

FOCUS ON: BIOTECHNOLOGY

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STUDY IN JAPAN

JAPANESE SCHOLARSHIPS FOR INTERNATIONAL STUDENTS

INTRODUCTION :

Seeing India as a powerful global hub for biotechnology in future, the very first important factor might be '*creation of world class human capital*'. In this quest, this e-book takes an initiative by bringing the recent and innovative articles with various flavors of fast growing and exciting biotechnology field. The main objective behind this is to aware students and so thus their enthusiasm towards the cutting edge knowledge, scientific discovery, and skill necessary for the science-based research, business, and careers for tomorrow.

Cutting edge biotechnology articles offer an approach to link the education and the world-of-work, particularly the specific opportunities and workforce required in biotechnology industry. This defines group of careers in biotech-nology industry and may help students to choose career in their area of interest and prepare themselves for building their own futures.

Research breakthrough highlight some remarkable scientific achievements in given field and up-tech technologies which can offer a huge potential in diagnosis, preventive healthcare, treatment of many diseases and inherited disordered and many other benefits to society. We also feature the interview of co-discover ((Dr. James Watson) of DNA structure with Dr. Francis whose far-reaching interests and achievement has been

left an enduring imprint on science. We hope, these qualities to be a great scientist "working hard and perseverance to make things happen" will students imbibe in their lives.

Booming economy of India, Government committed to science and innovation, and a well-developed drug industry all are representing a unique and an exciting time for Indian science. However, long term success depends on Indian scientists advancing past endemic poverty, poor public health infrastructure and a rising disease burden. In outlook India, we explore some challenges in India and how a handful scientists and biotech companies are overcoming them to transform India's research landscape.

Additionally, we include News features to well-connect the students with the research advancement and programs in life sciences globally and Education link with the intention of disseminating students a depth and pertinent knowledge of cutting edge science.

Finally, we hope, our efforts will motivate and encourage students aspiring to pursue a career in scientific field. We would like to compliment Biyani group colleges for start-up in sharing the knowledge and awareness campaign among students and staff, will definitely boost up their confidence to take the next steps in education and promote an appropriate implementation in the way of learning and teaching also.

My best wishes to the students of Biyani group colleges for their great start in life!

Sincerely,

Madhu Biyani

CUTTING EDGE: BIOTECHNOLOGY

AN INDUSTRY FOR THE
FUTURE

***work with your hands
and your mind***

***work with new ideas
and new products***

***work in many careers
and build your future***

“....it is important that biotech is the one industry that’s poised to grapple with every major human and environmental challenge, from global hunger to global warming...” G. Steven Burrill, *biotech 2003*(life sciences: revolution and restructuring)

You have been read headlines lots that biotechnology is emerging as a fast growing sector in our country and biotech based industries are expanding at a scorching pace. But in fact, biotechnology has been around us a long time.

Traditional biotechnology was (and still is) the use of living organisms to solve problems and make useful products. Domesticating crop plants and farm animals through selective breeding, and using yeast to make bread rise and produce

wine are examples of traditional biotechnology.

New biotechnology is based on scientific advances over the last 50 years that have enabled us to understand how living organisms work- and how can work for us. Now, our understanding of how cells work makes it possible to create new varieties of plants with better nutrients for our diet, and the traditional fermentation processes used to make wine or beer have been re-tooled to produce cutting edge pharmaceuticals for previously incurable diseases.

Biotechnology in Industry

There is a broad range of industries using the tools of biotechnology to fight disease, feed the world and save our environment. For example:

- A pharmaceutical company developing new ways to cure diseases;
- A chemical company making plastic from corn instead of petroleum;
- An environmental company finding new microorganisms to clean up oil spills;
- An agricultural company developing drought- resistance crops;

- An energy company using fermentation to make ethanol for fuel.

Biotechnology industry is well advanced in the developed countries and offering a wide variety of career opportunities. Presently, biotechnology industry sector is also fast emerging in India and biotechnology Industry is experiencing a tremendous growth rate of nearly 40% with annual turnover in 2005 being US \$1.07 billion. The consumption of biotech products in India is expected to grow to the tune of \$ US 4270 million by 2010. So, this revolution in biotechnology will open many doors for young generations.

Biotechnology's Toolbox

Biotechnology is not just one technology, but many. Biotechnology is a toolbox filled with many different kinds of living cells and their component molecules, and different way to use them. Because there are millions of different species of plants, animals, and microorganisms in the world, each having cells and molecules with unique characteristics, there are a lot of potential tools in the toolbox! That is why biotechnology is so powerful and can be applied in so many different ways.

There are three basic kinds of biotechnology tools.

- **Working with cells:** a cell is the smallest unit of life and

contains billions of molecules of many different kinds. You can think of a cell as a tiny chemical plant in which thousands of chemical reactions are going on every minute. This complex chemistry is what makes cells useful. For example, we can use chemical reactions in cells to break down pollutants or to synthesize antibiotics to cure infections. While a single cell can not produce enough of a product such as an antibiotic to do any good, we can grow billions of cells in bioreactors. This is called bioprocessing, and people who work in this field need to know biology, engineering and manufacturing technology.

- **Working with proteins:** many of molecules in cells are proteins. These are the molecules that actually do the chemical work inside a cell and make it useful. Many of these proteins are enzymes. Even a simple cell such as a bacterium contains about 2,000 different proteins, each one with a unique job. When we grow cells to make protein products. These range from the enzymes added to laundry detergents, to insulin for diabetics, to vaccines used to prevent disease. Chemists, biochemists, and molecular biologists study the intricate structure of protein molecules and develop new ways to use these molecules.

- **Working with genes:** You know that DNA is molecule

responsible for inheritance. The sequences of chemical building blocks strung together to make up a DNA molecules are instructions, blueprints, for a cell. These instructions, or genes, tell the cell how to make each of its proteins. These instructions are “written” in a chemical language called the genetic code. Because we have also learned how to change the code in DNA molecules, we can give a cell new instruction, telling it how to make the protein we want or how to do some other job. This is called genetic engineering. For example, geneticists have inserted the gene for a human protein called interferon into hamster cells that can be grown in bioreactors. The interferon is used to treat multiple sclerosis.

Now, our understanding of how cells work makes it possible to create new varieties of plants with better nutrients for our diet, and produce cutting- edge pharmaceuticals for previously incurable diseases.

A career with many choices

Biotechnology offers a wider range of career choices than many other fields, you can choose among different types of employers, different roles within organization, different work environments, and different paths for future advancement.

Whatever your career goals are, whatever you enjoy doing, wherever you want to work, and biotechnology offers some great career choices for you.

A choice of employers : The knowledge and skill required for a job in biotechnology are highly transferable. In industry, you can work for a pharmaceutical, medical device, food, agricultural, or chemical company. You might also work for a government agency or in a university.

A choice of work : Biotechnology careers have expanded well beyond the research laboratory as innovative ideas move to practical applications in the marketplace. Today there are many different jobs you can do in a biotechnology or related bioscience company as a scientist, a laboratory technician, an engineer, a process technician, a clinical research associate.

A choice of environments : Jobs are available in many different types of industries, companies, and organizations. You can work in fast – paced business environment, a cutting – edge research lab, a high-tech manufacturing facility, agricultural research station. You can work in a classroom educating future scientists and technicians.

A choice of futures : Because biotechnology is an evolving field, it holds excellent promise for long-term career growth. You can advance by pursuing a management position. You can advance by obtaining additional

education. Biotechnology requires life-long learning. You can expand your knowledge more broadly by pursuing a higher degree

Preparing for the Future:

If you want to remain competitive over the long term in today's changing workplace, you will need to continuously expand your knowledge and upgrade your skills. This is especially true of biotechnology; where many new discoveries are anticipated in the coming decades. If learning excites you, biotechnology will offer you many opportunities to acquire new knowledge and learn new skills both now and throughout your career.

It is not surprising that solid career skills are equally as important as scientific or technical training in the eyes of a prospective employer. So it is critical that you begin sharpening your career skills early.

Learning for success

Skills

- Communication skills including strong writing and presentation skills
- Flexible interpersonal skills such as working effectively alone, with a partner, or as a member of a team.
- Leadership skills including the ability to organize, motivate, and manage people and projects.

- Organization skills including attention to detail, troubleshooting ability, and time management.

Attributes

Successful employees in the biotechnology industry are:

- Self-motivated
- Resourceful
- Reliable
- Punctual
- Eager to learn
- Problem solvers
- trustworthy

OUTLOOK: INDIA

Reaching for the top

The classical image of India that most people can conjure has cows, beggars, small children and sari-clad women all jostling for space on crowded streets. That image still reflects reality- but with palpable differences.

Along some of those streets now are gleaming, modern buildings where men and women churn out medicines for poor countries. Many children are being immunized with affordable vaccines produced by India's own biotechnology industry. And if the country continues to prosper as it has for the past decade, there soon may not be many beggars left. Since 1991, when India discarded its socialist past and institutes broad reforms, its economy has been growing rapidly. By 2032, India's economy could be larger than those of all but the U.S. and china, according to an estimate by the investment banking firm Goldman Sachs.

In the following pages, we look at what effect these changes have had on India's life sciences. Indian biotechnology companies have been remarkably successful, but they have made most of their money copying patented drugs. To sustain growth, they will have to become more innovative. The same is true for the basic-research

institutes, which have only recently begun to be globally competitive.

While developed nations are seeing their populations shrink, half of India's growing population is under the age of 25. The govt. must improve India's ailing universities to educate and train these young people and stem the haemorrhage of its brightest students to the United States and Europe. It must also untangle the still-rampant red tape that stifles creativity and set up ethics panels to monitor clinical research.

Most important, it must find a way to protect its people from grave health crises. India has among the highest rates of HIV/AIDS, diabetes and tuberculosis, which threaten to sap the country's resources and derail its progress.

This is critical juncture for India. The opportunities, whether in partnership with multinational pharmaceutical companies or as an outsourcing centre for clinical trials, are many and they can allow India to build a scientific and technological future to be proud of.

