FOCUS ON LIFE SCIENCES
Synthesis & Analysis of Millions of Genomes & Nanostructures for Novel Therapies and Materials

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Speaker
George Church, Ph. D.
Professor of Genetics, Harvard Medical School, Director of the Center for Computational Genetics

Moderator
Stuart A. Borman.
Senior Correspondent, C&EN

About the Speaker
George Church, Ph.D., is a Professors of Genetics at Harvard Medical School, and the Director of the Center for Computational Genetics. Professor Church’s 1984 Harvard PhD studies consisted of the first direct genomic sequencing, molecular multiplexing and barcode tags. These lead to automation and software used for the first commercial genome sequence (of the pathogen Helicobacter) in 1994. He has since founded PersonalGenomes.org, which provides the world’s only open-access information source for human genomic, environmental and trait data (GET). He is director of the NIH CCV Center for Excellence in Genomic Science and is a member of NAS and NAE, and a Hoogendijk Prize awardee and Franklin Laureate for Achievement in Science.

The Life Science Series
This is the second production of C&EN Webinar’s new Life Science Series. As C&EN readers know, the interface between chemistry and biology is one of the most dynamic and important areas of modern science, and one that C&EN covers regularly in its reporting. Through this webinar series, we hope to expand our coverage of the life sciences, by enlightening and engaging our audience in topics of cutting edge technology and research in areas such as Next Generation Sequencing, PCR, and the study of Biomarkers. Contact cenwebinars@acs.org for more information about this and other upcoming C&EN webinars.

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WELCOME TO June issue of “Focus On Life Sciences.” This edition is a compilation of news and feature stories that appeared in March, April, and May 2012 issues of C&EN, the weekly newsmagazine published by the American Chemical Society, the world’s largest scientific society.

We’re distributing the “Focus On Life Sciences” series because C&EN, like the chemistry enterprise it is devoted to covering, is deeply involved in all aspects of modern life sciences—from bench research on the fundamental chemistry of living organisms to breakthrough biopharmaceuticals, from the analytical instrumentation that makes life sciences discoveries possible to the tough policy choices some of those discoveries pose. Our audience of more than 164,000 chemical professionals knows that the interface between chemistry and biology is one of the most dynamic and important areas of modern science. It’s where many of them work, and C&EN is the magazine they rely on to keep them informed of advances in the field and of the products and services they use in their labs.

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I hope you enjoy “Focus On Life Sciences.” With its large global circulation and loyal readership, C&EN provides a tremendous opportunity for advertisers who want to communicate with top scientists across many disciplines. C&EN reaches more than 164,000 readers each week, and C&EN Online (www.cen-online.org) has grown to more than 12 million page views per year.

C&EN’s Life Sciences Webinar Series is hosting guest speaker George Church on July 12 at 11 AM EDT. The webinar topic is “Synthesis & Analysis of Genomes & Nanostructure for Novel Therapies & Materials.” Register for this free webinar at www.cen-online.org/webinar.

We think you will find C&EN, with its broad coverage, readership, and outstanding editorial quality, to be an ideal vehicle for reaching your customers.

Thanks for reading.

Rudy M. Baum

Rudy M. Baum
NEWS OF THE WEEK

3 ION CHANNEL IN ACTION
Record-breaking computer simulation provides a first look at protein’s opening and closing.

4 MORE REVIEW OF GENE PATENTS
Supreme Court remands an appeals court decision on Myriad Genetics’ patents.

4 EPGENETICS TOOL
Technique quantitatively differentiates two common changes to cytosine in genomic DNA.

5 UNDERSTANDING A PUTRID PATHWAY
Studies of enzymes that make 2-methylisoborneol could help mitigate malodors in food and water.

5 BIOLOGICS JOINT VENTURE
Angen, AstraZeneca together will pursue new antibody therapies for inflammatory diseases.

6 REVERSIBLE COVALENT TIES
Strategy targeting noncatalytic cysteine residues could lead to safer drugs, especially for cancer.

6 DO-IT-YOURSELF BLOOD TYPING
New paper-based device answers the question, “What’s my blood type?” in writing.

BUSINESS

7 UNIQUE CONSORTIUM
Five major drug firms seek to prevent a rare disease that has emerged as a side effect of potential blockbuster drugs.

9 PAUL HERRLING
C&EN talks with the Novartis executive about new ways to fund drug development for neglected diseases.

GOVERNMENT & POLICY

10 PATENT DECISION SURPRISES BIOTECH
Supreme Court limits patent claims for diagnostic tests.

11 STRUCTURAL BIOLOGY CENTER
NIH partners with instrumentation firm FEI to accelerate structure determination of medically relevant proteins.

SCIENCE & TECHNOLOGY

12 PROBING PROTEINS
Advances in mass spectrometry raise method’s popularity as a tool for structural biology.

16 HEREDITARY EPGENETICS
In utero chemical exposures can trigger changes in gene expression, study confirms.

17 SPELUNKING IN A SPACE SUIT
Researcher explores caverns in the Austrian Alps that serve as proxies for caves on Mars.

EMPLOYMENT

19 CHEMICAL BIOLOGY
Opportunities exist at the dynamic interface of chemistry and biology.

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Serve the chemical, life sciences, and laboratory worlds.
ONE OF THE MOST extensive biomolecular simulations ever has allowed researchers to visualize the opening and closing of a voltage-gated potassium ion channel for the first time.

Voltage-gated ion channels in cell membranes help propagate nerve impulses, time heartbeats, and synchronize muscle contractions. The findings could thus aid drug design for heart disease, paralysis, migraine, and other conditions caused by ion-channel malfunctions. The work also shows that new levels of computer power are becoming available to study biomolecules.

Structures of voltage-gated ion-channel open states have been obtained, and many other studies have revealed much about channel behavior. But closed-state structures have remained elusive, making it difficult to nail down the channels’ overall mechanism.

Now, computational biochemist David E. Shaw of D. E. Shaw Research, in New York City, and Columbia University and coworkers including Morten Ø. Jensen have used a customized computer called Anton to perform all-atom calculations on a long-enough timescale to simulate ion-channel opening and closing (Science, DOI: 10.1126/science.1216533). The study was funded by Shaw Research and not supported by government grants.

The study of a system of more than 100,000 atoms was made possible by Anton’s ability to perform molecular dynamics simulations about 100 times faster than those carried out by any other computer. The longest simulation time in the new study is 230 microseconds, whereas comparable simulation times on other computers have been about 10 microseconds at most.

To make their computationally demanding simulations of channel opening and closing fast enough to be practical, the Shaw group applied membrane voltages several times higher than normal. That maneuver could spark controversy about whether the simulations elicited realistic channel behavior.

S4 helices on each of the channel’s four voltage-sensing domains are the main moving parts. The simulation shows them twisting as they open and close the channel. The group also simulated the activity of a channel with a known heritable mutation and proposed a mechanism for its aberrant ion flow, which is believed to cause heartbeat irregularities and neurological problems.

“Amazing!” said ion-channel expert Frederick J. Sigworth of Yale School of Medicine after viewing a movie of the normal process. “It’s like seeing for the first time something that until now has existed only in imagination. There are going to be things shaken out about whether Shaw and company got the details right, but it’s very impressive that they were able to put together a pretty convincing physical system and let it run.”

The new findings agree with a general consensus about the mechanism that has developed in the past couple of years, Sigworth and others tell C&EN. However, researchers disagree or are uncertain about some mechanistic details, such as how much S4 moves and whether or not it twists. Shaw’s simulation could help resolve such points of contention. — STU BORMAN

See a potassium ion channel close and open at http://cenm.ag/simulation.

& VIDEO ONLINE

ION SWITCH As potassium ion channel closes, S4 helices in voltage-sensing domains (VSDs, only one of four of which is shown) twist down toward the cell interior. S4 linker helices then loosen their hold on pore gate domains (two of four of which are shown), allowing pore closure. In channel opening, S4s twist upward, causing linkers to pull pore gate domains open. Insets show (from above) all four VSDs (circles), pore gate domains (squares), and linkers (lines). Also shown are a key VSD phenylalanine (Phe) and important basic (+) and acidic (−) side chains.
**GENE PATENTS UNDER REVIEW**

**SUPREME COURT:** Patentability of DNA-based inventions is at stake

The Supreme Court last week voided an appeals court ruling that allows human genes to be patented. The justices further instructed the U.S. Court of Appeals for the Federal Circuit, in Washington, D.C., to reconsider its July 29, 2011, decision.

That appellate court decision allowed patents on two “isolated” human genes used in tests for breast and ovarian cancer developed by Myriad Genetics, a biotechnology company based in Salt Lake City.

In its 2011 ruling, the Federal Circuit overturned a March 2010 decision by the U.S. District Court for the Southern District of New York that ruled the patents had been improperly granted because they encompassed nothing more than a “law of nature.” The Federal Circuit said in its decision that the genes isolated by Myriad are eligible for patent protection.

“It’s inconceivable that a company can own a patent on something as naturally occurring as DNA.” —CHRIS HANSEN, ACLU STAFF ATTORNEY

“Because access to DNA is tightly controlled, hair doesn’t grow on bone and toenails don’t appear in the spleen. Control comes from a system that includes chemical modifications to DNA bases, or epigenetic marks, that ensure the right genes are expressed in the right place at the right time. Two widely known chemical modifications are 5-hydroxymethylcytosine (5hmC) and 5-methylcytosine (5mC). What they do can now be better understood with the first tool to measure, with single-base resolution, their relative amounts (Science, DOI: 10.1126/science.1220671).

