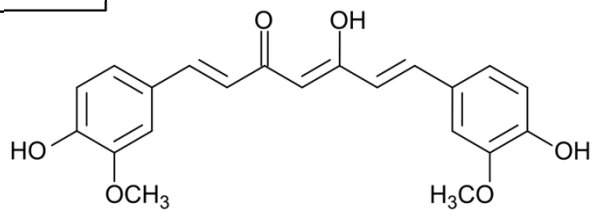
Super-Curcumin Story

Chapter 1: Curcumin is excellent compound for various medicinal usages
Chapter 2: Discovery of Super-Curcumin analog
Chapter 3: Anti-tumor activities of Super-Curcumin analog
Chapter 4: Molecular targets of analogs
Chapter 5: Oncogenes & analogs
Chapter 6: Apoptosis & analogs
Chapter 7: Cancer stem cells & analogs
Chapter 8: Analogs lead drug discovery
Supplement: Super-Curcumin analog & Sleeping sickness (African trypanosomiasis)

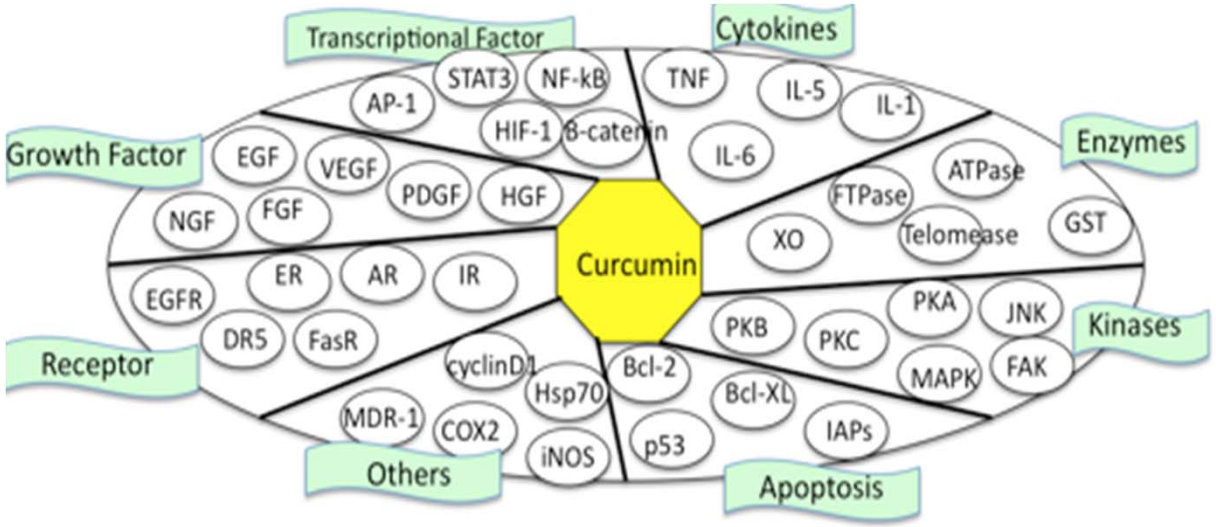
Chapter 1: Curcumin is excellent compound for various medicinal usages

Curcumin



IUPAC name; (1E,6E)-1,7-bis (4-hydroxy-3-methoxyphenyl) -1,6- heptadiene-3,5-dione

