



THE NOVOZYMES PRIZE

BERNARD HENRISSAT

2015

NOMINATION OF BERNARD HENRISSAT

” The Novozymes Prize 2015 is being awarded to Bernard Henrissat for his groundbreaking and systematic investigations of carbohydrate-active enzymes and their potential in biotechnology and human health.

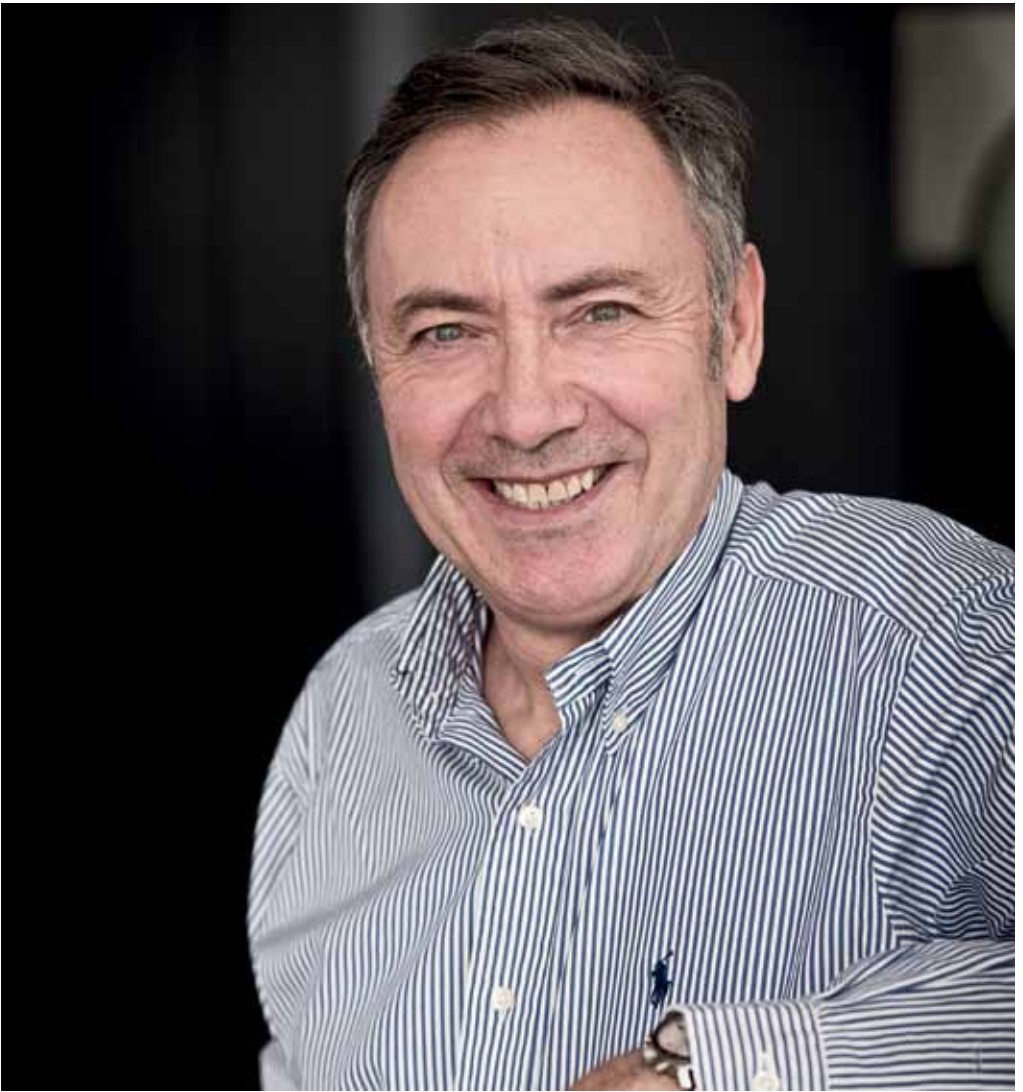
The Novozymes Prize 2015 is being awarded to Bernard Henrissat for his groundbreaking and systematic investigations of carbohydrate-active enzymes and their potential in biotechnology and human health.

