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OMICS Group has organized 500 conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.

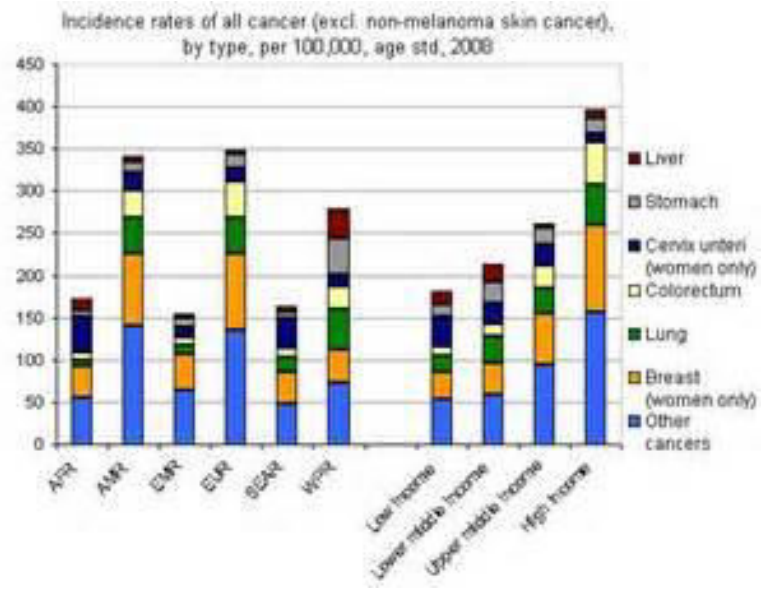
OMICS Group Conferences
Accelerating Scientific Discovery
Conference Guide
3rd International Conference and Exhibition on
Biosensors & Bioelectronics

Fluorescence Imaging of Cancer by Molecular Response to COX-2 Enzymes

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Cancer : One of the Major Causes of Death World-wide



In 2008 resulted in 7.6 million deaths (13% of the total)

China's Population Motality in 2010

Disease Name	Percentage	Ranking
Cancer	27.01%	1
Heart Disease	20.77%	2
Cerebrovascular Disease	20.36%	3

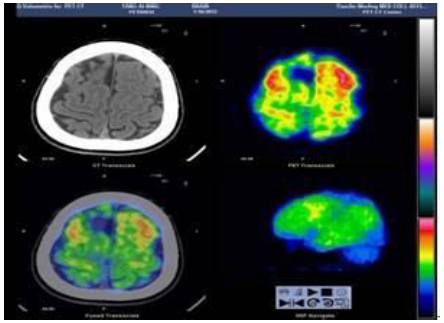
- **Cancer is a major public health problem, although progress has been made in reducing incidence and mortality rates, it still causes numerous deaths world-wide**
- **Early diagnosis of cancer is particularly important for reducing cancer mortality.**

Cancer diagnostic methods

- Magnetic Resonance Imaging (MRI)
- B Ultrasound
- Positron Emission Tomography (PET) imaging
- Computed Tomography (CT)
- X-ray imaging



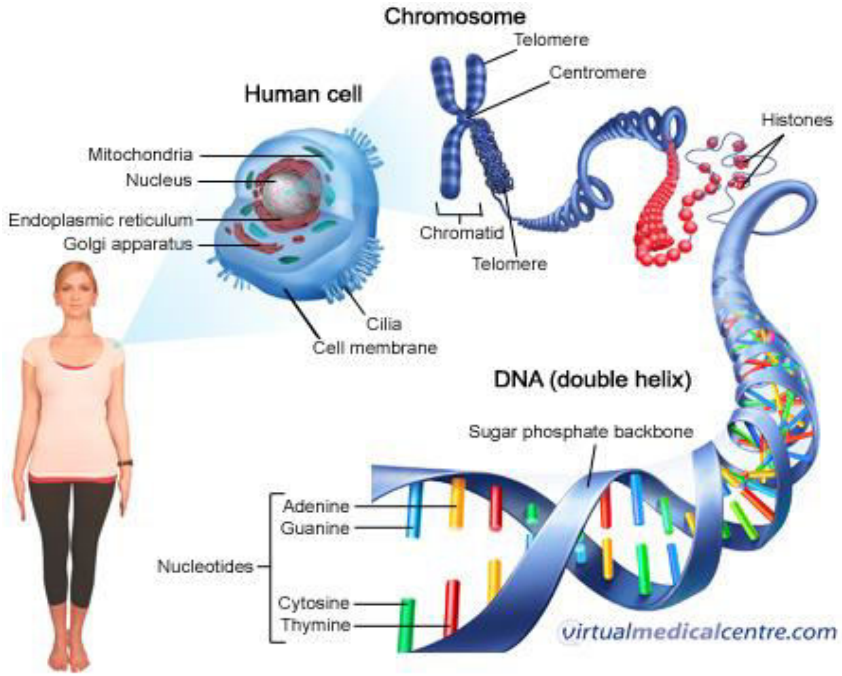






Each of these methods has its drawbacks, such as relatively low resolution, narrow time window, high instrument cost and injection of radioactive agents. **Apart from that, they are often not effective until the middle and terminal cancer**.