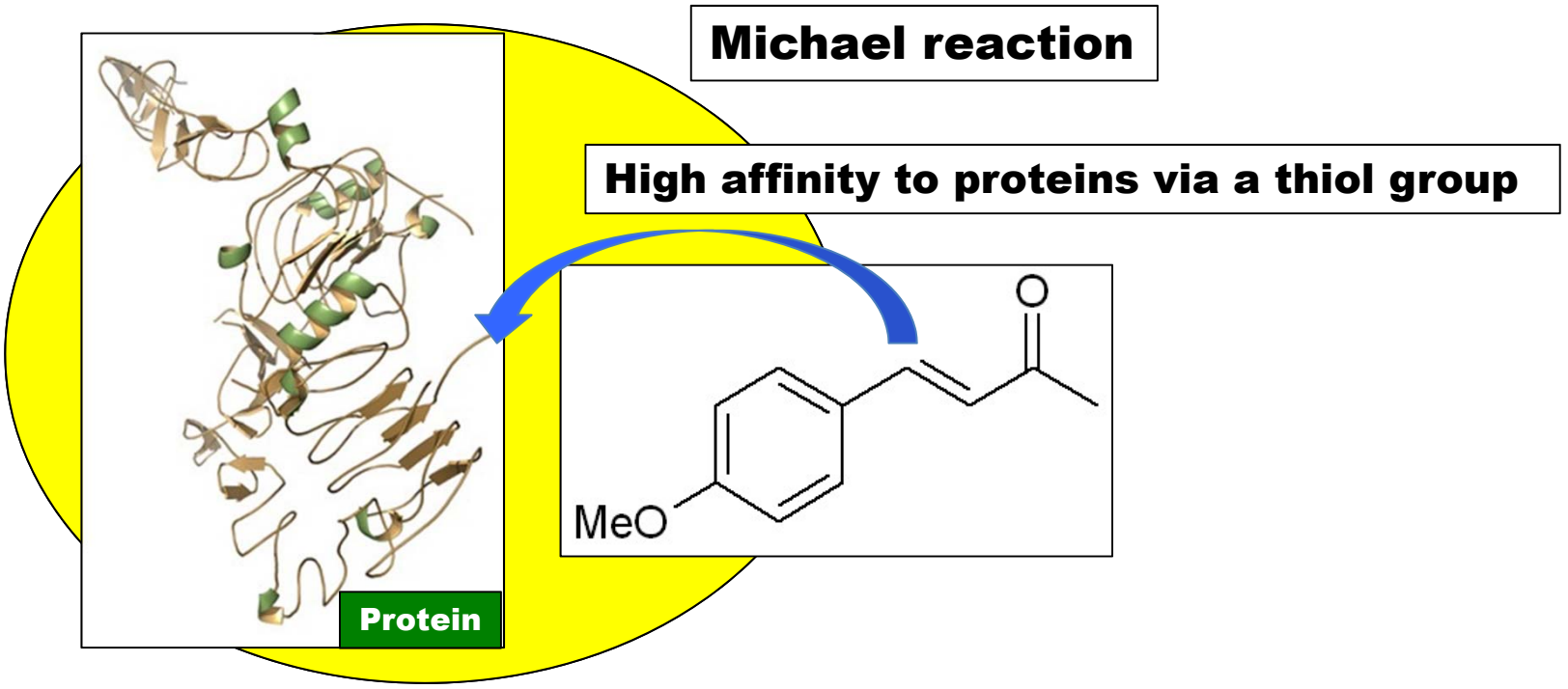
Curcumin is a multi-targeted compound



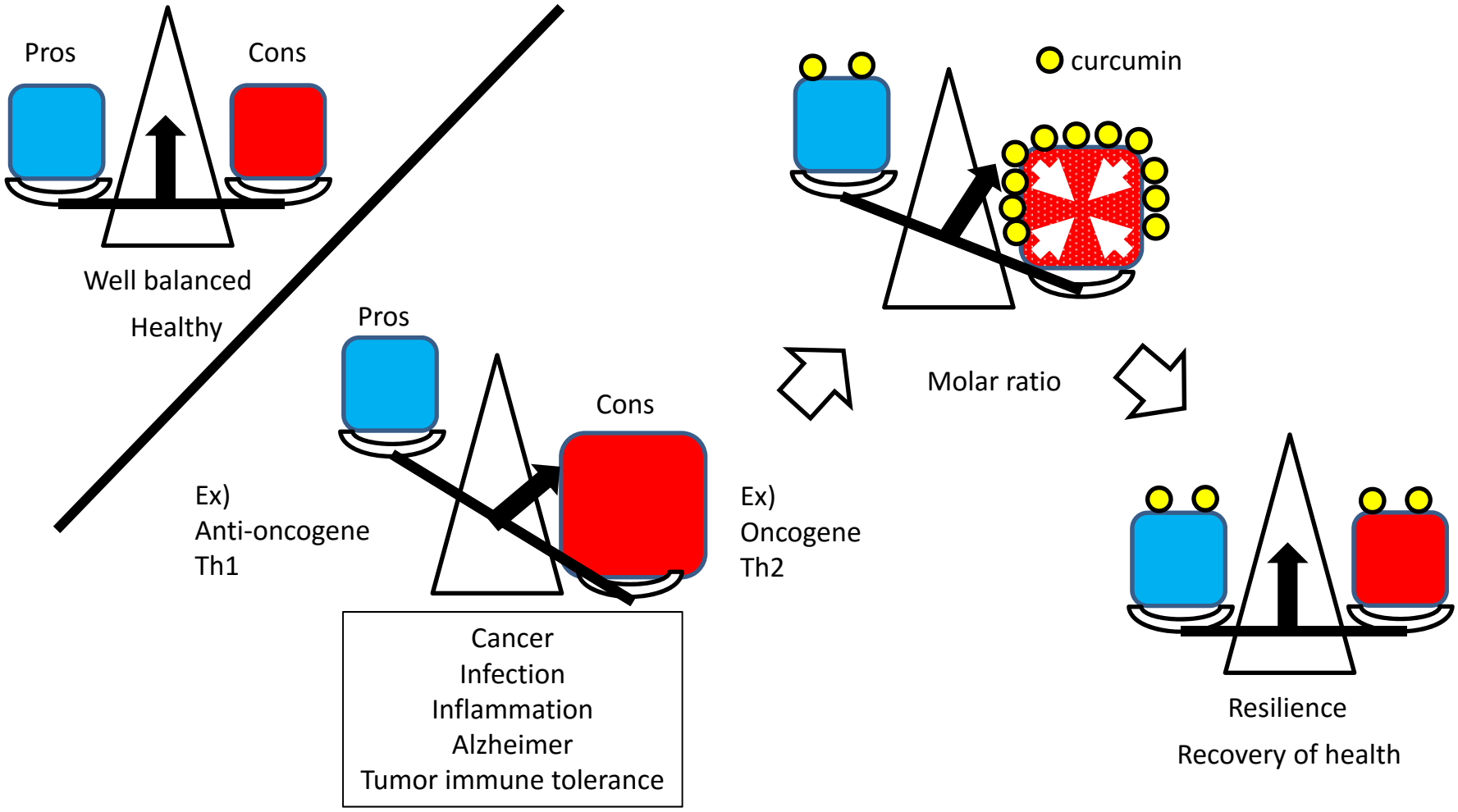
Curcumin can stop the individual gears of wheels in cancer.

Curcumin man

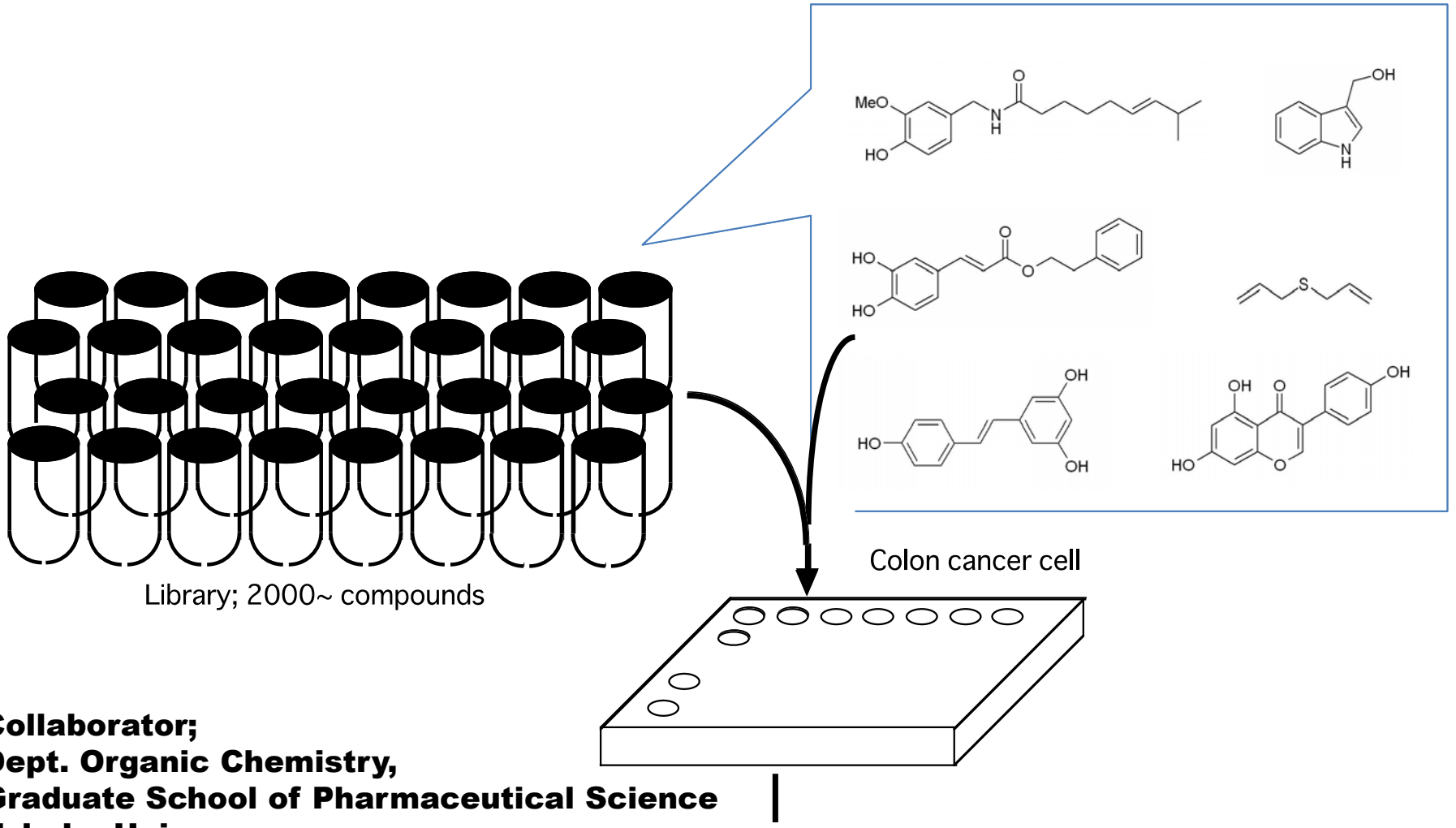
Why does curcumin have a multiplicity of targets?



How can curcumin control multiple targets? – “Resilience”-



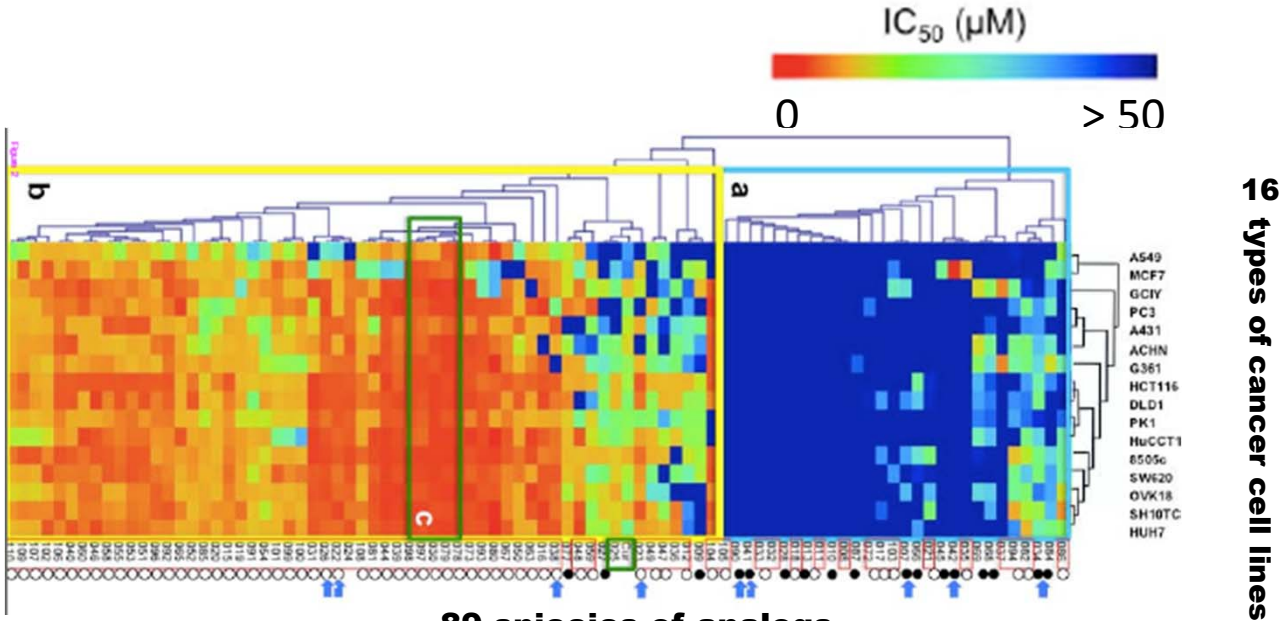
Chapter 2: Discovery of Super-Curcumin analog



Collaborator;
Dept. Organic Chemistry,
Graduate School of Pharmaceutical Science
Tohoku Univ.

