4. Support for Research and Development

R&D Incentive

Tax Deduction & Exemption:
- Tax credit- **15%** of the investment in R&D against business income tax payable (Max: 30%)
- Business income tax- 25% → **17%**

Direct Funding

Human Resource Support:
- The enlisted personnel- Minimum 3 years in R&D center
- R&D headcount- subsidize up to **50%** (Max: 20 people)

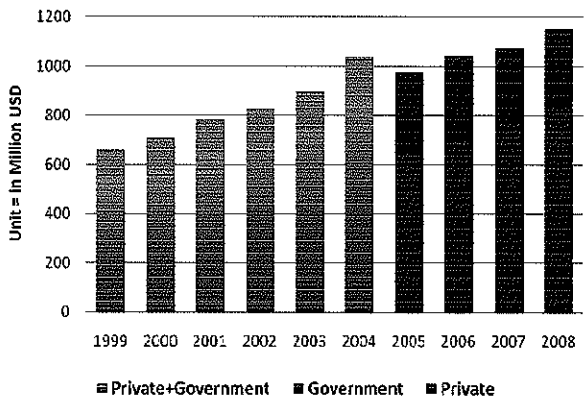
Supported by MOEA

4. Support for Research and Development

● **Additional tax incentive for R&D:**
- **For foreign investment-**
  - Tax benefits: **17%** business income tax
- **For domestic investment-**
  - Tax deduction:
    - up to **30%** of the R&D and HRD expenses
    - **5-7%** for the investments in automation, pollution control, energy-saving, etc.

● **Direct funding programs:**
- National Science & Technology Program
- Industrial/Academic/Organization Technology Development Program -by MOEA
- Technology Development Program -by DOH
- Small Business Innovation Research (SBIR)

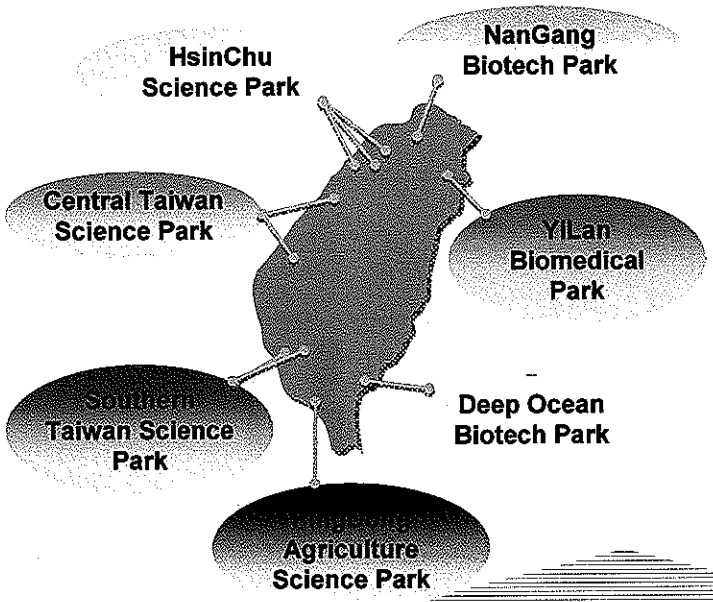
Gross R&D Expenditure for Medical and Agricultural Science:



Source: STPI

4. Support for Research and Development

Distribution of R&D clusters:



- **Chinese Taipei tops world in the "State of Cluster Development" for 3 consecutive years!**
  - WEF, 2006-2009
- **Benefits of clustering:**
  - Reduce risk for the start-up companies by sharing both the resource and the overhead cost
  - Encourage public-private partnership
  - Facilitate transition from basic to applied research and commercialization

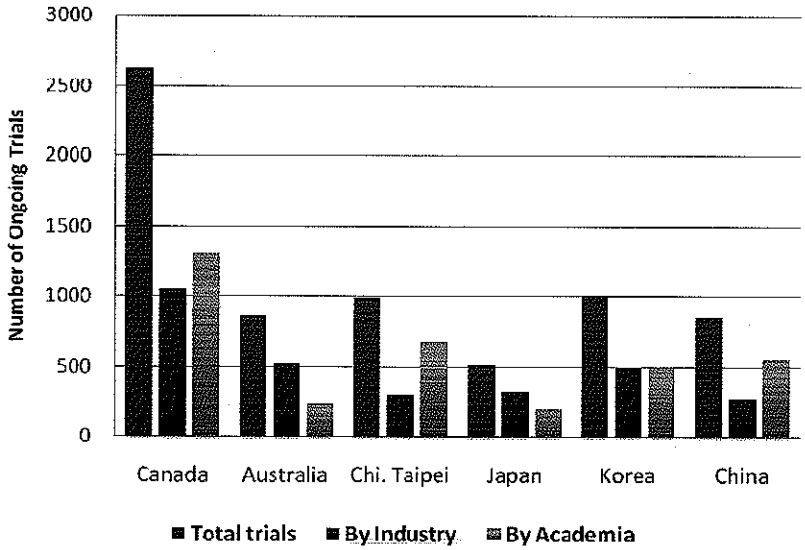
5. Efficient and Internationally Harmonized Regulatory Systems

- **Harmonizing effort towards international standards**
  - Actively participation in many global forum toward regulatory harmonization- APEC (AHWP/GHTF), WHO, ICH/GCG
  - Chinese Taipei is one of the 8 non-ICH countries regularly participating in international regulatory forum
- **A regulatory framework that allows for speedy introduction of new medical products**
  - Organizational reform to streamline the process
  - Relaxation of requirement for pharmaceutical product registration such as technical review without certified purchasing professionals (CPP)
- **An efficient clinical trial regulatory regime**
  - Simplification of clinical trial protocol review adapting the spirit of CTN/CTX system

Source: CDE

5. Efficient and Internationally Harmonized Regulatory Systems

Clinical Research in Asia Pacific:



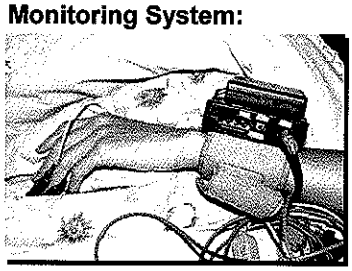
Source: CDE, Comparison Data accessed from www.clinicaltrials.gov on Sep.13,2010

6. A Holistic and Transparent Approach to Healthcare Policy

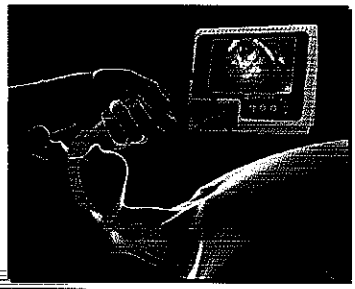
- **Rapid Prototyping Service Center (RPC) for Medical Devices**
  - ☑ Mechanisms to align research activities with health priorities
  - ☑ Process for coordination of life science research
  - ☑ Appropriate prioritization of the health needs of the population
  - ☑ Holistic approach for the speedy introduction into the market
- **Bridging the gap between concept and clinic-ready: by combining engineering with business strategy**
  - A Need-Driven prototyping model
  - Platform for clinical and engineering expertise to interact
  - Identify R&D direction based on need
  - Integrate strategic planning for commercialization, including intellectual property and regulatory management

Current projects:

Home-use Sleep Quality Monitoring System:



Curved Videolaryngoscope:

