

# Convergence Revolution – Piloting the Third Scientific Revolution through Start-Ups for Breast Cancer Cure

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## Abstract

Convergence revolution integrates various academic disciplines with wide spectrum of activities and also connects them with translation and innovation ecosystem thereby going well beyond traditional collaborations. This is the third revolution in the life science arena, first being DNA discovery and second genomics where almost entire human genome has been sequenced. The third revolution, convergence revolution has the potential to lead to a solution for breast cancer cure. Breast cancer is the second largest mortality causative agent among women. In United States, nearly 40,000 women die of breast cancer every year. Till date (March 2017), 3.1 million women have been medicated for breast cancer. On an average every 2 minutes, a woman in the U.S. is diagnosed with breast cancer. Convergence may provide a more effective solution for cure breast cancer by multipronged approach using nanotechnology (targeted delivery with controlled release), imaging protocols (Raman spectroscopy) and biomarkers detection involving physicists, chemists, bioengineers, radiologists, clinical oncologists and entrepreneurs and proposing for a National Cancer Data Ecosystem. This work is a classic example of convergence involving multi-disciplinary researchers and technology developers. Several start-ups are working in the direction of breast cancer therapy onto clinical trials which can pave way for translation to clinics for the cure of belligerent types of breast cancers which affect young women.

**Keywords:** Convergence Revolution; Cancer Moonshot; Nanotechnology; Start-Ups; Breast Cancer

## Introduction

“For the loved ones we’ve all lost, for the family we can still save; let’s make America the country that cures cancer once and for all.” - President Barack Obama.

The first revolution involved the discovery of DNA by Watson and Crick which lead to diagnosis, prognosis, treatment and cure of many diseases. The second revolution pertained to genomics by which the cost of whole genome sequencing has fallen from in the range of millions of dollars per genome to below \$1,000 resulting in blueprinting nearly the entire human genome sequence. The third revolution integrates research and development of academia and industries involved in nano/bio/info/cogno areas of independent discipline to converge to commercialize personalized precision medicine and therapy, in particular for oncological interventions [1, 2]. Achievement of success relies on the prosperity of the evolved hub of start-up companies such as in Silicon Valley or Greater Boston area.

## Healthcare revolution

Chronic morbid condition of the American adult population, arising due to cancer, cardiac irregularities, stroke, diabetes and obesity account for 85 percent of U.S. healthcare spending. This corresponds to roughly 17.5 percent of Gross Domestic Product (GDP) approximately to \$3 trillion in 2016 Projections are that this will increase to 19%. Global R&D Funding forecast report [3] describes the gross expenditures on R&D by different countries with United States of America estimated to spend US \$514B in 2017 (Table-1). Convergence revolution: The future of health [4-7] provides solution for the ever increasing healthcare expenditures by piloting state of the art technologies through start-up companies offering cutting edge innovations for early diagnosis, prevention and cure. If not supported by adequate financial backup, American competitive dominance leading to global supremacy in the transnational platform may be subverted or even undermined. In this report oncological interventions are discussed since cancer

**Table – 1:** Forecast Gross Expenditures on R&D

Year		2014			2015			2016		
Rank	Country	GDP (Bil,\$)	R&D as % GDP	Value (Bil,\$)	GDP (Bil, \$)	R&D as % GDP	Value (Bil, \$)	GDP (Bil, \$)	R&D as % GDP	Value (Bil, \$)
1	USA	17,460	2.78%	485	18,001	2.76%	496	18,559	2.77%	514
2	China	17,630	1.95%	343	18,828	1.98%	372	20,015	1.98%	396
3	Japan	4,807	3.40%	163	4,855	3.39%	164	4,913	3.39%	166
4	Germany	3,621	2.85%	103	3,678	2.92%	107	3,741	2.92%	109
5	South Korea	1,786	3.60%	64	1,844	4.04%	74	1,909	4.04%	77
6	India	7,277	0.85%	61	7,822	0.85%	66	8,409	0.85%	71
7	France	2,587	2.25%	58	2,618	2.26%	59	2,657	2.26%	60
8	Russia	3,568	1.50%	53	3,432	1.50%	51	3,396	1.50%	50
9	U. K	2,435	1.81%	44	2,500	1.78%	44	2,558	1.78%	45
10	Brazil	3,073	1.21%	37	3,042	1.21%	36	3,072	1.21%	37

Source: 2016 Global R&D funding forecast R&D Magazine, winter 2016 [2]

is chronic and very painful leading to psychological burden not only on the patient but on the near and dear ones also resulting in reduced productivity and negative impact on the quality life.

