How do Cancer Researchers Perceive the Future of Cancer in Asia?

Cross-boundary Cancer Studies at the University of Tokyo: Opening a Path Through Research to the Future of Cancer Treatment

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LECTURER PROFILE
Tetsuo Noda graduated from Tohoku University Faculty of Medicine in 1980, before going on to receive a doctorate from the same university in 1984 (doctor of medicine). After engaging in research at the National Cancer Institute of the USA, the Institute for Virus Research of Kyoto University and the Whitehead Institute for Biomedical Research of Massachusetts Institute of Technology (MIT), he become the director of the cellular biology laboratory of the Cancer Institute of the Japanese Foundation for Cancer Research in 1990. After being appointed as professor of molecular genetics at Tohoku University in 1997, he has been serving in his current post since 2006. He has achieved many cutting-edge outcomes in the course of his gene analysis research relating to carcinogenesis. In addition to serving as president of the Japanese Cancer Association (JCA) he also serves as the leader of the Project for development of Innovative Research on Cancer Therapeutics.

OPENING A PATH THROUGH RESEARCH TO THE FUTURE OF CANCER TREATMENT

No matter how many discoveries are achieved in cancer research, the current situation is that many of these discoveries do not filter through to cancer patients. What is the cause of this situation? What needs to be done to achieve a breakthrough? ‘Medicine’ is only ‘medicine’ if it can actually be received by patients. A measure of national competence is actually therefore the degree to which medicines can be manufactured that are provided not to a single cancer patient, but to many patients. In order to achieve such a goal, it is likely that ‘science’ alone will not be sufficient to denote a country’s competence, but rather a comprehensive approach will be required.

THE DAWN OF CANCER RESEARCH

The major characteristic of cancer research in the 20th century was that it was carried forward with a focus on the life sciences, including genome and molecular biology research. This focus had one demerit, in that research was concentrated on the identification of cancer cells, which slowed discoveries about the nature of individual cancers. It has only been in the 21st century that cancers have come to be treated as individual diseases, which has seen the inauguration of scientific research into cancer cells.

The discovery of the tumorigenic retrovirus marks the dawn of cancer research. It was in this research that the virus oncogene was discovered. It was subsequently understood that oncogenes exist in our own genome. There came to be a general recognition, based also on the results of university-based experiments, that the activation of genetic mutations was the cause of cancer. This backstory has been a source of courage and inspiration to scientists, who believed that if we could identify, study and understand cancer then it could be controlled, cured and beaten. The reality has been, however, that the process of understanding cancer has not run so smoothly.

Cancer research traces its genesis to around the year 1900. Given that infectious diseases were predominant at that time,
it was not until 1926 that the first Nobel Prize for cancer-related research was won by Prof. Johannes Andreas Grib Fibiger, a Danish scholar who had published a treatise on parasitic oncogenesis. The results of Fibiger’s research are, however, now discredited. At this time, another person on the shortlist for the Nobel Prize was Prof. Katusaburo Yamagwa of the University of Tokyo. In his paper, he discussed scientific methods of inducing cancer and reported that he had been able to induce squamous cell cancer by smearing coal tar on the ears of rabbits. This was the first time that cancer had been induced by artificial means, but in the race for the Nobel Prize, it was thought at the time that the University of Tokyo was a more reliable source of research than the University of Tokyo.

It would be a further 40 years until a Nobel Prize in Physiology or Medicine would be granted again for cancer-related research. In 1966, Prof. Peyton Rous of the USA won the Nobel Prize for his discovery of tumor-inducing viruses (retroviruses) and his work on viral oncogenesis. In his experiments, Prof. Rous ground up cancer cells that had developed in chickens and injected disease-free birds with a cell-free filtrate that only viruses could cross, the result being that cancer developed in the previously disease-free chickens. At the time that Prof. Rous was engaged in his research it was not possible to culture cells and only possible to test the theory on specimens. Following the Second World War it became possible to culture and alter cells, enabling the creation of cancerous cells through viral transmission under laboratory conditions. It was at this time that the oncogene was first discovered.

If the oncogene of a virus is brought into contact with normal cells, it causes cancer, demonstrating that the virus has entered the cancerous cells. However, it was also found that substances similar to the cancer-carrying virus were also present in cells where cancer had not developed. This discovery was announced in 1976 by Prof. J. Michael Bishop and Prof. Harold E. Varmus. Theirs was a startling paper, noting that oncogenes were originally present in normal cells and it was these proto-oncogenes that viruses extracted and used to cause cancer. Bishop and Varmus were presented with the Nobel Prize in Physiology or Medicine in 1989. Prior to the Nobel Prize, in 1982 Bishop and Varmus had also received the Albert Lasker Basic Medical Research Award in the same year as Prof. Hidesaburo Hanafusa of Japan, who was awarded the prize for demonstrating how RNA tumor viruses cause cancer, and elucidating their role in combining, rescuing and maintaining oncogenes in the viral genome.

