



Erbsubstanz: Grundlagen und Klinik mi-RNA, zirkulierende DNA

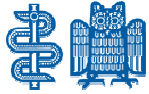
26.11.2010

Ingolf Juhasz-Böss
Homburg / Saar



Klinische Erfahrungen

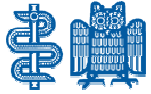
- zirkulierende miRNA erstmals 2008 im Serum von B-Zell Lymphomen beschrieben
(Lawrie et al., Br J Haematol 2008)
 - Septische Patienten
 - Diabetes mellitus
 - KHK
 - Lebererkrankungen (z.B. Hepatitis)
 - Karzinomen
 - Rechtsmedizin
- > 200 miRNAs im Serum Gesunder nachweisbar



Nachweis von miRNA

Table 1. Differential Expression of Circulating miRNAs under Various Dysfunctional Conditions

miRNA	Body fluids	Diseases	Alteration	Refs.
miR-155, miR-210, miR-21	Serum	DLBCL	UP	59
miR-141	Plasma	Prostate cancer	UP	38
miR-25, miR-223	Serum	NSCLC	UP	37
miR-155	Serum	Breast cancer	UP	64
miR-155, miR-21	Plasma (exosomes)	Lung cancer	UP	65
miR-21, miR-141, miR-200 family	Plasma (exosomes)	Ovarian cancer	UP	67
miR-17-3p, miR-92	Serum	CRC	UP	68
miR-1, miR-122, miR-124, miR-133a, miR-192, miR-208	Serum	Acute tissue injuries	UP	70–73
miR-146a, miR-223	Serum	Sepsis	Down	74
miR423-5p	Serum	Heart failure	UP	75
miR-208a	Serum	Artery occlusion	UP	76
miR-526a, miR-527	Serum	Pregnant	UP	77
miR-141, miR-149, miR-299-5p, miR-135b	Serum	Pregnant	UP	78
miR-126, miR-182	Urine	Bladder cancer	UP	79
miR-125a, miR-200a	Saliva	Oral squamous cell carcinoma	UP	80



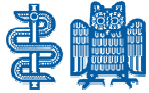
Wo kann man miRNA nachweisen?

- Serum
- Plasma
- Urin
- Speichel
- Sperma
- Vaginalsekret
- Menstruationsblut



The **ideal biomarker** should be:

- easily accessible such that it can be
- sampled relatively noninvasively,
- sensitive enough to detect early presence of tumors in almost all patients, and
- absent or minimally present in healthy, tumor free individuals.



Welche miRNA beim Mammakarzinom?

All participants (Case vs. Control)

MicroRNA name	Log2 FC	P value	AUC
hsa-miR-595	2.395719	0.002393	0.75
hsa-miR-589	2.155282	0.006985	0.6
hsa-miR-504	1.915404	0.025783	0.68
hsa-miR-518b	1.600464	0.035285	0.67
hsa-miR-483-5p	1.385806	0.037231	0.56
hsa-miR-425*	1.197242	0.027131	0.68
hsa-miR-493	1.144993	0.032888	0.7
hsa-miR-187	1.144919	0.038317	0.62
hsa-miR-431*	1.107432	0.025801	0.62
hsa-miR-1231	1.028423	0.023928	0.68
solexa-9655-85	1.003729	0.026531	0.7
hsa-miR-668	-1.00174	0.038456	0.68
hsa-miR-377	-1.08111	0.048523	0.66
hsa-miR-410	-1.17687	0.039992	0.64
hsa-miR-922	-1.24073	0.029972	0.64
hsa-miR-155	-1.26546	0.014117	0.72
HS_169	-1.29076	0.023019	0.69
hsa-miR-340*	-1.50691	0.019858	0.66
HS_200	-1.53419	0.049367	0.7
hsa-miR-432	-1.60309	0.047606	0.65
hsa-miR-574-3p	-1.66389	0.037904	0.67
hsa-miR-148a	-1.68157	0.034794	0.66
hsa-miR-181a	-2.00397	0.004354	0.72
hsa-miR-1275	-2.00526	0.008116	0.72
hsa-miR-1304	-2.51079	0.002657	0.7
hsa-miR-151-5p	-2.81719	0.000542	0.76

