Animal Drugs, Animal Studies, and MicroPhysiological Systems

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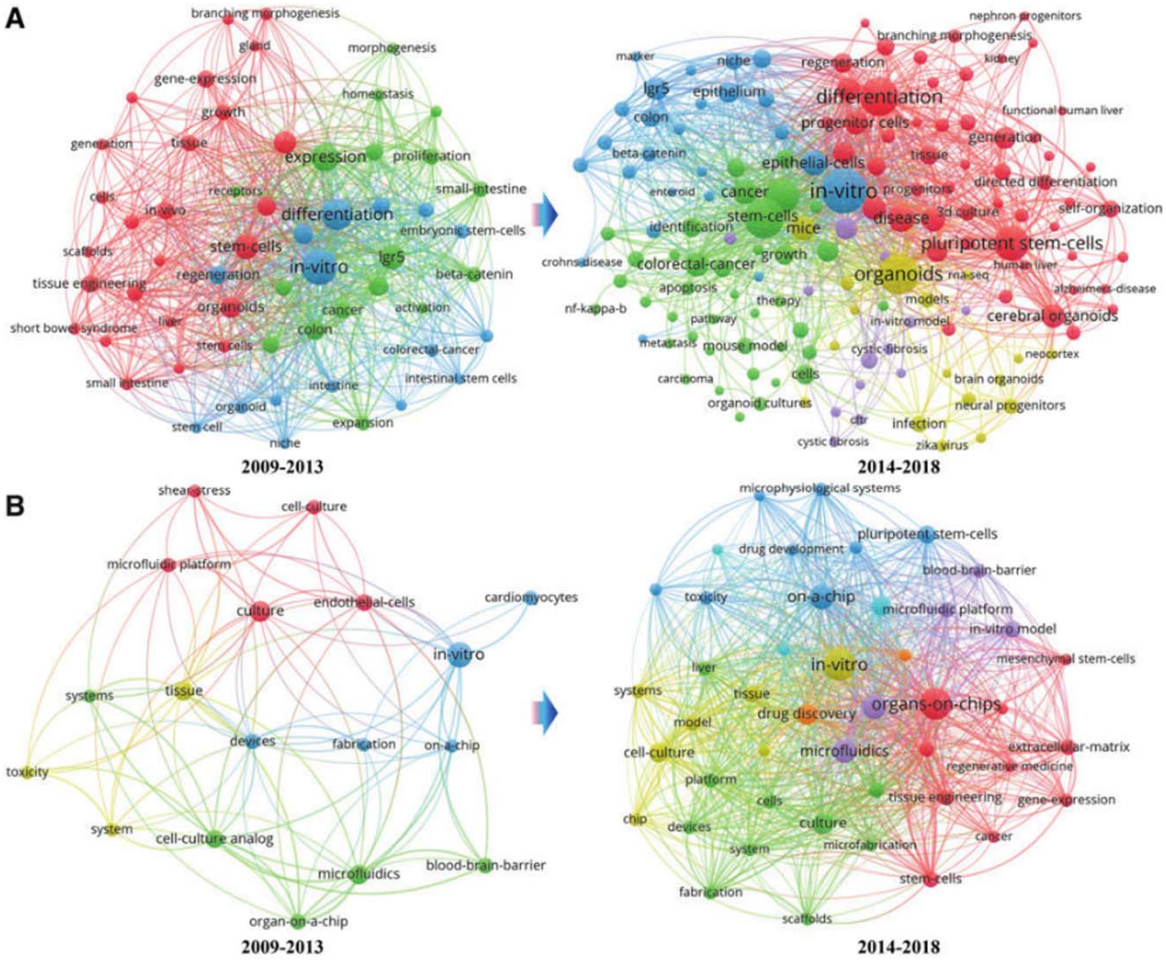

Global trends of organoid and organ-on-a chip in the past decade: a bibliometric and comparative study. **Wang et al. 2019. Tissue Engineering Part A vol 26 no 11-12.**

FIG. 6. Mapping and clustering keywords in co-occurrence networks based on documents in the periods of 2009–2013 and 2014–2018. (A, B) Keyword co-occurrence networks related to organoid and organ-on-a-chip, respectively.

