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R&D Sustainability of Biotech Start-ups in Financial Risk

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Abstract This paper's objective is to draw a decision guideline to continue research and development (R&D) investments in biotech start-ups facing the "Valley of Death" syndrome - a long negative profit period during a financial crisis. The data include financial indices as Net income, Revenues, Total stockholders' equity, Cash & equivalents, and R&D expenses of 18 major biotech companies (nine in negative profit and nine positive, in FY2008) and 15 major pharmaceutical corporations as benchmarks both in FY2008 and in FY2016 derived from the US SEC Database, EDGAR. A first methodology dealing with real options analysis assumes Total stockholders' equity as a growth option. And a second methodology, Bayesian Markov chain Monte Carlo (MCMC) analysis, is applied to test the probability relationship between the Total stockholders' equity and the R&D expenses in these three groups. This study confirms that Total stockholders' equity can play the role of a call option to support continuing R&D investments even in negative profits.

Keywords Biotech start-ups, valley-of-death, R&D sustainability, Bayesian MCMC, financial crisis

I. Introduction

While stock prices of large pharmaceutical corporations (large pharma) have been recovering to the level prior to the 2008 Financial Crisis related to Lehman Brothers' bankruptcy, the stock prices of many pioneering biotech start-ups (and established companies) have shown much stronger resilience with respect to the shock and they have maintained growth thereafter. For example, the NASDAQ Biotechnology Index has maintained a more steady growth compared with the Dow Jones U.S. Pharmaceuticals Index, after the Lehman Brothers collapse. Basically, when commercializing the findings of basic research by universities, the biotech start-ups get superior results in many respects including speed, lower cost, and a more flexible management structure than large-market-oriented pharmaceutical corporations. However, it is extremely difficult for biotech start-ups constrained with resources to overcome the so called "Valley of Death" as

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an initial negative profit period within the whole drug development period from compounds at basic research to government approval for a drug on the market. For example, it takes an average of 12 years, a cost of around 3 million US dollars - 2 billion dollars and a rare success probability of one thirty thousandth during this period (Teconomy Partners LLC, 2018).

Research questions regarding the biotech start-ups facing the Valley-of-Death include, first of all, why can many biotech start-ups continue their R&D investment while in a regular deficit and even in a financial crisis? In particular, if biotech start-ups in deficit were further increasing R&D expenses regardless of the deficit spreading, what kind of mechanism would enable such entrepreneurship to be implemented? Second, why is it possible to increase the growth rate of R&D investment for biotech-start-ups with more resource constraints as compared with large pharmaceutical companies with abundant resources? And thirdly, why can such a more constrained group have a higher rate of increase in shareholder value?

As a main concept, a biotech start-up is defined as a portfolio of real options, regarding the investment opportunity of commercialization of a life science idea with the underlying asset.

With data from the EDGAR database of the United States Securities and Exchange Commission (SEC), this paper selected 18 growing biotech companies, excluding BioMarin Pharmaceutical and Alnylam Pharmaceuticals, which are outliers in view of their extremely outperforming R&D investment in FY 2016, out of 20 biotech companies with larger corporate value as of September 2017. Also selected for the study were the 15 larger pharma, excluding AbbVie, which spun off from Abott Laboratories in 2013, out of a group of pharmaceutical companies with high corporate value. The research uses the following indices: the Net income, Total shareholders' equity value, Cash equivalent assets, and R&D expenditures in FY 2008, close to the Lehman Brothers collapse, and FY 2016 as the present time (USA SEC, 2017).

As a methodology, we apply Real Options Analysis to evaluate the potential of a biotech start-up company as a growth option and Bayesian Markov chain Monte Carlo (MCMC) method to explore the signaling function under an asymmetric information situation (Kruschke, 2014).

The objective is to try each verification, firstly, where the shareholders' value has a function of growth option when biotech start-ups overcome the Valley-of-Death; secondly where the emerging biotech start-ups are investing in flexible R&D to promising possibilities among high birth and high death rates of companies at start-up ecosystem; and thirdly, where the growing biotech start-ups specialize in high added value niche markets.

II. Review of Literature

Some previous studies look at the Valley-of-Death as an initial negative profits period for biotech start-ups from both academic and practical perspectives, Pisano (2006), and practical inside information perspectives, Binder et al. (2008), Hughes (2011), and Werth (2014). They are just identifying problems for biotech start-up to survive in deficit for a long time, however without proposing any specific solutions.

The majority of studies looking at solutions about this problem are examining social institution approaches. For example, the first group of studies is focusing on locational ecosystems as, for example, the paradox between proximity and globalization for innovation, Audretsch (1998); necessity of stable relation between universities and industry for combining resources from different clusters, Waluszewski (2004); and the flexibility and specialization in UK Cambridge regional success, Garnsey et al. (2006).

The second group of studies is dealing with government policy as Advanced Technology Program (ATP) for SME, Auerswald et al. (2003); public sector support necessity to bridging the Valley of Death, Moran (2007); and Federal government's expanding capacity for U.S. national innovation system, Block (2008).

The third group of studies emphasizes the partnership between university and industry as the established anchor firms being expected to create externalities for biotech start-up by using the upper stream knowledge, Feldman (2003); a triple helix of university-industry-government relations for assisted linear model from research to commercial potential, Etzkowitz (2006); the continuity of regenerative medicine study through a crisis condition, Brindley et al. (2009); the organizational problem for commercialization of findings from basic research, Finkbeiner (2010); the accelerator and social capital, Audretsch at al. (2011); and the collective entrepreneurship between university-based start-ups and corporate spin-offs, Auerswald (2003).

However, these approaches are still qualitative, and more quantitative analysis on investment is necessary, especially for proving the validity to continue R&D investment even in a long-term deficit period. Then, there are real options analysis studies about the valuation of biotech start-ups at the Valley-of-Death not only just as a practical concept and figure explanation, Perlitz et al. (1999), Amram et al. (2000); practical revision of anti-failure bias, McGrath (1999); and proposing conceptual and binomial model, Jägle (1999); but also modeling a growth option for strategic investment, Ottoo (1998); proposing a customized model for strategic analysis based on the case of Merck, Bowman et al. (2001); evaluating project portfolios, Vassolo et al. (2004); and offering more comprehensive and fundamentally sophisticated approaches, Bogdan et al. (2010).

Real options analysis is one of the financial engineering tools, but it still needs a signaling function at the early stage of biotech start-ups as asymmetric condition for an investment decision. However, there are very few studies about real options for overcoming the Valley-of-Death to biotech start-ups from Bayesian MCMC analysis, except Castellaneta et al. (2014), Zhong et al. (2018), and Aktekin et al. (2017). Accordingly, this study's objective is to apply Bayesian MCMC analysis to find the signaling function of growth option for continuing R&D investment in a deficit condition.

