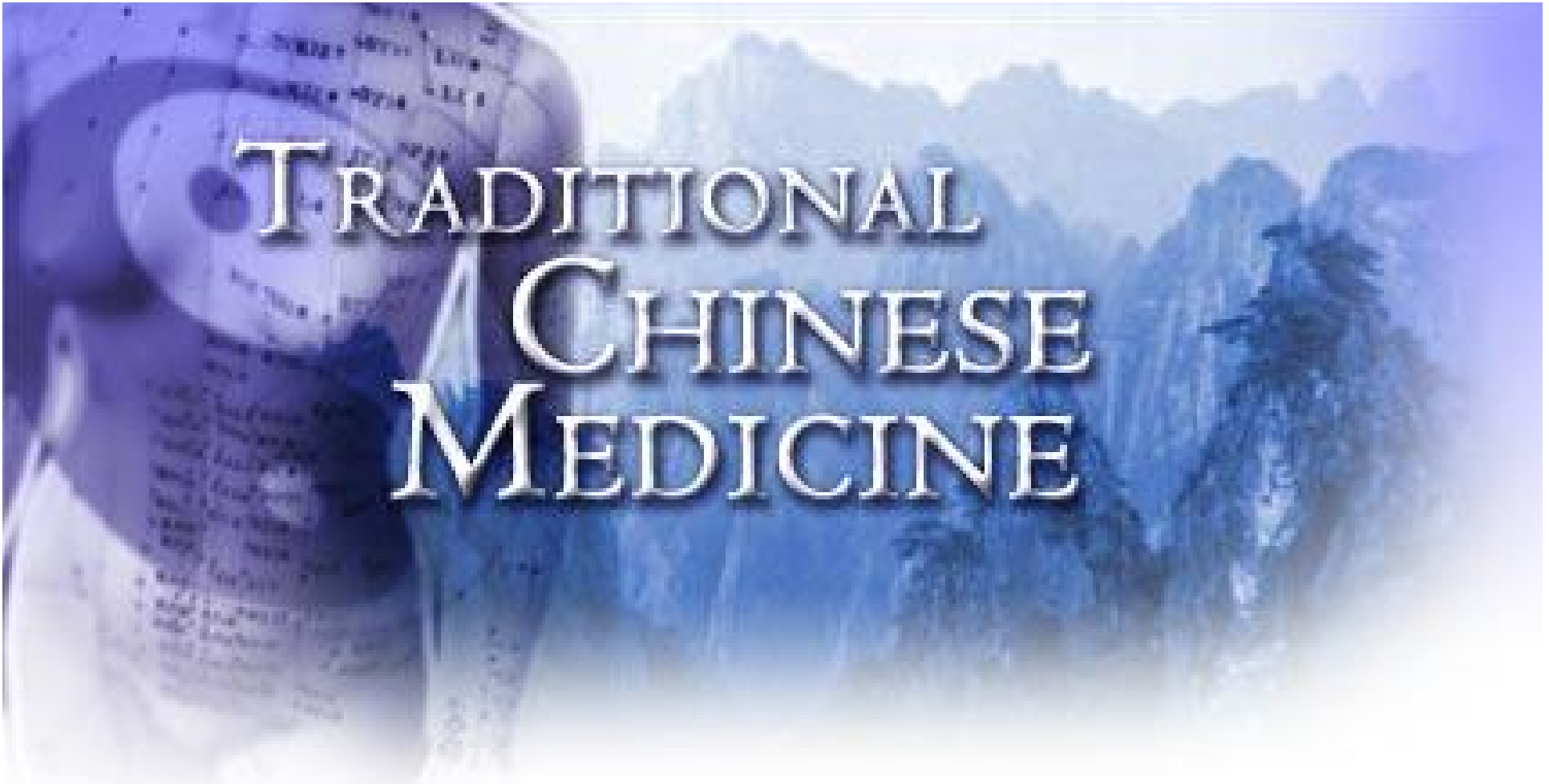




TRADITIONAL CHINESE MEDICINE

Anti-tumoraler Effekt von Artesunate
Thomas Efferth
Johannes Gutenberg-Universität Mainz



Agenda



1. Die Grundlagen der TCM
2. Molekulare Pharmakologie
3. Klinische Studien



TCM im Westen



Alternativmedizin
und Esoterik

Exportschlager
2004: 98 Mio \$
2009: 160 Mio \$

€ \$

€ \$

€ \$

€ \$

€ \$

€ \$

TCM in Fernost

TCM ersetzt die fehlende
medizinische Grundversorgung in
unterentwickelten ländlichen Regionen Chinas



Begriffs- definitionen

- **Gesundheit:**
 - Yin und Yang im Gleichgewicht
 - Ausgewogenheit von Körper, Geist und Seele
- **Krankheit:**
 - Disharmonie von Yin und Yang
 - Energiefluss von Qi in den Meridianen ist gestört
 - löst Krankheiten aus



Beeinflussung der Meridiane

Akupunktur



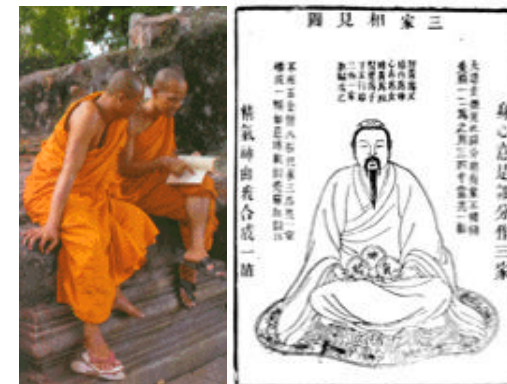
Ernährung



Arzneien



Meditation



Physiologische Funktionen sekundärer Pflanzenmetaboliten

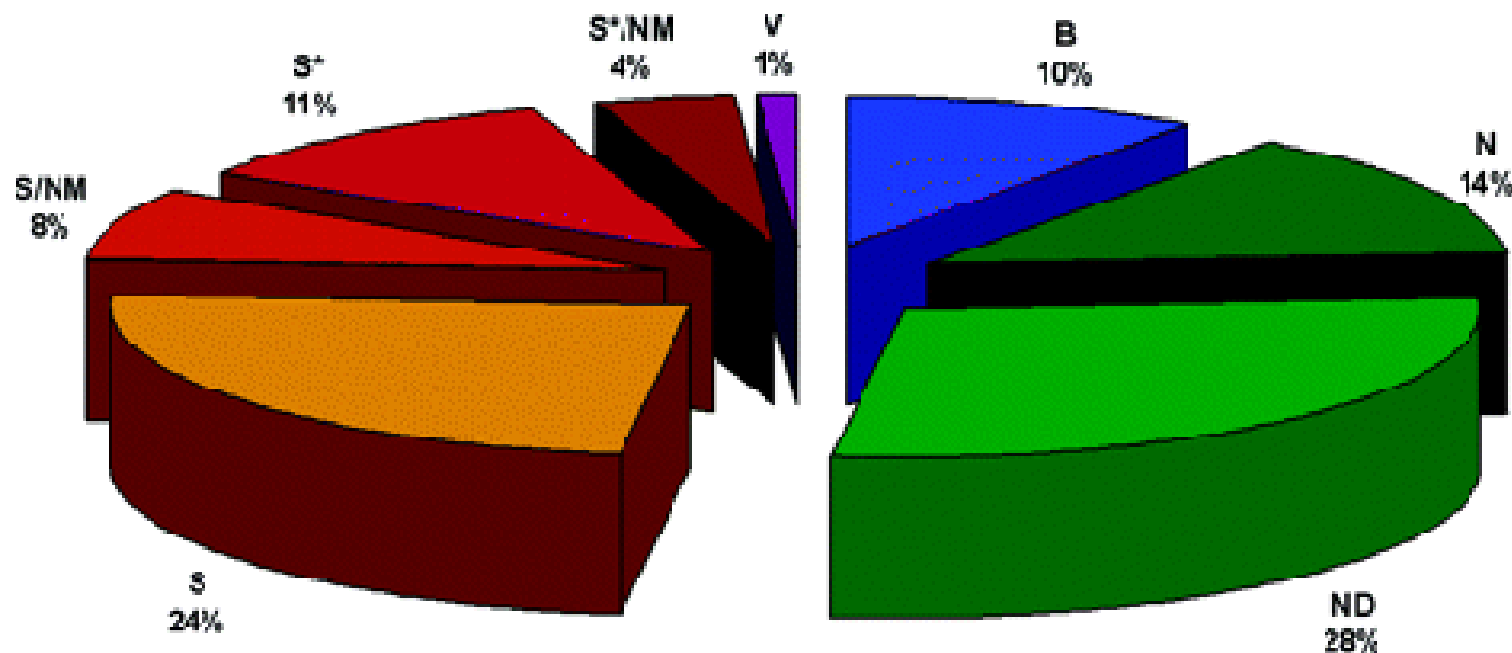


1. Schutz vor Parasiten
(Insekten, Würmer etc.)
2. Schutz vor mikrobiellen Infektionen
(Viren, Bakterien, Pilze, etc.)
3. Schutz vor Herbivoren
4. Anlocken von Bestäubern (Insekten)



