Settle in… this will take some time.

**Before the Curtain Rises:**

**A Prologue**

Drug development is a pain in the neck, with twists and turns at every point in time. But it’s of vital importance to me—and I know the same is true for you. I follow the comments on the community website—from discussions about Project Catalyst (where is the utrophin compound?) to Shire (what’s happening with ACE 031, and what is the big deal with bleeding gums, nosebleeds, or red dots on the skin?) to the AVI webinar and recent calls and presentations (there is protein expression, but no functional improvement at 12 and 24 weeks… meaning more waiting) to GSK/Proensa (anticipation about the Phase III pivotal trial, with recruitment expected to close 4th quarter 2012), and Ataluren (what’s next?) and Catabasis (what’s the timing for a Duchenne study?), and then ReveraGen, Pfizer, and Summit (what’s the timeline for trials?).

Recently, I attended several meetings: the Rare Disease Leaders’ Forum in San Francisco and the World Orphan Drug Congress/ USA. I participated in discussions about drug development; partnerships with families and foundations, relationships with biotech and pharmaceutical companies, working with clinical site teams; the impact of social networking; and finally, access to therapies within healthcare systems. The good news is that Rare Disease is now viewed as important… interesting… the new frontier. Biotech and Pharmaceutical companies are developing and expanding their rare disease portfolios, convinced we will see dramatic increases in the number of approvals for rare diseases. Discussions around the ‘Genzyme model’ (referring to enzyme replacement therapies that while expensive, are available for patients who need them, whether reimbursed or through patient access programs) are tossed around as if it will be easy and sustainable; everyone acknowledges that therapies for rare diseases are likely to be expensive.

The good news is that rare disease is now “center stage.” But that focus demands that we ask difficult questions about the next steps after drug approval. Of course the patients deserve these therapies. They have the potential to improve the quality of life, lengthen lives, save lives. But today, with increased promise or hope of treatments in an ever increasing number of rare diseases, will the model be sustainable? Will it be true for Duchenne? Will all patients have access to these expensive therapies? Will access to a therapy depend upon meeting certain functional criteria based on disease progression?
And what about the use of combination therapies, understanding that many rare conditions (including Duchenne) may be best managed using combinations of expensive therapies? Is that approach sustainable in the US? In other countries?

The Stage is Set

I’m in the Brooks Atkinson Theater on 47th Street in NY, waiting for the curtain and smiling in anticipation for “Peter and the Starcatcher,” a re-telling of one of my children’s favorite stories: Peter Pan, the orphan who never grew up, caring for the Lost Boys, recruiting Wendy to help, and flying with Tinkerbell, sprinkling the world with fairy dust. And who can forget Peter’s plea, calling out to all in the universe to clap their hands to save Tinkerbell’s life? The curtain rises, and I become part of the show, the totality of the story as each actor plays his or her role, synchronized, harmonized, and in perfect step as the story unfolds. It looks easy, natural, effortless, and real. I’m drawn in, carried off with them to Never Never Land as I experience the feeling of being lost with no map and no stars to guide me. I imagine myself on the stage... ever the aspirant, the wannabe... actor, dancer, director. It looks easy.

During the show I’m invited backstage, wishing for a peak at the glamour, the chance to meet the actors who seem to effortlessly get into character, changing from joy to sorrow, from laughter to tears in a single moment. But backstage was far different than expected. It was not at all glamorous, with hundreds of people rushing about, each essential for the show to go on. And while the talent is obvious and even extraordinary, without the team – without the producers, directors, creative staff, without the stage crew – there would be no show.

The Theater of Duchenne

As is typical of so many of us, my thoughts crisscrossed to real-life, always returning to Duchenne. And as I walked from the theater, I saw Duchenne on stage and thought about all of the actors on our stage and how each actor, and each word, each phrase, each movement affects all of the others onstage. I wondered if I were to interview all of the players on our stage, our theater of Duchenne, would I be able to identify the glitch, the malfunction, the problem – to point a finger specifically at the cause for the delays, the barriers, the problems? The reason it takes so damn long to develop treatments… to understand the biology of a given disease… to test the hypothesis, to figure out the pathological cascade of events, to pick a target, to search for a compound… to test and test until there is something that is sufficiently convincing… to advance through the regulatory process… to develop the right clinical study, determine the ‘right’ outcomes that will define some meaningful change in the participants’ lives? Would I be able to pinpoint issues related to achieving statistical relevance, indicated by the p-value… needing to recruit sufficient numbers of subjects (eligible patients) willing to participate and having a primary outcome that is sufficiently sensitive to show change during a trial, all needed to convince regulatory authorities that in fact, this compound or biologic delivers measurable benefit without intolerable risk when tested in the relevant population?