From Fluorescent Dyes to Diseases Diagnosis and Surgery



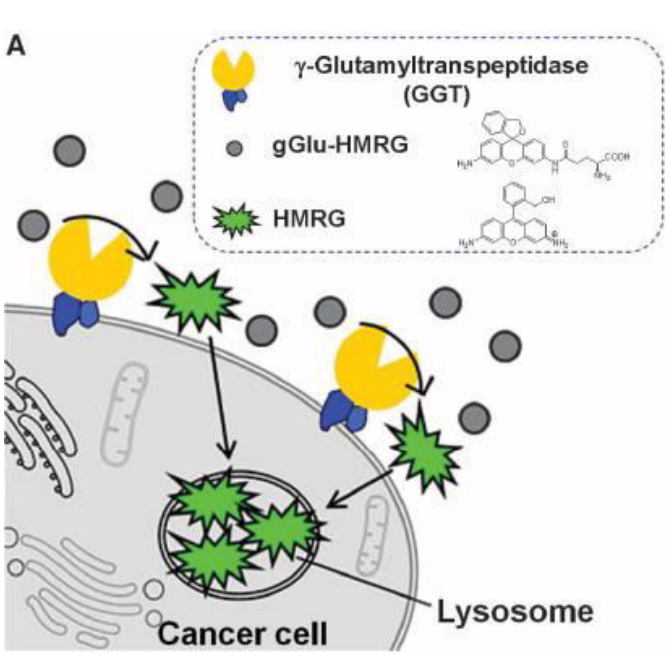
Macro → Micro

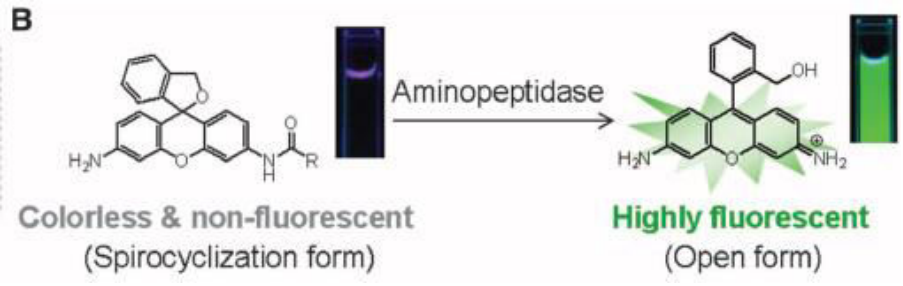
Fluorescent Dyes & Probes

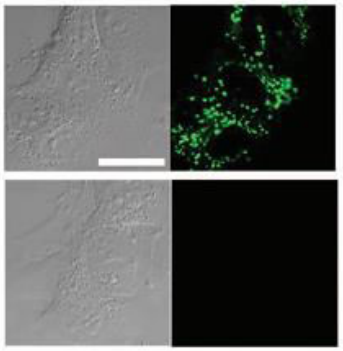
- Lesions have produced in your body for a long time when you feel a pain.
- Occurrence of diseases is from mutations of DNA, RNA and enzymes to body's pain
- A few probes for surgery using DNA, RNA or enzymes as imaging targets have been reported.

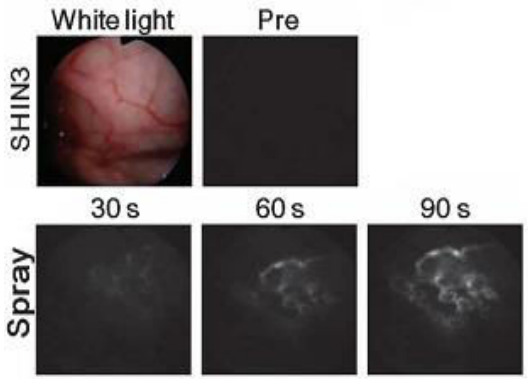
For the early diagnosis of cancer due to its high-selectivity, high-resolution, and noninvasive capabilities.

GGT targeted probe





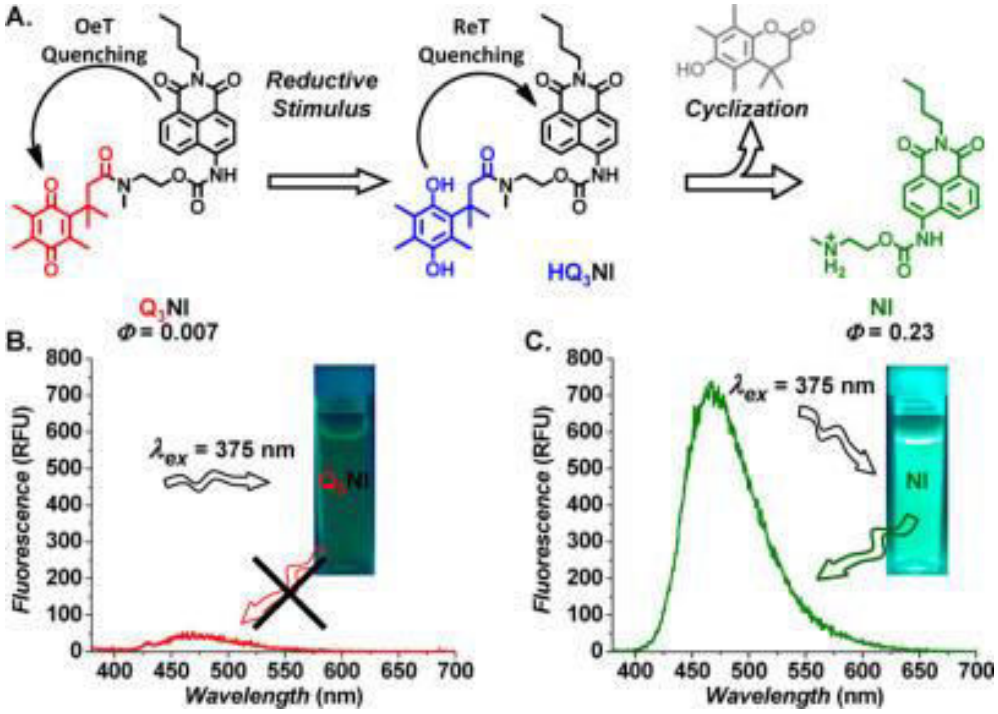


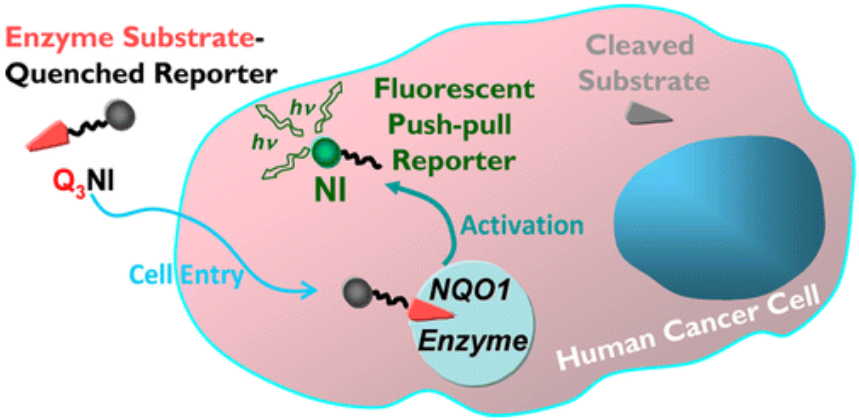


- **GGT : g-glutamyltranspeptidase, a cell surface–associated (or bound) enzyme involved in cellular glutathione homeostasis, overexpressed in several human tumors, including those from cervical and ovarian cancers.**
- **A small-molecule fluorescent probe for detection of cancer using GGT as target can be used in not only fluorescence imaging but also endoscopy system (ESS)**