Innovation driven biotechnological sector

We are celebrating the recent success of India's biotech industry and applaud the

increased investment but will the current high levels of investment enough to secure its future?

The first prime minister of India, Jawaharlal Nehru, believed that science is the way out of poverty. The scientific opportunities in India may well prove him to be a true visionary, but there is much work to be done first.

It should be delighted and impressed us that scientists in India are publishing their papers in top-tier journal and biotechnology and pharmaceutical industry having the desire to undertake novel challenges. The top Indian companies provide copies of brand-name drugs and also manufacture a significant proportion of vaccines made for developing world. True, that still needs considerable sophistication and know-how.

But how do we encourage such innovation? The govt of India established the department of biotechnology in mid-1980s with well defined objectives to furnish state-of-art laboratories, provide increased funds for research, reduce the bureaucracy required for importing research materials, initiate projects that promote sharing the expensive equipments, offer visiting fellowship and build manpower to support the biotech industry. These initiatives have provided a strong foundation and the skilled resource pool vital for creating a sustainable biotechnology based businesses. DBT released an ambitious plan to

create a biotechnology industry that would generate revenues of about \$5 billion and creating one million skilled jobs in the next five years through products and services. As a part of strategy, the DBT is planning to make it easier for foreign-owned companies to set up in India. The DBT has also subsidized the construction of three biotechnology parks and aims to help finance at least ten such parks by2021. The science ministry has already announced a 50% increase in its budget over past year for drug discovery research and to encourage small businesses the DBT gives out grants of Rs 5 million for proof-of-concept research and low interest loans for product development and commercialization.

- 40 national research laboratories employing 15,000 scientists.
- 300 college level education and training institutes offering degrees and diplomas in biotechnology, bio-informatics and biological sciences, producing 300,000 students annually.
- 100 medical colleges qualifying 17000 medical practitioners per year.
- 100,000 postgraduate and 1500 PhD qualify I biosciences and engineering each year.

Despite this, India will not succeed unless it encourages innovation and reward excellence. Most Indian

universities still operate under a feudal system, which stifles creativity. Although country grants 300,000 degrees and diplomas in biotechnology, bioinformatics and the biological sciences each year, companies struggle to find skilled staff most of them get their degrees without seeing a biotech lab. Senior scientists are too often selected by seniority and rank, rather than their ability and achievements. Most scientists who train abroad return to India for family reasons and are loath to live away from their home town. They would sooner go back abroad than swap cities or states within India.

But science thrives when there is a nucleus of scientists striving for excellence. The Indian institute of science in Bangalore and national institutes of immunology in New Delhi have achieved this. To be competitive on a global scale, India needs to nurture such centers rather than worry about equitable distribution of the country's resources. The govt should provide incentives for interdisciplinary research because modern biology requires the expertise of scientists from many different fields. It should also encourage academics to forge alliances with industry, market their inventions and set up technology-transfer offices. Govt officials are always coming up with catchy slogans, such as 'IT today, BT tomorrow' but often they do not follow through on those ambitious plans. India is still far behind the United States, Europe and Japan. Although India has advantage that its citizens know English, it still lags

behind other Asian countries such as china and South Korea.

Companies worldwide and their innovative spirit should inspire biologists to be more adventurous. The time is ripe for life sciences to blossom in India, every day, newspapers carry headlines reporting Indian successes in information technology, tales of rich Indian biotech tycoons and highlighting the enormous purchasing power of the growing middle class.

India is not a poor country- indeed, it is rich in natural and intellectual resources- but it has many poor people. More than 700 million people, nearly 70% of the population, live in rural areas but contribute only 20% of the GDP. Until this disparity changes, vast sectors of Indian population will never see the benefits of biotechnology or modern medicine. It is very clear what India needs to do to become a world player in the life sciences, but unless the govt, researchers and the industry work together to put solutions into practice, all their best laid plans will not succeed.

Breathing life into Biology

Mriganka Sur says that life science will prosper in India once research and teaching connect.

Mringanka sur, a head of the dept. of brain and cognitive sciences at the Massachusetts institute of technology presently, was grown up in Allahabad in the northern state of Uttar Pradesh like most of students who were asked to choose between two careers - to be a doctor or an engineer and never considered any other options. So, for him becoming biology researcher did not figure on the list.

As it turns out, he eventually became a neuroscientist due to mainly his interest to understand how the brain works. He never had a university-level course in biology. He studied electrical engineering as an undergraduate in the early 1970s from Indian institute of technology (IIT) in Kanpur.

India must build excellence in life science training to capitalize on the life sciences and biotechnology revolution but in most countries, this is the task of universities. Unfortunately, the Indian universities system is in serious decline.

Only the exception of IIT most Indian universities are ill-equipped to tackle the complex, interdisciplinary nature of modern biology. Faculty members at both undergraduate teaching college and universities offering advanced degrees are largely concerned with teaching, and tend to focus more on theory than on experiment science. But research and teaching are inseparable components of a

modern science education according to most scientists view.

Most Indian universities don't have the equipment or faculty members and staff to give students a solid grounding in techniques and instruments. At some biology department, even introductory procedures such as DNA extraction are merely described.

This unfortunate division between research and teaching runs deep. The Indian govt decided more than 50 years ago to create focused research institutes. The scheme set up distinct priorities: universities would concentrate on teaching, and the institutes would concentrate on research. The policy led to a handful of excellent scientific institutes but also impoverished university-based research. There is no shortage of funds for university research or teaching laboratories, but a heavy teaching load, an overly bureaucratic system of appointments and promotions, and the lack of infrastructure have all made it difficult to recruit capable researchers.

Many institutes have begun training students by evolving graduate-level courses for small classes. Unfortunately, the top students who train at these institutes often choose to leave India and complete their PhDs abroad.

What might be done? There little question that the govt should actively support universities-based

research. Universities need help in upgrading their research infrastructure and laboratories, and in recruiting scientists with dedicated research space and healthy start-up packages. The govt could contribute to these costs.

There are signs that the govt is responding to these concerns. In march 2005, the science Advisory council recommended setting up a national science and engineering research foundation, on the lines of US national science foundation, to support research in various disciplines.

As founding for these universities increases, there should be accompanying changes in culture. Research and teaching should be values as mandatory components of faculty appointments and promotions.

The particular structure of Indian science also suggests solutions. For instance, funding agencies might consider establishing long term research faculty positions within universities. New research centers could be closely allied with or even located on university campuses. The researchers would be required to teach in the university, and university students would have access to research labs.

One model for effectively integrating research and teaching already exists within the IITs. These institutes continue to attract the best Indian undergraduates in engineering and physical sciences,

and give them world class education. Their success has positioned India as a key player in the IT industry. One small step towards boosting the life sciences may be to encourage the IITs to expand their biological sciences curriculum. But that cannot be only solution, if only because a wider transformation is needed.

Innovation in universities is part of a broader theme in how a society educates not only its elite but all of its citizens. A hard look at education in the life sciences is particularly urgent for a country such as India, which has both strong need for development and the ambition to match it..

Traditional medicine system

Science and business are racing to tap the 3000-year old system of medicine for new drugs.

In number 1997, ethno botanist Palpu pushpangadan was trekking through the tropical forests in the southern Indian state of kerala. Pushpangadna and his colleague were struggling to keep up, but their guides, men from local kani tribe, kept popping brownish- black fruit about the size of a cardamom pod into their mouths and walking briskly ahead. Curious, scientists ate the fruits and felt a surge of energy.

Locally known as *arogyapacha*, meaning 'evergreen health', the

fruit, *trichopus zeylanicus*, is noted in ancient Indian texts as a source of health and vigor. With the tribe's help, this scientist and his colleagues studied the plant extracts, isolated the active ingredients and developed an energy-boosted drug, Jeevani, combining *T. zeylanicus* with two other herbs mentioned in the texts.

The jeevani story is one often told in India as a success both in scientifically validating traditional knowledge and in setting up a model that benefits the local population.

Upgrading traditional remedies

Today, several laboratories and private companies are racing to tap ancient Indian system of medicine, ayurveda, for new drugs. The CSIR and health ministry are jointly digitizing ayurvedic knowledge and translating the information into English, Spanish, German, French and Japanese to forestall contentious patent application. CSIR has funded three ayurveda-based projects seeking drug candidates for arthritis, type-2 diabetes and liver diseases.

The ayurvedic system of medicine is nearly 3,000 years old and prescribes remedies for a range of problems from diarrhea to contraception. Classical texts describe more than 700 medicinal herbs with their taste, appearance and digestive effects to safety, efficacy, dosage and benefits.

For example, neem (*Azadirachta indica*) as an antidiabetic, *withania*

somnifera or the Indian ginseng as an antitumour agent and *curcumin*-the active ingredient in the spice turmeric- as an anti-infective, anti-inflammatory and anti-diabetic. Scientists are following intriguing leads that *curcumin* might have antimalarial activity and inhibit the replication of viruses. The Ayurvedic database in classical texts can be used for bioprospecting and new drug discovery but that task is easier said than done. Some species have become extinct. Time and environmental factors, as well as pesticide and heavy-metal contamination of soils and waters, may also have wrought subtle, but important, alterations in the plant products. In some cases, there is simply not enough raw materials to meet market demand. For example, the central drug research institutes in Lucknow developed an anticholesterol drug, *guggul*, from the resin of the tree *commiphora mukul*. The institute patented the drug in Europe and the United States, and in 1987 licensed it to a Mumbai-based company. The company was forced to stop making it because the slow-growing tree failed to produce fast enough. The institute has since developed a synthetic version of the drug.

With the herbs in hand, scientists must correctly identify the active ingredient, standardize the manufacturing process, and conduct clinical trials to test their effectiveness.

Data Mountain

There is no centralized database of the herbs under investigation, but one database of tribal traditional knowledge at the national botanical research institute in Lucknow catalogues more than 10,000 plant species. Of these, fewer than 200 have so far been investigated.

