Entering A Renaissance for Drug Development
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Healthcare hasn't felt like an innovative industry for quite some time. Patients and doctors, company management and scientists, and investors in the space have felt more frustration than excitement over the last decade. The drug development conversation has largely been dominated by headwinds like patent expirations, decreasing R&D productivity, and rising costs. While there certainly have been bright spots, like the coming of age of antibodies, successful drugs for orphan diseases, and a near unlimited freedom to increase price, the challenges have roughly outweighed the successes. Even today, much of the conversation still surrounds these challenges, not to mention the entitlement reform gorilla, which has added even more doom and gloom. In the midst of all this, there is a quiet renaissance taking place in the labs across the country. The most important fundamental driver for the future of the industry is quietly taking shape - a research productivity boom.

Research productivity is just beginning to gain momentum in a way we haven't seen since the birth of drug development. Last year the FDA approved 39 novel drugs, the highest in 16 years. Skeptics might attribute the banner year as a benefit of the FDA's current policy making, or simply statistical noise. To try to gain better insight into potential longterm fundamental trends we examined the approvals for molecularly targeted drugs, which are defined by a clear link between a drugs effect and a patient's genetics. Their approvals can be used as a rough proxy for the industry's ability to generate drugs stemming from a deeper understanding of the underlying biology behind disease. During the first eight years of the last decade, about two percent of drugs approved were molecularly targeted (five out of a total of 205). This jumped to 10% of approvals (seven out of 69 to be specific) over the last two years. We believe the statistics will continue to improve.

The primary driver of increased productivity is the plummeting cost of genetic information. Many of us remember the Human Genome Project and the race between the U.S government and Celera Corporation to sequence the first human genome. It cost Celera $300 million and the government $3 billion to complete a first draft in 2001. Today, the cost of sequencing a human genome is roughly $3,000, and it will likely fall below $500 within the next couple of years. Running genetic studies to identify high value targets is becoming cheaper and more efficient at a blistering pace. Together with continuously maturing lab tools and multiple ways to drug a target, we may actually see the cost of drug development decline for the first time since the industry was born.

Time is money in drug development. For those seven molecularly targeted drugs approved in 2011 and 2012, the average amount of time it took to get from the clinic to approval was six years, with a median of five years. The current industry average is longer than six years. We anticipate the time spread between molecularly targeted drugs and the broader industry will widen, as the development of targeted therapies should have significant advantages. When drug developers are able to redefine a disease by its underlying genetic causes a targeted therapy can be designed, and only the genetically targeted patient population who might benefit can be singled out to be studied. As a result, observed drug effects are larger and more obvious, allowing smaller studies and translating into higher success rates. The end result is faster drug development and substantial cost savings.

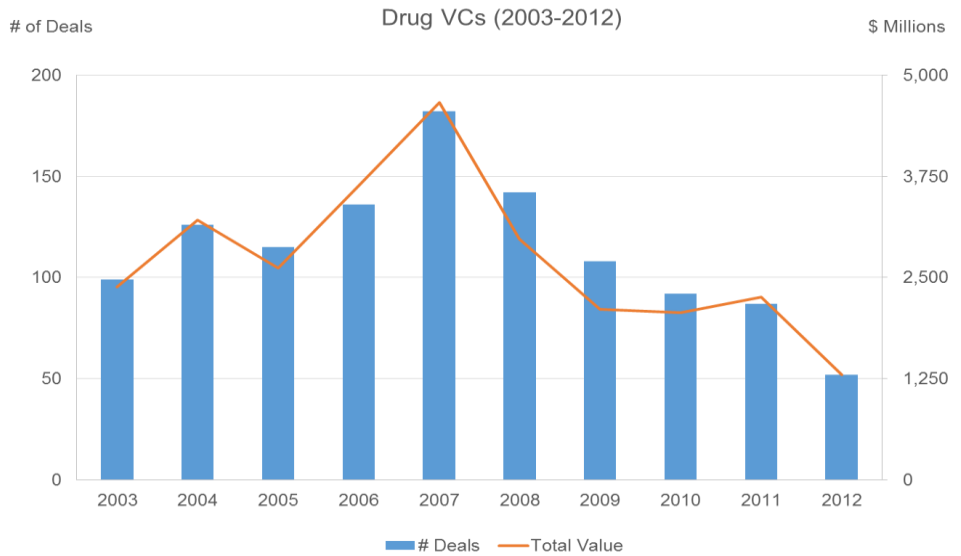
Looking at real life examples, let's take Vertex Pharmaceutical's Kalydeco, a drug approved by the FDA last year. Kalydeco was studied in a small subset of cystic fibrosis patients who have a specific mutation