What we know now is that oncogenes are present in the body and once activated these genes go on to cause cancer. The type of cancer known as anaplastic lymphoma kinase (ALK) lung cancer is created by the ALK gene forming a fusion gene with any of several other genes, which then causes lung cancer. The activation process for this oncogene is qualitative and quantitative, but it is possible to differentiate it from normal genes.

The process of drug discovery in cancer is focused on the search for a chemical compound that when brought into contact with a cancer cell will kill it off. However, whether it be rats or other animals, if you give them a poison they will die. Poisons used to date have all been cytotoxic and have targeted cell growth. If given to human patients, the cytotoxic poison will cause blood plasma, intestinal and hair cells, all of which proliferate at a rapid rate, to die. However, the molecularly targeted therapies of recent times have been created to specifically target the molecules involved in carcinogenesis, leaving other rapidly-dividing cells alone.

The typical pathway for the creation of molecularly targeted drugs is composed of a three-step process: (i) search for target molecules, (ii) search for an antibody and low molecular compound that will constrain the functions of targeted molecules and (iii) scientifically and critically examine whether the compound identified can be used in humans. Since 2000 there have been two further Nobel Prizes awarded relating to cancer research. One of these was for the discovery of Helicobacter pylori and how it may be a cause for viral cancerogenesis in human papilloma virus (HPV) cervical cancer. However, as the mechanism of H. pylori is still not fully understood, what we currently know is used to prevent cancer. One of the reasons the mechanism has not been clarified is because the bacteria is an exogenous gene. Endogenous genes are used as the target for treatment, but exogenous genes are targeted as a preventive measure. A challenge for the research community is to understand the mechanism of the bacteria in the near term and target it molecularly.

Looking back through history we can see that the oldest form of cancer treatment was through surgical methods. An excavated human skeleton found at the base of a pyramid in Egypt with a hole in its head has told us of the history of such methods. The next method to be used was radiotherapy, which has a history dating back more than a century. Japanese research in this area was particularly notable and garnered global attention. Even now, Japan is one of the top-three countries in the world in terms of the volume of radium it possesses.

The next method for treating cancer to appear during the course of history was the use of drugs, namely chemotherapy. The famous story about the first use of chemotherapy related to nitrogen mustard gas. Towards the end of the First World War a German U-boat sank an American ship loaded with large quantities of mustard gas in a British port. Sailors affected by the sinking had ingested or come into contact with large quantities of mustard gas and medical examination showed that all of them had decreased counts of white blood cells, as a result of which many fell prey to infectious diseases and died. The doctors who discovered this effect considered that if the mustard gas could cause white blood cell counts to drop so dramatically, mustard gas could be used in the treatment of leukemia and it was used as a drug against malignant lymphoma. As can be seen from the above anecdote, although the processes at work may have not been fully understood, a drug treatment was developed that had been shown to work on human subjects. However, given that a drug treatment cannot be used on humans without due testing, it was further developed through use on animals. Even now, cancer research
involves gathering chemical compounds from around Japan and testing them against cancer cells to gain a profile for that compound.

A more recent trend in cancer research has been to analyze cancer cells and identify molecules that can be targeted in treatment. Although molecularly targeted drugs are said to have few side effects, epidermal growth factor receptors (EGFR) can cause terrible skin complaints.

Since the start of the 21st century we have entered an era in which >90% of cancer drugs that have been discovered and approved are molecularly targeted drugs. It can be expected that further new and innovative molecularly targeted drugs will be discovered from now and countries wishing to produce such drugs must enhance their basic research capacity.

**Research and Development in Japan**

When thinking about drugs, it is necessary to consider not only molecularly targeted drugs themselves, but also the companies that produce them. No matter how promising the discovery of a targeted therapy may be, if no companies exist to produce such a therapy it will never materialize, and if companies are not interested in the drug it will naturally not find its way to the patients who need it. So how does a pharmaceutical company go about creating a drug? If we look back to the 20th century we can see that a total of 26 types of drugs were brought to the market in Japan. These were created through a process of basic research, animal testing prior to clinical trials, and clinical trials targeting patients before being approved. In order to realize these 26 types of drugs it was the case that 60,000 different compounds were screened. As you can see drug creation has an extremely poor ‘batting average,’ and drug development presents real risk. It is still the case that almost all drugs are produced in Europe, the USA and Japan, and emerging economies have yet to catch up. To put this in context, take the example of television production. Today 90% of all televisions produced globally are flat-screen television, of which 30% are made in China. In contrast, the process of drug discovery and creation is an extremely difficult one that requires comprehensive skill and know-how. The drug manufacturing sector is one that emerging economies have yet to get a foothold in.

