UNIVERSITY OF COPENHAGEN

Pharmaco-miR.org:

A web server to probe the interactions of miRNAs and traditional drugs

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Introduction

miRNAs are small non-coding RNAs, prevalent in metazoans, that negatively regulate gene expression in many cellular processes. By regulating the expression of drug metabolizing or transporting genes and drug targets, miRNAs have recently been shown to play a pivotal role in drug efficacy and toxicity and have potential clinical implications for personalized medicine. Also, a new generation of drugs target the miRNA system, either by mimicking miRNAs or inhibiting miRNA function. Like endogenous miRNAs, such novel miRNA drugs may potentially interact with existing, more traditional drugs in combinatorial treatment. We have launched a web server, named Pharmaco-miR, which allows for the probing of putative associations of miRNAs, their target genes, and drugs that rely on these genes for their function. Users can, for instance, enter a miRNA name and retrieve a list of target genes and drugs associated with these genes. This will ease the prediction of which miRNAs may interact with the function of traditional drugs and suggests that currently identified cases of miRNA-drug interactions only represent the tip of the iceberg. Furthermore, Pharmaco-miR provides access to a custom built database of experimentally verified miRNA-gene-drug interactions, named Pharmaco-miR VerSe (for Verified Sets). Pharmaco-mir is available at www.pharmaco-mir.org.

Website and Results

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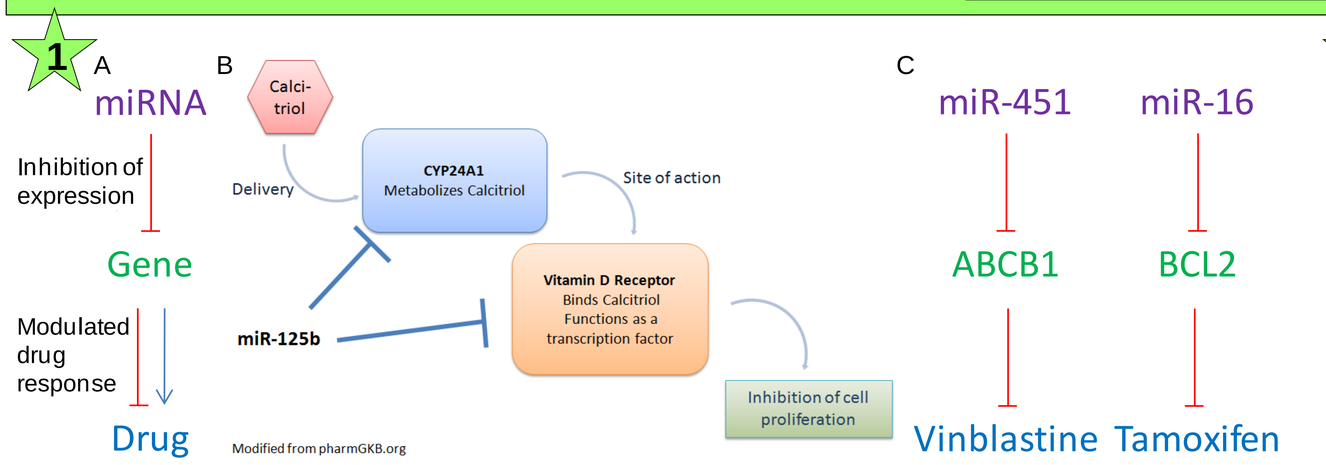

Figure (1) Principle and examples of miRNA-drug interactions for miRNA drug candidates

A) Pharmaco-miR combines information on miRNA targeting and gene-drug associations, based on the databases listed in Table 1 (below). miRNAs alter protein levels which in turn either increases or decreases drug response, depending on protein function.
B) Several examples of miRNA pharmacogenomics have been described in literature. miR-125b inhibits the calcitriol metabolizer CYP24A1 and thereby increases calcitriol levels [1]. miR-125b furthermore inhibits vitamin D receptor (VDR) expression. VDR is a co-factor for calcitriol and lower protein levels decrease calcitriol efficacy [2]. **C)** Similarly, the drug candidates miR-451 [3] and miR-16 [4] have been shown to affect vinblastine and tamoxifen efficacy through regulation of ABCB1 and BCL2, respectively [5,6].