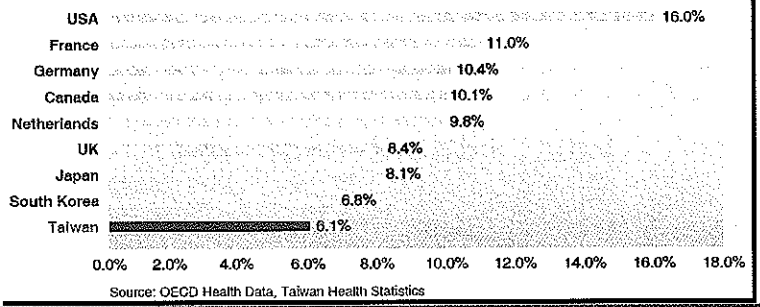


Source:: Industrial Technology Research Institute (ITRI)

6. A Holistic and Transparent Approach to Healthcare Policy

- **Universal national health insurance legislation -1995**
  - ☑ Mechanism for inter-agency/ministry coordination of budgetary allocation
  - ☑ Transparent government processes
  - ☑ Policies
  - ☑ Health system infrastructure
- **Coverage has increased from 57% to 98% of the population**
- **Increase in life expectancy even after 10 years of implementation:**
  - Male: +1.11 years (1985~1995) to +2.56 years (1995~2005)
  - Female: +1.98 years (1985~1995) to +2.99 years (1995~2005)

Healthcare System in Comparative Perspective:



Source: TFDA

Lessons Learned

	Advantage	Disadvantage
Human Capital	High capacity	Inadequate professionals
IPR System	Comprehensive IPR system	Inefficient processing
Open and Competitive Market	Strong government incentive	Small domestic market
Support for R&D	Strong government support	Inadequate resource
Harmonized Regulatory System	Strong clinical trial regulatory regime	Weak internationalization and approval efficiency
Holistic Approach to Healthcare Policy	Strong healthcare policy	Insufficient effort in translational medicine

- **How Can the Checklist be Improved:**
  - **Include evaluation of demand in human capital into the "Increasing Human Capital" section**
  - **Include detailed instruction or specify the overall purpose for each section**
  - **Include a final evaluation across 6 sections for a global perspective**

Thank you for your attention!

Contact: Dr. Chien-Hsin Daniel Cheng
E-mail: chcheng1@moea.gov.tw
Tel.: +886-2-2394-6000 ext. 2553
Fax.: +886-2-2356-9547

附件三：大會結論
暨建議

Asia-Pacific
Economic Cooperation

2010/SOM3/LSIF/008

Notes for Discussion on Potential Conclusions and Recommendations, LSIF VIII

Submitted by: Chair

JAPAN 2010

Life Sciences Innovation Forum
Sendai, Japan
18-19 September 2010

Notes for Discussion on Potential Conclusions and Recommendations, LSIF VIII

These notes are for discussion purposes only, and are organised in terms of Japan's three priority areas for APEC 2010.

Health Innovation and New Economic Growth Paths

It is necessary to distinguish between the existing level of health spending in a given economy - based on the specific institutions, skills and technology in place at a given time - and the role of innovation to do things better across the whole health system, including in risk detection, prevention, treatment and cure.

LSIF VIII concludes that increased spending on health and life sciences innovation should be treated as an investment with strong economic and social returns and not just as a cost. Such innovation will be a central driver of the new growth path.

LSIF VIII recommends that the governments of APEC economies, as part of their pursuit of new growth paths, encourage significantly increased investment in health innovation. This should be both public and private investment, including international investment coming in part through regional collaborations. Some of the priority areas for investment in innovation are:

- *Preventive measures -protecting the health of the healthy.* These measures are of high priority, and range from basic lifestyle and public health measures to advanced processes (such as large cohort studies) to identify and manage disease and healthcare acquired infections risk.
- *Reform and development of life sciences innovation system.* Major change is taking place in life sciences innovation systems, even in major countries such as the USA and Japan. APEC economies need to adjust their innovation systems in the light of these changes, invest further in the various components of those systems and increase their conformity with global best practice.
- *Financial reforms, to extend coverage and manage costs.* These reforms, while complex, remain of the highest priority for many governments. Effective reform will generate strong social benefits.
- *Efficiency initiatives.* LSIF VIII concludes that a wide range of innovations are possible which will both improve both efficiency and the quality of health care. These include the strengthening of primary care and the creation of more open, collaborative health systems. The development of IT to transform the flow of medical information will be an important component of such innovations.
- *Regulatory reforms to speed access to innovations and encourage investment.* LSIF VIII concluded that improved regulatory processes, and the adoption of international best practice, can often generate better health and greater economic activity at little cost, while facilitating investment.
- *Investment by firms in programs to improve the health of their own employees.* LSIF VIII accepts that wellness and other programs at the firm level can generate strong health benefits and much improved productivity. LSIF VIII recommends that APEC governments consider ways in which they can accelerate the adoption of such programs and create steps that can take in partnership with business to reduce costs.

While health costs will continue to rise, as incomes and health needs rise, LSIF VIII concludes that such an enhanced program of investment in health innovation will generate strong economic and social returns, and will spur new growth activity in the region.

Regional Economic Integration and Openness

LSIF VIII concludes that further steps towards regional integration and openness for health products and services are necessary for increased innovation in health, and to allow health to play its full role in the new growth path. Four forms of increased integration have been highlighted.

Regulatory harmonization. LSIF VIII finds that regulatory harmonization in the region, in line with international standards and for both medicines (including biologicals) and medical devices, can offer major health and economic benefits. Perhaps targets going ahead? LSIF VIII's harmonization work is

playing a leading role in the region, and LSIF VIII recommends that it be strongly supported by member governments including a target date.

Openness to trade in health services. LSIF VIII also concludes that systematic measures to reduce formal and informal barriers to trade in health services are necessary, to achieve more efficient and effective service delivery to patients. LSIF VIII recommends that this be treated as a priority area within APEC, especially given APEC's historic commitment to trade openness.

Increased collaboration in life sciences innovation. LSIF VIII notes that collaboration in life sciences is growing in the region and globally

Collaboration to address the neglected infectious diseases and healthcare acquired infections in the region . LSIF VIII concludes that increased regional collaboration to address neglected infectious diseases would have significant health and economic benefits. As an example of such an initiative, the LSIF VIII leadership will undertake further discussions with the Sabin Vaccine Institute about their proposal to set up a facility in the region for the development and production of vaccines for these diseases.

Improving Human and Economic Security

Many aspects of health and health innovation relate directly to human and economic security.

Anti-counterfeiting activities; regulations for safe and early access to treatment. LSIF notes the importance of these issues and the value of work being done in APEC forums, including LSIF.

The challenges to human and economic security arising from the triple burden of infectious and chronic diseases in many economies. LSIF VIII recommends that Leaders support the establishment by LSIF of a tripartite working party, in conjunction with the APEC Health Working Group, to document the challenges arising from this triple burden and to make recommendations about how the APEC community can support economies dealing with these challenges.

Value of protecting health expenditure from cuts in economic downturns. LSIF VIII notes the importance of protecting health care spending in downturns, when the need for care rises, and that those economies that did so during the financial crisis benefited significantly from doing so.

附件四：Professor Miyata
簡報

New era for the discovery and development of drugs in renal disease

Toshio MIYATA

Tohoku University School of Medicine
United Centers for Advanced Research and Translational Medicine (ART)

Fact

Nephrologists have only a limited number of therapeutic options...

