# Small molecule immunomodulators:

# New targets and opportunities

Eric Kool - Department of Chemistry, Stanford University

# Eric Kool experience

- organic chemistry / chemical biology expertise
- published >300 papers; received several national awards
- >30 patents, multiple licensed commercial technologies
- invented founding technology of 4 companies
- co-founded genomics venture Cell Data Sciences (2014; multiple products currently on the market; and diagnostics startup Ascella Biosystems (2020)

DxTerity

CELLDATA

ascella BIOSYSTEMS

## Our goal: Immune modulation by targeting DNA repair

- multiple targets for disease intervention
- opportunities in diseases with millions of patients
- near-term applications with IP already developed
- long-term development also promising

Large patient populations are underserved

## Acute inflammatory diseases:

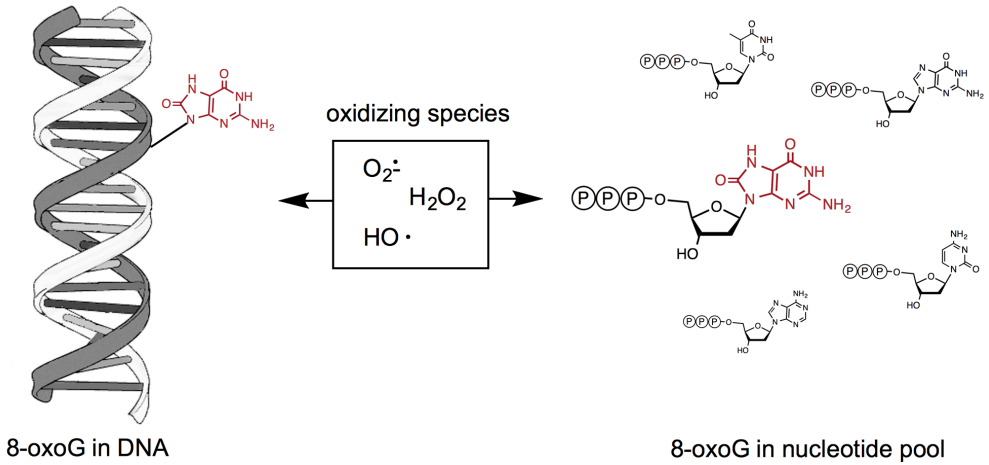
| | |
|---|---|
| sepsis | 1.6M /y (US) |
| acute pancreatitis | 90K /y |
| neuroinflammation | |
| (e.g. stroke) | 795,000/y |
| lung inflammation | |
| (ARDS; COVID) | millions/y |

cytokine release syndrome (CRS) (“cytokine storm”) in:

| | |
|---|---|
| -bone marrow stem cell transplant | ~20K / y) |
| -CAR-T therapy | thousands of pts; rapidly growing |

## Our targets: DNA repair pathways as controllers of inflammation

> e.g. **the "GO" system** (guanine oxidation)




- control of the GO pathways offers many therapeutic opportunities
- multiple enzyme targets in the pathway (OGG1, MTH1, MutYH, ...)
- currently undrugged: multiple chances for 1st in class

*Cancer Sci*. **2007**, *98*, 465

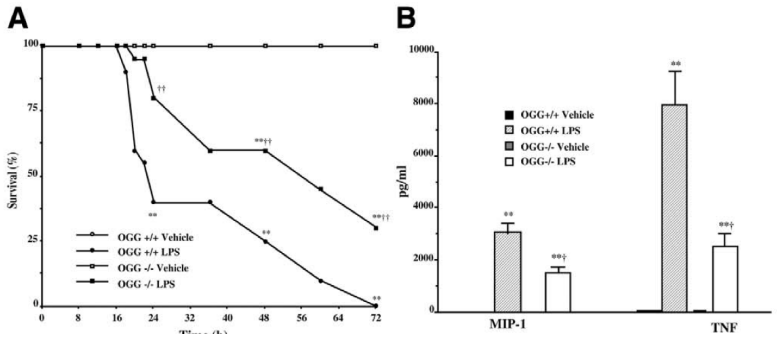
# Biological connections between DNA repair and inflammation. (1)

*The FASEB Journal* express article 10.1096/fj.04-2278fje. Published online December 1, 2004.