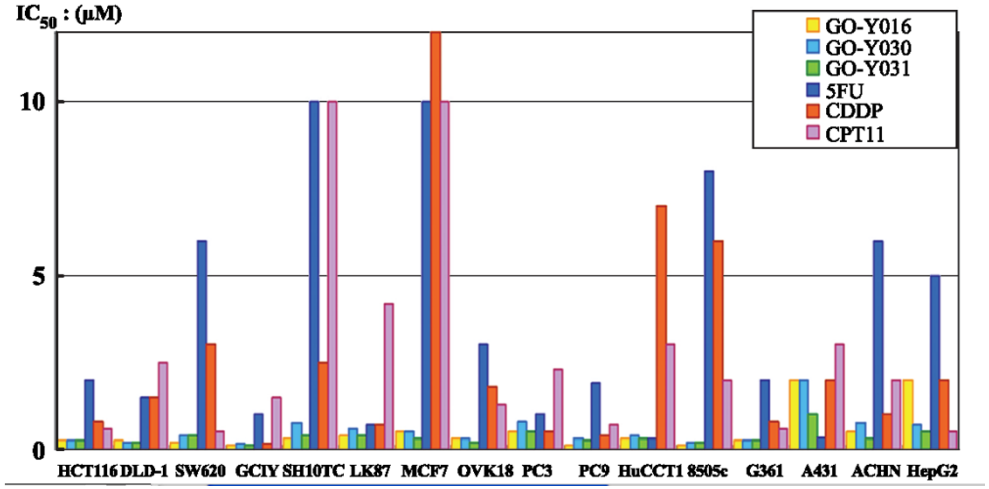
Analog screening was started from the chemical library stored in Dept., Organic Chem.

Chapter 3: Anti-tumor activities of Super-Curcumin analog

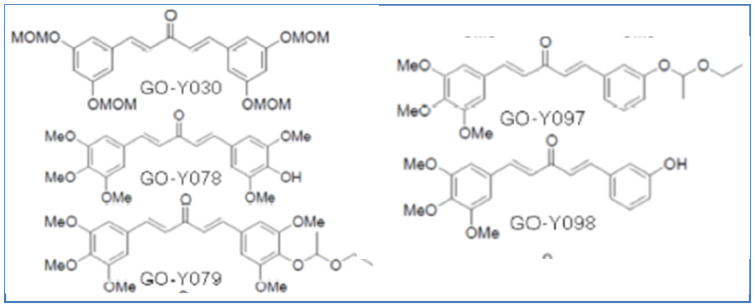


Over 100 species of analogs were synthesized from one lead compound, and the anti-tumor activities against 16 types of cancer cell lines were examined.

Analogs can kill the cancer cells at concentrations 30 – 60 times lower than 5-FU, cisplatin, irinotecan.



Analogs bearing strong anti-tumor activities

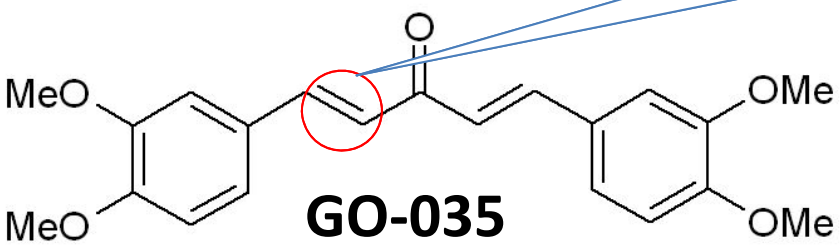


They have a 84 times stronger activity than Curcumin.

Chapter 4: Molecular targets of analogs

Analogs have different mechanisms from approved cytotoxics.

This structure is important.

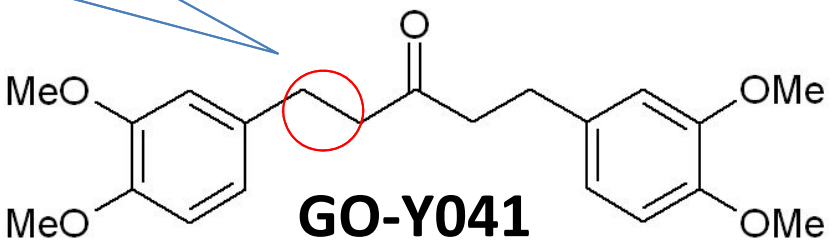


GO-035

IC_{50} : 1.6μM

Stronger anti-tumor activities

>>



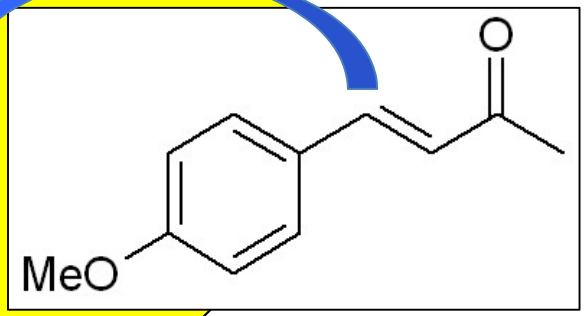
GO-Y041

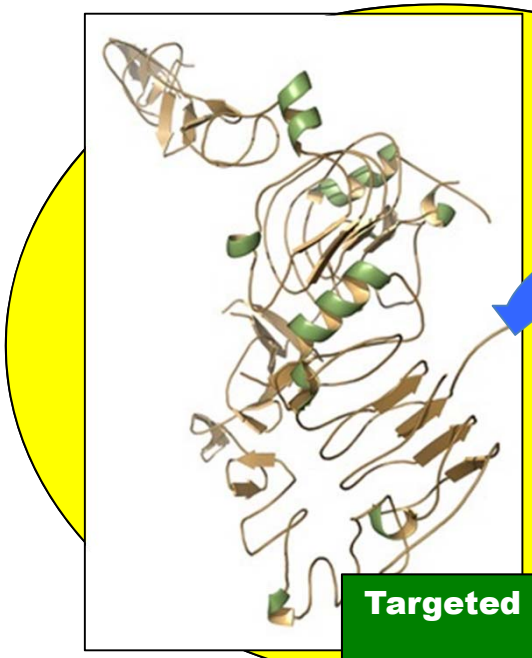
IC_{50} : >100μM

No anti-tumor activities

Michael reaction

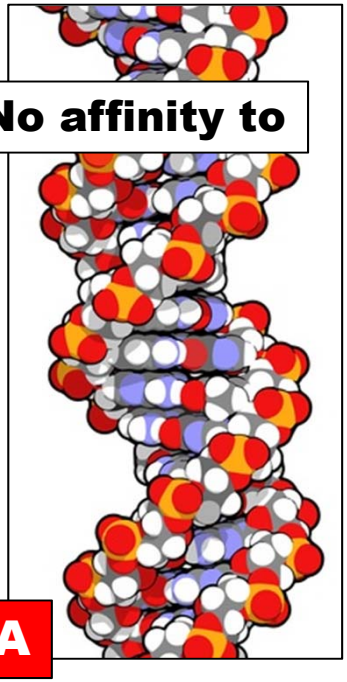
High affinity to





Targeted to Oncogene products (protein)

No affinity to



DNA

Chapter 5: Oncogenes & analog

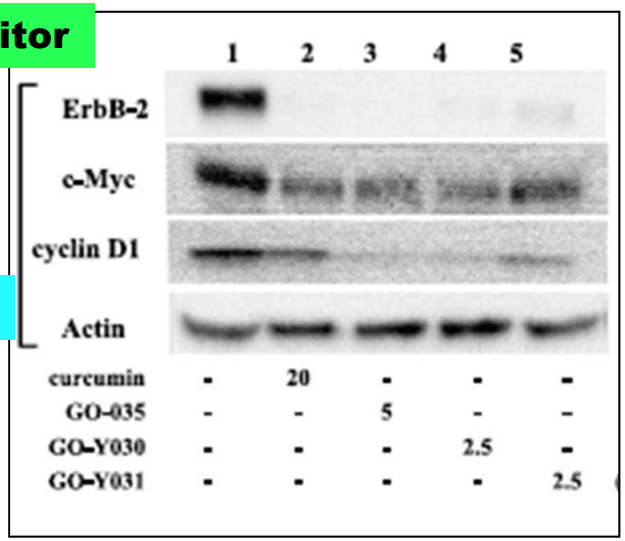
Analogs target oncogene products.