### Strategies and Solutions for Cancer

First and Second life science revolutions played a very critical role in diagnosis, prognosis, treatment and to cure (only upon early diagnosis) in terms of differentiating types of cancer. Many types of cancer can be treated with the existing therapy regimen, including chemo and radiation. Convergence leaps several steps forward for oncological interventions by providing innovative advanced protocols and approaches.

### Biomarkers

Biomarkers technology is the major pathfinding step for cancer diagnosis, prognosis, treatment and cure. Non invasive methods by urine analysis or with minimal invasive methods using few drops of blood testing, for any types of cancer detection more of a paper based technique which needs no sophistication for inference. One of the largest urine biosample repositories of patients is maintained at Harvard [8] with a hope that biomarkers for breast cancer can be discovered for early diagnosis using urine sample of the individual. Currently, such a non-invasive or minimally invasive biomarker technology is available for pregnancy and diabetes. Big data analytics and machine learning techniques proposed by convergence approach could definitely accelerate the cure for all types of breast cancer using the biosamples frozen in one of the largest clinical biosample repository.

### Targeted drug delivery

Convergence may provide solution further from diagnosis to cure. Nanotechnology drug delivery system is a key technology for cancer [9] which is used not only for diagnosis but also for treatment regimens. Targeted delivery coupled with controlled release minimizes side effects and lower impact on the normal cells and tissues.

### Immunotherapy

The third innovative approach to cure cancer is by redirecting the patient's own immune system [10] to identify, recognise from malignant to benign and kill the tumour cells. This type of therapeutic approach uses antibodies tagged with different characteristic heavy ions. These antibodies identify specific cellular characteristics of the tumour cells. High volume of complex set of data will be generated, which by using integration of ICT discipline can be resolved for precise immune therapy leading to personalized nanomedicine.

### Cancer Moonshot

Convergence approach needs to accelerate the pathway with a specific timeline the scientific skillsets which has been accumulated over decades. This accumulated skillsets are built upon vast intellectual creativity and innovation of the American technology developers (researchers and pharmaceutical companies) for more than 200 types of cancer. U.S. former Vice President started cancer moonshot [11] to accelerate the efforts for the prevention, diagnosis, treatment and further cure with a specific timeframes. Currently researchers, pharmaceutical companies and start-up entrepreneurs have access to large amounts of clinical data, thanks to the previous revolution, namely the genomic

revolution. Convergence style research approach using electronic health records, and large datasets of clinical, environmental, and public health information for sure will herald the success of cancer moonshot. Milestones of cancer moonshot are now available at the National Cancer Institute website [12].

Bench to bedside translation of new drug discovery for one new small molecule (new chemical entity) is amounting to US \$1b approximately which requires perennial funding. The timeline to reach the commercial market to reach to the patient from laboratory bench is around nine to twelve years. For sure convergence revolution can provide a much shorter timeline for bench to bedside with the integration of huge quantum of genomic data.

Global healthcare industry comprises of pharmaceuticals, biotechnology firms, medical instruments, diagnostic devices, veterinary therapeutics, agronomy and clinical research. In terms of the R&D, 85 percent of the R&D spending is for the biopharmaceutical sector more towards disease treatment and cure. Core chemical engineering based small molecule chemical moiety pharmaceutical industry more towards generic manufacturing have plateaued in their R&D spending or even cut size to several folds. Utilizing sophisticated informatics and big data in-

frastructure biopharmaceutical sector is on the high in terms of R&D spending.

The Nobel Prize has been bestowed to researchers since 1901 and the research awards are from 73 different countries ever since its inception. U.S. researchers have dominated the Nobel Prize Awards; with 356 awards overall and from 2000 onwards 102 U.S. researchers have been awarded the pinnacle of research award and have become Nobel Laureates. One of the founders of the convergence revolution is also a Nobel laureate. Academic R&D capabilities are still dominated by U.S. institutions. 60% of the top ten global universities are located in the U.S. and 70% of top 100 global universities are also located in the U.S. Johns Hopkins University was the first academic institution in the world to surpass \$1 billion in R&D and now is the first to surpass \$2 billion—the bulk of which is funded by the federal government for healthcare and life science research (Table-2).

