Biotech Industry in La La Land

By Yi Liu, PhD (yi@bc-la.org)
Yi is a project scientist at UCLA, biotech blogger at bioequity.org and associate at BCLA.

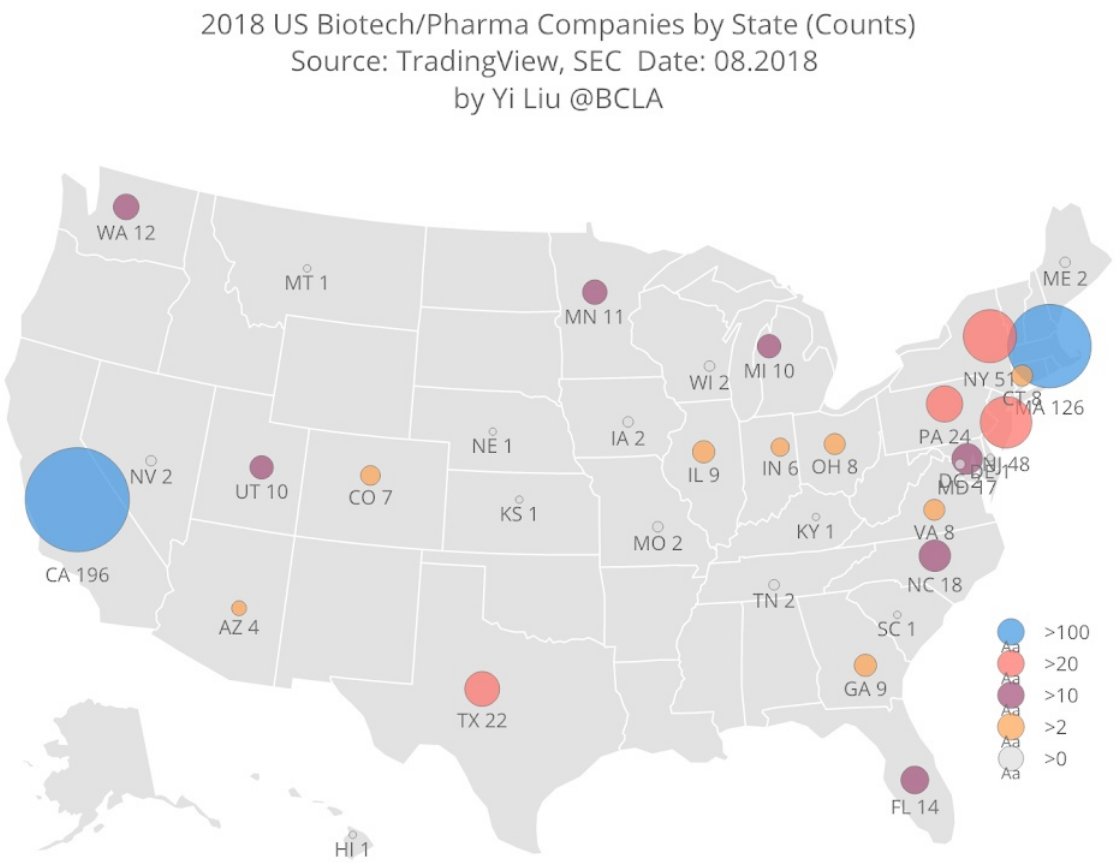
How strong is the biotech industry in Los Angeles?