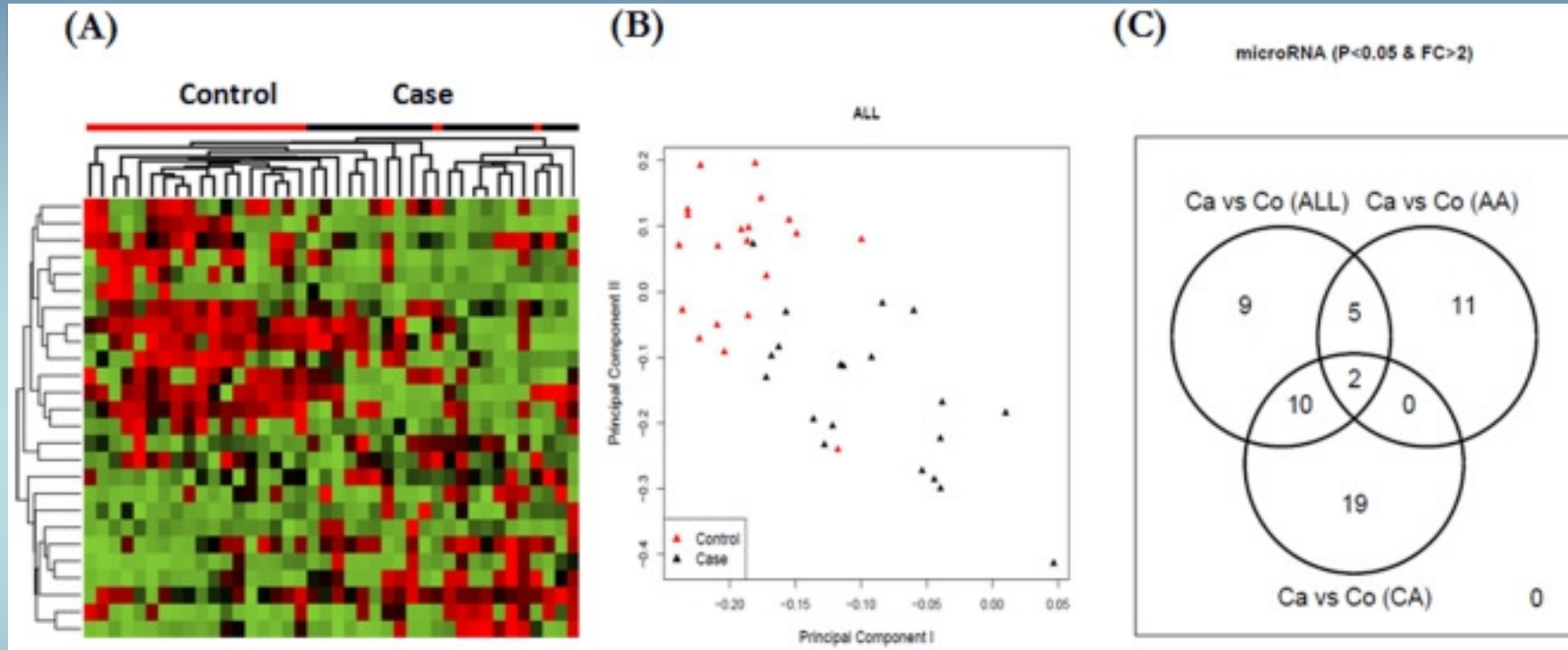
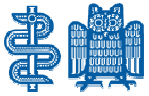
n = 40 Patientinnen

n = 20 gesund

n = 20 Mammakarzinom

26 unterschiedliche miRNA
Expression zw. gesund vs. krank

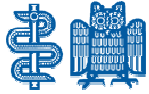
sowohl „Up-Regulation“ als auch
„Down-Regulation“ möglich



