PNAS Plus Significance Statements

Accounting for inhomogeneous broadening in nano-optics by electromagnetic modeling based on Monte Carlo methods

Herman Gudjonson, Mikhail A. Kats, Kun Liu, Zhihong Nie, Eugenia Kumacheva, and Federico Capasso

The advent of nanotechnology has enabled the study of physical phenomena in structures with nanoscale dimensions. Pushing the limits of fabrication techniques inevitably leads to uncertainties—for example, an array of nanoscale resonators may be designed to be identical, but in fact has a distribution of sizes due to fabrication imperfections, leading to a distribution of responses. In optical experiments involving collections of nanostructures these effects are often acknowledged but rarely quantified. We demonstrate (pp. E639–E644) a technique that combines electromagnetic simulations with a Monte Carlo sampling technique to rigorously account for "inhomogeneous broadening" of optical resonances as a result of fabrication or synthesis imperfections. This approach has wide applicability to any experiments involving collections of structures designed to be identical.

Identifying and mapping cell-type-specific chromatin programming of gene expression

Troels T. Marstrand and John D. Storey

In order for genes to be expressed in humans, the DNA corresponding to a gene and its regulatory elements must be accessible. It is hypothesized that this accessibility and its effect on gene expression plays a major role in defining the different cell types that make up a human. We have only recently been able to make the measurements necessary to model DNA accessibility and gene-expression variation in multiple human cell types at the genome-wide level (pp. E645–E654). We develop and apply a new quantitative framework for identifying locations in the human genome whose DNA accessibility drives cell-type-specific gene expression.

Structure of signaling-competent neurotensin receptor 1 obtained by directed evolution in *Escherichia coli*

Pascal Egloff, Matthias Hillenbrand, Christoph Klenk, Alexander Batyuk, Philipp Heine, Stefanie Balada, Karola M. Schlinkmann, Daniel J. Scott, Marco Schütz, and Andreas Plückthun

Only a tiny fraction (<2%) of the unique structures in the protein database correspond to membrane proteins, and only a few of these are of eukaryotic origin, representing potential drug targets. The difficulties in structure determination of these proteins are due to two specific complications, which are unique for membrane proteins: first, low expression levels and, second, the necessity for detergent micelles, which are often destabilizing as they mimic the hydrophobic membrane environment only poorly. We prove (pp. E655–E662) that directed evolution has the potential to overcome these problems by determining several structures of evolved eukaryotic G protein–coupled receptor variants. High functional expression levels and superior receptor stability in harsh detergents allowed us to gain deeper insights into this important receptor family.

Structural determinants for ligand capture by a class II preQ$_1$ riboswitch

Mijeong Kang, Catherine D. Eichhorn, and Juli Feigon

Riboswitches are structured RNA elements, generally found 5′ to protein-coding regions that control gene expression by binding metabolites or other RNAs. The class II prequeuosine riboswitch (preQ$_1$-II) enfolds preQ$_1$ to form a rare example of a pseudoknot with a conserved hairpin embedded in loop 3. The solution NMR structure and dynamics studies of the preQ$_1$-bound *Streptococcus pneumoniae* preQ$_1$-II riboswitch presented here reveal the key functionality of the embedded hairpin in ligand recognition. We show that this hairpin destabilizes formation of the pseudoknot before ligand capture, thereby preventing premature sequestration of the Shine–Dalgarno region, and blocks ligand exit on capture. Our studies show (pp. E663–E671) that the preQ$_1$-II riboswitch uses a previously unknown mechanism to harness exquisite control over queuosine metabolism.

www.pnas.org/cgi/doi/10.1073/pnas.ss11106

Whole-genome sequencing identifies genomic heterogeneity at a nucleotide and chromosomal level in bladder cancer

Carl D. Morrison, Pengyuan Liu, Anna Woloszynska-Read, Jianmin Zhang, Wei Luo, Maochun Qin, Wiam Bshara, Jeffrey M. Conroy, Linda Sabatini, Peter Vedell, Donghai Xiong, Song Liu, Jianmin Wang, He Shen, Yinwei Li, Angela R. Omilian, Annette Hill, Karen Head, Khurshid Guru, Dimiter Kunnev, Robert Leach, Kevin H. Eng, Christopher Darlak, Christopher Hoeflich, Srividya Veeranki, Sean Glenn, Ming You, Steven C. Pruitt, Candace S. Johnson, and Donald L. Trump

