The fidelity of translation is dependent on the specificity of the aminoacyl-tRNA synthetases (aaRSs). But in some cases aaRSs unable reliably discriminate amino acids with similar structures. To overcome this problem some aaRSs have specific editing activities that clear the wrong amino acid: misactivated noncognate amino acids (pre-transfer editing) or mischarged tRNA (post-transfer editing). Both reactions are depend on a tRNA cofactor and required translocation to the editing site located in the separate domain.

In this work we have studied molecular mechanisms of editing by synthetases from two different classes: *Thermus thermophilus* leucyl-tRNA synthetase (LeuRSTT) from class I and *Enterococcus faecalis* prolyl-tRNA synthetase (ProRSEF) from class II. Crystal structures of the LeuRSTT revealed that the same site in CP1 domain can bind analogues of both pre- and post-transfer editing substrates. To define the possibility of pre-transfer editing in the editing site and mechanism of editing we have used biochemical, X-ray crystallography methods and methods of molecular dynamics. To define the possibility of pre-transfer editing in the editing site and mechanism of editing we have used biochemical, X-ray crystallography methods and methods of molecular dynamics. We have shown that editing of norvaline by LeuRSTT occurs mainly through post-transfer pathway. We prove the existence of tRNA-independent pre-transfer editing (hydrolysis of norvalyl-adenylate), which occurs in the editing domain. For class II ProRSEF we have found that pre-transfer editing against alanine occurs in the synthetic center of enzyme in the presence of tRNA<sub>Pro</sub>.

Crystal structures of the editing domains of LeuRSTT and ProRSEF have been used as the platforms for intensive alanine scanning mutagenesis of the key elements of the deacylation activity for that type of enzymes. In fact, we have failed to identify catalytic residues for hydrolysis within the active sites. At the same time the role of the tRNA A76 hydroxyls in ester hydrolysis has been tested and the tRNA-assisted mechanisms of post-transfer editing by leucyl- and prolyl-tRNA synthetase are proposed.

Specific Peptides (SPs) are deterministic amino-acid motifs, extracted from Swiss-Prot data, that serve as sequence markers for enzymatic functionality. When found on large strings of genomic or proteomic origin SPs provide quick enzymatic annotations. Using the criterion of coverage length (overall number of amino-acids in consistent SP hits) $\geq 7$ to provide EC annotations at levels 3 or 4, we specify the biochemical function of an enzyme on the basis of its sequence. This method has been applied to Sargasso Sea Data uncovering 220K enzymes among 1 M protein sequences, and providing an enzymatic spectrum of the metagenome.

A user-friendly tool that displays occurrences of SPs on any protein sequence that is presented as a query, together with the EC assignments due to these SPs, is available at http://adios.tau.ac.il/DME11.html.

Recently SP usage has been extended to direct search on short reads. By collecting all short reads where SPs of a given EC can be located, an estimate is provided for the abundance of its relevant genes, thus generating an enzymatic spectrum of its genomic or metagenomic source. Moreover, some of its taxonomic decomposition can be deciphered using a subset of SPs belonging to aaRS enzymes.

A subset of SPs facilitates the task of taxa counting in metagenomic data. Using a list of 4000 SPs of length $\geq 9$, belonging to a subset of EC:6.1.1. aaRS enzymes that are single genes in bacterial genomes, we identify their occurrences on given lists of short reads or contigs. Identifying the largest number of reads associated with one SP, we propose an algorithm that constructs a minimal number of fused strings that differ from each other, thus serving as estimates for the different genes that could have led to the observed reads or contigs. Short reads lead to bounds on numbers of families, while long reads or contigs lead to lower-bound estimates of numbers of strains and species.
Abstracts

L3.3 Application of bioinformatics in pharmacogenomic research
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The therapy of psychotic, depressive and anxiety disorders is related to cellular and molecular mechanisms in the brain regions controlling motivation, mood and emotions. It is believed that psychotropic drugs regulate gene transcription and translation of new proteins that are required for treatment-induced plastic changes and readaptation of the target neural systems. The aim of our research is to investigate genetic networks regulated in the brain, in response to psychoactive drugs from various clinical and pharmacological classes. We applied whole-genome microarray profiling to evaluate time-course (4 time points) of transcriptome alterations following the drug treatment (18 drugs). The gene expression data were stored in a data integration system, based on MySQL in the data layer, Java in the logic layer and AJAX (GWT) in the presentation layer. Implemented tools allow for the identification of drug-specific genomic signatures and drug-regulated transcriptional modules. Further inspection and visualization of the signatures is possible using multidimensional data analysis (PCA), co-expression analysis and heatmaps. Transcriptional modules were identified by hierarchical clustering using the metric of distance between nodes on the whole transcriptome correlation tree. The tree was built as minimal spanning tree using a Pearson correlation between the expression profiles. Using the bioinformatic tools we reveal drug-regulated gene expression networks in the brain that are formed by inducible transcriptional networks, as for example group of CREB/SRF-dependent genes that appears to be related to drug-induced neuronal activity. The observed alterations are connected to various drug-receptor interactions and pharmacological effects of the drugs on dopamine, serotonin and histamine systems. New candidate genes and novel transcriptional variants with drug and time specific gene expression profiles were identified.

