The Narrow Upward Path towards Neuroprotection

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In the ensuing articles, we find a nicely linked series in which a drug development programme that has been moving forward slowly but extremely carefully for over a decade is described and placed in the context of the clinical problem, the laboratory approaches needed to select a compound for development and the importance of close attention to clinical trial design and analysis. No programme is perfect, and hindsight will reveal flaws that the investigators have not appreciated or had hoped to evade. Nevertheless, the logical and rigorous approach that is needed in science must not be disregarded in the field of stroke medicine: the inherent difficulties in finding a neuroprotectant that is well tolerated and effective underscore the need for extra vigilance and rigour in the conduct of the clinical development. Over the next few years, the degree to which the SAINT programme has been successful will become known. Data presented following the symposium on which these articles are based are encouraging. In the meantime, here are lessons upon which we can build.

Davalos and Millán set the scene, providing us with a timely overview of the effectiveness and limitations of thrombolysis for acute ischaemic stroke. We see that rt-PA is a highly efficacious treatment and yet practical difficulties over its widespread use, concerns over its safety (more perceived than real, according to recent registry data) and time window, and theoretical considerations around glutamate excitation together conspire to limit its contribution in public health terms. The authors show

that even with a conservative estimate of the number needed to treat with rt-PA of 7, the impact on the disease is limited because such a low proportion of stroke patients presently receive the treatment. It is apparent that a modest benefit that could be delivered to a majority of patients would be more valuable to society than a substantial benefit derived by only a few. In practice, both approaches are required – specific and general, and as the authors point out, there is good reason to believe that the benefits of thrombolysis may be extended to later times through careful selection of patients, through different drugs and through co-administration of a neuroprotectant. The challenge now is to develop the neuroprotectant.

Shuaib develops the theme, illustrating the many reasons why previous excitement over potential neuroprotectants may have been premature, and describes the measures suggested by the STAIR group to bring a rational, if yet unvalidated, approach to drug development in this field. Using the example of NXY-059, he shows how the STAIR criteria are attainable. We learn the importance of using a comparable time window in the laboratory to that which can be achieved in patients. We note the relevance of white matter, often disregarded in rodent models. Above all, he shows us how function can be assessed in the laboratory using tests that are easily recognisable to clinicians. The correspondence between infarct volume assessed weeks after neuroprotective treatment for an acute ischaemic insult, and the gradual (and enhanced) recovery of motor and visuo-spatial problems in

these animals offers a signal that NXY-059 may be a suitable compound for clinical use. He emphasises the importance of adequate dosing, and of matching the pharmacological effects and tolerability in animals to the clinical situation. We are left with hope that NXY-059 has risen higher through the preclinical mist than most previous compounds.

Davis takes on the challenge of lifting the chosen candidate from the darkness of the laboratory and guiding it through the murky field of clinical trials. He begins with an optimistic note. Recent years have seen several major developments in acute stroke care: we are clearly in an era where treatment of stroke has not only become possible but is being delivered around the world. Only neuroprotection has so far eluded us. Small sample sizes, long time windows and insufficient doses have each contributed to the failure of clinical trials. Outcome measures have not always been assessed rigorously or analysed in ways that reflect clinically likely effects. He describes the SAINT programme, which is developing NXY-059 as a novel neuroprotectant for acute stroke, where a number of these potential pitfalls have been sidestepped. First, Phase II studies demonstrated that doses adequate to attain and maintain drug levels known to be neuroprotective in animals were well tolerated by patients. Phase III trials have taken account of lessons from elsewhere. Stroke severity is assessed before entry and included as a randomisation factor to ensure a broad range of patients, all of whom have potential to contribute to the function-

al outcome assessment. Time from stroke onset to treatment is controlled to give information on treatment up to 6 hours without compromising efficacy by permitting 'bunching' at the outer limit of the time window. The chosen primary outcome measure, modified Rankin Scale, is one that has resonance with clinicians, patients and regulators alike; and the analysis of this is based on the logical assumption that meaningful benefits can be seen across a range of disability levels. Careful efforts were taken to ensure that investigators were trained in use of the mRS. On the understanding that neuroprotection aims to deliver relatively modest benefits that can be offered to a wide range of patients, the sample size was initially chosen to include over 3,400 patients in the Phase III programme.

These steps along the steep path of developing a neuroprotectant have been described with authority and clinical relevance. The relevance is highlighted by the announcement following the symposium at the ESC that the first of the two SAINT trials, SAINT I, was positive on its primary end point. As a result, SAINT II has been expanded to include 3,200 patients and to take account of the other encouraging findings from the first positive neuroprotectant trial. It takes more than a single step to achieve a distant goal: the stairway to success needs solid foundations and a firm footing at every stage. The SAINT programme is picking its way cautiously. We hope that we may yet rise above the clouds.