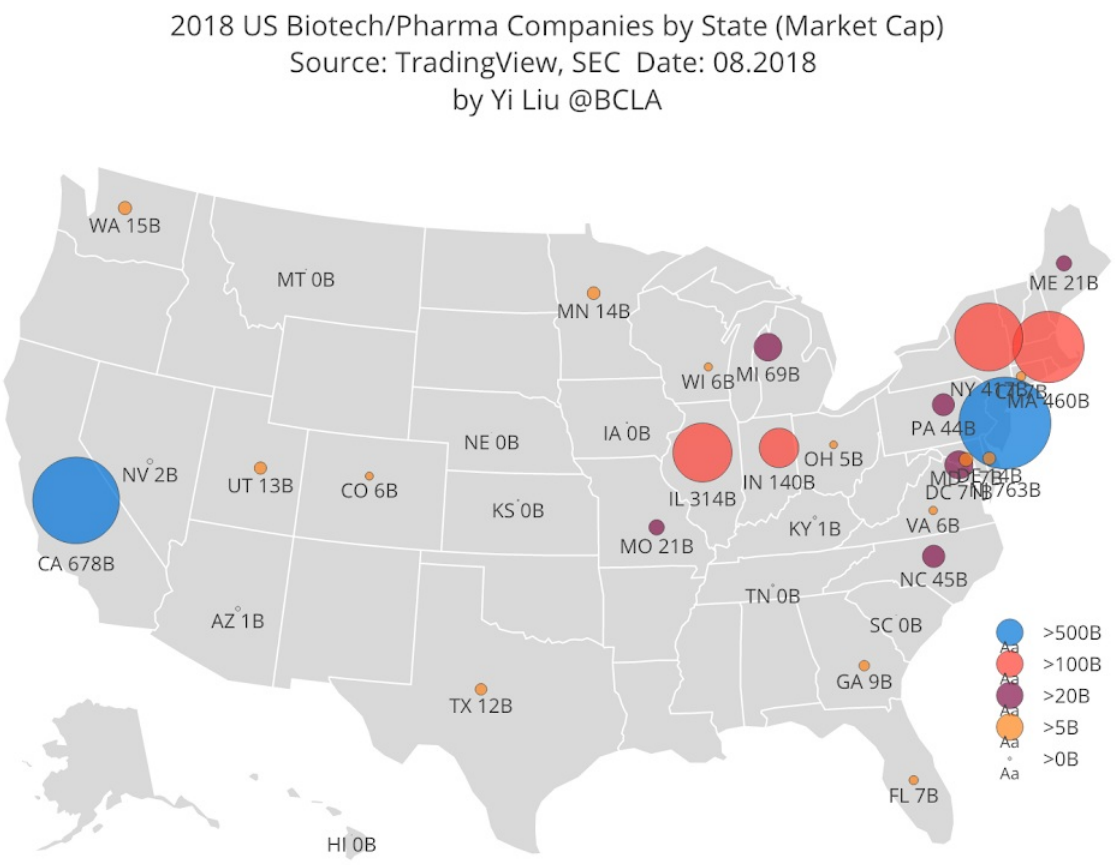
Admit it, when we talk about biotech, the City of Stars is overshadowed by major hubs such as Boston and San Francisco, or even our neighbor San Diego. Different methods have ranked LA as 9th (GEN 2016), 6th (BioSpace Life Sci Jobs ranking 2015) or 15th (FierceBiotech VC funding 2014) in the USA.

Here, I used a different angle to answer the same question. I took a snapshot of current independent public biotech companies and located each headquarter city and state.

I only looked for independent public biotech companies. Private companies, or wholly owned subsidiary companies such as Kite Pharma (Gilead, $12B buyout) are not included here. Though they represent a significant part of the biotech industry, it is hard to find accurate information about them.

Here are two graphs representing the geographical distribution of Biotech/Pharma companies in the United States, by company counts and market cap, respectively.





The method is detailed below.

Method

Using TradingView's screener, I looked for US based healthcare companies in these four industries:

- Biotechnology & Medical Research
- Pharmaceuticals
- Advanced Medical Equipment & Technology
- Medical Equipment, Supplies & Distribution

This yielded 643 companies. Then I looked for their headquarter addresses using the U.S. Securities and Exchange Commission (SEC) 's company search tool. 195 of company headquarters are located in California, 87 in Southern California, and 13 in Los Angeles County.