miRNA Unterschied ist
Rassen-abhängig

CA: 31
AA: 18

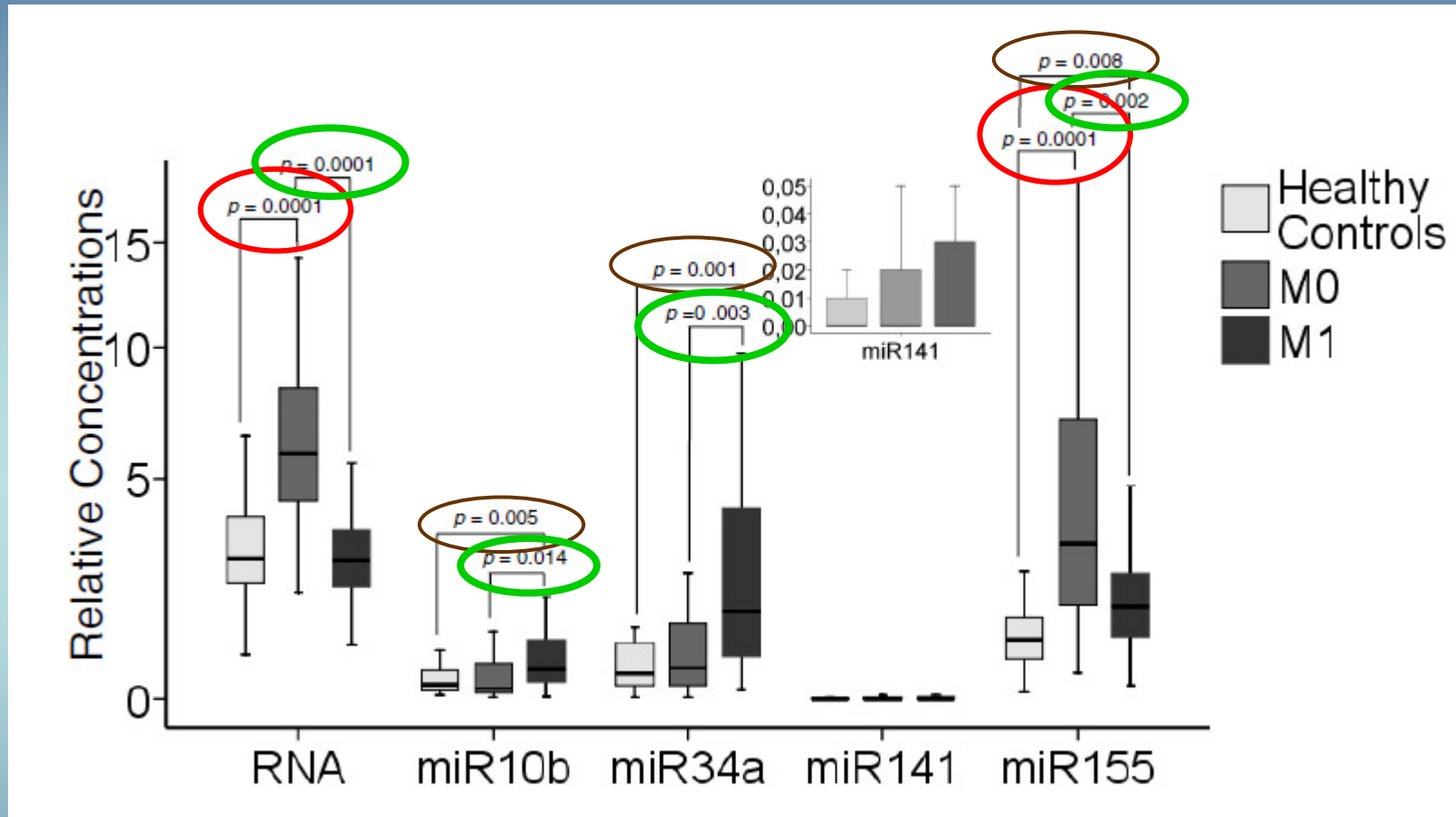
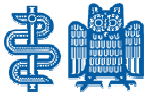
	up	down
CA	17	14
AA	9	9



miRNA & Mammakarzinom

Unterscheiden sich miRNA Spiegel
in Abhängigkeit von:

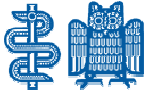
- Tumorstadium bzw.
- Metastasierung?!?



