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Doing it all - How Families are Reshaping Rare Disease Research

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Abstract

The face of rare disease drug discovery and development is changing right before our eyes. The outliers of the past were the plucky parents who summoned up the courage to try to treat their children against all odds. Think of the rare disease focused movies ‘Lorenzo’s Oil’ and ‘Extraordinary Measures’ but now accelerated to develop treatments even quicker. Parents, patient advocates and their collaborators are now capable of doing it all themselves. We think this will have profound implications for everyone from the incumbent rare disease foundations that have held sway for decades to the multibillion dollar rare disease market, BioPharma companies, VCs and angel investors that inhabit this space. The repercussions of this disruption will no doubt impact healthcare in general and ultimately influence how we develop treatments for major diseases as well. We present several lines of evidence for our viewpoint from our personal experiences interacting with many rare disease families and patient advocates in recent years.

I just did what I thought I had to do’ John Crowley Pompe Disease patient advocate and serial biotech entrepreneur Chairman and CEO Amicus Therapeutics

Exhibit A.

After completing the frequently multi-year diagnostic odyssey, parents of a child with a rare disease now quickly form their own teams of researchers and clinicians from scratch, raise money to fund a portfolio of complementary research strategies, and then increasingly use external companies to independently replicate their findings. Those capabilities have all been learnt from earlier trailblazing families as far as we can tell. This new generation of rare disease parent / patient advocates understands that they must assemble a preclinical data package for novel small molecules or biologics they discover, perhaps partnering with a company that pursues NIH funding to translate to the clinic, or even raising capital from investors to spin out new companies focused on clinical development (1). In parallel, many

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of these foundations are also building their own valuable patient registries and finding more patients for themselves.

Rare disease family foundations today are smaller and nimbler than the bigger rare disease foundations of the past, sometimes forming consortia in which they combine with others to multiply resources and fund larger ticket *in vivo* efficacy studies. This agility provides them with the option of pivoting quickly and making more bets on different scientific approaches while in some cases spreading the risk over many small exploratory studies. In addition, they leverage the resources of nonprofits that are also increasingly reaching out to the rare disease community e.g., Jackson Labs and other CROs have started to target rare disease groups offering their services and expertise. The new rare disease ecosystem involves the rare disease family making relatively small investments to academics or companies to develop animal models (yeast, nematodes, flies, fish, mice) most likely using gene-editing technology. The creation of these “patient avatars” is followed by drug screening campaigns and the potential to identify known or novel molecules that may become a treatment. Families pursuing gene therapy approaches are also taking to crowdfunding sites like GoFundMe and setting ambitious multi-million goals to fund preclinical or clinical proof of concept studies e.g., Project Alive and Saving Eliza.

Exhibit B.

This current generation of rare disease foundations is rebuilding the scientific networks of the past in a way that serves their needs today. Whereas previously the key rare disease opinion leader was the hub drawing in patient families (Figure 1), now we are seeing the families as the hub and the researchers are just one of many spokes that may be supplemented by small biotechs, consultants, CROs, non-profit labs, etc. In fact, rare disease families or patient advocates are actively recruiting researchers from academia and BioPharma companies to their cause, a marked change from their more passive stance historically. The families are now the catalysts that organize the research, culling ideas from the team then funding the work via direct investments or submission of research proposals which they solicit directly.

Exhibit C.

Examples of families going from basic research to the clinic are still rare themselves, but we see more families taking it upon themselves even when it may not result in a treatment for their own child. For example, like so many others, the ultra-rare disease multiple sulfatase deficiency (MSD) has no treatment. MSD is caused by mutations in the gene that encodes the human C(alpha)-formylglycine generating enzyme, sulfatase-modifying factor 1 (SUMF1) (2). This deficiency is present at birth, although symptoms of the disorder don't become noticeable until the first or second year of life. It is a very rare disorder. Two parents – Alan Finglas and Amber Olsen from Ireland and the USA, respectively – came together to pool their resources and tackle treatment development for their children (Figure 1). In the space of a year, they organized a scientific meeting of experts on MSD as well bringing in scientists from outside the field to tackle different aspects. They had an open call for proposals, and are now funding multiple strategies in parallel, from animal and cellular

models for drug screening to gene therapy. In addition, they worked with our companies to develop fly models of the disease and pursue NIH small business grants to develop small molecule modulators. This was all done in just their first year organizing research. In the past this would have taken many times longer to reach this point, if at all. Importantly, they are standing on the shoulders of the ‘giants’ in the rare disease space, namely the parents who came before them and who have helped to mentor them. This family-to-family network enables them to exploit shortcuts and learn from the prior iterations of success and failures.

Exhibit D.

There are now more research options on the table than ever before. Rare disease families are exploring cheaper disease models. Where the mouse was once the go-to or exclusive animal model for their disease of choice, we are now seeing the worm, fly and zebrafish increasingly being deployed for rare disease treatment screening (3). Whereas previously every foundation aspired to run massive HTS screens with hundreds of thousands of compounds against their target of choice, today the focus is on repurposing an FDA or other approved drug library, or exploring a small focused library to pick a small number of lead compounds. The new dawn is machine learning to accelerate discovery (or rediscovery, as the case may be) of new treatments for the countless rare diseases still awaiting treatments as we have seen already with neglected diseases (4).

For example, consider the rare disease Charcot-Marie Tooth 1A (CMT1A), which is caused by mutations in the gene PMP22 that was first identified in 1992 (5). While there is at least one treatment in the clinic (6) there is no FDA approved drug. Several years ago, the Charcot-Marie Tooth Association (CMTA) funded drug screens at NIH NCATS, which identified several potential compounds of interest as starting points for drug discovery (7,8). More importantly there is a large dataset in PubChem which can be used for machine learning. This can now be used to find additional compounds for testing, as yet we are not aware that this has even been attempted.