Researchers have known that when cytosine bases are methylated, the gene is silenced. The precise role of 5hmC is still debated, but it’s clear it has enormous biological importance, says Shankar Balasubramanian, a chemical biologist at Cambridge University.

Most researchers believe that 5hmC marks are an epigenetic “on” switch for genes. Others think that 5hmC is an intermediate in so-called active demethylation, which occurs in the first moments after a sperm fertilizes an egg. During this process, cytosine bases on the newly combined DNA are rapidly demethylated to create an embryonic stem cell.

Resolving the debate has been difficult because current genome-sequencing methods can’t distinguish between the two decorated cytosines with single-base resolution, says Skirmantas Kriaucionis, a biochemist at Oxford University. Now, Balasubramanian and colleagues have developed a technique that can do so.

The technique first uses a DNA-sequencing method that doesn’t differentiate the two. In this method, called bisulfite sequencing, both decorated cytosines are measured as cytosine, while naked cytosine bases are recorded as thymine. Next, the team repeats the sequencing after oxidizing 5hmC; this time 5hmC is recorded as uracil instead of cytosine. Because the first sequencing round tabulates both 5hmC and 5mC, while the second sequencing round tabulates only 5mC, the difference provides a quantitative measurement of 5hmC.

The new technique is “an elegant strategy,” says Chuan He, a chemist at the University of Chicago, who says his alternative method for quantitatively sequencing 5hmC will be published soon.—SARAH EVERTS

**SEQUENCING AN EPGENETIC MARK**

**CHEMICAL BIOLOGY:** Technique locates modified cytosines in genomic DNA with single-base resolution

because the company is testing for distinctive chemical forms of the genes, which are not as they appear naturally in the body.

In a terse order, the Supreme Court nullified that decision and sent the case back to the appellate court for further consideration in light of the justices’ ruling on March 20 in a similar dispute. In that case, the justices invalidated gene-related patents on a medical test held by Prometheus Laboratories, ruling the patents were ineligible because they simply described naturally occurring activities in the body (see page 20). Natural phenomena cannot be patented.

Myriad holds patents on two genes: BRCA1 and BRCA2. Its BRACAnalysis screen looks for gene mutations in extracted DNA that indicate a high risk of a woman developing breast or ovarian cancer.

The American Civil Liberties Union (ACLU) filed a lawsuit against Myriad in 2009 that sought to have the patents invalidated, arguing that genes are “products of nature.” The suit contends that the patents stifle research and limit access to potentially lifesaving genetic tests for at-risk women.

Peter D. Meldrum, president and CEO of Myriad, says the case is important to the medical, pharmaceutical, and biotechnology industries, and to the “hundreds of millions of people whose lives are bettered by the products these industries develop based on the promise of strong patent protection.”—GLENN HESS

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**NEWS OF THE WEEK**

**PUTRID PATHWAY PROBED**

**NATURAL PRODUCTS:** Studies of odorant biosynthesis could aid water remediation

**STRUCTURAL AND MECHANISTIC** analyses have revealed how two bacterial enzymes bio-synthesize the terpenoid odorant 2-methyliso-borneol (MIB) (*Biochemistry*, DOI: 10.1021/bi300109c and 10.1021/bi201827a). The work could lead to an improved understanding of factors promoting MIB production and ways to mitigate MIB odors and off-flavors in food, beverages, and the water supply.

MIB is a volatile terpenoid produced by microorganisms. Its musty odor can be detected at low concentrations. It contributes to the scent of moist soil and Brie and Camembert cheeses. But its odor can also taint fish and cause off-taste and odor in drinking water.

“We expect that the structures of the enzymes responsible for MIB biosynthesis will lead to new approaches for inhibiting the generation of this contaminant, which threatens the public water supply and causes multi-million-dollar annual losses in the food and beverage industry,” says chemistry professor David W. Christianson of the University of Pennsylvania. He carried out the work with Penn postdoc Mustafa Köksal and chemistry professor David E. Cane and postdoc Wayne K. W. Chou of Brown University.

The structures show that one enzyme, geranyl diphosphate C-methyltransferase (GPPMT), is a hexamer resembling a Star of David and that the other, MIB synthase (MIBS), is a homodimer of 13-α-helix bundles.

Scientists already knew that GPPMT methylates a 10-carbon monoterpene substrate and that MIBS then cyclizes the product to MIB. In all other terpenoid biosyntheses, methylation occurs only after cyclization.

The new studies have uncovered further details about this unique biosynthetic process. For example, they show the three-dimensional relationship of reacting species in GPPMT’s active site.

MIB is currently removed during water treatment by activated carbon filtration; biological filtration with immobilized bacteria; or UV-, ozone-, or hydrogen peroxide-based oxidation. But MIB contamination is difficult and expensive to remedy by such means, and water utilities are seeking better methods.

Christianson believes the new studies could aid rational design of GPPMT or MIBS inhibitors that might mitigate MIB generation in water sources.

Research scientist Susan B. Watson of the National Water Research Institute, in Burlington, Ontario, believes jurisdictions are unlikely to permit treatment of water with enzyme inhibitors. However, she adds, the studies aid understanding of factors controlling expression of genes for the two enzymes, which could lead to better mitigation methods.—STU BORMAN

**NATURAL PRODUCTS:** Studies of odorant biosynthesis could aid water remediation

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**PHARMACEUTICALS** AstraZeneca, Amgen join to advance monoclonal antibodies

In the wake of cutbacks in their respective research operations, AstraZeneca and Amgen say they hope to advance biologic therapies for inflammatory diseases in a development and commercialization joint venture. They will work on a portfolio of five clinical-stage Amgen monoclonal antibodies, including one, brodalumab, that has completed Phase II trials as a psoriasis treatment.

The partners say AstraZeneca brings the expertise in developing respiratory, inflammation, and asthma therapies housed at MedImmune, its biologics arm, as well as its commercial inroads in respiratory and gastrointestinal diseases. The Amgen molecules have the potential to impact multiple indications, they say.

Under the terms of the agreement, AstraZeneca will make a one-time payment of $50 million to Amgen, and the companies will share the cost of development and profits on any drugs commercialized. AstraZeneca will fund approximately 65% of development costs for the first two years of the joint venture, after which the partners will share costs equally.

Bahija Jalal, head of R&D for MedImmune, tells C&EN that the partnership is in keeping with AstraZeneca’s strategy for advancing biologics. “Our portfolios are complementary, and we are capitalizing on the strength of the two companies,” she says.

The partnership follows the announced elimination of 2,200 research positions at AstraZeneca earlier this year and 380 research jobs at Amgen last October.—RICK MULLIN
COVALENT TIES REVERSED

**DRUG DESIGN:** Dual activation groups lead to rapidly reversible covalent kinase inhibitor

**REVERSIBLY TARGETING** noncatalytic cysteine residues could lead to covalent drug molecules with improved potency and selectivity but with less potential for off-target adducts, Jack Taunton of the University of California, San Francisco, and coworkers report (Nat. Chem. Biol., DOI: 10.1038/nchembio.925).

The researchers say the strategy could lead to safer drugs.

Several acrylamide-based inhibitors that covalently bind noncatalytic cysteine residues in kinases are currently in clinical development as cancer treatments. These inhibitors have the potential to form irreversible adducts with glutathione and other off-target thiols that can raise safety concerns.

Hoping to reduce such off-target adducts, Taunton’s team made inhibitors with two electron-withdrawing groups for Michael addition reactions. Because of their dual activating groups, the new inhibitors bind to protein cysteines more quickly than do the ones currently in the clinic, which have only one activating group. But the reverse reaction is also swift, Taunton says.

“By increasing the intrinsic reactivity of the electrophile,” Taunton says, “you cross into a kinetic regime in which both the forward and reverse rate constants are intrinsically very fast.”

Despite the speed of the reverse reaction, the new inhibitors form stable complexes with their protein targets, thanks to a network of specific interactions between the inhibitor and the protein. Off-target cysteines lack such stabilizing interactions, and the speedy reverse reaction prevents permanent adducts from forming.

As a test case, Taunton and his coworkers made inhibitors for one of the domains of a kinase called RSK2. They targeted a cysteine in the enzyme’s active site. The approach should work for any “druggable” site as long as there’s a nearby cysteine, Taunton says.

“This is an exciting and potentially general approach for making reversible covalent inhibitors that possess unique pharmacology,” says Nathanael S. Gray, who develops kinase inhibitors at Dana-Farber Cancer Institute.

BLOOD TYPING MADE SIMPLE

**BIOANALYSIS:** Paper-based device spells out blood type

For anyone who has ever wondered what their blood type is, a new paper-based device will literally write the answer, providing an inexpensive and unambiguous way to determine blood type (Angew. Chem. Int. Ed., DOI: 10.1002/anie.201201822).

