细胞信号转导研究技术新进展

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一、背景介绍

二、细胞信号通路研究技术新进展

三、总结

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一、背 景介 绍

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细胞信号转导大事记

1955年，Sutherland，cAMP第二信使学说，获1971年诺贝尔生理和医学奖

1963年， cGMP作为胞内信使的发现

1978年，Rasmussen，Ca^{2+}第二信使学说

1983年，IP_3和DG作为胞内信使的发现

1992年，酪氨酸蛋白激酶与信号转导的研究获诺贝尔生理和医学奖

1994 年，Gilman和Rodbell G蛋白的研究获诺贝尔生理和医学奖

2000年 阿尔维德·卡尔森（Arvid Carlsson，瑞典），保罗·格林加德（Paul Greengard，美国），Eric R Kandel（美国） 关于神经系统信号传导方面的研究诺贝尔生理和医学奖

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细胞信号转导异常与疾病的关系

一、 肿瘤

1.促细胞增殖的信号转导过强

(1) 生长因子产生增多

多种肿瘤组织能分泌生长因子

(2)受体的改变

①某些生长因子受体表达异常增多

如多种肿瘤组织中发现有编码EGFR的原癌基因c-erb-B的扩增及EGFR的过度表达

②突变使受体组成型激活

如多种肿瘤组织中证实有RTK的组成型激活

二、 胰岛素受体与胰岛素抵抗性糖尿病

1.遗传性胰岛素受体异常，包括受体合成减少

受体与配体的亲和力降低，如受体精氨酸735突变为丝氨酸

受体TPK活性降低，如甘氨酸1008 突变为缬氨酸，胞内区TPK结构异常

2.自身免疫性胰岛素受体异常

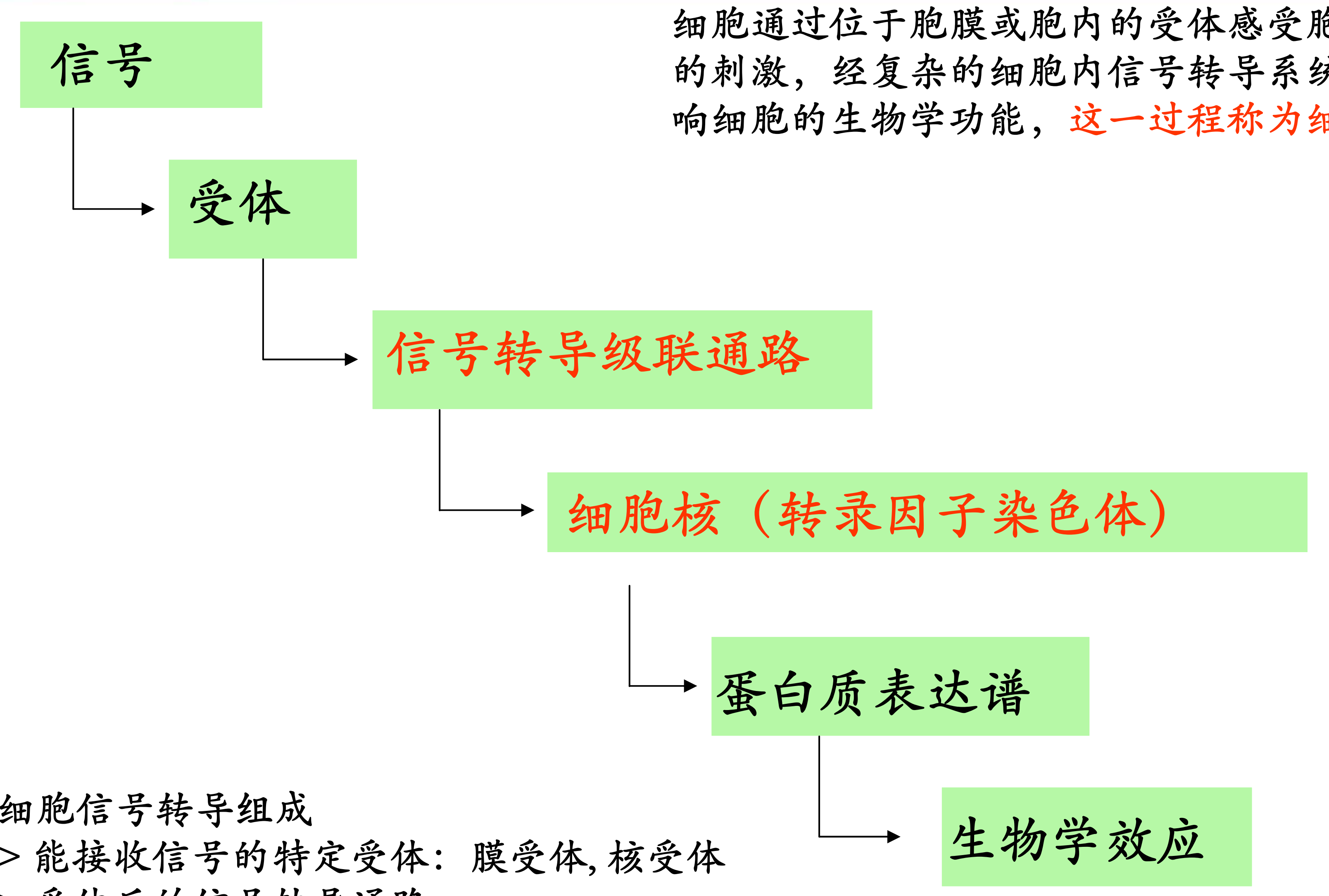
血液中存在抗胰岛素受体的抗体

三 、 雄激素受体缺陷与雄激素抵抗征

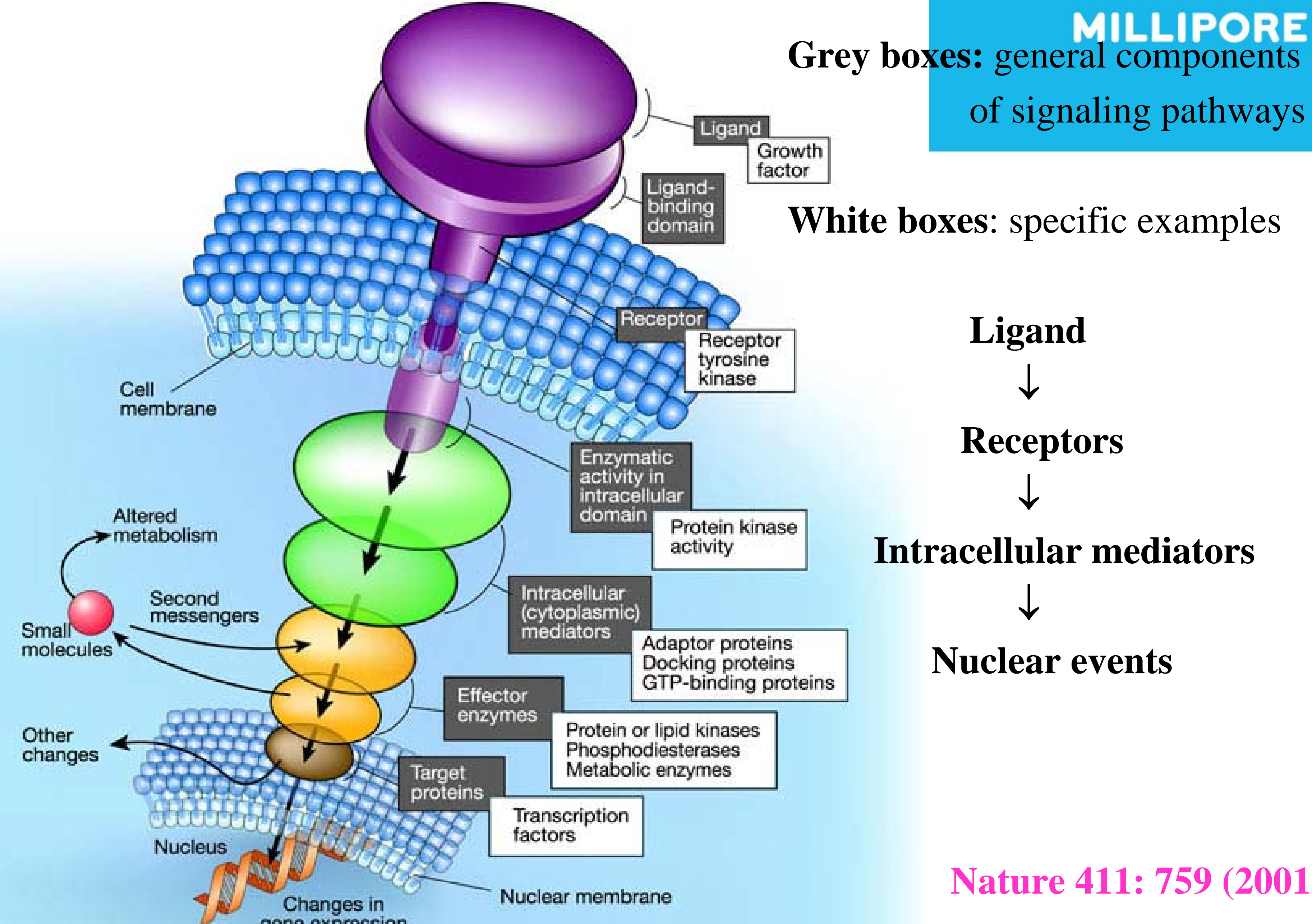
AR减少和失活性突变

什么是细胞信号转导

细胞通过位于胞膜或胞内的受体感受胞外信息分子的刺激，经复杂的细胞内信号转导系统的转换来影响细胞的生物学功能，这一过程称为细胞信号转导



细胞信号转导组成
> 能接收信号的特定受体：膜受体,核受体
> 受体后的信号转导通路
> 信号的生物学效应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Grey boxes: general components of signaling pathways
White boxes: specific examples
Ligand
↓
Receptors
↓
Intracellular mediators
↓
Nuclear events
Nature 411: 759 (2001)
Ligand
Growth factor
Ligand-binding domain
Receptor
Receptor tyrosine kinase
Cell membrane
Enzymatic activity in intracellular domain
Protein kinase activity
Altered metabolism
Second messengers
Small molecules
Intracellular (cytoplasmic) mediators
Adaptor proteins
Docking proteins
GTP-binding proteins
Effector enzymes
Protein or lipid kinases
Phosphodiesterases
Metabolic enzymes
Other changes
Target proteins
Transcription factors
Nucleus
Nuclear membrane
Changes in gene expression

细胞信号转导的基本方式和特点

细胞信号转导网络的构成

- 多条信号转导途径(pathway)
- 交互调控(cross talking)
- 形成网络(network)

