肝癌新正子掃描製劑初報

New PET Agents for the Detection of HCC

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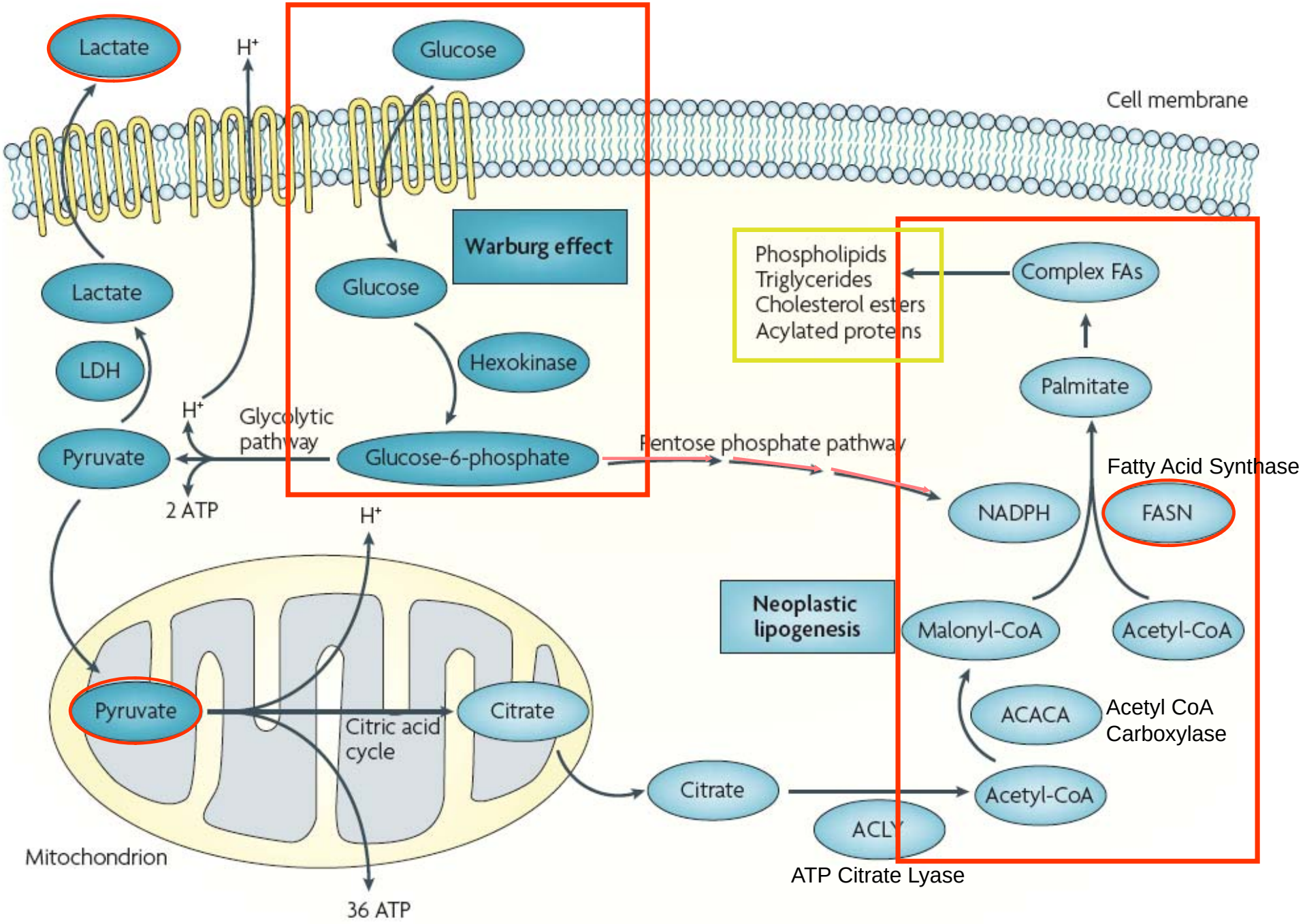
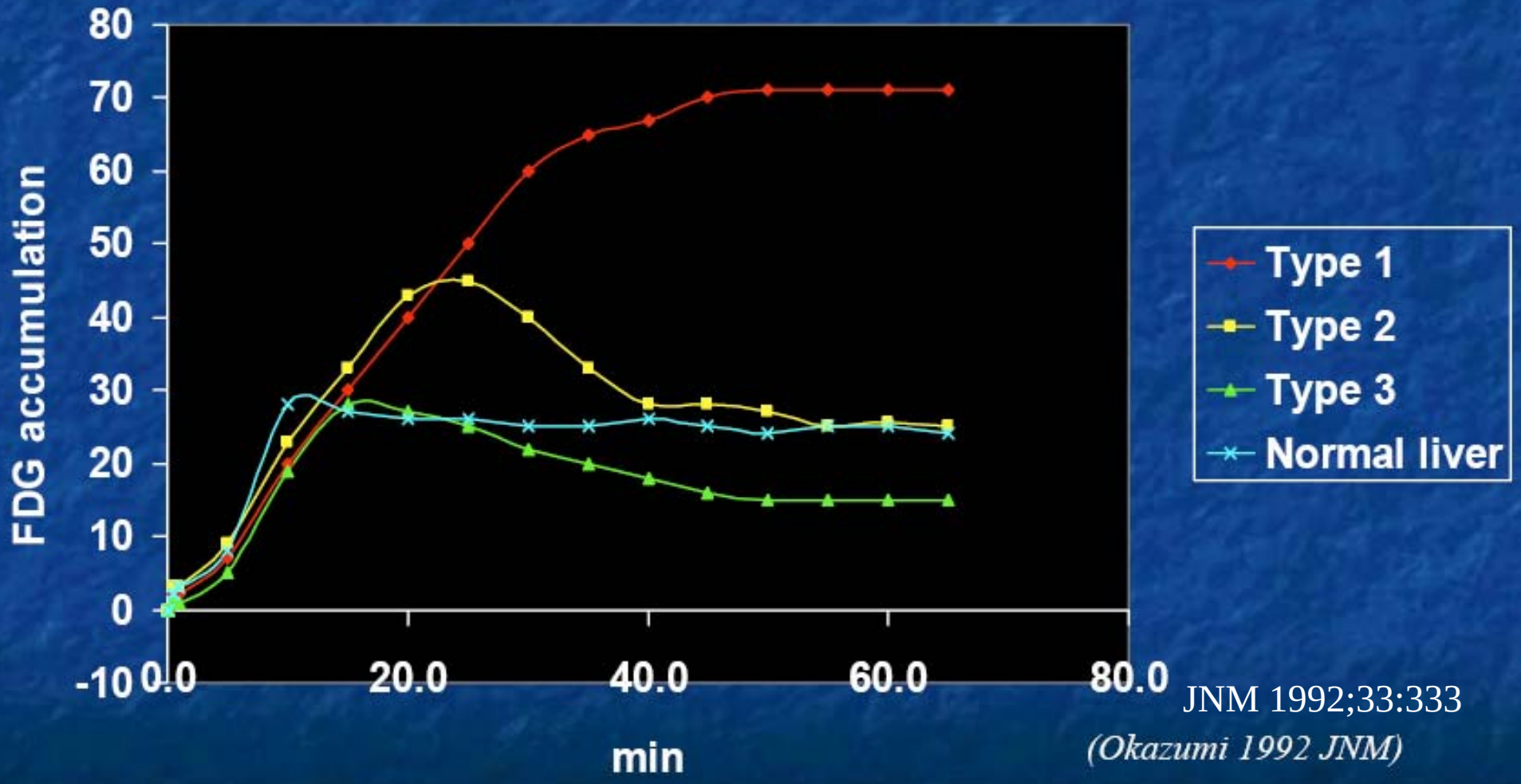
12/16/2009