Bernard Henrissat was born in 1954 in the Netherlands. He received his scientific education at the University of Grenoble, France, where he obtained his PhD degree in 1979. He was recruited for a permanent researcher position at the Centre National de la Recherche Scientifique (CNRS) in December 1980 and received a DSc degree in 1985. After several postdoctoral and sabbatical positions in Canada, France and Denmark during 1986–1997, he earned a Directeur de Recherche position at the Centre National de la Recherche Scientifique (CNRS). He then moved to Marseille, where he joined the Architecture et Fonction des Macromolécules Biologiques (AFMB) laboratory, jointly operated by CNRS and Aix Marseille University, in 1998. Since 1999, he has been group leader of Glycogenomics at the AFMB laboratory. In 2004, Henrissat became the Director of the AFMB laboratory, and for the period 2008-2012 Deputy Director of the Fédération de la Recherche Infectiologie: du Malade à la Molécule, also associated with CNRS and Aix Marseille University in Marseille.

Carbohydrate-active enzymes are ubiquitous in all kingdoms of life and vital in an abundance of cellular processes, including structural integrity; interactions between cells and between cells and pathogens; and protein folding. Many carbohydrate-active enzymes catalyse biotechnologically important reactions more efficiently and specifically than chemical reactions and can be exploited for industrial processes such as making biofuels. The enzymes that build and break down complex carbohydrates and glycoconjugates for a diverse spectrum of biological functions include glycoside hydrolases, glycosyltransferases, polysaccharide lyases, carbohydrate esterases and others. Understanding the catalytic mechanisms and specificity determinants, and relating them to the three-dimensional structure of these enzymes are fundamental to all areas of carbohydrate engineering.

Bernard Henrissat performs highly original research focusing on identifying, characterizing and classifying carbohydrate-active





enzymes. He started out studying protein structures and enzyme mechanisms and subsequently turned towards classifying carbohydrate-active enzymes. A crowning achievement of Bernard Henrissat's research is his systematic classification scheme and organizational framework for glycoside hydrolases. In addition to including cellulases, which catalyse the hydrolysis of insoluble cellulose into soluble sugars, glycoside hydrolases are involved in numerous processes of significant scientific interest and of great importance for biotechnology as well as for human health. The original catalogue of glycoside hydrolases has since expanded to include a wide range of other carbohydrate-active enzymes, for which Henrissat has developed and is maintaining the CAZy database, which is used by numerous scientists worldwide and is of enormous scientific and technological impact and value.

The true scientific value of the database developed and maintained by Bernard Henrissat relies on the profound knowledge about the enzymes, from their biochemical functions to the detailed protein structures at atomic resolution, which Bernard Henrissat and his colleagues have explored over the years. A biotechnology example is the classification of cellulase "families" based on their con-

served mechanisms (such as the stereochemistry of catalysis) and shared protein folds. As more crystal structures became available, the informational synergy and logic of this scheme became even more apparent. Analysis of 3-D protein structures within the family framework has provided unprecedented insights into the structure, function and catalytic mechanisms of these enzymes.

During the 1990s, as the number of glycoside hydrolase genes being sequenced began to outpace experimental characterization of the encoded enzymes, Bernard Henrissat began to compare and catalogue these enzymes based on their primary amino acid sequence. This new paradigm was guided by the premise that fundamental relationships between sequence and structure would prove most useful for deriving mechanistic information about newly discovered enzymes and hence enable proteins of uncharacterized function to be accurately classified. This classification scheme also exploited and benefited from the explosive increase in the number of available sequences and the concurrent development of new sequence comparison methods that dealt with low sequence identity. In recent years, Bernard Henrissat has published an ever-increasing number of high-impact articles reporting detailed analysis of genome sequences, focusing most strongly on analysing the carbohydrate-acting enzymes present, their classification and possible functional *in vivo* contributions. This has provided strong new insight into the ability of organisms to assemble and break down complex glycans. It has also provided highly useful information for possible biotechnology exploitation.

Bernard Henrissat has made significant recent contributions in gut microbiome research. His contributions are numerous and include analysis of the bacteria colonizing the human gut and the effects of in-feed antibiotics on the pig microbiota at different gut locations, just to mention a few. In this domain, he is at the forefront of analysing the role and impact of microbial carbohydrate-acting enzymes on food digestion and the associated effects on nutrition and health. Some of these digestive enzymes have obvious biotechnology potential.

Over the years, Bernard Henrissat has performed outstanding research that is strongly relevant for the development of the biotechnological sciences and provides clear scopes for innovative solutions in such fields as white biotechnology, biobased economy, environmental biology, systems biology, human nutrition and gut health. His work and contributions are original, with a strong impact especially in the field of carbohydrate-active enzymes. The quality of his work continues to be very high. Bernard Henrissat has published more than 300 articles in scientific journals, and his output in recent years continues to be very great. He frequently publishes in the highest-ranking scientific journals. The topics of his research draw strong attention from the international scientific community, and he is very frequently invited to join large international projects. His great output is accompanied by an impressively high citation index, showing the high impact of his research.

