

Creating a Biotechnology Hub: Lessons from the BioForest

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Four states in northwest USA – Washington, Oregon, Montana, and Idaho, and British Columbia in Canada comprise the BioForest¹. The BioForest is ranked as a ‘second-tier’ life-sciences hub, the first-tier hubs comprising the San Francisco area and Boston. The greater Seattle area (Washington state), is the Mecca for immunology, cancer biology, proteomics and systems biology. Ultrasound and cardiac technologies round up the region’s base.

This paper traces the history of the BioForest, identifies the factors contributing to the growth of the region into a life-sciences hub and goes on to draw lessons for the setting up of such regional hubs and the issues and challenges therein. Since most of the activity in the first 20 years from 1970 to 1990 was concentrated in the greater Seattle area, this paper will focus on the narrower region of the BioForest flanked by the Puget Sound.

Over the past quarter century, Seattle has used the following ingredients to build a competitive life-sciences hub:

- an excellent academic research foundation which understands technology transfer
- the critical mass of people and the connections they have formed over the years
- early stage companies that try new ideas and concepts, improve on existing platforms, and find the people to fund it
- core science funding from the federal government and charitable foundations
- mid-stage and later stage companies that have gone through the FDA process, and
- lifestyle: mountains, ocean, rivers, trails, parks.

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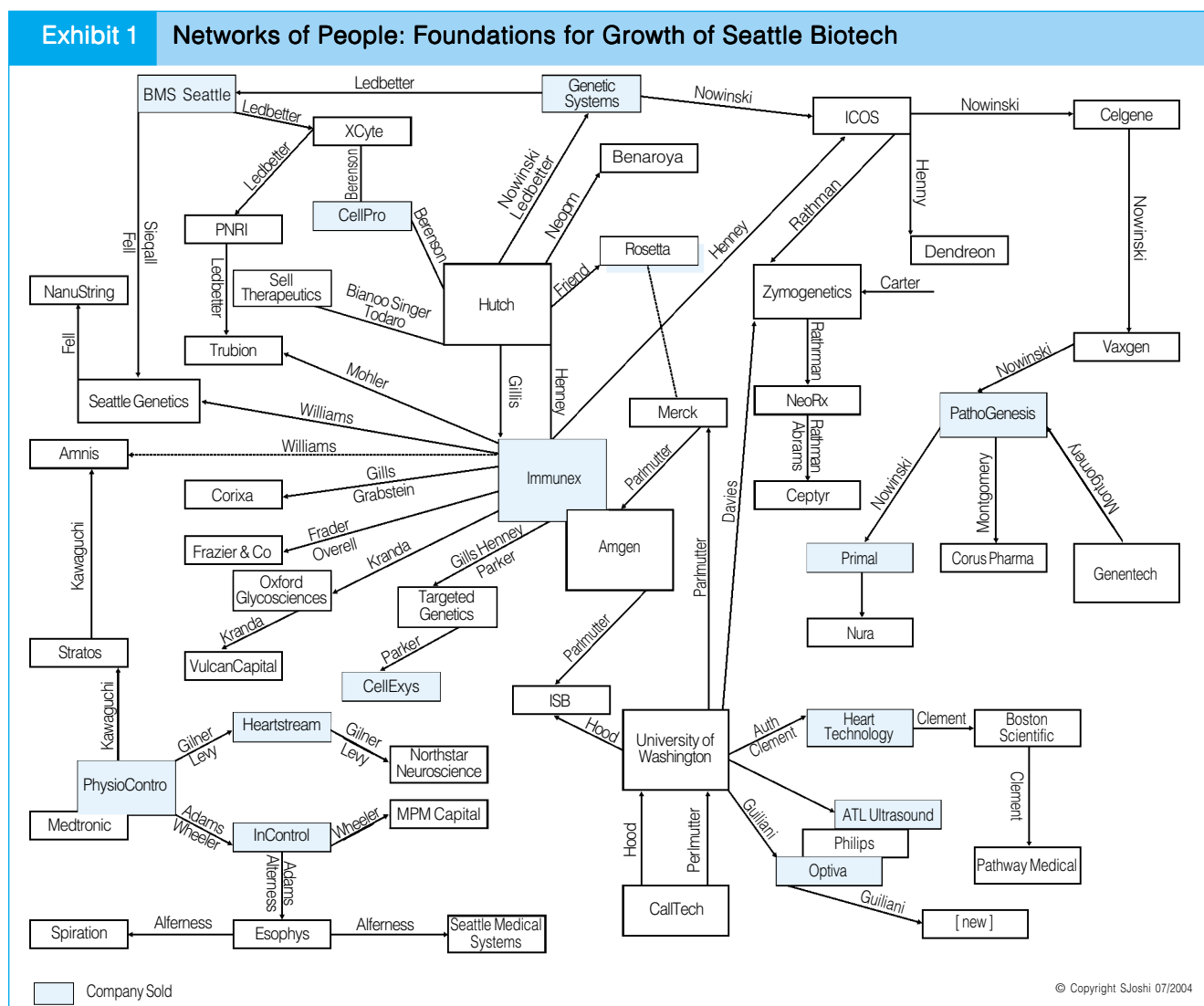
Sustaining, funding and nurturing the hub and the connections of the people that are its backbone requires the kind of innovation and leadership that biotechnology itself needs.