Molecular characteristics of malignancy

- Proliferation
- Hypoxia
- Glycolysis
- Phospholipid synthesis
  - Fatty acid synthase
  - Choline metabolism
- Angiogenesis
- Receptor expression
- Transporter expression
- Antigen expression
- Apoptosis
- Gene delivery
- Multi-drug resistance


Lactate
H+
Glucose
Cell membrane
Warburg effect
Lactate
Glucose
LDH
Hexokinase
H+
Glycolytic pathway
Pyruvate
Glucose-6-phosphate
Pentose phosphate pathway
2 ATP
Phospholipids
Triglycerides
Cholesterol esters
Acylated proteins
Complex FAs
Palmitate
Fatty Acid Synthase
NADPH
FASN
H+
Neoplastic lipogenesis
Malonyl-CoA
Acetyl-CoA
Pyruvate
Citric acid cycle
Citrate
ACACA
Acetyl CoA Carboxylase
Citrate
Acetyl-CoA
ACLY
ATP Citrate Lyase
Mitochondrion
36 ATP

Time activity curve of different types of HCC in FDG accumulation



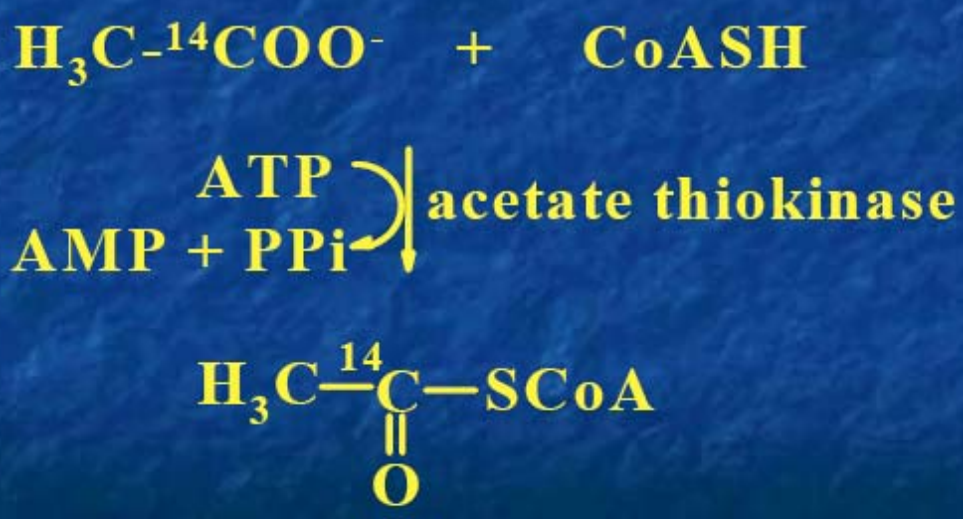
JNM 1992;33:333

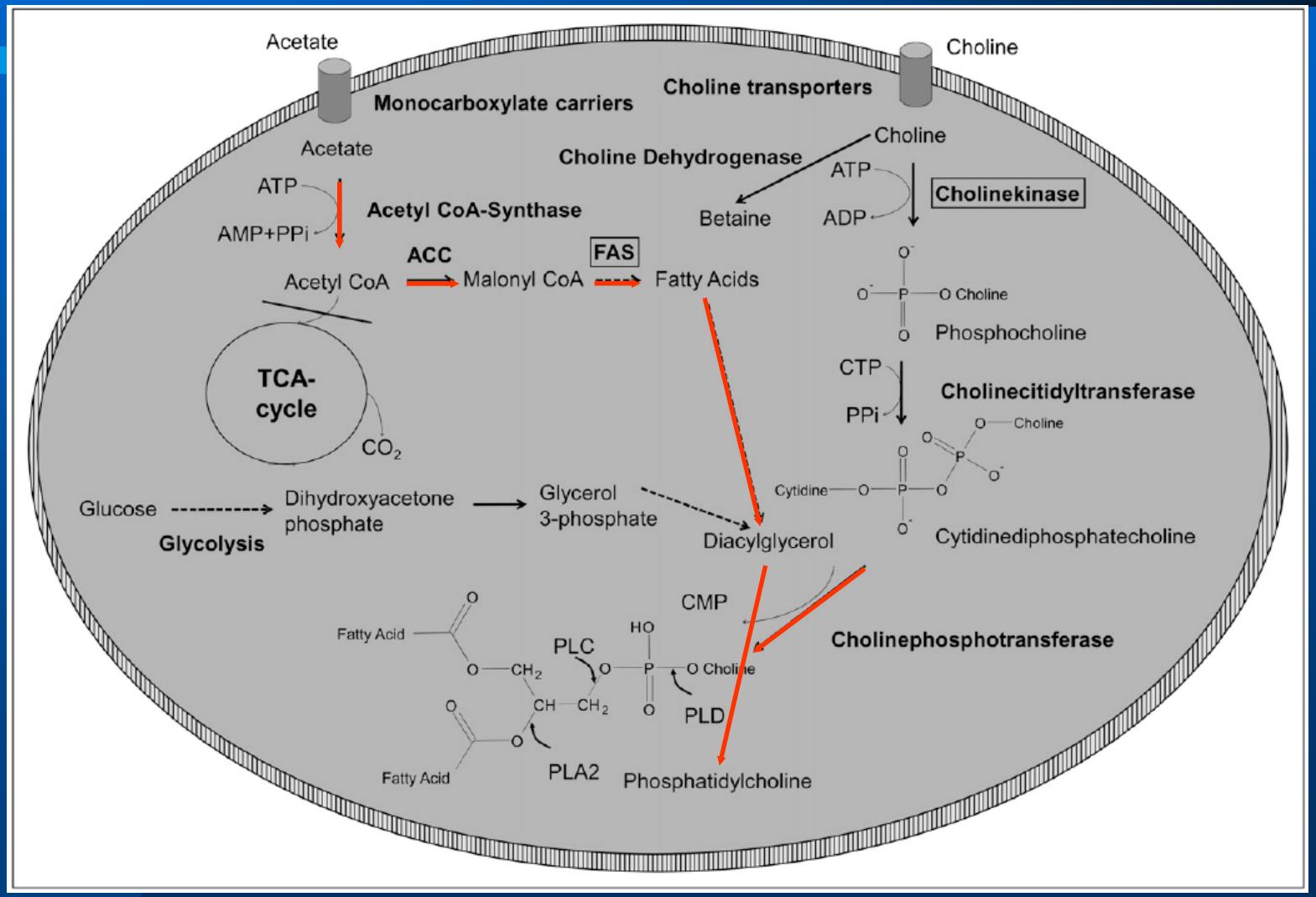
(Okazumi 1992 JNM)

