Franziska Michor, PhD

**Program for Evolutionary Dynamics,
Harvard University, Cambridge, MA**

Ausbildung

1992 - 2000	Bundesgymnasium Klosterneuburg in Austria
2000 - 2002	Undergraduate studies at the University of Vienna (molecular biology and mathematics)
2002	Università degli Studi di Trieste, Italy (medical biotechnology)
2002	First Diploma (Bachelor of Science) from the University of Vienna
2002 - 2005	Graduate studies at Harvard University in the Department of Organismic and Evolutionary Biology and the Program for Evolutionary Dynamics
2002 - 2003	Institute for Advanced Study, Program in Theoretical Biology
2005	PhD from Harvard University, Department for Organismic and Evolutionary Biology

Labortätigkeit

2001	Laboratory of Rudolf Schweyen, Institute of Genetics and Microbiology, University of Vienna
2001/02	Institute for Hematology and Leukemia Research, Hanusch Hospital, Vienna
2002	Laboratory of Kim Nasmyth, Institute of Molecular Pathology, Vienna
2002	Laboratory of Roland Foisner, Institute of Biochemistry and Cell Biology, University of Vienna

Stipendien und Auszeichnungen

2000	Prize of the Austrian Mathematical Society for the paper *The Mathematics of Planetary Movement*
2004	Harold M. Weintraub Graduate Student Award of the Fred Hutchinson Cancer Research Center, Seattle, Washington
2005-2008	Junior Fellowship of the Harvard Society of Fellows

Invited talks and lectures

Feb. 13th, 2003	Biomathematics Summer School, IMPA, Rio de Janeiro, Brazil
March 13th, 2003	Department of Pure and Applied Sciences, University of Tokyo, Japan
March 17th, 2003	Fukuoka Workshop of Theoretical Biology: Coevolutionary Aspects in Ecology and Medicine, Kyushu University, Fukuoka, Japan
May 20th, 2003	Program for Women in Mathematics: Mathematical Biology, Institute for Advanced Study, Princeton, New Jersey
June 4th, 2003	Department of Medicine, University of California at Los Angeles
Sep. 9th, 2003	Institute for Molecular Pathology, Vienna, Austria
Oct. 20th, 2003	Centre for Mathematical Biology, Department of Mathematics, Oxford University, England
Feb. 11th, 2004	Workshop on Biomathematics and Evolutionary Dynamics, IMPA, Rio de Janeiro, Brazil
March 5th, 2004	Department of Ecology and Evolutionary Biology, Yale University
March 8th, 2004	Department of Organismic and Evolutionary Biology, Harvard University
May 7th, 2004	Weintraub Symposium, Fred Hutchinson Cancer Research Center, Seattle, Washington
May 10th, 2004	Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington
May 12th, 2004	Pacific Institute of the Mathematical Sciences, University of British Columbia, Vancouver, Canada
July 14th, 2004	Mathematical Models Applied to the Biological Sciences, Economics, and Complex Systems, Siena, Italy
Sep. 28th, 2004	Royal Society Discussion Meeting: Chromosome Segregation, Royal Society, London, England
Oct. 1st, 2004	Department of Mathematics, University of Massachusetts at Boston
Dec. 16th, 2004	Brigham and Women's Hospital, Harvard Medical School, Boston
Jan. 19th, 2005	University of Natural Resources and Applied Life Sciences (BOKU), Vienna
Feb. 2nd, 2005	Program for Evolutionary Dyamics, Harvard University
Feb. 18th, 2005	Summer School on Evolutionary Dynamics, IMPA, Rio de Janeiro, Brazil
Feb. 22nd, 2005	Mathematical Methods and Modeling of Biophysical Phenomena, IMPA, Rio de Janeiro, Brazil
March 8th, 2005	Program for Evolutionary Dynamics, Harvard University
April 14th, 2005	Program for Evolutionary Dynamics, Harvard University
April 15th, 2005	Department of Organismic and Evolutionary Biology, Harvard University
April 28th, 2005	Vienna ASCINA Conference, Austrian Academy of Sciences, Vienna