III. Basic Theory

Based on the Black-Scholes-Merton formula for the valuation of financial options shown as Figure 1 (Black & Scholes, 1973; Merton, 2007), this paper follows the basic idea of S. Myers who firstly used shareholders' equity value as a call option in real options by regarding the assets as the underlying asset and the liability as the exercise price in a balance sheet shown as Figure 2 (Myers, 1977). Additionally, there are fundamental studies about real options analysis (Kester, 1984; Dixit, 1994; Copeland, 2001). European call option is valued by the following equation:

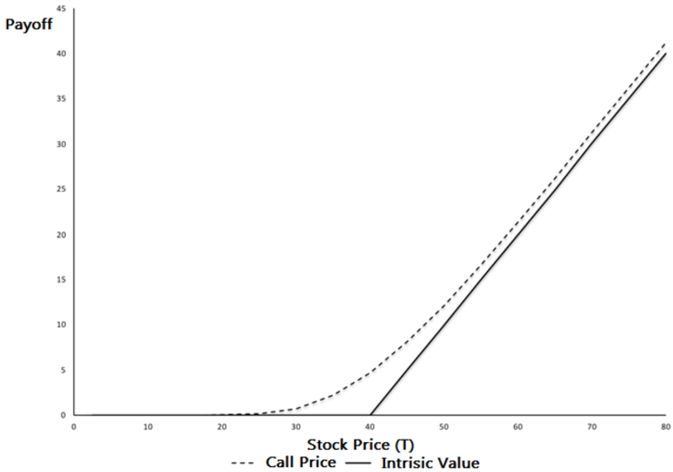
$$C_0 = S_0 N(d_1) - X e^{-r_f T} N(d_2)$$

$$d_1 = \frac{\ln\left(\frac{S_0}{X}\right) + \left(r_f + \frac{\sigma^2}{2}\right) T}{\sigma\sqrt{T}}$$

$$d_2 = d_1 - \sigma\sqrt{T}$$

where S_0= present stock price, $N(\cdot)$= standard normal cumulative distribution function, X= exercise price, r_f = risk-free rare, T= maturity time, and σ= volatility (Merton, 2007).

However, it is expected that in the case of biotech start-ups facing the Valley-of-Death, the shareholders' equity value has a function of a growth option in real options, and especially the cash equivalents, can be regarded as a new growth option in terms of the shareholders' equity as the underlying asset, and the R&D expenses as the strike price due to the instability of the capital market at the time of the financial crisis.



Source: Author

Figure 1 Call option and intrinsic value

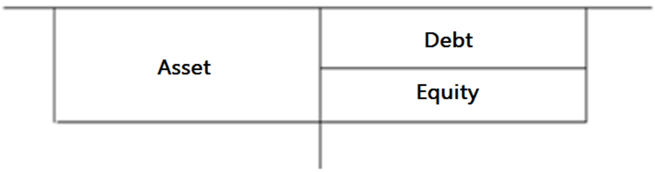


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Figure 2 Balance sheet and equity as call option

IV. Summarized Analysis of Data

This paper classifies the negative profits (Red-Bold) biotech companies and the positive profits (Black-Regular) biotech companies based on the net loss or net income in FY 2008 from the EDGAR database of the US SEC (see Table 1). While these biotech companies' values are sometime comparable with large pharma due to their development success, they have still some common characteristics with biotech start-ups as either listing in the NASDAQ or on the NYSE, or their R&D-oriented investment to mass manufacturing or selling. In addition, the paper selects 15 major pharmaceutical corporations as comparison benchmarks (Table 2).

Here, we try to analyze the dataset including the R&D expenditures as investment and the indicators related to return outcomes in these three groups between FY2008 and FY2016 according to the research questions above.

Table 1 Data of biotech companies

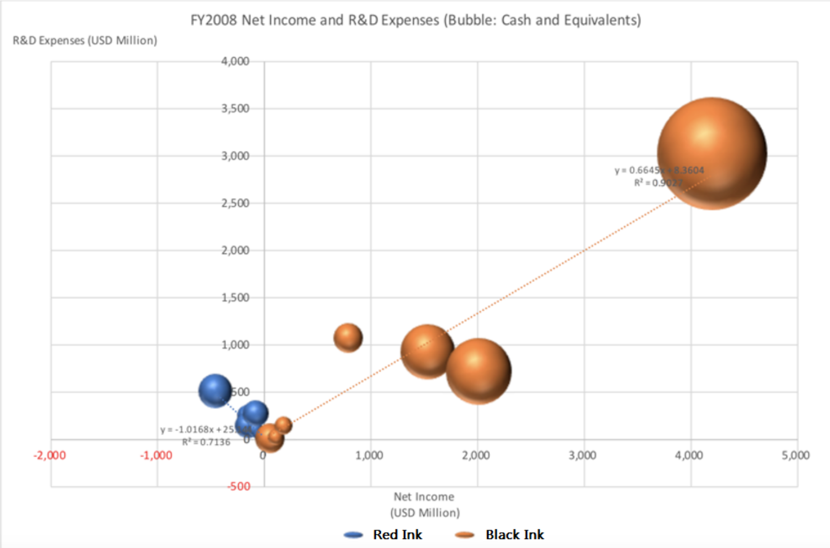
2017.09.06		Market Cap.	FY2008(USD Million)					FY2016(USD Million)				
Company	Ticker	USD Billion	Net Income	Revenues	Stockholders' Equity	Cash & Equivalents	R&D Expenses	Net Income	Revenues	Stockholders' Equity	Cash & Equivalents	R&D Expenses
Vertex Pharmaceuticals	VRTX	40.1	-460	176	239	832	516	-84	1702	1338	1184	1048
Jazz Pharmaceuticals	JAZZ	8.9	-184	68	-93	26	70	397	1,488	1,877	366	162
Exelixis	EXEL	8.3	-163	118	-57	284	257	-70.2	191	89	152	96
Nektar Therapeutics	NKTR	3.4	-155	218	227	467	149	-154	165	88	60	204
Seattle Genetics	SGEN	7.4	-86	35	79	161	111	-140	266	634	109	379
Regeneron Pharmaceuticals	REGN	52.7	-83	238	419	527	278	896	4,860	4,449	535	2,052
ACADIA Pharmaceuticals	ACAD	4.3	-64	2	53	60	57	-271	17	518	164	99
Halozyme Therapeutics	HALO	1.8	-49	9	15	64	44	-103	53	-32	67	151
Sarepta Therapeutics	SRPT	2.7	-27	0	26	25	35	-267	5	337	122	188
Alexion Pharmaceuticals	ALXN	32.3	33	259	247	138	63	399	3,084	8,694	966	757
Repligen	RGEN	1.9	37	19	64	61	7	12	105	169	122	7
Illumina	ILMN	30.3	50	573	849	640	14	63	2,398	2,270	735	504
Bio-Techne	TECH	4.5	104	257	487	167	22	76	563	950	92	54
Incyte	INCY	27.8	179	4	-221	218	146	104	1,106	419	652	582
Biogen	BIIB	66.8	783	4,098	5,806	622	1,072	3,696	11,449	12,129	2,327	1,973
Celgene	CELG	109.0	1,534	2,255	3,491	2,222	931	1,999	11,229	6,599	6,170	4,470
Gilead Sciences	GILD	107.8	2,011	5,336	4,152	3,240	722	13,488	30,390	19,363	8,229	5,098
Amgen	AMGN	129.0	4,196	15,003	20,386	9,552	3,030	7,722	22,991	29,875	3,241	3,840

