

# THE PRECURSOR FOR NERVE GROWTH FACTOR AND INNERVATION IN THYROID CANCER



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*The discovery of the growth response elicited by a soluble tumoural agent revealed the receptivity of developing nerve cells to hitherto unknown humoral factors, and in this way opened a new area of investigation.*

Professor Dr. Rita Levi-Montalcini, Nobel Lecture, 1986.

## DECLARATION

### STATEMENT OF ORIGINALITY

I hereby certify that the work embodied in the thesis is my own work, conducted under normal supervision. The thesis contains no material which has been accepted, or is being examined, for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made. I give consent to the final version of my thesis being made available worldwide when deposited in the University's Digital Repository, subject to the provisions of the Copyright Act 1968 and any approved embargo.

### THESIS BY PUBLICATION

I hereby certify that this thesis is in the form of a series of papers. I have included as part of this thesis a written declaration from each co-author, endorsed in writing by the Faculty Assistant Dean (Research Training), attesting to my contribution to any jointly authored papers.

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## ABSTRACT

The precursor for nerve growth factor (proNGF) has recently been shown to be expressed in thyroid cancer, suggesting that neurotrophins and nerves may contribute to thyroid malignancy. Nerves and neurotrophins are emerging as important mediators of cancer initiation and progression, and may represent new biomarkers or therapeutic targets.

It was first hypothesized that proNGF may be a diagnostic biomarker for thyroid cancer, either in serum or solubilised thyroid-biopsy material, in patients with benign and malignant nodular thyroid disease. ProNGF was detected in a minority of specimens, but there was no correlation with thyroid malignancy. However, serum proNGF correlated with hyperthyroidism, a relationship that is supported by animal data.

It was then considered whether proNGF could have a functional role in thyroid cancer, examining first the evidence for innervation of thyroid cancer. Nerve density in papillary thyroid cancers was found to be twofold higher than in benign thyroid (12 nerves/cm<sup>2</sup> [IQR 7-21] vs 6 nerves/cm<sup>2</sup> [IQR: 3-10],  $p=0.001$ ). Most nerves were of the adrenergic subtype. Nerve density in papillary thyroid cancers was positively associated with extrathyroidal invasion ( $p<0.001$ ). Nerves in the thyroid cancer microenvironment expressed the neurotrophin receptor TrkA, as did a subset of primary thyroid cancers. Whilst proNGF expression in thyroid cancer was again demonstrated, it was not shown to be associated with neo-innervation ( $p=0.07$ ), although this relationship warrants further exploration in light of the near-significant result. ProNGF was shown to be expressed in thyroid cancer nodal metastases, which correlated with expression in paired primary tumours, although it did not correlate with markers of aggressiveness or high risk features.

The key finding of increased nerve density in the papillary subtype of thyroid cancer suggests that nerves may have biological relevance in thyroid cancer and invites further study. The presence of neurotrophin receptors in thyroid cancer raises the possibility that nerve-cancer crosstalk may be mediated by neurotrophins, however this relationship remains incompletely understood. This work establishes that proNGF is not a diagnostic biomarker for thyroid cancer in serum or biopsy material.

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Rowe CW, Haider AS, Viswanathan D, Jones M, Attia J, Wynne K, Acharya S. (2017) **Insulin resistance correlates with maculopathy and severity of retinopathy in young adults with Type 1 Diabetes Mellitus**. Diabetes Research and Clinical Practice. <https://doi.org/10.1111/cen.13114>

Rowe CW, Arthurs S, O'Neill CJ, Hawthorne J, Carroll R, Wynne K, Bendinelli C. (2018) **High-dose cholecalciferol to prevent post-thyroidectomy hypocalcaemia: a randomized double-blind placebo-controlled trial**. Clinical Endocrinology. <https://doi.org/10.1111/cen.13897>

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Marlow A, Rowe CW, Anderson D, Wynne K, King B, Howley P, Smart C. (2019) **Young children, adolescent girls and women with type 1 diabetes are more overweight and obese than reference populations, and this is associated with increased cardiovascular risk factors**. Diabetic Medicine. <https://doi.org/10.1111/dme.14133>

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Blefari N, Rowe CW, Carroll R, Weigner J, Bendinelli C, O'Neill CJ. (2019) **Long term quality of life outcomes in thyroid cancer survivors.** Royal Australasian College of Surgeons Annual Scientific Congress. Bangkok, Thailand.

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Croker E, Tan HLE, Rowe CW. (2017) **Diabetic ketoacidosis (DKA) in patients on maintenance dialysis: case series and literature review.** Australian Diabetes Society Annual Scientific Meeting, Perth, Australia.

Croker E, Chew CYM, Weigner J, Tan HLE, Bendinelli C, McGrath S, Rowe CW. (2018) **The whole is greater than the sum of its parts: synthesised triple-assessment of thyroid nodules optimises pre-operative risk-stratification.** Endocrine Society of Australia Annual Scientific Meeting, Adelaide, Australia.

Kuehn J, Rowe CW, Amico F, Ward A, Bendinelli C. (2018) **Management of an intrathyroidal cystic parathyroid gland with post-traumatic haemorrhagic transformation causing acute airway compromise.** Endocrine Society of Australia Annual Scientific Meeting. Adelaide, Australia.

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## LIST OF ABBREVIATIONS AND ACRONYMS

### A

AJCC American Joint Cancer Committee

ANOVA Analysis of Variance

ATA American Thyroid Association

ATC Anaplastic thyroid cancer

AUROC Area under the receiver-operating characteristic curve

### C

cAMP Cyclic adenosine monophosphate

CI Confidence Interval

CNS Central Nervous System

### D

DAB 3,3'-Diaminobenzidine

DTC Differentiated thyroid cancer

### E

ETE Extra-thyroidal extension

### F

FNA Fine needle aspiration biopsy

FTC Follicular thyroid cancer

### I

IgG Immunoglobulin G

IHC Immunohistochemistry

IgM Immunoglobulin M

### M

MTC Medullary thyroid cancer

mRNA Messenger Ribonucleic acid

MW Molecular weight

## **N**

NGF Nerve Growth Factor

NT Neurotrophin

## **P**

P75<sup>NTR</sup> p75 Neurotrophin receptor

PBS Phosphate buffered saline

PCR Polymerase chain reaction

PGP9.5 Protein gene product 9.5

PI Protease inhibitor

PTC Papillary Thyroid Cancer

## **R**

ROC Receiver Operating Characteristic

RNA Ribonucleic acid

RTK Receptor tyrosine kinase

## **S**

siRNA Small/short interfering RNA

SORT Sortilin

## **T**

TGCA The Cancer Genome Atlas

TMA Tissue Microarray

Trk Tropomyosin-related kinase

TSH Thyroid stimulating hormone (thyrotropin)