

ATP Metabolism as Biomarker Target for Cardiovascular Protection and Toxicity

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Biomarkers Symposia – My involvement



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- *“Biomarkers as surrogate endpoints in pre-clinical and clinical drug development” at the 6th Annual Symposium of the Canadian Society of Pharmaceutical Sciences, Montreal, QC, May 28 - 31, 2003.*
- *“Can Biomarkers for Cardiovascular Drug Therapy and Cardiac Toxicity be Effectively Integrated in Drug Development?” at the 110th Annual Meeting of the American Society of Clinical Pharmacology and Therapeutics (ASCPT) in Washington DC (National Harbor, MD), March 18 -21, 2009.*
- *“Predicting Clinical Outcome Events using Biomarkers for Drug Development” at the 2010 FIP/AAPS Pharmaceutical Sciences World Congress, New Orleans, LA, USA, Nov 14 - 18, 2010.*
- *“Optimizing Drug Development using Biomarkers and Biowaivers ” at the Annual Meeting and Symposium of the Canadian Society of Pharmaceutical Sciences, Toronto, ON, June 12 - 15, 2012.*

Drug development is a science, art, or both?



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- *1970's - Application of pharmacokinetics*
- *1980's - Controlled clinical studies for efficacy*
- *1990's - Pharmacodynamics and pharmacogenetics*
- *2000's - Focus on drug safety*
- *2010's - Biomarkers?*

Potential Impacts of Biomarkers (Pharma 2010)



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IBM Business Consulting Services

Pharma 2010:
The Threshold of Innovation



IBM

- Revitalize and sustain a vibrant pharmaceutical, biotechnology, and diagnostic industry.
- Develop more targeted drug therapies and reduce cost of drug development.
- Form the scientific basis of personalized medicines.

Definition of biomarkers

Biomarkers Definitions Working Group. *Clin. Pharmacol. Ther.* 69: 89 – 95, 2001

- **Biological marker (biomarker):** *“A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.”*
e.g. Blood pressure, blood glucose, body weight, etc.
- **Clinical endpoint:** *“A characteristic or variable that reflects how a patient feels, functions, or survives”*
e.g. Feeling depressed

Processes of New Drug Discovery & Development

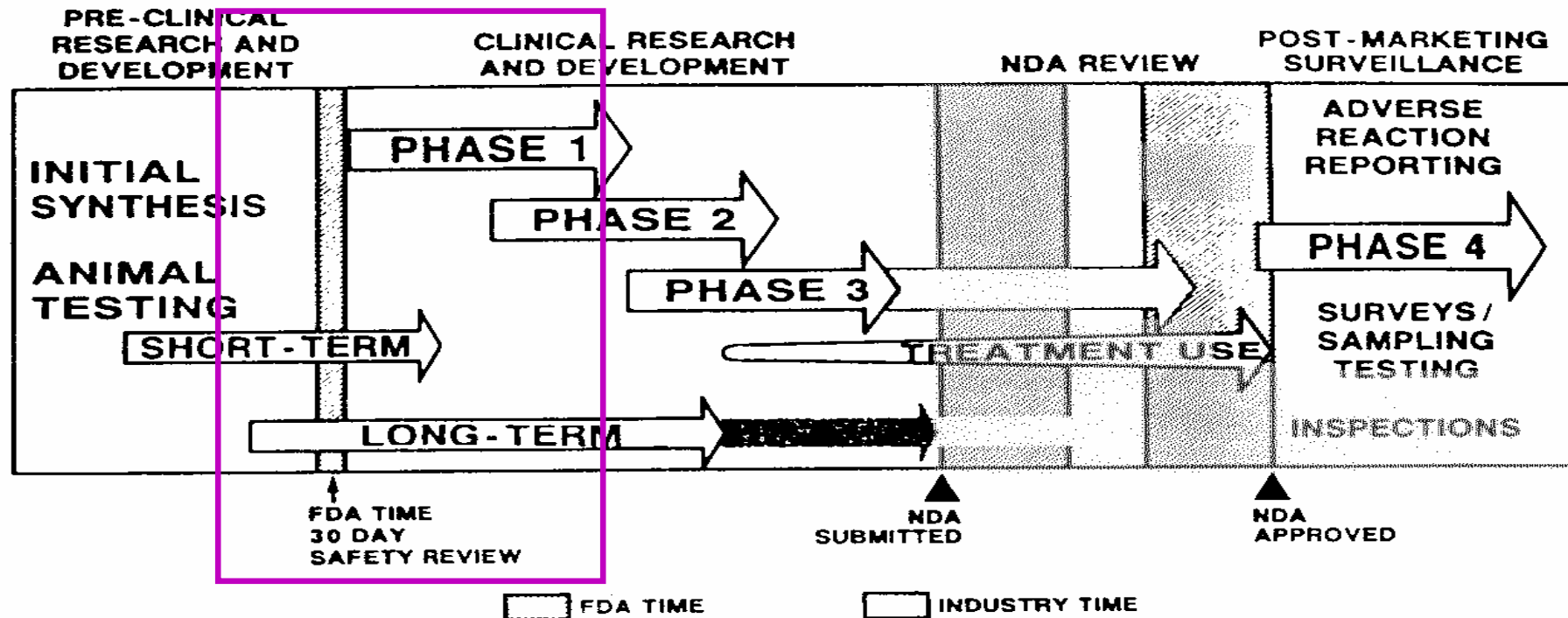
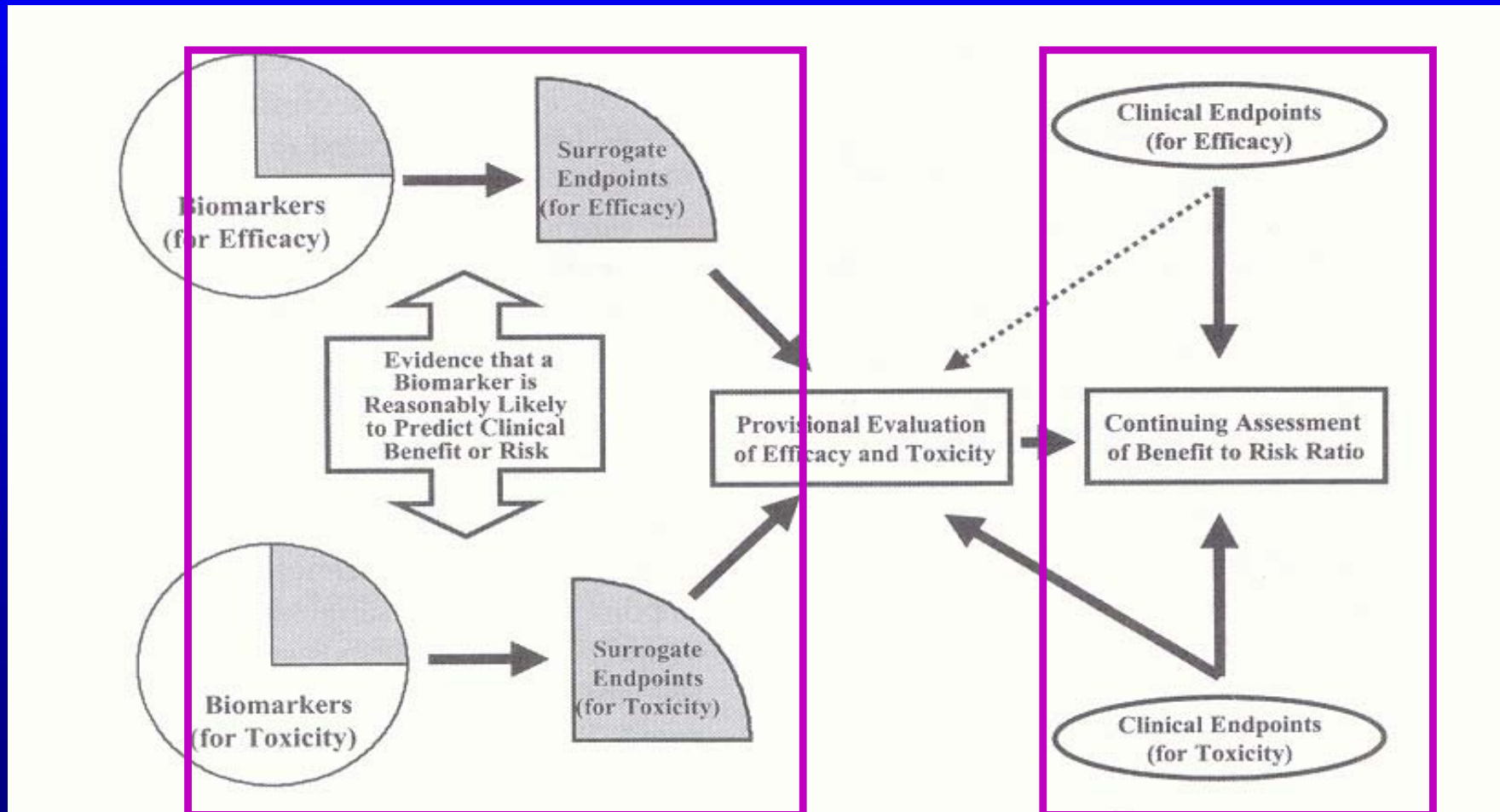


Fig. 1. A schematic depiction of the new drug development process.

