1 Neuroscience Hypotheses and Translation into Neurosurgery Practice

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1.1 INTRODUCTION

1.1.1 CONCEPT OF TRANSLATIONAL NEUROSCIENCE

The concept of “translational” research is based on the effective rendering of research ideas into actual clinical practice — in other words “translating” the research finding into clinical usefulness.\(^1,2\) This concept has many different definitions, depending upon the location along a continuous axis that extends from preclinical experimental work to what would be considered purely clinical research. In a recent review, translational research is considered to occur when an endpoint is measured in a patient rather than via a preclinical experiment.\(^2\) A team is usually involved, including
the preclinical scientists developing the idea for the treatment strategy, the clinicians involved with providing care to patients and using the treatment, and the formal clinical trial necessities such as trial statisticians and research nurses. However, a broader definition is provided by The American Physiological Society, which defines translational research as “the transfer of knowledge gained from basic research to new and improved methods of preventing, diagnosing or treating disease, as well as the transfer of clinical insights into hypotheses that can be tested and validated in the basic research laboratory.”

The team concept has evolved through necessity because basic neuroscience tends to be very focused on cellular and genetic mechanisms, whereas clinical trials and subsequent applications to humans are now unique specialties in their own rights, with clinicians and neurosurgeons providing patient care in the middle course between the new specialties. In a way, almost all biological research is translational, but the timelines for clinical applications may differ considerably, i.e., 1 year, 10 years, 100 years, etc.

Neurosurgeons tend to prefer more rapid relevance (within 1 or 2 years) because of inherent impatience. However, many of the great clinical advances stem from older basic science research findings applied outside their original fields. For example, microbiologists were cataloguing bacteria for years before the process had any clinical relevance. The advent of antibiotics created an immediate need to classify and understand organisms due to their differing sensitivities to antibiotics.

The three aspects of translational research include first a great preclinical idea developed often from laboratory findings that appear to have significant potential (Figure 1.1). This seminal idea may have been tested in rodents or in nonhuman primates and hopefully a side effect profile and likely therapeutic range are in hand. For many neurosurgery devices and products, no dose-response curve is available or applicable, and often Phase I trials for side effects in normal patient populations are obviated and the device or product instead moves rapidly into Phase I/II trials in the target patient population. Thus, information obtained about side effects and dosage (if applicable) from preclinical studies can be very helpful.

The preclinical idea must then have an enthusiast or sponsor willing to do the work to begin human testing. The sponsor must obtain a relevant investigational device exemption (IDE) for a device or an investigational new drug (IND) application for a drug from the U.S. Food and Drug Administration (FDA), and usually requires an industry cosponsor to handle manufacturing compliance, assist in defraying costs, and set up the initial testing format. Individuals and companies may have varying motivations to proceed to initial clinical testing, but usually the motivation is a mix of altruism (to improve some medical condition) and a profit incentive based upon the possibility of a marketable product at some point in the future.

Many pitfalls are present in the transition from idea or preclinical data into a clinical concept. In many cases a “translator” person may serve as an intermediary. Such a person is familiar both with the basic science and clinical concepts inherent to the product and the business aspects related to marketability. From the view of the translator, preclinical data may not necessarily be needed to evaluate a hypothesis but may be needed to decrease the risk of failure of the product through more extensive testing. The involvement of a basic science person in this transition may
sometimes be difficult because such scientists often do not have a full picture of clinical relevance and marketing aspects and, in many cases, may not understand why a product is not developed or is suppressed by a company for business reasons or because of side effects.

The second aspect then is to look for (usually) academic neurosurgery collaborators willing to apply the device or product to patients in the proscribed clinical trial format. This initiation of clinical testing in humans also requires significant paperwork and oversight, including obtaining institutional review board (IRB) approval for human research and enrolling patients — tasks for which the clinical investigator is often paid. The type of clinical trial format and patient enrollment are then closely monitored by both the institution and the FDA.