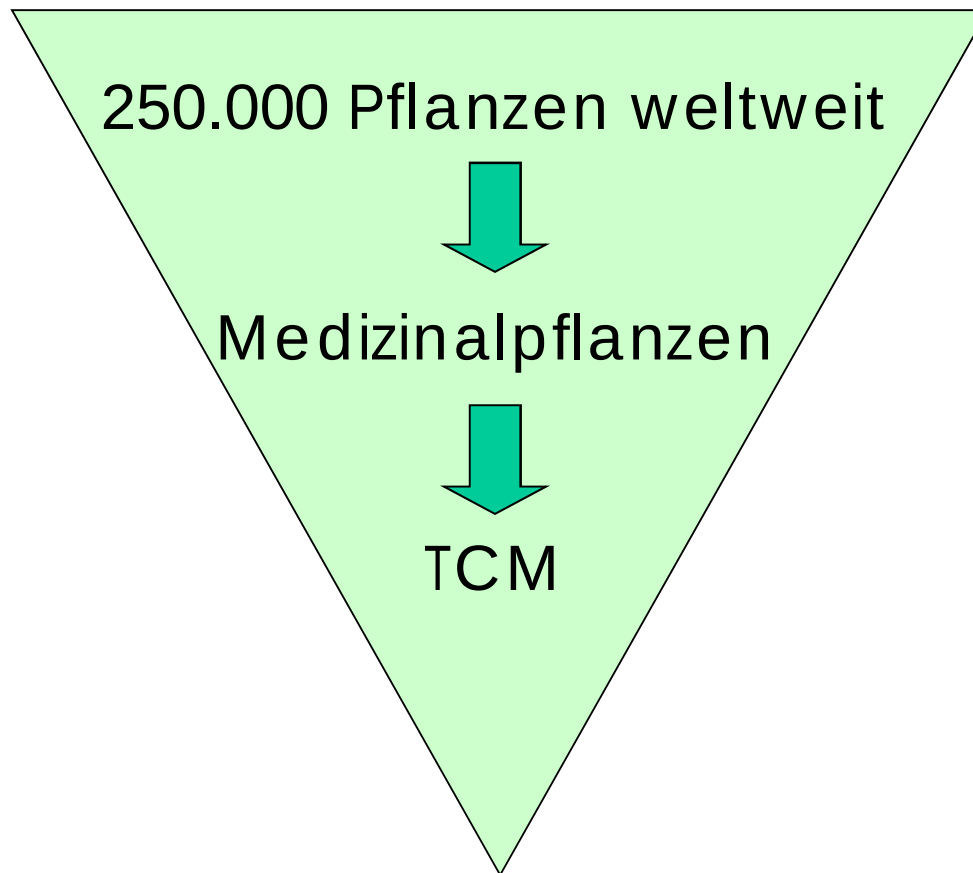
Vinca rosea
(*Catharanthus roseus*)

Krebsmedikamente (1940 – 2006)



B, biological drugs: peptides or proteins (> 45 residues)
N, natural product
ND, derived from natural product, semi-synthetic modification
S, totally synthetic drug
S*, synthetic with pharmacophore from natural product
V, vaccine
NM, natural product mimic

Traditionelle Chinesische Medizin: Anti-Tumor Screening



Medizinalmarkt Kunming





Medizinalpflanzen



Bioaktivitätsgeleitete Isolation von Pflanzeninhaltsstoffen

Phytochemie



Molekulare Pharmakologie

Pharmakogenomik,

Validierung von Zielstrukturen mit Transfektanten und *knock outs*

In vivo Validierung

Bioactivity-Guided Isolation of Natural Products



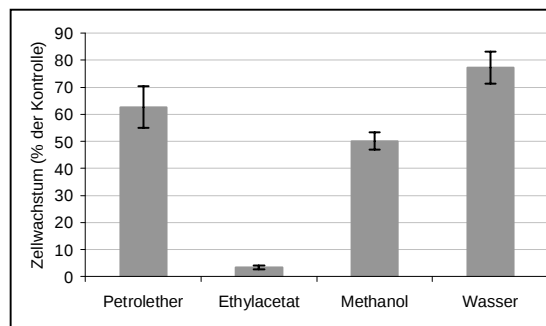
1

Quisqualis indica L.