(rearranged CL Ho)

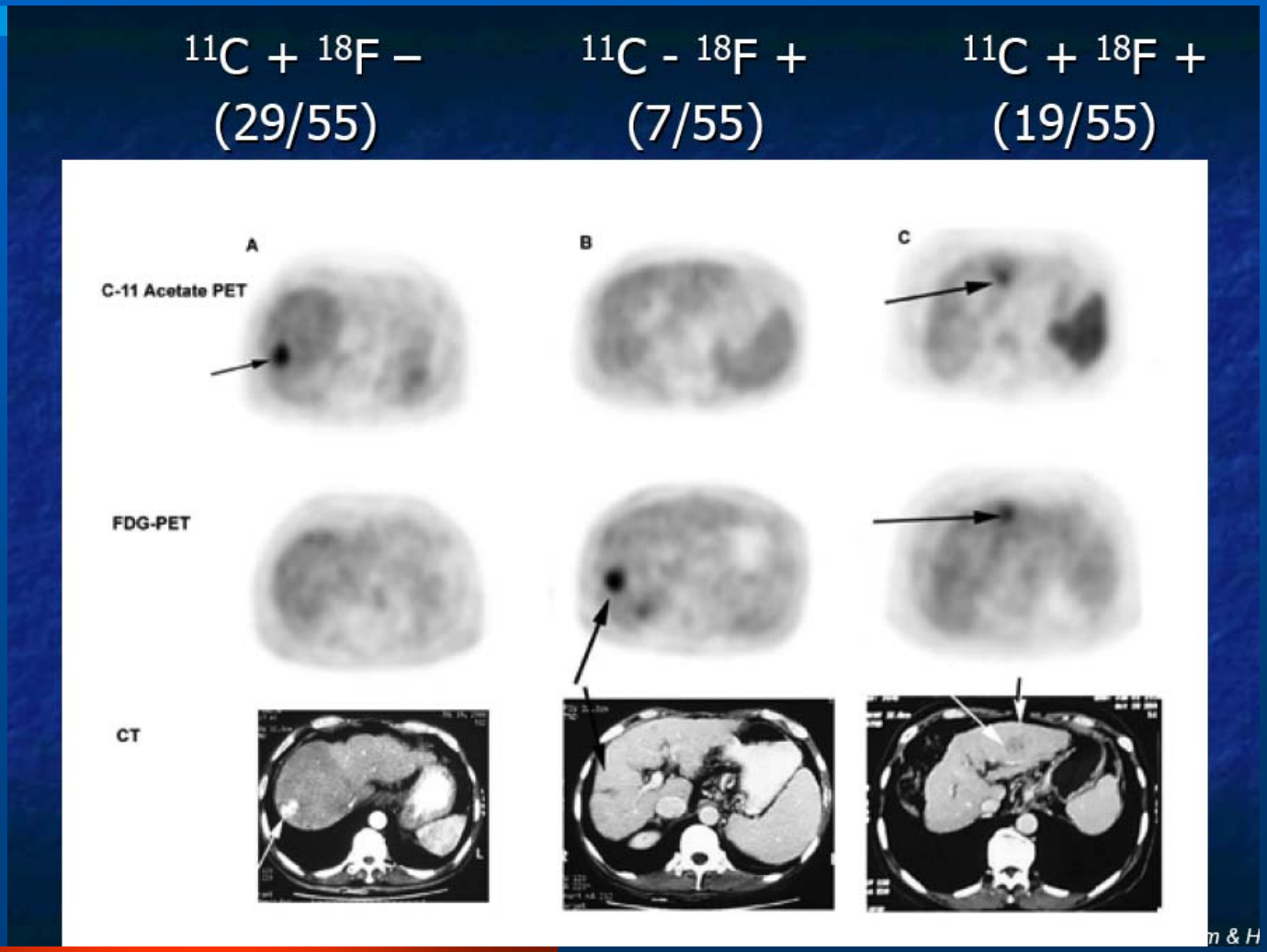
Acetate is a precursor of acetyl-CoA

Experiment: 1-[^{14}C]acetate is converted to 1-[^{14}C]acetyl-CoA by cells




Acetate
Choline
Monocarboxylate carriers
Choline transporters
Acetate
Choline
Choline Dehydrogenase
ATP
AMP+PPi
Acetyl CoA-Synthase
Betaine
ATP
ADP
Cholinekinase
ACC
FAS
Acetyl CoA
Malonyl CoA
Fatty Acids
O Choline
Phosphocholine
TCA-cycle
CO_2
CTP
PPi
Cholinecitidyltransferase
Choline
Cytidine
Glucose
Glycolysis
Dihydroxyacetone phosphate
Glycerol 3-phosphate
Diacylglycerol
Cytidinediphosphatecholine
CMP
Fatty Acid
PLC
HO
O Choline
Cholinephosphotransferase
PLD
Fatty Acid
PLA2
Phosphatidylcholine

^{11}C-acetate vs. ^{18}F-FDG scan



Hepatocellular Carcinoma (=< 3 lesions, size > 1.8 cm) **32 patients, 55 lesions**