Table 2 Data of large pharmaceutical companies

2017.09.06		Market Cap.	FY2008(USD Million)					FY2016(USD Million)				
Company	Ticker	USD Billion	Net Income	Revenues	Stockholders' Equity	Cash & Equivalents	R&D Expenses	Net Income	Revenues	Stockholders' Equity	Cash & Equivalents	R&D Expenses
Johnson & Johnson	JNJ	356.1	12,949	63,747	42,511	10,768	7,577	16,540	71,890	70,418	18,972	9,095
Roche	RHHBY	216.7	3,402	16,797	14,191	2,910	3,621	9,576	51,789	23,526	4,096	11,346
Pfizer	PFE	201	8,104	48,296	90,446	2,122	7,945	7,215	52,824	59,840	2,595	7,872
Novartis	NVS	197.5	8,233	41,459	50,437	6,117	5700	6,698	48,518	74,891	7,777	8,402
Merck	MRK	175.3	1,903	18,502	10,529	3,373	3,529	3,941	39,807	40,308	6,515	10,124
Sanofi	SNY	123.8	4,621	33,082	53,839	2,160	5,490	4,967	36,608	60,705	10,835	5,455
Novo Nordisk	NVO	109.4	1,543	7,288	5,277	1,396	1,254	6,068	17,885	7,243	2,990	2,336
Bayer(Euro)	BAYN	107.4	2,063	39,502	19,608	2,444	3,184	5,791	56,123	39,433	2,279	5,599
GlaxoSmithKline	GSK	106	5,983	31,658	10,310	7,310	4,785	1,127	34,461	1,389	6,051	4,483
Bristol-Myers Squibb	BMY	91.8	5,247	20,597	12,241	7,976	3,585	4,457	19,427	16,177	4,237	4,940
Eli Lilly	LLY	90.8	-2,072	20,378	6,835	429	3,841	2,738	21,222	14,081	4,582	5,244
AstraZeneca	AZN	86.3	6,130	31,601	16,060	15,869	5,179	3,406	23,002	16,669	5,018	5,890
Abbott Laboratories	ABT	84.4	4,881	29,528	17,480	4,112	12,612	1,400	20,853	20,717	18,620	1,422
Allergan	AGN	81.6	621	4,447	4,050	1,110	706	14,973	14,570	76,192	1,724	2,575

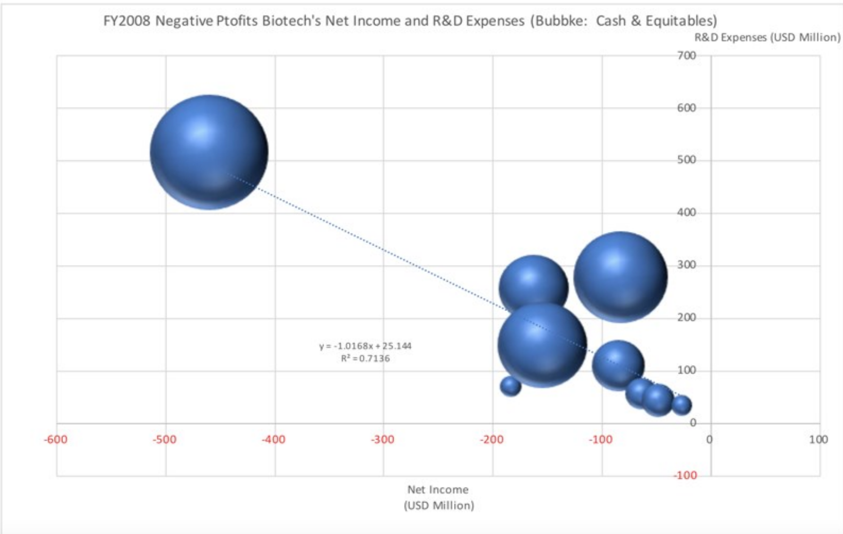
1. Growth Option

Even if some biotech start-ups have net losses, they can continue their R&D investment based on stockholders' equity as technological potential valued in capital market in the data (shown in Table 1). However, in Figure 3, it is natural to observe that positive profits biotech companies could improve their R&D investment with both increases of net income and cash equivalents. On the contrary, the negative profits biotech companies increased their R&D investments with increases of not only cash equivalents, but also net losses even in a financial crisis. In such a severe financial condition, in addition to usual stockholders' equity, cash equivalents can play a greater role as a growth option for immediate challenge or as an R&D investment increase for their survival (Figure 3, Figure 4).



Source: Author

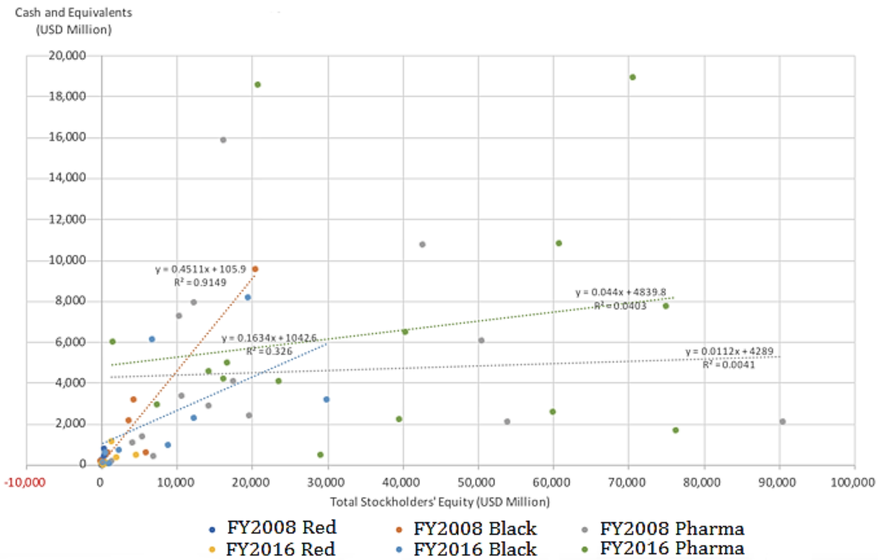
Figure 3 FY2008 net income and R&D expenses



Source: Author

Figure 4 2008 negative profits biotech companies' net income and R&D expenses

As for the output side, regarding the shareholders' equity value as an independent variable and the cash equivalents as a dependent variable, we examine the linear regression analysis of each data of the deficit biotech companies, profitable biotech companies, and large pharma (Figure 5). Then, the slope as cash preference to stockholders' equity is steepest in the FY2008 deficit biotech companies, followed by FY2016 deficit biotech companies, FY2008 profitable biotech companies, FY2016 profitable biotech companies, FY2016 large pharma, and FY2008 large pharma. Thus, the cash preference to stockholders' equity is the strongest at FY2008 deficit biotech companies because of cash necessity subject to financial resource feasibility based on potential valuation. Coefficients of determination are very low for large pharma in both fiscal years, because of relative financial affordability.



Source: Author

Figure 5 Total stockholders' equity and cash & equivalents

2. R&D Productivity

Each slope of linear function as R&D productivity is 0.0271 for deficit biotech companies, 0.0228 for profitable biotech companies, and 0.0194 for large pharma with regard to the market capitalization as a dependent variable and R&D expenses as an independent variable in FY2016 data (Figure 6).

