Neuroscience is the Next Oncology

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Prominent and expensive failures in Alzheimer's disease therapies have led to a contagious belief system in some parts of the biopharma industry that neuroscience is just too hard, too risky, and too uncertain. But, might this belief system itself be a residual bias of the past? Close inspection reveals all the signs of a coming era of neurotherapeutics.

Regardless of therapeutic area, drug discovery and development is a long, difficult, and failure-ridden journey. Even in those areas where success blossoms—most recently in immuno-oncology—it is easy to forget that the landscape once looked different to the casual observer. Indeed, just a few years ago many biopharmaceutical companies eschewed immuno-oncology as a marginal area with limited potential for clinical impact. Hindsight is 20-20, but a look into the rear view mirror identifies the signs and signals that foretold the advent of the new wave of immuno-oncology therapeutics. Starting with the identification of central molecular pathways for lymphocyte activation or suppression, more detailed understanding of the tumor microenvironment, the development of targeted checkpoint inhibitors, and identification of responsive patient populations, what began as a "high risk" area has culminated in a torrent of clinical investigation, combination therapies, and increasingly refined treatment options that are changing the field of medicine.

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As much as oncology has recently reigned supreme in the biopharma firmament, the development of neuroscience therapeutics has lagged over the past 15 years. The prominent and expensive failures in Alzheimer's disease therapies, in particular, have led to a contagious belief system in some parts of the biopharma industry that neuroscience is just too hard, too risky, and too uncertain. But, might this belief system itself be a residual bias of the past? Close inspection reveals all the signs of a coming era of neurotherapeutics.

First, arguably no other area of biomedical science is advancing as rapidly as neuroscience. From our understanding of core molecular and cellular processes that contribute to brain development, plasticity, function, and aging, to our unprecedented ability to monitor and manipulate neural circuits, we are witnessing a revolution. Second, we are defining the genetic architecture of complex neurological and neuropsychiatric disease that is unraveling pathways and creating therapeutic hypotheses more causally rooted in human

biology. Third, molecular and functional access to the human brain through neuroimaging, mobile or digital assessment technologies, and fluid biomarkers are enabling much richer patient phenotyping and more quantitative objective assessments of complex brain function. Fourth, we are seeing the emergence of new drug modalities, including intrathecal antisense oligonucleotides, adeno-associated virus gene therapy, cell therapies, and brain penetrant biologics that are opening entirely new target spaces for therapeutic intervention in the central nervous system. Fifth, regulatory agencies are providing new paths, supporting novel endpoint development and trial design, and helping to reshape the definition of disease states. And, finally, in response to all of these signs, the flow of venture capital and new biotech start-up activity in neuroscience has taken off.

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Taken together, these signs suggest that neuroscience at an inflection point. Indeed, looking over the past year or so, as well as looking forward to events in the coming year, the field of neuroscience is experiencing a suite of treatment paradigm changes in therapeutics. An entirely new class of migraine drugs, the anti-calcitonin gene-related peptides (CGRPs) that have the potential to significantly impact this widespread disease, will reach patients and the market in the coming year. The first drug for tardive dyskinesia, a disabling effect of chronic antipsychotic use, is now available. The past year saw the launch of the only approved drug for Parkinson's disease psychosis as well as a transformative therapy for spinal muscular atrophy (SMA), the most common genetic cause of childhood death. We are on the verge of new drug approvals for rare, intractable, genetic epilepsy syndromes, and last year had the second ever approved therapeutic for amyotrophic lateral sclerosis (ALS). Drugs are now available, or might soon be available, for select genetic subsets of Duchenne muscular dystrophy (DMD), and we can anticipate the launch of the only approved therapeutic for postpartum depression.

Beyond newly approved therapeutics and those that are likely to be approved in the near future, we are witnessing promising examples of progress in clinical development. There is tantalizing evidence for direct lowering of the toxic huntingtin (htt) protein by intrathecal antisense oligonucleotides in Huntington's disease. Adeno-associated virus-based gene therapy is showing great promise in SMA and might reach the clinic for DMD. And promising early clinical data suggest the prospect of rapid-acting antidepressants effective in treatment-resistant populations.

But it doesn't stop there. Outside traditional molecular therapeutics, treatment paradigm changes are happening across different modalities in neuroscience. Last year, the United States Food and Drug Administration (FDA) approved the first app to treat substance use disorder. The first algorithm-based therapeutic delivered via a tablet interface for attention deficit hyperactivity disorder (ADHD) is likely to be approved this year by the FDA. Endovascular thrombectomy has substantially improved clinical outcomes in ischemic stroke. And brain-machine interfaces are restoring neural functionality in patients with spinal cord injury. And this list is not exhaustive.

When examined more broadly, beyond the narrow lens of Alzheimer's disease, one begins to see the dramatic progress that has been achieved in just the last year or so, with more expected in the very near future.

Will the promise hold? Only time will tell with certainty, but what is clear is that diseases of the nervous system, long considered impervious to therapeutic advances, are now being addressed successfully. With continued focus, propulsive thinking, scientific rigor, and clinical innovation, neuroscience will be the next oncology. And that is great news for patients.

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