BY KIM RIBBINK

ONE for ALL

The oncology-focused biotech company Millennium is thriving under the collaborative direction that is being driven by Chief Medical Officer Dr. Nancy Simonian, who is also bringing synergy and interactivity to R&D activities.

There's no place for the arch ego in today's most progressive biotechnology companies or for that matter, at pharmaceutical companies. Rather, scientific leaders such as Nancy Simonian, M.D., are leading the charge toward collaborative ingenuity.

Teamwork is very much Dr. Simonian's mantra. Indeed, it is the collaborative spirit of biotechnology that spurred Dr. Simonian to join the industry in the first place, and it is how she has been working ever since.

"Integration of cross functions is very much in the DNA of small biotech companies, and I like working with interdisciplinary, collaborative teams and bringing people with many different backgrounds and opinions to the table to try to solve the complex problems of drug development," Dr. Simonian says.

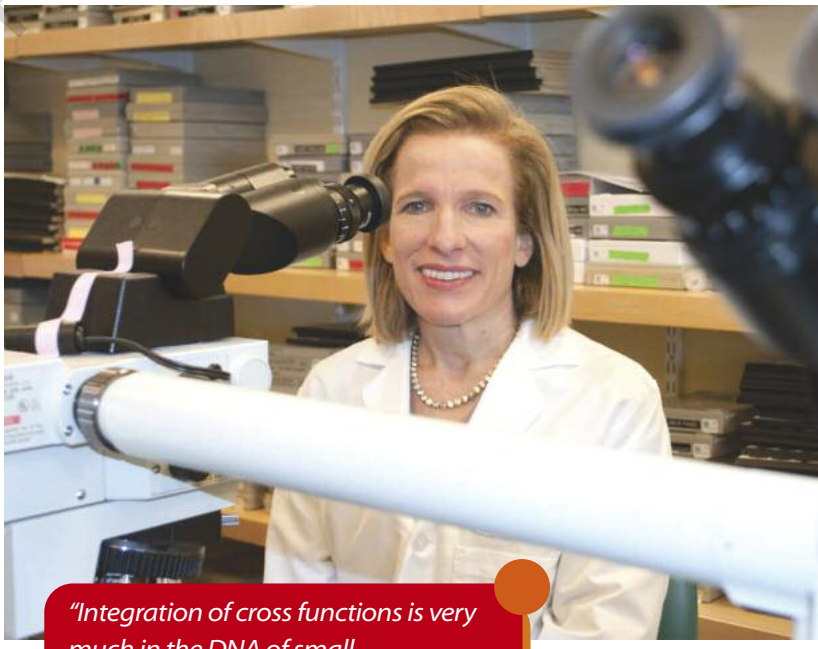
At Millennium: The Takeda Oncology Company, where she is chief medical officer, Dr. Simonian is a key member of a team that shrugs off departmental protectiveness and builds synergies that deliver tangible results in research and development.

"I'm a strong believer that to create innovation in R&D there has to be very close integration and collaboration across the R&D chain," she says.

To that end, rather than having a single head of R&D, a team comprising Dr. Simonian, as chief medical officer, Joseph Bolen, Ph.D., as chief scientific officer, and Peter Smith, Ph.D., as senior VP of nonclinical development sciences, works in tandem to run the R&D organization. The three meet regularly to discuss what's going on across the R&D organization and the areas requiring the greatest focus. In so doing, they also drive collaboration among members of their own teams.

"We make sure that what is being done in research is going to be important for what will be done in development and ultimately what we think is important for the patient," she says. "Likewise, we take learnings from the clinic and feed those back to research, which helps us improve the way we are working."

Dr. Simonian says this approach extends beyond the company walls into strong allegiances with academic institutions and nonprofit organizations, such as the National Cancer Institute and the Multiple Myeloma Research Foundation.



"Integration of cross functions is very much in the DNA of small biotechnology companies, and I like working with interdisciplinary, collaborative teams and bringing people with many different backgrounds and opinions to the table to try to solve the complex problems of drug development."

"Success requires having some level of understanding of the broad number of components that go into the business. Leaders don't necessarily need to be technically proficient in all areas, but it's important to have enough of a sense for why they are important and how they influence decisions."

Today, Millennium is delving into many exciting and evolving areas of cancer research and building a pipeline of products that potentially mark a turning point in the treatment of many cancers. (To read more about Millennium's pipeline, access the digital edition at pharmavoice.com.)

ENABLING THE PROCESS

The complexity of the life-sciences industry, particularly in today's highly regulated and competitive market, means leaders must not only be able to thrive in a collaborative, team-oriented environment, but must have an understanding of the bigger picture.