And once you reach the “promised land”—get a result that meets the right p-value, submit the data to regulatory authorities and with luck receive the stamp of approval and have an approved drug in hand and available for the eligible patients – then can you ensure access to every individual with the diagnosis? Can we ensure that healthcare systems (better known as the payers) will cover the cost of the drug, so that this gift of treatment does not financially devastate families with a price so high that it is unattainable? Imagine the heartbreak of patients who are unable to access a therapy that slows down or stops disease progression.

I got home and decided to analyze the theater of Duchenne, looking for answers.

ACT I

Center Stage: The families, the boys (and some girls).

This is us. You’ve lived it. We are confronted with a ‘to do’ list that extends to the moon and back, appropriate for the size of the gene responsible for the word Duchenne, which has recently broken down the door of home and heart. We have to learn how to say the word DUCHENNE out loud without letting on that our heart is breaking in a million pieces. We have to say it to the world we live in, our spouse or partner, our children, our extended family, the school, and our community. We have to search for our own version of optimal care, a team of physicians we feel confident have sufficient expertise and experience to care for our sons. We search the internet and connect with the Duchenne community – an amazing group of individuals that have a role, play a part, have a connection to or an interest in Duchenne. We reach out in search of new actors: academics, biotech and pharmaceutical companies, telling our story with the goal of generating interest or incentivizing research. We spend days, weeks, months, years searching and searching into a world both familiar and unfamiliar. We continually review and update the Arithmetic of Duchenne: my son is x years of age and if this happens and that happens by y age, he will continue to walk, to transfer, to move his arms, to breathe, to live.

Stage Right: The academics. The biologists, physiologists, geneticists, biochemists – the world of PhD ‘-ists’. They are the ideas folks, the people who think in terms of exons, introns, genes, molecules, cells and cell structure, communication pathways, systems biology, what system is affected, when, how and to what degree and how it interacts with other systems. They go up the chain from molecules to systems… back and forth, back and forth. The academics discover genes and protein products, they understand how cells ‘talk’ to each other, and figure out how to interpret the language of cells. At times they know exactly what they are looking for and at other times, backtrack through the systems until they find the gene, the protein, the enzyme the base pairs (Adenine, Thymine, Guanine, Cytosine) in our DNA, the science of our lives. They are the discovery people, developing a hypothesis and step by step try to figure out if they were right, backward and forward, and sometimes by serendipity they find they were wrong but have found something more interesting or more amazing. They look at single cells in culture, single cell organisms such as the amoeba, to zebra fish, to mice, to rats, to monkeys, up and down through the chain of life. They are inspired by curiosity, by people, by a specific interest. They are thinkers, discoverers, dreamers. They operate under grants given by people, foundations, companies, governments. These grants are finite (1 year, 3 years, 5 years), not an open checkbook with an unidentified timeline. The academics develop assays, identify targets for drug discovery, test approved drugs, test biochemical reactions, and test animals. Some experiments work out exactly as predicted. Some hit the wall. Major labs
have post-doctoral fellows who work on projects and design experiments or the primary investigator (PI) takes the lead. Successful labs have multiple projects, some fully funded. Others start and stop depending on available resources, lab priorities, and changes within.

