Translational research: what is the value of experimental studies in comparison with clinical studies to help understand clinical problems?

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Along with the development of sophisticated methods to assess parameters in experimental animal and laboratory studies, the meaningfulness of these studies has increased. Clinical studies alone may be difficult to obtain [1, 2] and patient numbers may represent an issue [3]. This may get to a point where research organizations stop providing the financial support if the patient numbers are not met on time [4]. Other publications provide subsets of data studies that may suffer from type II errors and lack of long-term impact [5, 6] (Table 1).

Therefore, approaches from ‘bench to bedside’ have been emphasized. They are thought to facilitate the gathering of knowledge, allow to be more cost effective and provide rapid results [7]. Animal studies are more standardized, whenever a standardized model is available. Until the late 1990s, sophisticated methods to study the impact of trauma on an organism mimicking the human situation was merely possible using primates [8].

Translation in the field of traumatic brain injury (TBI) seems to be especially challenging, most probably due to (I) the heterogeneous TBI population in clinical trials, (II) the necessity of an appropriate TBI severity classification beyond the initial Glasgow Coma Scale, (III) suitable outcome parameters, and finally (IV) the problem of choosing the right experimental TBI model.

It is well known that TBI is still the most common cause of disability and mortality in industrialized countries and even more prevalent than stroke. But in contrast to stroke, TBI mainly affects the young and working populations,

thereby causing tremendous personnel and socio-economic burdens that underline the need for neuroprotective and causal treatment targeting the secondary brain injury cascades and the sequels of chronic traumatic encephalopathy. Thus, TBI is a silent epidemic resulting in diverse neuropsychiatric long-term sequels including behavioral and cognitive deficits [9].

Since Klatzko brought up the concept of vasogenic and cytotoxic brain edema, experimental TBI research successfully elucidated the histopathological and molecular changes of the secondary brain injury cascade following TBI [10]. However, more than three decades of experimental TBI research brought up promising neuroprotective compounds—primarily targeting secondary brain edema and raised intracranial pressure (ICP) including inflammation, oxidative stress, excitotoxicity, mitochondrial dysfunction, cell death and blood–brain-barrier disruption—that unfortunately failed in more than 30 clinical trials [11, 12]. As mentioned, translation in the field of TBI is challenging and well-established experimental and primarily rodent TBI models that mainly mimic focal or mixed closed brain injury need to be reassessed [13]. Furthermore, new concepts of multipotential approaches in rodents and gyrencephalic species according to the STAIR criteria—known from translational stroke research—are crucial [14]. Certainly, long-term outcome studies might help to further elucidate the chronic sequels of traumatic encephalopathy and might help to better classify TBI for clinical and research purposes.

Whenever the cardiovascular system was to be studied, sheep or dog models were used, but none of them provided results of inflammatory parameters or other clinically relevant results [15, 16]. To mimic results of surgical procedures, systemic parameters were difficult to obtain and secondary parameters were utilized [17]. The current issues provide examples from a scientifically active and ongoing group named TREAT [18]. This group has been working in multiple research centers, such as Vienna,

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Table 1 Documentation of recruitment conditions in clinical studies dealing with trauma patients

References	<i>n</i> (pat.)	Study duration (years)	Inclusion criteria	Power analysis	No. of centers
[4]	34	2.5	4 ^b	–	> 10
[2]	165	6	3 ^a	150	10

Inclusion criteria in detail

^aNew injury severity score ≥ 16 points, or three fractures and abbreviated injury scale score. 2 points and another injury (abbreviated injury scale score 2 points), and age 18–65 years

^bInjury of at least two body regions with an injury severity score (ISS) ≥ 16 , a femoral shaft fracture which can be treated in principle by nail or fixateur externe (surgical treatment beginning within 24 h after trauma), age ≥ 18 years, and a calculated probability of death between 20 and 60%

Marburg, Aachen, Ulm, Frankfurt, Utrecht and Zurich [19–21]. The unique feature of this group is a cooperative effort of multiple researchers that have shared the burden of gathering data along with the results of their cooperation. It hopefully will serve as a role model for research cooperations in multiple places in the future.

In this FOCUS ON issue, four translational research papers are included.

The manuscript of Verboket/Marzi et al. [22] demonstrates how stem cell therapy for bone defects could be developed from cell cultures via animal experiments to a phase 2 clinical study within a few years. The requirements and hurdles for such a process are very nicely described in this story. The authors mention how they managed to develop cell lines that yield the way into a multi-center, three-arm, prospective clinical study, e.g. the perfect way of performing medicine from bench to bedside.

The review by Greven et al. [23] summarizes the current evidence of the involvements of neutrophils in the pathogenetic changes after trauma. There is an ongoing body of literature that supports the translational aspects of trauma care.

Qiao et al. [24] performed a systematic review and metaanalysis on the relevance of proinflammatory cytokines, such as interleukins. They reconfirm the meaningfulness of inflammatory changes in trauma research. The authors conclude that they continue to be of importance.

Kalbas et al. [25] used the TREAT animal model and performed studies on microcirculatory changes during and after intra- versus extramedullary instrumentation in an established pig model. Their results reconfirm the importance of studying pathogenetic changes in controlled experimental conditions that resemble the human situation.

Compliance with ethical standards

Conflict of interest All Authors declare that they have no conflict of interest.

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