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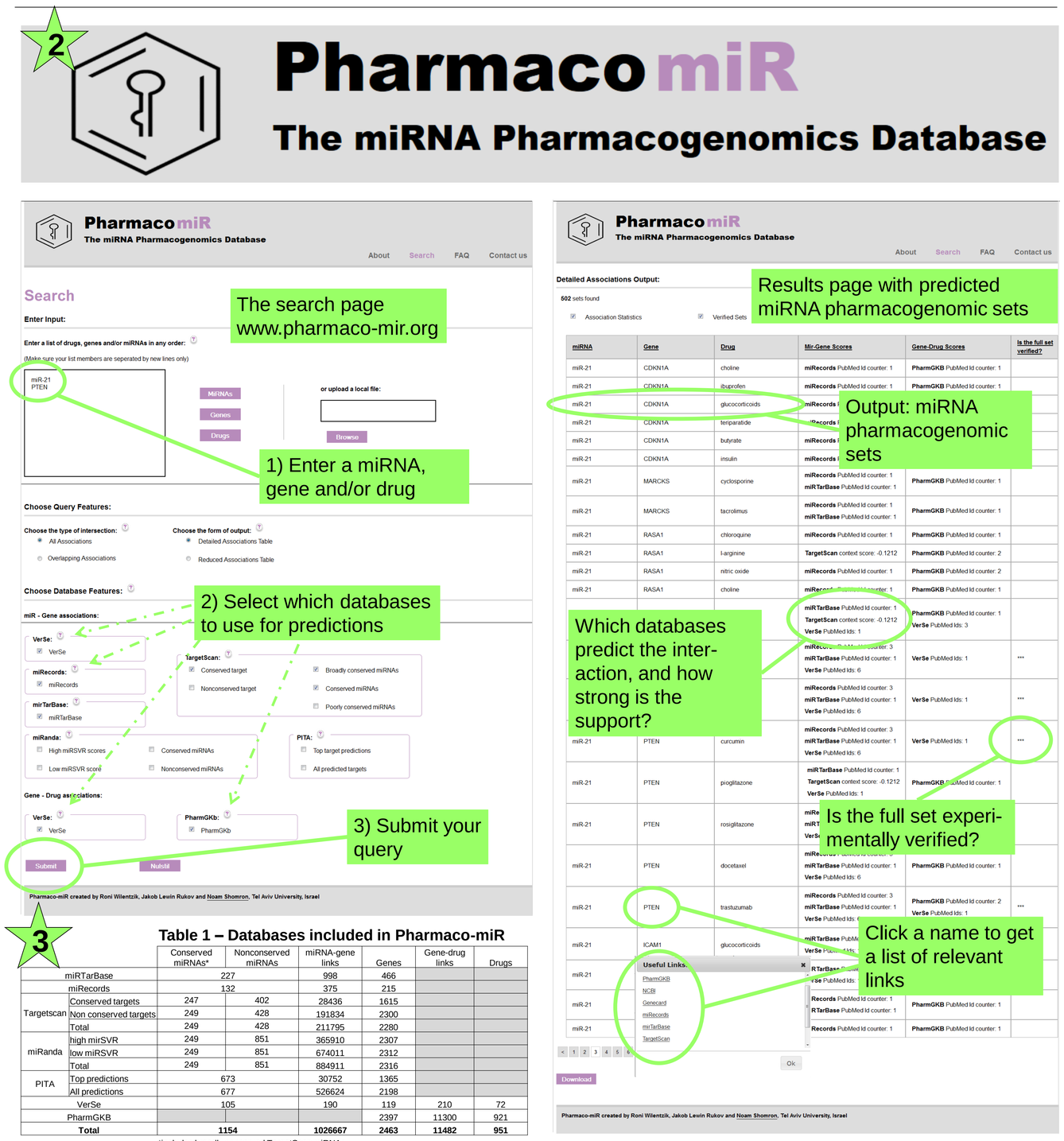

3

Table 1 – Databases included in Pharmaco-miR

		Conserved miRNAs*	Nonconserved miRNAs	miRNA-gene links	Genes	Gene-drug links	Drugs
miRTarBase		227		998	466		
miRecords		132		375	215		
Targetscan	Conserved targets	247	402	28436	1615		
	Non conserved targets	249	428	191834	2300		
	Total	249	428	211795	2280		
miRanda	high mirSVR	249	851	365910	2307		
	low miRSVR	249	851	674011	2312		
	Total	249	851	884911	2316		
PITA	Top predictions	673		30752	1365		
	All predictions	677		526624	2198		
VerSe		105		190	119	210	72
PharmGKB					2397	11300	921
Total		**1154**		**1026667**	**2463**	**11482**	**951**