(Peck et al. (1993) *Integration of Pharmacokinetics and toxicokinetics in rational drug development*. Edited by A. Yacobi et al. Plenum Press, N.Y.)

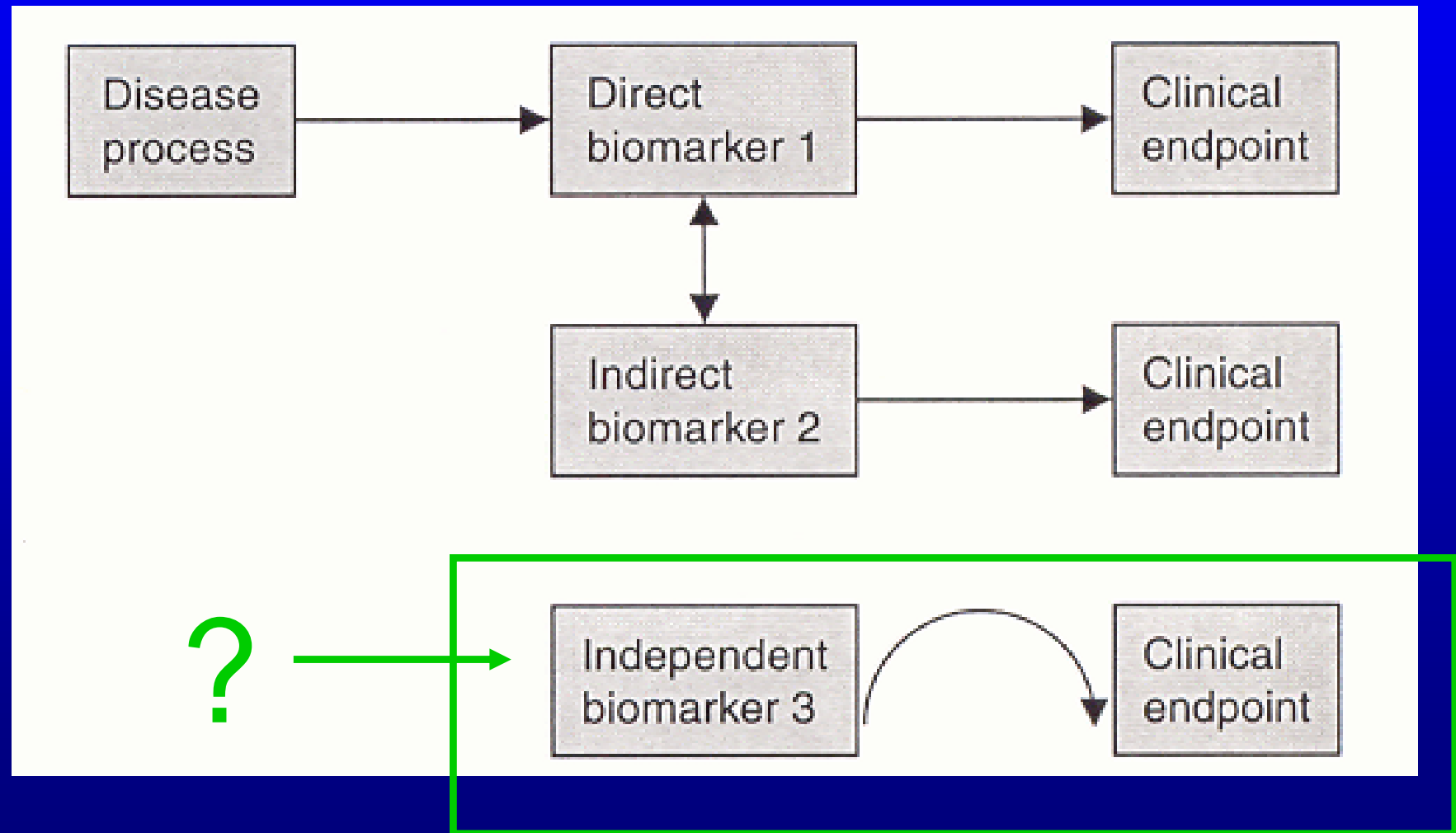
CONCEPTUAL MODEL FOR BIOMARKERS AND SURROGATE ENDPOINTS



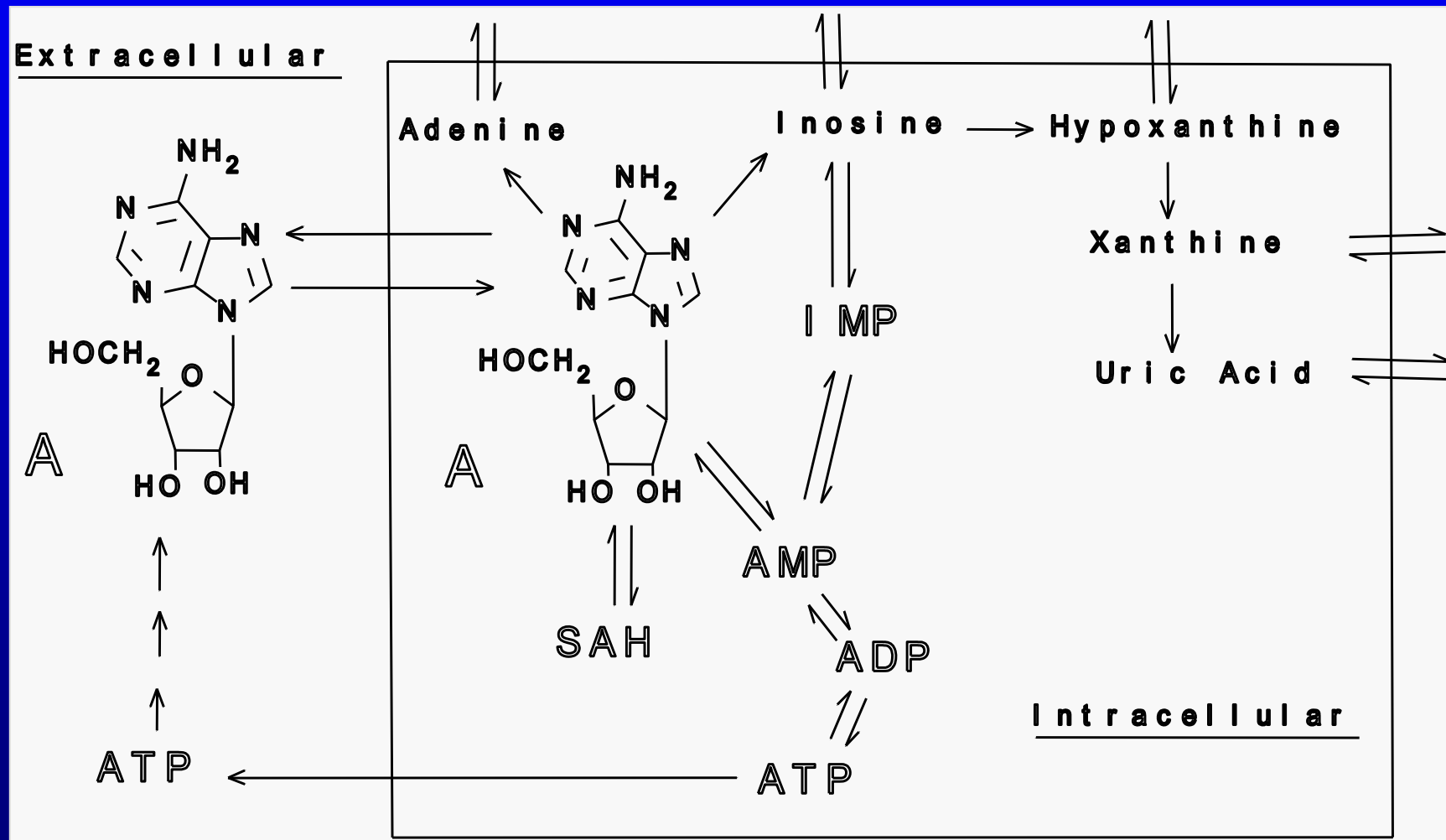
Biomarkers Definitions Working Group. Clin. Pharmacol. Ther.69:

89 – 95, 2001

Selection of Types of Biomarkers



ATP Metabolism (Yeung, et al. 1997)



Physiological Roles Adenosine and ATP



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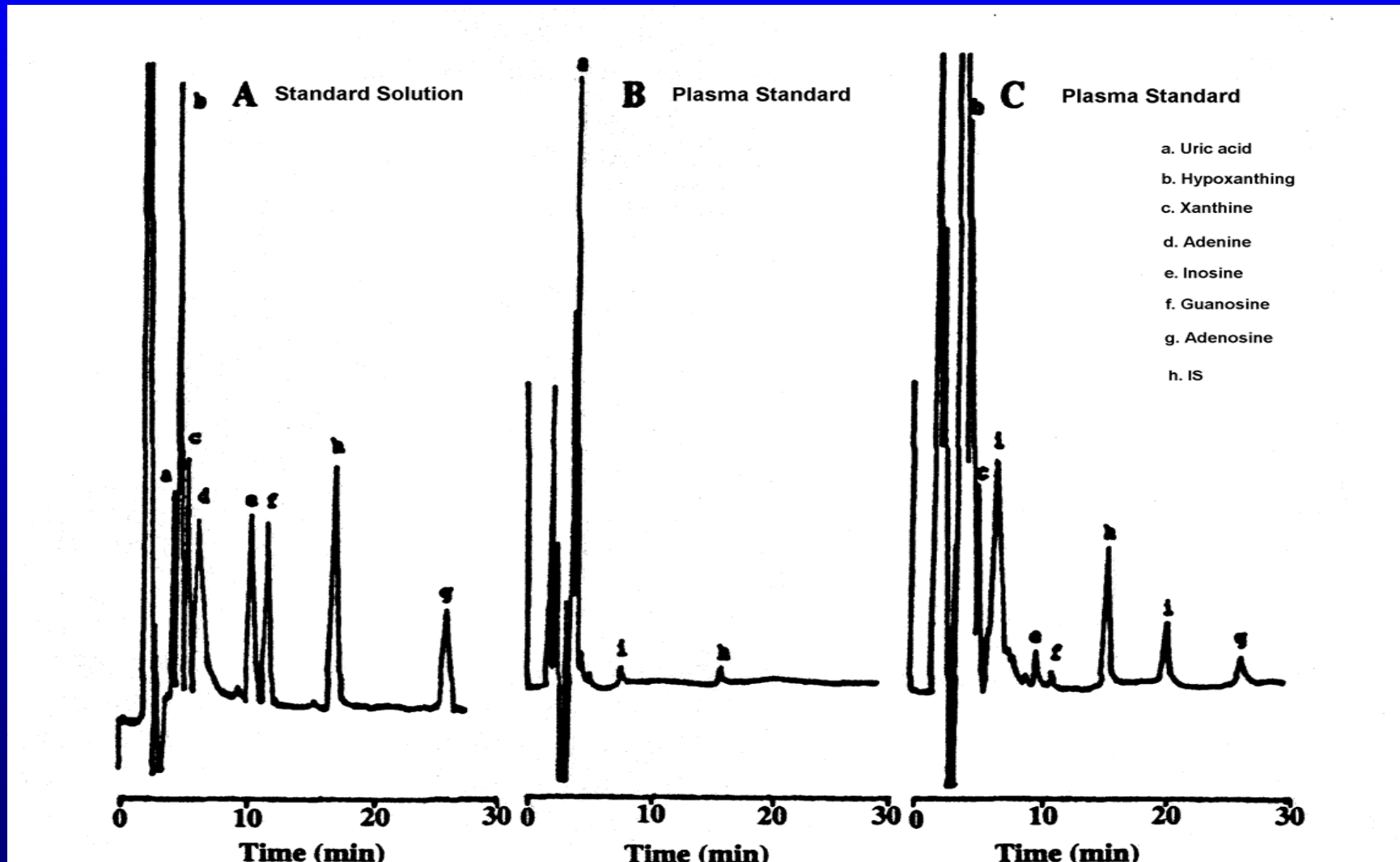
- **Regulate coronary blood flow**
- **Inhibit platelet aggregation**
- **Cardioprotection**
- **Neuro- and immuno- modulation**
- **Attenuate tissue necrosis (limit size of infarct)**
- **Mediator of ischemic or exercise preconditioning**
- **Others?**

HPLC of Adenosine and its Oxypurine Metabolites in Plasma

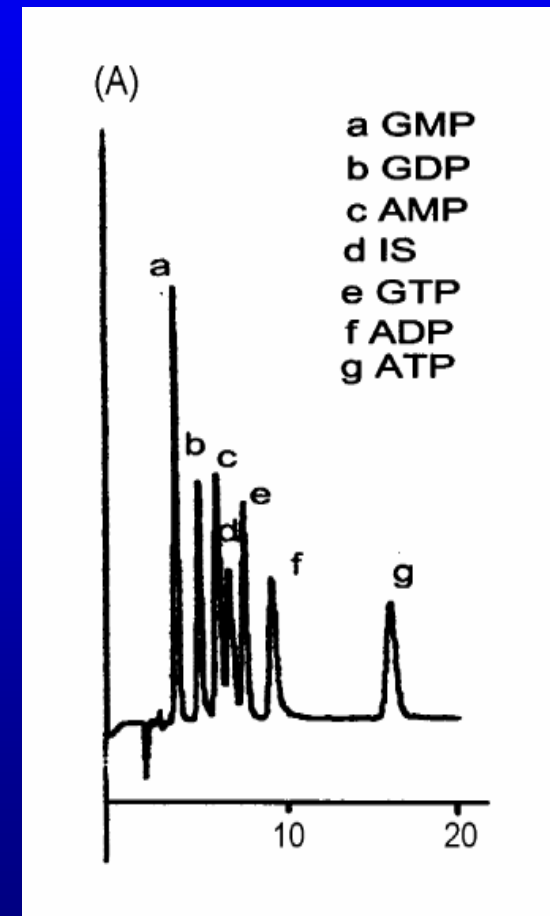
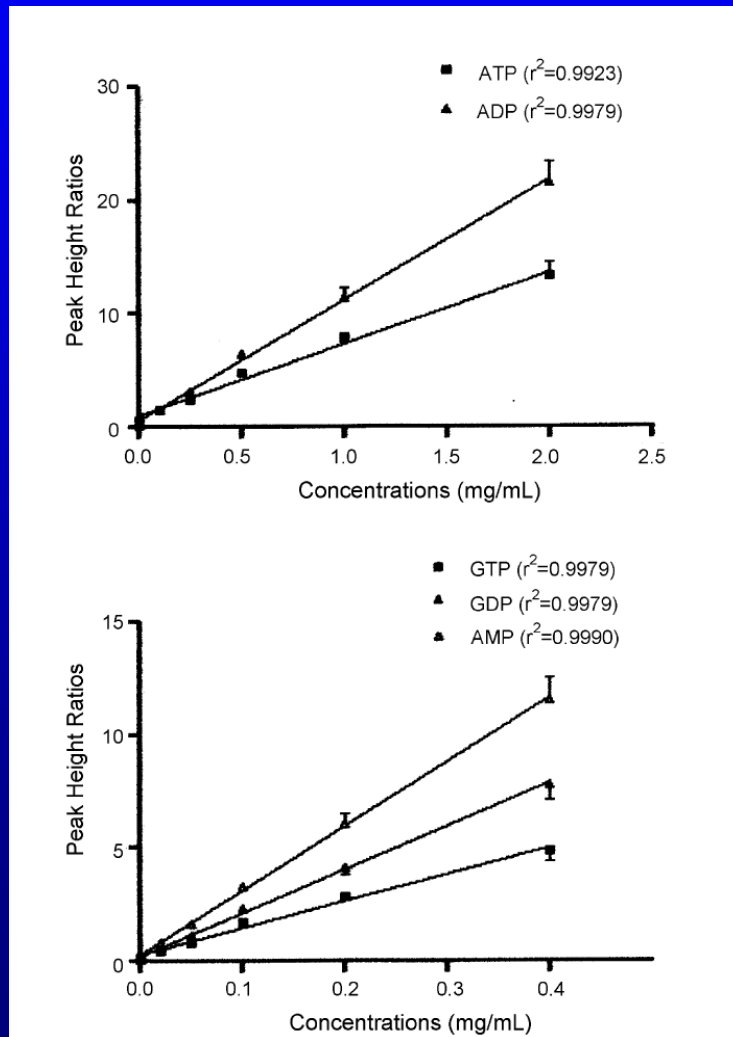
Feng and Yeung, *Ther Drug Monit* 22:177 - 183, 2000