The presence or absence of certain antigens on red blood cells determines a person’s blood type. Specific antibodies will react with these antigens and make the red blood cells clump. Researchers led by Wei Shen, of Australia’s Monash University, use an ink-jet printer to apply these antibodies in the shapes of letters A, B, and X as well as a vertical line onto postage-stamp-sized pieces of paper towel. O and rhesus-negative blood types don’t have antigens that react with these antibodies, so the researchers preprint an O in the same spot as the X and a horizontal line intersecting the vertical line on the paper in red waterproof ink.

Place a few drops of blood on the paper, wash it with saline, and in under a minute, the blood type appears in text. For example, if the blood type is A-positive, antigens will react with printed A antibody to produce a clump of red blood cells in the shape of the letter A and with antibody in the vertical line to form a + sign. The antigens will also cause a red X to form over the preprinted O. For O-negative blood, no reaction with the antibodies would occur, and the preprinted paper would simply read O above a – sign.

Shen got the idea after seeing the film adaptation of J. K. Rowling’s book “Harry Potter and the Chamber of Secrets,” in which the characters query a diary that responds in writing. Shen realized technology he had previously helped develop could be modified to respond in writing to the question: What’s my blood type?

“The ability to form letters that directly report blood type makes it possible for nonexperts to interpret the results rapidly, which is of particular importance in rapid-response scenarios,” comments John D. Brennan, an expert in bioanalytical chemistry at McMaster University in Ontario. “This method also shows the advantage of implementing simple ink-jet printers to produce paper assays rather than conventional lateral flow printers, which produce only lines.”—BETHANY HALFORD
DRUGMAKERS JOIN TO STUDY A VIRAL THREAT

A rare and deadly BRAIN INFECTION could derail a range of immune system-modulating drugs

RICK MULLIN, C&EN NORTHEAST NEWS BUREAU

BIG PHARMA drug development collaborations, such as Pfizer and GlaxoSmithKline’s Viiv Healthcare HIV/AIDS joint venture, have become fairly commonplace. The Alzheimer’s disease pact among Pfizer, Johnson & Johnson, and Eli Lilly and the diabetes partnership between AstraZeneca and Bristol-Myers Squibb (BMS) are two other examples of two or three big drug companies joining forces against a huge therapeutic target.

In contrast, a unique consortium of five major drug companies is aiming at an extremely small target: progressive multifocal leukoencephalopathy (PML), a rare and often fatal viral brain infection associated with immunodeficiency that has primarily affected HIV/AIDS patients.

PML is caused by an apparently benign virus, called John Cunningham virus, present in 50% of all adults, she says. In rare cases of immunodeficiency, the virus mutates and begins a demyelinat-

ing neurodegenerative process. It is not known where the virus resides in the body before mutation, Banzet says. And not much attention has been paid to it, given that the disease affects “one or two out of 100,000 people, depending on the underlying disease,” Banzet says. “It’s worse than an orphan disease.”

ROCHE AND GENENTECH began paying attention to PML, however, after they voluntarily pulled Raptiva, a psoriasis therapy, from the U.S. market in 2009 on the basis of its association with increased risk for PML. This followed the withdrawal of Eli Lilly and Biogen Idec’s Tysabri for the same reason in 2004. In both cases, the number of patients diagnosed with PML in trials was small—three in the case of Tysabri and in four in the case of Raptiva—and the Food & Drug Administration allowed Tysabri back on the market in 2006. Roche and Genentech have not reintroduced Raptiva.

Roche, Eli Lilly, and other companies concerned about PML as a side effect of their drugs were in a difficult position, Banzet says. No reliable diagnostic tool existed for physicians, most of whom were unaware of PML, to determine which patients might be affected. A recently developed blood test indicates only whether a patient carries the virus (C&EN, Feb. 13, page 26). And the drug companies had information on only a small number of patients. None of the companies was equipped to develop any kind of diagnostic guideline on its own.

“Some companies decided that in order to mitigate the risk, there is value in putting together data and resources and expertise,” Banzet says. Five companies eventually formed the consortium “to try to put together everything we can to understand the disease, to predict the disease. Basically, it is around sharing resources.”

The group is established as a legal entity in which competitors share data in a noncommercial venture. “This, to me, is unique,” she says.

Nicki Vasquez, vice president of program and portfolio management at Eli Lilly and the Alzheimer’s disease pact among corporate safety and research groups. “With Roche and Genentech, we have this serious opportunistic infection that can be linked with immunomodulatory drugs. We are all looking at this problem. How can we get together and make some headway?”

The focus, Vasquez says, is on developing a means of controlling PML as a side effect of a range of immunotherapies. “The issue for patients as well as drug companies is that PML raises the specter of derailing a therapeutic that might otherwise be effective,” she says. “If we stop the development of a particular drug because it might result in PML as an adverse event, we may be hurting patients by blocking access to a potentially beneficial drug.”

It was unlikely that industry would band together to cure PML rather than prevent it as a side effect for drugs, Vasquez acknowledges. “Companies aren’t going to be particularly motivated to find cures for PML per se,” she says, “even with the increased frequency with immunomodulatory drugs. It is not on the radar of antiviral companies because it really is extremely rare.”

The group, which formed in 2009, “hit its stride” last year, Vasquez says, awarding grants to laboratories at Harvard University, the University of Kentucky, Penn-

“It was surprising to me that companies would band together to share research efforts and data about patients.”
The PML Consortium, led by Penn State University, is fostering collaboration and data sharing among multiple companies to better understand and develop treatments for progressive multifocal leukoencephalopathy (PML). This virus-targeted disease is often associated with the use of monoclonal anti-inflammatory drugs, and the consortium is working to prevent it from becoming a major industry problem.

David B. Clifford, a neurologist in clinical neuropharmacology at Washington University in St. Louis, chairs the PML Consortium’s scientific advisory board. He notes, “I have worked in the development of AIDS therapies for years, and I have seen nothing like this group in that field.” Clifford emphasizes that the challenge of PML is also unique. The biological mechanism of the virus, for which there is no animal model, is a mystery.

There are all these monoclonal anti-inflammatory drugs that are very exciting possibilities to move therapy forward for MS, arthritis, inflammatory bowel syndrome—drugs for big, big markets,” Clifford says. “And FDA is sweating every one of these things for the risk of PML. It has become a common industry problem.”

Although the PML Consortium has no commercial objective, “in the future we would like to support the development of drugs to treat PML,” Vasquez says. “But this is not a commercial collaboration in the sense of what you see with drug companies where they band together to pool resources for commercial purposes. Our intent is not commercial. Because PML is so rare, we see this as the only real way to get our heads around it and really advance the field.”

For now, the consortium is a group effort to navigate uncharted biology around the John Cunningham virus. That should keep it busy, notes Clifford, who is skeptical that any commercial drug company would bear down on developing a therapy for the disease itself. “This is not something that will result in a blockbuster drug,” he says.

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Reprinted from C&EN, March 5, 2012
Imagine a biotech company with too many promising drug candidates and not enough cash to pay for their development. It’s a problem that could be solved pretty quickly by any number of strategies: license some compounds, go public, or get acquired by a bigger firm.

But for companies working to find new medicines for diseases that affect the developing world, a full drug pipeline is both a blessing and a curse. When there’s no profit at the end of the road, it’s a stretch to pay for full-scale development of even one promising compound, let alone an entire portfolio of drug candidates. The question is not only how to decide which one goes forward but also how to justify not pushing all of them forward when so many people are affected by—and will die from—diseases like malaria and tuberculosis.

Paul Herrling, chairman of the board of the Novartis Institute for Tropical Diseases (NITD), the neglected-disease arm of the Swiss drug company, is trying to come up with ways to bring as many new drugs for neglected diseases to market as possible. Time is of the essence. If a drug gets stuck in the pipeline because of lack of funds, “the patients will have the bad luck,” Herrling says, shrugging his shoulders. “That’s life.”

To some observers, his words might sound cynical. But Herrling’s matter-of-fact explanation of the realities of the developing world belies his commitment to finding new drugs for neglected diseases.

In fact, if the Swiss executive has developed a certain cool remove when discussing the challenges of funding drugs for neglected diseases, his eyes light up when he talks about progress in discovering them. Novartis researchers have come up with three new approaches to treating malaria. Two of them are already in clinical studies, one of which, a spiroindolone that Novartis calls NITD609, is the first antimalarial compound with a novel mechanism of action to enter Phase II clinical trials in 20 years.

The NITD malaria drug candidates are part of a pipeline of more than 100 drugs and vaccines for neglected diseases that in the past decade have emerged from a variety of public-private partnerships, including NITD (which is a partnership with the Singapore Economic Development Board), Medicines for Malaria Venture, and the Global Alliance for TB Drug Development.

Not all will succeed. As Herrling points out, the attrition rate for drug development is the same whether a medicine is intended for the rich or the poor. “But there is now a sufficiently large pipeline that a few of these projects will need to go into full development, where costs go up exponentially,” he says.

So far, funding for the drugs has come from a mix of nonprofits and pharmaceutical companies. But those backers “seem to have difficulties in funding the full development,” Herrling says. Without a new model for how to pay for Phase III trials and registration with regulators, “there is a real danger some of this pipeline will be stalled because there are no funds.”

The funding gap is particularly acute for diseases such as malaria and tuberculosis, for which a new drug needs to be paired with other medicines to combat resistance. Assessing both the new compound and the combinations in patients is an expensive undertaking. For example, if NITD609 moves forward to Phase III, as is expected, the clinical trials would likely cost hundreds of millions of dollars, Herrling notes.

