Could you tell us about your work and its significance?

Throughout my career I have focused on developing treatments for rare genetic diseases. My primary focus has been using techniques of gene therapy to treat and potentially cure patients with rare diseases.

My work in gene therapy has spanned over three decades, from the inception of the concept of using gene therapy to treat patients. During this time we have had a number of phases in the development of gene therapy, beginning with an early evaluation of gene therapy based on existing technologies at that time, which led to results that were not that encouraging.

This was followed by a period of discovery and basic research to develop better platforms for delivering genes and their evaluation in animal models, and then finally more recently the introduction of these new platform technologies into clinical trials that have really been quite encouraging.

My work has toggled between discovery, animal model studies and clinical trials. And in the paradigm of bedside to bench, learning from the clinical trials to come back to the laboratory to improve the technology, as well as modify or focus our work in animal models to more accurately reflect what we would predict in those patients.
Could you elaborate a little bit on how you used lessons from clinical trials in the lab to improve the models that you use?

The initial development of in vivo gene therapy, that is, directly injecting gene delivery vehicles into patients, utilized common viruses to deliver the genes. Therefore, our initial work took advantage of attenuated viruses based on the family of adenoviruses, which were shown in preclinical models to achieve fairly efficient gene transfer when delivered directly into the animals. In the context of this work we identified some challenges, including the immune responses of the host to the gene delivery vehicle or the genetically modified cells. After extensive work in animal models and attempts to mediate any potential side effects, we moved into the clinic in multiple indications.

During this period we learned that the human response to the vector was qualitatively different between animals and humans in certain ways, specifically as it related to the initial inflammatory response. This then helped us to refocus on a different delivery platform that was based on another family of viruses called adeno-associated viruses, or AAV. We then perfected the application of AAV in animal models and in selected cases moved these into humans, with much more insight and experience to what could be predictive. The area where animal models have fallen short is predicting what the immune response of the host would be to the gene therapy vehicle. In general, we’ve been able to predict these responses when focusing on primate models, but even then there have been some surprises in the clinic.

What do you think are the biggest drawbacks in animal models of human diseases?

The bottom line is that animal models aren’t perfect, but can be used to address specific questions regarding the safety and efficacy of gene therapy. What I’ve learned over the years is that animal models have predicted with a high degree of accuracy the efficiency with which we can transfer genes into humans. In the short term I don’t really see any immediate impact. In the long term, genomic data may create and identify new targets and new strategies. But then they’ll need to be evaluated in more traditional settings for developing novel therapeutics.

What single change do you think would have the greatest impact on our approach to modeling diseases for drug discovery?

I believe that nontraditional animal models, i.e., species other than rodents and nonhuman primates, may turn out to be useful. Some of these other species, in particular larger animals, can be incredibly helpful, such as dogs, cats and pigs. The advent of genome editing to engineer the germ line of these species and a better understanding of their genomes will markedly enhance their utility.
Could you give us a broad overview of the subject of your presentation and its significance?

I will be speaking about understanding where we are with regard to the development, characterization, evaluation and introduction of emerging innovations in medicine; be they innovations in diagnostics, in therapeutics, devices, drugs or biologics.

These issues of development in themselves represent a distinct scientific discipline. And, as a science, they can be taught. They can be quantified. They can be passed along to other people. And they can be used within a quantitative framework to determine objectively how emerging technologies should be considered before market introduction and afterwards. That's the 30,000-foot view.

One can then move in a variety of directions to ask not only if the field is optimized for delivering on promises but the extent to which society should or should not be supporting the efforts of individuals and organizations in this regard. For example, should the National Institutes of Health, the federal government, foundations, charities and other institutions be funding this kind of work? Or should this be industry-supported only?

In terms of research, what do you think about basic animal studies versus translational research and human studies?

Research is not a linear but a cyclical process. There is therefore no distinction between the phases you mentioned. Bench-top, animal and clinical research meld into each other. And they naturally feed off each other. I don't believe, for example, that there is such a thing as preclinical work and clinical work. And, for that matter, there is no such thing as basic and applied work. Each discipline and domain are like individual paints on a palette that can be used to come together in a harmony of color to more fully depict a scene and tell a story.
There is a desire to understand the root of disease and this is best done using every tool available. The more you know the better you can proceed to try to alleviate the ravages of disease.”

When I see patients, and I see the sickest of people in an intensive care unit, I’m always wondering how my science can help me understand better what they’re suffering from. And therefore how best to treat them. So the answer to your question is there is no such thing as only one model. There is the desire to understand the root of disease and this is best done using every tool available. The more you know the better you can proceed to try to alleviate the ravages of disease.

How do you think big data will help us in this direction?

What big data help us do, amongst many things, is to provide greater fidelity and precision with respect to clinical events. Big data means that we can collect, analyze and correlate multiple factors for multiple events in large numbers of people over large spans of time. The promise of big data resides moreover not only in the ability to house data from large numbers of observations, from large numbers of people, but in the incredibly innovative means of displaying and associating these data one with each other and with their governing forces. The power of the resources and potency of the big data tools enable us to find associations and even causal relationships that would otherwise remain buried in the mass of information or infrequency of events. And the harnessing of big data by those steeped in medicine, biology and physiology make the data relevant.

