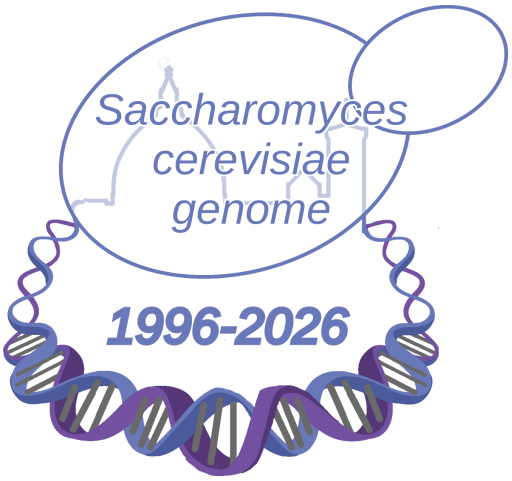

LIFE WITH 6000 GENES

celebrating 30 years since
the sequencing of the *Saccharomyces cerevisiae* genome

FLORENCE 31 AUGUST – 1 SEPTEMBER 2026

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Waste-derived carbon utilization in *Yarrowia lipolytica*: quantitative insights for sustainable biotechnology

Eugenia Messina, Serena Barile, Isabella Pisano, Luigi Palmieri, Pasquale Scarcia, ***Gennaro Agrimi***

Department of Biosciences, Biotechnologies and Environment, University of Bari "Aldo Moro", Bari, Italy

The transition toward a circular and sustainable bioeconomy increasingly depends on biotechnological processes capable of converting waste streams into valuable products. A major challenge in this context is understanding how microorganisms process unconventional, waste-derived substrates at the cellular level. *Yarrowia lipolytica*, a non-conventional yeast already used in several industrial applications, is particularly attractive because it can grow on a wide variety of low-value carbon sources that are inaccessible to many traditional production organisms. Among such substrates are short-chain fatty acids generated during anaerobic digestion of organic waste, as well as small molecules derived from plastic degradation, such as ethylene glycol. These compounds represent promising, sustainable alternatives to sugar-based feedstocks, but their intracellular fate and contribution to cellular growth remain poorly understood, limiting their rational use in industrial bioprocesses. In this work, metabolic flux analysis combined with stable carbon isotope tracing (13C-MFA) was applied to quantitatively follow how carbon from waste-derived substrates is redistributed inside *Y. lipolytica*. By integrating measurements of substrate uptake, by-product secretion, and isotopic labeling patterns in biomass components, this approach reconstructs carbon flow through central metabolic processes involved in energy generation and biomass formation. The analysis reveals how different waste-derived substrates interact metabolically and how carbon is dynamically partitioned between intracellular pools. Overall, this study highlights the importance of quantitative metabolic approaches to understand how *Y. lipolytica* transforms waste-carbon into cellular material. Such knowledge is essential for developing more efficient and predictable biotechnological processes that rely on waste substrates, reducing dependence on food-grade resources and supporting sustainable industrial biotechnology.

Mapping genetic networks and cellular phenotypes on a genome-wide scale: from yeast to humans

Brenda Andrews

Donnelly Centre and Department of Molecular Genetics University of Toronto

Our collaborative research integrates systematic yeast genetics and high-content single-cell screening to illuminate the functional architecture of the eukaryotic cell. When the *Saccharomyces cerevisiae* deletion collection was being constructed, we were inspired to develop the synthetic genetic array (SGA) platform, which automates yeast genetics and enables the construction of more complex mutants on a large scale. Measuring colony size as a proxy for growth, we scored double mutants for both negative (synthetic lethal or sick) and positive (masking and suppression) genetic interactions. Over ~15 years, we constructed almost all ~18 million possible yeast double mutants and we mapped a genome-wide genetic network, revealing a hierarchical model of cell function and pathway organization. In parallel, we expanded our systematic genetics pipeline to include single cell image-based readouts and arrays of yeast strains expressing GFP-tagged proteins for exploration of proteome dynamics and the effects of genetic perturbations on subcellular compartment morphology. Together, these complementary approaches establish a comprehensive framework for linking genotype to phenotype at scale. By combining network-level genetic data with detailed cell-level phenomics, our work defines the structure of genetic interaction networks, uncovers functional modules, and provides general principles governing cellular robustness. These integrative strategies serve as a model for systems-level genomics, offering both conceptual and methodological blueprints that extend to more complex organisms.

The role of branched-chain amino acid aminotransferases in yeast–insect interactions: impact of *BAT2* deletion on *S. cerevisiae* Volatile Organic Compounds profiles.

Matilda Bellini[1], Stefano Nenciarini[2], Alessandro Russo[1], Monica di Paola[1], Agnese Gori[1], Niccolò Meriggi[3], Michela Pivetti[1], Beatrice Bernardi[4], Federico Cappa[1], David Baracchi[1], Irene Stefanini[5], Stefano Turillazzi[1], Duccio Cavalieri[1]

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The symbiotic association between *Saccharomyces cerevisiae* and social insects has emerged as a key driver of yeast evolution and dispersal. While the ecological implications of these interactions have been explored, the genetic basis of yeast-derived chemical signals remains poorly understood. This study aims to investigate how the genetic diversity of *S. cerevisiae* strains isolated from different natural reservoirs influence their production of Volatile Organic Compounds (VOCs) and their effects in mediating the attractiveness toward social insects, focusing on the branched-chain amino acid aminotransferase gene *BAT2*, acting upstream of the Ehrlich pathway. In this context, the selected yeast strains were grown in nectar-like substrate, to mimic natural dispersion on flowers, and tested for their ability to attract social insects (*Polistes dominula*, *Apis mellifera* and *Bombus terrestris*). Behavioral assays confirmed species-specific responses to *S. cerevisiae* strains and VOCs, highlighting differential ecological effects. To confirm the mechanistic role of fusel alcohols in driving the attractiveness of a wasp-gut isolated strain (ET32) toward *P. dominula*, monoallelic and null mutants of the *BAT2* gene were obtained and VOC profiles were analysed using GC–MS. Deletion of *BAT2* resulted in significant metabolic shifts, including altered production of branched-chain alcohols and acetic acid, which in turn led to changes in insect behavioral responses. The null mutant showed the most pronounced changes in VOCs emission compared to the wild-type and monoallelic strains. These findings demonstrate that *BAT2* plays a key role in shaping yeast volatile profiles, providing a mechanistic link between genetic variation and ecologically relevant chemical signaling.

Saccharomyces pastorianus: past, present and the future……

Ursula Bond

Trinity College Dublin

Saccharomyces pastorianus, are the major yeasts used in the production of lager beers. Originating from the hybridisation of *S. cerevisiae* and *S. eubayanus* species, the resultant hybrids possess traits that confer a selective advantage in the fermentation environment. The complex aneuploid genomes underpin the unique physiological traits. The genome era has allowed us to investigate the genetic make-up and gene expression of the hybrids. The polyploid genomes confer immense genetic redundancy and appear to still be in flux with chromosome copy number and composition subject to alteration especially when the yeasts are subjected to environmental stress. Gene expression analyses reveal dose dependency on gene copy number and there is no evidence of dosage compensation. While genetic redundancy poses challenges to altering the physiological traits of the lager yeasts, we developed a stress-induced mutation strategy, coupled with trait selection, to generate strains with improved flavour profiles. The strategy is adaptable to other hybrid yeasts. While we have learned a lot about lager yeasts, much remains to be explored. There still persists a large number of GOUFs, ‘genes of unknown function”, that require analysis. We have developed a pipe-line to characterise GOUFs to update the annotation of the reference genome for *Saccharomyces pastorianus*. Finally, much needs to be done to explore cross-talk between parental transcription factors to improve our understanding of gene expression patterns and to determine what role does the hybrid genome play in generating hybrid multi-subunit protein complexes. Is this the trick to the vigour and robustness of lager yeasts?