In conclusion, the Novozymes Prize Committee is awarding Bernard Henrissat the Novozymes Prize 2015 for his groundbreaking research in carbohydrate-active enzymes and the internationally recognized impact of his contributions to the field of biotechnology.





” I love what we can do with CAZy. With the database, we have integrated the genomic and structural data. Our work both benefits from and guides experimental investigations. and we strengthen the link between basic research and industrial development. Every day we hope to make a difference both for the research community and for society.”

CURRICULUM VITAE

BERNARD HENRISSAT

PROFESSOR, DIRECTOR

BORN FEBRUARY 18, 1954 IN KERKRADE, THE NETHERLANDS

- 2014 – Thomson Reuters “Highly Cited Researcher” in two different disciplines (“Biology & Biochemistry” and “Plant & Animal Science”)
- 2013 – Honorary Professor, University of Copenhagen, Denmark
- 2007 – Pierre Desnuelle Award (French Academy of Sciences)
- 2004 – Director of the Laboratory “Architecture et Fonction des Macromolécules Biologiques” (AFMB) (CNRS and Universities of Aix-Marseille)
- 2000 – Deputy Chairman of the Editorial Board of the Biochemical Journal
- 1998 – Creator and curator of the Carbohydrate-active enzymes database (www.cazy.org)
- 1996 – Sabbatical stay, Novo Nordisk A/S, Bagsværd, Denmark
- 1985 – D.Sc. University of Grenoble, France (Physical Sciences)

Professor Bernard Henrissat has 358 publications and has an h-index of 87; >32,000 citations.

HE DIGS THE LANGUAGE OF LIFE

BY MORTEN BUSCH

Along with genes and proteins, carbohydrates have been called "life's third language." No one understands how this language is created and should be understood better than Bernard Henrissat. He therefore helps researchers and companies worldwide daily to comprehend the complex world of carbohydrates, which has been dubbed the glycome.

In 1977, Fred Sanger and his team published the world's first complete DNA sequence of an organism: bacteriophage phiX174. The 5386-base-pair DNA sequence started an exponential race. Rather than one new gene sequence per year, several whole genome sequences from new organisms appear every single day in 2015.

"The quantity of new sequence data is so enormous that no human mind can keep up. Since the sequences as a starting-point are only useless rows of letters, the need to develop tools and methods to analyse the huge quantity of data is greater than ever before," Bernard Henrissat explains.

Bernard Henrissat is a CNRS Director of Research at the AFMB laboratory in Marseille and one of the absolute experts at finding useful data among the endless quantities of sequences. For more than 30 years, he has grouped, systematized and analysed carbohydrate-active enzymes, ensuring that each one is registered correctly in his huge database CAZy.

Through his work and experience, he has developed the necessary methods to analyse sequences and enzymes from all living organisms. He thus finds the enzymes that researchers or biotechnology companies should analyse for further use. Bernard Henrissat's database and abilities are therefore useful to

health researchers, biotechnology companies and numerous other scientists worldwide.

NATURE IS BROKEN DOWN

It began somewhere completely different for Bernard Henrissat. Not physically, since his career began only a few 100 miles away at the University of Grenoble at the foot of the French Alps. But scientifically, he had, however, only a faint idea which mountain he was going to climb.

"I studied chemistry, one of the most exciting fields of science, since it is central to understanding how nature's chemical reactions are set in motion and accelerated. My PhD project thus tried to understand how enzymes interact with their substrates."

About 10 years earlier, David Chilton Phillips had succeeded for the first time in determining the X-ray structure of an enzyme – lysozyme. The new three-dimensional understanding of nature's catalysts had thus created great interest in understanding enzyme mechanisms and how they could perform many complicated processes in human cells and nature around us.

"The enzymes that came and took me in Grenoble were called cellulases. Cellulose is the most abundant polymer in the world and a significant structural component of plants. We tried to understand how these long chains of carbohydrates were assembled and tried to understand

how, for example, microbes can break down these long chains of up to thousands of sugar units."

A GREAT DANE

A major problem in enzyme research at the time, however, was finding sufficient pure enzyme to perform exploratory research. This was necessary to investigate the mechanisms in detail to explore how cellulase enzyme can degrade cellulose. This challenge was solved for Bernard Henrissat by something of a coincidence.