Genetic alterations are frequently observed in bladder cancer. In this study (pp. E672–E681), we demonstrate that bladder tumors can be classified into two different types based on the spectrum of genetic diversity they confer. In one class of tumors, we observed tumor protein p53 mutations and a large number of single-nucleotide and structural variants. Another characteristic of this group was chromosome shattering, known as chromothripsis, and mutational heterogeneity. The other two bladder tumors did not show these profound genetic aberrations, but we found a novel translocation and amplification of the gene glutamate receptor ionotropic N-methyl D-aspertate, a potentially druggable target. Advancements in bladder cancer treatment have been slow. Understanding the genetic landscape of bladder cancer may therefore help to identify new therapeutic targets and bolster management of this disease.

Mistimed sleep disrupts circadian regulation of the human transcriptome

Simon N. Archer, Emma E. Laing, Carla S. Möller-Levet, Daan R. van der Veen, Giselda Bucca, Alpar S. Lazar, Nayantara Santhi, Ana Slak, Renata Kabiljo, Malcolm von Schantz, Colin P. Smith, and Derk-Jan Dijk

Disruption of the timing of the sleep–wake cycle and circadian rhythms, such as occurs during jet lag and shift work, leads to disordered physiological rhythms, but to what extent the molecular elements of circadian rhythm generation are affected is not known. Here, we show that delaying sleep by 4 h for 3 consecutive days leads to a sixfold reduction of circadian transcripts in the human blood transcriptome to just 1%, whereas, at the same time, the centrally driven circadian rhythm of melatonin is not affected. Genes and processes affected included those at the core of circadian rhythm generation and gene expression. The data (pp. E682–E691) have implications for understanding the negative health outcomes of disruption of the sleep–wake cycle.

Noninvasive positron emission tomography and fluorescence imaging of CD133$^+$ tumor stem cells

Simone Gaedicke, Friederike Braun, Shruthi Prasad, Marcia Machein, Elke Firat, Michael Hettich, Ravindra Gudihal, Xuekai Zhu, Kerstin Klingner, Julia Schüler, Christel C. Herold-Mende, Anca-Ligia Grosu, Martin Behe, Wolfgang Weber, Helmut Mäcke, and Gabriele Niedermann

Cancer stem cells (CSCs) are thought to be responsible for growth and dissemination of many malignant tumors and for relapse after therapy. Therefore methods for the noninvasive imaging of CSCs could have profound consequences for diagnosis and therapy monitoring in oncology. However, clinically applicable methods for noninvasive CSC imaging are still lacking. The AC133 epitope of CD133 is one of the most intensely investigated CSC markers and is particularly important for aggressive brain tumors. Here (pp. E692–E701) we describe the development of clinically relevant tracers that permit high-sensitivity and high-resolution monitoring of AC133$^+$ glioblastoma stem cells in both subcutaneous and intracerebral xenograft tumors using positron emission tomography and near-infrared fluorescence imaging, two clinically highly relevant imaging modalities.

Critical role for IL-1β in DNA damage-induced mucositis

Naama Kanarek, Sergei I. Grivennikov, Michael Leshets, Audrey Lasry, Irit Alkalay, Elad Horwitz, Yoav D. Shaul, Matthew Stachler, Elena Voronov, Ron N. Apte, Michele Pagano, Eli Pikarsky, Michael Karin, Sankar Ghosh, and Yinon Ben-Neriah

Deletion of the E3 β-TrCP in the mouse gut epithelium deregulates enterocyte cell cycle, induces a DNA damage response (DDR), and abolishes the epithelium barrier function, resulting in a lethal mucosal inflammation. Epithelial-derived IL-1β, likely induced by DDR independently of NF-κB, is a major culprit, and initiates the pathology by compromising epithelial tight junctions (TJs). Anti–IL-1β treatment secures the TJs and prevents the fulminant mucosal inflammation. IL-1β secretion accompanies human mucositis, a severe mucosal inflammatory reaction caused by chemoradiation therapy-induced DNA damage, which often results in treatment suspension. We propose (pp. E702–E711) that anti–IL-1β preventive treatment may ameliorate mucositis, as well as multiple disorders associated with epithelial barrier permeability, including burn injuries, head and neck trauma, alcoholic intoxication, and graft-vs.-host disease.