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HPLC Assay of Purine Nucleotides in RBC

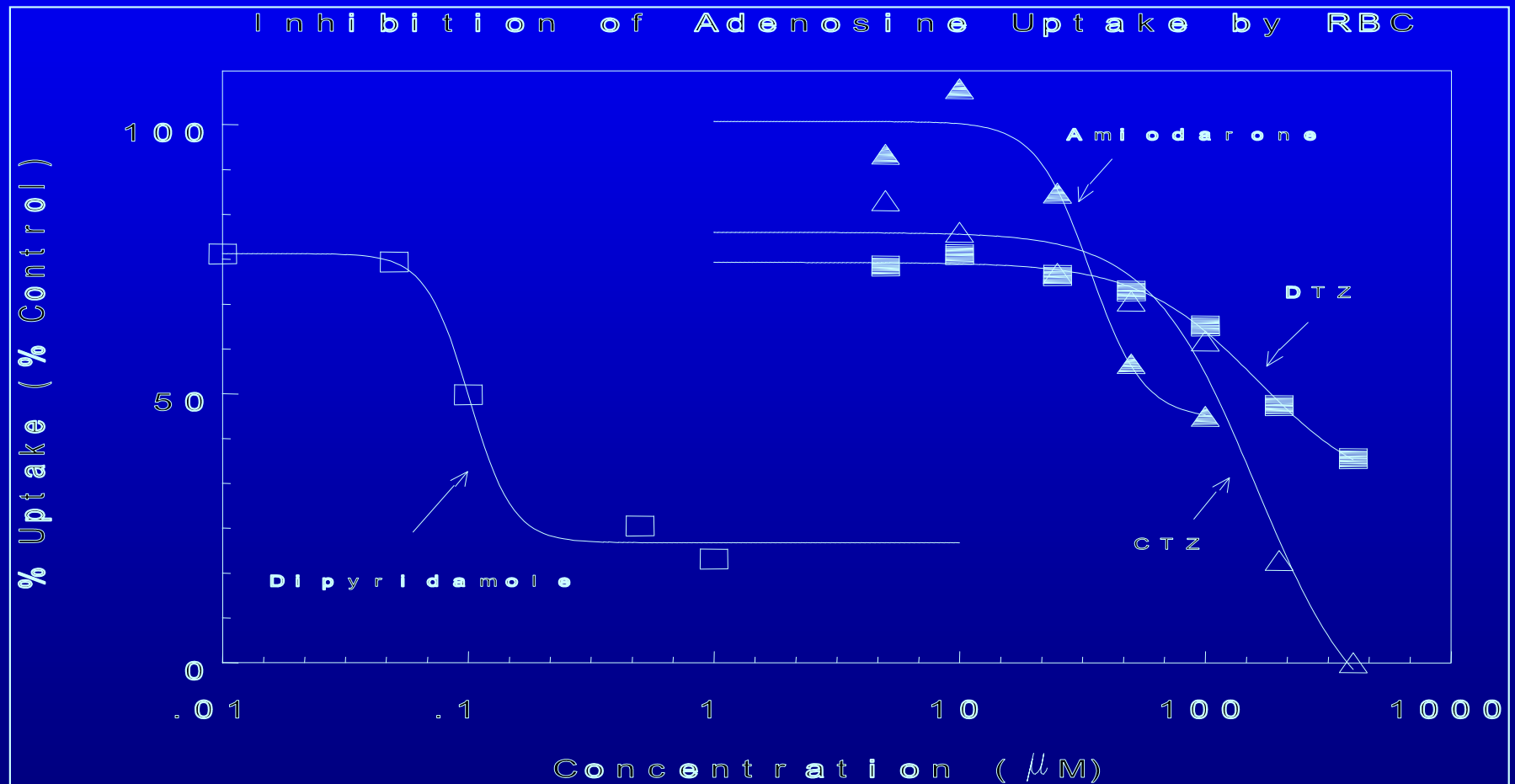


Yeung P, Ding L, Casley W. Journal of Pharm Biomed Anal 2008;47:377-382.

Inhibition of RBC uptake of adenosine



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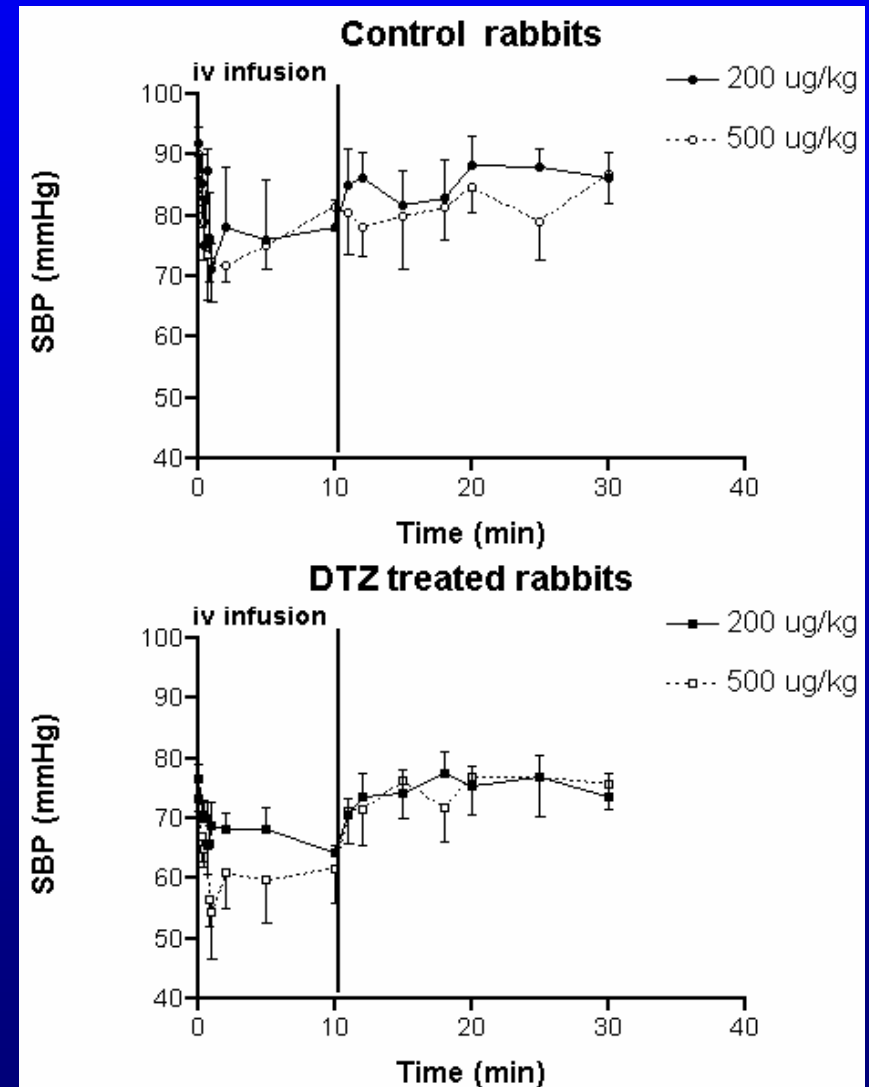
Yeung, Mosher, MacRae, Klassen. *J. Pharm. Pharmacol.* 43:685 - 689, 1991

Adenosine and Diltiazem Interactions *in vivo* (Yeung et al., *Current Topics in Pharmacology* 9 (1): 117 - 121, 2005).

