Supplemental Table 1: A summary of advantages, disadvantages and resources available regarding various trauma models leveraged in the translational effort to advance trauma patient care and outcomes [human clinical, human volunteer, veterinary clinical, pre-clinical (induced animal models) and other]

|  |  |
| --- | --- |
|  | **MODELS AND RESOURCES FOR INTEGRATED SOLUTIONS** |
|  |  | **Human Clinical** | **Human Volunteer** | **Veterinary Clinical** | **Pre-clinical** | **Other (*in vitro*, *in silico,* etc.)** |
| **Resuscitation of the haemorrhaging patient** | **Advantages** | Species of interest | Species of interest: No cross-species confoundersStudies of relevant co-morbidities possible1 | Similar demographics, mechanisms of injury2–5 Similar pathophysiological responses6,7Resource-rich hospitals with specialists, blood banks, and trauma focus8  | Range of trauma severities possibleHomogenous insults (results with fewer animals)Pathophysiological response to haemorrhage similar across a range of species. 9,10 | Minimal if any ethical challenges / constraintsCheapHigh throughput |
| **Disadvantages** | Heterogeneity of injuries (may need large numbers for clinically meaningful results)ConsentCo-morbidities Which outcomes?11 | Must be no long-lasting effects: modelling mild haemorrhage only.Lower body negative pressure does not fully model concurrent effects of tissue injury seen in trauma. | Species differences may limit translationDifferent clinical practices impacting outcomes Welfare concerns and use of euthanasiaConsent | Species differences may limit translationEthical challenges frequently limit studies to acute, anaesthetised, non-recovery models (long-term outcomes not assessed)Rat as a trauma translational model12 | Response to haemorrhage involves multiple body systems and not possible to re-create all aspects *in vitro*Validation requiredClarity on limitations/boundaries required |
| **Resources available** | Trauma networkdatabases13,14Evidence-based Clinical Practice Guidelines15,16  | Lower body negative pressure (LBNP) to simulate physiological effects of haemorrhage17,18 | VetCOT trauma registry19 Future/underway: Clinical Practice Guidelines | Many research laboratories worldwide utilizing various species20–22 | Model of endotheliopathy23Mathematical models of haemorrhagic shock24 |
| **Trauma -induced coagulopathy (TIC)** | **Advantages** | Species of interest | Species of interest: No cross-species confoundersStudies of relevant co-morbidities possible | Incidence is similar (approx. one third of moderate/severely injured in dogs) | Use of anaesthetised animal models enables replication of severe injury | Minimal if any ethical challenges / constraintsCheapHigh throughput |
| **Disadvantages** | Improvements in trauma care, early use of ‘blood’ and TXA for example Prevalence (defined by laboratory tests) is lower as demonstrated in the ITACTIC study8 | Most prevalent in severe injury therefore modelling in volunteers not a viable option | Evidence of breadth of manifestations needs to be further definedFocus of multi-center projects | Species differences in coagulation factor levels and laboratory test values as well as the relative contributions of fibrinogen and platelets exist; exact translation of temporal changes in the different species is deficient | The complex interaction between systems is difficult to replicate and validate  |
| **Resources available** | Resuscitation protocols guided by viscoelastic testing25,26 Evidence-based Clinical Practice Guidelines15,16,27 | Acute hypercoagulation has been observed following LBNP17 | Similar clinical tools (viscoelastic testing)28 | Reviews29–34 | *Ex vivo* model35–37State of the science review38 |
| **Traumatic brain Injury (TBI)** | **Advantages** | Species of interest | N/A | Similar range of mechanisms of injurySimilar validated scoring systems (MGCS) | A variety of models available with different mechanisms of injury39Able to control severity of injuryUse of genetically engineered species to elucidate mechanisms40 | Minimal if any ethical challenges / constraintsCheapHigh throughputMechanistic studies |
| **Disadvantages** | Heterogeneity of injuries (may need large numbers for clinically meaningful results)ConsentOnset of symptoms / progression of diseaseClinical meaningful outcomes? | N/A | Natural disease less well-characterisedLong-term effects not characterisedLess cognitive needs so may be better able to cope with enduring disability | Species variation in anatomy (e.g. lissencephalic and gyrencephalic brains) Clinically meaningful outcomes can be difficult to replicate in animal modelsPoor translation of therapeutics from animal models to human TBI patients41 | Current systems are deficient in many areas (e.g. *in vivo* microenvironment)42  |
| **Resources available** | Evidence-based Clinical Practice Guidelines15,43 |  |  | Animal model reviews44Large animal model review45,46Animal and non-animal models review47Diagnostics/prognostics48 | Systematic review of *in vitro* models of TBI49Non-mammal models of TBI50,51*In vitro* and *ex vivo* models of TBI52Review of computational models of TBI53 |
| **Translational Systems Biology** | **Advantages** | Biobanks / data repositories available for interrogation  | Species of interest: No cross-species confoundersStudies of relevant co-morbidities possible | Similar demographics and mechanisms of injury | Wide range of models available for sample collection andbiobanking of samples feasible | Potential for a large amount of data generated from animal models that could be interrogated *in silico*Modelling ‘cytokine storm’ Increasing field due to COVID-19 with potential opportunities to leverage models for trauma |
| **Disadvantages** | N/A | Most prevalent in severe injury therefore modelling in volunteers not a likely option | Currently a poorly studied fieldValidity of companion animals as a model of post-trauma ‘omics unknown‘Self-selection’ (most severely injured die ‘pre-hospital’) | Long-term outcomes usually not assessed so translation may be limited |  |
| **Resources available** | Human studies54–58  |  |  | Mouse models59,60Porcine model61Rat model62 |  |
| **Trauma Immunology** | **Advantages** | Species of interest | Species of interest: No cross-species confoundersStudies of relevant co-morbidities possible | Similar demographics and mechanisms of injury for translationStudies of relevant exposures and co-morbidities possible  | Pre-injury status known |  |
| **Disadvantages** | Heterogeneity (age, sex, exposure, and genetic impacts; may need large numbers for clinically meaningful results) | Only observations in mild injury will be possibleHeterogeneity (age, sex, exposure, and genetic impacts; may need large numbers for clinically meaningful results) | Limited data available to understand trauma immunology in companion animalsLimited availability of suitable reagentsHeterogeneity (age, sex, exposure, and genetic impacts; may need large numbers for clinically meaningful results) | Limited volume of blood available in small mammals for longitudinal analysisLimited availability of suitable reagents especially for large animal trauma modelsEffects of stress and decreased immune exposures related to research environment | The complexity of the immune response is difficult to replicate *in vitro* |
| **Resources available** | Review56 | Experimental endotoxemia as a model of trauma63 |  | Review of animal models64 |  |

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