	Lesions	*Percentage*
^{11}C-Acetate +ve ^{18}FDG -ve	29/55	52.7%
^{11}C-Acetate + ^{18}FDG both positive	19/55	34.5%
^{11}C-Acetate -ve ^{18}FDG +ve	7/55	12.7%
^{11}C-Acetate -ve ^{18}FDG -ve	0/55	0.0%
Total ^{18}FDG positive (Sensitivity)	26/55	47.3%
Total ^{11}C-Acetate positive (Sensitivity)	48/55	87.3%
Either ^{11}C-Acetate or ^{18}FDG positive	55/55	100.0%

Choline

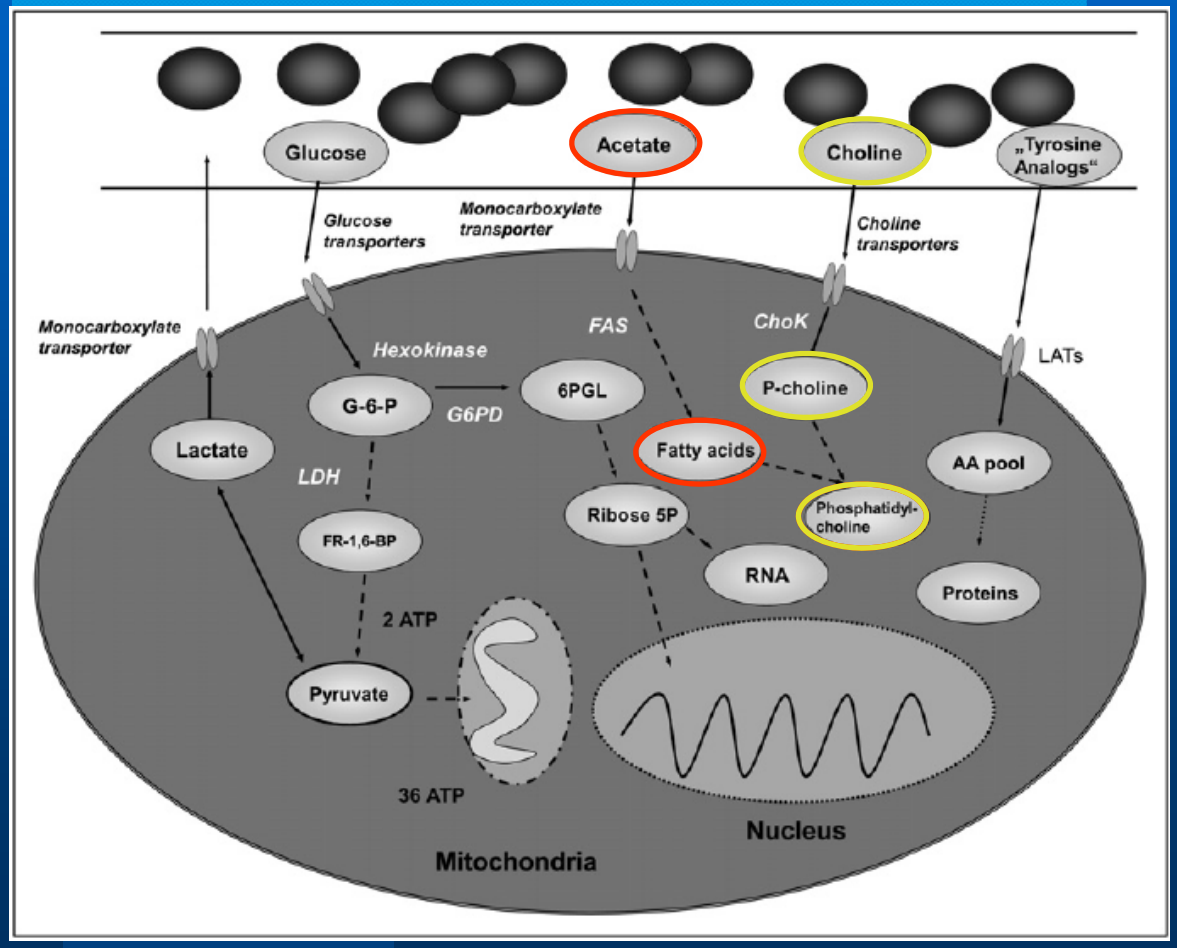
Eur J Nucl Med Mol Imaging (2006) 33:1285–1289

- An essential nutrient;
- Transported through choline transporter into cells;
- Phosphorylated to phosphoryl choline by choline kinase;
- Trapped into phospholipid pool.
- Correlated with cellular membrane phospholipid synthesis rate indicating proliferation.

Choline metabolism in cancer

- **Overexpression of choline kinase in multiple tumor cell lines;**
- **Choline kinase increased in breast ca, colon ca.**