"I remember that Mary Mandels, a scientist in the United States who had worked with cellulases for years, told us she knew who could solve my problem. She knew someone who could give me all the cellulases I needed," Bernard Henrissat remembers.

It was Bernard Henrissat's first, but certainly not last, meeting with Danish researcher Martin Schülein, who worked for Novo Nordisk and

later Novozymes. He gave Henrissat more purified cellulase than he could have ever dreamed of and more than enough for researchers to examine the cellulase enzyme in detail.

"My interest in the carbohydrate-modifying enzymes was born. At the same time I realized that it was also a scientific field of major development and enormous importance in many contexts."

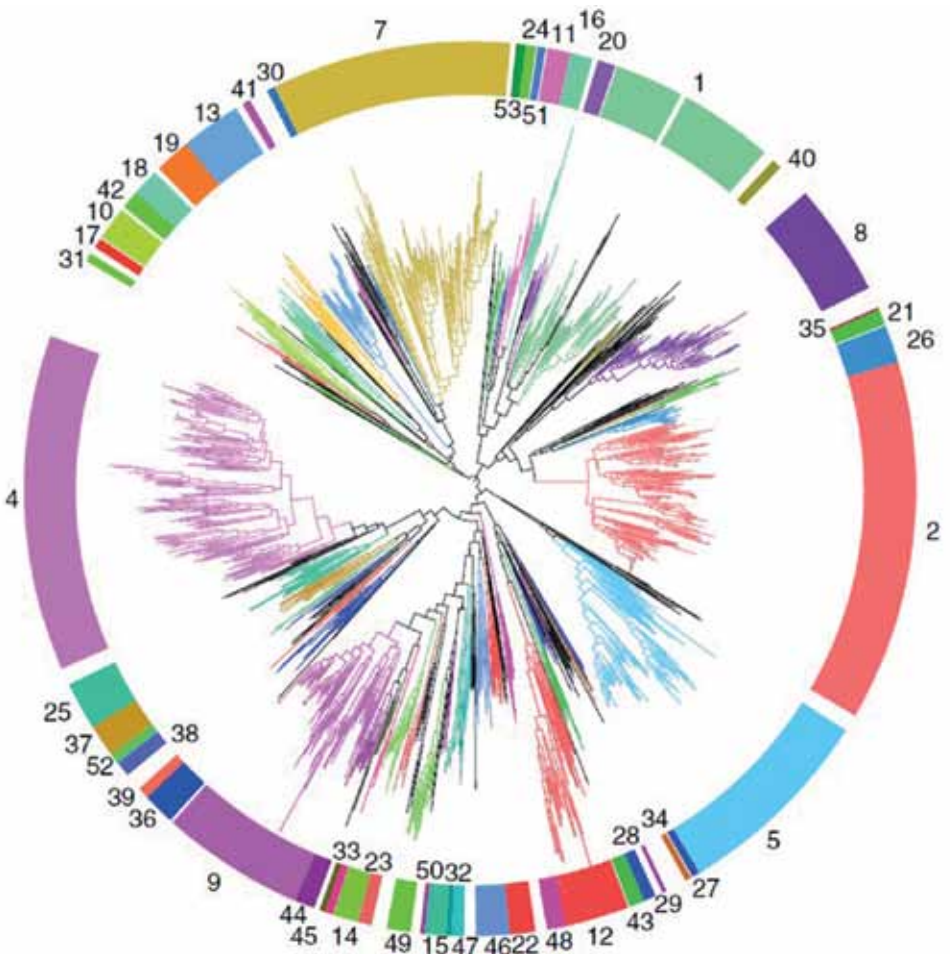
FRENCH IMPRESSIONIST

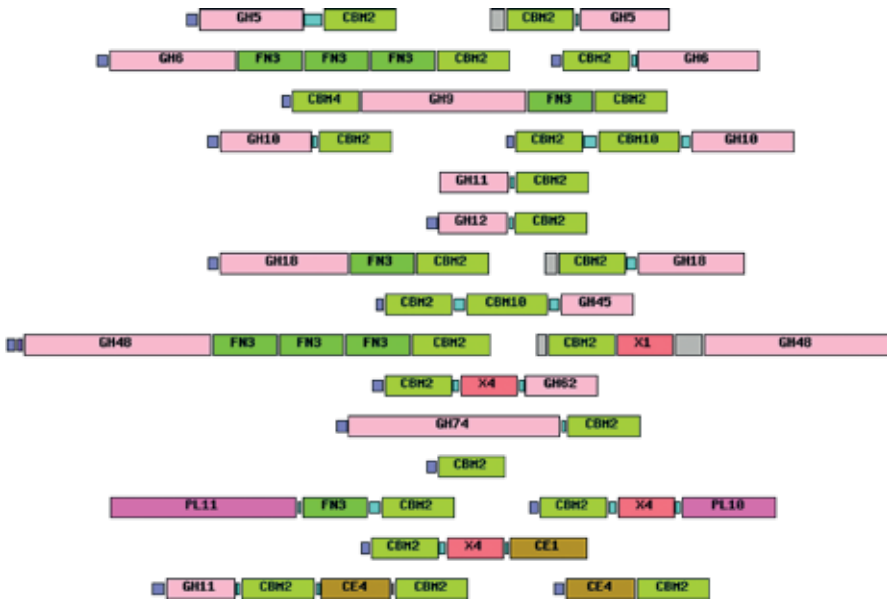
Cellulose is also a key component of pulp in the paper industry, so after he completed his DSc studies, Bernard Henrissat spent a postdoctoral year at the Xerox Research Centre of Canada to find out how to remove toner from paper surfaces.

"The job at Xerox mainly opened my eyes to the fact that I – like the rest of the world – needed to know much more about enzyme structure. And when the first protein sequence of a cel-

PHYLOGENETIC TREE

Phylogenetic tree of a family of glycosidases showing multiple subfamilies. About 40% of the subfamilies in this tree have no known functional representative and therefore offer discovery potential.





CARBOHYDRATE-ACTIVE ENZYMES

often display variable modular structures whereby different catalytic domains (hereby shown as GH, PL, CE) can be attached in different ways to a particular carbohydrate-binding module (here CBR2) as well as to modules of unknown function

lulase was published shortly thereafter, I knew that I should specialize in precisely that."

Before long, Bernard Henrissat turned out to have a very special talent that gave him the lovingly meant nickname "the French impressionist" among his closest colleagues because he uses a very graphic – almost pictorial – approach. Bernard Henrissat thus found a solution to a problem that other researchers had previously unsuccessfully attempted – finding the similarities in the protein sequences of cellulases.

"At that time, in 1988, we had the amino acid sequences of only 21 β -glycanases from different organisms. Evolutionarily, we would expect that important sequence features are preserved if they are important, but the sequences were unlike each other – at least until I came across a new method that Jean-Paul Mornon had developed in 1987 in Paris."