二、细胞信号传导方法研究方法介绍

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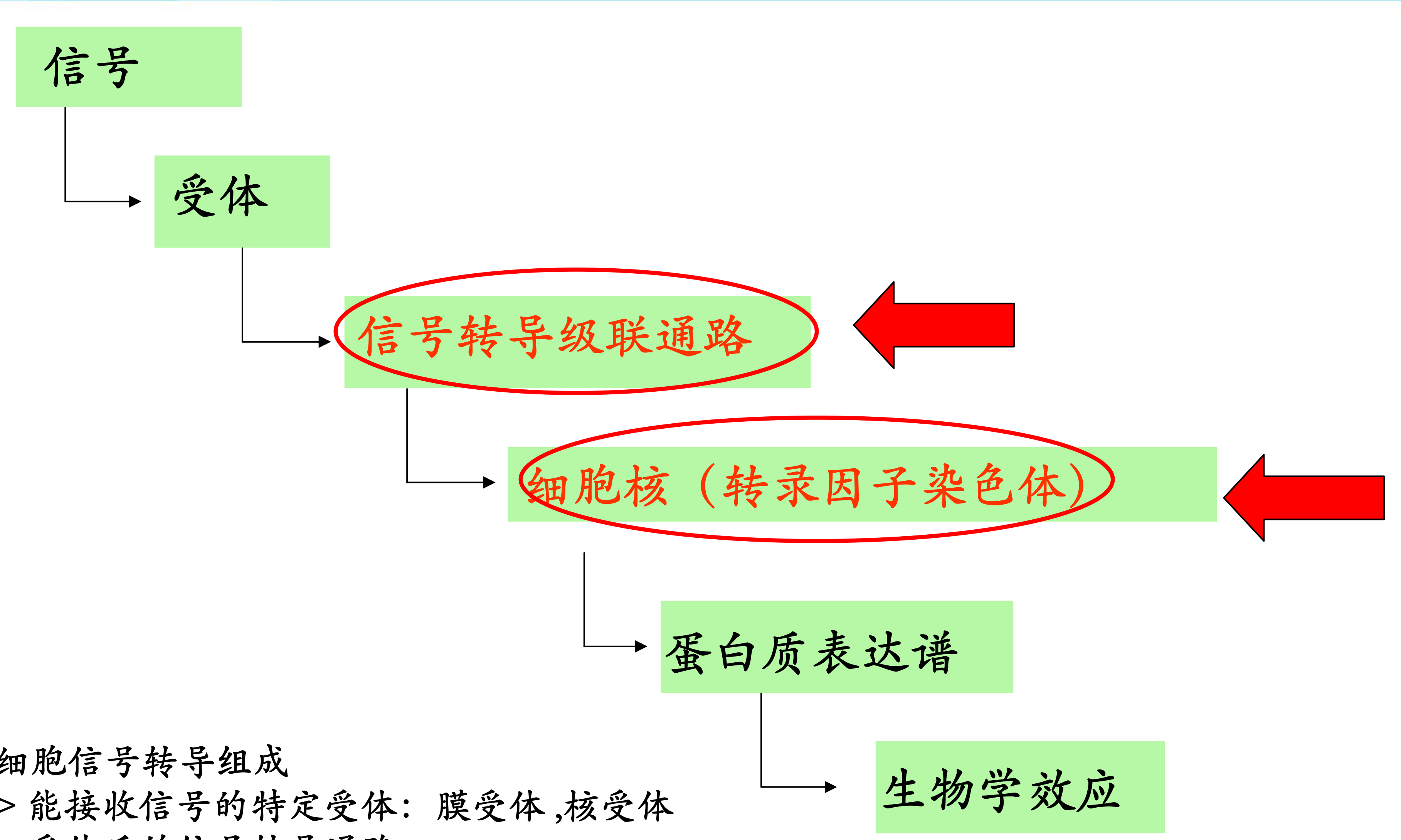

细胞信号转导组成

> 能接收信号的特定受体：膜受体,核受体
> 受体后的信号转导通路
> 信号的生物学效应

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信号转导级联通路

信号转导过程中的生物化学

- 化学修饰（磷酸化-phosphorylation与去磷酸化-dephosphorylation)
- 变构效应
- 蛋白质-蛋白质相互作用

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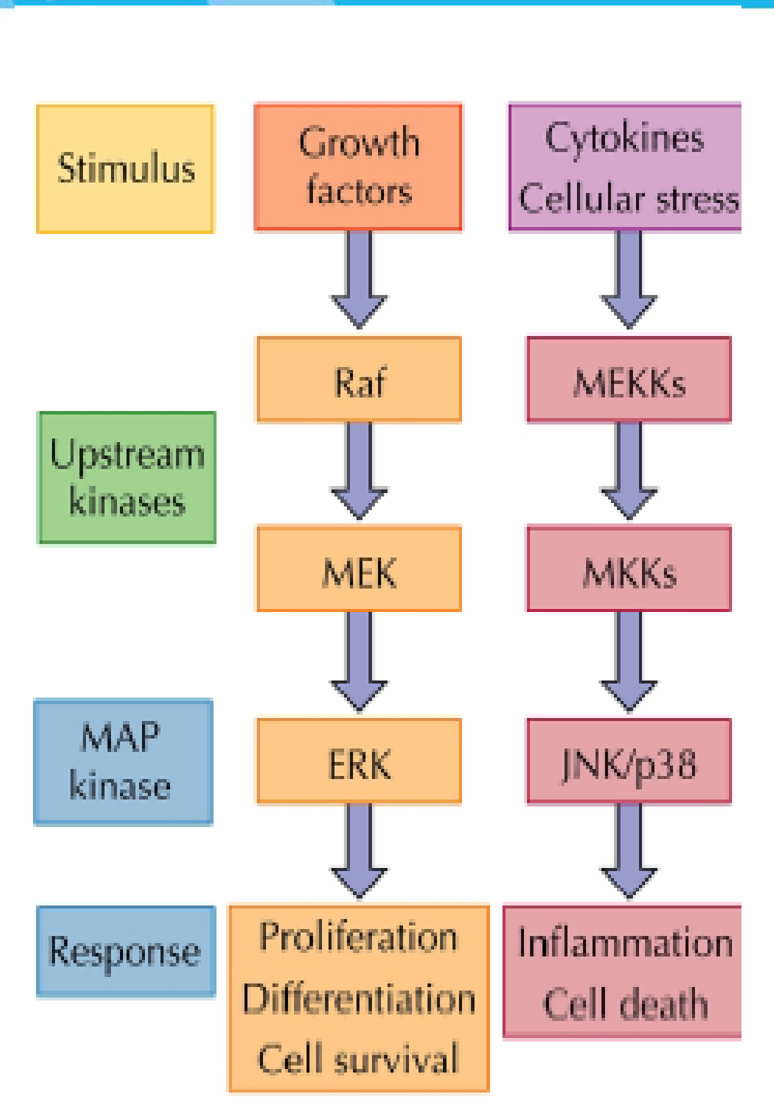
Kinases and Phosphatases

- **Is reversible**
- **Does not require new proteins to be made or degrades**
- **Occurs very rapidly and sometimes continuously**
- **Provides a vast assortment of proteins to support the cell**
  - **508 kinases in Human**
  - **Known targets include: structural cell receptors, enzymes, ion channels and signaling molecules**

Note:
蛋白激酶A(protein kinase A,PKA)；蛋白激酶G(PKG)；蛋白激酶C(PKC)；钙调素依赖的蛋白激酶；蛋白酪氨酸激酶(protein tyrosine kinase)；有丝分裂原激活的蛋白激酶(mitogen activated protein kinase,MAPK)

MAPK家族酶的激活机制都通过磷酸化的三级酶促级联反应



Polypeptide hormone
Receptor tyrosine kinase (RTK)
Active Raf
Ras
Ras
Tyrosine kinase
ATP
ADP
Raf
GTP
GDP
Tyr
P
Tyr
GRB2
SOS
MAPKK
Active MAPKK
P
MAPK kinase
2 ATP
2 ADP
MAPK
Active MAPK
Thr
P
Tyr
P
Mitogen-activated protein kinase
Nucleus
Transcription factor phosphorylation
Myc
Jun
ATF-2
Fos
Gene transcription
Protein synthesis

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信号转导级联反应的研究方法之一——Western Blotting

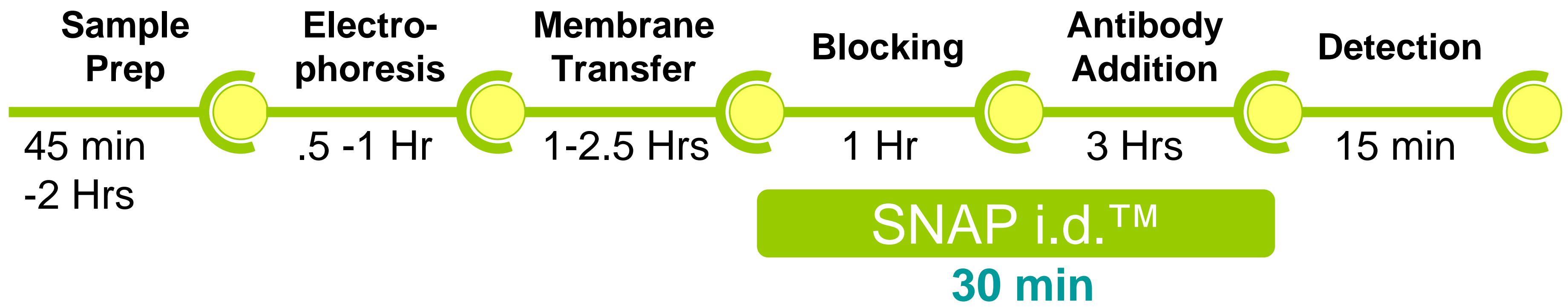
目的：检测化学修饰（磷酸化-phosphorylation与去磷酸化-dephosphorylation),

蛋白质表达量或者活性状态

Sample Prep	Electro-phoresis	Membrane Transfer	Blocking	Antibody Addition	Detection
45 min -2 Hrs	.5 -1 Hr	1-2.5 Hrs	1 Hr	3 Hrs	15 min

