Why our patients (and we) need basic science research

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ABSTRACT

In times of fiscal austerity, the tendency is to seek instant, inexpensive gratification. In the case of biomedical research, this means the shortest path to practical clinical implementation. But fueling the translational pipeline with discovery depends critically on allowing the biomedical research community to follow their science where it takes them. Fiscal constraints carry with them the risk of squelching creativity and forfeiting the power of serendipity to provide the substrate for the translational engine in the future. *Neurology*® 2013;80:2070-2075

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GLOSSARY

p75NTR = p75 neurotrophin receptor; PD = Parkinson disease.

The translation of research from the laboratory to the clinic has become a benchmark of success. The NIH has recently launched a new institute for translational medical research,¹ funded a national network of clinical and translational science institutes,² and emphasized translational and clinical research on their new, engaging Web site.^{3,4} In a 2010 National Science Foundation survey,⁵ 82% of participants agreed or agreed strongly that research that advances the state of knowledge is necessary and should be funded by the federal government. In response to a 2009 survey by the Pew Charitable Trusts, 73% said spending on basic scientific research usually pays off “in the long run.” Despite this understanding of the lay public and the assertion of the US Senate of the critical importance of basic research in the life sciences, 3 reasons are given for the shift of many funding agencies, foundations, and corporate funds away from basic research and toward research of immediate and obvious consequence for human health: 1) the health benefits of basic research derive from layers of noncontemporaneous research and are therefore hard to trace, 2) basic research is a high-risk enterprise vis-à-vis the prediction of yield for human health, and 3) shareholder and donor pressure for short-term results limits enthusiasm of corporations and foundations for making investments in research with a long-term potential benefit. Recently, some federal agencies have felt similar pressure from voters and elected officials.⁶

Then why is it that investment in basic research remains important? Why does the public realize at some level that this investment is worth it in the long term? The answer to these questions lies in the complexity of the human organism and its interaction with its environment. There is virtually no question involving human health and disease to which the answer is a universal “yes” or “no.” Context, both intrinsic and extrinsic, is everything. Whether an effect is “off-target” or “on-target” depends on what the target in that particular circumstance happens to be. Whether assembly of a receptor-ligand pair triggers the life or death of a cell depends on which of its downstream effectors is plentiful, activated, or available in the right cellular compartment at the time of assembly. It is these complex equations that make basic and translational science so essential to development of safe and effective therapies. Furthermore, it is these complex equations, as well, that account for the inefficiency and unpredictability of the process that leads from discovery to practical implementation. Hundreds of attempts to hit a target may

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result in tens of trials that go nowhere and a handful of trials that either hit a worthy target other than the one at which they were originally aimed or teach us something about the system that aids in subsequent development of other successful trials. This is not exactly a prospectus likely to tempt the timid investor. But if we are to constantly fuel the discovery-to-treatment pipeline, it is critical.

THE RELATIONSHIP BETWEEN BASIC SCIENCE AND DISEASE PREVENTION AND TREATMENT

The development of symptomatic therapies for Parkinson disease (PD) is perhaps one of the best known examples of how a search for solutions to a common clinical problem can fuel basic science and how that science, in turn, can inform the search for clinical solutions. It is, at times, a story of intentional dialogue and, at times, a story of serendipitous intersection of purpose. The clinical description of PD was refined and augmented over the 1800s. Pathologic descriptions followed in the early 1900s. But not until the basic neuroscience notions of neural circuits and connectivity, also refined in the late 1800s and early 1900s, were juxtaposed with these clinicopathologic observations did the idea of interruption of the neural signal between brain loci make its way into explanations for clinical conditions. Even so, the observations that belladonna and other anticholinergic agents calmed the tremor and that a powder of anticholinergic hyoscyamine and dopaminergic ergot suppressed the symptoms of patients with PD were made empirically, and it was not until much later that the concept of maintenance of a balance between cholinergic and dopaminergic circuits evolved.⁷

