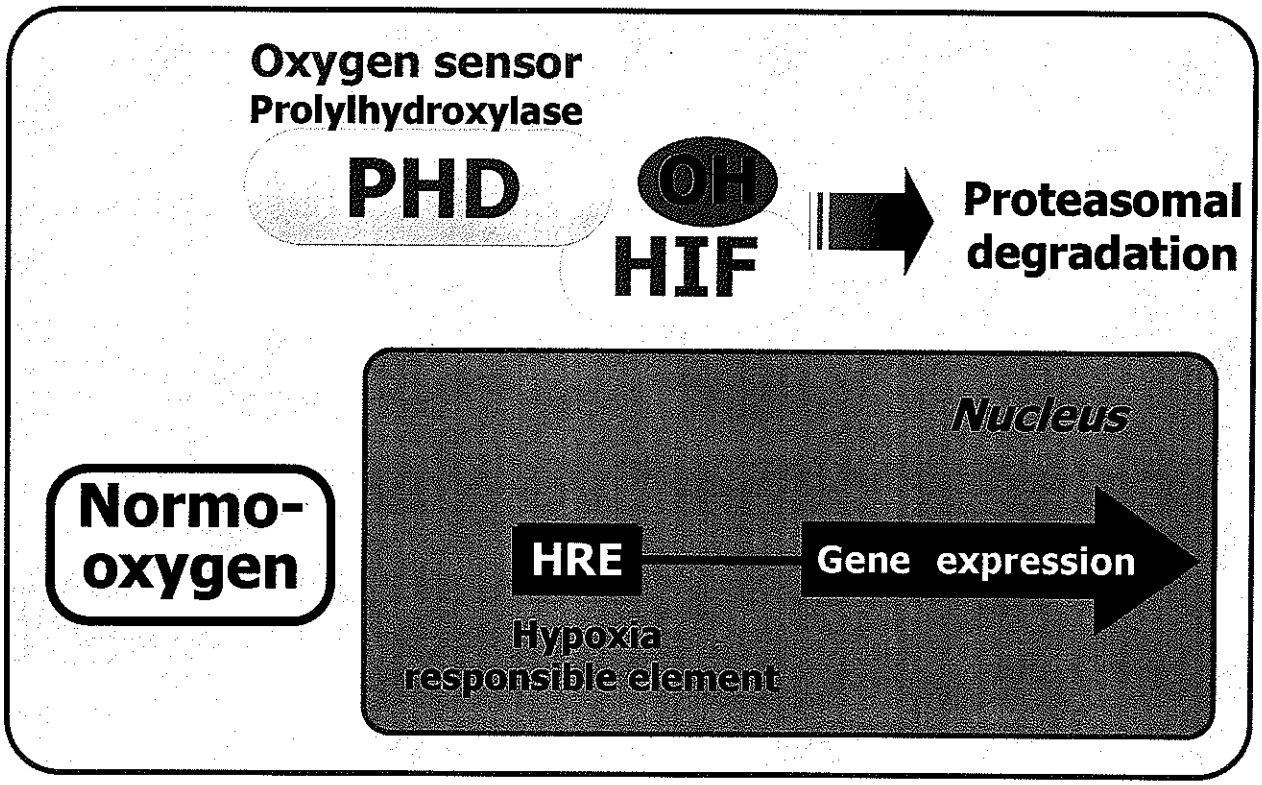
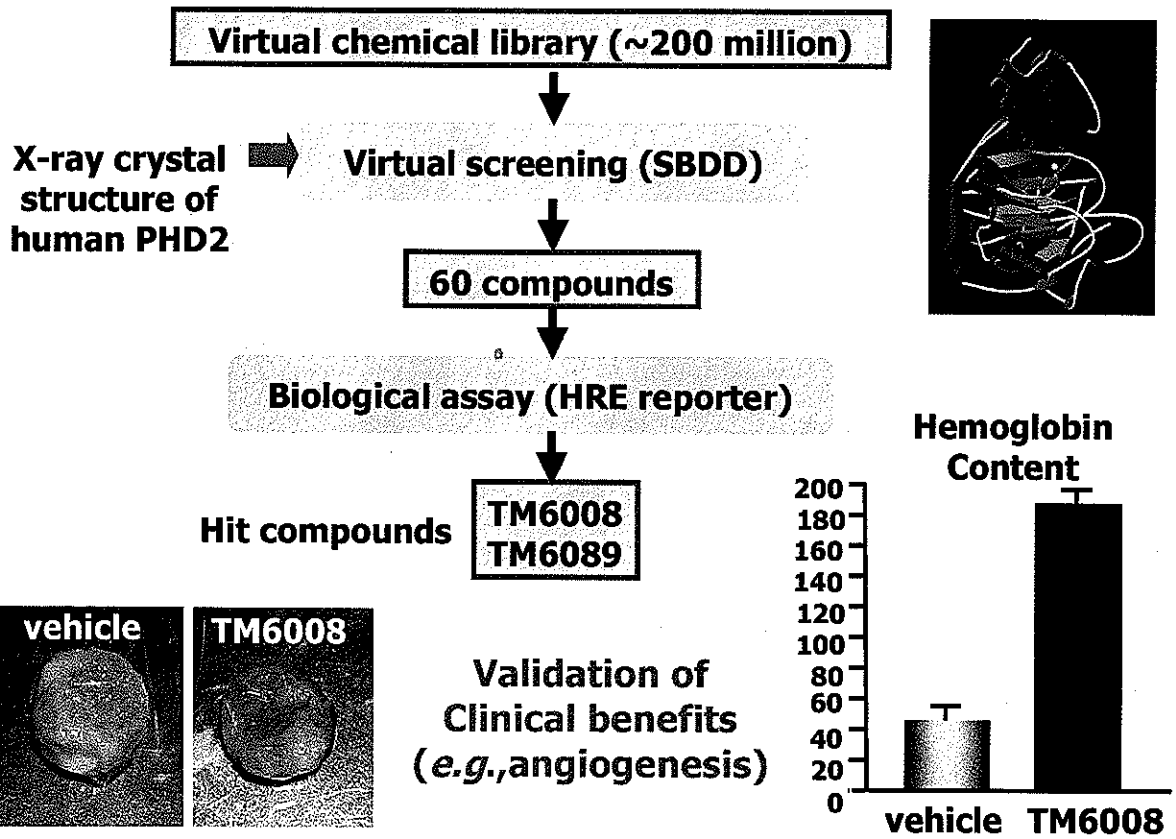
PHDs are 'oxygen sensors' regulating HIF activity