信号转导级联反应的研究方法之一——Western Blotting

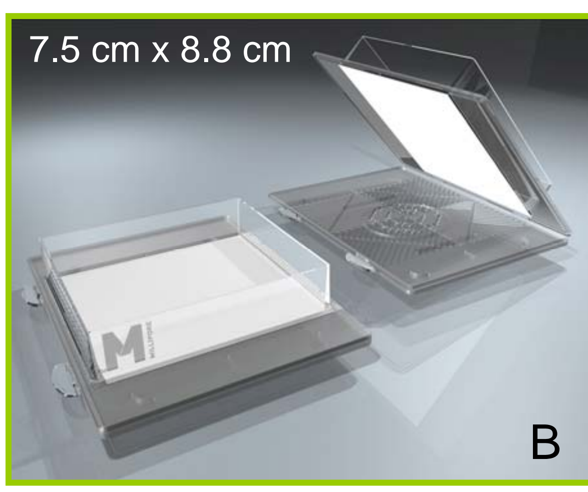
SNAP i.d. Value Proposition



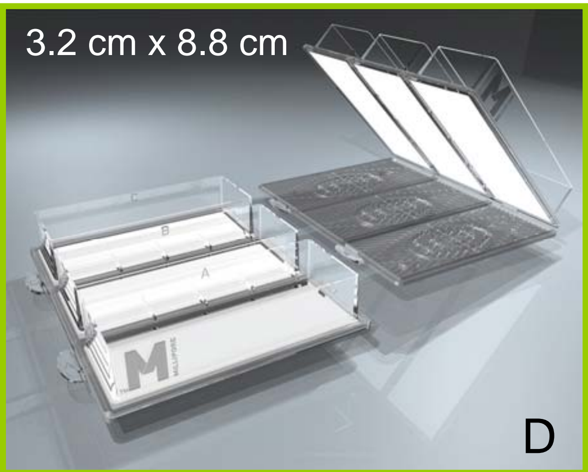
Immunodetection occurs in 30 min vs. 4 hrs

- Reduces incubation times in Western Blotting
- Compatible with all reagents and membranes
- No directly competitive product on the market

SNAP i.d. Components



A. SNAP i.d. Base
B. Single Blot Holder, 30/pk
C. Double Blot Holder, 30/pk
D. Triple Blot Holder, 20/pk
E. Antibody Collection Tray, 20/pk



Detection Substrates

Primary Ab (400mg/ml) 1:10,000

Secondary Ab 1:100,000

Choose high sensitivity substrates if
- detecting low abundance proteins
- sample amount is limited
- antibodies have weak affinities

High-quality Antibody (Upstate and Chemicon)

Advantage:

- Higher quality with significantly more products to completely fulfill the customers needs
- More modification state-specific antibodies
- Kinases/Phosphatases
- more modification state-specific (i.e. phospho-specific) antibodies

High-quality Antibody (Upstate and Chemicon)

Key Products in Tyrosine Phosphorylation

4G10, 4G10 platinum, EGFR, Src, FAK ,JAK2, PTP1b, SHP2

Key products for Ser/Thr Phosphorylation

MAPK pathway, AKT, GSK3 , phosphoserine (AB1603)

Lipid pathway

Insulin pathway

Ubiquitin-Proteasome pathway

G-protein activation assay

cAMP/cGMP assay

Reference:

1. Zhengxing Qu, David M. Goldenberg, Thomas M. Cardillo. Bispecific anti-CD20/22 antibodies inhibit B-cell lymphoma proliferation by a unique mechanism of action. *Blood*, Vol. 111, No. 4, 2211-2219, 2008.

2. Risaku Fukumoto,Miroslav Dundr, Christophe Nicot.
Inhibition of T-Cell Receptor Signal Transduction and Viral Expression by the Linker for Activation of T Cells-Interacting p12I Protein of Human T-Cell Leukemia/Lymphoma Virus Type. *Journal of Virology*, Vol. 81, No. 17, 9088-9099,2007.

3. Sebastien Tauzin1, Heidrun Ding1, Karim Khatib. Oncogenic association of the Cbp/PAG adaptor protein with the Lyn tyrosine kinase in human B-NHL rafts. *Blood,* Vol. 111, No. 4, 2310-2320, 2008.

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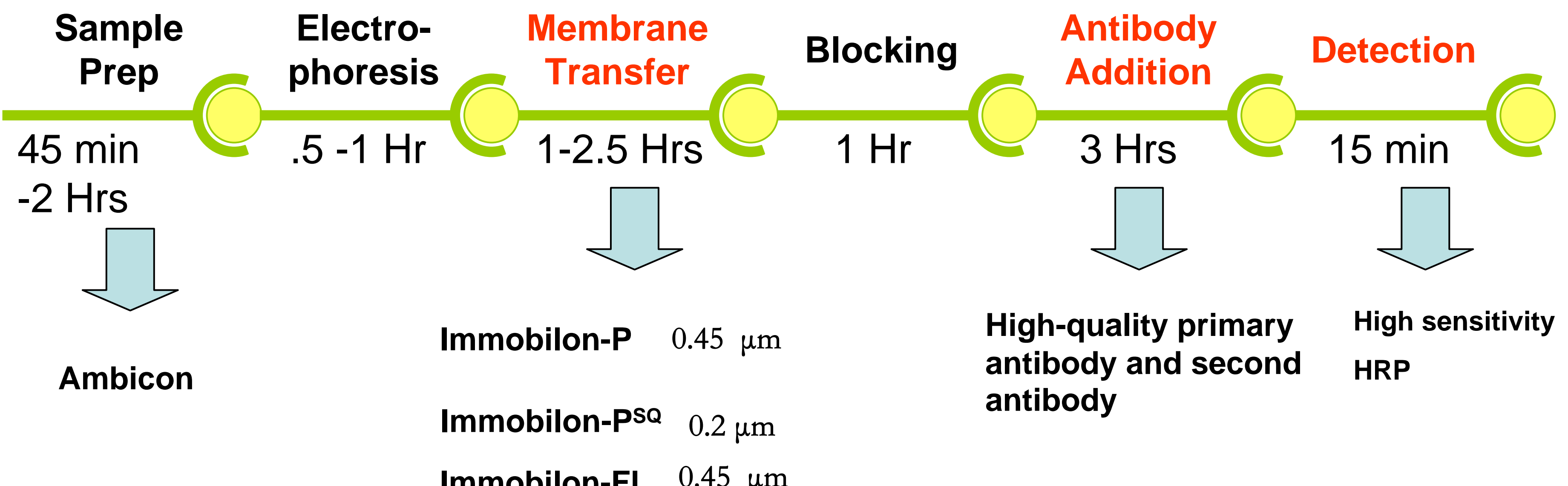
信号转导级联反应的研究方法之一——Western Blotting



检测标本很多的情况?

— Western 无法满足高通量的需求

信号转导级联反应的研究方法之二 — ELISA

ELISAs (Enzyme Linked Immunosorbent Assay)

目的:蛋白质表达量或者活性状态(检测化学修饰（磷酸化-phosphorylation与去磷酸化- dephosphorylation)

What?

ELISAs are used for detecting protein levels in a sample in a faster, more efficient method than western blot.

Phosphospecific-ELISAs show the relative phosphorylation differences in different samples.

ELISAs
STAR (traditional sandwich)
cAMP/cGMP (competitive)

Overview: ELISA Technique: Schematic

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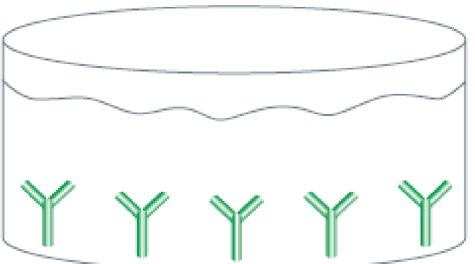
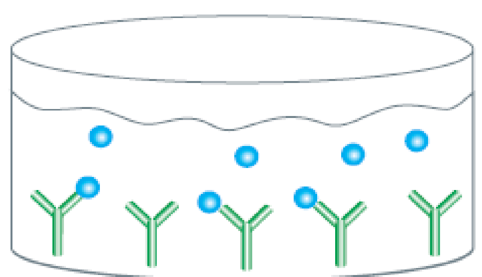
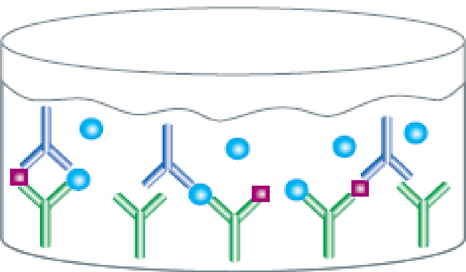
ELISA Diagram



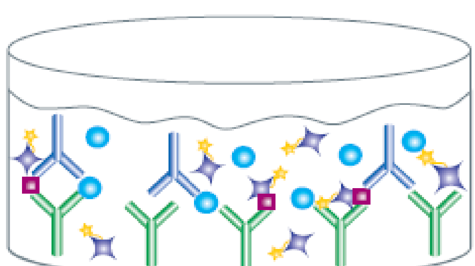
STEP 1: 96 well clear plates-coated with a specific mouse monoclonal capture antibody



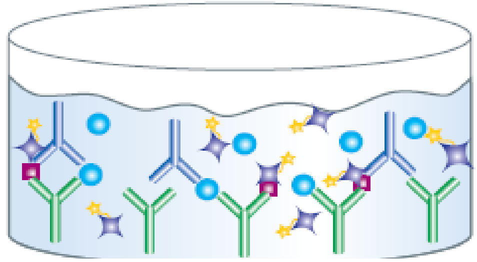
STEP 2: Sample lysate (or standard) is incubated in the microwells allowing the target to be captured in the plate wells



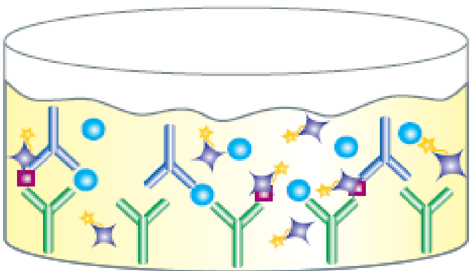
STEP 3: Wash away unbound, non-specific material. Add specific rabbit total or phosphospecific Antibody in each sample well.



STEP 4: Wash unbound detection Ab and add HRP-conjugated anti-rabbit antibody.



STEP 5: Wash unbound HRP Ab and incubate with TMB enzymatically activated detection reagent.



Step 6. Add stop solution and read. This stops the reaction and changes the blue solution to yellow. Measure the color change.

STAR ELISA Kit-Overview

STAR (Signal Transduction Assay Reaction)

- **Fast, sensitive method (<50% time and 2X more sensitive than western blot)**
- **Detects either total or active/inactive (phosphorylated) signaling targets**

Kits for top signaling targets (based on publications and current sales)

- **32 assay kits**
- **widest customer base**
- **primarily for kinases (with the exception of IRS and p53)**

Highlights

Kit is in a ready-to-use format, unlike some competitors

- **Open the box and run.**

Enzymatic detection measured at 450 nm using a standard plate reader

- **i.e. broad customer base**

Assay takes less than 5 hours with minimal hands-on time.

includes standard-used for positive control and to develop a standard curve.