Foundations of the Seattle Biotech Hub

The critical mass of people and their connections set up networks of growth in Seattle, spanning over thirty years. The seeding of the early biotechnology industry came from the Fred Hutchinson Cancer Research Centre (the 'Hutch') in the late 1970s. The founders of the early biotech companies formed most of the biotech companies through the late 80s and early 90s. The early high-risk climate at the Hutch also fostered the serial entrepreneurs of the area, who went on to found several companies successively. (Exhibit 1 shows the networks of people and companies in the Seattle biotech landscape who created the foundations for its growth).

Several world-renowned academic institutions had their roots in the area: The University of Washington, 1861 – from which the medical device industry of the 1970s spun off; Pacific Northwest Research Institute (PNRI), 1956; Benaroya Research Institute at Virginia Mason (BRI), 1957; The Pacific Northwest National Laboratory (PNNL), 1965; Programme for Appropriate Technologies in Health (PATH), 1975; The Seattle Biomedical Research Institute (SBRI) in 1976²; and later, in 1999, the Institute for Systems Biology, an academic non-profit organisation. The last is now the Mecca of proteomics and systems biology with an increasing focus on the essence of the BioForest: immunology.

It was in the Seattle BioForest that the first commercial direct current cardiac defibrillator was produced in 1961; Spacelabs collaborated with the US Air Force (NASA) in developing systems to monitor the vital signs of astronauts in space³; and the first treadmills designed specifically for cardiac testing were built.



Since Seattle had invested heavily in the high-tech bubble economy, the loss of jobs was one of the highest in the country. Other countries and regions may need to pay close attention to this: steep wage increases within a short period in specific industries usually do not last long.

The 1980s were the boom years for Seattle biotech and 1981 saw the birth of many companies. The University of Washington (UW) was active in contributing intellectual capital for the ventures. After the Stock Market Crash in October 1987⁴, speculation in futures seems to have been the basis for the 'feel-good' investments in early-stage biotechnology companies⁵. Hutch alumni figured prominently in the late 80s and early 90s, focussing on AIDS vaccines, cancer biology, cystic fibrosis and automated systems for purifying large quantities of specific cells for therapeutic and diagnostic applications.

In 1990 the Human Genome Project—an international effort to map all the genes in the human body—was launched⁶. The Breast Implant Lawsuits started in 1992 and culminated with the March 1994 class action suit finalised by the manufacturers, the largest class action settlement in history, with Dow Corning being the largest contributor. The settlements, a little less than \$5 billion⁷, sent a chill to the early stage companies that Dow Corning and other companies had funded. The Biotechnology Industries Organisation (BIO) was established in 1993 to provide a leadership and political forum for the issues in the biotechnology industry. The period between 1995 to 1998 saw the takeover of Seattle medical device companies and the reasons for the spate of these acquisitions would make an interesting study⁸.