To compound the situation in this global era is the fact that companies must engage in efforts to protect their intellectual property rights. These efforts take up a significant proportion of R&D costs. In contrast to what happened in the past, in today’s world if it becomes known that a promising molecularly targeted therapy had been found, a mega-pharmaceutical steps in, thus initiating a process of intense global competition.

However, this process of creation and competition presents a very serious issue. The longest period of a substance patent is 25 years. This means that once a drug is successfully developed and marketed its patent life will only be ~10 years, after which a company in India, or other countries will create a generic version, making it uneconomical for the original developer to sell. It is for this reason that companies are now taking out patents for specific elements of a compound and methods, and only applying for a substance patent when a drug reaches the clinical testing stage. However, this process of patent applications also presents its own problems, in that a doctor may have made all preparations for a clinical trial, but due to the patent application process the start of the trial is delayed, thus taking up more precious time.

Given the above factors, development of drugs on the national level must respond to the following imperatives: (i) how fast can a promising therapy be developed? (ii) How fast can scientific evaluation of clinical trials be attained? Although there are many revolutionary therapeutic agents for cancer coming on to the market, there is a danger that there will only be one treatment therapy that has originated in Japan. On the other hand, Japan is an extremely attractive market for the mega-pharmaceutical companies of other countries. Given that Japan has a National Health Insurance scheme in place, if a treatment is approved as being of a suitably high standard it is possible for patients to receive that treatment at low cost. In the USA and other countries there is no linkage between approval of drugs and medical insurance, meaning that only people who are paying into a very good private insurance scheme have full access to the full range of new drugs. In terms of market scale Japan is second in the world after the USA for pharmaceutical products and given that the health insurance system makes it easy to calculate how much revenue can be gained if a drug were taken by x number of patients each year, it is easy for companies to contemplate business in Japan. However, in an environment in which new diagnostic technologies are being utilized and where overseas companies have a monopoly on business, if medical treatment costs are permitted to continue to appreciate naturally, ultimately the National Health Insurance scheme will be bankrupted. The only other option is to introduce a form of mixed treatment that involves patient co-payment for some treatments or drugs, which would create disparities in the standard of care received by high and low income sectors of society.

The worst thing about the current situation is that it is insurance companies that are making the greatest profits. Money is also finding its way to practitioners of alternative medicine. Current total medical care expenditure in Japan amounts to 30 trillion yen, of which 3–4 trillion yen is accounted for by cancer treatment costs. However, people who are concerned about the system and their treatment are throwing more money at alternative therapies and insurance policies. I believe that such people who have money to spare should invest in organizations that are creating medical care solutions in Japan and ensure that drugs can continued to be created in Japan, by Japanese hands.

The fundamentals of any molecularly targeted drug must be strong, and this is not possible without implementing scientific clinical trials, prior to which pre-clinical trials are required. This requires some sort of a bridge by which to link the pre-clinical and clinical phases, but scientists are often unsuited to providing such a bridge. The type of person who is required is
someone with business sense, and unless such a person is involved in the process a drug will not ultimately be able to be created. There is a well-known story that concerns the antibody drug Herceptin, or Trastuzumab. Approximately 25% of all cases of breast cancer are treated with Herceptin at a cost of around 400 000 yen per month. All of that money goes to F. Hoffmann-La Roche Ltd (Roche). However, it was in fact Prof. Kumao Toshima and Prof. Tadashi Yamamoto of The Institute of Medical Science of the University of Tokyo who discovered the EGFR that is the target for Herceptin. Unfortunately their discovery was not taken further and was not developed into a drug. In contrast, various antibodies are being trialed in clinical tests overseas. This demonstrates clearly that without the backing of a venture company it is not possible to press ahead and further develop a medical discovery. In Japan there is little attempt made to advance from the academic stage. Venture companies are adept at thinking about how to implement clinical trials and technologies with a view to achieving a cure for a disease, but before that stage it is science that clarifies and elucidates the actual mechanism by which a cure is achieved. Ultimately the rights to the discovery by Yamamoto and Toshima were bought by Roche. Although people in Japan are engaged in outstanding basic research and have achieved excellent results, there are no bioventures in Japan whatsoever and no people capable of taking a discovery through to the R&D stage.