Ayurveda- based drug discovery uses 'reverse pharmacology', in which drug candidates are first identified based on large -scale use in population, then validated in clinical trials. Experts say this approach can cut the time for drug discovery from 12 years to 5 years or less, and for a fraction of the usual cost.

India can benefit enormously if it can build a golden triangle between traditional medicine, modern medicine and modern science.

Women scientists in India

A tough journey

To outsider, Vijaylaxmi Ravindranath's story might seem a resounding success. Vijaylakshmi Ravindranath is one of the very few high- achieving women scientists in India. In 2000, she was appointed director of nascent national brain research centre in Manser, on the outskirts of near New Delhi, but her achievement did not come easily. When Ravindranath was a post doc at the US national institute of health, her husband, also a scientist remained in India. She

initially took her two-year-old son with her, but, unable to arrange for his care when she was in the lab, she sent him to be looked after by her parents. She had to be away during two critical years of her son's childhood.

Twenty years later, she was once again faced with a difficult choice. The offer to head the new centre was a rare opportunity, but it meant a five-year separation from her husband and son. With the cooperation of her husband and son it would have been possible.

Ravindranath is one of the lucky few. Unable to juggle professional and domestic demands and sometimes coping with nepotism, most Indian women scientists give up early in their career. According to a 2004 report of the Indian National science academy (INSA), only nine of 398 shanti swarup bhatnagar awards, India's highest honor for science, went to women. Within the INSA, women have only 14 of the academy's awards and medals, and no woman has ever led the academy.

Like their counterparts worldwide, Indian women scientists fare better in biology than in engineering or physics. In 2000, women accounted for 32% of medical students, compared 16% in engineering. But, as elsewhere, those who continue opt for a career in medicine or teaching, rather than research.

Apart from the usual factors, such as marriage and lack of adequate

childcare, Indian women also have to endure the country's staunch patriarchal culture. Many complain that male colleagues don't treat them as peers and often assign them to reception committees or to choosing menus for conferences.

Women also face considerable bias in the interview process and a tendency to ignore the excellent career records of women scientists when it comes to selecting top positions.

The govt is beginning to take action. In 2003, the DST initiated a scheme to offer fellowships to women whose careers were interrupted by their husbands' geographical moves.

"Women scientists particularly need assistance when they are struggling to balance their early career with a growing family. If the women tide over the period of marriage and child rearing, a critical mass of women scientists can develop in biology", Ravindranath says. Today, her son and husband are among the proudest and happiest about her success.

How I became a Successful Entrepreneur

**Dr. Viloo Morawala Patel
(Founder, Chairman &
Managing Director of
Avesthagen)**

In my experience it has been the 3Ps of entrepreneurship that has catapulted me into the success zone- the 3Ps being Passion, Plunge and Persevere. I have always believed in dreaming big and doing so passionately. Having followed that, there is very little that has stopped me from achieving what I have today.

It is all about setting goals, dreaming big and then pulling all stops to realize the dreams. I loved sciences and molecular pathways have always fascinated me. This is an important aspect for biotech sphere.

Fortunately, I come from a family deep rooted in both academy and business. Therefore, though I came across many skeptics in my quest for setting up a pure R & D company, I believed in myself and took the plunge. I had promised myself to deliver India to the global market. The seeds of innovative science at Avesthagen are intended to improve the quality of life in rural India.

I have always been proud of my identity as a woman and have been a non conformist throughout my life. Of course, there are pitfalls too. As a woman I have had to work twice as much and be double as convincing. In my life, women members from my family have been strong supporters. Being a strong believer in woman power, there was a guiding force encouraging me to go ahead. When people see you making a difference they tend to support you. When

this happens, the funding agents see your mettle, and come forward with concrete offers.

For those who have chosen the biotech field, they will find themselves in the thick of a sunrise and happening industry. There is a lot of talent that needs to be developed and entrepreneurs will find themselves donning dual caps of training people and managing business. Learning and constantly evolving are key parameters that would define success. Keeping an eye on the ball whether it is administration, finance, research or people and focusing on the big picture is a sure shot formula. This has been my experience.

Finally, I would like to be an inspiration for other women. If you have a dream, it is never too late to chase it. When I did my PhD in France at 33, my two daughters aged 6 & 8 moved with me to this new country. They have been with me through trials, tribulations and tributes. Besides my husband and family, my girls have been my pillars of strength. If your family is supportive there is nothing that can stop you from touching the stars that you aim for!

INTERVIEW

**Dr. James Watson, Ph.D
(Co-discoverer of the
structure of DNA with Dr.
Francis)**

**The following is an excerpt
from an interview with Dr.**

**James Watson that took place
at the "Winding Your Way
through DNA" symposium at
the University of California San
Francisco.**

Interviewer: Why did you decide to head the NIH's Human Genome Project?

Dr. James Watson: I thought NIH [was] game to it, and I wanted the Project to succeed and someone had to lead it. I had the advantage that I wasn't doing science so it wasn't going to take me away from the lab bench. I wasn't doing human genome research so I wouldn't be competing with other people. And I'm well known so I've had a good track record for proposing to do stupid things. So I guess my reputation was good and I actually wanted it done. I had lobbied quite a bit actually to get the money for it, so when I was asked I really couldn't turn it down, although I had another job and that always made it difficult because I never really could give it the time that I should have.

Interviewer: What were you trying to accomplish with the Human Genome Project? What was the ultimate goal?

Dr. James Watson: Well, the goal was just to understand life better and when you understand life better you understand disease better. Everyone in their families has particular diseases you'd like to come to grips with. The goal of the Human Genome Project is to understand the genetic instructions

for human beings. In doing that, we want to understand the instructions for the mouse, as a comparison with humans and then go down even to bacteria, so we get a whole series of genetic constructions and get some idea how man evolved: How did we start? And how did we get all this complexity? Getting the instructions is a big job; understanding those instructions can consume many hundreds of years....

Interviewer: Let's pretend it's 2042, fifty years from now, and we're looking back on this period of time, these last three or four decades. What are people going to say about this time?

Dr. James Watson: Well, the last fifty years we've been, sort of, coming to grips with DNA. It was in 1944 that Avery published the famous paper which said that bacterial heredity can be changed by adding a DNA molecule to bacteria. The whole century will probably be known as the century of genetics so we will go on from just knowing that genes exist to knowing what the genes are, chemically, to really finding out how their instructions are carried out, in theory, and then finally, by the end of this century, producing a complete set of instructions which then can be used by a whole variety of other biologists in studying other problems.

Interviewer: In terms of evolution, different species have been manipulated in their genetic codes, perhaps not as willfully as we do,

but certainly other species have been doing mutations and surviving. We now have a species (human) which has learned to understand its genetic code on a more intimate level. What does that mean?

Dr. James Watson: I think that human beings evolved to the point where we know our instructions occurred by DNA. I think it says that humans are pretty bright! The human brain is pretty remarkable. You know, whales will never know where their instructions come from. They wouldn't be able to pose the question that way, so, it's pretty extraordinary what human beings have done.

Interviewer: You were 25 years old when you helped elucidate the structure of DNA?

Dr. James Watson: I was 24.

Interviewer: That's fairly young-- your counterparts were a little bit older. How did that make you feel to be a young scientist doing such profound work?

Dr. James Watson: It was rather a thrill knowing you're five or ten years younger than the other people, just keeping up with them. It was fun-- they would call me by my first name or something so I was lucky I got into sciences at such a young age. But also I had the advantage that I needn't be in a hurry. I was younger than other people so, actually, I didn't have to produce.

I try to get people doing real science at an early age because for most things you don't have to be in school for ten years before you do something important. In school you learn a lot of things you don't ever use in life so one thing it's very lucky if you know what interests you early in life because then you don't take courses on things [you're not interested in].

Interviewer: How did you get interested in science?

Dr. James Watson: I think I was curious about why things happened and I was curious, really, about what life was. You couldn't discuss it in any rational way. You could say, "Living things move," or "Living things have nerves." But finally when we got to genes and found out what the genes are, we can actually see what happened. All biologists have to think in terms of evolution and the building blocks of evolution are the genes.

Interviewer: Are you still curious about life?

Dr. James Watson: Oh, very curious. I eagerly await the next issue of Nature or Science....I just have always loved facts. I guess if I have any vices [one is that] I read too many newspapers each day. I get pleasure from knowing what's happening.

Interviewer: I assume that you are a curious person. Is that a good trait to have?

Dr. James Watson: Oh, yes, if you want to be a scientist. It depends

what you're doing. There are similar occupations that I won't name where curiosity might be harmful.

Interviewer: Why is curiosity important to a scientist?

Dr. James Watson: Scientists try to explain why things happen. Why one cell becomes two. Why blue eyes or brown eyes. So, you're trying to explain--in the old days--why the sun came up in the morning, why the days got longer in the summer. You know, there is a whole set of questions [based on what] you saw, things you wanted to know why they happened.

Interviewer: Going back to your position at 24, making the discovery that would win the Nobel Prize, do you think today that biology is a field for young scientists?

Dr. James Watson: Oh, sure. I think you're unlikely to make an impact unless you get into a really important lab at a young age, because you're unlikely to know what problem to work on. We had a nineteen year old boy living with us last year from England. He'd done very well in school and hadn't gone to college but he left our lab and he's going to publish a paper. He was doing the work of a post doc. But, you know, he was narrowly focused. He didn't know about everything but sure, you can do things young. People used to be kings when they were nineteen, generals. Now you're supposed to wait until you're virtually senile. In

fact, we sometimes choose senility because it doesn't threaten anyone.

Interviewer: How do you know when you've really made an important discovery as opposed to following a wild goose chase?

Dr. James Watson: In some sense when you can make predictions. You can predict something you don't know and, in the case of the double helix it just looked so good and we thought it was right....We didn't have an x-ray structure of proof for about 25 years, but we knew it was right even though we didn't have this formal method of proof.