Conferences and Summer Schools

1996	Junior Mathematical Conference, Miskolc, Hungary
2000	European Science Days: Biological Evolution of Cooperation and Communication, Steyr, Austria
2002	Theoretical Course: RNA Structure and Function, Trieste, Italy
2002	Workshop on Theoretical Ecology: Natural Resource Management and Conservation Biology, Trieste, Italy
2002	Biomathematics Euro Summer School: Dynamical Systems in Physiology and Medicine, Urbino, Italy

2002	Frontiers in Science, University of California at Irvine
2003	Biomathematics Summer School, Rio de Janeiro, Brazil
2003	Fukuoka Workshop of Theoretical Biology: Coevolutionary Aspects in Ecology and Medicine, Fukuoka, Japan
2003	Program for Women in Mathematics: Mathematical Biology, IAS, Princeton, New Jersey
2003	Mathematics of Language Conference, Bloomington, Indiana
2003	Conference of the Academia Europaea, Karl Franzens University, Graz, Austria
2004	Workshop on Biomathematics and Evolutionary Dynamics, IMPA, Rio de Janeiro, Brazil
2004	International Conference on Research in Computational Molecular Biology (RECOMB), University of California at San Diego
2004	Stem Cell Symposium, Harvard Stem Cell Institute, Harvard University
2004	Weintraub Symposium, Fred Hutchinson Cancer Research Center, Seattle, Washington
2004	Genomic instability and cancer: biological and mathematical approaches, IAS, Princeton, New Jersey
2004	Fourth European Congress of Mathematics, Stockholm, Sweden
2004	Mathematical Models Applied to the Biological Sciences, Economics, and Complex Systems, Siena, Italy
2004	Royal Society Discussion Meeting: Chromosome Segregation, Royal Society, London, England
2004	Recent Developments in Evolutionary Game Theory, Program for Evolutionary Dynamics, Harvard University
2004	Language Conference, Program for Evolutionary Dynamics, Harvard University
2005	Summer School and Conference: Mathematical Methods and Modeling of Biophysical Phenomena, IMPA, Rio de Janeiro, Brazil
2005	Mathematical Modeling and Analysis of Language Diversification, Harvard University
2005	Vienna ASCINA Conference, Austrian Academy of Sciences, Vienna

Forschungsgebiet

Evolutionary concepts such as mutation and selection can best be described when formulated as mathematical equations. Cancer arises as a consequence of somatic evolution. Therefore, a mathematical approach can be used to understand the process of cancer initiation and progression. My research focuses on evolutionary dynamics of cancer and includes the following research projects:

(1) Dynamics of alterations in gatekeepers, caretakers and landscapers:

Cancer arises due to mutations in cancer-susceptibility genes. These genes belong to one of three classes: gatekeepers, caretakers and landscapers. Gatekeepers directly regulate growth and differentiation pathways of the cell and comprise oncogenes and tumor suppressor genes. Caretakers, in contrast, promote tumorigenesis indirectly. They function in maintaining the genomic integrity of the cell. Mutation of caretakers can lead to genetic instability, and the cell rapidly accumulates changes in other genes that directly control cell birth and death. Landscaper defects do not directly affect cellular growth, but generate an abnormal stromal environment that contributes to the neoplastic transformation of cells. But what are the fundamental principles that govern the dynamics of activating oncogenes, inactivating tumor suppressor genes and alterating genetic instability genes in populations of reproducing cells? (see publications 3, 9, 10, 11, 13, 17)

2) Genetic instabilities and their role in tumorigenesis:

Genetic instability is a defining characteristic of most human cancers. Two types of genetic instability have been identified. In a small fraction of colorectal and some other cancers, a defect in mismatch repair results in an elevated mutation rate at the nucleotide level and consequent widespread microsatellite instability (MIN). The majority of colorectal and most other solid cancers, however, have chromosomal instability (CIN). CIN refers to an increased rate of losing or gaining whole chromosomes or large parts of chromosomes during cell division. The consequence of CIN is an imbalance in chromosome number (aneuploidy) and an increased rate of loss of heterozygosity (LOH). An elevated rate of LOH is an important property of CIN, because it accelerates the inactivation of TSGs. A crucial question of cancer biology is whether CIN is an early event and thus a driving force of tumorigenesis. How does a quantitative theory of somatic mutation and selection help us to evaluate the role of genetic instability in human tumorigenesis? (see publications 3, 9, 10, 16, 18)

(3) Dynamics of Chronic Myeloid Leukemia:

Chronic myeloid leukemia (CML) is a malignant clonal disorder of hematopoietic stem cells that leads to increased numbers of myelocytes, erythrocytes and thrombocytes in peripheral blood. The molecular hallmark of CML is the Philadelphia (Ph) chromosome, a t(9;22) translocation resulting in the fusion of the BCR (breakpoint cluster region) gene on chromosome 22 to the ABL (Ableson leukemia virus) gene on chromosome 9. The chimeric oncogene BCR-ABL encodes a constitutively active cytoplasmic tyrosine kinase. This protein activates growth and differentiation pathways in hematopoietic cells and initiates a process to transform hematopoietic cells such that their growth and survival become independent of cytokines. The revolution in CML treatment came about with the discovery of the tyrosine kinase inhibitor imatinib (STI-571, Gleevec). Imatinib binds competitively with ATP to BCR-ABL and blocks its abnormal signalling. It selectively kills or inhibits the proliferation of BCR-ABL positive cell lines. However, acquired resistance to imatinib develops in a substantial fraction of patients. In 70-80% of these cases, acquired resistance is caused by point mutations in the ABL kinase domain. So far, about 40 different point mutations have been discovered, each of which is sufficient to cause resistence to imatinib. But what are the in vivo kinetics of this disease? Can imatinib eradicate leukemic stem cells? And what are the dynamics of relapse due to imatinib resistance mutations? (see publication 20)

(4) Tissue architecture and stem cell dynamics

The development of multicellular organisms requires the organization of cells in morphologically stable functional units. Such units are made up of seperate families of multiplying cells that are organized hierarchically. The most primitive cells are pluripotent stem cells capable of proliferation, self-renewal, and production of a large number of differentiated progeny. The most primitive stem cells produce more committed progenitor cells. Progenitor cells in turn produce even more committed cells etc. Differentiated cells typically proliferate to fulfill their organ-specific tasks. The maintenance of homeostasis, i.e. constancy in cell number, reflects a highly regulated balance between the rates of cell proliferation and cell death. If the balance is shifted towards uncontrolled proliferation, cancer occurs. Therefore, cancer is breakdown of homeostasis. But how does tissue design influence the probability to develop cancer? What is the optimum tissue architecture to minimize the probability of cancer initiation and progression? (see publications 4-6, 10)

(5) Evolution of resistance to cancer therapy

Acquired drug resistance is a major limitation for successful treatment of cancer. Drug resistance can result from two general causes: (i) host factors such as poor absorption and rapid metabolism reduce the maximum achievable serum levels of the drug - this is sometimes referred to as intrinsic resistance, and (ii) specific genetic or epigenetic alterations enable resistant cancer cell clones to outgrow and escape from otherwise effective treatment. Some of these mechanisms, such as loss of a cell surface receptor or transporter, specific metabolism and an increase or alteration in the drug target, result in resistance to only a small number of related chemotherapeutic agents. Other mechanisms, however, lead to simultaneous resistance to many structurally and functionally unrelated drugs. This phenomenon is known as multidrug resistance and can result from changes

that limit accumulation of drugs within cells by decreasing uptake, enhancing efflux, or affecting membrane lipids, block apoptosis which is activated by most anticancer drugs, induce general response mechanisms that detoxify drugs and repair DNA damage, and modulate the cell cycle and checkpoints. If a genetically diverse population of replicating cancer cells is subjected to chemotherapy that has the potential to eradicate it, what is the probability of emergence of resistance? Can we estimate the probability of success for any treatment regimen? (see publications 7, 8, 19)