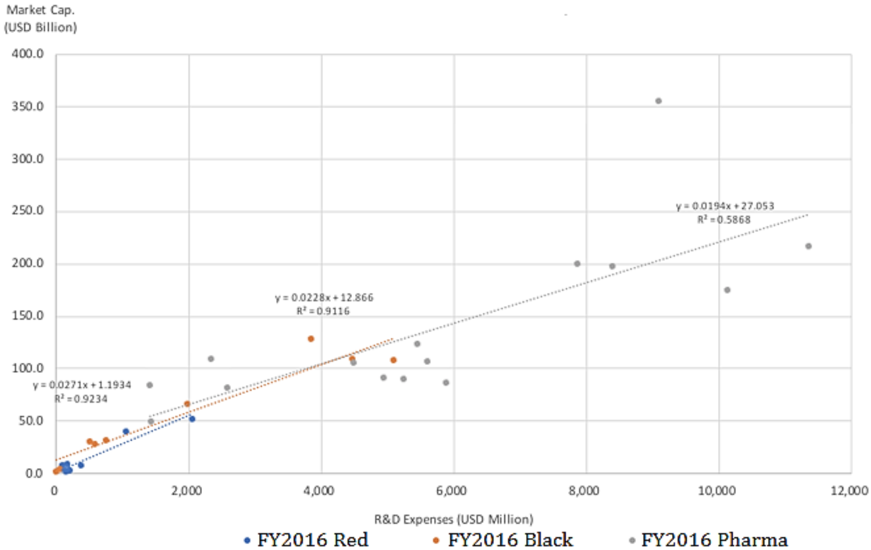


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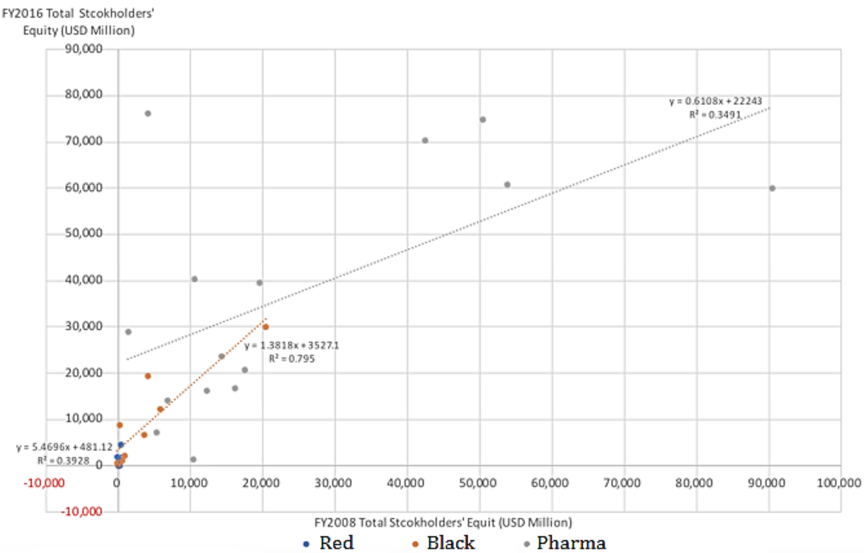
Figure 6 FY2016 R&D expenses and market cap



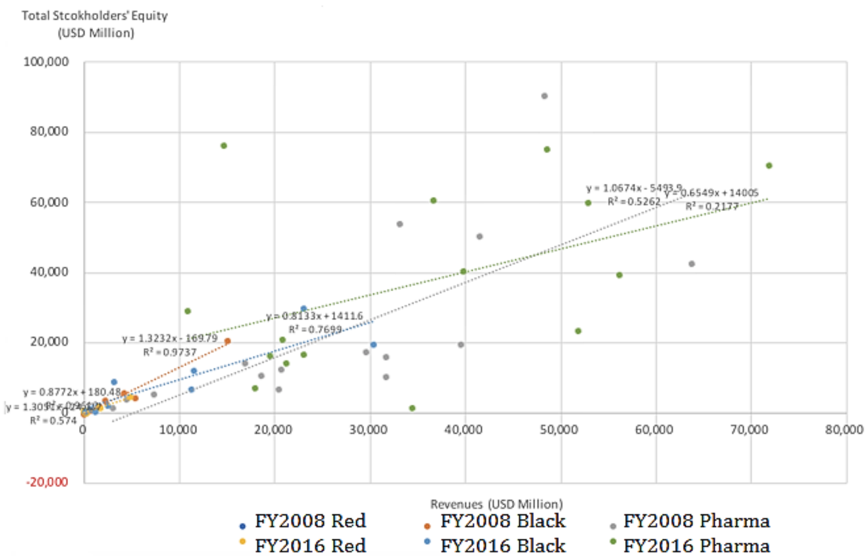
Source: Author

Figure 7 Shift of total stockholders' equity between FY2008 and FY2016

Next, the output improvement as each shift of output stockholders' equity between FY2008 and FY2016 resulted each with slope of 5.4696 for deficit biotech companies, 1.3818 for profitable biotech companies, and 0.6108 for large pharma (Figure 7). Thirdly, at the input side, each shift of R&D expenses is 2.5014 for deficit biotech companies, 1.3182 for profitable biotech companies, and 0.1354 for large pharma between FY2008 and FY2016. Both the slope and the coefficient of determination of large pharma are much lower, because they are more interested in mass manufacturing-and-selling and acquiring patents and biotech start-ups themselves. Thus, R&D productivity is greatest at deficit biotech companies amongst the three groups.

3. Signal of Success

Regarding the stockholders' equity as dependent variable and the sales as independent variable, for FY2008 each slope is 1.3232 for profitable biotech companies, 1.3051 for deficit biotech companies, and 1.0674 for large pharma (Figure 8).



Source: Author

Figure 8 Revenues and total stockholders' equity

Between FY2008 and FY2016, each group's slope is always declining. Even deficit biotech companies can acquire some revenue by contracted R&D to large pharma. Then, this kind of information can play the role of signaling as a promising technology from these biotech companies, even if their drugs are not yet on the market. However, this analysis result shows both the slope and range of profitable biotech companies are a little bit higher than that of deficit biotech companies, because the signal information of deficit biotech companies is insufficient in this data.

V. Bayesian MCMC Analysis on “Valley-of-Death”

Software packages MacOS10.12.6, R3.4, and Rstan2.16.2 were used based on CPU 4 GHz Intel Core i7. Here we examine the analyzed results of re-parameterization method of hierarchical Bayesian MCMC to get the R-hat values less than 1.1 as simulation convergence criterion. Linear regression model with stockholders’ equity as dependent random variable and R&D expenses as independent random variable is represented as the following:

$$Y_n \sim Normal\ (a[Group\ [n]] + b[GroupR\ [n]X[n]], \sigma_Y) \qquad n = 1, \cdots, N \qquad (1)$$

$$a[k] = a_{Total\ Average} + a_{Group\ Residual}\ [k] \qquad k = 1, \cdots, K \qquad (2)$$

$$a_{Group\ Residual}\ [k] \sim Normal\ \ (0, \sigma_a) \qquad k = 1, \cdots, K \qquad (3)$$

$$b[k] = b_{Total\ Average} + b_{Grou\ Residual}\ [k] \qquad k = 1, \cdots, K \qquad (4)$$

$$b_{Group\ Residual}\ [k] \sim Normal\ \ (0, \sigma_b) \qquad k = 1, \cdots, K \qquad (5)$$

where Y= random variable (r.v.) of stockholders’ equity, X= r.v. of R&D expenses, a= r.v. of intercept, b= r.v. of slope, n= each real data of total sample population, N= total real data of total sample population, k= each real data of each group sample, K= total real data of each group sample, Group=1 (Negative profits biotech companies), Group=2 (Positive profits biotech companies), Group=3 (Large pharma), Group=0 (Whole groups), and σ=standard deviation.