LOTS OF EXCEL SPREADSHEETS

The method was called hydrophobic cluster analysis. The method gave Bernard Henrissat an edge in identifying the similarities in protein sequences over everyone else in the field. Described very simply, the method focuses on the areas in proteins with numerous hydrophobic amino acids.

"From the known 3-D structures of proteins, one could see that the hydrophobic amino acids of helix structures have a particular distribution,

different from that of strands. A central feature of protein structure is that the hydrophobic amino acids end up facing inwards in the protein to stay away from the aqueous environment. This gave us a clearer picture of the protein structures and thus indicated the important features that were repeated in several of the 21 beta-glycanases."

The new method defined six families of cellulases, which attracted considerable attention in the scientific community and made Bernard Henrissat renowned overnight. Using this method, he managed to find the sequence similarities in numerous carbohydrate-active enzymes. Other researchers in the field had been eager to find this system for years.

In the late 1980s and early 1990s, the number of protein sequences increased significantly. This meant that the experimental studies of enzyme mechanisms were superseded by what could be derived from protein sequences and structures. Data on carbohydrate-active enzymes were stored on large Excel sheets, where Bernard Henrissat and others tried to keep track of them. But soon a more lasting solution had to be found to this challenge.

CAZy

In the mid-1990s, Bernard Henrissat became a visiting researcher in Denmark for 6 months. Here he visited his good colleague Martin

Schülein, who had previously provided Bernard Henrissat with cellulase. Martin Schülein tried together with Bernard Henrissat over the next 6 months to bring an end to the many Excel sheets.

"At the time, the growth of sequence data was so immense that something had to be done. Along with Schülein and his colleague Kim Vilbour Andersen, we tried to convert all the data in the Excel spreadsheets to HTML format so they could be presented and browsed with navigators on the – at that time – booming Internet."

Bernard Henrissat was again ahead of his time in this matter. When he came back to France and settled in Marseille, he took the HTML project an important step further. And in 1998, with the help of his postdoctoral fellow Pedro Coutinho, he launched his website to present his classification of all known carbohydrate-active enzymes. He named the database CAZy (Carbohydrate-Active EnZymes).