Urano Y, et al. Sci. Transl. Med., 2011, 3, 110-119.

hNQO1 targeted probe

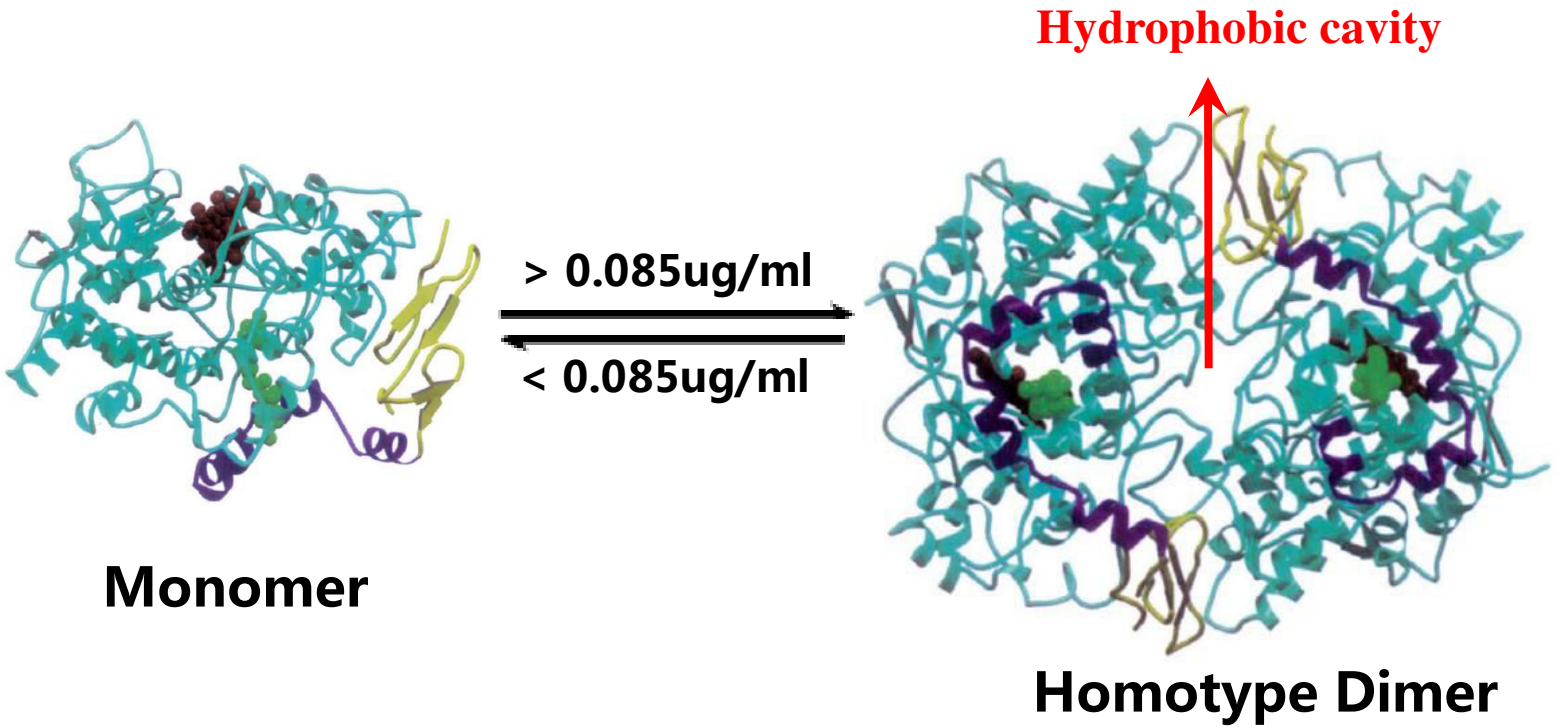




- **hNQO1 : the cancer-associated human NAD(P)H, quinone oxidoreductase isozyme 1.**
- **Quenching of molecular probe fluorescence is achieved through unique photoinduced electron transfer between the naphthalimide dye reporter and a covalently attached, quinone based enzyme substrate. Fluorescence is turned on by rapid removal of the quinone quencher highly selectively by HNQO1.**

McCarley R. L. et al. J. Am. Chem. Soc., 2013, 135, 309-314.

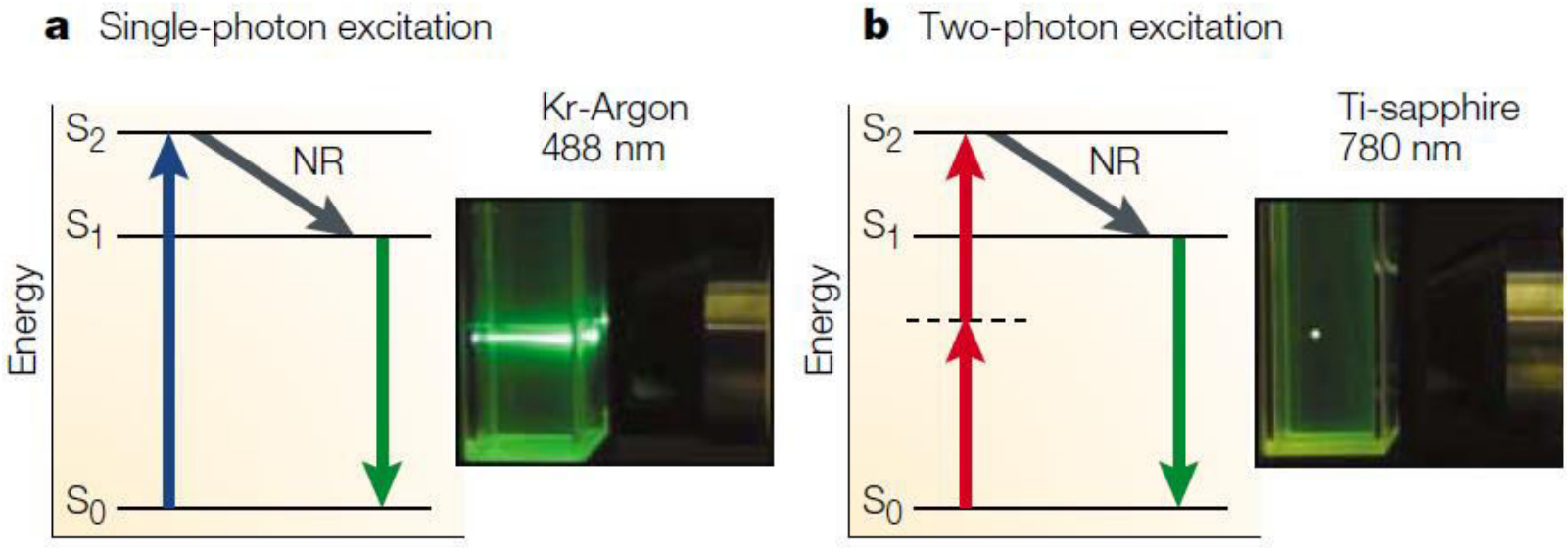
The different crystal structure in the different concentration