1. FY2016 R&D Investments and Growth Option

At first, we start the simple regression analysis of present R&D productivity of each group by regarding the R&D expenses as investment and the stockholders’ equity as growth option. As to intercept, we got [6.14 (USD million): expected value, 1457.20: standard deviation {-2908.35(2.5%): 3007.11(97.5%)}] for deficit biotech companies, [1062.01, 2088.57{-2705.94: 5817.28}] for profitable biotech companies, and [3125.90, 6401.41{-6614.80: 19902.74}] for large pharma (Table 3). Thus, the intercept shows a sort of threshold or entrance barrier for drug discovery or drug development. Especially, the expected value of profitable biotech companies is almost one third that of large pharma. But the expected value of deficit biotech companies is one hundred seventieth for that of profitable biotech companies. Then, it seems there is a huge gap in the cash amount at the initial condition between deficit biotech and profitable biotech companies (Figure 9, Figure 10).

Next, the slope value as R&D productivity shows as [2.45, 2.09{-1.85: 6.46}] for deficit biotech companies, [3.69, 1.43{1.16: 7.18}] for profitable biotech companies, and [3.11, 1.44{0.61: 7.13}] for large pharma (Table 3). The R&D productivity of profitable biotech companies is steepest 3.69 at the expected values. The comparison of the slope distribution of profitable biotech companies with large pharma shows their focus on more added value drug development rather than just large market size drugs displayed with the expected value and both tails (Figure 11, Figure 12). The expected value of deficit biotech companies is lowest at 2.45 amongst the groups. However, comparing the difference of the expected values with the other groups, the distribution of this group is most dispersed in the groups. It means they are challenging drug discovery by trial and error type R&D to find any promising drug candidates.

Thus, there is a technology transfer path from university's basic research to large pharma through deficit biotech companies and profitable biotech companies by a dynamic portfolio management method for phased screening in probability of success.

Table 3 FY2016 print (fit)

	mean	se_mean	sd	2.5%	25%	50%	75%	97.5%	n_eff	Rhat
a0	1582.18	285.44	7455.11	-14327.73	-1003.09	734.83	3321.33	20622.28	682	1.01
b0	3.07	0.10	2.88	-3.16	1.98	3.08	4.08	9.29	816	1.00
a_raw[1]	-0.23	0.01	0.76	-1.76	-0.71	-0.22	0.27	1.27	5639	1.00
a_raw[2]	0.02	0.01	0.77	-1.46	-0.50	0.01	0.50	1.59	5703	1.00
a_raw[3]	0.17	0.01	0.86	-1.58	-0.39	0.18	0.72	1.87	8277	1.00
b_raw[1]	-0.20	0.02	0.84	-1.87	-0.73	-0.20	0.31	1.58	1368	1.00
b_raw[2]	0.25	0.02	0.79	-1.34	-0.24	0.23	0.75	1.88	1888	1.00
b_raw[3]	0.00	0.01	0.78	-1.60	-0.50	0.01	0.51	1.51	2844	1.00
s_a	9455.45	572.15	14186.66	134.10	1553.52	4214.73	10897.12	53729.25	615	1.00
s_b	3.71	0.16	5.26	0.08	0.79	1.94	4.38	19.10	1034	1.01
s_Y	4515.95	22.91	1714.82	2060.73	3259.45	4222.90	5450.86	8622.71	5603	1.00
a[1]	6.14	10.56	1457.20	-2908.37	-832.54	-5.76	824.42	3007.11	19029	1.00
a[2]	1062.01	16.70	2088.57	-2705.94	-211.99	857.93	2143.04	5817.28	15640	1.00
a[3]	3125.90	90.73	6401.41	-6614.80	-546.48	1497.01	5538.63	19902.74	4978	1.00
b[1]	2.45	0.02	2.09	-1.85	1.44	2.54	3.54	6.46	9737	1.00
b[2]	3.69	0.01	1.43	1.16	2.85	3.57	4.35	7.18	9667	1.00
b[3]	3.11	0.02	1.44	0.61	2.27	3.03	3.76	7.13	3536	1.00
lp__	-310.33	0.06	3.23	-317.26	-312.34	-310.14	-308.15-	304.45	2807	1.00

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Samples were drawn using NUTS(diag_e) at Sun Sep 17 23:58:21 2017.
For each parameter, n_eff is a crude measure of effective sample size,
and Rhat is the potential scale reduction factor on split chains (at
convergence, Rhat=1).
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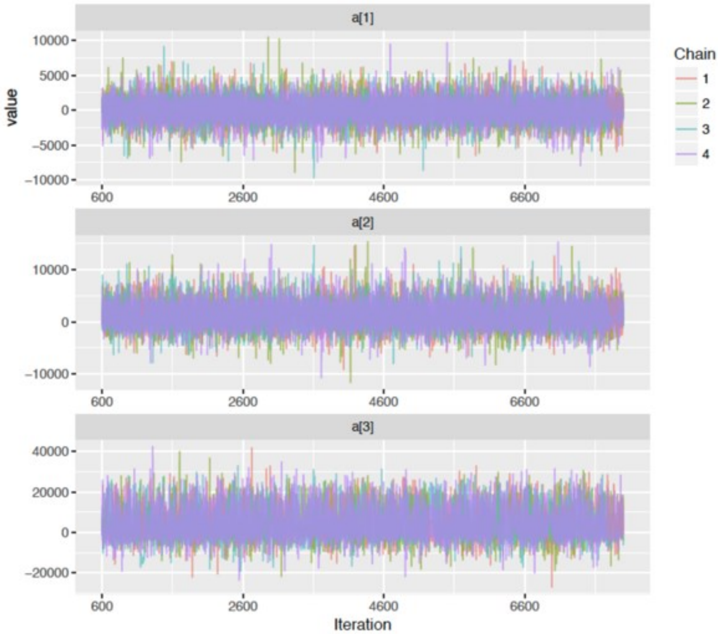
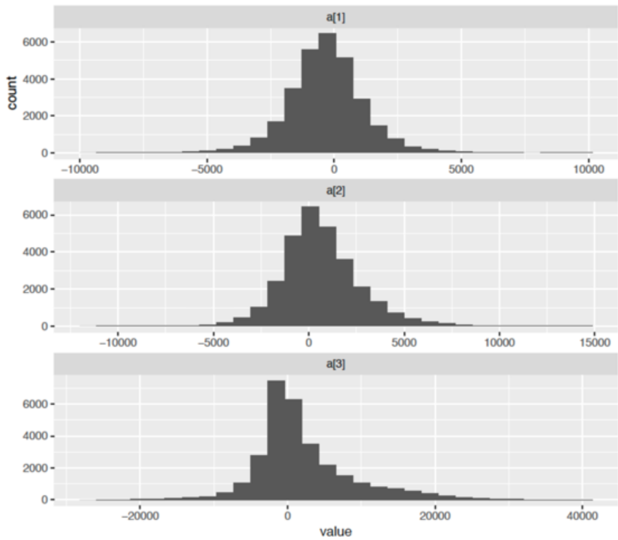