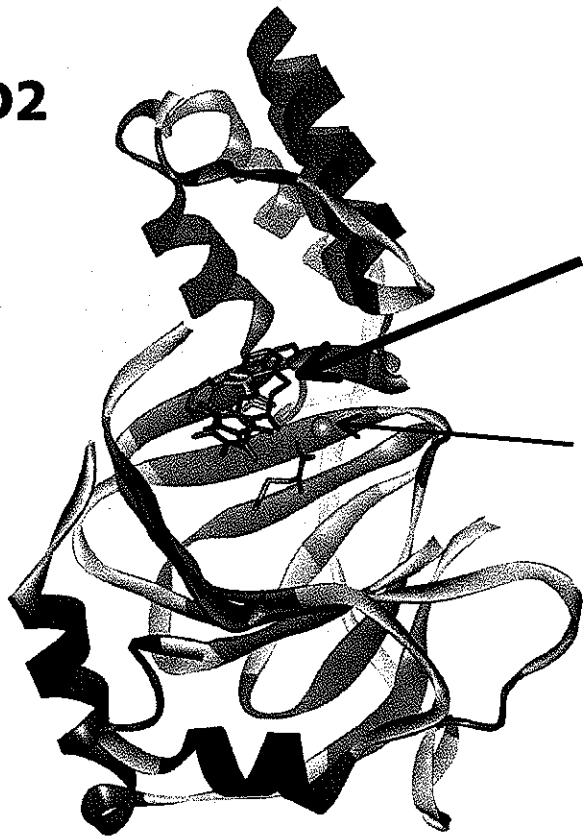


In silico discovery of inhibitory compounds for 'oxygen sensors'



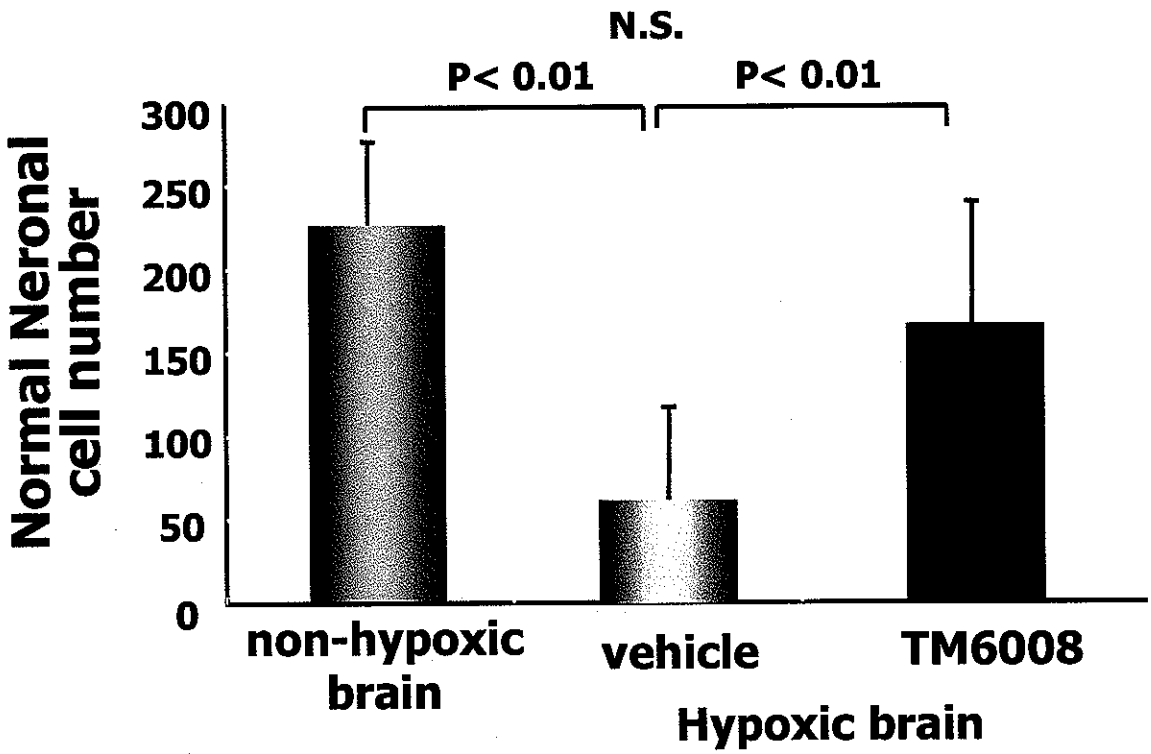
Nangaku et al. Arterio Throm Vas Biol 27, 2007

