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# Cell-based Therapies for Stroke: Promising Solution or Dead End?

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### *Contribution to the field*

Stroke is a leading cause of serious long lasting disability. For many years nearly all therapeutic approaches to stroke were failing. The discovery of stem cells has brought up a lot of hope to overcome daunting outcomes of stroke. Though, no stem cell-based approach has been translated to a routine clinical treatment, Surprisingly, mechanical thrombectomy rapidly became a mainstay of stroke management as it overwhelmingly superseded efficacy of any other therapeutic approach. Therefore, the question arises if stem cell-based therapy is still a promising solution or a dead end. We have collected most recent evidence of the advances in the field of stem cells for stroke. While the replacement of damaged brain tissue by stem cells seems still to be a distant objective, we are witnessing an explosion of novel paradigms including combination therapies. Interestingly, while mechanical thrombectomy is indeed radically improving outcomes, still many patients experience some neurological deficits, which prevent their return to pre-morbid status. Notably, clot removal provides a gateway for therapeutic agents including stem cells to the infarcted tissue. Moreover, the smaller tissue damage due to thrombectomy may actually be easier repaired by stem cells, so regenerative medicine seems to be more promising solution than ever.

1 **Editorial: Cell-based Therapies for Stroke: Promising Solution or Dead End?**

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51 The introduction of recanalization procedures has revolutionized acute stroke  
52 management, although the narrow time window, strict eligibility criteria and logistical  
53 limitations still exclude the majority of patients from treatment. In addition, residual  
54 deficits are present in many patients who undergo therapy, preventing their return to  
55 premorbid status. Hence, there is a strong need for novel, and ideally  
56 complementary, approaches to stroke management.

57 In preclinical experiments, cell-based treatments have demonstrated  
58 beneficial effects in the subacute and chronic stages following stroke [1; 2; 3] and  
59 therefore are considered a promising option to supplement current clinical practice.  
60 At the same time, great progress has been made in developing clinically feasible  
61 delivery and monitoring protocols [4]. However, efficacy results initially reported in  
62 clinical studies fell short of expectations [5] raising concerns that cell treatment might  
63 eventually share the 'dead end fate' of many previous experimental stroke therapies.  
64 This Research Topic reviews some of the latest and most innovative studies to  
65 summarize the state of the art in translational cell treatments for stroke.

66

### 67 *New mechanistic insights from preclinical experiments*

68 Umbilical cord blood (UCB)-derived cells are a widely available and rich  
69 source of relatively young cells. However, it is unclear which fraction of this  
70 heterogeneous population is responsible for the therapeutic effects reported after  
71 stroke. Gornicka-Pawlak and colleagues investigated CD34<sup>+</sup> mononuclear cells  
72 (MNCs) either freshly prepared or cultured for 3 days versus a UCB derived neural  
73 stem cell line (<https://www.frontiersin.org/articles/10.3389/fneur.2019.00786/full>) [6].  
74 The study particularly focused on restoring cognitive functions after stroke what is a  
75 novel endpoint for the UCB derived neural stem cell line. Freshly prepared cells were

76 found most effective, which is in line with what has been reported for motor and  
77 sensory functions using UCB-MNCs after stroke [7]. An enriched environment was  
78 provided to the animals, further fostering cognitive recuperation in a clinically  
79 meaningful setup. Mu et al revealed that a combination of adipose stem cells and  
80 rehabilitation after experimental stroke is beneficial  
81 (<https://www.frontiersin.org/articles/10.3389/fneur.2019.00235/full>) [8]. This approach  
82 follows the newest STem Cells as an Emerging Paradigm in Stroke (STEPS)  
83 recommendations and is expected to provide more translationally relevant data [9].  
84 Hwang et al. proved that a combination of UCB-MNC and erythropoietin is also  
85 beneficial (<https://www.frontiersin.org/articles/10.3389/fneur.2019.00357/full>)  
86 [10]. Green and colleagues stereotaxically applied neural stem cells in the subacute  
87 stage after large cortico-striatal and smaller striatal strokes  
88 (<https://www.frontiersin.org/articles/10.3389/fneur.2019.00335/full>)  
89 [11]. Cell graft vitality was better preserved in smaller, striatal lesions, which are  
90 associated with a stabilization of functional neuronal networks. However, this effect  
91 was only transient, indirectly pointing to other long-term degenerative mechanisms  
92 and processes that thus far have not been identified. Encouraging results were  
93 reported regarding the efficacy of bone marrow-derived mesenchymal stem cells  
94 (MSCs) which have been applied in numerous preclinical trials for almost two  
95 decades. Satani et al. performed a systematic review and meta-analysis on 141  
96 preclinical studies, confirming robust efficacy in acute and subacute time windows  
97 (<https://www.frontiersin.org/articles/10.3389/fneur.2019.00405/full>) [12]. It is  
98 noteworthy that comparable effects were seen in multiple labs around the world.  
99 Based on these robust data, the authors suggest that this approach should advance  
100 to carefully planned and implemented clinical trials.