The information technology bubble started in 1995 and ended in 2000⁹. The period 1997-2000 was the heyday of bioinformatics companies¹⁰. Commercial bioinformatics withered in 2002 and 2003, despite the continuing accumulation of gene and gene expression data that needed analysis. High-flying software companies failed and others reinvented their business models as drug discovery firms¹¹.

The bubble had led to too many bioinformatics companies being formed, resulting in a saturation stronghold, which meant companies that sold products survived. The year 2001 saw a lot of activity, among other things the 'lab-less company', with Corus, a new kind of drug company with a focus on the business of biotech licensing and data management (from outsourced biology and clinical trials).

The terrorist attacks of Sep 11, 2001 on the financial and national capital froze venture investing for two years. Early stage companies that did not show great promise withered and died. The recession was officially announced as ended in June 2003¹². From March 2004, the economic and venture activity has picked up again in Seattle. Seasoned scientists and veterans of the Seattle biotech market started the most touted company in 2002, Trubion Pharmaceuticals and have received \$45 million to date in investments¹³. Washington State's first large manufacturing plant is being built and it is planning a \$60 million manufacturing facility to the north of Seattle¹⁴. With \$100 million in seed money, Microsoft co-founder Paul Allen created the Allen Institute in 2003 and the Allen Brain Atlas as its first endeavour¹⁵.

Since Seattle had invested heavily in the high-tech bubble economy, the loss of jobs (and therefore the unemployment rate) was one of the highest in the country. It is estimated that the greater Seattle area lost about 100,000 jobs (most of them high-paying high-technology jobs) that were not replaced¹⁶. Other countries and regions may need to pay close attention to this: steep wage increases within a short period in specific industries usually do not last long.

Forming and Sustaining a Hub

Technology Transfer

Technology transfer from universities into the commercial arena, a major factor in hub creation, can be very complex, and the process requires intermediaries to have a good understanding of many technical, business and legal issues. The process often requires patience and strategic thinking as the interval from 'proof of concept' to commercial success can take anywhere from 4 to 10 years, especially in the life-sciences.

Licensing of intellectual property to an existing business can be rewarding (both for the university and the commercial entity), and is likely to be the preferred option if a ready route to market exists. Technology training and strategy programmes offer an excellent route for technology transfer

Exhibit 2 The Technology Transfer Process	
Area	Function
Technology Consulting	Advice provided to industry for a fee by staff from a university or research organisation
Contract Research	Work at a research organisation funded by a company exploiting the technology
Technology Licensing	Patents and know-how held by the university or research organisation
Technology Resources	Transfer of personnel from the technology developer to the company exploiting or utilising an idea
Partner Collaboration	Programmes which bring together several partners to produce a viable technology transfer activity
Sales Promotion	Activities to raise awareness about a technology, including entries on technology transfer databases
Networking	Processes where interactions are key to solving a problem or creating a new technology
Training	Usage and explanation of value of technology
Direct Marketing	Proactive marketing of a technology to potential users/exploiters (in contrast to awareness raising)
Spin-off Creation	Appropriate when an idea can form the basis of a business and when other routes are less rewarding

in many circumstances, and for building long term industry-academia relationships. The application of a technology often ends up being different from the one conceived during the development stage¹⁷.

The difficulty, however, is in defining the metrics for identifying opportunities with specific inventions, the quality of the invention and determining the legal agreement for spinning off the invention into a company¹⁸.

A focused Biotechnology Venture Fund created by the state government could help increase the available funding toward the very early stages of the development of the IP from the academic institutions¹⁹. The management and the decision making process are critical, starting with the attitude of the university toward entrepreneurial scientists²⁰. Exhibit 2 shows the ingredients needed for the technology transfer process.

Spin-off companies can be very effective at getting a new technology into the market place, making significant returns for the institution and individuals involved and giving positive feedback into the quality of research. For a spin-off event to occur, there needs to be a strong technology base and the mother-organisation has to allow the IP to be licensed or released.