Human PHD2



Miyata and van Ypersele, Nature Review Nephrology 6,2010

Oxygen sensor inhibitor protects neurons
Gerbil acute stroke model



Nangaku et al. Arterio Throm Vas Biol 27, 2007

Table 1 | **Selected list of prototypical inhibitors of oxygen sensors PHD and FIH**

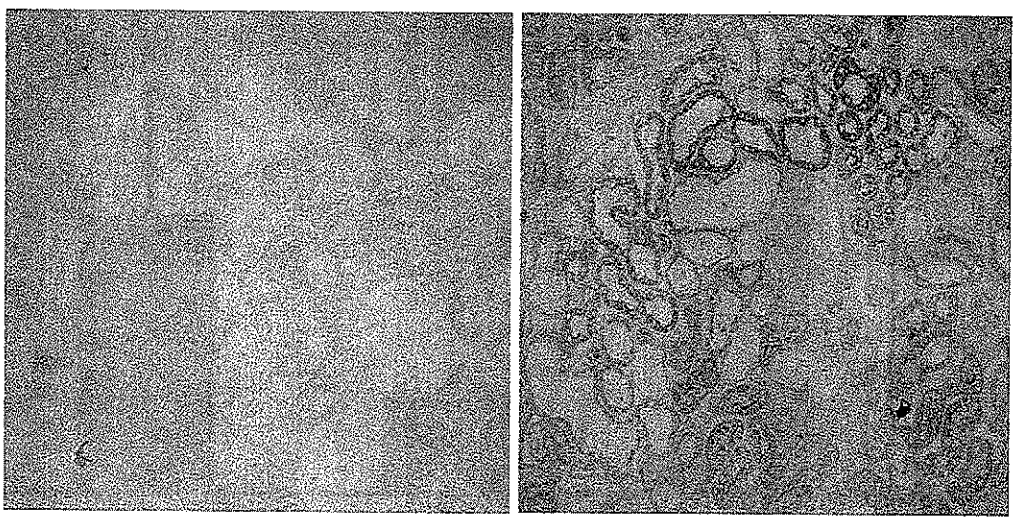
Inhibitor	Principle of inhibition	Specificity (IC_{50})	Physiological effect	Therapeutic application	Refs
Dimethyloxalylglycine	Mimics 2-OG	PHD, FIH, CPH (>30 μM)	Promotes angiogenesis, confers hypoxia tolerance, ischaemic preconditioning, suppresses inflammation, blocks adipocyte differentiation	Ischaemic disorders (cerebral/myocardial), inflammatory bowel diseases, metabolic disorders	19,31,73,142, 152,181–183
N-Oxalyl-D-phenylalanine	Mimics 2-OG	FIH (not determined) over PHD2	Not determined	Not determined	154
Desferrioxamine	Chelates Fe^{2+}	Fe^{2+}-requiring enzymes	Confers hypoxia tolerance	Ischaemic disorders	34,93,95, 96,184
Metal ions (for example, Co^{2+} and Cu^{2+})					95
Hydralazine		CPH		hypertension	30
Ethyl 3,4-dimethylbenzoate	Blocks active site, chelates Fe^{2+}	PHD2 (330 μM), PHDs, FIH	Confers hypoxia tolerance, blocks adipocyte differentiation	Ischaemic disorders	35,94,152, 185–188
FG-0041	Blocks active site, chelates Fe^{2+}	PHDs, FIH*, CPH (2 μM)	Confers hypoxia tolerance	Myocardial ischaemia	182,189
FG-2229 (ciclopirox olamine)	Blocks active site, chelates Fe^{2+}	PHDs, FIH*, CPH (1 μM)	Promotes angiogenesis, antifungal properties	Ischaemic disorders, mycosis	182,190
FG-4497	Blocks active site	PHDs (not determined), FIH*	Confers hypoxia tolerance, suppresses inflammation	Kidney failure, inflammatory bowel	97,143
TM 6008	Blocks active site, chelates Fe^{2+}	PHD2 (0.57 μM), PHDs*, FIH*	Promotes angiogenesis, neuroprotective	Ischaemic disorders	162
TM 6089	Blocks active site	PHDs (not determined), FIH*	Promotes angiogenesis	Ischaemic disorders	162
Compound A	Blocks active site	PHD2 (3.8 μM), PHDs*, FIH*	Neuroprotective	Cerebral ischaemia/ stroke	35,156
L-Mimosine	Blocks active site, chelates Fe^{2+}	PHD, CPH and others e.g., DOHH (455 μM)	Promotes angiogenesis, induces HIF1α in kidneys, inhibits DNA replication	Kidney failure, ischaemic disorders	188,191,192
Dealanylalahocin analogues	Block active site	PHD2 (up to 1,000 μM), PHDs*, FIH*	Not determined	Not determined	193
8-Hydroxyquinolines	Block active site	PHD2 (3.2–28.7 μM),	Not determined	Not determined	194