"Success requires having some level of understanding of the broad number of components that go into the business," Dr. Simonian says. "Leaders don't necessarily need to be technically proficient in all areas, but it's important to have enough of a sense for why they are important and how they influence decisions. I believe today's leaders need to be able to work in a team-oriented setting. It's not about one individual with particular knowledge; it's how to turn a group of people with different technical expertise into a group that can be greater than the sum of its parts."

Since women tend to be more collaborative and team oriented by nature, Dr. Simonian says the demands of today's business can serve women very well as future leaders. Her own success at Millennium, where she is responsible for clinical development, regulatory affairs, pharmacovigilance, and development project and portfolio management, is testament to that.

As she guides her team of innovators, Dr. Simonian looks to challenge her staff with ideas and questions while providing them with the autonomy to get the job done.

"The way I learn as a leader is by asking questions and understanding how people think about a problem," she says. "This not only helps me understand how my team members are thinking about challenges, it helps them to think, in some circumstances, differently than they may have otherwise. I believe having the right people in place creates a dynamic that encourages constructive challenging; that's the optimal scenario."

In addition, Dr. Simonian looks beyond the confines of the workplace to gather ideas. She is on the board of Arqule Pharmaceuticals, a publicly traded biotech company, as well as the board of a nonprofit organization, the Personalized Medicine Coalition.

"These other opportunities help me to think differently and broaden my horizons in terms of networks and ideas," she says. "As a board member, I am able to step back and view things a little differently. Then when I return to my day-to-day job I am able to put a different lens and perspective on my own company. It is often difficult for leaders and managers to step back, view things in the broader context, and look down the road to the future. Any opportunities to get out of the here and help to make us better leaders and keep our companies competitive."

PLUNGING INTO NEW TERRITORY

There's one thing that's abundantly clear about Dr. Simonian: she's not afraid to take risks. From the move that took her from academia to biotech to the decision to leap into a challenging role at Millennium, Dr. Simonian has steered her career toward new opportunities.

In fact, even her decision to move into the field of neurology research, rather than surgery, was a deviation from what might have been a predefined path.

The daughter of a surgeon, Dr. Simonian says medicine has always been a part of her life, and from an early age she remembers watching her father perform surgeries. It was no surprise when she chose to go to medical school, but while she had anticipated following the surgical route, she found she was not as excited by

Keeping Productive

For Millennium's progressive Chief Medical Officer Nancy Simonian, M.D., the problem of shrinking pipelines that faces much of the industry points to a need for a greater focus on true innovation.

"The biggest challenge we face, overall as an industry, is R&D productivity," she says. "We have a wealth of information and lots of potential targets to go after. The difficulty facing companies is how to choose what to invest in, and how to invest in them most effectively and efficiently."

Dr. Simonian believes that having the ability to be focused at a deep level in certain biologies is critical to success. Companies that focus on their expertise, while also looking to external opportunities, will do best.

"But the challenge is choosing where to focus these efforts, and knowing how to combine a specific area of biology and the instinctual aspect of where the next important ideas lie," she says. "This is why it's important to have a deep expertise and a culture of innovation. Companies that are just turning the crank and aren't innovating won't be successful in the long run."

One of the biggest challenges facing companies today, however, is that factors beyond good science and good data can impinge on decision making.

"Sometimes issues, such as politics and changing regulations, can start to play a role," she says. "Our industry has to stay focused on the science and what the data are, and accept that there is always uncertainty. By making the development of new medicines a science and data-based endeavor, we can continue to innovate."

A big challenge facing the industry, she says, is the loss of revenue as patents expire.

"This will put greater pressure on R&D investing," she says. "Also, the explosion of new science and biology in so many areas that require investment based on outcomes and skyrocketing costs of clinical development continue to put pressure on being successful as an industry and impact how we are able to bring those exciting next new molecules to the clinic and then patients."

She warns that any cutbacks on the industry's ability to invest in R&D could have a detrimental impact on human health down the road.

"A lot of important advances have been made but there's so much more we need to do, and my concern is how do we appropriately weather the storm over the next several years to ensure the industry has the long-term ability to turn incredible science into new medicines," she says.

"When I think about drug development I don't think about it purely from an R&D standpoint; I think about it from the perspective of the unmet need, the customer's need, what physicians want, and what patients want."

the area as she had anticipated and found herself drawn to science and research around medicine, particularly neuroscience. This interest is what led her into academia at Massachusetts General Hospital, Harvard Medical School.

"While I enjoyed the aspect of seeing patients, my passion was directed toward science and research," she says.