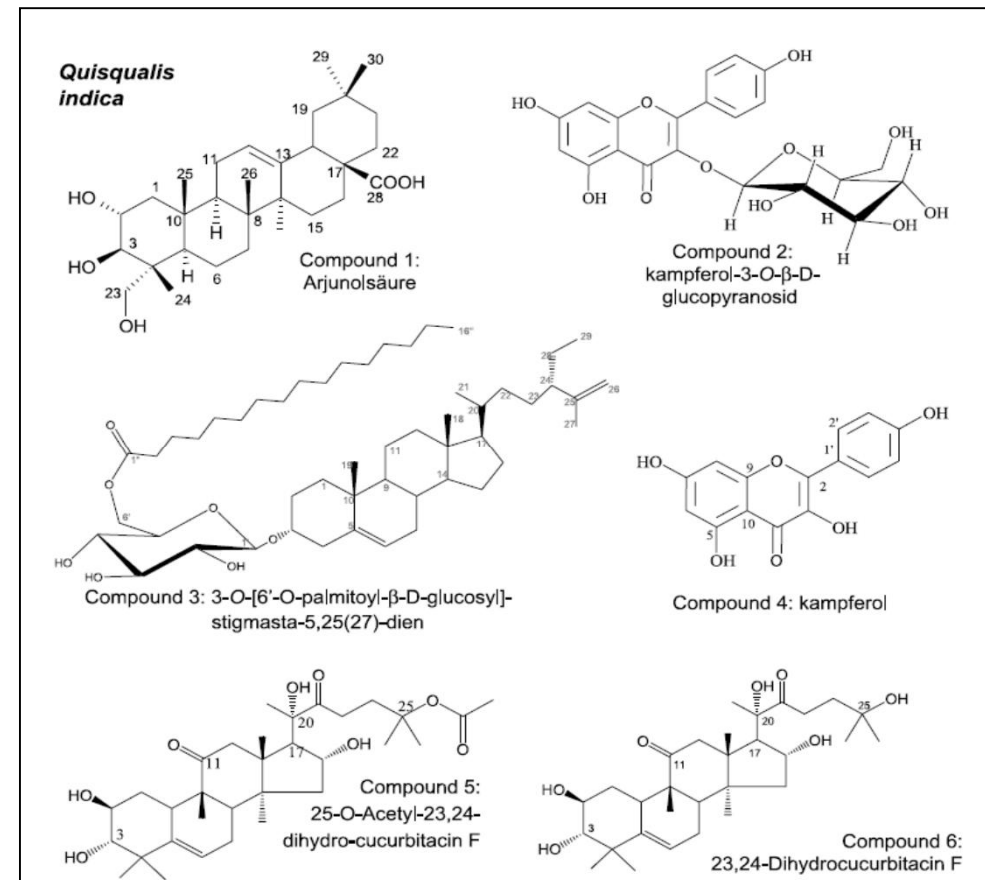
2

Extract Testing and Fractionation

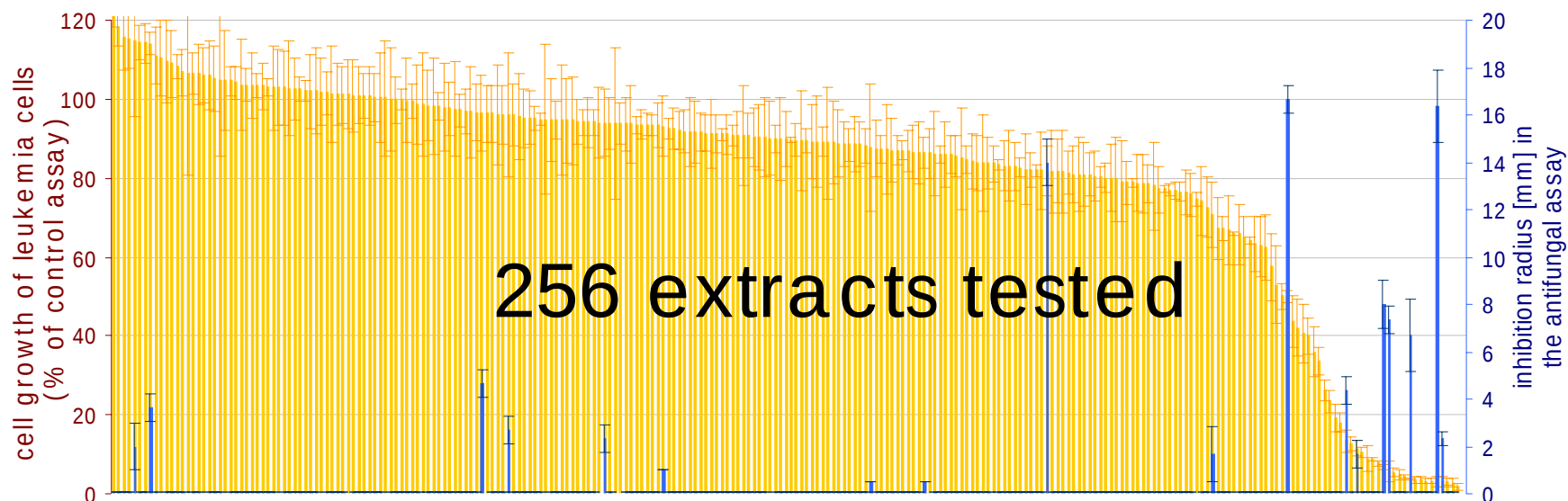


3

Structure Elucidation



Anticancer Screening of TCM Plants



- *Artemisia annua* L. (Compositae)
- *Caesalpinia sappan* L. (Caesalpiniaceae)
- *Curcuma longa* L. (Zingiberaceae)
- *Eleutherococcus senticosus* Maxim (Araliaceae)
- *Hydnocarpus anthelmintica* Gaertner (Flacourtiaceae)
- *Lonicera japonica* Thumb. (Caprifoliaceae)
- *Quisqualis indica* L. (Combretaceae)
- *Salvia miltiorrhiza* Bunge (Lamiaceae)

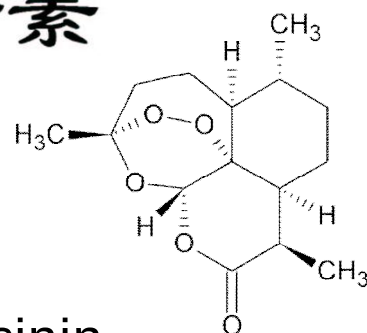
Artemisia annua L. (Qinhao)