Malignant phenotypes

1. **Loss of growth control**
2. **Resistance to apoptosis**
3. **Immortality**
4. **Angiogenesis**
5. **Invasion**
6. **Metasatasis**

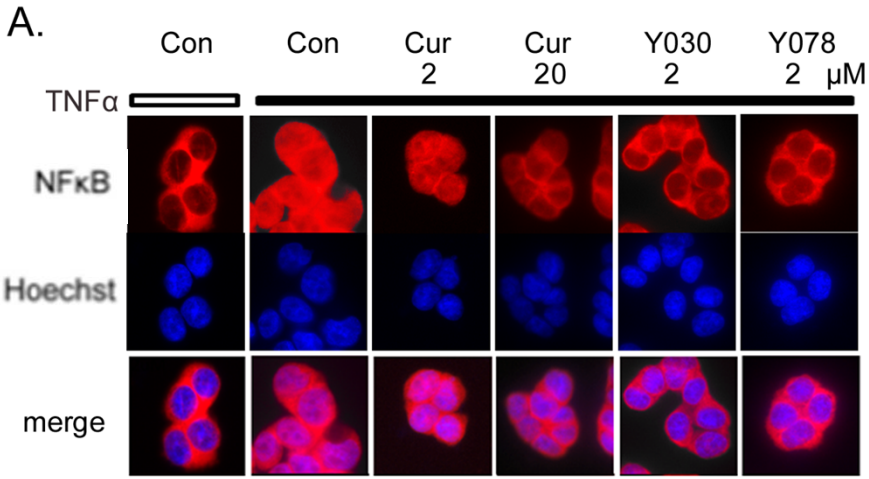
Her2 inhibitor

Myc inhibitor



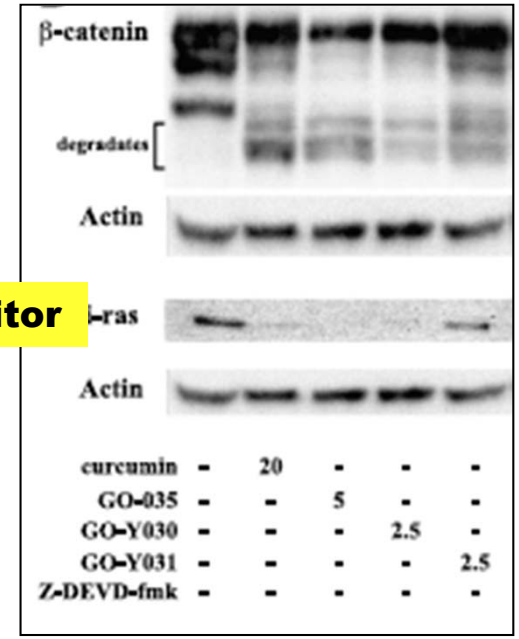
Analogs can regulate overexpressed oncogene products such as ,,,.

c-Myc, KRAS, CyclinD1, ErbB2, β-catenin, COX-2,, (examined).



NF-kB inhibitor

KRAS inhibitor

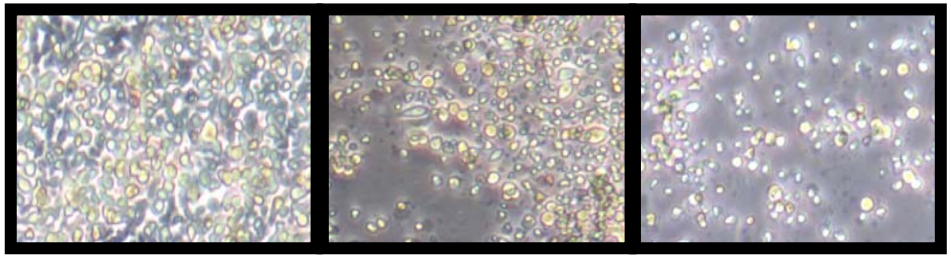


Analogs can induce apoptosis.

Malignant phenotypes

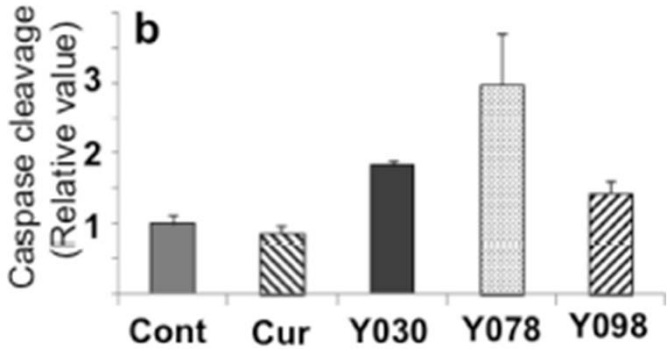
1. Loss of growth control
2. Resistance to apoptosis
3. Immortality
4. Angiogenesis
5. Invasion
6. Metasatasis

Analogs can induce apoptosis related proteins such as ,,,,,,,.
Caspases, PARP, TP53, XIAP, DR5,, (examined).

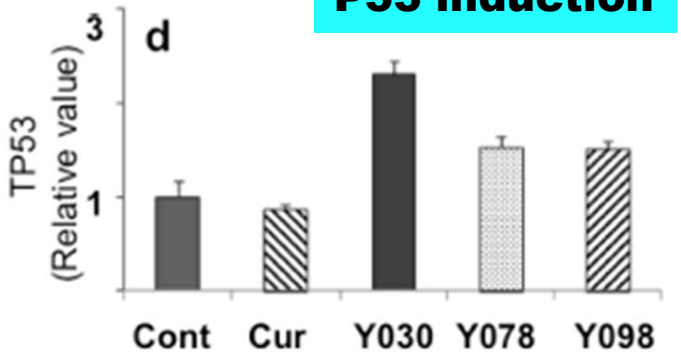


Apoptotic DLD-1 cells

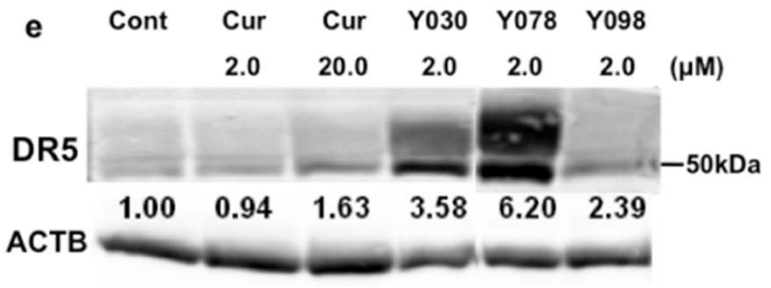
Caspases induction



P53 induction



Death receptor induction



Chapter 7: Cancer stem cells & analogs

Analogs can kill cancer stem cells.

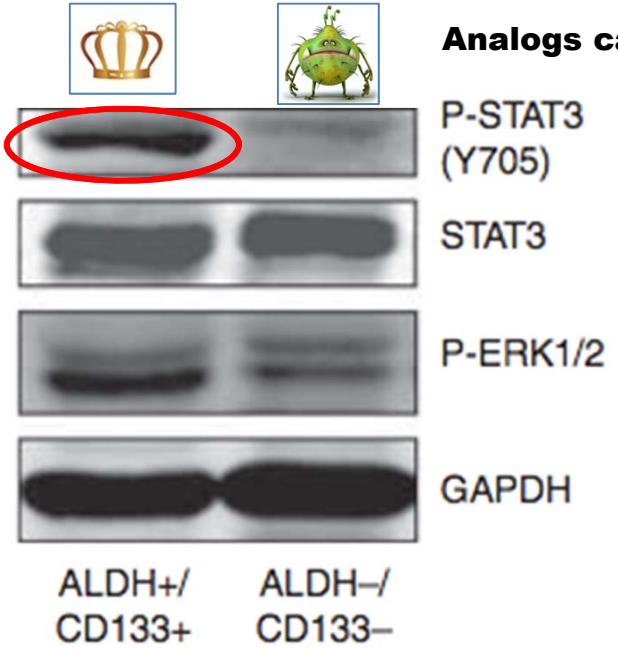
Cancer stem cell is like a queen bee. She is resistant to chemotherapy.

sensitive

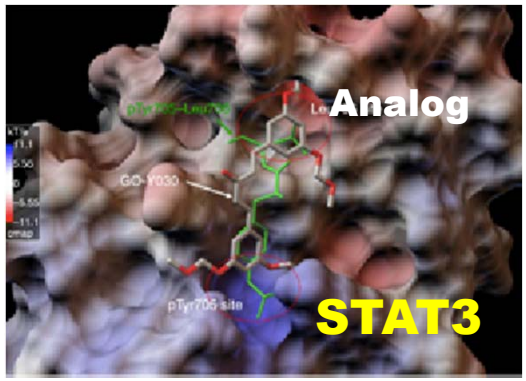
resistant

Killer Queen

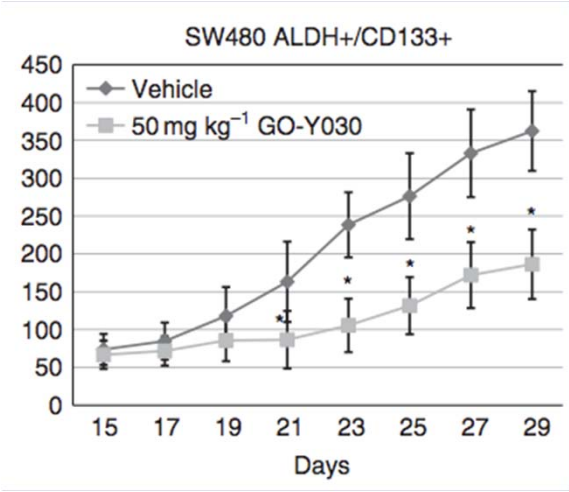
Phosphorylation of STAT3 is characteristic to cancer stem cells.