At the time, professors of medicine — the men and women who were Dr. Simonian's role models — were expected to have a trifecta of skills: they taught, conducted research, and saw patients. But it became clear to Dr. Simonian that in order to do research at the highest level, it was difficult to juggle teaching and patient care. At the same time, she wanted her work to be applied to helping people.

"At first I didn't realize I could achieve these goals by being part of a biotech or pharma company, because those who I trained and interacted with at Mass General had little first-hand knowledge of the opportunities that biotech presented and considered going into industry a questionable career choice," she says.

But Dr. Simonian is not someone so easily swayed by opinion and when she got a call from a recruiter looking for a neurologist to join Biogen, she decided to go for the interview.

"Biogen had a very science-driven culture and its clinical team was staffed with people from academic medicine," she says. "I soon realized that I could get some of the things that were important to me outside the world of academic medicine, so I took the plunge."

Despite some of the misgivings of her colleagues at Massachusetts General, she has never looked back.

A researcher by nature, Dr. Simonian has found that biotech is her natural home. To test her theory, she did go for an interview at a pharmaceutical company before joining Biogen.

Dr. Simonian says she is inspired by all things that define biotech: its science-centric focus, the strong collaboration and integration across research and development, and the fact that, unlike large pharma companies, there is very little hierarchy and bureaucracy, and each person feels he or she can have a broader impact across the organization.

"My job at Biogen was to lead the clinical efforts on interferon-beta and the company's first product Avonex, which gave me a broad perspective across the company: research, development, and commercial," she says.

PULLING TOGETHER

While the change from academia to industry can be a challenge for many people, Dr. Simonian found she adapted fairly effortlessly.

"In the academic setting, the physician can be at the center of decision making, but in a company the clinical or medical person is one of many equally important voices at a table and it's necessary to work more collaboratively," she says. "I found this to be refreshing. At a company, we all have a common goal and work toward that."

Nevertheless, her academic background has stood Dr. Simonian in very good stead, encompassing a network of colleagues as well as laying the foundation for scientific rigor. This experience forms the basis of how she tackles a scientific problem, how she solves hypotheses, and how she conducts experiments.

All of this has contributed to many significant breakthroughs and achievements during the six years she spent at Biogen.

The company's first marketed product, Avonex for multiple sclerosis, was approved based on a single Phase III study.

"What I found most satisfying was being able to see the evolution of Avonex, the additional indications that we received, as well as additional research on brain atrophy, cognition, and other different areas," Dr. Simonian says.

Aside from the clear benefit to patients, Dr. Simonian was very proud that she and her col-

Collaborative Growth

NANCY A. SIMONIAN, M.D. — RESUME

2006 – PRESENT. Chief Medical Officer, Millennium: The Takeda Oncology Company
2005 – 2006. Senior VP, Clinical, Medical & Regulatory Affairs, Millennium
2003 – 2005. VP, Clinical Department, Millennium
2001. VP, Medical Research, Biogen
2000 – 2001. Senior Director, Medical Research, Biogen
1997 – 2000. Director, Medical Research, Biogen
1995 – 1997. Associate Director, Medical Research, Biogen
1997 – 1999. Assistant Professor, Neurology, Harvard Medical School, Massachusetts General Hospital
1994 – 1997. Instructor in Neurology, Harvard Medical School, Massachusetts General Hospital

EDUCATION AND TRAINING

1992 – 1994. Clinical & Research Fellow in Neurology, Harvard Medical School, Massachusetts General Hospital
1989 – 1992. Resident in Neurology, Harvard Medical School, Massachusetts General Hospital
1988 – 1989. Intern in Internal Medicine, Harvard Medical School, Massachusetts General Hospital
1988. M.D., University of Pennsylvania Medical School
1983. B.A. Princeton University

HONORS AND AWARDS

1995. Physician Scientist Award, National Institutes of Health
1994. Ellison Scholar
1989. Academic Medicine Prize, University of Pennsylvania School of Medicine
1988. Neurology Prize, University of Pennsylvania School of Medicine
1987. Charles A. Dana Fellowship
1987. Alpha Omega Alpha

"I am continually interested in broadening and challenging my sphere; I like to be on the learning curve."

leagues were able to make some big changes in how the field thought about clinical trials and treatment in MS.

One of the huge career benefits of working on Avonex from early on was that Dr. Simonian got a bird's-eye view of the clinical, commercial, and marketing interface and the importance of not just having good data but being able to communicate clinical data, understand customer needs, and provide patients with what they need in the most appropriate way.

"Coming from an academic medicine background, this was a new learning and I was very fortunate to have the experience early on," she says. "Now, when I think about drug development I don't think about it purely from an R&D standpoint; I think about it from the perspective of the unmet need, the customer's need, what physicians want, and what patients want. It's important to keep all of these in mind, because increasingly companies are going to need to provide products that create true value over what already exists."