Herba Artemisiae annuae

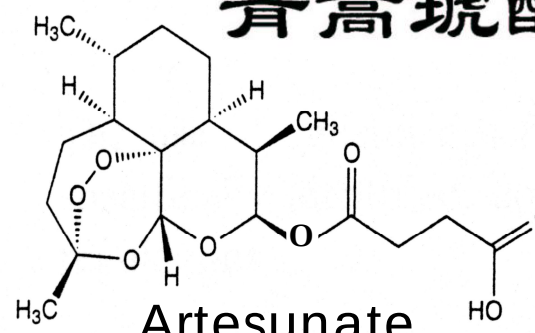


青蒿素



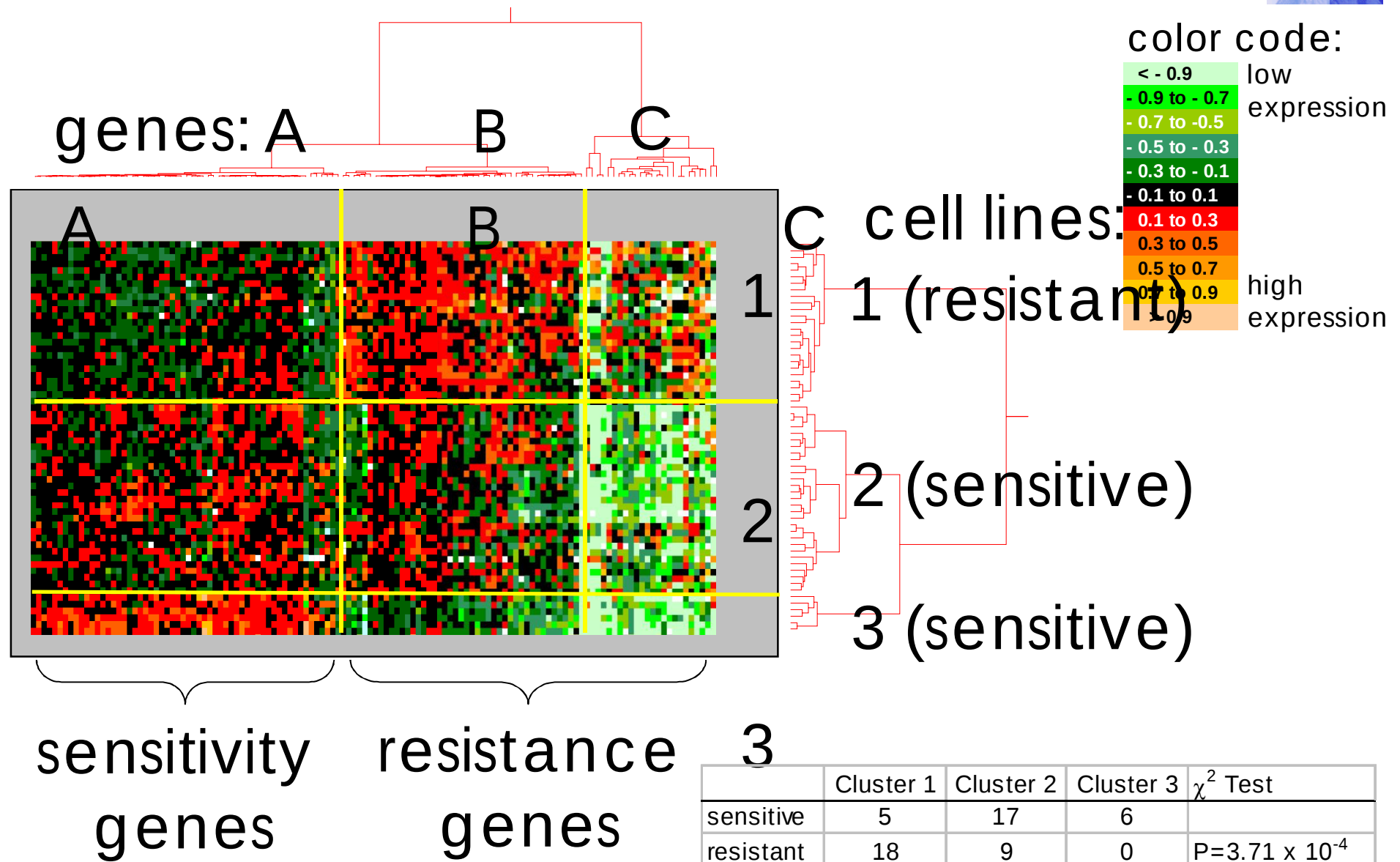
Artemisinin

青蒿琥酯

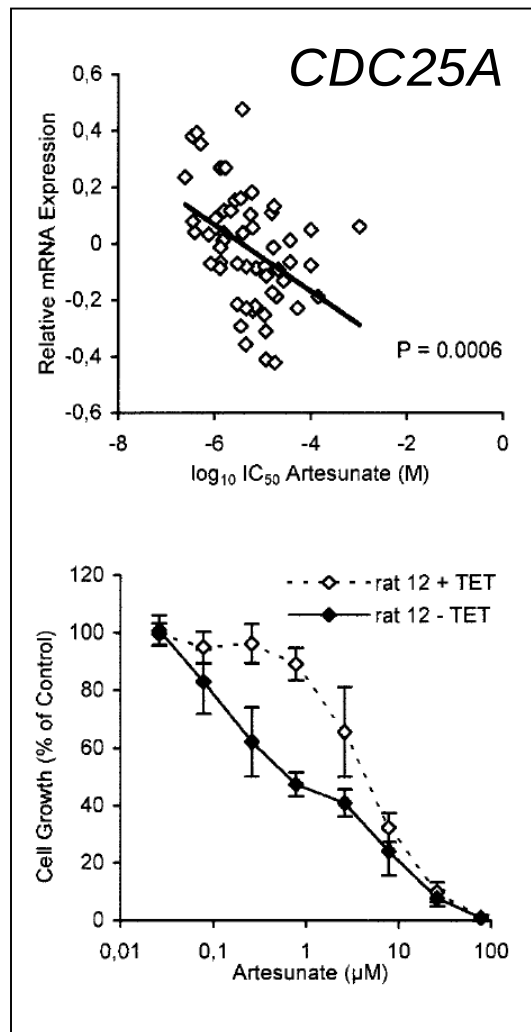


Artesunate

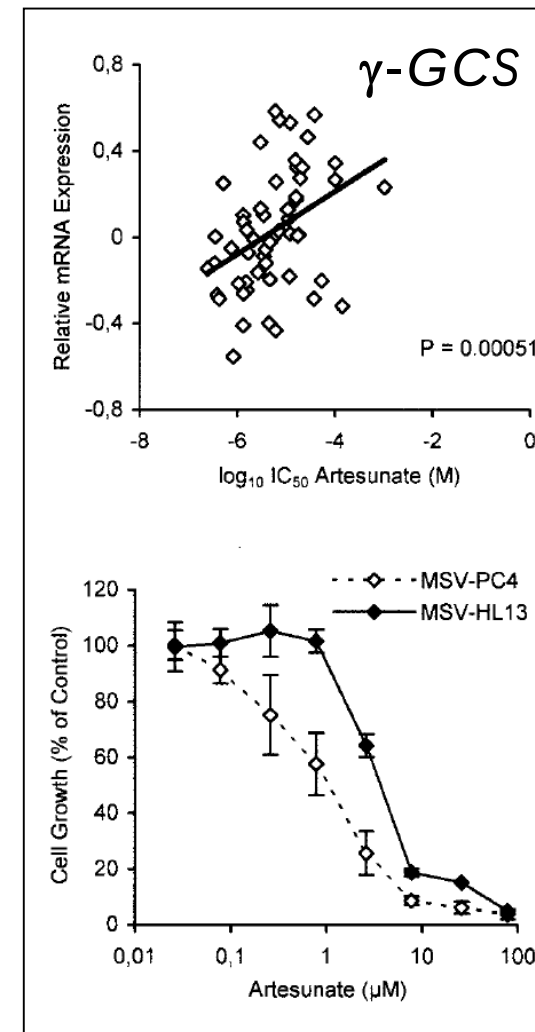
Microarray and Cluster Analysis



Activity of Artesunate Towards Transfected Cell Lines



sensitivity gene

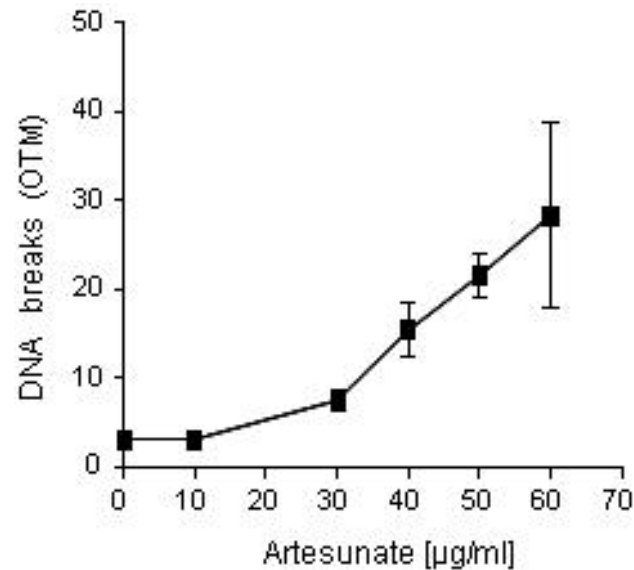


resistance gene

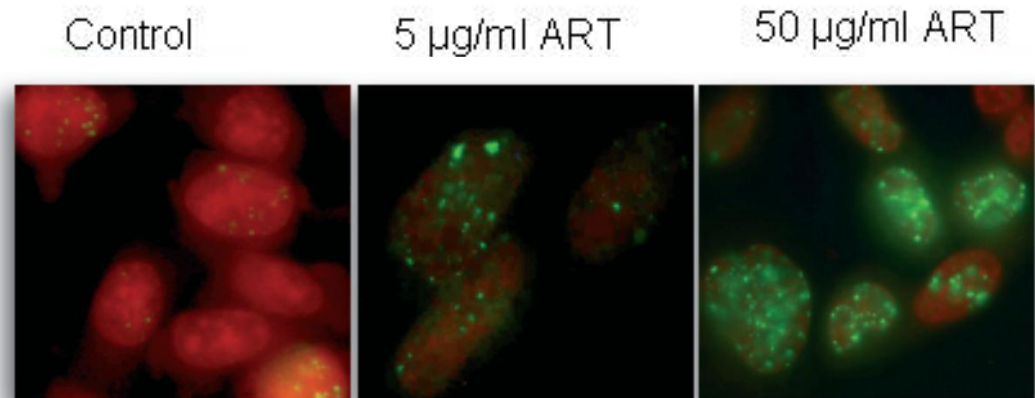
Induction of DNA Strand Breaks by Artesunate