101 *Translational and clinical considerations*

102 Defining the best-suited cell source is crucial to taking the translational  
103 process from the preclinical to the clinical stage. Ideally, the respective cells should  
104 be applicable for autologous and allogeneic use, and should exert beneficial effects  
105 via indirect ('bystander') effects while also exhibiting the potential for replacement of  
106 brain cells including astrocytes, oligodendrocytes and, most challenging, neurons  
107 thus covering all potential aspects of brain tissue regeneration [13]. Recent research  
108 by Gancheva et al. revealed that dental pulp stem cells may perfectly fill this role  
109 (<https://www.frontiersin.org/articles/10.3389/fneur.2019.00422/full>) [14]. Another  
110 relevant aspect to translation is the safety of cell applications. Potential adverse  
111 events such as secondary microinfarction were reported when intraarterially  
112 administering large diameter cell populations such as MSCs. However, this  
113 phenomenon seems to depend on infusion speed and, in particular, cell dose, since  
114 lower doses can be safely delivered to the brain [15; 16]. Cell engineering is another  
115 approach used to mitigate these potential adverse effects, for instance by increasing  
116 cell egress from cerebral capillaries [17]. Moreover, no strong evidence of such  
117 complications has been observed after MSC delivery in clinics [18]. The use of MSC-  
118 derived extracellular vesicles in place of MSCs also may help circumvent this  
119 problem. Bang and Kim, both working at the forefront of clinical translation,  
120 summarize the state of the art in this field, focusing on emerging clinical applications  
121 and remaining challenges  
122 (<https://www.frontiersin.org/articles/10.3389/fneur.2019.00211/full>) [19].

123 Results from clinical cell therapy studies in stroke have been reported for  
124 intravenous injections [20; 21] and intracerebral grafts [22]. Although overall safety  
125 has been confirmed, analysis of efficacy endpoints suggests that magnitude of effect



126 may be smaller in human than animal studies, and a number of logistical challenges  
127 also have been identified. Krause's group reviewed such problems, providing an  
128 unbiased overview of bottlenecks in the translational process, and discussing  
129 relevant aspects such as cost-to-benefit ratios and the role of industry-driven clinical  
130 research (<https://www.frontiersin.org/articles/10.3389/fneur.2019.00656/full>) [23].  
131 Despite the moderate collective tepid enthusiasm regarding cell-based approaches,  
132 encouraging clinical data is available. Haque et al. report metabolic changes  
133 observed by magnetic resonance spectroscopy in the brains of patients being  
134 treated with autologous bone marrow-derived MNCs  
135 (<https://www.frontiersin.org/articles/10.3389/fneur.2019.00656/full>) [24]. These  
136 changes correlated with NIHSS scores and might not only indicate efficacy, but could  
137 also be used as surrogate markers for treatment efficacy in future clinical trials.

138

### 139 *Summary and outlook*

140 Although clinical translation of cell-based therapies is clearly gaining  
141 momentum, a number of open questions remain. One is the role of co-morbidities,  
142 which are abundantly present in human patients but are rarely modelled preclinically.  
143 Laso-Garcia and colleagues have analysed this discrepancy and provide a  
144 comprehensive summary on effects of the most relevant comorbidities including  
145 hypertension, diabetes, and obesity both from clinical and preclinical perspectives  
146 (<https://www.frontiersin.org/articles/10.3389/fneur.2019.00332/full>) [25]. Aspects  
147 such as potential cell-drug interactions also await clarification [26]. Finally,  
148 remarkable developments towards precision stem cell medicine have been achieved,  
149 which may facilitate stem cell-based therapies. Stem cell labelling and real-time  
150 imaging are capable of improving precision of transplantations [27]. Progress in

151 biomarker research [28] and artificial intelligence [29] may soon revolutionize  
152 research on outcome assessment, which will be pivotal to the future success of stem  
153 cell therapies. In summary, the road on which we travel with cell therapies for stroke  
154 is probably not a dead end but the journey remaining is challenging and long.  
155 Nevertheless, the overall research progress may finally shed light on the path, with  
156 this Research Topic identifying some of the most important past and future  
157 milestones along the way.

In review

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