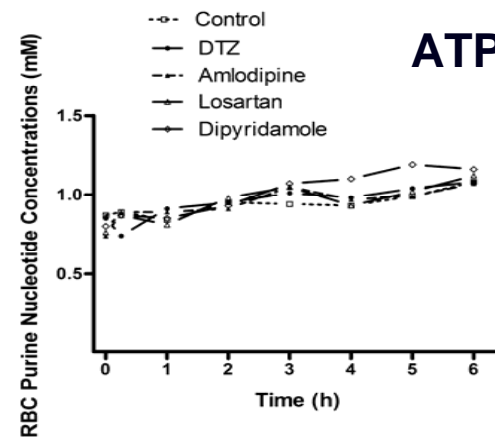
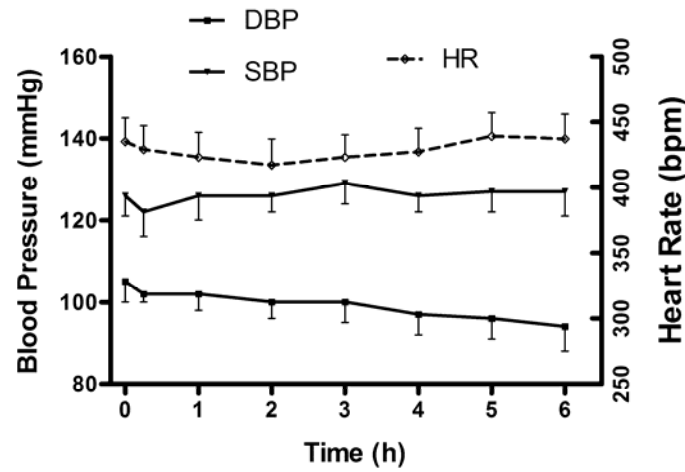
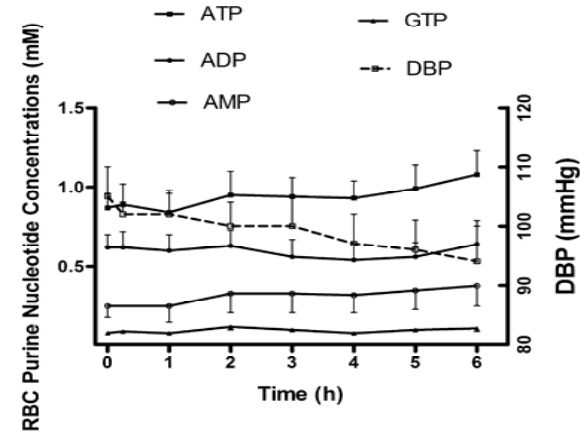


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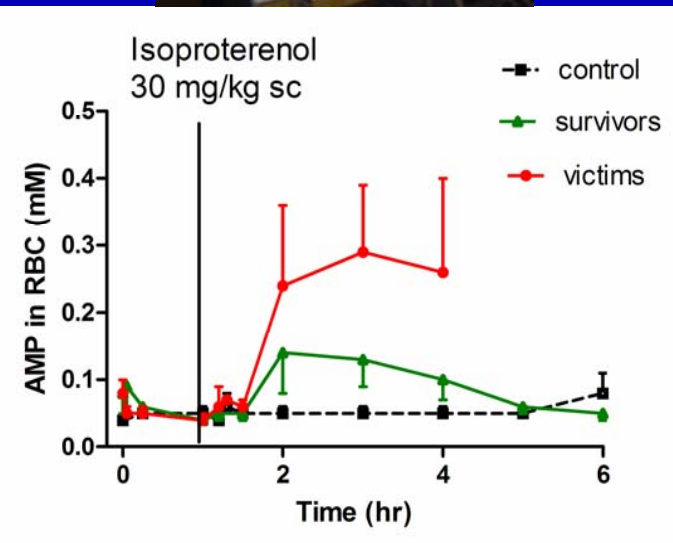
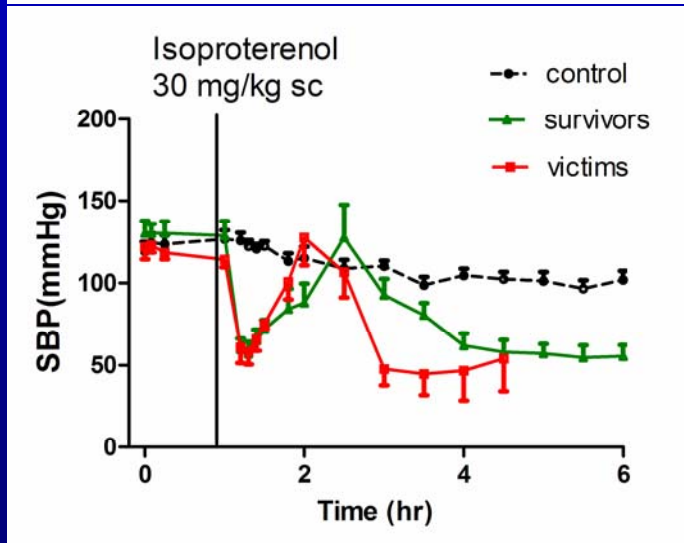
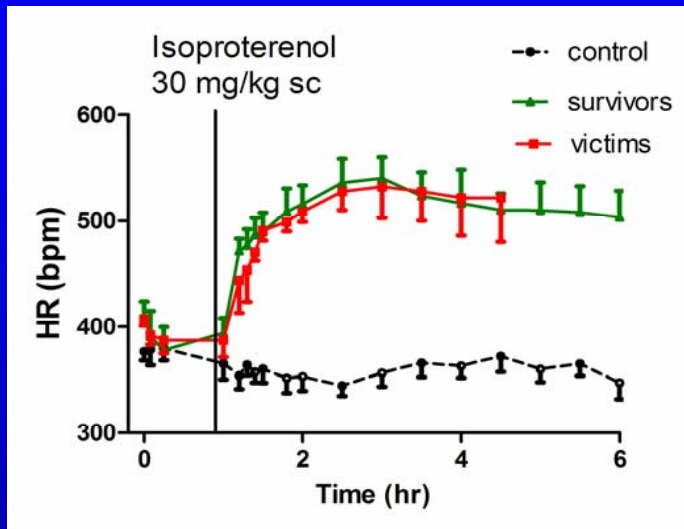
- Rabbits (n = 6) pretreated with saline or DTZ (5 mg/kg sc bid for 5 doses).
- Adenosine administered by rapid iv infusion (over 10 min)



Effect of Anti-ischemia Drugs on ATP Metabolism in RBC (Yeung et al., 2011)



Effect of Isoproterenol (Yeung et al., 2012)



ATP Metabolism in Rats treated with isoproterenol (Yeung and Seeto, 2012)



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Biomarker variables	Control (n=9)	Isoproterenol treatment (n=10)	Victims ^a (n=5)	Survivors ^b (n=5)
ATP vs. AMP r^c	-0.051 ± 0.312*, ^e	-0.515 ± 0.421	-0.717 ± 0.362	-0.262 ± 0.380
ATP vs. AMP β^d	0.002 ± 0.032*	-0.202 ± 0.204	-0.318 ± 0.190	-0.058 ± 0.115**
ATP vs. ADP r	0.299 ± 0.306*	-0.277 ± 0.569	-0.429 ± 0.654	-0.088 ± 0.456
ATP vs. ADP β	0.103 ± 0.117*	-0.294 ± 0.542	-0.523 ± 0.642	-0.008 ± 0.194
ADP vs. AMP r	0.579 ± 0.260	0.787 ± 0.253	0.812 ± 0.248	0.767 ± 0.285
ADP vs. AMP β	0.132 ± 0.124*	0.392 ± 0.277	0.296 ± 0.282	0.469 ± 0.278