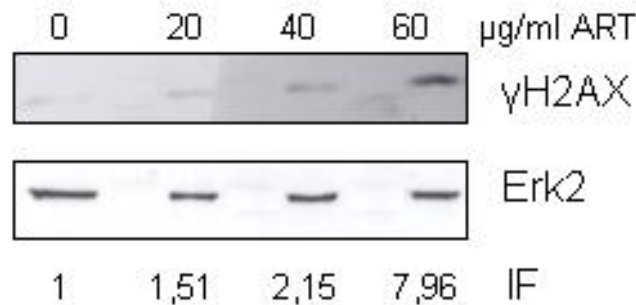
A. Single Cell Gel Electrophoresis



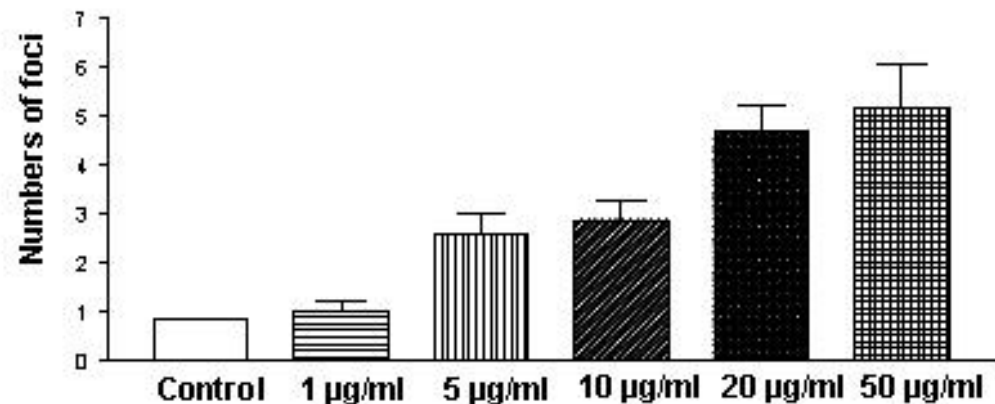
C. Immunofluorescence of γ -H2AX Foci



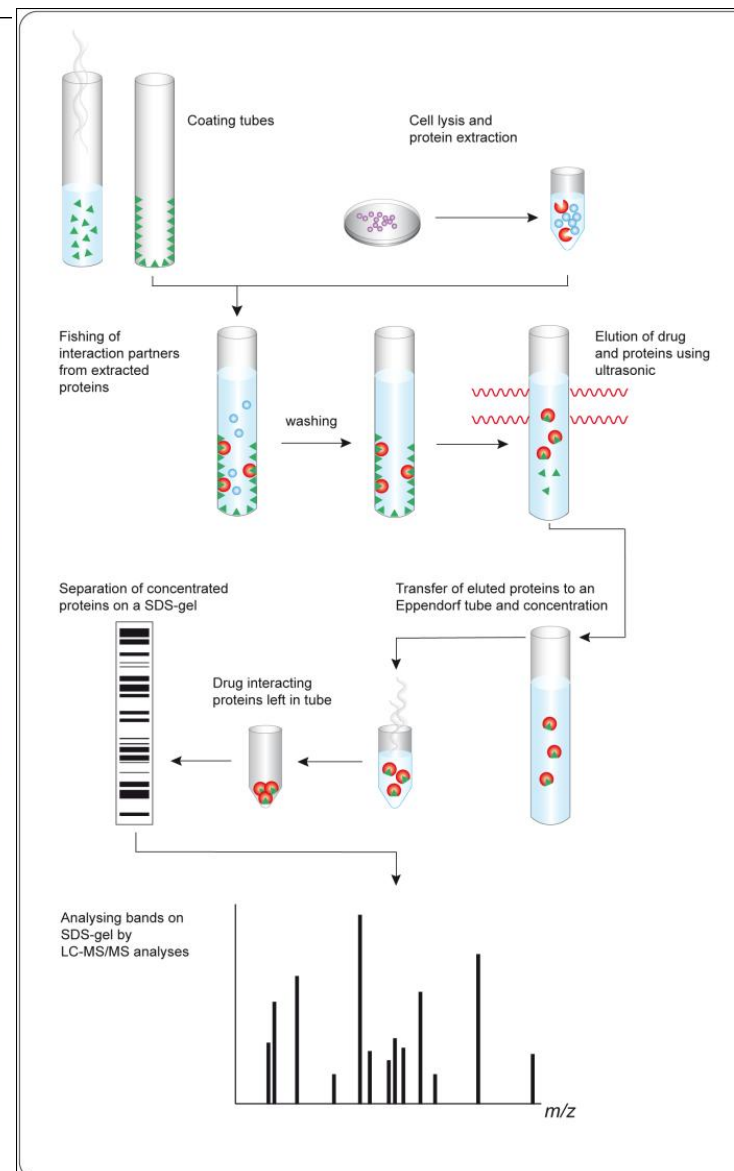
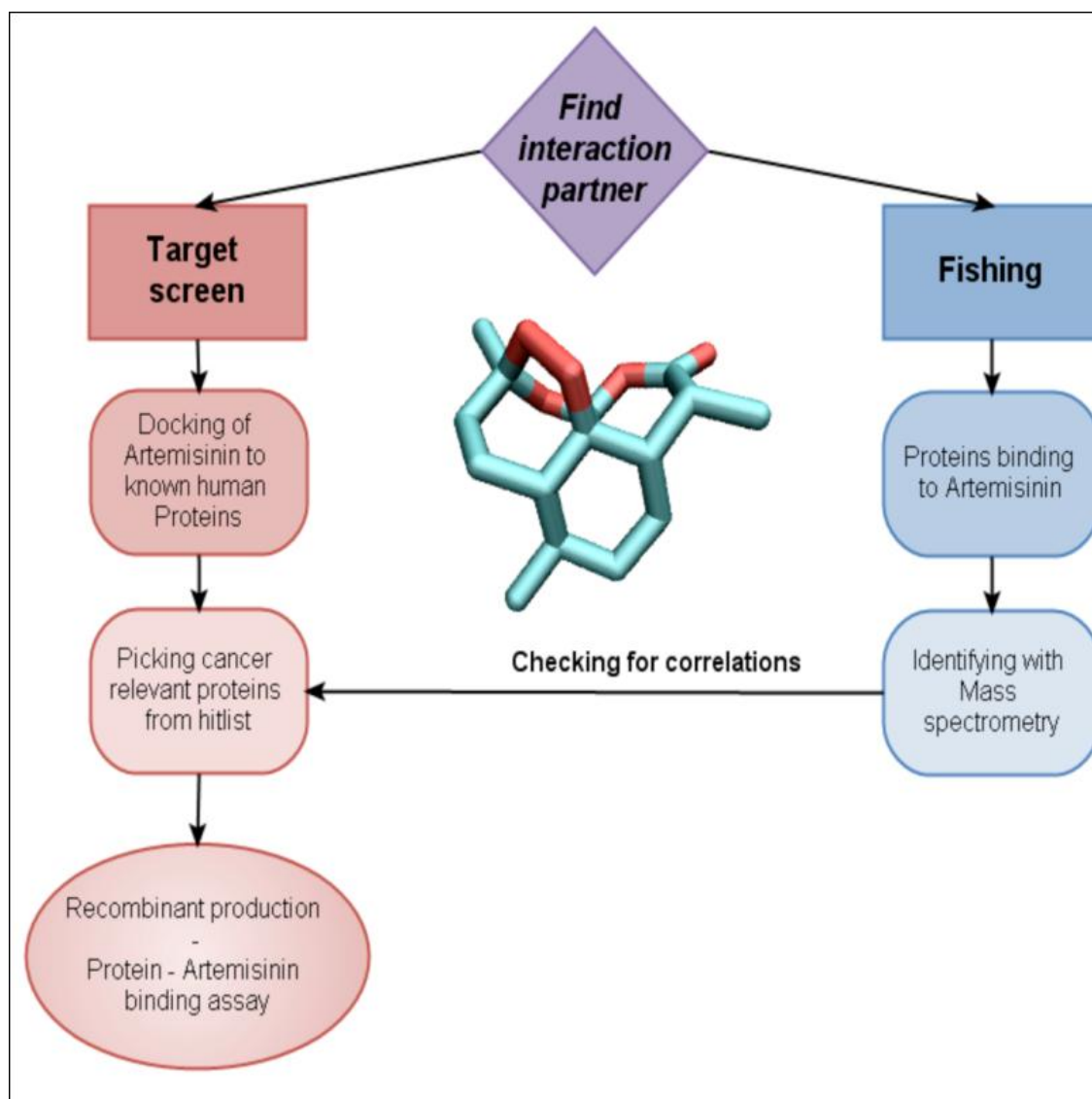
B. Westernblot of γ -H2AX