University Research

The Bayh-Dole Act of 1980²¹ illustrates the possibilities of a symbiotic relationship between the government, universities,

and corporations. The Bayh-Dole Act established a uniform Federal policy in favour of allowing universities to own the results of government-funded research, enabling universities to profit from research results by licensing them to companies that could bring the results to market. Technology transfer offices are now common in universities and federal laboratories and are the technology foundation for numerous biotechnology and medical device companies.

The Bayh-Dole Act does have its drawbacks: a 'significant' portion of the 'manufacturing' has to be done in the US ('significant' is not defined, and only 'manufacturing' is mentioned, not 'research and development').

The FDA: Cornerstone of Competitiveness?

The US FDA is illustrative of the pro-active role played by the government regulatory authority. The original 'Food and Drugs Act' was passed in 1906²². The Food and Drug Administration Act of 1988 officially established FDA as an agency of the Department of Health and Human Services, with a Commissioner of Food and Drugs, and broadly spelt out the organisation's responsibilities for research, enforcement, education, and information. The Food and Drug Administration Modernisation Act of 1997 mandated the most wide-ranging reforms in agency practices since 1938. Provisions included measures to accelerate review of devices, regulate advertising of unapproved uses of approved drugs and devices, and regulate health claims for foods.

Some of the FDA's impetus to act may have come from the *Los Angeles Times*' investigation in 2000 of the diet drug 'Redux' that caused fatal heart defects and the diabetes drug 'Rezulin', which induced liver failure. This investigation caused the FDA to pull from the market unsafe drugs that had been previously approved.

Companies and organisations sometimes neglect the assessment of the risk and the negative press when something goes wrong. This is more evident if the company is publicly traded. The FDA was involved in several events: to quote a few cases – the shutting down of the PhysioControl plant in Redmond, Washington in 1992 after two deaths were attributed to one of its defibrillator models. About 1700 units were recalled and losses to PhysioControl's parent Eli Lilly were estimated at between \$125 million and \$140 million, causing Lilly to put the troubled subsidiary up for sale²³. Complaints about the biased connection between the Hutch physicians conducting a study into the deaths of 20 terminally ill patients, and the Hutch spin-off company, Genetic Systems, led to the Hutch receiving a warning letter from the FDA in 2001. Corixa's marketing campaign was delayed by almost two years when the FDA asked Coulter Pharmaceuticals, a company that Corixa had acquired, to resubmit data for its clinical trials of Bexxar.

Some of the FDA's impetus to act may have come from the *Los Angeles Times*' investigation in 2000 of the diet drug 'Redux' (fen-phen) that caused fatal heart defects and the diabetes drug 'Rezulin',²⁴ which induced liver failure. This investigation caused the FDA to pull from the market unsafe drugs that had been previously approved²⁵.

The FDA needs to keep pace with the tremendous research advancements funded by the NIH on the clinical and phenotypic effects of these developments. This means smooth transition in leadership, decentralised management and a lot more funding to keep up with the growing demand for approvals of drugs.

The Federal and State Funding Processes

Within the purview of the 'mature' federal funding process is

the Small Business Innovation Research (SBIR) programme by the National Institutes of Health (NIH)²⁶, a programme for US small business concerns to engage in Research/Research and Development (R/R&D) that has the potential for commercialisation. Other funding organisations like the Howard Hughes Medical Institute, the Scripps Research Institute and the Whitaker Foundation provide funding equal to the tax-payer funded federal institutions²⁷.

The dilemma of the state funding process is revealed by the difference in approach to the early stage companies, as compared to the big- or mid-to-large-pharma company. The Brookings Institution released a report in 2002 on what it takes to build and grow biotechnology centres in the US²⁸. While in a big pharma company, it is expected that multiple projects will fail and failure is quite the norm²⁹, the focus for funding is on the irreverently termed, 'sphincter of biotechnology'³⁰ – the early stage companies that lie between the large academic institutions and mid-to-large-size biotechnology industry. These are the 70% or so of companies locally that have fewer than 25 employees³¹.