Industry is beholden to shareholders and can fund only so many trials without the promise of a financial return. Novartis, for example, devotes more resources to neglected diseases than many drug companies, but it has limits to how much money it will spend on such efforts. Nonprofits, meanwhile, have limited resources and would be hard-pressed to sink such a large sum into just one drug.

Herrling is trying to come up with solutions. He sees two distinct challenges to getting drugs for neglected diseases onto the market. The first is clear-cut: finding the money to pay for trials. The second is more subjective: ensuring the best projects in the overall pipeline are moving forward.

Next month, Herrling and a group of delegates from various countries will present to the World Health Organization (WHO) the results of a yearlong study of how best to address the first challenge. In response to a call, the committee received 109 proposals; it whittled them down and made general recommendations. Its main conclusion is that all countries should devote at least 0.01%—more for developed countries—of their gross domestic product to government-funded R&D related to health issues of the developing world. “We want all countries, including the poor ones, to take ownership of this,” Herrling says. “But on the other hand, it’s clear that everyone should participate according to their paying power.”

Herrling is also part of a team that submitted a proposal addressing the second challenge. Their Fund for R&D in Neglected Diseases would pool neglected-disease funding from all sources to enable the kind of science-based portfolio management that goes on in big pharma firms. Herrling argues that dispassionate management of the many drugs under development would eliminate duplication of effort and help cut out projects that get pushed forward for political rather than scientific reasons.

Now WHO member states will need to reach a consensus on how to move forward. It’s a process that “will take time,” Herrling says. “But any step we take in the right direction is worth it.”

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**PATENT RULING DISMAYS BIOTECH**

**Supreme Court limits PERSONALIZED MEDICINE claims**

**THE SUPREME COURT’S** ruling last month, striking down two patents for a diagnostic test that helps doctors set drug dosages for patients with certain diseases, is being hailed by doctors and other medical professionals as a victory for patients.

But the justices’ unanimous decision in *Mayo Collaborative Services v. Prometheus Laboratories* has alarmed the biotechnology industry, which fears the decision will hurt the emerging field of personalized medicine (C&EN, Jan. 16, page 26).

Also called targeted therapy, personalized medicine entails the use of a patient’s genetic information to select medicines and treatments that precisely match the needs of the individual.

Prometheus, a San Diego-based biotech firm that is now part of Switzerland’s Nestlé Health Science, obtained patents on a medical invention—a blood test that helps doctors determine optimal drug dosages for patients with gastrointestinal disorders such as Crohn’s disease and other autoimmune ailments. The legal dispute began in 2004 when Prometheus filed a patent infringement lawsuit against Mayo after Mayo tried to market a similar test. In March 2008, the U.S. District Court for the Southern District of California invalidated the patents, finding that Prometheus’ invention was no more than “a natural body process preexisting in the patient population.”

The U.S. Court of Appeals for the Federal Circuit reversed that ruling in September 2009, saying the claims are patent-eligible because they describe a specific method for improving the treatment of certain diseases through a series of concrete and transformative steps.

After that decision was appealed to the Supreme Court, the justices concluded that Prometheus had attempted to patent laws of nature that could not be made exclusive. “Upholding the patents would risk disproportionately tying up the use of the underlying natural laws, inhibiting their use in the making of further discoveries,” Justice Stephen G. Breyer wrote in the Court’s 24-page opinion.

The American Medical Association (AMA), the nation’s largest physician group, welcomes the ruling. Robert M. Wah, chair of AMA’s Board of Trustees, says the verdict is “a clear legal victory that ensures critical scientific data remain widely available for sound patient care and innovative medical research.”

Had the Court found the patents to be valid, Wah contends that physicians would have encountered a “vast thicket of exclusive rights” that would prevent them from considering all relevant scientific information when reviewing diagnostic test results.

But the Biotechnology Industry Organization, an industry trade group, finds the decision disappointing. “We are concerned that it introduces new and confusing concepts into the traditional body of patent law, which patent examiners and lower courts will struggle to consistently and rationally implement,” says Hans Sauer, the group’s deputy general counsel for intellectual property (IP).

The industry is troubled that the Court’s opinion “fails to appropriately recognize” the importance of personalized medicine and the research and investment incentives needed to develop new individualized therapies for untreated diseases, Sauer says.

**IN THE DECISION**, the justices acknowledge the competing interests of securing patent rights to reward significant investment on one hand and the ability to freely conduct research on the other, notes Paul M. Rivard, a patent attorney in the Washington, D.C., office of Banner & Witcoff, an IP law firm. “But they essentially punted on this issue, leaving it up to Congress to fashion any special rules for personalized medicine,” he says.

With a more challenging legal environment for patents broadly directed to diagnostic methods, investors in personalized medicine “may revisit the value proposition for investments already made and may curtail or redirect future investments in new projects,” says Kendrew H. Colton, a partner at Chicago-based IP law firm Fitch, Even, Tabin & Flannery.

The Supreme Court’s decision will “significantly impact how patent applications in the field of personalized medicine are drafted, and the scope of protection that may eventually be obtained,” Colton adds.

Patent applicants in this area “probably will need to identify and claim more specific protocols to avoid being found to preempt a law of nature,” Rivard says.

Additionally, the thousands of patents issued for diagnostic tests in the past two decades could be affected by the Court’s ruling. “The decision may expose broadly drafted diagnostic method patents to increased legal risk,” Colton says. Over time, he adds, the challenges will be tempered by a new generation of patents drafted in the aftermath of the high court’s decision.

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LIVING LAB

Public-private effort creates a STRUCTURAL BIOLOGY CENTER

THE NATIONAL Institutes of Health and Oregon-based instrumentation company FEI have teamed up to create a novel structural biology facility on the NIH campus in Bethesda, Md. Called the Living Lab Structural Biology Center, the center brings together experts from FEI and multiple NIH institutes, including the National Cancer Institute (NCI) and the National Institute of Diabetes & Digestive & Kidney Diseases, to accelerate structure determination of molecular complexes and proteins that are important in human diseases.

This public-private partnership is unique in terms of the complexity of the project and the speed at which the agreement was completed. The concept for the Living Lab started with FEI, which went looking for a partner. NIH was interested, and after only a few months of discussions the partnership got off the ground earlier this year. For its part, FEI provided the lab with a fully automated Titan Krios transmission electron microscope, optimized for cryogenic electron microscopy.

The instrument is a workhorse for high-resolution imaging. The basic microscope is used around the world for all kinds of research, but the cryogenic capability is well suited to “soft and squishy” medical samples, says Srimat Subramaniam, a senior scientist at NCI and codirector of the Living Lab.

Cryoelectron microscopy is gaining popularity in structural biology because it allows samples to be imaged in their native environment. FEI hopes the partnership will open new markets for the technique, making it as commonplace in structural biology as more traditional complementary techniques such as nuclear magnetic resonance spectrometry and X-ray diffraction.

NIH researchers are optimistic that the five-year collaboration will lead to new vaccines and medical treatments. To make that happen, Subramaniam is hoping the work will result in key technical improvements that will allow him to obtain structures of dynamic protein complexes or enveloped viruses in their native state.

NIH investigators have a long history of knowing what structures are medically important to study, Subramaniam says. Instead of trying to answer questions using existing technologies, “we try to identify what the important questions are and develop technologies to actually go after them,” he explains. “By having FEI engaged with us, they have a better understanding of what it is we are trying to do,” he says.

Subramaniam is particularly interested in the structures of the proteins that HIV uses to get into cells in order to design better vaccines. “We want to get structures of proteins without having to crystallize them first,” he says. This is important, he explains, because “crystallizing a protein changes its native form.”

The Living Lab was formed quickly because “there had been a lot of groundwork laid by the investigators before they approached the more formal process of getting an agreement in place,” says Kathleen Higinbotham, a specialist at NCI’s Technology Transfer Center, in Frederick, Md.

“I knew a fair bit about what FEI was doing, and they knew a fair bit about what we were doing,” Subramaniam says. The relationship had been formed over several years, he says.

Before the company reached an agreement with NIH, “FEI did a thorough analysis of who we wanted to partner with in the Living Lab,” says Annette Kolodzie, strategic programs director at FEI and codirector of the Living Lab. One reason FEI chose NIH is the agency’s speed in achieving scientific results, Kolodzie says. In many cases, NIH scientists have much more flexibility in how they choose and pursue scientific projects than do university researchers, she tells C&EN.

Another important deciding factor was NIH’s expertise in determining what is medically important, Kolodzie says. “Having access to someone who can immediately tell us what is biologically relevant and will bring successes for the Living Lab quickly” is critical for the firm, she says.

SOME PEOPLE don’t realize that it can be easy to work with the government, Subramaniam says. NIH’s mission—to improve the health of the country—is clearly defined, he notes. “We are not in this to make a profit,” Subramaniam stresses. “The company is here to make a profit. The lines are clear.”

The broad nature of the Living Lab presented the biggest challenges in getting agreement, Higinbotham says. NIH typically sees collaborations that involve a particular compound or technology, she notes. “In this case, the collaboration actually advances an entire field,” she says.

Part of the difficulty was getting multiple projects from multiple investigators at multiple NIH institutes wrapped into one agreement, Higinbotham adds. But in the end, NIH was able to make the Living Lab project fit into a standard Cooperative Research & Development Agreement.