"After I had presented CAZy at a conference in Japan in September 1998, we had a quiet start with a few hundred hits a month initially. Nowadays, we have about a couple of million hits a year on the CAZy website from researchers and companies around the globe in many various scientific disciplines. The only common denominator is that they work with carbohydrates."

THE CONSTANT DATA MINER

The original catalogue of glycoside hydrolases has since expanded to include a wide range of other carbohydrate-active enzymes Bernard Henrissat has classified. Another reason for CAZy's success is that the database is maintained every day and that new genomic sequences are automatically downloaded directly from GenBank and analysed.

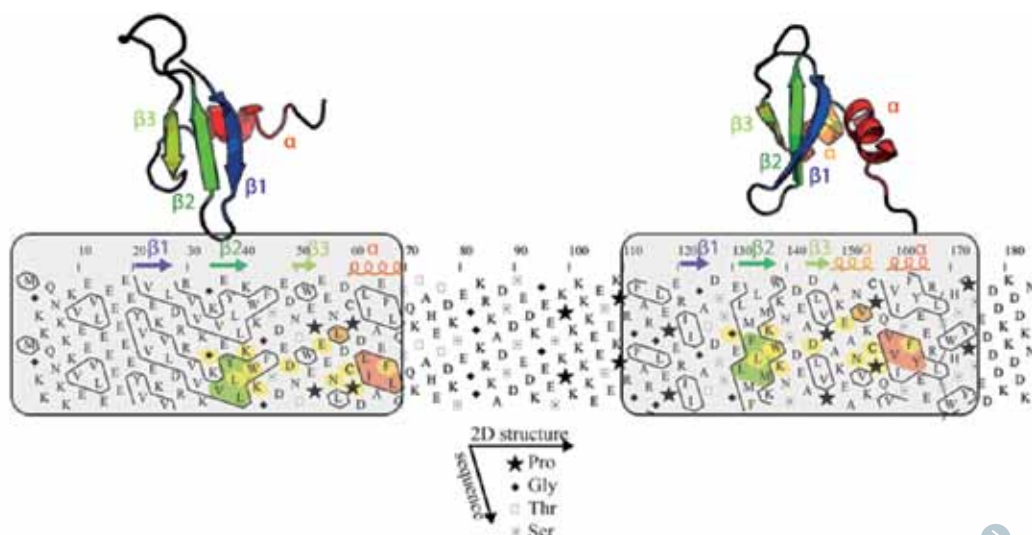
"Every single day the genomic sequences of several new organisms are released and the candidate carbohydrate-active enzymes are identified and classified in the database. We are constantly trying to improve our tools for analysing sequences so that we can both improve our throughput and generate scientific value and technological development."

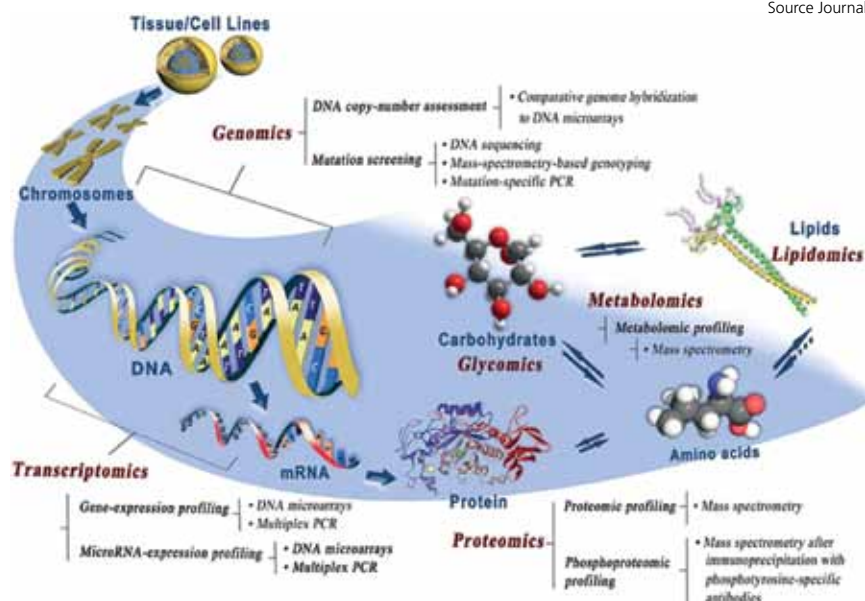
The analysis is more than full-time employment. Other research groups who need his abilities to identify enzymes relevant to their research often approach him. And it is always a pleasure for Bernard Henrissat to dig into the large sequence mine and find the newest nuggets of gold.