Western Blot Analysis

Company	STAR ELISA	Western Blot
TIME:	<5 hours with little hands-on time	>8 hours (often longer) with much greater hands on time
Sample amount	Lower limit of detection Less sample needed	2x More sample needed
Sample Number	48 samples (ran in duplicate using 96 wells for greater accuracy)	No more than 14 at one time (run as singlets)
Reliability	Optimized No parameters to work out	Wasted sample and time on optimizing Few parameters worked out

SUMMARY:

Easier, faster, more sensitive

SOLUTION IN A BOX

Existing Signaling ELISA Offering

New STAR ELISAs-32 assays
17-315 Phosphotyrosine (colorimetric)
17-182 Cellular Phosphotyrosine ELISA (4G10)
17-426 phospho-Src (Tyr418) (chemiluminescent)
17-424 Ras GTPase Activation ELISA
17-327 H2A.X Phosphoryaltion Assay Kit (chemilum)
17-155 MESACUP Protein Kinase Assay
SGT410 Tyrosine Kinase Activity Assay

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STAR ELISAs – NEW!

Cat. No.	Description		Cat. No.	Description
17-455	AKT1 (Total) ELISA kit		17-473	MEK1 ELISA
17-456	phospho-Akt (Thr308) ELISA Kit		17-474	phospho-MEK1 (Ser218/222) ELISA
17-457	phospho-Akt (Ser473) ELISA kit		17-475	phospho-p53 (Ser15) ELISA
17-458	IRS-1 (Total) ELISA kit		17-476	p53 ELISA
17-459	phospho-IRS-1 (Ser312) ELISA kit		17-477	PRAS40 ELISA
17-460	EGFR ELISA kit		17-478	phospho-PRAS40 (Thr246) ELISA
17-461	phospho-EGFR T(yr1173) ELISA		17-479	FAK ELISA
17-462	phospho-EGFR (Tyr1068) ELISA		17-480	phospho-FAK (Tyr397) ELISA
17-463	ERK 1/2 ELISA		17-481	IGF-1R ELISA kit
17-464	phospho-ERK 1/2 (Thr185/Tyr187) ELISA		17-482	phospho-IGF-1R (Tyr1135/Tyr1136) ELISA
17-465	JNK 1/2 ELISA		17-483	IR ELISA
17-466	phospho-JNK 1/2 (Thr183/Tyr185) ELISA		17-484	IR (Tyr1162/Tyr1163) ELISA
17-467	Src ELISA		17-485	IκB ELISA
17-468	phospho-Src (Tyr418) ELISA		17-486	phospho-IκB (Ser32) ELISA
17-469	Met ELISA		17-487	p38α ELISA
17-470	phospho-Met (Tyr1230/34/35) ELISA		17-488	phospho-p38a (Thr180/Tyr182) ELISA
17-471	GSK-3β ELISA			
17-472	phospho-GSK-3β (Ser9) ELISA			

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信号转导级联反应的研究方法之三 — IP

1. Yeast Two Hybrid: BD and AD

2. GST pull down

3. IP

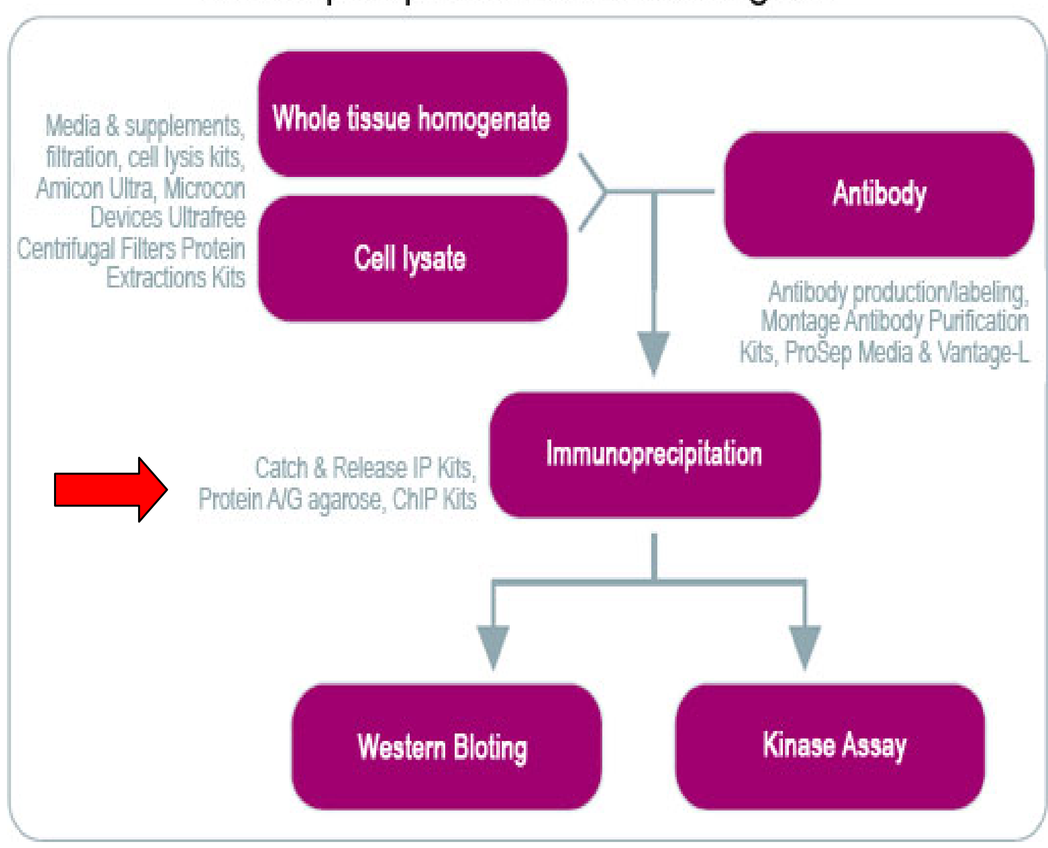
Immunoprecipitation (IP)

Immunoprecipitation (IP):

- Separates proteins from other molecules in a cell lysate
- Isolates proteins in their native conformation
- Studies protein: protein interactions known as co-IP

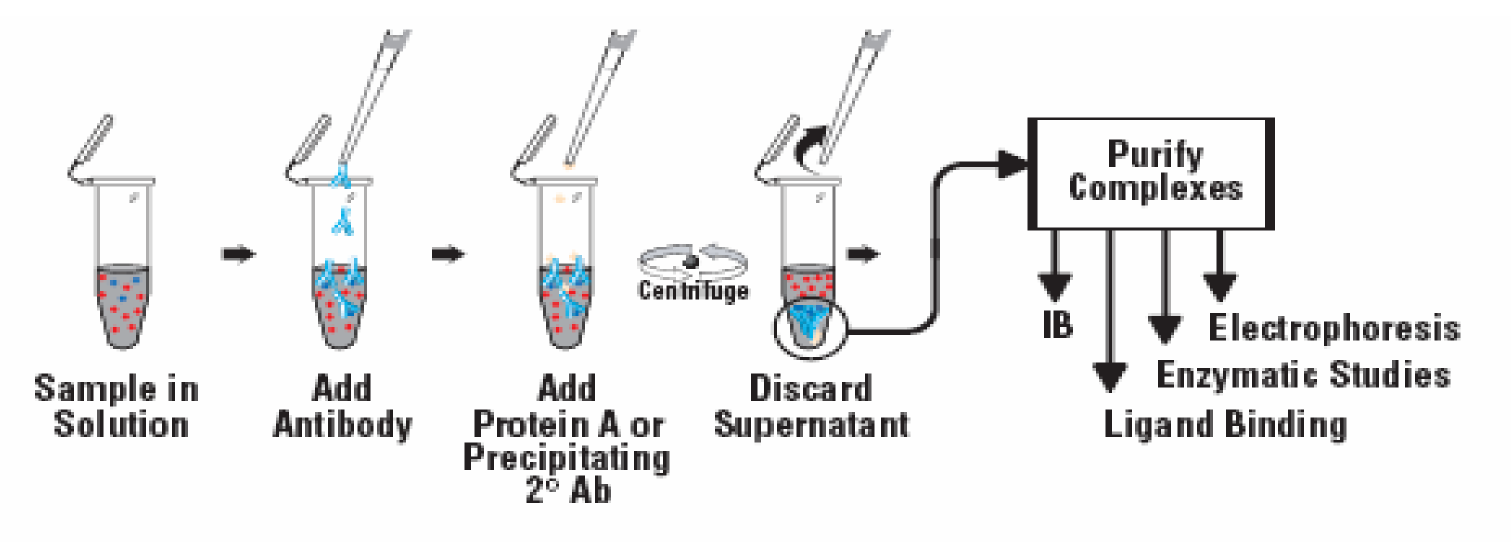
What is Unique about IP?

- Binding of protein in its native state leading to purification



Traditional IP

Preparation → Antigen/ Antibody complex → Precipitation of complex → Centrifuge → Analysis → Purify,WB Etc.



如何解决实验结果重复性的问题?

如何节约免疫共沉淀的时间?