Mapping genetic networks and cellular phenotypes on a genome-wide scale in yeast

Charles Boone

Donnelly Centre and Department of Molecular Genetics University of Toronto

Our collaborative research integrates systematic yeast genetics and high-content single-cell screening to illuminate the functional architecture of the eukaryotic cell. When the *Saccharomyces cerevisiae* deletion collection was being constructed, we were inspired to develop the synthetic genetic array (SGA) platform, which automates yeast genetics and enables the construction of more complex mutants on a large scale. Measuring colony size as a proxy for growth, we scored double mutants for both negative (synthetic lethal or sick) and positive (masking and suppression) genetic interactions. Over ~15 years, we constructed almost all ~18 million possible yeast double mutants and we mapped a genome-wide genetic network, revealing a hierarchical model of cell function and pathway organization. In parallel, we expanded our systematic genetics pipeline to include single cell image-based readouts and arrays of yeast strains expressing GFP-tagged proteins for exploration of proteome dynamics and the effects of genetic perturbations on subcellular compartment morphology. Together, these complementary approaches establish a comprehensive framework for linking genotype to phenotype at scale. By combining network-level genetic data with detailed cell-level phenomics, our work defines the structure of genetic interaction networks, uncovers functional modules, and provides general principles governing cellular robustness. These integrative strategies serve as a model for systems-level genomics, offering both conceptual and methodological blueprints that extend to more complex organisms.

S. cerevisiae Whole Genome Sequencing and the recognition of inter-specific hybrids in fungal evolution

Gianluigi Cardinali

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When *S. cerevisiae* S288C and its derivates were chosen for the first ever whole genome sequencing, most biologists considered inter-specific hybridization very rare or even “illegitimate” among yeasts, suggesting that fertile offsprings could be obtained only (or mostly) by intra-specific crosses. On one side, this belief suggested using the Biological Species Concept as a tool for species delimitation, on the other it directed geneticists and phylogeneticists efforts toward the idea that yeast species are genetically impermeable groups of strains. Although evidence of inter-specific hybrids was mounting even before the publication of the whole genome, most of what we know about this topic was possible only after the whole genome was available and novel techniques allowed to massively sequence hundreds of strains from various yeast species. Keeping its nature of “model organism”, *S. cerevisiae* has been a forerunner to shed light on this fundamental genetic phenomenon among yeasts and other organisms. Now we know that this widespread phenomenon is a major driver of evolution, posing several challenges to phylogenetic reconstruction and to the understanding of gene flow among genetically-plastic organisms as the fungi. Recognition of this process has transformed perspectives in fungal genetics, influencing taxonomy, medical mycology, yeast biotechnology, and multiple fields within eukaryotic microbiology. The collective research efforts initiated thirty years ago have had a transformative impact on both the theoretical understanding and practical application of yeast genetics and related disciplines.

Phenotypic and immunogenic diversity of gut fungal isolates in pediatric Crohn's disease

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Intestinal fungal communities play a complex role in health and the pathogenesis of Inflammatory Bowel Diseases (IBD). While the contribution of fungi to IBD progression is well recognized, the mechanisms by which certain yeast strains amplify inflammation and acquire pathogenic features remain poorly understood. In this study, fecal samples were collected from 23 pediatric Crohn's disease patients, and metagenomic analyses were performed to identify microbial signatures associated with the disease and yeast species were isolated. The isolates were phenotypically characterized and stratified based on the risk of aggressive disease progression and were used in immunological tests to assess cytokine profiles. For strains with higher clinical relevance, the cell wall was analyzed by measuring structural sugars and evaluating their interaction with human immune receptors such as Dectin-1 and Dectin-2, which are known to play key roles in immune response modulation. These findings highlight the critical importance of strain-level analysis in understanding the relationship between microbial composition and the risk of disease progression. Moreover, they provide a strong foundation for developing targeted therapies, paving the way for precision medicine and personalized management of Crohn's disease.

From sequence to knowledge: thirty years of the *Saccharomyces* Genome Database

J. Michael Cherry, Stacia Engel, Gavin Sherlock

Department of Genetics, Stanford University

The completion of the *Saccharomyces cerevisiae* genome sequence was a defining moment in biology, the first fully sequenced eukaryotic genome and a catalyst for modern genomics. What followed was not simply a sequence, but a global community effort to interpret it, gene by gene and experiment by experiment, transforming raw DNA into biological understanding. Over the past three decades, this achievement has evolved from a static reference into a richly functional view of a eukaryotic cell. Central to this transformation has been the Saccharomyces Genome Database (SGD), the community resource for budding yeast genetics and biology. Since its inception, SGD has curated and maintained the reference genome sequence, genetic nomenclature, chromosome maps, and functional annotations for *S. cerevisiae*, integrating experimental results from the peer-reviewed literature with validated large-scale datasets. Through intuitive web interfaces, genome browsers, and analysis tools, SGD has enabled generations of researchers to explore gene function, phenotypes, and molecular interactions. This presentation reflects on the evolution of SGD alongside the yeast genome era and on how sustained community curation has turned a landmark genome into a living, enduring scientific resource.

The Italian microbial research platform: a model for collaborative, FAIR, and sustainable data infrastructure.

Sandro Gepiro Contaldo[1], Francesco Venice[2], Francesco Pantini[1], Dora Tortarolo[1], Antonio d'Acierno[3], Elisa Li Perottino[1], Lorenzo Bosio[1], Luca Simone Cocolin[4], Ilario Ferrocino[4], Andrea Peano[5], Patrizia Nebbia[5], Davide Carmelo Spadaro[4], Vladimiro Guarnaccia[4], Pierluigi Aldo Di Ciccio[5], Alessandra Dalmasso[5], Irene Stefanini[2], Cristina Costa[6], Fateme Sadeghian[2] , Francesca Cordero[1], Marco Beccuti[1], Giovanna Cristina Varese[2]

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In microbial research, sustainable and interoperable data sharing is essential for collaboration and reproducibility. In Europe, these efforts are led by MIRRI-ERIC, with Italy's integration driven by the SUS-MIRRI.IT project. Coordinated by the Turin University Culture Collection (TUCC), the project aims to develop research, services, and training within the Italian network of culture collections (MIRRI-IT). Through the project, a considerable amount of genomic and metabolic data has been added to the stored bioresources, unlocking their potential and increasing their relevance for the bioindustry. These activities lead to the creation of a national catalog, thereby strengthening the national and EU network of microbial biobanks. Beyond catalog development, the initiative achieved two additional outcomes. First, it defined standardized operating procedures for microbial wet-lab analyses and supported the sequencing of 390 microbial genomes generated according to high-quality standards. These resources were contributed by multiple collections with specialized objectives focused on addressing critical knowledge gaps in fungal genomics in plant and animal pathogens, including human beings, food, and environmental niches. Second, the project developed a high-performance bioinformatics service hosted at the University of Turin. The platform currently provides two workflows. The Microbial Genome Assembly workflow is optimized for long-read data and integrates multiple assembly tools to ensure high-quality genome reconstructions and enable protein prediction. The Metagenomic Analysis workflow is designed for taxonomic annotation and characterization of microbial communities and is organized into three main stages: (i) quality control and preprocessing of sequencing data, (ii) taxonomic classification, and (iii) downstream functional and diversity analyses.

Don't mess in God's backyard – Cloning comes to two cities

Terrance G. Cooper

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1976, a new era in yeast. Davis reported cloning yeast DNA into *E. coli*. With a dozen well-characterized genetic loci in hand, we wanted clones! Initially, I was off to Fink's lab to learn the yeast transformation method he and Al Hinnen were developing. When the colonies appeared, I was all in! Unfortunately, 1978 was a bad time to begin cloning. Michigan County Government imposed strict prohibitions on recombinant DNA work, halting experiments entirely. Principals met in Asilomar in search of guidelines. To avoid similar restrictions in Pittsburgh, we took a proactive, public-facing approach. I invited Paul Berg to launch the Provost's Distinguished Lecture Series—a five-day affair complete with TV interviews and radio talk show appearances. The strategy worked! Political problem solved, we initiated cloning research without public outcry or impediment. Meanwhile, Carbon's lab was cloning yeast genes by complementation, so I was out to California in 1979. The first gene I cloned was *CAR1*, followed by the *DAL* and *DUR* genes. Returning to Pittsburgh, each grad student received their own gene. DNA Sequencing? They sequenced 54Kb using the Maxam-Gilbert method, an impressive amount at the time. Sanger sequencing was reported in 1977, yet almost no one used it. Why? Fast forward to 1985. We moved to Memphis. Same political problem, you're messing in God's backyard! Headline news. Same solution, transparent public engagement. Once again, it worked! Celebration rather than resistance, including the State putting up funds for its first endowed chairs and the UTHSC MRC (Molecular Resource Center).