The most important factor that made the collaboration come together is “the passion to get the science to go forward,” Higinbotham tells C&EN. “That passion was ignited by the investigators,” she says, and it was transferred to all the other people who worked on getting this project established. —BRITT ERICKSON

Reprinted from C&EN, March 26, 2012
X-RAY CRYSTALLOGRAPHY and nuclear magnetic resonance spectrometry (NMR) have long been the star players in structural biology. Now, mass spectrometry (MS) is finding its own place in the starting lineup, filling gaps left by other methods.

Crystallography provides atomic-resolution images of protein structures, but those images are snapshots of a single state frozen in time. And a protein must form crystals to get that picture, often not an easy thing to do.

NMR, in contrast, can capture dynamic information without crystals. But it requires high concentrations and doesn’t work well for aggregation-prone proteins. Plus, despite some success with large complexes, most conventional NMR is best suited to relatively small proteins.

MS avoids many of these problems. A protein need not crystallize, making MS suitable for such recalcitrant protein classes as membrane proteins and intrinsically disordered proteins. MS doesn’t have the same size and concentration restrictions as NMR. And MS can analyze complex mixtures of proteins, which is particularly important for complexes that can exist in multiple oligomeric states.

Even with these strengths, mass spectrometrists have struggled for more than a decade to gain acceptance of MS as a suitable tool for structural biology. One important question has been whether gas-phase structures have any relevance to solution-phase structures.

Oxford University chemistry professor Carol V. Robinson, a pioneer in applying mass spec to structural biology, still runs into skeptics. “Sometimes we get comments saying, ‘It’s just in the gas phase. Who’s going to believe that?’ That’s always a bit disappointing because I’ve been doing this so long.” Over the years, Robinson’s group and others have published many examples showing that a protein’s solution structure is preserved in the gas phase.

Brandon T. Ruotolo, whose group at the University of Michigan, Ann Arbor, studies multiprotein complex topology and stability using a combination of gas-phase ion-mobility separation and MS, suggests that MS is now at a stage similar to that of crystallography in the 1950s.

“Crystallography in the 1950s was struggling to assert itself as a method for structural biology. Crystallographers had to go through a lot of basic experiments to prove to people that the structure of a protein within a crystalline packing structure accurately represents what it might look like in a solution or in a cell,” Ruotolo says. Now, mass spectrometrists are “still trying to convince people that the models we come up with using our technology have rele-
Mass spec can also help identify intermediates that other methods miss. Albert J. R. Heck, a professor at Utrecht University, in the Netherlands, studies the assembly of viral capsids using mass spec. Virologists hadn’t been able to figure out how a virus gets from its monomeric or dimeric building blocks to a complete capsid, a process so fast that virologists couldn’t find stable intermediates.

By tweaking various parameters and by combining ion mobility with MS, Heck and his coworkers found that the hepatitis B virus forms a hexamer on the way to its 180-subunit capsid. Before that, researchers had been able to see only monomers, dimers, and the intact capsid, because those high-abundance structures swamped the low-abundance intermediates. Ion-mobility spectrometry, which provides a shape-based separation, helped them show that the intermediates have a sheetlike structure (Nat. Chem., DOI: 10.1038/nchem.947).

In the case of the Triatomina virus, which infects the Chagas disease-causing Trypanosoma cruzi, its capsid consists of 60 copies each of three proteins. Using MS, Heck’s group found that the capsid is actually assembled from 12 building blocks that contain five copies of each of the proteins. In dissociation experiments, they could see two of the proteins but not the third one. The one that doesn’t dissociate at all is likely in the core of the building block, Heck says.

So far Heck has looked at relatively simple viruses that contain multiple copies of only one or a few types of capsid protein. Now he is starting to look at viruses that are more complicated such as the adeno-virus, which has 12 different proteins in its capsid, some of which have 700 copies and some of which have only one. MS can also reveal information about protein complexes that exist in many different stoichiometries at equilibrium. For example, the small heat shock protein αB-crystallin exists in about 40 states, each differing from the others by only a few percent in size. Such a complicated mixture isn’t a good candidate for conventional structural methods.

COURTESY OF ALBERT HECK

Mass spectrometrist Vicki H. Wysocki of the University of Arizona sees structural biology colleagues turning to mass spec as a frontline tool. “I have colleagues who years ago rarely looked at their complexes by mass spec. Now, it’s the first tool they use.”

Nobody is suggesting that MS will replace other structural methods. In fact, many researchers think the best understanding will come from combining information from multiple methods.

“NO TECHNIQUE seems to work for everything,” says Justin L. P. Benesch, a mass spectrometrist at Oxford University. Modern structural biology “really is about trying to use as much information as you can glean from as many different techniques as possible.”

John R. Engen, a chemistry professor at Northeastern University, agrees. Mass spec is “most powerful when you combine it with other structural techniques,” he says. For example, mass spec can provide dynamic information that can flesh out otherwise static crystal structures. “It actually increases the value of the crystal structure,” Engen says. And in the interplay between the two techniques, interpretation of that dynamic mass spectral information becomes much easier with a known crystal structure.

“You get a beautiful view of electron density from protein crystallography,” says Gregory A. Petsko, a structural biologist at Brandeis University. “But then you have to interpret that electron density in terms of a chemical structure. That’s not always so obvious. Mass spec is great for that. It tells you what chemical species you’ve got in there.”

“Mass spec has become an indispensable tool in structural biology,” says David S. Eisenberg, a structural biologist at the University of California, Los Angeles. “We use it routinely to examine the homogeneity of protein samples and to learn the stoichiometry of complexes. It reveals post-translational modifications of proteins that are hard to detect by other means.”

Indeed, MS is providing answers to structural biology questions that are difficult to approach with other methods. A key example is membrane proteins, which are notoriously difficult to crystallize.

For example, Robinson is using MS to study intact ATPases, membrane-associated molecular machines that use adenosine triphosphate hydrolysis to power rotary motors. Researchers have used cryo-electron microscopy (cryoEM) and X-ray crystallography to look at pieces of the complex, but they’ve been unable to see the whole structure in detail.

At first, Robinson just wanted to learn the subunit stoichiometry of these 600-kilodalton-plus complexes. With MS, she was able to provide evidence to settle a disagreement between cryoEM and crystallography about the stoichiometry of the complex’s ring. CryoEM suggested that the ring contained seven subunits, whereas crystallography suggested 10. Initially, Robinson thought both methods were wrong, because the mass spectrum seemed to suggest 11 subunits. But with an improved mass assignment algorithm, Robinson’s postdoc Nina Mogner realized that the complex contains 10 protein subunits and 10 tightly bound lipids (Science, DOI: 10.1126/science.1210148).

“I hadn’t expected to see the very specific and tight binding of lipids,” Robinson says. “When I started, I didn’t want to see lipids at all. But then I realized they were holding the key to how these things were functioning.”

In ATPase, the lipids form a plug that adapts the ring so that it can turn the machine’s rotor. Without seeing the proteins and lipids together, Robinson’s team wouldn’t have been able to figure that out, she says.
Benesch uses MS to figure out the oligomeric distribution and, by monitoring incubation with a heavier counterpart, how the oligomers interconvert. By coupling MS with ion mobility, he can also determine how the shapes change.

He manipulates conditions such as temperature and pH to mimic various stresses and then sees how the protein responds. “The protein becomes much more dynamic,” Benesch says. The monomeric subunits “hop around” faster between oligomers.

He finds that only certain geometries fit his ion mobility data, and these explain the ability of αB-crystallin to interconvert so easily. His data suggest, for example, that the 24-subunit oligomer forms an octahedron. Getting from the 24-mer to a collision-induced dissociation (CID), in which the complex crashes into gas molecules, which transfer energy and make the complex fall apart.

The problem with CID is that it provides somewhat limited information. It usually results in just the loss of an unfolded, highly charged monomer, yielding easily discernible monomer and \((n-1)\)-mer peaks, where \(n\) is the total number of monomers. That pattern makes it easy to figure out the oligomeric state of the intact complex but doesn’t provide much other information about how the pieces fit together.

Another method, called surface-induced dissociation (SID), addresses CID’s problems. In this method, pioneered by Wysocki for more than a decade, complexes slam into a surface and break into pieces that give additional information about how they fit together.

For example, Wysocki used SID to figure out the architecture of the complex toyocamycin nitrile hydratase, a heterohexamer comprising two each of three different subunits (Anal. Chem., DOI:10.1021/acs.analchem.1c03068). With CID, all she saw were two types of monomers and the associated pentamers. With SID, the same heterohexamer dissociated into trimers with one each of the three subunits.

“SID is giving us substructure we’ve never been able to see with CID,” Wysocki says. “It could have been various arrangements, but the only things that popped out were these trimers.”

With even more energy, the trimers dissociate and pop out the third kind of monomer. Because that monomer comes only from the trimer and not the hexamer, it might be more tightly bound or buried in the hexamer’s core, Wysocki says.

Wysocki thinks that SID fragments retain their compact, nativelike structure (Angew. Chem. Int. Ed., DOI: 10.1002/anie.201108700). Collision cross sections of SID fragments measured by ion mobility are approximately the same as calculated cross sections based on known crystal structures.