Analogs can bind phosphorylation site of STAT3, and inhibit STAT3 signaling.



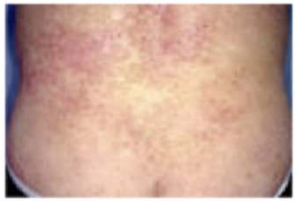
Analogs can inhibit cancer stem cell growth *in vivo*.

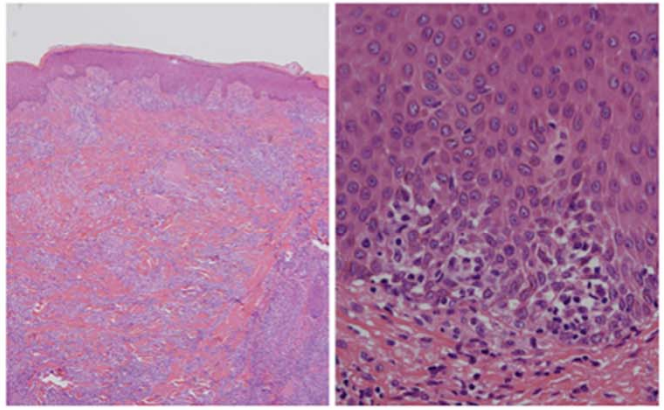


Chapter 8: Potential against rare cancers

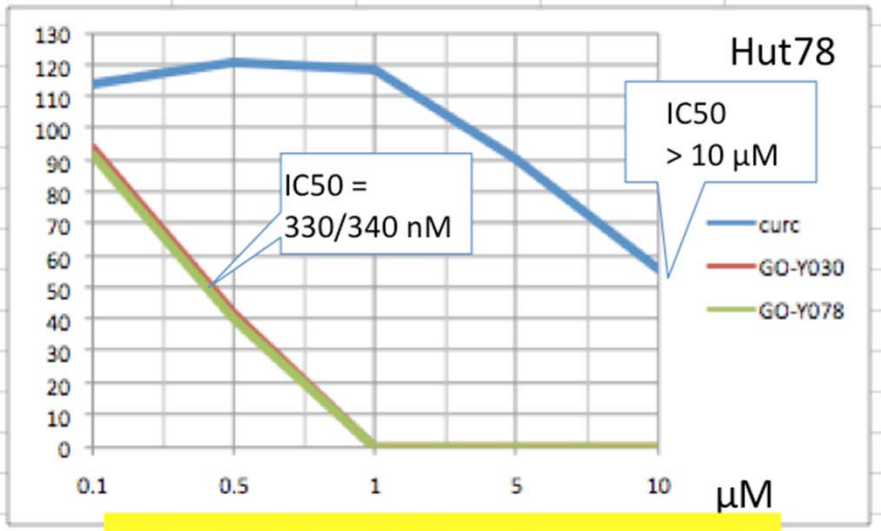
Rare cancers
- CTCL -

The incidence; < 1 / 100 000
in the United States

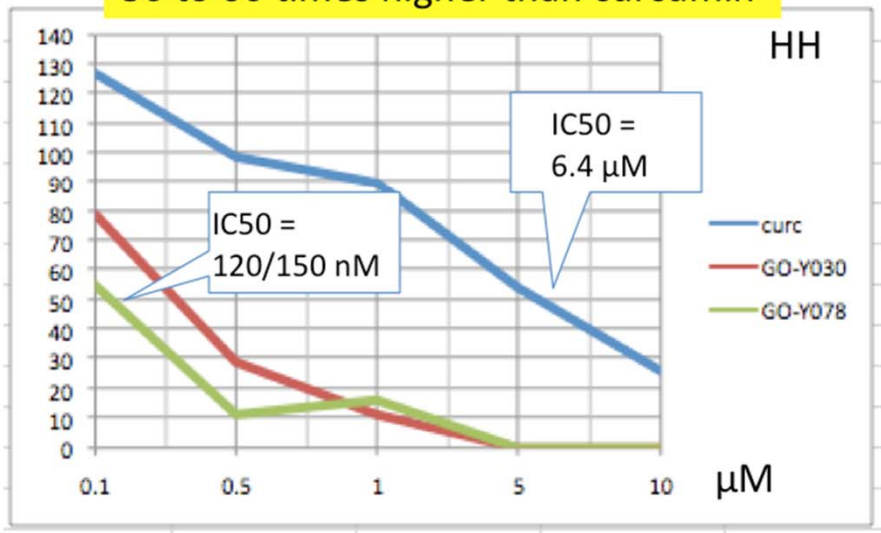




Growth-suppressive potentials – CTCL cell lines -

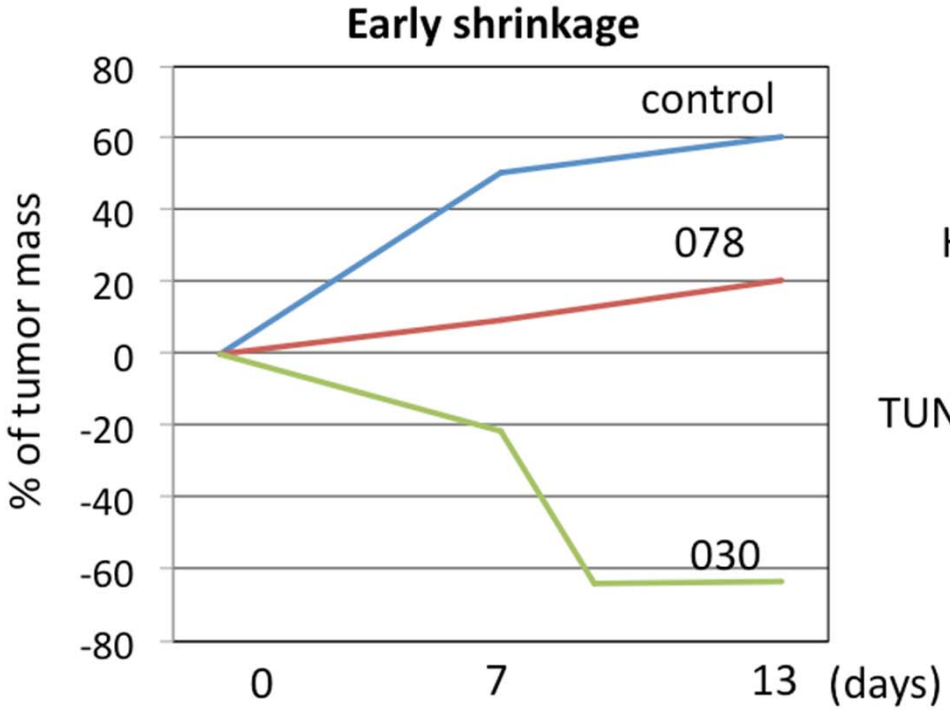


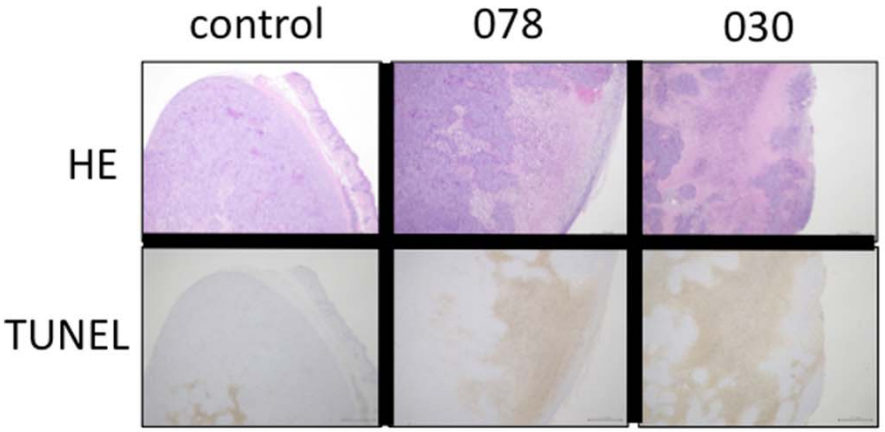
30 to 60 times higher than curcumin



Analogs have no HDAC inhibitory effects. Combination with SAHA?