Most clinical trials, especially in a device domain, do not have more than 200 to 400 patients in each arm. If an event occurs on the order of 1 to 2 percent per year and you have 200 patients, then you’re talking about two to four patients. And it becomes impossible sometimes to discern these events. Which means that, when you begin to poll data, you have the potential of increasing your fidelity and precision; increasing your ability to detect the infrequent but important events. Such opportunity is particularly important for events that are not only infrequent but also potent and potentially fatal. But it is important to remember that the data analysis has to be done in a scientifically verifiable, physiologically appropriate and technically valid manner. Once performed in this way, the results can then be tremendously helpful to the development, evaluation, characterization and optimization of diagnostics and therapies. They can also help direct animal models.

Have you been using these techniques in your work?

Yes I use these techniques all of the time. Take the case of clotting of stents for example. Stents are an extraordinary invention and the failure mode of these devices has shifted from inability to be placed to almost complete success at placement, and then from inability to remain patent to almost complete patency. However, patients who get these devices may also suffer from complications like clotting of the device. We now have a situation where 1 percent to maybe 3 percent of patients will clot those devices. And clotted stents are associated with about a 50 percent chance of not making it to the hospital. While the frequency of such events is low, they are highly fatal. And it took data polling, first to understand when stent thrombosis occurs or that it does occur, and also to identify the risk factors. Finally, the information was used through directed animal models, to understand how to potentially create technologies that avoided these issues or develop adjunctive therapies that would lessen their impact.

What single change do you think would have the greatest impact on our approach to modeling diseases for drug discovery?

I think moving away from the desire to predict to the need to understand; moving away from promising risk-free technologies, innovations, therapies, to explaining to people that all technologies have risk, and to explain what the risks are. If we move from a perspective of, “We will make something for you that is absolutely safe and 100 percent efficient,” to one that’s says, “This technology works well, very well, but not in the same way for everyone. For some the benefit clearly outstrips the risk but in others this is not the case and risk dominates.” Our responsibility is to help people understand that there is a threshold that everyone could potentially exceed where benefit is damped by potential harm, and that it is assumption of risk rather than promise of benefit that should come front and center. If we explain the when and why and how the risk-benefit calculus, then people and healthcare providers can make a decision as to whether it is appropriate to assume the risk for the given benefit. I think these changes in mindset and the way we use animal models could go a long way in understanding their value.
Disorders of the central nervous system (CNS) such as Alzheimer’s disease, Parkinson’s disease and Huntington’s disease have become more prevalent as people live longer. So far, few effective therapies have been developed against these devastating conditions.

The traditional “bench to bedside” approach has fallen short in part because animal models widely used in basic research have limited ability to replicate human disease. But by using the right tools and asking the right questions, drug discovery researchers can assemble the information they need to make progress.

Secrets of the Elders

One solution is to start at the bedside and work back to the bench—a process some call “reverse translation.” One of us pursues this strategy by studying the extremely healthy elderly to understand what allows some individuals to avoid disease. A proprietary platform is used to generate recombinant human-derived monoclonal antibodies from these donors to analyze their immune response to the misfolded proteins characteristic of Alzheimer’s and other neurodegenerative diseases of aging.

The presence of plasma antibodies against misfolded proteins indicates active humoral immune responses and the formation of B cell memory. The memory B cells of healthy donors were analyzed and used to generate antibodies to target miscoded or abnormal protein structures that can lead to a variety of diseases. These
antibodies appeared to neutralize toxicity, block cell-to-cell propagation of misfolded proteins and trigger the removal of protein aggregates by microglia or macrophage-mediated phagocytosis. This finding was confirmed in transgenic animal models. These studies provide scientific basis for a technology in recombinant human monoclonal antibody design, resulting in a novel class of effective and safe biopharmaceutical products. Aducanumab is one such human monoclonal antibody, currently in phase III clinical trials for the treatment of Alzheimer’s disease. Other candidates are in phase I for Parkinson’s disease and tauopathies, and in preclinical development for amyotrophic lateral sclerosis.

Improving Animal Models

Animal models have a number of drawbacks as models for preclinical CNS disease drug development, some of them unavoidable. For example, rodents have lower brain function, far smaller bodies and shorter lifespans than humans. But other drawbacks are introduced by researchers and could be avoided. For instance, while CNS strikes a heterogeneous population of humans at different ages living in a wide variety of environments, rodent models are often derived from a homogeneous population living in very similar, controlled environments.

Researchers can increase the relevance of animal models by using similar tools and tests to evaluate humans and rodents. The same types of imaging techniques used in the clinic, such as positron emission tomography (PET) and magnetic resonance imaging (MRI), can be used in rodents, for example. In addition, advanced animal behavioral techniques used in rodents, such as touch screen operant assays and kinematic motion analysis, have been developed to administer tests comparable to those used in humans.