Acknowledgements

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Oral presentations

O3.1 Changes in gene expression profile in primary culture of rat hepatocytes treated with interferon alpha
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Interferon alpha (IFN-α) is a cytokine of innate immune system. IFN-α is widely used in clinical practice for antiviral and anticancer therapy. Nowadays IFN-α in combination with ribavirin is the most effective therapy for viral hepatitis and associated hepatocellular carcinoma. The majority of former and current investigations of IFN-α effects on liver cells are conducted on transformed cell lines arguably stressing its importance in treatment of liver cancer but clearly omitting physiological relevance. In this work, we aimed to determine the pure response of hepatocytes to IFN-α. We cultivated primary rat hepatocytes and treated them during 3 and 6 hours with 250u/ml IFN-α — dose similar to the IFN-α concentration observed during liver regeneration (LR). The gene expression profile was assayed with Affymetrix Rat Genome 230 2.0 microarrays. In-house bioinformatics analysis included custom Bioconductor pipeline, computational identification of transcription factor binding sites, pathways and GO enrichment analysis using 3rd-party tools. 124 genes with the fold change greater than 2 were defined as differentially expressed. Validation with real-time qPCR confirmed high correspondence with the results of microarray experiment. Differently expressed genes were attributed, substantially, to GO categories related to “immune response”, but considerable enrichment was also observed in GO category “modification dependent protein degradation” pointing to IFN-α activated catabolic processes. We have analyzed whether the differential expression occurs as a result of activation of Jak/STAT, Jak/STAT/ISGF3 and p38 signaling pathways involved in IFN-α response. For this purpose we conducted the search of appropriate transcription factor binding sites for STATs (1, 3, 4, 5, 6), ISGF3, IRF1, CREB1, CEBP, NFκB, Max/Myc, MEF2A/C, NFAT, SP1, ELK1 within promoter regions of differentially expressed genes. Our results support the activation of multiple signaling pathways and corresponding transcription factors by IFN-α. The signaling pathways Jak/STAT, Jak/STAT/ISGF3 and p38 are represented in descending order according to the extent of their involvement in IFN-α response. Majority of differentially expressed genes contained binding sites for more than one of the transcription factors listed above, which may be a base for more precise regulation of gene expression, activated by IFN-α, where each transcription factor makes certain contribution to the activation of transcription. Current work is the first step towards elucidation of IFN-α role in the triggering of LR.
**O3.2**

**Structure-based characterization of GntR superfamily regulators of *Streptomyces coelicolor* A3(2)**

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Streptomycetes are soil-living bacteria with a complex life cycle. Members of this genus have large genomes and the ability of producing a broad spectrum of biologically active substances, in particular, many known antibiotics. The genome of the main model strain, *Streptomyces coelicolor*, contains more than 20 secondary metabolite gene clusters and 965 regulatory genes. Given the fact that streptomycetes are of enormous industrial importance (production of antibiotics and other products), it is essential to further elucidate regulatory mechanisms of metabolic and morphological differentiation in this taxon.

One of the most abundant and widely distributed groups of transcriptional factors in actinobacteria is the GntR superfamily of regulators. They regulate numerous processes of primary metabolism and cell differentiation. The *S. coelicolor* genome encodes 60 putative GntR-like regulatory proteins (GntRs) but, so far, no exhaustive classification of this regulators has been undertaken.

We use comparative genomic analysis to describe and characterize the putative GtnRs. Regulators of this superfamily possess a conserved N-terminal domain involved in the DNA binding and a quite diverse, heterogenous C-terminal domain involved in effector binding and/or oligomerization. Based on diversity of C-terminal domain, GntRs are divided into a few families with conserved secondary structure. The sequence analysis of these regulators showed distinguishable predicted secondary structure features. The majority of these proteins represent features of FadR, HutC, MocR and YtrA subfamilies. Several GntRs show additional secondary structure elements, suggesting a possible origin of new subfamily within GntR superfamily.