Ranking

If Los Angeles county was a state, with 13 companies and $8B market cap, it would have ranked 10th by count, after Florida and before Washington State; 20th by market cap, after Georgia and before Connecticut.

If we include Orange, Santa Barbara, Ventura, Riverside, San Bernardino counties, the Greater LA metro area has 33 companies and a $188B market cap. This would rank 5th by count and 6th by market cap among all states.

If Southern California were a state, with 87 companies and a $317B market cap, it would rank 3rd by count and 5th by market cap.

The rankings above are always lower by market cap than by count. It is because Los Angeles and other California companies are newer and smaller by comparison to the larger and more established Big Pharma in NJ, NY or IL.

Enough ranking, you get the idea.

Now let's focus on the 13 Los Angeles county-based public biotech companies individually. I will write about biotech companies in other Southern California counties later here at BCLA blog (think Amgen, Illumina).

Click the ticker to go to that company

Ticker	Name	Market Cap (M)	Employees No.	Product & Service	City	Zipcode
XNCR	Xencor	2,321	114	BiTE, Ab Fc Engeneering	Monrovia	91016
STAA	STAAR Surgical	1,918	353	Implantable lenses	Monrovia	91016
PBYI	Puma Bio	1,645	318	in-licensed TKI for Breast Cancer	Los Angeles	90024
ARWR	Arrowhead	1,740	93	RNAi	Pasadena	91101
SNNA	Sienna Bio	325	54	Small molecule PEG and Photothermolysis	Westlake Village	91362
NH	NantHealth	257	494	Genomics, precision medicine	Culver City	90232
MNKD	Mannkind	168	250	Inhalable insulin	Westlake Village	91362
FLGT	Fulgent Genetics	78	98	NGS genetic testing	Temple City	91780
OPNT	Opiant	62	n/a	opioid overdose	Santa Monica	90401
CYTR	CytRx	37	20	doxorubicin LADR	Los Angeles	90049
CAPR	Capricor	34	29	Cardiac cell therapy and exosome	Beverly Hills	90211
RTTR	Ritter	11	5	Microbiome for lactose intolerance	Los Angeles	90067
IMUC	ImmunoCellular	10	4	Stem-to-T-cell	Westlake Village	91362

- Market cap data as of 8.23.2018

Xencor

The largest company by market cap and the only mid-cap (>$2B) company in the list, Xencor is currently the leader (by market cap) of independent biotech in LA.

Stephen L. Mayo, PhD, Caltech professor, protein design expert, the only African American faculty member in 1995 CalTech and the first tenured African American faculty member at CalTech, co-founded Xencor with his student Bassil I. Dahiyat, PhD, in 1997.

Xencor's XmAb technology enables the rapid creation of more powerful, more effective antibodies by simply changing a few amino acids in the Fc domain to the amino acids identified by our structure-based design. So far, Xencore can engineer 4 types of Fc domains: bispecific, immune inhibitor, cytotoxic, and Xtend.

Since initial public offering (IPO) in 2013, Xencor has grown steadily. Its XmAb Fc antibody engineering core strength has attracted a series of major Big Pharma/biotech collaborations, including:

Partner	Upfront	Upto	Year	Indication
Novartis	150M	2.5B	2016	Oncology
Amgen	45M	1.7B	2015	Immu-Onco, Inflammation
Morphosys	13M	N/A	2010	CLL/NHL
Boehringer Ingelheim	N/A	N/A	2007, 2012	Oncology
CSL	N/A	N/A	2009, 2013	Leukemia
Alexion	N/A	N/A	N/A	N/A

With capital supplied by these partnerships, Xencor has developed its own pipeline, currently including one Phase II, five Phase I and two pre-clinical drug candidates. The successful combination of partnerships and fully-owned candidates makes Xencor an example of a **Genus 1 Product (Therapeutic Modality) Platform Company** according to Steven Holtzman's *Early-Stage Biotech Value Creation*

The following four are small cap companies (between $300M and $2B)

STAAR Surgical

STAAR Surgical is an example of the rich medical device community in Los Angeles and Orange County. The company developed, patented, and licensed the first foldable intraocular lens, or IOL, for cataract surgery. Made of pliable material, the foldable IOL permitted surgeons for the first time to replace a cataract patient's natural lens with minimally invasive surgery.

