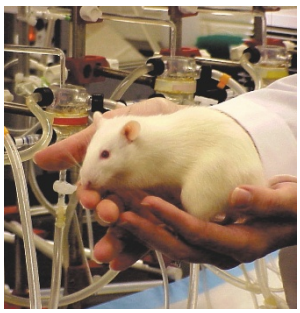
New rats set physiologists' hearts aflutter

Under a new agreement, Massachusetts-based laboratory animal provider Charles River Labs is to begin selling 'consomic' rats developed at the Medical College of Wisconsin (MCW) in Milwaukee. Although many physiologists remain unaware of the significance of the new strains, MCW researchers claim they will revolutionize research in fields ranging from cardiovascular disease to asthma.

The concept of a consomic—or chromosome-substitution—strain is relatively straightforward: a single chromosome from one rat strain is introduced into another rat strain, allowing researchers to study multigenic phenotypes in a controlled genetic background. For example, individual chromosomes from the well-studied brown Norway rat could be substituted one at a time into the Dahl salt-sensitive rat model of hypertension, and the resulting consomic strains could be compared to normal Dahl salt-sensitive rats. If one chromosome confers a difference in susceptibility to hypertension, gene mappers, physiologists and pharmaceutical companies would be able to use the new strain as a model for future hypertension studies.



Courtesy of MCW

Some of the strains have already produced interesting results. For example, replacing chromosome 13 in the Dahl salt-sensitive rat with chromosome 13 of the brown Norway strain essentially abolished hypertension. Another consomic strain sustains substantially less myocardial damage than its parent strain after 25 minutes of global ischemia, potentially making it a valuable model for studies on heart failure.

Generating a consomic strain is also theoretically simple, but laborious. "I wish I could tell you it was a fascinating technological breakthrough, but it's really just agricultural genetics," says Howard Jacob, director of the Human and Molecular Genetics Center at MCW, "you back-cross, you select the animal for the next round of back-crossing that's heterozygous for the whole length of the chromosome, and you then just serially wash away the rest of the genome" in subsequent crosses. Only the genotyping of the strain, which is done with markers spread along the chromosome, involves modern molecular techniques.

Once each strain is generated, MCW researchers engage in what they call "high-throughput physiology," measuring and comparing over 200 quantifiable physiological traits—ranging from kidney function to ischemia response—in the consomic strain and its parental strain. The scale of the effort, which is being financed with a $13.3 million, four-year grant from the National Heart, Lung, and Blood Institute (NHLBI) of the NIH, is impressive. "In the last 9 months ... we have studied 1,256 rats and we've generated over 29,000 data points of physiological characteristics," says Jacob, adding that "two technicians are generating the amount of data equal to a physiology paper a week."

Rather than publishing all of the data in the form of papers, the program, named PhysGen, releases results quarterly in an online public database (http://pga.mcw.edu/). The MCW program received pilot funding from the Merck Genome Institute, but in January PhysGen became part of a $37 million NHLBI-funded effort called Programs for Genomic Analysis.

So far, six consomic rat strains have been generated and subjected to the battery of physiological tests, but by 2004 the MCW researchers expect to have generated a panel of 42 strains. Each of the 21 rat chromosomes will be substituted from the brown Norway rat into both the Dahl salt-sensitive strain and the fawn-hooded strain. Allen Cowley, chair of the department of physiology at MCW, says that the three parental strains represent at least 75% of the total allelic diversity of the rat genome.

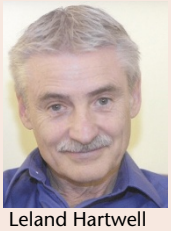
Although consomic mouse strains are being developed for genetics research (*Nature Genet.* **3**, 221; 2000), the rat is the standard model system for physiology. "We know very little physiology for the mouse," says Cowley, adding that "a mouse is a lot more than a small rat, it's really a different mammal, separated by 40–50 million years of evolution."

Although larger animals such as dogs and pigs are better suited for some types of cardiovascular research, consomic rats will offer several advantages for most studies. Besides being more affordable, "this will really be the first controlled strain where you can have a fixed genetic background except for the thing you're interested in, so you can have all of your genetic controls" in one system, according to Cowley. The completion of the rat genome sequence, currently projected for 2003, will further increase the utility of the system for gene mapping.

Alan Dove, Philadelphia

Cell cycle scientists are centenary Laureates

This year marks the 100-year anniversary of the Nobel Prizes and the committee for Physiology or Medicine has chosen to honor three scientists who have elucidated genes and proteins crucial to cell-cycle control. Leland Hartwell, president and director of the Fred Hutchinson Cancer Research Center in Seattle, is widely credited with pioneering the field through studies in baker's yeast, *Saccharomyces cerevisiae.* He has identified over 100 cell-division cycle (*CDC*) genes including those that stop and start the cell-division process.



Leland Hartwell

Tim Hunt

Two honors went to British researchers at the Imperial Cancer Research Foundation: Sir Paul Nurse (see page 1172) has isolated genes corresponding to those that Hartwell found in human cells and Tim Hunt discovered cyclin proteins in the cytoplasm which associate with kinases to control the passage of a cell through the cell cycle. The winners share 1 million Swedish krona ($96 million). For more details, see http://www.nobel.se/medicine/laureates/2001/press.html.

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