# Investigative toxicology services 2024

www.ipstherapeutique.com

## *“It’s about knowing your strengths.”*

Dan Salvail, Ph.D
Vice-President, IPST

Or, rather, discovering them.

Since 1999, we’ve built IPS Therapeutique Inc. around preclinical efficacy and safety pharmacology. Not toxicology. Ultimately, we are experts at defining the conditions necessary for a future drug to help, and do no harm. Not toxicologists.

Yet as I look back upon 25 years of achievements, I can’t ignore the investigative toxicology we have been involved in: The study with the hemorrhaging primates; the syncope cases in the paused Phase II trial; the respiratory distress study when animals crashed within 5 minutes of being dosed…

With access to IPST’s physiological monitoring platforms, we discovered that optimising efficacy in a preclinical candidate is very similar to investigating an unexpected toxicity later in development.

Every one of our 30+ investigative tox projects has been unlike the others, and the key to their success has been the flexibility of IPST services as well as the experience of its scientists.

A “catalogue of investigative toxicology” services is therefore an oxymoron: it ignores the unique nature of toxicology findings and fails to provide a clean slate from which to create an appropriate investigative strategy. Therefore, you’ll find herein a pair of case studies that highlight various aspects of IPST’s toxicology work.

I look forward to discussing how our teams can work together on your next toxicological investigation.

# Investigative toxicology

Generally triggered by an unanticipated toxicology finding, it's a hypothesis-driven, customized investigation of the mechanism of toxicity of a preclinical drug candidate.

Once the mechanism of toxicity is identified, it can be used retrospectively to select next-generation candidates, or quantify the possibility of a clinically-relevant liability.

IPST a comprehensive toolbox to define and qualify the toxic mechanisms:

| **Functional measurements:** | **Biomarkers of damage:** | **Cellular and molecular biology:** | **Histopathology:** |
|---|---|---|---|
| • Electrophysiology<br>• Telemetry<br>• Hemodynamics<br>• Ventilation<br>• Imaging | • Cardiac<br>• Renal<br>• Hepatic<br>• Inflammatory<br>Metabolic… | • Gene expression<br>• Cell distribution<br>• Cell differentiation<br>• Proteomics | • Bright-field staining<br>• Immunohistochem.<br>• Confocal and fluorescence microscopy |

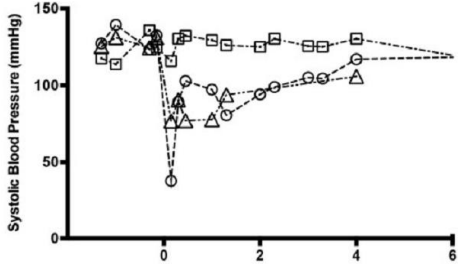
# Case study 1: the hemorrhaging antibody

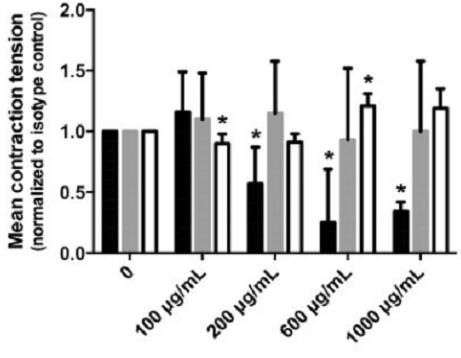
## The toxicity finding:

A monoclonal antibody administered to primates induced unexpected hematemesis, hematochezia, and intestinal hemorrhage.

## The investigative toxicology:

- *In vitro* studies demonstrated off-target effects on vascular endothelial cells including activation of nitric oxide synthase.
- *Ex vivo* vascular tension measurements utilizing segments from cynomolgus aorta and femoral artery confirmed the induction of endothelium-dependent smooth muscle relaxation and vasodilation mediated via NO.
- *In vivo*, cynomolgus monkeys exhibited a rapid and pronounced increase in NO in the portal circulation that corresponded temporally with systemic hypotension, associated with non-inflammatory, localized hemorrhage in the gastrointestinal tract detected by histology.



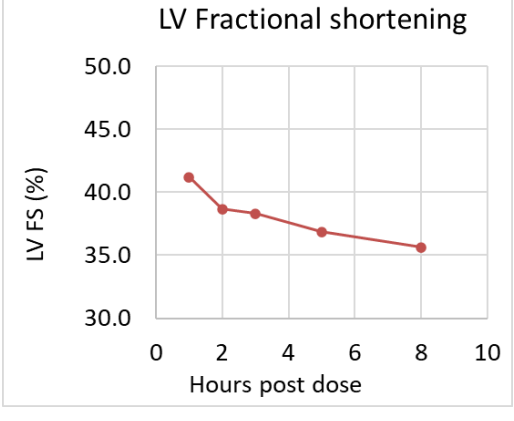
# Case study 2: the sudden heart failure

## The toxicity finding:

A small molecule with a clean safety profile led to rapid suffocation and death in the toxicology study's dogs.

## The investigative toxicology:

- *In vitro* studies failed to reveal off-target receptor affinity in commercially-available high-throughput panels using human targets.
- Isolated heart preparations revealed an acute drop in contractility in dogs, but none in rodents. Blood vessel tension measurements confirmed an acute coronary vasoconstriction in dogs, but not in human tissues.
- Isolated lung experiments revealed no pulmonary vasoconstriction which could lead to cardiac hypoxia and coronary constriction.
- *In vivo*, pulmonary gas exchange was ruled out as a cause of death: Rather, cardiac dysfunction leading to hypoperfusion led to acute cellular respiration deficit and mortality.



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