Grace Roxas | Contributing Writer

Nobel Prize demystified

Israeli-born 2004 Nobel Prize for Chemistry Dr. Aaron Ciechanover talks about what it took to hail from a small, besieged country and win a plum of humanity

In his baggy khakis and loafers, topped only by a formal dark coat as a nod to ceremony, Dr. Aaron Ciechanover shuffles in front of the audience with the homely charm of a professor coming in for the day's lessons.

But the task he had in mind went somewhat contrary to the expectations of an audience of mostly college students who gathered to listen to him in a forum organized by the International Peace Foundation and the University of Santo Tomas. Instead of giving an impromptu chemistry lesson on one of the decade's most important scientific finds, of which he happened to be codiscoverer, he set out to knock this very discovery off its pedestal with a self-avowed intent to "demystify the Nobel Prize"—arguably humanity's most prestigious plum—by finding some personal common ground.

Much was made of the parallel between the Philippines and Ciechanover's native Israel, two small countries that emerged into modern nationhood at roughly the same time after World War II.

Then the paths of the two countries began to diverge, even if Ciechanover's own smooth journey in life was not so ruffled by the extraordinary circumstances of his perennially besieged homeland.

He studied to be a physician and did a stint with the army as required by Israeli laws. Then after some career vacillation that involved trying out a career in surgery, he decided to become a scientist instead.

Going against the grain

The decision to do science went against the grain of what seemed to be right and expected from him. It started with going against every Jewish mother's fondest dream.

"The ultimate dream of any Jewish mother is to have a son or a daughter who is a physician. I decided to be a doctor and my family was happy. But then I decided I wanted to be a doctor of science, and my family thought that there are real doctors and fake doctors. I was a real doctor who became a fake one," he quipped.

And then there was the matter of national context. He won the Nobel (alongside Profs. Avram Hershko and Irwin Rose) for a discovery that is life-affirming and not one that primes the opposite instinct in a country that has arguably developed the best defense-technology industry in the world under constant threat of annihilation by its neighbors.

"We've undergone 11 full-scale wars. But in between lots of buses, restaurants, and fa-

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cilities blown up, I still managed to get a Nobel Prize. It keeps you busy," Ciechanover said.

A couple of important career judgments he made were in the spirit of breaking away from the herd to find his niche: going back to his country to do science, and trailblazing a different path in research.

Not only did these decisions lead him down the winning path, they were also judgment calls made by someone whose circumstances are not unlike those faced by Filipinos trying to make it big abroad: a talented professional from a small country who felt like a small fry swimming with the big fishes in a pond called the US of A.

Working in the native land

After undergoing the bulk of his studies in his native country, Ciechanover capped his research training in the US, at the Massachusetts Institute of Technology (MIT).

MIT is probably the best place in the world for anyone to take wings as a fledgling scientist, but the young Ciechanover knew he would probably be only one of so many talented hatchlings there who would have to fight for his place under the American sun.

So he went back to a highly receptive welcome in his country and never looked back since. Just how receptive is an object lesson that Ciechanover wanted to impart to Filipinos and other nationalities laboring with a small-town complex.

"I wouldn't have gone back if my institute didn't have the start-up funds for me, the laboratory and the infrastructure. I got a package deal that made it attractive for me to come back. And it [was] the government who [had] to set up this infrastructure," he pointed out.

There was also the less quantifiable fact that Israelis have always been a patriotic lot, although patriotism for Ciechanover is not a vehicle that runs on its own gas.

"We build national aspiration, but that won't help you. You need to build your pipeline to burn the oil and put the energy into it," he said. "So we work closely with the government and we put money aside to bring young people in."

His future is now his past, he says. As senior research mentor at Technion Israel Institute of Technology in Haifa, Israel, Ciechanover is personally involved in ensuring that young Israeli scientists are getting as good a package deal as he did or even better.

Kiss of death, promise of life

The crucial insight that also led to their award-winning discovery of the ubiquitin system, the process of molecular labeling that bestows a "kiss of death" on the proteins that need to be destroyed, was also a product of thinking along a track different from the rest.

In the early '80s when Ciechanover started with his life's work, most scientific inquiries focused on how proteins are generated and transferred from one generation to the next. No one even knew that proteins are being degraded at all or even if they are, that it would be significant enough to merit major research focus.

"You don't want to be on the main road with Harvard, University of California, MIT, or the others. You want to be original and do something that nobody else is doing. So we decided to go the opposite way," he recalled.

It was not a fast, nor an easy way. "First of all, you don't know that what you discovered is important and it's typically not the discoverer who realizes the importance," he said. "Furthermore, we have to circumvent many doubts in the scientific community because I didn't go into the scientific discovery itself. But it was shown nonetheless that once you put the 'kiss of death' on the protein, the protein changes its molecular weight dramatically."

It took two to three years before he and his colleagues even realized they had something novel and true, though not necessarily important. The true significance of the discovery unfolded a decade later.

And when it did, it was like a gold rush, landing Ciechanover and his colleagues in biology and medical textbooks and providing the science for at least one cancer treatment to date, with more to come not only for the different types of malignancies but for almost every disease that has a possible link with a digression from the normal rate of protein degradation in the body.

Glaring contrast

A two-time visitor of the Philippines to date, Ciechanover is all too aware that the part of his story about using one's talent in the home turf stands in contrast to the local situation.

He calls attention to the fact that countries that employ Filipino nurses, doctors, and other professionals are actually getting these imported professional services on a silver platter, not having to invest themselves in training such professionals among their population.

Again, he implied that a case can be made for more government support in education because the interest of privately owned Philippine schools catering to the overseas demands for jobs is not tempered by a national agenda to reserve the best talents for the country's own development.

"All good things can be said about Filipinos [working abroad] except that they are not serving the country, or serving it only by sending back money," he said. "This is important but life is not only about money. And if they were here, they could have generated more money by helping boost the economy." **M**

A new lode of cure

It already has one novel cancer treatment to show for itself, a therapy against multiple myeloma and non-Hodgkin's lymphoma that has been shown to greatly improve prospects of long-term remission for patients that had previous bouts with chemotherapy.

And the Nobel Prize–winning discovery by Profs. Aaron Ciechanover, Avram Hershko, and Irwin Rose of a mechanism by which cells of most living organisms cull unwanted protein is holding out more promises of cure not only for other types of cancers but for a host of known degenerative disorders including the notorious Alzheimer's disease, inflammatory diseases, infectious, and even viral diseases.

This mechanism is mediated by a molecule called ubiquitin, which fastens itself to the proteins that need to be destroyed for either being spoiled or useless. Thus labeled for destruction, the proteins are accompanied to their death among enzymes called proteasomes, which chop them into pieces and destroy them. Shortly before the protein is squeezed into the proteasome, its ubiquitin label is disconnected for reuse.

According to Ciechanover, there are thousands other enzymes in the body that act like policemen by targeting specific proteins for destruction. They are thus themselves individual targets for drug development.

"It is very promising but it will be slow," Ciechanover said of the future, "because we are trying to understand more of the system and identifying the enzymes that will become drug targets." **M**