Animal models - CTCL -





CTCL can be cured in animal model.

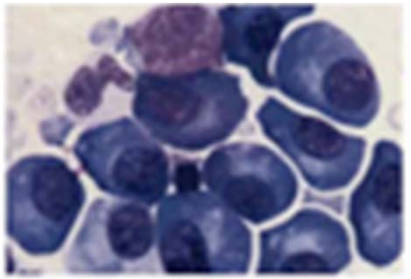
Anti-tumor effect (at sacrifice)

	Complete Regression	Regression	No change	Enlargement
Cont (n=8)	0 (0)	0 (0)	1 (12.5)	7 (87.5)
030 (n=10)	6 (60.0)	0 (0)	3 (30.0)	1 (10)
078 (n=11)	1 (9.1)	0 (0)	3 (27.3)	7 (63.6)

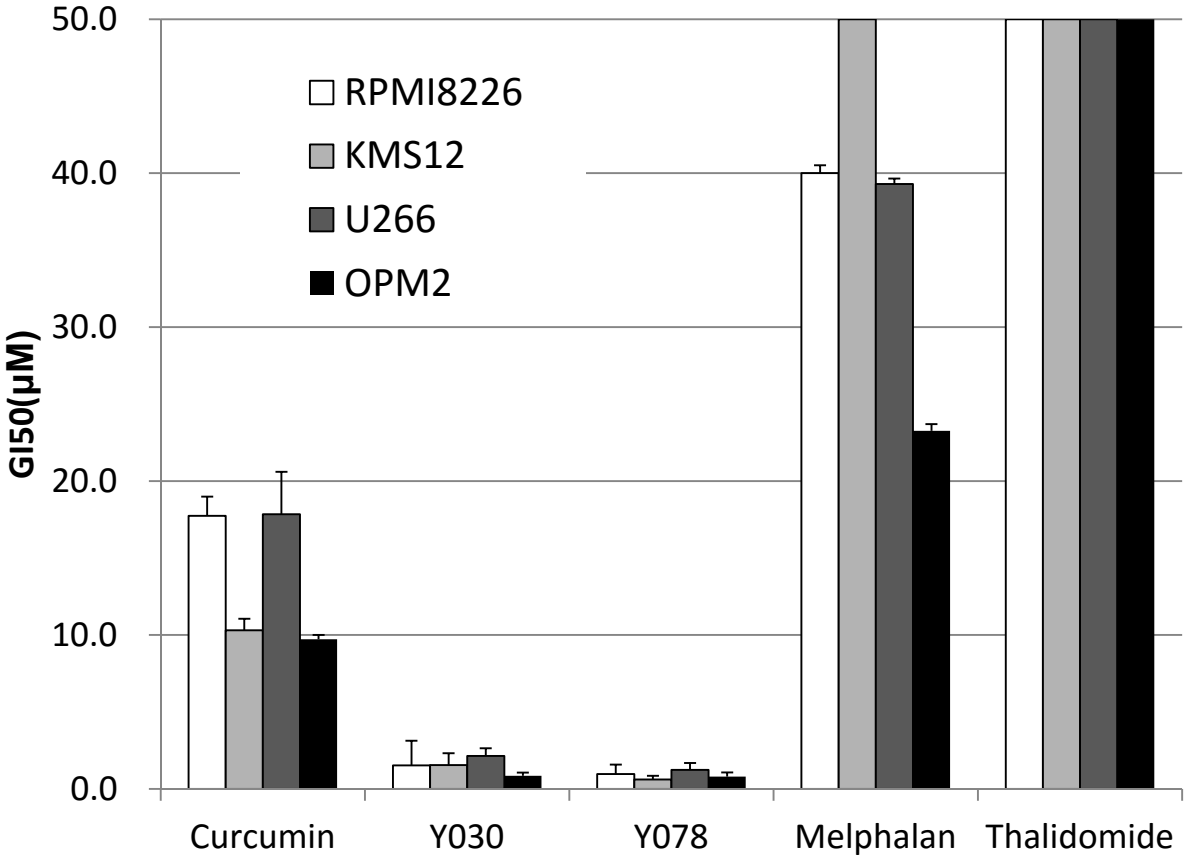
P=0.001176

P=0.00565
(Kruskal-Wallis)