Medicines are not always developed for fields in which they are needed...

Limitations of drug D&D in the field of renal disease

- **Lack of experimental animals mimicking human nephropathy**

- **Absence of appropriate surrogate clinical biomarkers able to substitute for time-consuming, hard end-points (e.g., renal death, Cr doubling time)**

3

Current processes of discovery and development of investigational new drug (IND)

A series of leads — Derivatives (2,000~) — Physical & Toxicological

Animal → Human →

Several years →

Problem

- **Time- and cost-consuming**
- **Unable to pursue many promising compounds**
- **Late introduction to human study**
- **A model with a high risk**

4

Key

A *priori* understanding of disease pathophysiology so as to pin-point the critical underlying issues, and test our hypothesis in man as early as it is safe and practicable to do so.

A more holistic approach should be developed before embarking on expensive development program (*e.g.*, lead optimization, preclinical studies in animals, etc).

5

New ICH Harmonized Tripartate Guideline

GUIDANCE ON NONCLINICAL SAFETY STUDIES FOR THE CONDUCT OF HUMAN CLINICAL TRIALS AND MARKETING AUTHORIZATION FOR PHARMACEUTICALS

M3(R2)

Current *Step 4* version

dated 11 June 2009

European Union, Japan and the USA

Administration of a total dose of 100 μg of IND in any subject including patient, provided that its safety is demonstrated in an extended single dose toxicity study in one species, usually rodent.

5 administrations of a mamimum of 100 μg of IND in any subject including patient, provided that its safety is demonstrated in a 7-day repeated-dose toxicity study in one species, usually rodent.

6

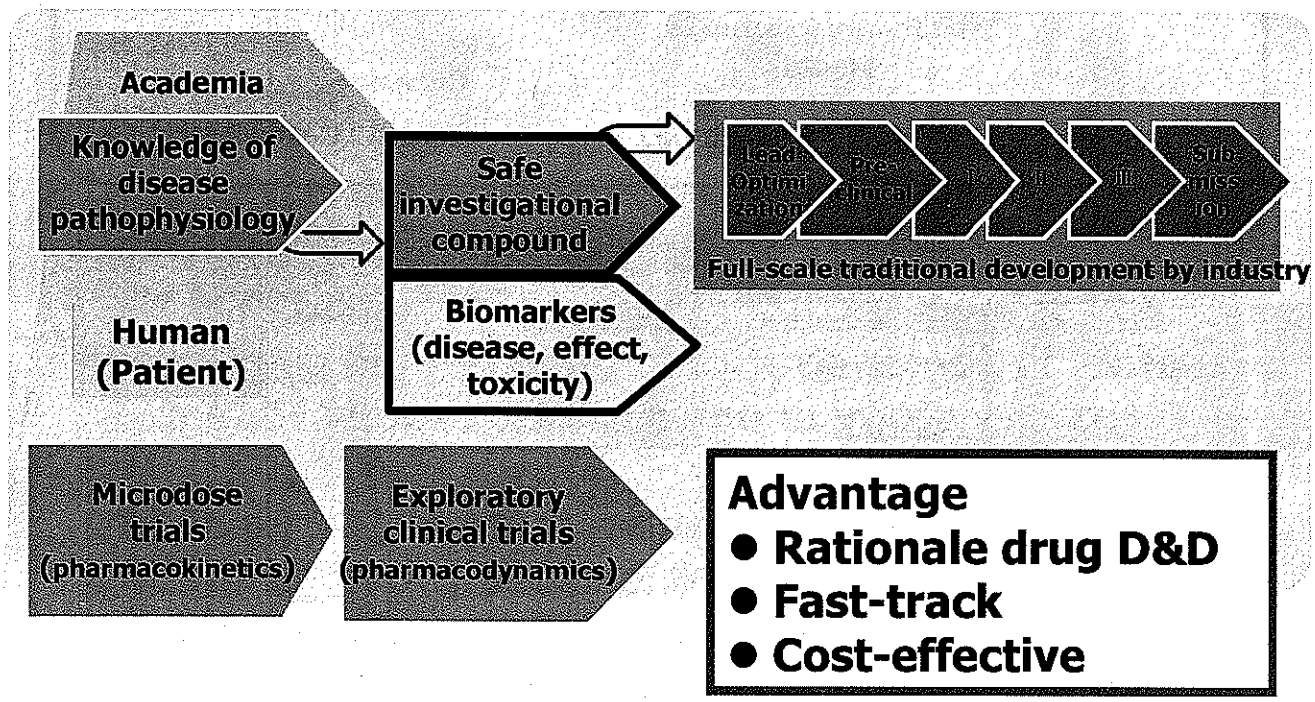
New ICH Harmonized Tripartate Guideline

'Exploratory clinical trial' or 'Microdose trial'

Earlier access to human data should improve

- **Insights into human physiology/pharmacology**
- **Document the drug candidate's characteristics**
- **Therapeutic targets relevant to disease**

Researchers in academia (medical university), with <u>knowledge for disease pathophysiology</u> as well as <u>patients</u>, is now able to contribute to the drug D&D!

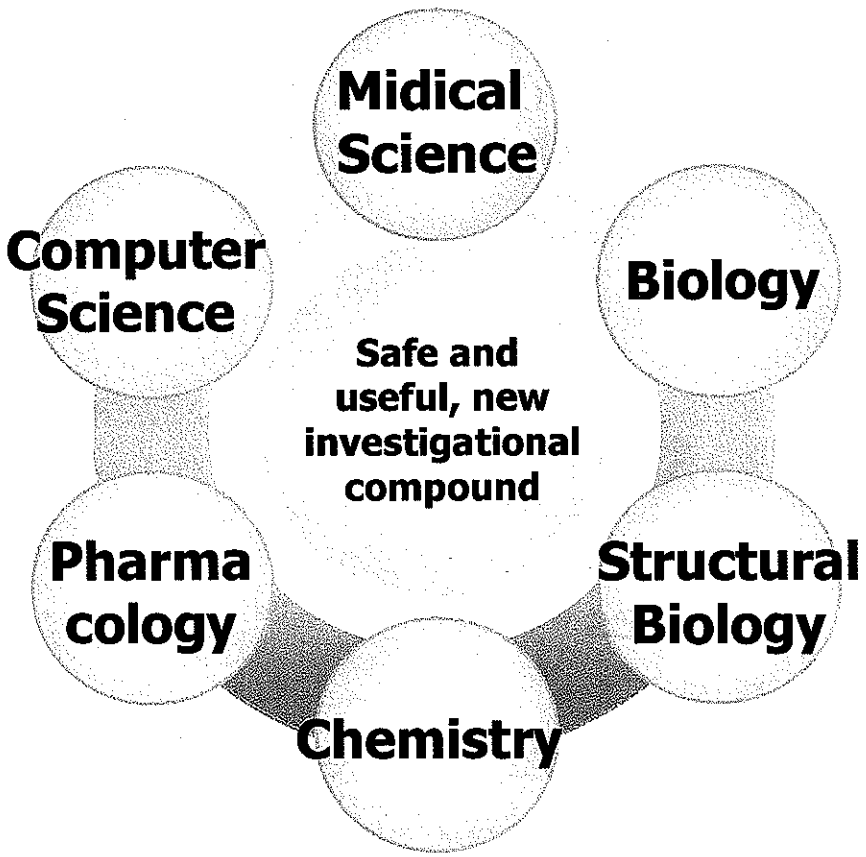


Important tools
for more efficient drug D&D

A safe investigational compound (a seed for promising drug)