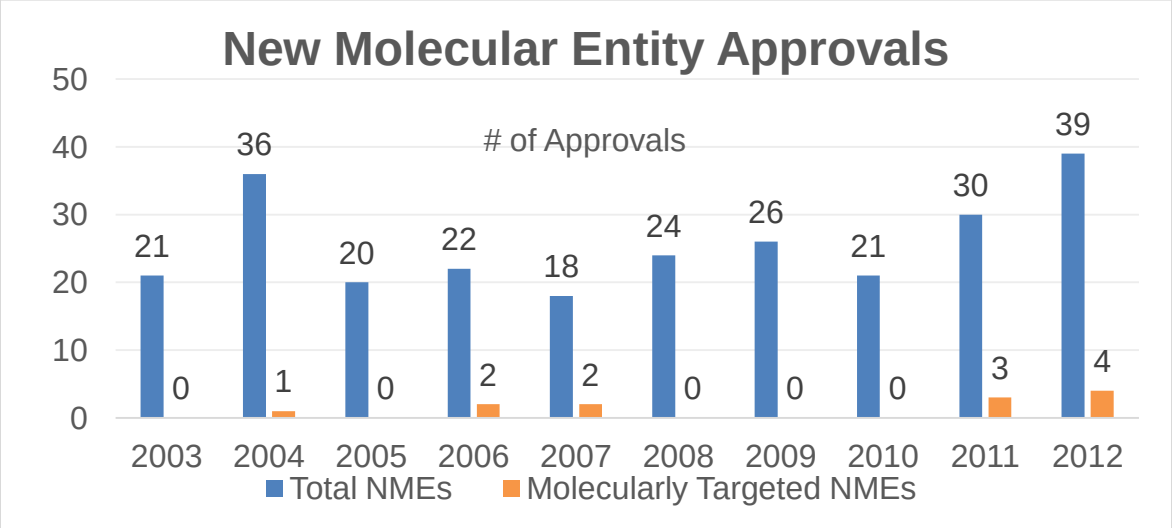
in the CF gene called the G551D mutation. Cystic fibrosis is caused by defective chloride channels in patients, which regulates fluid flow. Roughly five percent of these patients have the G551D mutation, where the chloride channel does not open properly. Kalydeco specifically potentiates the action of these defective channels, and was approved based on striking results from a pivotal trial of only 39 G551D patients.

Bristol-Myers Squibb successfully developed the drug Zelboraf for a subset of metastatic melanoma patients. Metastatic melanoma has historically been one of the toughest cancers to treat, and was a graveyard of drug development until very recently. Roughly one-half of metastatic melanoma patients have tumors with a specific genetic mutation called V600E, which activates an enzyme called B-Raf that in turn causes uncontrolled cell proliferation. Zelboraf was designed to inhibit the B-Raf enzyme. Bristol conducted a single 675 patient pivotal trial in B-Raf V600E mutated metastatic melanoma patients, and saw a result that has eluded drug developers for decades – an impressive doubling of survival.

There will be an increasing number of drugs like these two in the years to come. Drugs that target a clear genetically validated target will move quickly and more cheaply through to market. Most importantly many of these drugs will have a larger impact on diseases than our generation has grown accustomed to. The next generation will have the good fortune of having access to a great many more drugs that are cures. This kind of progress will undoubtably change the tone of the cost benefit discussion in the future.

It would be a mistake to extrapolate the experience of the last decade and underestimate the tremendous promise for scientific progress that is on the horizon. However, an unfortunate consequence of the poor historical return on investment from drug companies has been a decline in venture capital funding and IPOs. Perhaps like most things in life, it is darkest before the dawn. I do not think it is a stretch to suggest that 20 years from now we may look back and say one of the largest value creating forces of the next two decades is the boom in drug development enabled by cheap genetic information. In the near term, until this potential becomes more widely accepted, many entrepreneurs and scientists will need some creative solutions to move their promising new projects forward.





* Molecularly targeted NME ≡ a novel targeted therapy to a biologically important process where the target is measurable in the clinic, and measurement of the target correlates with clinical outcome when drug is administered.