COX-2: Cyclooxygenases, absent or expressed at very low levels in most normal cells but expressed at high levels in inflammatory lesions and many tumors

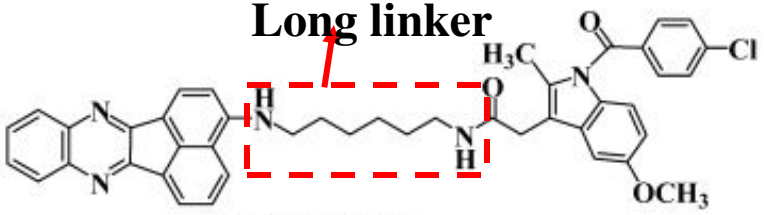
Curr Opin Struct Biol 2001, 11,752-760.
Nature 1996, 384,,644-648.

The advantages of two-photon technology

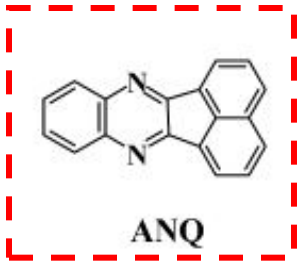


Excellent fluorescence with two-photon features such as increased penetration depth, localized excitation and prolonged observation time.

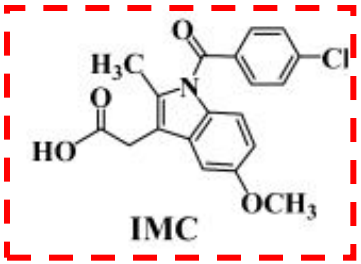
Long linker



ANQ-IMC-6

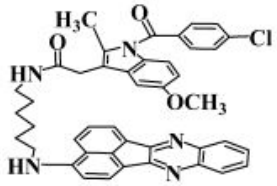


ANQ



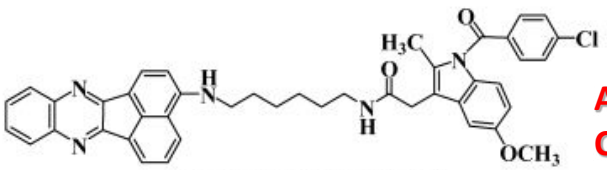
IMC

Fluorophore **Recognition group**



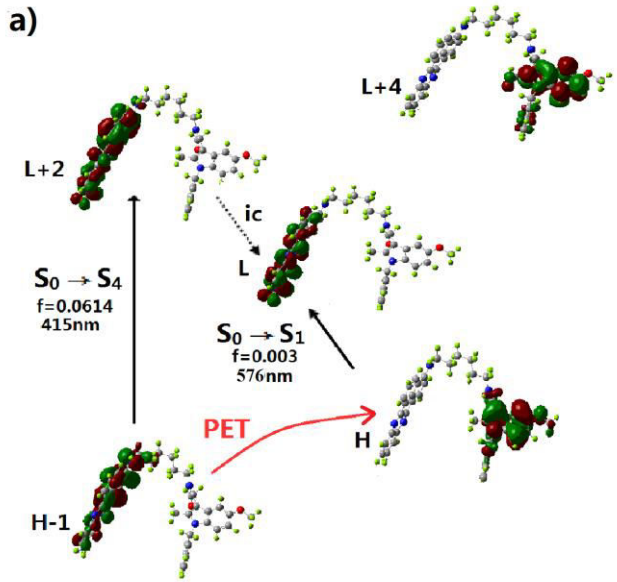
ANQ-IMC-6 (folded)