Sensitive surrogate biomarkers

Interdisciplinary research

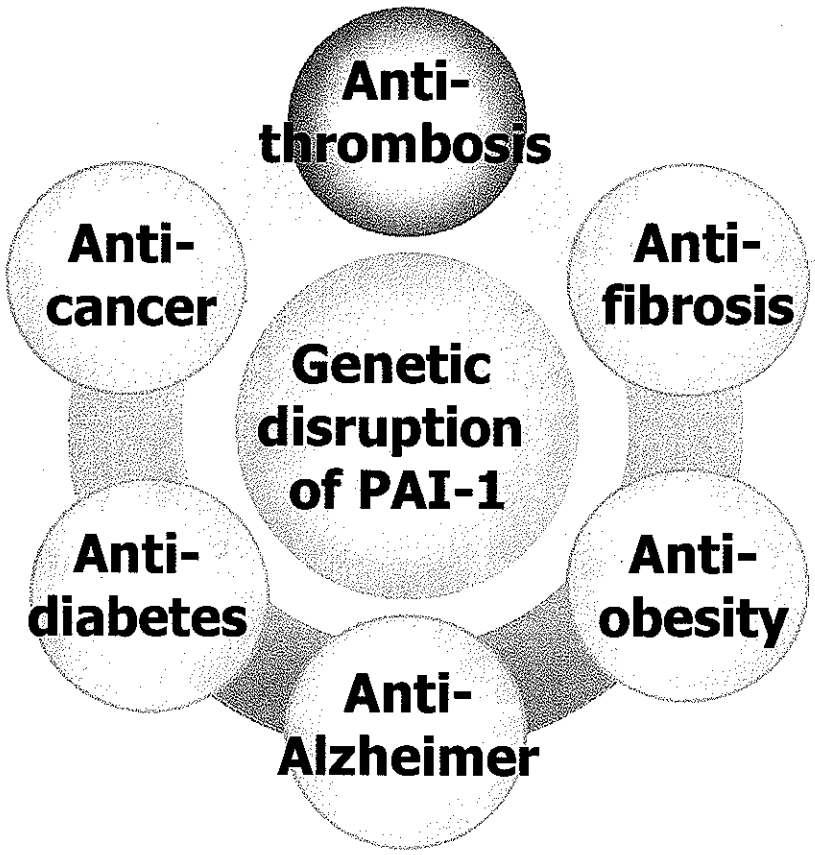


Target 1

Plasminogen activator inhibitor-1 (PAI-1)

PAI-1 inhibits tissue plasminogen activator (t-PA) involved in the fibrinolytic process.

PAI-1 inhibitor (cure-all?)



The role of plasminogen activator inhibitor 1 in renal and cardiovascular diseases

Hunjoo Ha, Eun Y. Oh and Hi B. Lee

Abstract | The 50 kDa glycoprotein plasminogen activator inhibitor 1 (PAI-1) is the major physiological inhibitor of tissue-type and urokinase-type plasminogen activator. These two molecules convert inactive plasminogen into its fibrin-degrading form, plasmin. Plasma and tissue concentrations of PAI-1 are extremely low under normal circumstances but increase under pathologic conditions. This increase is mediated by many factors, including reactive oxygen species. Increased PAI-1 activity is associated with an increased risk of ischemic cardiovascular events and tissue fibrosis. Whereas the antifibrinolytic property of PAI-1 derives mainly from its inhibition of serine proteases, its profibrotic actions seem to derive from a capacity to stimulate interstitial macrophage recruitment and increase transcription of profibrotic genes, as well as from inhibition of serine proteases. Despite studies in mice that lack or overexpress PAI-1, the biological effects of this molecule in humans remain incompletely understood because of the complexity of the PAI-1–plasminogen-activator–plasmin system. The cardioprotective and renoprotective properties of some currently available drugs might be attributable in part to inhibition of PAI-1. The development of an orally active, high-affinity PAI-1 inhibitor will provide a potentially important pharmacological tool for further investigation of the role of PAI-1 and might offer a novel therapeutic strategy in renal and cardiovascular diseases.

Ha, H. *et al. Nat. Rev. Nephrol.* **5**, 203–211 (2009); doi:10.1038/nrneph.2009.15

Introduction

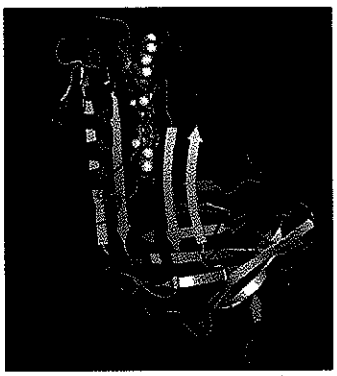
Plasminogen activator inhibitor 1 (PAI-1) is a 50 kDa single-chain glycoprotein (Figure 1) that acts as the primary physiological inhibitor of the two main mammalian plasminogen activators, tissue-type plasminogen

Regulation of PAI-1 expression

PAI-1 can be synthesized by various cells, including hepatocytes, adipocytes, glomerular mesangial cells, glomerular epithelial cells, tubular epithelial cells, vascular endothelial cells, vascular smooth muscle cells (VSMCs),

Ha, H. et al. Nat. Rev. Nephrol. 5, 203–211 (2009)

In silico discovery by structure based drug design (SBDD)