FIGURE 1.1 The transition path of a great basic science idea from preclinical studies to product. First, clinical need, commercial interest, and animal data must be sufficient before one can consider proceeding to initial human protocols. Initial consideration of human studies requires further evaluation of other factors including intellectual property rights, ability to devise a suitable human manufacturing process, market surveys to indicate clinical marketing likelihood, and initial FDA interactions. If initial feasibilities of Phase I/II clinical trials are approved, an investigation device exemption (IDE) must be obtained and the manufacturer must choose a premarket approval (PMA) or 510 K approval pathway. A PMA requires considerable additional data and clinical studies for an entirely new treatment approach; a 510 K links the product to existing FDA-approved products to show equivalence. If a pivotal trial is convincing, the FDA may finally approve marketing; then the product can be sold freely for FDA-approved indications.
The third aspect is to then assemble the data, often from multiple sources, decide on a Phase III format for a randomized trial, obtain FDA approval to proceed based on the initial side effect and dose-response profiles, and then perform the definitive trial. Even after FDA approval, a product must still meet the FDA burden of registry of late side effects and long-term issues, particularly for implanted surgical products that may involve unknown consequences years after implantation. At some point after FDA approval, more open clinical trials are often initiated by other groups, usually those with considerable skepticism about the clinical worth of the product. After these external trials are performed, many devices and products are never commonly used due to lack of efficacy, difficulty in use by those other than the core enthusiasts, or because of unanticipated side effects despite FDA approval and availability.

Since the process of translation into even simple clinical practice requires a significant burden in complying with regulations at both the institutional (IRB, ethical board, etc.) and FDA levels, the translational process also requires a clinician familiar with the treatment scheme and capable of delving adequately into regulations for approval and often a corporate entity to advance the significant FDA-required costs. Thus, a heavy burden is borne by the medical care system and clinicians who participate in the process of translational medicine.

Translational research also implies a mechanistic understanding at the molecular, cellular, and systemic levels of the function or action of the therapy in relation to the disease mechanism or target. Many clinical advances are not translational or hypothesis-based, but rather are evolutionary or simply empiric. Thus, the concept of translational research is usually applied primarily to a situation where a hypothesis is generated, tested at the preclinical level, and then applied in sequence to initial and then final stages of clinical testing for human use. In many instances, drug development has followed this approach whenever possible, although many notable failures occurred as well.

Translational research depends critically upon an animal model of the disease for preclinical testing of the proposed therapy, and the translational process can fail, for example, by applying results from an inappropriate animal model to a human disease. Thus, translational research continues to evolve and, in many cases, further understanding as to why a treatment does not work in an intact individual may lead to the opening of additional preclinical research avenues.

A recent review on translational neuroscience focused on the concept of designer drugs generated by hypotheses and new information about the nervous system and the mechanisms by which such preclinical hypotheses can be applied to human medical care. The field of neuroscience has developed many promising new treatment strategies now in the process of testing, and arising from basic neuroscience advances. In many ways such a hypothesis- and data-driven approach contrasts with traditional drug screening in which many compounds are subject to blind screening via a validated technique. However, in both empiric and hypothesis-driven treatment development, many pitfalls and development problems can arise, particularly unforeseen side effects, when new therapeutics are applied to clinical treatment schemes.
All applications into the clinical arena depend upon ample (and willing) supplies of patients for testing and clinicians willing and sufficiently enthusiastic to spend their time (beyond ordinary clinical care) for such testing. Some clinicians may also have sufficient understanding of the therapy at both the basic science and clinical levels to serve as a bridge to facilitate the transfer of the treatment to clinical care.  

1.1.2 TRANSLATIONAL NEUROSURGERY VERSUS TRANSLATIONAL NEUROSCIENCE

In many ways, neurosurgery is very different from neuroscience in general. First, it involves far less emphasis on systemic drug treatment, although, of course, considerable crossover and use occur, as in the cases of anticonvulsants, antibiotics, chemotherapeutic agents, and drugs in general medical care. Second, in addition to therapeutics, a whole field of devices, most of which require FDA approval, serve as aids to surgeons performing procedures and are not directed at patient therapy. Third, many therapeutics in development and use are devices and permanent implants that may require an invasive form of delivery. The safety and efficacy requirements that must be met for FDA approval may be quite different for such therapeutics from requirements for oral or systemic drug delivery.

Because the FDA treats devices very differently from drugs, the requirements for specific types of clinical trials also differ and the entire process of translation from a preclinical state to clinical use requires different forms of expertise and knowledge of clinical trials. The focus of most of this volume is on these various categories of therapeutics, devices, and approaches to translation of preclinical advances into clinical usefulness — in other words issues more relevant to ordinary neurosurgical practice and research. These issues are rarely covered in print because the number of devices and their applicability are far fewer than medical applications for new drugs.

Another category of clinical development and advances includes the rationalization of existing therapy. For example, most neurosurgery procedures such as craniotomy and laminectomy involve a few standard approaches that have been in development for more than a century. Since the FDA regulates surgeons in contrast to drugs and devices, little data exists on many neurosurgery procedures, their relative efficacy and safety, and their indications.