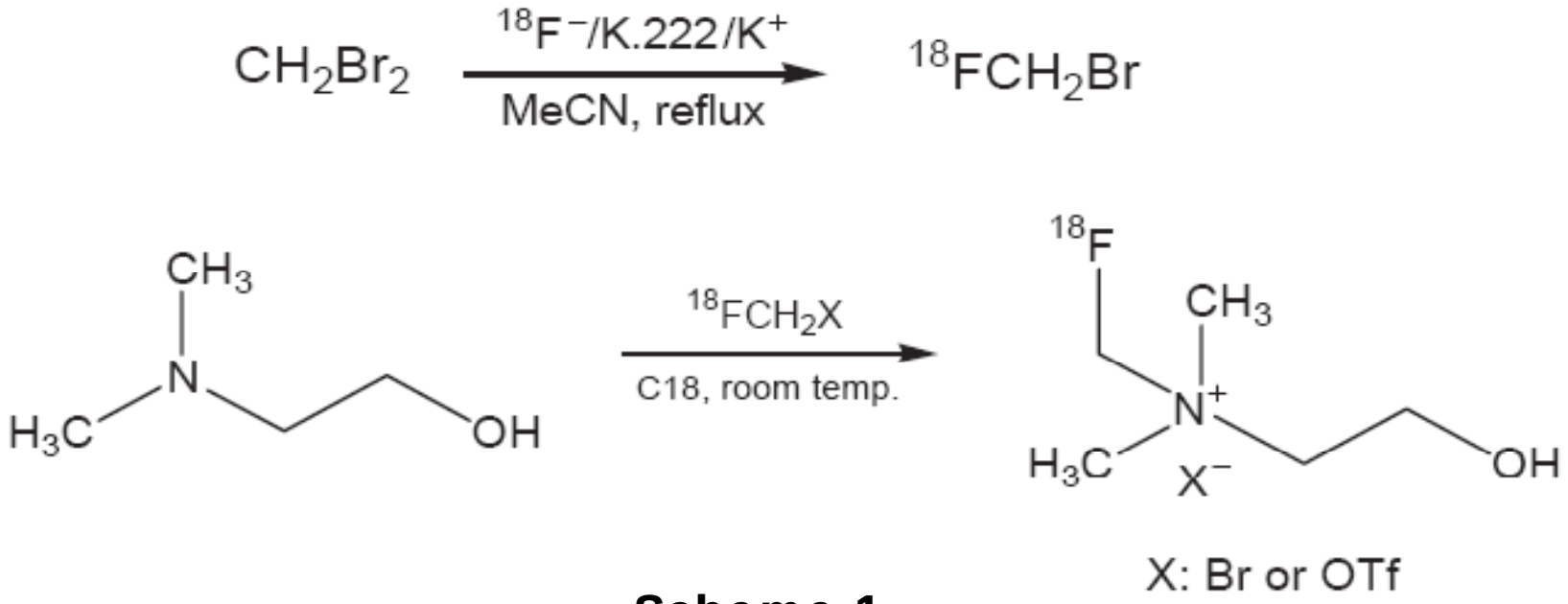
Lipid metabolism in cancer cells



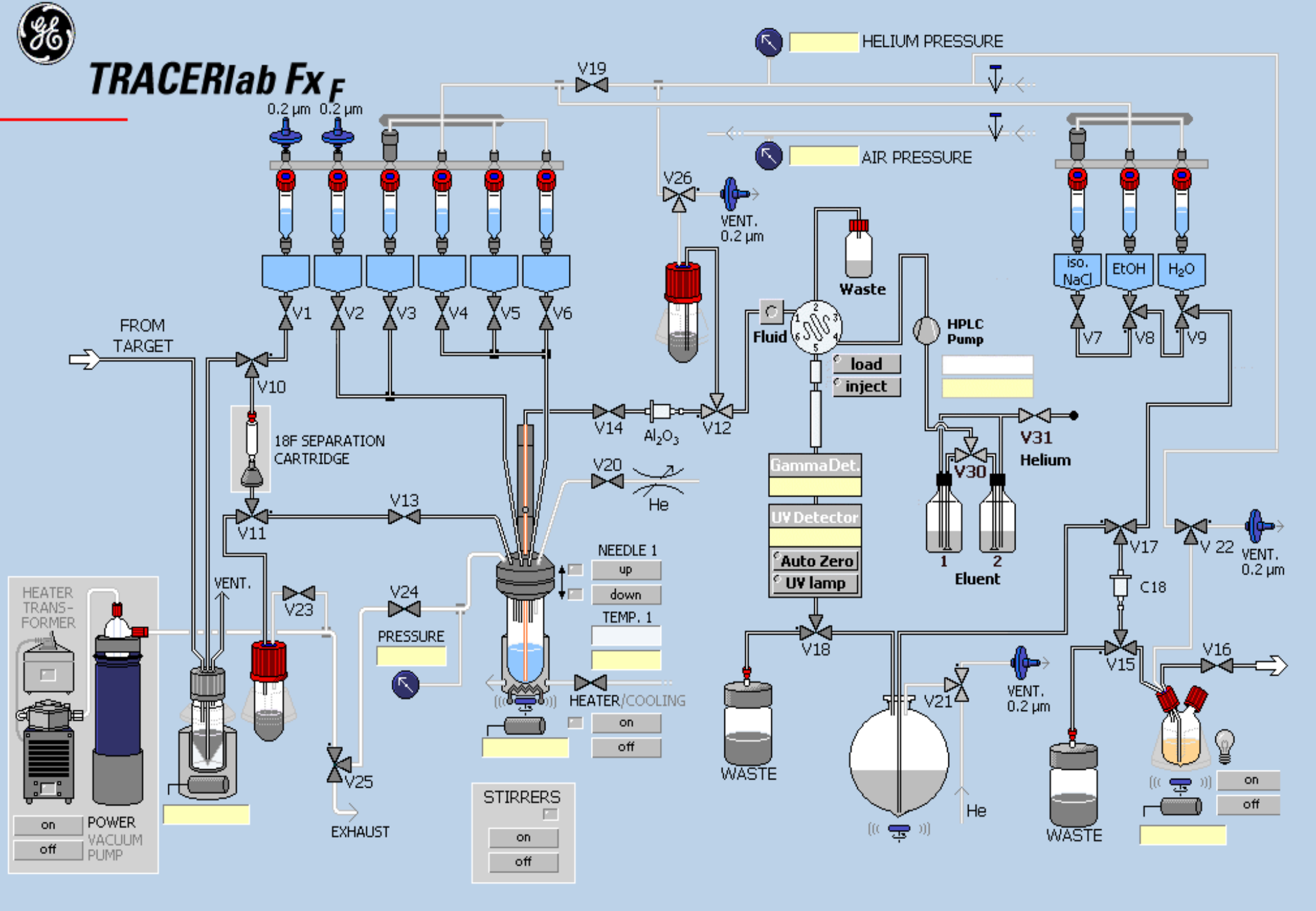
- **Overexpression of fatty acid synthase (FAS);**
- **Overexpression of choline kinase (ChoK)**

Synthesis of ^{18}F-Choline

18F-Choline was synthesized in two steps as reported with some modifications (scheme 1)



Scheme 1

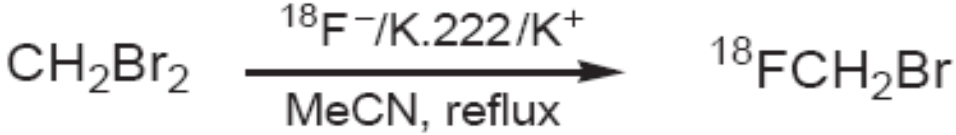

TRACERlab Fx F
HELIUM PRESSURE
AIR PRESSURE
V19
V26
VENT.
0.2 µm
0.2 µm
0.2 µm
V1
V2
V3
V4
V5
V6
FROM
TARGET
V10
18F SEPARATION
CARTRIDGE
V11
V13
V14
Al2O3
V12
V20
He
Waste
Fluid
load
inject
HPLC
Pump
GammaDet.
UV Detector
Auto Zero
UV lamp
V30
V31
Helium
1
2
Eluent
iso.
NaCl
EtOH
H2O
V7
V8
V9
V17
V22
VENT.
0.2 µm
C18
V15
V16
V18
V21
VENT.
0.2 µm
WASTE
He
WASTE
on
off
NEEDLE 1
up
down
TEMP. 1
HEATER/COOLING
on
off
PRESSURE
V24
V23
VENT.
V25
EXHAUST
HEATER
TRANS-
FORMER
on
POWER
off
VACUUM
PUMP
STIRRERS
on
off