(based on analysis of 2790 publication)

Outline

- How are animal studies used for evaluation of animal drugs?
- Highlight of some unique considerations.
- How can MPS inform animal drug evaluation?

TARGET ANIMAL STUDIES

Target Animal Studies

1. Target animal effectiveness (substantial evidence of effectiveness).
    a. Clinical studies of effectiveness (Field trials).

Target Animal Studies

1. Target animal safety
   (all studies reasonable; evaluated by experts qualified by training and experience).
   a. Margin of safety studies.
   b. Target animal safety.

HUMAN SAFETY STUDIES

Human Food Safety

(Reasonable certainty of no harm)

1. Toxicological studies (typically in animals) to establish a human health protective value (e.g., acceptable daily intake (ADI) or acute reference dose (aRFD).
2. Animal studies to determine the nature, deposition, and depletion of residues in edible tissues of the treated target animal.

Human Food Safety

(Reasonable certainty of no harm)

1. Comparative metabolism studies to determine the relevance of the toxicological study to the residues in edible tissues.
2. Animal studies to inform risk of antimicrobial resistance.
3. Animal studies to inform potential exposure to human gastrointestinal microbiome to antimicrobial residues.

Human User Safety

1. Limited studies to inform potential exposure (e.g., dermal absorption, inhalation) and toxicity.
2. Qualitative risk assessment for labeling.

Some unique considerations

- Multiple species; multiple breeds within species:
  - 7 major animal species – many minor species,
  - 195 breeds of dogs, 44 breeds of cats.
- Widely different biological physiological systems:
  - Homeotherms (cattle, pigs, poultry, dogs, cats) to poikilotherms (fish, shellfish, reptiles).
  - Ruminants (cattle, sheep) to monogastric non-ruminants (pigs, dogs, cats, horses).
- Wide range in size (mass):
  - pheasants to dogs to beef cattle to elephants.

Some unique considerations

- Very limited toxicity data in humans to inform human safety considerations (safety to the human consumer, safety to the human treating the animal).
- Need to establish residue exposures safe for the human consumer (similar to the considerations for additives for human foods).
- Very heavy reliance on extrapolation from in-vitro and in-vivo (and in-silico) non-human models.

HOW CAN MPS INFORM ANIMAL DRUG EVALUATION?

Start with the goal in mind..

- What are the regulatory questions being asked?
- What is the target population?
  - For veterinary drugs, this can be:
    - the treated animal,
    - the human exposed while treating, working, or living with the animal,
    - the human consumer of foods derived from the treated animal.
- Is the model intended to provide a definitive data for a decision, or offer additional data to inform a decision?

Some areas of promise

- Organoid/organ-on-a-chip models can
  - inform adverse outcome pathways – whether for target animal or human safety;
  - offer insight into important breed differences for companion animals;
  - offer multiple organ-on-a-chip models for extrapolation across breed especially for target animal safety (dog on a chip concept);
  - offer insight on the impact of inflammation and disease on drug uptake and depletion for target animal safety an human food safety;
  - develop human gastrointestinal tract/microbiome model to inform impact of antimicrobial animal drug residues on the human gastrointestinal microbiome.

An example…

- Regulatory requirement to establish a human health protective level for residues of antimicrobial veterinary drugs based on concern for impact on the human gastrointestinal microbiome.

An example…

- Internationally harmonized guidelines (VICH GL36/FDA GFI 159) clearly outline the minimal data requirements recommended to estimate a human health protective value.
- Approaches are provided to estimate a microbiological Acceptable Daily (mADI) Intake for residues of the antimicrobial in human food.
- Currently recommends use of 10 bacterial species from 10 human subjects evaluated using:
  - MIC data from traditional plate microbiology,
  - MIC and population data using invitro flask-culture,
  - MIC and population data from mice with humanized gut microbiome.

An example…

- FDA is currently collaborating with an industry partner to develop a model using a human intestinal-organ-on-a-chip, incorporating multi-species bacterial population.
- Goal to provide a model more representative of the human gastrointestinal microbiome for the estimation of the mADI.

Thank you


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