Interviewer: What would be your advice to a young high school student that might be considering biology?

Dr. James Watson: I would go to a good university where you think the students are brighter than you are.

Interviewer: Why?

Dr. James Watson: Because then you test yourself. I think if you're intelligent, you underestimate yourself because you know all you don't know. So, if you want to play tennis, you'd better go to a good tennis camp, because you won't know really to what level you can go. I was very lucky; I hadn't planned it that way but I had courses by world experts when I was eighteen and I was in one of the best labs in the world when I was twenty.

So, I first went to a university where the students were bright and I was scared but then, you know, by the time of my senior year I wasn't scared. You have to go through a period where you find yourself. Then, you go to the place where people are interested in what you're interested in. You've got to go to find people that you want to be around. Not just that they're famous, that doesn't help you. You've got to go to a place where [your interests are]. I was interested in genetics and there were two good places for genetics and when I finished college, I went to one of them and, then I ended up where we found the double helix and it was in the best lab in the world. So it wasn't as if the discovery was made in a place where people didn't know what was up. It was the best.

Interviewer: Once you elucidated the structure of DNA, did you look at life differently? Did it answer a lot of questions for you?

Dr. James Watson: Well, it told us that we were right in thinking that DNA was a chain. It also told us how it replicated. So, yeah, we've gone a long way and the satisfaction only lasted a couple of months because then you had to go to the next problem which was "How did the gene really work?" So that occupied me for the next 15 years of my life.

Interviewer: How do you want to be remembered? For the DNA discovery, the Genome Project, as an author, something else?

Dr. James Watson: I guess for a little of all of them.

Interviewer: As a rebel?

Dr. James Watson: I guess I never felt a part of the establishment. Conventional wisdom is often wrong. What you read in the newspaper is often wrong so I guess I'm a fighter. I want to know the truth and I'm not satisfied with people who avoid the truth.

Interviewer: So, in terms of telling that to a biology student, it's OK to buck conventionalism.

Dr. James Watson: You know, if you're going to make the next step in a major scientific thing, no one knows how to do it so you have to, in a sense, reject your professors and say, "They're not getting anywhere, I'm going to try something else." Crick and I did that at one stage and we're famous practically because we thought that what other people were doing won't get anywhere. So, you know, that's part of your education, to know what things won't work and then try to get something to work.

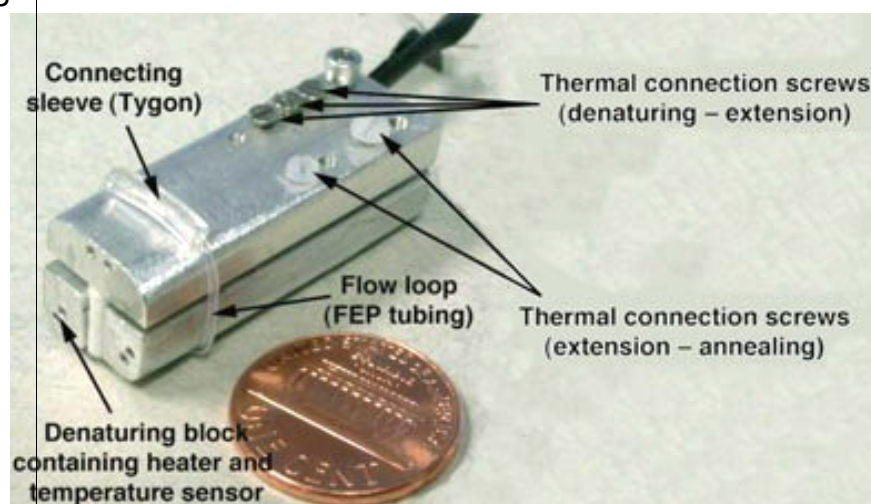
We were, of course, pretty lucky.

Breakthrough in research

Pocket-sized PCR machine:

A pocket-sized device that runs on two AA batteries and copies DNA as accurately as expensive lab equipment has been developed by researchers in the US. The device has no moving parts and costs just \$10 to make. It runs polymerase chain reactions (PCRs), to generate billions of identical copies of a DNA strand, in as little as 20 minutes. This is much faster than the machines currently in use, which take several hours.

Running a PCR requires treating DNA strands, along with chemical materials needed to make new DNA strands, at three different temperatures. The highest temperature (95°C) causes two strands of a DNA molecule to separate. The lowest temperature (60°C) makes DNA building blocks stick together. Then, holding the temperature in the middle (72°C), allows an enzyme to quickly assemble replica DNA strands.



To cycle through these temperatures, a conventional PCR machine heats and cools a large metal block holding multiple tubes containing samples of DNA and the material needed to make copies.

In the new device, created by graduate student Nitin Agrawal, a centimetre-wide loop of tubing wraps in a vertical ring around a set of three metal rods. The rods, together the size of an AA battery, are kept at three different temperatures. With this set-up, the parts of the tube closest to each block are heated differently.

This keeps the liquid flowing through the millimetre-wide tube, and so the DNA and building blocks cycle automatically through the three temperatures needed for PCR. It's similar to how a lava lamp works.

As the fluid is heated, it becomes less dense and more buoyant, so it flows upward. When the fluid cools in another part of the loop, it becomes denser and moves down. And because the device only heats the three small blocks of metal, it also runs off just two AA batteries.

The device shows promise for a variety of tests, including monitoring levels of HIV virus in a person's body or diagnosing tuberculosis.

This system could enable DNA-and RNA-based tests to be carried out in the field or in developing countries, where large, expensive laboratory equipment is neither practical nor affordable.

Reprogramming cells:

Induced pluripotent stem cells are not just functionally identical to embryonic stem cells. They also have identical biological structure, express the same genes and can be coaxed into giving rise to the same cell types as human embryonic stem cells, but are easier to create and free of the heavy ethics baggage.

The riddle of Dolly the Sheep has puzzled biologists for more than a decade: What is it about the oocyte that rejuvenates the nucleus of a differentiated cell, prompting the genome to return to the embryonic state and form a new individual? This year, scientists came closer to solving that riddle. In a series of papers, researchers showed that by adding just a handful of genes to skin cells, they could reprogram those cells to look and act like embryonic stem (ES) cells. The ES cells are famous for their potential to become any kind of cell in the body. But because researchers derive them from early embryos, they are also infamous for the political and ethical debates that they have sparked. The new work is both a scientific and political breakthrough, shedding light on the molecular basis of reprogramming and, perhaps, promising a way out of the political storm that has surrounded the stem cell field.

The work grows out of a breakthrough a decade ago. In 1997, dolly, the first mammal cloned from an adult cell, demonstrate that unknown factors in the oocyte can turn back the developmental clock in a differentiated cell, allowing the genome to go back to its embryonic state.

Various experiments have shown how readily this talent is evoked. Recently, researchers showed that a fertilized mouse egg, or zygote, with its nucleus removed could also reprogram a somatic cell.

Meanwhile, the identity of the reprogramming factors continued to puzzle and tantalize biologists. In 2006, Shinya Yamanaka's team at Kyoto University, Japan produced cells what they called induced pluripotent stem cells (iPS). Yamanaka had identified genes that are particularly active in embryonic stem cells, and used retroviruses to transfect mouse fibroblasts with a selection of those genes. Eventually, four key pluripotency genes essential for the production of pluripotent stem cells were isolated; Oct-3/4, SOX2, c-Myc, and Klf4. Cells were isolated by antibiotic selection for Fbx15⁺ cells. However, the team could not at that time demonstrate that these reprogrammed cells would differentiate into a variety of adult cells after having been introduced into a mouse embryo which then developed into an adult mouse. Being able to do this would verify the pluripotency of the reprogrammed cells. ([Pluripotency](#))

is the ability of a cell to develop into any type of fetal or adult cell. It is characteristic of embryonic stem cells.

However, in June 2007 Yamanaka's team, along with two American groups, reported that they had been able to provide the missing demonstration of pluripotency. They showed that the iPS cells made from mouse skin could, like ES cells, contribute to chimeric embryos and produce all the body's cells, including eggs and sperms. The crucial step, of course, was being able to reprogram adult human cells in the same way. For all anyone knew, this might be quite difficult.

However, just five months later, in November 2007, Yamanaka's team, together with another led by James Thomson of the University of Wisconsin, announced that their mouse recipe could work in human cells.

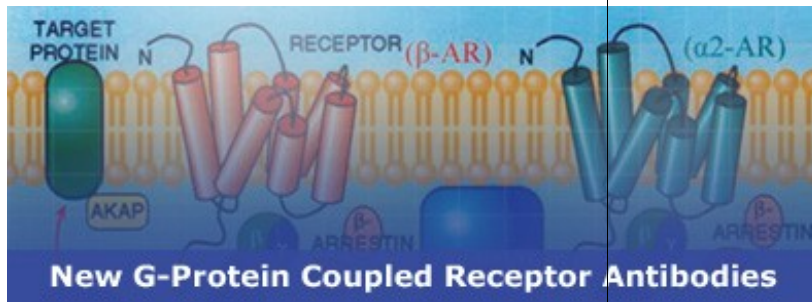
The advance seems set to transform both science and the politics of stem cell research.

In early December, scientists reported that their mouse iPS cells could treat a mouse model of sickle cell anemia. The next big challenge will be finding a way to reprogram human cells without using possible cancer-causing viruses (retroviruses) to insert the genes.

Some researchers say they still need to be able to do research cloning to find out just what proteins the egg uses for its

reprogramming magic. And now science has come a step closer to the long-term goal of stem cell therapy, mouse models won't be adequate for animal studies. Rather, researchers will need to test cell transplantation approaches with primates, a move that will inevitably stir up resistance from animal-rights activists.