This lack of data perplexes both rational care providers and medical consumers because many different approaches to the same clinical problem may be suggested by various surgical specialists. Because the neurosurgical literature mostly involves anecdotal case series and little data generated by randomized controlled trials, few guidelines based on such data apply to management of typical problems, particularly complex issues such as brain tumors and spine therapy.

Where therapy has beenrationally studied, as in the case of carotid endarterectomy and cerebral aneurysm, less contention exists, but many technical and timing issues remain. While many neurosurgical procedures will never be thoughtfully studied because of insufficient patient populations or lack of contention about treatment choice, many treatment options could be studied rationally and various
formats of clinical trials continue to percolate and develop, particularly those that go beyond traditional randomized clinical trials.

New clinical advances depend on the ability to rationally and efficiently translate new understanding of brain function into clinical neuroscience practice. Currently, most clinical neuroscience advances are purely empiric, and often are subject to clinical testing without full identification of the cellular mechanisms involved. Thus much time, energy, and money have been allocated to new treatments with minimal examination of their scientific bases and applicability. However, for many reasons, it is critical to define the hypotheses underlying the application of neuroscience to clinical use.

This definition may lead to reexamination of the data underlying advances in terms of the adequacy of support of the hypotheses and may lead to a fresh approach. However, in spite of a rational approach, the transition from preclinical studies to clinical medicine may still be difficult because of unanticipated potential side effects, clinical trial flaws or inadequacies, inappropriate disease translation, and lack of sufficient market potential.

Most current neurosurgery procedures developed from both clinical hypotheses and practice-related outcome measures to assess the worth of the hypotheses. Many stable and confirmed clinical hypotheses are common in the practice of neurosurgery, particularly the concept that “mass effect” or pressure, if relieved, may improve brain, spinal cord, or peripheral nerve functioning. However, such simple hypotheses do not work for more complex abnormalities, such as intrinsic brain tumors that involve both infiltration and mass effect. As a result, more complex hypotheses often encompassing cellular, systemic, and organ level concepts have been developed.

In many situations, neurosurgery is moving away from the simplistic mass effect hypothesis that has dominated clinical thinking for many years and into specific mechanistic approaches requiring further insight into anatomical, physiological, and pathological factors unique to the brain. This book focuses on such fresh approaches in a variety of neurosurgical fields.

Compared to pharmaceutical mechanisms of translational research, neurosurgery presents many challenges. The first is a small market throughout the world for most conditions under the neurosurgery umbrella, particularly compared to neuroscience diagnoses not involving surgical treatment, for example, Alzheimer’s disease and cardiovascular disease. This is particularly true for clinical products intended for neurosurgery centers rather than for patients (surgical instruments, diagnostics, and other intraoperative aids). This small market may preclude effective development and commercialization because its potential is often insufficient.

A second factor is that experimental surgical procedures are far more expensive to study than experimental pharmaceuticals. A typical price for an experimental surgery, for example, a cell transplant procedure, may reach $150,000 in direct costs in addition to the great amount of liability coverage required and the need for sham or placebo surgical implant procedures. The cost per patient is much higher than the cost of testing experimental drugs and a high level of preliminary efficacy must be demonstrated prior to engaging in clinical trials. Other requirements are substantial financial backing and significant market potential.
Because of these burdens, rarely has an experimental surgical procedure been developed commercially, except as a direct derivative of an existing procedure for which clinical payment coverage may be obtained. Examples are pain or deep brain stimulators. Rarely has a sponsoring company paid clinical study expenses except for the costs of the devices because in most cases the patients may have obtained some benefits. Obviously, this clinical coverage scheme would not be workable for a randomized, placebo-controlled clinical trial.

1.1.3 EXAMPLES OF TRANSLATIONAL PRODUCTS

Collagen nerve guide tubes — For years, neuroscientists have tried to improve the recovery capability and ease of repair of peripheral nerves. A number of different nerve guide tubes were developed. The first used autologous materials (such as arteries and veins) because many injuries allowed insufficient autologous peripheral nerve for cable grafting of a long lesion. A simple collagen nerve guide tube was developed by Archibald et al.\(^\text{10}\) to aid in regrowth of peripheral nerves, with the advantage of absorption over time (see Chapter 3). This absorption obviated some of the problems of permanent materials such as silicone that eventually became restrictive to the nerves. After extensive testing in nonhuman primate median nerves across large gaps, the nerve guide tubes were also compared with conventional cable grafts. However, the initiation of human feasibility trials was difficult in the U.S. and European trials that were conducted first. After several years, a corporate sponsor became interested, pursued additional clinical trials, and eventually the product became FDA-approved for nerve injury repair. This time span from bench to bedside application exceeded 15 years, and the device clearly was a hypothesis-based translational product.