FundingUniverse has a thorough recap of STAAR Surgical Company History from its origins in 1980s, and its struggles and recovery in 1990s, through 2003.

STAAR received FDA approval for IOLs in 1991, and implantable collamer lens (ICLs) in 2005. However, profits did not immediately follow and share price fell under $1 during the financial crisis in 2009. Its share

price has been under $20 for decades since 1990.

This year, the Vision ICL product sales took off. Share price broke the $20 mark and 36 years of innovation is now finally beginning to pay off.

Puma Biotechnology

Puma was founded by Alan H. Auerbach, who previously served as founder, chief executive officer and president of Cougar Biotechnology, Inc., which was acquired by Johnson & Johnson in 2009 when he was 39.

Founding another company named after a Big Cat, Auerbach at Puma in-licensed its single asset - neratinib, a pan-HER inhibitor for breast cancer from Pfizer in 2011. He impressed the oncology field again in 2014 with Phase III results and re-negotiated a deal with Pfizer for lower royalties.

With that news, PBYI stock price reached an all-time high of $279.37 in August 2014. It then started a three-year decline, as it struggled through the regulatory process with the FDA. Wikipedia has a brief summary of related events. It was finally approved for a narrow indication in August 2017.

Neratinib brought in $50M revenue in Q2 2018. Puma needs to realize its commercial potential and expand into broader indications, before we see an upwards trajectory of its stock price again.

Arrowhead Pharmaceuticals

Arrowhead Research went public, in Jan 2004, via a reverse merger transaction. Its business plan at the time was to finance CalTech research in the “nano-technology” field.

In 2005, it co-founded a subsidiary company Calando Pharmaceuticals, Inc. to develop nano-engineered RNAi therapeutics. In the context of RNAi history, the leading company Alnylam was founded in 2002, and the Nobel Prize in Physiology or Medicine 2006 was awarded jointly to Andrew Z. Fire and Craig C. Mello “for their discovery of RNA interference - gene silencing by double-stranded RNA”.

For a long time, Arrowhead reported to the SEC as a holding company of various subsidiaries. In December 2010, Calando moved to the top of the reports. In October 2011, Arrowhead acquired Roche’s RNAi business, including its RNA therapeutic assets, related intellectual property and research facility in Madison, Wisconsin. That year, the company’s SEC 10K report started to focus on RNAi. In April 2016, the company finally changed its name to Arrowhead Pharmaceuticals to reflect its focus on RNAi.

After a sizable deal with Amgen in September 2016, Arrowhead went into a period of depressed share price to the end of 2016. It then discontinued all ongoing clinical programs to start from scratch, due to a long term toxicity issue with the previous generation of technology.

Now that almost two years have passed, Arrowhead has returned with promising clinical data of its newer technology. In October 2018, it signed a deal valued at up to $3.7B ($175M upfront) to license its HBV drug to Johnson & Johnson (J&J) and collaborate on three other programs.

Following market optimism after Alnylam won first RNAi FDA approval, Arrowhead is on an uptrend in both its business and share price.

Sienna Biopharmaceuticals

Sienna Bio is a relatively new company. Todd Harris, an MIT PhD, founded Sienna Labs in July 2010 and developed its Silver Plasmonic Therapy (SPT). This technology has promising applications for treating acne and permanent hair removal. After two rounds of VC financing (2016, 2017) and acquisition of Creabilis in 2016, Sienna Bio went public in July 2017. The acquisition of Creabilis brought in another technology platform, known as:

Topical by Design. This process uses polymer (PEGylation) to convert approved small molecule oral drugs for topical use. Currently, Sienna has a TrkA inhibitor and a Jak3/TrkA dual inhibitor in the pipeline.