ANOTHER TRICK That mass spectrometrists use to obtain structural information is labeling proteins in various ways. These labeling strategies can help reveal dynamic changes in protein structure.

Foremost among these labeling methods is hydrogen-deuterium exchange (HDX). In this method, a protein is placed in \(\text{D}_2\text{O}\), and deuterium from the solvent exchanges with accessible hydrogen atoms in a protein’s amide backbone and some of the amino acid side chains. A hydrogen atom’s accessibility is dictated by both its location and its hydrogen-bonding state. Unprotected hydrogen atoms on the protein surface will undergo rapid exchange, whereas those that are buried or involved in holding together secondary structures such as \(\alpha\)-helices and \(\beta\)-sheets will undergo sluggish HDX, says Lars Konermann, a professor of chemistry at the University of Western Ontario.

For unprotected hydrogens, the HDX reaction occurs quickly in both directions. That means that deuterium is just as quickly lost in the back-reaction. Researchers slow down the reverse reaction by cooling the solution and lowering the pH.

After the exchange reaction is quenched, proteins are digested into peptides just as they would be in a standard proteomics experiment, and the peptides are analyzed by MS. Every deuterium increases a peptide’s mass by a single mass unit, revealing how much exchange occurred.

Many people find the protocol difficult, but that needn’t be the case. “You have to work fast at zero degrees. You don’t have an hour to do chromatography at room temperature to make a beautiful separation because all of the label would be gone,” Northeastern’s Engen says. “People think that’s hard because many are used to pro-

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**SHAPE SHIFTING** The small heat shock protein αB-crystallin interconverts between oligomeric states. The 24-mer complex forms an octahedron (left). Adding an edge—a dimer—forms a 26-mer augmented triangular prism (center). Adding another edge results in a gyrobifastigium, two triangular prisms joined at square faces with one prism rotated 90° (right).

26-mer involves adding an edge—two subunits—to form an augmented triangular prism. Adding another edge yields a 28-mer gyrobifastigium, which consists of two triangular prisms joined at square faces with one prism rotated by 90° (Structure, DOI: 10.1016/j.str.2011.09.015).

**MASS SPECTROMETRISTS** have a number of tricks in their playbook for acquiring structural information. For example, they can put energy into a system to make complexes fall apart into fragments that reveal information about the intact complex. The most common fragmentation method is...
teomics experiments where they do overnight digestions at 37 degrees followed by a long separation gradient. You just have to get your mind into this mode: You have to go fast, and you have to be cold.”

Improvements in high-speed chromatography have made it possible to apply HDX to larger proteins (see page 16). Previously “you could only work with a 20-kDa protein,” Engen says. “Now, we can work with 350-kDa proteins.”

Other people, such as Michael C. Fitzgerald at Duke University, are turning to other labeling methods that work with conventional proteomics methods.

“We decided you need to be able to do the experiment that people always do—the bottom-up proteomics,” Fitzgerald says. Those methods “can resolve and detect hundreds and thousands of proteins in a mixture.”

Instead of conventional HDX, Fitzgerald uses covalent labeling reactions that are irreversible on the timescale of his experiments. For example, he focuses on the denaturant dependence of reactions such as oxidation of methionine and deuterium exchange of hydrogen in the histidine side chain. Unlike HDX of the amide backbone, HDX of the histidine side chain is a slow reaction with a half-life of about two days.

IN THE METHOD. Fitzgerald uses denaturant to unfold the protein. The unfolding exposes previously buried sites, and those are the only sites whose labeling depends on the denaturant concentration. Because it is restricted to global unfolding reactions, the method reveals only those sites that were protected within the protein structure. “Methionine is attractive because a lot of methionine residues are buried in the hydrophobic core of a protein,” he says.

The denaturant experiment provides relatively coarse resolution, but that makes things easier from an experimental perspective. “We don’t have to get high peptide coverage of a protein,” Fitzgerald says. “We can identify just one methionine peptide, and that tells us about the whole domain from which it came.”

But methionine represents only about 2.6% of amino acids. Fitzgerald is trying to find similarly slow labeling reactions for other amino acids, which would allow him to get such information for additional proteins.

Konermann uses oxidative labeling of methionine, cysteine, and other residues to determine which parts of membrane proteins are exposed or protected. Solvent-exposed residues will be modified, whereas protected ones will not.

Konermann considers HDX and covalent labeling to be complementary methods. He used both methods to understand how glycerol facilitates, a member of the aquaporin family of channel proteins, transports glycerol and water across cell membranes (J. Mol. Biol., DOI: 10.1016/j.jmb.2011.12.052). Crystal structures have shown that glycerol interacts with specific binding sites, but those structures don’t explain why the glycerol doesn’t get stuck in the channel, Konermann says. His team found that the binding sites are actually the most dynamic parts of the protein. “There is enough structure to ensure specificity but enough dynamics to prevent glycerol from getting stuck,” he says.

Even with all these successes, sometimes the best use of MS is in partnership with other methods. Brian T. Chait, a mass spectrometrist at Rockefeller University, has long worked with structural and cell biologists to guide their use of techniques such as X-ray crystallography.

MS IS USED. At every step of the process, Chait says. It’s used to find the best conditions for expressing and stabilizing proteins. It’s used to figure out the domains in a molecular machine. And it’s used to provide restraints for building models, with or without X-ray structures or cryoEM images.

Chait’s group has collaborated for more than a decade with cell biologist Michael P. Rout, also of Rockefeller, and computational structural biologist Andrej Sali of UC San Francisco, to figure out the workings of the nuclear pore complex. This 50-megadalton molecular machine, which is more than 10 times bigger than the ribosome, provides the only way in or out of the nucleus in eukaryotic cells. Despite its large size, the nuclear pore complex has many fewer types of proteins—only about 30—than the ribosome, which has about 80 different types of proteins.

Many of those parts occur in multiple copies in the nuclear pore complex. Because it’s so large, crystal structures have been solved only for pieces of it. Chait and his collaborators combine low-resolution techniques such as MS and cryoEM to build high-resolution models of pieces of the complex, some of which are pretty big themselves. With MS, they can find out how the pieces of a subcomplex associate with one another. Recently, they deduced a model for the structure of the 600-kDa, seven-protein complex Nup84, 16 copies of which form the outer ring of the yeast nuclear pore complex (J. Cell Biol., DOI: 10.1083/jcb.2011099008).

Mass spec is getting better and better at looking at isolated protein complexes, but people ultimately want to see what these complexes look like in their native environment—the cell. Plenty of work will be needed before that’s possible though.

Nonetheless, mass spec is finding its place in the structural biology starting lineup. “Structural biology is changing to an era where you have a problem and you will study it using different techniques,” Heck says. “Mass spec will definitely be one of them.”

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HERITABLE EPIGENETICS

A STUDY ON FOUR CLASSES of chemicals—plastics, pesticides, dioxins, and hydrocarbons—has confirmed that exposure of a fetus to man-made chemicals in the womb can result in heritable changes in gene expression, even to offspring generations later that were not directly exposed to the chemicals (PLoS One, DOI: 10.1371/journal.pone.0031901).

The work is the latest from the lab of Michael K. Skinner of Washington State University, Pullman. Skinner’s research is helping change preconceptions in the field of epigenetics, which is the study of the still-mysterious biochemical processes that switch genes on and off. Scientists believe that understanding epigenetic changes holds the key to understanding the mechanisms of disease.

Epigenetic marks such as methylation of cytosine bases in DNA leave a permanent lifetime imprint without mutating the underlying DNA sequence. These marks were initially thought to be transient and erased in germ-line cells, which develop into eggs and sperm, and therefore not passed on to subsequent generations.

But in a 2005 paper in Science, Skinner’s lab reported the first experimental evidence that chemical exposures can cause permanent epigenetic changes in the germ line (DOI: 10.1126/science.1108190). They exposed pregnant female rats to the fungicide vinclozolin and the insecticide methoxychlor and found that 90% of the male offspring after three generations still exhibited a decrease in fertility. Because military personnel are regularly exposed to an array of chemicals in their work environments, Skinner’s research attracted the attention of the Department of Defense, which prompted the new study.

“DOD asked us to test sets of chemicals with our protocol to see if there is any chance that certain chemical exposures could promote epigenetic transgenerational inheritance of disease in people,” Skinner explains. DOD’s primary concern is drinking water, which can contain bisphenol A and phthalates that leach from plastic containers. Other concerns are the insecticide permethrin and insect repellent N,N-diethyl-m-toluamide (DEET); dioxins, which are chlorinated compounds that are released into the environment when burning trash; and jet fuel, a mixture of C8 to C20 hydrocarbons that the military often sprays on the ground to control dust.

Skinner’s team injected pregnant rats with high, but nonlethal, doses of the four sets of chemicals. They used an abnormal route of exposure and doses well above normal environmental exposure amounts, Skinner points out, because his group was trying to induce the epigenetic phenomenon.

The researchers found consistent sets of epigenetic marks in the next three generations of rats, none of which were exposed to the chemicals. Furthermore, in the female offspring they observed earlier than normal puberty and fewer ovarian follicles, which later become eggs. In the male offspring they found increased decay and death rates of sperm cells, similar to the findings in the Science study.