Frameless stereotactic devices — While stereotactic frames have been in common human use since the early 1950s, the difficulties in using a frame and the discomfort to the patient led to consideration of other techniques for surgical navigation. As digital scans such as magnetic resonance imaging (MRI) and computerized tomography (CT) and algorithms to reconstruct the scans and provide three-dimensional representations became more readily available, it became possible to align a patient’s brain in the three-dimensional space of an operating room with the patient’s own computed images. The critical pieces needed to accomplish this alignment are rapid three-dimensional representations of computerized brain images and an accurate and robust three-dimensional digitizer.\(^\text{11,12}\) A variety of three-dimensional digitizing systems were developed and continue to evolve to accomplish intraoperative navigation. FDA approval of frameless stereotactic devices has been expanded to require evidence of clinical usefulness because the devices are used solely by surgeons to aid intraoperative navigation. The devices have evolved into clinical products in wide use and include the Stealth (Medtronics) and BrainLAB systems. Both systems were built upon rapid advances in three-dimensional localizer technology, computer systems, and graphics. The entire laboratory-to-operating-room translational process took less than 10 years.

GDNF for Parkinson’s disease — Glial-derived neurotrophic factor (GDNF) was the primary dopamine growth factor discovered in the 1980s and purified as a
recombinant human protein. After several years of experimentation, nonhuman pri-
mate experiments showed considerable promise for GDNF in initiating regrowth of
dopaminergic collaterals within the striatum. Initial human clinical trials were begun
in 1996, but ended prematurely due to unexpected severe side effects. After further
work in nonhuman primates with both direct GDNF infusion into the putamen and
gene therapy for GDNF transfection, initial human clinical trials with both methods
of administration are in progress. GDNF continues to show significant promise
and further pivotal trials will likely be conducted for at least one of these two novel
methods of administration (see Chapter 8). Although FDA approval has not yet been
granted, GDNF is another example of a hypothesis-driven bench-to-bedside product.

1.2 CATEGORIES OF NEUROSURGERY ADVANCES

Neurosurgery advances can be divided into three basic categories. The first category
involves drugs and devices that are therapeutic and typically involve obtaining an
IND or IDE for initial human use and some form of clinical trial sequence prior to
full FDA approval. Examples of drugs include the Gliadel wafer (BCNU; 1,3-bis(2-
chloroethyl)-1-nitroso urea), which is directly deposited into a brain tumor cavity
at the time of craniotomy, the intracerebral infusion of GDNF for the treatment of
Parkinson’s disease, and adenovirus vector delivery of gene therapy for GDNF
enhancement in the striatum.

Many of these new approaches are based on neural regeneration, biological
plasticity, tissue grafts, and new engineering approaches. Examples of devices
include implants such as cerebrospinal fluid (CSF) shunts, hardware for spine
fixation, and deep brain stimulating (DBS) electrodes for movement disorders.
Because this category generally involves permanent implants for therapy and the
devices are highly invasive, extra consideration is usually involved to ensure long-
term safety.

The second category involves aids to treatment and the performance of proce-
dures. These devices are not directly involved in therapy; they are diagnostic and
surgical tools are meant to facilitate the surgeon’s application of the patient’s
primary therapy. For example, diagnostic tools include MRI scanning of the nervous
system in radiology and potentially in the operating room suite, ultrasound for
intraoperative diagnosis, and newer computer-based tools such as the Stealth com-
puter-aided intraoperative navigation system and other devices. Other diagnostic
tools recently approved by the FDA include microelectrodes and associated phys-
iological recording apparatus for movement disorder surgery, evoked potential
devices, and Licox (Integra Neurosciences) oxygen recording catheters for intrac-
cerebral use. Most of the general instrumentation (retractors, scissors, clamps, etc.)
used during procedures is not individually FDA approved; the manufacturer may
have a general FDA approval for manufacturing techniques in a global sense. Many
other common devices are not FDA approved. One example is the operating micro-
scope that is so important to most surgeons. Because neurosurgery involves proce-
dures, it also involves many devices used by surgeons as therapeutic approaches.
Thus, the FDA recently added a new category of approval for surgeon’s aids; the
primary criterion is usefulness.
The third category is rationalization of established products the FDA has already approved and older procedures already in common clinical practice for which efficacy was not established.