This basic scientific notion of opposing neurotransmitter forces ensuring homeostatic motor control in the case of normal CNS function led to further pursuit of dopaminergic and anticholinergic therapies for PD. The recognition that dopamine was itself a neurotransmitter and not just a precursor for norepinephrine⁸ and the discovery that dopamine levels were particularly high in the basal ganglia were followed by the identification of dopamine deficiency⁹ in the substantia nigra of patients with PD. Subsequently, basic laboratory studies defined the transport system that brings L-dopa, but not dopamine, into the CNS; the enzyme that converts L-dopa to dopamine in the periphery; the modulating effects of serotonergic, adenosinergic, GABAergic, and glutamatergic transmission on motor control; and the synaptic recycling of catecholamines in the CNS. These studies have enhanced the bioavailability and effectiveness and diminished the side effects of symptomatic therapy for PD. Current basic laboratory

studies hold the promise of understanding the contributors, both endogenous and environmental, to the pathogenesis of PD and development of preventive strategies for those at risk.^{7,10,11}

Sometimes the basic science evolves before its application to human health and disease is clear. In that case, basic science discovery can drive, rather than grow out of, the search for understanding and treatment of human disease. A recent example is the discovery that RNA serves many functions aside from its traditional role as an intermediate for conversion of genomic material to cellular proteins. In the late 1970s, it was discovered that RNAs are frequently and variably spliced and that in between transcribed segments of the genome are segments called introns. The notion of “one gene, one polypeptide” was clearly excessively simplistic.¹² The 1980s brought our understanding of RNAs as enzymes,¹³ and the 1990s afforded us the concepts of RNAs as regulators of transcription and translation.¹⁴ More recent basic studies have identified the cytotoxicity of aberrant or overabundant RNAs.¹⁵

In this context, and armed with the new knowledge that some diseases of the nervous system are associated with a stretch of DNA that contains a large number of trinucleotide repeats, previously cryptogenic disorders began to be discovered to involve toxicity or regulatory aberrancy of RNA. Toxic RNAs contribute to type 1 myotonic dystrophy and spinocerebellar ataxia type 8. The absence of an RNA-binding protein required for RNA shuttling between the nucleus and the cytoplasm and for regulation of translation and synaptic protein synthesis is thought to be responsible for the manifestations of fragile X mental retardation syndrome.¹⁶ Conversely, double-stranded RNAs, shown to interfere with translation, have been proposed as therapeutic agents for disorders involving overproduction of a normal protein or production of a toxic protein.¹⁷ The 90 years or so between the clinical description of these disorders and the discovery of trinucleotide repeats as a pathogenetic mechanism were paralleled by 3 or 4 decades of basic science aimed only at discovering mechanisms of normal function in organisms as diverse as the fruitfly *Drosophila melanogaster*, the worm *Caenorhabditis elegans*, and the laboratory mouse.¹⁸ Without this basic scientific exploration, at the time seemingly aimed at knowledge for knowledge's sake alone, no one would have imagined that the RNA, rather than the protein, produced from a gene could be responsible for the clinical pathology of genetic aberrancy.

Finally, sometimes the quest for an understanding of one disorder leads to basic science discovery that is of unanticipated relevance to another. Early studies of the p75 neurotrophin receptor (p75NTR) characterized its independent signaling activity as inducing cell

death by the process of apoptosis.¹⁹ In the embryonic human brain, p75NTR is ubiquitously expressed. As the brain develops, however, its expression is increasingly restricted. When hypoxic-ischemic injury to the adult brain occurs, p75NTR is once again expressed.²⁰ It has been hypothesized that the cell death that ensues depends on p75NTR, and downregulation of p75NTR has been demonstrated to contribute to attenuation of hypoxic-ischemic injury-related neuronal death.²¹

p75NTR is also expressed in embryonic peripheral neurons, and its expression has been noted in tumors, such as neuroblastoma, that arise from these neurons.²² It has therefore been proposed^{23,24} that p75NTR agonistic ligands be used to induce the death of neuroblastoma cells. Other studies^{25,26} have shown, however, that p75NTR signaling is variably lethal or protective to neuroblastoma cells. Prediction of the function of p75NTR in a given cell and environment would require knowing which of many signaling pathways triggered by this receptor are relevant in that case. Furthermore, within a single tumor, the expression and function of p75NTR likely vary from cell to cell. Clearly, p75NTR is not the most tractable of therapeutic targets for neuroblastoma. But in the course of studies^{27,28} of neuroblastoma cells that do or do not express p75NTR, it was noticed that expression of p75NTR is associated with altered concentrations of the same set of cellular proteins that exhibit altered concentrations in the brains of mice that express familial Alzheimer mutant presenilin.