G protein- coupled receptors (GPCRs): Receptor visions



G protein-coupled receptors (GPCRs), also known as seven transmembrane domain receptors, 7TM receptors, heptahelical receptors, and G protein-linked receptors (GPLR)

As one of the largest and most diverse protein families in nature, the G-protein coupled receptor (GPCR) super family play important roles in a variety of biological and pathological processes such as development and proliferation,

neuromodulation, angiogenesis, metabolic disorders, inflammation, and viral infection. By detecting light, odors, and tastes, the receptors clue us in to our surroundings and also help manage our internal conditions by relaying messages from hormones, the neurotransmitter serotonin, and myriad other molecules.

All members of this superfamily are grouped on the basis of shared sequence motifs into the following broad classes:

- Class A Rhodopsin-like
- Class B Secretin-like
- Class C Metabotropic

glutamate/pheromone

- Class D Fungal pheromone
 - Class E cAMP receptors
 - Frizzled/
 - Smoothed
 - Vomer nasal receptors
 - Putative/
 - unclassified

Not surprisingly, it is one of the most targeted protein families in pharmaceutical research today. Their fundamental role is highlighted by the fact that of the around 500 currently

marketed drugs, more than 30% are GPCR modulators. GPCR agonist and antagonist drugs have therapeutic benefit across a broad spectrum of diseases, including pain (opioid receptor agonists), asthma (β 2-adrenoceptor agonists), peptic ulcers (histamine H2 receptor antagonists), migraine (serotonin 5-HT1B/1D agonists), hypertension (angiotensin AT2 receptor antagonists), schizophrenia (serotonin 5-HT2 receptor agonists and dopamine receptor antagonists), rhinitis or allergy (histamine H1 receptor and chemokine receptor antagonists), etc. Besides, no single class of proteins ranks higher than GPCRs in terms of new drug discovery potential. It has been estimated that of the around 400 GPCRs considered to be potential drug targets, only ~30 are targeted by currently marketed drugs. The natural ligand has been identified for a further 210 receptors, which leaves around 160 orphan receptors with no known ligand or function.

The pharmaceutical industry has focused on development of modulators to this protein family, but GPCRs also represent an attractive target as biomarkers. Recent studies have implicated endothelin receptors, chemokine receptors and lysophosphatidic acid receptors in tumorigenesis and metastasis, and a recent *in silico* analysis found a number of GPCRs that were up-regulated in

various cancers which suggests not only targets of therapeutic value, but of diagnostic and prognostic value as well. A summary of these up-regulated receptors is below.

Lung cancer

Edg2, P2Y purinoceptor 6, PAR-2, PAR-3, GPR68

Breast cancer

CCR1, CXCR-4, PAR-2

Prostate cancer

Beta 2 adrenergic receptor, CXCR-3, CXCR-4, GPR68

Melanoma

Edg6, PAR-2, mGluR1

Gastric cancer

CXCR-4, P2Y purinoceptor 5

Lymphoma

Beta 2 adrenergic receptor, Edg1, CCR7

While research continues, it is evident that GPCRs are critical in countless biological functions—and disfunctions. While the emphasis is on their role in drug development, it is becoming increasingly clear that G-protein coupled receptors will play a critical role as indicators of disease with diagnostic and prognostic potential.

Recent breakthrough in GPCR structure, the crystallographers have nabbed a close-up of adrenaline's target, the B2-adrenergic receptor for the visual pigment rhodopsin. Its structure has long been on the to-do list but

feat got because of the molecule's family connections with G-protein-couple receptors. Now a clear picture of receptor's binding site might be helpful for the researchers to develop more potent and safer drugs.

Next-generation sequencing-by-hybridization

A new hybridization-based technology offers advantages in sequencing genomes for which a reference genome exists.

In the quest for the \$1,000 genome, every imaginable approach is being explored to develop sequencing technologies with improvements in miniaturization, parallelism and simplification. This new method describe a miniaturized, highly parallel resequencing platform in which universal oligonucleotide probes are hybridized sequentially to a genomic sample immobilized in 200-bp fragments on a glass surface. This is termed shotgun sequencing-by-hybridization (shotgun-SBH), is rapid, accurate, and appears to offer significant cost advantages for straightforward resequencing applications.

Once the entire genome sequence of a species is known, the task of sequencing the DNA of an individual is simplified because any new sequencing result can be

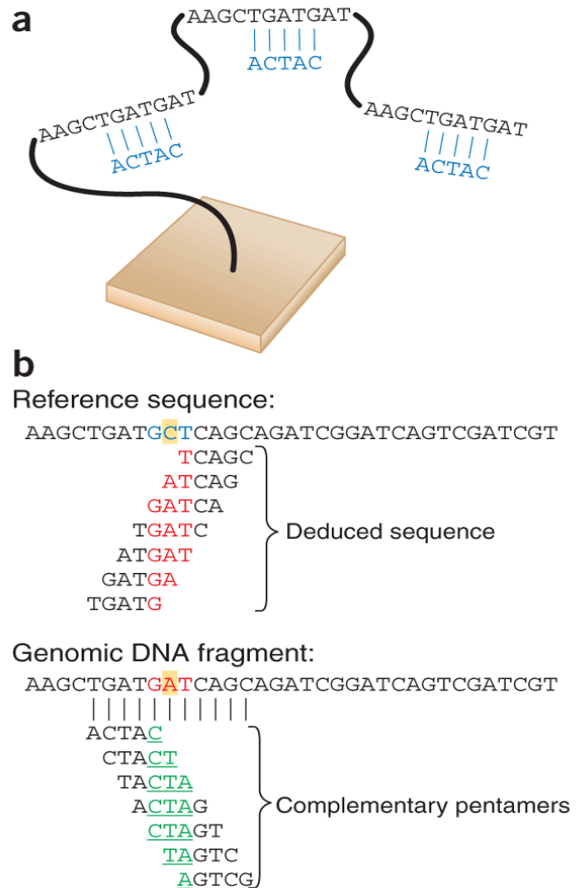
compared to the reference genome. Standard SBH, formally proposed in the late 1980s by Southern and Drmanac, consists of determining the occurrence in a DNA sample of many short 'words', or oligonucleotide sequences, which are hybridized to the genomic DNA to form perfect duplexes. These individually detected DNA words are then compared to a reference genome with appropriate algorithms to assemble the longest perfect matches. SBH is a sound resequencing approach for identifying sequence variants but can stumble when probing long sequences, tandem DNA repeats or unexpected sequence insertions. Moreover, SBH has so far failed to sequence even viral genomes, because DNA-word recognition can be error prone when hybridization conditions are identical for all oligonucleotide probes.

The shotgun approach developed by Pihlak solves some of the problems of standard SBH. Hybridization conditions are tailored to each probe, and the probe design includes locked nucleic acids to increase probe stability and specificity for the universal set of 582 probes. Another improvement is the use of a library of overlapping DNA fragments, which increases the accuracy of the sequence assembly process. Remarkably, shotgun-SBH correctly decodes ~96% of the 48.5-kbp Bacteriophage λ genome and ~80% of the 4.6-Mbp *Escherichia coli* genome, thereby

greatly outperforming standard SBH.

Shotgun-SBH starts by random cutting of genomic DNA and isolation of 200-bp fragments, which are circularized into a library. This library is subsequently displayed on a surface as a collection of discrete, single-stranded DNA molecules. DNA immobilization by rolling circle amplification facilitates imaging of clonal DNA fragments on glass surfaces and enhances SBH signal intensity because each genomic DNA fragment is repeated many times within one tiny, loosely coiled fuzz ball (Fig. 1a). Each square centimeter of the surface can accommodate several million DNA fuzz balls, yielding the desired parallelism for subsequent sequence decoding.

Figure 1: Shotgun sequencing-by-hybridization (shotgun-SBH)



- (a) Rolling-circle amplification results in tandem repeats of identical ~200-base DNA fragments immobilized as a fuzz ball on a glass surface. Shotgun-SBH relies on sequential hybridization of different pentamers; one hybridization round with the 3'-ACTAC-5' pentamer is depicted.
- (b) Detection of a point mutation in the trinucleotide sequence GCT (colored in blue in the reference sequence), which shows a change to GAT (colored in red) in a genomic DNA fragment by shotgun-SBH. The single base change is deduced

from five independent complementarity matches (underlined, green) using antiparallel pentamer sequences detected by sequential hybridization and image snapshots during the shotgun-SBH process. The deduced sequence for the trinucleotide is shown in red

Next, 582 fluorescently labeled oligonucleotide probes, each harboring a different pentamer sequence, are placed in contact with the glass surface sequentially, enabling optimized hybridization conditions for each probe. The probe design incorporates locked nucleic acids⁶ for higher DNA helix stability and superior sequence discrimination. For each pentamer cycle, an image records the local signal intensity at each DNA fuz ball.

Finally, based on analysis of the full spectrum of partially overlapping DNA fragments and of the five independent pentamer-binding events that recognize each base position ([Fig. 1b](#)), the pentamer binding information is compared to the reference genome sequence to identify changes or identities. The authors report that 97.3% of single-base changes in the sequence could be detected in a test genome. Given its high throughput, shotgun-SBH could work well as a resequencing platform for the discovery of single nucleotide polymorphisms or mutations in coding and noncoding exons, which represent nearly 2% of the human genome (55 megabases) and can

be harvested using exon-capture technologies:

How does shotgun-SBH compare with other DNA sequencing platforms? Whereas other platforms require polymerases or ligases, shotgun-SBH uses only a universal set of synthetic locked nucleic acid oligonucleotides, which are stable and inexpensive reagents. Although loss of DNA fragments during sample preparation produced gaps in the *E. coli* genome sequence, this loss is not an inherent property of the method, and new sample preparation techniques could substantially improve assembly beyond the observed 80%.