Nature Review Drug Discovery

by the group of Peter Carmeliet 8, 2009

Biomarker for tissue hypoxia

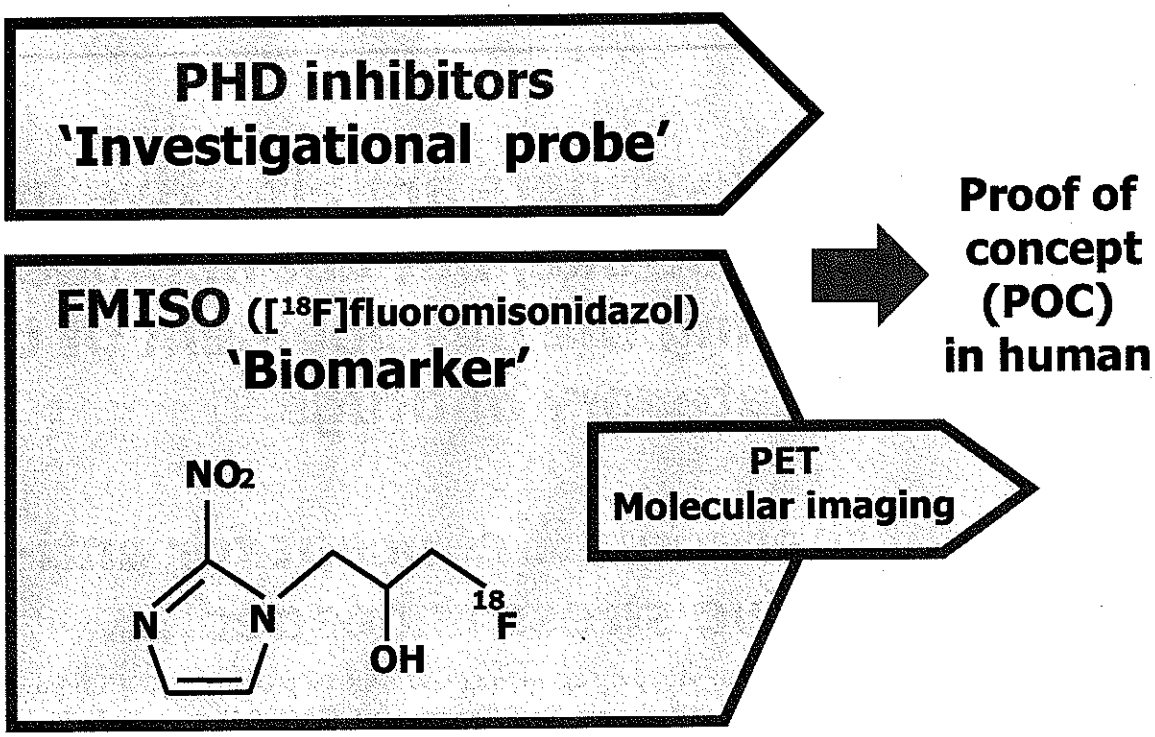
Pimonidazole



Normal | **Type 2 diabetic rat (SHR/ND) 33 wk**

Izuhara Y et al. J Am Soc Nephrol 16, 2005

Drug discovery and development platform for anti-hypoxic injury agents will be ready....



An old paradigm revisited.....

Oxidative stress

ORIGINAL ARTICLE

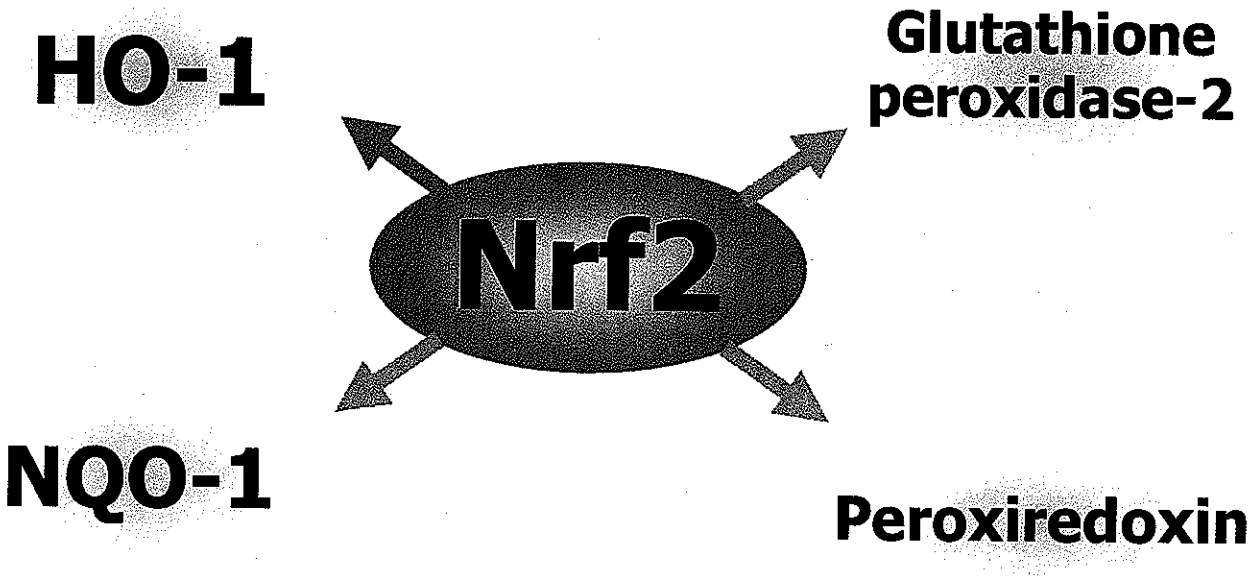
Radical scavengers are effective in experimental stroke, but not in humans, thus hampering the development of this category of drugs.