Publikationen

1. Michor F, Nowak MA (2002) The good, the bad and the lonely. *Nature* **419**, 677-679. (PDF)
2. Michor F, Nowak MA (2002) Immunology tomorrow. *Nature* **420**, 741-742. (PDF)
3. Michor F, Iwasa Y, Komarova NL, Nowak MA (2003) Local regulation of homeostasis favors chromosomal instability. *Curr Biol* **13**, 581-584. (PDF)
4. Michor F, Nowak MA, Frank SA, Iwasa Y (2003) Stochastic elimination of cancer cells. *Proc Roy Soc Lond B* **270**, 2017-2024. (PDF)
5. Michor F, Frank SA, May RM, Iwasa Y, Nowak MA (2003) Somatic selection for and against cancer. *Jour Theor Biol* **225**, 377-382. (PDF)
6. Nowak MA, Michor F, Iwasa Y (2003) The linear process of somatic evolution. *Proc Natl Acad Sci U S A* **100**, *14966-14969.* (PDF)
7. Iwasa Y, Michor F, Nowak MA (2003) Evolutionary dynamics of escape from biomedical intervention. *Proc Roy Soc Lond B* **270**, 2573-2578. (PDF)
8. Iwasa Y, Michor F, Nowak MA (2004) Evolutionary dynamics of invasion and escape. *Jour Theor Biol* **226**, 205-214. (PDF)
9. Michor F, Iwasa, Y, Nowak MA (2004) Dynamics of cancer progression. *Nat Rev Cancer* **4**, 197-206. (PDF)
10. Michor F, Iwasa Y, Rajagopalan H, Lengauer C, Nowak MA (2004) Linear model of colon cancer initiation. *Cell Cycle* **3**, 358-362. (PDF)
11. Iwasa Y, Michor F, Nowak MA (2004) Stochastic tunnels in evolutionary dynamics. *Genetics* **166**, 1571-1579. (PDF)
12. Iwasa Y, Michor F, Nowak MA (2004) Some basic properties of immune selection. *Jour Theor Biol* **229**, 179-188. (PDF)
13. Nowak MA, Michor F, Komarova NL, Iwasa Y (2004) Dynamics of tumor suppressor gene inactivation. *Proc Natl Acad Sci U S A* **101**, 10635-10638. (PDF)
14. Jones, NA, Wei X, Flower DR, Wong M, Michor F, Saag MS, Hahn BH, Nowak MA, Shaw GM, Borrow P (2004) Determinants of Human Immunodeficiency Virus type 1 escape from the primary CD8+ cytotoxic T lymphocyte response. *Jour Exp Med* **200**, 1243-1256. (PDF)
15. Iwasa Y, Michor F, Nowak MA (2005) Virus evolution within patients increases pathogenicity. *Jour Theor Biol* **232**, 17-26. (PDF)
16. Michor F, Iwasa Y, Lengauer C, Vogelstein B, Nowak MA (2005) Can chromosomal instability initiate tumorigenesis? *Seminars in Cancer Biology* **15**, 43-49. (PDF)
17. Iwasa Y, Michor F, Nowak MA (2005) Population genetics of tumor suppressor genes. *Jour Theor Biol* **233**, 15-23. (PDF)
18. Michor F (2005) Chromosomal instability and human cancer. *Proc Roy Soc Lond B*, in press.
19. Michor F, Nowak MA, Iwasa Y (2005) Evolution of resistance to cancer therapy. *Curr Pharm Design*, in press.
20. Michor F, Hughes TP, Iwasa Y, Branford S, Shah NP, Sawyers CL, Nowak MA (2005) Dynamics of chronic myeloid leukemia. *Nature*, in press.

Weiterführende Links

http://www.people.fas.harvard.edu/~michor/index.htm - Homepage at Harvard
http://www.ostina.org/NfA/0312/ixUS1203.html#i3 – Interview