Rare cancers
- Multiple myeloma -

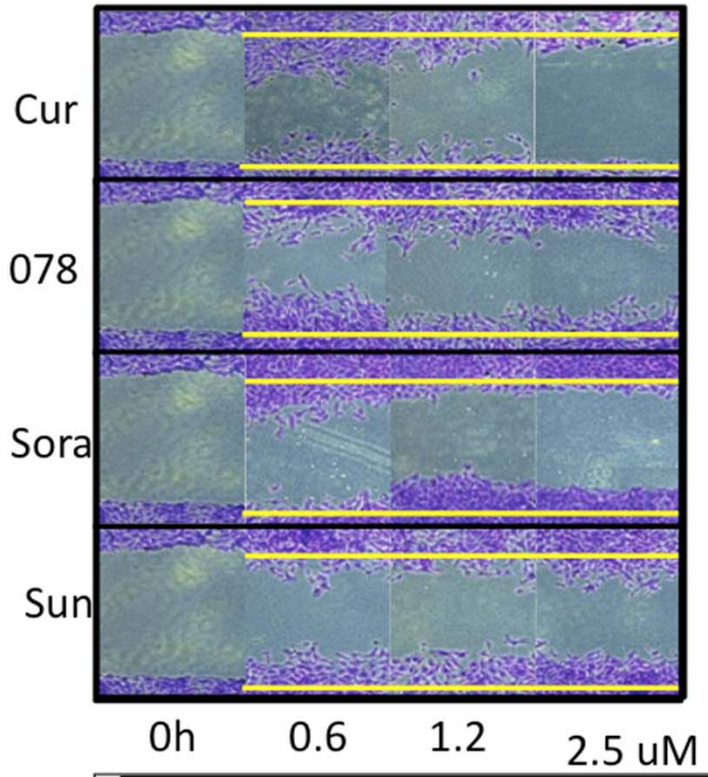


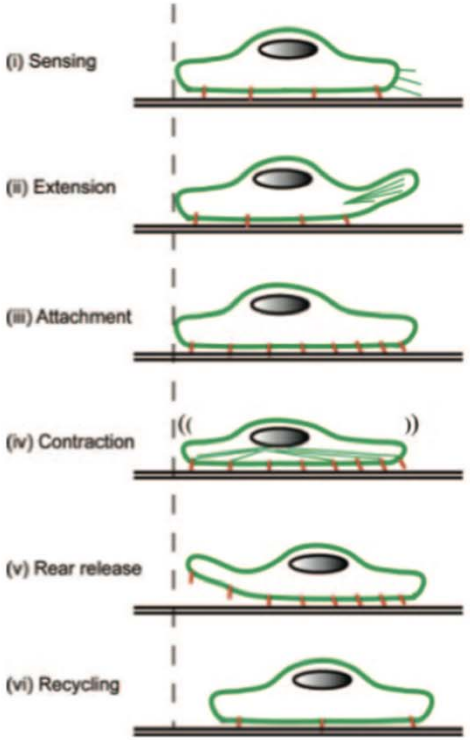
MTT Assay

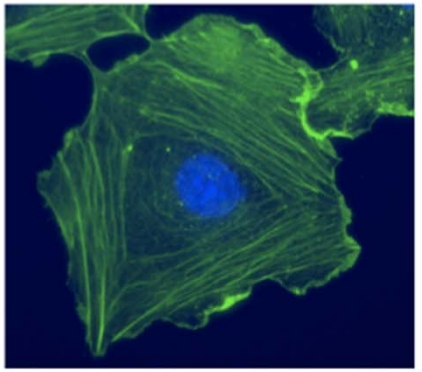


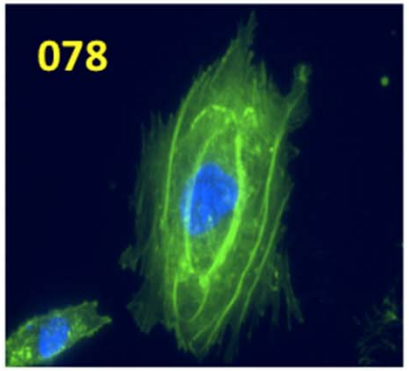
72hr treatment

Chapter 9: Anti-angiogenic potential of analogs

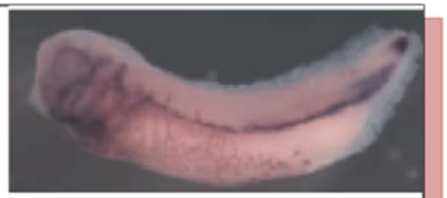


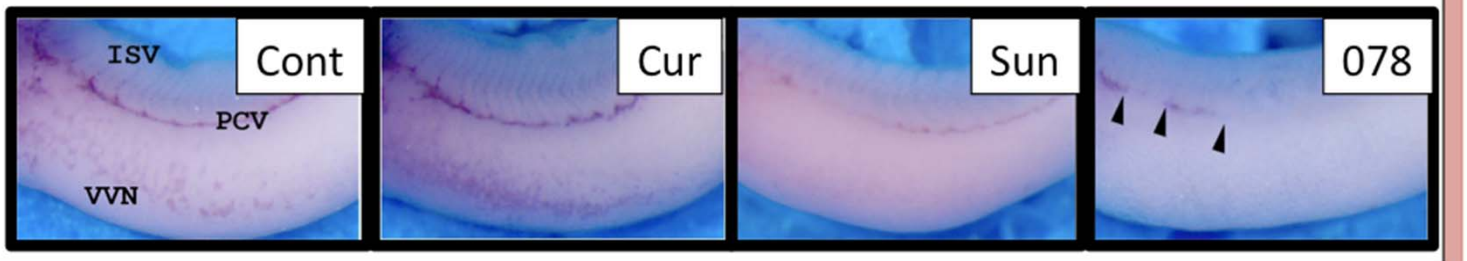




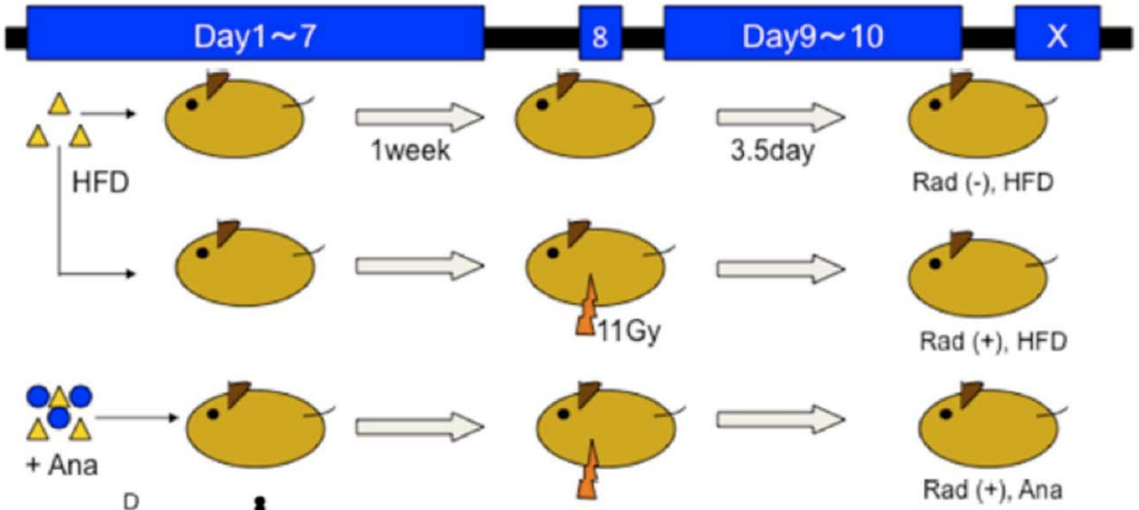


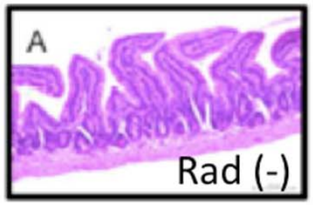
Angiogenesis inhibition (Xenopus Embryo)
/GO-Y078 (20 μM)

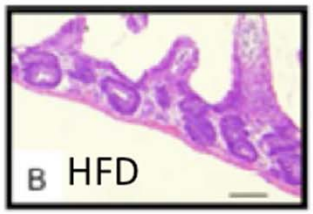


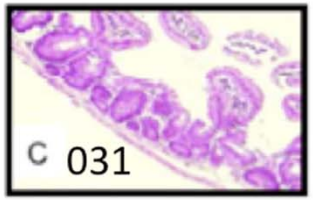


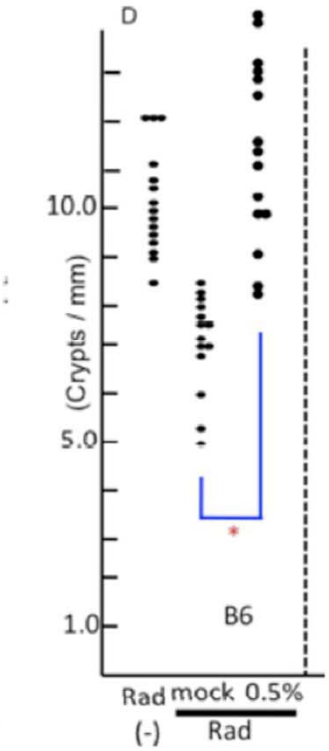
Chapter 10: Radioprotection

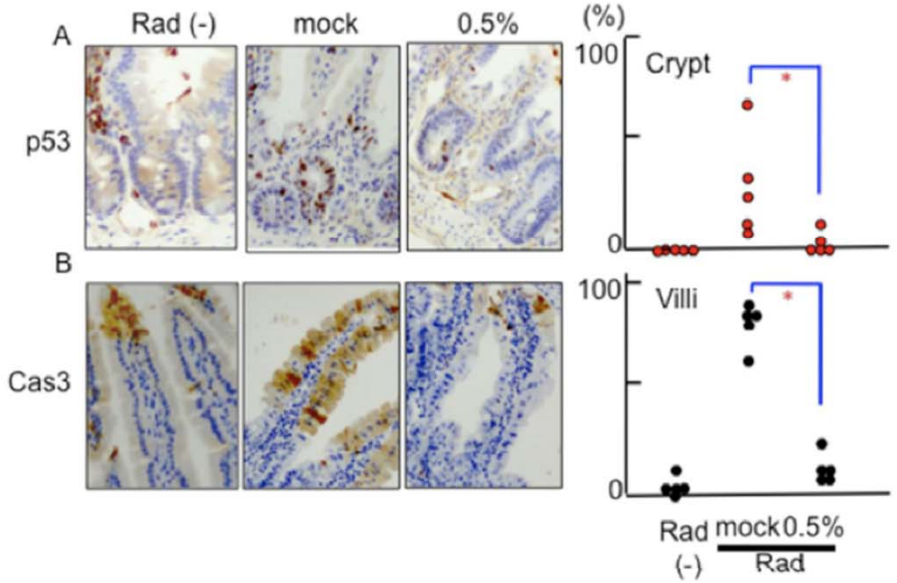








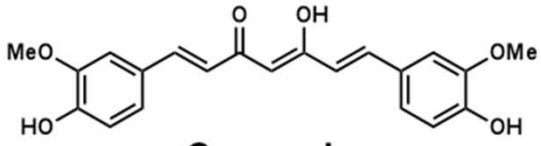




Chapter 11:

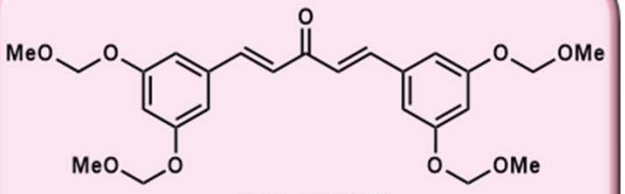
1. Improvement of solubility

Curcumin is low bioavailable (insoluble in water, poor absorption).