Novel therapeutic concept for anti-oxidative stress is needed.....

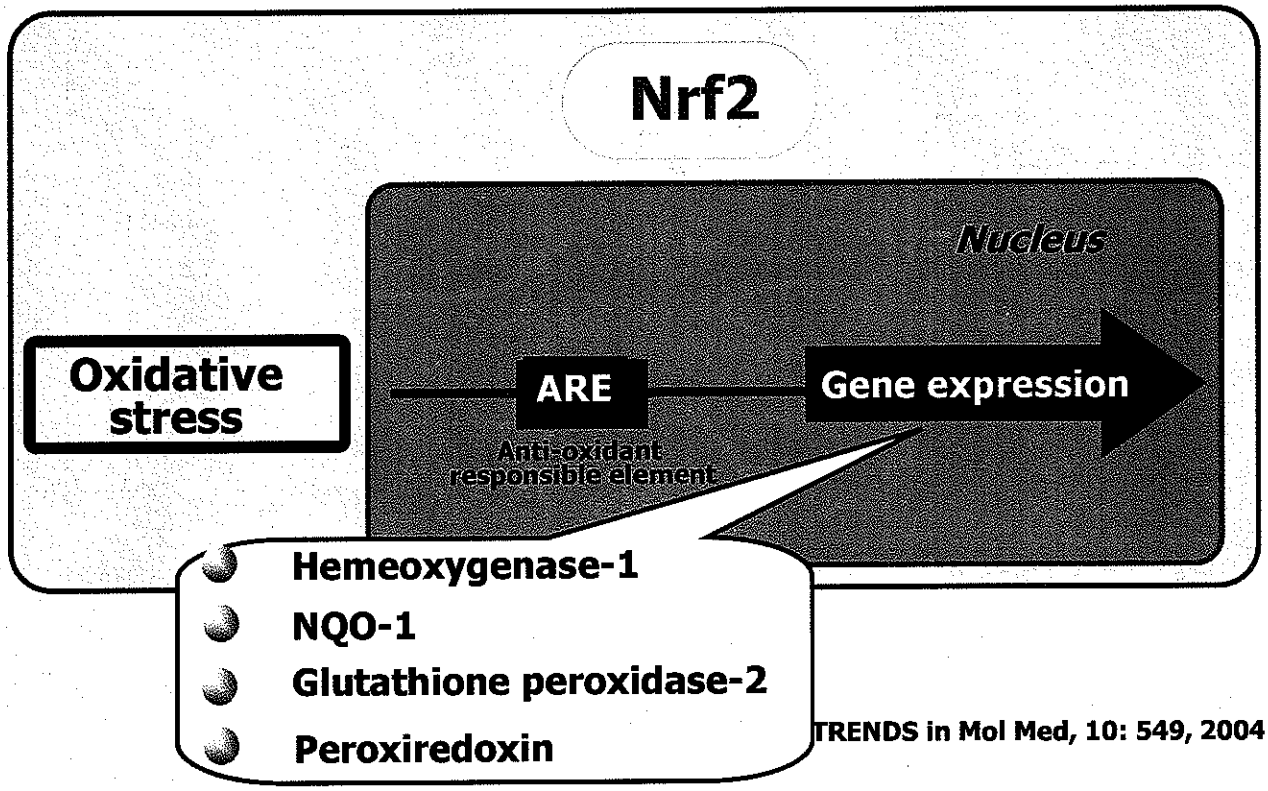
Division of Neurology, University of Alberta, Edmonton, Canada (A.S.); Stroke Unit and Cerebrovascular University Department of Med-

The free-radical–trapping agent NXY-059 showed promise as a neuroprotectant in the Stroke–Acute Ischemic NXY Treatment I (SAINT I) trial, reducing disability when given to patients who had acute ischemic stroke. We sought confirmation of