During her time at Biogen, Dr. Simonian was also involved in the decision to in-license Tysabri for the treatment of MS.

"We now know the compound carries some risk but the efficacy is spectacular, and it has made a big difference for a lot of patients in a very positive way," she says.

The experiences that perhaps helped most in preparing her for further leadership roles were building teams and ensuring the right people were in place.

"Bringing in and developing great talent are important capabilities but the corollary to those are being able to identify the individuals who aren't working out well in the team, for whatever reason," she notes. "It's better to deal with these situations earlier rather than later. At the end of the day, it's how the whole group works together and how individuals pull together for the overall benefit of the company."

SETTING NEW GOALS

Though Dr. Simonian was not particularly looking to leave Biogen, she realized after six years that she was ready for a new challenge. She had been looking internally for new opportunities when she received a call from a former Biogen colleague, who was consulting for Millennium and had been put in charge of finding a new clinical head for the company.

On first hearing about the position, Dr. Simonian didn't think she was the right person for the job since the company was looking for someone with at least 15 years of industry experience. But her former colleague put her name forward and she went for interview.

"Similar to the experience I had when I went to Biogen, I really connected with the people I met and was drawn to the culture, and this was an important component for me," she says. "I got the job and looking back, maybe it was a bit of a stretch to hire me, but ultimately I was given this wonderful opportunity."

This "wonderful opportunity" has worked out well for both Dr. Simonian and Millennium. She moved fairly quickly from VP of the clinical department, to senior VP of clinical, medical, and regulatory affairs, to her current position as chief medical officer.

"When I joined the company, there wasn't much of a department and I quickly had to figure out how to build a team from within the organization and by hiring externally," she says. "Because there wasn't much of a foundation, I could build the team in the way I felt was best; I didn't have to deal with a lot of legacy."

Such challenges are a perfect fit for Dr. Simonian.

"I am continually interested in broadening and challenging my sphere; I like to be on the learning curve, and often I 'get what I asked for,' but in a positive way," she says.

Aside from her day-to-day role as Millennium's chief medical officer, Dr. Simonian chairs the company's portfolio review committee, helping to decide how to allocate resources for everything in oncology development.

Even as a wholly owned subsidiary of Takeda, Millennium remains an autonomous biotech entity. With the money that the overall Takeda corporation allocates to oncology R&D, Millennium's senior management determines how much should be allocated to research versus development.

"We want to make sure we have the right balance; we want to invest enough in research to make sure we have the appropriate flow of programs into development for the long-term profile, while ensuring there is enough money in development to be able to optimally develop each program," she says

Millennium has more than 300 projects under way and more than 17 drug candidates in the areas of protein homeostasis, angiogenesis, growth signaling inhibition, hormone regulation, cell cycle inhibition, and apoptosis in development.

To determine how much to spend across this vast array of projects, the portfolio review committee conducts a rigorous portfolio prioritization, conducting analytics on the target product profile, including what the molecule is; what kind of attributes it has, including is it first in class, best in class, etc.; what the market potential is; what spend is required to get through the various development stages; and what the probability of success is.

"Then we look at the strategic factors that are most important to us in terms of revenue, time frame, and level of risk," Dr. Simonian says. "One of the exercises we employ is to prioritize the portfolio, and while part of this is quantitative, there is also a qualitative piece. We look at the numbers and ask does the ranking make sense? Does our understanding of the biology fit with the data? Should some projects be shifted to a high, medium, or low priority, and then we take that prioritization and figure out how to allocate the dollars accordingly."

This is much like any investment decision: a constant juggle of risk and reward, she says. There could be drugs with major revenue potential but may have a lot of risk while others may have more certainty but aren't going to have the huge revenue potential.

"This is a very collaborative effort with the folks in finance who do a lot of the modeling, as well as teams involved in the research, commercial, and clinical areas," Dr. Simonian says. "This is a very integrated portfolio process that tries to bring in all the various components; the goal is to maximize the way we make investments to better our chance of delivering innovative new medicines to patients." ✦

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BY KIM RIBBINK

A Pipeline of POSSIBILITIES

When Millennium was acquired by Takeda Pharmaceutical Company Ltd. in May 2008, the company became an oncology-focused enterprise, and merging the oncology resources of both companies has resulted in a more robust pipeline of investigational drug candidates.

"This whole class of 17,20 lyase inhibitors, of which we have the second one in the running, is one of the most exciting new drug classes for treating prostate cancer."