*includes broadly conserved TargetScan miRNAs

4

Table 2 – miRNA candidates for oligonucleotide drugs, target genes and potential interacting drugs

miRNA	Target genes (selected)	Drugs associated with target genes (selected)
let-7a	APP, BCL2, CASP3, CASP8, E2F1, IGF2, IL6, ITGB3, KRAS, MYC, NEFM	5-fluoroucil, aspirin, beta blocking agents, cisplatin, cyclophosphamide, cytarabine, daunorubicin, dienestrol, docetaxel, doxorubicin, epinephrine, estrogens, etoposide, fluorouracil, gemcitabine, glucocorticoids, ibuprofen, irinotecan, methotrexate, paclitaxel, tamoxifen, topotecan, vincristine, warfarin
miR-122	ADAM10, ANK2, CCNG1, CDK4, CYP7A1,GYS1, IGF1R, MAPK11, NFATC1, RAC1, SLC7A1, SLC7A11,	antiarrhythmics, antipsychotics, chloroquine, cisplatin, clarithromycin, doxorubicin, erythromycin, estrogens, mercaptopurine, metformin, methadone, progesterone, quinidine,sparfloxacin, tacrolimus, trastuzumab,
miR-132	CDKN1A	celecoxib, choline, cisplatin, cyclophosphamide, docetaxel, fluorouracil, gemcitabine, glucocorticoids, ibuprofen, insulin, metformin, methotrexate, paclitaxel, trastuzumab
miR-155	APC, BCAT1, CTNNB1, CYP51A1, CYR61, FOXO3, KRAS, MSH2, MSH6NARS, PDE3A, PPL, RAB5C, SELE, SMAD2, SOCS1, VAMP3	5-fluoroucil, angiotensin ii antagonists, calcium channel blockers, antihypertensives, biotin, celecoxib, cetuximab, choline, cisplatin, docetaxel, doxorubicin, estrone, glycine, ibuprofen, imatinib, losartan, mercaptopurine, methotrexate, norepinephrine, olanzapine, progesterone, pyrimidine analogues, tamoxifen,
miR-15/16/195	APP, BCL2, BMI1, BRCA1, CCND1, CCNE1, CCND1, CDK6, EGFR, F2, CDC25A, JUN, MSH2, NFKB1, TP53, UCP2, VEGFA, WT1, BCLW, CDK6,SIRT1, VEGFA	5-fluoroucil, antiinflammatory and antirheumatic products, beta blocking agents, cannabinoids, chloroquine, cisplatin, cyclophosphamide, daunorubicin, docetaxel, doxorubicin, epinephrine, estradiol, gefitinib, gemcitabine, ibuprofen, imatinib, methotrexate, metformin, mitomycin, navitoclax, omega-3 polyunsaturated fatty acids, paclitaxel, pyrimidine analogues, sorafenib, tamoxifen, topotecan, vincristine, warfarin
miR-208	CDKN1A	choline, cisplatin, cyclophosphamide, docetaxel, fluorouracil, gemcitabine, ibuprofen, insulin, methotrexate, trastuzumab
miR-21	BCL2, CDC25A, CDK6, CDKN1A, E2F1, EGFR, FAS, ICAM1, IL1B, MSH2, PDCD2, PDCD4, PTEN, RASA1, RECK, SLC16A10, TGFB1, TGFBR2	5-fluoroucil, antineoplastic agents, celecoxib, cetuximab, chloroquine, cisplatin, cyclophosphamide, cytarabine, daunorubicin, docetaxel, estrogens, etoposide, gefitinib, geldanamycin, gemcitabine, glucocorticoids, ibuprofen, imatinib, insulin, irinotecan, losartan, methotrexate, oltipraz, opioids, paclitaxel,tacrolimus, tamoxifen, taxol, topotecan, vincristine
miR-33a/b	ABCA1, NPC1	allopregnanolone, atorvastatin, fenofibrate, fluvastatin, hmg coa reductase inhibitors, metoprolol, phospholipids, rosiglitazone, torcetrapib, tretinoin
miR-34	BCL2	5-fluoroucil, cisplatin, cyclophosphamide, cyclosporine, daunorubicin, docetaxel, doxorubicin, etoposide, gemcitabine, mitomycin, paclitaxel, tacrolimus, tamoxifen, topotecan, vincristine
miR-451	ABCB1, AKT1, MAD2, MIF	amitriptyline, caffeine, calcium channel blockers, citalopram, codeine, daunorubicin, docetaxel, erlotinib, erythromycin, escitalopram, folic acid, gefitinib, grapefruit juice, heroin, insulin, irinotecan, methadone, methotrexate,nicotine, paclitaxel, progesterone, protease inhibitors, pyrimidine analogues, quinine, tamoxifen, testosterone, tetracycline, vincristine, vitamin d and analogues, warfarin