What to Ask When

Choosing appropriate models and tests is only one part of the equation in successful drug development. It is also essential to ask the right questions at the right time in order to build the layers of knowledge that lead to a successful drug. To aid drug development against CNS and other diseases, a guide has been developed to the discovery process. The guide provides a strategic planning framework for research teams to ask productive questions at each of three key stages: target, dose, and patient. First, it counsels, identify the right biological target for the selected disease and increase understanding of its role. Second, identify the molecule that delivers the right exposure at the target site of action and elicits the desired target modulation without compromising patient safety. In other words, pick the molecule with the right therapeutic window. Finally, select the right patient population and use the right diagnostic tests for the selected disease.

Strategies like taking a systematic approach to identify the right target, dose and patient; learning from healthy humans how to fight off disease; and building sturdier translational bridges between animal models and humans can all improve the success rate in translational medicine. By using such new approaches, we can make advances against diseases that have been resistant to existing therapies.

References

1. Neurimmune’s Reverse Translational Medicine™ platform.
For years, the trend in translational medicine has been to study biology at finer and finer levels to understand disease and develop drugs that effectively treat it.

This reductionist approach, with its laser-like focus on tissues, cells and proteins, has delivered diminishing returns and contributed to the accelerating costs of making drugs. As an alternative, animal models are receiving renewed attention as a way to test and validate theories that come off the bench. While not perfect analogs for humans, animal models offer promise in recreating the systems that underlie many complex diseases such as atherosclerosis, diabetes, fatty liver disease or cancer.

Modeling Atherosclerosis
Animal models such as mice are especially useful in identifying and evaluating targets associated with atherosclerosis. Animal studies, especially those involving genetically modified mice, have already provided extensive insights into atherosclerosis. Examples include the discovery of genes that regulate triglyceride-rich lipoprotein metabolism and a better understanding of the role of those lipoproteins in atherogenesis.

To be sure, there are drawbacks to animal models. For instance, atherosclerosis takes a lifetime to develop in humans, while disease induced in laboratory mice is comparatively nascent. Studies involving animal models are often inconsistent, perhaps due to differences between strains or lack of standardization in measuring lesion size. Ultimately, we cannot always be confident that the effects of drugs on mice can be reproduced in humans.

Nevertheless, animal models are an efficient and often effective way to understand diseases and how to fight them. By using human genomic data to identify targets, cherry-picking drug compounds and using genetically altered mice, we can elucidate the mechanisms of atherosclerosis or diseases of the aorta. The two-way flow of information between mouse and human studies has already furthered our knowledge of atherosclerosis and has helped to validate therapeutic targets.
A recent study shows that aging animal models can also mimic the human metabolic system in studies of conditions such as fatty liver disease and diabetic neuropathy. To understand the role of exercise in these metabolic conditions, two contrasting rat models have been developed—one with high capacity and the other low capacity for physical activity.

Created through two-way artificial selection, these models test the hypothesis that variation in the capacity to convert stored energy into function is the central mechanistic determinant of the divide between disease and health. Studies show that rats with a high capacity for exercise are very resistant to cardiovascular and metabolic disease, while those with a low capacity for exercise are more subject to these diseases and die earlier.

A recent study shows that aging increases DNA breaks and activates DNA-dependent protein kinase (DNA-PK) in skeletal muscle, which suppresses mitochondrial function, energy metabolism and physical fitness and leads to weight gain and chronic diseases. In the rat models, there is 60 percent less DNA-PK activity in the High-Capacity Runners than in the Low-Capacity Runners. This observation suggests that DNA-PK inhibitors may have therapeutic potential in reversing obesity and increasing exercise capacity.

Recapitulating Mutations in Mouse Cancer Models

In the rapidly growing field of targeted cancer therapies, mouse models acquired a decade ago are inadequate to test drugs for effectiveness, resistance or interaction with other cancer drugs. For that reason, it is important to have a patient-derived mouse model that can recapitulate the complexity of tumors seen in today’s clinics.

Because cancer drugs are intended to be used at different stages of disease, it’s important to understand the effect of a drug compound on a tumor in combination with other drugs. If the drug is a third line of treatment for a particular cancer, how will it act after a patient’s first and second lines of treatment? Mouse models that keep pace with drug development efforts can help us answer such questions.

In addition, patient-specific mouse models—or “patient avatars”—are being developed to study how a particular patient would respond to a drug or combination of drugs.

All too often, drug companies bring compounds to the clinic before gaining a deep understanding of their mechanisms of action. These types of mouse models can help us develop that understanding.

Cardiovascular disease and cancer are the top two causes of death in the developed world. By improving the quality of animal models designed to reproduce various aspects of these conditions, reverse translation has the potential to advance our understanding of these disease types and develop more effective therapies to treat them.

Low- and High-endurance Rat Models

Studies show that rats with a high capacity for exercise are very resistant to cardiovascular and metabolic disease, while those with a low capacity for exercise are more subject to these diseases and die earlier.

References