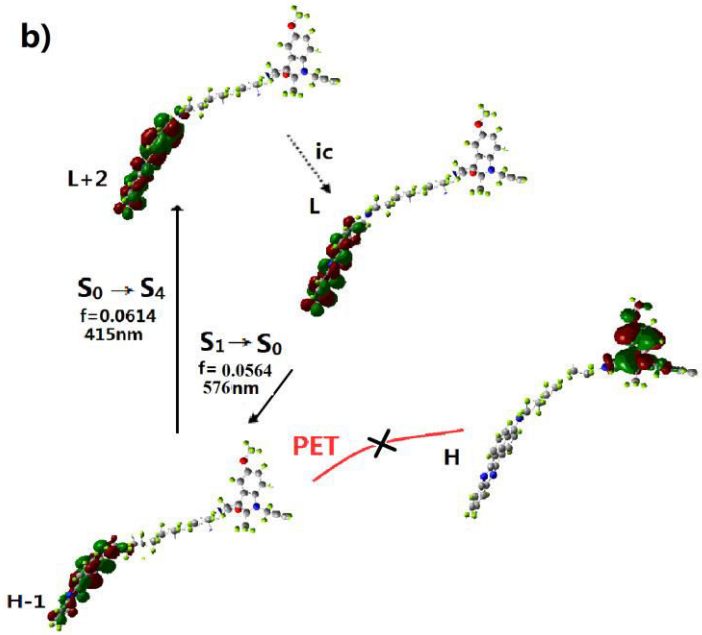
Free ANQ-IMC-6

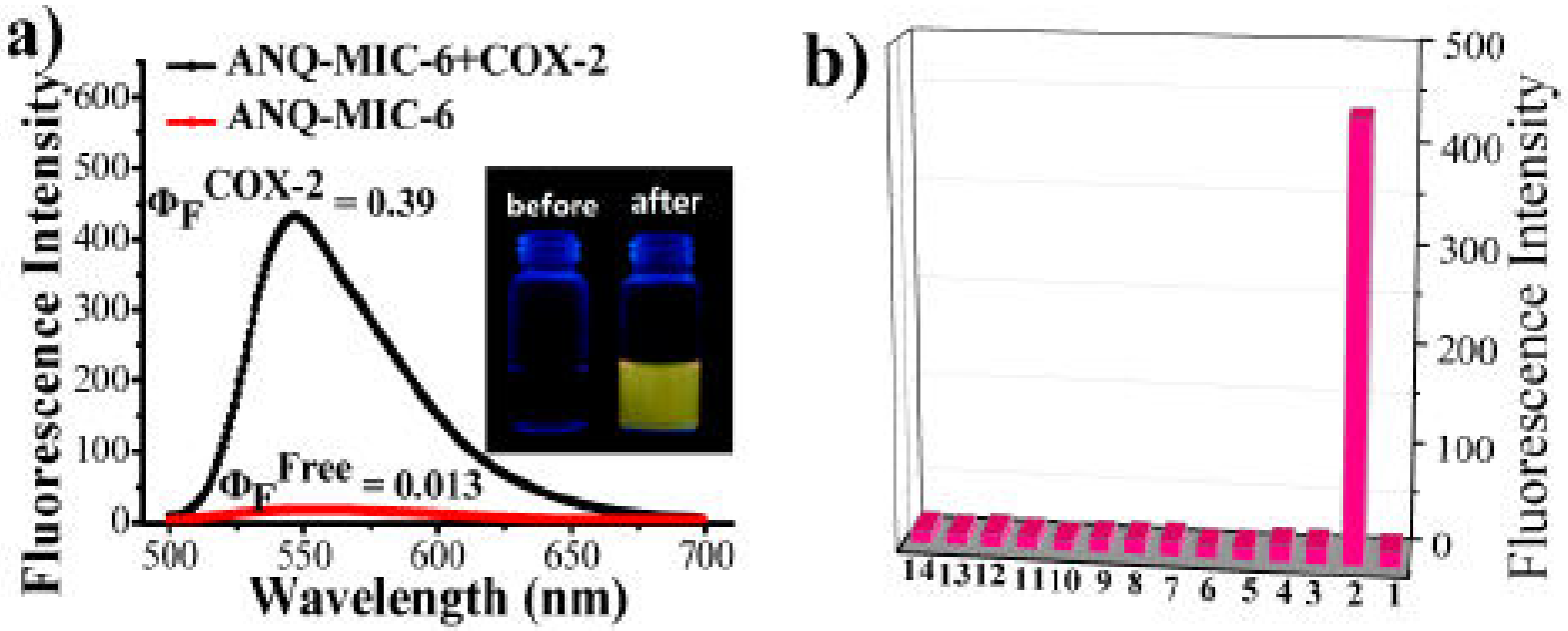


ANQ-IMC-6 (unfolded)

After combined with COX-2

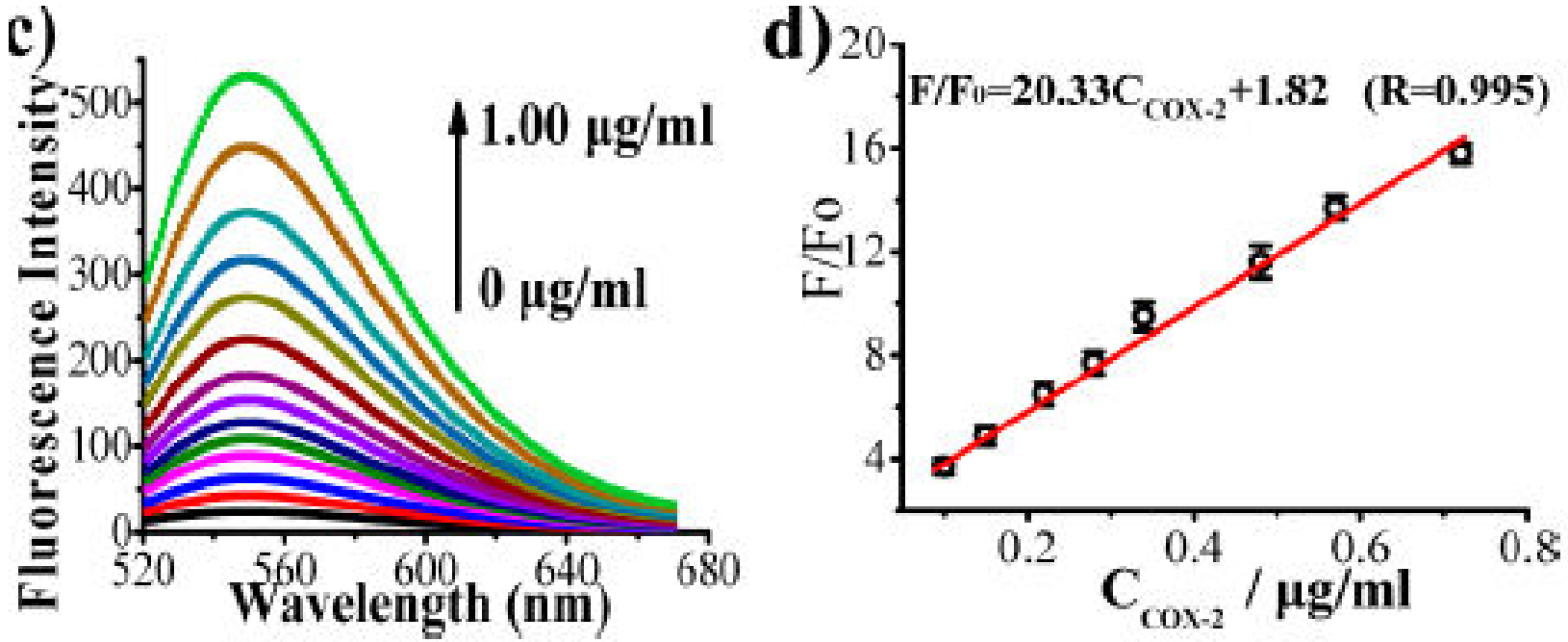






a. Fluorescence emission spectra of **ANQ-IMC-6** (2.0 μM) in the absence and presence of COX-2 (0.50 μg/ml) in buffer at 25 °C.