Read more about the technologies here. It is anticipated that critical clinical data will be available around year-end 2018.

The next four are micro cap companies (between $50M and $300M)

NantHealth

Founded by the "richest doctor" on earth - Patrick Soon-Shiong - in 2007, NantHealth aimed to provide fiber-optic, cloud-based data infrastructure to share healthcare information. Over the years, its focus has evolved to "leverage the latest advancements in precision medicine and software technology to enable true value-based care". NantHealth provides a portfolio of solutions including cancer insights, healthcare information flow, and payer platforms.

The company IPOed in 2016, and lost 90% of its value since, likely due to stalled revenue and increasing operating loss.

You can read more about NantHealth, Soon-Shiong, and his other companies at Wikipedia.

Mannkind

Mannkind was founded by and named after Dr. Alfred E. Mann (1925 – 2016), an American physicist, inventor, serial entrepreneur, and philanthropist. Mannkind came to its present form after a merger of three of Mann's companies: Pharmaceutical Discovery Corporation (PDC), a cancer vaccine developer CTL ImmunoTherapies, Inc., and an allergy vaccine company Allecure Corp. From PDC, MannKind acquired the Technosphere molecule and Medtone Inhaler, based on which Mannkind developed its lead product, Afrezza (inhalable insulin).

The development of Afrezza is one of the most dramatic cases in biotech history. After two complete response letters (CRLs) in 2010 and 2011, Afrezza finally earned FDA approval in June 2014. As an inhalable insulin, Afrezza generated heated enthusiasm among the media and investment community, with sensational headlines including "revolutionary" and "mega-blockbuster" spreading among social networks in the US and abroad. The market cap of Mannkind reached more than $4B at its peak.

Despite FDA approval and an initial deal with Sanofi, Afrezza failed commercially as previously predicted by concerned experts. Few doctors are prescribing this drug device and few patients want to use it. It failed in a similar fashion to Pfizer's inhalable insulin product - Exubera, despite that Afrezza uses a much smaller and more convenient inhaler. After little more than a year, Sanofi terminated the commercialization

deal. Shortly after, Dr. Mann passed away.

Mannkind has struggled since FDA approval, losing 96% its share price. With reverse stock-split and rounds of secondary offering bringing in new funds, Mannkind is not giving up. It is developing a next generation inhalation technology, a miniature, breath-powered inhaler used in combination with single-use cartridges containing pre-metered doses.

Read more about the story of Afrezza: Inhalable Insulin — A Breathtaking Development

Fulgent Genetics

Fulgent was founded by the billionaire Chinese-born American entrepreneur and philanthropist Ming Hsieh in 2011. It was shortly after he sold Cogent Systems (the best automated fingerprint identification systems, including scanner and software algorithms used by the government) to 3M.

Moving from real fingerprints to genetic "fingerprints", Hsieh's new company inherited from Cogent the ability to efficiently acquire, process and analyze complex data. It is now in the diagnostics genetic testing business using next-gen sequencing (NGS) and proprietary algorithms and databases for *accessible pricing, high accuracy, and competitive turnaround times.*

Still a young and small company, it hasn't brought in much revenue yet, about $5M per quarter. Genetic testing is a crowded and competitive business. There are established diagnostic businesses, including Lab Corp, Quest, and GeneDx, as well as many startups. Can Ming Hsieh do it again and emerge as the leader?

Opiant

Opiant CEO Roger Crystal was the keynote speaker at 2018 BCLA Healthcare Symposium: Opioid Epidemic and Alternative Pain Treatments. The company, formerly known as Lightlake Therapeutics, was founded in 2009 by the late Dr. David Sinclair and based upon his pioneering research demonstrating that opioid antagonists could be used as a symptom-driven treatment for alcoholism, a.k.a. The Sinclair Method.