**Table 2:** Top Universities by R&D Expenditures (Millions of U.S. Dollars)

S. #	University	R&D	Fed obligations	% Share
1	Johns Hopkins Univ.	\$2,169	\$1,539	71%
2	Univ. Michigan, Ann Arbor	\$1,375	\$610	44%
3	Univ. Washington, Seattle	\$1,193	\$663	56%
4	Univ. Wisconsin, Madison	\$1,124	\$440	39%
5	Univ. California, San Diego	\$1,076	\$566	53%
6	Univ. California, San Francisco	\$1,043	\$574	55%
7	Harvard Univ.	\$1,013	\$459	45%
8	Duke Univ	\$993	\$454	46%
9	Univ. NC, Chapel Hill	\$973	\$442	45%
10	Univ. California, Los Angeles	\$967	\$481	50%

**Source:** 2016 Global R&D Funding Forecast and National Science Foundation

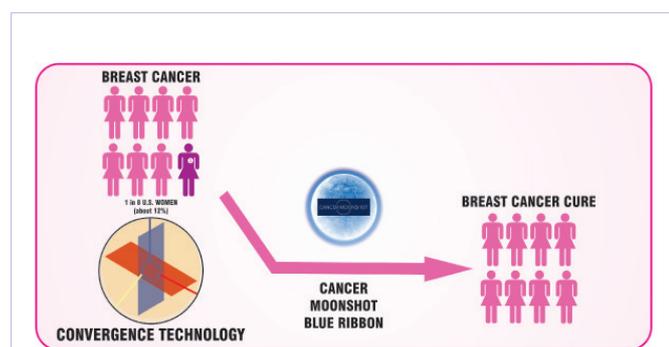
As an outcome of very rich intellectual inputs given by the academia large number of start-ups has emerged for personalized medicine. California and Massachusetts lead the world in terms of financially sustainable life science based start-ups. These two regions are the major drivers for global biotechnology innovation.

According to a popular website (Lab Rat) there are 195 bio companies in Massachusetts and 240 around the San Francisco Bay. Hence these companies are going to be the leading hand for convergence revolution. In 2015, biotechnology sector's financing started to drive north with unprecedented heights. Biotechnology companies raised nearly US\$71 billion in 2015, easily surpassing the record-setting US\$56 billion amassed in 2014. Clinical trials and FDA regulatory approval procedures consume 75% or more of all the funds raised by a life science start-up. Few start-ups have planned to enter IPO market pretty soon. Audentes Therapeutics a three-year-old biotechnology company located in California plans to raise \$86.3 million offering. This company develops and commercialize gene therapy products. Edit as

Medicine, Massachusetts based company which is only two years old Plans to offer up to \$100 million in stock. They develop treatments to modify disease-causing genetic defects. Corvus Pharmaceuticals, founded in Q4 2014 which is California based attempts to raise \$115 million in an IPO for its business. Core activity is on immune-oncology which is the keystone project for convergence revolution.

### Breast cancer

As of March 2017, there are more than 3.1 million women with a history of breast cancer in the U.S. and about 40,610 women in the U.S. are expected to die in 2017 because of breast cancer [13]. Convergence approach embedded with cancer moonshot program will be a curative approach, for in The U.S. About 8 U.S. women (about 12%) will develop invasive breast cancer over the course of her lifetime (Figure – 1).



**Figure 1:**Convergence revolution with cancer moonshot for breast cancer cure

Approach for cure for breast cancer needs multifaceted understanding of the occurrence and proliferation mechanisms at the molecular level than at the cellular or tissue level. Convergence revolution creates a platform for multidisciplinary integration for providing a solution for breast cancer cure. First life science revolution played a very critical role in diagnosis, prognosis, treatment and to cure (only upon early diagnosis) in terms of differentiating types of cancer and the second revolution discovered Trastuzumab.

Convergence revolution is not an interdisciplinary collaboration but taking science, research and technology development into next revolution by interdisciplinary integration. Thereby, major barriers confronted can be surmounted. Creation of largest patient database (one million patients), incorporating genetic, behavioural (societal) and clinical information is currently in progress. Using big data analytics and machine-learning techniques, the results obtained from the largest patient database (one million patients) are to be disseminated to researchers in engineering, physical, biological and clinical sciences for them to be interpreted. Government agencies like National Science Foundation (NSF), National Institute of Health (NIH), Defense Advanced Research Projects Agency (DARPA) [14] and other funding agencies to formulate a denotative interdisciplinary convergence guidelines so that, the major barrier of long standing revenues generations can be crossed over.