Nrf2 regulates basal and inducible expressions of anti-oxidant genes

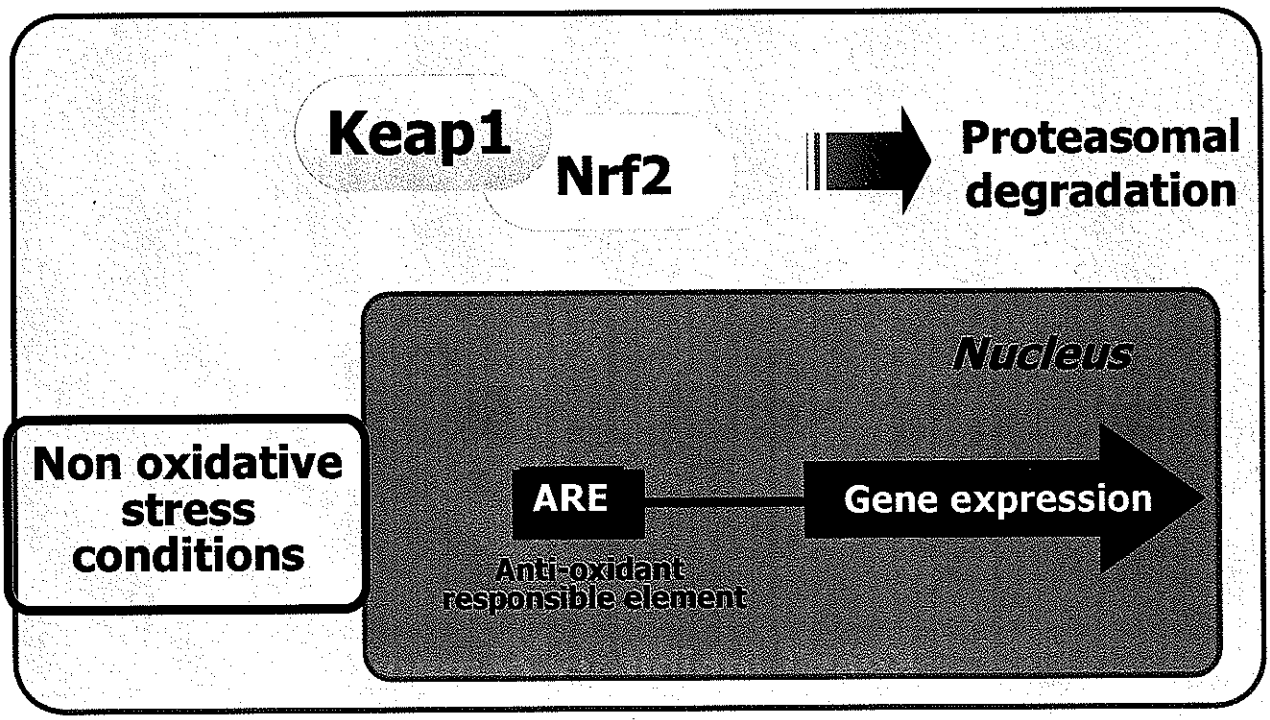


Defensive mechanisms against oxidative stress injury
'The Keap1-Nrf2 system'