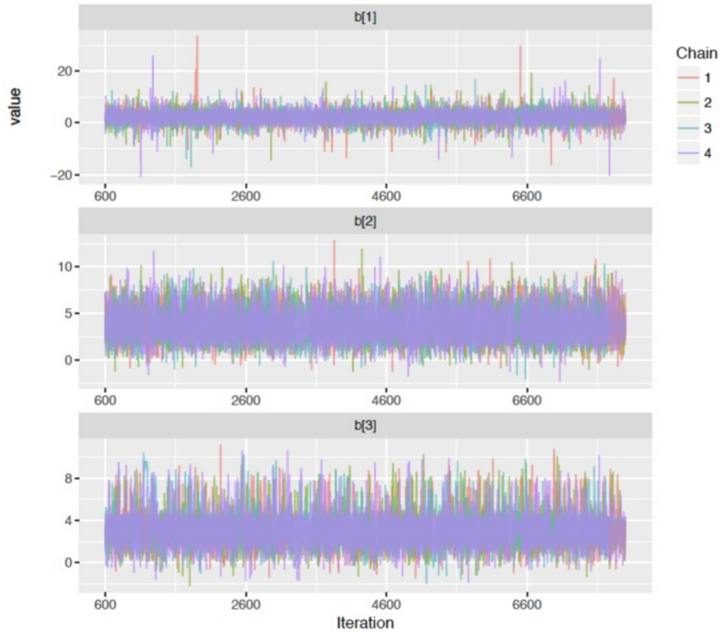
Source: Author

Figure 9 FY2016 trace-plot of intercept



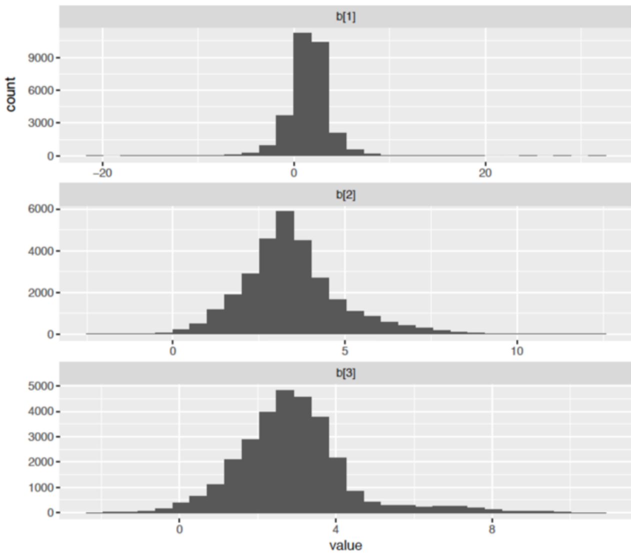
Source: Author

Figure 10 FY2016 fit-summary of intercept



Source: Author

Figure 11 FY2016 trace-plot of slope



Source: Author

Figure 12 FY2016 fit-summary of slope

2. FY2008 R&D Investments and Growth Option

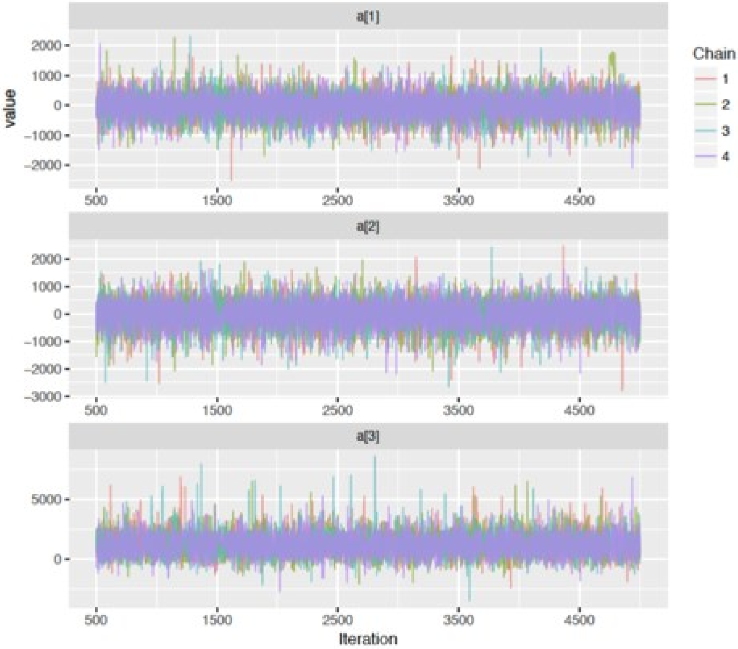
Here, we examine each group's R&D investment behavior in the financial crisis FY2008 in comparison with present time FY2016 results as the benchmark. Firstly, with a similar type of analysis with FY2016, each intercept result is [-36.60, 381.11{-812.12: 733.93}] for deficit biotech companies, [8.91, 450.59{-966.74: 852.42}] for profitable biotech companies, and [1153.81, 919.79{-362.88: 3042.90}] for large pharma (Table 4). All expected values are lower than each corresponding value of FY2016, reflected by the financial crisis. However, a negative expected value of -36.60 million USD of deficit biotech companies means a pure Valley-of-Death status or prior investment in a future opportunity. Furthermore, each group intercept's location of expected value and probability distribution are shown as Figure 13, and Figure 14.

Table 4 FY2008 print (fit)

4 chains, each with iter=5000; warmup=500; thin=1;
post-warmup draws per chain=4500, total post-warmup draws=18000.