^aRats died within 5 hrs after isoproterenol

^bRats survived longer than 5 hrs after isoproterenol

^cCorrelation coefficient

^dRegression coefficient

^eData represent mean ± SD

* $p < 0.05$ vs. isoproterenol (t-test)

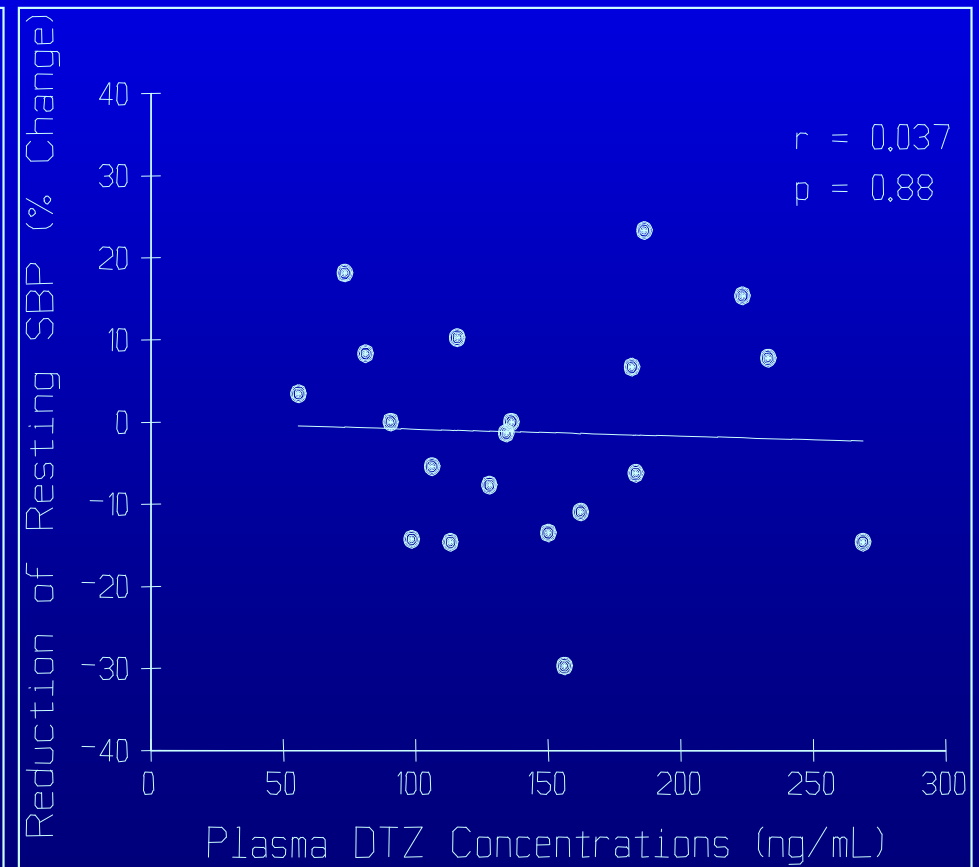
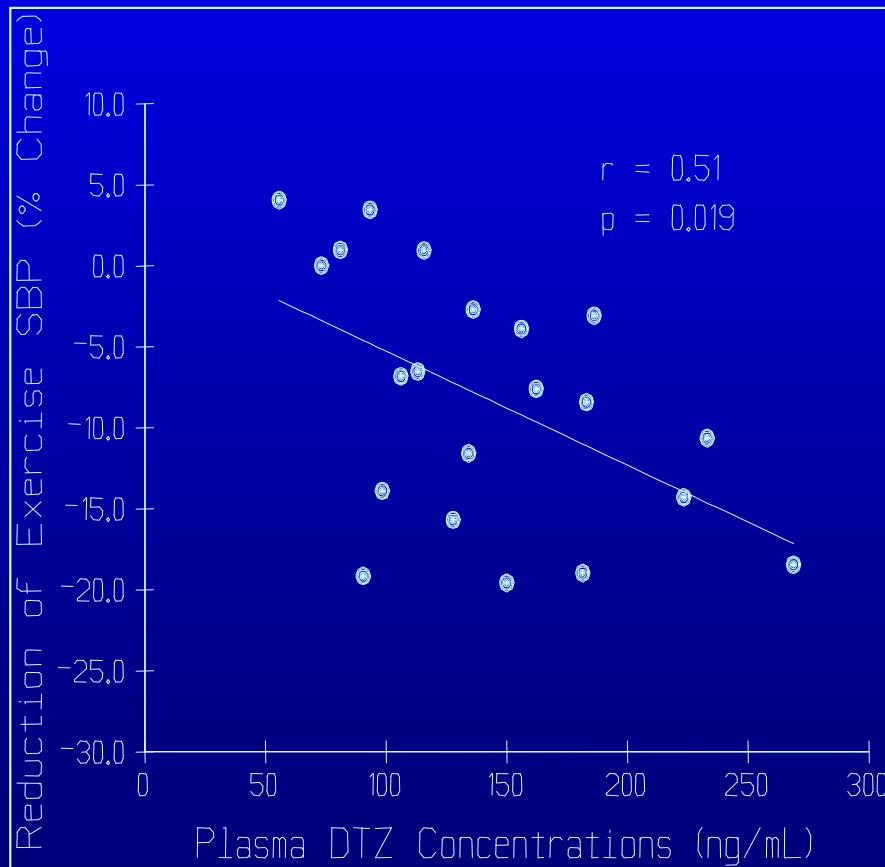
** $p < 0.04$ vs. victims (t-test)

Table 3: Correlation between RBC concentrations of adenine nucleotides in rats after isoproterenol (30 mg/kg sc).

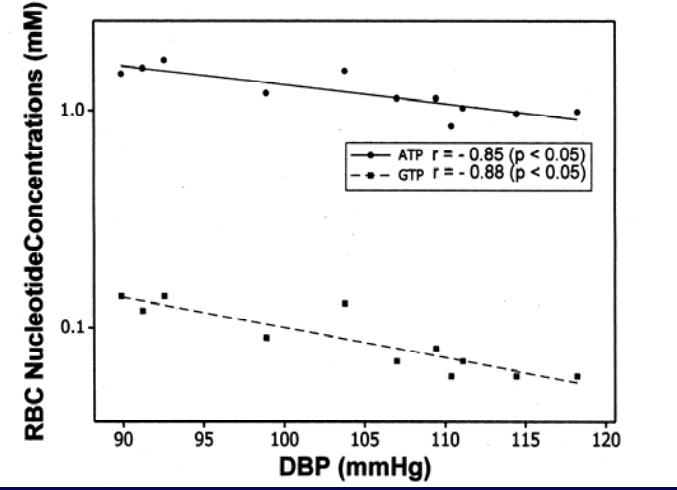
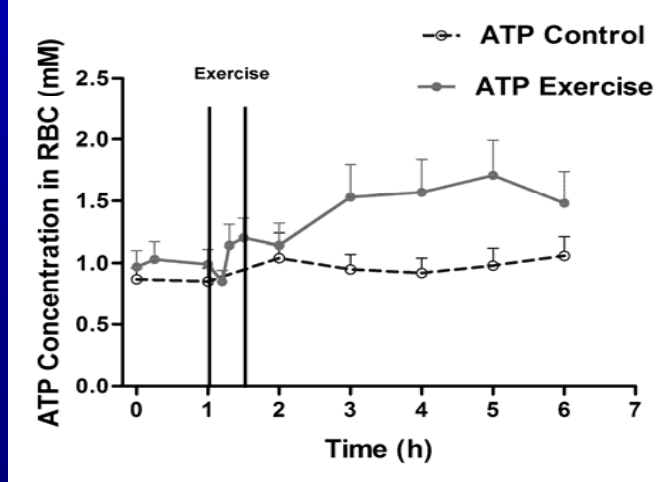
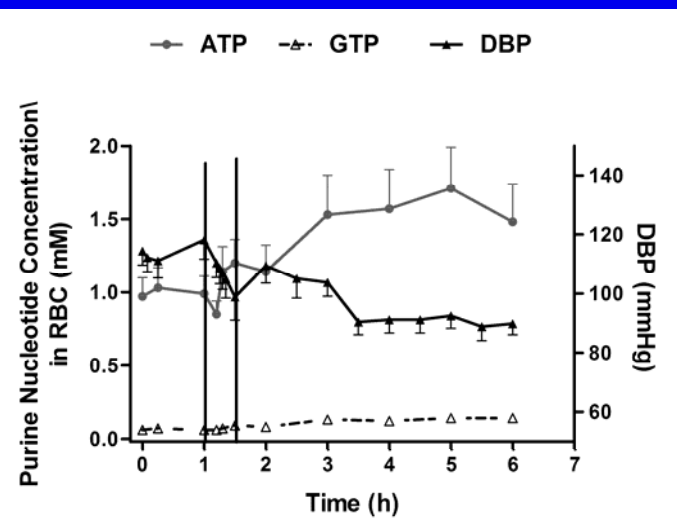
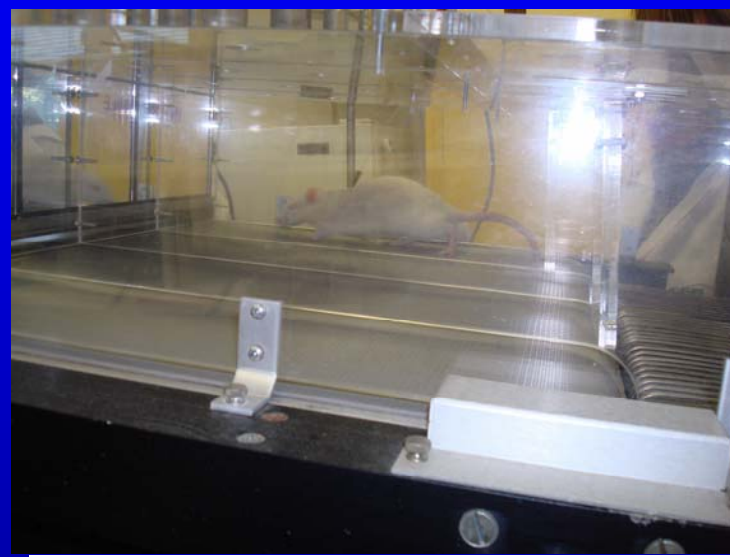
Effect of exercise on Correlation between plasma DTZ concentrations and SBP