2,240,000 compounds

↓ **Filter selection (size/charge)**

3000 compounds

↓ **Docking simulation (Ph4Dock)**

Virtual screening

95 compounds

↓ **Purchase/synthesize**

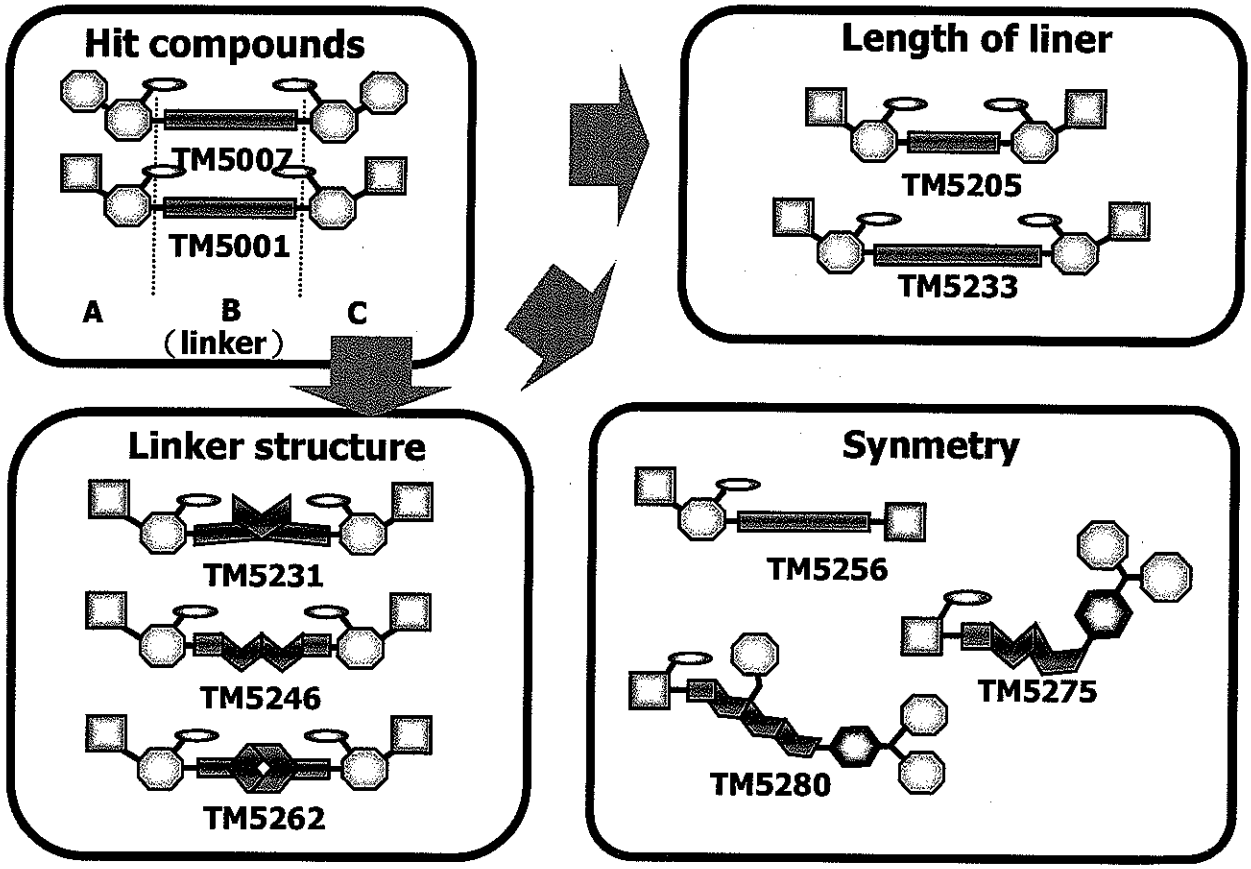
Biological screening

28 compounds

↓ **In vitro bioassays**

Hit compounds → **TM-5001, TM-5007**

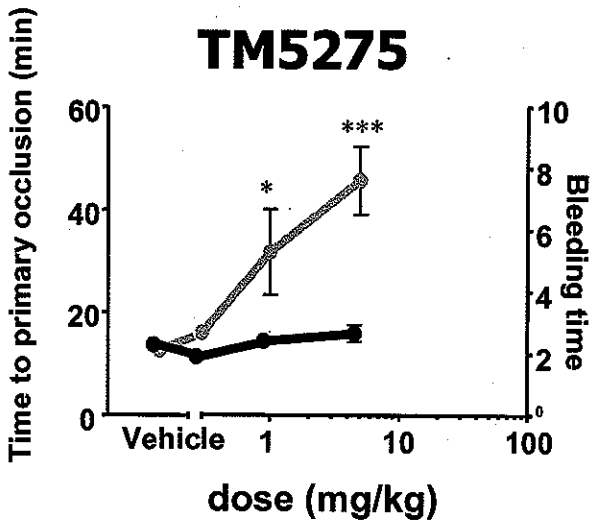
Lead optimization (185 compounds)



Validation of benefits in animals (rodents)

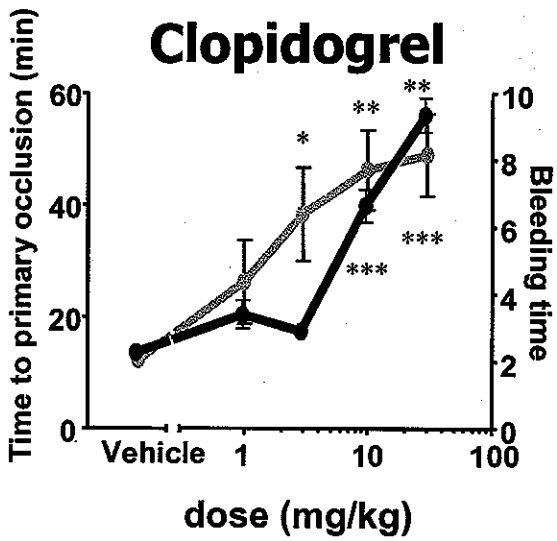
Anti-thrombosis (Benefit)

TM5275



Bleeding time (Side effect)

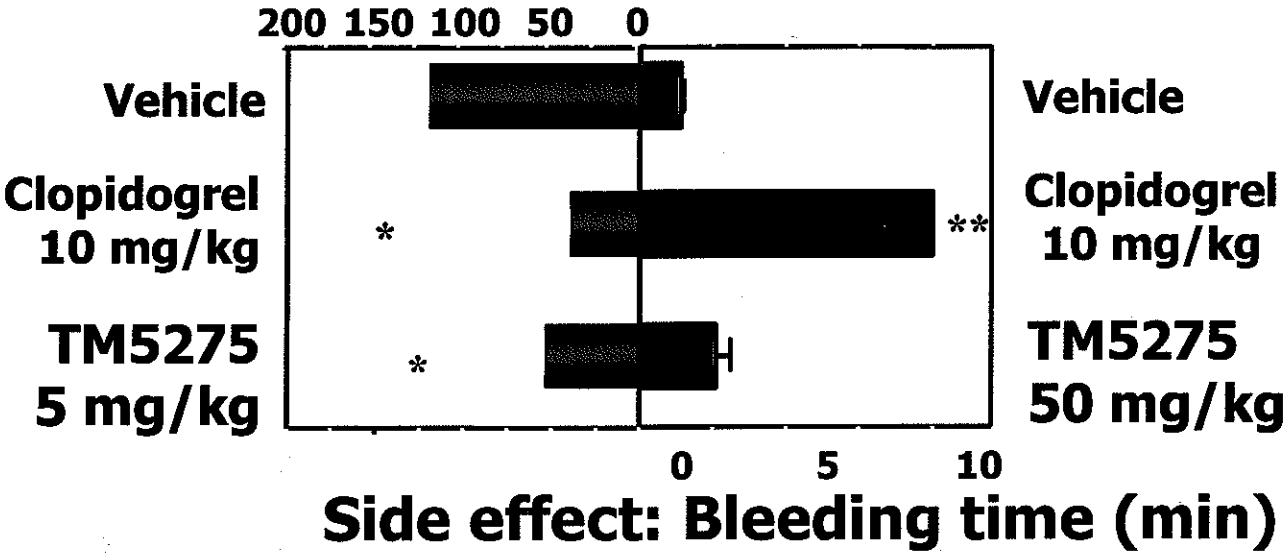
Clopidogrel



*P<0.05, ** P<0.01, ***P<0.001 vs Vehicle group (n=8)