Proceeding with a clinical trial for established surgery requires significant contention about the worth of the procedure, as when carotid endarterectomy began to be carefully scrutinized. For example, the reasons for the carotid endarterectomy trials in the 1980s included the high cost to society for the multiple procedures performed, the lack of any valid data regarding what would happen if the procedure was not performed (contemporary natural history studies), and the prophylactic nature of the procedure, i.e., to prevent a bad event despite the risks of the procedure. Many common products have been applied to additional disease mechanisms without adequate studies of the appropriateness or risk-to-benefit ratio, and thus the great need to establish the proper patient population and determine whether existing procedures are indeed efficacious, safe, and appropriate continues to exist.

1.3 CRITICAL QUESTIONS IN TRANSLATIONAL NEUROSURGERY

1.3.1 WHEN IS PRECLINICAL DATA SUFFICIENT TO PROCEED TO HUMAN EXPERIMENTATION?

Because devices and products involving surgical application or implantation usually involve more risk than drugs, manufacturers have somewhat higher burdens to demonstrate product worth in preclinical research before they move on to clinical trials. The pace at which a preclinical treatment or device is applied to initial patient experimentation is often dictated more by the entity developing the treatment rather than by any rational approach to quality of the preclinical data. For drug development, the FDA has established a rigorous process of IND application and development. For devices, it uses a parallel structure of IDE approval prior to clinical trial. However, many aspects of neurosurgery and translational research are not covered by these regulatory pathways if they do not involve drugs or devices. The definition of experimental surgery has always been a complex issue for surgeons. Standard clinical practice varies considerably among surgeons. Thus, is a slight difference in surgical technique an “experiment”?

An example of a new surgical development was the rapid application of autologous adrenal medullary tissue grafts to patients with Parkinson’s disease, beginning in 1987, after a report from a foreign medical center that they were beneficial. Although linked indirectly to preclinical research suggesting benefits from this procedure, no preclinical studies supported the transition of the procedure to initial clinical experimentation. However, because the tissue was autologous (came from the patient) and the procedure involved only slight variation from an ordinary craniotomy, no regulatory agencies or issues were directly involved. The primary critical issue was whether sufficient informed consent could be obtained for such a blatant experimental procedure.
If a procedure is clearly labeled experimental, insurance carriers usually do not pay for it. This places a great burden on the patient to provide payment for an experimental procedure and assume significant risk without a known benefit. There are many examples of such deviations from surgical practice that to many observers clearly represent experimental surgery and to others constitute only small departures from current practice. The rapidity of clinical application of a new advance continues to be a highly contentious issue, clearly requiring institutional backup from the IRB and ethical support whenever a neurosurgeon engages in some form of human research.

If a corporate entity is involved with a therapeutic, then the rapidity of entry into clinical trials may be more dictated by the need for a marketable product than necessarily the quality of the preclinical evidence. Examples include many of the proprietary neural tissue graft trials. Companies have developed both porcine embryonic cell transplants (as replacements for human embryonic cells) and tumor-derived cell lines for human neural grafting protocols. These cases usually proceed from initial rodent preclinical data directly to clinical trial because of the cost and time required to adequately assess the therapy in nonhuman primates.

One example is a trial of cultured human neuronal neurons for deep hemorrhagic stroke; they were applied to humans in early clinical trials after only a few rodent studies showed cell survival and presence of grafted cells. Because the therapy may be headed for FDA approval, the promoters usually have a burden to demonstrate safety and efficacy before the therapy reaches final clinical trials. However, if a corporate entity is less involved or is not as enthusiastic as the investigators, as was the case with GDNF gene therapy trials for Parkinson’s disease, much more careful nonhuman primate work may be performed before initial human experimentation is considered. Thus, the source of the therapeutic, the need for clinical product development, and marketing for later commercialization may all dictate both the manner and pace of the translational process.

Do neurosurgeons jump too quickly to human experimentation without proper consideration for appropriate human risk and benefit? Clearly, the example discussed earlier of autologous adrenal medulla transplants for Parkinson’s disease involved premature human application, and fairly rapid abandonment of the procedure because of significant risk and lack of efficacy. Thus, convincing preclinical data in a validated animal model of the disease (whenever possible) is required to support the transition to initial clinical trials.