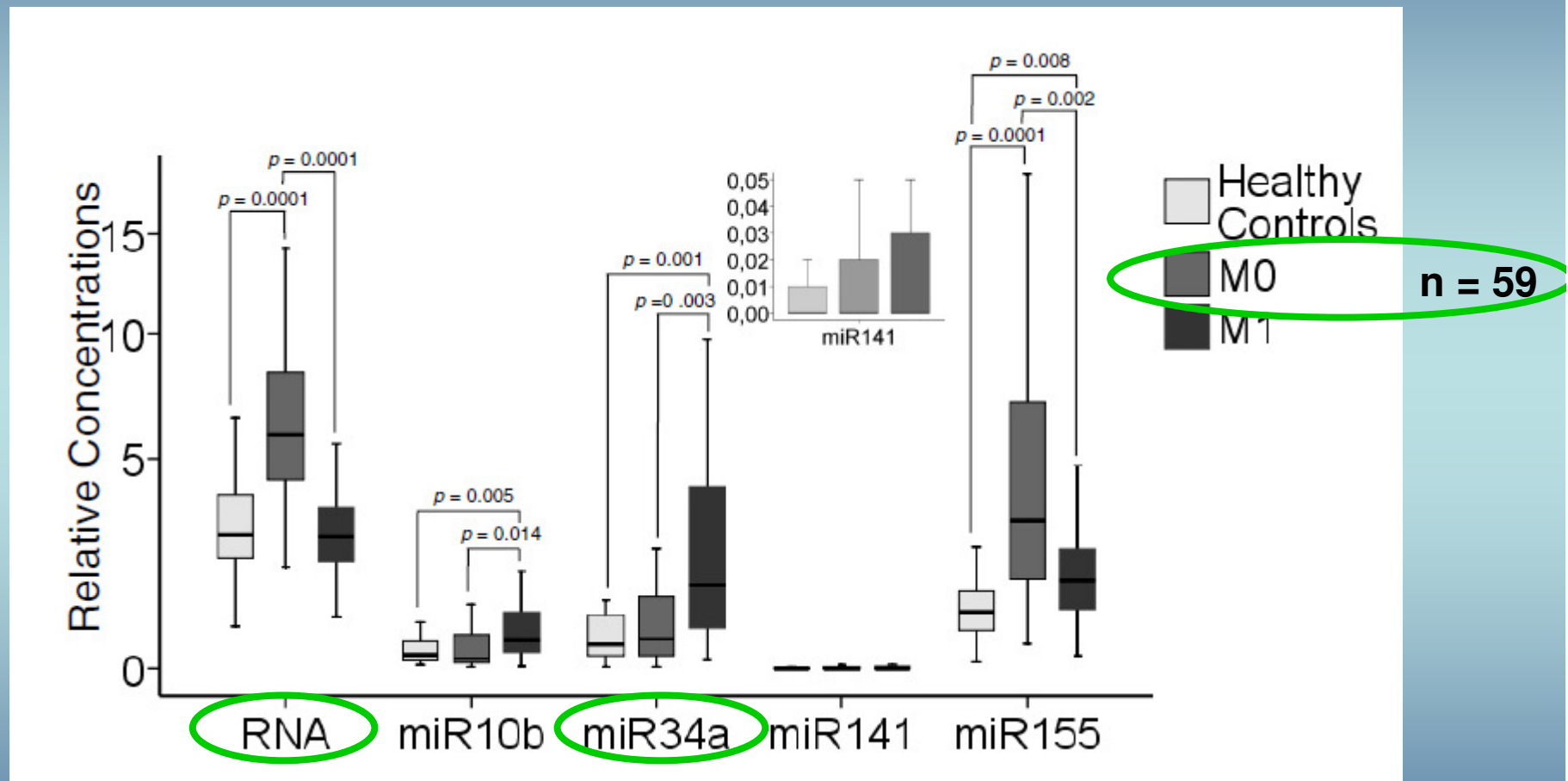
Healthy vs. M0

Healthy vs. M1

M0 vs. M1



miRNA Spiegel in Abhängigkeit von Tumorstadium



pT3 / 4 had significantly more total RNA ($P = 0.0001$) and miR34a ($P = 0.01$) than pT1 / 2



Korrelation miRNA & Mammakarzinom Tumoreigenschaften

Östrogen Rezeptor / ER:

ER positiv vs. negativ:
Heneghan et al., Ann Surg 2010

miR10b



Progesteron Rezeptor / PR:

PR positiv vs. negativ:
Zhu et al., BMC Res Notes 2009

miR155



HR positiv vs. negativ:
Roth et al., Breast Cancer Res 2010

miR155

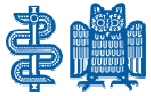




miRNA & Mammakarzinom

Eignen sich miRNA Spiegel zum

Therapie-Monitoring?!?



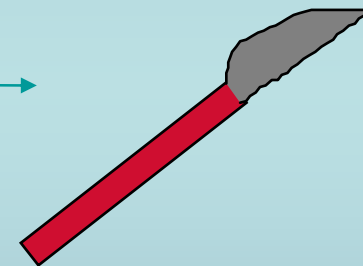
miRNA & Therapiemonitoring

Kolonkarzinom:

Ng et al., Gut 2009

- miR-17-3p:
- miR-92:

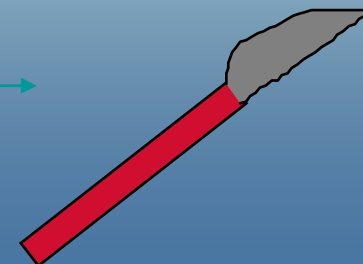
signifikant
erhöht



signifikant
erniedrigt

Mammakarzinom:

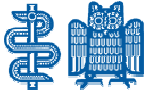
- miR-195:
Heneghan et al., Ann Surg 2010



