Nicotinamide for Skin Cancer Chemoprevention

Professor Diona Damian

Dermatology, University of Sydney
Investigator-initiated studies:

NHMRC, Cancer Council NSW, CINSW, SMS Foundation, Australasian College of Dermatologists Scientific Research Fund
DNA Damage → DNA repair → Genomic Stability

UV immunosuppression (↓ anti-tumour immunity) → Mutations → Cancer

Inflammation
Skin cancer prevention

- Prevent DNA damage
- Enhance DNA repair
- Protect skin immunity
- Replenish cellular energy
Sunscreens are good

- Reduce AKs/SCC by ~40% in 2 years
- May reduce BCC and melanoma after ~8 years
  *(Green, Lancet 1999; Green, J Clin Oncol 2011)*
- 8 or 80- It’s never too late for sunscreens!

*BUT YOU HAVE TO APPLY THEM*
Sometimes sunscreens just aren’t enough
Chemoprevention options

- Retinoids
- NSAIDs
- Botanicals
Chemoprevention wish-list

Effective
Non-toxic
Inexpensive
Available
Nicotinamide

- Amide form of vitamin B3
- No vasodilatory side effects (unlike NIACIN)
- Anti-inflammatory effects
- Precursor of NAD$^+$
  - cofactor in ATP production = ENERGY
Nicotinamide unblocks glycolysis and prevents UV-induced ATP depletion (replenishes cellular energy) 

(Park et al, 2010)
Nicotinamide enhances DNA repair

- Human keratinocytes
- Melanocytes
- *ex vivo* human skin

*Surjana, Carcinogenesis 2013*
*Thompson, Exp Dermatol 2014*
*Thompson, PLOS One 2015*
Cyclobutane Pyrimidine Dimers

No UV
Nicotinamide reduces UV immunosuppression

- Protects from both UVB and UVA
- Placebo-controlled crossover studies (Mantoux model):
  - immune protective at 500mg tds & 500mg/day

Damian, J Invest Dermatol 2008;
Sivapirabu, Br J Dermatol 2009;
Yiasemides, Carcinogenesis 2009
Does nicotinamide reduce skin cancer?
Oral Nicotinamide to Reduce Actinic Cancer

A double-blind, multi-centre, phase 3, randomised controlled trial

N=386 immunocompetent adults

≥2 non-melanoma skin cancers (NMSCs) in past 5 yrs
Endpoints

Primary endpoint:

new histologically confirmed NMSCs
(BCC + invasive or *in situ* SCC) to 12 months
## Study Sites and Procedures

**Royal Prince Alfred Hospital and Westmead Hospital**

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Treatment Period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 m</td>
</tr>
<tr>
<td>Skin cancers</td>
<td>X</td>
</tr>
<tr>
<td>AKs</td>
<td>X</td>
</tr>
<tr>
<td>AEs</td>
<td></td>
</tr>
<tr>
<td>Labs</td>
<td>X</td>
</tr>
<tr>
<td>Baseline Characteristics</td>
<td>Placebo (N=193)</td>
</tr>
<tr>
<td>--------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Age</td>
<td>66 [30-91]</td>
</tr>
<tr>
<td>Male</td>
<td>63%</td>
</tr>
<tr>
<td>Skin cancers in past 5y</td>
<td>8.2 [2-52]</td>
</tr>
<tr>
<td>AKs</td>
<td>46 [0-214]</td>
</tr>
<tr>
<td>Sunscreen in past week</td>
<td>51%</td>
</tr>
</tbody>
</table>
## Treatment (12 months)

<table>
<thead>
<tr>
<th>NMSCs</th>
<th>Mean Rate</th>
<th>Relative rate reduction (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO vs NIC</td>
<td>2.4 vs 1.8</td>
<td>0.23 (0.04 to 0.38)</td>
<td>0.02</td>
</tr>
<tr>
<td>BCCs</td>
<td>1.7 vs 1.3</td>
<td>0.20 (-0.06 to 0.39)</td>
<td>0.1</td>
</tr>
<tr>
<td>SCCs</td>
<td>0.7 vs 0.5</td>
<td>0.30 (0.00 to 0.51)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Post-Treatment (6 months)

<table>
<thead>
<tr>
<th>Mean Rate</th>
<th>Relative rate reduction (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMSCs</td>
<td>0.80 vs 0.81</td>
<td>0.3</td>
</tr>
<tr>
<td>BCCs</td>
<td>0.55 vs 0.48</td>
<td>0.7</td>
</tr>
<tr>
<td>SCCs</td>
<td>0.25 vs 0.32</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Negative binomial model; relative rates, relative rate reductions, and p-values from model with centre and 5y skin cancer history as covariates.
How quickly does it work?