Using the reciprocal BLAST search, we identify that 12 GntRs have the orthology in all sequenced to date *Streptomyces* genomes and suggest that they are the most important for morphogenesis and/or secondary metabolism. Since the expression of many genes for GntRs is autoregulated, we've tried to find potential operator sites of GntRs by analyzing the upstream regions of these genes. Most of the examined promoters do not possess operators inferred for each GntR subfamily from *in silico* analysis of non-actinomycete GntRs. New operators are proposed for the studied genes. Further identification and verification of these sites is needed to underpin the functional roles of the studied genes.

**Posters**

**P3.1**

**Comparison of binding of 44 transcription factors to putative regulatory regions identified by histone modifications, open chromatin and conservation**

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We designed and implemented a database, named TRAM (Transcription Regulatory Areas and Motifs database), unifying representation of the data from Ensembl schemas relevant for cis-regulation (funcgen, compara and core) to the analysis layer. Among the key features of TRAM are pre-computed data on pairwise overlap on the genomic sequence of putative regulatory areas of different types, in several different cell types.

Here, we report analysis of pairwise overlap among 41 histone modifications, 44 transcription factors (TFs), two markers of open chromatin, and regions of sequence conservation from two algorithms. We focused on the overlap between the chip-seq data for the 44 transcription factors represented in funcgen v60 and the remaining putative regulatory regions. We found that the binding of TFs is highest in regions of histone modifications associated with active promoters (H3K4me2-3, H3K9ac, Pol II), high in the regions of modifications associated with active enhancers (H3K27ac) and in cis-RED promoters; and low in the regions associated with poised enhancers (H3K27me1-3). We report a notable difference between the high binding of TFs to the regions of open chromatin identified by DNase-seq and lower binding to the regions identified by FAIRE.

TF binding to the regions identified by sequence conservation was lower than to the regions identified experimentally. Interestingly, it was also low for the 400 VISTA enhancers verified experimentally, confirming that enhancer occupancy by TFs is cell and developmental stage specific.

The highest conservation of the same feature localization in different cell types was found for the markers of active promoters (H3K4me2-3) and insulators (CTCF); intermediate conservation for regions identified by Dnase1 (but not FAIRE) and markers of active enhancers (H3K27ac); whereas localization of histone markers of poised enhancers (H3K27me1-3), as well TFs binding was variable among the different cell types. To conclude: TF binding correlates well with regions of regulatory activity computationally predicted from gene expression data. TF binding is higher, and more conserved across cell types, in promoters than in enhancers. Regions of open chromatin identified by Dnase1 are more enriched in TF binding than regions identified by FAIRE.
P3.2

GenomeGems: evaluation of genetic variability from deep sequencing data

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Deep Sequencing (also known as Next Generation Sequencing or Massive Parallel Sequencing) is a revolutionary method that allows myriad amounts of short DNA fragments to be read simultaneously. Deep Sequencing of the human genome for detection of disease-causing mutations possesses great challenges. In particular, organizing the great amount of sequences generated so that mutations, which might possibly be biologically relevant, are easily identified is a difficult task. Yet, for this assignment only limited automatic tools exist. GenomeGems comes to gap this need by evaluating variability in Deep Sequencing generated genetic data in a simple tabular depiction, graphical representation and visualization for comparing multiple sequencing datasets. GenomeGems integrates well with the UCSC Genome Browse in order to create an annotated display of the genetic changes in the acquired data. As such, via automatic, clear and accessible presentation of processed Deep Sequencing data, our tool aims to facilitate ranking of genomic variance calling. GenomeGems runs on a local PC and is freely available at http://www.tau.ac.il/~nshomron/GenomeGems.

P3.3

Analysis of consequently changed signaling pathways — a novel method for analyzing microarray data

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Signaling pathways belong to a complex system of communication that governs cellular processes. They represent signal transduction from an extracellular stimulus via a receptor to intracellular mediators, as well as intracellular interactions. Perturbations in signaling cascade often lead to detrimental changes in cell function and they are a major cause of many diseases, including cancer. Identification of deregulated pathways may advance understanding of complex diseases and lead to improvement of therapeutic strategies.