When the Dystrophin gene and protein product were discovered, several young and talented scientists believed this monumental discovery would quickly pave the way to therapies, some suggesting it was likely we would be able to deliver Dystrophin via an adenovirus or by using stem cells within a few years. That was 20+ years ago. Many academics have made predictions over time, anxious to see change. Few of them have been correct because the path of drug development is impossible to predict. In a strange sort of way, it is another side of the Arithmetic of Duchenne. The prediction... if X happens and the experiment works out exactly and the animal data is positive, then Y will happen. X and Y may be dependent on money, on university technology transfer, on toxicity data, on production, on regulatory issues, on clinical study design, on clinical site selection, on Institutional review boards (IRB), on 100 other next steps... all variables and all influence the predicted timeline. Academic scientists are part of the team to develop drugs, but typically not directly involved in the business of drug development. Predictions, while well-meaning, are often inaccurate, because in scientific research as in life, we sometimes don’t know what we don’t know.

Stage Left: Biotech and Pharma (Industry). These folks typically hesitate to make predictions, being so familiar with the process and the hiccups that can change the plans and timeline by months or years. Industry collaborates with academia, sharing ideas and hypotheses. Industry has access to libraries of compounds, with the capability of performing high throughput screens (HTS) in search of specific drug targets. They assign a team of individuals to perform or repeat experiments and to move forward on the path of drug discovery and development.

An idea is born, an assay developed, a high throughput screen run (HTS) on specific targets. Robotics have increased the speed of the HTS, robotic arms delivering microscopic amounts of various compounds to thousands of ‘wells’ containing cells, hoping to identify ‘hits,’ biochemical scaffolds identifying a ‘set’ of compounds that to some degree have an effect on the target assay. Progress!

The next step is to determine if those hits are really hits: if the compound achieves an effect, and to learn if the identified compounds are toxic. Lead optimization is the silent period, where the sifting and sorting is done, where each hit is methodically screened, examined for toxicity and efficacy, and tested over time in the relevant animal model. It’s called lead optimization because the goal is to find a lead compound or compounds that appear to achieve the most significant desired effect, and to begin testing in relevant animal models in order to fully understand exactly what the compound is doing, sorting out the PK, the pharmacokinetic data in the animal model. The experiments in animals are repeated and often in another lab, because results can vary from one lab or one investigator to another. Researchers use terms such as ‘in our hands’ (as in, ‘our lab’) to describe a particular set of experiments with the compound, which are sometimes difficult or impossible to recapitulate in another lab. It happens.

While at the Rare Disease Leaders Forum in San Francisco, one of the pharmaceutical companies suggested that frequently they are unable to reproduce data or arrive at the same conclusion found in an academic lab. Then what? They start again, collaborate with the academics, sort through all of the nitty gritty details and try to figure out what happened and why and then try again, repeating the experiment. This process continues on and on and there is no lab or company willing to report on daily successes or frustrations. I am certain there are times when they finally leave their respective labs in the evening, imagining they have something, only to return to in the morning and find it actually looks different, better or worse. And if they are lucky enough to believe they may have something, that the lead compound has an effect, confirmation of proof of concept without significant toxicity, the compound will need to be formulated for human use and in parallel, tested in several animal models as they prepare the required data package for regulatory agencies. Relevant animal models – rodents and primates – are typically required before testing in people.

In parallel, medicinal chemists begin the work of formulating the compound, to figure out how to add molecules capable of maintaining the integrity of the compound and, at the same time, ensure it is able to be delivered via the desirable route of administration: by injection (subcutaneous, intra muscular, intra peritoneal, IV), by mouth, by inhalation, or by skin patch to ensure that whatever system sees the compound first does not degrade it and excrete it before it gets where it needs to go and is able to achieve the desired effect.

Then compound is tested once again in a series of relevant animal models and often in non-human primates that may more closely represent or mimic what might be anticipated in people, in an effort to generate sufficient data for the investigational new drug (IND) enabling studies, including:

- Pharmacokinetic (PK) – how the compound acts in the body
- Pharmacodynamic data (PD) or ADME (administration, digestion, metabolism, excretion) – how the body reacts to the compound

And finally, designing a clinical protocol for conducting the human study, and preparing for the IND meeting with regulatory authorities (FDA, EMA) where it is hoped the regulators will give the thumbs up, the head nod, the all clear, the sign to go forward, to test in people. Phase I. Often the Phase I safety study consists of healthy volunteers and at other times, Phase I is tested in the relevant patient population.