"I love what we can do with CAZy. With the database, we have integrated the genomic and structural data. Our work both benefits from and guides experimental investigations. And we strengthen the link between basic research and industrial development. Every day we hope to make a difference both for the research community and for society."

Example of the use of Hydrophobic Cluster Analysis of mouse chromobox homolog 1. Globular domains (boxed), containing approximately one third of hydrophobic amino acids gathered into clusters that are separated by a hinge, which is less hydrophobic. The comparison of the HCA plots of the two domains indicates similar shapes of clusters (shaded green and red), suggesting a structural relationship

Source: IMPMC, Sorbonne Universities





The emerging field of glycomics is gathering momentum to earn its place alongside other established 'omics' fields such as genomics and proteomics, as envisioned by experts in the field.

FIRING UP THE BIOFUEL BUSINESS

CAZy's potential in optimizing the production of biofuels is especially obvious. Cellulases convert cellulose, which is found, for example, in plant stems, to soluble sugars, the basic precursors of biofuels. CAZy provides an overview of the various microbial cellulases, to make searching as effective as possible.

"First-generation biofuels have already had a great impact in the quest for renewable and safe energy sources. For example, breaking down starch from maize can produce bioethanol. But, we have realized that using valuable land to grow energy rather than food is not sustainable. New solutions are needed."

Last year, Gideon Davies and Paul Walton of the Department of Chemistry at York University discovered through a partnership with Bernard Henrissat a new family of enzymes with the potential to break down hard-to-digest stems, wood, cardboard and even insects shells to sugars for biotech applications.

"If we could use biowaste to generate energy, this would have a huge impact on the second generation of biofuels. Hopefully producers of bioethanol can in this way ensure that they become a competitive source of transport biofuels."

MIND THE GUTS

Another study in which CAZy and Bernard Henrissat have played an important role was in collaboration with Jeffrey I. Gordon's team from Washington University in St. Louis, United

States. Gordon's group investigates bacteria, which are important in human digestion. This is interesting because an understanding of the bacteria's importance can help us to understand and eliminate the worldwide obesity epidemic.

"It is noteworthy that the human genome encodes a tiny number of enzymes for digesting carbohydrates. This means that, without the aid of bacteria, humans can only digest three types of carbohydrates: table sugar, lactose and a portion of starch. For all other types of dietary sugars, whether of vegetable, fruit or animal origin, we need help from bacteria to derive energy."

Given the paucity of human enzymes that can break down carbohydrates, the human gut is home to microbes – the microbiota – that benefit from a rich supply of sugar and water at a temperature of 37°C. This is the perfect breeding ground for the approximately 1000 bacterial species that typically grow in the human gut. Via CAZy, scientists can rationally organize the 50,000 to 60,000 genes from these bacteria that encode enzymes for digesting carbohydrates from food.

"This research is still in its very early stages, but there are already some very interesting and surprising results. Scientists have looked at twins who are genetically identical. The difference between their gut flora therefore only results from the bacteria that live in their gut. Preliminary results indicate that gut flora is less diverse in obese subjects. And if we can learn to cor-

rect this, it may be possible to restore a healthy intestinal flora."

THE LANGUAGE OF LIFE

The number of ways CAZy can be applied to the world of carbohydrates seems almost infinite, and it is therefore reasonable that carbohydrates are called life's third language. Moreover, the structural and chemical diversity of carbohydrates seems to make this language one of the most complicated ones.

If you only put two glucose molecules together, they can be combined in a dozen ways. Since there are many types of simple sugar molecules other than glucose, the number of combinations rises above 1000 for a molecule made of two sugars. In nature, carbohydrates sometimes assemble in polymers that can contain thousands of simple sugars, resulting in huge diversity, which is reflected in the numerous different roles of carbohydrates in nature.

Carbohydrate-mediated interactions are not only critical for the communication of healthy cells but they also play key roles in disease, including during viral or bacterial attack. For example, influenza virus haemagglutinin binds to the sugar sialic acid on the surface of human cells.

"Another great application of knowledge about carbohydrates was found by the Henrik Clausen, a professor from the University of Copenhagen. The main differences between the blood types A, B, AB and O are some simple sugars on cell surfaces. During one of our collaborations, Henrik Clausen found enzymes that could selectively remove sugars at the surface of red blood cells and thus convert all blood groups to type O, which all people can tolerate."