Here was a completely unexpected finding in a seemingly unrelated disease and animal model system. Could p75NTR be relevant for both neuroblastoma and Alzheimer disease? The answer came with the realization that the life-or-death decision-making activity of p75NTR in neuroblastoma cells required cleavage of the p75NTR molecule by any of the enzymes in the γ -secretase class. Presenilin is one such enzyme. Changing the activity of presenilin by mutating it has the same effect on expression of many cellular proteins as changing the expression of its substrate, p75NTR, because presenilin affects cellular function, in part, by cleaving p75NTR. Presenilin and p75NTR are sequential components of the same cellular signaling pathway.²⁷

Why is this important? Knowing this suggests that there may be therapeutic targets for both diseases in this signaling pathway. For example, altering p75NTR expression or mutating presenilin changes the expression of all 5 major enzymes involved in cholesterol biosynthesis. The effect of statins on resistance of neuroblastoma cells to chemotherapy and the role of statins in the therapy of Alzheimer disease underscore the importance of this mechanistic observation. Furthermore, basic laboratory studies make it clear that

p75NTR is far from the only target of presenilin and that presenilin is far from the only γ -secretase in the nervous system.^{29,30} Clinical implementation of the mechanistic findings will therefore likely require development of specific drugs that target specific γ -secretases or that affect specific branch points off of the cholesterol biosynthetic pathway.³¹

The pathway from the laboratory to the clinic is rarely linear or predictable. Clinical advances have been made from bidirectional exchange of information and from co-opting of findings from studies of one disease in service of the therapy of another.

THE RELATIONSHIP BETWEEN BASIC SCIENCE AND THE TRAINING OF NEW NEUROLOGISTS

The process of clinical reasoning involves accruing an evidence base and weighing alternative interpretations against newly accrued fact and is exactly what a clinician does with each patient he or she sees in the office. One hears the chief complaint and begins to formulate hypotheses as to what could be causing that symptom or concern. Soliciting the history from the patient and asking targeted questions tests each of these initial hypotheses and allows one to refine the list of hypotheses to a manageable size. One then tests these hypotheses by doing a physical examination and putting some lower on the list or rejecting them outright on the basis of positive and negative findings on that examination. Then, with one or two remaining hypotheses, one obtains laboratory data aimed at testing each hypothesis in turn and narrows the field to a single hypothesized diagnosis. This final hypothesis is tested by treatment, observation, and outcomes assessment.³²

As a neurologist, one hears the chief complaint and begins instantly to formulate two sets of hypotheses—one for localization and one for process. The localization hypotheses are largely determined by the location and nature of the symptoms themselves. The process hypotheses are determined by the timing of the onset, the time course of the evolution, and the specific character of the symptoms. The history tests each hypothesis, eliminating some and elevating others to the top of the list. The laboratory studies chosen may be done sequentially or simultaneously depending on such things as likelihood of a particular diagnosis, invasiveness or cost of the study, availability of the technology required, potential impact of a particular diagnosis on the treatment and outcome, and the patient's wishes. A treatment plan is arrived at using a blended literature and personal experiential evidence base, and its implementation and the subsequent monitoring of outcomes tests the final diagnostic hypothesis.³³

All through this process, communications are key. One communicates with the patient and the patient's caregivers in a language and with an intent that are

decidedly different from those with which one communicates with the pharmacist or the physical therapist or one's physician colleagues.³²

This process does not differ significantly from that of hypothesis-driven research or critical analysis of a journal article. What better training and testing ground for the analytical and logical thought, evidence-based decision making, and communication to varying audiences that are the hallmark of modern neurology than the critical evaluation of research results, whether they are generated in the course of one's own mentored research or read in peer-reviewed journals? The conduct or review of research teaches one to think in an intellectually rigorous manner, to question the status quo, to acquire and integrate new data, to revisit previous conclusions in the light of these new data, to weigh the cost of uncertainty against the cost of experimentation, and to communicate findings and conclusions clearly, in an organized fashion, and in a language that is appropriate for a particular audience. Is that not what we expect of every neurologist we train?³⁴

As the community charged with training and accrediting the next generation of clinical neurologists, we need basic research as one mechanism for instilling the cognitive and communication skills required for the exemplary practice of clinical neurology into our trainees.^{32,34}