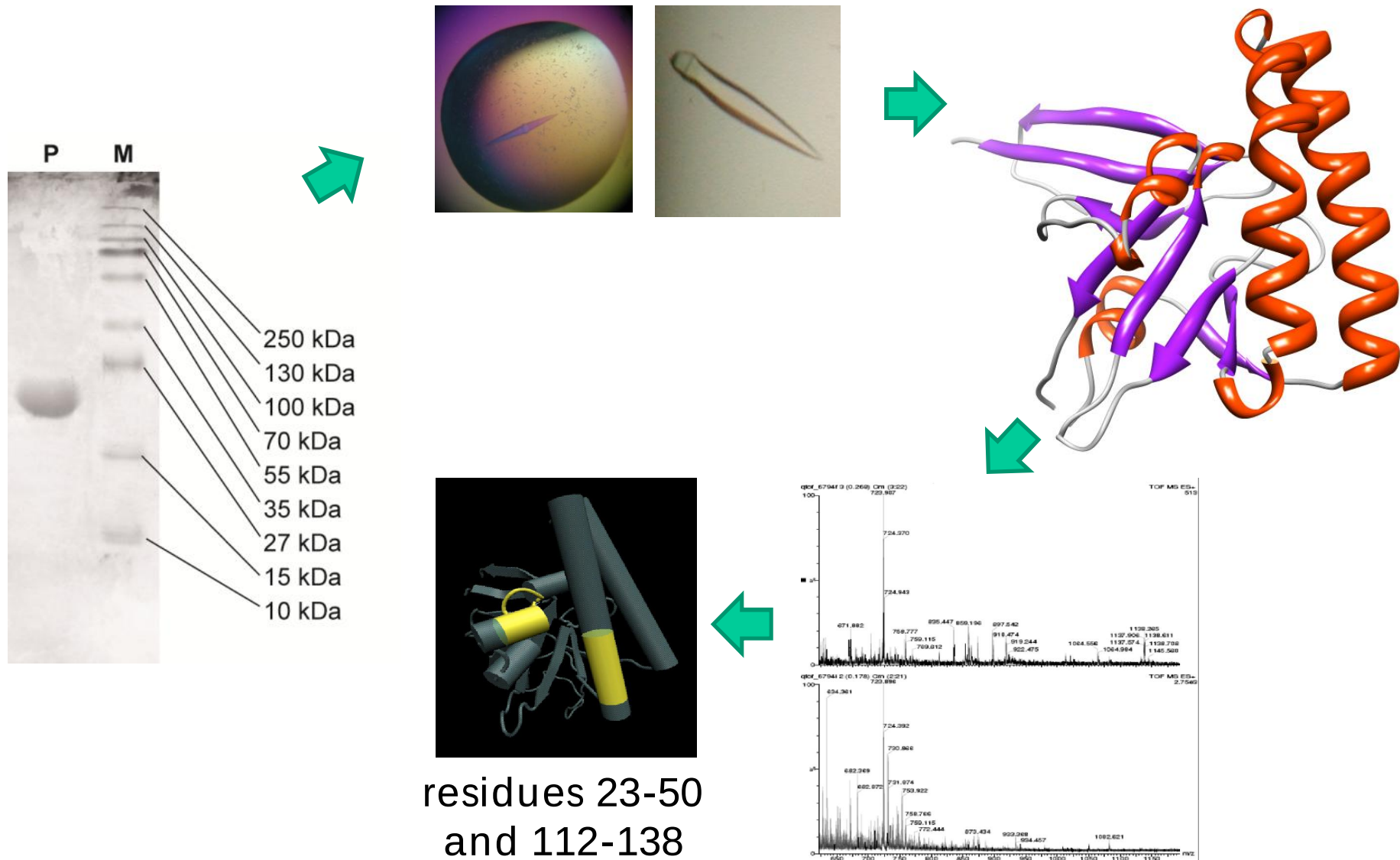
D. Quantification of γ -H2AX Foci



Identification of Artemisinin-Binding Proteins *in silico* and *in vitro*

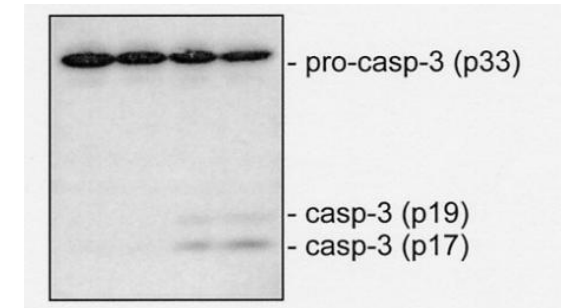
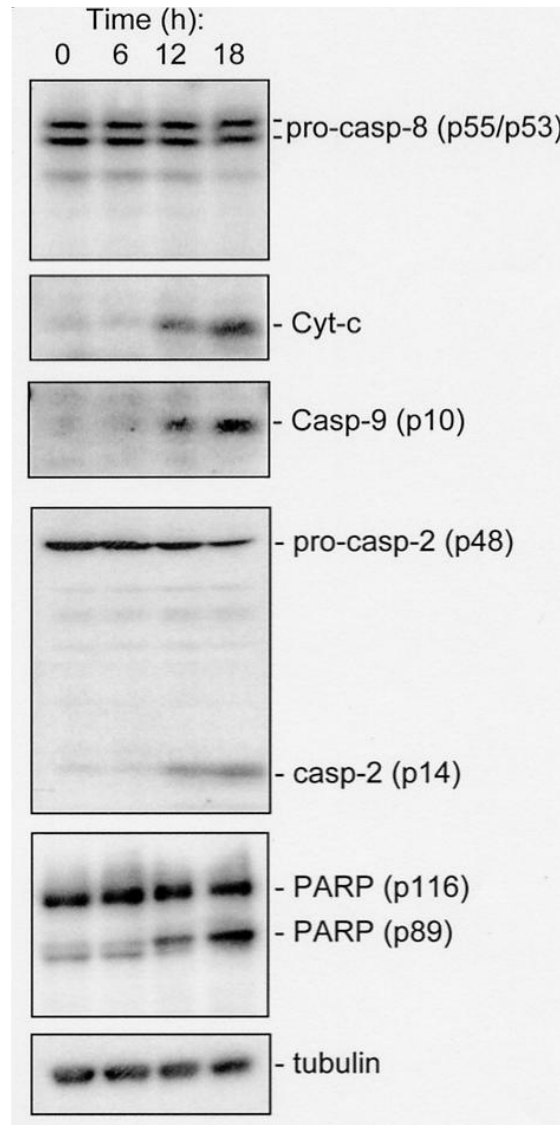
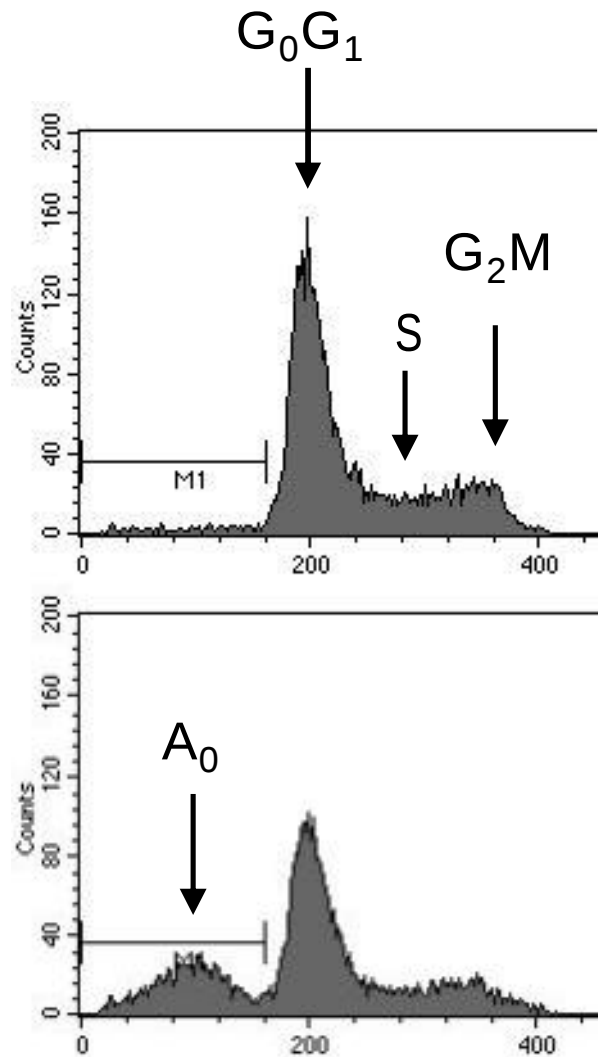


Binding of Artemisinin to TCTP (Translationally-Controlled Tumor Protein)