The DNA fragment length used in shotgun-SBH is 200 bases, functionally analogous to the read-length of other methods and roughly comparable to the 300-base reads obtained with Roche's Genome Sequencer FLX. Compared with Roche's FLX technology, shotgun-SBH achieves greater parallelism because the density of sequencing features can be as high as 10 million per square centimeter. Other commercial next-generation sequencers—Illumina's Solexa sequencing-by-synthesis platform and Applied Biosystems' SOLiD sequencing-by-ligation platform—offer a similar degree of miniaturization, but the reads are only 30–40 bases long. However, paired-end sequencing, achievable with the Roche FLX, Illumina and ABI SOLiD platforms, captures genomic fragments of known length, facilitating *de novo*

assembly of complex genomes—a task that remains beyond the capabilities of shotgun-SBH.

In a recent report from Helicos Biosciences, Harris describe the first single-molecule sequencing-by-synthesis technology. Is shotgun-SBH single-molecule sequencing? Yes and no. The DNA fuzz balls interrogated during shotgun-SBH are indeed single molecules of DNA with the caveat that each fuzz ball contains many tandem copies of the same sequence; thus, this is not single-molecule sequencing in the strict sense. Nonetheless, it is interesting to compare shotgun-SBH with the Helicos technology. Harris reported a novel cycling chemistry for DNA sequencing-by-synthesis that generated 30-base reads with high parallelism (280,000 simultaneous reads) and enabled sequencing of a viral genome. The method requires washing steps for each cycle but does not require cloning or DNA amplification and is therefore not prone to loss of DNA fragments. The success rate for detecting base substitutions was 98%, slightly better than shotgun-SBH, whereas the throughput and read lengths were lower in the Helicos report.

On the horizon are other single-molecule sequencing technologies from Visigen Biotechnologies and Pacific Biosciences. These companies are developing different approaches based on real-time massively parallel imaging of single-molecule base-addition events catalyzed by DNA

polymerase. Data are generated at a rate of 10–50 bases per second per polymerase molecule, as tens of thousands of polymerases read DNA templates. Read lengths of 8,000 bases may be within reach, making these technologies ideal for the most challenging applications, like sequencing of structurally rearranged cancer cell genomes. Although shotgun-SBH may not be well suited to tackling genome rearrangements, its potential for extremely high parallelism through inexpensive scaling of the imaging area could give it a cost advantage in standard genome resequencing applications.

Nearly 20 years have elapsed since SBH was first envisioned and the sequencing of single molecules of DNA was proposed. We are now on the cusp of a new era in which widely available high-throughput platforms will generate DNA sequence information from any organism at a cost of pennies per megabase.

Human genetic variation: Spice of our individuality

Equipped with faster, cheaper technologies for sequencing DNA and assessing variation in genomes on scales ranging from one million of bases, researchers are finding out how truly different we are from one another

The unveiling of the genome almost 7 years ago cast the faint light on our complete genetic makeup. Since then, each new genome sequenced and each new individual studied has illuminated our genomic landscape in ever more detail. In 2007, researchers came to appreciate the extent to which our genome differ from person to person and the implications of this variation for deciphering the genetics of complex diseases and personal traits.

Less than a year ago, the big news was triangulating variation between us and our primate cousins to get a better handle on genetic changes along the evolutionary tree that led to humans. Now, we have moved from asking what in our DNA makes us human to striving to know what in my DNA makes me me.

Techniques that scan for hundreds of thousands of genetic differences at once are linking particular variation to particular traits and diseases in ways not possible before. Efforts to catalog and assess the effects of insertions and deletion in our DNA are showing that these changes are more common than expected and play important roles in how our genome work- or don't work. By looking at variations in genes for hair and skin color and in the "speech" gene, we have also gained a better sense of how we are similar to and different from Neandertals.

Already, the genome of several individuals have been sequenced, and rapid improvements in sequencing technologies are making the sequencing of "me" a real possibility. The few "celebrity genome" like Watson's and Venter's have been sequenced. The potential to discover what contributes to red hair, freckles, pudginess, or a love of chocolate-let alone quantifying one's genetic risk for cancer, asthma, or diabetes- both exhilarating and terrifying. It comes not only with great promise for improving health through personalised medicine and understanding our individuality but also with risks for discrimination and loss of privacy.

Turning on the flood lamps

Even with most of the 3 billion DNA bases lined up in the right order, there was still much that researchers could not see in the newly sequenced human genome in 2001. Early conserved regulatory regions, RNA genes, and other features into relief, bringing meaning to much of our genome, including the 98% that lies outside protein-coding regions. These and other studies, including a pilot study called ENCODE, completed this year, drove home how complex the genome is.

There are an estimated 15 million places along our genomes where one base can differ from one person or population to the next. By mid 2007, more than 3 million such locations, known as single-nucleotide polymorphisms (SNPs),

had been charted. Called the HapMap, this catalog has made the use of SNPs to track down genes involved in complex diseases- so-called genome-wide association studies- a reality. More than a dozen such studies were published in 2007.

Traditionally, geneticists have hunted down genes by tracking the inheritance of a genetic disease through large family or by searching for suspected problematic genes among patients. Genome-wide association studies go much further. They compare the distribution of SNPs- using arrays that can examine some 500,000 SNPs at a time- in hundreds or even thousands of people with and without a particular disease. By tallying which SNPs co-occur with symptoms, researchers can determine how much increased risk is associated with each SNP.

In the past, such links have been hard-won, and most have vanished on further study. However, researchers linked variants of more than 50 genes to increased risk for a dozen diseases. Almost all the variants exert relatively small effects, in concert with many other genetics factors and environmental conditions, and in many cases the variant's real role has not yet been pinned down. But the sheer numbers of people studied have made even skeptics hopeful that some of these genetics risk factors will prove real and will help real underlying causes.

The Wellcome Trust, the U.K.'s largest biomedical charity, began to put its weight behind genomic-wide association studies in 2005 and recruited 200 researchers to analyse the DNA of 17,000 people from across the United Kingdom. In June 2007, the consortium published a mammoth analysis of seven diseases, including rheumatoid arthritis, bipolar disorder, and coronary artery disease. It also found several gene variants that predispose individual to type 1 diabetes and three new genes for Crohn's disease.

Several large studies have also pinpointed type 2 diabetes genes. One French study involving nonobese diabetics found that a version of a gene for a protein that transports zinc in pancreas increased the risk of this disease. Three simultaneous reports involving more than 32,000 participants uncovered four new diabetes-associated gene variants, bringing to 10 the number of known non Mendelian genetic risk factors for type 2 diabetes. These finds strongly point to pancreatic beta cells as the source of this increasingly common chronic disorder.

New gene associations now exist for heart disease, breast cancer, restless leg syndrome, atrial fibrillation, glaucoma, amyotrophic lateral sclerosis, multiple sclerosis, rheumatoid arthritis, colorectal cancer, ankylosing spondylitis, and autoimmune diseases. One study even identified two genes in which particular variants can slow the

onset of AIDS, demonstrating the potential of this approach for understanding why people vary in their susceptibility to infectious diseases.

Genomic hiccups

Genomes can differ in many other ways. Bits on DNA ranging from a few to many thousands, even millions, of bases can get lost, added, or turned around in an individual's genome. Such revisions can change the number of copies of a gene or piece of regulatory DNA or jam two genes together, changing the genes' products or shutting them down. The year 2007 marked a tipping point, as researchers became aware that these changes, which can alter a genome in just a few generations, affect more bases than SNPs.

In one study, geneticists discovered 3600 so-called copy number variants among 95 individuals studies. Quite a few overlapped genes, including some implicated in our individuality- blood type, smell, hearing, taste, and metabolism, for example. Individual genomes differed in size by as many as 9 million bases. This fall, another group performed and extensive analysis using a technique, called paired-end-mapping, that can quickly uncover even smaller structural variations.

These differences matter. One survey concluded that in some populations almost 20% of differences in gene activity are due to copy-number variants; SNPs

account for rest. People with high-starch diets- such as in Japan- have extra copies of a gene for a starch-digesting protein compared with members of hunting-gathering societies.

New technologies that are slashing the costs of sequencing and genome analyses will make possible the simultaneous genome-wide search for SNPs and other DNA alterations in individuals. Already, the unexpected variation within one individual's published genome has revealed that we have yet to fully comprehend the degree to which our DNA differs from one person to the next. Such structural and genetic variety is truly the spice of our individuality.

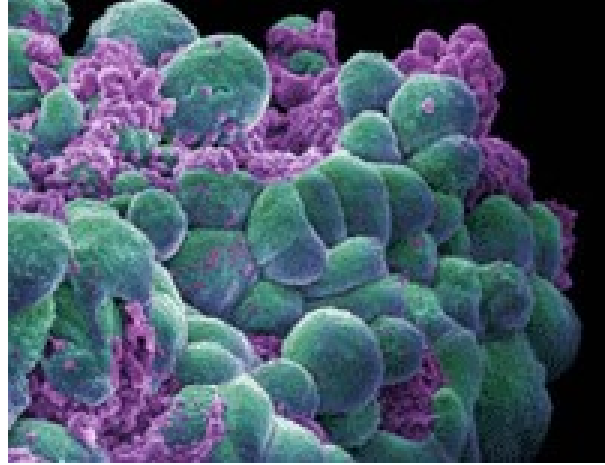
News Features

Global genetics consortium launches major cancer research initiative

Researchers from four continents have come together to launch the 'International Cancer Genome Consortium' (ICGC), a major collaboration designed to identify the key genetic mutations involved in up to 50 types of cancer. The consortium will group researchers from the US National Institutes of

Health, as well as cancer and genetic research groups from Australia, Canada, China, France, India, Japan and Singapore. The consortium, which includes the Wellcome Trust and the Wellcome Trust Sanger Institute in the UK, will generate a valuable resource enabling the development of new and better ways of diagnosing, treating and preventing cancer.

The ICGC hopes to build on the success of the UK's Cancer Genome Project at the Wellcome Trust Sanger Institute. The team will use the DNA sequencing of thousands of cancer genomes to catalogue all the changes and obtain a complete picture of the abnormalities that lead to cancer.



A research team of the Cancer Genome Project led by Mike Stratton at the Sanger Institute had found far more mutations to be involved in cancer than originally thought. The research team also established that the BRAF gene is commonly mutated in malignant melanoma and some other tumors.