LAST FRONTIER OF MOLECULAR AND CELL BIOLOGY

Once you know the many challenges and applications, it is immediately easier to understand why the well-known Israeli researcher Nathan Sharon called carbohydrates "the last frontier of molecular and cell biology". The enzymes that are necessary for synthesizing and breaking down carbohydrates reflect the complexity and diversity of the carbohydrates themselves.

This last frontier of molecular and cell biology is currently being explored at the Copenhagen Center for Glycomics at the University of Copenhagen. The Center explores the complex carbohydrate surfaces of human proteins and cells, since small changes in these carbohydrates are a major cause of hereditary diseases. And like

many other places around the world, Bernard Henrissat is on the list of employees – as an Honorary Professor.

"It has been an amazing journey into the world of carbohydrate. From the time it started, almost by chance, to now, when I get to travel the world to so many exciting research groups and help to solve the large and important challenges they face. Although the techniques for investigation have changed over the more than 30 years, my fascination with carbohydrates is still intact."

Together with the Copenhagen Center for Glycomics, he hopes to explore and map the changes in the complex carbohydrates that cause metabolic diseases or cancer and perhaps learn how to turn on and off the responsible genes. These researchers hope that this insight into the universe of carbohydrates can lead to new diagnostic tools and more targeted medicines and vaccines.

EVER-GROWING DICTIONARY

Bernard Henrissat's success mainly results from his ability to predict trends and needs in the scientific community. He realized before anyone else that carbohydrate-modifying enzymes need to be classified, which gave him his breakthrough.

And he recognized before anyone else in his field that tools need to be compiled and created to analyse the many new genome sequences produced at the end of the last millennium. Nevertheless, Bernard Henrissat is overwhelmed to receive the Novozymes Prize for his great contributions to science.

"It was a huge surprise and a tremendous honour to receive this prize. It is a special honour because I am getting the award from Denmark, the homeland of enzyme research. It motivates me to continue diving into the fascinating world of carbohydrates and to try to predict how and which enzymes best perform their carbohydrate chemistry. In this way, I can guide other researchers in the direction of potential candidates for their own experimental work."

Where in the scientific and physical world the next trip will take Bernard Henrissat remains to be seen, but he always brings CAZy: his ever-growing dictionary of life's third language – the language of carbohydrates. A language that Henrissat, through his longstanding career and everyday training, knows better than anyone else.





THE NOVOZYMES PRIZE COMMITTEE

The Novozymes Prize is a new European research award instituted by the Novo Nordisk Foundation. The Novozymes Prize is awarded in the name of the foundation and using the funds of the foundation. The purpose of the Prize is to raise awareness of basic and applied biotechnology research.

The Novozymes Prize is awarded to recognize outstanding research or technology contributions that benefit the development of biotechnological science for innovative solutions. It consists of a funding amount for the awardee's research (DKK 2.5 million) and a personal award (DKK 0.5 million). An additional part of the Prize is an international symposium within the awardee's field of research.

Awardees must have a current position at a public or non-profit research institution in a European country. They can previously have worked anywhere and have any nationality.

The Novozymes Prize is awarded by a prize committee that selects the awardee based on scientific achievements after a confidential nomination and review process.

The members of the Novozymes Prize Committee are appointed by the Novo Nordisk Foundation Board of Directors, and presently the committee consists of 6 members:

- Professor Søren Molin, chair
- Professor Henrik Callesen
- Professor emeritus Liisa Viikari
- R&D Director Claus Hviid Christensen
- Professor Michael Broberg Palmgren
- CEO Birgitte Nauntofte

The award event takes place in the Spring at the Novo Nordisk Foundation Prize Celebration, at which occasion also the Novo Nordisk Prize is awarded.

In addition, in celebration of the award, the awardee gives a lecture lasting about 1 hour at his or her workplace. Before the end of the year, the recipient and the Foundation arrange an international symposium within the scientific field of the prize winner.

Candidates for the Novozymes Prize can be nominated by the prize committee and former prize winners.

Additionally a "Call for nominations" is published in the Spring and candidates can be nominated on the basis of this call.

At the committee meetings the nominated candidates are thoroughly discussed with regard to their research contribution and impact, and a comprehensive bibliometric report is produced. A limited number of candidates are then selected for a thorough international peer review. On the basis of the international peer reviews the committee reaches a decision about the year's prize winner.



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