A consensus emerged from interviews with the local leaders³² on the ways of allocation of state money through the following funding vehicles:

- A few companies (5 to 10 a year) to be funded through a State Life-Sciences Venture Fund. This is a 'graded' process. Since this is capital intensive, the companies should be supported till they can raise venture funding or partnering/licensing revenues. Universities should look at equity participation as a licensing arrangement too³³.
- Pre-clinical, process sciences, pre-manufacturing service infrastructure: To be run like a corporation. State government provides a large percentage of the funding and Board of Directors seats. Create a conglomerate of professors and departments that creates new technologies in process science, purification and manufacturing.
- Provide funding for process sciences and pre-manufacturing for local companies.
- Give grants to academia and non-profit organisations, specifically as non-restricted funds with peer review.
- Use the money for local health programmes or specific non-technology initiatives.

It has been suggested that the state government needs to decide a funding formula based on the above-mentioned funding mechanisms³⁴.

Since NIH funding has been dropping over the past few years³⁵

Exhibit 3 Summary of Company Histories					
Company	Early Tech Transfer	Early Funds	Mid- Funds	Key Early Players (Ex. 1)	Notes
Immunex	No	Mayfield, NEA, Cable& Howse, Domain	Public	Henney, Gillis	Sold to Amgen 2003: \$10 billion
ICOS	Yes, UW	Private (led by Gates)	Public	Nowinski, Rathman, Henney, Gates	Partnered with Lilly to produce Cialis
Zymogenetics	Yes, UW	Rathman	Warburg Pincus, Patricof, Novo, Frazier	Rathman, Davie, Hall, Smith	Major share Novo Nordisk, reacquired
Corixa (Immunex spinoff)	No	Gillis	Public	Gillis, Grabstein	2 year delay due to FDA issues, sold to Glaxo Smith Kline
Heart Technology	Yes, UW	E.R. Squibb and Sons	Boston Scient.	Auth, Clement	Sold to Boston Scientific 1985: > 0.5 billion

and moving more to Centre grants, greater cooperation is needed between local organisations³⁶, and between academic research and industry³⁷ in particular. Exhibit 3 summarises the histories of a few companies in the Seattle hub.

Building and Sustaining a Hub: Issues and Challenges

Out of the experience of 18 of the Seattle region's leaders and innovators, the following emerged as key to the development of a biotech hub:

- The three legs of the regional innovation stool are: a strong education system, a non-profit base funded by a consistent tax base (and charity) and incisive technology transfer with early stage capital that ensures success (through participation by venture capital and the state government).
- Bringing entrepreneurial thought leaders into the region and providing networking connections and mentorship through them is very important for leadership and innovation.
- The regulatory industry spearheaded by the FDA, the tax-base that provides the funding for early stage fundamental research and the market purchase power will ensure the lead maintained by the USA.
- Funding for early-stage companies, however, remains a challenge.
- Regions and companies change directions due to unplanned events.

Other factors contributing to the formation of life-sciences hubs are: an immediate need or a crisis, political or state government initiatives, evangelists and champions for a cause, angel investors and mission oriented organisations³⁸. Exhibit 4 provides the *hub-metrics*.

However, each region should find a way to:

- define its own pulse, its heartbeat and capitalise on it. Trying

Exhibit 4 Tracking Hub Performance	
Metrics	
1.	New company births
2.	New company births per 100,000 residents
3.	High-tech company births per 100,000 residents
4.	Percentage employment of companies less than 5 yrs old
5.	VC investment (in select industry areas)
6.	Number of scientists and engineers
7.	Number of Life and Physical sciences workers per 100,000
8.	PhDs in workforce
9.	Gazelle (fast growing) firms
10.	Number of Inc 500 companies per 10,000 businesses
11.	Research by \$ invested: Academic, Federal, Industry, Non-Profit

Source: 'Drivers for a Successful Technology-Based Economy: Benchmarking Washington's Performance', A Technology Alliance Report, Somers P, May 2003. Available at http://www.technology-alliance.com/resources/publications/benchmark_report_final.pdf,

With the current investment climate, we are now looking for the ‘Clinician-Scientist-Manager’. The trend is evident in education: the Professional Science Master’s degree programme (PSM) now being offered in some of the state colleges and universities in the US, with a focus on life-sciences and a strong ‘real-world’ emphasis.

to mimic successes of other life-sciences hub does not necessarily work.