The international alliance would use high-speed technology to scan the DNA of tumor cells in order to pinpoint genetic coding errors linked to different cancers.

This research is uncovering a dramatic view in which the human genome in cancer cells is ravaged by changes. With the advent of new faster DNA sequencing technologies the ICGC now has set the hugely ambitious aim of fully sequencing thousands of cancer genomes to catalogue all the changes in DNA and obtain a complete picture of the abnormalities that lead to cancer with the aim of improving diagnosis and treatment. The new research will have clinical significance around the globe, aiming to study cancers of all major organs,

including breast, ovary, prostate, and lung and blood cancers.

ICGC members will assume responsibility for specific cancers, and facilitate the exchange of information to avoid duplication of effort. All the data generated will be made rapidly and freely available to the global research community.

In 2007, more than 7.5 million people died of cancer worldwide and more than 12 million new cases of cancer were diagnosed; these numbers are expected to rise to 17.5 million deaths and 27 million new cases by 2050.

The Wellcome Trust Sanger Institute announced results from the first ever genome-wide study of cancer samples using new technology sequencing of the type that will be the backbone of the ICGC. The research, published in Nature Genetics, shows that in some cancers the human genome has been rearranged to a remarkable extent with hundreds of fractures being reset wrongly, resulting in an extraordinary reshuffling of DNA. This ground-breaking research will set the stage for the ICGC.

The ICGC, which is extending an invitation to all nations to participate, currently includes:

- **Australia:** National Health and Medical Research Council (Observer Status)
- **Canada:** Genome Canada; Ontario Institute for Cancer Research
- **China:** Chinese Cancer Genome Consortium
- **France:** Institut National du Cancer
- **Europe:** European Commission (Observer Status)
- **India:** Department of Biotechnology, ministry of science and technology
- **Japan:** RIKEN; National Cancer Center
- **Singapore:** Genome Institute of Singapore
- **United Kingdom:** The Wellcome Trust; Wellcome Trust Sanger Institute
- **United States:** National Institutes of Health (NIH).

Each ICGC member will conduct a comprehensive, high-resolution analysis of the full range of genomic changes in at least one specific type or subtype of cancer, with studies built around common standards of data collection and

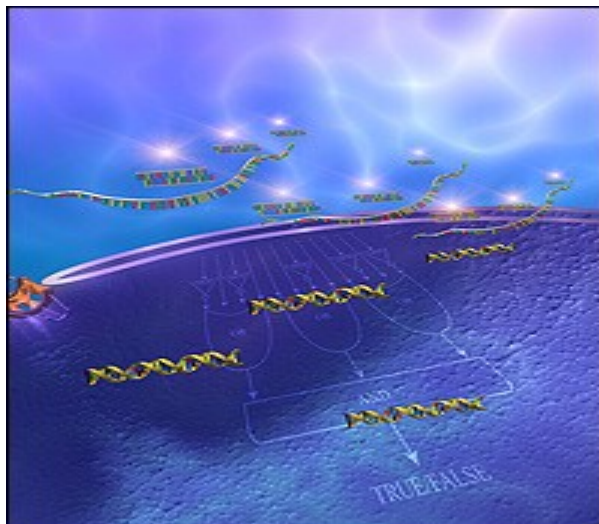
analysis. Each project will require cancer specimens from 500 patients and have an estimated cost of \$20 million.

To help meet that need, the Consortium will use new genome analysis technologies to produce comprehensive catalogues of the genetic mutations involved in the world's major types of cancer. Such catalogues will be valuable resources for all researchers working to develop new and better ways of diagnosing, treating and preventing cancer.

Development of tiny implantable Biocomputers- the molecular doctor

Molecular devices' remarkably precise scans of cellular activity could revolutionize medicine

Imagine a "biocomputer" inside your body monitoring what's going on inside, identifying the unhealthy



cells, and even releasing treatment dose. Researchers at Harvard and Princeton universities have taken a crucial step toward building biological computers, tiny implantable devices which can one day be implanted in human cells to monitor the activities and characteristics. The information provided by these "molecular doctors," constructed entirely of DNA, RNA, and proteins and hold the promise of revolutionize medicine by targeting only diseased cells or tissue, leaving healthy ones completely unaffected.

Evaluating Boolean logic equations inside cells, these "biocomputers" are designed to detect anything from the presence of a mutated gene to the activity of genes within the cell. The biocomputers' "input" is RNA, proteins and chemicals found in the cytoplasm; "output" molecules indicating the presence of the telltale signals are easily discernable with basic laboratory equipment. To create a "molecular computer" capable of making decisions is a big challenge in itself and getting them to work in human cells is likely to be even trickier.

Currently, there are no tools for reading cellular signals. These biocomputers can translate complex cellular signatures, such as activities of multiple genes, into a readily observed output. They can even be programmed to automatically translate that output into a concrete action, meaning they could either be used to label a cell for a clinician to treat or they

could trigger therapeutic action themselves.”

A biocomputer’s calculations, while mathematically simple, could allow researchers to build biosensors or medicine delivery systems capable of singling out very specific types or groups of cells in the human body. Biocomputers could allow doctors to specifically target only cancerous or diseased cells via a sophisticated integration of intracellular disease signals.

Cells have short interfering RNA (siRNA) molecules which recognize corresponding DNA sequences in genes, causing them to shut down. This system is based on the process RNA interference (RNAi)

A new world of RNAi discovery:

Thermo scientific DharmaconAccell™ siRNA: New delivery technology of siRNA

siRNAs’ ability to knock down of any gene of interest by RNA interference (RNAi) pathway, has generated a great deal of interest in both basic and applied biology. There are an increasing number of large-scale RNAi screens that are designed to identify the important genes in various biological pathways. As disease processes also depend on the activity of multiple genes, it is expected that in some situations turning off the

activity of a gene with a siRNA could produce a therapeutic benefit.

However, applying RNAi via siRNAs to living animals, especially humans, poses many challenges. Over the years, gene silencing by RNAi has relied on the use of cationic lipid-based delivery reagents for transfecting cells with siRNAs. In many cases, lipid-based transfection is sufficient and provides efficient levels of gene knockdown. Yet in a significant fraction cases, cells are either refractory to lipid mediated delivery of siRNA or aversely sensitive to the presence of lipids. In addition, this approach can induce brief (24-72hrs) changes in the state of innate immune response.

Over the course of investigations, it is often necessary to knockdown gene expression for long time to assess the contribution of a particular protein to a given biological event. Under these circumstances, reagents that induce long-term gene knockdown are needed to sufficiently deplete internal cellular store for extended period of time. To address these needs, Thermo Fisher Scientific has developed Thermo Scientific DharmaconR Accell™ siRNA product line with novel modifications enabling uptake by any cell types without the aid of lipid tranfection reagents and extraordinary ease-of-use for rapid results. This innovative delivery technology allows repeated application of Accell siRNA to provide extended duration gene

knockdown with only minimal effects on cell viability and the innate immune response.

New delivery technology. New possibilities

The passive nature of Dharmacon Accell siRNA uptake lends itself to gene silencing applications not possible with other delivery techniques:

- Repeated dosing for extended duration knockdown-useful for study of long-lived protein and downstream cellular responses
- Transient silencing of multiple genes with multiplex delivery (with lipid based delivery or viral vector)
- combinatorial approaches to silence in cells stably transduced using SMART vector™ shRNA technology

Thereby, these attributes will greatly broaden the range of biological questions and cell types that can be investigated by researchers using RNAi.

Educational link:

System Biology:

The next frontier in biological research

Systems biology is the study of an organism, viewed as an *integrated* and *interacting*

network of genes, proteins and biochemical reactions which give rise to life. Instead of analyzing individual components or aspects of the organism, such as sugar metabolism or a cell nucleus, systems biologists focus on all the components and the interactions among them, all as part of one system. These interactions are ultimately responsible for an organism's form and functions. For example, the immune system is not the result of a single mechanism or gene. Rather the interactions of numerous genes, proteins, mechanisms and the organism's external environment, produce immune responses to fight infections and diseases.

Systems biology emerged as the result of the genetics "catalog" provided by the Human Genome project, and a growing understanding of how genes and their resulting proteins give rise to biological form and function. The study of systems biology has been aided by the ease with which the internet allows researchers to store and distribute massive amounts of information, plus advances in powerful new research technologies, and the infusion of scientists from other disciplines, e.g. computer scientists, mathematicians, physicists, and engineers.

Traditional biology — the kind most of us studied in high school and college, and that many generations of scientists before

us have pursued — has focused on identifying individual genes, proteins and cells, and studying their specific functions. But that kind of biology can yield relatively limited insights about the human body.

As an analogy, if you wanted to study an automobile, and focused on identifying the engine, seat belts, and tail lights, and studied their specific functions, you would have no real understanding of how an automobile operates. More important, you would have no understanding of how to effectively service the vehicle when something malfunctions. So too, a traditional approach to studying biology and human health has left us with a limited understanding of how the human body operates, and how we can best predict, prevent, or remedy potential health problems. Biologists, geneticists, and doctors have had limited success in curing complex diseases such as cancer, HIV, and diabetes because traditional biology generally looks at only a few aspects of an organism at a time.

As scientists have developed the tools and technologies which allow them to delve deeper into the foundations of biological activity — genes and proteins — they have learned that these components almost never work alone. They interact with each other and with other molecules in highly structured but incredibly complex ways, similar to the

complex interactions among the countless computers on the Internet. Systems biology seeks to understand these complex interactions, as these are the keys to understanding life.

The individual function and collective interaction of genes, proteins and other components in an organism are often characterized together as an interaction network. Indeed, understanding this interplay of an organism's genome and environmental influences from outside the organism (nature and nurture) is crucial to developing a — systems — understanding of an organism that will ultimately transform our understanding of human health and disease.

Why system biology?