Leveraging the yeast genome to dissect conserved pathways in aging and disease

Vitor Costa and Vitor Teixeira

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The complete sequencing and annotation of the *Saccharomyces cerevisiae* genome had a transformative impact on the yeast research community. It enabled the systematic use of reverse genetics alongside genome-wide resources such as the deletion collection, tagged-ORF libraries, epistasis mapping strategies, and transcriptomic and proteomic profiling approaches. This powerful experimental framework enabled us to dissect molecular mechanisms underlying fundamental cellular homeostasis, particularly on lipid metabolism, redox homeostasis, organelle dynamics, autophagy, ion homeostasis, stress responses and regulated cell death. In parallel, we explored the intricate signalling networks orchestrating these processes, predominantly on pathways governed by protein kinases, phosphatases and transcriptional regulators that coordinate cellular adaptation and stress-responsive gene expression. Our work has advanced the understanding of how cells integrate environmental and metabolic cues to regulate survival, and how disruption of these processes contributes to aging and disease. Importantly, the use of genome-wide methodologies and the integration of multi-omics data with functional genetics enable a shift toward systems-level analysis, allowing the identification of key regulatory networks and cellular functions that coordinate metabolism, stress responses, and survival, including during chronological aging. Moreover, the high degree of evolutionary conservation between yeast and human genes enabled us to develop and characterize yeast models for human diseases, such as Niemann-Pick type C and seipinopathies. These models facilitated the identification of genetic modifiers and potential therapeutical targets, highlighting the translational relevance of yeast research.

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Biotechnological exploitation of biodiversity and hybridisation processes in strain development

Daniela Delneri

Manchester Institute of Biotechnology, University of Manchester, UK

Yeasts are a key class of microorganism used in industrial biotechnology. Sterility of *Saccharomyces* inter-species hybrids has been the main obstacle to any attempt of strain improvement via breeding. Breakthroughs in yeast genetics have overcome infertility and generated a large number of hybrid progenies with diverse traits allowing for quantitative genetic analysis. Such approach opens the door to an unprecedented large phenotypic space that can now be subjected to further selection and exploited for commercial biotechnological purposes. Moreover, non-conventional yeasts, with their great genetic and phenotypic diversity, represent an untapped biotechnological resource which offers significant potential for industrial strain development in the production of green chemicals. In recent years, advances in large-scale genome sequencing and the development of improved molecular tools have enhanced our understanding of fundamental biological processes and accelerated the optimisation of these yeasts for industrial applications in sustainable bio-production.

Yeast genome-scale metabolic models as a framework for multi-omics integration and metabolomics interpretation

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Metabolomics is the omics discipline devoted to the comprehensive study of metabolites, the small molecules that act as substrates and products of metabolic reactions within biological systems. As the metabolome reflects intracellular biochemical processes and environmental influences, it represents a key link between genotype and phenotype, capturing interactions among molecular layers, including the genome, transcriptome, and proteome. Within the framework of systems biology, metabolomics plays a crucial role in providing a holistic understanding of cellular functions through the integration of multi-omics data. Untargeted metabolomics approaches allow the large-scale detection of metabolites in biological samples. However, the complete identification and characterization of detected compounds remain a challenge, and no cellular metabolome has yet been fully experimentally characterized. In this context, artificial intelligence (AI) is emerging as a promising strategy to support metabolite annotation and improve the interpretation of complex metabolomics datasets. Focusing on the model organism *Saccharomyces cerevisiae*, this study evaluates recent community-supported AI-informed approaches for metabolomics data analysis, including global optimization methods, reference data-driven strategies, and machine learning–based metabolite annotation. However, the effectiveness of AI in metabolomics is constrained by limited curated datasets and heterogeneous annotation resources. Integrating metabolomics within systems biology frameworks, including genome-scale metabolic models, may therefore provide a more robust strategy for data interpretation. Accordingly, we optimized a workflow based on the genome-scale metabolic model Yeast9 to facilitate the integration of metabolomics data within a multi-omics framework. This workflow highlights the importance of well-curated, species-specific genome-scale metabolic models for supporting metabolomics interpretation within systems biology studies.

Horizontal gene transfer and adaptive evolution in wine yeasts: insights from the EC1118 genome

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The sequencing of the *Saccharomyces cerevisiae* reference genome marked a milestone in biology, providing a framework for understanding eukaryotic genome organization and function. However, early genomic studies focused mainly on laboratory strains and did not capture the diversity of industrial yeasts. To address this gap, we performed whole-genome sequencing and comparative analyses of wine strains, starting with the commercial wine strain EC1118 and extending to additional isolates. The EC1118 genome revealed large genomic regions (A, B and C) acquired from distant yeast species, providing a clear example of horizontal gene transfer (HGT) in *S. cerevisiae*. These regions are widespread among wine yeasts and are enriched in genes involved in sugar and nitrogen metabolism, supporting their role in adaptation to the winemaking environment. Some of these regions show variation in gene content and structure across wine and related fermented beverage strains. Region C, in particular, reflects a complex history of large genomic region acquisition followed by gene rearrangements and losses.

Region C contains *FOT* (Fungal Oligopeptide Transporter) genes, a key example of adaptive innovation in wine yeasts. These transporters, acquired from *Torulaspora microellipsoides*, enable utilization of oligopeptides as an additional nitrogen source in grape must and are conserved in wine yeasts, suggesting an adaptive role. Functional studies demonstrated that *FOT* genes confer a selective advantage under enological conditions by improving nitrogen uptake and fermentation performance.

Altogether, these findings challenge the classical view of strictly vertical genome evolution and establish HGT as a major driver of adaptation in wine yeasts.

A genome sequence of the species *Saccharomyces cerevisiae*

Fred S. Dietrich

Duke University, Molecular Genetics and Microbiology Department

Our completion thirty years ago of the first eukaryotic genome, that of a strain of *S. cerevisiae*, was a milestone in modern biology, in particular when coupled with the development of the *Saccharomyces* Genome Database (SGD). This was followed by a period of sequencing of one species, one strain. Now with the massive improvements in computer hardware, DNA sequencing technology, and artificial intelligence over the subsequent decades it is possible to move into a new period of genomics. For any fungal species it is now quite feasible to sequence thousands of complete genomes. For *S. cerevisiae* the thousands of genomes sequenced reveals the core genes and genes of variable occurrence; the central region of the genome where gene order is extremely stable and the variable sub-telomeric regions. In addition, there are new transposons, new genes, novel tRNA genes, sequence variation, exchange of genes between related species, annotation errors, and numerous other stories. An ongoing challenge is how to take 10,000 genome sequences, 60 million genes, and build a “genome sequence of a species”. Once again *S. cerevisiae* is the perfect model organism for this research. We are currently trying an approach to structure a database of *S. cerevisiae* “curated” and searchable with AI and other tools. This is particularly important for fungal pathogens where what is important is not the sequence of a reference genome but understanding the diversity in the genomes of the species, and how those variations correlate with pathogenicity, drug resistance, and other clinically relevant traits.

Unveiling the microbiome biodiversity and biogeography of spontaneous wine fermentations through shotgun metagenomics

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Modern winemakers commonly inoculate grape must with commercial *Saccharomyces cerevisiae* strains to obtain controlled fermentations and reproducible products. However, wine has been produced for thousands of years using spontaneous fermentations (SP) from wild strains, a practice experiencing a revival among small producers. Despite widespread historical usage and some recent geographically scattered metabarcoding studies, much remains to be known about the ecology, evolution, and functional potential of the microbial communities in SP. Here, we investigate the microbial biodiversity of 33 SP must metagenomes from 21 Italian estates and compare them with publicly available shotgun datasets from Germany, Spain and Australia. We reconstructed MAGs for functional analyses, inferred strain-level phylogeny of *S. cerevisiae*, and curated a wine-specific Kraken2 database for taxonomic profiling to overcome the under-representation of oenological taxa in reference databases. We found clear country-level biogeographical structure, with a small global core microbiome within a large variable pan-microbiome. The *S. cerevisiae* phylogeny placed most SP strains within the wine clade and revealed no clear geographic structuring or distinction between spontaneous and commercial strains. We are currently testing the stability of the microbial profiles over time and the ecological origin of *S. cerevisiae* strains (grapevine versus cellar) by analysing multiple time points and microvinified samples. Overall, our results support a microbial terroir of spontaneous wine fermentations microbiomes across countries, while *S. cerevisiae* populations are genetically homogeneous within the wine clade.