Trend to reduction in NMSCs within 3 mths

<table>
<thead>
<tr>
<th>Visit Duration</th>
<th>Relative Rate Reduction</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 month visit</td>
<td>25%</td>
<td>0.11</td>
</tr>
<tr>
<td>6 month visit</td>
<td>27%</td>
<td>0.09</td>
</tr>
<tr>
<td>9 month visit</td>
<td>18%</td>
<td>0.29</td>
</tr>
<tr>
<td>12 month visit</td>
<td>29%</td>
<td>0.09</td>
</tr>
</tbody>
</table>
### Actinic keratoses

<table>
<thead>
<tr>
<th>Time point</th>
<th>Relative reduction (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3m</td>
<td>0.11 (0.18 to 0.03)</td>
<td>0.01</td>
</tr>
<tr>
<td>6m</td>
<td>0.14 (0.21 to 0.07)</td>
<td>0.0005</td>
</tr>
<tr>
<td>9m</td>
<td>0.20 (0.27 to 0.13)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>12m</td>
<td>0.13 (0.2 to 0.05)</td>
<td>0.001</td>
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</table>

Estimates from repeated measures model
Subgroup Analyses NMSCs to 12 Months

- Male: P=0.6
- Female: P=0.6
- <68 years age: P=0.6
- ≥68 years age: Cont. P=0.9
- (Ex) Smoker: P=0.7
- Never smoked: P=0.7
- <6 NMSCs: P=0.2
- >=6 NMSCs: Cont. P=0.02
- < 34 AKs: P=0.4
- ≥34 AKs: Cont. P=0.5
- No NSAID: P=1.0
- NSAID: P=0.5
- No statin: P=0.5
- Statin: P=0.5
- Overall: P=0.5

Tests of effect modification

Subgroup Analyses NMSCs to 12 Months
Nicotinamide was safe

No clinically or statistically significant differences in:

- Adverse events
- Blood pressure
- Blood parameters
  (full blood count, renal or liver function)
- Weight ($mean -0.5kg; p=0.15$)
Nicotinamide reduced skin cancer by 23% in heavily sun damaged people

Similar efficacy against SCCs and BCCs

Reduced keratoses by ~15%

No effect beyond treatment period
A Phase 3 Randomized Trial of Nicotinamide for Skin-Cancer Chemoprevention


DOI: 10.1056/NEJMoa1506197
Wide media coverage:

Global audience reach ~81 million

University of Sydney International Media Report Jan-Jun 2015
“vitamin in beer and Vegemite can prevent skin cancer”

New study .. research reveals that Vitamin B3 reduces skin cancer. Picture: Supplied
Sue DunlevyNews Corp Australia Network
Tablets are widely available

Many patients already know about it
Well tolerated

Inexpensive (~$10/month)

Instantly translatable to clinical practice
Nicotinamide in the clinic

For patients who have already had (non-melanoma) skin cancer

Ensure nicotinamide, **NOT** niacin / nicotinic acid

We still need sunscreens and skin checks
Can nicotinamide prevent melanoma?

ONTRAC did not assess melanoma incidence

Enhances DNA repair in melanocytes

Reduces UV immunosuppression

Does NOT enhance melanoma cell viability, proliferation or invasion in vitro

(Thompson Exp Dermatol 2014)

(Minocha et al)
Is nicotinamide chemopreventive in the immune suppressed?

ONTRAC excluded immune suppression
No Phase 3 level efficacy or safety data in transplant recipients: not recommended for transplant patients outside of a trial setting.

ONTRANS

Oral Nicotinamide after Transplant

254 heart, lung, liver and kidney transplant pts

NHMRC Project Grant 1108328
Team ONTRAC

Dr Andrew Chen  Dr Andrew Martin  Prof Gary Halliday

Dr Bonita Choy  Dr Robyn Dalziell  Prof Richard Scolyer  Dr Catriona McKenzie

A/Prof Pablo Fernandez-Penas  Prof Janette Vardy  Dr Haryana Dhillon  Dr Anne Kricker  Dr Gayathri St George  Dr Nira Chinniah