It is now recognized that biological systems are extremely complex and that they show emergent behavior. In layman's term emergent behavior implies that $2+2$ need not always be 4. Rather the sum could range anywhere from 1 to 9 depending upon the context in which the calculation is made. Similarly, biological responses are rarely ever all or none but frequently modulated in a context-specific manner. And such context-specific manner can never be rationalized by detailing the properties of individual molecular constituents. Rather, it requires a global understanding of the structure and dynamic of the molecular networks that control

such behavior. Since the goal of the system biology approach is to understand the properties of the system and that of its components, the longer term hope is that one will be able to manipulate the system in a specific way. Every biological process is complex, be it cell cycle regulation, signal transduction, cell motility, regulation of gene expression, metabolism, or the cellular response to external perturbation. These processes are governed by mutually redundant subsets of biomolecules that continue to process information in a precise manner under a given set of circumstances. The system biology approach is endeavoring to address such remarkable aspects of biological systems.

Another important feature of a system-biology based approach is that it permits an exploration of biological processes at different scales simultaneously.

An important application of system biology is in the development of new drugs. We anticipate that deciphering the cellular networks will help to point out the key factors that are responsible for its aberrant function. Similarly, system biology is emerging with exciting applications in community biology. One area is the ability to predict the rate and direction of spread of infectious diseases in a population.

In short, system biology aims to transform biology into a predictive science. And its beauty lies in the fact that this can be applied at all levels of resolution of biological systems. However, one of the foremost challenges to initiate, is to bring together experts from diverse disciplines viz. computer scientist, physicist, mathematician and biologist to interact and synthesize views in a productive manner. System biology needs an interdisciplinary network.

The power of proteomics:

Effectiveness of the analytic methods used in proteomics

Proteome was first coined by Mark Wilkins in 1994 in the symposium "2D Electrophoresis: from protein maps to genome" in Siena Italy. The term proteome initially was used to refer to total proteins of a cell or an organism. It means much more now. Proteomic today implies, systematic separation of proteins, quantification and determination of modification state, interaction partners, activity, sub-cellular localization and structure in a given cell type and at a particular time.

The transfer of information from genes to proteins is not linear. One gene-one protein concept is

no longer valid. Indeed the increase in information content from gene to protein is exponential. And analysis of this information is an emerging and exciting area of research. Apart from the fact that a single gene could give rise to several protein products by differential splicing at the level of transcripts and proteins, multitude of post-translation modification of proteins, makes the proteome a very complex entity. An additional feature, unique to the proteome, is the variable abundance of individual proteins. This characteristic is one of the most difficult issues to analyze, since in many cases there is no correlation between respective levels of mRNA and protein abundance. Because of this, high throughput proteome analysis is as yet not as effective as in the case of genome analysis.

The experimental approaches to proteome analysis can be divided into distinct groups namely, top down, bottom-up and shot-gun proteomics. The classical two-dimensional (2D) separation of the given proteome followed by mass spectrometric identification of separated proteins is a top down approach. In this approach, the information regarding the proteins such a molecular weight, post translation modification can also be used for supplementing the identification process. In the bottom-up approach, peptide of the whole proteome are generated by enzymatic digestion first (using a

proteolytic enzyme such as trypsin). This peptide mix is purified by gel electrophoresis and then identified using mass spectrometry. In the shot gun approach, crude protein extract is digested directly and then separated by liquid chromatography. The choice of approach depends on the experimental design. There are advantages and disadvantages of these approaches. Here we examine 2D gel based electrophoresis.

2D electrophoresis is evolved into a reproducible methodology. The main problem faced by researchers using isoelectric focusing is the non-reproducibility of the pH gradient using carrier ampholytes. The introduction of immobilized pH gradient IEF strips largely eliminated this major problem. Coupled with increasingly sophisticated 2D gel analysis software one could easily produce reproducible gels with minimal effort. The commercial availability of a wide range of IPG strips, covering the entire pH range, is a boost to 2D analysis. Further, large format gels, allow the separation of a large numbers, maintain reproducibility and minimize gel to gel variation. Good 2D analysis software helps in removing the background intensity, and one can easily overcome minor variation in spot location during matching process using alignment option from software.

In order to achieve separation of a large number of spots, several strategies can be used. Removal of highly abundant protein allow loading of more protein leading to separation and detection of low abundance proteins. Sub cellular fractionation is non-intrusive method for reducing the complex of the proteins. Separation of membrane fractions from cytoplasmic fractions helps in handling the complexity as well as identification of these special group proteins of similar nature and to reduce the complexity of lysate. One such strategy is solution isoelectric focusing, which is promising as a prefractionation strategy. Coupled with narrow range IPG strips, the zoom gels can resolve about 15,000 proteins as of now.

Detection of proteins is an important step in 2D analysis. Sensitivity is still a major problem. The sensitivity staining methods using silver, such as ammoniacal silver staining, are not compatible with mass spectrometric identification. There are several silver staining methods which are modified to make them compatible with mass spectrometry. In spite of all these developments fluorescent staining is a method of choice since this staining does not interfere with mass spectrometry. The modified colloidal coomassive blue staining, also called "blue silver staining" is less expensive but is not as sensitive as the silver based and fluorescent stains.

Protein identification is mainly based on mass spectrometry of peptides generated by enzymatic digestion of gel- separated proteins. There are two major approached, one using Electro Spray Ionization (ESI) and the other is Matrix Assisted Laser Desorption ionization (MALDI).

MALDI as a method is user friendly and fast and in addition, today one can even get a bench top MALDI machine at a affordable cost. We will focus here on the use of MALDI in proteome identification.

The four main steps after the separation of protein on one/two dimensional gels are:

1. In-gel digestion of proteins

The spots cut out from the gel are dehydrated and incubated with trypsin or other suitable proteolytic enzyme. Care must be taken to use good quality enzyme since the auto digest products of the enzyme will interfere with the identification process.

2. Extraction of peptides, desalting, mixing with appropriate matrix and spotting

The use of appropriate matrix is a critical factor. The matrix suitable for the ionization of whole protein may not be suitable for ionization of peptides. There are, in addition, several matrix enhancers which also help in better ionization and suppression of matrix adducts. Standard peptides should also be spotted, for calibration, as close as possible to the actual spot. The use of internal standards, at times, masks the real peaks and hence this method may not be useful. In addition, if the trypsin used for digestion is good, one may not find any auto digest products.

3. MALDI analysis

Through fairly straight forward, it is important that one knows about the instrument to a certain extent. Care is needed in the

calibration of the instrument, laser power, and resolution used for analysis.

4. Peptide mass list analysis using search engine

In the final step, the list of peaks is filtered to remove the contaminating keratin peaks. Removal of these peaks will improve the score. One should also use more than one database for identification purpose. MASCOT is the most common search tool, but protein prospector also has a good search tool. The interpretation of the results from these search tools is fairly simple and good online help is also available for each of the tools.

Peptide mass fingerprint is most commonly used identification method. However, the availability of MS/MS data of the selected peptides will help further in the identification process. Apart from the analysis of unmodified peptides one can also identify post-translational modifications such as glycosylations and phosphorylations in MALDI.

Both 2D and MALDI are now being used as very sensitive quantitative tools for discovering minute variations at expression level. The applications of proteome analysis, particularly in biomarker discovery and

clinical proteomics, have
immense commercial
potential.

expenses or tuition fee. Here, the
brief description of Japanese
scholarships is listed below which
can be applied from your home
country.

STUDY IN JAPAN

Japanese scholarships for international students

Japanese Govt. and many private
organizations offer a number of
scholarships to international
students who wish to study
particularly in Undergraduate,
Researcher, Master, Doctorate,
Japanese language and specialized
training and technology programs.
A majority of scholarships only
sponsor parts of the student's daily

Scholarships applied overseas

| Types | | Target students/ No. of scholarship-grant bodies | Monthly sum |
|--|---------------------------|--|-------------|
| Japanese government (Monbukagakusho:MEXT) scholarship | Embassy recommendation | Research students/ teacher trainees | ¥170,000 |
| | | Students in Undergraduate Programs/Colleges of technology/Specialized training colleges/ Japanese language, Japanese studies | ¥134,000 |
| | | Students in the Young Leaders' Program (YLP) | ¥258,000 |
| | University recommendation | Research students Japanese language, Japanese studies | ¥170,000 |
| | | | ¥134,000 |
| JASSO reservation program for Honors scholarship for private financed international students | | Students who have taken the EJU exam and plan to enroll in regular | ¥50,000 |

| | | |
|--|---|----------|
| | program at Universities/Junior colleges/Professional training colleges | |
| Private organization scholarships | 13 private organizations | ¥149,000 |
| Short-term students Exchange Promotion Program (inbound) | (Target is short-term international students under inter-University Exchange Program agreement) | ¥80,000 |

The detailed guidelines for Japanese scholarships, you may check this website: http://www.jasso.go.jp/study_j/scholarships_sfisij_e.html

Resources

Cutting edge biotechnology

North Carolina Department of Public instruction, “Focus on biotechnology”

Break through in research

“Pocket size PCR machine” Chemistry world, May 01, 2007.

“Reprogramming cells, GPCRs and Human genetic variation”, science, December 21, 2007.

“Next generation DNA sequencing by hybridization” Nature Biotechnology, May 25, 2008.

Outlook India

Articles: Innovation for Indian biotechnology sector, breathing life into biology, a traditional medicinal system, Women scientist in India, A tough journey; “Inside: Indian life sciences” Nature, July 28, 2005.

“How I become a successful entrepreneur” **Villo Morawala Patell** (chairman & Managing director of Avesthagen). Newsletter of DBT, India, December, 2007.

News features

“Global genetics consortium launches major cancer research initiative” B-domain, Industry monitor, April 29, 2008.

“Development of tiny implantable Biocomputers” MediNew.Direct, May 26, 2007.

“A new world of RNAi discovery” Thermo scientific, Inc, 2008.

Educational links

Newsletter of DBT, India, August, 2006