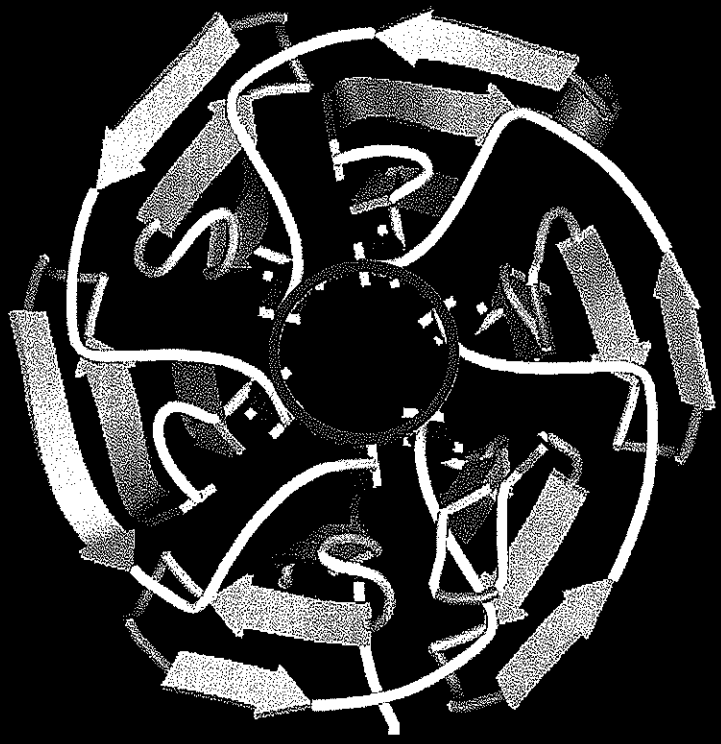


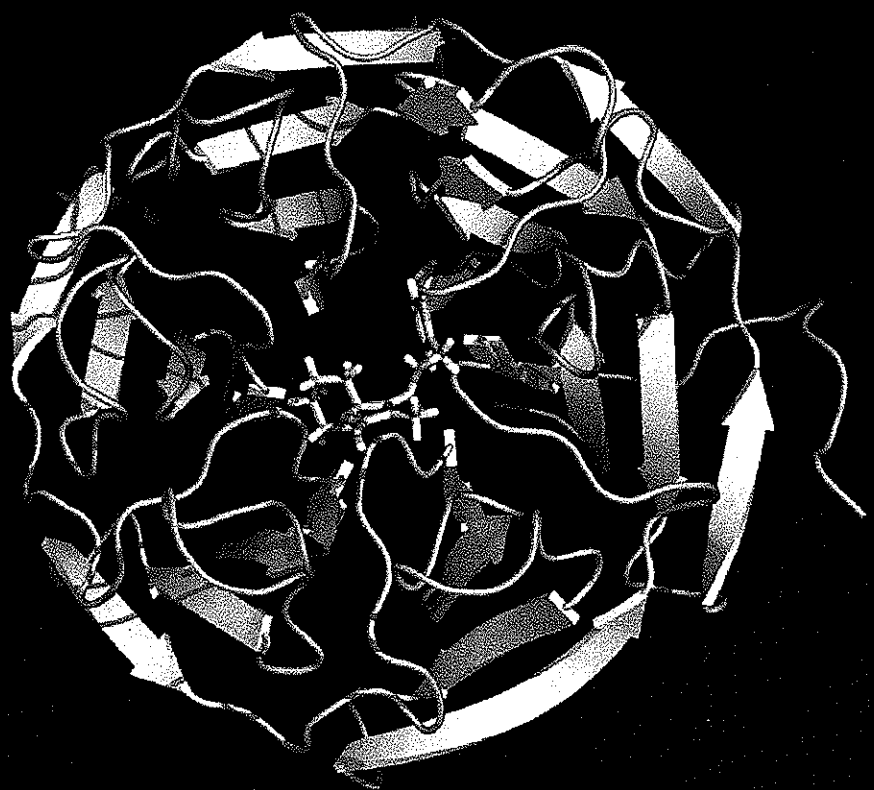
TRENDS in Mol Med, 10: 549, 2004

Keap1 is a sensor of oxidative stress and regulates the activity of Nrf2



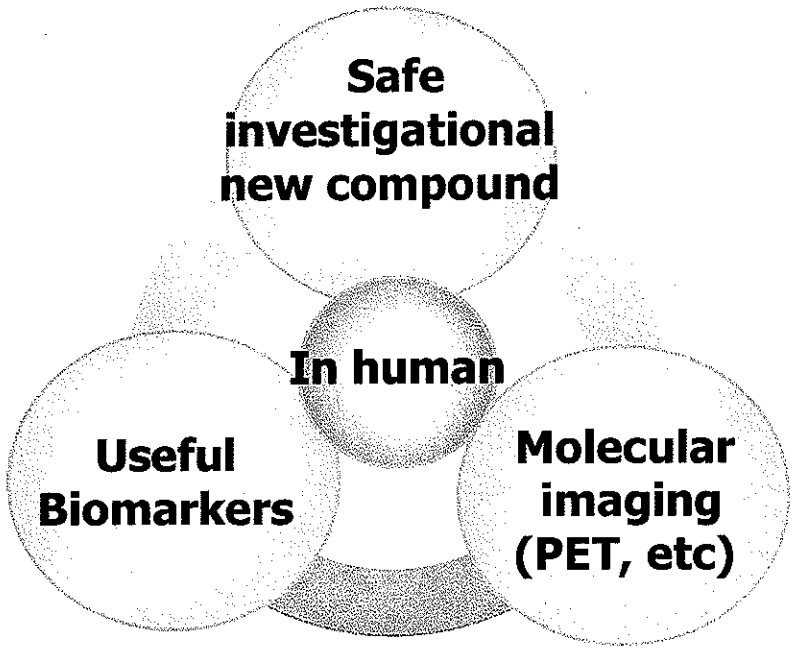
Keap1 crystal structure



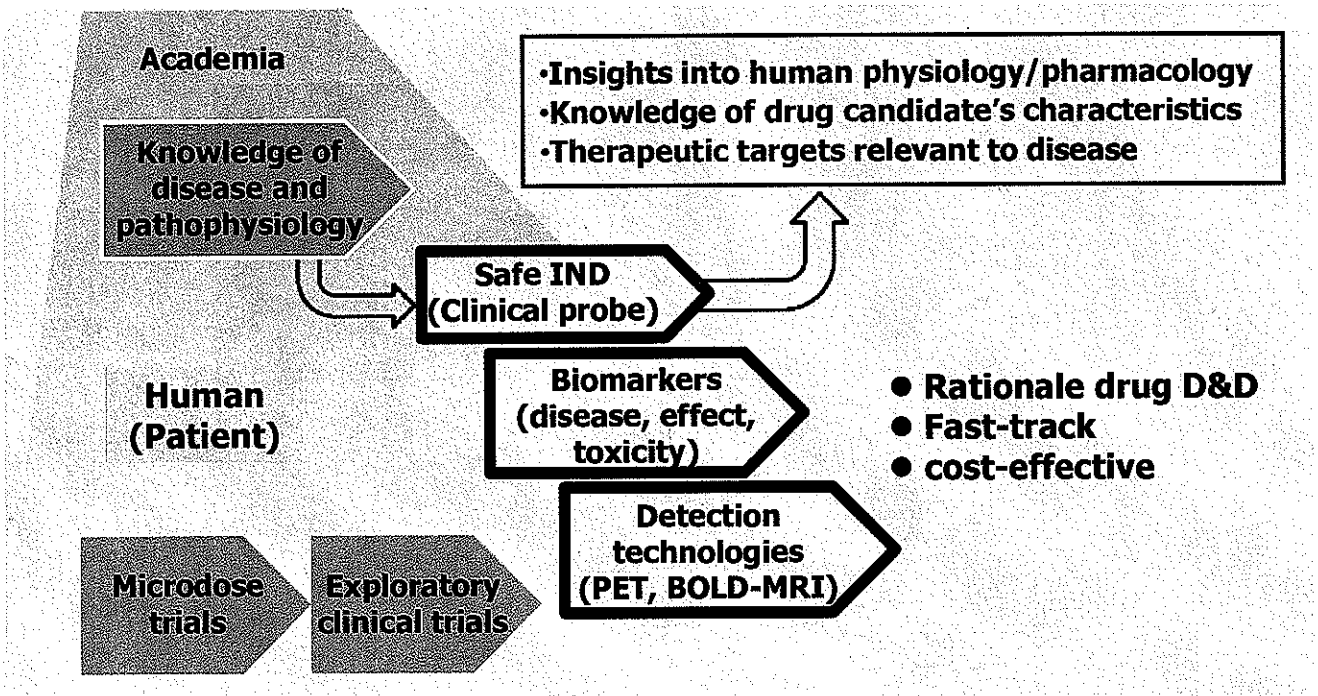


Keap1 inhibitory compound

Exploratory clinical trials for understanding of human pathophysiology and for more efficient drug D&D



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



附件2

Asia-Pacific
Economic Cooperation

2010/SOM3/LSIF/RHSC/002

Promoting Regulatory Harmonization in the Medical Device Sector in the APEC Region

Purpose: Consideration
Submitted by: United States

JAPAN 2010

Life Sciences Innovation Forum Regulatory Harmonization Steering Committee Meeting
Sendai, Japan
17-18 September 2010

Promoting Regulatory Harmonization in the Medical Device Sector in the APEC Region

Trend Towards Regulatory Harmonization Worldwide

The Global Harmonization Task Force (GHTF) was created in 1992 to enhance patient safety and increase access to safe, effective and clinically beneficial medical technologies around the world through harmonization of regulatory systems. Since then, the Task Force has created a set of regulatory guidelines that form the basis for promoting the harmonization of regulatory requirements in many economies in Asia (the Asian Harmonization Working Party) and in Latin America (Latin American Harmonization Working Party). Four of the five founding members of the GHTF are members of the Asia-Pacific Economic Cooperation (APEC) forum (Australia, Canada, Japan, and United States)[1].

The Challenge Faced by Medical Device and Technology Companies in the APEC Region

APEC economies impose varying regulatory requirements for controlling the safety and effectiveness of medical technology – the medical devices, diagnostic products and health information systems that are transforming health care through earlier disease detection, less invasive procedures and more effective treatments. Government regulations are one measure to provide patients high quality and safe products. However, differing regulatory requirements within the APEC region create unnecessary market entry hurdles, which slow patient access and impose additional costs.

Recommended solution: A Program To Achieve Harmonization by 2020

An APEC commitment to harmonize regulatory requirements for medical technology products by 2020, on the basis of GHTF, will facilitate trade in life-saving medical devices and promote innovation in this field region-wide. This is an opportune time to launch this initiative, because many APEC economies are in the process of developing regulations for medical devices

The benefits of such a commitment are compelling:

- For APEC member economies: Facilitates an environment conducive towards the growth of the medical device sector, enhancing innovation and growing knowledge-based jobs. Promotes patient access to life-saving medical technologies.