Yeung, Hung, Pollak, and Klassen. Int. J. Clin. Pharmacol. Therap. 37:413 - 416, 1999)



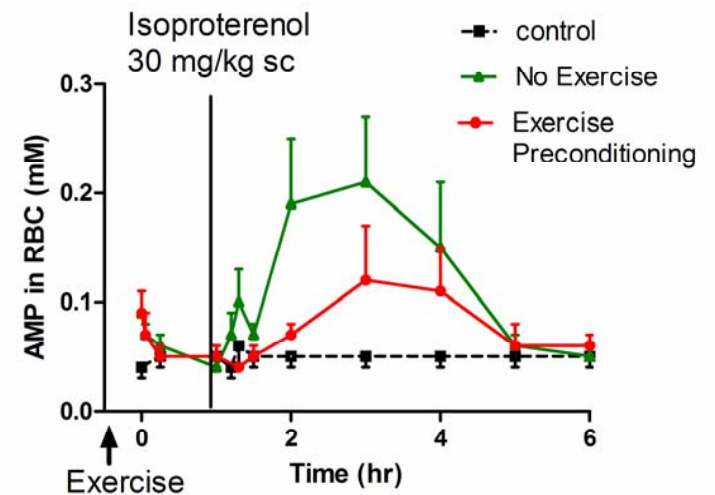
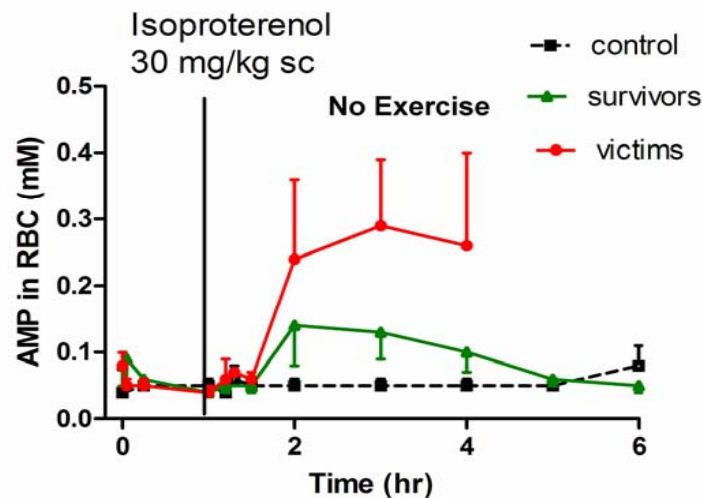
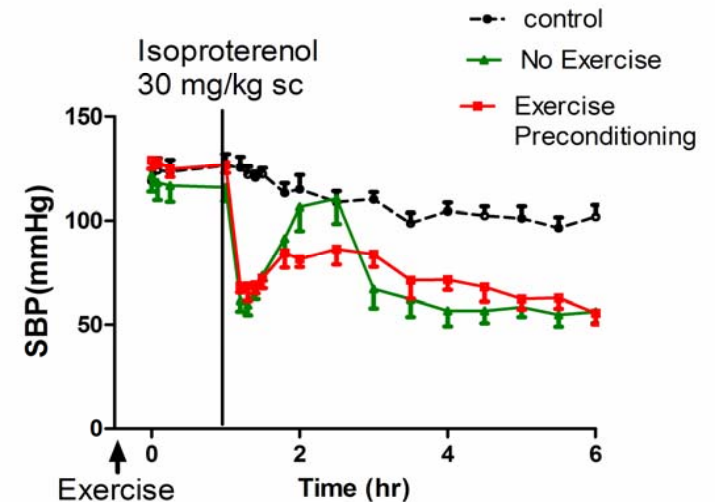
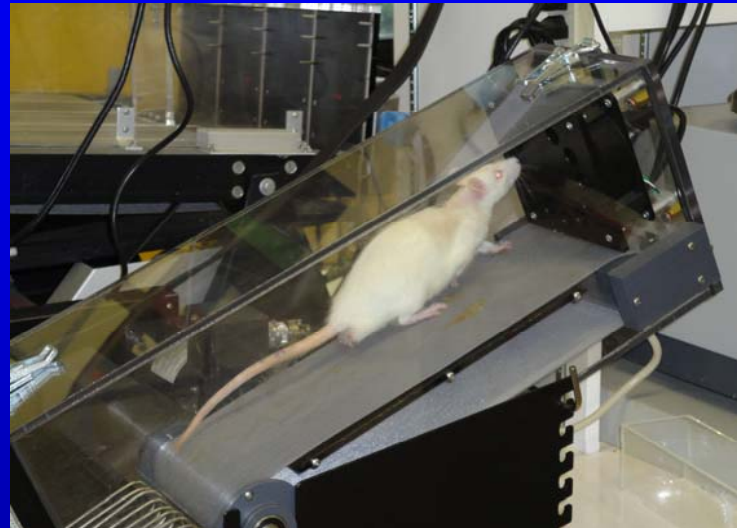
Effect of Exercise (Yeung, et al., 2010)