And then... breathe a sigh of relief, issue a press release, reach out to clinical sites, post notices about the trial on ClinicalTrials.gov, sign contracts, get IRB approval, start recruiting and screening patients who fit certain criteria (called the inclusion and exclusion criteria) and who will agree to certain tests at certain intervals, will be compliant, and will sign the ‘informed consent’ (which means they understand what is required, what is expected, and agree to the obligations and rigor required for conducting clinical studies).

Industry and clinicians wonder if families actually read the informed consent, or simply view it as one more paper to be signed to get to the real stuff, the nuts and bolts of the trial, and access to the compound. They worry about the impact of social networking on clinical studies, very aware of blogs where families talk about the experience and express their view of how things might be done more
efficiently, express their fears about certain tests and discuss results, as well
as make predictions about whether their child is on active drug vs. placebo.
Industry worry that comprising the integrity of the trial through these participant
discussions will result in disaster resulting in years of delay, perhaps requiring
them to start once again at the beginning of the process.

And everyone, all the players, patients, families, clinicians, biotech, pharma…. all
saying the silent prayer to their god: ‘please let this work, let this compound
deliver the intended benefit without harm.’

The Musicians: The foundations. They provide seed money, investment capital, incentives, information, exposure. These are foundations willing to do whatever is necessary to accelerate the process. The people who advocate for equity for those with rare conditions. Those voices that managed to engage Congress to pass the Orphan Drug Act so many years ago, never realizing at the time that this legislation would be adopted around the world. Foundations who investigate opportunities, initiate drug development, start registries, start companies, advise pharma, and help design services. Foundations who carry their mission and vision to governments, to healthcare providers, to the world to ensure rare disease (in our case Duchenne) receives accurate and timely diagnosis, access to optimal care, acceleration of the development of therapies, and access to them in an effort to change the predicted outcome. Foundations – people, patients, primary stakeholders. Those who live with Duchenne or those who love someone who has Duchenne.

The Stage Crew: The clinicians. The clinicians who regularly care for Duchenne, those with expertise, insight, knowledge, and experience. Clinicians who we hope provide a certain basic standard of care, based on the Care Considerations, published after 2 years of deliberation. These guidelines, certainly not aggressive, but driven by consensus and most definitely a move in the right direction, provide a roadmap for clinicians around the world. Clinicians who realize that as the knowledge of specific genetic mutations, physiologic pathways, and genetic modifiers expands, our knowledge and understanding about care and available treatments will continue to improve. And there is no disagreement that care varies considerably within the United States and around the world.

These clinicians work with parents who want and need to do something, because doing nothing feels wrong, harmful, a waste of time. These clinicians are willing to engage in discussions about nutraceuticals, supplements, and alternative therapies that may offer hope (or fulfill the need to do something) with perhaps only a slight possibility for benefit.

These same clinicians will conduct the clinical trials and must fulfill the obligation and rigor required. And their clinical coordinators and clinical teams are trained and re-trained so that whatever tests are conducted to measure efficacy are done in the same way and consistently across sites so the data can be compared.

The clinicians are now on the hot seat to gather the data and to understand the patient population, the clinical variability, the behaviors: to understand the necessary rigor required in clinical trials, to remain objective, blinded, not to notice if one or another child is doing something differently or looks better, not to raise an eyebrow, to smile, to give off any indication. They are the Jack of All Trades: to be sufficiently and professionally close to the families while at the same time, distant, objective, observant, and simultaneously recognize the burden on participating families… listening to stories, concerns, worries, fears, to understanding the parents’ pain and anxiety as they watch their child participate in endless testing, blood draws, and biopsies, knowing full well that this is the only path forward.

ACT II
Curtain Up: The patients and families participating.
Clinical Trials. The words the community has waited for, wished for, hoped for, never perhaps fully understanding what would be required, sitting on the edge of their seats, pain in the pit of their stomach, heart in hand, as they or their child is screened for a trial, perhaps THE trial. The trial that is believed and hoped will change the predicted outcome that accompanied the Duchenne diagnosis yesterday, last week, last year. The words that are on rewind every night, every day, every occasion, every birthday.