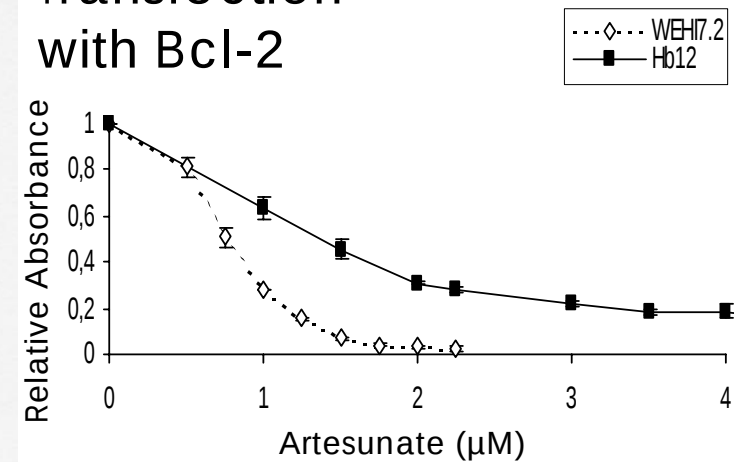


residues 23-50
and 112-138

Artesunate Induces the Intrinsic Pathway of Apoptosis



Transfection with Bcl-2



Artesunate Inhibits Angiogenesis and Tumor Growth *in vivo*



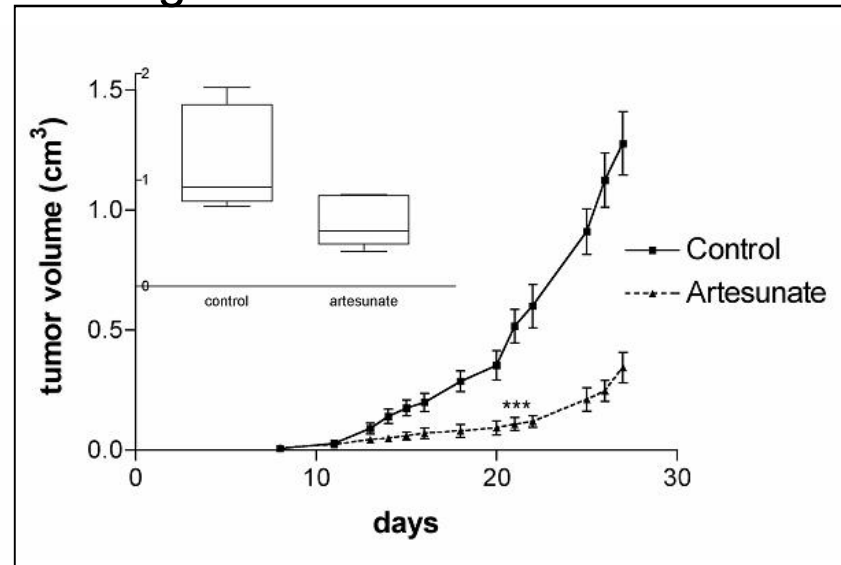
Matrigel Plug Assay



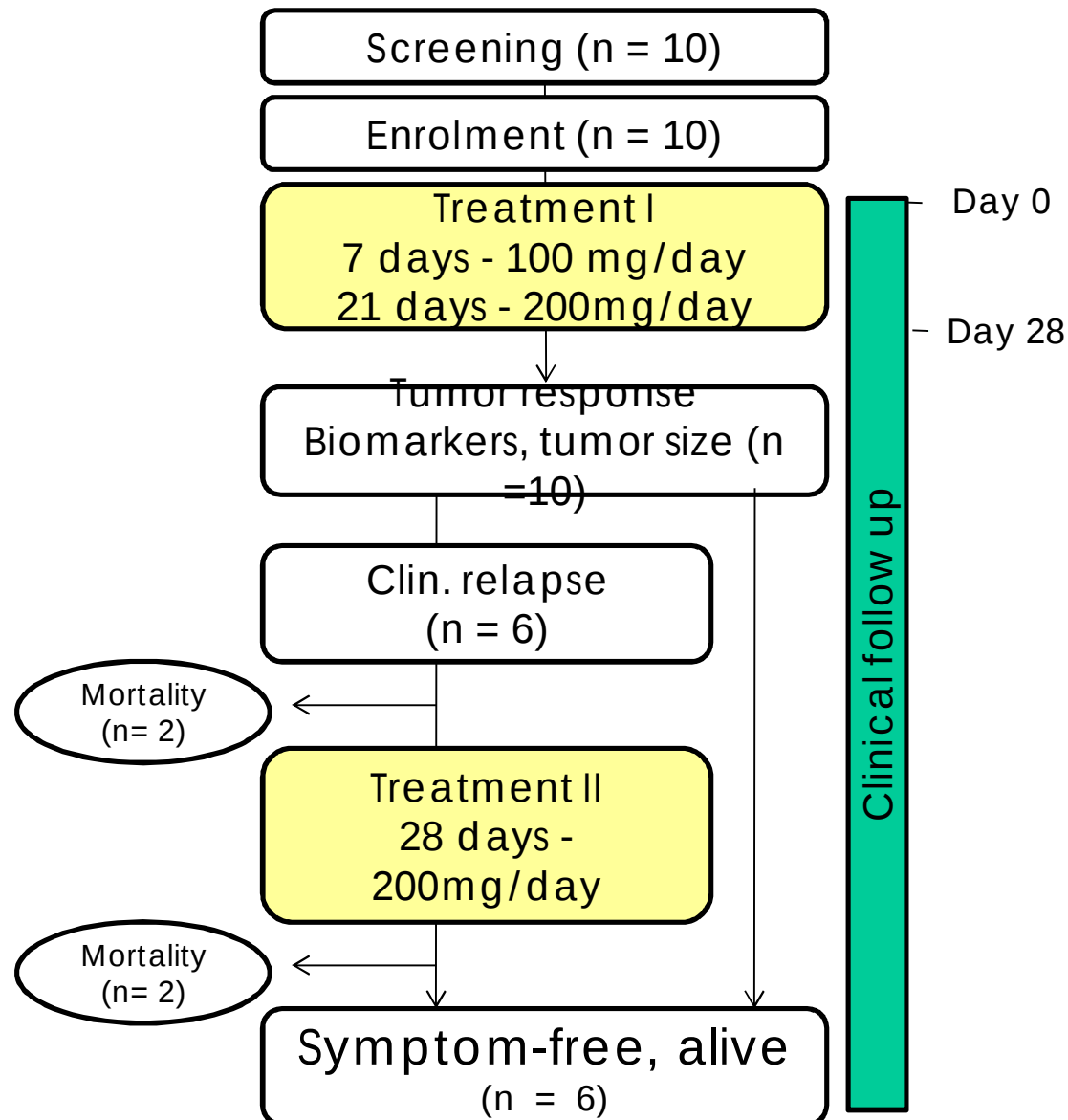
Microarray Analysis

- Angiostatin
- Collagens 18A1 and 4A2
- Fibronectin 1
- Hypoxia-inducible factor 1
- Matrix metalloproteins 9 and 11
- Nitric oxide synthase 2A
- Plasminogen activator (urokinase)
- Thrombospondin
- Tissue factor (thromboplastin)
- Vascular endothelial factor C

Xenograft Nude Mice Model



Clinical Phase I/II Trial: Activity of Artesunate in Cervix Carcinoma



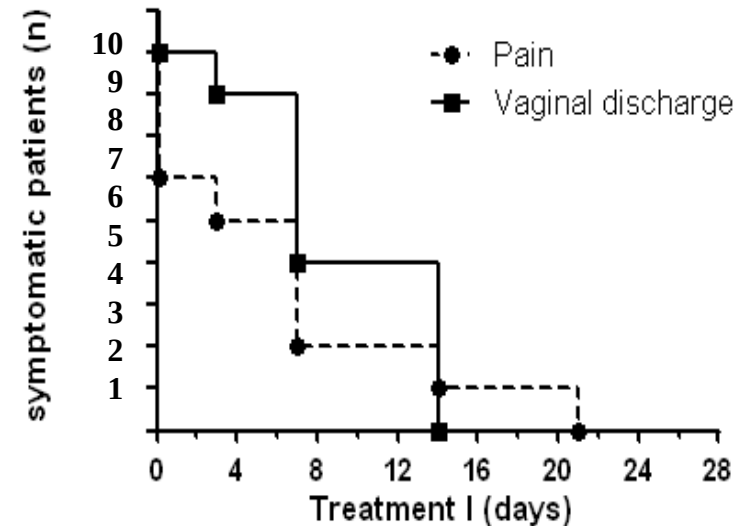
- Open label, single center pilot study
- Service de Cancerologie, CHU Treichville, Abidjan, Côte d'Ivoire
- Ten women with cervical carcinoma (stage: 1 x IIIa, 4 x IIIb, 4 x IVa, 1 x IVb)

Clinical Phase I/II Trial: Activity of Artesunate in Cervix Carcinoma



Response: 10 x remission.

Median time for the disappearance of vaginal blood loss, watery discharge and pain = 7 days (min 3, max 21).