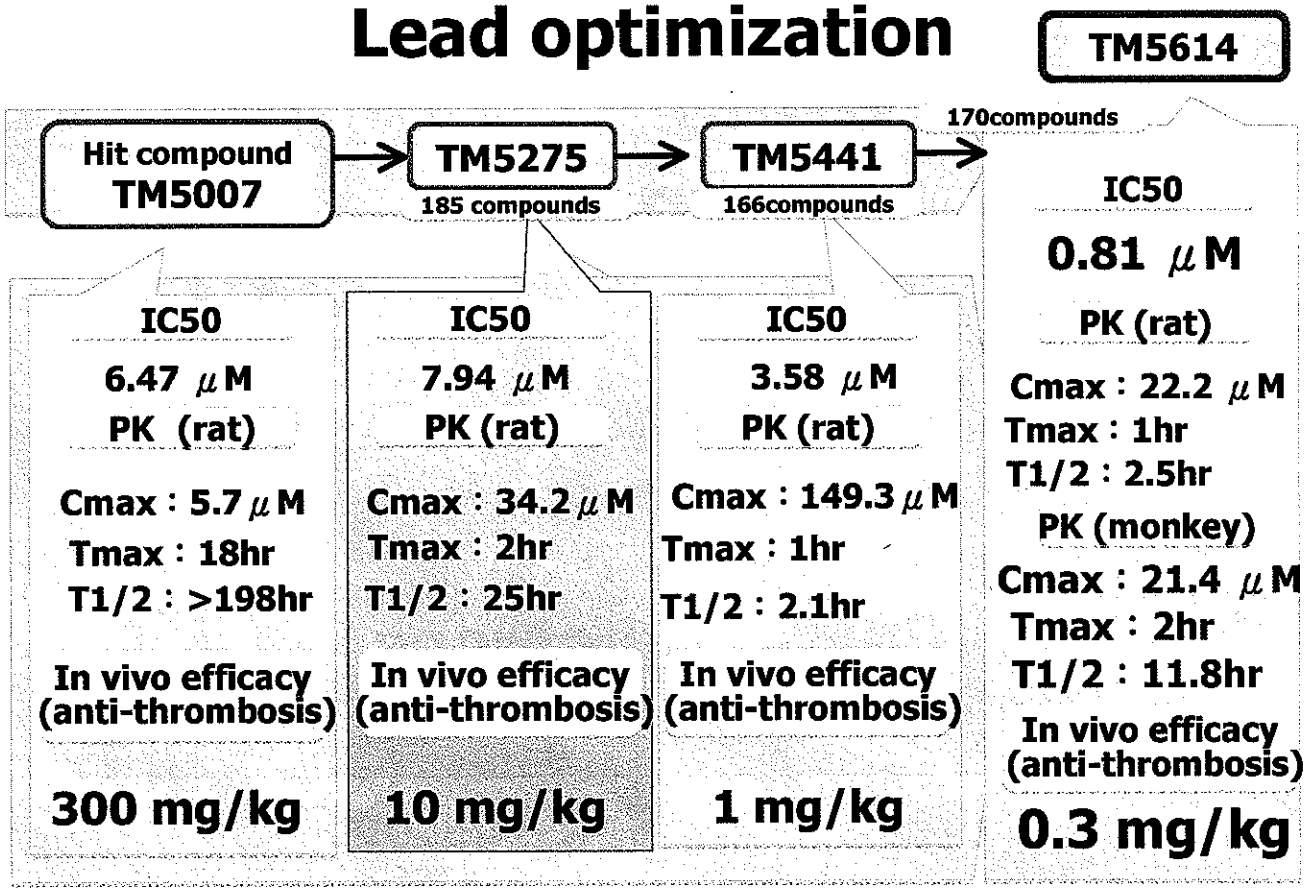
Validation of benefits in animals (monkeys)