**Drug Manufacturing, Companies and Government Administration**

So what can be done in the face of this situation? The total budget for research in Japan is a mere fraction of the budget available in Europe and the USA. Each year the Cancer Measures and Health Promotion Division of the Ministry of Health, Labour and Welfare (MHLW) announces the ‘Basic Plan to Promote Cancer Control.’ The seventh point on the list in this plan is ‘cancer research,’ but the budget allocated for such research is \( \sim 45 \) billion yen. In contrast, the research budget of the National Cancer Institute (NCI) of the USA is \( \sim 10 \) times larger, at \( \sim 500 \) billion yen. The Japanese Cancer Association has no research expenditure, whereas the NCI disburses 4 billion yen in research expenses. In the USA it is a practice to hold academic gatherings and collect donations from companies, which are then made available for research expenses. The Japan Cancer Society receives \( <1 \) billion yen in donations, whereas its US counterpart receives almost 100 billion yen. Although Japan’s GDP is one-third that of the USA, the differences in research funding is not by any means one-third. One of the reasons for these differences lies in the issue of keeping down medical expenses overall. For example, a patient having an operation at the University of Texas MD Anderson Cancer Center would have to pay between 7 and 10 times the cost of the same operation in Japan. In addition, given that hospitalization costs are also expensive, patients tend to leave hospital much quicker than in Japan. In return for such high-cost the doctors and paramedical staff in the USA are all outstanding. In terms of an analogy you could say that medical treatment in the USA is attempting to alter the course of a wide, vast river. To use a similar analogy to describe Japan, you would have to say that medical treatment is like a dam or levee being built around a river to contain its flow and keep down medical costs, while also attempting to create innovation and new ideas. However, there is a limit to how much this can be implemented. It is for this reason that Japanese pharmaceutical companies are seeking to advance overseas, but their efforts have been half-hearted. In many cases, they do not make a full-fledged entry into overseas markets, but first go abroad to seek out seeds for new development and then have clinical trials implemented overseas. The far better way would be to completely globalize, engage in M&A activities and to work with foreigners to create new drugs, just like other foreign companies, but this is not happening.

Nonetheless, Japanese pharmaceutical companies are hard at work. According to science and technology indices, the public funding of Japanese pharmaceutical companies stands at 17.5%, with R&D budget from the private sector accounting for 82.2% of funds. Even in the worst case Japanese pharmaceutical companies allocate 20% of their budget to R&D expenses. In the general case in Japan, companies like the East Japan Railway Company (JR East), for example, develop shinkansen trains and rolling stock for sale overseas, but their R&D expenses account for no \( >2.5\% \) of total budget. There are no companies other than pharmaceuticals where R&D expenses are \( >5\% \) of total budget.

One of the most serious problems is the vertical way in which cancer research is structured. The budgets for cancer research of the Ministry of Education, Culture, Sports, Science and Technology (MEXT) and the Science and Technology Agency are separate and these government bodies cling doggedly to their own budgets. Even if the Science and Technology Agency had a budget surplus it would not release it for the use of MEXT, even if the ministry had found promising seeds for development. Although MEXT has developed a research organization that works well, it is just one of a number of ministries involved in cancer research, including the Ministry of Economy, Trade and Industry and the MHLW and all these organizations work separately from each other.

The USA also often complains about a lack of funding, but it was President Nixon who said that there was no need to put man on the moon, and funds should be focused on curing cancer. Nixon was responsible for the establishment of a national cancer program in the USA and by ensuring that cancer research-related budgets were appraised on a nationwide basis, he ensured that cancer funding would flow flexibly and organically. Within the grounds of the National Institutes of Health (NIH) there are almost 100 buildings, all containing different research institutes, including for infectious disease and cancer. Cancer-related matters in Japan, however, are covered by a multiplicity of government bodies, including the Ministry of Economy, Trade and Industry, MHLW, and the Ministry of Education, Culture, Sports, Science and Technology and just...
where the budget for measures to control cancer is being allocated and whether it is achieving results is unclear.