The new gold rush is beginning, with the data that’s been accreting over the last 20-30 years now held in publicly assessable databases like PubChem and ChEMBL. This is represented not just by the large high-throughput screening data but also the accumulation of small-scale experiments from many individual labs that can be combined and then used to build computational models for thousands of targets. It is not just rare diseases but also some of the neglected diseases and more common diseases as well that can benefit. As an example, NIAID ChemDB has over 270,000 compounds tested against HIV, TB as well as rare pathogens associated with HIV. PubChem has over 300,000 compounds tested against TB alone. There is likely as much data on malaria in public databases that has yet to be used in this way. ChEMBL has data on many targets for monogenic rare diseases. It is nearly at the point where you could pick your favorite rare disease, find a dataset for your target and then use a computational model to predict new compounds you might want to test. While it is not yet a turnkey solution, it is feasible without too much trouble using open source software (9).

Exhibit E.

New business models are revealing themselves. We could invert the current process in this data-rich world. Let's start with the rare disease focus on the target gene or disease modifier gene, depending on the biology. Find the dataset that would enable one to build a model that would then be used to filter drugs and available compounds to hone in on a promising chemotype. Find the rare disease foundation or family that might benefit from said molecule. Partner that small-molecule asset to develop a treatment, and then license it to an established BioPharma company. Now imagine if we are using computational approaches, we could mine all the data on every rare disease and have a database of rare diseases and potential treatments ready to offer to respective foundations or companies in that particular space. The key tools for the new gold rush are data, machine learning and faster and cheaper animal models. Together, they form a near perfect engine for drug discovery, where the cost is shrunk for multiple iterative cycles and thus this may help to industrialize the process of orphan drug development (10).

Exhibit F.

Who else is going to do it? There is no Edison or Jobs of rare disease research; there is no one person driving the innovations we need. Instead today's rare diseases families are a powerful force and are in the process of dislodging the larger legacy foundations from their perches. Unfortunately, many of those large foundations are retreating into family support and pulling back from what they perceive are risky investments in basic and translational research. Researchers sense there may be a more direct route to funding their labs than big foundations and NIH funding, and hence their increased accessibility to families. This push and pull as the incumbents exit the fray of drug discovery has brought new investment at a time when the long-term sustainability of government-supported biomedical research is in question. Certainly, the large foundations have historically funded basic research that has led academics to get grants from the NIH and move the science along, but these incumbent foundations are generally just as risk averse as some areas of the NIH when it comes to funding true breakthrough discoveries. The small foundations are translating the basic research and are currently seeding the new discoveries on their own.

Looking to the future

The Cystic Fibrosis Foundation is the benchmark for how a large rare disease foundation previously could help bring a treatment to market and see a return on investment. But the past does not predict the future. They may represent the last of a dying breed. So, let's make a few predictions. The ALS Association (ALSA) raised a small fortune from the Ice Bucket Challenge but did they invest the money in a way that they could get a treatment for ALS? A sequel to the Ice Bucket Challenge called the Hot Pepper Challenge is currently raging on social media and being spearheaded by ALS-TDI, which is focused exclusively on research. The cure for ALS will not be funded entirely by them, in our opinion. Similarly, the cures for many rare diseases will likely not come exclusively from crowdfunds to the legacy rare disease foundations because in many cases they just have not evolved as fast as the smaller rare disease foundations, which are stealing away with the youngest, freshest, likely most

original scientific ideas. Could this put pressure on established scientists so that they get the message that the goal is translation and not more open-ended blue sky research?

If rare disease families can help to foster and develop treatments on their own, where does this leave VCs and traditional funders of biotech startups? Certainly, they have to shift direction and consider the new generation of rare disease foundations as the raw materials to form NewCos, as they will have already de-risked the science. Angel investors should perhaps also think creatively about how they can assist the families to develop treatments given their patience and long-term investment approach. Last but not least, the rare disease pharmaceutical and biotech companies need to face up to the reality that the families of the very patients they should be developing treatments for are actually besting them at their own game. These families have found a way to do research cost effectively, faster and without the overhead of a massive corporate structure. BioPharma has two choices: wait for the treatments to be fully de-risked and in-license them, or try to beat them at their own game. As we know, these multibillion dollar companies do not turn on a dime and it is unlikely they could do what the families are doing. There might be a third way forward. Perhaps they could partner with the families. In exchange for some first right of refusal, they could help to fund the research or proffer their internal expertise or resources. Do nothing and they risk new upstart companies or non-traditional investors seizing the opportunity and building valuable portfolios from underneath their nose – and taking their potentially valuable patient registries with them.

If today's families are able to fund and bring treatments to the clinic without institutional capital, then tomorrow's families will likely come up with additional approaches to shave more time off the process and do it more cost effectively. They are already evolving the process of drug discovery, something big companies have tried unsuccessfully to do for decades and that has ultimately saddled society with increased healthcare costs. It seems ironic that families of patients helping their children with rare diseases might have found a way to ultimately lower healthcare costs for everyone, fund academic researchers and create new companies. Now that is innovation anyone would be proud of.

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Disease expert research network

Patient centered research network

Figure 1.

Traditional 'rare disease expert' (blue) research network driven predominantly by a single group / institute with a clinical collaborator (green) and rare disease patient foundations (black) at arms-length. Patient centered research network made up of more diverse collaborating clinical, molecular biology, animal model, small biotech partners, non-profit research institutes, CRO, chemistry, biologic development groups, drug delivery, patient advocates and others. Willow and Dylan, Multiple Sulfatase Deficiency patients (photos provided with parental permission).