Convergence revolution provides solution using multi-pronged approach for breast cancer diagnosis, treatment and a potential cure. In terms of early diagnosis, Raman spectroscopy added to the existing repertoire of diagnostic imaging methods and for treatment and potential cure, nanobiotechnology for targeted controlled drug release nanomedicine. Any adult in the age group from birth to 50 years occurrence of cancer risk is higher for our female folks (5.4%) than their male counterparts (3.4%). Major reason being, the comparative high encumbrance of breast, gynaec and thyroid cancers in young women during their conceptive fertile time period. From last three decades onwards, exponential incremental rise in breast cancer incidence may be because of changes in female reproductive choice of intimacies and crumby food intake habits. Also to an accessible dazzling mammography screening, of the susceptible population, leading to the increased detection of breast cancer.

## Raman spectroscopy necessitates convergence revolution

Convergence revolution provides solution for early breast cancer diagnosis and breast cancer treatment which has great potential as a cure drug regime. In terms of early breast cancer diagnosis, imaging technique Raman spectroscopy is utilized. Raman spectrum observed for clinical biological samples fall in the range of 400 – 2000  $\text{cm}^{-1}$ . Spectrum interpretation and inference necessitates convergence revolution for the interpretation and of distinctive biological ‘fingerprint’ obtained from the clinical specimens [15]. They are:

- (i)Physicists (skill set on Raman technique)
- (ii)Chemists (sample processing and readiness for analysis)
- (iii)Bioengineers (spectrum inference)
- (iv)Clinical Oncologists (prognosis of the spectrum) and finally
- (v)Technologists (testing and training the equipment for nearly nil false positive/ negative results)

Clinical trials have been initiated in this direction for example NCT00918788 [16] and NCT00918216 [17] fall under this category. This technique is currently planned to shift and elevate to clinical settings whereby the ability to differentiate between benign and malignant tumors apart from its cost effectiveness lies the success of the clinical protocol for breast cancer early diagnosis.

## Targeted Delivery Nanoformulation

Nanoparticles can move to the target site (breast tissue) from the site of parenteral route of administration, by virtue of its structural morphology of spherical in shape conforming the principle of classical chemical engineering fluid dynamics principles. Upon its arrival at the destination the offloading of the drug molecules under controlled release is mastered by calibre and intellectual skills of chemists, biochemists, bioengineers, radiographers clinical oncologists. Convergence revolution has been pioneered at MIT’s Koch Institute for Integrative Cancer Research located in Boston, Massachusetts for conquering cancer for a cure. Nanoparticles as nanoformulation are being tried across continents for breast cancer using targeted delivery mechanism. Several therapeutic proteins Trastuzumab [18], being an important trillion dollar molecule, are used as targeted controlled release nanoformulations. Biocompatible and biodegradable polymers play a very critical role in the controlled delivery of the drug load to the targeted site by engineered porosity [19, 20]. Further to the existing of single molecule functionality, MIT’s Koch Institute for Integrative Cancer Research is working on “smart” nanoparticles to deliver more than one drug molecule to the targeted breast cancerous tissue [21]. Hydrophilicity and hydrophobicity of the drug chemical nature is taken advantage to come up with the nanoformulation embedded to biocompatible, biodegradable polymers which carry the drug load to the breast cancerous tissue and off-loads at a precise rate. First drug molecule released shrinks the tumor by shutting down the cellular growth pathway. The off-loaded second drug which is released after several hours’ maybe days targets the tumor DNA.

By using big data analytics and machine learning techniques of patient’s data of precise clinical manifestations, may be possible to identify precise biomarkers in blood or urine which

can be used for early diagnosis of breast cancer. Upon early diagnosis, administration of precise personalized nanomedicine is quite possible which can reduce the time and cost of drug regimen. By the next decade because of big data analytics, time and cost of bench to bedside drug discovery lifecycle can be drastically reduced from 9 – 12 years and current value of around \$1.1 billion.

### Valley of death

Academia and corporate working set-up are placed on different ends of the deliverable spectrum to overcome the “valley of death” [22]. Industrial based R&D is very time specific for real-world problems with an exit plan, whereas academic research is more often towards basic science. Risk sharing of funds is slowly coming to existence, academia had the luxury of non-accountability of research failures, of late, this is slowly started to co-exist with industrial set-up of financial accountability. Blockbuster breast cancer drug, Trastuzumab (Herceptin™) discovery is a perfect example of the success of academic – industry collaboration between UCLA and Genentech.