The most urgent and overriding issue is the lack of any biotech corporations in Japan. The thinking in Japan tends to be that there are no small companies like bio-ventures that are engaged in the process of drug development, but that sort of thinking is mistaken. The reality is that when such small companies launch clinical trials, they are bought out by mega-pharmaceuticals who buy the rights to the intellectual property created. From time to time I meet researchers who left Japan to engage in research in the USA 10 years ago or so and ended up staying in the USA, and when I receive their business cards they invariably have the names of small, unknown bio-venture companies also written there. However, we have now reached a point where these types of venture capital-incubated drugs are being bought out by mega-pharmaceuticals. Incidentally, it should be mentioned that the total investment in venture capital in Japan stands somewhere between the level of investment in Hungary and Slovakia. Although even only 10 years ago there was still a momentum towards university-launched ventures, the result has been a ‘Death Valley,’ rather than a ‘Silicon Valley.’ Bio-ventures in particular have had a dismal track record. On the upside Japanese companies are investing R&D expenses in overseas bio-ventures, but domestically there is very little funding. One of the reasons for this is because clinical trials are so difficult to implement in Japan, leading to a lack of incentive for overseas investors to place an R&D division here.

**Promoting Clinical and Therapeutic Trials**

Another problem in Japan lies in the promotion of clinical and therapeutic trials. Although Japanese doctors work to a very high standard, their experience and implementation of clinical and therapeutic trials is still not well developed. Trials in Japan are not unified or integrated legally or qualitatively and they are also small in scale. Given the severe regulations and requirements concerning clinical trial data, it is not possible to implement trials speedily in Japan. ‘Clinical research’ refers to research that utilizes patient samples and data. A clinical trial is the result of research and is the means to get a drug approved. However, the quality of clinical trials in Japan is poor in comparison to those overseas and the data are not readily usable. It is for this reason that foreign-manufactured drugs are ultimately sold.

Another issue is the ‘drug lag,’ the major problem with which is Japan’s participation in international joint clinical trials. Unless the scale of a drug market can be perceived as a whole it is impossible for a company to make business calculations, but there are very few facilities in Japan where it is possible to implement joint trials.

Finally, I would also like to point out that there is no structure in Japan that would enable the large-scale implementation of clinical trials. Although the quality of doctors engaged in clinical research is extremely good, as there is no concrete research or trial implementation system in place, research does not match the needs of R&D. The MHLW has been engaged in measures to respond to this issue for the last 5 years, but no progress has yet been made.

One of the other issues for clinical trials is the size of hospitals. Hospitals overseas are very large. Even in Korea hospitals are large in size and can conclude a critical trial three or four times faster than in Japan. In China also, there are hospitals in Shenzhen and Shanghai that have 3000 or 4000 beds. Medical innovation is a key part of government policy in China and the government speaks in terms of providing one-stop support for the medical sector. In Japan we have a system where Japanese companies take on the work that was started in academia, but we must work to create a system that will enable companies to embark immediately on Phase I work. It will likely be difficult to compete with overseas companies and over the next 5–10 years innovation will change. If all that is done is to tell Japanese pharmaceutical companies to come up with innovation in a market that is focused only on keeping down medical expenses, the future for drug development in Japan does not look bright. Unless we go out and face the world we will become unable to compete.

**DISCUSSION**

Q: Which do you think is more important, that drugs are produced in Japan, or that the lives of patients are extended?

**Noda:** I would say the former. Unless drugs are produced by Japanese companies no profits will be generated and Japanese patients will have to take expensive foreign drugs, which will be to the further detriment of the Japanese medical economy. If Japan is merely perceived as a market by overseas companies, the number of drugs available for healthcare purposes is liable to decrease, or new drugs will only become available outside the national health insurance scheme, at the expense of the patient.

Q: Do you think that graduate school education should be more segmentalized and specialized for the purpose of developing cancer treatments?

**Noda:** I don’t think that would be beneficial as clinical research responds to the needs of various specialties. There are many outstanding professors at the University of Tokyo and other institutions who are engaged in excellent basic research, and there are many outstanding clinicians who become university professors. The clinical researchers of the future will be those who seek how fast their ideas and clinical trials can be realized through clinical research as human biology.

Q: So if you aim to become a clinical doctor it is still necessary to study biological sciences at graduate school?

**Noda:** Of course. It is necessary to learn the skills and concepts that will enable you to draw out evidence from the bio-field.

Q: What do you think is the best way to motivate people who have been brought up as basic researchers to seek to create drugs?

**Noda:** Basically I think that the motivation to develop drugs comes from a desire to know and the interesting nature of drug development. The desire to put your energy and desire to help to a good cause and see how far you can go is not something that can be taught. It is also not something that a person can engage in alone, it requires a strong network of people.

Conflict of interest statement

None declared.