without the need for additional satellite groups.

The optimisations comprise:

- reduction of sample volumes of blood, serum, and plasma by miniaturization of assays
- improvement of assays to make all parameters accessible in the mouse (e.g. complement activity)
- aseptic removal of lymphatic organs for functional end-point assays

The CITT-28 protocol is highly flexible with regard to the route of application of test compounds (e.g. oral, parenteral, topical)

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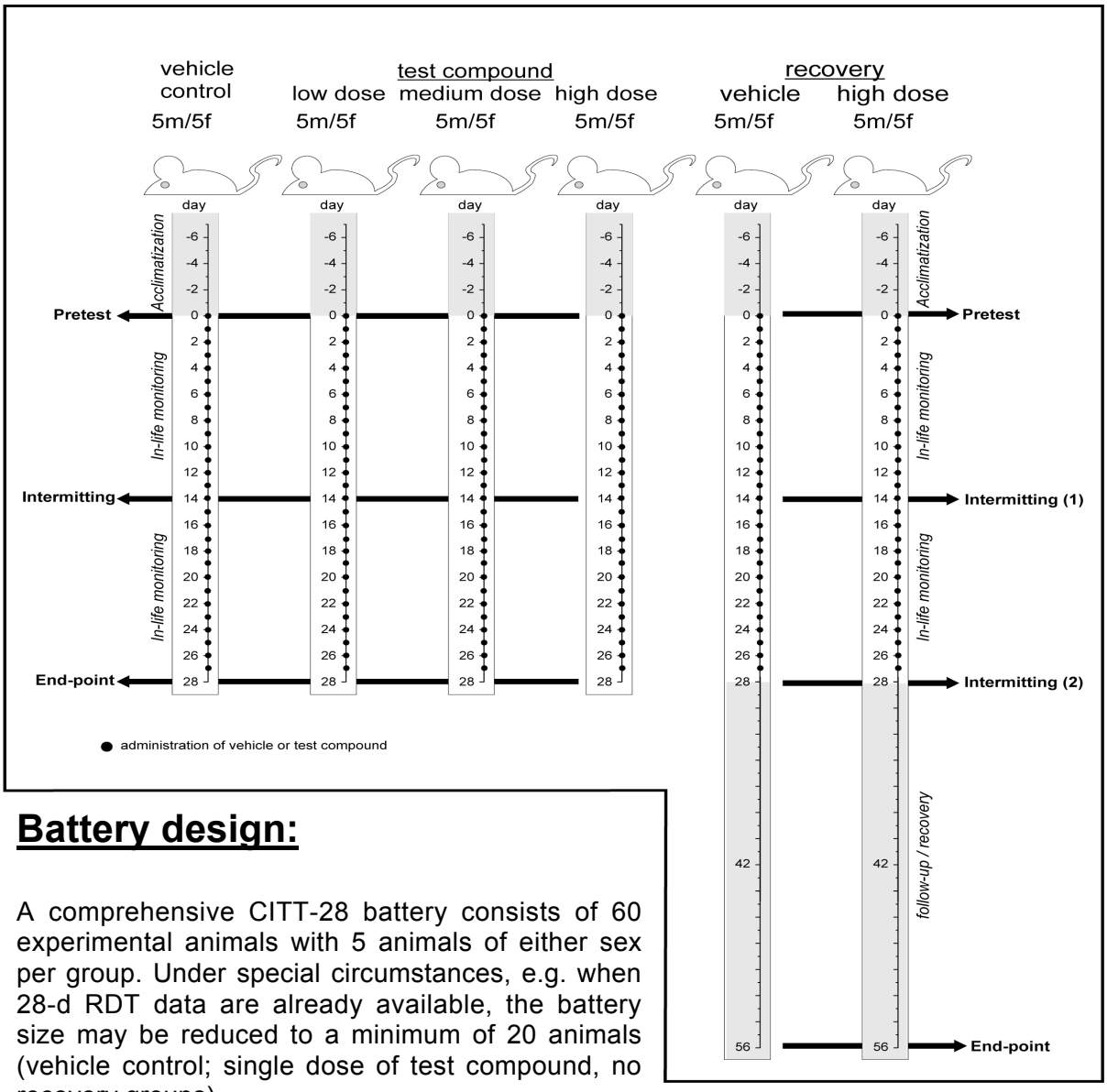

Battery design:

A comprehensive CITT-28 battery consists of 60 experimental animals with 5 animals of either sex per group. Under special circumstances, e.g. when 28-d RDT data are already available, the battery size may be reduced to a minimum of 20 animals (vehicle control; single dose of test compound, no recovery groups).

Humoral-mediated immunity
- Humoral responses to T-dependent antigens
- Humoral responses to T-independent antigens

Cell-mediated immunity
- Delayed-type hypersensitivity
- Antigen-specific T cell proliferation
- Mixed leukocyte response
- Cytotoxic T lymphocyte responses against allogeneic tumour cells

Host resistance models
- Syngeneic tumour models
- Bacterial infection models
- Viral infection models

Upgrade to tier-2 testing:

In contrast to the basal immune parameters measured during tier-1 testing, tier-2 protocols are assessing effects on antigen-specific immune responses.

In most cases a tier-1 immunotoxicity testing meets the requirements of regulatory agencies. In case a drug compound directly targets the immune system, or when a test compound shows immunotoxicity during tier-1 testing, regulatory agencies may request additional tier-2 studies. A comprehensive panel of tier-2 immunotoxicity tests is offered by PARA BioScience.

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