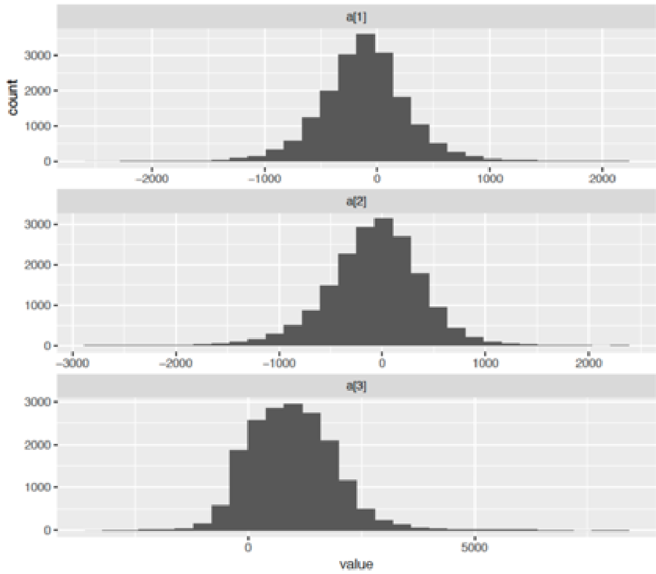
	mean	se_mean	sd	2.5%	25%	50%	75%	97.5%	n_eff	Rhat
a0	343.20	67.63	2320.33	-4583.49	-240.67	255.44	907.45	5074.98	1177	1.00
b0	3.27	0.19	4.76	-6.86	1.52	3.27	4.93	15.57	647	1.01
a_raw[1]	-0.27	0.01	0.72	-1.74	-0.73	-0.25	0.20	1.11	3399	1.00
a_raw[2]	-0.22	0.01	0.73	-1.71	-0.68	-0.20	0.24	1.19	3444	1.00
a_raw[3]	0.52	0.01	0.79	-1.00	0.00	0.50	1.01	2.15	3816	1.00
b_raw[1]	-0.49	0.01	0.72	-1.97	-0.94	-0.46	-0.01	0.87	3750	1.00
b_raw[2]	0.61	0.02	0.71	-0.69	0.11	0.57	1.06	2.12	1946	1.00
b_raw[3]	-0.11	0.01	0.63	-1.43	-0.50	-0.09	0.31	1.09	3039	1.00
s_a	2811.79	124.80	4836.44	55.47	621.68	1340.78	2920.13	15452.69	1502	1.01
s_b	7.12	0.35	8.02	0.88	2.59	4.54	8.49	29.11	524	1.00
s_Y	909.81	5.96	321.70	435.58	682.05	859.18	1080.98	1695.14	2913	1.00
a[1]	-36.60	5.18	381.11	-812.12	-258.28	-35.05	181.08	733.93	5406	1.00
a[2]	8.91	4.38	450.59	-966.74	-248.70	32.09	294.21	852.42	10575	1.00
a[3]	1153.81	14.01	919.79	-362.88	476.58	1108.67	1744.78	3042.90	4309	1.00
b[1]	1.07	0.03	2.03	-2.88	-0.08	1.03	2.24	5.13	5046	1.00
b[2]	5.64	0.01	0.99	3.35	5.02	5.74	6.42	7.12	9064	1.00
b[3]	2.92	0.00	0.39	2.08	2.73	2.93	3.13	3.64	6229	1.00
lp__	-272.65	0.09	3.74	-280.69	-275.06	-272.30	-269.94	-266.30	1775	1.00

Samples were drawn using NUTS(diag_e) at Thu Sep 28 01:50:30 2017.
For each parameter, n_eff is a crude measure of effective sample size,
and Rhat is the potential scale reduction factor on split chains (at
convergence, Rhat=1).



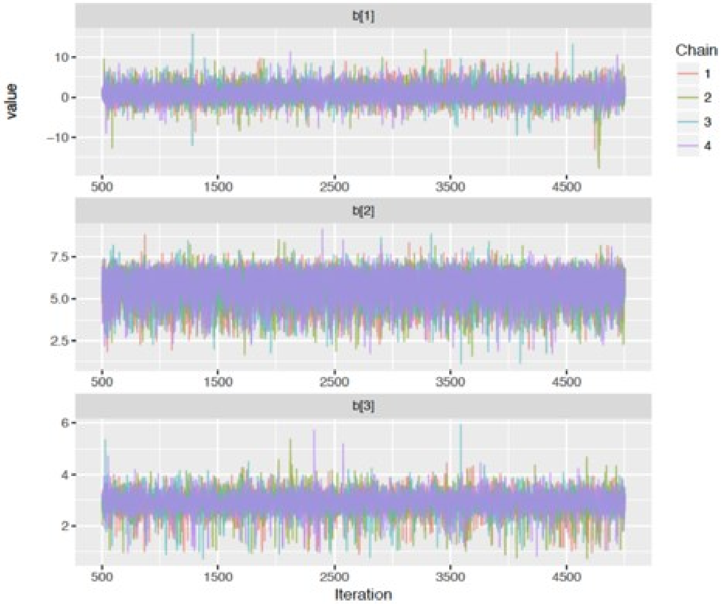
Source: Author

Figure 13 FY2008 trace-plot of intercept



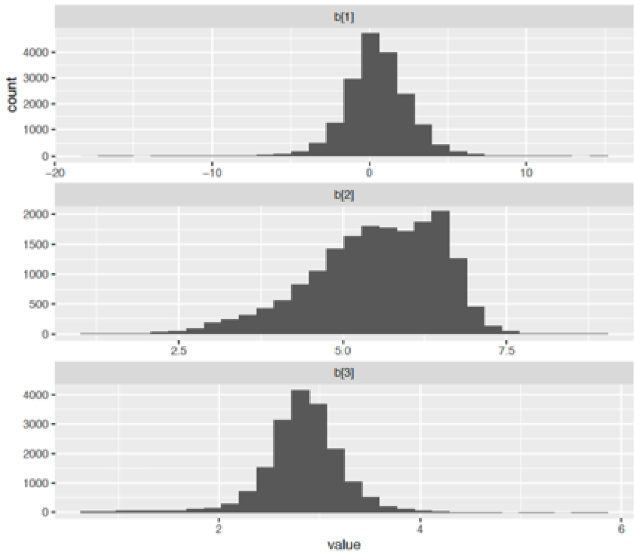
Source: Author

Figure 14 FY2008 fit-summary of intercept



Source: Author

Figure 15 FY2008 trace-plot of slope



Source: Author

Figure 16 FY2016 fit-summary of slope

Secondary, each slope result is [1.07, 2.03{-2.88: 5.13}] for deficit biotech companies, [5.64, 0.99{3.35: 7.12}] for profitable biotech companies, and [2.92, 0.39{2.08: 3.64}] for large pharma (Table 4). FY2008 expected value 5.64 of the slope of profitable biotech companies is higher than the 3.69 of FY2016 of this group. The distribution figure is also biased into higher value (Figure 15, Figure 16). That means they focused more on much higher added value drugs or market. Their strategy is robust and successful even in a financial crisis. The standard deviation and the range between 2.5% and 97.5% of deficit biotech companies are biggest and broadest in the three groups. So, although basic condition as intercept and average productivity as expected value are not so good as shown in the intercept mentioned above, their distribution range is the broadest in the three groups. Their range of 75-97.5% is much higher than that of large pharma. It means this group's portfolio is a mixture of wheat and chaff. The expected value of the large pharma is middle size in the three groups and the standard deviation is very small. So, even in a financial crisis, there is a phased screening path from basic research at university to manufacturing and selling at large pharma through trial and error type R&D at deficit biotech companies and next, more R&D focused on high added value drugs and markets at profitable biotech companies.

VI. Conclusion

This study confirms the possibility that Total stockholders' equity can play the role of call option to support continuing R&D investments even in negative profits. For example, as analyzed results about deficit biotech companies at the present time, and especially in a financial crisis as in FY2008, stockholders' equity can be a guideline for R&D investment continuity in a negative profits situation as "Valley-of-Death" and even at the severe capital market condition with the bankruptcy of Lehman Brothers. Especially, for deficit biotech companies, not only stockholders' equity, but also cash equivalents can exceptionally become a growth option in such an emergent condition. So, patient capital is necessary to be enhanced by some new instrumental creation like LTSE (Long Term Stock Exchange) in Silicon Valley or "Public Interest Capitalism" initiative by Mr. Jorge Hara in Japan.