Curcumin

GI_{50}= 16 μM

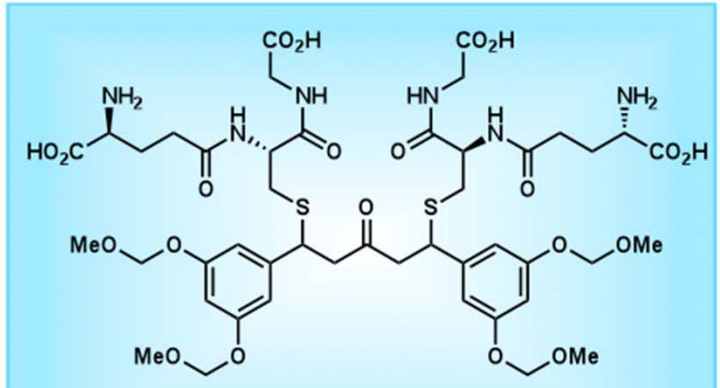


GO-Y030

GI_{50}= 0.3 μM

Low solubility

C_5-Curcuminoid-thiol adduct as prodrug (12 compounds)



GO-Y140

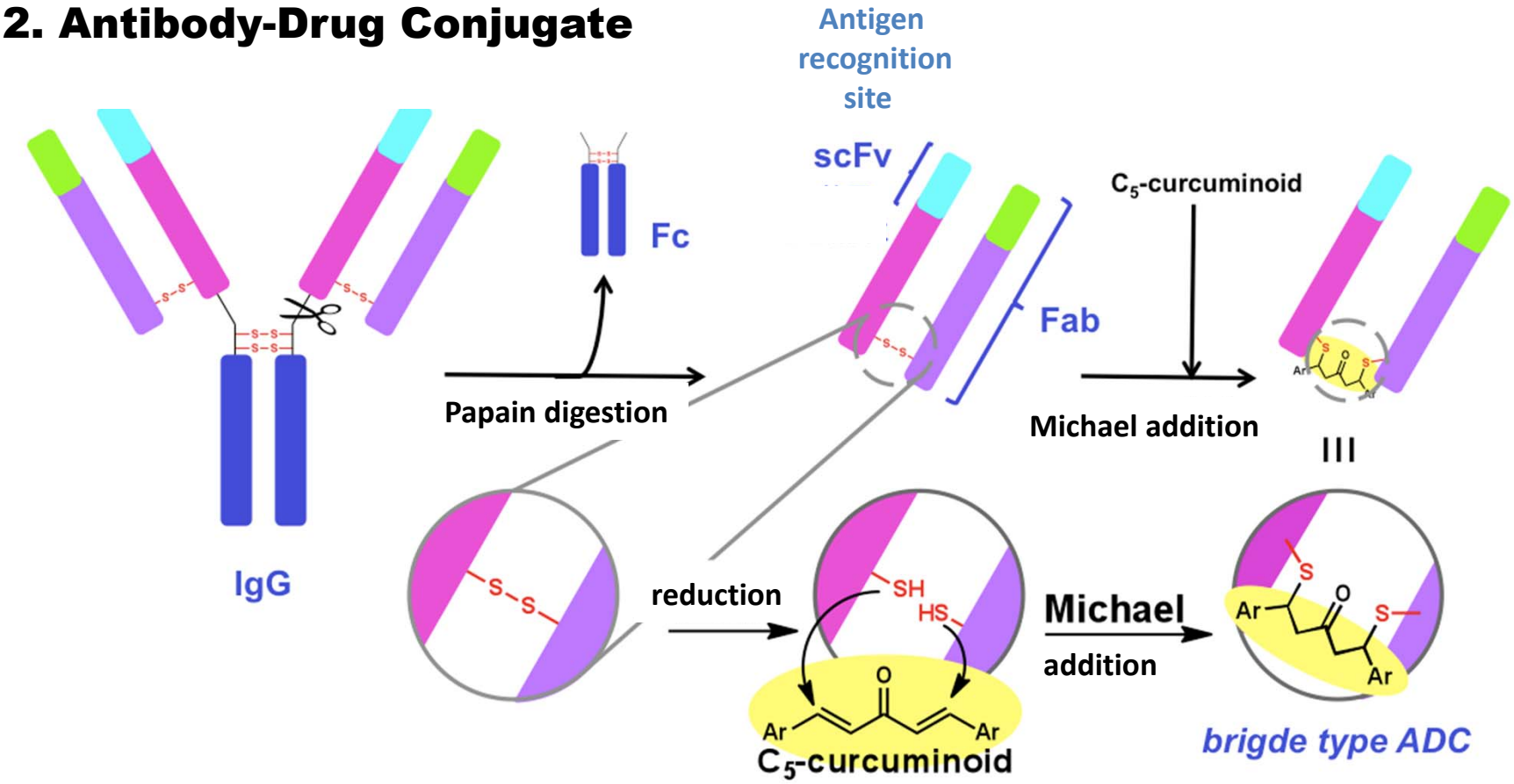
GI_{50}= 3.3 μM

GO-Y030 GO-Y140

30 mg compound in pH8 PBS buffer

Solubility ↑

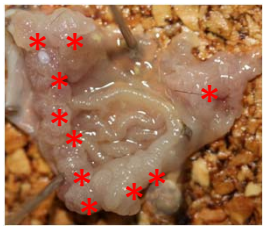
2. Antibody-Drug Conjugate



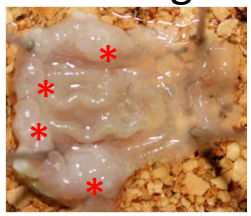
Chapter 12: Future Directions

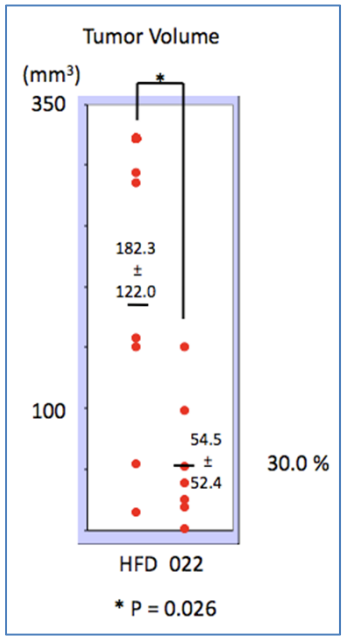
1. An analog was detected in curry.
It is potent to suppress gastric cancer *in vivo*.

control



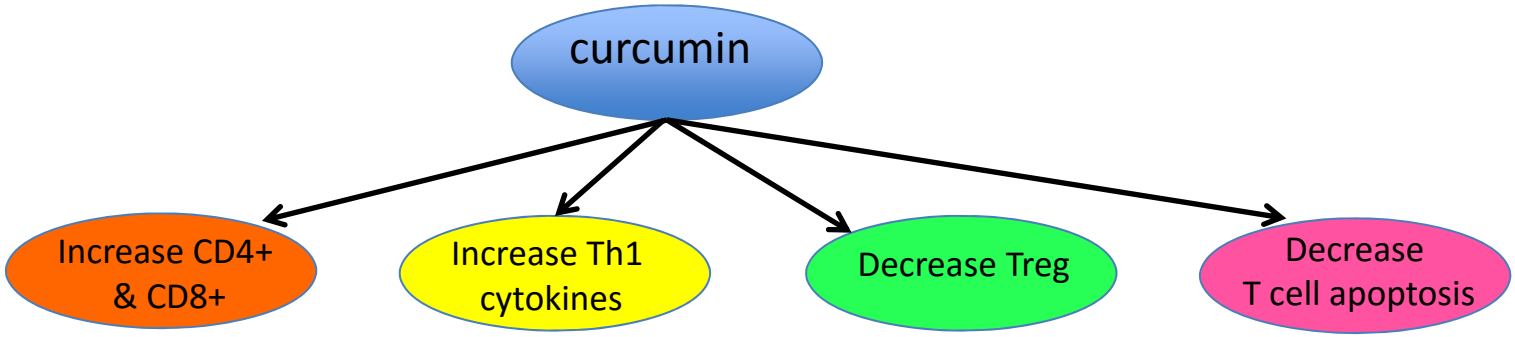
analog





Functional Food

2. Analogs could induce anti-tumor immunity, like curcumin.



Apendix (1): Patent Right

We got US and Japan patents.

(19)日本国特許庁(JP)　(12)特　許　公　報(B2)　(11)特許番号
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Analog man

Appendix (2): Analog & Sleeping sickness (African trypanosomiasis)

Analogs may be effective for trypanosomiasis (sleeping sickness).

In vitro anti-trypanosomal activity against *Trypanosoma brucei brucei* GUTat 3.1 and cytotoxicity in MRC-5 cells of curcumin and GO-Y0xx compounds

	Growth inhibition IC50 (μg/ml)		
Analogs	**Anti-trypanosomia activity**	**Cyto-toxicity**	**Safety Index**
Curcumin	0.66	3.32	5.0
GO-Y015	1.32	38.37	29.1
GO-Y023	0.53	13.19	24.9
GO-Y038	0.078	5.09	65.3
GO-Y050	0.33	13.62	41.3
GO-Y052	0.46	10.99	23.9
GO-Y056	0.21	5.33	25.4
GO-Y057	0.44	7.17	16.3
Suramin	1.58	>100	>63
Eflornithine	2.27	>100	>44

Recruit Collaborators!!