DNA sequencing in the early 1990s

Bernard Dujon

Sorbonne Université & Institut Pasteur, Paris, France

The systematic sequencing of the genome of a reference strain of the yeast *Saccharomyces cerevisiae* started in 1989 and was completed 7 years later as the result of a collaborative effort of 633 authors from 96 laboratories in 20 different countries. Such an enterprise, hardly imaginable with today's technological standards, played a most important role at its time not only by delivering the first complete sequence of a eukaryotic genome to the scientific community but also by promoting a friendly collaborative spirit within the yeast research community. Using documents still available in my files, I will try to illustrate this period that now belongs to history and to imagine how our present may be perceived in 3 decades after now.

Decoding yeast life cycle complexity from genomes

Cintia Gómez Muñoz, Louis Ollivier, Nina Vittorelli, Guillaume Achaz, Fanny Pouyet, ***Gilles Fischer***

CNRS – Sorbonne Université

The canonical life cycle of *Saccharomyces cerevisiae*, established over 80 years ago, predicts predominantly homozygous diploid populations because frequent inbreeding through haploselfing and intratetrad mating should rapidly eliminate heterozygosity. Yet natural populations are often highly heterozygous and frequently polyploid, with polyploidy strongly associated with heterozygosity. To resolve this paradox, we first investigated mating-type switching, the process enabling haploselfing in homothallic strains. We identified multiple independent losses of switching caused by *HO* loss-of-function mutations and structural variation at the *HML*/*HMR* loci. At least 27% of strains are heterothallic, representing a minimum of 13 independent evolutionary transitions. We showed that heterothallism is strongly associated with both elevated heterozygosity and polyploidy. We next discovered a previously undescribed route to polyploidization, termed Sporulate-Endoreplicate-Mate (*SEM*). During germination, postmeiotic endoreplication produces mating-competent diploid spores that mate with sibling spores, generating stepwise transitions from diploidy to triploidy and tetraploidy. Hallmarks of natural polyploids, including frequent triploidy and characteristic allele balance ratio are consistent with iterative *SEM* cycles being the predominant natural route to polyploidy in yeast. Finally, population genomic analyses reveal pervasive admixture among ancestral lineages, indicating that outcrossing has played a much greater role than previously recognized. Together, these findings show how genomes uncover unexpected reproductive strategies that maintain heterozygosity and drive polyploid evolution in yeast.

A multi-omics characterization of marine basidiomycete yeasts with plastic-degrading potential

Matteo Florio Furno[1], Francesco Venice[1], Sadeghian Fateme[1], Matteo Chiarello[2], Federica Spina[1], Costanza Torchia[1], Angelica Laera[1], Giovanna Cristina Varese[1]

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Microplastic (MP) pollution represents a critical environmental challenge, severely impacting marine ecosystems and biodiversity. This study investigates the genomic, metabolomic and phenotypical traits of four marine basidiomycete yeasts isolated from sediment-associated MPs in the Livorno region (Italy), highlighting their potential role in plastic depolymerization. The genomes of *Cystobasidium slooffiae* and *Sakaguchia dacryoidea* (Cystobasidiomycetes), *Vishniacozyma carnescens* (Tremellomycetes), and *Kondoa aeria* (Agaricostilbomycetes) revealed a high abundance of genes encoding putative plastic-degrading enzymes, including esterases, laccases, and hydrophobins potentially involved in MP adhesion. Notably, evidence of horizontal gene transfer, such as a bacterial-derived plastic depolymerase identified in *C. slooffiae*, suggests evolutionary adaptation to MP-rich environments. Metabolomic profiling by mass spectrometry revealed a diverse array of bioactive compounds, including terpene-like molecules with potential biotechnological relevance. In parallel, transcriptomic (RNA-based) analyses are currently ongoing to identify the enzymes actively involved in the degradation of polyurethane, including both polyester- and polyether-based formulations. Overall, these findings support the contribution of marine yeasts to MP degradation processes and provide new insights into their adaptive strategies in polluted marine ecosystems. The studied strains emerge as promising candidates for sustainable bioremediation approaches and bio-based innovation.

The accidental genomicist: the importance of being in the right place at the right time

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How did a journeyman yeast geneticist come to play a role in the worldwide project to determine the sequence of the yeast genome? The short answer comes from Isaac Newton: he stood on the shoulders of giants. I will make the case that my colleague Maynard Olson was the first person to “do genomics,” and tell how that led Bob Waterston to build a large-scale DNA sequencing center at Washington University in St. Louis. I will describe how I came to have the privilege of helping that sequencing center contribute to the sequencing of the yeast genome.

Post-translational modifications of ATP synthase modulate mitochondrial bioenergetics in yeast

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Post-translational modifications (PTMs) are key regulatory mechanisms that modulate protein activity, stability, localization, and interactions. Phosphorylation is a well-characterized, reversible modification that controls signaling, metabolism, and stress responses. In contrast, AMPylation (adenylylation) has recently emerged as an important PTM, involving covalent attachment of AMP to residues that can also be phosphorylated. Evidence suggests that AMPylation and phosphorylation may act cooperatively or competitively, adding complexity to cellular regulation. Using a large-scale approach to identify AMPylated mitochondrial proteins in wild-type cells and in strains lacking Fmp40—the only known AMPylase in *Saccharomyces cerevisiae* —we identified seven AMPylated subunits of ATP synthase, many modified at sites also known to undergo phosphorylation, underscoring the complex PTM-based regulation of this enzyme. We demonstrate that AMPylation/phosphorylation of Ser29 in the δ subunit (Atp16) modulates ATP synthase activity and oxidative phosphorylation (OXPHOS) coupling under both fermentative and respiratory conditions, resulting in increased respiratory control ratios and enhanced ATP production relative to oxygen consumption (P/O ratio). This regulatory mechanism is critical for maintaining mitochondrial membrane potential (ΔΨ). In contrast, blocking AMPylation/phosphorylation of Atp4 ATP synthase subunit, leads to a more pronounced decrease in ΔΨ, whereas alterations in respiratory control ratios are opposite to those observed for the Atp16-S29 substitution. Our findings indicate that OXPHOS coupling is regulated in a complex manner by PTMs of ATP synthase subunits. Given that mutations in ATP synthase genes underlie numerous inherited disorders, elucidating the interplay between AMPylation and phosphorylation is essential for understanding the molecular mechanisms governing OXPHOS and its disease-associated dysregulation.

About wine yeast diversity: adaptation to grape must and its unexpected consequences

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What drives the diversity of *S. cerevisiae* yeast strains that perform wine fermentation? Genetic and genomic studies over the past 20 years have shown that wine and flor strains form differentiated populations. Using genomic approaches, we identified and demonstrated the role of the alleles of several genes in the adaptation to the velum of biologically aged wines and confirmed the role of others in the wine environment. In order to better understand how yeast adapted to the wine environment, we sought to recapitulate wine yeast adaptation using three recombinant populations derived from wine strains, Mediterranean oak strains (as a grape must-naive population), or crosses between strains from both origins. These populations were grown for 24 consecutive fermentations in a typical Sauvignon grape must. This experimental evolution improved the fitness of the recombinant Mediterranean oak/wine populations and revealed shifts in allelic frequencies at specific regions, including *SSU1* and *ECM34*, which are involved in sulfite resistance; *MET10*, which is involved in sulfide reduction, as well as other regions. Finally, while studying the characteristic copper adaptation of wine yeast we observed an unexpected consequence: amplification of the *CUP1* genes activates the sulfur assimilation pathway, which may lead to excessive H_2S production. In conclusion, adaptation of *S. cerevisiae* to the wine environment has been a complex process involving variation across multiple genomic regions, with some adaptive genetic changes impairing wine quality.