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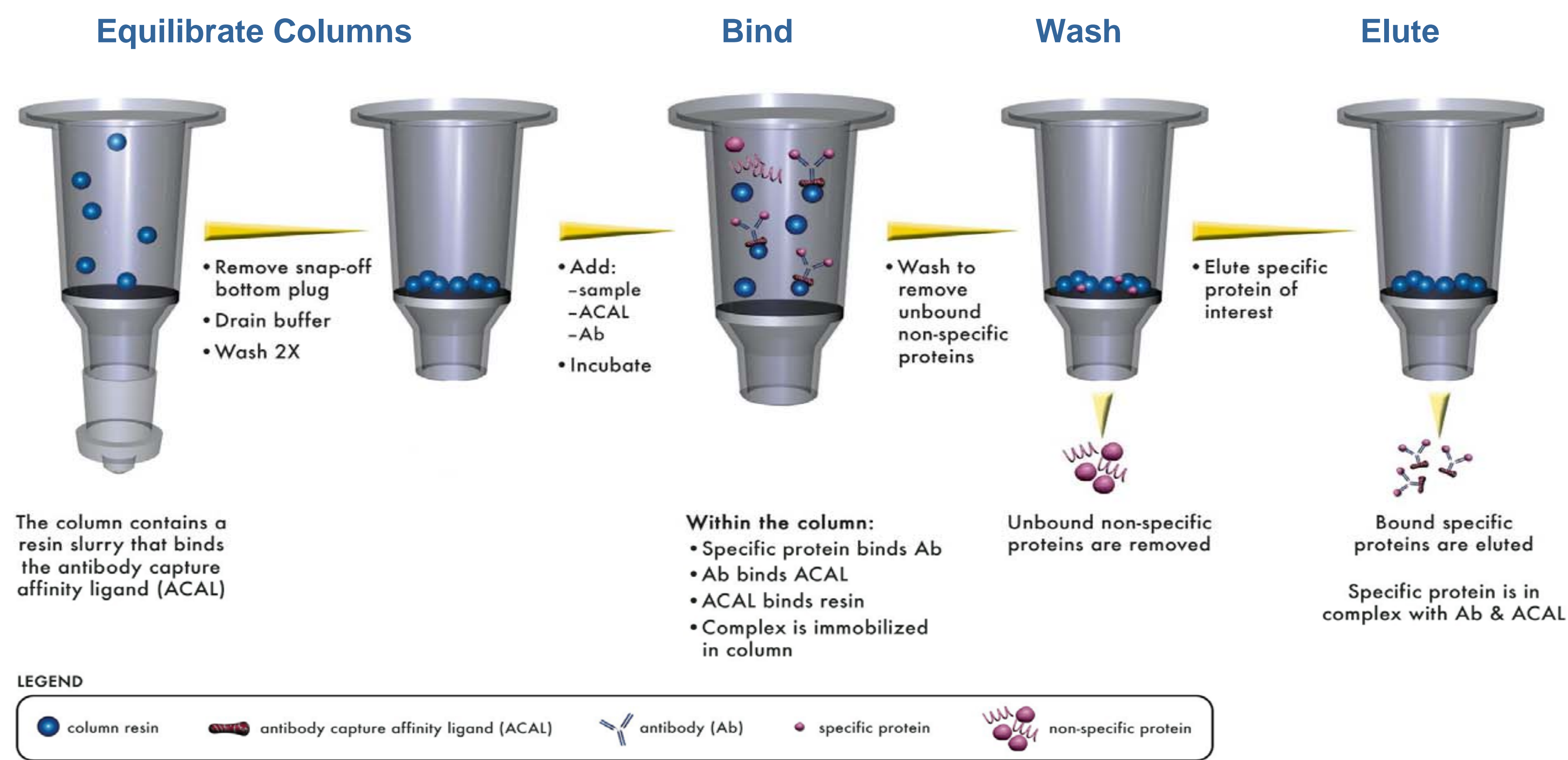
Catch & Release® IP System



Cell lysate 500ug+Antibody 1-4ug+ACAL 10ul +1Xwash buffer = 500ul→RT 30min→ 5000rpm 15-30s→ 3Xwash→ elute

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Competition

Traditional IP
Protein A/G agarose

Catch & Release Advantage over Traditional IP

- **Minimize contamination:** resin filled spin columns offer less non-specific binding than traditional protein A or G agarose
- **Reproducible**: eliminates aspiration steps that typically lead to sample loss
- **Native or denatured elution:** choice of elution buffer allows purification of active enzymes for functional assays or denatured proteins for Western blot analysis
- **Convenient**: spin column format ensures ease-of-use with a 30 minute incubation and streamlined protocol
- **High throughput process**
- **Saving primary antibody (1-4ug)**

Note: C&R is suitable to immunoprcipitate protein expression

Flag, GFP, HA and Myc.

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Reference

1. **Jun Ho Lee, Young Mi Kim, Nam Wook Kim et al.**

   Phospholipase D2 acts as an essential adaptor protein in the activation of Syk in antigen-stimulated mast cells. *Blood*, Vol. 108, No. 3, 956-964, 2006.

2. **Wei jie Li, Christine Marshall, Lijuan Mei et al.**

   Srcasm Modulates EGF and Src-kinase Signaling in Keratinocytes. *J. Biol. Chem*. Vol. 280, 6036-6046, 2005.

3. **Hong wei Li, Tibor Rauch, Zhao-Xia Chen et al.**

   The Histone Methyltransferase SETDB1 and the DNA Methyltransferase DNMT3A Interact Directly and Localize to Promoters Silenced in Cancer Cells. *J. Biol. Chem*., Vol. 281, 19489-19500, 2006.

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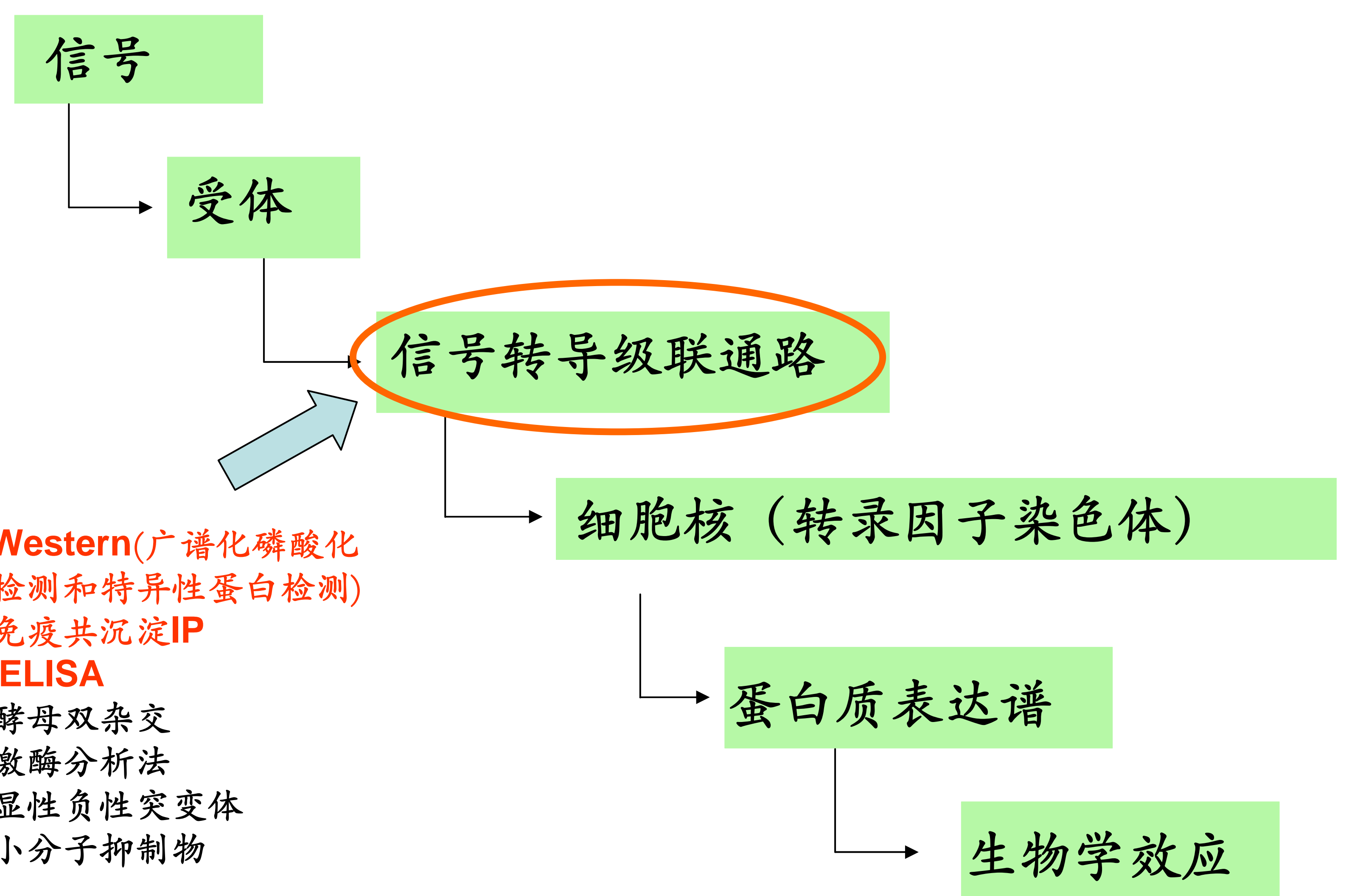
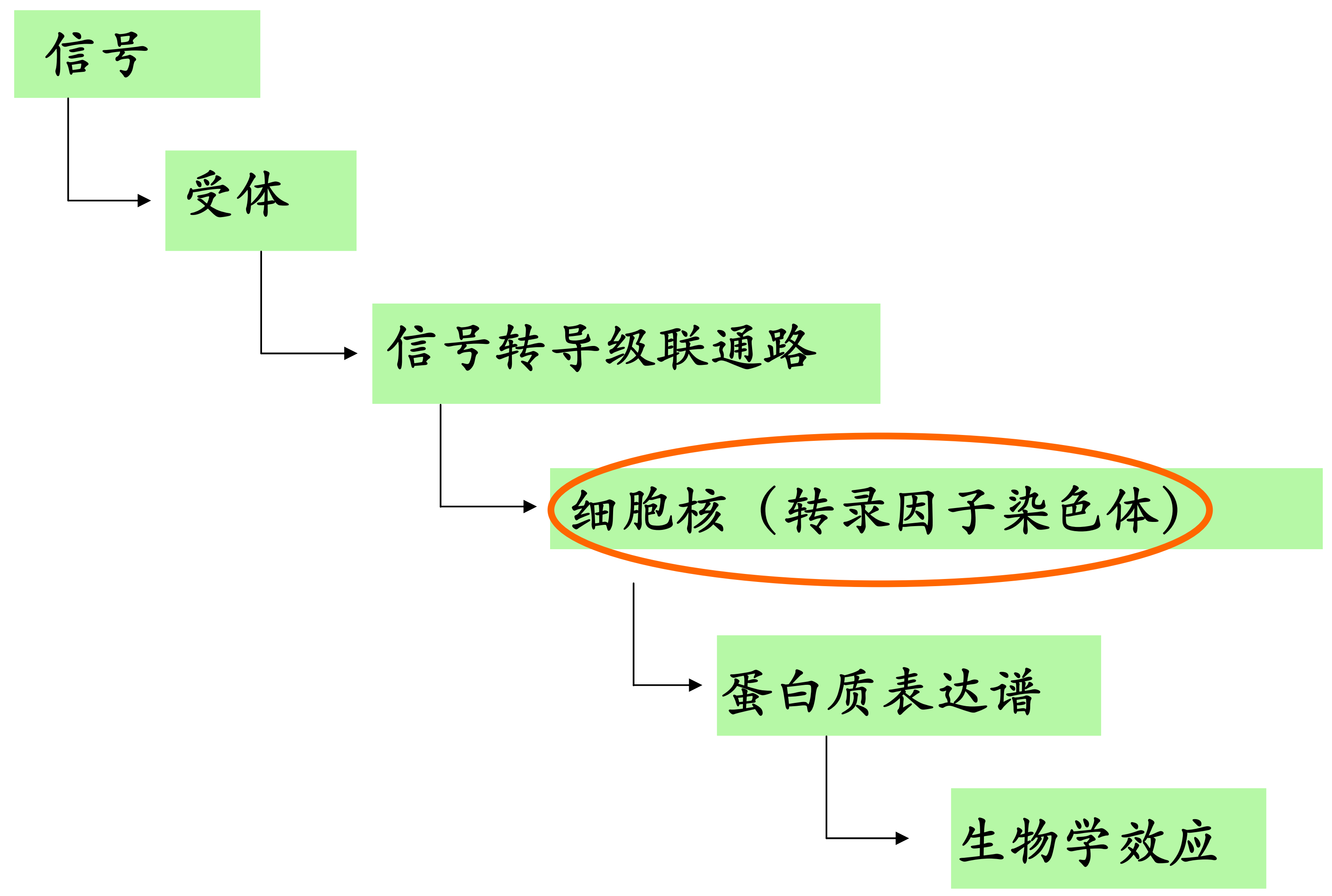
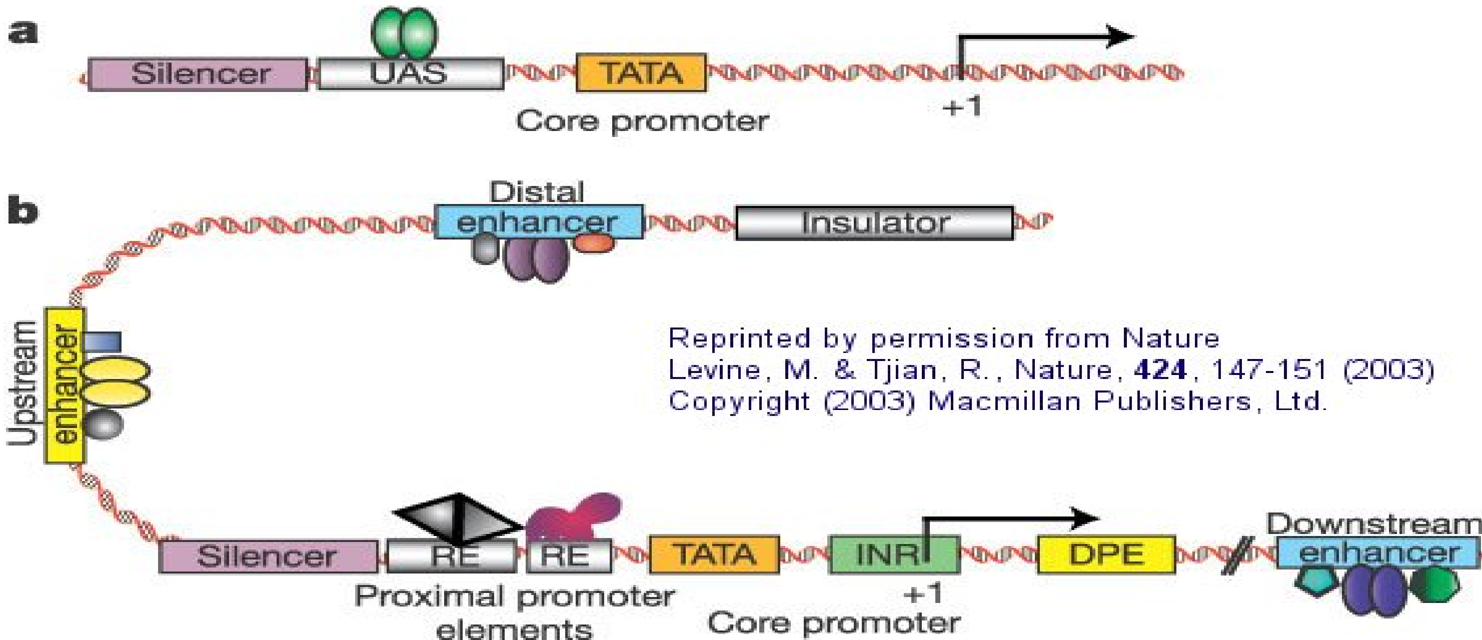
细胞信号转导常用方法