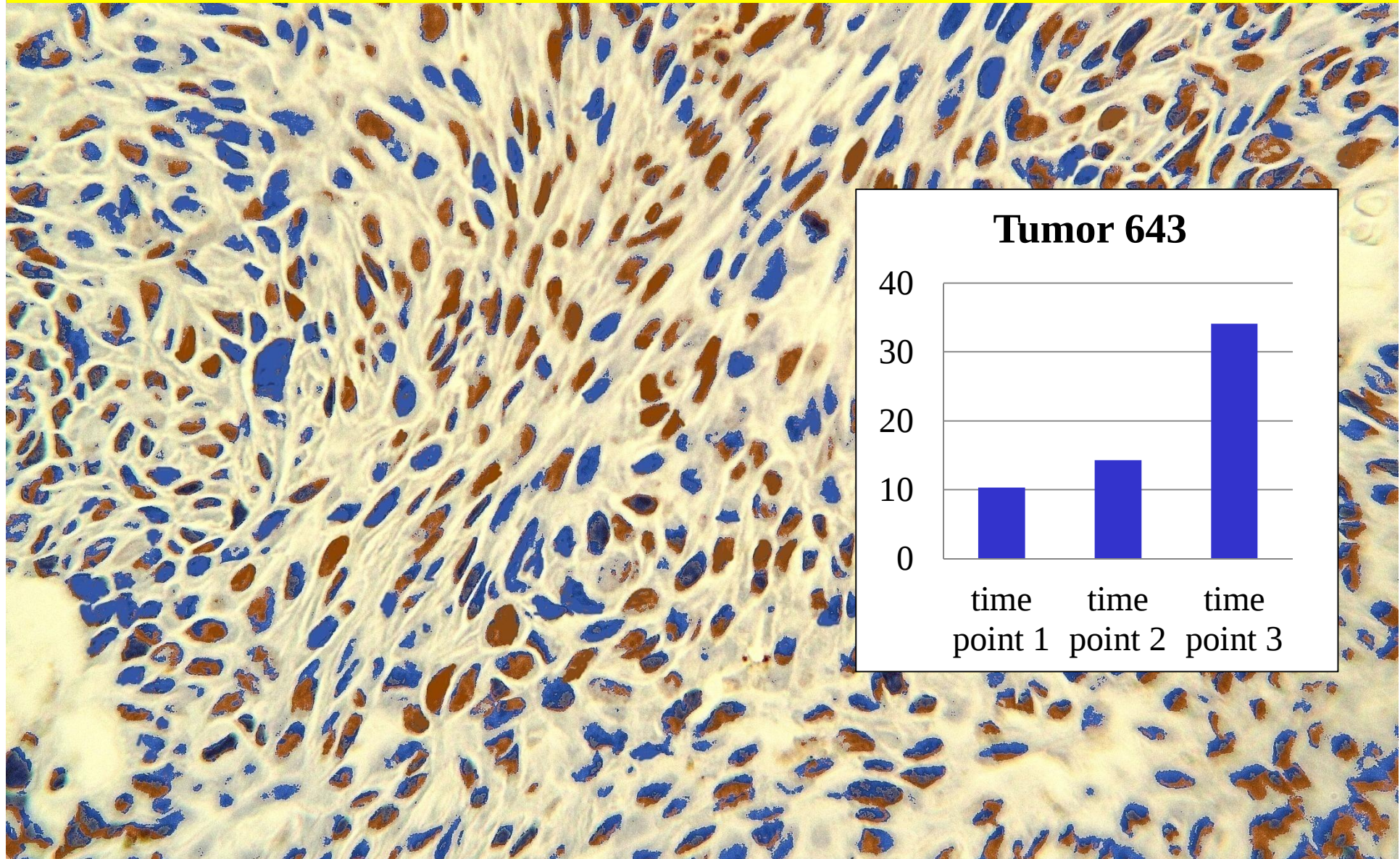


Adverse effects: Grade 1 or 2: 5 patients with “flu-like syndrome”, headache and abdominal pain
No grade 3 or 4 adverse events

Average time for clinical relapse: 6 months (min 4, max 8)
4 refractory tumors treated again: 2 patients died, 2 in remission

Survival time : 12 months (min 8, max 13), (expected: 4)

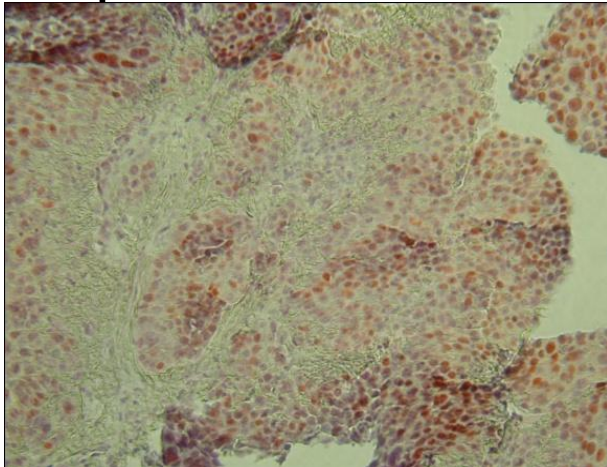
(TUNEL-Assay (Apoptosis): Activity of Artesunate in Cervix Carcinoma



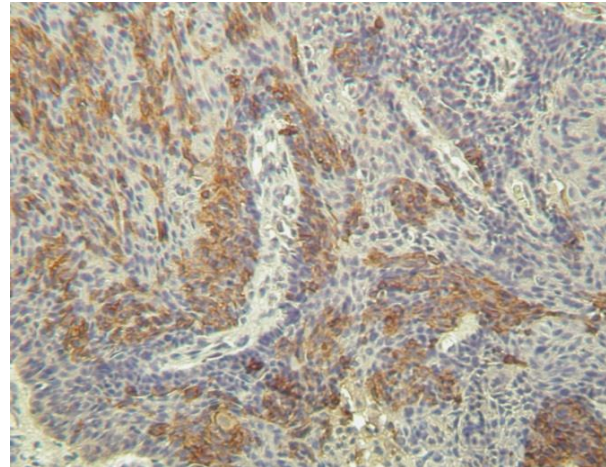
Immunohistochemical Biomarkers: Activity of Artesunate in Cervix Carcinoma



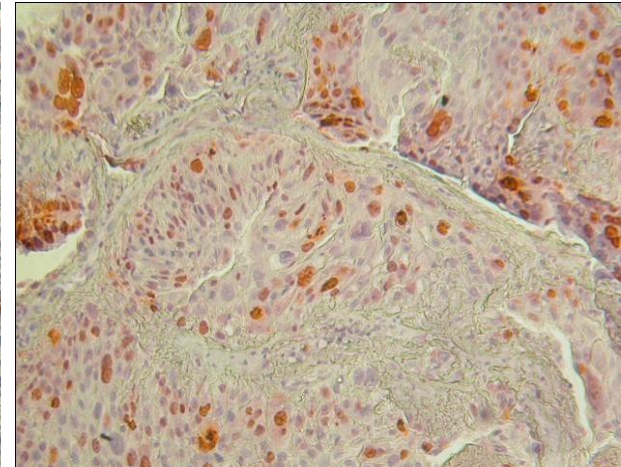
A. p53



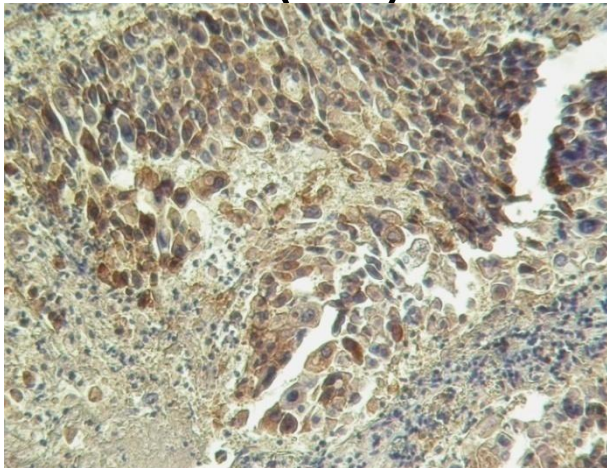
B. EGFR



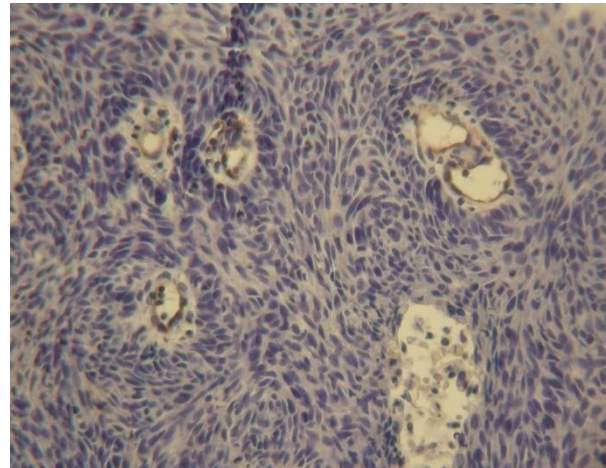
C. Ki-67



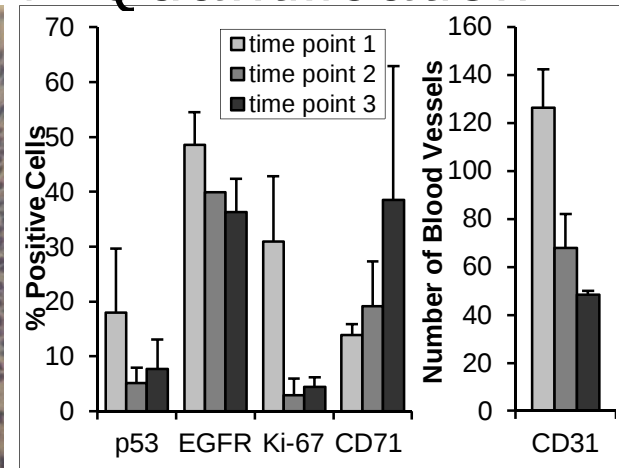
D. CD71 (TfR)



E. CD31



F. Quantification





1. Die Grundlagen der TCM

Jahrtausendealte Geschichte und Philosophie

2. Molekulare Pharmakologie

Phytochemie von Wirkstoffen

Molekularbiologische Aufklärung der Wirkmechanismen

3. Klinische Studien

Nachweis der Wirksamkeit in Tumorpationen



Vielen Dank
für Ihre Aufmerksamkeit!