The company now serves as a global center of excellence in oncology under its new name: Millennium: The Takeda Oncology Company.

A key area of focus for Millennium's scientists is protein homeostasis, where the company is one of the world leaders.

The company's first-in-class proteasome inhibitor Velcade for the treatment of patients with multiple myeloma and relapsed mantle cell lymphoma continues to be investigated for other indications.

The compound currently is in pivotal trials for treating follicular lymphoma and has revolutionized the way hematological malignancies are treated.

In addition, the company has a second-generation proteasome inhibitor program that's in the clinic now. Proteasome inhibition constitutes a unique approach to targeted therapy. Inhibition of the proteasome prevents the degradation of numerous regulatory proteins, affecting multiple signaling cascades within the cell.

"This compound has different properties than Velcade, and preclinically it works in Velcade-resistant models," says Nancy Simonian, M.D., chief medical officer at Millennium. "It is also an oral molecule so we think this could be an advantage in the marketplace for treating myeloma and lymphoma especially in the maintenance setting."

"Also from the protein homeostasis platform is the NEDD8-Activating Enzyme (NAE), which is a target upstream of the proteasome that was discovered by Millennium scientists," Dr. Simonian says. "The biology is beautiful; it speaks to the innovation and the science, and hopefully this will translate into a new treatment for cancer patients."

That project is currently in early clinical trials.

In addition, Millennium has a molecule called TAK-700 that arose out of the strong research efforts at Takeda in the area of hormonal regulation.

"Takeda discovered Lupron, the mainstay for hormonal treatment in prostate cancer and now we have this other molecule, TAK-700 a 17,20 lyase inhibitor and it has shown promising data in early-phase clinical research," she says.

The progression and growth of prostate cancer cells requires the production of testosterone — the result of a long signaling cascade that begins with the secretion of the gonadotropin-releasing hormone and lutenizing hormone by cells in the pituitary gland, which in turn induce cells in both the adrenal glands and the testes to secrete testosterone. Testosterone then travels to the prostate, stimulating the growth of cancer cells.

While existing therapies target testosterone production in the testes, it is also secreted by cells in the adrenal cortex. Testosterone is synthesized in the mitochondrial membrane of adrenal cells by a series of enzymes, including 17,20 lyase. In preclinical studies, TAK-700 has been shown to bind to and inhibit the enzyme 17,20 lyase in both the testes and adrenal glands.

This is a molecule in the same class as abiraterone, which was developed by the biotech company Cougar, which was acquired by J&J last year for $970 million.

"The whole class of 17,20 lyase inhibitors, of which we have the second one in the running, is one of the most exciting new drug classes for treating prostate cancer," Dr. Simonian says.

Another Millennium program that excites Dr. Simonian is an inhibitor of Aurora A kinase. During mitotic cell division, Aurora A is a protein kinase involved in centrosome function and spindle assembly. It is required for faithful chromosome segregation. Aurora A kinase is over-expressed in a wide range of cancers, although the significance of this is not known.

In vitro, over-expression of Aurora A resulted in neoplastic transformation of certain cell lines, leading to Aurora A kinase's designation as an oncogene.

In preclinical studies, MLN8237 has been shown to selectively bind to and

potently inhibit Aurora A kinase.

"We've seen single agent activity in early clinical trials on advanced cancer patients, and we now have a very broad program going on in Phase II; this is a first-in-class oral molecule that has the potential to be very important in cancer," she says.

For all of its clinical programs, Millennium works closely with academic institutions and nonprofit groups. With its ongoing work on Velcade, the company works with multiple cooperative groups and foundations, including the Multiple Myeloma Research Foundation (MMRF), on a variety of different studies.

"The MMRF is also supporting our Aurora A kinase inhibitor program in a trial in combination with Velcade, and the group has been instrumental in moving new therapies forward in myeloma," Dr. Simonian says.

From a clinical-trial perspective, Millennium also works early on with the National Cancer Institute through a process whereby investigators at the NIH can access the company's molecules and conduct investigator-initiated studies.

"We work very closely to conduct clinical trials with the National Cancer Institute, and with cooperative groups for Velcade and some of our pipeline molecules," she says. "We are working with the Children's Oncology Group on our Aurora A kinase inhibitor for the development of 8237 in childhood cancers, in parallel with our adult program."

Dr. Simonian says the company believes it is important to form collaborations during the development of products since broader study results can pay dividends in greater development potential.

"For example, with Velcade after we pursued studies related to myeloma there were some investigator-initiated studies to research its use in lymphoma, and through those studies we had data that showed very strong signals in mantle cell lymphoma and follicular lymphoma; from those studies we decided to pursue company-sponsored studies." ✦