细胞信号转导常用方法



Typical DNA Response Elements



Silencer = Repressor Binding Site
UAS = Upstream Activating Sequence
TATA = TATA Box (PolII recognition)
Enhancer = Trans Factor Binding Site
INR = Initiator sequence
DPE = Downstream Proximal Element
Insulator = sequence defining a chromatin regulatory domain

Transcription Factors

- They are the ultimate target of many signaling pathways
- Proteins that bind to DNA and mediate the translation of RNA (with RNA polymerases).
- Often bind in the promoter region of the gene
  - (before the open reading frame of the gene really starts)
  - They bind to a consensus sequence in DNA. This means that certain TF family member recognize the same DNA sequence (6-12 bases) and bind to it when activated.
- Work to either stimulate or repress transcription of a gene
- Regulation is dependent on the presence of other DNA binding proteins (including other transcription factors) as well as local chromatin structure.

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Methods to Study Gene Regulation

Electrophoretic Mobility Shift Assay, DNAse I footprinting, *in vitro* transcription reactions

Transfection Analysis
- Promoter Mutagenesis + Reporter Vectors
- cDNA overexpression and mutagenesis

Biochemical purification of nuclear complexes

RNA Analysis
- Northern Blot, RT-PCR, SAGE, microarray

Immunoprecipitation of proteins associated with nucleic acid
- a variety of protocols

CHIP

-ReChIP = performing a ChIP and then taking isolated chromatin and applying a second antibody to further select the ChIPed species

- ChIP:ChIP is chromatin IP coupled with microarrays

- ChIP:PET is chromatin IP in conjunction with high throughput sequencing

- RIP ChIP is a method of isolating RNA associated with RNA binding proteins by immunoprecipitation.

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Traditional methods — EMSA

EMSA quick overview:

1. Treat cells and prepare nuclear lysate just as you would for our assay (we offer a very easy kit for this Cat. No. 2900)
2. Lysates incubated with radio-labeled (P32) double-stranded oligonucleotide
3. Run a very large gel (10X the size of a western) for hours
4. Expose the gel to X-ray film at -80C for 1-3 days
5. Develop film and determine the amount of radioactivity (band intensity) on the X-ray film showing the gel shift.

Shortfalls:

- **Radioactive**: very messy and dangerous
- **Very time consuming**, both hands-on time (hours vs. minutes) and assay completion time (days vs. hours)
- **Not target specific**
  - Ex. All 5 NFκB family members bind to the same sequence.
    Can not differentiate how much of each one.
    This assay differentiates the amount of each.

EZ-TFA
Transcription Factor Assay
(70-5x0 and 70-6x0)

EZ-TFA kits are used to detect specific transcription factor DNA binding activity in cell/nuclear extracts

Protocol

Double stranded biotinylated oligonucleotide with consensus sequence for TF binding is mixed with nuclear extract, and TFA assay buffer

During incubation, the active TF in the nuclear extract binds to its consensus sequence

Transfer to streptavidin coated plate
- Biotinylated oligonucleotide with active protein bound to consensus sequence is immobilized
- unactive, unbound material is washed away

Probe for specific TF bound (antibody)
- Detect with spectrophotometric plate reader (colorimetric detection) or luminometer (chemiluminescent detection)

Assay Overview

Step 1: *Treated whole cell or nuclear extract is added to the Capture Probe in solution. The Capture Probe is a double stranded biotinylated oligonucleotide containing the consensus sequence for transcription factor binding.*

Step 2: *After incubation, the extract/probe/buffer complex mixture is transferred to the streptavidin coated plate. The biotinylated Capture Probe is immobilized and any inactive, unbound material is washed away.*

Step 3: *The bound transcription factor subunit is detected with a specific primary antibody.*

Step 4: *The HRP-conjugated secondary antibody binds to the specific primary antibody.*

Step 5: *After a chromogenic substrate reaction the relative quantity of DNA bound transcription factor is measured using a spectrophotometric plate reader.*

EZ-TFA

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Combines the principles of ELISA (Enzyme-Linked Immunosorbent Assay) with EMSA (Electrophoretic Motility Shift Assay)

- **Fast**
  - <4 hours with minimal hands on time.
    - EMSA is 2-4 days.
- **Sensitive**
  - Chemiluminescent can go to pg levels of nuclear lysate protein. Colorimetric to μg levels.
  - More sensitive than EMSA
- **Flexible**
  - Strip-well format (12x8)
    - Can use some now, some later-multiple runs.
    - Allows for manual through put or HTS.
  - Use included capture probe (canonical sequence) or create new ones yourself (potential binding sites)
  - Titration of capture and competitive probes
- **Safe (Non-radioactive)**
  - Colorimetric and Chemiluminecesnt kit available for all targets.
    - EMSA use large amounts of P32