**Potential role for 8-oxoguanine DNA glycosylase in regulating inflammation**

Jon G. Mabley,*,† Pál Pacher,†,‡ Amitabha Deb,† Rebecca Wallace,† Rhoderick H. Elder,§ and Csaba Szabó†,‖

- OGG1-deficient mice have reduced inflammatory responses
- lower responses to endotoxin (LPS) and to allergen sensitivity
- KO mice have prolonged survival after endotoxin
- decreased levels of chemokines and cytokines IL-12, IL-1, and TNF-α




*FASEB J.* **2005**, *19*, 290

# Biological connections between DNA repair and inflammation. (2)

**The Role of 8-Oxoguanine DNA Glycosylase-1 in Inflammation**

Xueqing Ba [1,2], Leopoldo Aguilera-Aguirre [1], Qura Tul Ain Nmi Rashid [3], Attila Bacsi [1,4], Zsolt Radak [1,5], Sanjiv Sur [3,7], Koa Hosoki [3], Muralidhar L. Hegde [6] and Istvan Boldogh [1,7,*]

- OGG1-deficient mice have reduced allergic responses to ovalbumin
- lower levels of Th1 and Th2 cytokines
- siRNA to OGG1 in WT animals reduced allergic responses to ragweed pollen

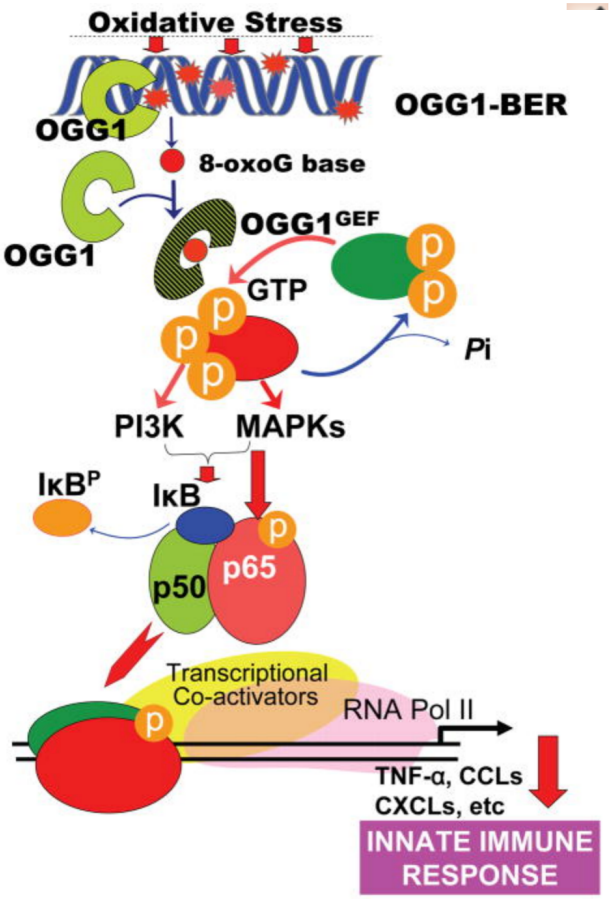
*Int J. Mol. Sci.* **2014**, *15*, 16975

# Biological connections between DNA repair and inflammation. (3)

**Innate Inflammation Induced by the 8-Oxoguanine DNA Glycosylase-1–KRAS–NF-κB Pathway**

Leopoldo Aguilera-Aguirre,* Attila Bacsi,*,[1] Zsolt Radak,*,[2] Tapas K. Hazra,[†,‡] Sankar Mitra,[†,3] Sanjiv Sur,[‡,§] Allan R. Brasier,[‡,§] Xueqing Ba,*,[4] and Istvan Boldogh*,[§]