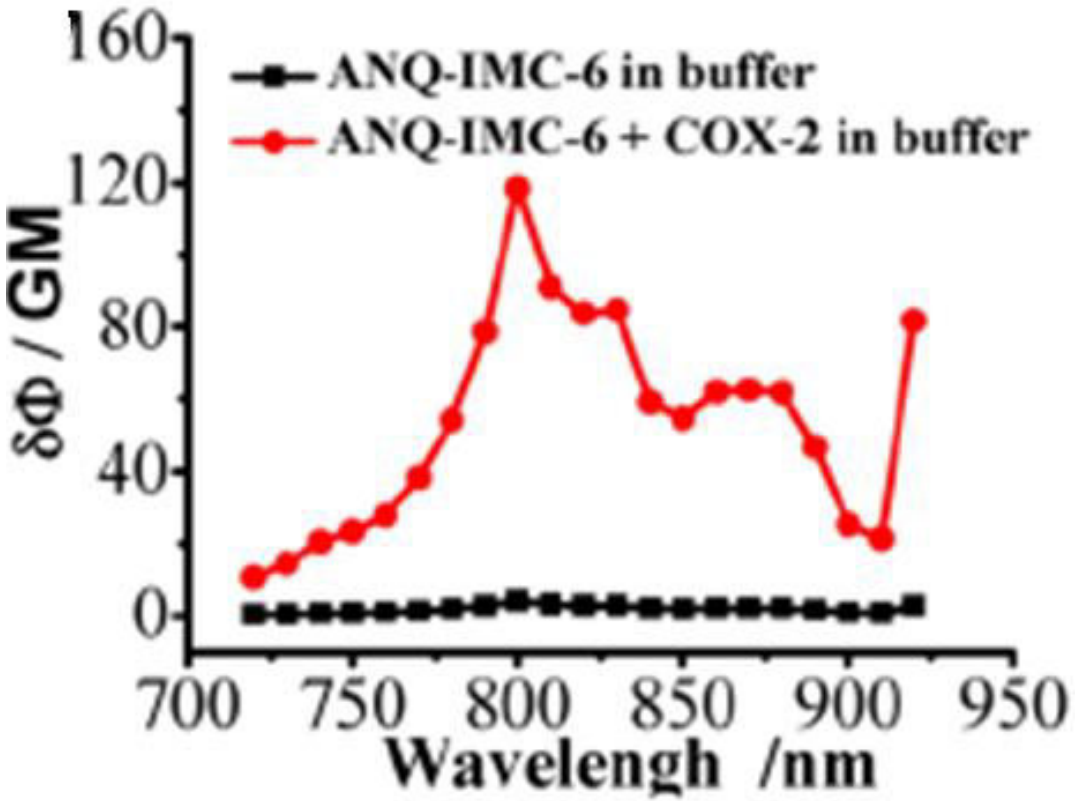
b. Changes in fluorescence with different biomolecules (0.050 μg/ml) in buffer. 1, control; 2, COX-2; 3, RNA; 4, DNA; 5, triacylglycerol acylhydrolase; 6, lysozyme; 7, proteinase k; 8, histone; 9, collagen; 10, hemoglobin; 11, BSA; 12, β-amylase; 13, trypsin; and 14, chymotrypsin.



c. Emission spectra of **ANQ-IMC-6** (2.0 μM) upon the addition of COX-2 (0-1.0 μg/ml.) in buffer.

d. The fluorescence of **ANQ-IMC-6** (2.0 μM) related to COX-2 concentration (0.05–0.72 μg/ml).

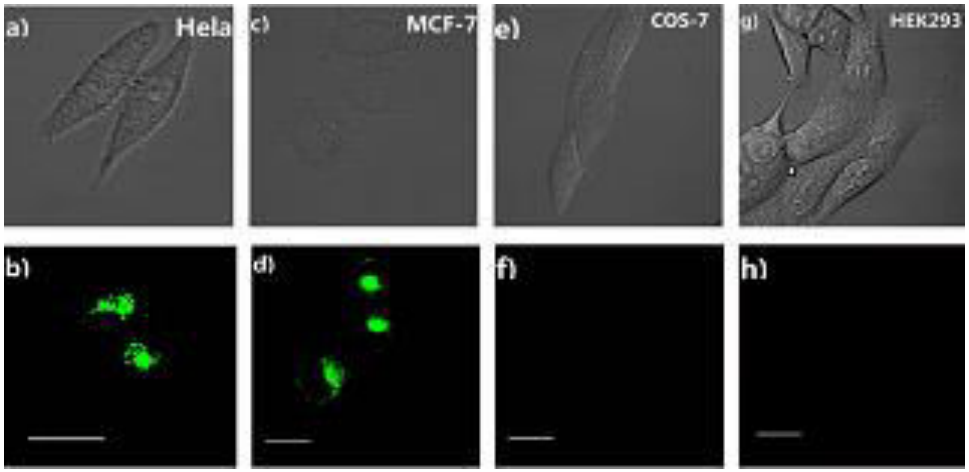
The detection limit for COX-2 was determined as 0.11 μg/ml , higher than the minimum expression of COX-2 (0.085 μg/ml) in cancer cells.



The activated two-photon action cross section $(\Phi\delta)_{max}$ of ANQ-IMC-6 is 118 GM (1GM= 10^{-50} cm^4 s/photon) when excited at 800 nm in the presence of COX-2 (0.50 μg/ml), and there was a 25-fold enhancement in the value $(\Phi\delta)_{max}$ compared with that seen in the absence of COX-2.