Occasionally the enthusiasm of a corporate entity to bring a therapeutic to market needs to be curbed by clinicians investigating the background and rationale for the transition. Because the data required for initial FDA approval to proceed to clinical trials are quite different in quality and type from those usually required for peer-reviewed publication (the information is often proprietary and difficult to access), external peer-reviewed scrutiny is rarely possible. Thus, neurosurgeons are commonly perceived as being on the edge of ethics, poorly defining experimental surgery as such, and stretching or breaking the (unwritten) rules as to when therapies should proceed to initial human testing.
1.3.2 Who Is Involved with Translational Neurosurgery?

Ideally, the application of devices, drugs, and surgeons’ aids should be performed by clinicians with sufficient background to understand and critically assess the value of a new approach and suggest optimal application.\textsuperscript{5,19} Because a preclinical team may have minimal clinical experience or knowledge, obvious clinical problems in the translational process may easily be avoided by an astute clinician who has the necessary experience. Also, clinicians involved in the translational process should understand FDA procedures and regulations, IRBs, and ethics and should have the expertise to fully validate initial clinical trials. Particularly for new approaches fresh from a preclinical scheme, knowledge of the goal of the underlying application may considerably aid the translational process because appropriate translation usually requires changes and scaling from preclinical applications.

Thus translational effort of taking a therapy or device from discovery to clinical application is generally provided by a team, and rarely by a lone neurosurgeon. The FDA requires rigorous consideration of the manufacture and construction of devices by a company with knowledge of human applications and materials to preclude “garage” level implementations. Thus, a team may include preclinical scientists who foster an idea and clinicians who are knowledgeable about the basic science side and the initial clinical application and who have access to appropriate patients, statisticians, trial designers, research nurses, and database and analysis personnel. This team usually requires outside funding to fully implement the translational advance, either through a grant or from a corporate entity with visions of a marketable and profitable product within a specific timeline.

Considering that training may be needed in a variety of disciplines beyond neurosurgery, the typical academic neurosurgeon often may be overwhelmed by the needs of even a simple clinical trial. The degree of paperwork, oversight, and IRB approval is astounding without significant administrative help, and often the design of a clinical trial from an industry-funded approach is insufficient to answer a scientific question even though it may be sufficient for FDA approval.

Academic neurosurgeons interested in translational approaches must be aware of and understand many of the basic neuroscience implications of the research, have captive patient groups who can be recruited, have the necessary clinical skills to adequately institute the methodology, and be aware of the relevant clinical trial needs for the study. This is a wide range of skills and the training to obtain most of them (beyond ordinary clinical skills) is not readily available through medical school or neurosurgery training — it requires additional time.\textsuperscript{19,20} As is the case for most academic medicine efforts, developing a team is critical, and a shortage of neurosurgeons interested in and sufficiently enthusiastic about such research to become translational “bridges” continues to exist.\textsuperscript{1}

1.3.3 Mechanisms of Translational Neurosurgery: University and Corporate Involvement

For a medical material such as an antibiotic or antiviral, the typical pathway consists of a scientific discovery that works well in a laboratory setting followed by trans-
lation through clinical trial into a treatment. Usually this approach is sponsored by a drug company, and therapies are developed because of market forces. An initial market survey is necessary to determine how much a drug would cost to develop, patent, and manufacture, how much profit is required to recapture development costs, and the size of the potential market. However, a large number of drug and device companies often take ideas from academics and then perform the translational work to prepare for clinical trials without actually proceeding on to clinical trials due to the cost. Instead, the marketable preclinical products may then be sold to more traditional drug firms or the translational companies themselves converted or sold into a different entity for further product development.

The drug field provides many examples of successes and failures. Many start-up drug companies went bankrupt in the search for new drugs, often at an initial level because the research was too far from a direct path to clinical development. In some cases, such as drug trials for stroke, a drug appeared promising in animal trials, but failed at the initial clinical trial level. This may have been caused by incorrect application of the animal model to the human situation (exploiting drugs that work in focal stroke to treat global ischemia), failure to understand how a drug may work in an intact system, side effects (a psychotropic profile for N-methyl-D-aspartate [NMDA] antagonist), or failure of clinical trial design. However, for devices and particularly for experimental surgeries, translational research often means something completely different. Obviously, a device may be patented, but it may be difficult ethically and legally to patent a surgical procedure.