We propose Analysis of Consistent Signal Transduction (ACST), a novel method for analysis of signaling pathways. Our method incorporates information regarding pathway topology, as well as data on the position of every gene in each pathway. To preserve gene-gene interactions we use a subject sampling permutation model to assess the significance of pathway perturbations. We applied our approach to four independent datasets of global gene expression profiling (vulvar epithelial neoplasia and endometriosis versus control and 2 sets of colorectal cancers-controls). The results of ACST, as well as three other methods used to analyze signaling pathways (SPIA, SEPEA and the maxmean), are presented in the context of biological significance and repeatability. We show that our method is characterized by biologically meaningful results, as well as strong repeatability between similar, yet independent, datasets.
P3.4
LEF1 and TCF7L2 are candidates for terminal selectors of thalamic neurons
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The concept of ‘terminal selectors’ that regulates terminal differentiation gene batteries (Hobert et al., 2010, Trends Neurosci), is an attractive way to envisage the role of master transcription factors in establishing characteristics of specific neuronal populations. We have recently shown that β-catenin, a cofactor of LEF1/TCF transcription factors, is constantly nuclear specifically in the thalamus and regulates expression of Cacna1g encoding an ion channel that is responsible for specific properties of thalamic neurons (Wistniewska et al., 2010, J Neurosci). We put a hypothesis that LEF1/TCF factors are terminal selectors of neurons of the thalamus.

Using Real Time PCR, we quantified expression level of genes encoding LEF1/TCF factors during postnatal thalamic development and observed that Lef1 and Tcf712 fulfill the most fundamental criterion for terminal selector genes, i.e. the maintained expression throughout the life of a neuron. Immunohistochemical analysis of β-catenin, LEF1 and TCF7L2 proteins in the adult mouse brain revealed the presence of these proteins in majority (although not all) of thalamic nuclei.

In parallel we defined thalamic regions of unique and correlated gene expression, using the Anatomic Gene Expression Atlas (AGEA) from Allen Brain Atlas. AGEA characterizes the multi-scale spatial relationship in the mouse brain as derived from gene expression data without a prior knowledge of classical anatomy. Then we collected 200 genes for each defined region using AGEA Gene Finder and visually inspected for false positives. The final lists of genes for each defined region using AGEA Gene Finder knowledge of classical anatomy. Then we collected 200 genes for each defined region using AGEA Gene Finder and visually inspected for false positives. The final lists of genes for each defined region using AGEA Gene Finder and visually inspected for false positives. The final lists of genes for each defined region using AGEA Gene Finder and visually inspected for false positives. The final lists of genes for each defined region using AGEA Gene Finder and visually inspected for false positives.

The concept of terminal selection, revealed its high therapeutic potential combined with low toxicity in the experimental mice (LD50=600 mg/kg). Thus, novel thiazolidones can be proposed for design of drugs targeting Bcl-XL antiapoptotic protein.

P3.5
Bio-evaluation of novel heterocyclic 4-thiazolidone derivatives designed for targeting Bel-XL, antiapoptotic protein
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Due to poor efficiency of classic cancer chemotherapy, more efforts are given to design of novel drugs, targeting tumor-specific vulnerabilities. In silico investigations have revealed that novel heterocyclic 4-thiazolidone derivatives can be used as effective inhibitors of Bel-XL-Bax dimerization, thus, enhancing apoptosis in tumor cells. More than 5000 compounds were synthesized at Lviv National Medical University and pre-screened in vitro at National Cancer Institute (Bethesda, USA). We have selected three compounds – Les-3120, Les-3166 and Les-3372 – that possessed the highest cytotoxicity towards tumor cells. Docking studies for their interactions with Bel-XL were performed using OpenEye software and protein Bel-XL structure (code 1YSI) taken from Protein Data Bank.

Western-blot analysis of signaling apoptotic pathways induced by these compounds in Jurkat T-leukemia cells has shown that different side chemical groups of thiazolidone molecules can determine specific mechanism of apoptosis (mitochondrial, receptor-mediated or caspase-independent) that was induced in tumor cells. Taking into account the results of our in vitro, in vivo and in silico studies, it was decided to combine in one compound two drug molecules that belong to Les-3120 and Les-3372. Earlier, we found that molecular mechanisms of pro-apoptotic action of these molecules was totally different.

As a result of such approach, two novel isomeric molecules were synthesized — Les-3661 and Les-3713 differing only in a place of substitution of phenylpyrazoline side group. While 2-substituted thiazolidone Les-3713 demonstrated modest cytotoxic activity (IC₅₀=5 μM), antitumor potential of Les-3661 (4-substituted thiazolidone) was increased more than 10 times (IC₅₀=1 μM) reaching a potential of gold chemotherapy standard – doxorubicin (IC₅₀=0.5 μM). Les-3661 acted towards target cells not only much quicker (3 h) comparing to Les-3120 (12 h). It also specifically cleaved initiator procaspases-9 and -10 involved in mitochondrial and receptor-mediated apoptosis, correspondingly. It is hypothesized that such “hybrid” molecule possesses not only tenfold elevated cytotoxicity, but combines potentials of two distinct apoptotic pathways available in its predecessors. In vivo studies of Les-3661 action towards murine NK/Ly lymphoma known by Bel-XL over-expression, revealed its high therapeutic potential combined with low toxicity in the experimental mice (LD₅₀=600 mg/kg). Thus, novel thiazolidones can be proposed for design of anticancer drugs targeting Bel-XL protein, and, thus, possessing high selectivity towards tumor cells.
Abstracts