Procedure 1

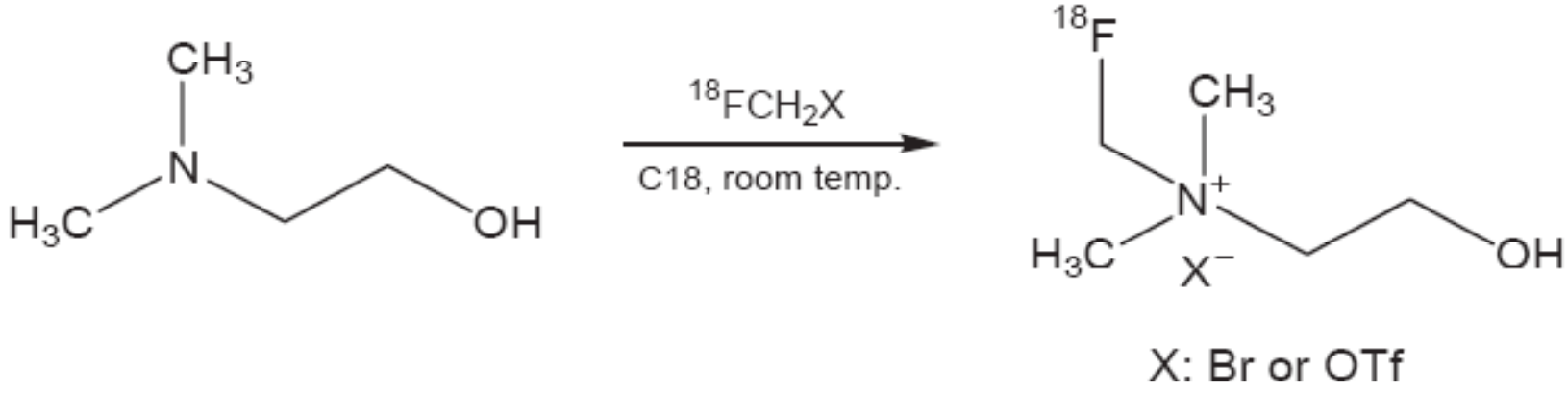
- The recovered [^{18}F]fluoride was passed through QMA.
- The eluent (vial 1) was used for elution of the absorbed fluoride.
- The reactor was then heated (110℃) for 2.5 mins and the solvent evaporated to dryness.
- The residue was dried by azeotropic evaporation with dry ACN (vial 2) to ensure complete removal of water.

Procedure 2

- Temperature of reactor was set to 65 ℃.
- CH_2Br_2 in dry ACN (vial 3) was then added to reactor.
- During reaction the unreacted CH_2Br_2 and product ($CH_2Br^{18}F$) were vented to three silica cartridges connected in series.
- $CH_2Br^{18}F$ was delivered to the dry tC18 cartridge which was loaded with DMAE.



- After the reaction, the tC18 cartridge was washed with ethanol (vial 7) followed by water (vial 8).
- The final procuct, [^{18}F]fluorocholine retained by CM cartridge (connected to tC18 cartridge) was then eluted with saline (vial 9).



- 外觀：最終產物在經由無菌過濾膜過濾後，其狀況以目視法觀察必須透明無顆粒狀態的 。
- 酸鹼度：以pH試紙測標準值在4.0-8.0之範圍。
- 放射性核種半衰期：以γ射線偵檢儀測標準值在110 ±5 min.之範圍。
- 放射化學純度與放射化學鑒別：用薄層層析法（TLC）以aluminium sheets Silica gel置於展開液（乙月青：水（95:5））中展開。以γ射線偵檢儀測放射化學鑒別R_f值 0.3 – 0.5，單一峰；放射化學純度標準值 > 90% 。
- Radionuclidic purity：以多頻分析儀（Multi-channel analyzer）測標準值 > 99.5%在0.511MeV and/or 1.022MeV。
- Kryptofix 2.2.2 ：用TLC測標準值< 50 μg/ml 。

- 殘餘溶劑：以氣相層析儀測DMAE ＜ 0.1 mg /ml ，Ethanol ＜ 0.5%（w/v）, Acetonitrile ＜ 0.04%(w/v)。
- 內毒素試驗：以動力比色儀（Kinetic Quantitative Chromogenic LAL Test）測標準值＜ 175EU/V(≦5EU/ml)。
- 無菌過濾膜：最終產物經無菌過濾膜過濾後，用氣體測試無菌過濾膜起泡點，標準須＞45psi 。
- 無菌測試： 在72小時內操作，將最終產物各注入FTM（Fluid Thioglycollate Medium ）、SCD（Soybean Casein Digest）培養，14天後觀察必須為清澈不混濁。