Yeast display technology enables rapid discovery of potent macrocyclic peptide ligands against diverse protein targets

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Macrocyclic peptides are valuable molecular scaffolds for drug development, bridging the gap between small molecules and large biologics. We recently developed a yeast-based combinatorial platform for the high-throughput screening and characterization of these ligands. By integrating flow cytometry with next-generation sequencing, our platform can screen millions of variants per hour, allowing for real-time monitoring and the precise tuning of binding properties. In this presentation, I will discuss our progress in applying yeast display technology to rapidly generate and molecularly evolve macrocyclic peptides with optimized binding properties for the development of potential therapeutics.

Sequencing subtelomeres: shedding light onto the dark matter of the genome

Ed Louis

University of Leicester

Through the end of last century and into this one, genome libraries were the basis of sequencing projects. The ends of chromosomes posed two problems for libraries and genome projects through those years with the yeast genome being the prime exemplar and the means to solving these problems. First, the nature of the telomere structure made them difficult to clone in any of the conventional library techniques of the time resulting in a 60-fold reduction in clones representing telomeres and the adjacent subtelomeric regions. Second, even if present in in a clone, the repetitive nature of subtelomeric regions makes them nearly impossible to map back to a unique genome location/chromosome end. Individual subtelomeric repeats had been studied by integrating unique sequences, allowing a specific repeat to be cloned and analysed. Modifying this technique to integrating unique sequences, including an *E. coli* vector, into the telomere tract itself allowed each chromosome end to be individually marked uniquely and mapped to specific locations. This solved both problems as the adjacent telomere and subtelomere could then be cloned directly into *E. coli* for subsequence sequencing or the unique sequence could be an anchor for long range PCR and sequencing of specific ends. The yeast genome was completed in this way. Modern long single molecule sequencing solves the problems today but for at least a decade the first yeast genome was the most complete.

A glimpse into cell death mechanisms for sustainable yeast biotechnology: the MSCA Doctoral Network “Understanding and Postponing Yeast cell Death (UPsYDe)”

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Yeasts are widely used as microbial cell factories to convert renewable feedstocks into valuable products, including biofuels, proteins, pharmaceuticals and lipid-derived compounds. While *Saccharomyces cerevisiae* remains the best-studied industrial yeast, non-conventional species such as *Komagataella phaffii*, *Yarrowia lipolytica* and *Debaryomyces hansenii* offer important traits for biotechnology, including methylotrophy, lipid production and tolerance to extreme conditions. The productivity and sustainability of yeast-based bioprocesses depend strongly on how long cells remain viable and productive. However, yeast cells have a limited lifespan and can die through distinct, regulated cell death (RCD) pathways. Although RCD has been extensively studied from a fundamental cell biology perspective, its role under industrial process conditions remains poorly understood, especially in non-conventional yeasts. UPsYDe (https://upsyde.eu/) aims to decipher how yeast cells die under industrially relevant conditions and to use this knowledge to improve yeast bioprocesses. By combining yeast cell biology, quantitative physiology, biotechnology, fermentation technology, systems biology and synthetic biology, UPsYDe will investigate cell death mechanisms, identify genetic and process-related triggers, and develop strategies to prolong productive lifespan. The network will use *S. cerevisiae* as a benchmark and extend its approach to *K. phaffii*, *Y. lipolytica* and *D. hansenii* and other species. Key objectives include developing rapid methods to distinguish yeast cell death phenotypes, identifying genetic and environmental factors involved in cell death, studying cell heterogeneity, and integrating these insights into dynamic metabolic models. UPsYDe will train a new generation of doctoral researchers able to connect fundamental yeast biology with industrial biotechnology. By presenting the network at this conference, we aim to increase the visibility of UPsYDe’s scientific objectives, share its interdisciplinary approach with the yeast research community, and highlight the relevance of yeast cell death for both fundamental biology and applied bioprocess development. This dissemination will help create awareness of the network’s activities and open opportunities for future scientific exchange, collaboration and translation of UPsYDe findings into more robust and sustainable yeast-based processes.

Identification and enrichment of extrachromosomal circular DNA (eccDNA) in *Saccharomyces cerevisiae* extracellular vesicles

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Extrachromosomal circular DNAs (eccDNAs) are independent, double-stranded DNA molecules derived from chromosomal loci that play a fundamental role in gene regulation, environmental adaptation, and genome plasticity by enabling rapid gene copy number variations. While extracellular vesicles (EVs) are established mediators of intercellular communication through the transfer of proteins and RNAs, their role as carriers of eccDNA in fungi is still unknown. In this study, we investigated the eccDNA cargo of EVs from four *Saccharomyces cerevisiae* strains isolated from diverse ecological niches: winery, fermented milk beverage, social insect gut, and human intestine. The cells were cultivated and harvested during the early stationary phase. EVs were purified at the same stage from culture supernatants using differential centrifugation and ultracentrifugation, with their size and concentration validated via Nanoparticle Tracking Analysis (NTA). We employed the Circle-Seq method to specifically enrich circular DNA by enzymatically digesting linear fragments, followed by rolling-circle amplification (RCA) using phi29 DNA polymerase and high-throughput Illumina sequencing. Our results provide the first evidence of eccDNA presence within yeast-derived EVs. Comparative bioinformatic analysis between cellular and vesicular DNA, performed using the Circle-Map++ pipeline, reveals that specific eccDNA species are significantly enriched in EVs rather than being a reflection of the internal cellular pool. These findings suggest the existence of a potential selective packaging mechanism for circular DNA into EVs. This discovery highlights a novel pathway for the horizontal exchange of bioactive genetic elements, potentially facilitating rapid adaptation and genomic plasticity across yeast populations.

Systems biology of yeast metabolism

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Metabolic Engineering relies on a thorough understanding of how the many different metabolic reactions in the cell to be engineered interacts. Genome-scale metabolic models offers a very strong tool for performing quantitative analysis of how the many different reactions in the metabolic network interacts, and through the addition of kinetic and proteome constraints to these models their predictive strength has significantly improved. However, these models can also be used for integrative analysis of quantitative data, e.g. proteomics and metabolomics data. In the lecture there will be presented progress on how kinetic and proteome constraints can improve the predictive strength of genome-scale metabolic models for use in metabolic engineering. Examples will be given of both identification of novel metabolic engineering designs and of using these models for gaining novel insight into the functioning of metabolism.

Life with more than 9000 genes- a genomic resource for *Rhodotorula* yeasts

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Introduction: The genus *Rhodotorula* has high biotechnological potential due to the ability to accumulate high amounts of lipids, carotenoids, and other interesting biochemicals. Still, tools for genetic and metabolic engineering are poorly developed and not much is known about genomics of *Rhodotorula* yeasts. These yeasts are highly diverse, with intraspecific variability sometimes as big as interspecific differences. Genes have several introns and alternative splicing variants.
Objective: Providing researchers access to comprehensive information about the genomes of a diverse set of *Rhodotorula* strains.
Method: Genome were sequenced using a combination of long-read (Nanopore) and short read (Illumina) techniques, enabling assembly of large contigs almost representing chromosomes. Genomes were annotated with a variety of annotation tools.
Results: The Rhodotorula Genome Database (RGDB) contains genomes of 19 strains. Users can search by gene name or perform BLAST searches. The integrated Genome Browser enables chromosome-level visualization of genomic features, and a built-in tool primer designing.
First investigations could correlate genetic changes (gene truncations) in one R. toruloides strain with diminished lipid- and carotenoid production. In another study, a first transformation system was established in another *Rhodotorula* species. Genome sequencing of transformants and comparison with the wild-type strain in the database resulted in identifying integration sites in the genome.
Conclusion: The RDGB provides a valuable tool for research in this biotechnologically interesting genus. Based on the information, systematic research can be performed, enabling establishment of novel microbial cell factories and cell models for fundamental research based on these yeasts.