### Start-ups

MIT’s educational efforts in entrepreneurship and innovation have an impressive impact at local, regional, and global levels. 30,000 companies have been founded by MIT alumni as per the report till the year 2104 [23], 4.6 million people employed and producing annual revenues of \$1.9 trillion, equivalent to the world’s 10th largest economy. Many numbers of start-ups have been found from Kock institute [24] (Figure -2).

Several start-ups are working in this direction onto clinical trials which can pave way for the cure of belligerent types of breast cancers which gravitates to onslaught the tender youth women folks. DARPA conducted a demo day [25] to exhibit products evolved of convergence approach in Pentagon (Figure-3).

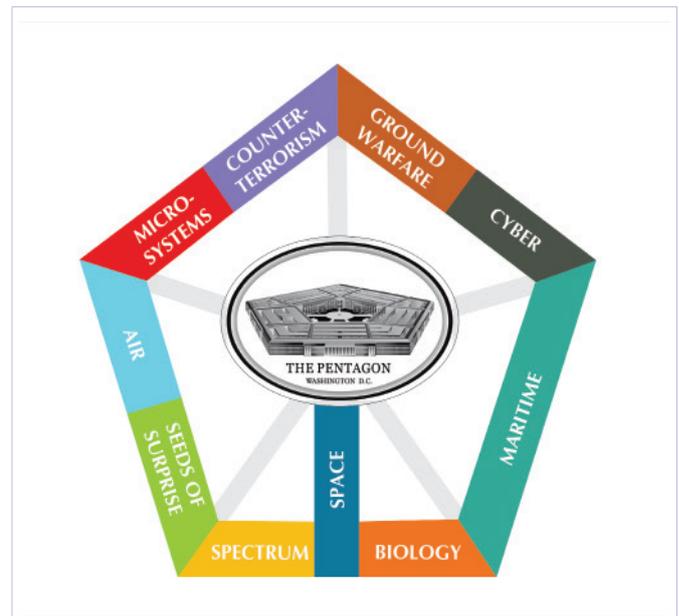


Figure 3: DARPA Demo day depicting convergence approach [25]

### Conclusion

Convergence technology integrates different disciplines for breast cancer cure involving academia, industry, government agencies, regulatory agencies and start-ups. Cancer moonshot facilitates the process for the translation of the nanomedicine to the clinics with the fact of achieving 10 years of progress in five years only which is very much a possibility with breast cancer data of the patients being shared rather than stored with very little use. Imaging protocols for early diagnosis by using Raman spectroscopy, onco-nanoformulation by targeted delivery of controlled release for treatment and by involving the regulatory bodies, bench to bedside at a quicker time for treatment and prospective cure for breast cancer is a reality by next decade.

### Conflict of interest

Balu Ranganathan discloses financial interest in Palms Connect LLC, Sandy, Utah 84094, United States of America, holds stock options as stakes in the company.

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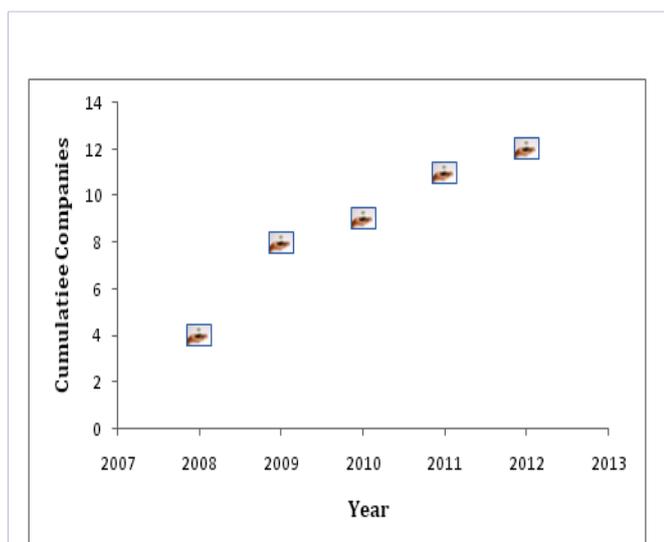


Figure 2: Number of Start – ups from Kock Institute

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