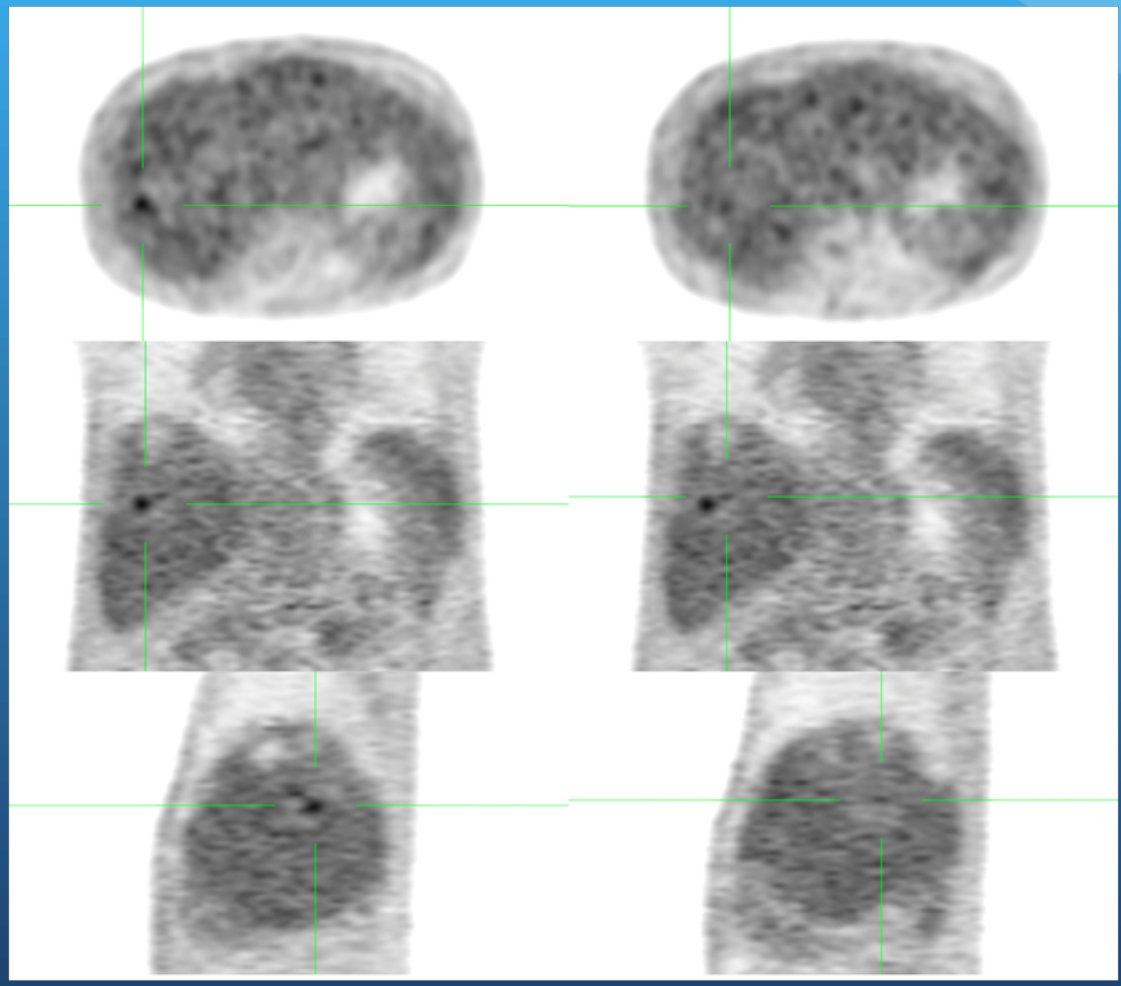
Results

Times	30 (5 failure and 25 success)
Success rate of synthesis	83.3 %
EOB	2 %
Time duration	40 mins
Radiochemical purity	> 90 %

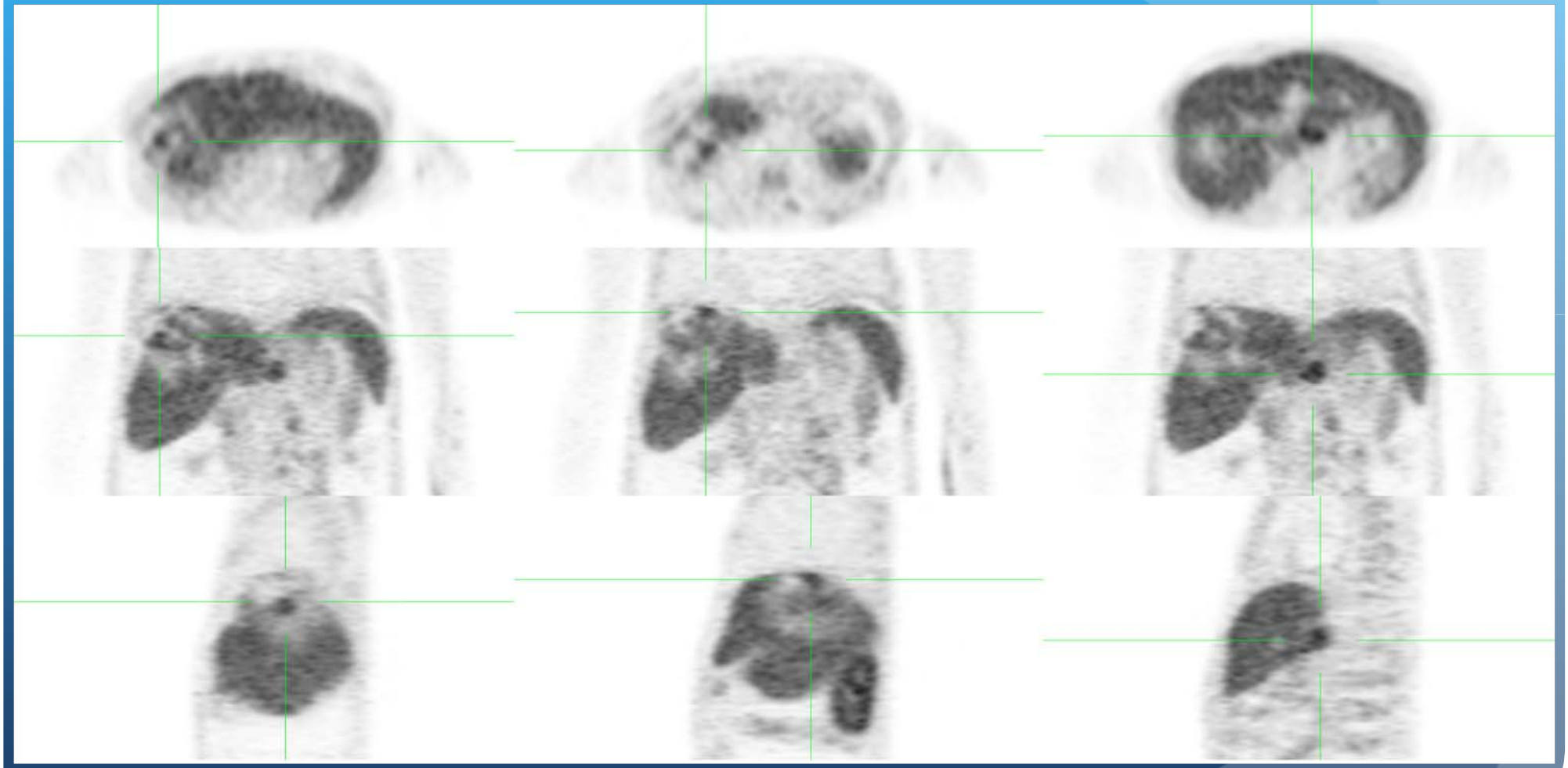
F-18 Choline in HCC research

- NTUH IRB passed on 8/29/2008
- NSC grant approved since 1/1/2009
- DOH approval on 4/21/2009
- 1st case enrolled on 7/17/2009
- Totally 9 cases enrolled till 11/25/2009