“It’s not surprising that you can treat pregnant female rats with an endocrine disruptor and see defects resulting from epigenetic problems in the offspring,” notes epigenetics expert John R. McCarrey of the University of Texas, San Antonio. “The big surprise in the results from Skinner’s original paper—the new study is an important validation of those results—is that the epigenetic changes persist in subsequent generations.

“That’s what’s scary,” McCarrey continues. “It means that something your great-grandmother was exposed to could impact you and your children or grandchildren.”

SKINNER SAYS he didn’t expect all the chemical mixtures to work, but they did. “That tells me it doesn’t matter so much what the signaling mechanism is,” Skinner says, “but that a large number of chemicals have the capacity to trigger heritable epigenetic changes during a critical window of fetal development.”

In addition, each of the chemical mixtures promoted a different DNA methylation pattern in the sperm, Skinner says. That means there are exposure-specific epigenetic biomarkers. “In the future, that might give us a way to analyze an individual’s epigenome and accurately predict adult-onset diseases or the possibility of passing on inheritable diseases to children,” Skinner suggests. “That concept is something we definitely didn’t expect when we began this study.”

With a better mechanistic understanding, scientists might figure out how to remove epigenetic marks from where they normally exist or create them where they normally don’t exist, McCarrey says. “For someone like me who is a basic researcher, it’s very exciting. We have a lot to learn.”—STEVE RITTER

Reprinted from C&EN, March 23, 2012
ON APRIL 28, as an unseasonably hot sun melted 8-foot-high chunks of winter snow in the Austrian Alps, a man in a space suit waited near the entrance of a cave.

Most visitors to the million-year-old Dachstein Giant Ice Cave prefer to wear standard winter coats during visits to its freezing, icy interior. But for five days the Dachstein cave system was a temporary lab for a squad of space scientists. Some 50 scientists assembled from three continents to use the UNESCO World Heritage site as a proxy for Mars—a first for the cave system, which normally hosts jazz concerts, modern art exhibits, laser shows, and a steady stream of tourists.

The space scientists used the Dachstein caves to practice 12 experiments that they hope to perform on future missions to the Red Planet. Those missions include Exo-Mars, an unmanned mission planned for 2018 by the U.S. National Aeronautics & Space Administration and the European Space Agency (ESA) as well as a potential human mission that ESA has predicted will take place by 2030. Space scientists typically travel to remote deserts to simulate Mars’s dusty, arid environment, or they go to Antarctica as a proxy for the planet’s frigid temperature, which averages around –35 °C but can range from 30 to –140 °C. While these locations are excellent mimics of the Mars surface, astrobiologists searching for life have their eyes on the Red Planet’s caves, which is where the Dachstein caves come in.

“If there is life on Mars—and it’s a big if—then it would likely be in the planet’s lava canals,” a network of underground caves in the planet’s basalt interior forged by lava during ancient volcanic eruptions, says Gernot Grömer, president of the Austrian Space Forum (ASF), the agency spearheading the field experiments at the Dachstein caves. Martian caves offer the best chance for life because they have a relatively stable temperature between –30 and –40 °C and they contain water—albeit in frozen form, Grömer explains. These underground passageways also offer protection from harmful ultraviolet radiation and solar flares that inundate the planet’s surface—protection that would probably be a prerequisite for life, says Bernard Foing, a space scientist at Free University of Amsterdam and with ESA. “If we want to go to the deepest caves in Mars, then we need to have some operational experience. This is the first time space scientists have tried simulating a Mars operation in a cave,” Grömer says.

The man in the shiny aluminum-coated suit at the cave entrance was 28-year-old Daniel Schildhammer, a physicist who works at ASF. His outfit is called Aouda.X, an approximately $2 million Mars mission space suit simulator made primarily of Panox and Kevlar. Aouda.X has been under development by ASF researchers for the past four years.

It’s called a simulator because the Aouda.X suit is not capable of protecting astronauts in space—at least not yet, says Grömer. For example, it doesn’t have a so-called pressure bladder, the air-tight barrier between the low-pressure Mars atmosphere that would boil an exposed astronaut’s blood and Earth’s atmospheric air pressure required to keep astronauts safe inside the suit.

WHAT THE AOUĐA.X suit does have is an advanced human-machine biomonitoring interface, which provides real-time information pertaining to the astronaut’s health. Information such as heart rate, body temperature, and CO₂ and O₂ levels are projected to a video screen in the helmet’s visor as well as being sent to mission control. The human-machine interface is “far more advanced than what is currently in space operations,” and it—or something like it—would be necessary for a Mars mission, Grömer says. “Because of the long distance to Mars, there’s a time delay of 26 minutes back to Earth in the worst-case scenario. That means when the astronaut says ‘Houston, we have a problem,’ it can take nearly an hour for mission control on Earth to respond, he explains. A Mars astronaut would need to have more real-time information about his or her health and to have more control over the space suit than in current versions, Grömer says.

The Aouda.X also has the overall frame and the 45-kg weight of a space suit so that space scientists can simulate and problem solve the difficulties of doing careful scientific experiments in the Mars caves given the nearly nonexistent dexterity offered by a space suit.

The Aouda.X suit “shows a great deal of potential” and has “revolutionary concepts,” comments Pablo de León, a space scientist at the University of North
Dakota. De León is working on two different space suit prototypes, called NDX-1 and NDX-2, that are funded by NASA as potential options for Mars or other planetary missions. In particular, de León’s NDX suits have a sophisticated pressurized layer, an important component currently missing from Aouda.X. “A possible collaboration between the Aouda.X and NDX research teams is in the works,” de León says. Grömer and de León are old friends who studied together at the International Space University in Houston in 1997.

IN ADDITION TO the Aouda.X and NDX suits, two other space suit prototypes have been under development with a human Mars mission in mind, Grömer says. One, NASA’s Constellation suit, which has exchangeable components such as arms and legs to fit many body sizes, had its funding slashed last year during NASA’s budget cuts. The other, a prototype developed by the Man Vehicle Laboratory at Massachusetts Institute of Technology, focuses on improving the poor ergonomics of current suits.

The Aouda.X suit’s intelligent interior required weeks of training to learn how to operate, Schildhammer told the dozens of journalists who swarmed around him at the cave’s entrance on April 28, rapidly firing questions. “I’m excited,” he answered. “I feel fine in the suit, but my day’s work has only just begun.”

“He’s going to get hot,” predicted Norbert Frischauf, an engineer at ASF, who has tried on the suit previously and who was watching from the sidelines. For example, just walking around in the 45-kg suit for four hours is an exhausting workout that burns approximately 3,000 calories, Frischauf explained. “If you want to lose weight, go to Mars,” he quipped.

Schildhammer’s mission that day was to walk deep into the cave while maintaining contact with scientists just outside the cave as well as scientists in New Zealand and the U.S. He also was supposed to collect a rock sample and carefully stick it into a plastic bag. The seemingly simple tasks are tricky in a suit where it is difficult to bend forward and to turn, Frischauf said. “If you are traveling down a slope, it’s also really hard to see anything in front of you,” he added. “And you don’t want to fall. Mars has one-third of Earth’s gravity, not one-sixth like the moon. If you fall, you can hurt yourself.”

Schildhammer entered the cave, followed by two technicians and the gaggle of journalists. His progress was slow, with periodic stops to rest, recharge batteries, fix dislodged earphones, and eventually practice the sample collection.

The suit’s three-layered glove system made fine-motor control difficult, which will be a challenge when taking martian ice and rock samples that will be evaluated for possible extraterrestrial microbial DNA using the polymerase chain reaction, says Luísa Rodrigues, a microbiologist at the University of Aveiro, in Portugal, and Free University of Amsterdam, to develop a microchip that could focus on conducting research inside the frigid Dachstein caves, plans for the Aouda.X space suit’s next practice mission were already afoot. The prototype suit will be tested in Morocco’s Sahara desert in early 2013.

As the scientists tried to ignore the perfect spring weather outside so they could focus on conducting research and other space-related technology. For example, as Schildhammer maneuvered by in the space suit, Stephen Clifford was in the Dachstein ice cave testing a rover called WISDOM (Water Ice & Subsurface Deposit Observation on Mars), which will use radar to map underground water deposits during the planned ExoMars mission.

But while researchers continue to improve space suits aimed for a potential human mission to Mars, the biggest hurdle for sending a person to the Red Planet may not be technology, but political will. “It is not a financial issue,” de León says. “We have spent many times more money on other things that bring way less benefit than a mission to Mars will. We humans could be by now a multiplanetary species. But try telling that to the politicians.” Perhaps that will change in 2030. ■

Reprinted from C&EN, May 14, 2012
SPEND ANY TIME at all with chemical biologists, and you’re likely to want to join their ranks. These researchers—who use chemical tools to understand biological systems, or who study the chemical reactions that take place in living organisms—are an enthusiastic bunch. And because their field is relatively young and is broad in scope, it offers appealing opportunities for chemists who want to blaze a new trail in science.

Chemical biologists apply the logical and intellectually satisfying tools and concepts of chemistry to fundamental and interesting problems in biology, says Lawrence J. Marnett, director of Vanderbilt Institute of Chemical Biology, by way of explaining the field’s hold on its practitioners. “In addition to creating new knowledge by interrogating biological function,” he says, “there’s always the potential for the use of that knowledge to create new drugs or diagnostic tests to improve human health.” Marnett, who is also a professor of cancer research, of biochemistry, and of chemistry at Vanderbilt University, studies the relationship between inflammation and cancer and uses that information to improve the detection and treatment of the disease.