A renaissance in yeast genomics: sculpting the future of *Saccharomyces cerevisiae* and precision winemaking

Isak Pretorius

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Just as the Renaissance Florentine artist Michelangelo believed that every block of marble contained a hidden masterpiece waiting to be revealed, the first genome sequence of *Saccharomyces cerevisiae* revealed the biological form encoded within ~6,000 genes. Inspired by the same visionary spirit, the international yeast community united more than 100 laboratories across 19 countries to reveal the first complete eukaryotic genome sequence (1996), catalysing a renaissance in yeast genomics. Three decades later, the field has entered a new era. Yeast genomics is no longer limited to reading and comparing genomes; it is increasingly about designing and sculpting them. This presentation traces that transformation through the lens of industrial wine yeasts. Since publication of the first commercial wine yeast genome (2008), followed by the genome of the wine spoilage yeast *Brettanomyces bruxellensis* (2012), comparative and population genomics have transformed our understanding of domestication, structural variation, hybridisation, fermentation performance, stress tolerance, and aroma production. Advances in telomere-to-telomere genome assembly, pangenomics, neochromosomes, functional genomics, and machine learning are now linking genomic diversity to industrial phenotypes with unprecedented precision, enabling predictable fermentations and precision winemaking. With the international Synthetic Yeast Genome consortium nearing completion of a fully synthetic *S. cerevisiae* genome, yeast is becoming a programmable engineering platform for iterative design-build-test-learn cycles and accelerated strain innovation. We stand at the threshold of a new renaissance in which yeast genomes are not merely read but intentionally sculpted to advance biology, and the next generation of precision-engineered industrial wine yeast strains, cell factories and biohybrid systems.

Citrate homeostasis and trafficking in osmoadadaptive response of *Saccharomyces cerevisiae*

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Inter-organellar cross talk is an important component of cellular stress response allowing adaptation and survival under different unfavourable conditions. In our laboratory we are studying the peroxisomes-mitochondria communication during osmotic stress induced by sodium chloride in *Saccharomyces cerevisiae* cells. We demonstrated that osmotic stress activates the mitochondrial retrograde (RTG) pathway in WT cells, as indicated by *CIT2* upregulation, encoding the peroxisomal citrate synthase, a prognostic marker of RTG activation. Interestingly, metabolomic quantification of TCA cycle intermedia showed that in WT cells treated with NaCl, intracellular citrate levels are increased compared to control cells. The synthesis of citrate mainly derives from peroxisomes, as indicated by the up regulation of *CIT2*, and not of *CIT1* and *CIT3*. Furthermore, the involvement of the mitochondrial citrate transporter, encoded by *YHM2*, in the osmoadaptive response, is demonstrated and preliminary results suggested that there is a modulation of cytosolic NADP-specific isocitrate dehydrogenase Idp2p activity. We propose that under NaCl-induced stress, RTG-dependent citrate synthesis occurs mainly in peroxisomes and cytosol. Cytosolic citrate might be converted to 2-oxoglutarate by Idp2p and then imported into mitochondria via the Yhm2 carrier in exchange with citrate. This would allow the replenishment of TCA cycle with 2-oxoglutarate. In the absence of *YHM2*, alternative pathways might be activated with the involvement of the mitochondrial transporter Odc2 for transport of 2-oxoglutarate in exchange with malate. Our data reveals a new layer of metabolic coordination among organelles and identifies citrate shuttling as a crucial adaptive mechanism upon osmotic stress.

The yeast saga: breakthroughs that shaped modern life sciences and arts

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The history of modern yeast research closely parallels the development of molecular biology, biotechnology, genomics, and systems biology. Long before 1966, yeasts were already central to baking, brewing, winemaking, and industrial fermentation, while also serving as important experimental systems in studies of metabolism, enzymology, cytology, physiology, and microbial taxonomy. European schools of fermentation science and yeast taxonomy — particularly in Western and Central Europe — established much of the conceptual and methodological foundation upon which modern yeast biology was built. Following the establishment of the **International Conference on Yeast Genetics** and Molecular Biology in Carbondale in 1961 and the activities of the **International Commission on Yeasts** beginning in Bratislava in 1966, yeast evolved from a fermentation organism into one of the most influential eukaryotic model systems in modern science. One of the defining milestones in this yeast saga was in 1996 the completion of the first fully sequenced eukaryotic genome, *Saccharomyces cerevisiae*, coordinated through a broad international consortium with major European participation. This phase culminated in the 1996 publication of the first fully sequenced eukaryotic genome, an achievement that fundamentally transformed genomics, systems biology, and computational life sciences. Based on this we can address yeast penetration from nature to science via food in decades, which correspond well with human advancement in science and culture.

Before 1966: **Yeast–the quiet herald of the invisible microcosm**: Yeasts were mainly recognized for their roles in baking, brewing, winemaking, and industrial fermentation. They slowly penetrated into scientific focus and with their help many new scientific fields were established.

1966–1975: Foundations of Modern Yeast Genetics and Cell Biology: During this decade, advances in genetics, cytology, taxonomy, mating-type analysis, and recombination established key principles of eukaryotic inheritance and cellular regulation. Sacch. cerevisiae emerged as a tractable experimental system for studying gene regulation, mating pheromones, mitochondrial genetics, and cell-cycle organization.

1976–1985: Recombinant DNA and the Rise of Modern Biotechnology: The emergence of recombinant DNA technology transformed yeast into a central platform for molecular biology and industrial biotechnology. Yeast cloning vectors, shuttle plasmids, and heterologous gene-expression systems enabled the production of recombinant proteins and expanded the possibilities of experimental genetics. Consequently, yeast became a preferred eukaryotic host for biotechnology and industrial fermentation research.

1986–1995: Cell-Cycle Control and the Pre-Genome Molecular Revolution: Studies of yeast cell-cycle regulation identified highly conserved molecular mechanisms controlling eukaryotic cell division, discoveries that profoundly influenced cancer biology and

biomedical research. During this period, molecular genetics, gene mapping, and early large-scale sequencing efforts developed the technological and conceptual foundations required for genome-scale biology. This phase was characterized by the transition from classical molecular genetics to systematic biological analysis. It culminated in the establishment of international genome initiatives and collaborative sequencing strategies that enabled the completion of the first fully sequenced eukaryotic genome in the following period. Yeast became firmly established as the reference system for eukaryotic cell biology and molecular genetics.

1996–2005: Post-Genome Functional Genomics and Systems Biology: Following the completion of the first fully sequenced eukaryotic genome in 1996, Sacch. cerevisiae, yeast research entered a new phase in which the genome became the central reference framework for all cellular processes. This period marked a transition from individual gene studies to systematic, genome-wide analysis of biological function. High-throughput approaches including transcriptomics, proteomics, interaction mapping, deletion libraries, and computational modeling enabled functional annotation of genes at genome scale. Systems-level analysis revealed the modular and networked architecture of the eukaryotic cell, establishing yeast as the leading model organism for integrative and quantitative biology and laying the foundations of systems biology.

2006–2015: Synthetic Biology, Metabolic Engineering, and Bioart: Synthetic biology and metabolic engineering transformed yeast into a programmable cellular factory for the production of pharmaceuticals, biofuels, fine chemicals, flavors, fragrances, and recombinant biomolecules. Genome engineering, pathway optimization, and evolutionary engineering expanded industrial applications. In parallel, artists, architects, and designers increasingly incorporated microbial systems, including yeasts, into experimental cultural practices and bioart.

2016–2026: CRISPR, Biodiversity, Ecology, and Medical Mycology: This decade has been characterized by the widespread adoption of CRISPR-based genome engineering, expanded exploration of global yeast biodiversity, and growing recognition of the ecological roles of yeasts within natural and host-associated microbial communities. Research on emerging pathogenic yeasts, antifungal resistance, and multidrug-resistant species such as Candida auris underscored the medical importance of yeast biology. Simultaneously, advances in precision fermentation and sustainable biomanufacturing further broadened the industrial applications of yeasts.

Beyond 2026: Sustainable Biotechnology and Living Systems: Looking beyond 2026, yeast research is expected to remain central to sustainable biotechnology, synthetic ecosystems, precision fermentation, alternative food systems, and environmentally responsive biomaterials. Future developments will likely integrate artificial intelligence, automation, evolutionary design, and ecological engineering with synthetic genomics and systems biology. Yeast will continue to serve as a unifying experimental system demonstrating how microbial model organisms can profoundly shape both science and culture.