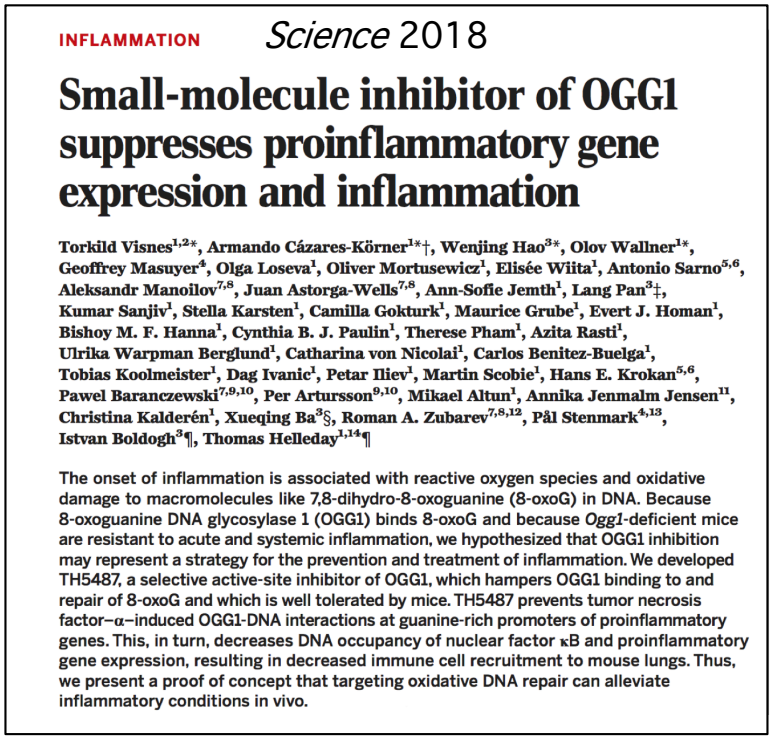
- 8-oxoguanine (released by OGG1) is a proinflammatory signaling agent
- Repair by OGG1 creates ss DNA breaks, which are also proinflammatory via cGAS / STING pathway
- Binding of OGG1 to DNA increases NF-κB occupancy of proinflammatory promoters




*J. Immunol.* **2014**, *193*, 4643

# Validation of OGG1 as a target for inflammation in mouse model

- study in *Science* late '18
- OGG1 small-molecule inhibitor reduces inflammation in LPS-treated mice
- inhibitor reduces TNF, IL6 expression
- our inhibitor also shown to be active in the supporting data
- (note: our inhibitor is more potent)



INFLAMMATION *Science* 2018

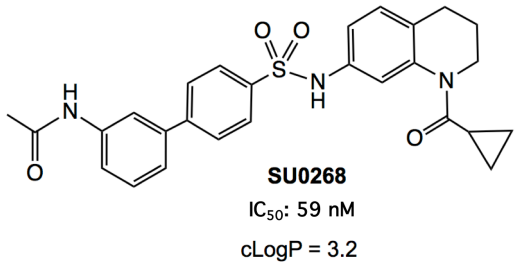
## Small-molecule inhibitor of OGG1 suppresses proinflammatory gene expression and inflammation

Torkild Visnes[1,2*], Armando Cázares-Körner[1*†], Wenjing Hao[3*], Olov Wallner[1*], Geoffrey Masuyer[4], Olga Loseva[1], Oliver Mortusewicz[1], Elisée Wiita[1], Antonio Sarno[5,6], Aleksandr Manoilov[7,8], Juan Astorga-Wells[7,8], Ann-Sofie Jemth[1], Lang Pan[3‡], Kumar Sanjiv[1], Stella Karsten[1], Camilla Gokturk[1], Maurice Grube[1], Evert J. Homan[1], Bishoy M. F. Hanna[1], Cynthia B. J. Paulin[1], Therese Pham[1], Azita Rasti[1], Ulrika Warpman Berglund[1], Catharina von Nicolai[1], Carlos Benitez-Buelga[1], Tobias Koolmeister[1], Dag Ivanic[1], Petar Iliev[1], Martin Scobie[1], Hans E. Krokan[5,6], Pawel Baranczewski[7,9,10], Per Artursson[9,10], Mikael Altun[1], Annika Jenmalm Jensen[11], Christina Kalderén[1], Xueqing Ba[3§], Roman A. Zubarev[7,8,12], Pål Stenmark[4,13], Istvan Boldogh[3¶], Thomas Helleday[1,14¶]