THE ROLE OF SERENDIPITY The conduct of science and the achievement of advances in medicine require a combination of targeted, systematic posing and testing of hypotheses and serendipitous juxtaposition of seemingly unrelated ideas and concepts. Off-target advances are advances nonetheless, and generation of new knowledge may find its purpose many decades remote from and in unanticipated applications of the original studies.³⁵

As such, advances in science and medicine are born of their practitioners having freedom to think creatively and broadly, time to pursue promising or intriguing leads, venues and time in which to network with a diverse array of other creative thinkers, and rewards that are not linked to the applicability of their findings to only a specific problem or clinical disorder.³⁶ Without time, funding, and human resources dedicated to intellectual pursuit without topical boundaries, scientists find only what they specifically seek to find and answer only concrete, derivative, narrowly applicable questions.³⁵⁻³⁷

SCIENCE AS A SOCIAL ENTERPRISE An entire generation of children grew up seeing the scientist Beaker on the Muppet Show speak in a language no one else could understand and work on cryptic experiments in relative isolation.³⁸ Nothing could be further

from the truth. Laboratory science is an intensely social enterprise. Without networks of colleagues who bring new ideas and knowledge to the table, without the critical eye of others on one's own body of work, without the new approach, the new vantage point, and the new questions, science would be monotonic, linear, and subject to interpretations influenced by persistent preconceived notions and prejudices.³⁹

The optimal conduct of science and its application to problems in medicine therefore require a critical mass of investigators who regularly collaborate, critique each other's work, and serve as each other's sounding boards for new ideas and techniques. Although electronic means of communication have facilitated collaboration at a geographic distance and in nonsynchronous modes, the best scientific communities foster serendipitous interaction, creating physical venues for members to congregate at will; lecture and seminar series at which members present their own work, hear others' work, and interact with visiting speakers from other scientific communities; and training programs in which there is a bidirectional exchange of ideas between the current and future generations of the greater scientific community.³⁷

The diminution of available funds for basic scientific research may strike some as a selection pressure that allows only the very best of the community to survive. But the shrinking of the scientific community below the critical mass necessary for the exchange of ideas and viewpoints will eventually cripple even the best and most "independent" scientific enterprise.

WHY OUR PATIENTS (AND WE) NEED BASIC SCIENCE RESEARCH

Four overarching points underscore the need for unfettered, intellectually free conduct of basic science research. First, because scientists only ask questions to which they do not know the answers, science often takes us in unanticipated directions. Sometimes these directions lead to dead ends. More often, they lead to more questions or, if we are lucky, to answers to questions we did not even think to ask. Efficiency is not the strong suit of science. Knowledge and understanding are. Knowledge and understanding without action and service are perhaps less than optimally useful. But action and service without knowledge and understanding are, at best, unwise and, at worst, dangerous.

Second, the science of the past 2 decades is only now technically translatable in service of the good of humankind. Having translatable information 2 decades from now will depend upon the science we develop now. We must extend our pipeline from the laboratory all the way to the clinic. It is critical, precisely because of this, that we continue to fuel the laboratory end of that pipeline.

Third, clinical and translational research that is not informed by and that does not, in turn, inform mechanistic understanding is less likely to produce clinically effective results and more likely to produce unwanted, off-target effects. This makes investment in translation without continued basic science an unwise investment.⁴⁰

Finally, the funders of research, be they public or private, are like venture capitalists. They must look at the research prospectus and decide whether to take a particular risk and fund a particular enterprise. Their decision is based on their assessment of the relative magnitudes of the risk and the potential payoff and the likelihood of the payoff's coming to fruition, either in the traditional, linear sense or because of some unanticipated, different application of the knowledge and understanding generated. There can be no question that the latter situation poses an almost impossible problem for the risk-averse. How can the likelihood of an unanticipated, "off-target" advance be quantified and assessed? It cannot. And in times of fiscal restraint, in times of more tangible, mission-critical priorities, perhaps ventures with unquantifiable risk/benefit ratios ought not to be pursued. But if we make this decision, it must be with full realization that not taking this risk today poses an equally unquantifiable but inevitable risk for tomorrow. To build a bridge that extends from the laboratory to the clinic to the community and to simultaneously close the entrance to the bridge is to forfeit the future of translational medicine.

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