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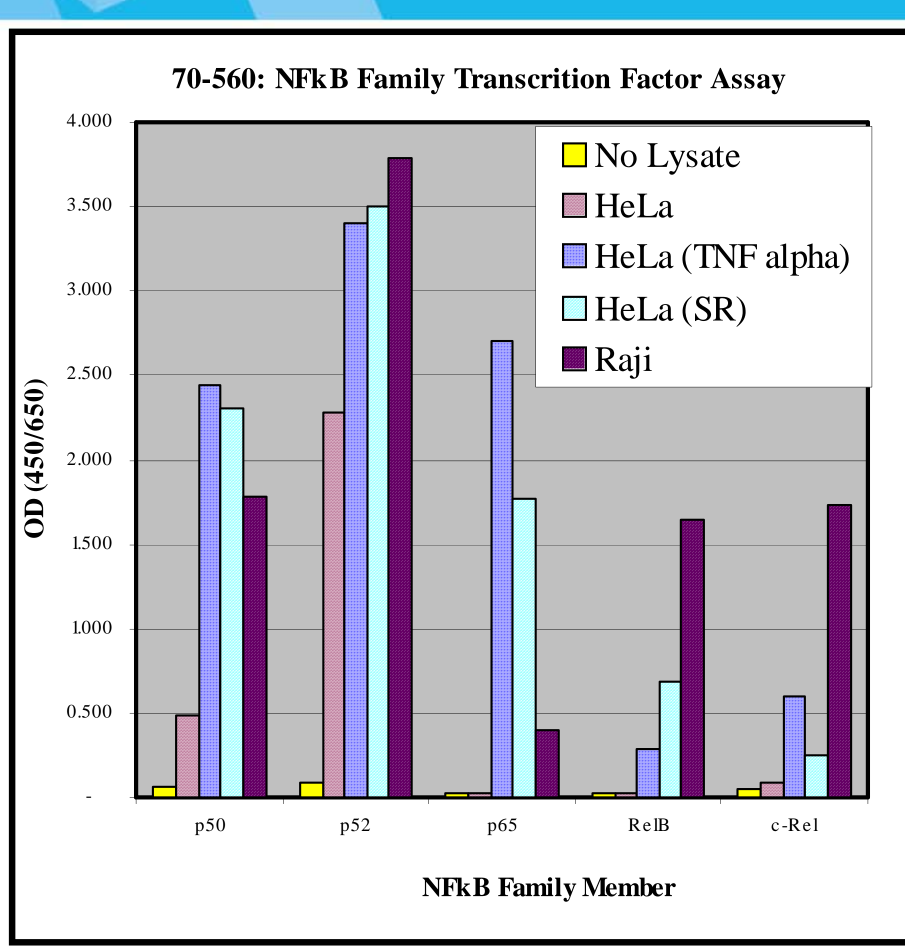
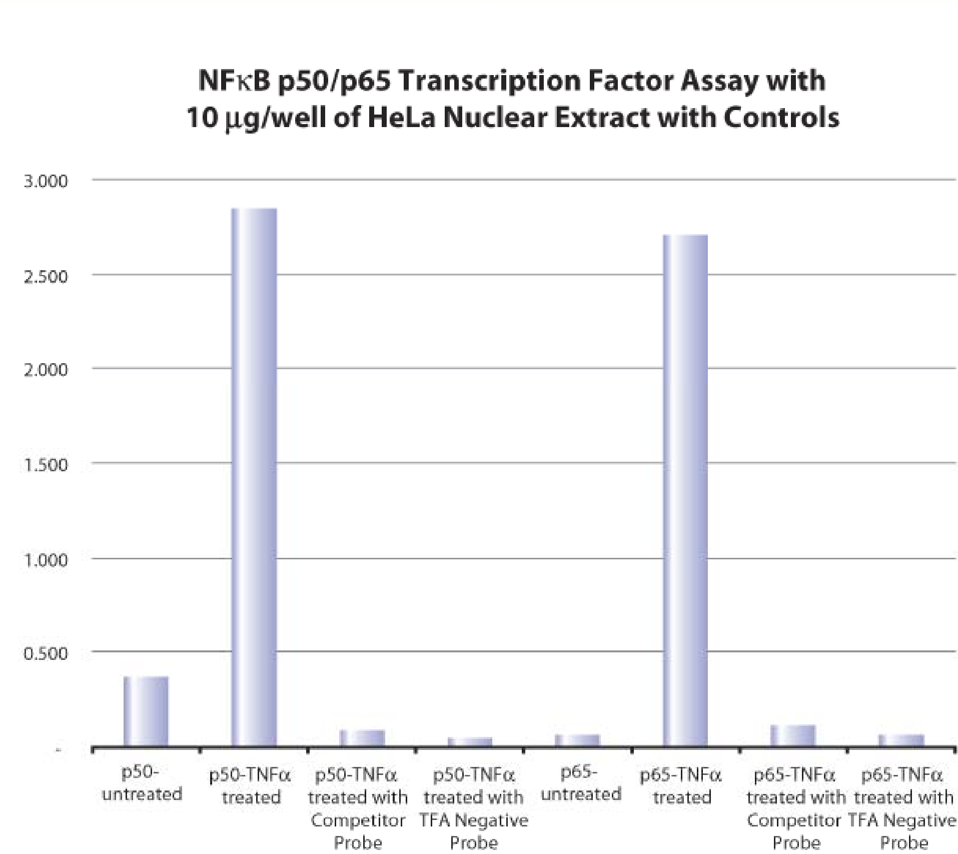
EZ-TFA Profiling Data





EZ-TFA
Non-radioactive Transcription Factor Activity Assay Kits

Millipore EZ-TFA Kits

Description	Catalogue Number: Colorimetric	Catalogue Number: Chemiluminescent
c-Fos	70-545	70-645
c-Jun	70-540	70-640
Jun/Fos	70-546	70-646
CREB	70-575	70-675
NFκB p50/p65	70-510	70-610
NFκB p50	70-515	70-615
NFκB p65	70-520	70-620
Fox01	70-555	70-655
FoxO3a	70-553	70-653
ATF2	70-585	70-685
HIF-1α	70-570	
Oct-4	70-565	
p53	70-525	70-625
STAT1α	70-535	70-635
STAT3	70-530	70-630
AP-1 Family (Jun, Fos, JunB, JunD, FosB, Fra-1, Fra-2) 192 assays	70-550	70-650
NFκB Family (p50, p52, p65, c-Rel, and RelB) 192 assays	70-560	70-660

Universal EZ-TFA Kits

Description	Catalogue Number: Colorimetric	Catalogue Number: Chemiluminescent
Universal EZ-TFA 96 assays	70-500	70-600
Universal EZ-TFA 192 assays	70-501	70-601

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Methods to Study Gene Regulation

Electrophoretic Mobility Shift Assay, DNAse I footprinting, *in vitro* transcription reactions

Transfection Analysis

- **Promoter Mutagenesis + Reporter Vectors**
- **cDNA overexpression and mutagenesis**

Biochemical purification of nuclear complexes

RNA Analysis

- **Northern Blot, RT-PCR, SAGE, microarray**

Immunoprecipitation of proteins associated with nucleic acid

- **a variety of protocols**

CHIP

-ReChIP = performing a ChIP and then taking isolated chromatin and applying a second antibody to further select the ChIPed species

- ChIP:ChIP is chromatin IP coupled with microarrays

- ChIP:PET is chromatin IP in conjunction with high throughput sequencing

- RIP ChIP is a method of isolating RNA associated with RNA binding proteins by immunoprecipitation.

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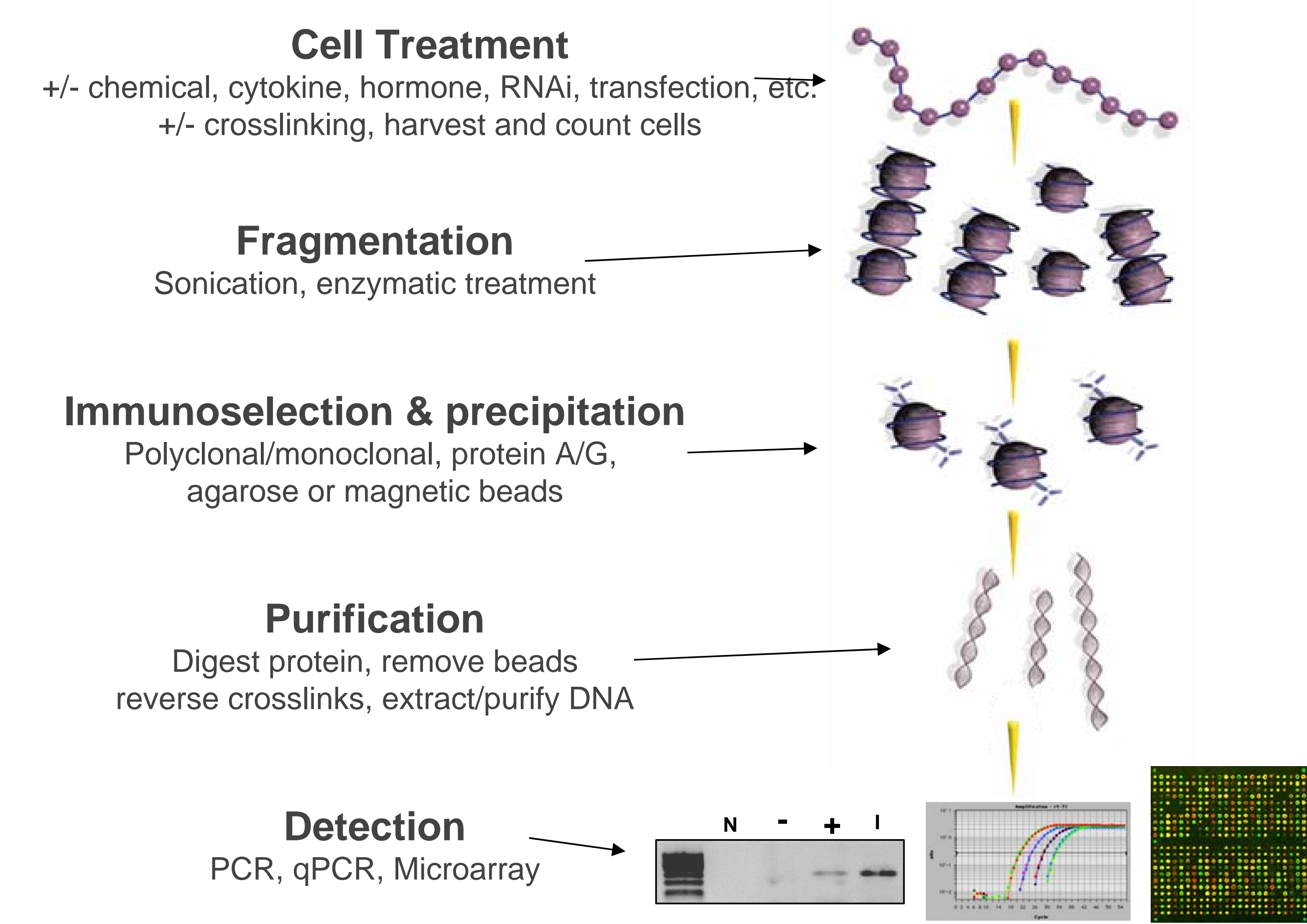
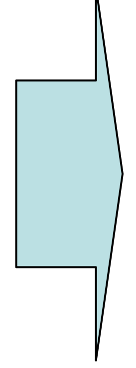
ChIP: An application for probing protein: DNA, protein: RNA and protein: protein interactions using antibodies



ChIP Challenges

Cell Treatment
Fragmentation
Antibody Selection
Immunoprecipitation
Purification



Formaldehyde for crosslinking, Native ChIP
Sonication or Enzymatic
Choose carefully, use all available information
Use blocked beads, careful washing
proteinase K and DNA purification columns

ChIP (bare bones—experienced users)

3rd Generation of ChIP Kits

17-295 ChIP Kit
17-245 ChIP Acetyl H3
17-229 ChIP Acetyl H4

<u>EZ-ChIP</u> **(controls, buffers, spin filters—New users)**

17-371 EZ-ChIP
17-375 EZ-Zyme

<u>Magna ChIP</u>

17-610 Magna ChIP Protein A (buffers, spin filters)
17-611 Magna ChIP Protein G

17-408 EZ-Magna ChIP A (Acetyl H3) (complete)
17-409 EZ-Magna ChIP G (RNA Pol2)

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Reference:

1. Arati Khanna-Gupta, Theresa Zibello, Hong Sun, Peter Gaines. Chromatin immunoprecipitation (ChIP) studies indicate a role for CCAAT enhancer binding proteins alpha and epsilon (C/EBP and C/EBP) and CDP/cut in myeloid maturation-induced lactoferrin gene expression. *Blood*,Vol. 101, No. 9, pp. 3460-3468 ,2003.

2. Lee Gary, Donald H. Gilden, and Randall J. Cohrs. Epigenetic Regulation of Varicella-Zoster Virus Open Reading Frames 62 and 63 in Latently Infected Human Trigeminal Ganglia. Journal of Virology,4921-4926, Vol. 80, No. 10, 2006.

