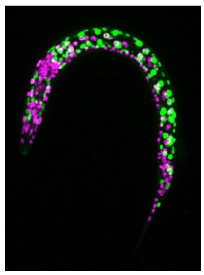
MODEL ORGANISMS

A nervous system from Mom and a gonad from Dad

A simple tweak on the zygote's mitotic spindle generated hybrid *Caenorhabditis elegans* with certain tissues (such as those of the nervous system) consisting of entirely maternal genomes and others (such as the germline) consisting of entirely paternal genomes.



A hybrid worm expressing maternal (purple) and paternal (green) markers separately in different tissues. Adapted with permission from Besseling and Bringmann (2016).

In 1865, Gregor Mendel devised three principles describing transgenerational inheritance, which has formed the cornerstone of modern genetics. The basis of Mendelian inheritance is that in sexually reproducing organisms, each parent contributes to 50% of the offspring's genome. But now, Judith Besseling and Henrik Bringmann of the Max Planck Institute for Biophysical Chemistry in Göttingen have rewritten the rules of inheritance in *C. elegans*. They generated hybrid worms with certain cells containing only the maternal genome and others containing only the paternal genome, simply by overexpressing one protein to disrupt the mitotic spindle during the zygote's first cell division. This work is likely to open new possibilities in epigenetics and transgenerational inheritance.

In the wild-type zygote, the chromosomes delivered by the oocyte and the sperm come together during the formation of the bipolar spindle. Then the spindle pulls the sister chromatids apart, eventually resulting in two daughter cells—an anterior cell (AB) and a posterior cell (P1)—with an identical genotype. The expression level of GPR-1, a microtubule force regulator, controls the pulling force of the mitotic spindle. Besseling and Bringmann found that in zygotes overexpressing GPR-1, instead of one

DATABASES

CROWDSOURCING FOR NATURAL PRODUCTS RESEARCH

The Global Natural Products Social Molecular Networking knowledgebase facilitates community sharing and curation of mass spectrometry data from natural products.

Interest in natural products—active compounds produced by organisms—for applications in biotechnology and medicine is being renewed. A key technique in natural product analysis is mass spectrometry. Research in this field has been inhibited, however, by the lack of an electronic mechanism to share mass spectrometry data, according to University of California, San Diego (UCSD) researchers Nuno Bandeira and Pieter Dorrestein. "The knowledge that is generated through structure elucidation by the natural product community is important for many in the life sciences as well as the metabolomics community," they write in a joint e-mail. "Structures are shared, but not the data that led to the structure."

Together, they aimed to collate, curate and make available such valuable raw data in a searchable resource by developing the Global Natural Products Social Molecular Networking knowledgebase (GNPS), available at http://gnps.ucsd.edu. "We wanted to create an infrastructure that has the ability to store, analyze and disseminate both data and knowledge in an integrated manner to make data continuously more informative," they say. They liken GNPS to GenBank, which facilitates the sharing of DNA sequence data, and BLAST, which facilitates searching of such sequence data.

GNPS allows users to make their raw tandem mass spectrometry (MS/MS) data for natural products available through UCSD's MassIVE (Mass Spectrometry Interactive Virtual Environment) repository. It also contains a spectral library of known natural product spectra, aggregated from their own libraries as well as third-party public libraries. At the time of publication, the GNPS spectral library contained more than 220,000 spectra for more than 18,000 compounds. All data sets uploaded to GNPS are subjected to an automated analysis that compares the experimental spectra against the library spectra, a process known as dereplication.

bipolar spindle, two monopolar spindles often formed, pulling apart the maternal and paternal chromosomes prematurely. This resulted in two daughter cells with distinct genotypes. Usually AB contained only maternal DNA, and P1 contained only paternal DNA.

Disrupting the mitotic spindle in the zygote usually leads to embryonic lethality. However, "the thing that was amazingly surprising was that the embryos that formed two monopolar spindles could survive," says Bringmann.

In *C. elegans*, AB and P1 develop into different lineages. The team crossed GPR-1-overexpressing worms whose chromosomes were decorated with a red fluorescent marker with wild-type males whose chromosomes were labeled by a green fluorescent marker. In the F1 progeny, the team frequently found hybrid worms, the majority of which expressed only the maternal (red) marker in the AB lineage (such as neurons) and the paternal (green) marker in the P1 lineage (such as the germline). These presumably developed from zygotes with monopolar spindles and unequal segregation of maternal and paternal DNA during the first cell division. The F2 progeny of the F1 hybrid worms carried genetic information from either only the grandfather or only the grandmother, thus demonstrating non-Mendelian inheritance.

Non-Mendelian inheritance can potentially be harnessed to study epigenetics, imprinting or signaling between tissues or genomes. Because GPR-1 function is highly conserved throughout evolution, in principle similar approaches could be developed in other organisms.

The study demonstrates that it is possible to rewrite the rules of inheritance by changing the properties of the mitotic spindle—a cellular structure that so far has not been widely recognized as 'engineerable'. "To my view what has been overlooked in the past was to engineer cell division, cell biological structures, macromolecular complexes, to really change basic cell biological properties and ultimately to engineer animals that have properties that we have not seen before," Bringmann says. The team named this field "synthetic zoology."

Kate Gao

RESEARCH PAPERS

Besseling, J. & Bringmann, H. Engineered non-Mendelian inheritance of entire parental genomes in *C. elegans*. *Nat. Biotechnol.* **34**, 982–986 (2016).

However, the chemical structure space of natural products is much, much greater than the current spectral library in GNPS (or any other spectral library, for that matter), which prevents the identification of most spectra in a data set for a particular organism. Uniquely, GNPS relies on crowdsourcing to not only help grow its spectral library but also help annotate unknown spectra in submitted data sets. At the time of publication, contributors had added spectra representing 1,325 new compounds to the spectral library and had revised the annotations of 563 library spectra. Each spectrum added to the library is given a gold, silver or bronze quality rating depending on how it was derived.

GNPS also includes a molecular networking tool that enables users to visualize related molecules, similarly to how sequence alignment is used to reveal related genes and other coding sequences. Network analysis can help reveal connections between data sets from disparate data sources that would otherwise remain hidden.

GNPS implements the concept of 'living data': as the spectral library grows, all public data sets in GNPS are periodically reanalyzed by the dereplication and molecular networking tools. This allows the data to become more annotated over time, say Bandeira and Dorrestein. Data contributors are automatically notified of new spectral matches made to their data sets, and users can 'follow' specific data sets of interest. "GNPS changes the way we interact with the data as the data starts to interact with the user," note Bandeira and Dorrestein.

In the future, they plan to expand GNPS to include other types of MS data, provide tools to support automated metadata capture and 3D visualization, and add analysis capabilities for specific applications such as microbiome research.

"Unfortunately too many groups in the natural product community or in the metabolomics community still do not share their data," Bandeira and Dorrestein lament. GNPS could help change this, as individual researchers can reap the positive feedback loop that crowdsourcing offers in return for sharing their precious data.

Allison Doerr

RESEARCH PAPERS

Wang, M. *et al.* Sharing and community curation of mass spectrometry data with Global Natural Products Social Molecular Networking. *Nat. Biotechnol.* **34**, 828–837 (2016).