1.3.4 Device Development Process

Specific device or therapeutic development begins with a great idea, but a complex process usually involving commercialization must be followed before considering human application of the concept (Figure 1.1). Commercialization of an idea for clinical use involves consideration of many critical issues before development proceeds further. The critical issues include exclusiveness and the availability of patent rights, market size and access to markets, and the feasibility of commercial production. Once a process is deemed feasible for production using accepted standards for devices and drugs (good laboratory and manufacturing practices), a number of parties may decide whether to proceed with initial human feasibility trials. For most devices, no equivalent of Phase I volunteer testing in healthy subjects exists, so most initial trials for feasibility follow Phase I/II in patient populations relevant to the product.

Considerable interaction with the FDA is required during design and performance of feasibility and then pivotal clinical trials. Finally, the path to FDA approval can include a full premarket application (PMA) or a comparison of equivalence to an existing device or therapeutic (510K application). Defining the selected indications for use and patient populations for potential use are critical in order to obtain the widest FDA approval possible.

After FDA approval is received, postapproval market selection proceeds. Percutaneous discectomy devices (numerous after chymopapain approval in the 1980s) suffered rapid fall-offs in clinical use after FDA approval because of difficulty of use or perceived (or real) lack of efficacy in many surgeons’ hands. Thus, many
products are essentially dormant despite FDA approval. It may take several years
for a product to find a market niche, even though the FDA approved it. Further
rigorous clinical studies for postmarket approval may be required to fully define
indications, risks, and efficacy.

1.3.5 GUIDELINES FOR EFFICACIOUS TREATMENT SCHEMES

In many instances, a product becomes a standard aspect of clinical treatment
schemes, for example, immunization vaccines for many childhood diseases. Multiple
studies confirmed high degrees of efficacy and the clinical evidence was consider-
able. Clinical guidelines developed for many medical care situations and diseases
usually incorporate treatments that are generally agreed to be efficacious as parts of
the standard clinical treatment scheme. However, a second type of translation\(^8\)
involves convincing practitioners to routinely provide care based on guidelines. This
requires considerable education of practitioners. However, family practitioners now
face so many guidelines, particularly for long-term health care maintenance, that
the time required merely to follow the guidelines is considerably more than that
required to provide ordinary health care. In a way, postmarket guideline development
is critical for the transference of information from tight clinical trials with rigorous
patient populations to the general patient population at large.

1.4 OUTLINE OF TOPICS OF NEUROSURGERY

This volume is not meant to be all-inclusive. It is intended to provide an overview
of several exciting areas of neurosurgery. We selected fields that lend themselves to
translational work and discuss examples of translational products. For example, little
translational science is now ongoing in the field of skull base surgery, but functional
neurosurgery to treat epilepsy and movement disorders, insert neuroprosthetics, and
perform neural grafting is well represented because of many hypotheses at the
preclinical level. Neurosurgery involves a broad range of subdisciplines, but is
generally divided into a few basic categories or mechanisms of disease:

Brain tumors and meoplasias — Examples of translational research include
new brain tumor therapeutics such as antibodies, radiation, infusions, drugs, Gliadel
wafer, and many promising new approaches (see Chapter 9).

Pediatrics and congenital — Examples include folic acid for prevention of
meningomyelocele, clinical trials underway on fetal surgery, and development of
new CSF shunt techniques (see Chapter 10).

Head injury, peripheral nerve regeneration, and trauma — A significant
amount of work is focused on central and peripheral regeneration, improved intensive
care unit (ICU) therapy, and enhanced recovery after injury (see Chapter 2, Chapter
3 and Chapter 13).

Stereotactic and functional — A number of new devices and treatments for
epilepsy and movement disorders have reached preclinical and clinical development
along with continued improvements in cell implants, such as stem cells. A host of
new neuroprosthetics devices including new stimulators and pumps for medicine delivery are also in development (see Chapter 2 and Chapter 5 through 8).

**Cerebrovascular, stroke, and endovascular** — Challenging topics include treatment of stroke, delayed cerebral vasospasm, new approaches for endovascular treatments such as catheters, balloons, and coils, and improved postoperative care in ICU settings (see Chapter 4 and Chapter 11 through 13).

**Spine and peripheral nerves** — A large number of spine implants have been approved and are now in common use; their usefulness is poorly characterized. Spine surgery needs considerable rationalization as to when it is appropriate, and what exactly should be done under various circumstances (see Chapter 3 and Chapter 14).