3. Melanie Amen,1 Xiaoming Liu,2 Usha Vadlamudi. PITX2 and ß-Catenin Interactions Regulate Lef-1 Isoform Expression. Molecular and Cellular Biology, 7560-7573, Vol. 27, No. 21, 2007.

Summary

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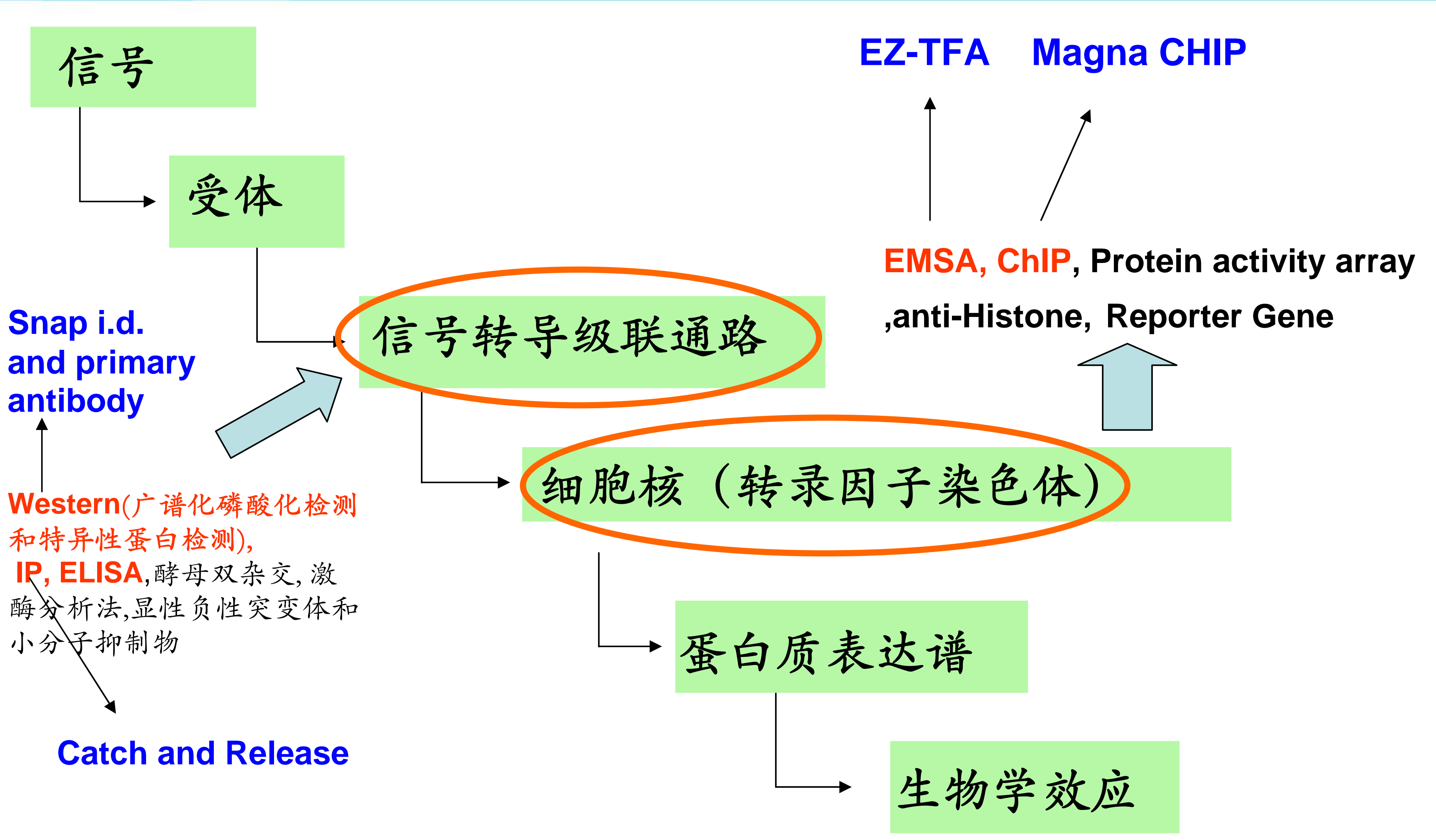

Framing the Workflow Modules

Obtain cells from Library, Supplier or Organism

Stem Cells

Protein Expression

Media

Supplements

Cultureware

Grow Cells / Tissue Culture

Sample Prep, Purify and Concentrate

Cell Analysis

Immunoprecipitation

Protein Analysis and Detection *(see ID Handbook)*

Western Blot

IHC and ICC

Flow Cytometry

ELISA/RIA/Milliplex

Gene Transfer

Cell Adhesion

Cell Migration

Cellular Pathways

Cell Function

- Focus of cell culture workflow module
  - *Epithelial CC*
  - *Neural Stem Cell Culture*

- Focus of protein research workflow module

- Not covered

Millipore : Products and services for Drug Discovery

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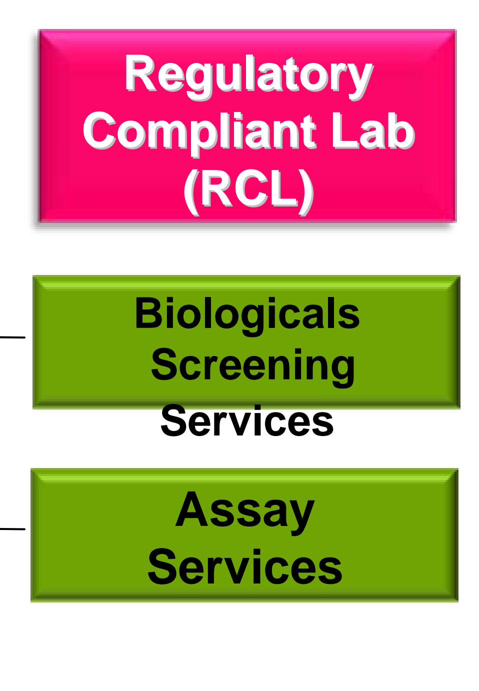
Biomarkers Immunoassays (BMIA)

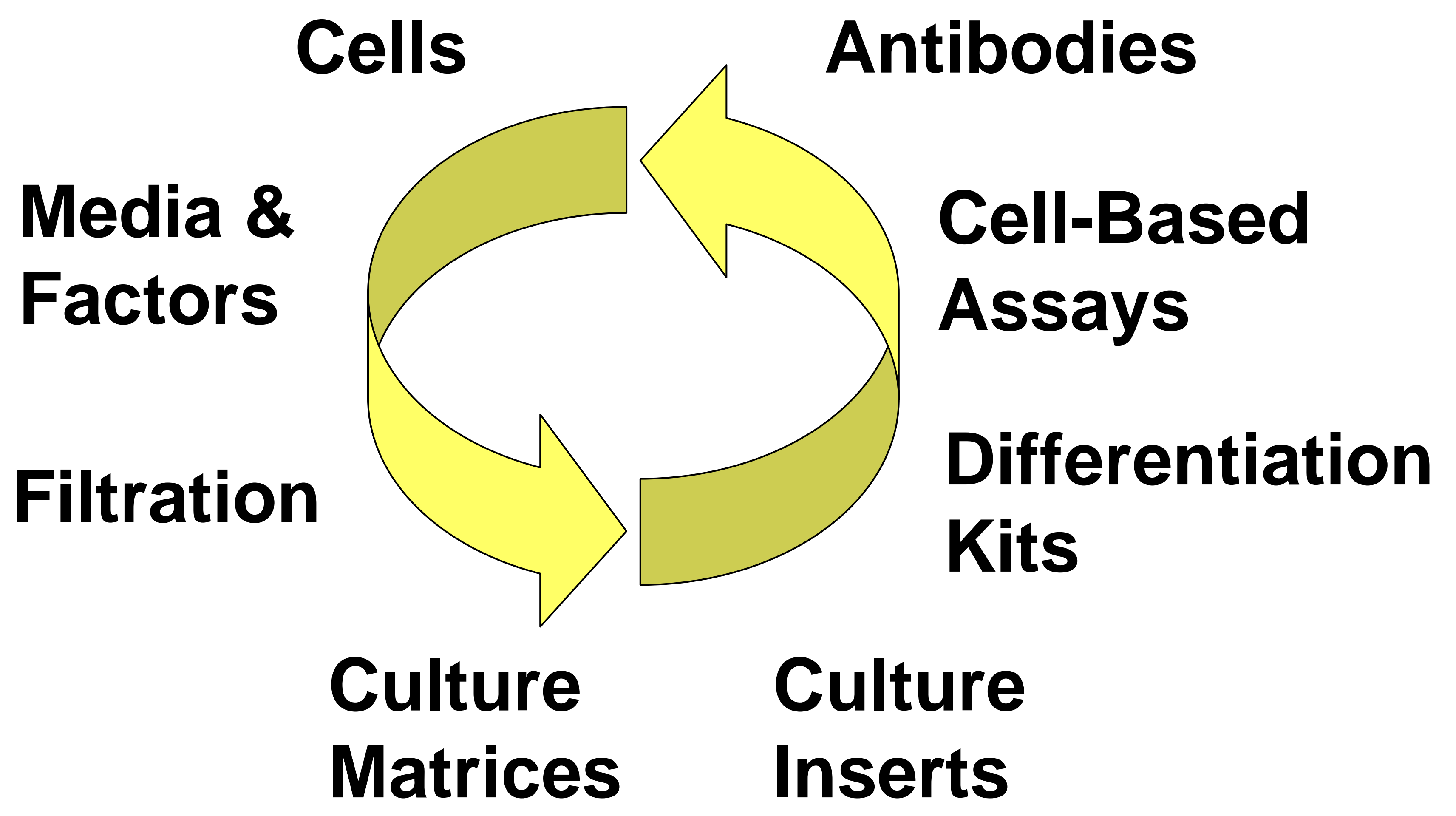
- Multiplex Instrument
- Assay Kits
  - ELISA
  - RIA
  - Milliplex

Target Profiling / Lead Optimization (TPLO)

- Products
- Services
  - GPCRs
  - Kinases
  - Phosphatases
  - Ion Channels



Integrated Solutions from Millipore



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Asia Technical Support Team Was Initiated to Build Since July, 2007

We are dedicated to provide valuable technical solution and advice by all kinds of ways in house for Asia customers and distributors.

- Tech Service Phone 400-889-1988
- Emails asiatechserv@millipore.com
- Millipore website inquiry collection
- Other communication ways, e.g. internal enquiry
- High quality team
    - 25% PhD. and 75% Master degree
    - Lily Zhang, PhD., from Serologicals
    - Hao Long & Jun Yin were trained in Temucula.

In Work

Team