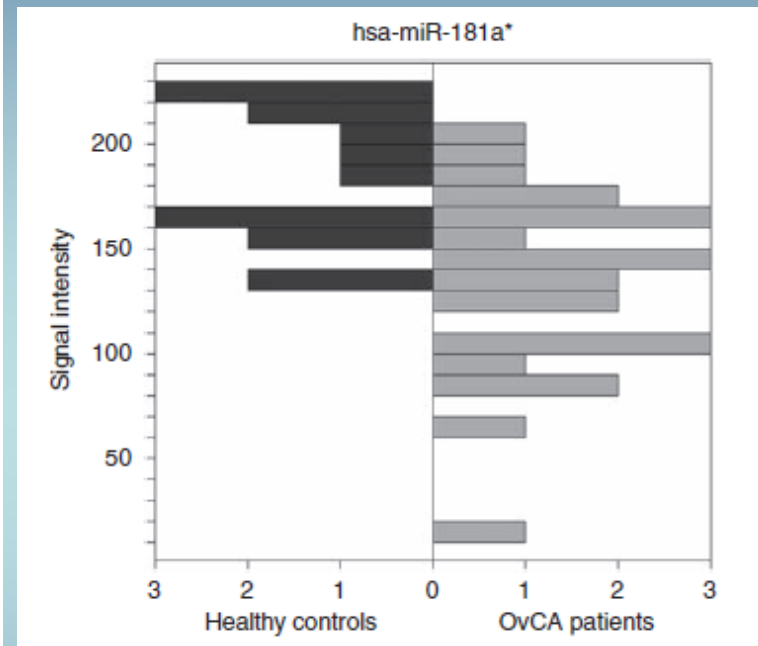
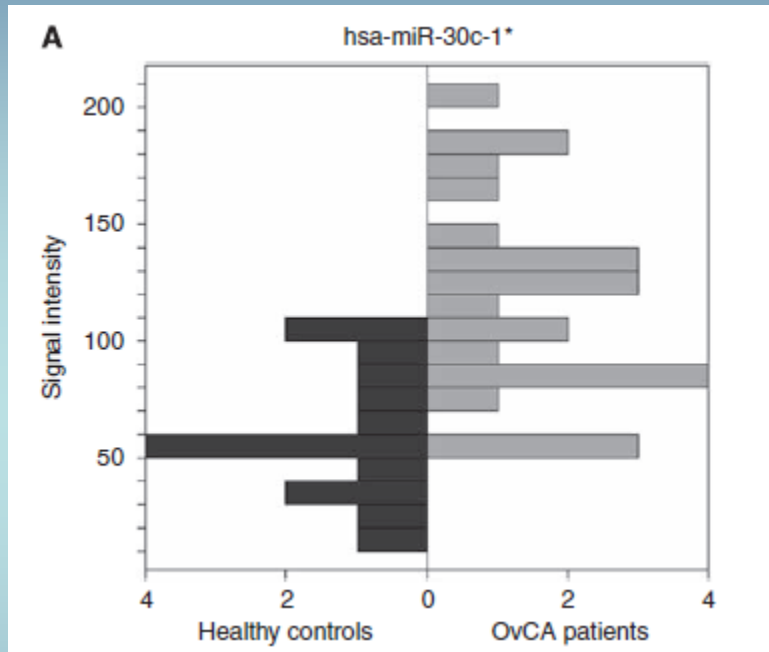
- Gesamt-RNA:

Roth et al., Breast Cancer Res 2010





miRNA & Ovarialkarzinom

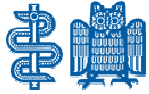


n = 15 OvCA

n = 24 healthy



147 significantly deregulated miRNAs



miRNA & Ovarialkarzinom

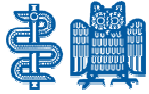
miR-200 family controls beta-tubulin III expression and is associated with paclitaxel-based treatment response and progression-free survival in ovarian cancer patients.

n= 72 ovarian carcinomas

Expression of: miR-141, miR-200a, miR-200b, miR-200c, miR-429, β -tubulin isotypes I, II and III

Patients without complete response had lower miR-200c levels than patients with complete response (HR=1.43, 95%CI=1.02-1.99, P=0.037)

Low miR-200 family expression had a trend towards poor progression-free survival (HR>2.0, P values 0.051, 0.054 and 0.079, for miR-200c, miR-141 and miR-429, respectively, multivariate analysis)



miRNA & Schwangerschaft

- Plazenta assoziierte miRNA:
miR-527 und miR-526a
- während der Schwangerschaft signifikant im Serum erhöht (vs. gesunde nicht Schwangere)

Gilad et al., PLoS One 2008

- Plazenta-miRNA sowohl in Serum als auch in Plasma nachweisbar
- miRNA-Level korrelieren mit der Schwangerschaftswoche

Chim et al., Clin Chem 2008



Kritische Zusammenfassung

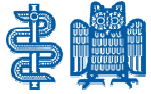
- miRNA bisher von Klinikern und Wissenschaftlern sehr getriggert
- Forschung erst in den Anfängen
- Studien:
 - kleine Fallzahlen
 - Unterschiedliche Methodik / Nachweis
 - Fehlender Standard bzgl. der Quantifizierung
- Validierung bisheriger Ergebnisse ausstehend





Zusammenfassung

- Stellenwert der miRNA in der Karzinogenese noch unklar
- miRNA als Biomarker zur frühen und minimal invasiven Diagnostik von Erkrankungen denkbar
- miRNA auch als Prognosefaktor, Therapiemonitoring usw. denkbar
- weitere Daten nötig!



Vielen Dank für Ihre Aufmerksamkeit!