Occlusion time (min): Benefit

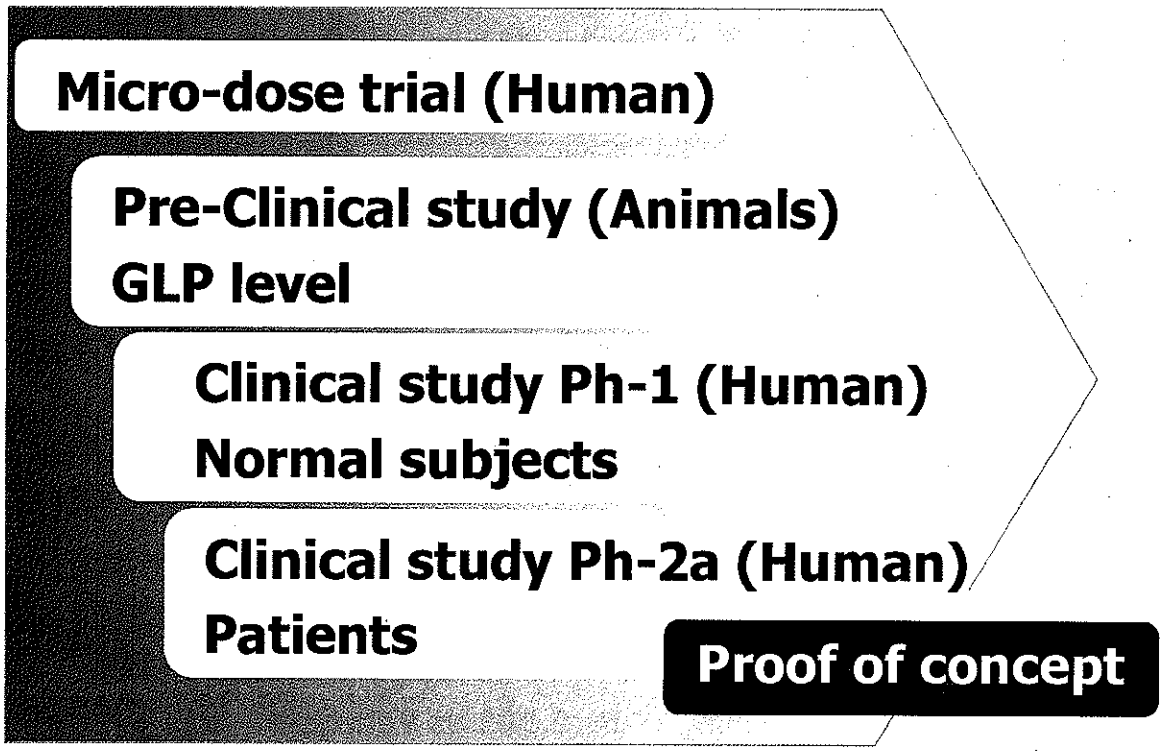


* P<0.05, ** P<0.001 vs Vehicle

Lead optimization



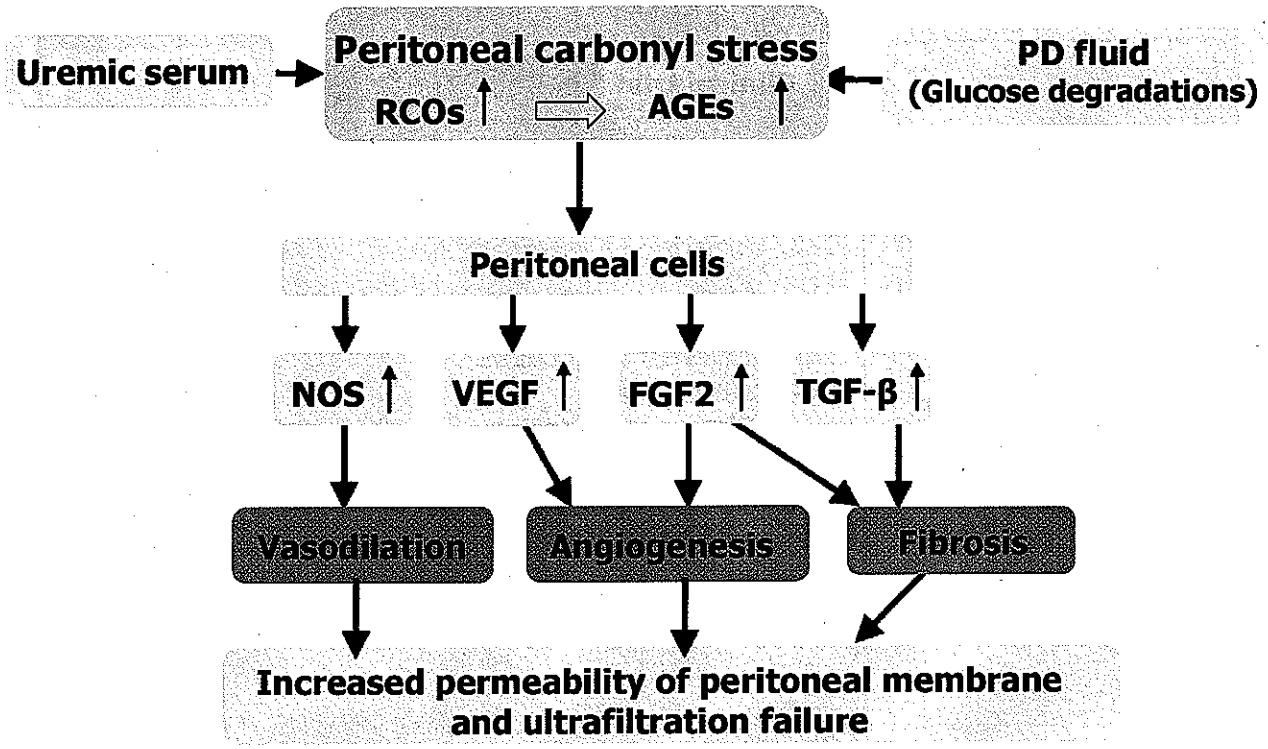
Processes needed to the 'Goal'



Target 2

Carbonyl stress

Structural, biochemical and functional alternations of the peritoneal membrane in long-term peritoneal dialysis patients



Miyata et al. Kidney Int 61, 2002

Kidney International, Vol. 68 (2005), pp. 1326–1336

Pyridoxamine improves functional, structural, and biochemical alterations of peritoneal membranes in uremic peritoneal dialysis rats

TAKATOSHI KAKUTA, REIKA TANAKA, YOSHINOBU SATOH, YUKO IZUHARA, REIKO INAGI, MASAOMI NANGAKU, AKIRA SAITO, and TOSHIO MIYATA

Department of Internal Medicine and Institute of Medical Science, Tokai University School of Medicine, Isehara, Japan; and Division of Nephrology and Endocrinology, Tokyo University School of Medicine, Tokyo, Japan

Pyridoxamine improves functional, structural, and biochemical alterations of peritoneal membranes in uremic peritoneal dialysis rats.

Background. We previously suggested that biochemical alterations of peritoneal membrane associated with long-term peritoneal dialysis might be, at least in part, accounted for by reactive carbonyl compounds overload originating both from uremic circulation and heat sterilization of glucose peritoneal dialysis fluid. In the present study, we utilized a uremic rat model on peritoneal dialysis and evaluated the protective effects of pyridoxamine, a recently developed inhibitor of advanced glycation end product (AGE), on structural, functional, and biochemical alterations of peritoneal membrane.

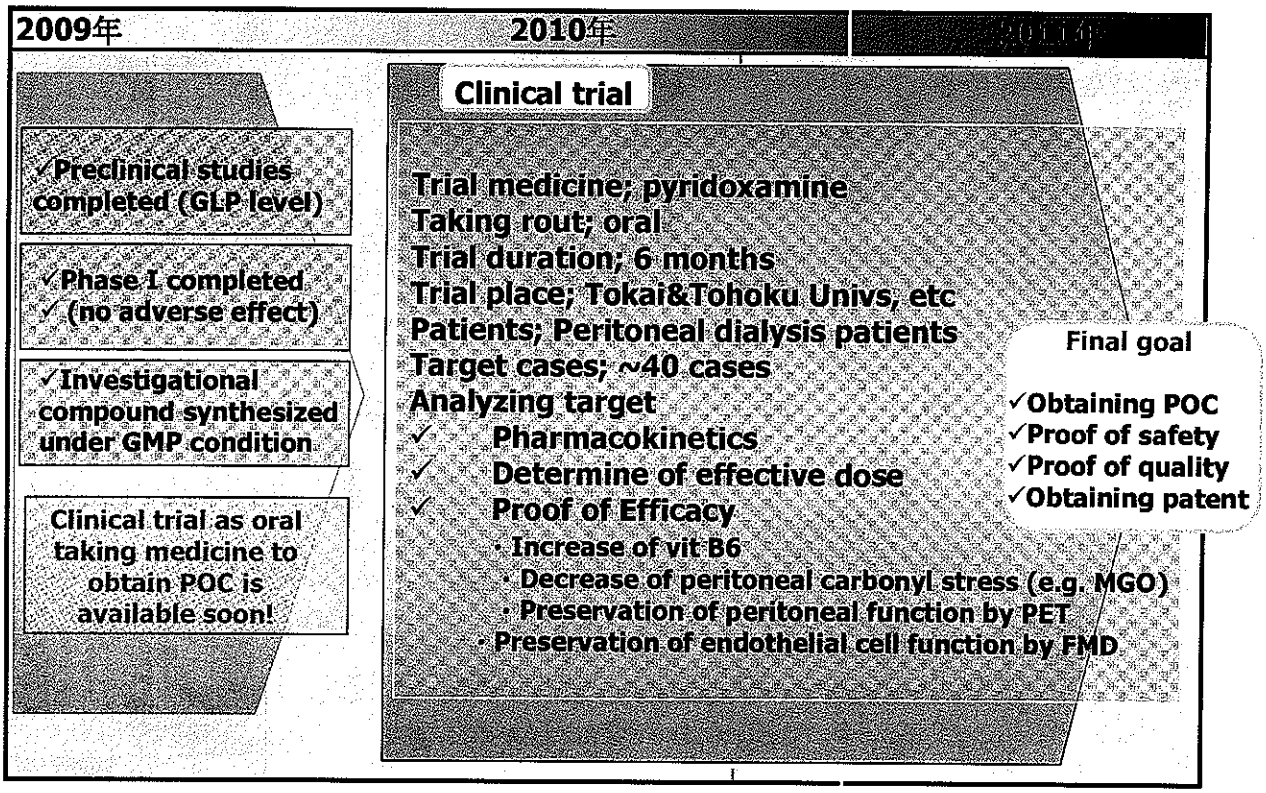
Methods. Uremic rats were generated by subtotal nephrectomy, some of which were undergone peritoneal dialysis with dialysate and/or given intraperitoneal pyridoxamine. Functional [illegible] ratio (D/P) [illegible]

by reduction of AGE accumulation and of angiogenic cytokines expressions.

Conclusion. Peritoneal carbonyl stress derived from uremia as well as peritoneal dialysis procedure might contribute to the vascular proliferation through induction of bioactive molecules and to an increased functional area, eventually leading to ultrafiltration failure. Pyridoxamine may be beneficial in protection of uremic peritoneal membrane on peritoneal dialysis.