Effect of Exercise on Cardiovascular Protection

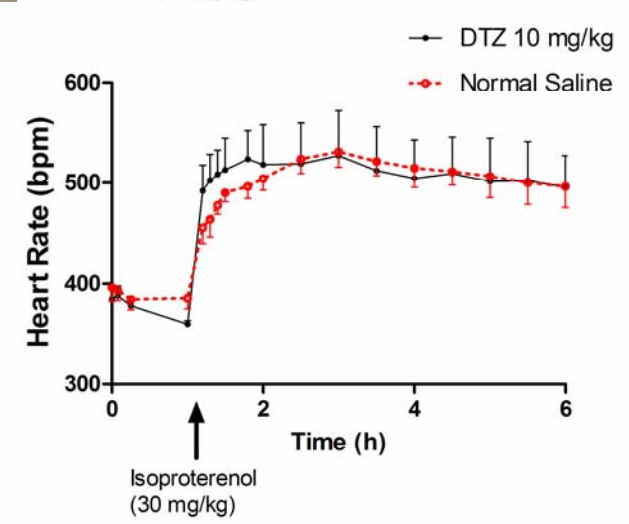
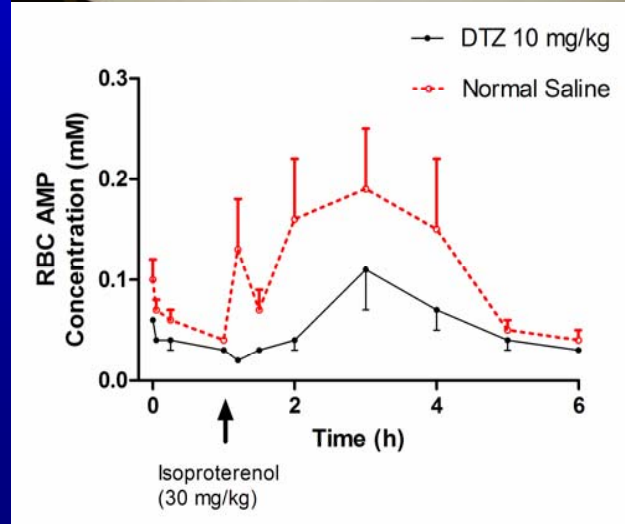
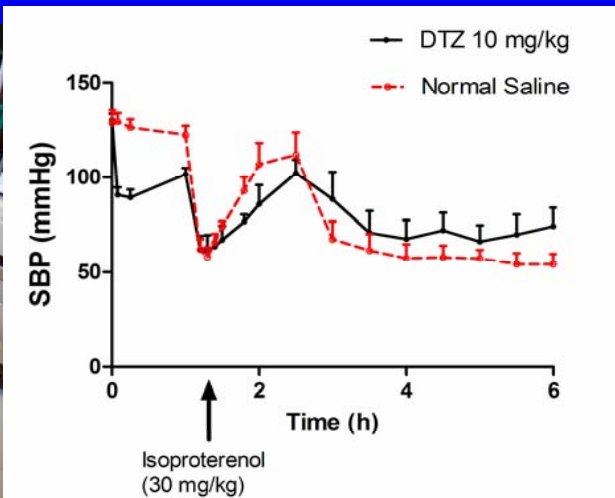
(Yeung et al., 2011)

Survival Rate increased from 50% to 80%



Effect of diltiazem on cardiovascular toxicity induced by isoproterenol (Yeung and Seeto, 2012)

After 10 mg/kg of DTZ bid for 4 doses, survival rate increased from 50% to greater than 80%



Opportunities for ATP metabolism as Biomarker target



- **Disease and health management:**
 - May be a measure of “Inner Energy”, “Reserves”, and “Cardiovascular homeostasis”
 - Cardiovascular and metabolic diseases, cancer, stroke, aging (inside age) and other neurodegenerated diseases.
 - Aging and other chronic illnesses.
- **Drug development:**
 - Cardiovascular protective agents (ARB, ACEI, CCB, Rennin and thrombin inhibitors, anti-platelet agent, B-blocker, ant-coagulant, NPH, and others)
 - Anti-cancer agents
 - Cardiovascular toxicities (cardio + vascular).
- **Complimentary medicine:**
 - Natural health products.
 - Traditional Chinese medicines
 - Energy supplements

Ideal biomarker of effect



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(Sistare 2003)

- **Should be drug or treatment related.**
- **Provide a diagnostic linkage to toxicity**
- **Represent a mechanistic intervention that may occur far upstream of actual toxicity for early detection of toxicity.**
- **Inter-species application.**

Biomarker Checklist for ATP Metabolism



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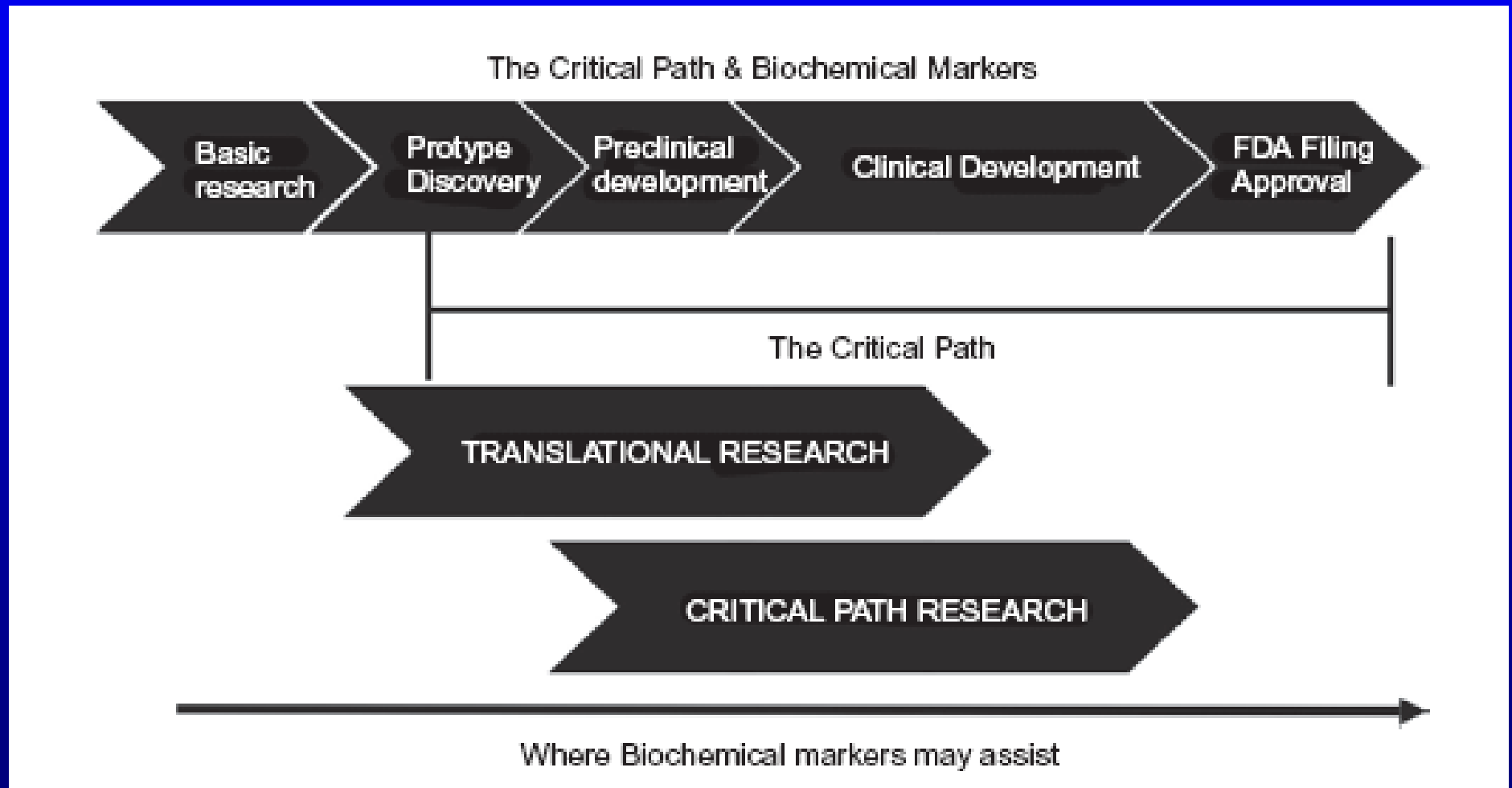
- **Is ATP metabolism applied across species (or species independent)?** ✓
- **Is ATP metabolism quantitative and measurable in systemic circulation for pharmacodynamic study?** ✓
- **Could ATP metabolism help lead candidate selection and reduce the risk of attrition?** ✓
- **Is ATP metabolism a sensitive and specific biomarker for disease or therapeutic intervention?** ?
- **Could ATP metabolism be studied in a routine clinical setting?** ✓ ?

Biomarkers and Critical Path

(Karsdal 2009)



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Challenges and Opportunities for use of biomarkers in drug development *(Woodcock, 2009)*



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- **The imperative to produce high-value, innovative drugs will intensify, creating a higher performance hurdle for new therapeutics.**
- **Basic biomedical science will churn out candidate biomarkers with tantalizing potential to improve value, whereas methods to use them effectively in drug development will evolve more slowly.**
- **The balance between these forces may well determine the success or failure of the drug development enterprise over the next decade.**

Acknowledgements

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Dalhousie University vs Lobster – which is better known for Nova Scotia?