- For APEC medical device companies: Creates a predictable regulatory framework so that companies can grow and export in a sustainable manner.

We propose a three-phase program to raise awareness of the GHTF guidelines, develop best practices for harmonizing regulatory processes, and conduct a gap analysis and organize targeted capacity building in order to close those gaps. The action plan would culminate in a commitment to achieving medical device regulatory harmonization by 2020, which would be a deliverable for the 2011 APEC Leaders' Meeting.

2010 (Japan host year): Working with the Life Sciences Innovation Forum (LSIF) Regulatory Harmonization Steering Committee, develop a strategic plan for harmonization in the medical device sector based on GHTF guidance. Present the strategic plan at the LSIF Annual Meeting. Seek Ministers' and Leaders' endorsement of the strategic plan and agree to work towards APEC-wide regulatory harmonization.

2011 (US host year): At the LSIF Regulatory Harmonization Steering Committee, build on the strategic plan to craft an action plan that includes the formulation of a harmonization check list that economies can use to generate self-reports on their degree of regulatory harmonization; a process for APEC to use these reports to identify harmonization gaps; and a procedure for developing targeted capacity building to close these gaps. Seek endorsement of an APEC Action Plan for Medical Device Regulatory Harmonization by 2020 as a deliverable for the APEC Leaders' Meeting. Such a political commitment will be a vital underpinning to the voluntary harmonization efforts of AHWP and GHTF.

2012 (Russia host year) and beyond: Using the harmonization checklist, identify member economies to undergo gap analyses and receive targeted capacity building in order to meet the goal of harmonization by 2020. The APEC Life Sciences Harmonization Center, established in 2009, will be central to the capacity building program during this period.

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[1] The European Union is the fifth founding member of GHTF.

Strong linkage to APEC goals

Since the founding of the Life Science Innovation Forum (LSIF) in 2004, Leaders and Ministers have endorsed measures to facilitate trade and investment in the APEC region by encouraging pro-innovation policies in the life sciences sector in APEC member economies, including regulatory harmonization. LSIF has consistently endorsed the GHTF as the foundation of APEC's work in the medical technology sector. In 2009, Ministers called for the development of a multi-year strategic plan, including capacity building projects, for achieving regulatory harmonization for medical devices.

Contact: Nancy Travis, Advanced Medical Technology Association, NTravis@AdvaMed.org