Patients undergoing long-term peritoneal dialysis suffer from a progressive deterioration of the peritoneal membrane function, and this condition is characterized by the enhanced dissipation of the glucose-dependent osmotic gradient [illegible]

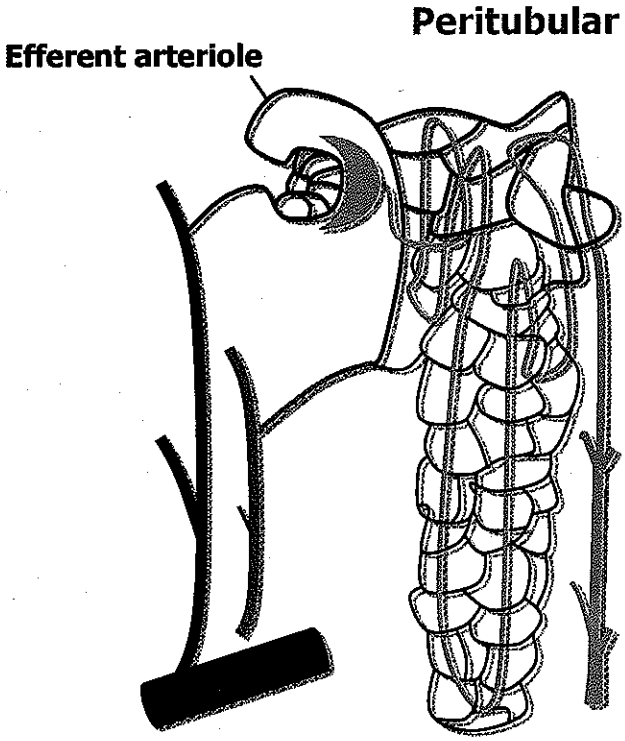
Development of pyridoxamine as a peritoneal protective agent



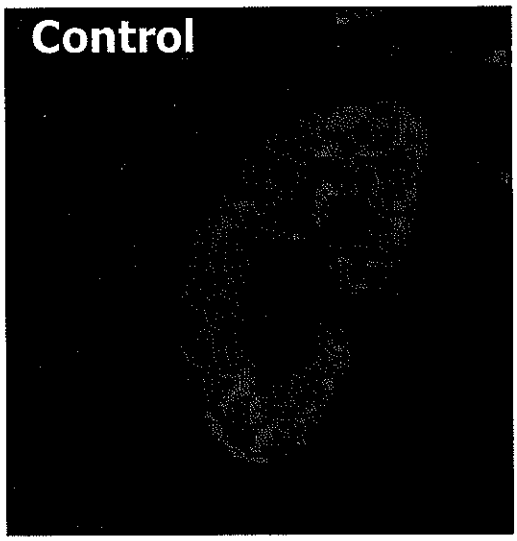
Target 3

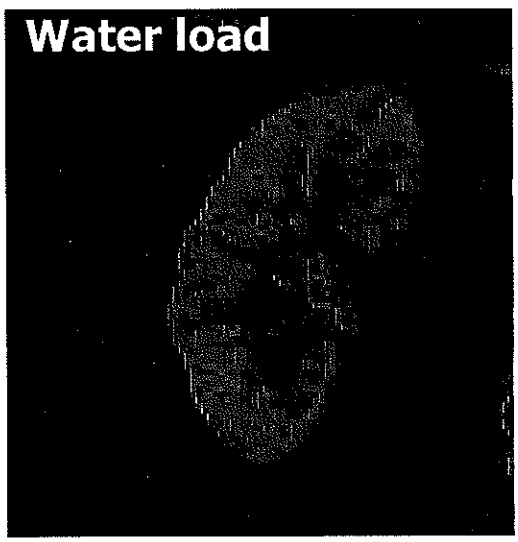
Oxygen sensors

Oxygen supply to the tubulointerstitial space



Renal BOLD-MRI in human
Renal oxygen level after 1L water load



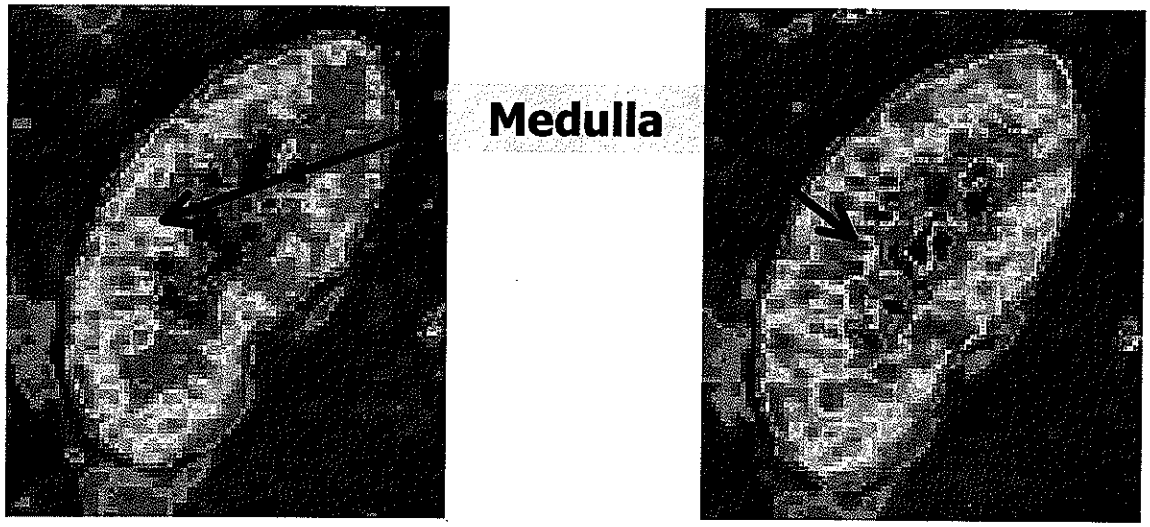


Water load increases medullary oxygen level
T2* imaging

Mori et al, unpublished observation

Renal BOLD-MRI in human
Renal oxygen level after furosemide i.v.

Before **15 min after i.v. of furosemide**

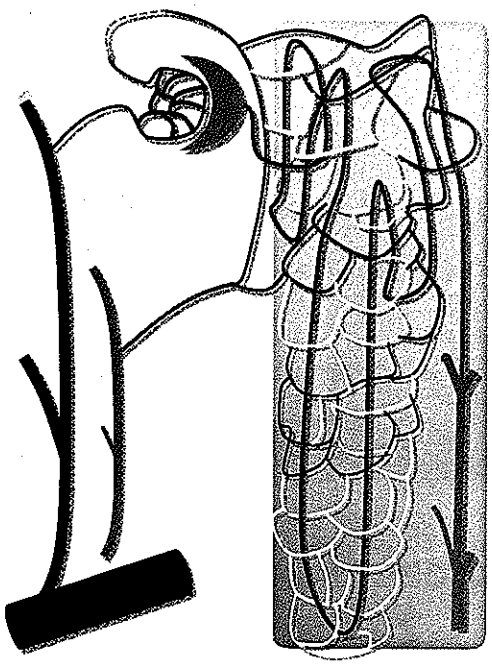


Furosemide increases medullary oxygen level at 15-min after administration

Mori et al, unpublished observation

Chronic hypoxia in the diabetic kidney

Diabetes **Tubulointerstitial hypoxia**



Miyata and van Ypersele, Nature Review Nephrology 6, 2010

Q

What are the cellular defensive mechanism against hypoxic injury?

'HIF' regulates reactions mitigating hypoxia