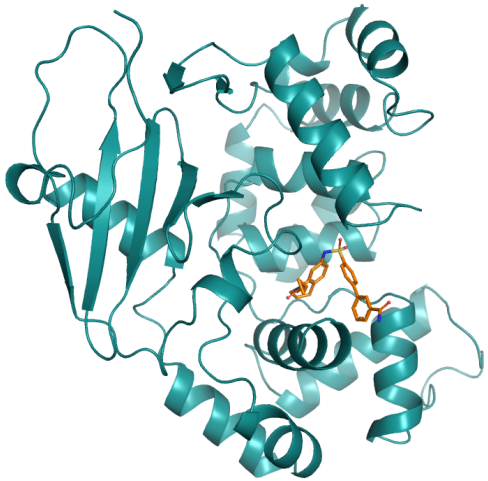
The onset of inflammation is associated with reactive oxygen species and oxidative damage to macromolecules like 7,8-dihydro-8-oxoguanine (8-oxoG) in DNA. Because 8-oxoguanine DNA glycosylase 1 (OGG1) binds 8-oxoG and because *Ogg1*-deficient mice are resistant to acute and systemic inflammation, we hypothesized that OGG1 inhibition may represent a strategy for the prevention and treatment of inflammation. We developed TH5487, a selective active-site inhibitor of OGG1, which hampers OGG1 binding to and repair of 8-oxoG and which is well tolerated by mice. TH5487 prevents tumor necrosis factor–α–induced OGG1-DNA interactions at guanine-rich promoters of proinflammatory genes. This, in turn, decreases DNA occupancy of nuclear factor κB and proinflammatory gene expression, resulting in decreased immune cell recruitment to mouse lungs. Thus, we present a proof of concept that targeting oxidative DNA repair can alleviate inflammatory conditions in vivo.

# IP position around this approach: potent inhibitors of OGG1

- HTS at Stanford, Novartis (Stanford owns IP)
- med chem optimization: potent compounds achieved and backup compounds/scaffolds in progress
- most potent existing modulators of these targets
- IP filed 2018




most potent and most bioactive OGG1 inhibitor

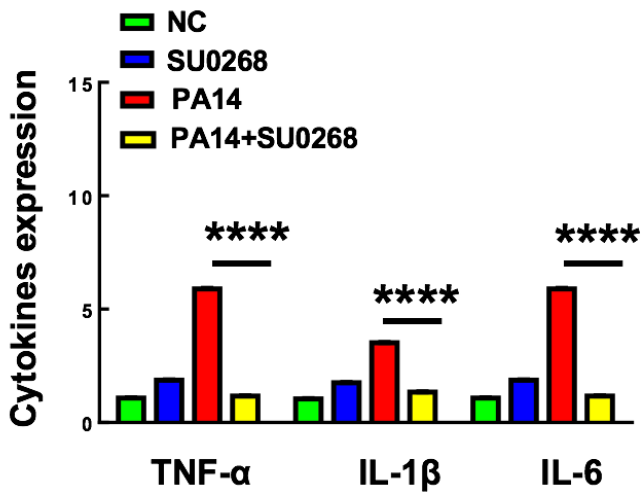


Kool lab, *J. Am. Chem. Soc.* 2018
and ongoing work

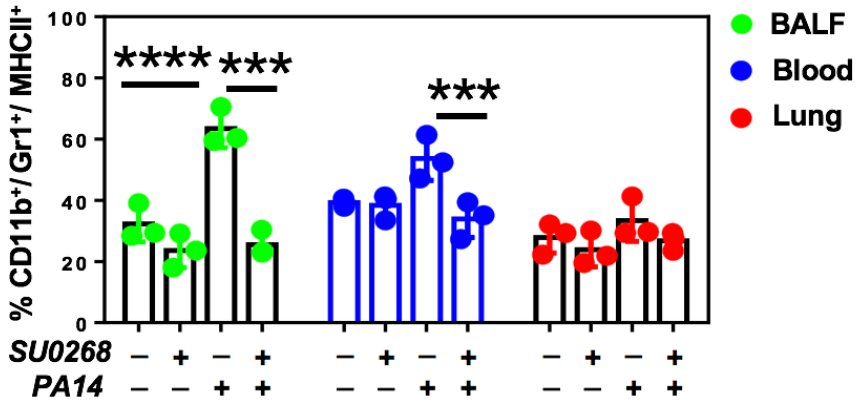
# SU0268 shows potent antiinflammatory activity in mouse model of sepsis

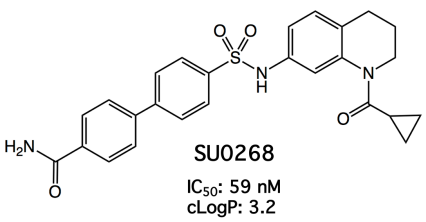
Lung infections with *Pseudomonas aeruginosa*

Cytokine levels in infected cells




Infected animals:
neutrophil counts




>Improved survival as well

with M. Wu,, *J. Immunol.* 2020

# Plans

- raise funds to support animal tox, IND filing for SU0268
- find clinical partner for phase I trial
- developing backup drug scaffold for OGG1
- optimize screening hits on second target