If he meets the inclusion criteria, he is one step closer to participation, to the informed consent and study participation. That document, the informed consent includes something like this: ‘I promise not to discuss specific parts of this trial with anyone, I promise not to blog and compare notes with other participants, not to post on social networking sites, not to communicate my thoughts and my opinions about the individuals, the study, the sponsor to anyone, except my family, the study doctor and medical professionals… I promise.’ (Easy to sign off on but difficult to do.) If the participant is a child, there is also an assent for the subject in the trial (a child, someone’s son) indicating his willingness to participate in the study. Often the assent is read out loud, each word spoken deliberately to make sure it is understood, while the parents wait and wonder what might be going through their young son’s mind, concerned that he might be frightened or worried or worse? It feels so incredibly unfair that this young boy, a child really, should have to be exposed to all of this and to put up with all of the tests that will be required. But, in fact, he usually does and does so willingly, trusting that his parents wants the best for him, and that his family collectively agrees that participation in this study IS the best for him.

And it begins.

First, the series of blood tests, procedures, and functional testing to show the ‘before’ picture. The day of… the day where the compound or placebo is finally given, by mouth, by vein, by subcutaneous injection.

The worries: Did he receive active compound? Is he in the Placebo group? Will there be any side effects? Will we be able to tell? Again, The Arithmetic of Duchenne… families can guess but are never certain, wondering and hoping their son will be on active compound, trying to imagine what to look for and when they might see an effect. Families wonder if their son will have access to the investigational compound once the study completes, and if so, for how long? How long might it take until the drug is approved, making the assumption that this investigational drug will provide benefit? Unfortunately for the parents and families participating in the trial, questions related to access programs and timing for approval cannot be answered until the study is well underway or, in terms of approval, the analysis is complete, the NDA filed and accepted and a decision is reached.
And week after week making plans for the next visit and the next, reorganizing the family so that the bases are covered: work, other children, meals, laundry, school, driving or flying to the clinical site, going through the testing, interrupted meals, interrupted sleep, receiving the compound or placebo and heading back home, worrying, watching, waiting, knowing this schedule will repeat and repeat for many weeks, and remembering other circumstances where trials were suspended, halted, terminated…hoping and believing that this study will be different.

And finally, completing the study and asking about the results; when or if access to individual data might be possible, when the New Drug Application (NDA) is expected to be submitted to the FDA or EMA, and what happens in the meantime? Will the subjects have access to the drug following completion of the study? Imagining or hoping that access means something positive, the path toward approval, translating and interpreting industry terms and making them their own, sometimes interpreting information as hope or an investigational compound as a medicine before trials and analysis are complete; others suggesting clinical trials are ‘treatments’ and misinterpreting treatment as Cure. The ‘Arithmetic of Duchenne’, translated, the need is great and the fear palpable.

The Critics: Regulatory Affairs. Bean counters, statisticians, physicians, researchers… a combination of expertise charged with evaluating data early on to determine if a drug or biologic has sufficient proof of concept, efficacy, quality, and safety to begin testing in people. They watch the story unfold on stage, meticulously observe every action and reaction, sorting, sifting, everything resting on the agreed upon metrics, the p-value, the statistical requirement of p= 0.05, which means that there is less than 5% chance that success of a given drug is by chance, happenstance, a fluke. The P-value: the regulatory agencies’ Arithmetic of Duchenne.

When clinical studies are complete and data have been analyzed, regulatory agencies receive the New Drug Application (NDA), the final data set, an encyclopedia of information required in order for regulators to make the final determination about whether a drug will receive approval and patients who fit the criteria as outlined on the label will have access to the drug.

Regulatory agencies are often criticized for many reasons: having little insight into a specific disease, lacking appreciation and understanding of disease burden, not understanding that risk/benefit is different in rare and common conditions, and potentially setting the bar too high in terms of expected benefit in rare progressive/disabling conditions. Regulators hear from patients and families who suggest they are willing to accept more risk, though there is no clear guidance on risk tolerance within a given rare disease community.

What is risk tolerance? Risk of developing another condition because of a drug, risk of exacerbating the current condition, risk of death? How much is the Duchenne community willing to tolerate?

“Risk adverse” is an accurate term for regulators– their ultimate worry, that if someone dies while participating in a trial, they might have prevented it; had they overlooked some piece of data that might have been informative?

Follow Pat’s blog at: http://community.parentprojectmd.org/profile/PatFurlong