Chemical biologists can apply their talents to a wide range of challenges. Some work in small-molecule screening and optimization for chemical probe or early-stage drug discovery, Marnett says. Others work on natural product biosynthesis and chemical modification to generate biologically active compounds with novel scaffolds, he adds. Many chemical biologists use high-throughput analytical chemistry in fields such as metabolomics and proteomics, which often rely heavily on mass spectrometry.

The work of Emily P. Balskus is representative of the wide-ranging scope of the field. She became an assistant professor of chemistry and chemical biology at Harvard University this past summer. In addition to establishing her research group, she is teaching a course she designed that examines the chemical aspects of natural product biosynthesis, biocatalysis, and metabolic engineering.

In the lab, Balskus and her team are unearthing new biosynthetic pathways and metabolic activities associated with mi-
croorganisms, including human symbiotic microbes, and their impact on health. They are also scouting along those pathways for enzymes that could be useful for organic synthesis.

Balskus has found that the field’s breadth stimulates interactions with colleagues in Harvard’s chemistry and biology departments as well as its medical school. “The boundaries of defined departments are starting to become a little more fuzzy as science gets more interdisciplinary,” she notes, and “working at the interface is a great place to be. People in multiple disciplines can appreciate what you do.”

The same cross-fertilization occurs in industry, whether a chemical biologist is working at a biotech company, a biofuels firm, a contract research organization, or a traditional pharmaceutical company. On drug discovery teams, for instance, “a very natural collaboration happens” between members, who come from several different backgrounds, says Nicola J. Clegg, an oncology research project manager at Novartis Institutes for BioMedical Research, in Emeryville, Calif. “I think a chemical biologist is valued there because they’re able to talk across those disciplines.”

START-UP COMPANIES are particularly likely to make good use of the assorted talents of chemical biologists. “A start-up often needs people with multiple skills, because the company doesn’t have the luxury of having a lot of employees,” Clegg says. Whatever route they follow, these chemists have to face the realities of an economy still recovering from recession. “In general, the job market is very tough for scientists,” points out Ronen Marmorstein, a professor and leader of the Gene Expression & Regulation Program at Wistar Institute, a private cancer research institute located on the campus of the University of Pennsylvania. But “being in chemical biology increases your chances, because it’s a new and upcoming and exciting field,” says Marmorstein, who also holds a joint appointment as an adjunct professor of chemistry, biochemistry, and biophysics at Penn. “A lot of departments are trying to hire more chemical biologists to build up that strength, and a lot of [companies are] also interested in chemical biologists.”

One reason that chemical biology may be suffering less than other fields, Marmorstein adds, is its potential for developing therapeutic compounds, an application he says the government is increasingly backing with funding. “Chemical biology provides some novel and interesting strategies toward developing new and effective therapeutic reagents,” he explains. “There are new tools for creating small-molecule inhibitors and drugs, and there are new chemical biology tools for identifying new protein targets to go after for therapy.”

Vanderbilt’s Marnett, in contrast, thinks that job prospects for chemical biologists are about the same as those for other chemists. But he believes several faculty positions will open up over the next 20 years as the stock market improves and professors who are currently in their 50s to 70s retire.

In the meantime, finding a job requires perseverance and flexibility. In Marnett’s lab, postdocs are staying an extra year to bulk up their curricula vitae so they can be more competitive. They’re also considering nontraditional jobs outside the lab. One of his postdocs went the regulatory route by joining the Food & Drug Administration, and another postdoc is applying for a job as a congressional fellow.

In fact, for chemical biologists who want to move away from the lab bench, “there are plenty of options at the interface where communication or collaboration needs to be facilitated,” Clegg points out. “I’m in one category of that: I’m a project manager in research, I work with a team of biologists and Chemists and protein engineers.”

Other chemical biologists are employed in technology transfer or intellectual property positions—or in sales. Chris McGee chose this path, though it wasn’t easy. While earning his Ph.D. in organic chemistry and chemical biology at the University of California, Irvine, in 2010, McGee realized he liked teaching better than life in the lab. He became an instructor for The Princeton Review, teaching organic chemistry to premed students preparing for the MCAT exam.

While looking for a full-time job after graduation, he spotted a recruiter’s ad for an opening at a Swiss company that produces peptides and other complex small molecules as active pharmaceutical ingredients. “I sent in a résumé, and never heard anything back, which was the usual story,” recalls McGee, who estimates he submitted at least 150 résumés during his job search. Eight months later, another position was open at the company, so he reapplied and got the job last March—18 months after he started looking.

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McGee is based in Torrance, Calif., but travels extensively for his job as a manager for the firm’s new chemical entity market segment. He visits emerging biotech and Pharma companies to identify products they’re working on that his company could help manufacture. “I use chemistry as a way in to understand what they’re doing and identify who I should be talking to,” McGee explains. “I like the interaction with other people, hearing what they’re doing, explaining what we can do.”

McGee limited his job hunt to positions that required a Ph.D. “You work hard for it, and you want to try and use it,” he explains. In hindsight, he believes the restriction limited his search unnecessarily.

**IN OTHER ADVICE** for students interested in a chemical biology career, McGee recommends that they obtain “a really good foundation in organic chemistry and then build biology on top of that.” He also suggests they find departments with a chemical biology curriculum, rather than “going off to graduate school to do chemistry and then read biology on the side.”

Clegg benefited from this type of program at the University of California, San Francisco. There, she synthesized compounds to investigate estrogen receptor signaling. She graduated with a Ph.D. in chemistry and chemical biology in 2004. During a subsequent five-year stint as a postdoc with Charles L. Sawyers, she picked up genetic and molecular biological techniques while studying androgen receptor signaling related to prostate cancer—first at UCLA, and then, when the lab relocated, at Memorial Sloan-Kettering Cancer Center in New York City. Her chemistry background facilitated the group’s collaboration with a UCLA chemistry lab that was developing potential therapeutics to inhibit the receptor, and later with the synthetic chemistry facility at MSKCC that was developing methods for scale-up.

During her time at MSKCC, she essentially managed the transition of one of the compounds through preclinical studies in collaboration with pharmacologists, analytical chemists, synthetic chemists, pharmacists, and clinicians. She then helped the lab partner with a biotech company that is now testing the drug in Phase I/II clinical trials. After an eight-month job search, she took up her current position managing cancer research projects at Novartis in 2011.

Clegg, like many in the field, acquired a lot of skills along the way. But as they prepare for the working world, chemical biologists need to guard against “superficial training in everything,” she says. “One challenge that a chemical biologist may have is trying to find his or her niche. As a chemical biology graduate, you might end up being a jack-of-all-trades and a master of none. If you haven’t gone into enough detail in one of the disciplines, you’re not sure how to market yourself.”

At the same time, Shawn Tang, a principal staffing consultant for Genentech’s Research and early development divisions in South San Francisco, recommends that students who are finishing up their graduate studies or contemplating a postdoc position obtain a wide range of training, including experience with automation and informatics.

“That could make them more marketable than someone who knows one thing and one thing only,” she says.

Candidates who apply to Genentech typically have completed a two- to three-year postdoc in which they have designed and completed an independent project. The company employs chemists with a biological bent, including chemical biologists, on teams that tackle oncology, inflammation, and central nervous system disorders. Genentech hired quite a few biofocused chemists in recent years because of good growth in its small-molecule division, Tang says. Unfortunately that means the company has fewer openings available this year.

No matter where they apply for work, Tang recommends that job candidates invest some time in polishing their curricula vitae. “Make sure it’s clean, it’s precise, it’s concise,” she says. Rather than cramming every activity into the document, it’s best to highlight the most significant information. For instance, full journal articles should be listed separately from presentations at conferences, which carry less weight.

Chemical biologists who are looking for a job need to be able to communicate their science and explain why it’s important, including the big picture, Harvard’s Balskus advises. They can practice by explaining their work to graduate students who aren’t in the chemistry program. Balskus makes sure the students in her lab have opportunities to present their work at venues outside of group meetings. The university helps by providing several informal settings, including journal clubs, where students can give presentations to broader audiences.

Presenting talks has another benefit: The exposure helps postdocs become known by potential employers, Marmorstein says.

Candidates who are looking for their first job can also utilize the network of contacts they’ve established during their training, Clegg says. Sawyers and other mentors were critical to the success of her own job search. “None of the jobs I applied to blindly online led to anything,” she says. “Only the ones where my adviser was able to make an introduction for me led to interesting possibilities.”

Job seekers should also take advantage of social media including LinkedIn and Facebook, Tang says. Genentech posts frequent updates on its Facebook page. Both Genentech and Novartis utilize LinkedIn pages, and their recruiters also comb these sites for profiles of potential candidates. Recruiters at both companies have profiles on LinkedIn, and scientists are welcome to reach out to the recruiters for advice and networking, even if they aren’t currently on the job market.

Regardless of the path they take, the field’s practitioners appear to feel a calling to their work. As Vanderbilt’s Marnett puts it: “When we interview incoming graduate students, they say, ‘I really love chemistry and I want to keep doing chemistry, but I want to do something useful with it. I want to make a difference. I want to help people.’ And chemical biology is perfect for that.”
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