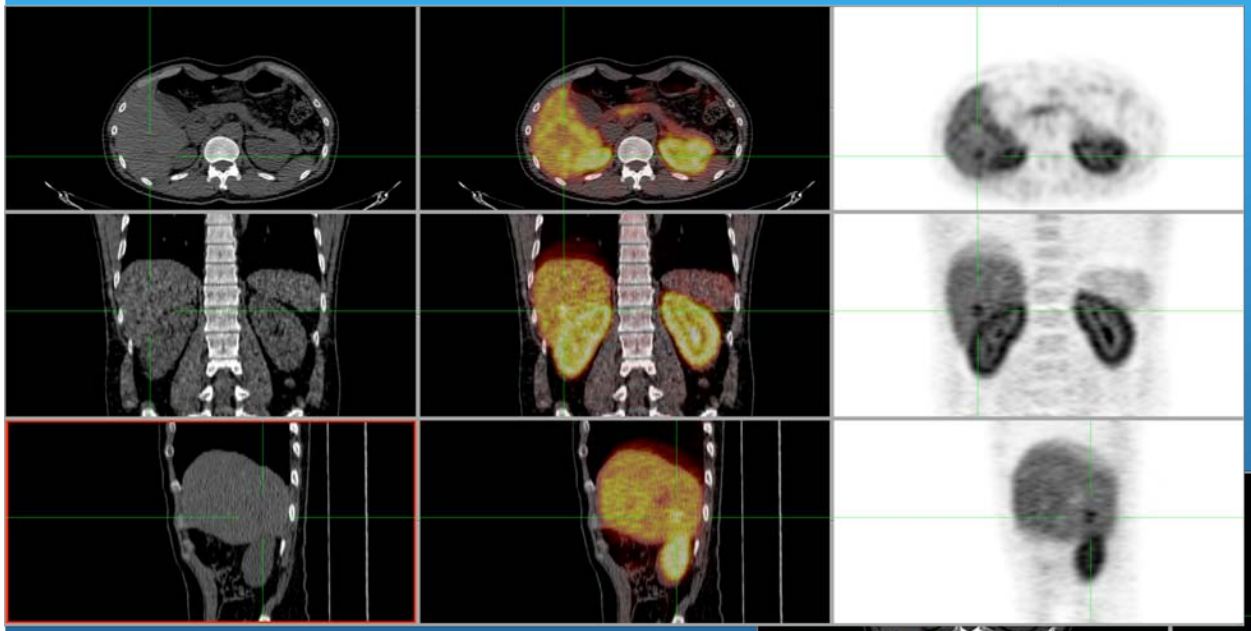
HCC FDG PET scan

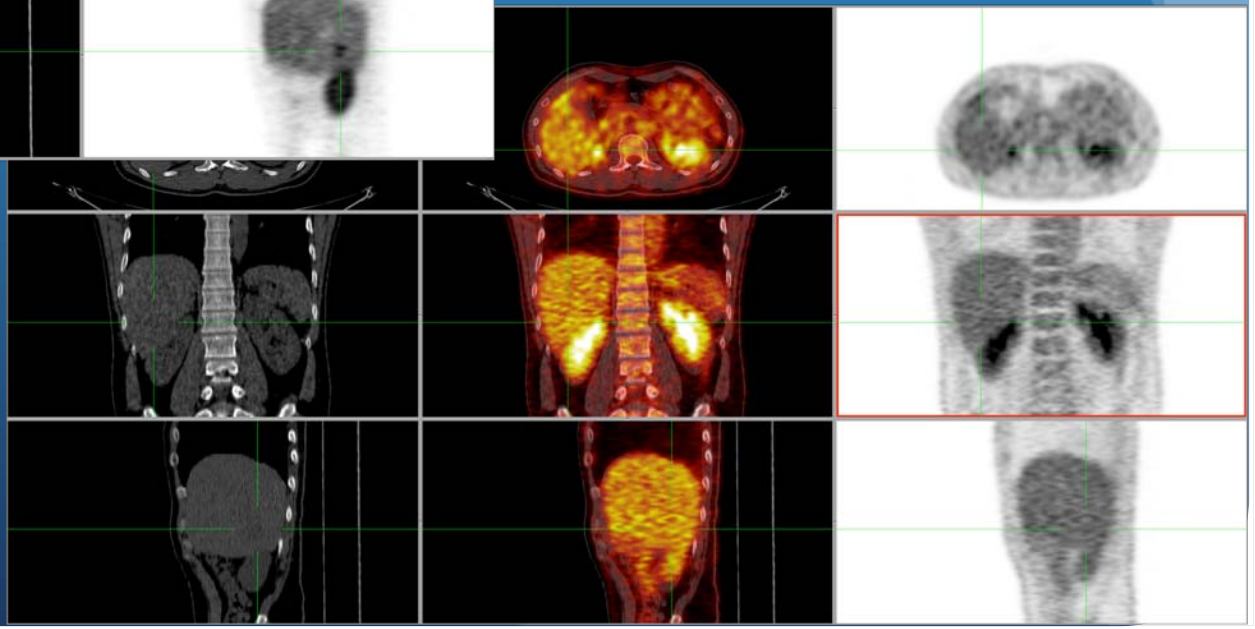


HCC F-choline PET scan



HCC ^{18}FCH (Lt.) vs. ^{18}FDG (Rt.)





寄件人: Nguyen Cong Duc
標題: **Nguyen Cong Duc - Cho Ray Hospital, Unit of PET-CT and Cyclotron.**
日期: 2009年11月2日 上午02時48分30秒
收件人: Kai-Yuan Tzen(曾凱元) <tzenky@ntuh.gov.tw>

Dear Dr. Kai-Yuan Tzen,

At first, I would like to send my warmest regards to you and your colleagues.

I would like to introduce myself again. I, Nguyen Cong Duc, have been working at the Unit of PET-CT and Cyclotron, Cho ray Hospital, Ho Chi Minh City, Vietnam. Now I would like to write to you for your assistance:

Dr. Nguyen Truong Son, Director of Cho ray Hospital and Dr. Hoang Hoa Hai, Head of Department of Training and Scientific Research had visited your institution and they are interested in the production and applications of F-18 Choline. We desire to develop this new PET radiopharmaceutical in our hospital.

Therefore, I wo ion of F-18 Choline and I would like to line and the other PET radiopharmac ease let me be informed the situation, th u about my study.

And I also woul arch this year and at present we are only prod

Please send m .

I wish you and y

Thank you ver

Nguyen Cong D

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12/1/2009 – 1/31/2010

Thank You Very Much for Your Attention