Yeast Researcher view: Modern yeast research was shaped by several influential scientific schools: the Carlsberg and Delft traditions of fermentation physiology and industrial

microbiology; the CBS/Dutch and Central European schools of yeast taxonomy and biodiversity; the American schools of molecular genetics and recombinant DNA research; the British fission-yeast cell-cycle tradition; and the European genome-consortium model that culminated in the first complete eukaryotic genome sequence in 1996. All this would not be possible without culture collections. The first public microbial culture collection was established in Prague in 1890 by František Král. Since then, culture collections evolved into a global infrastructure comprising nearly 800 registered microbial culture collections in more than 70 countries, preserving more than three million microbial strains, including numerous specialized yeast repositories located in 78 countries and regions as listed by the World Data Centre for Microorganisms (WDCM).

The yeast view: At the time of the completion of the first fully sequenced eukaryotic genome in 1996, yeast taxonomy recognized approximately 100 genera comprising more than 700 described species, according to the fourth edition of The Yeasts: A Taxonomic Study edited by Kurtzman and Fell (1998). By 2026, advances in molecular phylogeny, environmental sequencing, and global biodiversity exploration had expanded the recognized diversity to nearly 2,000 species distributed among more than 242 genera, reflecting a profound transformation in our understanding of yeast evolution and ecology (theyeasts.org).

Holistic view: Across more than six decades, yeast research has linked fundamental biology, technological innovation, ecology, medicine, industry, and culture, while also inspiring interdisciplinary collaborations with design, architecture, and bioart. Dedicated yeast research groups expanded from only a few dozen laboratories worldwide in the 1960s to several hundred by the time of the yeast genome sequencing in 1996. In the post-genomic era, yeast research became increasingly distributed across molecular biology, biotechnology, and systems biology laboratories, resulting today in approximately 150–250 core yeast-focused groups, embedded within a much larger global network of several thousand laboratories using yeast as a model system.

Ecological and metabolic characteristics of yeasts associated with the silverfish *Lepisma saccharina*

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Microbiomes associated with insects provide valuable systems for studying microbial adaptation to specialized ecological niches. Most available studies focus on insects feeding on simple sugars, whereas microorganisms associated with hosts exploiting polymer-rich substrates remain comparatively understudied. The silverfish Lepisma saccharina, a common indoor insect feeding on starch- and cellulose-containing materials, represents a suitable yet largely unexplored model for investigating such microbial communities. The fungal community associated with *L. saccharina* was analysed using ITS amplicon sequencing and complemented by cultivation-based isolation of yeasts. Isolates were identified using MALDI-TOF mass spectrometry, and selected strains were further characterized through morphological observations and functional assays assessing stress tolerance, carbon source utilization, and fermentative activity under oxygen-limited conditions. Sequencing revealed a fungal community of relatively low diversity dominated by Saccharomycetes, with *Candida* and *Nakaseomyces* species representing the most abundant taxa. Although taxonomically closely related, the isolated strains displayed pronounced differences in morphology, thermotolerance, halotolerance, and metabolic profiles. Several isolates were able to utilize a broad spectrum of carbon sources, including sugars associated with lignocellulosic biomass, and produced moderate amounts of ethanol during fermentation. These results indicate that the yeast community associated with *L. saccharina* is shaped by both host-related factors and selective pressures typical of indoor environments, while maintaining substantial physiological diversity. Silverfish-associated yeasts therefore represent a promising system for studying microbial adaptation to polymer-rich substrates and may constitute a source of strains with interesting metabolic capabilities.
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Tidal exposure shapes fungal and bacterial communities in tropical sandy beaches: evidence from Djibouti coastal sediments

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Tropical sandy beaches are known as unstable ecosystems characterized by dynamic fluctuations in environmental parameters. To understand microbial adaptation in these habitats, we explored the taxonomy of communities in the supralittoral and intertidal sediments of two contrasting beaches in Djibouti: rural Sagallou-Kalaf (SK) and urban Siesta Plage (SP), collecting samples along transects perpendicular to the shoreline reflecting the tidal gradient. Sequencing of 16S rRNA and ITS2 markers revealed divergent ecological adaptabilities. Bacteria showed marked site-specific taxonomic turnover driven by sediment grain size and anthropogenic pressure, with *Escherichia-Shigella* and *Staphylococcus* dominating the rural site, and marine-degrading Marinobacter in the urban site. In contrast, fungal and yeast diversity exhibited less geographical variability and resilience to variations in sediment types, but also notable shifts along the transects. PERMANOVA demonstrated that exposure to the tidal gradient predominantly drives these communities, explaining 63% of the total variance. At the rural site, Kluyveromyces emerged as the predominant genus (>45% of the fungal community), showing positive selection in the wettest zones. This suggests a crucial adaptive advantage for tolerating osmotic shocks. The urban site hosted a broader fungal association, including environmental yeasts such as *Pichia*, *Aureobasidium*, *Rhodotorula*, the latter known for producing protective UV-shielding pigments. In conclusion, tropical beaches act as strong selective filters. While bacteria respond rapidly to local perturbations, environmental yeasts reveal a more geographically resilient adaptation. Further exploring these niches could offer new perspectives regarding stress tolerance in yeasts.

From ancient fermentations to modern mycology: detecting yeasts across millennia

Mohamed S. Sarhan & Frank Maixner

Eurac Research Institute for Mummy Studies

The sequencing of the *Saccharomyces cerevisiae* genome transformed our understanding of yeast biology. Archaeological biomaterials now offer an unprecedented opportunity to explore the long-term evolution, ecology, and domestication of yeasts through time. Our studies apply molecular and cultivation-based approaches to detect and characterize yeasts in both ancient and modern samples, aiming to evaluate their significance for understanding yeast diversity, adaptation, and human–microbe interactions. We analysed archaeological and historical specimens from the Hallstatt salt mines (Austria) and the 5,300-year-old Tyrolean Iceman using metagenomics, ancient DNA authentication, genome reconstruction, phylogenetic analyses, and cultivation-based isolation. Whole-genome sequencing and comparative genomics were employed to characterize recovered fungal taxa. In Iron Age Hallstatt paleofeces, authenticated ancient DNA revealed domesticated *Saccharomyces cerevisiae* and *Penicillium roqueforti*, providing the earliest molecular evidence for beer brewing and blue-cheese production in Europe. In the Iceman, cultivation and genomic analyses recovered viable psychrophilic yeasts including species of *Glaciozyma*, *Mrakia*, *Phenoliferia*, and *Goffeauzyma*, demonstrating long-term microbial persistence in frozen environments. Combining ancient DNA, cultivation, and genomics enables the detection of both domesticated and environmental yeasts across millennia. These findings illuminate the evolutionary history of yeast domestication, adaptation to extreme environments, and the broader diversity of fungi, extending the legacy of the *S. cerevisiae* genome into paleogenomics and microbial ecology.

From one genome to thousands, and beyond

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Saccharomyces cerevisiae has played a central role in modern biology, evolving from the first eukaryote with a complete genome sequence into a premier model for exploring genome function, evolution, and systems biology. The emergence of high-throughput sequencing and functional genomics has shifted the field beyond a single laboratory reference strain toward the characterization of thousands of isolates spanning the species' ecological and evolutionary diversity. This wealth of genomic information has uncovered extensive variation in genome content, chromosome architecture, and structural organization, providing unprecedented insight into the forces shaping yeast evolution and domestication. I will discuss how recent developments - including telomere-to-telomere genome assemblies, pangenome representations, and integrative multi-omics datasets - are redefining our understanding of genetic diversity and enabling increasingly accurate links between genomic variation and phenotypic traits. These advances establish *S. cerevisiae* as a powerful framework for deciphering the genetic basis of complex traits and for developing predictive models of genotype-phenotype relationships across eukaryotes.