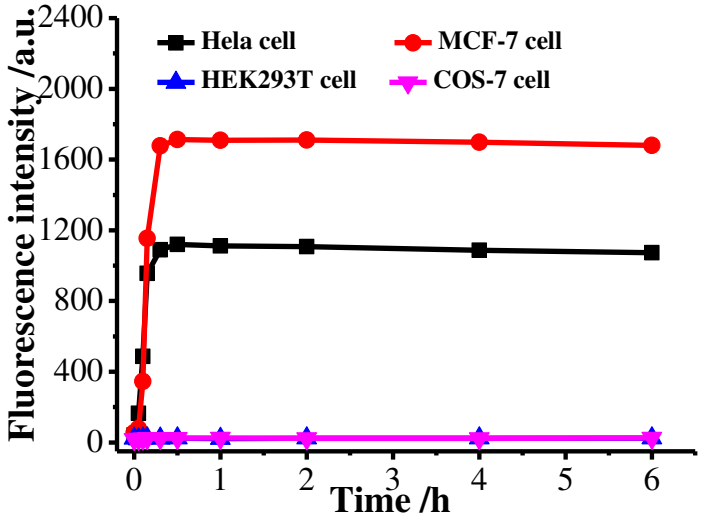
Selectively imaging living cancer cells

cancer cells　　normal cells



Incubation time 15 mins：

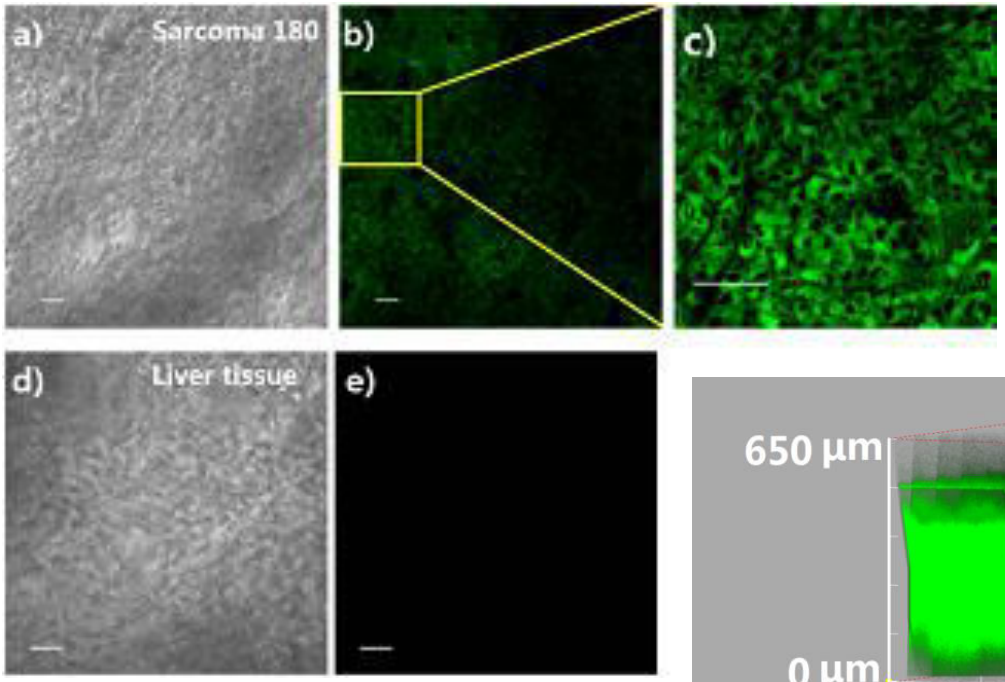
- **Strong and stable fluorescence in both cancer cells**
- **Negligible fluorescence in both normal cells**

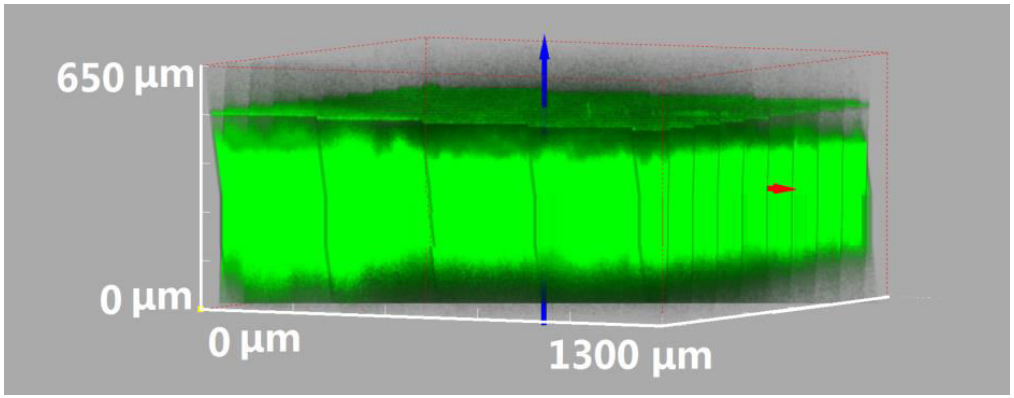


Prolong incubation time（6 h）：

- **Still obvious fluorescence in cancer cells**
- **Still negligible fluorescence in normal cells**