Opiant now has one FDA approved (in 2015, 2017) product, a nasal naloxone spray called NARCAN for opioid overdose in addition to three pipeline candidates in the clinical stage for substance abuse and alcoholism.

It began listing on NASDAQ in August 2017 and has limited revenue.

The last four are nano cap companies (<$50M)

CytRx

CytRx was an early generation biotech company: founded in 1985, IPO in 1986 (for reference, Amgen IPOed in 1983). It has struggled for decades with three stock reverse splits.

Over the last 10 years, CytRx has focused on aldoxorubicin - doxorubicin conjugated to an acid-sensitive linker. It gained this asset in a 2008 acquisition of Innovive. This modification is supposed to improve native doxorubicin including reduction of cardiac adverse events, improvement in efficacy and the ability to reach the tumor more quickly.

However, after a clinical hold demanded by the FDA disrupted the trial, it lost follow-up in 2/3 of the patients who initially enrolled. Limited results announced in July 2016 showed no significant improvement in *progression-free survival* (PFS) over doxorubicin. Unable to move this forward financially, CytRx licensed the drug to NantCell, one of Soon-Shiong's companies. The hope is that the Objective Response Rate nearly doubled in the Aldoxorubicin arm.

CytRx is also developing its Linker Activated Drug Release (LADR) technology for other anti-cancer payloads.

Capricor Therapeutics

Capricor was founded by Linda Marban, PhD in 2005. She brought the company public in December 2013 with a reverse merger.

Capricor originally worked on an "off-the-shelf" cardiac cell therapy based on Marban's experience on cardiac progenitor cells. They signed a deal in January 2014 with J&J. However, after a trial failure, J&J walked away and returned the rights back to Capricor.

Capricor has repurposed the failed therapy for Duchenne Muscular Dystrophy (DMD). It also has preclinical research based on exosome science.

Ritter Pharmaceuticals

At the age of 9, Andrew Ritter was diagnosed as lactose intolerant - a non-life-threatening, but annoying ailment. His father, businessman Ira Ritter has since started gathering human, financial, and R&D resources to end this problem for his son and others throughout the world. The LA Times has an interesting piece covering the story:

From Teenage Science Project to NASDAQ

Ritter is leveraging microbiome therapy to approach lactose intolerance. The lead candidate, RP-G28, a novel non-digestible oligosaccharide, is designed to "modulate the gut microbiome and stimulate growth of lactose-metabolizing colonic bacteria".

Like many pioneering microbiome companies, such as Seres ($MCRB) and Novan, Ritter suffered from disappointing clinical trial results. When their Phase IIb trial had insignificant results, Ritter determined that the primary endpoint can be optimized. It is now pushing forward with a Phase III trial to pave the way to FDA approval.

ImmunoCellular Therapeutics

ImmunoCellular was established in 2006 with cellular-based technology licensed from the Cedars-Sinai Medical Center in Los Angeles. In 2012, ImmunoCellular was listed on the NYSE.

Originally focused on developing a list of dendritic cell-based therapies for solid tumor, ImmunoCellular suffered substantially from trial failures and financial strain. It is not surprising if you know the story of

Dendreon. ImmunoCellular has shifted its focus to recently developed hematopoietic stem cell (HSC)-derived engineered T cell platform – " Stem-to-T-cell".

The Unsung Song in La La Land

Under the blazing lights of the entertainment industry, it may seem that biotech will never be the theme song in La La Land. Yet many of us know, in the dawning golden era of biotechnology, Los Angeles should not fall behind.

We already have 13 public biotech companies and the momentum of biotech in LA is growing. The sparks have been there. We can expect more companies to emerge from the numerous incubators that have become prominent in recent years. They provide a key component to the much needed startup infrastructure to continue to grow biotech in LA.

Soon, biotech will hit some high notes in La La Land. And we, at BCLA, will help you drive it there. □

---

* I thank BCLA team members Johnny, Stefanie, Adhi and Xiaoya for their inputs.