Although the subject is not disease based, the history of neurosurgery has also become a very popular topic at neurosurgery meetings over the past 20 years. While the history of neurosurgery is clearly beyond the scope of this volume, interesting failures of the past may provide excellent guidance as to how not to proceed in the future. Other topics are aspects of clinical trials as applied to developing translational approaches (see Chapter 15) and new approaches to the teaching of neurosurgery skills (see Chapter 16).

The focus is the discussion of advances beyond the current clinical domain for two main reasons. The first is that current and conventional treatments are well treated in many aspects of neurosurgery literature — both books and journal articles. The second is that much can be learned about flawed hypotheses, pitfalls of the translational approach in general, and untested hypotheses and clinical advances from past (and now unused) treatments. This volume focuses on promising new concepts still in preclinical development, those already applied to some clinical trial phase, and those that failed during application to patients. It should provide a worthwhile opportunity to review whether the basic mechanisms, animal models, and translational processes were flawed. Clearly, many of these topics fall outside the scope of a traditional, detailed, and comprehensive neurosurgery textbook.

### 1.5 LEVELS OF NERVOUS SYSTEM FUNCTIONING: CELLULAR TO SYSTEMS

Diseases are caused by mechanisms and affect levels ranging from subcellular (genetic, mitochondrial, etc.) to organ. In general, most surgical disciplines primarily consider therapeutics aimed at the organ level (e.g., resecting brain tumors), whereas medical disciplines often test cellular or subcellular approaches involving medicines and drugs. Because knowledge about brain function is accumulating at every level, the approaches at different levels such as subcellular (genetic, molecular, organelle), cellular (electrical integration, channels, and regeneration), local circuits, systems, and organs should be considered. Eventually all translation from preclinical findings to clinical testing depends in one form or another on clinical hypotheses and appropriate clinical trial design for adequate testing of hypotheses and devices where a hypothesis rests at one particular level.

Although pharmaceutical development is usually at the cellular level of functioning, most neurosurgery treatments stem from system or organ level structures
or functions. In many cases translational research in neurosurgery can take advantage of all three levels of brain functioning loosely defined as follows:

1. **Brain function at the cellular level** — The primary cell type and basic functional building block of the nervous system is the neuron. Neurons are assembled together in local circuits. Important additional types include glial cells and Schwann cells. Several disorders are based on disturbed aspects of cellular and local circuit function (epilepsy, movement disorders, demyelinating diseases, and aberrant regeneration). In many situations, treatment schemes for these disorders may include pharmacotherapy directed at single neurons or circuits, gene therapy to alter individual cell functioning, cellular replacement and transplantation, and other forms of restorative treatment.

2. **Brain function at the system level** — Systems within the nervous system include various local circuits and regions working together for a common modality. Examples of modalities include a variety of motor planning, modulation, and execution systems, sensory systems dedicated to particular types of inputs, cognitive and memory systems, and basic systems that control alertness, respiration, and cardiac status. Each system forms a unit of functioning based on a certain modality and assembled for cooperative nervous system functioning. When a system dysfunctions, for example with movement disorders, treatment such as deep brain stimulation may be directed at the systems level to alter the function of the system.

3. **Brain structure and function at the organ level** — Regardless of the function of the nervous system, the brain remains an organ that requires adequate nutrition, blood flow, oxygenation, removal of waste products, and mechanical support from the skull and spinal column. It can also develop mass lesions such as tumors. The treatment of such disorders, although specific to the brain, is similar to other clinical treatments at the organ level, i.e., resecting of mass lesions, enhancement of blood flow, CSF diversion, and mechanical restoration of the spinal column. Many of these treatments are empirical and may require assessment of their clinical efficacy separate from any cellular basis for the treatment scheme.

1.6 CONCLUSIONS

Neurosurgeons have long been eager to develop “designer” surgical procedures to solve specific problems and perform “experimental” surgical procedures. Much medical knowledge has been gained from these (usually) rational approaches. For example, most of our current dermatome maps were derived from single root and multiple root dorsal rhizotomy procedures performed in the 1920s and 1930s to eliminate cancer pain; sensory losses were carefully mapped postoperatively. Likewise, many of the “fad” surgical procedures performed to help Parkinson’s disease patients and most of our clinical knowledge of the function of the basal ganglia derive from a long line of experimental procedures (see Chapter 8). However, many newer advances resulted from the basic neuroscience that blossomed over the past 20 years and are being tested more rationally. This volume covers many of these exciting new advances, with the caveat that trying to peer into the future is not necessarily an exact science, and many of the products and devices mentioned may fail in application or development and some will succeed.

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