

DSM Press Release

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Heerlen (NL), 29 September 2008

DSM publishes DNA genome sequence of penicillin producer *Penicillium chrysogenum*

Major landmark in the 80 year history of Penicillin

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Royal DSM N.V., the global Life Sciences and Materials Sciences company headquartered in the Netherlands, today announces that the renowned scientific journal "Nature Biotechnology" is publishing a paper in its October 2008 issue on a breakthrough analysis of the DNA sequence of the fungus *Penicillium chrysogenum*. The paper is the result of a major research project initiated by DSM in which seven international research groups participated.

The unraveling of the DNA sequence of *Penicillium chrysogenum* is a major landmark in the history of penicillin, arguably the most important drug of the 20th century and discovered by Sir Alexander Fleming 80 years ago this month.

Gerard de Reuver, President of DSM Anti-Infectives, comments: "The insights gained through this research will help DSM Anti-Infectives to improve current production methods for β -lactam antibiotics. It will also allow greater innovations in the development of production mechanisms from which our customers and the patients in need of these products will benefit too. We are committed to sustaining our world leading position in these very important pharmaceutical products".

In order to gain a better understanding of the mechanisms by which *Penicillium chrysogenum* produces antibiotics, and to improve the efficiency of this organism in the fermentation processes, DSM started a research project in 2004 to determine the complete DNA sequence of *Penicillium chrysogenum* and to elucidate of the functions of the different genes. The project has resulted in a high-quality genome sequence of 32.2 million base pairs with 13,653 unique genes. The functions of around 6,000 of these genes could be predicted and the first functional analysis of the genome has been reported.

Scientific breakthrough

"The unraveling of the DNA sequence enables us to study the highly complex physiology of *Penicillium chrysogenum*", explains Dr. Marco van den Berg, principal scientist Metabolic Engineering and Screening at DSM Anti-Infectives. "Never before has the sequence of this strain been mapped to this level or such important knowledge extracted. It is an absolute leap forward in the field of these antibiotics and it will generate many innovative development opportunities for both classical and new products. This project confirms DSM's leading role in fungal biotechnology following last year's publication on another production workhorse of DSM, *Aspergillus niger*."

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In February 2007 DSM published, also in *Nature Biotechnology*, a paper in which the company released the DNA sequence of the fungus *Aspergillus niger*, a micro-organism that DSM uses for the production of enzymes and other compounds that are mainly used in food ingredients. This research resulted in numerous patent filings by DSM and a whole range of new DSM products.

Follow-up research for the *Penicillium chrysogenum* project is now being carried out by DSM in collaboration with academic partners in a number of public-private partnerships in the Netherlands. This research has already resulted in several new patent filings by DSM.

DSM – the Life Sciences and Materials Sciences Company

Royal DSM N.V. creates innovative products and services in Life Sciences and Materials Sciences that contribute to the quality of life. DSM's products and services are used globally in a wide range of markets and applications, supporting a healthier, more sustainable and more enjoyable way of life. End markets include human and animal nutrition and health, personal care, pharmaceuticals, automotive, coatings and paint, electrics and electronics, life protection and housing. DSM has annual sales of almost EUR 8.8 billion and employs some 23,000 people worldwide. The company is headquartered in the Netherlands, with locations on five continents. DSM is listed on Euronext Amsterdam. More information: www.dsm.com

For more information:

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Forward-looking statements

This press release contains forward-looking statements. These statements are based on current expectations, estimates and projections of DSM management and information currently available to the company. The statements involve certain risks and uncertainties that are difficult to predict and therefore DSM does not guarantee that its expectations will be realized. Furthermore, DSM has no obligation to update the statements contained in this press release.

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Notes to editors and background information:

- *Penicillium chrysogenum* is a micro-organism that is used for the production of β -lactam antibiotics, such as penicillins and cephalosporins. These are converted into active pharmaceutical ingredients like amoxicillin, ampicillin, cephalexin and cefadroxil.
- The importance to humanity of penicillin should not be underestimated. Penicillin-derived antibiotics are still the world's most significant weapon against infectious diseases. This research has provided a landmark breakthrough in our understanding of *Penicillium chrysogenum* - the micro-organism that is used for the production of antibiotics – and this will be of benefit to all of humanity as it will help create purer products produced more sustainably and at a cheaper price, making these crucially important drugs more easily and widely available for all. This is important, because penicillin-derived antibiotics are likely to remain one of our most potent defenses against infectious diseases for several decades to come.
- The exact number of people using penicillin around the world every year is almost impossible to quantify but is more than a billion. Antibiotics account for about 8% of the world pharmaceuticals market.
- Last year's research into *Aspergillus niger* by DSM grew into one of the most important industrial genomics projects in Europe, and earned DSM a position among Europe's leading biotechnology companies. DSM products that were developed as a result of this research include: PeptoPro® (ingredient for muscular recovery after physical exertion); Brewers Clarex™ (enzyme for preventing chill-haze in beers); and PreventASe™ (enzyme for preventing the formation of the toxic compound acrylamide during baking or frying of certain foodstuffs).

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Partners

DSM scientists carried out the research on the *Penicillium chrysogenum* genome in collaboration with research partners in the Netherlands, Germany, Spain and the USA.

Delft University of Technology, Professor Jack Pronk, head of the Industrial Microbiology department: *"This genome sequence will help us to identify the many mutations that, over the course of half a century of intensive strain improvement, have transformed naturally occurring Penicillium chrysogenum, which produces only negligible amounts of penicillin, into a highly efficient antibiotics producer. Insight into the mechanisms and dynamics of genome change in this unique model system will be invaluable for the rational design of other strain improvement programs."*

Groningen University, Professor Arnold Driessen, head of the Molecular Microbiology - department: *"With the aid of the genome sequence we will now be able to elucidate the last unresolved mechanistic questions in antibiotics biosynthesis that have proven to be difficult to tackle otherwise. This for instance concerns the elusive transport of penicillins and cephalosporins out of the cell. These insights will be instrumental for the future synthetic biology based development of novel production processes."*

Title of the paper published in Nature Biotechnology

"Genome sequencing and analysis of the filamentous fungus *Penicillium chrysogenum*"

END