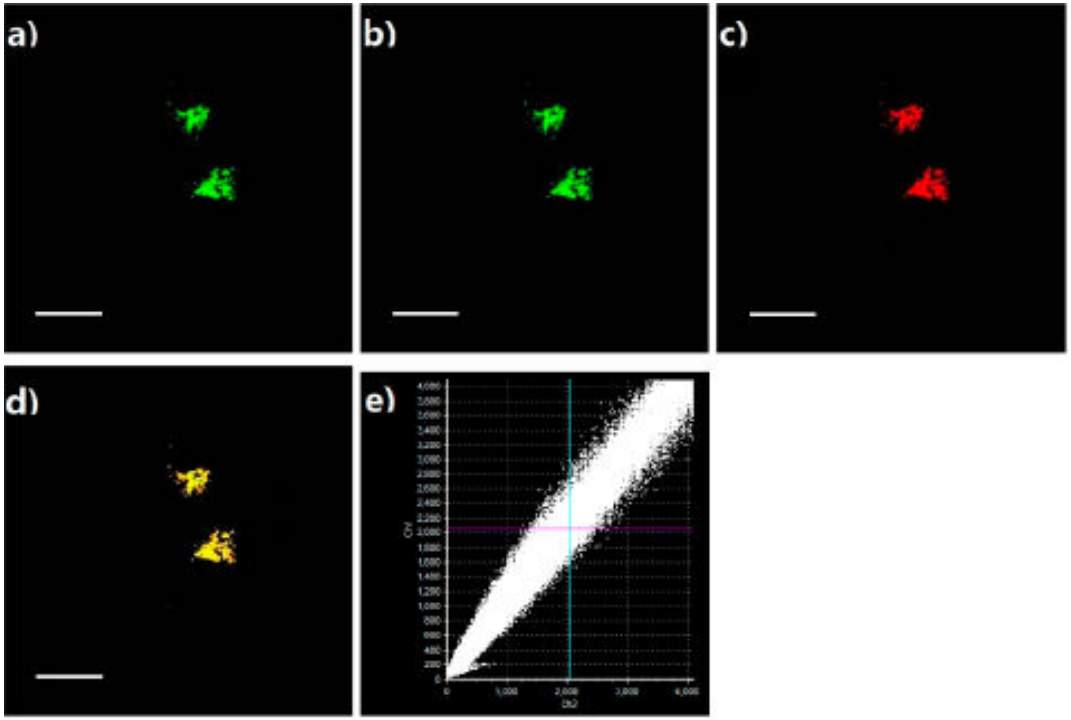
Selective 3D depth imaging of living cancer tissues





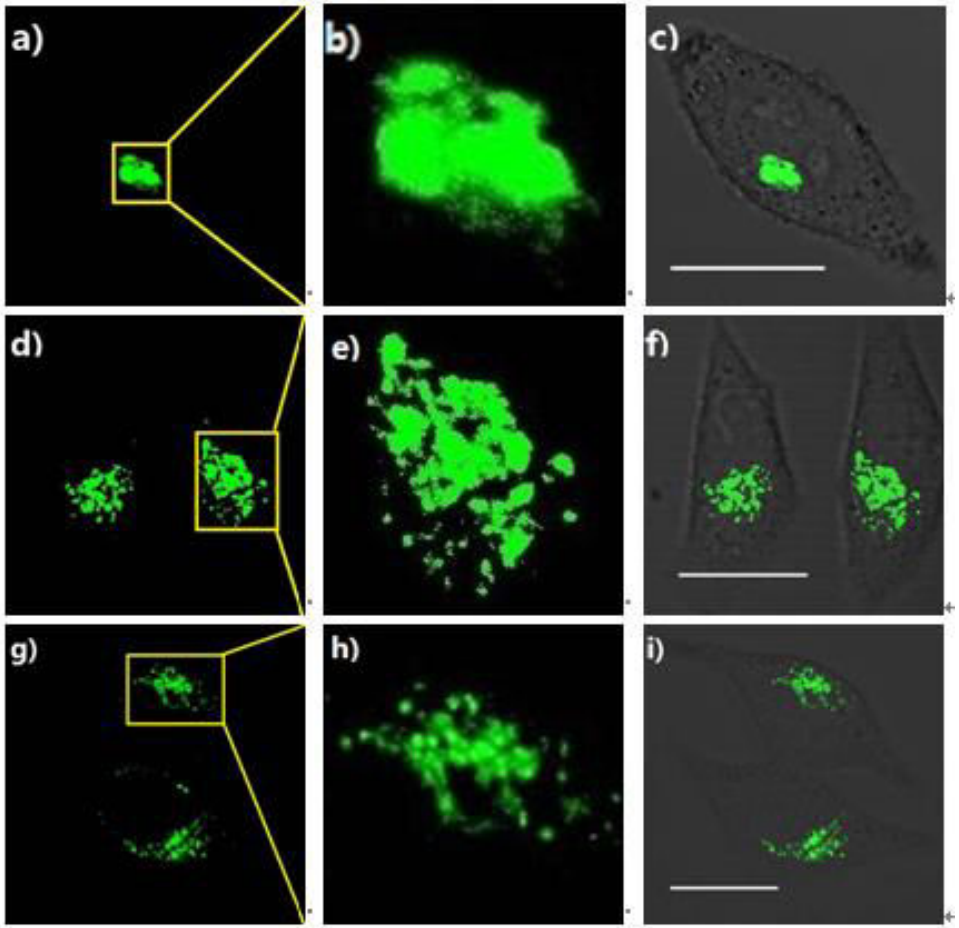
The sarcoma 180 tissue slices could be clearly visualized by green fluorescence at 50-550 µm depth . Only negligible fluorescence was observed in normal liver tissue slices.

Specific localization of Golgi Apparatus of cancer cells.



Fluorescence images of **ANQ-IMC-6** (5.0 μM) and BODIPY TR C5-ceramide (5.0 μM) in HeLa cells. a, and b, Stained with **ANQ-IMC-6**. a, excitation wavelength = 800 nm, scan range = 530-570 nm. b, excitation wavelength = 488 nm, scan range = 530-570 nm. c, Stained with BODIPY TR C5-ceramide, excitation wavelength = 543 nm, scan range = 600-640 nm. d, Merged image of b, and c. e, Intensity correlation plot of stain **ANQ-IMC-6** and BODIPY TR C5-ceramide.

Imaging morphological changes of the Golgi apparatus during the cancers cells apoptosis.



- Golgi body gradually disintegrated, to form the apoptotic bodies

- Fluorescent dye can be used to *in situ* real-time observe changes of cancer cells golgi apparatus

Fan JL and Peng XJ, J. Am. Chem. Soc., 2013, 135, 11663-11669.

Summary

- A PET-quenched molecular probe (ANQ-IMC-6), a fluorogenic derivative of a COX-2 inhibitor was reported, whose fluorescent signal is selectively and quickly generated by interaction with COX-2 accumulating in the Golgi apparatus of cancer cells.
- The push-pull charge-transfer structure of ANQ-IMC-6 provides significant two-photon properties permitting the selective identification of and screening for cancer cells.
- We anticipate that ANQ-IMC-6 could serve as a practical tool for the early diagnosis of cancers.

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Dr. Jianjun DU

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Benhua Wang

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Education Ministry of China

Ministry of Science and Technology of China

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