As the result of Bayesian MCMC Analysis, deficit biotech companies showed very low average intercept in the R&D productivity equation with stockholders' equity as a dependent variable and R&D expenses as an independent variable, not only at the present time, but also in financial crisis. It means their drug candidates are far from market and they have to endure such events as the Valley-of-Death as a negative profits period. The expected value of slope as R&D productivity is lowest in the three groups, but its standard deviation and range is very broad. This means that negative profits biotech start-ups are showing broader slope distribution of R&D productivity, because search portfolios are rich in alternatives. That is, deficit biotech companies are seeking trial and error type R&D efforts and then the part of their higher value tail is much better than that of large pharmaceutical corporations.

Successful biotech start-ups, positive profits firms, are showing a focus on higher added-value niche markets rather than big pharma in slope distribution of R&D productivity. That is, the expected intercept of profitable biotech companies is the middle size in the three groups. They have some brand value or some advantage even before R&D investment. The slope of R&D productivity equation is highest in these groups. It means they have focused on higher added value drugs on the market than those of mass-market oriented large pharmaceutical corporations. The distribution asymmetry or skewness of this group changed from negative to positive values between FY2008 and FY2016.

Then, it might be possible to imagine some virtual bridge from fundamental research by university to large pharmaceutical firms' manufacturing and selling through the deficit, but exploratory R&D of biotech start-ups and then profitable and higher added value-oriented biotech companies if smoother technology transfer was enabled by FinTech innovation for the gap between angel and venture capital investments.

The future challenge is to expand into including non-financial indexes as patents and R&D manpower. Furthermore, there may be a possibility to integrate not only real options and Bayesian MCMC analysis, but also to include game theory for a more general methodology. Practical implication is a potential to utilize the signaling function of Bayesian MCMC analysis for the above-mentioned gap by shortening between angel and venture capital investments. This paper confirmed that not only Total Stockholders' Equity, but also Cash & Equivalents could be a sort of growth option in very severe condition in financial crisis, since cash liquidity might be necessary for R&D investment resources in an emergent state.

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References

Aktekin, T., Dutta, D.K. and Sohl, J.E. (2017) Entrepreneurial firms and financial attractiveness for securing debt capital: a Bayesian analysis, Venture Capital, 20(1), 1-24.
Amram, M. and Kulatilaka, N. (2000) Strategy and shareholder value creation: the real options frontier, Journal of Applied Corporate Finance, 13(2), 15-28.
Audretsch, B. (1998) Agglomeration and the location of innovative activity, Oxford Review of Economic Policy, 14(2), 18-29.
Audretsch, D.B., Aldridge, T.T. and Sanders, M. (2011) Social capital building and new business formation: a case study in silicon valley, International Small Business Journal, 29(2), 152-169.
Auerswald, P.E. and Branscomb, L.M. (2003) Valleys of death and darwinian seas: financing the invention to innovation transition in the united states, Journal of Technology Transfer, 28(3-4), 227-239.
Binder, G. and Bashe, P. (2008) Science Lessons: What the Business of Biotech Taught Me about Management, Cambridge, MA: Harvard Business School Press.
Black, F. and Scholes, M. (1973) The pricing of options and corporate liabilities, Journal of Political Economy, 81(3), 637-659.
Block, F. (2008) Swimming against the current: the rise of a hidden developmental state in the united states, Politics and Society, 36(2), 169-206.
Bogdan, B. and Villiger, R. (2010) Valuation in Life Sciences: A Oractical Guide, Berlin: Springer.
Bowman, E.H. and Moskowitz, G.T. (2001) Real options analysis and strategic decision making, Organization Science, 12(6), 772-777.
Brindley, D. and Davie, N. (2009) Regenerative medicine through a crisis: social perception and the financial reality, Rejuvenation Research, 12(6), 455-461.
Castellaneta, F. and Gottschalg, O. (2014) Does ownership matter in private equity? the sources of variance in buyouts' performance, Strategic Management Journal, 37(2), 330-348.
Copeland, T.E. and Antikarov, V. (2001) Real Options, New York: Texere.
Dixit, A. and Pindyck, R.S. (1994) Investment Under Uncertainty, Princeton, NJ: Princeton University Press.
Etzkowitz, H. (2006) The new visible hand: an assisted linear model of science and innovation policy, Science and Public Policy, 33(5), 310-320.
Feldman, M.P. (2003) The locational dynamics of the US biotech industry: knowledge externalities and the anchor hypothesis, Industry and Innovation, 10(3), 311-328.
Finkbeiner, S. (2010) Bridging the valley of death of therapeutics for neurode-generation, Nature Medicine, 16, 1227-1232.
Garnsey, E.W., Galloway, S.C. and Mathisen, S.H. (2006) Flexibility and specialization in question; birth, growth and death rates of Cambridge new technology-based firms 1988-92, Entrepreneurship and Regional Development, 6(1), 81-107.
Hughes, S.S. (2011) Genentech: The Beginnings of Biotech (Synthesis), Chicago: University of Chicago Press.

Jägle, A.J. (1999) Shareholder value, real options, and innovation in technology-intensive companies, R&D Management, 29(3), 271-288.
Kester, W.C. (1984) Today's options for tomorrow's growth, Harvard Business Review, 62(2) March-April, 153-160.
Kruschke, J. (2014) Doing Bayesian Data Analysis: A Tutorial with R, JAGS, and Stan, 2nd ed., London: Academic Press.
McGrath, R.G. (1999) Falling forward: real options reasoning and entrepreneurial failure, Academy of Management Review, 24(1), 13-30.
Merton, R.C. (2007) Theory of rational option pricing, Bell Journal of Economics, 4(1), 141-183.
Moran, N. (2007) Public sector seeks to bridge 'valley of death', Nature Biotechnology, 25(3), 266.
Myers, S.C. (1977) Determinants of corporate borrowing, Journal of Financial Economics, 5(2), 147-176.
Ottoo, R.E. (1998) Valuation of internal growth opportunities: the case of a biotechnology company, Quarterly Review of Economics and Finance, 38(3), 615-633.
Perlitz, M., Peske, T. and Schrank, R. (1999) Real options valuation: the new frontier in R&D project evaluation? R&D Management, 29(3), 255-270.
Pisano, G.P. (2006) Science Business: The Promise, the Reality and the Future of Biotech, Cambridge, MA: Harvard Business School Press.
Teconomy Partners LLC, (2018) Strengthening Biopharmaceutical Innovation, PhRMA.
USA Securities and Exchange Commission (2017) EDGAR, Retrieved from https://www.sec.gov/edgar.shtml.
Vassolo, R.S., Anand, J. and Folta, T.B. (2004) Non-additivity in portfolios of exploration activities: a real options-based analysis of equity alliances in biotechnology, Strategic Management Journal, 25(11), 1045-1061.
Waluszewski, A. (2004) A competing or co-operating cluster or seven decades of combinatory resources? what's behind a prospering biotech valley?, Scandinavian Journal of Mangement, 20(1-2), 125-150.
Werth, B. (2014) The Antidote: Inside the World of New Pharma, New York: Simon & Schuster.
Zhong, H., Liu, C., Zhong, J. and Xiong, H. (2018) Which startup to invest in: a personalized portfolio strategy, Annals of Operations Research, 263(1-2), 339-360.