- build direct connectivity to the state and central regulatory agencies.
- foster apolitical and non-business networking amongst its thought leaders. This network should also provide a forum for informal mentorship.
- attract star-power to its region, once the pulse and the heartbeat of the region has been identified. Continuing the process of bringing more star-power takes money and consistent effort.

Despite the fact that so many factors are in place, there still remain several issues and challenges to be faced in the region.

Intellectual Capital

If the Seattle region grows again, one of the consistent worries is priming the next generation of scientists. 50 to 60% of PhDs awarded in the US (for all disciplines) are to foreign students³⁹. This contributes a large labour pool for the post-doctoral programmes. With the current climate of ‘tightening the borders’ and tightening or reduction of all visa categories⁴⁰, there is a real worry that the post-doctoral scientists and the vast majority of PhDs that stay behind to perform high quality research and start new companies will dry out. ‘I am already seeing the effects of the visa restrictions’ said Gerald Nepom, President of Benaroya Research Institute. If the local PhD candidates do not pick up the slack, the US brain-trust will feel the shortage before the next 10 years.

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programme (PSM) now being offered in some of the state colleges and universities in the US, with a focus on life-sciences and a strong ‘real-world’ emphasis. Instead of conducting pure research and dissertation as in a PhD programme, students embark on industry internships, learn business and patent law and work on real-world clinical projects in the classroom. There is, however, a worry that the PSM programme is diluting the thought, creativity and multi-disciplinary understanding needed for research and development of drugs which is provided with the PhD and MD PhD programmes⁴¹.

Teaching entrepreneurship, especially in the life-sciences, requires immersion. Seasoned mentors who have ‘been there and done that’ are an integral part of finding and coaching entrepreneurial scientists, clinicians and engineers. Failure of the firm is not necessarily failure of the individual⁴².

Training for Entrepreneurship

Training for entrepreneurship, according to several heads of academic institutions and companies, poses several issues and challenges. To quote John Castle, Professor of Entrepreneurship, UW, biotechnology is a very high risk game for entrepreneurship.

Empirical versus Cognitive

Interviewees perceived a basic difference in the ‘empirical’ approach of scientists and the ‘cognitive’ approach of physicians. According to Bruce Montgomery, CEO, Corus Pharma, ‘Physicians are trained a lot in understanding humans, whereas scientists tend to think: why is that person behaving that way. A scientist reasons: if the numbers don’t make sense, it is a bad experiment. A physician is trained to look at signals whereas scientists are trained to look at patterns. Physicians are trained to work within insufficient information and uncertain data’.

Apprenticeship and Social Skills

Universities and academic organisations do not reward behaviour that leads to becoming a good leader, holds Bruce Montgomery. According to John Castle, ‘Entrepreneurship is best taught in a conflict resolution class. It teaches negotiation and communication skills leaders must have to be better entrepreneurs’.

Decision Making Skills

The correlation between entrepreneurship, risk, individuality,

opportunity, trust and communication has been and continues to be the subject of study⁴³. Leadership by consensus versus leadership by trust is an issue mentioned by Bruce Carter, CEO, Zymogenetics. According to Jeffrey Ledbetter of Trubion Pharmaceuticals, companies can get too big. Bigger isn't better to foster entrepreneurship. Large pharma is sub-divided into sections: research to manufacturing, and is also divided by disease processes. This is neither conducive to research nor leadership. The right company size should be found for productive research.

Conclusion

There has been much lamenting about the investment in early-stage companies by the less than handful of the local venture capital companies. But then, it is the job of venture capital to realise short-term returns, not to promote the local economy or 'hang-on' to companies for periods of 10 to 15 years.

The issues discussed above need seasoned leadership (and perhaps more 'out-of-the-box' thinkers) and not the 'group-think' that seems to be more formulaic than regional.

We are in the second golden era of medicine. The time for innovative leadership is now.

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