Selective autophagy of cytosolic proteins in the methylotrophic yeast *Komagataella phaffii*

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Eukaryotic cells use two primary protein degradation pathways: proteasomal degradation and autophagy. Typically, autophagy is a non-selective process, responsible for enwrapping and degradation of random pieces of cytoplasm. Selective autophagy is well documented for degradation of cell organelles, like peroxisomes, whereas selective autophagic degradation of single cytosolic proteins is poorly documented. We study selective autophagy of cytosolic proteins in the methylotrophic yeast *Komagataella phaffii* (*Pichia pastoris*). It was found that cytosolic enzymes of methanol metabolism fructose-1,6-bisphosphatase, formaldehyde dehydrogenase, formate dehydrogenase are inactivated after cell shift from methanol to glucose (but not ethanol) medium and that this inactivation occurs due to vacuolar degradation of the corresponding proteins. Similar process was found to occur for model recombinant protein β-galactosidase from the yeast Kluyveromyces lactis expressed under control of *K. phaffii* promoter of formaldehyde dehydrogenase *FLD1*. The mutants of K. phaffii defective in inactivation of β-galactosidase were isolated which permitted to identify new gene *ACG1* involved in autophagy of both cytosolic and peroxisomal proteins. It was found that knock-out of several key *ATG* genes (*ATG1*, *ATG6*, *ATG15*) leads to defects in autophagic degradation of cytosolic proteins formaldehyde and formate dehydrogenases. This means that selective autophagy of cytosolic enzymes uses standard Atg proteins. Using β-galactosidase activity monitoring in cell colonies, the new mutants defective in selective degradation of the studied cytosolic proteins were isolated. Part of them was defected in selective degradation of both peroxisomal and cytosolic enzymes of methanol metabolism whereas several mutants showed defects only in selective degradation of the cytosolic enzymes of this pathway. Full genome sequencing of the isolated mutants was carried out to identify the mutated genes. The selective autophagy of the recombinant β-galactosidase was studied depending on control of the corresponding genes by promoters induced by methanol (*FLD1*) or by constitutive (*GAP*) promoters. Degradation of β-galactosidase was observed only in the case it was expressed under control of inducible by methanol *FLD1* promoter. Obtained data suggest on ties between regulation of the particular gene expression and selective autophagy of the cytosolic product of this gene in the yeast *K. phaffii*.

30 years with lovely yeasts: back to the future

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Thirty years have passed since the genome sequence of the yeast *Saccharomyces cerevisiae* was completed as the first eukaryotic genome, a milestone famously described as “Life with 6000 genes.” This achievement marked the beginning of post-genomic biology. Over the past three decades, yeast has continued to serve not only as a premier model organism for fundamental research but also as a versatile platform for biotechnological applications. My research during this period has explored both fundamental and applied aspects of yeast biology, spanning studies with model yeast and the development of industrial strains. We have investigated stress tolerance mechanisms of *S. cerevisiae* under harsh fermentation environments, including ethanol, freezing, drying, and osmotic stresses. These studies revealed that the amino acid proline plays a key role in enhancing stress tolerance and fermentation performance. Based on these findings, we proposed a new breeding concept termed “functional amino acids engineering,” aimed at developing yeast strains that accumulate specific amino acids with beneficial functions. Using this strategy, we created mutant strains overproducing proline, ornithine, leucine or phenylalanine and successfully brewed alcoholic beverages such as sake, awamori, and craft beer, with improved fermentation performance, enhanced flavor, and added a health-related image. Recently, our work has expanded toward emerging foodtech applications, including yeast-based sustainable proteins and plasmid-free genome editing technologies for precision fermentation. Looking back on “30 years with lovely yeasts,” this lecture will highlight how discoveries from fundamental yeast research can drive industrial innovation and discuss future perspectives for yeast biotechnology—truly “back to the future.”

The impact of the yeast genome on biotechnology

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The sequencing of the yeast genome had a spectacular impact on the progress of fundamental research in yeast but similarly also on applied research. Industrial yeast strains have been engineered to expand substrate consumption with xylose fermentation for second-generation bioethanol production as a classical example. The field of yeast 'cell factories', in which yeast cells are engineered to produce specific industrial bio-based chemicals, has boomed. Availability of the yeast genome sequence has facilitated enormously improvement in performance of these yeast strains. Some of these cell factories have made it to commercial application with lactic acid producing yeast as a prominent example. It enables lactic acid production at low pH avoiding the massive gypsum production associated with bacterial lactic acid production. The expansion of knowledge on the functionality of the 6000 gene products has led to new technologies with huge commercial potential, like the engineering of recyclable yeast cells with high activity of cell wall bound enzymes. Yeast with high activity of cell-wall bound sucrose isomerase enables sucrose to isomaltulose conversion in just a few hours and recycling of the yeast strongly reduces enzyme costs. The high cost of enzymes is a major bottleneck for their application in industrial biotechnology such as plastic recycling and plant fiber degumming. The most unfortunate bottleneck for expansion of these novel yeast-based technologies is still the attitude versus GMOs, whether it is a real barrier like in the food and feed industry, or just a perceived bottleneck in yeast applications with contained production processes.

From the genome sequence to modeling of biological functions: metabolism, growth, and cell cycle

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As the first sequenced eukaryote (1996), *Saccharomyces cerevisiae* is a vital model for understanding conserved cellular mechanisms in higher organisms [1] because fundamental processes—such as metabolism, cell growth, and the cell cycle—are highly conserved between budding yeast and higher eukaryotes. The *S. cerevisiae* genome sequence catalyzed the shift from classical single-gene genetics to modern functional genomics and systems biology. Whole-cell modeling is an advanced computational systems biology approach that aims to simulate the comprehensive physiological, biochemical, and biophysical processes of an entire living cell within a single unified mathematical framework. By integrating diverse, heterogeneous datasets across multiple networks, these multiscale models transition biology from a descriptive science to a highly quantitative discipline [2]. While traditional whole-cell computational modeling relies on bottom-up aggregation of individual gene products, we developed a low-resolution, top-down multiscale approach. This low-granularity framework integrates metabolism, cell mass growth, and cell cycle progression to efficiently simulate yeast populations and provide a scaffold for molecularly detailed models [3]. Our model predicts that cells with constitutive respiration fail to modulate size in response to growth conditions—a finding we experimentally validated using glycolysis and glucose-transport mutants. The model can be used as a scaffold for plugging-in models of increasing granularity, potentially allowing for a molecular description of one or more biological functions, improving the predictions from the cellular to the molecular level. We will exemplify this concept by showing data regarding the G1/S transition [3] and the ribosome assembly pathway [4]. Finally, we are extending the model to transient conditions, such as an ethanol-to-glucose shift-up. Incorporating In summary, this hybrid multiscale approach provides a robust framework for predicting cell phenotypes under diverse genetic and environmental conditions.

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Work with 6000 genes – understanding & exploiting the genomes of industrial yeasts

Kevin J. Verstrepen

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Our research focuses on characterizing, comparing and understanding industrial yeasts, and using these insights to generate superior yeasts for fermentation processes, from beer and wine to precision fermentation for biofuels, lipids, proteins and chemical compounds. Over the past years, we collected, sequenced and characterized hundreds of yeast strains from various traditional and industrial fermentation processes. Comparative genomics revealed the history and domestication patterns of today's yeasts, showing how they adapted to various industrial niches and thereby opening the door to understanding and further improving industrially-relevant phenotypes. In addition to giving an overview of the strategies we use to generate better industrial microbes, the talk will also cover a few examples of novel molecular tools that we developed to optimize genetic engineering and directed evolution approaches.

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The origin of HO endonuclease and its role in Whole Genome Duplication

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The whole-genome duplication (WGD) that occurred in an ancestor of *Saccharomyces cerevisiae* profoundly altered the biology of this species by forming hundreds of pairs of duplicated genes, many of which have diverged in function. We now know that the WGD was a hybridization between two divergent parental species, from different parts of the budding yeast phylogenetic tree. Interspecies hybrids are increasingly being detected by yeast genome sequencing projects, but the key thing that distinguishes the ancient WGD from most of the other (more recent) hybridizations is that the WGD hybrid managed to regain a complete sexual cycle, whereas many of the recent interspecies hybrids are unable to make viable ascospores. Based on data from naturally fertile interspecies hybrids in the genus *Zygosaccharomyces*, we postulate that the key steps in regaining fertility are damage to one copy of the *MAT* locus, which converts a diploid hybrid cell into a functional gamete, followed by mating-type switching, which allows two gametes to mate and form a zygote in which every chromosome can pair with an identical partner during meiosis, making the hybrid fertile. HO endonuclease, which catalyzes mating-type switching in *S. cerevisiae*, originated shortly before the WGD and we propose that it was instrumental in regaining fertility after WGD. We have discovered that HO is a domesticated member of a new type of homing genetic element – called WHO elements – that normally home into the glycolytic gene *FBA1*.

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