P3.6
Identification of transcription factor STAT3 target genes and epigenetic modifications in glioma cells using whole genome chromatin immunoprecipitation

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Signal transducer and activator of transcription 3 (STAT3) is a transcription factor constitutively activated in diverse human tumors (including gliomas) and contributing to malignant transformation, tumor progression and resistance to apoptosis. Screening of small molecules inhibitors (caffeic acid derivatives) targeting Jak2/STAT3 signaling revealed inhibition of proliferation and induction of cell death, suggesting a pivotal role of STAT3 in glioma survival. Global gene expression profiling revealed modulation of numerous genes as a result of treatment and hundreds of genes were identified as potential STAT3 targets, however a small fraction of those genes was proven to be direct STAT3 targets. We mapped the genome-wide occupancy of active, phospho-STAT-3 and epigenetic modifications (H3K4me3; H3K27me3) in glioma cells by hybridization of immunoprecipitation-enriched genomic DNA to promoter microarrays (3x720K RefSeq Promoter microarrays, NimbleGen) or analysis by massively parallel sequencing (ChIP-Seq). Furthermore, putative STAT binding sites and motifs were identified computationally in a genome-wide study. Data from H3K4me3 chromatin immunoprecipitation was intersected with the data on STAT3 ChIP-chip. This analysis identified a list of 800 genes which promoters have both STAT3 binding site and H3K4me3 modification suggesting these are actively transcribed genes. Gene Ontology analysis revealed several groups of genes, including a few interesting and expected groups such as inflammatory response, cell migration, cell differentiation, positive regulation of cell proliferation, regulation of blood vessel size. The data from STAT3 and H3K4me3 study were also intersected with three sets of expression data: a set identifying genes differentiating C6 glioma cells from non-transformed glial cells and two sets of microarrays data from C6 glioma cells treated with inhibitors of JAK/STAT signaling. From this analysis we obtained a list of 250 genes which are likely to be STAT3 transcriptional targets. The most interesting hits, representing new identified STAT3 targets, are verified by chromatin immunoprecipitation followed by qPCR.

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P3.7
Short peptide sequences inhibit prokaryotic translation

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The ribosome is a highly conserved nucleoprotein machine whose function is to translate information encoded in an mRNA into a protein. All nascent polypeptides must pass through the ribosomal exit tunnel. The tunnel is lined with chemical groups which can potentially interact with the growing polypeptide, thus potentially arresting translation. We hypothesized that the incidence of certain short amino sequence might be reduced by evolutionary pressure, since these short amino acid sequences could form strong interactions with the ribosomal exit tunnel leading to translational arrest and loss of cell viability. The existence of many complete proteomes has afforded us the ability to search for sequences that exist at frequencies below their expected frequency (based on each amino acids total usage in the proteome). We have used “reverse bioinformatics” and indeed identified such highly under-represented sequences (URSs) in the proteome of E. coli and other organisms. When these URSs were experimentally incorporated into a protein expressed in E. coli, the rate of translation of the URS embedded protein, was radically diminished, both in vivo and in vitro. In addition we found that the presence of these URSs in one protein also inhibits the translation of other proteins in vitro, indicating that the rate of ribosome recycling is also inhibited. Arrest of ribosome translation by the protein containing URSs also inhibits the translation of other proteins in vivo, to an extent that causes cell death. We thus propose that knowledge of the chemical attributes of the URSs may lead to the development of a completely novel class of antibiotics. We also propose that the identification of factors lacking from an organisms, using reverse bioinformatics can be a new and useful tool for understanding the overall physiology of the organism.
Laser microdissection — how to obtain a homogeneous material for gene expression research?

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Molecular analysis are mostly carried out in heterogeneous biological material, and results obtained in this way illustrate the situations that exist in different cell types, also in cells that are not the object of our interest. An important need of many research projects is the availability of high-quality, pure and well defined cell — for example normal and cancer cells. These challenges can be overcome via the use of laser microdissection which allows separation of single cells or defined groups of cells from complex tissues almost unchanged, both morphologically and biochemically. Nowadays, this technique is increasingly used for profiling gene expression by methods such as quality real-time RT-PCR, microarrays and most recently by RNA-sequencing, what is important for characterizing molecular profiles of cell population within a heterogeneous tissue, especially in cancer research.