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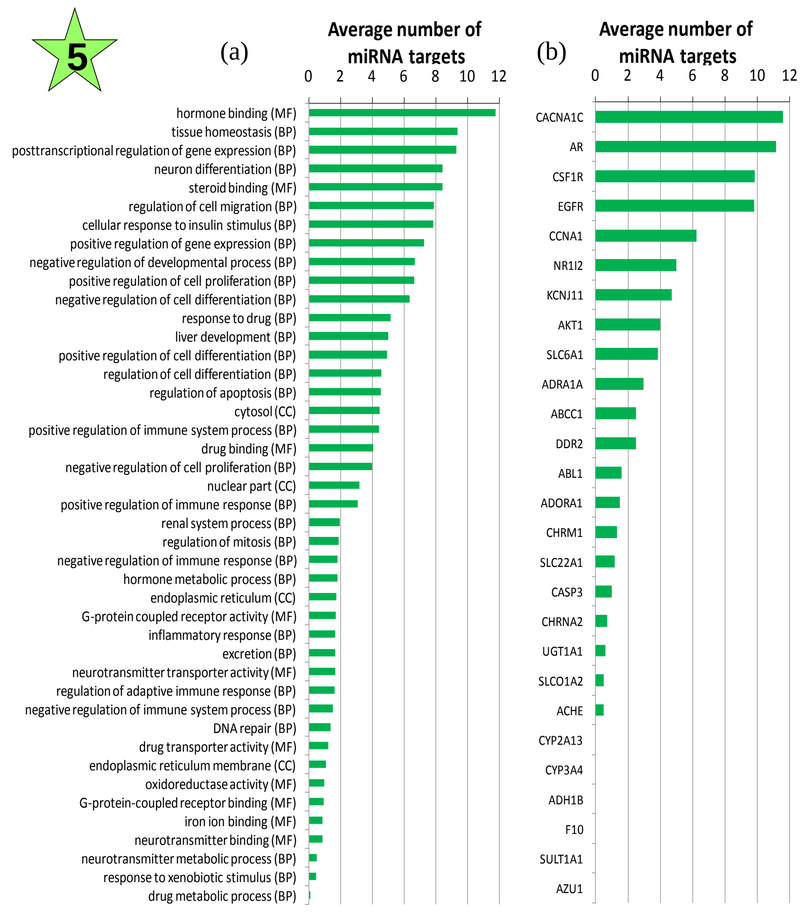

Figure (3) Average number of genes in selected Gene onto-logy (GO) groups and gene families.
(a) Gene ontologies (GOs) consist of genes grouped by a shared biological process (BP), molecular function (MF) or cellular compartment (CC). GO therefore allow for comparison of trends between groups of genes with shared features. We have identified GO groups with an overrepresentation of pharma-cogenomics relevant genes using Pharmacogenomics Knowledge Base [7] annotations. For each group the average number of conserved miRNA target sites (as predicted by TargetScan [8]) was calculated. See [9] for further details. (b) Target number distribution in genes grouped in families. Genes were grouped with closest paralogs into gene families. Each family is shown with a representative gene symbol. See [10] for further details.

Conclusions

miRNA-pharmacogenomics studies the impact of miRNAs on drug function. The advent of miRNA therapeutics introduces the question of how miRNA drugs may interact with (and modulate the function of) more traditional drugs. In fact, several miRNAs undergoing drug development have been shown to affect drug function. Pharmaco-miR makes it possible to predict interactions between miRNAs, target genes and drugs that rely on these genes for their function. It therefore facilitates the prediction of drug interactions in combinatorial treatment including miRNA drugs. A wide range of drugs (Table 2) and drug related functions and families (Figure 3) are predicted to be affected by miRNAs, many of which are candidates for miRNA drugs. Pharmaco-miR is available at www.pharmaco-mir.org.

References

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